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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.


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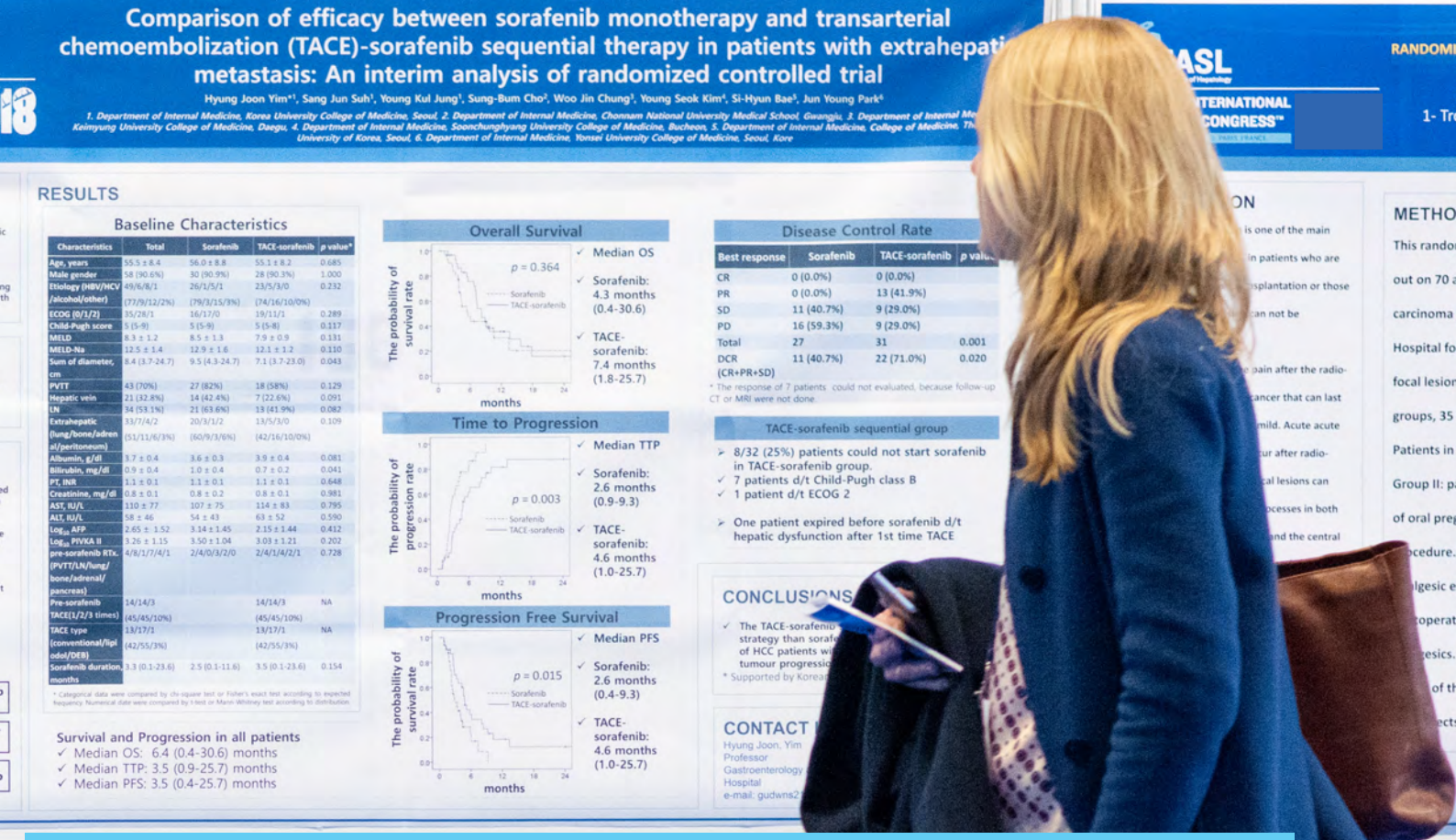

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GS-01

Efficacy, safety, and tolerability of lubiprostone for the treatment of non-alcoholic fatty liver disease: The LUBIPRONE, double-blind, randomized, placebo-controlled, phase II study

Takaomi Kessoku[1], Kento Imajo[1], Yuji Ogawa[1], Takashi Kobayashi[1], Yasushi Honda[1], Takayuki Kato[1], Wataru Tomeno[1], shingo Kato[1], Takuma Higurashi[1], Masato Yoneda[1], Hiroyuki Kirikoshi[2], Kazumi Kubota[3], Masataka Taguri[3], Takeharu Yamanaka[3], Haruki Usuda[4], Koichiro Wada[4], Satoru Saito[1], Atsushi Nakajima[1].
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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disorder, and its progression is associated with increased gut-permeability. Lubiprostone is a type 2 chloride channel activator indicated as a laxative for the treatment of patients with constipation. We have previously reported that lubiprostone ameliorated the increased intestinal permeability (PlosOne 2016). This study is a first proof of concept study that uses lubiprostone to demonstrate improvement of NAFLD by controlling gut-permeability. The aim of study is to evaluate the efficacy, safety, and tolerability of lubiprostone on this disorder (Protocol Paper, Kessoku T, contemporary clinical trial 2018).
Method: In this double-blind, placebo-controlled, randomized, phase II trial, patients with NAFLD (ALT ≥ 40 IU/L, MRI-PDFF ≥ 5.2%, MR elastgraphy < 6.7kPa) were enrolled. 12μg or 24μg of lubiprostone or placebo were administered orally for 12 weeks. The primary end point was defined as the improvement in ALT level from the baseline to the end of treatment. A planned key secondary end point was defined as the improvement in the change of lactulose-mannitol ratio (LMR), which was used as the golden standard for the measurement of gut-permeability. The other end points were blood endotoxin activity, MRI-PDFF and liver stiffness measured by MR elastography. Analyses were done by intention-to-treat. This trial was registered with UMIN000026635.
Results: 150 NAFLD patients were randomly assigned. 41 patients in the placebo, 47 in the 12 μg lubiprostone, and 51 in the 24 μg lubiprostone were included in the full analysis population. After 12 weeks of treatment, the lubiprostone group showed significantly greater improvements in the mean ALT levels (placebo vs 12 μg lubiprostone: p = 0.0096, placebo vs 24 μg lubiprostone: p = 0.0025), LMR (placebo vs 12 μg lubiprostone: p = 0.0125, placebo vs 24 μg lubiprostone: P = 0.0017), blood endotoxin activity (placebo vs 12 μg lubiprostone: p = 0.0008, placebo vs 24 μg lubiprostone: P = 0.0002), MRI-PDFF (placebo vs 12 μg lubiprostone: p < 0.001, placebo vs 24 μg lubiprostone: P = 0.001) and liver stiffness (placebo vs 12 μg lubiprostone: p = 0.0207, placebo vs 24 μg lubiprostone: P = 0.0002). But no statistically significant difference was observed between the 12 μg and 24 μg lubiprostone group. In safety and tolerability, drop-out ratio of placebo, 12 μg lubiprostone, 24 μg lubiprostone, were 5%, 0%, and 9%, showing that 24 μg lubiprostone had significantly higher rates of adverse events (placebo vs 12 μg lubiprostone: no significant, placebo vs 24 μg lubiprostone: P = 0.0025), especially diarrhea, compared to the other groups.
Conclusion: Lubiprostone showed favourable efficacy and tolerability when administered at 12μg doses to NAFLD patients, suggesting manipulating gut permeability may be a promising novel treatment target for the treatment of NAFLD.

GS-02

Efficacy of GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid: Interim efficacy results of a phase 2 clinical trial

George Dalekos[1], Pietro Invernizzi[2], Frederik Nevens[3], Van Vlierberghe Hans[4], Ehud Zigmond[5], Raul J. Andrade[6], Ziv Ben Ari[7], Michael Heneghan[8], Jonathan Huang[9], Stephen Harrison[10], Gerald Minuk[11], Schattenberg JörnPD Dr.[12], Christophe Moreno[13], John Vierling[14], Catherine Vincent[15], Christopher Bowlus[16], Yoav Lurie[17], Luigi Muratori[18], Grazia Niro[19], Gideon Hirschfield[20], Anthony Post[21], Stefan Zeuzem[22], Tania Welzel[22], Chin Lye Ch'ng[23], Cynthia Levy[24], Michael Miller[25], Agustin Albillos[26], Jane D. Collier[27], Lynsey Corless[28], Douglas Dieterich[29], Andreas E Kremer[30], George Papatheodoridis[31], David Romeo[32], Marina Silveira[33], David Bernstein[34], Michal Cohen-Naftaly[35], Annarosa Floreani[36], Brian Borg[37], Elizabeth Carey[38], Coral Hollywood[39], Benedict Maliakkal[40], Marco Marzioni[41], Mordechai Rabinovitz[42], Christian Rupp[43], David Sheridan[44], Carmen Stanca[45], Mark G Swain[46], Ella Veitsman[47], P Spyridon Dourakis[48], Philippe Wiese[49]. *[1]University of Thessaly,*

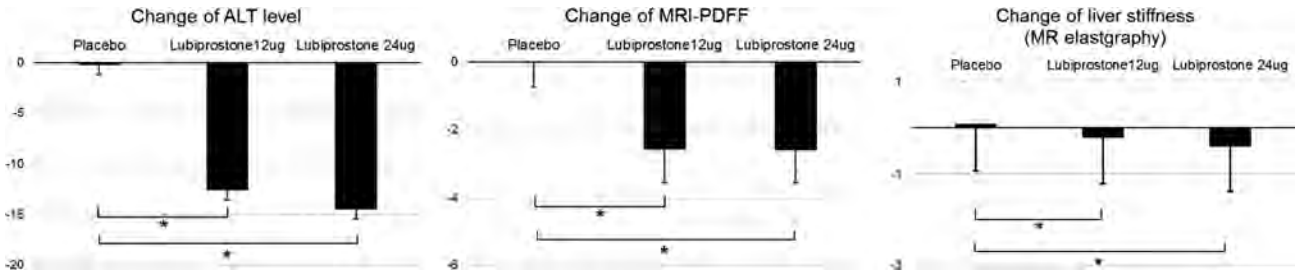

Figure: (abstract: GS-01)

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Background and aims: GKT831 is a potent inhibitor of the nicotinamide adenine dinucleotide phosphate oxidases 1 and 4 (NOX1/4). NOX1/4 produce reactive oxygen species and modulate intracellular signaling pathways through oxidation of target proteins. In response to cellular stress including cholestatic injury to cholangiocytes and hepatocytes, NOX1/4 coordinate the activation of multiple inflammatory and fibrogenic pathways. GKT831 has shown marked anti-inflammatory and anti-fibrotic activity in multiple models of advanced cholestatic diseases. We are conducting a 24-week, randomized, double blind, placebo controlled trial to assess the safety and efficacy of GKT831 in patients with primary biliary cholangitis (PBC) and inadequate response to ursodeoxycholic acid (UDCA).
Method: PBC patients on a stable dose of UDCA and with alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) levels ≥ 1.5 times the upper limit of normal (ULN), and normal bilirubin were randomized to GKT831 400 mg once a day (QD), 400 mg twice a day (BID), or placebo. All subjects continued UDCA treatment during the treatment period. A predefined interim efficacy analysis was conducted when 92 patients completed 6 weeks of treatment.
Results: 111 patients with high baseline disease activity were randomized (female = 91%, mean ALp = 312 IU/L, mean GGT = 225 IU/L). Changes in the primary efficacy end point GGT, a marker of liver and bile duct injury, were-7%, –12%, and-23% in the placebo, 400 mg OD and 400 mg BID groups, respectively ($p < 0.01$ for 400 mg BID vs placebo). GKT831 achieved even greater GGT reductions (29% for GKT831 400 mg BID vs 8% for placebo, $p < 0.01$) in patients with higher baseline GGT (≥ 2.5 × ULN, n = 68), suggesting that GKT831 may also benefit patients with more advanced disease. Changes in ALP were-2%, –8% and –17% in the placebo, 400 mg OD, and 400 mg BID groups, respectively ($p < 0.001$ for 400 mg BID vs placebo). Although patients had low baseline levels of liver transaminases and high sensitivity C-reactive protein, dose dependent reductions were achieved. Total and conjugated bilirubin remained unchanged.
Conclusion: GKT831 achieved rapid, dose and time dependent reductions in markers of cholestatic bile duct and liver injury. These reductions in disease activity were highly significant for both ALP and GGT in the 400 mg BID group at week 6. Quality of life and markers of liver fibrosis will be assessed at week 24.

GS-03

Global real world evidence of sofosbuvir/velpatasvir as a simple, effective regimen for the treatment of chronic hepatitis C patients: Integrated analysis of 12 clinical practice cohorts

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Background and aims: The WHO estimates that 71 million people are chronically infected with hepatitis C (HCV) globally and has a goal to eliminate HCV by 2030. SOF/VEL is a pangenotypic, panfibrotic, protease inhibitor (PI)-free, single duration, single tablet regimen (STR), offering a simplified treatment option to address this goal.
This integrated analysis of real-world data from clinical practice cohorts representing a heterogeneous patient population evaluates the efficacy of SOF/VEL for 12 weeks, without ribavirin (RBV), in patients with HCV across all genotypes (GT) and fibrosis stages, including patients with compensated cirrhosis (CC).
Method: Data from 12 clinical practice cohorts across North America and EU, representing 8 countries, are included. Adults were treated according to local standards of care, with CC determined by the treating physician according to local clinical practice. Data on GT1-6 patients with CC or without CC (NC), treatment naïve (TN) or treatment experienced (TE) [pegIFN + RBV±PI], who initiated SOF/VEL for 12 weeks prior to November 2018 were included. Patients with a history of decompensation, prior NS5A inhibitor exposure, treatment duration > 12 weeks or addition of RBV were excluded. For patients who completed treatment and with virological outcome data available at abstract submission, sustained virological response (SVR; ≥ 12 weeks after end-of-treatment) was assessed.
Results: Overall, 5760 patients with HCV GT1-6 were included. At abstract submission, virologic outcome was available for 4491 patients. The median age was 56 years, 58.4% were male and GT distribution was as follows: 31.5% GT1, 30.9% GT2, 30.8% GT3, 6.0% GT4-6, 0.9% mixed or unknown GT. CC was present in 889 (20%) patients. 1998 (44%) TE patients were included. 98.9% of patients (4442/4491) achieved SVR, with 99.1%; 98.4%; 98.4% SVR respectively in NC, CC patients and patients with unknown cirrhotic status, and 98.5%; 99.5% and 97.1% SVR respectively in TN patients, TE patients and DAA naïve patients with unknown treatment history. Demographics, SVR results and subgroup analyses of the full cohort will be available at the conference.
Conclusion: Simplicity is key in reaching the WHO goals for HCV elimination. SOF/VEL for 12 weeks is a simple and highly effective regimen that cures HCV patients, irrespective of GT, cirrhosis status or treatment history, with a manageable drug interaction profile, which will contribute to the implementation of test and treat strategies.

GS-04

Addition of stent placement to angioplasty for Budd-Chiari syndrome improves recanalization patency and reduces symptom recurrence with adequate safety: A randomised controlled trial

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Background and aims: Angioplasty is recommended by guidelines as the first-line interventional treatment for Budd-Chiari syndrome (BCS), the long-term patency of which consequently determines symptom recurrence, ensuing treatment and patient outcome. Although previous retrospective studies indicated that angioplasty with metal stents is conducive to maintain patency, this issue has not been investigated in prospective studies due to the rarity nature of the disease. We therefore designed the current randomized controlled trial to test the hypothesis that the addition of stent placement to angioplasty for BCS could improve patency and reduces symptom recurrence with adequate safety.
Method: From July 2014 to September 2017, 150 consecutive BCS patients were screened. Eighty-eight patients with short-length stenosis were finally enrolled and then randomly assigned to angioplasty (AP, n = 45) or angioplasty with stent placement group (AP+SP, n = 43). Primary end point was patency of recanalized veins. Secondary end points included symptom recurrence, procedure-related complications, hepatocellular carcinoma (HCC) incidence, and survival.
Results: During a median follow-up of 27 months in the entire cohort, incidence of recanalized veins restenosis were significantly lower in AP+SP group than in AP group (0% vs. 24% at 1 year and 4% vs. 40% at 3 years, respectively; HR = 21.5, 95% confidence interval [CI] 2.9-161.4, p < 0.001, Figure A, C). Noteworthy, symptom recurrences were also less frequent in AP+SP group (symptom recurrence-free survival being 5% vs. 33% at 1 year and 11% vs. 60% at 3 years, HR = 4.4, 95%CI 2.0-9.8, p < 0.001, Figure B, D). Meanwhile, procedure-related complications were not significantly different between the two groups (2% vs. 0%, p = 0.489), with no cases of stent fracture or migration during follow-up. HCC incidence (4.6% vs. 2.2%, p = 0.612) as well as 3-year survival (97% vs. 98%, p = 0.550) were similar between the two groups.
Conclusion: As the only randomised controlled trial regarding BCS to date, the current study indicated that the addition of metal stents to angioplasty significantly improves patency of recanalized veins and, more importantly, lessens symptom recurrence without increasing the risk of procedure-related complications, thereby relieving the burden of revision and reducing the necessity of procedures with higher invasiveness. Therefore, stent placement should be preferred in angioplasty for BCS patients.

GS-05

MHC-II invariant chain adjuvanted chimpanzee adenoviral and MVA hepatitis C vaccines elicit unprecedented levels of anti-viral T-cell immune responses in humans

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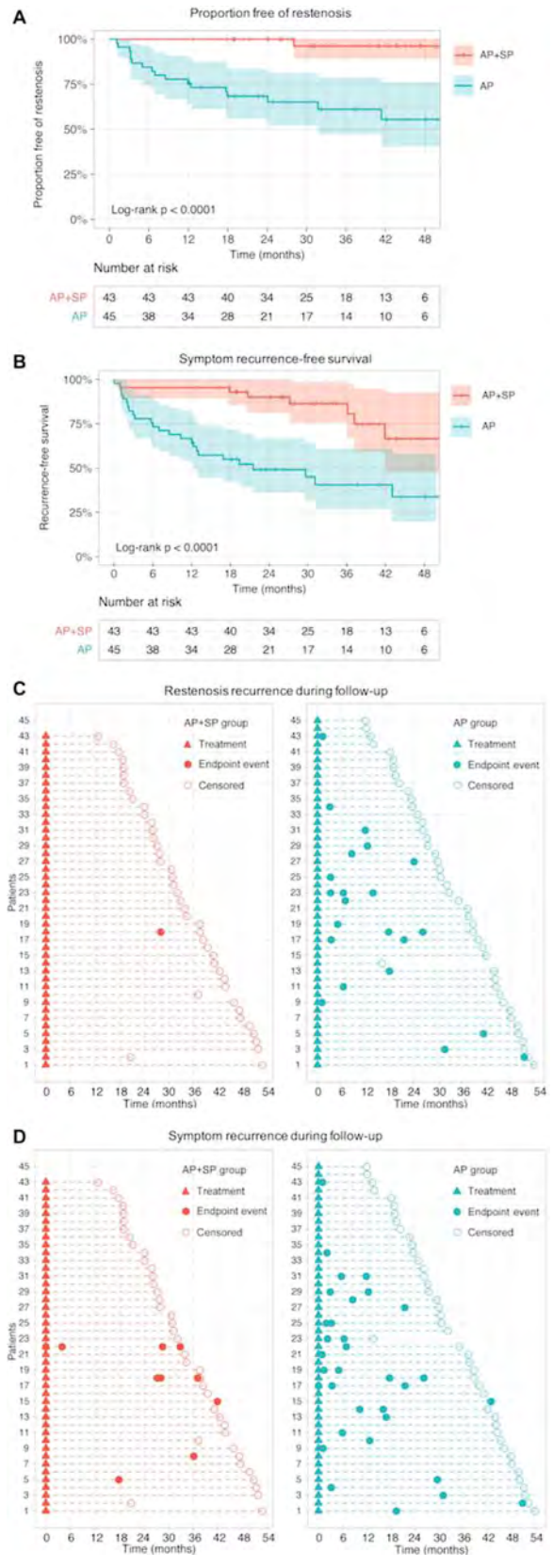

Figure: (abstract: GS-04)

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Background and aims: A vaccine for HCV prevention is highly desirable. Pre-clinical studies in mice and non-human primates have shown that linking MCH class II invariant chain (li) to an immunogen encoded by viral vectors enhances immunogen-specific T-cell responses. We evaluated this strategy in humans for the first time, using viral vectors chimpanzee adenovirus 3 (ChAd3) and modified vaccinia virus Ankara (MVA) encoding the HCV non-structural immunogen (NSmut) linked to human (h)li.

Method: ChAd3-hliNSmut and MVA-hliNSmut were given 8 weeks apart in 17 healthy volunteers aged 18-65 in two doses i.m. (n = 6; ChAd3-hliNSmut 5×10^9/MVA-hliNSmut 5×10^7 viral particles[vp], n = 11; ChAd3-hliNSmut 2.5×10^{10}/MVA-hliNSmut 2×10^8vp). HCV specific T cell magnitude, breadth and polyfunctionality was assessed using fresh PBMCs in ex-vivo IFN-ɣ ELISpot assays, ICS and Class I multimers. We monitored anti-Ii T cell and antibodies. HCV immune responses were compared to those elicited using non-Ii vaccines. Adverse events (AEs) were reported.

Results: Side effects were typical of those observed after Ad/MVA vaccination and were generally mild. No serious AEs, persistent grade 3 solicited AEs, or clinically-significant changes in laboratory parameters were reported. Following low dose vaccination high magnitude HCV specific responses were observed (mean ±SD) 555SFU/10^6PBMC (±784) post prime and 4209SFU/10^6PBMC (±3968) post boost. At high dose, the magnitude and breadth of HCV specific T cell responses were further enhanced at 2538SFU/10^6PBMC (±2137) post prime and 6869SFU/10^6PBMC (±3667) post boost). These were significantly higher and more sustained than those seen at the same dose in non-Ii vaccines ($p = 0.015$). Polyfunctional HCV specific CD8+ and CD4+ responses were induced (> 20% CD8+/CD3+ in some individuals) (fig 1). Class I multimer analysis showed that up to 8% of CD8+/CD3+ targeted single HCV epitopes; these were mostly "effector memory" with high levels of T cell activation and cytolytic markers. No volunteers developed anti-Ii T cell or antibody responses.

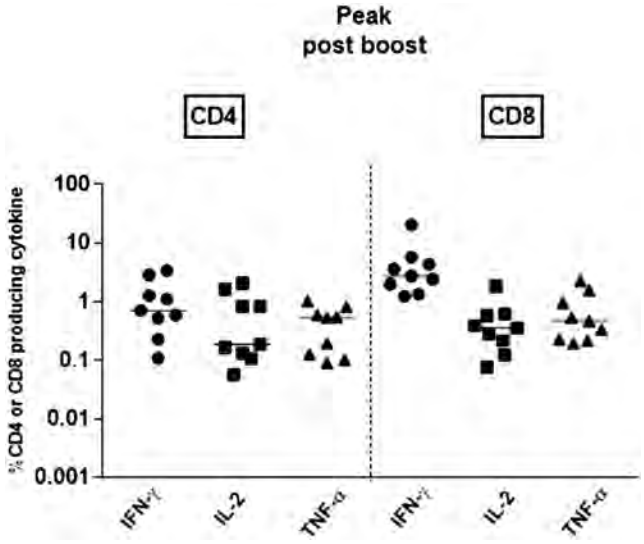

Figure 1: Functionality of vaccine induced HCV specific CD4+/CD8+ T cells.

Conclusion: Class-II invariant Ii adjuvanted chimpanzee adenoviral and MVA vaccines were well tolerated and elicited unprecedented levels of HCV specific T cell immune responses in humans. This new strategy could be developed to contribute to the HCV elimination targets, and paves the way for developing class-II Ii chain vaccines against cancer and other infections.

GS-06

Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH

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Background and Aims: Obeticholic acid (OCA), an FXR agonist, improved both fibrosis and histologic features of nonalcoholic steatohepatitis (NASH) in the Ph2 FLINT study. This Month 18 pre-specified interim analysis of the ongoing Ph3 REGENERATE study evaluated the effect of OCA on liver histology in patients (pts) with biopsy-confirmed NASH.

Method: Pts with NASH and fibrosis stages F2-3 (ITT), and an exploratory group of F1 pts with metabolic syndrome, were randomized to placebo (PBO), OCA 10 mg, or OCA 25 mg QD. Primary endpoints were fibrosis improvement (≥1 stage) with no worsening of NASH, or NASH resolution with no worsening of liver fibrosis per liver biopsy. The safety population included all randomized and dosed pts (F1-3, N = 1968). Clinical outcomes will be evaluated at the end-of-study.

Results: The ITT population included 931 pts (PBO [n = 311], OCA 10 mg [n = 312] or OCA 25 mg [n = 308]), comprised of 44% F2 and 56% F3. Baseline characteristics were well-balanced across groups. Results in Table. The primary fibrosis endpoint was met by 11.9% PBO, 17.6% OCA 10 mg (p = 0.0446 vs PBO), and 23.1% OCA 25 mg (p = 0.0002 vs PBO) pts (ITT). The primary NASH endpoint was not statistically significant (ITT); however, in a pre-specified analysis that included F1-F3 pts (N = 1218), more OCA 25 mg pts achieved NASH resolution. Significantly more pts on OCA 25 mg showed improvements in hepatocellular ballooning (p = 0.0011 vs PBO) and lobular inflammation (p = 0.0322 vs PBO). Dose-dependent reductions in ALT, AST and GGT were observed. Pruritus was the most common AE (19% PBO, 28% OCA 10 mg, 51% OCA 25 mg) and was predominantly mild to moderate in severity (severe pruritus: < 1% PBO, < 1% OCA 10 mg, 5% OCA 25 mg). More OCA 25 mg pts discontinued due to pruritus (< 1% PBO, < 1% OCA 10 mg, 9% OCA 25 mg; protocol mandated discontinuation of treatment with severe pruritus). SAEs occurred in 11% PBO, 11% OCA 10 mg and 14% OCA 25 mg pts. Increases in LDLc with OCA were observed by Week 4, but approached baseline by Month 18 (OCA 25mg: LS mean change Wk4 +22.6 mg/dL, M18 +4.0 mg/dL). Cardiovascular SAEs were similar across groups (2% PBO, 1% OCA 10 mg, 2% OCA 25 mg). Cholelithiasis or cholecystitis were reported in 1% PBO, 1% OCA 10 mg and 3% OCA 25 mg pts. Hepatic disorder SAEs were uncommon but occurred more frequently in OCA 25 mg pts (<1%). Three deaths occurred; none were considered treatment-related (PBO n = 2; OCA 25 mg n = 1).

	Placebo	OCA 10 mg	OCA 25 mg
Primary: ITT Population (F2 + F3)	n = 311	n = 312	n = 308
Fibrosis improvement + no worsening of NASH	11.9%	17.6% p = 0.0446	23.1% p = 0.0002
NASH resolution + no worsening of fibrosis	8.0%	11.2% p = 0.1814	11.7% p = 0.1268
Improvement in hepatocellular ballooning	23.2%	27.2% p = 0.2423	35.1% p = 0.0011
Improvement in lobular inflammation	35.7%	39.1% p = 0.3380	44.2% p = 0.0322
Additional: Full Efficacy Analysis (ITT + F1)	n = 407	n = 407	n = 404
Fibrosis improvement + no worsening of NASH	10.6%	15.7% p = 0.0286	21.0% p < 0.0001
NASH resolution + no worsening of fibrosis	7.9%	11.3% p = 0.0903	14.9% p = 0.0013

Overall study discontinuations (ITT): 16% PBO, 17% OCA 10 mg, 15% OCA 25 mg.

Conclusion: Treatment with OCA 25 mg improved liver fibrosis, key histologic features of steatohepatitis and liver biochemistry, demonstrating consistent efficacy with an overall AE profile similar to previous studies.

NAFLD Pathophysiology – Target identification

PS-001

Roles of CC chemokine receptor 9 in the progression and carcinogenesis of murine non-alcoholic steatohepatitis

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Background and aims: The number of non-alcoholic steatohepatitis (NASH) patients are increasing globally. Recently, many researches focus on CCR2/CCR5 for therapeutic target for NASH. Our group has demonstrated the pathogenic role of $CCR9^{+}$ macrophages in a murine model of acute hepatitis and its effect was greater than CCR2. This research aimed to examine a role of CCR9/CCL25 axis and reveal the therapeutic potential against NASH and NASH-based hepatocarcinogenesis.

Method: 50 biopsy-proven NAFLD patients were recruited in this study. With written informed consent, blood sample were obtained and serum CCL25 level was measured by ELISA, which was compared

with healthy volunteers. For further study, Male C57BL/6 (WT) and CCR9 deficient ($CCR9^{-/-}$) mice were fed either a 60% high-fat and 1% high-cholesterol diet (HFHC) or a normal diet for 24 weeks as a NASH model. Bone marrow transplantation was performed to generate Ly5.1 mice with Ly5.1 or Ly5.2 $CCR9^{-/-}$ bone marrow (BM), and Ly5.2 $CCR9^{-/-}$ mice with Ly5.1BM, and they were fed with HFHC diet for 6 months. In other experiments, WT mice fed with HFHC diet for 18 weeks were subsequently administrated CCR9 antagonist for 6 weeks. Furthermore, we analyzed carcinogenesis with WT and $CCR9^{-/-}$ mice administrated diethylnitrosamine (DEN) intraperitoneally at 3 weeks old and fed 60% HF diet (HF+DEN) for 45 weeks.
Results: First, serum CCL25 level was significantly higher in NAFLD patients than that of healthy volunteer. To elucidate the role of CCR9, we analyzed WT and $CCR9^{-/-}$ mice fed with HFHC diet and found that $CCR9^{-/-}$ mice fed with HFHC demonstrated ameliorated NASH progression both in serologically and histologically compared with WT mice. To clarify the immunological mechanism, we analyzed liver infiltrating cells and found the increased TNF-α-producing $CCR9^{+}CD11b^{+}$ macrophages in WT mice fed with HFHC. Besides, CCR9 expression was significantly higher on hepatic stellate cell (HSC) in WT fed with HFHC by immunofluorescence analysis, and the expression of fibrosis-related genes were significantly decreased in HSCs derived from $CCR9^{-/-}$ mice fed with HFHC. WT mice reconstituted with $CCR9^{-/-}$ mice-derived BM developed severe steatohepatitis compared to $CCR9^{-/-}$ mice reconstituted with WT mice-derived BM, reinforced the role of CCR9 in resident liver cells rather than in BM cells in the progression of liver fibrosis. Reduction of liver fibrosis in mice administered with CCR9 antagonist further support the pathogenic role of CCR9 in NASH development. Finally, we investigated HF+DEN-induced carcinogenesis model, and revealed that development of hepatocellular carcinoma was suppressed both in the number and the diameter in $CCR9^{-/-}$ mice.
Conclusion: CCR9/CCL25 axis mainly in HSCs plays a pathogenic role both in murine NASH progression and NASH-based HCC development, suggesting a potential clinical therapeutic target against NASH in the future.

PS-002
Persistence of hepatic and adipose tissue alterations in T helper 17 cells, CD8+ cytotoxic T cells and regulatory T cells despite metabolic and histological improvement upon diet reversal in a high-fat high-fructose mouse model of NAFLD

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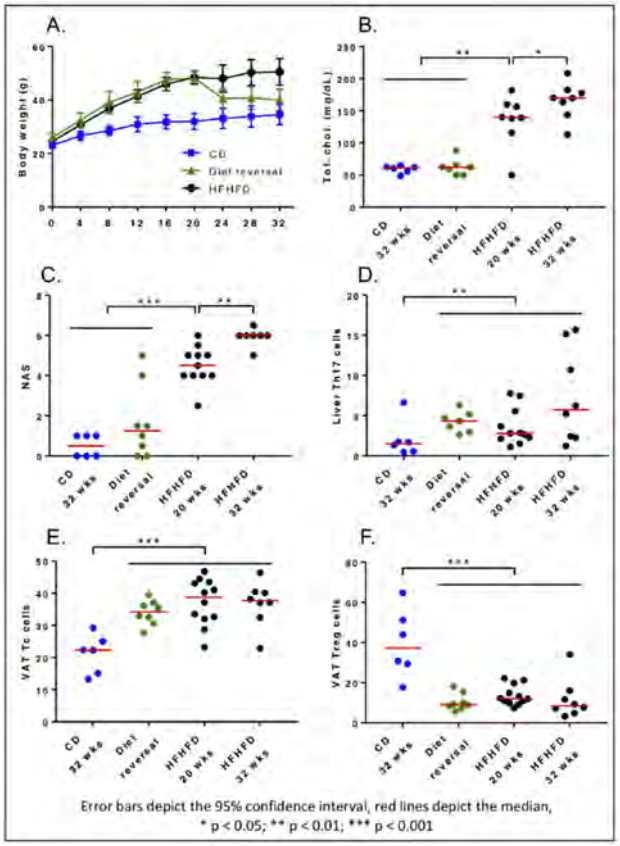
Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a multisystem condition in which the liver, adipose tissue and the immune system are involved. T cells form a part of the adaptive immune system and can be subdivided in several subsets with distinct functions. We previously demonstrated that mice with severe NAFLD exhibit elevated hepatic T helper 17 cells (Th17, CD4+ RORγt+) cells, an abundance of visceral adipose tissue (VAT) CD8+ cytotoxic T cells (Tc) and a reduction of VAT regulatory T cells (Treg, CD4+ CD25+ Foxp3+). This study aimed at investigating the potential reversibility of these alterations upon diet reversal.
Method: Male 8-week old C57BL/6J mice were fed a high-fat high-fructose diet (HFHFD) for 20 weeks. Subsequently, a diet reversal (DR) was performed by substituting the HFHFD with control diet (CD) and continuing the CD for 12 additional weeks. Three control groups were included: mice fed CD for 32 weeks, HFHFD for 20 weeks and HFHFD for 32 weeks. Liver tissue was assessed histologically and the NAFLD Activity Score (NAS) was calculated. T-cell subsets were characterised in liver and visceral tissue (VAT) via flow cytometry. Tc cells were expressed as a percentage of CD45+ CD3+ cells, Treg and Th17 cells as a percentage of CD3+ CD4+ cells.
Results: HFHFD-feeding for 20 and 32 weeks confirmed the previous findings of metabolic alterations and NAFLD development (Figure 1A-C), and the associated hepatic and VAT T-cell alterations, specifically an increase in hepatic Th17 cells (Fig. 1D) and VAT Tc cells (Fig. 1E), as well as a reduction in VAT Treg cells (Fig. 1F), compared to CD-fed mice. DR induced weight loss (Figure 1A, $p < 0.001$), a decrease in cholesterol levels (Figure 1B, $p < 0.001$) and a decrease in NAS (Figure 1C, $p < 0.001$). No significant difference was observed in NAS between CD-fed mice and DR mice ($p = 0.160$). Conversely, the alterations in hepatic and VAT T cell subsets were not affected by DR. Hepatic Th17 cell and VAT Tc levels were significantly higher in DR mice compared to CD-fed mice ($p = 0.015$ and $p = 0.003$ resp.), whereas no difference existed between the DR group and mice fed HFHFD for 20 and 32 weeks (Figure 1D-E). VAT Treg levels were significantly lower in DR mice compared to CD-fed mice ($p = 0.003$), whereas no difference existed between the DR group and mice fed HFHFD for 20 and 32 wks (Figure 1F).



Conclusion: Although diet reversal induced a metabolic and histological normalisation in HFHFD-fed mice, the HFHFD-induced alterations in hepatic Th17 cells, VAT Tc cells and VAT Treg cells were not reversed within a timeframe of 12 weeks. This finding challenges our current understanding of the reversibility of NAFLD-related inflammation upon life style modification.

PS-003

Activation of the miR-34a/SIRT1:AMPK axis contributes for insulin resistance and mitochondrial dysfunction in the NAFLD muscle

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) pathogenesis associates with intramyocellular lipid deposition, mitochondrial dysfunction and insulin resistance (IR). microRNAs (miRNAs/miRs), including pro-apoptotic miR-34a, also contribute for disease progression and are found modulated in liver tissue and plasma.
We aimed to investigate the functional role of miR-34a-dependent signalling pathways in modulating mitochondrial function and IR in the skeletal muscle of human and experimental non-alcoholic steatohepatitis (NASH).
Method: Skeletal muscle biopsies were obtained from morbid obese NAFLD patients undergoing bariatric surgery. C57BL/6N mice were fed different NAFLD-inducing diets, including a fast food diet for 25 weeks; a choline-deficient, high-fat diet for 14 weeks; and a choline-deficient amino acid-defined diet for 32 weeks. C2C12 muscle cells were incubated with palmitic acid (PA) in the presence or absence of an AMP-activated protein kinase (AMPK) specific activator, or upon miR-34a functional modulation.
Results: Our results showed that different muscle miRNAs, including myomirs miR-1; –26a, –27a, and –27b, as well as miR-34a, increased with human NAFLD progression. Activation of the miR-34a/SIRT1:AMPK pathway, concomitant with the development of IR and deregulation of mitochondrial-shaping proteins, was evident in C2C12 cells incubated with PA, as well as in the skeletal muscle of all three diet-induced NAFLD mice models. Functional studies established the association between miR-34a- and PA-induced muscle cell deregulation. Of note, activation of AMPK almost completely prevented miR-34a- and PA-induced cellular stress. In addition, the miR-34a/SIRT1:AMPK pathway and mitochondrial dynamics dysfunction were also found amplified in the human NAFLD muscle. Finally, muscle miR-34a expression and Mitofusin 2 protein levels correlated with hallmarks of NAFLD and disease progression.
Conclusion: Our results indicate that activation of the miR-34a/SIRT1:AMPK pathway leads to IR and mitochondrial dynamics dysfunction in skeletal muscle of human and experimental NAFLD, representing an appealing prospective target in metabolic syndrome.
(Gilead Sciences International-Research Scholars Program in Liver Diseases and SFRH/BD/104160/2014, FCT, Portugal).

PS-004

Western diet triggers a unique inflammatory phenotype of myeloid leukocytes in bone marrow and liver

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Background and aims: Changes in the composition and polarization of hepatic myeloid leukocytes, especially infiltrating monocytes and macrophages, are central features in the development and progression of metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD). Single cell RNA sequencing has been emerged as a powerful method for analyzing gene expression profiles across distinct populations especially regarding disease associated changes. We therefore aimed to elucidate the characteristic changes in immune-metabolic pathways of myeloid leukocytes that promote the development of NAFLD.
Method: Experimental NAFLD was induced in C57BL/6J mice by feeding a high-fat, high-sugar, high-cholesterol Western diet for 16 weeks. Myeloid leukocyte populations from bone marrow and liver were then purified by fluorescence-activated cell sorting and subjected to single cell RNA sequencing. Further, bone marrow derived macrophages from lean and obese mice were stimulated *in vitro* towards an inflammatory or anti-inflammatory phenotype. To analyze the relevance of TLR4 mediated fatty acid recognition, an inhibitor of TLR4 signal transduction, TAK-242, was added to macrophages stimulated with fatty acids.
Results: Analyses of single cell RNA expression showed that Western diet feeding for 16 weeks induced a characteristic gene expression profile in myeloid leukocytes that was reflected across all myeloid subsets, comprising monocytes, macrophages and dendritic cells in liver as well as bone marrow. In the liver, the inflammatory phenotype was primarily characterized by a down-regulated expression of inflammation-associated markers *S100a8* and *S100a9* in Western diet fed mice, whereas differentiation markers like *Id3* and *Chil1* were highly expressed. Strikingly, myeloid populations in the bone marrow revealed similar changes. Moreover, *in vitro* experiments showed that macrophages isolated from lean and obese mice exhibited a unique polarization in response to inflammatory stimuli which was maintained even after cultivation for 7 days. *In vitro* stimulation of macrophages with fatty acids could partially mirror the *in vivo* observed phenotype and was found to depend on TLR4 signaling.
Conclusion: Hepatic myeloid leukocytes, as well as their precursors in the bone marrow, exhibit a unique NAFLD phenotype, consistent with an attenuated inflammatory response of monocytes and monocyte dependent liver macrophages. This phenotype was maintained *ex vivo* and could be partially mirrored by TLR4-dependent fatty acid stimulation of monocytes. Taken together, these data suggest that the diet-induced inflammatory polarization of monocytes and myeloid precursors is already stably imprinted in the bone marrow and determines pathogenic responses driving NAFLD in the liver.

PS-005

Evaluation of neuromedin-B receptor variants effect on iron metabolism and liver disease

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Background and aims: A significant proportion of iron overload heritability remains unexplained. By exploiting next generation whole exome sequencing in three cases of hereditary hemochromatosis (HH) and iron overload not accounted for by known genetic risk loci, we identified rare mutations predicted to alter protein activity in Neuromedin-B receptor (NMBR) in all patients. NMBR gene encodes for a G-protein-coupled receptor involved in the regulation of appetite, the hypothalamus-pituitary axis, cell contraction and proliferation. Aim was to validate the role of NMBR in the modulation of iron metabolism.

Method: *Genetic analysis:* NMBR coding sequence was fully sequenced in 129 unrelated HH/iron overload patients and 100 blood donors with normal iron metabolism. The L390M NMBR low-frequency variant was assessed in 191 patients with non-alcoholic fatty liver disease (NAFLD) and in 68 individuals who underwent oral iron tolerance test (OITT) with hepcidin measurement. *Functional analysis:* NMBR and its natural ligand Neuromedin B (NMB) gene expression was assessed by qRT-PCR on cDNA derived from human hepatoma HepG2 cells and murine primary hepatocytes. Serum NMB was assessed by ELISA.
Results: Rare NMBR mutations were significantly enriched in HH patients as compared to both local controls (15.5% vs. 5%, $p = 0.0038$) and 1000Genomes Non Finnish European subjects ($p = 0.02$ at burden test) and were associated with higher transferrin saturation in blood donors ($p = 0.04$). In patients at risk of iron metabolism alterations due to NAFLD, the L390M variant was independently associated with higher circulating ferritin ($p = 0.03$). In the OITT cohort, L390M-variant carriers without HH had higher iron absorption (s-iron-AUC 4016 ± 741 vs 2750 ± 844, $p = 0.002$; TS%-AUC 1057 ± 192 vs 716 ± 205, $p = 0.0006$) and lower hepcidin release index (0.26 ± 0.12 vs 0.43 ± 0.23, respectively, $p = 0.033$) as compared to non-carriers following iron challenge. In a subgroup of 20 individuals, serum NMB was significantly down-modulated by iron challenge at 8 hours, corresponding to the hepcidin release peak, and was decreased in L390M-variant carriers and HH individuals in parallel with increased TS%.
Conclusion: NMBR mutations may contribute to explain a fraction of still unexplained predisposition to iron overload.

PS-006
MBOAT7 downregulation induces hepatic lipid accumulation
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Background and aims: The rs641738 C > T variant in Membrane bound O-acyltransferase domain-containing 7 gene (MBOAT7), involved in phosphatidylinositol acyl-chain remodeling, increases the risk of non-alcoholic fatty liver disease (NAFLD), inflammation and fibrosis due to lower protein expression. Our preliminary results demonstrated that the Fatty Acid Transport protein 1 (FATP1) was upregulated upon Mboat7 silencing in mice. Aim of this study was to evaluate the impact of MBOAT7 downregulation and FATP1 overexpression on hepatic fat accumulation.
Method: We examined hepatic MBOAT7 and FATP1 in 119 obese patients. We silenced MBOAT7 in HepG2 hepatoma cells (MBOAT7$^{-/-}$) by Crispr/Cas9 technology. Then, MBOAT7$^{-/-}$ cells were exploited to produce a double stable model of full knockout MBOAT7 and heterozygous FATP1 (MBOAT7$^{-/-}$/FATP1$^{\pm}$).
Results: In obese patients, hepatic mRNA levels of MBOAT7 were inversely correlated with FATP1 ($p < 0.05$). As expected, MBOAT7 mRNA and protein levels were strongly dampened in MBOAT7$^{-/-}$ cells ($p < 0.01$). These cells showed also a phospholipidic composition pattern suggestive of altered MBOAT7 overall enzymatic activity, revealing reduced levels of lipid species associated to arachidonic and docosahexaenoic acids ($p < 0.05$). MBOAT7$^{-/-}$ cells displayed a spontaneous increase in intra-cellular fat content ($p < 0.05$), related to enhanced expression of genes involved in *de novo* lipogenesis (i.e. SREBP1, FAS, ACC) ($p < 0.05$) and increased FATP1 ($p < 0.01$). In addition, they retained activation of mTOR signaling in response to insulin (0.33μM), while AKT phosphorylation was hampered ($p < 0.05$), mirroring the condition of insulin resistant hepatocytes. FATP1 partial genetic deletion on this genetic background normalized FATP1 expression and rescued the phenotype, ameliorating fat accumulation ($p < 0.05$), *de novo* lipogenesis ($p < 0.01$) and improving insulin sensitivity.
Conclusion: These data suggest that downregulation of MBOAT7 is causally implicated in the pathogenesis of liver disease by inducing hepatocellular fat accumulation. Upregulation of FATP1 seems required to allow fat deposition associated with MBOAT7 downregulation. Further studies are needed to investigate the mechanisms linking reduced phosphatidyl-desaturation induced by MBOAT7 enzymatic activity impairment with the development of hepatic steatosis.

PS-007
Differential therapeutic effects of pan- and single PPAR agonists on steatosis, inflammation, macrophage composition and fibrosis in a murine model of non-alcoholic steatohepatitis
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Background and aims: Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors essential for the regulation of glucose and lipid metabolism in the liver and adipose tissue. Furthermore, they are also expressed in immune cells, notably macrophages, where they act as modulators of inflammation and fibrogenesis. Various single or dual PPAR agonists have been clinically evaluated in non-alcoholic steatohepatitis (NASH), yielding variable effects on aspects of NASH pathogenesis. We aimed to compare selective PPARα, γ and δ agonists with the pan-PPAR agonist lanifibranor in a therapeutic setting.
Method: Male C57BL/6 mice were fed a choline-deficient, amino acid-defined high-fat diet (CDAA-HFD) with 2% cholesterol for 12 weeks. After 6 weeks of diet, mice were treated via oral gavage with lanifibranor (30mg/kg/day) or selective PPARα (fenofibrate, 100mg/kg/day), γ (pioglitazone, 30mg/kg/day) and δ (GW501516, 10mg/kg/day) agonists for 6 weeks. Outcomes were assessed by liver histology, serum biochemistry, gene expression profiling and hydroxyproline assay. Liver and blood immune populations were investigated using flow cytometry and F4/80 immunohistochemistry.
Results: PPAR target engagement was confirmed by elevated circulating adiponectin levels in lanifibranor and pioglitazone-treated mice, and reduced serum triglycerides in lanifibranor and fenofibrate-treated mice, respectively. Lanifibranor attenuated hepatocyte ballooning, whereas both lanifibranor and, to a lesser extent, fenofibrate significantly improved histological steatosis and lobular inflammation. Fibrosis quantified on sirius red staining was ameliorated in all treatment groups, which was associated with decreases in liver hydroxyproline content and fibrogenic gene expression, most pronounced in the lanifibranor group. Hepatic monocyte-derived macrophages (MoMFs) and monocytes as well as circulating monocytes were significantly decreased following lanifibranor and partially fenofibrate treatment, alongside a shift towards Ly6C+ and MHC-II+ macrophages. Hepatic and blood lymphocyte populations remained unaffected. This coincided with a lower hepatic expression of the inflammatory mediators CCL2 and TNF-α, of the MoMF marker

CCR2, as well as a decreased F4/80 immunopositivity, particularly in mice treated with lanifibranor and fenofibrate.
Conclusion: Our data suggest that different PPARs play distinct roles in the pathogenesis of NASH. Pan-PPAR agonists combine the beneficial effects of selective PPAR agonists and may counter inflammation and disease progression more potently.

PS-008
E2F2 mediated repression of fatty acid B-oxidation is mitigated through CREB1 in progressive non-alcoholic fatty liver disease
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Background and aims: Obese patients with non-alcoholic fatty liver disease (NAFLD) are at increased risk of developing hepatocellular carcinoma (HCC). However, the mechanisms involved in the progression of NAFLD to HCC are still unclear. The role of altered fatty acid oxidation (FAO) in NAFLD progression is controversial. However, it has been described that carnitine palmitoyl-transferase II (CPTII) is decreased in steatohepatitic-HCC, which contributes to carcinogenesis. E2f2 gene expression is increased in HCC according to the oncomine database and E2F1 controls oxidative metabolism in adipose tissue. Thus, the aims here were to evaluate if E2F2 is required for the metabolic rewiring of NAFLD-driven HCC and to investigate the role of E2F2 transcription factor modulating FAO in NAFLD progression.
Method: E2f2$^{-/-}$ and wild-type mice (WT) were used. Liver disease in mice was induced by administration of diethylnitrosamine (DEN) (25 mg/kg) at 14 days-old plus high-fat (HFD) or HFD alone until sacrificed at 3 or 9 months-old. A group of chow fed (CD) mice was used. To a subgroup of DEN HFD treated mice of each genotype, CREB1 antisense oligonucleotides were injected to knockdown gene expression. AAV8 were used to decrease expression of E2F2 in vivo in liver of WT mice. E2F2 was also silenced in HepG2 cells. Lipid content, ChiP analysis, gene expression, protein levels and FAO rate were analyzed.
Results: We observed that E2f2$^{-/-}$ mice were resistant to lipid accumulation and to HCC development, which was linked to increased FAO as the oxidation rate of palmitate and the transcriptome showed. Besides, levels of CREB1 and CPTII were increased in the DEN HFD E2f2$^{-/-}$ mice. This metabolic profile was also evident when E2F2 was silenced in livers of 3 month-old WT mice fed a CD or in HepG2 cells, which demonstrate that E2F2 plays a role regulating FAO in liver hepatocytes. Knockdown of CREB1 in DEN HFD WT mice, in which E2f2 gene expression is increased, results in decrease FAO rate and CPTII levels; however, it had no effect in DEN HFD E2f2$^{-/-}$ mice, in which FAO and CPTII levels remained increased. The ChIP analysis using E2F2 or CREB antibodies did not show enrichment in the corresponding binding sites of CPTII promoters when liver disease was induced or avoided in the E2f2$^{-/-}$ mice suggesting a E2F2-CREB mediated but indirect effect.
Conclusion: E2F2 transcription factor, required for NAFLD-HCC development, cooperates with CREB1 to regulate FAO in progressive NAFLD. Absence of E2F2 avoids the metabolic rewiring of NAFLD-driven HCC arising as a target for treatment.

Autoimmune and cholestasis I

PS-009
Proteome of primary biliary cholangitis in naïve and UDCA treatment patients
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Background and aims: Primary Biliary Cholangitis (PBC) is a rare, autoimmune liver disease affecting women and men at a ratio of 9:1. Currently, there are two approved therapies: Ursodeoxycholic acid (UDCA) and Obeticholic acid to tackle the abnormal bile acid pool, cholestatic injury and chronic immune cell infiltrate. 40% of patients do not respond to UDCA thus increasing their predicted risk of liver failure according to the UK-PBC risk score.
Method: As part of the UKPBC consortium serial sampling from a prospective nested cohort of patients, proteomic profiling was carried out on (A) n = 444 UDCA-treated, (B) n = 68 Naïve treatment and (C) n = 102 controls via the Olink platform. Through a ΔΔ-Ct method 356 analytes were quantified in 4 µl serum. By multivariate analysis comparing cohorts and linear regression against risk scores and Alkaline Phosphatase (ALP) we have identified a distinct PBC proteome and close associations with biochemical responses.
Results: Interestingly, PBC proteome remains largely unchanged between naïve and treated patients. 44 analytes were significantly changed ($p < 0.05$) between these cohorts indicating that the cholestatic injury-based therapy is not affecting the systemic inflammatory profile in 77% of the protein panel. The UDCA-Modified PBC Proteome shows significant pathway clustering ($p < 5 \times 10^{-12}$). Cytokine/cytokine receptor interaction and chemokine signalling pathway remained significant (9 proteins @ FDR 2×10^{-9} and 4 proteins @ FDR 0.005). Highly significant clustering ($p < 1 \times 10^{-16}$) was seen for the proteins not significantly changed with UDCA treatment.
Correlation of this serum proteome in UDCA-treated patients with UK-PBC risk score demonstrated significant association of risk at 10 years with 172/356 (48%) proteins. Analytes such as uPA (adjusted p value = 1.52×10^{-14}) and MMP-2 (adjusted p value = 7.18×10^{-12}) correlating with risk at 5, 10 and 15 years. This is the first validation of the UK-PBC risk score utility with respect to PBC-central biological processes rather than just clinical end points. Delineating the risk score into its respective serum components has indicated the association of ALP with 197 analytes ($p < 0.05$). Of the 223 proteins in the PBC proteome unchanged in treated patients 60% showed a significant correlation with ALP.
Conclusion: This analysis is the first instance of a defined PBC Proteome. Cytokine/cytokine receptor interaction, chemokine signalling, TLR signalling, TNF signalling and JAK-STAT are associated with PBC, UDCA non-response and ALP presenting potential candidates for a mechanistically stratified second-line therapy.

PS-010
24-nor-ursodeoxycholic acid ameliorates inflammation by reshaping mTOR proteome and immunometabolism sensing programs in CD8 T-cells
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Background and aims: Hepatic lymphocyte accumulation is a common immunopathological feature in many inflammatory liver diseases including primary sclerosing cholangitis (PSC) where nor-ursodeoxycholic acid (*nor*UDCA) has shown promising results. We previously reported anti-inflammatory mechanisms of *nor*UDCA via mTOR, distinct from UDCA in CD8 T cells. How *nor*UDCA potentially modulates dynamic signaling networks and bioenegergetic pathways underlying lymphocyte immunity remains unidentified. Therefore, we aimed to explore how *nor*UDCA impacts on CD8 T cell proteome, phosphoproteome and metabolic sensing programs in context of activation.
Method: Using mass spectrometry (MS) we generated in-depth profiling of *nor*UDCA shaped CD8 T cell proteome and phosphoproteome revealing a redirection of metabolic sensing programs, migration and functions. MS data were further validated in vivo, in lymphocytic choriomeningitis virus (LCMV) model of CD8 T cell driven hepatic immunopathology and in Mdr2 (Abcb4) KO model of PSC.
Results: Our MS data confirmed our previous finding of *nor*UDCA mTOR inhibitory effect as evidenced by reduced phosphorylation of mTOR substrate S6 kinase (Ser235/236) by 43% ($p < 0.05$). Consequently, *nor*UDCA reduced abundance of mTOR regulated glycolytic enzymes such as hexokinase2 and lactate dehydrogenase B ($p < 0.05$). Subsequently, *nor*UDCA treatment reduced abundance of effector molecules GranzymeB and IFNγ by 43% ($p < 0.005$) and 21% ($p < 0.05$), respectively and increased abundance of lymphatic retention patterns, like CD62L and CCR7 ($p < 0.05$). Conversely, fatty acid (FA) oxidation was enhanced by *nor*UDCA as shown by higher abundance of long-chain FA transport protein4, Fatty-acyl-CoA synthase, Cpt1α and Cpt2 ($p < 0.005$), while FA synthesis was reduced as shown by lower abundance of FA synthase. Interestingly, glutaminolysis was unaffected. Supporting MS finding, in vivo *nor*UDCA ameliorated hepatic injury and inflammation induced by LCMV as shown by lower ALT ($p < 0.005$), decreased liver expression of GranzymeB by 41% ($p < 0.005$) and Cxcl10 by 40% ($p < 0.005$), and reduced CD8 effector T cell hepatic infiltration without compromising virus control. Similarly, *nor*UDCA reduced CD8 T cell infiltration in liver of Mdr2 KO mice.
Conclusion: Overall, we unraveled novel metabolic modulatory potency of *nor*UDCA by reshaping mTOR proteome and phosphoproteome, indicating *nor*UDCA may represent a promising immunometabolic drug for treatment of T-cell based inflammatory liver diseases.

PS-011
New synthetic conjugates of ursodeoxycholic acid inhibit hepatorenal cystogenesis in experimental models of polycystic liver disease

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Background and aims: Polycystic liver diseases (PLDs) are inherited genetic disorders characterized by the development of multiple fluid-filled biliary cysts. We have previously shown that ursodeoxycholic acid (UDCA) inhibits hepatic cystogenesis in experimental models and patients with PLD. Furthermore, histone deacetylase 6 (HDAC6) inhibitors reduced hepatorenal cystogenesis in PCK rats. However, both therapies showed limited efficacy. Since UDCA does not display any HDAC6 inhibitory activity, and most of the available HDAC6 inhibitors are potentially toxic, we aimed to design new synthetic UDCA conjugates with selective HDAC6 inhibitory capacity (HDAC6i-UDCA) and evaluate their dual therapeutic potential for PLD.
Method: Eleven synthetic HDAC6i-UDCA#1-11 conjugates were designed, analysed *in silico*, synthesized and tested for their inhibitory activity on HDAC6 and HDAC1. After lead selection, PCK rats were orally administered 15 mg/kg day of HDAC6i-UDCA#1 for 5 months. After sacrifice, serum, bile, liver and kidney were collected and analysed. The molecular mechanisms of HDAC6i-UDCA#1 were investigated in PLD cholangiocytes.
Results: 4 of the 11 designed HDAC6i-UDCA conjugates presented highly selective HDAC6 inhibitory activity, with HDAC6i-UDCA#1 emerging as the most promising molecule. *In silico* experiments predicted an active contribution of UDCA to the HDAC6 inhibitory activity of HDAC6i-UDCA#1, which was confirmed by IC50 determination. HDAC6i-UDCA#1 treatment significantly reduced liver and kidney weights, respective tissue to body weight ratios and liver cystogenesis. In parallel, increased serum levels of albumin and reduced serum levels of urea were found in treated PCK rats. Administration of HDAC6i-UDCA#1 increased the liver and kidney alpha-tubulin acetylation, a HDAC6 target, and restored the related primary cilium length in cystic cholangiocytes. UDCA-HDAC6i#1 treatment also resulted in increased UDCA concentration in liver, bile, peripheral and portal blood. *In vitro*, HDAC6i-UDCA#1 inhibited the 2- and 3-dimentional growth of cystic cholangiocytes and decreased ERK1/2 phosphorylation, in a greater extent than its forming components [i.e. UDCA and 4- (aminomethyl)-N-hydroxybenzamide hydrochloride], alone or in combination. HDAC6i-UDCA#1 was transported into cells through NTCP, OCT1 and OCT3 transporters.
Conclusion: HDAC6i-UDCA#1 inhibited hepatorenal cystogenesis in an animal model of PLD and displayed greater antiproliferative effects on PLD cholangiocytes than UDCA alone, while retaining the UDCA hepatotropic characteristics. In addition to the HDCA6 inhibitory capacity, increased UDCA concentrations in treated animals, suggest a release of UDCA upon metabolism of HDAC6i-UDCA#1, minimizing potential toxicity of metabolites and highlighting the relevance of this promising dual therapy for the treatment of PLDs.

PS-012
Validation of histologic and non-invasive measures of fibrosis as surrogate end points of disease progression in patients with primary sclerosing cholangitis

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Background and aims: Surrogate end points that predict complications are necessary for approval of new therapies for PSC. We assessed associations between histologic and non-invasive fibrosis markers with disease progression in PSC.
Method: We included 209 adults with non-cirrhotic PSC from a 96-week phase 2 trial of simtuzumab. Liver fibrosis (baseline [BL], week 48 [W48], and W96) was staged by Ludwig classification, hepatic collagen and α-SMA expression were quantified by morphometry, liver stiffness (LS) was measured by transient elastography (TE), and ELF was calculated. Cox regression determined associations between these end points with PSC-related events (i.e. progression to cirrhosis, decompensation, transplantation, ascending cholangitis).
Results: Median age was 44 years, 62% were male, 48% had ulcerative colitis, 61% were on UDCA, and the median serum ALP was 248 U/L. At BL, 29% had F0-1 fibrosis, 71% had F2-3, and median LS by TE (n = 52) was 8.2 kPa. By W96, 56 (27%) developed a PSC-related event (progression to cirrhosis [n = 29], ascending cholangitis [25], ascites [1], variceal hemorrhage [1]). Among BL factors, F2-3 fibrosis (HR 4.13; 95% CI 1.77-9.64) and greater hepatic collagen, α-SMA expression, and ELF were associated with disease progression (Table). After adjustment for BL factors, non-worsening of fibrosis (HR 0.31; 95% CI 0.18-0.53) and fibrosis improvement (HR 0.04; 0.01-0.31) were associated with a reduced risk of progression. On the contrary, increases in hepatic collagen, α-SMA, ELF (and TIMP-1, PIII-NP, and hyaluronic acid), and LS by TE were associated with an increased risk of events. BL ALP, but not its change, was associated with progression.

Table: Predictors of Disease Progression

	HR (95%CI)*	P value
Ludwig stage		
BL F2-3 vs F0-1	4.13 (1.77-9.64)	**0.001**
Non-worsening vs worsening	0.31 (0.18-0.53)	**< 0.001**
Improvement vs no change/ worsening	0.04 (0.01-0.31)	**0.002**
Hepatic collagen, %		
BL	1.09 (1.03-1.16)	**0.006**
Change	1.14 (1.10-1.17)	**< 0.001**
α-SMA, %		
BL	1.15 (1.07-1.24)	**< 0.001**
Change	1.05 (1.04-1.07)	**< 0.001**
ELF		
BL	1.80 (1.47-2.22)	**< 0.001**
Change	1.86 (1.37-2.53)	**< 0.001**
LS by TE, kPa		
BL	1.02 (0.99-1.05)	0.21
Change	1.08 (1.03-1.13)	**0.003**
Serum ALP, per 10-U/L		
BL	1.02 (1.01-1.03)	**< 0.001**
Change	1.01 (1.00-1.03)	0.16

*Hazard ratios for changes from BL adjusted for BL value.

Conclusion: Disease progression in non-cirrhotic patients with PSC is associated with more advanced fibrosis at baseline and greater increases in fibrosis, measured histologically or with non-invasive markers.

PS-013
Evaluation of serological markers of extracellular matrix remodeling in primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease with progression to liver cirrhosis in the majority of patients. PSC shows a remarkably variable course making it challenging for clinicians to identify patients at risk for rapid disease progression. We aimed to evaluate the prognostic utility of three biomarkers of interstitial extracellular matrix (C3M, PRO-C3) and fibril-associated collagen (PRO-C16) remodeling in patients with primary sclerosing cholangitis.
Method: Serum samples from 250 large-duct primary sclerosing cholangitis patients (of which 183 [72.3%] with IBD) recruited 2004-2016 and 20 healthy controls were analyzed. In 27 PSC patients a follow-up serum samples (mean 5.5 years, 3-10 years) were assessable. neo-epitope biomarkers of collagen type III formation and degradation (PRO-C3 and C3M, respectively) and type XVI formation (PRO-C16) were assessed and compared with regard to laboratory and clinical parameters.
Results: The final study cohort comprises 250 PSC patients. 183 (73.2%) patients had concomitant IBD and 69 (27.6%) patients presented dominant strictures at time of serum collection. Of the evaluated biomarkers PRO-C3 and PRO-C3/C3M ratio were significantly elevated in PSC patients compared to healthy controls (24.6 ng/ml vs. 8.1 ng/ml, $p < 0.0001$). PRO-C3 and PRO-C3/C3M were elevated in all PSC subtypes, independent of presence of concomitant IBD phenotypes (PRO-C3: control: 8.1 ng/ml; no IBD: 20.4 ng/ml; UC: 26.8 ng/ml; CD: 20.1 ng/ml, $p < 0.01$; PRO-C3/C3M ratio control: 0.8; no IBD: 2.0; UC: 2.5; CD: 1.8, $p < 0.05$;). Only PRO-C16 could separate PSC patients with and without IBD, ($p = 0.007$) After a mean follow-up period of 5.5 years in a subgroup of 27 patients C3M showed an significant increase during the course of disease, when compared to baseline (C3M: baseline 10.4 ng/ml vs. FU 12.7 ng/ml, $p = 0.04$) In patients with presence of dominant strictures in the bile ducts at serum collection PRO-C3/C3M ratio were significantly elevated (PRO-C3/C3M: no DS 1.79 vs. DS 3.32; $p = 0.003$).
Conclusion: Serum markers of extracellular matrix remodeling are elevated in primary sclerosing cholangitis patients compared to healthy controls. Collagen type III formation and turnover (PRO-C3, PRO-C/C3M) is significantly elevated in PSC patients with dominant strictures, while PRO-C16 specifically related to the IBD phenotype of the patients irrespective of PSC status. These results indicate that specific ECM biomarkers might relate to different pathophysiological aspects of PSC-IBD, and assessement of serum markers of extracellular matrix remodeling might be a valuable tool for early identification of patients at risk for rapid disease progression.

PS-014
Disease clustering in autoimmune liver diseases points towards environmental factors being important in their aetiology

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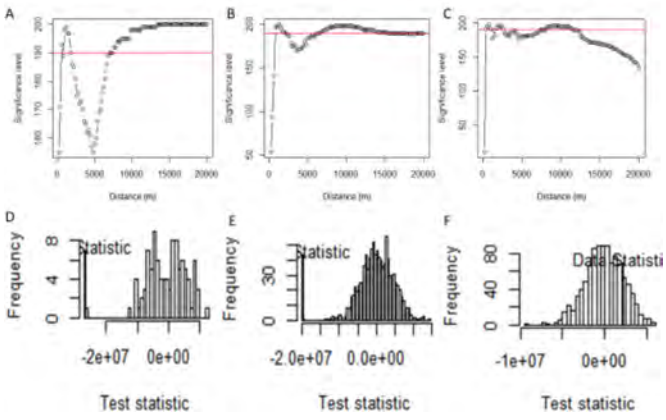
Background and aims: Autoimmune liver diseases have a complex aetiology with the interplay of genetic and environmental factors. Disease clustering has been reported in primary biliary cholangitis (PBC) but equivalent studies have not been performed in autoimmune hepatitis (AIH) or primary sclerosing cholangitis (PSC). This study aimed to examine if there is spatial and/or temporal clustering in a comprehensive cohort of patients in the North-East of England and North Cumbria with PBC, AIH and PSC.

Method: All patients with PBC (n = 2150), AIH (n = 963) and PSC (n = 472) in a defined geographical region within England were identified using multi-source case-finding methodology. Spatial point analyses (k function) were used to investigate for the presence and patterns of disease clustering (using postal addresses) after controlling for population size. For those with a known year of diagnosis (1780 PBC, 889 AIH and 451 PSC), spatio-temporal analyses were undertaken. The time range was based on first and last years of diagnosis in 1-year steps.
Results: Significant spatial clustering was found at approximately 1-2 km in all 3 diseases (Figure 1A/B/C-red line defining 95%). Further clustering was identified for AIH and PSC with a peak distance of approximately 10 km. In PBC, the clustering appeared again at 7.5 km and was sustained to the limits of the spatial range (20 km). No significant temporal clustering was found in any of the diseases (Figure 1D/E/F). However, for PSC the test statistic was in the right hand tail of the histogram suggesting some evidence of temporal clustering.

Figure 1. A: Spatial clustering in PBC, B: Spatial clustering in AIH, C: Spatial clustering in PSC, D: Temporal clustering in PBC, E: Temporal clustering in AIH, F: Temporal clustering in PSC



Conclusion: Evidence of spatial clustering in PBC, AIH and PSC implies that exposure to an environmental agent may play a role in disease pathogenesis, with increased prevalence in areas reflecting increased exposure risk or exposure levels. The lack of temporal clustering does not support the theory of more transient environmental components such as infection. The presence of spatial, but not temporal, clustering suggests a persistent and low level environmental trigger for disease. Varying distances of peak clustering between the diseases raises the concept of different environmental factors being important in PBC, AIH and PSC. The suggestion of temporal clustering in PSC needs further exploration in a larger cohort and analyses for 'acute' AIH should be undertaken using shorter time steps (months versus years). Confirmation of spatial clustering emphasises the need to explore potential environmental factors that are associated with areas of high disease prevalence.

PS-015

Role of methylation-controlled J-protein, endogenous repressor of the mitochondrial respiratory chain, in cholestatic liver disease

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Background and aims: Mitochondrial dysfunction contributes to CLD pathogenesis, in fact bile acids are cytotoxic, capable of emulsifying lipid membranes such as mitochondrial, causing ROS overproduction and hepatocyte death. MCJ is a mitochondrial protein that represses the function of the mitochondrial respiratory chain (MRC), so that its deficiency could mitigate the oxidative stress caused by cholestasis. Our aim is to study the effect of MRC inhibition by MCJ on bile acids induced liver toxicity.
Method: Bile duct ligation (BDL) in WT and MCJ-KO mice was used as an animal model of cholestasis. Liver injury was assessed by histology. The protein and gene expressions were measured by Western blot and qPCR respectively. The MCJ expression in WT mice was transiently knockdown injecting MCJ siRNA (siMCJ). In vitro studies, primary hepatocytes were treated with deoxycholic acid (DCA), MCJ was silenced using a ShRNA for MCJ (shMCJ), assessing the apoptosis by caspase3 activity. Total ROS and superoxide production, and active mitochondria were measured by CellROX®, MitoSOX® and MitoTraker® stain respectively. Mitochondrial membrane potential was analysed by flow cytometry, and ATP levels were measured by luminescence. MCJ levels were analysed by immunohistochemistry in patient liver biopsies with primary biliary cholangitis (PBC).
Results: Hepatic MCJ expression are significantly induced in PBC patients and WT mice after BDL. *In vivo*, we saw greater survival of MCJ-KO mice after BDL compared with WT, and lower inflammatory hepatic infiltrate at 48 hours after BDL. The liver injury was evaluated 7 days after BDL showed minimal levels of necrotic areas and inflammation in mice treated with siMCJ relative to those that did not receive siMCJ. Both *in vivo* and *in vitro*, MCJ-KO have lower JNK activation. In fact, we found less apoptosis after adding DCA in hepatocytes MCJ-KO and ShMCJ. This lower apoptosis is due to lower depolarization of mitochondrial membrane, lower ROS production and higher ATP production that we saw in hepatocytes MCJ-KO after DCA treatment. In addition, MCJ-KO hepatocytes showed higher expression of genes related to bile acids transport (MDR2, FXR), and lower expression of inflammatory genes (IL1b, TNF).
Conclusion: Loss of MCJ protects hepatocytes against JNK activation, ROS production, mitochondrial membrane depolarization, and ATP depletion as a result of bile acid toxicity. Our results identify MCJ as a potential therapeutic target to mitigate liver injury in CLD.

PS-016

Prospective evaluation of serum alkaline phosphatase variability and prognostic utility in primary sclerosing cholangitis using controlled clinical trial data

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Background and aims: Serum alkaline phosphatase [ALP] is a prognostic biomarker in primary sclerosing cholangitis [PSC], however biovariability as part of the natural history of disease has not been formally or prospectively studied. Herein, we quantify, using high-quality controlled clinical trial data, the degree of ALP variability in patients [pts] with PSC.
Method: Data were analysed from 234 PSC pts enrolled in a 96-week, placebo-controlled trial of simtuzumab [SIM] (64% men, median age 45 yrs, 61% taking ursodeoxycholic acid, cumulative follow-up 371 pt-yrs) to evaluate the magnitude of ALP fluctuation and associations with clinical outcome. Since SIM did not influence ALP or other end points, treatment arms were combined.
Results: At study entry, baseline [BL] ALP values were widely distributed: ≤ 1xULN (n = 57), > 1xULN (n = 177), > 1.5xULN (n = 145), > 2xULN (n = 121), and 3xULN (n = 71). 26% of pts with normal BL ALP developed elevation > ULN at week-96 (W96). Conversely, a decrease by ≥ 30% occurred in 18%, 18%, 21%, and 25% of pts with a BL ALp > 1xULN, > 1.5xULN, > 2xULN, and > 3xULN, respectively. Overall, ALP spontaneously declined to ≤ 1.5xULN in 10.4% of pts at the end of study. Median intra-individual (per-pt) coefficients of variation approximated 12%, irrespective of fibrosis stage and BL value, with ranges exceeding 30% over a 4-week period (Fig 1A). Mean serum ALP did not improve significantly from BL to W96; however, variability as reflected by the standard deviation of relative change progressively increased from 25% at W12, to 37% at W48, and 42% at W96. The observed variability in ALP was applied to create a reference tool to power future clinical trials according to target ALP thresholds, end points, and magnitude of effect size (1B). Of 209 pts with a BL Ishak fibrosis stage 0-IV, 30 developed cirrhosis by W96. In univariate logistic regression analysis, changes in serum ALP by W12, W24 or W48 were not associated with progression to cirrhosis (all p > 0.05). In total, 47 pts (20%) experienced a PSC-related clinical event. However, changes in ALP at W12, W24, or W48 were not predictive of event-free survival (Cox regression, all p > 0.05).

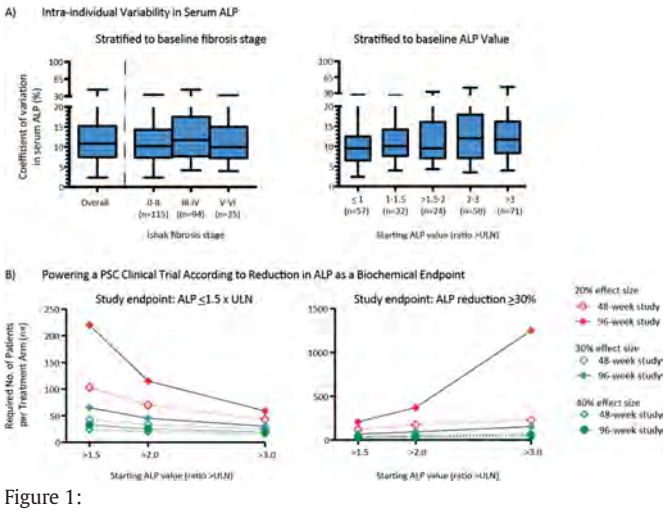

Figure 1:

Conclusion: The degree of fluctuation in ALP, wide per-pt coefficients of variation, and substantial proportion of pts who spontaneously attain specific thresholds, highlight significant implications relevant to the design of future trials in PSC, using ALP as part of a treatment efficacy end point.

Portal Hypertension – Refining risk stratification and therapy

PS-017
Long-term impact of sustained virological response on systemic and pulmonary hemodynamics in HCV-cirrhotic patients with portal hypertension

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Background and aims: Some case series suggest an association between antiviral therapy and the development of pulmonary hypertension (PH:mPAP ≥ 25mmHg) (Chest, 2016). Our previous data showed that early after therapy there was an improvement in systemic parameters but an increased prevalence of PH, although without fulfilling criteria for porto-pulmonary hypertension (PHH) (Gastroenterology, 2017). We aimed to assess the long-term impact of HCV cure (SVR) on systemic and pulmonary hemodynamics in patients with clinically significant portal hypertension (CSPH, HVPG ≥ 10mmHg).
Method: Prospective multicenter study of patients with HCV-related cirrhosis and CSPH at baseline (BL) who obtained SVR after treatment with all-oral antivirals (n = 226). Patients with CSPH 24 weeks after therapy underwent a new hemodynamic evaluation at 96 weeks (SVR24 and SVR96, respectively). Data from the subgroup of patients with right-heart catheterization at BL, SVR24 and SVR96 (n = 84) are presented.
Results: The majority (79%) were Child-A; 84% had esophageal varices and 31% previous hepatic decompensation. Most (70%) received sofosbuvir based-regimens. BL-HVPG 15.5 (13-18) mmHg decreased – 2 ± 3mmHg at SVR24 and – 4.1 ± 4mmHg at SVR96 (both, p <.01). However, 76% of patients still presented CSPH at SVR96. At this time point, an increase in mean arterial pressure (+7%, p = .07) and systemic vascular resistance (+12%, p <.05) as well as a reduction in cardiac output (– 9%, p <.01) were observed. There was also a significant increase (p <.05) in mean pulmonary arterial pressure (mPAP:16 ± 5 to 19 ± 6mmHg, +12%), pulmonary vascular resistance (PuVR:98 ± 52 to 110 ± 58 dyn/s/cm-5, +10%) and pulmonary capillary wedged pressure (10 ± 4 to 11 ± 4mmHg, +20%). At baseline, 7 (8%) patients had pulmonary hypertension, although none met the PPH criteria. At SVR96, pulmonary hypertension remained in 4/7 patients and developed in 12 additional patients. Only 4 presented high PuVR (> 240 dyn/s/cm-5). Two other patients had elevated PuVR but no significant PH (mPAP 22 and 21 mmHg). Neither the type of treatment nor the presence of previous decompensation or persistent CSPH had an influence on the hemodynamic response.
Conclusion: SVR after all-oral antiviral therapy is associated with an improvement in systemic hemodynamics in patients with CSPH. However, an increase in the prevalence of pulmonary hypertension was detected, although of post-capillary characteristics. No association with the type of antiviral therapy was found.

PS-018

Paroxysmal nocturnal hemoglobinuria and Budd Chiari syndrome: Impact of Eculizumab therapy on survival and liver outcome in 54 patients: A multicentric valdig study

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Background and aims: Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by intravascular haemolysis and in 2-10% by Budd Chiari syndrome (BCS). This study aimed at assessing characteristics and outcome of patients with PNH and BCS, with the impact of Eculizumab (currently indicated in PNH with hemolysis with clinical symptom indicative of high disease activity (ie thrombosis), while administration varies according to availability in each country).
Method: Retrospective analysis of patients with PNH and BCS diagnosed in centers of the VALDIG network between 1987 and 2017. Primary end point was survival. Data are presented as median [IQR] and n (%). Features associated with survival were assessed using univariate Cox proportional hazards model. Survival curves were obtained using the Kaplan-Meier methods, and compared treated patients using the log-rank test.
Results: Fifty-four BCS patients (28men, 52%) were included (16 with portal vein thrombosis), 23 [0-51] months after PNH diagnosis, aged 40 [33-52] and followed-up after BCS diagnosis 5 years, 95%CI [1-11]. In 22 patients, PNH was revealed by BCS. Clone size was 87% [74-4], hemoglobin 10 [8-11] g/dl, LDH 783[564-16071]IU. Three had associated myeloproliferative neoplasms. Thirty-five (62%) had ascites, 20 (37%) oesophageal varices (6 variceal bleeding). All received a stepwise therapeutic strategy, including, anticoagulation (n = 50; 92%), vein angioplasty/stent (n = 4; 6%), transjugular Intrahepatic Portosystemic Shunt (n = 20, 37%) and/or liver transplantation (n = 2; 4%). Venous thrombosis elsewhere at diagnosis and during follow-up occurred in respectively 9 and 15 patients including 6 and 2 cerebral thrombosis. Arterial thrombosis occurred in 8 patients at diagnosis and 6 during follow-up. Complications were severe bleeding n = 17, sepsis n = 14, recurrent thrombosis n = 15; Overall, 17 (31%) patients died (infection, cancer, multiple organ failure, haemorrhage and other causes), including 8 from liver complications and 4 (7%) treated with Eculizumab. Thirty-three (61%) patients received Eculizumab treatment, for 1254 days, CI 95% [766-2130], 73 days[37-210] after BCS diagnosis in 31 patients. In univariate analysis, Eculizumab treatment was significantly associated with a better survival (HR 0.29 IC 95% (0.09-0.90) p = 0.03).Of note, patients treated or not with Eculizumab had similar prognosis scores at BCS diagnosis: Meld score 13 [12-16] vs 15 [13-22], Child-Pugh score 9 [7-10] vs9 [7- 10], Clichy score 6[4- 6] vs 5 [4- 6]

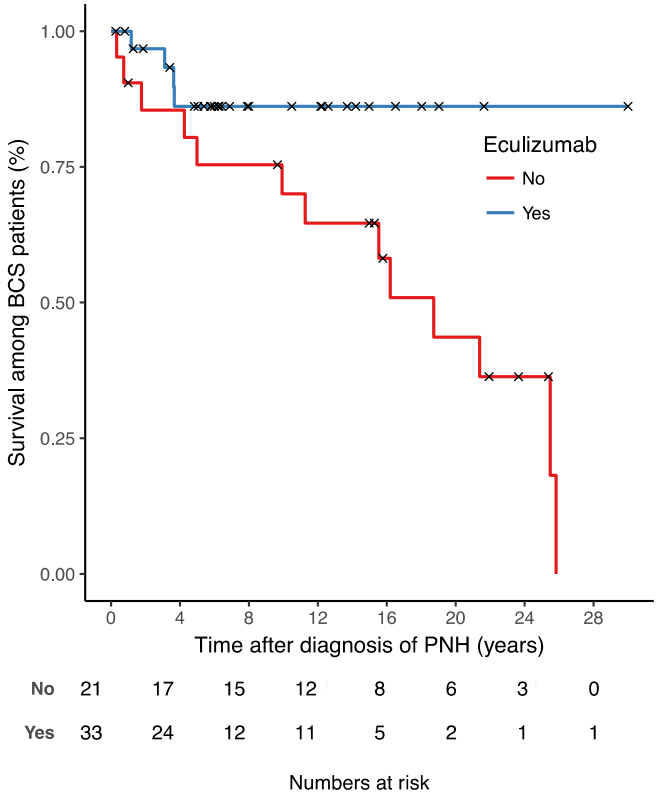

Figure: Overall survival according to Eculizumab therapy

Conclusion: Patients with PNH and BCS have frequent thrombosis outside the splanchnic vascular bed, bleeding and severe septic complications. Patients treated with Eculizumab have a significantly better survival. Nevertheless, close follow-up is still needed in these patients who may still have severe, lethal complications

PS-019

Response of liver and spleen stiffness to portal pressure lowering drugs in a rat model of cirrhosis

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Background and aims: Liver stiffness (LS) is increasingly used to screen for liver fibrosis, in addition, spleen stiffness (SS) is an established parameter to assess portal hypertension which is tightly related to the hemodynamics of blood flow and vascular resistance. Little is known about the response of LS and SS to vasoactive

substances. We here studied LS and SS in an TAA-induced cirrhosis rat models after exposure to various vasoactive drugs using a miniaturized Fibroscan platform (µFibroscan).

Methods: We induced cirrhosis in 24 wildtype 8 weeks old adult male Wistar rats with 200 mg/Kg dosage of Thioacetamide (TAA) through intraperitoneal injection of 50 mg/ml solution 2 times per week for 6 weeks. The six groups consisted of control (sodium chloride), metoprolol, udenafil, enalapril, terlipressin and carvidelol. LS and SS were measured by µFibroscan (Echosens, Paris). The rats underwent general anesthesia with isoflurane inhalation. After anesthesia, abdominal aorta, inferior vena cava and portal vein were cannulated with 24-gauge cannula and connected to Power lab device (AD instruments) to continuously measure the mean arterial pressure (MAP), heart rate (HR) and portal vein pressure (PVP). Drugs were injected systemically and data were collected at time points 0, 15 and 30 mins.

Results: LS and SS was significantly higher in TAA treated rats than in the control group (23.8 vs 3.8 kPa and 19.6 vs 47.8 kPa, P < 0.0001). In addition, they had significantly bigger and heavier spleens (6 vs 4 cm and 2.7 vs 1 gm, P < 0.0001, respectively). In all drugs, LS and SS followed tightly the change of the portal vein pressure (r = 0.681and 0.622, P < 0.01, respectively). Also, SS was significantly correlated with spleen size and weight (r = 0.723 and 0.663, respectively < 0.01). Noteworthy, a significant decrease of PVP ranging from 22% to 34% (p < 0.05) was seen after 15 to 30 minutes with metoprolol, udenafil, enalapril and carvedilol which was accompanied with a significant decrease in LS and SS ranging from 18.2 to 44% (p < 0.05). (see the Table) Interestingly, with terlipressin, LS and SS only slightly decreased which could be explained by counteracting PVP and MAP. Thus, while PVP decreased by 20% (p < 0.001), MAP increased by 35% (p < 0.001). Overall, carvedilol showed the best response regarding the decrease of PVP, LS and SS. Of note, the heart rate increased after metoprolol and udenafil injection (ca. 10%, P < 0.05), while it decreased in response to terlipressin and carvedilol by ca 30% (p < 0.01).

Drug/Parameter	Delta LS (P Value)	Delta SS (P Value)	Delta PVP (P Value)	Delta MAP (P Value)	Delta HR (P Value)
Metoprolol	-19% (<0.05)	-21.9% (<0.001)	-22% (<0.001)	-20.1% (<0.01)	+7.5% (<0.01)
Udenafil	-18.2% (<0.05)	-27.7% (<0.001)	-26.2% (<0.001)	-16.5% (<0.05)	+7.9% (0.105)
Enalapril	-34% (<0.05)	-22.3% (<0.001)	-25.4% (<0.001)	-13.5% (<0.01	-0.3% (=0.125)
Terlipressin	-3.7% (=0.08)	-15.8% (=0.19)	-20.1% (<0.001)	+35.2% (<0.01	-27.6% (<0.01)
Carvedilol	-44.6% (<0.05)	-29.7% (<0.001)	-33.1% (<0.001)	-35.8% (<0.05)	-42.1% (<0.01)

Conclusion: LS and SS strongly correlates PVP and responded differently to various vasoactive drugs. Combined non-invasive LS and SS measurement could be useful to monitor the patient's response and compliance to portal pressure lowering drugs.

PS-020

Spleen T1 and spleen diameter criteria can identify and exclude oesophageal varices accurately

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Background and aims: Application of Baveno VI criteria (platelets > 150 × 10^9/l, liver stiffness < 20 kPa) can avoid 10-34% of screening endoscopies for oesophageal varices needing treatment (VNT) in compensated advanced chronic liver disease (cACLD), but still > 46% endoscopies will be performed unnecessarily with no VNTs detected. Magnetic resonance imaging (MRI)-derived spleen T1, cT1, extracellular fluid volume fraction (ECV) and size measures have been associated with portal hypertension. This study explores these spleen MRI measures to improve the identification of patients with cACLD with and without VNTs.

Method: Ninety-one patients with cACLD of mixed aetiologies had spleen MRI, blood and liver stiffness assessment within median 30 days (IQR 11-117) of endoscopy screening for varices. MRI with gadoxetic acid administration was used to measure spleen T1, extracellular fluid volume fraction (ECV), volume and diameter. Measures were explored for the identification of VNTs. New criteria were derived to minimise the number of screening endoscopies for VNTs subject to accepting that < 5% of VNTs will be missed. Baveno and other published criteria were also tested.

Results: Patients had median age 61 years and 70% were male. VNT prevalence was 14%. Spleen T1 × spleen diameter had the highest accuracy for the identification of VNTs (area under the receiver operator curve 0.87, p < 0.001). Spleen T1 < 1307 ms or spleen diameter < 137 mm was the best performing criteria to avoid screening endoscopies for VNTs, saving 66% of endoscopies (table 1).

Table 1: Ability of non-invasive criteria to avoid endoscopy screening for VNTs in cACLD.

	Endoscopies avoided (%)	VNTs missed (%)
New criteria		
Spleen T1 < 1307 ms or spleen diameter < 137 mm	60 (66%)	0
Spleen diameter < 159 mm and platelets > 112 × 10^9/l	52 (57%)	0
Platelet/spleen volume < 0.267 × 10^9/l/ml	49 (54%)	0
Spleen T1 × spleen diameter < 185088 msmm	46 (51%)	0
Spleen T1 < 1307 ms	41 (45%)	0
Spleen cT1 < 1252 ms	37 (43%)	0
Spleen diameter < 137 mm	36 (40%)	0
Spleen volume < 403 ml	33 (36%)	0
Platelet/spleen diameter < 1.27 × 10^9/l/mm	24 (26%)	0
Platelets > 213 × 10^9/l	15 (16%)	0
Spleen ECV < 0.317	13 (14%)	0
Published criteria		
Baveno VI (platelets > 150 × 10^9/l and liver stiffness < 20 kPa)	16 (20%)	0
Expanded Baveno (platelets > 110 × 10^9/l and liver stiffness < 25 kPa)	39 (48%)	2 (5%)
MELD = 6 and platelets > 150 × 10^9/l	15 (16%)	0
LSPS < 1.33	23 (28%)	1 (4%)

Abbreviations: MELD, modified end stage liver disease score; LSPS, liver stiffness and platelet count/spleen diameter ratio score; ECV, extracellular volume fraction.

Conclusion: Spleen T1 and spleen diameter criteria have high accuracy for the identification of VNTs and could reduce endoscopy screening requirements for VNTs compared with published criteria.

PS-021

The development of portosystemic shunts depends on liver dysfunction rather than on PlGF-driven neoangiogenesis

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Background and aims: Portosystemic shunts (PSS) are common in patients with advanced chronic liver disease (ACLD). However, the relative impact of liver dysfunction, portal pressure and splanchnic neoangiogenesis in the pathophysiological development of PSS remains unclear. The pro-angiogenic placental growth factor (PlGF) has been associated with the development of liver fibrosis and portal hypertension in experimental studies. We assessed the association between the extent of PSS and hepatic dysfunction, portal pressure and PlGF levels in ACLD patients.
Method: 107 patients with ACLD were prospectively enrolled. Portal hypertension was evaluated by hepatic venous pressure gradient (HVPG), severity of hepatic dysfunction was evaluated by ALBI score, FIB-4 score, MELD score and Child-Pugh score (CPS). PSS were semiquantitatively categorised as mild, moderate and severe on contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) scans by two experienced radiologists.
Results: N = 51 (47, 7%) showed mild PSS, while n = 38 (35, 5%) showed moderate and n = 18 (16, 8%) severe PSS. The extent of PSS (mild vs. moderate vs. severe) correlated with a higher prevalence of portal vein thrombosis (PVT: 3.9% vs. 26.3% vs. 44.0%; $p < 0.001$), higher ALBI score (-2.41 vs. – 1.96 vs. – 1.90; $p = 0.002$) and FIB-4 score (3.9 vs. 5.2 vs. 8.8; $p < 0.001$). There was a significant association of PSS severity with HVPG (12 vs. 19 vs. 15 mmHg; $p = 0.0095$) and MELD score (10 vs. 13 vs. 14; $p = 0.0022$). However, there was no significant association between PSS and CPS ($p = 0.1024$). Also, PlGF levels were not significantly different between patients with mild vs. moderate vs. severe PSS.
Conclusion: The development and extent of portosystemic shunts seems to be determined by severity of portal pressure and hepatic dysfunction. Importantly, the presence of PVT, i.e. prehepatic portal hypertension may be a major trigger for PSS development. Surprisingly, PlGF levels did not correlate with the extent of PSS.

PS-022

Optimal timing of endoscopy is associated with lower 42-day mortality in variceal bleeding

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Background and aims: The optimal timing of endoscopy in patients with variceal bleeding from the upper gastrointestinal tract is unknown. Current guidelines recommend performance of endoscopy within 12–24 hours from hospital admission, but the evidence is limited. Our aim was to describe the association between timing of endoscopy and 42-day mortality in variceal bleeding.
Method: Analyses were performed on prospective collected data on patients admitted with variceal bleeding at 34 centres in Europe and Canada during in the period October 2011 to May 2015. Patients transferred with bleeding from other hospitals and patients bleeding from post-banding ulcers, or non-specified sources, were excluded. Logistic regression analyses were used to investigate the association between timing of endoscopy and 42-day mortality following adjustment for confounding factors including age, sex, comorbidities, liver function, previous decompensation, laboratory values, haemodynamic parameters, and treatment with vasopressors. We evaluated the association in: 1. All patients with variceal bleeding; 2. Patients with Child-Pugh A or B-cirrhosis; and 3. Patients with systolic blood pressure (SBP) < 90mmHg.
Results: A total of 2, 138 patients were considered for inclusion. Following exclusion of transferred patients (n = 607) and patients with other sources of bleeding (n = 163), 1, 373 patients were included with mean age 59 years, and mean Child-Pugh score 8.2. 69%, 18%, 8% and 5% underwent endoscopy in the periods < 6, 6-12, 12-24, and > 24 hours, respectively. Mortality at 42 days was 26.2%. Following adjustment for confounding factors, performance of endoscopy within 24 hours from time of hospital admission was associated with lower mortality in patients with Child-Pugh A or B cirrhosis (Odds ratio (OR) 95% confidence interval (CI): 0.38 [0.16-0.86]; p = 0.020) and patients with SBp < 90 mmHg (OR [95% CI]: 0.053; [0.006-0.51]; p = 0.011). Performance of endoscopy within 6 or 12 hours was not associated with further reduction in mortality compared with endoscopy within 24 hours. We did not find a significant association between timing of endoscopy and mortality in the overall group of patients (OR [95% CI]: 0.51 [0.24-1.09]; p = 0.082).
Conclusion: Our data suggest that in patients presenting with variceal bleeding, performance of endoscopy within 24 hours is associated with reduced 42-day mortality in patients with Child-Pugh A or B cirrhosis and in those with SBp < 90mmHg.

PS-023

Factors predicting survival in patients with high-risk acute variceal bleeding treated with pre-emptive (Early)-TIPS

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Background and aims: Pre-emptive TIPS (p-TIPS) improves outcomes in patients with acute variceal bleeding and high-risk of treatment failure (HR-VB) compared to those receiving medical/endoscopic treatment (Drug+Endo). However, current studies have included a low number of p-TIPS patients precluding the evaluation of factors predicting outcome after TIPS that may optimize its use.
The aim of the study is to identify prognostic factors in patients with HR-VB treated with p-TIPS. In addition, if different risk-groups are identified, the outcome observed in patients with p-TIPS will be compared with that in patients sharing the same prognostic factors, but receiving Drug+Endo.
Method: Individual data of all patients with HR-VB treated with p-TIPS included in 4 published studies (2 randomized, 2 observational) comparing p-TIPS vs Drug+Endo were analyzed to identify prognostic factors of survival. Liver transplant was considered as a competing event. Different prognostic models were developed avoiding redundant variables. Continuous variables were considered as continuous but also as categorical according to cut-off values identified by Youden index.
Results: 169 HR-VB p-TIPS patients were included. At one year, 30 died and 15 were transplanted. Cumulative survival at 6 weeks and at a 1 year was 91.2% and 76% respectively. At Cox uni and multivariate analysis, age, alcoholic etiology, bilirubin, creatinine, Child and MELD were associated with p-TIPS survival. From all significant models, the one with best "c-statistic" index, and consequently with better adjusted survival, entailed age ≥ 65; Creatinine ≥ 1.3 mg/dl; Child ≥ 12 and alcoholic etiology. A score of 3.5, 3.5, 4 and 4 points was given to each variable respectively. The model classified p-TIPS patients in low (total score < 4 points: n = 46), medium (score from 4-7.5; n = 68) and high (score > 7.5; n = 55) risk groups with a 1-year survival of 91, 83 and 55% respectively. Survival for all these 3 groups were better for p-TIPS when, by using the same scoring system, we classified the 692 patients treated with Drug+Endo included in the previous studies (low risk; n = 383: 70%: p < 0.02; Medium; n = 124: 53%:p < 0.01; High; n = 185; 44%:p < 0.05).
Conclusion: In HR-VB patients treated with p-TIPS, 3 different prognostic risk groups can be identified. For all 3 groups of risk, prognosis is better using p-TIPS than Drug+Endo. This fact strengthens and reinforces the use of p-TIPS in patients with cirrhosis and HR-VB.

PS-024
Early TIPS with covered stent versus standard treatment for acute variceal bleeding among patients with advanced cirrhosis: A randomised controlled trial

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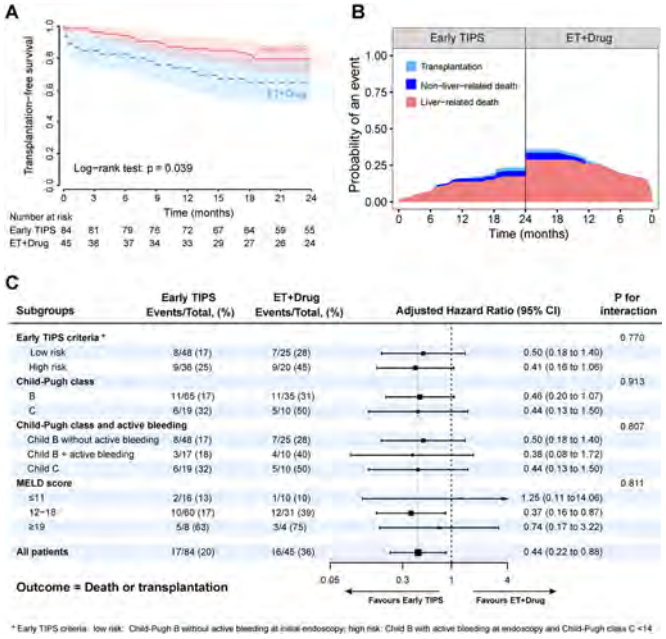
Background and aims: Early placement of transjugular intrahepatic portosystemic shunt (TIPS) has been shown to improve survival in high-risk patients (Child-Pugh B + active bleeding at endoscopy or Child-Pugh C10-13) with cirrhosis and acute variceal bleeding (AVB). However, whether the same results can be validated and achieved in a broader population remains to be assessed.
Method: Consecutive patients with advanced cirrhosis (Child-Pugh B or C) and AVB who had been treated with vasoactive drugs plus endoscopic therapy (ET) were randomly assigned in a 2:1 ratio to receive early TIPS treatment (performed within 72hours after initial endoscopy, early TIPS group) or continuation of vasoactive drug therapy to day 5, followed by propranolol plus long-term endoscopic band ligation for the prevention of rebleeding and a TIPS placement as rescue therapy when needed (ET+ Drug group), respectively. Primary end point was transplantation-free survival. Secondary end points included failure to control bleeding or rebleeding, new or worsening ascites, overt hepatic encephalopathy (OHE), other complications of portal hypertension and adverse events.
Results: From May 2011 to September 2017, a total of 129 patients were randomly assigned to the early TIPS group (n = 84) or the ET+ Drug group (n = 45). The transplantation-free survival rate was higher in the early TIPS group compared with the ET + Drug group (6 weeks: 99% vs 84%; 1 year: 86% vs 73%; 2 years: 79% vs 64%; p = 0.039, Figure A). Similar results were observed in a post-hoc competing risk sensitivity analysis (Figure B). After adjusting the severity of liver disease in the Cox regression analysis, early TIPS was associated a 56% relative risk reduction in the mortality or transplantation at 2 years (adjusted HR, 0.44; 95% CI: 0.22 to 0.88). Moreover, the beneficial effect tending to favour the early TIPS was homogeneous across the most of subgroups (Figure C). Finally, early TIPS placement was associated with decreased risks of failure to control bleeding or rebleeding as well as new or worsening ascites, without increasing the frequency and severity of overt hepatic encephalopathy and other adverse events.
Conclusion: Among patients with advanced cirrhosis and AVB, early TIPS is superior to drugs plus endoscopic treatment in improving transplantation-free survival rates, reducing failure to control bleeding and new or worsening ascites without increasing the risk of overt hepatic encephalopathy. Our results favour the early use of TIPS in patients with advanced cirrhosis and AVB. (Trial registration: ClinicalTrials.gov: NCT01370161)



Liver disease immunology

PS-025

Elevated tissue homing of monocytes and increased cytotoxic activity of CD8+ T-cells in immune checkpoint inhibitor-induced hepatitis

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Background and aims: Checkpoint inhibitors (CPIs) targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) are a novel class of cancer treatment which stimulate anti-tumour immune responses. CPI treatment is frequently complicated by immune-related adverse events, including CPI-induced hepatitis (CPI-Hep) in up to 25% of patients on dual therapy. Here, we sought to characterise the profile of circulating and hepatic immune cells of patients with CPI-Hep.

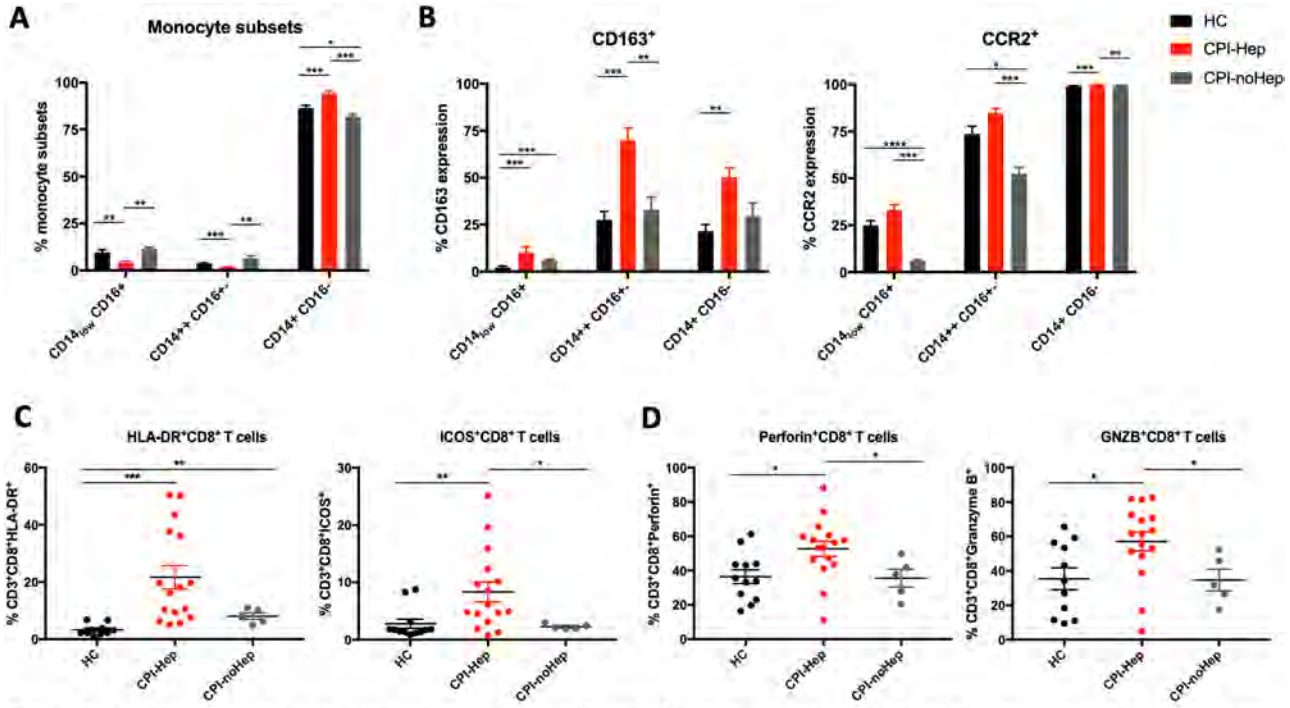

Figure. Flow cytometry analysis of circulating monocytes and T cells of healthy controls (HC), CPI-treated cancer patients with hepatitis (CPI-Hep) and without hepatitis (CPI-noHep). **A)** Frequency of circulating monocyte subsets. **B)** Expression levels of CD163 and CCR2 in monocyte subsets. **C)** Expression of HLA-DR and ICOS in CD8+ T cells. **D)** Granzyme B and Perforin production by CD8+ T cells. Non-parametric (Mann-Whitney) statistical analysis was used. Data shown as median values with IQR. *p<0.05, ** p<0.01, *** p<0.0001, **** p<0.0001.

Figure: (abstract: PS-025)

Method: Using multi-colour flow cytometry, we phenotypically and functionally characterized circulating immune cells from healthy controls (HC; n = 12), CPI-treated cancer patients with and without hepatitis [CPI-Hep, grade 3-4 hepatitis, (n = 16); CPI-noHep, (n = 5)]. Monocytes were screened for activation and tissue-homing markers as well as microbial clearance (phagoburst, pHrodo). Lymphocytes were monitored for activation (HLA-DR, CD25, ICOS) and function [CD127, perforin, granzyme B (GZMB)]. Immunohistochemistry (IHC) was performed on liver tissue from CPI-Hep/noHep (n = 3 each) and pathological controls (PC) [resection margins of colorectal metastases, (n = 2)].
Results: Patients with CPI-Hep had a lower proportion of non-classical and intermediate and a higher frequency of classical monocytes, compared to controls **(A)**. Circulating monocytes in CPI-Hep showed a higher proportion towards a $CD163^{high}CCR2^{high}$ phenotype **(B)**, but unaltered microbial clearance capacity. Proportions of CD4, CD8 and Tregs were comparable between CPI-Hep/noHep and HC. However, in CPI-Hep, $CD8^+$ T cells presented an activated $HLA\text{-}DR^{high}ICOS^{high}$ phenotype **(C)** with increased GZMB and perforin production, compared to controls **(D)**. Patients with CPI-Hep showed lobular liver inflammation and focal aggregates of CD68 with CD3/CD8/CD25/GZMB positive cells whereas macrophages and $CD8^+$ T cells were evenly distributed in PC and CPI-noHep. Double-IHC revealed colocalization of cytotoxic $CD8^+$ T cells with $CD68^+$/$CCR2^+$ macrophages in livers of patients with CPI-Hep.
Conclusion: CPI-Hep is an emerging problem with the development and wider application of cancer immunotherapy. Our novel data suggest that CPI-Hep is associated with changes in both the myeloid and $CD8^+$ T cell compartments. The coexistence of activated circulating monocytes and increased $CCR2^+$ hepatic macrophages, suggests monocyte recruitment to the liver may be important in disease pathogenesis. Further studies will focus on the interaction between cytotoxic T cells and monocyte-derived macrophages within the liver and mechanisms of altered immune cell phenotype and dysfunction during CPI-Hep.

PS-026
FOXO1-activitiy controls effector function of CXCR6+CD8+ T-cells and prevents liver immune pathology during viral hepatitis and non-alcoholic steatohepatitis

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Background and aims: Recognizing foreign antigens as peptides in a complex with MHC class I is indispensable for $CD8^+$ T-lymphocytes to eliminate infected cells. Tight cellular co-regulation of metabolism and immunity is required to control effector function, but the mechanisms regulating organ-specific immunity in tissues rich in nutrients such as liver remained unclear. $CD8^+$ T cells expressing the chemokine receptor CXCR6 are important for staying as tissue-resident memory T cells (T_{rm}) in the liver and providing front-line defense for infections. T_{rm} express high levels of effector molecules like GzmB or IFN-γ but how T_{rm} regulates their effector function in order to avoid immune pathology is largely unknown. Here we identify Foxo1-activity in $CXCR6^+CD8^+$ T cells as critical regulator of CXCR6 expression, metabolism and effector function during liver disease states.
Method: Extracellular flux analysis, cytokine expression, cytotoxicity assays were performed to study co-regulation of metabolism and immunity of $CXCR6^+CD8^+$ T cells and its dependence on Foxo1 in vitro and ex vivo studies. Murine models of viral hepatitis and non-alcoholic steatohepatitis (NASH) were used to explore Foxo1-dependent T cell immunopathology.
Results: RNA-seq and KEGG pathway analysis of $CXCR6^+$ memory $CD8^+$ T cells of the liver compared to memory $CD8^+$ T cells from other tissues revealed high GzmB level accompanied with downregulation of Foxo1-dependent pathways. Flow cytometric analysis of liver-specific lymphocytes revealed a $Foxo1^{low}CXCR6^+GzmB^{high}CD69^+CD8^+$ T cell population. Using germ-free mice and *in vitro* studies we found that high GzmB level in Foxo1lowCXCR6+ CD8+ T cells were dependent on the the presence of microbiota. We further identified TGFβ and IL15 as critical cytokines that downregulate Foxo1 via PI3 K/pAkt pathway and inducing $CXCR6^+CD8^+$ T cells derived from $CXCR6^-CD122^+CD8^+$ T cells. To address the functional consequence of $CXCR6^+Foxo1^{low}Gzmb^{high}$ $CD8^+$ T cells we performed in vitro killing assays of infected and non-infected hepatocytes demonstrating antigen-independent immune pathology against hepatocytes in the presence of elevated levels of IL15 and acetate. This development of autoimmune $CD8^+$ T cell effector function was also be observed in NASH where we detected high numbers of $Foxo1^{low}CXCR6^+GzmB^{high}CD69^+CD8^+$ T cells that caused liver damage. Since TCR sequencing of hepatic T cells did not reveal presence of particular T cell-clones in NASH, we assume that increased effector function in $CXCR6^+$ $CD8^+$ T cells in the absence of Foxo1-control caused antigen-independent hepatic immunopathology.
Conclusion: Our results provide evidence for a critical role of Foxo1 in controlling metabolism in $CD8^+$ T cells that is required to prevent liver immunopathology and may explain metabolic $CD8^+$ T cell activation in NASH causing sterile inflammation.

PS-027
The LLT1-CD161 interaction : An important inhibitory interaction for NK cells in cirrhosis

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Background and aims: Immune profiling is important to understand the increased risks of hepatocellular carcinoma (HCC) in cirrhosis. Lectin-like transcript 1 (LLT1) interacts with CD161, a receptor expressed on most NK cells. Here we investigate LLT1 in the liver and determine its effect on NK cell function.
Method: LLT1 expression in the liver was characterised with immunohistochemistry (IHC) on formalin fixed liver tissue, and quantified with real-time PCR using RNA extracted from liver tissue snap frozen at the time of liver resection. GAPDH was the housekeeping gene. Peripheral blood mononuclear cells (PBMCs) from healthy donors and cirrhotic patients were surface stained for CD3, CD56, CD161. Function was assessed against K562 targets (PBMCs:K562, 5:1) with intracellular staining for Interferon gamma (IFNγ), and staining for degranulation (CD107a). CD107a was also measured on healthy donor NK cells (n = 3) cocultured with target cells expressing different surface levels of LLT1: Huh7 cells (low levels of LLT1), Huh7 cells overexpressing LLT1 (achieved by transfection), and Jurkat cells (lacking LLT1). Statistical analysis of variance (ANOVA) was performed to compare each condition.
Results: Relative quantification (RQ) demonstrated a significant upregulation of LLT1 in cirrhotic liver (median RQ of LLT1:371.7 vs. 1.0, cirrhotic liver (n = 5) vs. normal liver (n = 6), $p < 0.001$). IHC confirmed a homogenous expression of LLT1 on cirrhotic liver hepatocytes, but no expression on normal hepatocytes (n = 23 cirrhotic livers vs. n = 18 normal liver margins). Circulating NK cells had a significantly higher proportion expressing CD161 in cirrhosis compared to healthy donor NK cells (91.3% vs. 87.2%, p = 0.05, n = 29 vs. n = 25). NK cells from cirrhotic donors also had attenuated functional responses when co-cultured with K562 targets (cirrhotic (n = 25) vs. healthy donors (n = 24): percentage positive expressing

CD107a 59.8%vs69.3%, $p < 0.05$; percentage positive producing IFNγ 41.8%vs48.3%, $p < 0.05$). CD161+NK cells from healthy donors had reduced CD107a expression, compared to CD161-NK cells, when cocultured with Huh7 cells expressing LLT1. When cocultured with transfected Huh7 s overexpressing LLT1, as seen in cirrhotic livers, there was a further significant reduction in the proportion of healthy donor CD161+NK cells expressing CD107a ($p < 0.05$) compared to CD161+ NK cells cultured with non-transfected Huh7s. In contrast, CD107a expression in CD161+ and CD161-NK cells was not significantly different when the target cell did not express LLT1 (Jurkat cells).

Conclusion: LLT1 inhibits NK cytotoxicity via the CD161 receptor. Upregulation of LLT1 in cirrhotic livers, coupled with the increase in circulating CD161+NK cells contribute to the inhibitory NK cell profile in cirrhosis. Future NK-mediated HCC immunotherapies may need to overcome this inhibitory LLT1-CD161 interaction in cirrhosis.

PS-028

Viral escape contributes to the failure of hepatitis D virus-specific CD8+ T-cells and drives evolution of HDV

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Background and aims: Hepatitis D virus (HDV) super-infection of hepatitis B virus (HBV)-infected patients is associated with rapid progression to liver cirrhosis and hepatocellular carcinoma. Treatment options are limited, and no vaccine is available. Although HDV-specific CD8+ T cells are thought to mediate viral control, little is known about the repertoire of targeted epitopes, and it remains unclear why HDV-specific CD8+ T cells ultimately fail during persistent infection. We aimed to define how viral escape impacts the efficacy of HDV-specific CD8+ T-cells.

Method: 104 patients with chronic HDV/HBV infection were analyzed for HLA class I associated viral sequence polymorphisms. Candidate HDV-specific CD8+ T-cell epitopes overlapping these sequence polymorphisms were predicted, tested, and characterized in patients with resolved (n = 12) or chronic (n = 13) HDV infection. One of the validated epitopes was used for phenotypical characterization of HDV-specific CD8 T cells using a highly sensitive tetramer-based enrichment strategy.

Results: 21 HLA class I-associated viral sequence polymorphisms were identified as highly significant ($p < 0.005$). Five of these polymorphisms were found to co-localize with experimentally confirmed HDV-specific CD8+ T-cell epitopes. Importantly, variant peptides were only partially cross-recognized, indicating viral escape. Similarly, CD8+ T cells targeting escape variants display a 'memory-like' phenotype, indicating a loss of antigen drive. These newly identified epitopes were restricted by relatively infrequent HLA class I allotypes, with a preference for HLA-B. In contrast, frequent HLA class I alleles were not associated with viral sequence polymorphisms.

Conclusion: Using a viral sequence-based approach, we identified new HDV-specific CD8+ T-cell epitopes, indicating a role for viral escape as a determinant of immune failure. In turn, viral escape was associated with uncommon HLA class I alleles, suggesting population-level evolution of HDV.

PS-029

Eradication of HCV by DAAs provides patients with immunological benefits by the restoration of antigen-presenting dendritic cells

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Background and aims: In an era of DAA against HCV, controversial arguments have been prevailed in the recurrence and/or occurrence of post-SVR HCC. Rapid and complete clearance of HCV from infected hepatocytes by DAAs is reported to reduce the expression of ISGs, thus probably resulting in the impairment of anti-malignancy potential. An interaction between BDCA3$^+$ dendritic cells (BDCA3$^+$DC/cDC1/mDC2) and NK cells is recently reported to play important roles in immune surveillance against cancer cells. We thus aimed to clarify whether the gene expression and function of antigen-presenting DCs, including BDCA3$^+$ subset, are restored or not in patients with HCV infection after successful DAA treatment.

Method: At the baseline before the DAA therapy, we enrolled 53 patients with chronic HCV infection and age-matched 21 healthy volunteers. In addition, we enrolled 14 patients with chronic HCV infection who achieved SVR with glecaprevir/pibrentasvir. PBMCs were collected at before, end of treatment (EOT) and 12 weeks thereafter. Phenotypes of immune cells and degree of apoptosis were analyzed by FACS. We performed the focused gene expression analysis on peripheral DCs (CD3-CD14- CD19- CD56-HLA-DR+) by single-cell RNA-seq (10X system). Alternatively, plasmacytoid DCs (pDCs) and BDCA3$^+$DCs were sorted from PBMCs and subjected to qPCR and functional analyses with TLR ligands.

Results: At the baseline, the frequency of pDCs and BDCA3$^+$DCs was significantly lower in HCV-infected patients than in healthy volunteers (HVs) (pDCs, 0.18 vs 0.28%; BDCA3$^+$DCs, 0.03 vs 0.06%). The proportion of apoptotic cells were significantly higher in pDCs and BDCA3$^+$DCs in HCV-infected patients, suggesting that HCV provides pro-apoptotic nature to DCs. IFN-α production by pDCs and IFN-λ production by BDCA3$^+$DCs were decreased in patients with HCV infection. RNA-seq revealed that, after DAA, downregulation of ISGs (IFI44L, ISG15, LY6E), cancer-related genes (KLF6, PRMT9, MALAT1) and maturation markers (NR4A2, CXCR4) were observed in BDCA3$^+$DCs. In this setting, enrichment analysis showed that pro-apoptotic pathway gene sets were downregulated. By the qPCR analysis at the baseline, we found that BCLX expression on BDCA3$^+$DCs was significantly decreased in patients compared with

HVs, while the expressions of the other anti- or pro- apoptotic genes, BCL2, MCL1, and BIM were comparable. After attaining SVR in treated patients, the frequency, function, and BCLX expression on BDCA3$^+$DCs were restored to the pretreatment levels.
Conclusion: In patients with chronic HCV infection, dendritic cells are decreased and functionally impaired, one of the reasons of which is apoptosis-prone nature of immune cells. Attaining SVR with DAAs restored the number, function and pro-survival BCLX expression in BDCA3$^+$DCs, supporting the notion that the eradication of HCV by DAAs provides some immunological benefits to patients.

PS-030
Cure of hepatitis C virus has limited impact on the functional and mitochondrial impairment of HCV-specific CD8+ T-cell responses
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Background and aims: Hepatitis C virus (HCV)-specific CD8+ T cells are functionally impaired in chronic hepatitis C. Even though HCV can now rapidly and sustainably be cleared from chronically infected patients, reverberation of HCV clearance on virus-specific CD8+ T cells still remains elusive. Here, we aimed to investigate if HCV clearance by direct acting antivirals (DAA) could restore the functionality of exhausted HCV-specific CD8+ T cell responses.
Method: HCV-specific CD8+ T cells in PBMC obtained during and 6 months following IFN-free DAA therapy of 36 chronically HCV infected patients were analyzed for comprehensive phenotypes, proliferation, cytokine production, mitochondrial function and response to immune-check-point blockades.
Results: We show that, unlike activation markers that decreased, surface expression of multiple co-regulatory receptors on exhausted HCV-specific CD8+ T cells remained unaltered after clearance of HCV. Likewise, cytokine production by HCV-specific CD8+ T cells remained impaired following HCV clearance. Proliferative capacity of HCV multimer-specific CD8+ T cells was not restored in the majority of patients. However, enhanced proliferative expansion of CD8+ T cells after in-vitro HCV peptide stimulation was more likely in women, patients with low liver stiffness and low ALT levels. Interestingly, HCV-specific CD8+ T cells that did not proliferate following HCV clearance could preferentially re-invigorate their proliferative capacity upon in-vitro immune-check-point inhibition. Remarkably, altered mitochondrial dysfunction exhibited by exhausted HCV-specific CD8+ T cell could not be normalized after HCV clearance.
Conclusion: Taken together, our data implies that exhausted HCV-specific CD8+ T cells during chronic HCV still remain functionally and metabolically impaired at multiple levels following HCV clearance in most patients. Our results might have possible implications for re-infection with HCV.

PS-031
RNAseq of liver biopsies following DAA-based therapy reveals a greater enrichment in immune, interferon, cytokine and cell cycle pathways compared to IFN-based therapy: Implications for DAA-related sequelae
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Background and aims: HBV reactivation (HBVr) and autoimmune disease (AID) are unexpected sequelae that emerged during interferon (IFN)-free direct-acting antiviral (DAA) therapy for HCV. The mechanism is unknown, particularly considering DAAs do not posses direct immunomodulatory properties. In contrast, HBVr and AID are well-recognized complications of IFN-based therapy, as IFN is directly immunomodulatory, and has some but limited anti-HBV activity. We sought to compare intrahepatic transcriptomic profiles before and after IFN-free DAA-based and IFN-based (DAA-free) therapy.
Methods: DAAs or pegIFN+ribavirin (PR)-treated patients who underwent liver biopsy before and at time of SVR assessment were retrospectively identified. RNA was extracted from RNAlater liver tissue and subjected to RNAseq. Pre and post-treatment transcriptomes were compared according to treatment group and response.
Results: 39 patients were enrolled: DAA-treated with SVR (n = 13), PR-treated with SVR (n = 13) and PR-treated non-SVR (n = 13). Patients were matched for sex, HCV genotype, HCV RNA, fibrosis stage and treatment history within each group. DAA patients were slightly older and had lower ALT levels ($p < 0.05$). At baseline, intrahepatic transcriptomic profiles did not differ among the three treatment groups. There was no difference in transcriptomic profiles before and after PR therapy in non-SVR patients. However, in DAA-treated patients, 518 genes were differentially expressed between pre and post-treatment liver biopsies. The top over-represented enriched pathways involved the immune system, IFN signaling, cytokine signaling, cell cycle and Rho effector pathways (FDR < 0.05). More than 1, 550 genes were differentially expressed between pre and post-treatment liver biopsies in PR SVR patients. The top over-represented pathways were immune system, cytokine signaling, IFN signaling, adaptive immune system, and cell cycle pathways. Interestingly, the fold enrichment of these pathways was significantly greater in DAA-treated patients.
Conclusion: We observed different patterns of changes in intrahepatic transcriptomic profiles between DAA-treated and PR-treated patients who achieved SVR, with significantly greater induction of immune-related and cell cycle pathways with DAA therapy. These findings may have implications for the mechanisms of several unexpected sequelae of DAA-based therapy, including HBVr itself and the severity of HBVr, as well as the development of AID.

PS-032
Impact of antigen recognition on memory-like HCV-specific CD8+ T-cells
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Background and aims: In chronic HCV infection, T-cell exhaustion is described as a functional impairment of virus-specific T cells. We have previously reported that exhausted HCV-specific CD8+ T cells are comprised of terminally exhausted CD127-PD1hi and memory-like CD127+PD1+ subsets. However to what extent memory-like HCV-specific CD8+ T cells resemble conventional memory or

exhausted cells and which impact viral antigen recognition has on the phenotype of these cells remain unclear.
Method: In order to define the molecular determinants of memory-like subsets, we conducted low-input RNAseq analyses of CD127/PD1-based HCV-specific CD8+ T-cell subsets obtained during and after chronic HCV infection targeting consensus and escaped epitopes (n = 5 patients) and after spontaneous resolution of acute HCV infection (n = 3 patients). Via unsupervised clustering, DESeq2 analyses and WGCNA, we investigated the similarities and differences among the different subsets and clinical conditions.
Results: Although in chronic HCV infection memory-like HCV-specific CD8+ T cells clearly exhibit characteristics of memory T cells, on a transcriptional level, however, an exhausted signature is dominant even after DAA-mediated viral clearance. Thus, memory-like HCV-specific CD8+ T cells are distinct from conventional memory T cells and rather resemble exhausted T cells. Furthermore, HCV-specific CD8+ T cells targeting escaped epitopes also showed a clear exhausted profile revealing an imprinted dysfunction and a fate of exhaustion.
Conclusion: Thus, chronic HCV infection is strictly linked to an "exhaustive" T-cell differentiation that is not simply reverted by removal of viral antigen or loss of antigen recognition. This has potential implications for the control of re-infection and therapeutic vaccines.

Mechanism of regeneration response to injury

PS-033
Hepatocyte-specific deletion of ERK5 modulates liver regeneration in mice

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Background and aims: Liver regeneration induced by partial hepatectomy (PH) involves several cell types and the activation of multiple signaling pathway. The extracellular signal-regulated kinase 5 (ERK5) is a member of the Mitogen-Activated Protein Kinase (MAPK) family implicated in cell survival, angiogenesis, differentiation and proliferation. ERK5 is critical for the development and growth of HCC, and we recently generated hepatocyte-specific ERK5 knock-out mice (ERK5ΔHep). The aim of this study to investigate the contribution of hepatocyte ERK5 to liver regeneration, in a model of PH.
Method: ERK5ΔHep mice were generated crossing ERK5 floxed mice with mice expressing Cre-recombinase under the control of albumin promoter. ERK5ΔHep mice animals of 16–24 weeks of age along with Alb-Cre littermates (control mice) were subjected to a 70% partial hepatectomy (PH). Mice were sacrificed at different time points. Serum ALT and AST in the serum were measured using standard assays. Intrahepatic gene expression was assayed by quantitative real time PCR. ERK5 activation was assessed using phosphor-specific antibodies.
Results: First we evaluated the activation state of ERK5 during liver regeneration, Increased phosho-ERK5 signal was found between 6 and 9 hours after PH, corresponding to transition from the priming phase, where hepatocytes prepare for cell cycle re-entry to the progression phase of DNA replication and hepatocyte proliferation. Next control and ERK5ΔHep mice were subjected to PH and sacrificed at 24, 48 and 168 hours. Liver-to body weight ratio showed that liver recovery was similar at 24 and 48 hours after PH, whereas at a late time point (168 hours) a reduced hepatic regeneration in ERK5ΔHep mice was observed. This late decrease of regenerative response of ERK5ΔHep mice correlated with reduced hepatic expression of cell proliferation markers such as PCNA and cyclin B1. Reduced liver regeneration was accompanied by severe liver damage at 24 and 48 hours, as indicated by elevated ALT and AST levels. Histologic analysis showed that ERK5ΔHep exhibited hepatic necrosis, associated with monocyte infiltration as indicated by evelevated intrahepatic expression of CD14 and CCL2 were elevated in ERK5ΔHep livers.
Conclusion: This study indicates for the first time that ERK5 exerts an important role in the liver regeneration process participating in the priming phase, that involves the activation of several proinflammatory pathways, and in the progression phase that activates the cell cycle machinery of hepatocytes.

PS-034
MCJ: A therapeutic target in hepatic ischemia and reperfusion injury

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Background and aims: Ischemia/reperfusion (IR) injury, a frequent pathological process during liver resection, is a leading cause of post transplantation organ dysfunction. The extent of the injury can determine the success of the procedure and the survival of the patient. Therefore, attenuation of pathology caused by the injury and improving liver function after the procedure would be critical for clinicians to diminish IR injury prevalence and improve the outcome. Mitochondria play a key role in liver homeostasis; indeed, more functional mitochondria induce hepatic regeneration. MCJ, also known as DNACJ15, is an endogenous negative regulator of complex I, located in the mitochondrial electron transport chain. While under normal conditions MCJ deficiency does not result in an altered phenotype in mice, its absence improves mitochondrial activity without increasing mitochondrial ROS. We present MCJ as a new target to minimize hepatic damage caused by IR injury and enhance the efficiency of liver regeneration during liver resection.
Method: Partial hepatectomies (PH) and PH combined with IR injuries were performed in MCJ-KO mice and in WT mice after *MCJ* silencing.

Results: We observed that the lack of MCJ reduced liver damage and induced hepatic regeneration after IR injury; MCJ-KO mice showed lower levels of Caspase 3 and a significantly higher Cyclin D1 expression. Moreover, we saw an improved metabolic response to hepatic insufficiency and an accelerated cell cycle progression during liver resection, which led to a faster recovery of the hepatic mass. In the initial phase after the PH, glucagon response was amplified in MCJ-KO mice, characterized by increased cAMP and AKT signaling, along with higher Ca^{+2} release from the endoplasmic reticulum (ER), glycogen synthase kinase (GSK-3beta) inhibition and nuclear factor-Kbeta (NFKbeta) translocation to the nucleus. In the proliferative phase, ablation of MCJ accelerated the induction of proliferative markers. Indeed, after MCJ silencing, an improved phenotype was detected in an aging mice model that underwent partial hepatectomy. Hepatic insufficiency was ameliorated, PCNA expression increased and steatosis reverted. Importantly, the combined procedure of PH and IR injury that resemble liver transplant procedure resulted in a 100% survival rate for MCJ-KO mice while just the 33% of MCJ-WT mice survived the operation. Increased levels of MCJ were found in liver biopsies from all liver donors at 60 minutes after normothermic regional perfusion (nRP) was started.
Conclusion: Overall, MCJ silencing during liver resection emerges as a promising therapy for IR injury and restoration of hepatic mass.

PS-035

The role of pericentral hepatocytes in homeostatic liver regeneration: Caveats to lineage tracing from Axin2

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Background and aims: The liver is a paradigm for organ regeneration, however there is still an incomplete understanding of which hepatocytes regenerate the liver. This has implications for liver regenerative therapy.
Quiescent hepatocytes repopulate the liver parenchyma after partial hepatectomy. However, during homeostasis or injury at least three new sub-populations of hepatocytes have been reported to have particular potential to regenerate. One is self-renewing Axin2+ hepatocytes which are adjacent to the pericentral veins. Lineage tracing has suggested these hepatocytes, with active Wnt signalling and Glutamine synthetase (GS) expression, are a major source of homeostatic liver regeneration.
Method: Our aims were to 1) examine regional differences in homeostatic hepatocyte proliferation and 2) to retest the role of pericentral hepatocytes using Axin2+ lineage tracing studies. Wild type and transgenic murine models, including lineage tracing from Axin2CreER mice, were given BrdU and analysed via multiplex immunohistochemistry, in-situ hybridisation and high throughput image acquisition/analysis. qRT-PCR was used for analysis of Wnt target gene expression.
Results: Quantification of homeostatic hepatocyte proliferation identified the area between periportal and pericentral zones, zone 2, as the area in which hepatocytes are most likely to proliferate (BrdU labelled/%total zonal hepatocytes: Ecad+ve zone 1, zone 2 and GS+ve zone 3; 0.13, 0.15 and 0.02 respectively). These phenotype was also seen with long term BrdU. When using established Axin2+ lineage tracing methodology we observed preferential labelling of zone 3 hepatocytes (GS+ve), however hepatocytes from all zones were labelled acutely in Axin2CreER LSL-tdTom mice. Increasing rates of hepatocyte labelling occurred between days 2 and 5 across multiple zones (labelled hepatocytes/%total zonal hepatocytes; GS+ve Days 2 and 5, 3.6 and 26.6 and GS-ve Days 2 and 5, 0.4 and 1.9 respectively). Finally we examined the effects of the presence of an Axin2CreER knock-in construct on the Wnt pathway, observing reductions in both Lgr5 and GS.
Conclusion: This study identifies zone 2, and not the pericentral zone 3, as the zone in which hepatocytes are most likely to proliferate. Previous Axin2 based lineage tracing reports pericentral restriction of these hepatocytes. However, we show that Axin2 is expressed across the lobule and the Axin2 reporter also labels hepatocytes across the lobule without pericentral restriction. Following induction, progressive labelling occurs which confounds attributing lineage tracing specifically to the pericentral population. Finally, we demonstrate that the Axin2CreER does not accurately reflect liver homeostasis, as it affects the Wnt pathway. These results help reconcile the discrepancies between differing lineage tracing studies in the liver.

PS-036

Optimization and validation of a novel three-dimensional co-culture system in decellularized human liver scaffold for the study of liver fibrosis and cancer

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Background and aims: Development of anti-fibrotic and anti-cancer therapies suitable for human use remains an elusive goal due to limitations in in vitro and in vivo models. Hence there is an urgent need for improved preclinical models using 3 Dimensional (3D) tissue-specific and disease-specific extracellular matrix (ECM) with co-culture systems to preserve the level of complexity found in human liver pathophysiology. The aim of this study was to develop and validate a co-culture model using human liver 3D healthy and cirrhotic scaffolds as a platform for drug testing.
Method: Decellularized 3D scaffolds obtained from healthy and cirrhotic human livers were recellularized with human hepatic cell lines LX2 and HEPG2 as single and co-cultures for up to 14 days. Protein secretion, gene/protein expression involved in fibrogenesis, hepatocyte functions and cytokine expression were compared between mono-and co-culture models in both 3D ECM models. To validate the system as a new drug testing platform, cultures were treated with Sorafenib (7 µM) w/wo TGF-b1 (5 ng/ml) for 48hrs.
Results: Gene and protein secretion/expression was significantly upregulated in co-cultures when cells were grown in 3D cirrhotic scaffolds in comparison to 3D healthy scaffolds indicating specific ECM-induced effects. Compared to the LX-2 monoculture in both 3D ECM models, LX2 co-cultures secreted significantly less pro-collagen1a1, and mRNA expression of *PDGFR-b*, *COL1A1*, *COL3A1*, *LOX* and *IL-6* was downregulated, whereas being upregulated upon TGF-b1 exposure. In contrast, HepG2 gene expression of *ALB*, *UGT1A1* and *HNF4a* was similar when grown in mono or co-cultures.
To optimize Sorafenib's anti-fibrotic effect, cell viability was not affected in co-cultures treated with Sorafenib and w/wo TGF-b1. In both 3D ECM scaffolds, co-cultures treated with Sorafenib showed a significant reduction in *PDGFR-b* protein expression and pro-collagen1a1 synthesis w/wo TGF-b1 exposure and demonstrated to significantly abrogate TGF-b1-induced upregulation of *COL1A1*, *LOX*, *FN-1* and *IL-6* gene levels. Ongoing experiments are performed to investigate Regorafenib's anti-fibrotic/anti-cancer effect.
Conclusion: Acellular human healthy and cirrhotic liver 3D ECM scaffolds represent a suitable platform that mimic the natural physio-pathological microenvironment. This new 3D platform constitute a more reliable platform to screen anti-fibrotic and anti-cancer drugs when compared to the standard 2D cell culture on plastic.

PS-037

SMURF1 aggravates liver steatosis by stabilizing SREBP-1C in an E3 catalytic activity independent manner

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder characterized by the accumulation of excessive lipid in liver. Although disturbance in energy homeostasis is the main cause of the disease, the precise pathogenesis of NAFLD is very complicated and remains largely unknown. Sterol regulatory element binding protein-1c (SREBP-1c) is the main transcription factor that mediates de novo lipogenesis. Smad ubiquitination regulatory factor 1 (Smurf1) is crucial for numerous processes including bone homeostasis, embryogenesis and pathogenic autophagy. However, the role of Smurf1 in NAFLD remains unknown.
Method: We generated *Smurf1*-deficient mice fed with high-fat-diet (HFD) to verify the function of Smurf1 in liver steatosis. Oil Red O staining was performed to reveal the liver steatosis in *Smurf1*-deficient mice or in *Smurf1*-knockdown cells. TG and ALT were measured in *Smurf1* WT or knockout mice. Immunohistochemistry and western blot were used to detect the changes of SREBP-1c and its target proteins. Gene expression patterns were characterized by quantitative reverse transcription PCR. The interaction of Smurf1 with SREBP-1c was identified by *in vivo* protein-protein interaction assays. The protein stability and ubiquitination modification of SREBP-1c was assessed by *in vivo* ubiquitination assay.
Results: Here we demonstrated that liver steatosis was obviously alleviated in Smurf1-deficient mice fed with high-fat-diet (HFD). Smurf1 deletion significantly reduced the accumulation of lipid droplets and triglycerides in hepatocytes. We showed that SREBP-1c levels were dramatically reduced in *Smurf1*-KO mice. Further investigation found that Smurf1 interacted with SREBP-1c both *in vivo* and *in vitro*. Smurf1 protected SREBP-1c from ubiquitination and degradation probably through inhibiting its binding with Fbw7a, which is a major ubiquitin E3 ligase for SREBP-1c. Additionally, Smurf1 stabilized SREBP-1c in an E3 ligase catalytic activity-independent manner.

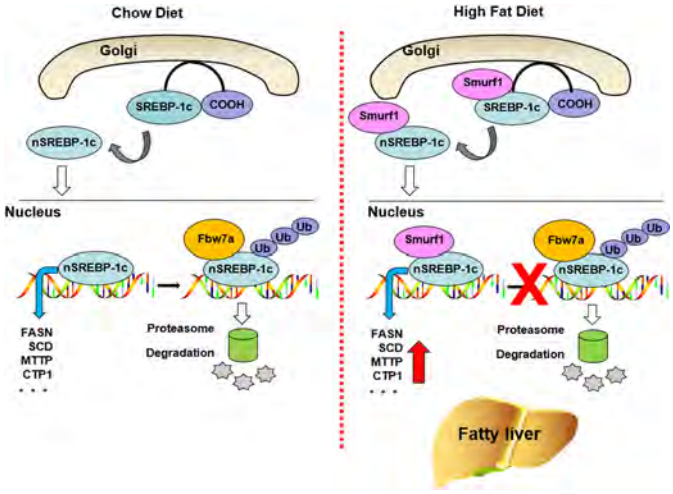

Figure legend: The proposed model for Smurf1 stabilizes SREBP-1c in E3-independent manner in fatty liver.

Conclusion: Results described in this study identify a previously unknown function of the Smurf1 in an E3-independent manner to regulate fatty liver development. Our findings unveil a novel mechanism underlying pathogenesis of liver steatosis and also provide a therapeutically potential target to combat NAFLD.

PS-038

A humanized bile acid pool induced by somatic CRISPR/Cas9-mediated deletion of Cyp2c70 modulates effects of pharmacological FXR activation in mice

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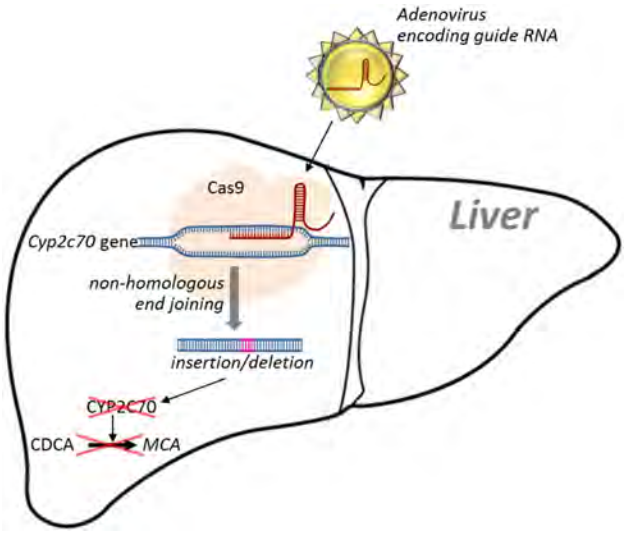
Background and aims: Bile acids (BAs) facilitate fat absorption but also modulate various metabolic pathways through activation of the BA receptors FXR and TGR5, which have been identified as targets for therapeutic interventions. However, fundamental differences in BA metabolism between humans and mice complicates translation of preclinical data. CYP2C70 was recently proposed to catalyze the formation of rodent-specific muricholic acids (MCAs). We generated an acute hepatic *Cyp2c70* knock-out mouse model, using somatic genome editing (see figure), to clarify the role of CYP2C70 in BA metabolism *in vivo* and to evaluate whether its activity modulates effects of pharmacological FXR activation on cholesterol homeostasis.
Method: The *Cyp2c70* gene was acutely ablated in adult mouse livers (*Cyp2c70*^{ako}) by CRISPR/Cas9-mediated somatic genome editing employing adenovirus-mediated delivery of single-guide RNA to Cas9-transgenic mice.
Results: Hepatic CYP2C70 protein levels were reduced by ~95% in *Cyp2c70*^{ako} mice. This translated into strongly increased contributions of chenodeoxycholic (CDCA) and ursodeoxycholic (UDCA) acids and a concomitantly reduced contribution of mouse-specific beta-MCA, resulting in a more hydrophobic BA pool ($p < 0.001$). Evaluation of *in vivo* CDCA and UDCA metabolism using D4-labeled tracers revealed 6beta-hydroxylase as well as C7-epimerase activity of CYP2C70, delineating its importance in generating the characteristic murine BA pool. Next, we assessed the impact of the humanized BA pool on the response to pharmacological FXR activation. The reduction of fractional cholesterol absorption observed in control mice upon FXR activation with PX20606 (54% to 20%, $p < 0.001$) was blunted in *Cyp2c70*^{ako} mice (47% to 34%, $p < 0.01$). Additionally, augmented fecal cholesterol disposal in response to FXR activation was impaired in *Cyp2c70*^{ako} mice ($p < 0.05$), predominantly due to reduced stimulation of transintestinal cholesterol excretion (TICE).



Conclusion: CRISPR/Cas9-mediated deletion of hepatic *Cyp2c70* in adult mice translates into a human-like BA pool composition and impacts the response to pharmacological FXR activation, emphasizing the importance to carefully consider the consequences of species-specific (BA) metabolism in pre-clinical studies.

PS-039

Role of ductular reaction on the hepatic microenvironment in chronic liver disease

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Background and aims: Ductular reaction (DR) expands in response to the loss of hepatocyte replicative capacity in chronic liver diseases. Yet, the role of DR in liver regeneration and its influence on the hepatic microenvironment is still not well understood. The aim of this study was to investigate the role of DR in tissue repair mechanisms such as inflammation, angiogenesis and fibrosis in the context of chronic liver disease.
Method: The hepatic transcriptomic profile was performed in normal liver tissue (n = 6) and patients with different stages of alcoholic liver disease (ALD) (n = 22). DR was obtained by laser microdissection of KRT7+ cells (n = 6) and analyzed by RNASeq. Hepatic organoids were generated from cirrhotic liver samples (n = 8), characterized by qPCR and ELISA and used as in vitro model of DR. The effect of organoids on: vasculogenesis was assessed on HUVEC cells cultured on Matrigel; neutrophils was evaluated by qPCR and Migratest; hepatic stellate cells (HSC) was evaluated by qPCR and wound-healing assay.
Results: Transcriptomic analysis of ALD samples showed the correlation of DR with the expression of inflammation, angiogenesis and fibrosis markers. Moreover, transcriptomic analysis of microdissected DR cells showed the expression of genes related to inflammation (*CXCL chemokines*), fibrogenesis (*LOXL, TIMP1, ACTA2*) and angiogenesis (*SLIT2, VWF, PECAM, VEGF*). Histological assessment showed that DR is associated with neutrophil infiltration, increased angiogenesis and fibrosis. Liver organoids generated from cirrhotic liver tissue expressed key markers of DR cells and showed a gene expression profile similar to DR cells. Moreover, organoids secreted inflammatory (CXCL5) and angiogenic factors (SLIT2), thus suggesting the potential of liver organoids as an in vitro system to model DR. Organoid conditioned medium promoted neutrophil migration and an increased expression of inflammatory cytokines (*IL1β* and *TNFα*). In addition, neutrophil conditioned medium up-regulated the expression of inflammatory chemokines (*CXCL chemokines*) in organoids, suggesting a crosstalk between DR and neutrophils. Regarding the potential role of DR in angiogenesis, organoid conditioned medium induced tubule formation in HUVEC cell cultures, which was dependent on SLIT2 production by organoids. Finally, organoid conditioned medium enhanced HSC activation and wound-healing response.
Conclusion: These results suggest that DR interacts with inflammatory cells, HSCs and vascular cells. In the context of chronic liver diseases, DR may exert an influence on the hepatic microenvironment and tissue repair mechanisms such as inflammation, angiogenesis and fibrosis.

PS-040

Bacterial infection upregulates TGR5 expression in a Krüppel-like-factor 5-dependent manner

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Background and aims: G protein-coupled bile acid receptor 1 (GPBAR1, TGR5) is one of the major effectors in bile acid sensing with demonstrated influence on metabolic, inflammatory, and proliferative processes. TGR5 is abundantly expressed in monocytes/macrophages and its activation in these cells is associated with a reduced nuclear factor kappa B (NFkB)-dependent inflammatory responses. The transcription factor Krueppel-like factor 5 (KLF5) has been shown to associate with NFκB to regulate genes involved in inflammation. Aim of our study was to investigate the role of KLF5 in the upregulation of TGR5 in inflammatory liver disease using different mouse models.
Method: TGR5 and KLF5 mRNA expression in *bone marrow-derived macrophages* (BMDMs) as well as in mice livers and human peripheral blood mononuclear cells (PBMC) were quantified by real-time PCR in relation to an endogenous control (HPRT1). Binding of the transcription factor KLF5 to the TGR5 promoter was verified by Chromatin Immunoprecipitation (ChIP). The survival of the TGR5 knockout (KO) and wildtype (WT) mice was monitored after the injections with 22, 5 µg/g BW lipopolysaccharide (LPS) or infection with 8×10^4 CFU/ml *Listeria monocytogenes (L.m.)*. Serum levels of AST and ALT were analyzed by using Spotchem-biochemical analyzer. Flow cytometry has been used to examine immune cells in non-lymphoid tissues.
Results: TGR5 and KLF5 mRNA expression was significantly upregulated in murine BMDMs or human PBMC as well as in livers from WT mice after LPS injection or *L.m.* infection. Furthermore, TGR5 staining in CD11 positive macrophages in the mouse liver was increased. Chromatin immunoprecipitation confirmed binding of KLF5 to the TGR5 promotor region. KLF5 increased the TGR5 promoter activity and the effect was lost when the binding sites for KLF5 in the TGR5 promoter region were mutated. LPS and L.m. injection resulted in severe liver injury in TGR5 deficient mice as determined by AST and ALT elevation. Moreover, mortality was significantly increased in TGR5 knockout mice. This phenotype was mirrored by immune-cell specific TGR5 knockout mice.
Conclusion: The TGR5 and KLF5 mRNA expression was significantly upregulated in murine and human macrophages and livers of WT animals after LPS injection or Listeria infection, indicating that TGR5 may confer protective effects in the WT animals, most likely through KLF5. In contrast, TGR5 deficient mice manifest increased mortality after LPS or L.m. injection underscoring the important role of TGR5 in inflammatory liver disease.

Liver tumours – Experimental

PS-041

Intense angiocrine crosstalk between liver endothelial cell subtypes leads to liver capillarization and recruitment of myeloid progenitors

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Background and aims: In hepatocarcinogenesis capillary endothelial cells (CECs) gradually replace liver sinusoidal endothelial cells (LSECs) in a tumour-supportive process termed capillarization. An in-depth molecular characterization of LSECs, CECs and liver macrophages in hepatocarcinogenesis is however still missing.
Method: An inducible mouse model with hepatocyte-specific expression of the constitutively active oncogene yes-associated protein (YAPS127A) was used to purify primary LSECs, CECs and liver macrophages. RNA was subjected to transcriptomic profiling. Predicted paracrine interactions were functionally tested in vitro. Kinase inhibition by Cabozantinib in vivo served as a model of HGF/c-Met axis perturbation.
Results: A progressive expansion of CECs from 4 ± 2% in healthy livers to 61 ± 30% in YAP induced hepatocellular carcinomas (HCCs) was observed. Transcriptome data revealed an intense paracrine crosstalk between CECs and LSECs including the ligand/receptor pairs VEGFC/Flt4, CXCL12/CXCR4, and the HGF/c-Met. Interestingly, a dynamic upregulation of c-Met was detected in CECs, while HGF was exclusively expressed by LSECs. Functionally, HGF stimulation of endothelial cells was associated with increased cell motility. In vivo, perturbation of the HGF/c-Met axis by Cabozantinib led to a 67% reduction of CEC sprouting. CEC expansion was also associated with an upregulation of myeloid recruiting genes. Indeed, a perivascular recruitment of CD11b+ F4/80+ macrophages was observed that lacked the typical Kupffer cell expression signature. Lastly, capillarization served as a prognostic biomarker in human HCCs and was associated with increased M0 macrophage infiltration.
Conclusion: A crosstalk between LSECs and CECs in hepatocarcinogenesis initiates capillarization. Angiogenesis perturbation could synergistically prevent tumour progressive capillarization and inhibit an influx of disease-modifying myeloid cells.

PS-042
Interventional targeting of cyclin E1 during hepatocarcinogenesis limits stem cell traits and hepatic myeloid cell homing and attenuates cancer progression

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Background and aims: Hepatocellular carcinoma (HCC) is one of the most severe tumor diseases with increasing incidence and limited treatment options. HCC initiation and progression are associated with persistent proliferation of hepatocytes and non-parenchymal cells. Proliferation is related to cell cycle activity, which is basically regulated by cyclins and Cyclin-dependent kinases (Cdks). E-Type cyclins (Cyclin E1, E2) and their canonical binding partner Cdk2 are key mediators of early cellular DNA replication. Own work demonstrated an essential role of Cyclin E1 and Cdk2 specifically for initiation of HCCs in a murine prevention model (Sonntag et al., PNAS 2018 Sep 11;115 (37):9282-9287). In the present study, we investigated the therapeutic benefit of Cyclin E1 or Cdk2 gene targeting after onset of hepatocarcinogenesis (intervention model).
Method: In this study, conditional Cyclin E1 (CcnE1f/f) or Cdk2 (Cdk2f/f) mice in a C57B6/J background with inducible Cre-recombinase under control of the Mx-gene promoter were used. For HCC induction, 14 days old male mice were intraperitoneally (i.p.) injected with diethylnitrosamine (DEN). Cre-negative littermates were used as controls. After 22 weeks (stage of early HCC), interventional inactivation of Cyclin E1 or Cdk2 in hepatocytes and the hematopoietic cell compartment was performed by three i.p. injections of poly-I:poly-C. Two weeks and 16 weeks after intervention, mice were analyzed for tumor burden, proliferation, stemness, DNA repair and the microenvironment composition to determine immediate and long term treatment effects.
Results: At the age of 40 weeks, interventional inactivation of Cyclin E1 resulted in a significant reduction of tumor numbers and size compared to DEN-treated control mice. This finding was associated with a decreased overall hepatic proliferation and intratumoral down-regulation of cell cycle activators, tumor markers, stem cell traits and vascularization. Already two weeks after intervention, Cyclin E1 deletion significantly reduced the expression of pro-proliferative genes. Importantly, Cyclin E1-independent growth in remnant tumors was associated with sustained expression of DNA repair genes. Moreover, Cyclin E1 inactivation also changed the composition of the myeloid HCC microenvironment (e.g. myeloid-derived suppressor cells) pointing to a new role of Cyclin E1 for immune progenitor cell homing during liver cancer development. In sharp contrast, interventional inactivation of Cdk2 after onset of hepatocarcinogenesis did not reveal any beneficial effect on tumor burden.
Conclusion: Cdk2 is essential for HCC initiation, but surprisingly fully dispensable for HCC progression. However, interventional inactivation of Cyclin E1 during early HCC progression attenuates disease development. Hence, Cyclin E1 presents a promising therapeutic target for treatment of HCC patients.

PS-043
Dual targeting of G9a and DNM-methyltransferase-1 for the treatment of experimental cholangiocarcinoma

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Background and aims: Cholangiocarcinoma (CCA) is a deadly disease usually diagnosed at advanced stages when treatment options are limited. CCAs are histologically and molecularly heterogeneous tumors highly resistant to systemic therapies, and targeted drugs are yet to prove their efficacy. Identification of novel targets for CCA treatment is therefore necessary. Epigenetic alterations are increasingly recognized in CCAs which may constitute druggable targets. DNA and histone methylation reactions functionally cooperate in fostering tumor growth. We evaluated the therapeutic efficacy of a first-in-class substrate-competitive dual G9a H3K9-methyltransferase and DNA-methyltransferase 1 (DNMT1) inhibitor in different *in vitro* and *in vivo* CCA models.
Method: G9a and DNMT1 mRNA and protein levels were examined in human CCA tissues by qPCR and immunohistochemistry. Dual targeting of G9a and DNMT1 was examined in CCA cells by

combination treatment with the G9a and DNMT inhibitors BIX-01294 and decitabine. Anti-CCA efficacy of our G9a/DNMT1 inhibitor lead compound, CM-272, was tested in human CCA cells, alone and in combination with cisplatin, Mcl-1 or ErbB inhibitors. Microarray transcriptomic analyses were performed in two CCA cell lines treated with CM-272. CM-272 was also tested in subcutaneous and orthotopic mouse xenografts of human CCA cells, and in a new model of cholangiocarcinogenesis (mice with JNK1/2 deletion in hepatocytes, $JNK^{\Delta hepa}$).

Results: G9a and DNMT1 expression was increased in human CCA samples and CCA cell lines compared to non-transformed tissues and cells. Combined treatment of CCA cells with BIX-01294 and decitabine resulted in synergistic growth inhibition. CM-272 showed GI50 values in the nanomolar range in six human CCA cell lines and markedly inhibited their colony formation capacity. CM-272 synergized with cisplatin, an Mcl-1 inhibitor, or the ErbB pathway inhibitors afatinib or lapatinib in the inhibition of CCA proliferation. CM-272 inhibited the growth of subcutaneous and orthotopic CCA xenografts, and the development of preneoplastic CCA lesions in $JNK^{\Delta hepa}$ mice. In CM-272 treated mice no systemic or hepatic toxicity were observed. Mechanistically, microarray analyses showed that CM-272 induced a strong metabolic reprogramming and interfered with growth factor signaling pathways in CCA cells

Conclusion: Pharmacologic interference with G9a and DNMT1 might be a promising strategy for the development of effective therapies against CCA

PS-044

Identification of a pan-gamma-secretase inhibitor response signature for notch-driven cholangiocarcinoma

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Background and aims: Cholangiocarcinoma (CCA) mortality rates are increasing. NOTCH pathway reactivation has been reported in CCA to conflicting degrees, hindering prioritization of therapeutic targets and identification of candidate responder patients for NOTCH-directed therapies. As 40% of NOTCH-directed clinical trials in cancer have been terminated or withdrawn, thorough guidelines for patient selection are clearly required. Here, we identified a transcriptomic signature capable of predicting pan-γ -secretase inhibitor (GSi) response across multiple patient cohorts and CCA models, as well as diverse cancer types.

Method: Transcriptomes were analyzed from 341 CCA patients. Models of GSi-sensitivity and -resistance were initially identified from 13 CCA cell lines *in vitro*, followed by subcutaneous CCA xenograft models. The responder signature was developed by transcriptome profiling of murine tumors and tested for enrichment across diverse hydrodynamic models and patient subgroups. Pan-cancer analysis of this signature was also pursued in 9409 patient tissues (31 cancer types) and 60 cancer cell lines.

Results: A *NOTCH1*^{high} CCA patient subgroup was identified, characterized by distinct stromal infiltration and lymph node metastasis. Extensive NOTCH network imbalance, including multiple ligand and receptor usage, identified the γ-secretase (GS) complex as an optimal therapeutic target. Treatment using two GSi classified HuCCT-1 and WITT as models of sensitivity and resistance, respectively. Subcutaneous transplantation of sensitive and resistant CCA cell lines pre-treated with a GSi cocktail demonstrated anti-neoplastic effects in the sensitive model only and led to development of a 225-gene responder signature. This signature was enriched in intrahepatic tumors developed by hydrodynamic injections of activated NOTCH as compared to AKT-RAS-driven tumors ($p < 0.001$), as well as in a subgroup of CCA patients ($p = 0.0232$). Candidate GSi-responder patients were characterized by grossly unique intra-tumoral stromal reaction and signaling pathways, as well as metastasis ($p = 0.0078$) and cancer stemness ($p = 0.0142$) signatures. Pan-cancer analysis identified 41.9% cancers to harbor prospective GSi-responder patients. This signature was also capable of discriminating nanomolar versus micromolar sensitivity of 60 tumor lines to GSi with an AUC of 1 (versus AUC:0.50-0.61 for *NOTCH* receptor expression).

Conclusion: Identification of this pan-GSi-responder signature may facilitate precision medicine application of NOTCH-directed therapy in CCA as well as prospectively across diverse malignancies. This is supportive of basket trial approaches using this theranostic signature.

PS-045

HCC promotes autophagy in hepatic stellate cells, leading to HCC progression via IL-6/STAT3 signaling

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Background and aims: Autophagy, a system of degradation of proteins and organelles, in hepatoma cells is supposed to promote the progression of cancer. However, the effect of autophagy in hepatic stellate cells on hepatocellular carcinoma (HCC) has not yet been clarified.

Method: HepG2 cells were used as human hepatoma cells and LX2 cells as human HSCs. Autophagy was examined from the ratio of the fluorescence intensities of GFP and RFP using LX2 cells overexpressing GFP-LC3-RFP-LC3ΔG probe. 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.

Results: When co-culturing LX2 cells with HepG2 cells, autophagy in LX2 cells was promoted and cell viability in HepG2 cells were increased. TaqMan Array using chemokine panel revealed WNT2, CER1, IL1B and IL6 expression levels were significantly increased in LX2 cells co-cultured with HepG2 cells. Among them, only IL-6 was detected by ELISA in co-cultured medium of LX-2 and HepG2 cells. Their IL-6 levels were significantly higher than those in LX2 mono-cultured medium, while IL-6 in HepG2 mono-culture medium was not detected. siRNA-mediated knockdown of Atg7 in LX2 cells decreased IL-6 levels in cultured medium. Co-culture with LX2 cells increased cell viabilities with pSTAT3 activation in HepG2 cells, which was attenuated by siRNA-mediated knockdown of Atg7 in LX2 cells. 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 LX2 cells. The acceleration was suppressed by Atg7 KO using CRISPR-Cas9 system in LX2 cells.
Wild-type (WT) mice or HSC-Atg7 KO mice were administrated with streptozotocin, and fed a high fat diet. Atg7 was efficiently inhibited in stellate cells isolated from HSC-Atg7 KO mice. At 20 weeks of age, there was no significant difference in fat body weight ratio, body weight, blood glucose level, serum ALT and insulin levels between them. Macroscopic tumor formation rate was lower in G-Atg7 KO mice than WT mice. The maximum size of liver tumors were significantly suppressed in G-Atg7 KO mice (2.0 ± 2.1mm v.s. 10.0 ± 5.8mm ($p = 0.002$)) with decrease in pSTAT3 expression levels of tumor lesions.The number of liver tumors were also significantly suppressed in G-Atg7 KO mice.

Conclusion: HCC promotes autophagy in stellate cell, which modulates inflammatory cytokine such as IL-6, leading to progression of HCCs.

PS-046

Suppression of complex protumorigenic phenotypes in chronic injury-associated hepatocarcinogenesis is dependent on IL-6/STAT3 signaling

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Background and aims: Hepatocelluar carcinoma (HCC) typically develops on a background of chronic hepatitis. Evidence from chemical-induced HCC associated experimental models with acute liver injury indicates that interleukin-6 (IL-6) is a crucial factor driving hepatocarcinogenesis. However, in chronic liver injury, where IL-6 is an established hepatoprotective factor, its role in hepatocarcinogenesis remains unresolved. We investigated the roles of IL-6 and signal transducer and activator of transcription 3 (Stat3) in liver cancer in multidrug resistant gene 2 knockout mice ($Mdr2^{-/-}$), which develop primary sclerosing cholangitis and are a physiologically relevant model of hepatitis-associated HCC.
Method: IL-6 knockout ($IL\text{-}6^{-/-}$) mice, and hepatocyte-targeted Stat3 knockout mice ($Stat3^{\Delta hep}$), were crossed into $Mdr2^{-/-}$ mice generating $Mdr2^{-/-}IL6^{-/-}$ and $Mdr2^{-/-}Stat3^{\Delta hep}$ mice, respectively. Additionally, the transgene encoding sgp130Fc (a selective inhibitor of soluble IL-6 receptor sIL-6R mediated trans-signaling) was introduced to generate $Mdr2^{-/-}$sgp130Fc mice. Mice were followed for the development of hepatitis and tumorigenesis over the course of 14 months.
Results: IL-6/Stat3 signaling deficient $Mdr2^{-/-}$ mice of both genders displayed increased liver injury (ALT) and fibrosis from an early age together with increased dysplastic nodule formation and uniformly presented with accelerated and increased tumorigenesis. Gene expression and bioinformatics analyses of female WT, $Mdr2^{-/-}$, and $Mdr2^{-/-}IL6^{-/-}$ mice revealed close associations of the aggravated tumorigenesis with the presence of four aberrant, HCC-linked phenotypes in the IL-6 deficient mice: i) reduced hormone-mediated protection; ii) hepatosteatosis; iii) inflammation and iv) cellular senescence. But, ovariectomy of $Mdr2^{-/-}$ mice reduced liver injury and tumorigenesis, and dietary restriction experiments, although reducing steatosis, did not affect tumorigenesis; thus ruling out loss of hormonal-protection and hepatosteatosis as underlying causes. Immunostaining analysis confirmed the increased inflammatory status, particularly involving macrophage (F4/80) infiltration. Cellular senescence, as indicated by levels of p21, γH2AX, and SASP factors (TGFβ, Mmp2, Timp1 and Timp2), was strongly reduced in young (3 months) IL-6 signaling deficient $Mdr2^{-/-}$ mice, but surprisingly increased in older mice (14 months). In contrast, expression of other SASP factors, including PAI-1, Cxcl14, cGAS and STING, were significantly reduced at all ages; together suggesting a strong, age-dependent disruption in cellular senescence and the SASP in IL-6 deficient strains.
Conclusion: Loss of IL-6/Stat3 signaling strongly aggravates hepatocarcinogenesis in $Mdr2^{-/-}$ mice associated with a profound age-dependent disruption in cellular senescence and increased macrophage infiltration.

PS-047

HSD17B13 loss of function variant protects from hepatocellular carcinoma developed on alcohol related liver disease

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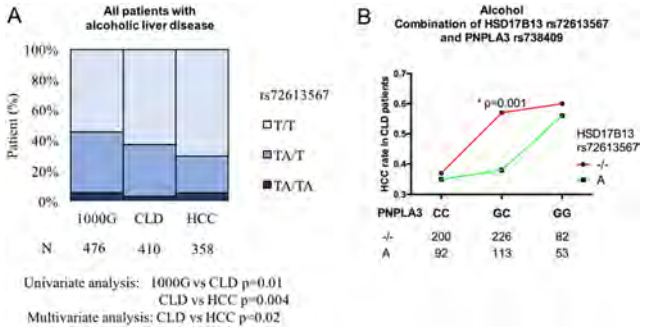
Background and aims: Recently, a loss of function variant (rs72613567) of 17-beta-hydroxysteroid dehydrogenase 13 (HSD17B13) has been identified as protective in non-alcoholic and alcoholic liver disease. However, the role of this SNP in hepatocellular carcinoma (HCC) development is currently unknown. We aimed to assess the impact of this variant in European patients with HCC developed on chronic liver disease (CLD) of various severities and etiologies.
Method: HSD17B13 rs72613567, PNPLA3 rs738409 and TM6SF2 rs58542926 were genotyped using a case control study design including 1018 patients with HCC (mean age 64 years, 83% of male, alcoholic liver disease 35%, hepatitis C 25%, non-alcoholic liver disease (NAFLD) 12%), 988 patients with CLD without HCC (mean age of 55 years, 68% of male, alcoholic liver disease 42%, hepatitis C 33% and NAFLD 18%) as well as 503 healthy individuals from 1000genome project all from European descent. We compared the genotype distribution between CLD patients and healthy controls from the 1000genome project, and between HCC patients and CLD patients using Chi-square test and logistic regression.
Results: Heterozygous T/TA of HSD17B13 were significantly less frequent in patients with CLD (32%, P = 0.001) and in cirrhotic patients (31%, P = 0.0008) compared to healthy control of 1000genome population (40%). Among etiologies of CLD, heterozygous T/TA of HSD17B13 was less frequent in patients with CLD due to chronic alcohol intake (34%; p = 0.03), chronic hepatitis C (32%, p = 0.01) and chronic hepatitis B (23%, p = 0.005) compared to healthy population (40%) suggesting a protective role of HSD17B13 rs72613567 in the progression of chronic liver disease.
In patients with HCC developed on alcoholic liver disease, T/TA genotype of HSD17B13 rs72613567 was less frequent (24%) than in CLD patients with alcoholic liver disease and without HCC (34%, P = 0.004) and the protective effect of the T/TA genotype remains significant after adjustment for age, gender and the stage of fibrosis in multivariate analysis (OR = 0.6 CI95% = 0.4-0.9 P = 0.03). In contrast, no robust association between HSD17B13 genotype and HCC risk was identified in other etiologies. PNPLA3 rs738409 (GC vs. CC: OR = 2.4 [1.6-3.6]; GG vs. CC: OR = 3.8 [2.3-6.3]) and TM6SF2 rs58542926 (CT +TT vs. CC: OR = 1.9 [1.3-2.9]) were both strongly associated with the risk of alcohol related HCC. Interestingly, the T/TA genotype of HSD17B13 rs72613567 was protective of HCC in patients with alcoholic liver disease harboring the at-risk CG allele of PNPLA3 rs738409 (OR = 0.4[0.2-0.7]; p = 0.001) but not in patients harboring the at-risk allele of TM6SF2.



Conclusion: Loss of function variant of HSD17B13 (rs72613567) is protective of HCC development on alcoholic liver disease, especially in patients harboring the at-risk allele of PNPLA3 rs738409.

PS-048

Definition of aneuploidy profiles and their impact on tumour progression and immune features in hepatocellular carcinoma

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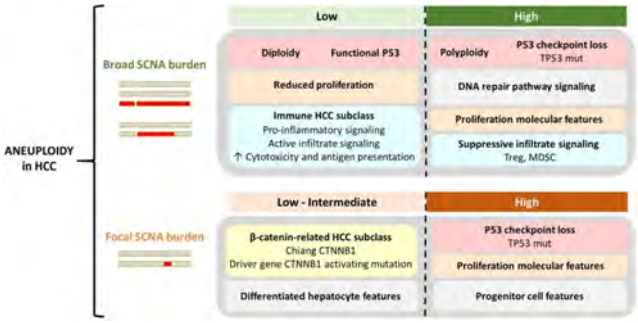
Background and aims: Aneuploidy is a hallmark of cancer that includes broad somatic copy-number alterations (SCNAs), being whole chromosome- or arm-level events, and smaller focal SCNAs. Pan-cancer studies suggest that distinctive molecular/clinical traits are linked to either broad or focal SCNA loads, with the first potentially interfering with tumor immune infiltrates. We aimed at assessing broad and focal SCNA burdens in hepatocellular carcinoma (HCC) to unveil associated clinic-molecular characteristics and immune cell profiles. We propose SCNA scores that predict low/high burdens and chromosomal instability.

Method: The study includes 520 paired tumor/adjacent surgically resected HCC samples: 150 of a training cohort (HEPTROMIC) and 370 of a validation cohort (TCGA). We extracted tumor ploidy and SCNAs from SNP array data using ASCAT and SAASCNV. Based on SCNA number, amplitude and length, we created a Broad SCNA Score (BSS) to assess broad SCNA loads in each sample, and a Focal SCNA Score (FSS) to determine focal SCNAs loads (being broad and focal those alterations spanning ≥ 50% and < 50% of a chromosome arm, respectively). The scores were integrated with gene expression profiling, clinic-pathological data from tumors and the composition of the tumor immune infiltrate, which was determined using the Immunophenoscore.

Results: HCC tumors characterized by a low BSS (25% of Heptromic, 15% of TCGA) were associated with the HCC Immune class and upregulation of genes related to inflammation, active infiltrate signaling, antigen presentation and cytolytic activity (FDR < 0.1, p < 0.05). Conversely, high BSS tumors (25% Heptromic, 45% TCGA) were linked to polyploidy, TP53 loss of function, were enriched in DNA repair and proliferation gene signatures and presented upregulation of genes from immune suppressor cells. On the other hand, tumors with high FSS (25% Heptromic, 49% TCGA) were associated with *TP53* loss of function and upregulation of genes related to proliferation and progenitor cells, whereas low-intermediate FSS tumors displayed higher β-catenin pathway activity, with enrichment in *CTNNB1* mutations. FSS was not associated with immunity profiles.



Conclusion: Broad are more informative than focal SCNA burdens in terms of molecular features and immune status. Tumors with low Broad SCNA Scores, thus with chromosomal stability, are enriched in the immune class of HCC, and might correspond to those tumors responding to checkpoint inhibitors.

Hepatitis B/D/E – Clinical aspects

PS-049

Tenofovir alafenamide for hepatitis B virus prophylaxis post-liver transplantation is associated with improved renal function: An interim analysis of a multicenter real-world experience

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Background and aims: Tenofovir alafenamide (TAF) has been shown to be equally efficacious in suppressing hepatitis B virus (HBV) but with less renal toxicity than tenofovir disoproxil fumarate (TDF). Post-liver transplantation (LT) patients are especially prone to renal effects due to calcineurin inhibitor immunosuppression. Therefore, we conducted a multicenter real-world study to evaluate renal function in post-LT patients on TAF.

Method: Post-LT patients receiving HBV antiviral therapy at 3 tertiary liver transplant centers in Southern California (University of California Los Angeles [UCLA], Cedars-Sinai [Cedars], University of Southern California [USC]) were enrolled. There were two arms: the intervention cohort underwent crossover from existing HBV antiviral agent to TAF; the control cohort remained on existing HBV antiviral agent. Study assessments were based on 48-week follow-up from baseline or time of conversion to TAF-based prophylactic therapy. We used the two-sample t-test to compare mean differences in serum

creatinine following one year of TAF therapy compared to the control group. 23 additional patients have yet to complete 48 weeks of TAF therapy and are not included in this interim analysis.
Results: There were 52 patients (UCLA: n = 26; Cedars: n = 13; USC: n = 13) in the intervention (TAF) cohort and 47 patients in the control cohort (TDF 70%; entecavir 26%; lamivudine 4%) (Table). Patients who transitioned to TAF had a significant mean decrease in serum creatinine, compared to the control cohort (-0.07 mg/dL 95% CI [−0.14 to −0.01] vs. 0.04 mg/dL [0.01 to 0.08]; p = 0.0043) after 48 weeks of therapy (Figure). In the TAF cohort, the mean serum creatinine decreased after 48 weeks at each center: UCLA −0.08 range [−0.58 to 1.03]; Cedars −0.08 [−0.31 to 0.06]; USC −0.03 [−0.36 to 0.18]. There were no differences in post-LT outcomes (rejection episodes, re-LT, death) between the two cohorts.

Table: Baseline characteristics

	Intervention (n = 52)	Control (n = 47)
Age	61 (9)	60 (10)
Sex		
Female	7 (13%)	15 (32%)
Male	45 (87%)	32 (68%)
Race/Ethnicity		
Asian	39 (75%)	28 (60%)
White	10 (19%)	11 (23%)
Hispanic	2 (4%)	8 (17%)
Black	1 (2%)	0 (0%)
Serum Cr at baseline	1.42 (0.44)	1.12 (0.31)
Serum Cr after 48 weeks	1.35 (0.45)	1.17 (0.32)

Data are n (%) or mean (standard deviation). Cr = creatinine.

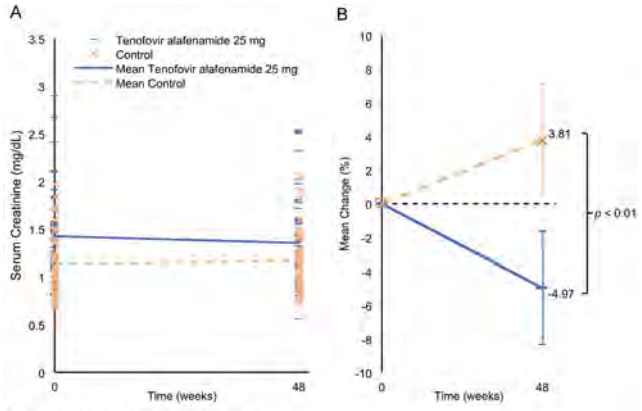

Figure: **Changes in serum creatinine**
(A) Mean serum creatinine and serum creatinine per patient at baseline and after 48 weeks of treatment.
(B) Mean percent change in serum creatinine at baseline and after 48 weeks of treatment. Bars are 95% CI.

Conclusion: Conversion to TAF in post-LT patients requiring HBV prophylaxis is associated with significant improvement in renal function, compared to a control cohort.

PS-050
Integrated analyses of both human and HBV genome to predict HCC Development

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Background and aims: Hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC). Clinical outcomes are induced by interactions between viral and host factor. Especially, a prediction marker of HCC development provides great benefits for clinician and patients. In the present study, we determined a host genetic factor associated with HBV-derived HCC, and discovered viral genetic factors corresponding to the host genetic variation.
Method: Total 2, 996 individuals were enrolled from 10 hospitals, 408 chronic hepatitis B (CHB) patients, 307 HBV-derived HCC patients, and 2, 281 healthy volunteer (HV). Human genetic data were obtained from SNPs array and Luminex method for HLA genotype. These genetic data were filled up by imputation techniques. For viral genome analysis, HBV DNA was extracted from serum of CHB or HCC patients and was prepared for next-generation sequencing (NGS). All sequence reads were converted from nucleic acid into amino acid (AA) sequences. Multiple comparisons were counteracted by statistical method.
Results: By genome-wide association study using SNPs and HLA genotype, HLA-DPB1*02:01 was an independent protection factor against HCC development ($p < 4.53x10-9$, OR = 0.53). HLA-DPB1*04:01 was statistically associated with the protection against CHB establishment ($p < 6.49x10-6$, OR = 0.31). Next, we focused on viral genomic factor related with HCC development. Patients with HLA-DPB1*02:01 homozygote were divided into HCC and non-HCC group with age-, sex-, HBV genotype-matched condition. The half of the samples was used for test set. AA variations of HBV protein were restricted to particular patterns in PreS/S protein in the HCC group with the HLA-DPB1*02:01. The ratio of S166 in CHB and HCC was 51.5% and 0%, respectively ($p < 0.05$). However, the ratio of L166 in CHB and HCC was 34.3% and 99.4%, respectively ($p < 0.05$). The mutation was confirmed using validation sample set. S166L mutation was also associated with HCC development ($p < 0.02$, OR = 18.2). In addition, we determined the effect of S166L mutation in HLA-DPB1*02:01 heterozygote with or without HCC. S166L mutation was statistically associated with HCC patients with the heterozygotes ($p < 0.05$, OR = 1.6). But, S166L mutation in PreS/S didn't change AA sequence in HBV polymerase.
Conclusion: We detected host and viral genetic factors related with clinical outcomes. Hepatitis B patients with both HLA-DPB1*02:01 allele and S166 in PreS/S were low risk for HCC development. However, when they had L166 mutation, they had high risk for HCC. A specific AA change in the HBV antigen could affect HCC development by interaction change between host and virus. This is a proof of concept study in order to predict a prognosis using genomic data in hepatitis B.

PS-051
Mortality and morbidity of hepatitis E in scotland: A multicentre study

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Background and aims: In the past decade Hepatitis E virus (HEV) infection has become the most common acute viral hepatitis in Scotland. Little is known about the burden of morbidity and mortality, which can be high in chronic liver disease and Immunosuppressed patients. Infection is also associated with nerve and kidney injury. The study aims to record the morbidity and mortality for all cases of HEV in four Scottish health boards.
Method: Demographic, clinical and laboratory data were collected retrospectively from all cases of HEV reported to virology departments within NHS Greater Glasgow and Clyde, NHS Grampian, NHS Tayside and NHS Lothian. Hospital records were reviewed by clinicians working within each hospital. Data was anonymised at hospital level.

Results: A complete, five-year dataset was obtained from Glasgow (n = 187) and Grampian (n = 96) between January 2013 and January 2018, further cases were included from Tayside (n = 72) and Lothian (n = 16) with data collection ongoing (n = 371, Mean age of 60yrs, 63% male). 41 (11.1%) cases had cirrhosis and 86 (23.2%) had diabetes. HEV infection affected 13 transplant patients in a total of 58 immunosuppressed cases (15.6%).
242 (65%) patients required admission, totalling 2255 inpatient-bed-days (median stay 3 days). 13 (3.5%) HEV related deaths were recorded, 10 with pre-existing liver disease and 3 with immunosuppression. 21 (5.7%) patients required admission to critical care. 27 (7.3%) patients developed acute, acute-on-chronic or decompensated liver failure with 2 requiring transplantation.
35 (9.4%) reported neurological symptoms with 8 developing neuralgic amyotrophy, 6 Guillain-Barré, and 2 encephalitis. 36 (9.7%) patients had a documented Acute Kidney Injury. 14 (3.8%) cases were documented as chronic HEV, 12 received Ribavirin therapy.

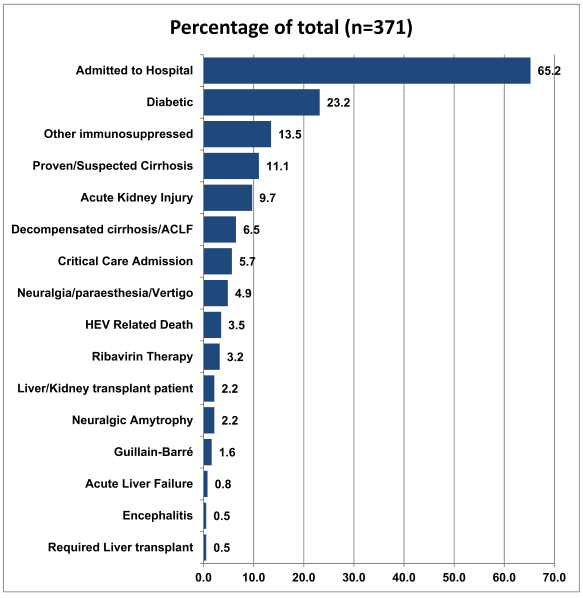

Figure: Morbidity and mortality expressed as percentage total of cases (n = 371)

Conclusion: Locally-acquired HEV causes a significant burden of disease, with a high number of inpatient days and a risk of organ failure or death. Cirrhosis, diabetes and immunosuppression are associated with symptomatic infection. Neurological and renal complications occur in a minority.

PS-052

End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection

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Background and aims: Hepatitis Delta Virus (HDV) infection leads to the most aggressive form of human viral hepatitis. There is no approved therapy. Worldwide prevalence of HDV infection is 15-20 million. PEG IFN-lambda-1a (Lambda) has previously demonstrated a good tolerability profile in >3000 HBV and HCV patients, with fewer cytopenias, flu-like and psychiatric symptoms compared to PEG IFN-alfa (Alfa). The goal of LIMT was to evaluate safety and efficacy of Lambda monotherapy in patients with HDV.
Method: Randomized, open-label study of Lambda 120 or 180 μg, weekly SC injections for 48 wks follow by 24 wks post-tx in patients with chronic HDV, conducted in Pakistan, Israel, and New Zealand. Major inclusion criteria: positive HDV RNA by qPCR (Robogene® 2.0, BLQ 14 IU/ml), ALT<10×ULN, and compensated liver disease. Tenofovir or entecavir were started at baseline (BL).
Results: 33 patients were randomized to Lambda 180 μg (n = 14) or 120 μg (n = 19). BL mean values: HDV RNA 4.1 log IU/ml (SD±1.4); ALT 106 IU/L (35-364) and bilirubin 0.5 mg/dL (0.2-1.2).

				48 Wk On-Treatment		24 Wk Post-Treatment	
Dose		N	Mean Wk 48 Log HDV RNA Decline	2 Log Decline or BLQ	BLQ	2 Log Decline or BLQ	BLQ
180 μg	All	14		9/14 64%	5/14 36%	7/14 50%	5/14 36%
	High BL VL	8	-2.3	7/8 88%	3/8 38%	4/8 50%	2/8 25%
	Low BL VL	6		2/6 33%	2/6 33%	3/6 50%	3/6 50%

ITT rates of durable virologic response (DVR = BLQ at 24 wks post-tx) for Lambda 180 μg (5 of 14, 36%) compare favorably to historic rates for Alfa 180 μg (28%) (Wedemeyer, NEJM, 2011). 50% DVR in low BL viral load (VL) patients ($\leq 4 \log_{10}$). Common on-treatment AEs included mild to moderate flu-like symptoms and elevated transaminase levels. Patients previously treated with Alfa noted significantly less side effects on Lambda. Cases of jaundice and increased incidences of bilirubin elevations were observed in the Pakistani cohort. No patients showed symptoms of decompensation, and all responded favorably to dose reduction or dose discontinuation. DILIsym® modeling of ALT and bilirubin dynamics indicate a transporter-based mechanism for the observed bilirubin elevations.
Conclusion: Lambda 180 μg had comparable antiviral activity with better tolerability, compared to historical data for Alfa. Durable BLQ virologic responses have been observed 24 weeks post-treatment. Lambda is a promising agent for mono or combo treatment of HDV. The LIFT study with Lambda + Lonafarnib is on-going at NIH.

PS-053

A rapid point-of-care device for the diagnosis of hepatitis delta virus infection

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Background and aims: Chronic Hepatitis Delta Virus (HDV) infection represents the most severe form of viral hepatitis. The detection of anti-HDV antibodies against Hepatitis Delta Antigen (HDAg) represents the recommended initial step in the diagnosis of HDV infection. Current assays for anti-HDV detection rely on manual ELISAs, which are time consuming and require laboratory equipment and trained

staff. Our aim was to develop a rapid pan-genotypic point of care (POC) test that allows fast and reliable detection of anti-HDV antibodies for all eight HDV genotypes and that can be used in hospitals and doctors' practices but also in remote areas.
Method: Using multiple sequence alignments, we designed and optimized a pan-genotypic consensus sequence of HDAg. The corresponding recombinant protein was expressed, purified and implemented as a detection antigen to assemble a POC device, based on the principle of lateral flow assay. The POC device was validated with a panel of 332 HDV-positive and 142 HDV-negative patient samples. Additionally, 18 serum samples from patients with non-genotype 1 HDV infection were used to evaluate pan-genotypic test performance.
Results: Application of serum containing anti-HDV antibodies to the POC test strips led to a visible positive test result already after 10-20 minutes of incubation. Positive signals could be detected even if the patient sera were diluted 100-fold, while no false positive signals were detected when HDV-negative control sera were applied. POC test validation on 476 samples led to a sensitivity of 94, 6 % and specificity of 100 %. All 18 serum samples from non-genotype 1 HDV-infected patients were positive in the POC test indicating pan-genotypic sensitivity. Multiplexing the test strip with HBsAg-specific antibodies allowed simultaneous detection of HBsAg and HDV infection on the same strip.
Conclusion: In light of the several novel HDV-specific drugs that are currently entering registration trials and might be available in the near future, fast and reliable diagnostics for HDV infection are of utmost importance. Here, we have developed and successfully validated a rapid test device for POC diagnosis in hospitals and remote areas or for epidemiological field studies.

PS-054

Quantitative antibodies against hepatitis B core antigen differ in NUC suppressed caucasian HbeAG-negative patients compared to patients who achieved either "NUC induced" or "spontaneous" functional cure of HBV

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Background and aims: IgG-antibodies against Hepatitis B core antigen (anti-HBc) persist lifelong in HBV subjects, independently of HBsAg loss. However, their quantitative assessment in different clinical settings of HBV including patients long-term treated with nucleos (t)ide analogs (NUC) or those who achieved a function cure, is lacking.
Method: This retrospective cross-sectional study evaluated three patients' groups: 1) 189 Caucasian HBeAg-negative HBV monoinfected patients under long-term TDF/ETV therapy; 2) 25 patients who cleared HBsAg after NUC therapy (functional cure group); 3) 60 HBsAg negative, anti-HBc patients referred for anti-HBV prophylaxis due to onco-hematological disease ("isolated anti-HBc" group). Quantitative anti-HBc levels (LG HBcAb-N, Fujirebio) and its ratio to WHO International Standard (Human NIBSC code 95/522) were evaluated.
Results: In the former group [age 66 (28-90) years, 75% male, 47% compensated cirrhosis, 100% HBeAg negative, 95% gt D, 65% NUC-experienced, TDF/ETV treated from 100 (15-127) months, undetectable HBV DNA since 118 (11-203) months, HBsAg 517 (1-11, 781) IU/ml] median anti-HBc levels were 127 IU/ml (6-282). Anti-HBc levels < 127 IU/ml were associated with older age, cirrhosis, longer TDF duration and HBV DNA suppression, and higher BMI; at multivariate analysis, only with longer HBV DNA suppression (OR 1.02, $p < 0.001$) and BMI (OR 1.10, $p = 0.047$).
In patients who achieved a functional cure following NUC therapy [age 59 (43-84) years, 80% male, 40% gt D, 36% compensated cirrhosis, 36% NUC-exp, treated from 67 (5-122) months, HBV DNA undetectable since 85 (0-153) months, 100% HBeAg neg, 84% anti-HBe, 44% with anti-HBs > 10 IU/ml (64 (13-461) IU/ml)], anti-HBc levels were 154 IU/ml (1-285).
In the "isolated" anti-HB-core positive patients [age 69 (46-84), 50% male, 25% anti-HBe, 93% with anti-HBs > 10 IU/ml (188 (11-1000) IU/ml)], median anti-HBc levels were 9 IU/ml (1-112). Anti-HBc levels < 9 IU/ml were associated only anti-HBe positivity ($p = 0.001$).
Among NUC suppressed CHB patient, anti-HBc levels were widely distributed independently of HBsAg levels. Despite a similar serological profile, anti-HBc levels were significantly higher in patients with NUC-induced compared to those with spontaneous-induced functional cure.
Conclusion: IgG anti-HBc levels differ in different phases of HBV infection suggesting that it may be useful to further characterize NUC suppressed patients and those achieving functional cure.

PS-055

The markers of HBV transcriptional activity-HBcrAg and pre-genomic HBV DNA during antiviral therapy with nucleos (t)ide analogue help to predict optimal timing of therapy withdrawal

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Background and aims: Nucelos (t)ide analogue (NA) withdrawal is a potential therapeutic strategy in long-term supressed HBeAg-negative non-cirrhotic chronic hepatitis B (CHB) patients. We previously demonstrated in 15 patients that 20% patients had severe post-withdrawal ALT flare (> 10 UNL) and required to re-start NA therapy. At time of NA withdrawal all patients with significant flare after stopping NA had detectable HBcrAg and pre-genomic (pg)HBV RNA, both markers of cccDNA transcriptional activity. Data regarding changes of HBV serological/virological markers during NA therapy prior to NA withdrawal are lacking and might provide valuable information about the timing of NA withdrawal. We aimed to compare the levels of HBV DNA, HBsAg, HBcrAg and pgHBV RNA and their kinetics during long-term NA therapy prior to NA withdrawal to evaluate whether on-treatment markers can help with timing of successful NA withdrawal.
Methods: We studied 25 CHB non-cirrhotic patients (64%males, median age 48yrs) were treated for a median duration 6.9 yrs (3.2-11.2) with tenofovir (TDF) and had undetectable HBV DNA for at least 3 years. TDF was stopped and patients were followed for at least 52 weeks (median 78, range 52-78). Based on type of ALT flare post NA withdrawal, patients were divided into 3 groups: no flare (n = 9), mild ALT flare (> 2 < 5 UNL and > 2 from NA stop baseline, n = 11) and 5 with severe flare (> 10UNL with HBV DNA > 100, 000IU/ml). Serum samples from NA therapy at baseline, years 1, 2 and 3 on therapy and at time of withdrawal were tested for HBV DNA and HBsAg levels, HBcrAg concentrations (by were CLEIA Fujirebio assay [LLDQ 2 $\log_{10}$U/ml]) and pgHBV RNA (using a real-time PCR research assay Abbott Diagnostics [LLDQ 1.65 $\log_{10}$U/ml]). The markers were compared between patients according to post withdrawal ALT flare status.
Results: At time of starting NA therapy patients with severe flares had significantly higher levels of HBV DNA, HBcrAg and pgHBV RNA, but quantitative HBsAg, ALT and degree of liver damage were similar. All serological/virological markers declines did not differ across the groups. By year 1 only HBcrAg and pgHBV RNA levels were higher in patients with subsequent severe flares and this remained the case until NA withdrawal (Figure 1). The proportions of patients with

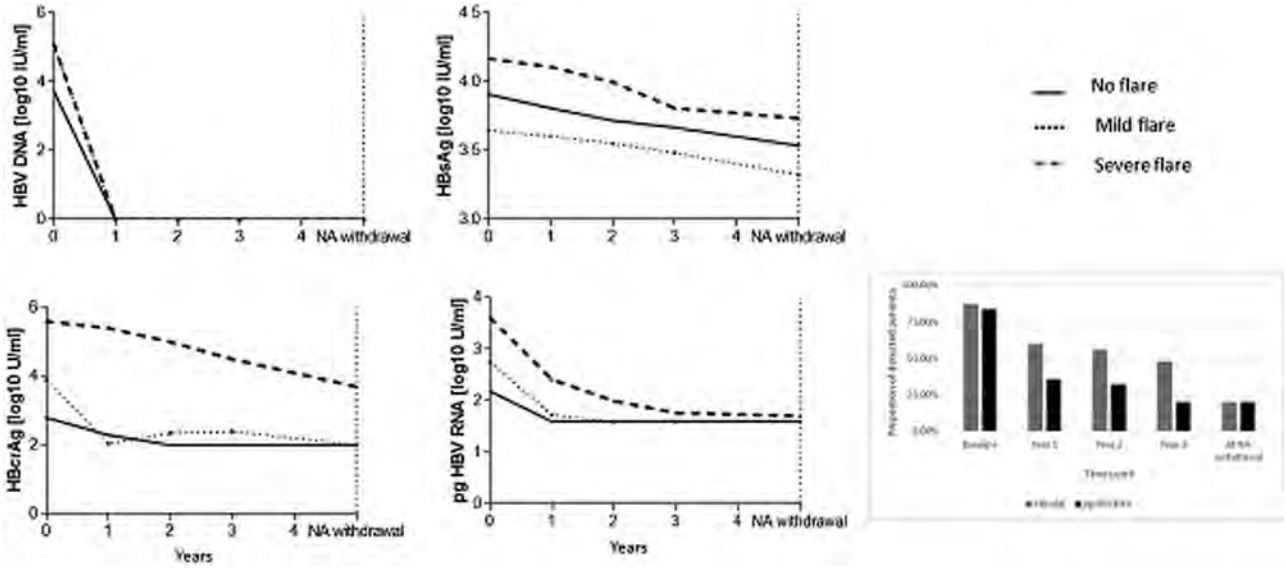

Figure 1: (abstract: PS-055): Medians of serological/virological markers during NA therapy

detectable HBcrAg and pgHBV RNA reduced during NA therapy (Figure 1); only patients who developed severe flares had detectable HBcrAg and pgHBV RNA at time of withdrawal.

Conclusion: During NA treatment of HBeAg negative patients, serum levels of HBcrAg and pgHBV RNA, ostensibly markers of transcriptional cccDNA activity were strong predictors of subsequent significant ALT flares after NA withdrawal and their monitoring on NA therapy might assist with appropriate timing of NA withdrawal to avoid relapse and related disease after NA withdrawal.

PS-056

Higher relapse and retreatment rates in patients who started as HBeAg positive than negative after stopping long-term nucleos (t) ide analogue therapy: results from the randomized controlled STOP study

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Background and aims: Patients with chronic hepatitis B (CHB) often receive long-term nucleos (t)ide analogue (NA) therapy. We compared outcomes after stopping NA therapy between patients who started therapy HBeAg positive or negative.

Method: In this prospective single-center randomized controlled trial, patients were included if they had received tenofovir/entecavir therapy for ≥ 12 months and achieved virologic suppression (HBeAg seroconversion and undetectable HBV DNA ≥ 12 months in HBeAg positive patients, or undetectable HBV DNA ≥ 36 months in HBeAg negative patients). Patients were randomized 2:1 to either stop or continue NA therapy for 72 weeks. Retreatment criteria were: HBeAg seroreversion, HBV DNA > 20, 000IU/ml twice or HBV DNA > 2, 000 with ALT > 5xULN twice. Sustained response (HBeAg negative, HBV DNA < 2, 000 IU/ml and normal ALT) was determined at week 72.

Results: Of 67 patients (60% male, 97% Asian), 45 (67%) patients were assigned to stop and 22 (33%) to continue NA therapy. At start of therapy, 18/45 (40%) stop patients were HBeAg positive. At randomization the mean duration of NA therapy was 8 (3) vs. 7 (3) years, 82% vs. 100% was anti-HBe positive and HBsAg level was 3.2 (0.9) vs. 3.0 (0.6) log IU/ml in HBeAg positive vs. negative patients. Time since HBeAg loss was 3.8 (2.3) in patients who started therapy as HBeAg positive. Sustained response was observed in 3/18 (17%) HBeAg positive vs. 7/27 (26%) negative patients (p = 0.35) (Table). HBsAg loss occurred in 1 HBeAg-negative patient.

Among patients who stopped, the mean HBsAg change from randomization to week 72 was –0.1 (0.4) vs. 0.2 (0.2) log IU/ml in HBeAg positive vs. negative patients (p = 0.10). 11/18 (61%) of the HBeAg positive vs. 5/27 (19%) HBeAg negative patients were retreated by week 72 (p < 0.005). ALT > 1/2/5/10xULN occurred in 89/72/61/50% vs. 70/48/37/15 % of HBeAg positive vs. negative stop patients. One HBeAg positive patient developed a bilirubin of 68umol/L, but none decompensated or died.

	Start of therapy		
Week 72 outcomes (%)	HBeAg positiven = 27	HBeAg negativen = 18	P
Sustained response	17	26	0.35
HBsAg loss	0	4	-
ALT > 5xULN	61	37	0.26
ALT > 10xULN	50	15	0.03
Virologic reactivation (lone HBV DNA > 20, 000 IU/ml)	83	56	0.14
Clinical relapse (HBV DNA > 2, 000 IU/ml +ALT > 1.5xULN)	6	19	0.10

Conclusion: Start of therapy HBeAg positive patients were more likely to relapse and receive retreatment than HBeAg negative patients. These findings in an Asian majority cohort suggest that patients do not benefit from stopping long-term NA therapy, particularly those who are HBeAg positive at the start of therapy.

NAFLD – Clinical burden natural history

PS-057

Redefining risk of liver disease in the general population: Analysis of the health survey for England 2016

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Background and aims: The health, financial and societal arguments for public health action to prevent lifestyle related liver disease are clear. Primary care has frequently been suggested as a key location for prevention strategies. Evidence on the most appropriate cut-offs for liver biochemistry and indirect fibrosis markers, which may be used for screening before more definitive assessment, has predominantly been gathered in patients with existing liver disease. These thresholds may not be suitable in community settings.
For the first time liver function tests, from a sample representative of the general population in England, are available. We explored the distribution of risk factors for liver disease, liver function test results and liver fibrosis scores in the Health Survey for England (HSE) 2016.
Method: Cross-sectional survey with interview, examination and blood tests. Multi-stage, stratified, random probability sample designed to be representative of the population living in private households in England.
Participants: 7, 826 adults aged 18 years and over, of whom 3, 791 had a blood test.
Exposures and markers: Risk factors were alcohol consumption > 14 units/wk, body mass index ≥ 25 and diabetes. Liver function tests were Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST). Liver fibrosis scores calculated were FIB–4 score (high >2.67), APRI score (high ≥ 1.0), AST:ALT ratio (high > 0.8), BARD score (high ≥ 2).
Results: 85.5% (84.4 to 86.7%, n = 5670) of the population representative sample have at least one risk factor for liver disease. 25.9% (24.4 to 27.5%, n = 4685) have two or more risk factors. 2.5% (2.0 to 3.1%, n = 3388) had a high FIB–4; 11.5% (10.3 to 12.8%, n = 3607) had a raised ALT; 86.0% (84.5 to 87.3%, n = 3424) had a high AST:ALT ratio. Only 5.1% (4.3 to 6.0%, n = 4031) of those with at least one risk factor and 7.9% (6.1 to 10.1%, n = 3749) of those with two or more risk factors had been told by a health professional that they were at risk of liver disease. 12.9% (11.8 to 14.1%, n = 4722) of the sample and 17.7% (10.9 to 27.3%, n = 85) of those with a high FIB–4 score report ever being tested for liver disease.

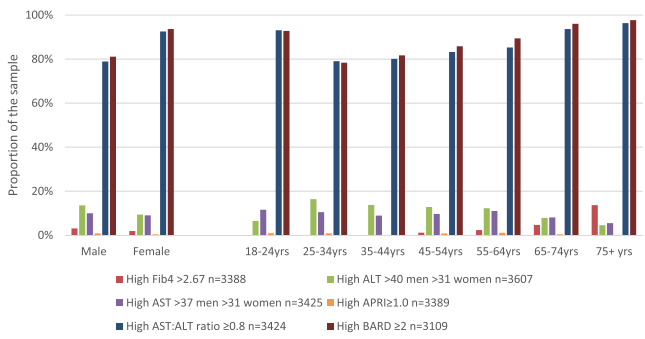

Figure 1: Distribution of 'high' liver function test and fibrosis marker results in the HSE 2016 sample, representative of the general population of England, by age and sex.

Conclusion: This is the first analysis of liver biochemistry and indirect fibrosis markers in a sample representative of the general population of England. Modifiable lifestyle risk factors for liver disease are present in more than 85% of participants. Multiple risk factors are common and may be synergistic. Commonly used liver function tests and fibrosis scores showed large variation in positivity. Awareness of risk and testing for liver disease was low, even in those with multiple risk factors. The best approach to achieve detection of liver disease in primary care remains unclear.

PS-058

The socio-economic burden of NASH in Europe and the United States: The gain study

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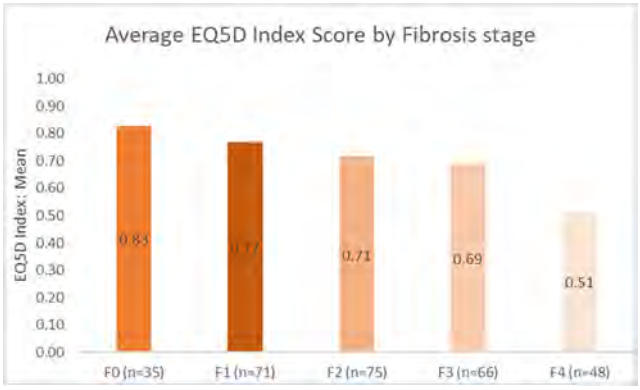
Background and aims: NASH is one of the most common chronic liver conditions yet, currently, no pharmacologic drug is available. The disease is associated with a significant socio-economic burden which, coupled with a steadily rising prevalence, is a growing public health threat. The Global Assessment of the Impact of NASH: a socioeconomic study (GAIN) study is a prevalence-based burden of illness study across Europe (France, Germany, Italy, Spain and the United Kingdom) and the United States to determine the socio-economic burden of NASH in the real-world.
Method: This study followed a retrospective and cross-sectional methodology that recruited a sample of physicians and provided demographic, clinical and economic information, including 12-month ambulatory and secondary care activity for patients via an online survey. Each patient was invited to provide corresponding patient questionnaire providing patient reported outcomes through validated tools (EQ–5DL, CLDQ-NAFLD, WPAI) as well as direct and indirect non-medical costs. Per-patient costs are calculated by multiplying the quantities of the resource use collected with the national unit price and then extrapolated to population level to calculate the economic burden. Patients with diagnosed by liver biopsy (n = 1, 619) were stratified by fibrosis score (F0-F4). Patients diagnosed by serum biomarkers and imaging techniques (n = 2, 135) were stratified with early (F0-F2) or advanced (F3-F4) fibrosis.
Results: Clinical reports for a total of 3, 754 patients were received. 767 patients (20% of the sample) provided information on indirect costs and health-related quality of life, of which 295 patients had a liver biopsy and confirmed fibrosis score (F0-F4). For these 295 patients, the average EQ–5D and CLDQ-NAFLD index scores were 0.70 and 4.70 respectively. Both indexes decreased with progression of fibrosis stage. For 2017, the total annual per patient cost of NASH was estimated at EUR 25, 512. The highest country per-patient costs were in the USA (mean EUR 73, 255) and the lowest were in France (mean EUR 4, 409). Costs increased with fibrosis stage driven by hospitalisations and a higher co-morbidity burden. Indirect costs are driven by patient and non-professional caregiver work loss.



Conclusion: The GAIN study significantly adds to the evidence base regarding the socio-economic burden in NASH. Results show a significant socio-economic burden associated with NASH that increases with progression of fibrosis stage.

PS-059

Increased healthcare resource utilization and costs in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients with liver disease progression: A multivariate analysis of french national hospital care

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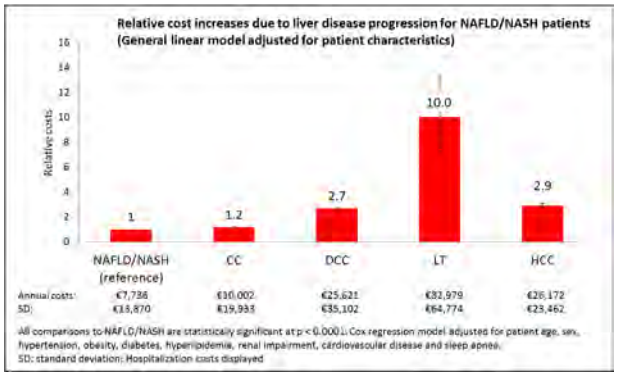
Background and aims: HCRU and healthcare costs increase in NAFLD/NASH patients who progress to compensated cirrhosis (CC). However, limited data on HCRU and costs exist for NAFLD/NASH patients with progression to decompensated cirrhosis (DCC), liver transplantation (LT), or hepatocellular carcinoma (HCC). This study evaluated increases in HCRU and costs in these hospitalized patients in France.

Method: Patients aged ≥ 18 years with NAFLD/NASH were identified from the French National Database on hospital care (PMSI) between 2009 and 2015, which captures all hospitalizations in France. Five study cohorts were identified via ICD–10-CM: (1) NAFLD/NASH overall, (2) CC, (3) DCC, (4) LT, and (5) HCC. Index date was defined as the earliest diagnosis date for each stage. Cohorts were not mutually exclusive; patients with other causes of liver disease were excluded. Patients followed from index date to earliest of 12 months, progression to new stage, death, or end of study. Costs were reported in 2015 €. Generalized linear models used to adjust for patient characteristics.

Results: 125, 052 hospitalized French NAFLD/NASH patients (mean age 55.9; 46.2% male) were identified, including 1491 CC (1.2%), 7846 DCC (6.3%), 52 LT (0.04%), and 1144 HCC (0.9%), with mean ages between 51.6 and 70.1. Rates of comorbidities were high across cohorts: ≥ 43% had diabetes, ≥ 41% had cardiovascular disease, ≥ 21% had renal impairment, ≥ 47% had hypertension. Mean length of stay generally increased with disease severity: NAFLD/NASH 4.1 ± 7.4 days, CC 3.5 ± 5.6, DCC 9.1 ± 15.4, LT 9.0 ± 7.6 and HCC 5.6 ± 6.3. Mean annual number of stays was 3.1 ± 5.6 in NAFLD/NASH and increased to 4.2 ± 8.6 in CC, 7.0 ± 11.1 in DCC, 7.1 ± 5.6 in LT and 5.5 ± 6.6 in HCC. Mean annual hospitalization costs were high for all groups and increased with disease progression: €7736±€13, 870 in NAFLD/NASH, €10, 002±€19, 933 in CC, €25, 621±€35, 102 in DCC, €82, 979±€64, 774 in LT, and €26, 172±€23, 462 in HCC. After multivariate adjustment, costs were 2.3 for DCC, 8.5 for LT, and 2.5 for HCC times significantly higher relative to CC (p < 0.0001). Similar significant increases were found relative to NAFLD/NASH (Figure).



Conclusion: Underdiagnoses of CC was apparent in hospitalized NAFLD/NASH patients in France. Along with a high comorbidity burden, HCRU and healthcare costs were significantly higher in patients with liver disease progression. Effective therapies to slow disease progression or reverse advanced disease are needed.

PS-060

Increasing risk of disease progression and mortality in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients with advanced liver disease: A german real-world analysis

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Background and aims: The presence of advanced fibrosis (F3/F4) is an independent predictor of all-cause mortality among NAFLD/NASH patients. This study aimed to quantify disease progression and all-cause mortality rates in NAFLD/NASH patients without and with advanced liver disease, including compensated cirrhosis (CC), decompensated cirrhosis (DCC), liver transplant (LT) and hepatocellular carcinoma (HCC), using a German claims database.

Method: Adult patients with NAFLD/NASH (ICD–10-GM) were identified retrospectively from 2011-2016 in the InGef database containing claims data of > 4 million individuals. Patients with other causes of liver diseases were excluded. Following NAFLD/NASH diagnosis, patients were identified with liver severity stages (NAFLD/NASH non-progressors (NN/NP), CC, DCC, LT, HCC) using first diagnosis as index date. Cohorts were not mutually exclusive with 6 years maximum follow-up. Patients were censored at disease progression to calculate the mortality rates. Kaplan-Meier curves were plotted for cumulative all-cause mortality rates for all liver stages except LT (low sample size).

Results: Of the 4, 580, 434 individuals in the database, the study identified 215, 655 (5%) NAFLD/NASH patients. Subsequent follow-up demonstrated, 100, 644 incident events of different liver severity stages were (NN/NP [79, 245 (78.7%)], CC [411 (0.4%)], DCC [20, 614 (20.5%)], LT [11 (0.01%)] and HCC [363 (0.4%)]). At 1 year follow-up, mortality rate was up to 50-times higher in patients with advanced liver disease than in NN/NP (p <.0001), including 1.2% in NN/NP, 8.8% in CC, 18.3% in DCC, 51.2% in HCC. This trend continued over 5 year follow-up, with significantly higher mortality in advanced liver disease patients than in NN/NP (p <.0001), with 2.8% in NN/NP deceasing, as compared to 14.8% in CC, 25.6% in DCC, and 64.5% in HCC. During the study period, 11.7% of the NAFLD/NASH patients progressed to advanced liver disease and 20.7% CC patients progressed to DCC.

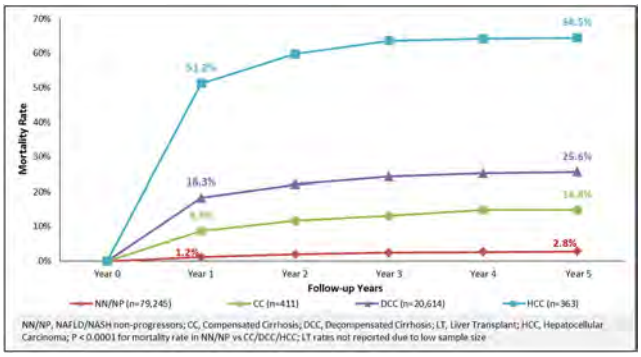

Figure: NAFLD/NASH Patients Cumulative All-cause Mortality Rate by Liver Severity Stages

Conclusion: Incident rates of CC and DCC indicate underdiagnosis of CC among NAFLD/NASH patients. Those with advanced liver disease in Germany had high mortality rate that significantly increased with disease progression ranging from 14.8% in CC to 25.6% in DCC to 64.5% in HCC. More than 20% of CC patients decompensate over 5 years of follow-up. Results suggest the need for early detection and effective interventions among NAFLD/NASH patients to prevent progression and potentially reduce mortality.

PS-061

Non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis patients with advanced liver disease had high burden of comorbidities, healthcare resource utilization and costs: Results from Italian administrative databases

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Background and aims: NAFLD/NASH may progress to advanced liver disease (AdvLD), which includes compensated cirrhosis (CC), decompensated cirrhosis (DCC), liver transplant (LT), and hepatocellular carcinoma (HCC). This study characterized the comorbidities, HCRU and associated costs among hospitalized patients with AdvLD due to NAFLD/NASH.

Method: NAFLD/NASH patients ≥ 18 years from 2011-2017 were identified from 8 administrative databases of Italian local health units with over 9 million inhabitants using ICD–9-CM codes. Following NAFLD/NASH diagnosis, development of CC, DCC, LT, or HCC was identified using their first diagnosis date for each severity cohort (index date). Eligible patients were followed from index date until the earliest of disease progression, end of coverage, death, or end of study period. Within each cohort, per member per month values were annualized to calculate the annual all-cause HCRU or costs in 2017 €.

Results: This study identified 9, 729 hospitalized NAFLD/NASH patients (mean age 62.0 years, 43% female). The majority (97%, N = 9, 470) did not have AdvLD, 1.3% (N = 131) had CC, 3.0% (N = 303) had DCC, 0.1% (N = 11) had LT, and 0.8% (N = 79) had HCC. The comorbidity burden was high across all cohorts—type 2 diabetes (34%–49%), renal impairment (15%–36%), cardiovascular disease (82%–94%), and hypertension (35%–47%). Mean annual number of hospitalizations was greater in patients with AdvLD vs. those without (4.2–4.4 vs. 2.9, p ≤ 0.05). Similar trends were observed in outpatient visits and pharmacy fills. Mean total annual costs also increased with disease severity, with post-index costs among patients with AdvLD due to NAFLD/NASH at least 86% higher than patients without AdvLD, driven primarily by higher inpatient costs (NAFLD/NASH without AdvLD was €10, 576, vs. CC €19, 681, DCC €19, 808, LT €65, 137, and HCC €26, 220, p < 0.001 for all) [Figure].

Figure: Total mean annual healthcare costs of hospitalized NAFLD/NASH patients by severity cohort in Italy (2017 €)

Conclusion: NAFLD/NASH patients in Italy have high comorbidity burden. Patients with AdvLD had significantly higher costs compared to those without, and costs increased significantly in patients with more severe disease. The lower prevalence of CC compared to DCC in this study suggests missed opportunity to diagnose at earlier stages. Early identification and effective management is needed to reduce the risk of disease progression and subsequent healthcare utilization and costs.

PS-062

The increasing importance of non-alcoholic fatty liver disease in human deficiency virus (HIV) positive patients

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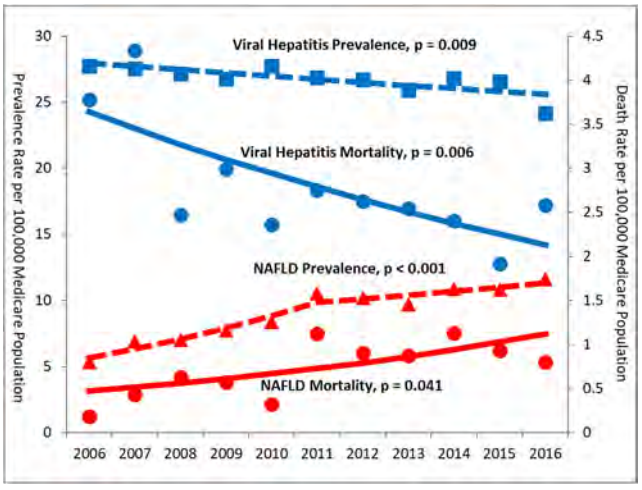
Background and aims: The development of highly effective antiretroviral regimens for HIV led to a decrease in the associated mortality. On the other hand, mortality from hepatitis C virus (HCV)-related liver disease (LD) became a leading cause of death in HIV (+) patients. The recent approval of new anti-HCV drugs have resulted in high cure rates in HIV-HCV co-infected patients. As viral hepatitis is effectively treated in HIV (+) patients, NAFLD could become a prominent LD. We aimed to assess the prevalence and mortality trends of NAFLD, viral hepatitis and other LDs in HIV infected Medicare recipients in the US.

Method: We used inpatient and outpatient data (random 5%) for the Medicare beneficiaries (1/1/2006 to 12/31/2016) with ICD–9 and ICD–10 diagnostic codes, resource utilization, and mortality rates. Prevalence rates for HCV, HBV, NAFLD, and other LDs (such as alcohol-LD, cholestatic LD etc.) were determined. Logistic regression models were used to assess 1-year mortality risk in NAFLD, HBV, HCV, and controls without LD.

Results: Among the 28, 675, 887 unique Medicare beneficiaries, there were 47, 062 HIV (+) subjects with 10, 474 having LD (5, 628 HCV, 1, 374 HBV, 645 HCV+HBV, 2, 629 NAFLD, 198 other LDs.). Between 2006 and 2016, rates for viral hepatitis decreased from 27.75 to 24.17 (p =.009) while, the rate for NAFLD in HIV (+) Medicare recipients doubled from 5.32 to 11.62 per 100, 000 (p <.001). During the study period, there were 2, 882 deaths within one-year of the encounter. Of these, 36.2% were related to LD (49.5% dying from HCV, 14.4% from HBV, 11.9% from HCV+HBV, 20.3% from NAFLD, and 3.9% from other LDs). During the study period, the death rates related to viral hepatitis in HIV (+) Medicare recipients decreased from 3.78 to 2.58 (p =.006), while the mortality for NAFLD in this group increased from 0.18 to

0.80 for NAFLD (p =.041). After adjustments for calendar year, age, sex, race/ethnicity, region, and beneficiary entitlement, presence of HCV (Odds ratio [OR] = 1.89, 95% CI: 1.69–2.11), HBV (OR = 2.25, 95% CI: 1.85–2.72), HCV+HBV (OR = 4.17, 95% CI: 3.31–5.24), and NAFLD (OR = 1.54, 95% CI: 1.33–1.80) were associated with increased risk of 1-year mortality in the HIV (+) Medicare recipients [vs. HIV (+) without LD].



Conclusion: As highly effective regimens for HIV, HBV and HCV lead to a reduction in associated mortality in HIV (+) patients, NAFLD is increasing as an important cause of LD and reason for liver mortality in this group of patients.

PS-063

Screening diabetic patients for non-alcoholic fatty liver disease: Is it cost-effective

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Background and aims: NAFLD is diagnosed in 70%–90% of diabetic patients. The EASL/EASD Guidelines recommend screening patients with diabetes for NAFLD. Recently, several novel interventions were shown to improve fibrosis stage. Our aim was to analyze whether screening individuals with diabetes for NAFLD may potentially be cost-effective.

Method: We constructed a Markov model (Figure 1) with an initial decision regarding screening diabetic patients for liver fibrosis (using elastography). The model is based on the natural history of NAFLD. We assumed that the hypothetical new treatment is relevant only for patients with NASH and significant fibrosis (F2-F3), whereas cirrhotics will be managed according to current guidelines. We assumed that the treatment will annually reduce the progression rate by 15% and increase the regression rate by 15%. The analysis was based on local costs and presented in USD. The annual cost of the new treatment ranged between 8, 000$ to 40, 000$. The primary outputs of the model included cost, life-years (LYs), and quality-adjusted LYs (QALYs), which were used to calculate the incremental cost-effectiveness ratio (ICER).

Results: For the base case where the new treatment cost was 10, 600$ the average cost of screening strategy was 54, 100$ and the No-screening strategy was 20, 454$, an increase of 33, 646$. The average QALY in the No-screening strategy was 15.25 QALY compared to 15.86 QALY in the screening strategy, an incremental of 0.61 QALY. The ICER was 55, 157$ per QALY. However, for annual cost of the new treatment of 40, 000$ the ICER increased to 208, 894$ per QALY. Sensitivity analysis of the annual cost of new treatment assuming annually reduce the progression rate and increase the regression rate by 15% and 20%, respectively, is shown (Figure 2).

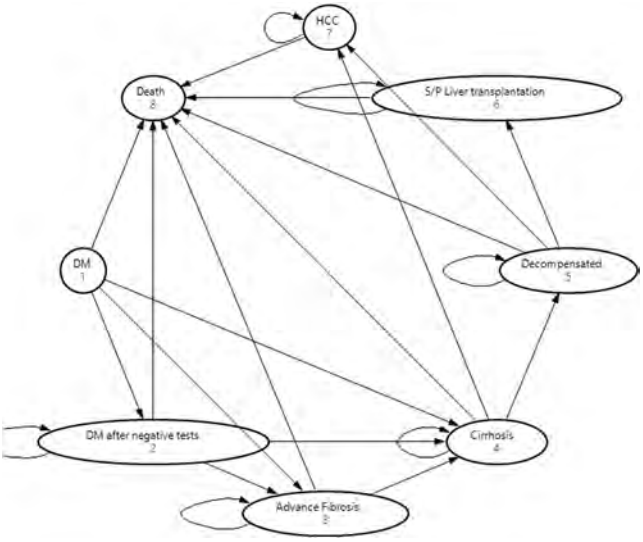

Figure 1: Markov Model for screening diabetics for NAFLD

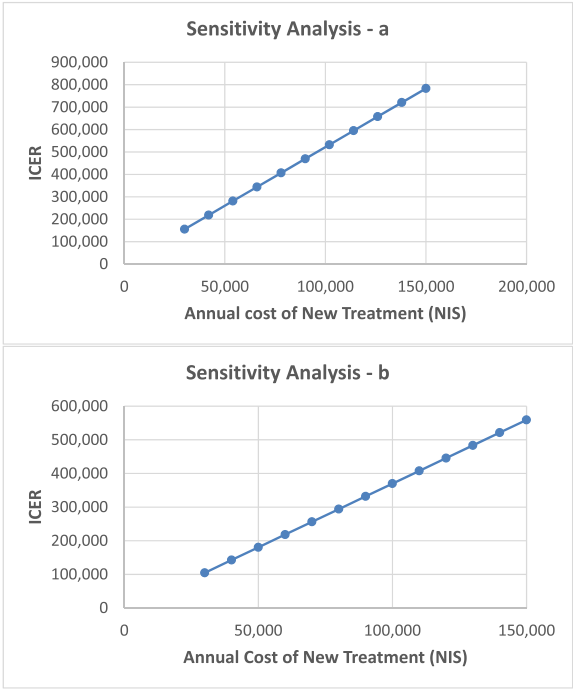

Figure 2: Cost-effectiveness of screening diabetic for NAFLD: a. 15% regression rate and 15% reduced progression rate b. 20% regression rate and 20% reduced progression rate

Conclusion: With the proposed screening strategy for NAFLD in diabetics the incremental QALY is marginal. Therefore, the costs of the novel therapeutic interventions have to remain relatively low (~10, 600$) to maintain cost-effectiveness. Cost-effectiveness of screening needs to be reassessed when more effective medications become available.

PS-064

NAFLD simulator: An interactive open-access tool for long-term risks of NAFLD and NASH

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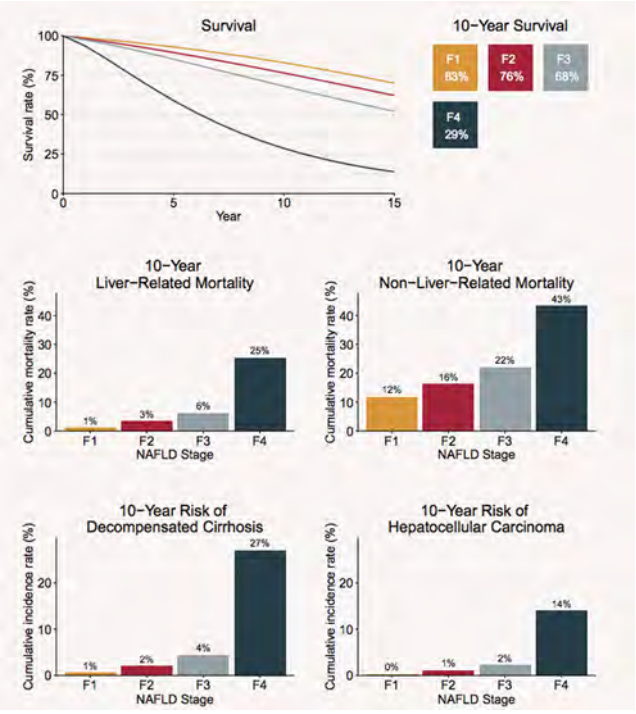
Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with an estimated prevalence ranging from 25% to 40%. Several pharmacological treatments that could potentially reduce the rising burden of non-alcoholic steatohepatitis (NASH), an aggressive form of NAFLD, are in early stages of development. Because NASH is a slow progressive disease, ongoing clinical studies use surrogate markers as primary end point. Our aim was to develop an open-access, interactive tool for patients and providers that help them understand the risk of short- and long-term adverse outcomes associated with NASH.

Method: We developed a mathematical model that simulated the life course of NASH patients as they progressed through the stages of the natural history: including NASH fibrosis states (F0-F4), decompensated cirrhosis, and hepatocellular carcinoma (HCC). Patient characteristics in the model were based on the NASH Clinical Research Network data. The model accounted for both liver-related and non-liver-related mortality in NASH patients. Disease progression rates and mortalities were derived from published meta-analyses and observational studies. Model-predicted patient survival was independently validated with three large observational studies. We created a large database of simulated NASH patients and their outcomes, and used it to create an interactive, web-based tool, NAFLD Simulator, that allows users to enter patient demographics and current NAFLD stage, and predicts survival, mortality (liver, non-liver, and background), cumulative incidence of liver cancer and decompensated cirrhosis.



Results: Figure 1 compares the predicted outcomes for a 50-year old patient having NASH fibrosis stages F1, F2, F3 and F4. For instance, the 15-year survival in patients with NASH F1, F2, F3, and F4 is 83%, 76%, 68%, and 29%, respectively. The 10-year non-liver-related mortality in these patients is 12%, 16%, 22%, and 43%, respectively. The NAFLD Simulator also shows that the 10-year risk of developing hepatocellular carcinoma increases from 2% to 14% in patients progress from F3 to F4.

Conclusion: NAFLD Simulator provides an innovative platform to disseminate the short and long-term risk associated with NAFLD and NASH to patients and providers. We envision that NAFLD Simulator will serve as an educational tool for patients and aid patient-physician decision-making; thereby increasing awareness of the long-term risks of NAFLD. The tool can be expanded to predict long-term outcomes of potential NASH treatments when they become available.

Cascade of care towards elimination of viral hepatitis

PS-065

The global investment case for hepatitis C elimination

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Background and aims: Approximately 71 million people globally are infected with hepatitis C, with an estimated 400, 000 deaths attributed to hepatitis C annually. Highly effective, well-tolerated treatment is available, making it possible to eliminate hepatitis C as a public health threat by 2030. Despite this, investment in hepatitis C programs has been slow. One potential reason for the limited investment in hepatitis C elimination is the lack of a strategic approach to investment in prevention, testing and treatment activities to achieve elimination. We proposed an investment framework, aligned with the Global Health Sector Strategy to guide policymakers and global funders in making investment decisions that will enable hepatitis C elimination.

Method: Our framework utilized a public health approach to identify national activities aimed at reducing hepatitis C transmission, morbidity, and mortality, and international activities necessary to provide an enabling environment for countries to achieve maximum effectiveness. Key enablers were highlighted including public support, community mobilization, and skilled workforces that can facilitate the rapid scale-up of national hepatitis C elimination activities.

We also modelled the health and economic (direct and indirect) benefits of scaling up hepatitis C elimination activities to meet the WHO global elimination targets of 90% of people diagnosed and 80% treated by 2030.

Results: Our models showed that investing to achieve elimination could reduce hepatitis C incidence by 85% and hepatitis C-related mortality by 68% by 2030, preventing a cumulative 2.1 million hepatitis C-related deaths and 12 million new hepatitis C infections. This required US $51 billion globally between 2018 and 2030, which included a peak of US $5.7 billion in 2021 before becoming cost-saving by 2027 due to substantive productivity gains (Figure 1). Overall, investing to achieve elimination produced a net US $19 billion return by 2030. Sharing staffing costs already invested within

the context of universal health coverage (UHC) reduced the cumulative costs of the elimination by $20.2 billion.

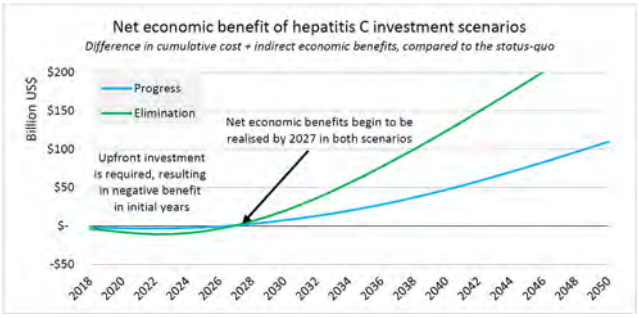

Figure: Net economic benefit of the elimination and progress investment scenarios compared to the status-quo

Conclusion: Achieving hepatitis C elimination requires a strategic approach nationally and internationally. However, investment in hepatitis C programs to achieve elimination is both cost-effective and becomes cost-saving by 2027.

PS-066

Patient flow across physician specialties over the course of the hepatitis C care cascade: A real-world analysis from the United States

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Background and aims: Hepatitis C virus (HCV) infection is a major cause of hepatic and extrahepatic morbidity and mortality. In spite of recommendations for HCV screening, diagnosis, linkage to care and treatment, significant gaps remain in the cascade of care for HCV. As the role of physician specialties for closing these gaps is poorly understood, this study assesses the flow of HCV patients across physician specialties in the US, over the course of the care cascade.
Method: This retrospective real-world study used two large de-identified national laboratory datasets (2013–2016). Screened patients had a HCV antibody (AB) test and/or HCV RNA viral load test. Diagnosed patients had a positive HCV RNA viral load test, and among this group, fibrosis assessment, genotype test and treatment were evaluated. Treatment was inferred with an algorithm based on changes in viral load. The number/proportion of patients at each step in the care cascade was calculated by physician specialty. Patient flow by physician specialty over the course of care cascade was assessed using Sankey Diagrams.
Results: Approximately 17 million patients received HCV screening, and 913, 529 were diagnosed. Over the course of the care cascade, there was an increase in the proportion of patients switching to HCV specialists (gastroenterologist, hepatologist, and infectious disease specialist). Generalists (primary care, family practice, internal medicine) ordered 37% of the AB tests, and 15% initiated treatment. HCV specialists ordered 3% of screening tests and 37% initiated treatment. Most of the fibrosis assessment (30%) and genotype tests (29%) were ordered by HCV specialists. Obstetricians/gynecologists ordered 11% of screening tests but only 0.3% initiated treatment. Among 974, 277 patients who received a positive AB test, 46% did not receive a confirmatory RNA test. Among diagnosed patients, 57% did not receive fibrosis assessment, 47% did not receive genotype test and 90% did not receive treatment.

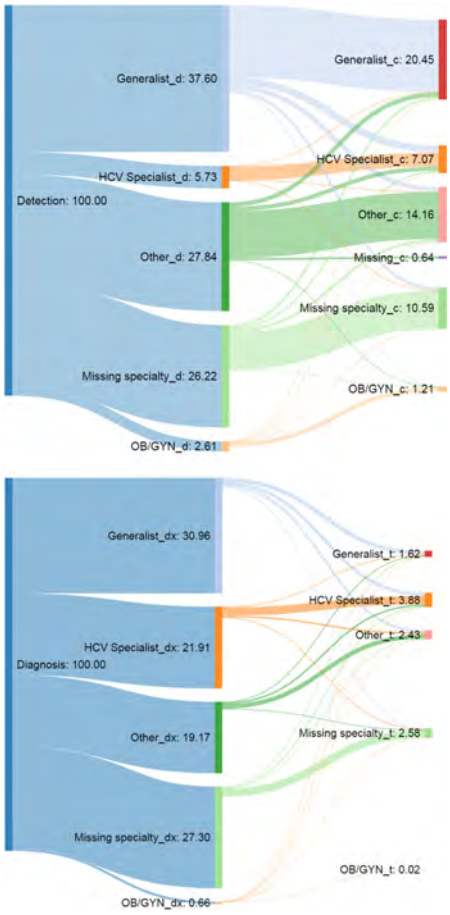

Figure: Sankey diagram of patient flow across physician specialties over the course of the care cascade. AB HCV detection to RNA confirmatory test (b) HCV diagnosis to treatment

Conclusion: Generalists account for more than one third of all HCV screening tests, however, HCV specialists play a more prominent role in patient assessment (fibrosis status, genotype testing) and treatment. Significant gaps remain in all stages of the cascade of care for HCV, and improved efforts are needed for every physician specialty to address them. Timely screening, monitoring and linkage to care by generalists coupled with early treatment by specialists could effectively reduce the hepatic and extrahepatic burden of HCV.

PS-067

Increasing incidence of HCV-GT2 as well as reinfections within the ongoing epidemic of acute HCV infections among MSM in Central Europe

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Background and aims: An epidemic of acute hepatitis C virus (HCV) infections (AHC) among men who have sex with men (MSM) is currently observed in high-income countries. While a recent study reported a declining incidence of AHC, potentially due to the broad

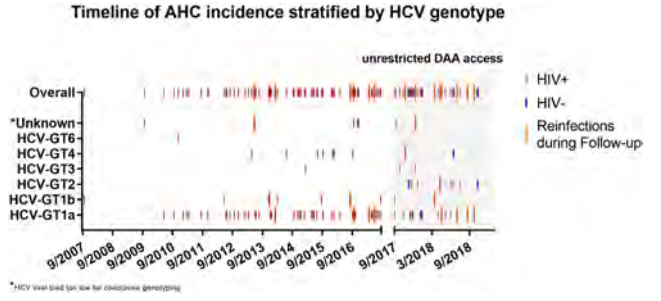
access to highly effective direct-acting antivirals (DAA), other studies found a further increase in AHC among MSM. As a consequence of these conflicting reports, we aimed to assess the characteristics of AHC patients at a large Central European tertiary care center in the era of unrestricted DAA-access.

Method: Patients presenting with AHC between 01/07 and 10/18 were retrospectively enrolled and followed after virologic clearance/eradication. AHC was defined by the European AIDS treatment network (NEAT) criteria.

Results: We identified 97 AHC patients with a mean age of 39 ± 8 years at inclusion. The majority of patients were male (95%, 92/97), HIV-positive (95%, 92/97), and MSM (87%, 84/97). After introduction of nationwide unrestricted DAA-access in Austria in 09/17 (DAA-era), a history of prior HCV infection at inclusion (i.e. previous episode of AHC or chronic HCV infection) was more frequent (33%, 8/24 vs. 7%, 5/73; p = 0.003). Importantly, when comparing infections occurring in the "pre-DAA-era" with infections after 09/17, we observed an increase in AHC incidence from 8.07 (95%-confidence interval (95-CI) 6.50–10.01) to 27.50 (95-CI 19.58–38.21) cases per year.

Patients were followed after spontaneous clearance or sustained virologic treatment response (SVR) for a total of 183.11 patient-years (PY; median 1.04). During follow-up, 15 reinfections were observed in 13 patients, corresponding to an incidence rate of 81.9 per 1000PY (95-CI 49.4-131.7) and a median time from SVR to reinfection of 1.51 years. Moreover, more than half of all reinfections (53% 8/15 vs. 47% 7/15) occurred in the DAA-era.

Interestingly, while HCV-genotype (GT)1a remained the most common HCV-GT (53%, 17/32 vs. 70%, 56/80), an outbreak of HCV-GT2 AHC was observed (25%, 8/32 vs. 0%, 0/80) in the DAA-era among both HIV+ and HIV- individuals (Figure).



Conclusion: We continue to observe a high incidence of AHC in Central Europe-primarily among HIV-positive MSM, but increasingly also in HIV-negative MSM. Notably, we also recorded an increasing number of reinfections and a significant rise in GT-2. Prevention strategies are urgently needed to confine further spread of HCV.

PS-068

The hepatitis C cascade of care and treatment outcomes among people who inject drugs in a Norwegian low-threshold setting: A real life experience

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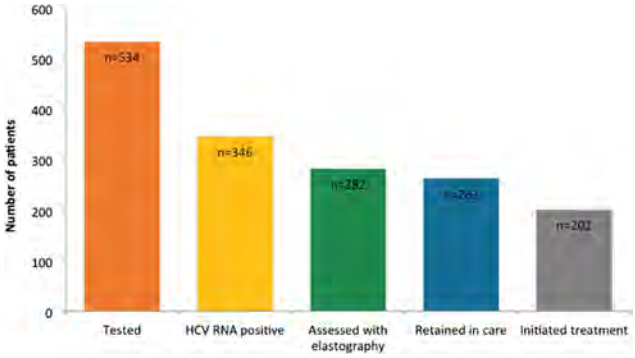
Background and aims: Improving hepatitis C virus (HCV) treatment uptake and outcomes among people who inject drugs (PWID) is crucial to achieve the World Health Organisation HCV elimination goals. The aim of this study was to describe the HCV cascade of care including treatment outcomes and reinfection rates in an urban cohort of PWID attending a low-threshold clinic.

Method: In 2013 a low-threshold clinic was established in downtown Oslo as an effort to provide HCV care for marginalised PWID. The clinic is located within the premises of the city's harm reduction services (including needle/syringe provision), and is staffed by a general practitioner and two nurses with specialist support. The nurses draw blood, operate a portable transient elastography device and provide individually tailored direct-acting antiviral (DAA) HCV treatment with emphasis on flexibility and ambulant work. In Norway, DAA treatment without fibrosis restrictions was available for all genotype 1 patients from February 2017, and for all HCV patients from February 2018.

Results: By September 2018 the clinic had tested 534 individuals, of whom 346 (65%) had chronic HCV infection. 282 of 346 (82%) were subsequently assessed with elastography (17% cirrhosis) and of those, 202 (72%) had initiated treatment. Cumulative treatment uptake among viremic individuals was 58% (202 of 346). Among 144 untreated individuals, 61 (42%) were retained in care, 76 (53%) were lost to follow-up and 7 (5%) had died. Among 110 individuals due for sustained virologic response (SVR) assessment by September 2018, mean age was 49 years, 76% were male, 29% had cirrhosis and 55% had genotype 1 infection. Injecting drug use during treatment was reported by 81% and 78% received opioid substitution treatment. In intent to treat analysis, SVR was observed in 93 of 110 (85%), one individual had virological failure, 6 discontinued treatment and 10 were lost to follow-up. In observed analysis, excluding discontinuations and loss to follow-up, 93/94 (99%) achieved SVR. Adherence of > 90% prescribed doses was reported by 91%. Follow-up data was available in 83 patients. Two cases of probable HCV reinfection (post-treatment HCV RNA recurrence in presence of risk factors) were observed over 71 PY of follow-up (incidence 2.8/100 PY [95% CI 0.34-10.2]).



Conclusion: HCV treatment uptake and virologic response was high among PWID attending a low-threshold clinic. This study provides real-life data on the feasibility of a model of care that could be disseminated to other urban areas.

PS-069

Towards HCV elimination: Feasibility of complete linkage to care by testing and treatment on the same day of screening: A pilot study

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Background and aims: We developed a community-based outreach model (Educate, Test and Treat) for prevention, diagnosis and

treatment of hepatitis C infection. (Lancet Gastroenterol Hepatol, 2018). To date the model has been implemented in 73 villages across 7 governates in Egypt. The program achieved high uptake of HCV testing and linkage to HCV RNA confirmation and treatment. We estimate coverage of treatment and cure in about 84% of all adult HCV viraemic persons across the 73 villages. The median time from serological diagnosis to treatment initiation was 2.1 weeks (IQR: 0 to 3.3), The availability of an FDA and WHO pre-qualified GeneXpert instrument for measurement of HCV Viral load in less than two hours (105 mins) and in the absence of sophisticated lab requirements presents an opportunity to offer a same day "test, evaluate and treat" on the same day of screening. Our objective was to establish the feasibility of a same day "test and treat" model through provision of point-of-care HCV viral load confirmation using GeneXpert, and on-site Fibroscan and clinical evaluation in one village in northern Egypt

Method: This pilot study was conducted on 7th October 2018 at Beeden village, Tanah district, Dakahlia, in northern Egypt, preceded by an awareness raising campaign one week earlier. Key portable laboratory instruments were transferred from the Egyptian liver research institute and hospital (ELRIAH) to the village, and calibrated the day prior to screening: This included: GeneXpert IV for HCV RNA; Mindray BA-88A chemistry analyzer; FibroScan Echosens Mini System and routine abdominal ultrasound Siemens Acuson P300. A team of 3 physicians, 2 radiologists, 2 fibroscan operators, 1 pharmacist, 4 lab specialists, 7 nurses and 2 data entry personnel were mobilised for the same day test and treat pilot in the village. Screening was done using HCV antibody RDT.

Results: All staff arrived at 8:30 am, and screening commenced at 9:00 am. Results of the first 100 RDTs were available by 10:00am, and 16 were HCV antibody positive. Their PCR results were available by 12:00 pm, 11 cases were positive HCV RNA. Results of liver functions, renal functions, CBC, AFP, abdominal ultrasound and Fibroscan were obtained by 12:00 pm. Treatment was offered to the first 11 patients by 12:30 pm. so the 11 cases received treatment 3.5 hours after screening. The same process was repeated, by the end of the day (6:00 pm), 475 individuals were screened by RDT, 56 had their HCV PCR done, 43 were positive for HCV RNA by PCR, and 40 patients received their treatment. Three patients were excluded, 2 had hepatic focal lesions and one pregnant female.

Conclusion: We report the feasibility of implementation of screening, testing, clinical evaluation and treatment on the same day with almost complete linkage to care.

PS-070

Uptake of testing, linkage to care, and treatment for hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage study

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Background and aims: People who inject drugs (PWID) are at high risk of hepatitis C virus (HCV) infection but have poor access to HCV treatment in most settings. Unrestricted direct-acting antiviral (DAA) therapy has been available in Australia since March 2016. Our objective was to evaluate burden of HCV and the extent of, and factors associated with, engagement with the HCV cascade of care among PWID in an era of unrestricted DAA therapy access.

Method: ETHOS Engage is an observational cohort study collecting demographic, behavioural and clinical data among PWID attending drug treatment clinics and needle and syringe programs in Australia. All PWID underwent point-of-care (POC) HCV RNA testing via Xpert® HCV Viral Load Finger-Stick assay. Multivariate logistic regression models were used to identify demographic and behavioural factors associated with treatment uptake.

Results: Between May and November 2018, 507 PWID were enrolled. Overall, 70% had injected drugs in the last month, and 70% were currently receiving opioid substitution therapy (OST). Of all enrolled, 73% (n = 370) were ever HCV-infected (Ab positive), and 58% (n = 296) were ever chronic HCV-infected (RNA positive or prior treatment). Among those Ab positive (n = 370), 76% had previously been tested for HCV RNA. Among those with evidence of current or past chronic HCV (n = 296), 86% had ever been linked to care and 68% had ever received treatment for HCV. Uptake of HCV therapy was high across sub-populations, including those with current and no OST (71%, 59%) recent injecting (last month) (70%), and heroin (68%), other opioid (57%) and amphetamine (70%) injecting in the last month. In adjusted analysis, no factors were associated with treatment uptake. Among those with a POC HCV RNA result at enrolment, 26% had current HCV infection (HCV RNA+ve), 33% had treatment-induced clearance, 17% spontaneous clearance, and 23% were uninfected (HCV Ab-ve) (Figure). The proportion with current HCV infection was similar across demographic and behavioural sub-populations.

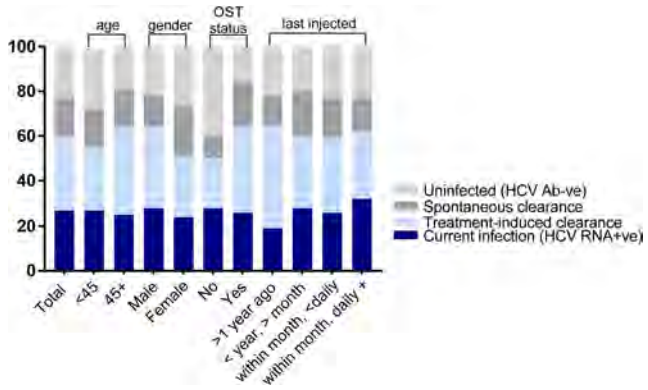

Figure: HCV prevalence among ETHOS Engage participants with known POC HCV RNA result at enrolment (n = 464)

Conclusion: The DAA era in Australia has produced high treatment uptake and lowered HCV viraemia among PWID attending drug treatment and needle syringe programs. To reach elimination targets, subgroups of PWID may require additional support to encourage further screening and engagement with HCV care.

PS-071

Piloting of integrated HCV, TB and HIV screening model at primary care level in Georgia

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Background and aims: In 2018, With support of the Global Fund Georgia started a pilot project in one of the regions of Georgia (Samegrelo-Zemo Svaneti) to test the potential for integration of HCV, HIV and TB screening services at the regional level and to engage primary healthcare providers in detection and management of all three diseases under the "one umbrella."
Method: The integrated screening protocol and training module were developed and almost all primary healthcare providers (440 professionals) in the region were trained to ensure the quality of diagnostic procedures, ethical conduct, and accurate recording and reporting through web-based platform. Trained primary health care physicians currently offer triple screening to patients seeking for care at medical facilities, and also pursue active case finding using door to door approach for individual houses, congregate settings or public establishments. In case of AB positive test result, individuals were asked to provide vein blood samples for RNA testing at the point of care. Local government has invested in incentives for physicians and nurses providing screening. The horizontal integrated model has involved local public health department staff as well that along with the National Family Medicine Training Center was providing supportive monitoring and supervision.
Results: In three years before the pilot initiation only 58 500 people were screened for HCV in Samegrelo-Zemo Svaneti Region. In 7 months of the pilot project implementation 88, 178 people (90% of the annual target) were screened, including 66% tested in the rural areas of the region. 2279 (2.58%) were HCV antibody positive (anti HCV+), 1393 (61%) were RNA tested, out of which 1277 (91.7%) were confirmed, 718 (56.2%) were registered at HCV treatment sites and 499 (39%) were enrolled in treatment. The integrated screening program has allowed 60% increase of the local population number screened on HCV infection. In addition, within the pilot 37 HIV AB positive individuals and 192 presumptive TB cases were identified and referred for further confirmation and treatment.
Conclusion: The project implementation enabled development of sustainable public-private partnership for effective integration of TB/HIC/HCV screening and early disease detection with engagement of Central government, the local municipalities, the Global Fund as a donor and local service providers. It has also become the first precedent of local government contribution to priority health initiatives. The pilot motivated service providers to explore patient-centered approaches to case detection and supported decentralization of diagnostic services (HIV and HCV confirmation tests) to district level non-specialized facilities. Based the promising results obtained during the pilot in Samegrelo-Zemo Svaneti, It is planned to standardize and roll-out the approach countrywide in 2019–2020.

PS-072

Is homelessness the biggest hurdle to treatment success in the management of HCV in the era of direct acting antivirals? Results from the TraP HepC nationwide treatment initiative in Iceland

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Background and aims: Hepatitis C virus (HCV) infection commonly affects people who inject drugs (PWID); injection drug use (IDU) is the driver of HCV transmission in many countries. Thus, special attention needs to be given to PWID in efforts to eliminate the disease. The Treatment as prevention for Hepatitis C (TraP HepC) program has provided access to direct acting antivirals (DAAs) without restrictions in Iceland since 2016, with the objective of eliminating domestic transmission of HCV in the country.
Method: From 01/2016 all HCV positive patients have been offered DAAs;-SOF/LDV ±RBV through 10/2016 and SOF/VEL±RBV thereafter. People with recent IDU, prisoners, and patients with advanced liver disease are prioritized. PWID receive additional support. Here, we analysed sustained virologic response rates at 12 weeks or later post treatment (SVR12+) using an intention to treat (ITT) design for all patients started on their first course of DAA during the first 24 months of TraP HepC.
Results: Treatment was initiated for 631 individuals, 80% of the estimated total HCV-infected patient population during the first 2 years of the project. Mean age was 43 years (range 19–83), males were 426 (67.5%). Recent (within 6 months) IDU was reported by 210 patients, 33.3% of the entire treatment cohort; of those 116 (55.2%) reported injecting within 30 days; 60 (28.6%) within 7 days. Overall, 40 (6.3%) were homeless, and 33 (5.2%) were incarcerated. Among those with history of recent IDU, stimulants were the preferred IV drugs by 86%, opiates by 14%, and 16% were receiving medication-assisted treatment. By ITT analysis, the overall cure rate (negative SVR12+) after the first treatment attempt was 89.2%, 82.9% among patients reporting recent IDU compared to 92.4% among those who did not ($p < 0.0001$). Those with recent IDU were more likely to discontinue treatment (15.2% vs 4.5%, $p < 0.0001$); if analysis is restricted to patients who completed treatment, their chance of cure on first attempt was nevertheless lower (89.9% vs 95.3%, $p = 0.025$). Homelessness was associated with a higher chance of persistent viremia at ≥ 12 weeks post treatment (relative risk RR, 2.42 (95%CI 1.34-4.37), $p = 0.007$), in contrast residence in a halfway house may be associated with lower risk (RR 0.37 (95%CI 0.12-1.16), $p = 0.068$). More than 90% of those who remained viremic after the first treatment attempt have been retreated.
Conclusion: Although rates of cure are lower among patients with recent history of IDU the vast majority of these patients are nevertheless cured on first treatment attempt with DAAs. Homelessness is associated with lower chance of treatment success, probably due to a higher chance of treatment discontinuation. This group needs to be targeted in order to curtail spread of HCV.

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Friday, 12 April 2019

General session II and award ceremony I

GS-07

Real-world safety, effectiveness, and patient-reported outcomes in patients with chronic hepatitis C virus infection treated with glecaprevir/pibrentasvir: Data from the German Hepatitis C-Registry

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Background and aims: The coformulated direct-acting antivirals glecaprevir (identifed by AbbVie and Enanta) and pibrentasvir (G/P) are approved to treat chronic HCV infection. Recent real-world data show that G/P is safe and highly effective, but patient-reported outcomes (PROs) are limited, particularly in subgroups key to achieving HCV elimination. Here we report real-world data from the German Hepatitis C-Registry (DHC-R) on the safety and effectiveness of G/P, and PROs in patients with psychiatric disorders, alcohol abuse, active drug use, on opioid substitution therapy (OST), and/or with HIV coinfection, for whom treatment is sometimes deferred.
Method: The DHC-R is an ongoing, non-interventional, multicenter, prospective registry study. Data were documented by 135 sites in Germany. The analysis included adult patients with HCV genotype 1–6 infection treated with G/P according to the local label. The primary end point was SVR12, assessed in patients who received at least one dose of study drug. Safety, tolerability, and PROs were also assessed.
Results: The analysis included 1242 patients, the majority of whom were treatment-naïve and without cirrhosis (84%), and thus treated for 8 weeks. Reported comorbidities included on OST (N = 311; 25%), with psychiatric disease (N = 178; 14%), alcohol abuse (N = 78; 6%), HIV coinfection (N = 74; 6%) and active drug use (N = 33; 3%). The SVR12 (ITT) rate was 97% (592/609), including 100% SVR12 in 11 patients with active drug use. There were 2 reinfections; one treatment-naïve patient with GT3 infection without cirrhosis relapsed. Thirteen patients discontinued treatment; 3 due to an adverse event (AE) or serious AE. Excluding non-virologic failures, the modified SVR12 rate was 99.5% (584/587). Ten serious AEs have occurred; 3 were considered possibly related to treatment. Patients with available data in key subgroups reported improvements in both their mental and physical SF-36 component scores; generally, patients with comorbidities reported lower scores at baseline, and showed more improvement at end of treatment, than those without comorbidities (Table 1).

Table 1. SF-36 Components at Baseline and End of Treatment (EOT)

	Mental Component, mean (SD)		Physical Component, mean (SD)	
Subgroup (N)	Baseline	EOT	Baseline	EOT
No OST (N=198)	42 (13.0)	44 (12.4)	50 (9.4)	51 (8.5)
On OST (N=49)	37 (13.8)	43 (11.5)	48 (8.9)	51 (7.4)
No psychiatric disease (N=204)	42 (12.8)	46 (11.1)	50 (9.1)	51 (8.1)
Psychiatric disease (N=43)	34 (13.6)	35 (14.0)	48 (10.0)	51 (9.2)
No alcohol abuse (N=218)	41 (13.2)	44 (12.2)	49 (9.2)	51 (8.3)
Alcohol abuse (N=29)	37 (13.2)	43 (12.2)	48 (9.7)	51 (7.8)
Without HIV (N=227)	41 (13.4)	44 (12.1)	49 (9.4)	51 (8.4)
With HIV coinfection (N=20)	45 (10.3)	44 (13.7)	52 (7.6)	53 (5.9)
Total (N=247)	41 (13.3)	44 (12.2)	49 (9.3)	51 (8.3)
	p=0.000		p=0.001	

Conclusion: In this real-world analysis, G/P treatment was safe and highly effective, and led to significant improvements in SF-36 component scores, including in patients with key comorbidities. Updated safety and efficacy data, including healthcare resource utilization data and PROs at time of follow-up, will be presented.

GS-08

The prevalence of non-alcoholic fatty liver disease in young adults: An impending public health crisis?

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has an estimated worldwide prevalence of 20%. This has major implications: increased cardiovascular disease related morbidity; greater burden on transplant services; a rising prevalence of hepatocellular carcinoma. The impetus is on early preventative measures to halt cirrhotic change. A cross-sectional analysis performed on the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in late teens, identified a NAFLD prevalence of 2.5% by ultrasound criteria. The aim of this study was to identify the prevalence of NAFLD within the same cohort, now young adults, using transient elastography to measure fibrosis and steatosis with controlled attenuated parameter (CAP).
Method: 4020 study participants (SPs) had fibroscans using the Echosens 502 Touch®. SPs with known alcohol use disorder or excessive daily alcohol intake were excluded. Results with interquartile range/median ratio (IQR/M) greater than 30% were excluded when analysing fibrosis, but not CAP. Data was collated on multiple variables including Metavir fibrosis (F) score, steatosis grade, body mass index (BMI), and serology including alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). Statistical analysis was performed using Stata MP 15.1.
Results: Mean age was 24 years (± 0.8). 3128 fibroscans were eligible for fibrosis analysis. 72 (2.4%) had fibrosis. 8 (0.3%) SPs had F4. ALT, AST and GGT were all associated with rising F score ($p = 0.002$, $p = 0.001$, $p < 0.001$ respectively). 3283 were eligible for analysis of steatosis. 780 (20.7%) SPs had steatosis; 377 (10.1%) had S3 steatosis. Females had significantly more steatosis than males ($p < 0.001$). ALT, AST and GGT all rose with CAP score ($p < 0.001$). CAP score was positively associated with F score ($p < 0.031$). Cholesterol levels,

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triglycerides, and low-density lipoprotein rose with increasing steatosis grade ($p < 0.001$) whilst high-density lipoprotein levels fell ($p < 0.001$). BMI rose significantly with F score ($p = 0.019$) and CAP score ($p < 0.001$).
Conclusion: This is the largest study to date to analyse fibrosis and steatosis in young adults with suspected NAFLD using transient elastography. 1 in 5 had steatosis and 1 in 40 had fibrosis at 24yrs. This is raised from previous estimated prevalence of NAFLD within the same cohort 6 years prior. The results suggest greater public health awareness of NAFLD is needed in young adults in the UK.

GS-09

Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein following sorafenib: Outcomes by liver disease aetiology from two randomised, placebo-controlled phase 3 studies (REACH-2 and REACH)

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Background and aims: Two global, randomized, blinded, placebo (PL)-controlled phase 3 trials have studied ramucirumab (RAM) in patients (pts) with advanced hepatocellular carcinoma (HCC) following sorafenib, with the REACH-2 (NCT02435433) study limiting enrolment to pts with an alpha-fetoprotein (AFP) ≥ 400 ng/ml. REACH-2 met its primary end point of overall survival (OS) for RAM treatment compared to PL, consistent with the benefit observed in the pre-specified population of pts with baseline AFP ≥ 400 ng/ml in REACH (NCT01140347). An exploratory analysis on pooled individual pt data (IPD) of REACH-2 and REACH pts with baseline AFP ≥ 400 ng/ml was performed by liver disease aetiology subgroups.
Method: Eligible pts had advanced HCC, Child-Pugh A, ECOG PS 0 or 1, AFP ≥ 400 ng/ml, and prior sorafenib. Pts received RAM 8 mg/kg or PL every 2 weeks. A pooled IPD meta-analysis (stratified by study) of REACH-2 pts and REACH pts with AFP ≥ 400 mg/ml was performed. Results are reported by aetiology subgroup (Hepatitis [Hep]B, HepC, Other [e.g. significant alcohol use, steatohepatitis, and cryptogenic cirrhosis]). In each subgroup, OS and progression-free survival (PFS) were evaluated using Kaplan-Meier method and Cox proportional hazard model. Aetiology subgroup-by-treatment interaction was tested using Wald test in the Cox model. Overall response rate (ORR) and disease control rate (DCR) were reported by treatment arms within each subgroup.
Results: Baseline pt characteristics were generally balanced between treatment arms in each aetiology subgroup. A consistent treatment benefit for RAM v PL (Table) was observed across aetiology subgroups (OS interaction p value = 0.29). Grade ≥ 3 adverse events (AEs) were consistent with observations from both individual studies; hypertension was the most frequent grade ≥ 3 AE.

	HepB	HepC	Other
Analysis Population (RAM v PL)	N = 225 (RAM 124, PL 101)	N = 127 (RAM 76, PL 51)	N = 190 (RAM 116, PL 74)
OS median, months	7.7 v 4.5	8.2 v 5.5	8.5 v 5.4
HR (95% CI)	0.74 (0.55, 0.99)	0.82 (0.55, 1.23)	0.56 (0.40, 0.79)
PFS median, months	2.7 v 1.4	3.6 v 2.7	2.8 v 1.6
HR (95% CI)	0.55 (0.41, 0.74)	0.58 (0.39, 0.88)	0.57 (0.41, 0.79)
ORR, %	3.2 v 1.0	7.9 v 2.0	6.0 v 0.0
DCR, %	53.2 v 28.7	65.8 v 52.9	53.4 v 37.8

Conclusion: A treatment benefit with RAM was observed for pts with advanced HCC and a baseline AFP ≥ 400 ng/ml, regardless of aetiology. RAM was well tolerated with no new safety concerns.

GS-10

A germline mutation in SEMA4D leads to a familial syndrome of sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a severe chronic cholestatic disease with unknown etiology and lacking effective treatment options. A group of PSC risk genes have been described in previous studies, but none are PSC specific or causal. Here we report the first monogenic form of PSC in a Swedish family and clarify the mechanism for disease causality.
Method: Germline DNA from 5 family patients and 19 controls were subjected to whole-exome sequencing to identify causal mutations. 3178 unrelated PSC patients and 5024 healthy controls were screened for the same mutation. Then functional studies were carried out on peripheral blood mononuclear cells by flow immune-phenotyping, functional tests, and RNA sequencing after cell subset purification. DDC diet was employed to induce cholangitis in CD100 deficient mice or mutation knock-in mice generated using CRISPR.
Results: The inheritance pattern in the family was consistent with an autosomal dominant disease. We identified a heterozygous missense mutation private to this family which affects a highly conserved region at the cytoplasmic tail of SEMA4D/CD100. Patients carrying the mutation had no obvious change in major immune subsets, but displayed altered T cell function by means of increased proliferation

and TLR1/2 dependent responses. CD100 deficient mice and mutation knock-in mice exhibited abnormal bile flow rate and were more sensitive to DDC-induced cholangitis. More body weight loss, higher serum cholestatic markers, and more server histological phenotypes were observed in them. Mutant mouse T cells also showed similar functional alterations as T cells from familial patients. Finally, adoptive transfer of wild type T cells to CD100 genetically modified mice attenuated cholangitis.

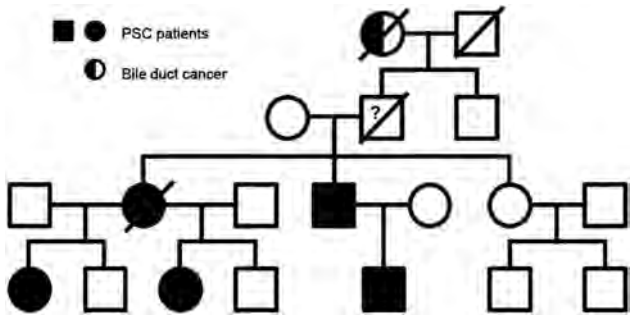

Figure: Pedigree of the Swedish PSC family. Squares: male subjects; circles: female subjects; black filled symbols: patients with PSC; half-filled symbols: patient with bile duct cancer but without a confirmed diagnosis of PSC; crossed-out symbols: deceased subjects.

Conclusion: We have identified the first monogenic variant of PSC and clarified potentially causal alterations in T cells. These findings suggest a role of CD100 in cholangitis pathogenesis which may represent a putative therapeutic target.

GS-11

Baseline neutrophil-to-lymphocyte ratio indicates both prevalent and incident infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis

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Background and aims: The Neutrophil-to-Lymphocyte Ratio (NLR) has been shown to reflect sepsis and inflammation in a variety of illnesses. We assessed the role of NLR in the prognosis of alcoholic hepatitis.

Method: The NLR was calculated from 789 patients who participated in the STOPAH trial with patients randomised to receiving prednisolone or not. Prevalent Acute Kidney Injury (AKI) was defined by an initial creatinine ≥ 133μmol/l and incident AKI was defined as either an increase of serum creatinine by 26.5μmol/l or by 50% by Day 7 in those without baseline AKI. Patients presenting with infections (prevalent infection) were treated prior to randomisation; incident infections were determined after inclusion in the trial. Odds ratio and *t*-tests were used for comparative analysis. with 95% confidence intervals shown.

Results: Those with prevalent AKI had higher NLR than those without (11.1 *cf.* 6.0; p = 0.001 [2.6, 7.6]) as did those with prevalent infection compared with those without (7.8 cf. 6.3; p = 0.02 [0.2, 2.8]). Higher NLR values were seen in those with both incident AKI and infection (Table). A favourable Lille score with Prednisolone treatment was more likely if NLR ≥ 5 *cf.* < 5: (56.5% *cf.* 41.1%: p = 0.01; OR 1.86 (1.16, 2.99)). The risk of developing infection after Prednisolone treatment was greater if NLR > 8 *cf.* < 8 after 7 days (17.3% *cf.* 7.4%: p = 0.006; OR 2.60 (1.32, 5.14)) and 28 days (30.6% *cf.* 20.0%: p = 0.031; OR 1.76 (1.05, 2.96)). The risk of incident AKI after Prednisolone treatment was greater for those with NLR > 8 *cf.* < 8: 20.8% *cf.* 7.0%: p = 0.008; OR 3.46 (1.39, 8.62).

	NLR		
Incident AKI	Present (n = 67)	7.5 (6.4, 8.7)	p = 0.0056
	Absent (n = 403)	6.0 (5.6, 6.4)	(0.5, 2.6)
Incident infection Day 7	Present (n = 94)	7.8 (6.3, 9.2)	p = 0.035
	Absent (n = 695)	6.1 (5.8, 6.5)	(0.1, 3.1)
Incident Infection Day 28	Present (n = 185)	7.1 (6.3, 8.0)	p = 0.025 (0.1, 2.0)
	Absent (n = 604)	6.1 (5.6, 6.5)	

*p < 0.05, **p < 0.01, ***p < 0.001

Conclusion: High NLR is associated with both prevalent and incident AKI and infection in alcoholic hepatitis. A Lille response to prednisolone is more likely if NLR ≥ 5, but development of infection or AKI after prednisolone treatment is greater if NLR > 8.

GS-12

Ascending dose cohort study of inarigivir - A novel RIG I agonist in chronic HBV patients: Final results of the ACHIEVE trial

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Background and Aims: Inarigivir, an oral dinucleotide RIG-I agonist has demonstrated anti-viral activity against HBV via a combination of activation of innate immunity and a DAA effect as a Non Nucleotide reverse transcriptase inhibitor (NNRTI). We report here the final results of the ACHIEVE trial, an ascending dose cohort study of 12 weeks of inarigivir followed by a switch to 12 weeks of tenofovir (TDF) 300 mg daily in treatment naïve HBV patients.

Method: 80 patients were randomized to inarigivir (25,50,100 and 200 mg) daily or placebo in a 4:1 ratio for 12 weeks and then all patients were switched to TDF. Primary endpoints were safety and efficacy measured by reduction in HBV DNA at week 12 from baseline. Secondary endpoints included HBV RNA, quantitative HBsAg, peripheral serum cytokines and change in ALT.

Results: Patient demographics are given in the table. Primary endpoint of HBV DNA reduction was achieved in a dose dependent fashion for both HBeAg positive and negative patients with a maximal reduction of 3.26 $\log_{10}$ in the 200 mg dose. HBV RNA paralleled HBV DNA reductions, with greater reduction in HBeAg

negative patients. Quantitative HBsAg response with a predefined threshold of a >0.5 log_{10} reduction at either week 12 or week 24 was seen in 22% of patients with a mean reduction of 0.8 log_{10} and a maximal reduction of 1.4 log_{10}. Unlike HBV DNA, HBsAg decline was not dose dependent and indicates the potential importance of the host response to inarigivir. Tolerability of treatment was good with 1 unrelated SAE of knee pain and 1 grade 3 non-sustained laboratory abnormality of hypertriglyceridemia. ALT flares (>200 IU) were seen in 6 treated patients (10%) and 4 placebo patients (25%) and 1 patient required dose discontinuation for ALT > 400 IU. No significant increases in bilirubin or INR were seen.

	Pbo E + ve	Pbo E – ve	Epos 25 mg	Eneg 25 mg	Epos 50 mg	Eneg 50 mg	Epos 100 mg	Eneg 100 mg	Epos 200 mg	Eneg 200 mg
n	8	8	9	7	11	5	13	4	8	7
Age	35	48	37	43	36	47	34	46	42	52
M: F	7:1	5: 3	5:5	3:3	9:2	5:0	7:6	3:1	4:4	2:5
ALT	85	53	82	75	75	65	75	90	54	73
HBVDNA	7.6 4	4.75	7.86	5.69	7.79	4.55	8.20	5.95	7.88	4.95
GTA		1		1						
GTB	2	6	4	3	3	4	4	3	2	5
GTC	6	1	5	1	7	1	8	1	6	2
GTD				2	1		1			

Conclusion: The ACHIEVE trial confirms the safety and anti-viral efficacy of inarigivir up to 200 mg daily and further studies at doses of up to 400 mg daily in combination with TDF or added to NUC suppressed patients are underway.

Hepatitis B – drug development

PS-073

Preclinical profile of HBV core protein inhibitor, ABI-H3733, a potent inhibitor of cccDNA generation in HBV infected cells

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Background and aims: Clinical cure remains elusive in chronic HBV (CHB) patients, despite prolonged treatment with current therapies. Core protein Inhibitors (CPIs) represent a novel class of direct acting antivirals that target multiple aspects of the viral life cycle. Here we characterize a newly identified CPI with enhanced potency in blocking cccDNA establishment.
Method: Antiviral activities were determined using the induced HepAD38 cell line (Gt D), and infection of HepG2-NTCP cells and Primary Human Hepatocytes (PHH). Pan-genotypic activity was established using transient transfection assays or HBV stable cell lines. Combination studies were performed using a range of inhibitory concentrations in HepAD38 cells. HBV DNA was quantified by Taqman PCR (qPCR) using primers and a probe specific to the HBV core gene. HBeAg and HBsAg were quantified by ELISA. HBV total RNA/encapsidated pgRNA, capsids and capsid-associated core DNA were detected by either RT-qPCR, Northern Blot or b-DNA, Western Blot, Enzyme Immunoassay (EIA) and Southern Blot, respectively, as previously described.
Results: ABI-H3733 exhibited potent inhibition of viral DNA replication in HepAD38 cells and PHH (EC_{50} 5 and 12 nM, respectively), and reductions in HBeAg, HBsAg and pgRNA in infected HepG2-NTCP cells and PHH (EC_{50} 43 and 61 nM, respectively). ABI-H3733 antiviral activity was pan-genotypic and activity was retained against a panel of known CPI resistant variants. No significant activity was observed against other viruses (EC_{50}s > 10 µM) or in cytotoxicity assays (CC_{50}s > 10 µM). Combination studies predict additive to synergistic inhibition when combined with Nuc therapy. ABI-H3733 possesses promising physical properties, low drug-drug interaction potential and favorable PK profiles in multiple species. Mechanism of action studies suggest enhanced potency in blocking encapsidation of pgRNA, and disruption of pre-formed capsids (EC_{50} 133 nM), leading to premature disassembly during trafficking of rcDNA containing capsids to the nucleus during infection. Using Southern blot analysis, ABI-H3733 inhibited cccDNA formation with an EC_{50} of 125 nM.
Conclusion: ABI-H3733 is a novel CPI, derived from a new chemical scaffold. It possesses potent inhibitory activity against multiple steps in the HBV infectious cycle, particularly those related to cccDNA generation. The enhanced potency and favorable preclinical profile support advancement of this next generation CPI into clinical development.

PS-074

A first-in-class orally available HBV cccDNA destabilizer ccc_R08 achieved sustainable HBsAg and HBV DNA suppression in the HBV circle mouse model through elimination of cccDNA-like molecules in the mouse liver

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Background and aims: The persistence of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes is a major barrier for achieving cure with existing therapies in chronic hepatitis B (CHB) patients. Therapeutic agents that can reduce the level of pre-existing cccDNA are needed to achieve the goal of cccDNA eradication. Here we report the discovery of a novel small molecule, ccc_R08, which reduces pre-existing cccDNA both *in vitro* and *in vivo*.
Method: Primary human hepatocytes (PHH) were used for HBV infection experiments and evaluation of antiviral activities. The HBVcircle mouse model was used to study in vivo efficacy. Compound treatment was initiated after viral persistence established. The levels of HBV DNA, pgRNA, HBsAg, HBeAg were measured by quantitative polymerase chain reaction (qPCR), HBsAg chemiluminescent immunoassay (CLIA), and HBeAg CLIA kits, respectively. cccDNA from infected hepatocytes and mouse liver was measured with Southern Blot or qPCR after Hirt DNA extraction.
Results: We observed potent and dose-dependent inhibition of HBV DNA, HBsAg, and HBeAg upon ccc_R08 treatment initiated two days after HBV infection in PHH. More importantly, the pre-existing level of cccDNA was reduced significantly by ccc_R08 in HBV infected PHH. ccc_R08 did not show any significant cytotoxicity in PHH or in multiple proliferating cell lines at up to 100 µM. No significant effect on mitochondrial DNA was observed, indicating a specific effect on cccDNA. In vivo efficacy was evaluated in the HBVcircle mouse model, in which HBV replication was driven by cccDNA-like molecules. ccc_R08 was orally dosed twice daily for two weeks. Notably, the levels of serum HBV DNA, pgRNA, HBsAg, HBeAg were significantly reduced, and sustained during the off-treatment follow-up period. Moreover, at the end of follow-up, levels of cccDNA molecules in the liver of ccc_R08 treated mice were reduced to below lower limit of quantification (LLOQ). As a control, entecavir did not impact cccDNA level in this model. In summary, these results demonstrate that ccc_R08 can reduce pre-existing cccDNA.
Conclusion: We have reported results that a novel small molecule ccc_R08 can substantially reduce cccDNA levels in HBV infected hepatocytes and in HBVcircle mouse model. These data encourage exploration of this type of molecule in the clinic to evaluate its potential for curing CHB infection.

PS-075

AAV-delivered IL-21 activates CD8+ T-cells to clear HBV replicon plasmid and cccDNA in mice

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Background and aims: Chronic hepatitis B virus (HBV) infection causes hepatitis, liver cirrhosis and hepatocellular carcinoma. HBV covalently closed circular DNA (cccDNA) is the sole viral transcription template in infected hepatocytes and is not cleared by current treatment options, thus constituting a key factor underlying HBV persistence in vivo. Previously, we established a mouse HBV persistence model based on hydrodynamic injection of HBV replicon plasmid and identified interleukin-21 (IL-21) as a potent regulator of HBV clearance in mice. We also recently described another HBV persistence mouse model based on cccDNA mimic termed recombinant cccDNA (rcccDNA) that is produced in vivo. Novel therapeutics with demonstrable effectiveness against cccDNA need to be developed.
Method: Antiviral effects of IL-21 were evaluated in HBV persistence models via adeno-associated virus (AAV)-IL-21 injection. Antibody block and adoptive transfer of immune cells were performed to investigate the cells involved in IL-21-mediated HBV clearance. To determine the long-lasting memory of antiviral effects, the cured mice were re-challenged with HBV.
Results: AAV-IL-21 treatments efficiently clears serum HBV markers and intrahepatic HBV replicon and rcccDNA. Antibodies against CD8+ T cells delayed IL-21-mediated HBV clearance. Adoptive transfer of splenic CD8+ T cells from the cured mice engenders clearance of HBV persistence in acceptor mice. IL-21-induced CD8+ T cell response harbors long-lasting memory that provides prolonged protection for the cured mice.
Conclusion: Our results demonstrate IL-21 as a sound basis for novel therapeutics against chronic HBV infection, with potential in removing cccDNA-harboring hepatocytes via activated CD8+ T cell responses and establishing subsequent long-term protection.

PS-076

Antiviral activity of JNJ-4964 (AL-034/TQ-A3334), a selective toll-like receptor 7 agonist, in AAV/HBV mice after oral administration for 12 weeks

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Background and aims: JNJ-64794964 (JNJ-4964), an oral toll-like receptor 7 (TLR7) agonist in clinical development for the treatment of chronic hepatitis B (CHB), may play an important role in restoring immune responses to hepatitis B virus (HBV). The ability of JNJ-4964 to restore anti-HBV immune responses was assessed preclinically in an adeno-associated virus/replicable HBV genome (AAV/HBV) mouse model.
Method: C57BL/6 mice infected with rAAV8-1.3HBV (genotype D) were treated orally with 20 mg/kg of JNJ-4964 weekly for 12 weeks and followed up for 4 weeks. The anti-HBV activity of JNJ-4964, and the capacity to induce HBV-specific immune responses, were evaluated by T and B-cell ELIspot assays.

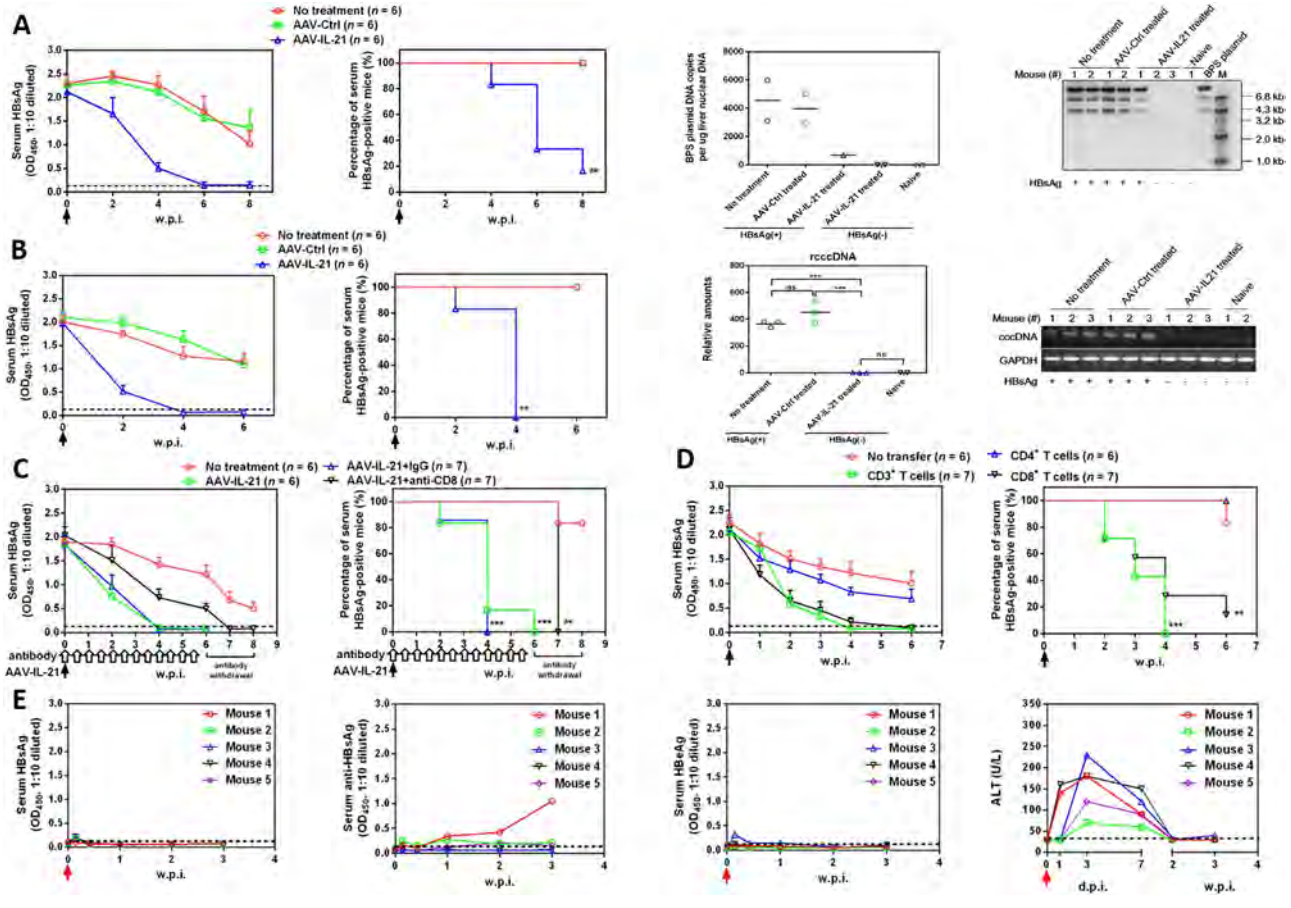

Figure: (abstract PS-075)

Results: JNJ-4964 showed potent anti-HBV activity in AAV/HBV mice treated for 12 weeks. HBV DNA and HBV surface-antigen (HBsAg) concentrations were undetectable for all animals 14 days after start of treatment with no alanine aminotransferase elevations. No rebound in HBV DNA and HBsAg was observed until the end of follow-up. Seroconversion (HBsAg under detection limit and with detectable anti-HBsAg antibody) was observed from 21 days after start of treatment through to the end of follow-up by which time liver HBV DNA and HBV RNA levels had dropped by 1.17 $\log_{10}$ and 0.5 $\log_{10}$, respectively. Four weeks after the last dose, HBV core-antigen expression was decreased and HBsAg became undetectable in the liver in half of the animals. Detectable T-cell and B-cell responses against HBsAg were observed at the end of treatment and the end of follow-up, suggesting sustained T and B-cell immunity in JNJ-4964-treated mice.
Conclusion: Oral administration of JNJ-4964 in AAV/HBV mice for 12 weeks resulted in potent and sustained anti-HBV activity resulting in HBsAg seroconversion and detectable HBsAg-specific T-cell and B-cell responses, supporting further investigation of JNJ-4964 in patients with CHB.

PS-077
Lenvervimab, a monoclonal antibody against HBsAg, can induce sustained HBsAg loss in a chronic hepatitis B mouse model
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Background and aims: Two billion people worldwide have been infected with hepatitis B virus (HBV) and 240 million people live with the chronic infection. Chronic hepatitis B (CHB) patients are at high risk of death, accounting for more than 750, 000 deaths each year. Sustained loss of HBV surface antigen (HBsAg) is regarded as a marker for functional cure. Since HBsAg is known to suppress immune responses against HBV, it was hypothesized that removal of HBsAg might result in restoration of the immune responses.
Method: Therapeutic potential of Lenvervimab was evaluated in hydrodynamic injection (HDI) based CHB mouse model with surrogate Lenvervimab (sLenvervimab) in this study.
Results: Sustained HBsAg loss for 6 months was observed after cessation of the sLenvervimab treatment in 5 out of 12 mice (41.7%). The replication of HBV and HBV core antigen positive hepatocytes was hardly detectable in the liver of those mice. More than 1 log reduction in the copy number of the injected DNA (pAAV-HBV1.2), which act as a template for HBV replication as cccDNA does in natural infection, was observed and the level attained was comparable to that of self-limited mice. Immunohistochemistry of liver tissues showed infiltration of lymphocytes and structural changes of hepatocytes, resembling ballooning degeneration. Also, upregulation of inflammatory markers, such as Cox-2, interleukin-1β and prostaglandin E2, were observed. Statistically meaningful increase of ALT level was observed in the mice. However, the level could be classified as mild or moderate. The existence of protective immunity was confirmed by further challenge experiments to the HBsAg loss mice.
Conclusion: These results indicated that removal of HBsAg by Lenvervimab resulted in the restoration of immune responses against HBV and sustained HBsAg loss was caused by elimination of HBV positive hepatocytes. This study provides proof of concept for applying antibody based therapeutics to achieve a functional cure of CHB.

PS-078
A phase 1b evaluation of HepTcell HBV-specific immunotherapy in nuc-controlled, eAg negative chronic HBV infection
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Background and aims: It is well understood that cellular immunity is key to HBV control. HepTcell is an immunotherapeutic synthetic

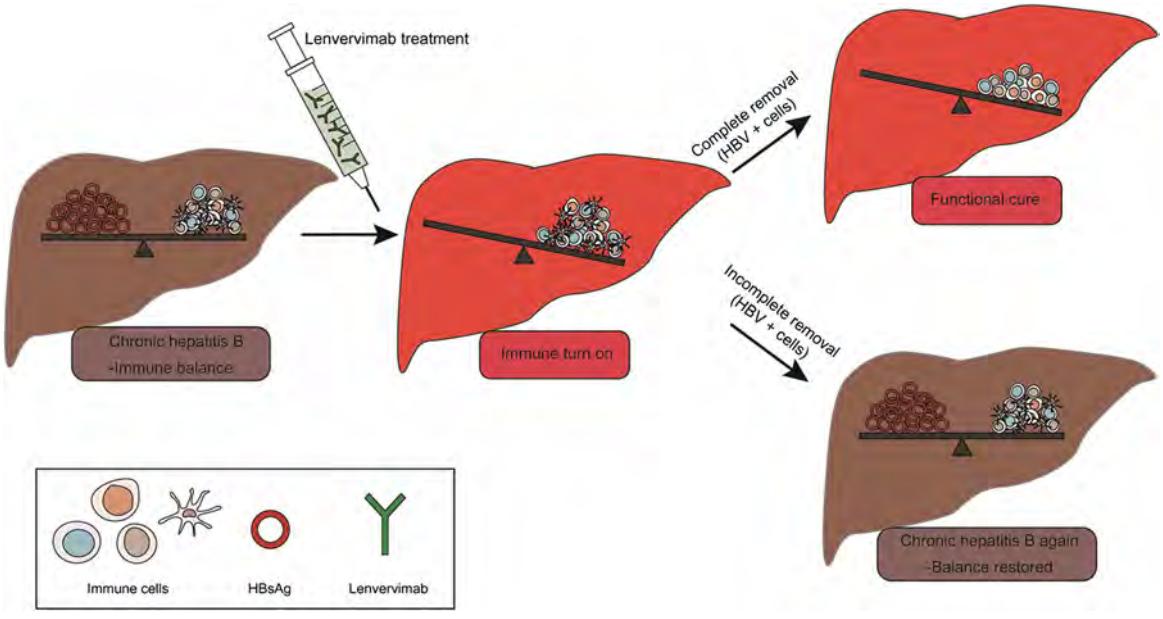

Figure: (abstract PS-077)

product composed of 9 peptides designed to drive T cell-immune responses against conserved regions of several HBV antigens. IC31® is a TLR-9 agonist-based adjuvant formulation designed to minimize systemic exposure.
Method: 60 HBeAg- subjects well controlled on entecavir or tenofovir were randomized to low and high dose peptides, with and without IC31, placebo, and IC31 alone across 3 dose-escalating cohorts. All subjects received 3 injections 28 days apart and were followed for 6 months after last injection. End points included patient and physician assessment of reactogenicity, adverse events including changes in transaminase levels, IFNγ-ELISpot of cultured PBMCs, and quantitative HBsAg.
Results: All doses were well tolerated with no SAEs or liver flares. The placebo group had higher baseline ELISpot responses, making immunology results difficult to interpret, but after the 3 injections, both adjuvanted peptide groups had increases in ELISpot spots/10^6 PBMC against the vaccine peptides compared to baseline values: Low + IC31 = +5608 (95% CI 0, +17483); High+ IC31 = +4804 (95% CI +2933, +10192); Placebo = +167 (95% CI −6717, +6692). Most of the response was driven by peptides derived from HBV polymerase antigen. Only one subject, a placebo recipient, had quantitative HBsAg decline > 0.5 log.
Conclusion: HepTcell immunotherapy was well tolerated and elicited HBV-specific immune responses in patients with well controlled HBeAg-negative chronic HBV. No effect on HBsAg was seen in this short course monotherapy study, but the safety and immunogenicity supports further evaluation in additional HBV populations and in combination with other novel products.

PS-079

HDV co-infection modifies the immunoproteasome profile of HBV infected hepatocytes leading to increased CD8 T-cell recognition: Implication for immunotherapy

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Background and aims: Patients with HBV/HDV co-infection are at risks to develop liver cirrhosis and cancer. Immunological therapy utilizing engineered virus-specific T cells might eradicate HBV/HDV infected hepatocytes. However, the impact that HDV might exert on the T cell recognition of HBV infected hepatocytes is unknown. Here we first analyzed *in vitro* how HDV modifies HBV antigen presentation to CD8 T cells. We then tested the antiviral efficacy of engineered T cells in HBV/HDV co-infected humanized chimeric mice.
Method: Quantity of HBV CD8 T cell epitopes were measured on primary human hepatocytes (PHH) infected with HBV alone or co-infected with HBV/HDV using antibodies and CD8 T cells specific for either core or envelope HLA-A0201 restricted HBV epitopes. HDV infection was concomitantly stained with a Primeflow RNA assay and expression of innate immunity genes were analyzed using Nanostring technology. HBV-specific TCR T cells were engineered using TCR mRNA electroporation on T cells of healthy and HDV chronically infected subjects. HBV/HDV co-infected uPA-SCID/beige/IL2rg$^{-/-}$ (USG) mice repopulated with HLA-A02-matched primary human hepatocytes were used for *in vivo* adoptive T cell transfer experiments.
Results: HBV/HDV co-infected hepatocytes displayed a selected increase presentation of HBV envelope (~100 times) but not of core CD8 T epitopes. The increased epitope presentation was linked with activation of type I IFN genes and modification of immunoproteasome profile, leading to an enhanced target recognition by HBV-envelope specific CD8 T cells. Adoptive transfer of T cells engineered with TCR specific for envelope/A0201 complexes into HBV/HDV co-infected human liver chimeric mice triggered a rapid decrease of both HDV (> 0.5 log) and HBV viremia (> 1 log) in only 12 days. Intrahepatic analysis indicated that the amplitude of anti-HDV effects correlated to the amount of HBV/HDV co-infected cells present at baseline. Of note, TCR-redirected T cells engineered utilizing T cells of HBV/HDV co-infected patients display identical functional profiles with TCR-T cells of healthy controls.
Conclusion: The ability of HDV to activate immunoproteasome activity in HBV infected hepatocytes and boost the presentation of envelope derived HBV epitope support the therapeutic use of HBV envelope specific TCR engineered T cells in HBV/HDV co-infection.

PS-080

Short term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg < 100 IU/ml threshold

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Background and aims: RNAi with JNJ-3989 (previously ARO-HBV) has shown promising reductions in circulating CHB viral parameters based on its design to silence mRNA from cccDNA and integrated sources (AASLD 2018). The ongoing phase 2 portion of AROHBV1001 assesses 3 doses of JNJ-3989 administered weekly to monthly in HBeAg pos (e pos) or neg (e neg) CHB patients. Herein we report reductions in HBsAg levels below important literature proposed thresholds and exploration of loading dose effect.
Method: CHB patients (n = 56) received 3 subcutaneous doses of JNJ-3989. CHB cohorts 2b–5b (n = 4, e pos or neg, NUC treated or not) received monthly doses of 100, 200, 300 or 400 mg. Cohorts of e pos, NUC naïve and experienced CHB (cohorts 8, 9 respectively, n = 4 each) received 300 mg monthly. Loading dose cohorts (all n = 4, e pos or e neg, NUC treated or not) received bi-weekly or weekly doses of 100 mg (cohorts 6 and 7) or weekly doses of 200 mg (cohort 10) or 300 mg (cohort 11). Baseline NUC untreated CHB in any cohort receive NUCs from day1, continuing after JNJ-3989 dosing ends. HBsAg results reported are through day 113, 56 days after 3rd monthly dose when available or most recent in patients with data at least 14 days data following 3rd dose. In total, current HBsAg data is reported for 40 patients and safety for 56. Further data will be available at time of presentation.
Results: No serious AEs or dropouts have been reported. Injection site AEs (all mild) occurred in ~12% of 171 injections. Mean max log10 declines in HBsAg were: 100 mg 1.9, 200 mg 1.7, 300 mg 1.7 and 400 mg 2.0 logs in cohorts 2b–5b and 2.3 in cohort 8, 2.5 in cohort 9.

Giving JNJ-3989 more frequently (cohorts 6, 7, 10, 11) did not increase rate or extent of HBsAg knockdown; duration persisted at least 6 weeks after last dose. 97% (34 of 35) of patients reaching day 85 after first dose have > 1.0 log HBsAg reduction. Of 40 patients with ≥ 14 days follow-up after 3rd dose 3 had HBsAg < 100 IU/ml at baseline while currently 32 have achieved HBsAg < 100, 14 ≤ 10, 5 ≤ 1. Other viral parameters (HBV DNA, RNA, HBcrAg, HBeAg) above LLOQ at baseline improved.
Conclusion: Monthly RNAi reduced all measurable viral products, including HBsAg in e pos and e neg CHB. JNJ-3989 rapidly reduces HBsAg to thresholds associated with improved chances of HBsAg sero-clearance with characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg clearance in CHB. JNJ-3989 has been safe and well tolerated.

Cirrhosis – Clinical aspects

PS-081
Systemic arterial blood pressure determines the therapeutic window of non selective betablockers in patients with decompensated liver cirrhosis

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Background and aims: Non-selective β-blockers (NSBB) remain the cornerstone of primary and secondary prophylaxis of variceal bleeding. However, the safety of NSBB has been questioned in patients with advanced liver cirrhosis and ascites. It has been suggested that there is a limited therapeutic window. Yet, the specific limits of this window still need to be better defined. This study aimed to evaluate different potential limits of the therapeutic window of NSBB treatment in patients with liver cirrhosis and ascites.
Method: The impact of NSBB on 28day (d)-mortality was analyzed in a cohort of 624 consecutive patients with decompensated liver cirrhosis and ascites. Four potential limits of the therapeutic window were investigated: development of a spontaneous bacterial peritonitis (SBP), acute-on-chronic liver failure (ACLF), mean arterial blood pressure (MAP) ≤ 82 mmHg and < 65 mmHg. To adjust for potential confounding factors a multivariate Cox regression, including MELD, platelet count, presence of esophageal varices and leukocyte count, was performed.
Results: NSBB treatment was independently associated with a lower 28d-mortality in the overall cohort as well as in the subgroup of patients with ACLF (adjusted HR: 0.621; p = 0.035 and adjusted HR: 0.578; p = 0.031, respectively). Of note, even in the group of patients with SBP a numerical lower mortality was documented among NSBB users (adjusted HR: 0.594, p = 0.073). In contrast, survival benefits were markedly extenuated in those with a MAP ≤ 82 mmHg and completely lost in those with MAp < 65 mmHg (p = 0.536). However, NSBB was still not associated with an increased mortality in these patients. Similar results were documented in ACLF and SBP patients with a MAp < 65 mmHg. In SBP patients with MAp < 65 mmHg NSBB treatment was associated with renal impairment as indicated by an increase in serum creatinine (p = 0.027) as well as a numerically higher risk of grade 3 acute on kidney injury (HR: 2.266, p = 0.078). In patients with a MAP ≥ 65 mmHg NSBB treatment was independently associated with a lower 28d-mortality regardless of the presence of SBP or ACLF (overall cohort: adjusted HR: 0.582; p = 0.029, SBP cohort: adjusted HR: 0.435; p = 0.028 and ACLF cohort: adjusted HR: 0.480; p = 0.034, respectively).
Conclusion: Neither ascites, ACLF nor SBP per se seem to limit the safe usage of NSBB in patients with cirrhosis. In contrast, a low MAP might be a more valid indicator to determine the therapeutic window of NSBB treatment.

PS-082
Plasma metabolomic changes modulate the impact of Middle Eastern versus Western Diet in an international cirrhosis cohort

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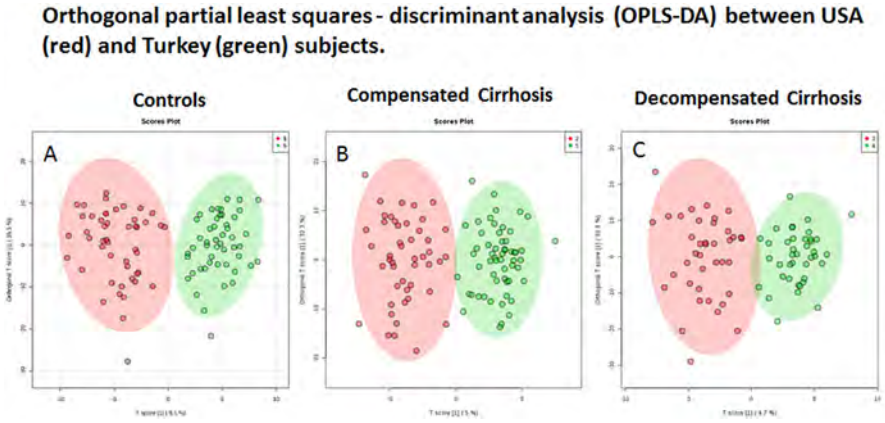
Background and aims: Diet affects gut microbiota and modulates hospitalization risk in a Turkish versus USA cirrhosis cohort, and these may also influence the metabolite composition of blood. This study aimed to define circulating metabolites in plasma associated with Western and Middle-Eastern diet in healthy and cirrhotic subjects across USA and Turkey.
Method: Compensated (Comp) and decompensated (Decomp) cirrhotic outpts and healthy controls (ctrls) were enrolled from Turkey and USA. A dietary history, cirrhosis severity (MELD score), stool (16srRNA diversity) and plasma (NMR spectroscopy at 600MHz) were obtained. Plasma metabolomics were compared between and within the country-based cohorts and $Q^2 > 0.4$ indicated good separation on multivariate analysis.
Results: 296 age-balanced subjects (157 USA [8 ctrls, 59 comp, 50 decomp]; 139 Turkey [46 ctrls, 50 comp, 43 decomp] were included. Cirrhotics between cohorts had similar MELD scores (11 vs 12) metabolic syndrome and diabetes (p = 0.42). Diet: All of the USA cohort consumed a high-fat Western diet. Coffee intake was higher in US subjects, while tea, fermented milk and chocolate intake were higher in the Turkish group (all p < 0.05). Microbiota: We found a significantly higher diversity in Turkish cohort than USA group regardless of cirrhosis; diversity similar in Turkish group between controls and cirrhotics (p = 0.16), but altered within the US-cohort being lowest in decomp pts (p < 0.001). Metabolomics: *Between countries*: There were differences between controls, comp and decomp pts of US vs Turkey (Figure, Q^2 0.62, 0.41 and 0.60 respectively) due to a higher lactate and lipid differences in Turkey compared to US. CH2 and CH3 lipids were higher in earlier stages but lower in decomp in Turkey compared to US (Figure). *Within countries:* there were differences in plasma metabolites within the Turkish cohort, despite similar microbial diversity, which was greatest between ctrls vs cirrhosis (Q^2 ctrl-comp 0.44, ctrl-decomp 0.70 and comp-decomp 0.26). Within the US group, the difference was greatest between ctrl-decomp (Q^2 0.58) rather than ctrl-comp (Q^2 0.21) and comp-decomp (Q^2 0.28). Phosphocholine and CH2 lipids were lowest in decomp followed by comp and ctrls regardless of country, suggesting systemic lipid derangement related to cell regeneration.
Conclusion: Plasma metabolomics showed systemic differences in circulating lipid metabolites in Turkish vs US cirrhosis and healthy cohort related to the dietary changes. These could modulate the potential benefits of the Middle Eastern diet in cirrhosis.



D. Turkey grouping compared to USA grouping: Relative metabolite levels contributing to differences

Metabolite Turkey Vs USA	Control	Comp	Decomp
Lipid CH_2	↓	↓	↑
Lipid CH_3	↓	↓	↑
Lactate	↑	↑	↑
Choline compounds	-	↑	-

Figure: (abstract PS-082)

PS-083

Serum albumin concentration as guide for long-term albumin treatment in patients with cirrhosis and uncomplicated ascites: Lessons from the ANSWER study

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Background and aims: The ANSWER trial[1] recently showed that long-term administration of human albumin (HA) to patients with cirrhosis and uncomplicated ascites significantly improves 18-mo survival. Under such treatment, mean serum albumin level (SA) increased from 3.1 to 3.7-3.8 g/dl within 1 month, remaining stable thereafter. This post-hoc analysis aims to determine whether SA at baseline and during treatment predicts patient outcomes.
Method: The entire ITT population (431 pts randomized to standard medical treatment [SMT] or SMT+HA) of the ANSWER trial was included in the analysis. 3rd grade polynomial regression was used to smooth K-M survival probability estimate for each SA. Factors influencing the achievement of 1-mo SA thresholds were determined with logistic regressions. Survival analysis (K-M estimation and Cox regression) was then performed on SMT+HA pts grouped by 1-mo SA.
Results: Baseline SA ranged from 2.2 to 3.9 g/dl in both arms. According to the different baseline SA (0.1 g/dl increase), 18-mo survival ranged from 35 to 98% in SMT arm and from 70 to 98% in SMT+HA arm. A survival benefit was seen in SMT+HA arm for baseline SA up to 3.7 g/dl, which was associated with a 84% survival in both arms.
To identify on-treatment SA associated with an improved survival, 1-mo SA was first assessed in the entire population. SA of 3.8 and 4.1 g/dl corresponded to 80 and 85% survival, respectively. Factors independently associated with these 1-mo SA thresholds were baseline SA, baseline MELD score, and HA treatment with the latter being the most powerful predictor (3.8 g/dl: OR 24.77 [95% CI 11.72-52.35], $p < 0.0001$; 4.1 g/dl: OR 33.69 [95% CI 10.03-113.11], $p < 0.0001$). In the SMT+HA arm, the survival probability was 86% in pts with 1-mo SA > 3.8 g/dl (n = 82) and 67% in those with 1-mo SA ≤ 3.8 g/dl (n = 96) ($p = 0.007$), while it was 93% in pts with 1-mo SA > 4.1 g/dl (n = 59) and 70% in those with 1-mo SA ≤ 4.1 g/dl (n = 122) ($p = 0.002$). Patients not reaching these 1-mo SA thresholds had lower SA and higher MELD score at baseline.
Conclusion: Long-term HA administration provides a survival benefit in patients with uncomplicated ascites presenting SA even in the low-normal range. More important, a 1-mo on-treatment SA of approximately 4 g/dl is associated with a significantly higher survival. Baseline SA and disease severity influence the response to treatment. These data can be used to guide dosage and timing of long-term HA treatment.

[1]The Lancet 2018;391:2417-29.

PS-084

Pregabalin for muscle cramps in patients with liver cirrhosis: A randomized, double-blind, placebo-controlled trial

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Background and aims: Muscle cramps are defined as a paroxysmal, involuntary, and painful contraction of skeletal muscle. Cirrhotic patients can encounter with muscle cramp frequently, which might

be associated with poor quality of life. However, cirrhotic patients have limited access to many therapeutic drugs metabolized primarily in liver due to decreased liver function. Indeed, to date, a well-established therapy for cramp in liver cirrhosis is still lacking. This is the first randomized placebo-controlled trial of pregabalin in the treatment of muscle cramps in patients with liver cirrhosis. Here, we aimed to assess efficacy and safety of pregabalin against frequent muscle cramp with liver cirrhosis. And we also investigate the relationship of muscle cramps with quality of life (QOL) using 36-item Short-Form Health Survey (SF-36) and Liver Disease Quality of Life instrument (LDQOL).

Method: In our randomized, double-blind, placebo-controlled study, we enrolled participants up to 75 years old with diagnosed liver cirrhosis at the Seoul Metropolitan Government Boramae Medical Center from July 2011 to Dec 2017. The patients randomly allocated into the treatment (pregabalin) and placebo (dummy) groups, by a web-based randomization program. The primary outcome was the reduction rate of the frequency of muscle cramps in both groups. We assessed the primary outcome in all participants who received at least one dose and had at least one LDQOL and SF 36 measurement. We monitored adverse events in all participants. This study is registered with ClinicalTrials.gov, number NCT01271660

Results: Between July 2011, and February 2018, we enrolled 63 participants (30 randomly allocated pregabalin, 30 randomly allocated placebo, and 3 withdrew). In the pregabalin group, the reduction rate of the frequency of muscle cramps was significantly higher than placebo group ($p < 0.005$). The reduction rate of pain and frequency of muscle cramp during sleep did not differ in both groups. Two domains of SF-36, "Role limitations due to physical health" and "Pain", and one domain of LDQOL scores, "Symptoms", showed significant differences between the placebo and the pregabalin group ($p < 0.05$).

Conclusion: Pregabalin is generally well tolerated in cirrhotic patients and reduces the frequency of muscle cramp over placebo. Our trial showed pregabalin will be good candidate for cramp treatment in cirrhotic patients.

PS-085

The impact of ABO blood group on von Willebrand factor levels and the prevalence of portal vein thrombosis in patients with advanced chronic liver disease

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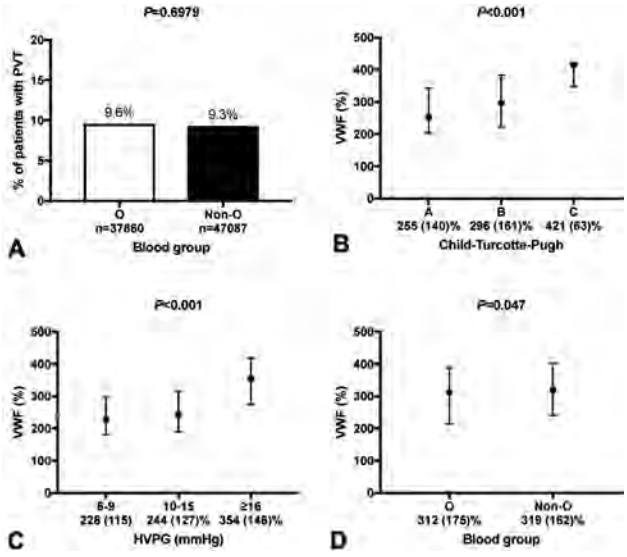
Background and aims: Non-O ABO blood group (BG) is a risk factor for arterial and venous thromboses in the general population, which has been attributed to the effect of BG on von Willebrand factor (VWF) plasma levels. Patients with cirrhosis commonly develop venous thrombosis, especially portal vein thrombosis (PVT). Procoagulant alterations, such as high VWF plasma levels, have been suggested as a risk factor. We aimed to assess **(1)** if BG is a risk factor for PVT and **(2)** whether BG impacts VWF plasma levels in patients with advanced chronic liver disease (ACLD).

Method: Retrospective analysis including two patient cohorts: **(1)** 'US' cohort including all adult liver transplantations in the US between 2002-2017 and **(2)** 'Vienna' cohort comprising patients undergoing hepatic venous pressure gradient (HVPG)-measurement at the Medical University of Vienna between 2006-2018 who had an HVPG ≥ 6mmHg and available information on BG and VWF plasma levels.

Results: (1) The 'US' cohort comprised 84947 patients. 55% had a non-O BG and except for ethnicity, we observed no relevant differences in patient characteristics between patients with BG O and non-O. Importantly, the prevalence of PVT at the time of liver transplantation was similar between groups (O: 9.6% vs. non-O: 9.3%; panel A).

(2) 420 patients were included in the 'Vienna' cohort; 64% with a non-O BG. Mean HVPG was 18 ± 6mmHg and 90% of patients had clinically significant portal hypertension (HVPG ≥ 10mmHg). VWF plasma levels were markedly increased, in a manner proportional to the degree of hepatic impairment (Child-Turcotte-Pugh: +16.5% VWF per point in adjusted analysis; panel B) and severity of portal hypertension (HVPG: +4.1% VWF per mmHg in adjusted analysis; panel C). VWF plasma levels were slightly higher in patients with a non-O BG (319 (162)% vs. 312 (175)%, p = 0.047 in unadjusted analysis; +23.6% VWF in adjusted analysis; panel D).



Conclusion: Elevated VWF plasma levels are related to the severity of liver disease with only a minor contribution of BG. BG was not a risk factor for PVT in a very large dataset, and this lack of association could be explained by the minor effect of BG on VWF plasma levels. Alternatively, hypercoagulability, for example caused by elevated VWF levels may only have a minor impact on PVT risk in patients with ACLD.

PS-086

Sustained virologic response in patients with cirrhosis from chronic hepatitis C leads to sustained and long-term improvement of health-related quality of life, fatigue, and work productivity

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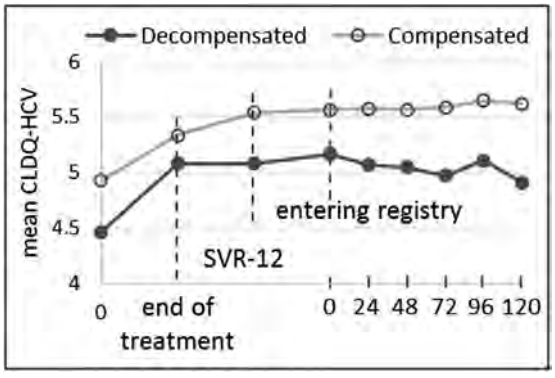
Background and aims: Patients with chronic hepatitis C (CHC) and cirrhosis have severe impairment of health-related quality of life

(HRQL) and other patient-reported outcomes (PROs). Although achieving sustained virologic response (SVR) leads to improvement in PROs, the long-term sustainability of this improvement in patients with cirrhosis has not been well established.
AIM: To assess long-term changes in PRO scores in patients with cirrhosis who have achieved SVR after treatment with a direct-acting antiviral.
Method: Patients with HCV and cirrhosis who had been treated in 14 clinical trials and had achieved SVR-12 were prospectively enrolled in a long-term registry (#NCT02292706). PROs were collected every 24 weeks for 120 weeks using Short Form-36 (SF-36), Chronic Liver Disease Questionnaire (CLDQ)-HCV, and Work Productivity and Activity Impairment (WPAI) instruments which collectively return 20 PRO domain scores.
Results: Data was available for 785 HCV cirrhotics with SVR-12: 659 compensated (CC) and 126 decompensated cirrhosis (DCC). Their pre-treatment characteristics include age 57.6 ± 7.3 years, 69% male, 22% with type 2 diabetes, 50% employed. Prior to their initial treatment, DCC patients had severely impaired PRO scores in comparison to CC patients (by average 5.8% to 15.6% of a PRO range size; $p < 0.05$ for 15/20 PRO domain scores); the most pronounced difference between DCC and CC patients was in physical health- and activity-related domains. After achieving SVR and enrollment into the registry, significant PRO improvements from their pre-treatment scores were noted in 19/20 PRO domains in CC patients (ranging from average +2.2% to +17.0% of a PRO range size) and in 10/20 PRO domains in DCC patients (from +4.4% to +20.5% of a PRO score range) (all $p < 0.05$). These PRO gains persisted or continued to improve over time up to 120 weeks after entering the registry in patients with both CC and DCC (Figure). In DCC patients, the presence of hepatic encephalopathy was the most important contributor to PRO impairment (up to −10.2%, $p < 0.01$ for 12/20 PRO scores).



Conclusion: Achieving SVR leads to significant and sustainable improvement of PRO scores in patients with pre-treatment cirrhosis.

PS-087
Fecal microbiota capsules are safe and effective in patients with recurrent hepatic encephalopathy: A randomized, blinded, placebo-controlled trial
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Background and aims: Recurrent hepatic encephalopathy (HE) can cause major morbidity despite standard of care (SOC; rifaximin/lactulose). Fecal microbial transplant (FMT) enema can be useful but patients prefer capsular FMT. FMT without pre-intervention antibiotics also needs to be studied with emphasis on small intestinal barrier function. Aim: Determine the safety, tolerability and impact on brain function and mucosal/stool microbiota in recurrent HE after capsular FMT vs placebo.
Method: Cirrhotic outpts with recurrent HE on SOC were randomized 1:1 into receiving 15 FMT capsules vs placebo from a single donor enriched in beneficial Lachnospiraceae and Ruminococcaceae. Endoscopies with duodenal/sigmoid Bx and stool analysis, cognitive function (EncephalApp and Psychometric hepatic encephalopathy score PHES) and duodenal anti-microbial peptide (AMP) mRNA expression were performed pre-, 2/4 weeks post with 5 mth follow-up. Pts remained blinded and those assigned to FMT underwent repeat endoscopies 4 weeks post-FMT.SOC was continued throughout the trial.
Results: 20 subjects on lactulose/rifaximin were randomized 1:1. MELD score was similar at baseline (9.6 vs 10.2) and study end (10.2 vs 10.5). Hospitalizations/Death: 6 pts in the placebo group required hospitalizations/died compared to one in FMT ($p = 0.05$). The number of hospitalizations was higher in placebo vs FMT (median 1.5 vs 0, $p = 0.02$). Infection/HE episodes not requiring admission was similar (median 1 vs 1, $p = 0.5$, Fig 1A). Microbiota changes: Baseline diversity was similar between gps in stool, sigmoid and duodenal mucosa ($p > 0.05$). Post-FMT, there was a significant increase in duodenal mucosal diversity [2.1 vs 2.6, $p = 0.01$) and relative abundance of Ruminococcaceae and Bifidobacteriaceae with decrease in Streptococcaceae and Veillonellaceae in FMT pts (Fig 1B). No change in stool/sigmoid diversity was seen pre/post FMT but reductions in

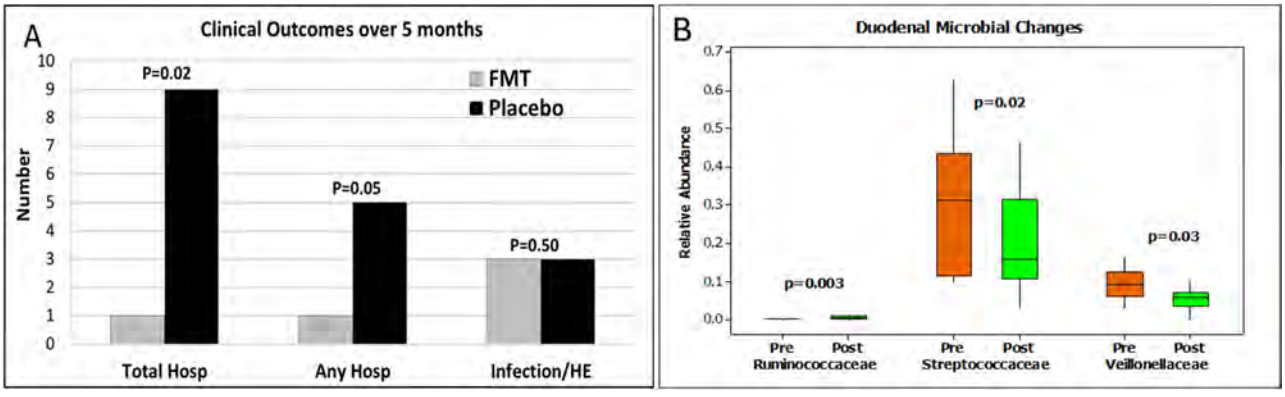

Figure: (abstract PS-087)

Veillonellaceae were seen post-FMT in sigmoid (p = 0.04) and stool (p = 0.05). Stool results over time were similar for placebo pts.
Duodenal inflammation/AMP expression: Baseline expressions were similar between groups. There was a significant increase in E-cadherin protein [pre 26700 (35500) vs post 43600 (35500) p = 0.03], reduced IL-6 [pre 146.4 (310.3) vs post 90.6 (117.4), p = 0.02] and increased Defensin A5 [pre 1821916 (271832) vs post 2430000 (3352500), p = 0.03] expression.
Brain function: Baseline EncephalApp scores were similar between groups (p = 0.57), which improved in the FMT group [250.2 (237.2) vs 224.9 (98.5), p = 0.02). PHES changes were similar at baseline and remained similar between groups post-intervention.
Conclusion: Oral FMT capsules were safely tolerated and associated with lower hospitalizations, improvement in duodenal mucosal diversity, dysbiosis and barrier function, and enhanced EncephalApp performance in cirrhosis and recurrent HE compared to placebo.

PS-088
Impaired cardiac contractile reserve on dobutamine stress echocardiography predicts development of hepatorenal syndrome

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Background and aims: Development of hepatorenal syndrome (HRS) in end stage liver disease is associated with poor outcomes. Identifying early predictors of HRS may allow an opportunity for intervention. Preliminary studies in small cohorts have suggested a potential role of myocardial dysfunction in its pathogenesis. We hypothesized that a diminished cardiac contractile reserve was associated with development of HRS.
Method: Consecutive patients without known cardiac disease that underwent dobutamine stress echocardiogram (DSE) for pre-liver transplant (LT) workup between 2010-2017 were recruited. HRS was diagnosed based on guideline-based criteria. Cardiac output (CO) (stroke volume by left ventricular outflow tract velocity time integral × heart rate; HR) was prospectively recorded at baseline and low-dose (10 μg/kg/min) dobutamine.
Results: Among the 560 patients that underwent DSE, 27 were excluded (cardiomyopathy n = 14, beta-blocker use n = 5, arrhythmias n = 8). Overall, 85 (15.9%) patients developed HRS over a mean follow-up of 1.8 (±2.4) years. The HRS cohort had higher baseline CO (7.9 L/min vs 6.7 L/min, p < 0.001) but demonstrated a significantly blunted response to dobutamine (% ΔCO; 29.7% vs 44.6%, p = 0.002). This was primarily driven by an impaired heart rate (HR) response in the HRS cohort (ΔHR: 13bpm vs 18bpm, p = 0.004). Impaired contractile reserve was defined as < 22% increase in CO with low-dose dobutamine (derived from the lowest quartile of % ΔCO at low-dose dobutamine). A significantly higher proportion of patients with impaired contractile reserve developed HRS, 34 (40%) vs 87 (25%), p = 0.006. On multivariable logistical regression, after adjusting for age, gender, model of end stage liver disease (MELD) and Child-Pugh score, impaired contractile reserve was the strongest predictor for development of HRS (Odds ratio 2.2 95%CI 1.2-4.0, p = 0.02).
Conclusion: Patients that developed HRS demonstrate an attenuated rise in CO with low dose dobutamine, driven primarily by an impaired chronotropic response. Impaired cardiac contractile reserve identified on DSE was the strongest predictor for HRS and may offer a novel non-invasive method for early identification of patients at risk for HRS.

Liver fibrosis

PS-089
Development of advanced alcoholic liver fibrosis involves intensive remodelling of a wide range of extracellular matrix proteins and is characterised by imbalance between collagen formation and -degradation and dysfunctional wound-healing

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Background and aims: Liver fibrosis is the driver of liver related mortality in alcoholic liver disease (ALD). In search of key mechanisms for progression, we aimed to investigate remodelling of extracellular matrix (ECM) proteins as a function of the histological severity of asymptomatic ALD.
Method: We measured 21 markers of fibrosis and ECM remodelling in a biopsy controlled study of 305 ALD patients and 50 gender, age and BMI matched healthy controls. We excluded decompensated cirrhosis or alcoholic hepatitis patients. We evaluated total fibrosis by elastography (FibroScan) and serum hyaluronic acid (HA). Specific ELISAs quantified collagen type III, V and VI formation (PRO-C3, PIIINP, PRO-C5, PRO-C6), tissue inhibitor of MMP1 (TIMP1), collagen type IV and V degradation (C4M, C5M), and collagen cross-linking (LOXL2, PRO-C3X). Additionally, we evaluated vascular and elastin remodelling (PRO-C18, ELM, ELM7, EL-NE), and wound-healing by markers of fibrinolysis (D-Dimer), fibrin formation (FPA), thrombin inactivation (F1) and activation (F1 + 2), von Willebrand factor degradation (vWF-A) and formation (vWF-N). We correlated all markers with central histological scoring of fibrosis, inflammation, ballooning and steatosis, as well as with alcohol consumption, age and gender (figure).

		Histological characteristics								
		Fibrosis stage (0-4)	Lobular inflammation (0-3)	Portal inflammation (0-1)	Ballooning (0-2)	Steatosis (0-3)	Healthy controls	Abstinent at inclusion (yes-no)	Age*	Gender
Total fibrosis	TE	0,759	0,540	0,455	0,565	0,279	-0,399	0,082	0,140	-0,058
	HA	0,662	0,509	0,378	0,558	0,209	-	-0,058	0,408	-0,069
Collagen formation	PRO-C3	0,670	0,511	0,451	0,519	0,201	-0,422	-0,016	0,087	-0,078
	PIIINP	0,587	0,409	0,381	0,451	0,081	-	0,050	0,187	-0,027
	PRO-C5	0,311	0,226	0,077	0,221	0,150	-0,117	0,069	0,109	0,015
	PRO-C6	0,434	0,230	0,282	0,302	-0,036	-0,347	0,191	0,117	0,047
	TIMP1	0,640	0,552	0,340	0,503	0,344	-	-0,169	0,201	-0,110
Collagen degradation	C4M	0,344	0,242	0,148	0,279	0,159	-0,150	0,071	0,104	0,044
	C5M	0,123	0,070	-0,031	0,080	0,009	-0,058	0,034	0,148	0,004
Cross-linking	LOXL2	-0,110	0,058	-0,101	-0,014	0,096	-0,065	0,047	0,050	-0,081
	PRO-C3X	0,560	0,381	0,280	0,483	0,119	-0,116	-0,041	0,087	0,077
Vascular remodeling and elastin	PRO-C18	-0,071	-0,022	-0,071	-0,092	-0,011	-0,197	0,037	0,023	-0,042
	ELM	0,089	0,009	0,111	0,018	0,023	0,167	-0,114	0,080	-0,057
	ELM7	0,120	0,157	0,082	0,122	0,115	0,083	-0,070	0,078	-0,068
	EL-NE	0,033	0,046	0,044	0,048	0,008	-0,309	0,170	0,032	-0,038
Wound-healing	D-Dimer	0,331	0,201	0,217	0,283	0,068	-0,026	0,014	0,202	-0,054
	F1	-0,372	-0,215	-0,246	-0,283	0,002	-0,026	-0,052	-0,141	-0,020
	F1+2	-0,115	0,001	-0,039	-0,019	-0,016	0,049	-0,027	-0,053	0,089
	FPA	-0,376	-0,253	-0,185	-0,228	-0,194	0,071	0,124	-0,024	-0,001
	vWF-A	0,103	0,073	0,038	0,143	-0,076	0,041	0,025	-0,046	0,353
	vWF-N	0,258	0,274	0,174	0,221	0,160	-0,176	0,065	0,087	0,004

Spearman's rho for pairwise correlations between the 21 markers and semiquantitative histological scores for fibrosis, inflammation and ballooning, together with drinking status at inclusion, age and gender. *Age in decades (<30, 30-39, 40-49, 50-59, 60-69 and ≥70)

Results: Mean age was 55 ± 10 years, 75% male, BMI 27 ± 7 kg/m^2. Compared to healthy controls, ALD patients had elevated levels of total fibrosis, collagen formation and degradation, and vascular and elastin remodelling, as a sign of ongoing ECM remodelling. This was irrespective of whether patients were actively drinking or abstinent

at inclusion. Patients with fibrosis stage F3-F4 showed an imbalance favouring collagen formation over degradation (34% higher PRO-C5 in F3-4 vs F0-2, compared to 6% higher C5M). A similar observation was seen in patients with severe ballooning and lobular inflammation (18% higher PRO-C5 vs 7% higher C5M). Also, fibrosis stage, lobular inflammation and ballooning correlated significantly with higher concentrations of fibrin degradation, low fibrin formation, lack of thrombin inactivation and more von Willebrand factor formation, as sign of a dysfunctional wound-healing cascade.
Conclusion: Alcoholic liver disease is characterised by extensive extracellular matrix remodelling, even after abstaining from alcohol. This study indicates that development of advanced fibrosis involve more collagen formation than degradation and dysfunctional wound-healing.

PS-090
SOX9 regulates extracellular matrix proteins in liver fibrosis that correlate with severity of fibrosis
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Background and aims: Extracellular matrix (ECM) deposition and resultant scar play a major role in the pathogenesis and progression of liver fibrosis. Identifying core regulators of ECM deposition may lead to urgently needed diagnostic and therapeutic strategies for disease. The transcription factor Sex determining region Y box 9 (SOX9) is actively involved in scar formation and its prevalence in patients with liver fibrosis predicts progression. We hypothesised that SOX9 regulated gene products could be utilised to predict severity of liver fibrosis.
Method: Primary rodent HSCs were isolated, and culture activated. Gene silencing was performed using short interfering RNA. Microarray was performed on *in vitro Sox9*-abrogated activated rat hepatic stellate cells (HSCs). *Sox9* deletion *in vivo* was induced in ROSACreER:*Sox9*$^{fl/fl}$ mice and fibrosis induced with injection of carbon tetrachloride or bile duct ligation. Chromatin immunoprecipitation (ChIP) assays were performed with a SOX9 antibody. Protein-DNA complexes were eluted, crosslinks reversed, and protein degraded prior to DNA purification and PCR. Serum paired with liver biopsy samples were obtained from chronic hepatitis C infected patients and assayed with sandwich ELISA for discrete proteins.
Results: In this study, transcriptomic approaches using *Sox9*-abrogated myofibroblasts identified > 30% of genes regulated by SOX9 relate to the ECM. Further scrutiny of these data identified a panel of highly expressed ECM proteins, including Osteopontin (OPN), Osteoactivin (GPNMB), Fibronectin (FN1), Osteonectin (SPARC) and Vimentin (VIM) as SOX9 targets amenable to assay in patient serum. *In vitro*, all identified proteins increased during HSC activation. SOX9 knockdown resulted in a commensurate reduction, suggesting regulation by SOX9. Moreover, *in silico* analysis revealed conserved SOX9 binding motifs in all identified ECM proteins, with 4 of the 5 demonstrating enrichment with ChIP. *In vivo,* all SOX9-regulated targets were increased in human disease and in mouse models of fibrosis and decreased following *SOX9*-loss in mice with parenchymal and biliary fibrosis. In patient serum samples, SOX9-regulated ECM proteins were altered in response to fibrosis severity.
Conclusion: These data support SOX9 as a key driver of the mechanisms underlying fibrosis and highlight SOX9 and its down-stream targets as new measures to stratify patients with liver fibrosis.

PS-091
Targeted disruption of TGF-B activation by an AVB1 integrin inhibitor significantly reduces liver fibrosis in CCl4 mice and Human NASH liver slices
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Background and aims: For many years, $\alpha_V\beta_1$ has been an elusive integrin as its distribution and expression levels were hindered by the lack of selective tools (integrin α_V can pair with 5 β integrins while β_1 integrin can pair with 12 α integrins). Although data in human tissue has been lacking, studies with a semi selective small molecule inhibitor has shown efficacy across multiple mouse models of fibrosis and suggested a prominent role of $\alpha_V\beta_1$ in TGF-β promotion of liver fibrosis.
Method: We have developed a sensitive electrochemiluminescence assay for the quantitation of $\alpha_V\beta_1$ in mouse models of liver fibrosis as well as human tissue samples from NASH and PSC patients. The efficacy of selective inhibition of $\alpha_V\beta_1$ was evaluated using an orally available, selective small molecule inhibitor of $\alpha_V\beta_1$ in vivo in CCl_4-treated mice and in precision cut liver slices from CCl_4-treated mice and explanted human cirrhotic liver tissue.
Results: In human livers $\alpha_V\beta_1$ expression (fig A) and SMAD3 phosphorylation (fig B) were significantly elevated in NASH and increased with increasing liver fibrosis stage. Integrin inhibition in precision cut human cirrhotic NASH liver slices reduced the expression of fibrosis related genes (fig C). In CCl_4 treated mice $\alpha_V\beta_1$ expression, SMAD3 phosphorylation, collagen gene expression and OHP concentration were significantly elevated. In vivo $\alpha_V\beta_1$ inhibition reduced SMAD3 phosphorylation, fibrotic gene expression and liver collagen content.

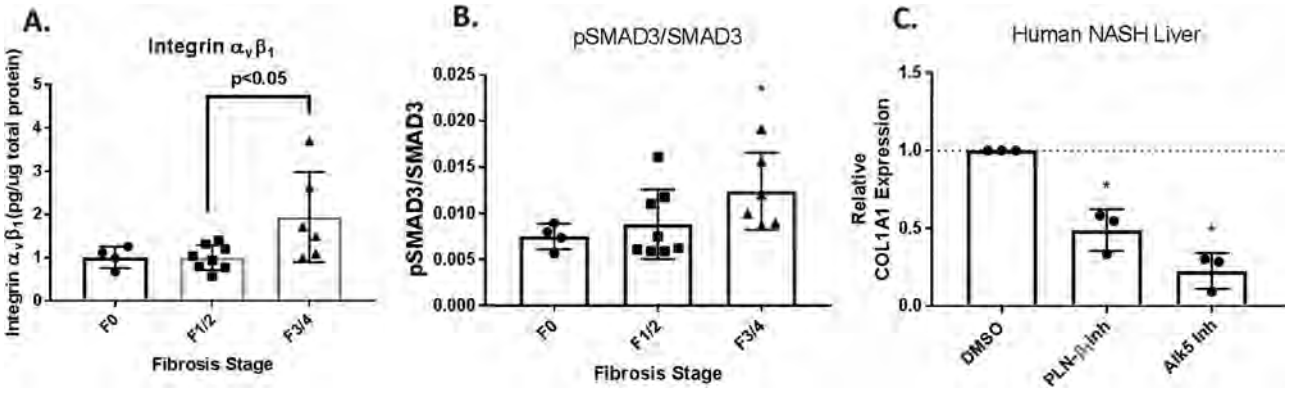

Figure: (abstract PS-091)

Conclusion: Inhibition of $\alpha_V\beta_1$-mediated activation of TGF-β significantly reduced expression of fibrotic genes in human precision cut liver slices and supressed liver fibrosis in mice warranting further evaluation.

PS-092

Lack of monoacylglycerol lipase protects from MCD-induced hepatic inflammation and fibrosis

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Background and aims: Monoacylglycerol lipase (MAGL) is the rate limiting step in the degradation of monoacylglycerols. It contributes to the production of arachidonic acid from endocannabinoid 2-arachydonoyl-glycerol (2-AG), thereby representing a metabolic hub between endocannabinoid and lipid signaling. NAFLD can progress to NASH and fibrosis with activation of hepatic stellate cells (HSC) as cellular source of fibrosis. Therefore, our aim was to explore the contribution of MAGL in HSC activation and metabolic liver fibrosis.
Method: Primary HSC and bone marrow derived macrophages (BMDMs) were isolated from wild type (WT) and MAGL knock-out (MAGL KO) mice and cultivated in vitro. To mimic NASH-induced fibrosis in vivo, we fed WT and MAGL KO mice a methionine-choline deficient diet (MCD) for 4 weeks. Fibrotic and metabolic markers were evaluated in primary HSC and total liver tissue by RT-PCR, western blot, immunohistochemistry (HandE, F4/80, Sirius Red, Oil Red O) and migration assays.
Results: After 4 weeks of MCD diet MAGL KO mice developed less steatosis (HandE), less inflammation (F4/80) and fibrosis (Sirius Red), compared to WT mice. In addition, analysis of hydroxyproline content (μg/mg) and total liver expressions of fibrogenic markers such as Collagen1α1, TGF-β, PDGFRβ and MCP-1 were significantly ($p < 0.05$) decreased in MAGL KO mice. Moreover, hepatic expression of de-novo lipogenesis related genes, such as SREBP-1c and FASN were significantly downregulated in mice lacking MAGL ($p < 0.05$), whereas PPARγ and its target gene CD36 were induced ($p < 0.05$), but there were no difference in bile acid synthesis (CYP7A1) and transporters expressions (BSEP, NTCP, MRP2, 3, 4) and cholesterol synthesis (SREBP-2, HMGCR). Interestingly, primary HSC isolated from MAGL KO mice displayed slower activation in vitro compared to WT HSC, supported by significant reduction of the fibrogenic markers Collagen1α1, PDGFRβ and α-SMA ($p < 0.05$) during the first 7 days of culture after isolation. Moreover, MAGL KO HSC showed less migration capacity and even stimulation with TGF-β (5 ng/ml) resulted in reduced amount of MCP-1, TIMP-1, Collagen1α1, SREBP-1c expressions in these cells ($p < 0.05$). BMDMs lacking MAGL have less migratory ability, also when stimulated with conditioned medium collected from activated HSC, compared to WT cells ($p < 0.05$). In addition, primary MAGL KO HSC accumulated less lipid droplets ($p < 0.05$) when challenged with oleic acid (100μM) and showed reduction of autophagic gene expression ATG7.
Conclusion: Lack of MAGL contributes to protect from hepatic inflammation and fibrogenesis in vivo and in vitro by reducing steatosis, inflammation and de-novo lipogenesis, thereby resulting in reduced HSC activation. Thereby, inhibition of MAGL may become a potential therapeutic strategy for NASH.

PS-093

The dynamics of elastin in collagen-based liver fibrosis: Accumulates late during progression and degrades slowly in regression

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Background and aims: Excessive deposition of elastin in advanced liver fibrosis may contribute to the declining reversibility of the disease. Our previous study has found that elastin crosslinking inhibition can effectively arrest liver fibrosis progression. To further understand the roles of elastin involved in liver fibrosis, we systematically investigated the expression, accumulation and degradation, and the ultrastructure of liver elastin and collagen, based on dynamic and bidirectional CCl_4-induced liver fibrosis mouse models.
Method: Dynamic and bidirectional liver fibrosis mouse model was established by CCl_4-intoxication. Multiple modalities were employed to observe and quantify liver elastin and collagen including cyto- and immunohistochemistry, immunofluorescence with 3D analysis, quantitative real-time PCR, western blot assays, biochemical analysis of collagen and elastin, and scanning electron microscopy.
Results: We found that the expression pattern of tropoelastin (soluble elastin) and collagen I was not completely comparable at both the transcriptional and posttranscriptional levels during liver fibrosis progression and regression. Elastin mainly accumulated onto the internodular fibrous septa and enlarged portal areas and intertwined with collagen I at the late stage of liver fibrosis. 3D analysis of elastin and collagen I by confocal immunofluorescence coupled, with biochemical analyses revealed that, with respect to collagen, elastin deposition was characterized by late aggregation in progression and slow turnover in regression. Based on the decellularized ECM scaffolds and in vitro models, scanning electron microscope analysis of the dynamic ultrastructures of elastin during ECM modeling and remodeling suggested that elastin globules physically interacted with collagen fibers in extracellular matrix.

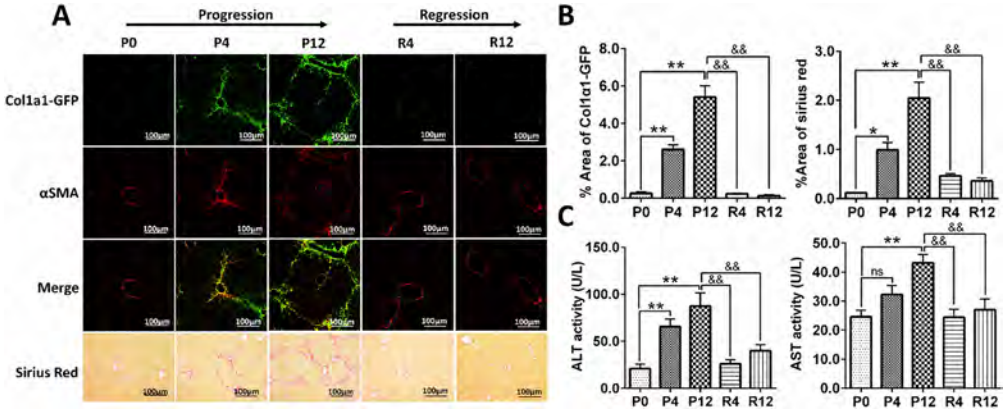

Figure 1: (abstract PS-093) Successful establishment of CCl4-induced liver fibrosis and spontaneously reversal model.

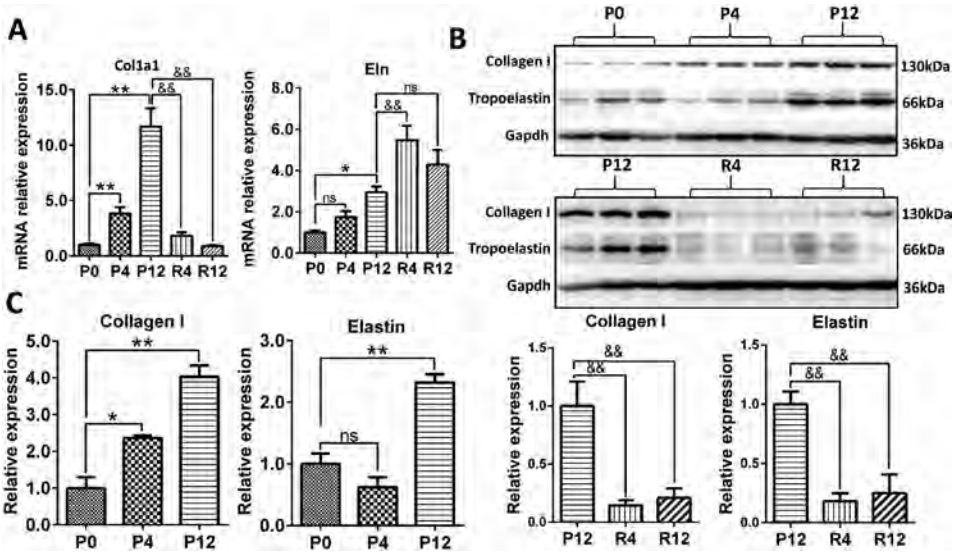

Figure 2: (abstract PS-093) Comparison of the expression pattern of collagen I and tropoelastin.

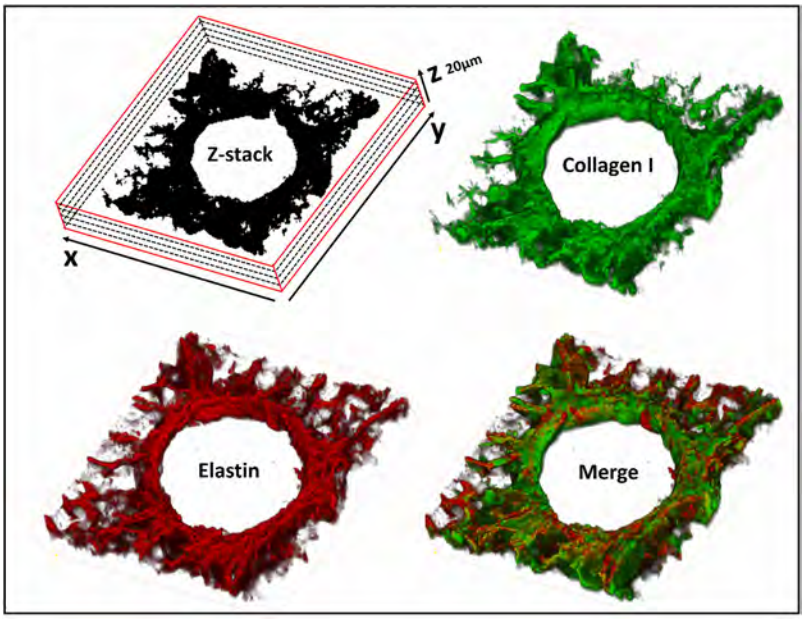

Figure 3: (abstract PS-093) 3D imaging model by laser scanning confocal microscopy.

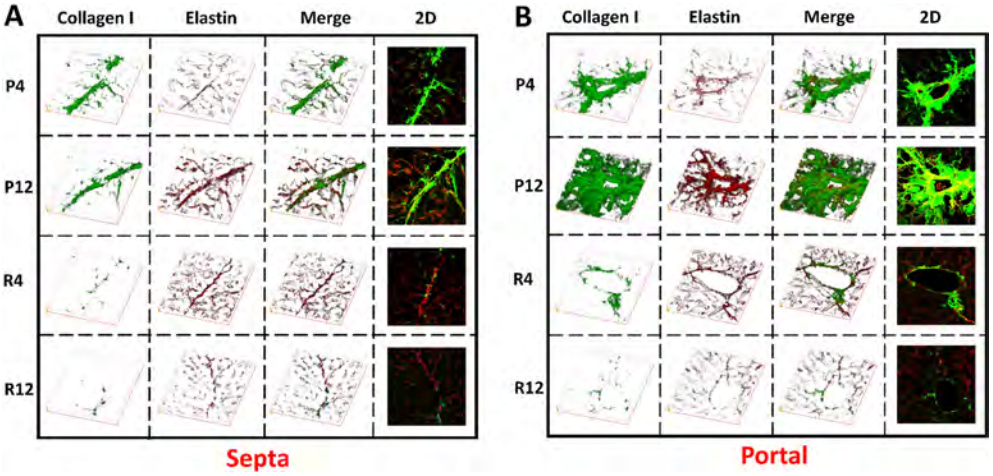

Figure 4: (abstract PS-093) 3D perspective views of extracellular collagen I and elastin colocalization in fibrotic and fibrolytic mouse livers.

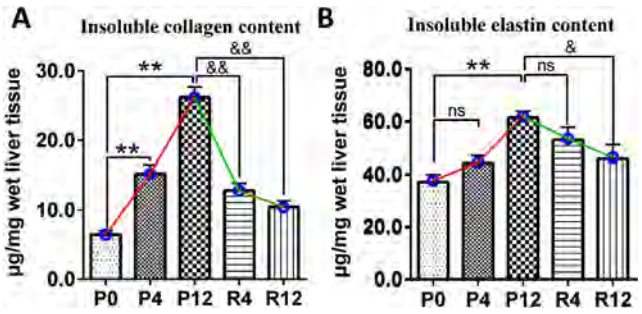

Figure 5: (abstract PS-093) Detection of liver insoluble collagen and elastin contents in bidirectional mouse models.

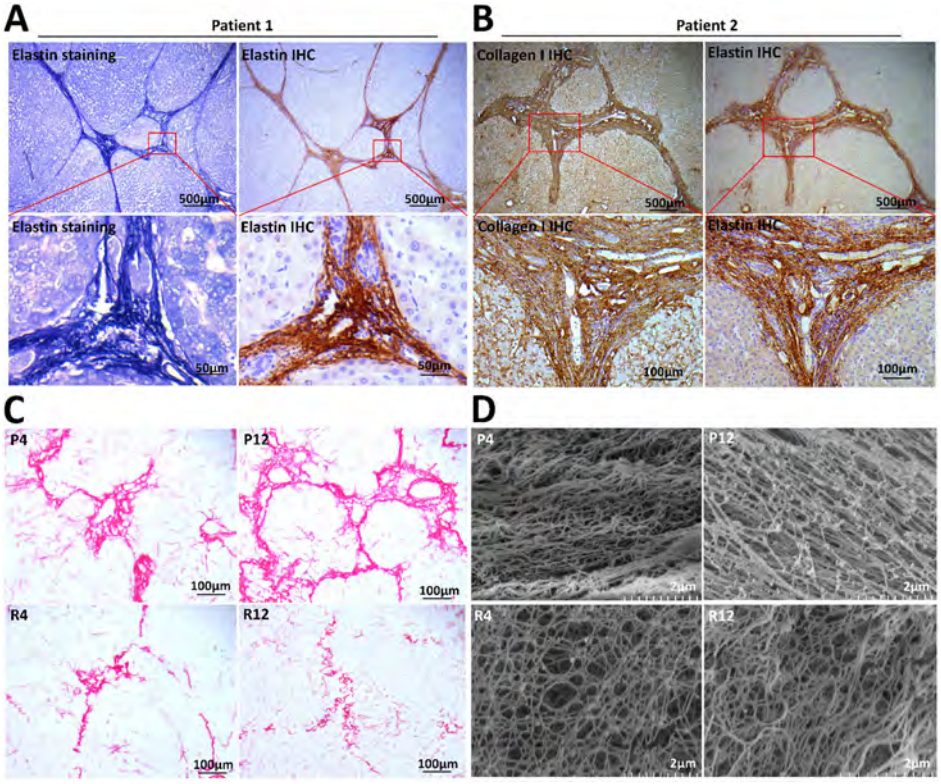

Figure 6: (abstract PS-093) Spatial localization of fibrotic liver collagen and elastin.

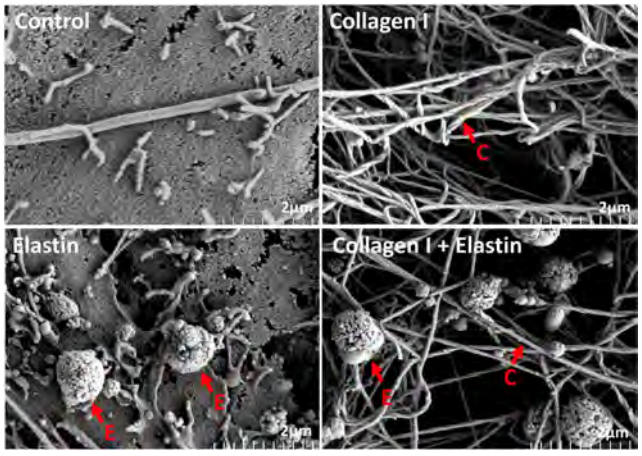

Figure 7: (abstract PS-093) Direct interaction between elastin globules and collagen fibers in ECM.

Conclusion: Our current study established new general hallmarks of elastin levels and forms in progressive and regressive liver fibrosis, and provided a foundation for further experimental investigation of the growing role of elastin in liver fibrosis regression.

PS-094

Selective activation of JAK-STAT1-mediated apoptosis in hepatic stellate cells as a new therapeutic option for liver fibrosis: Role of rilpivirine

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Background and aims: Increasing incidence of chronic liver disease and lack of effective therapeutic options represent a serious health problem worldwide. JAK-STAT1 and 3 signaling pathways have been proposed as possible therapeutic targets since they regulate cell proliferation and death within the liver. In general, JAK-STAT1 activation induces apoptosis, whereas JAK-STAT3 promotes cell proliferation. Rilpivirine (RPV) is a widely used antiretroviral drug whose beneficial effects in the liver have been previously described by our group. We aimed to study the involvement of JAK-STAT1 and JAK-STAT3 signaling pathways in the hepatoprotective effect of RPV, analyzing its actions on hepatic stellate cells (HSC) and hepatocytes.
Method: A nutritional model of non-alcoholic fatty liver disease (NAFLD) and a CCl_4-induced liver fibrosis model (both in C57BL/6 mice) were used; RPV was daily administered at clinical doses. Human cell lines of hepatocytes (Hep3B) and HSC (LX-2), as well as human primary HSC (hHSC) were also treated with RPV. Standard molecular biology and histology techniques were used to assess the progression of liver damage and the activation of STATs. Gene silencing and conditioned medium experiments were carried out to evaluate the implication of STATs and the crosstalk between different cell types in response to RPV.
Results: RPV significantly reduced hepatic inflammation and fibrosis *in vivo*, and produced an increase of STAT3 activation in hepatocytes and of STAT1 in HSC. These effects were accompanied by augmented numbers of proliferating hepatocytes and apoptotic HSC. *In vitro*, RPV did not directly alter the viability or STAT3 activation in hepatocytes, but it did induce a clear pro-apoptotic effect in LX-2 cells, together with a decrease in STAT3 and collagen 1 protein expression, and an increase in STAT1 activation. Interestingly, this selective cytotoxic effect completely disappeared when STAT1 was silenced. In addition, STAT3 was activated in hepatocytes incubated with conditioned medium from apoptotic LX-2 cells. All these results were reproduced in hHSC.
Conclusion: The hepatoprotective effect of RPV is directly mediated by the selective STAT1-dependent induction of apoptosis in HSC. Additionally, RPV activates STAT3 in hepatocytes, increasing its proliferation and favoring liver regeneration. These effects could be of great clinical relevance in the development of new effective therapies for liver diseases with a fibrotic component.

PS-095
MerTK-mediated cytokine secretion mediates a cross-talk between M2c macrophages and hepatic stellate cells to induce fibrosis

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Background and aims: Liver fibrosis is the consequence of chronic liver diseases caused by distinct etiologies, which can ultimately lead to cirrhosis and hepatocellular carcinoma. Among the main events initiating the fibrogenic process is the recruitment of inflammatory cells such as monocytes and macrophages, besides the activation of resident macrophages (Kupffer cells). These cells release several soluble mediators which induce the activation of various cells, including hepatic stellate cells (HSCs).
MerTK (Myeloid-epithelial-reproductive Tyrosine Kinase) is a receptor tyrosine kinase belonging to the TAM (Tyro3, Axl, Mer) subfamily of receptors and it is mainly expressed in M2c macrophages. In this study we evaluated a potential involvement of MerTK in the cross-talk between HSCs and M2c macrophages.
Method: Primary human HSCs and peripheral monocytes-derived macrophages were employed. M2c (CD206 + CD163 + CD209-) cells were differentiated by M-CSF, IL-10 and TGF-β and inhibition of MerTK expression was performed by UNC569, the first small-molecule Mer inhibitor. HSCs were exposed to Conditioned Medium (CM) of Gas-6-stimulated M2c macrophages. HSC Migration of was assessed by modified Boyden chamber, viability was measured by MTT assay, proliferation was evaluated by BrdU incorporation assay and gene expression by Real Time PCR.
Results: MerTK was phosphorylated in macrophages terminally differentiated towards the M2c phenotype, resulting in the activation of STAT3 and AKT, two downstream pathways. Moreover, exposure of M2c macrophages to Gas-6 further increased the phosphorylation of MerTK, that was reverted by pretreatment with UNC569. MerTK activation in M2c macrophages promoted HSC profibrogenic features, by inducing a significant increase in cell migration, viability, proliferation and in expression of profibrogenic genes, such as TIMP1, TGF-β1, IL-8 and VEGF-A. Furthermore, the treatment of HSCs with conditioned medium of Gas-6-stimulated M2c macrophages induced the activation of STAT3 and of two mitogen-activated protein kinases, ERK 1/2 and p38. These effects were specifically related to MerTK activity as indicated by pharmacologic inhibition.
Conclusion: Altogether, these data suggest the potential role of MerTK activation in M2c macrophages on HSC phenotype modulation.

PS-096
Validation study of the impact of hepatic iron concentration on the development of advanced hepatic fibrosis in HFE hemochromatosis

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Background and aims: HFE hemochromatosis (HH) is a common inherited disorder of iron overload in Caucasian populations. Phenotypic expression is variable with a minority of patients developing end organ damage such as liver fibrosis or cirrhosis, which when present reduces survival. Prior studies have shown that the hepatic iron concentration (HIC), and the product of HIC × age are associated with risk of advanced fibrosis. The aim of this study was to validate these predictors of the risk of fibrosis in an independent cohort.

Table 1: (abstract: PS-096).

	Mean HIC (umol/g)	95%CI	Mean HIC × age ([umol/g] × years)	95%CI	
Males	210.2	187.1–233.3	9066	7916–10217	P <
Females	155	126.8–183.1	7210	5719–8683	0.001
Males with advanced fibrosis	328.5	281–376	14443	12253–16634	p <
Males with no advanced fibrosis	173.9	153.4–194.4	7176	6143–8209	0.001
Females with advanced fibrosis	394.2	162.8–625.6	22061	12018–32104	p <
Females with no advanced fibrosis	135.4	114.4–156.3	5983	4988–6979	0.001

Method: We conducted a retrospective analysis of 140 male and 66 female subjects with HH who had undergone liver biopsy for diagnostic purposes. Baseline demographic data, alcohol consumption, biochemical results and liver biopsy histological assessments were available on all subjects. Statistical analyses including receiver-operator-curve (ROC) analyses and analysis of variance were performed using GraphPad Prism software and SPSS.
Results: The mean age at diagnosis was 42 yrs for males and 46 yrs for females. The mean values of HIC and the product of HIC × age in males were significantly higher compared with females (Table 1). In both males and females, these values were higher in the patients with advanced fibrosis (≥ F3) compared with those who did not have advanced fibrosis ($p < 0.001$). ROC curve analysis in males demonstrated that HIC alone had a sensitivity and specificity of 74% and 68% using a cut-off ≥ 200umol/g for diagnosis of advanced fibrosis (AUC = 0.79). In females, HIC alone had both a sensitivity and specificity of 80% using a cut-off > 197umol/g (AUC = 0.93). The ROC curve analysis in males for the product of HIC × age had both a sensitivity and specificity of 70% using a cut-off > 9152[mmol/g] × year for diagnosis of advanced fibrosis (AUC = 0.79). In females, the sensitivity and specificity for the product of HIC × age was 100% and 87% using a cut-off > 10400[mmol/g] × year (AUC = 0.97).
Conclusion: Levels of HIC above certain thresholds are predictive of increased risk of advanced fibrosis in HH. The product of HIC × age improves the prediction of advanced fibrosis predominantly in females, but adds little to predictions in males.

Acute and acute-on-chronic liver failure Translational aspects

PS-097

The association between liver type fatty acid binding protein serum levels and clinical outcomes in patients with non-acetaminophen acute liver failure: A cohort study

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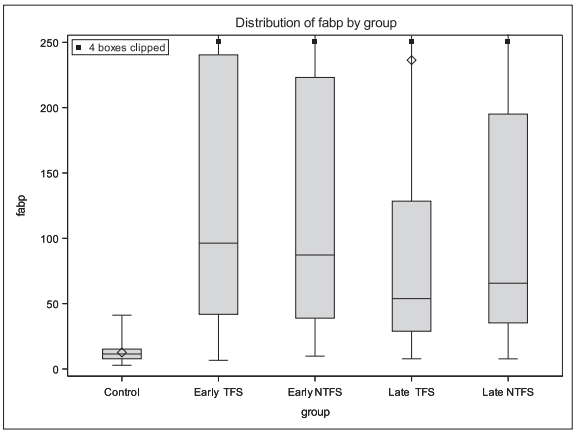
Background and aims: Acute liver failure (ALF) is associated with significant mortality. Failure to identify non-survivors results in preventable deaths, while misclassifying prospective survivors may lead to unnecessary transplants (LT). Liver-type fatty acid binding protein (FABP1) is a 15 kDa protein expressed in hepatocytes. It has previously been demonstrated to improve prognostic discrimination in acetaminophen (APAP)-induced ALF but has not been investigated in other etiologies of ALF. Our primary aim was too determine if serial FABP1 levels (early; admission or late; day 3–5) are associated with 21-day transplant-free survival in non-APAP ALF.
Method: FABP1 was measured in serum samples from 384 ALF patients (n = 88 transplant-free survivors (TFS), n = 296 died/LT~ NTFS) using solid-phase enzyme-linked immunosorbent assay (ELISA) and analysed with US ALFSG registry data.
Results: Of 384 patients, etiologies of ALF included autoimmune hepatitis (AIH, n = 125), drug-induced liver injury (DILI, n = 141) and Hepatitis B (n = 118). Overall, 177 (46%) ALF patients received LT. Transplant-free survivors (n = 88) were less likely to require mechanical ventilation (21 vs. 66%), vasopressors (10% vs. 35%) and or have Grade III/IV hepatic encephalopathy (30% vs. 73%, $p < 0.0001$ for all) compared with patients who died/required LT. FABP1 levels were significantly lower in TFS patients at day 3–5 (TFS 54 vs. NTFS 66 ng/ml; $p = 0.049$; see Figure) but not admission (TFS 96 vs. NTFS 87 ng/ml; $p = 0.67$). After adjusting for significant covariates, increased FABP1 levels at late time points (day 3–5) were significantly associated with worse outcomes (death/LT) in AIH patients (Log FABP1 Odds Ratio (OR) 3.93 (1.50–10.32), P = 0.0055; AUROC 0.89). Increased late FABP1 was associated with worse outcomes in HBV (Log FABP1 OR 1.85 (0.96–3.59), P = 0.068; AUROC 0.82) and DILI (Log FABP1 OR 1.36 (0.97–1.91), P = 0.079; AUROC 0.72), but these were not statistically significant after adjusting for covariates. Similarly, FABP1 on admission was not significant (adjusted $p > 0.15$ for all subgroups).



Conclusion: This is the first report of FABP-1 in non-APAP-ALF. Used in combination with existing prognostic scores, FABP1 may potentially help identify ALF patients with higher recovery potential at later time points after a period of organ support.

PS-098

Prevalence and risk factors of first line anti-tuberculosis drug induced liver injury: Large cohort study involving 4652 patients

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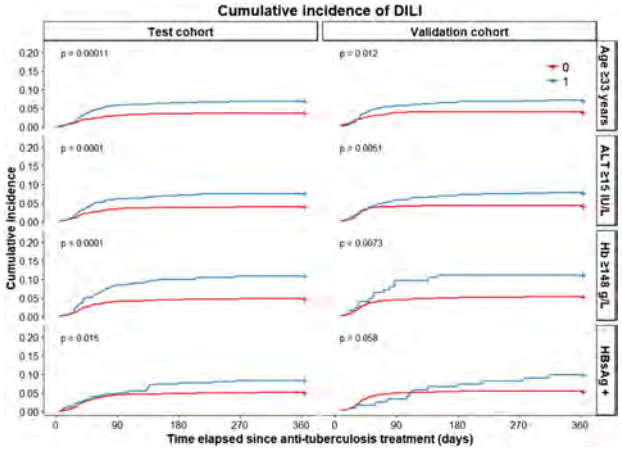
Background and aims: Reported prevalence of anti-tuberculosis drug-induced liver injury vary widely in the literature. The aim of this study was to investigate prevalence and risk factors associated with first-line anti-tuberculosis drug induced liver injury (DILI) in a large cohort of consecutive TB patients receiving first line intensive therapy.
Method: All patients diagnosed with tuberculosis from July 2011 to December 2015 in Ningbo No.2 hospital receiving a combination of isoniazid, rifampicin, ethambutol and pyrazinamide were enrolled. DILI was defined by serum alanine transaminase (ALT) levels of ≥ 5 times the upper limit of normal (ULN), or ≥ 3 times with 2 times ULN bilirubin or 2 times ULN levels of alkaline phosphatase (ALP). Risk factors for DILI were investigated using Cox regression analysis. A validation cohort (from January 2016 to July 2017) in Ningbo No.2 hospital was used to confirm our findings.

Table 1: Independent risk factors associated with DILI by multivariate Cox proportional hazard model in the training cohort

Variables	Regression coefficient	Hazard ratio (HR)	95% confidence interval (CI)	P value
Age	0.013	1.014	1.005–1.023	0.003
ALT	0.014	1.014	1.003–1.024	0.009
Hemoglobin (g/L)	0.012	1.011	1.002–1.020	0.02
HBsAg positive	0.461	1.516	1.004–2.290	0.05

Results: Of 3155 patients identified and followed, 170 (5.4%) developed DILI after a median 42.9 days from start of treatment. 143 (84.1%) was mild DILI; 27 (15.9%) developed jaundice; 9 (5.3%) was severe DILI (acute liver failure) and 2 died. Age, baseline ALT, hemoglobin and HBsAg positivity were independent risk factors for DILI. Age, baseline AST, active drinking and previous anti-TB treatment were independent risk factors for developing jaundice. In the validation cohort of 1497 patients, 87 (5.8%) developed DILI, age ≥ 33 years, baseline ALT (≥ 15 IU/l), hemoglobin (≥ 148 g/l) and HBsAg positivity were strongly predictive of DILI.



Conclusion: First-line anti-tuberculosis DILI and related death are lower than that has been reported in a large cohort of patients in China. Age, baseline ALT, hemoglobin and HBsAg positivity are risk factors for the development of DILI and these factors can be useful in choosing patients for close monitoring during therapy.

PS-099

PP100-01 (calmangafodipir) for overdose of paracetamol (The POP trial): Principal results

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Background and aims: Paracetamol (APAP) overdose is a common cause of acute liver failure. Calmangafodipir (trial drug PP100-01) is a superoxide dismutase mimetic that prevents APAP toxicity in mice. The POP Trial was a phase 1, open label, rising dose, randomised study which explored the safety and tolerability of PP100-01 co-treatment with a 2 bag, 12 h, N-acetylcysteine (NAC) regimen in APAP overdose.
Method: Patients were recruited in the Emergency Department of the Royal Infirmary of Edinburgh from 8th June 2017 to 10th May 2018 with full ethical and regulatory approval. The inclusion criterion was: adults within 24 h of a single or staggered APAP overdose that required NAC treatment. Patients were randomly assigned, with concealed allocation, into one of 3 sequential dosing cohorts of 8 patients (NAC+PP100-01 n = 6; NAC alone n = 2). The intravenous doses of PP100-01 were 2, 5 and 10µmol/kg, administered between NAC bags 1 and 2. Participants, study and clinical teams were not blinded. The primary outcome was the safety and tolerability of PP100-01 combined with NAC. Pre-defined secondary outcomes included alanine transaminase (ALT) activity, full-length keratin-18 (FLK18) and microRNA-122 (miR-122), measured at baseline, 10 and 20 h after starting NAC. FLK18 and miR-122 are hepatotoxicity biomarkers that have regulatory support for exploratory use in trials.
Results: All 24 participants received their allocated dose of PP100-01 and NAC. All were included in the analysis. All participants experienced at least 1 adverse event (AE). The numbers experiencing at least 1 serious adverse event (SAE) were: NAC alone, 2/6; NAC +PP100-01 (2µmol/kg), 4/6; NAC+PP100-01 (5µmol/kg), 2/6; NAC +PP100-01 (10µmol/kg), 3/6. There were no AEs or SAEs probably or definitely related to PP100-01.No treatment group had an increase in ALT (baseline to 20 h). Median FLK18 at 20 h was: NAC alone, 306U/L (range 118-2606); NAC+PP100-01 (2µmol/kg), 212U/L (98-572); NAC +PP100-01 (5µmol/kg), 163U/L (100-287); NAC+PP100-01 (10µmol/kg), 155U/L (103-508). The median fold increase in FLK18 (baseline to 20 h) with NAC alone was 1.71 (1.24-3.57). With NAC+PP100-01 co-treatment the fold increase in FLK18 was smaller (2µmol/kg: 1.41 (0.53-2.80); 5µmol/kg: 1.02 (0.43-1.45); 10µmol/kg; 1.17 (0.74-4.34)). miR-122 was similar to FLK18.
Conclusion: PP100-01 was tolerated in patients treated with NAC for APAP overdose and may reduce liver injury.
Clinicaltrials.gov NCT03177395
Funder: PledPharma AB

PS-100

Bench-to-clinical development of plasminogen as a novel prognostic biomarker for patients with hepatitis B virus related acute-on-chronic liver failure

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Background and aims: HBV related acute-on-chronic liver failure (HBV-ACLF) deteriorates rapidly in short term, which necessitates accurate initial clinical decision-making. Present study aims to develop a novel prognostic biomarker for HBV-ACLF patients.
Method: Three batches of Tandem Mass Tag (TMT) labelled quantitative proteomic were executed with 10 acute exacerbation (AE) and 20 ACLF patients. The biomarker candidates were preliminarily verified by a cross-sectional cohort (n = 144) and further verified by two prospective cohorts (n = 207, and n = 121 respectively).
Results: Plasminogen, a novel prognostic biomarker for HBV-ACLF patients, was identified by TMT quantitative proteomic and preliminarily verified by the cross-sectional cohort. In the further verification with a prospective cohort (n = 207), plasminogen was significantly lower in ACLF non-survivors than survivors ($p < 0.001$). The cumulative survival time in patients with higher plasminogen was significantly longer than whom with lower plasminogen ($p < 0.001$). During the 14-day longitudinal observation, the plasminogen level significantly decreased in the deterioration groups ($p = 0.008$), but significantly increased in the improvement group ($p < 0.001$). Additionally, the plasminogen level gradually increased in survivors ($p < 0.001$) but gradually decreased in non-survivors ($p = 0.019$) during patients' hospitalization. PHAIT, a novel prognostic score based on plasminogen, hepatic encephalopathy, age, international normalized ratio, total bilirubin was significant better than Child-Pugh, MELD, CLIF-C ACLF, COSSH, and HINT (all $p < 0.05$). This score was validated by another multi-centred prospective cohort (n = 121).
Conclusion: Plasminogen is a novel promising biomarker for HBV-ACLF, sequential plasminogen measurements may facilitate prediction of the clinical course of ACLF. PHAIT is a novel prognostic score and superior to Child-Pugh, MELD, CLIF-C ACLF, COSSH, and HINT.

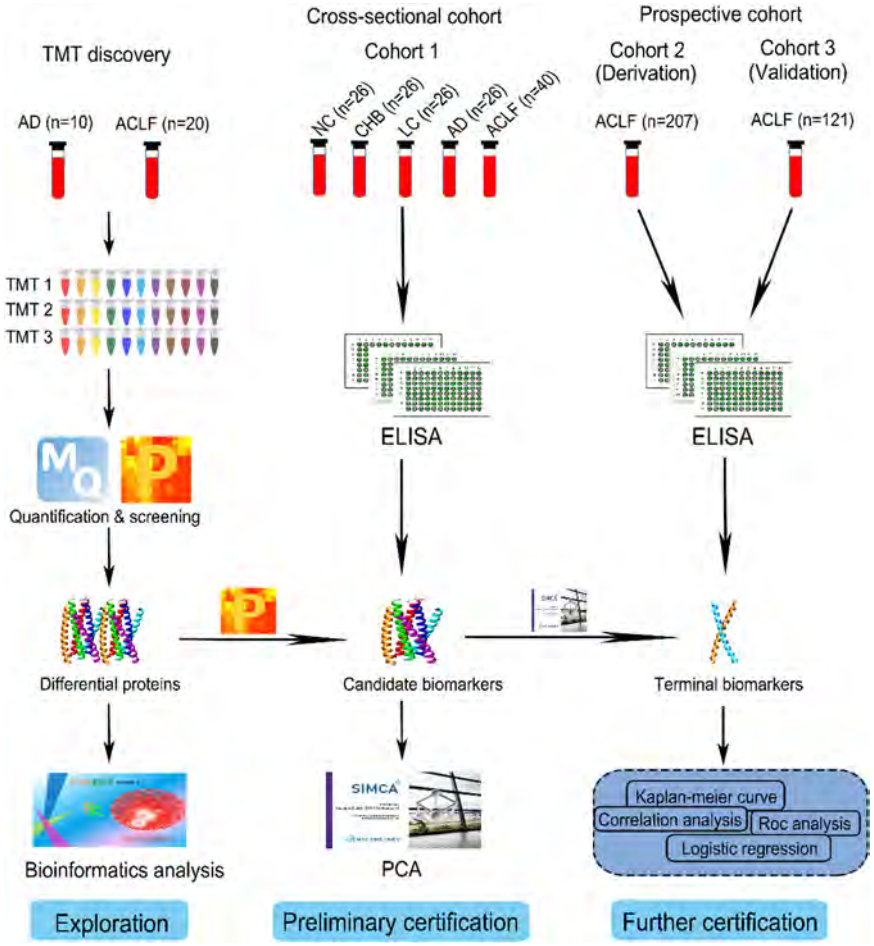

Figure: (abstract PS-100)

PS-101

Inhibition of toll-like receptor 4 using TAK-242 is a novel therapy for prevention and treatment of acute-on-chronic liver failure

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Background and aims: ACLF is characterized by acute deterioration of cirrhosis, systemic inflammation and multi-organ failure. Bacterial translocation, lipopolysaccharide (LPS) and cell death damage associated molecular patterns (DAMPS) are crucial players in the pathogenesis of ACLF. LPS and DAMPS transactivate toll-like receptor 4 (TLR4) resulting in pro-inflammatory cytokine release and systemic inflammation. The aims of this study were to assess whether inhibiting TLR4 signalling using a specific TLR4 antagonist, TAK242, can prevent the occurrence of ACLF and serve as potential treatment.
Method: Two models of ACLF were studied; (1) Bile duct ligated (BDL) SD rats, 4-weeks after ligation were administered LPS (i.p; 0.025 mg/Kg). TAK-242 (Takeda) (10 mg/Kg) or saline were given i.p 3 hours pre LPS injection (prophylactic [PX]) or at 30/60 minutes after ACLF induction (treatment [TX]) (n = 6-8 per group).
(2) C57BL/6 mice were gavaged carbon tetrachloride (CCl_4) over 6 weeks followed by i.p LPS (4 mg/Kg) (n = 4 per group). I.p TAK-242 (10 mg/Kg) was given 60 minutes and 22 hours post LPS (n = 4 per group). End points were: coma free survival at 6 hours after LPS injection (BDL) and at 24 hours (CCl_4), severity of liver and renal injury (biochemistry and TUNEL staining), plasma cytokines (LUMINEX), liver TLR4 protein (immunohistochemistry) and TLR signaling mRNA expression (qPCR).

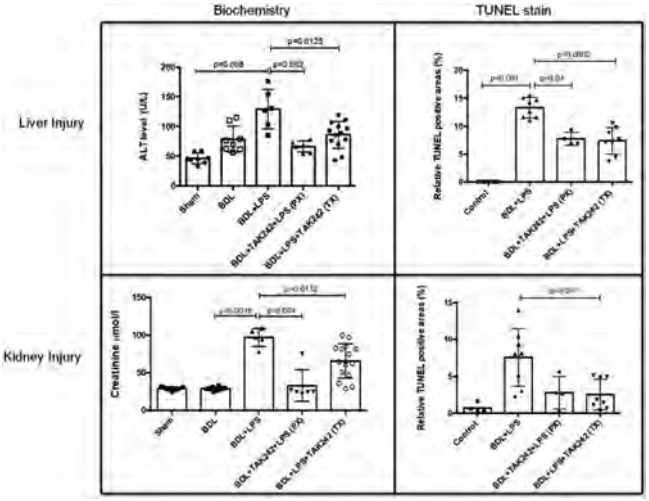

Figure: TAK242 reduces liver and kidney injury

Results: In the BDL model treatment with TAK-242 improved coma free survival from 13% to 100% (PX) and 53% (TX) and reduced the severity of liver and kidney injury (ALT, creatinine and TUNEL) significantly (Figure 1). TAK-242 led also to a reduction in plasma cytokines (pg/ml); TNF alpha 466 (± 137) vs 16 (± 0) (p = 0.001) [PX] vs 200 (± 50) (p = 0.04) [TX], IL-6 1518 (± 486) vs 36 (± 0) (p = 0.001) [PX] vs 3052 (± 1603) (p = 0.01) [TX] and IL −1 beta 1518 (± 486) vs 136 (± 43) (p = 0.005) [PX] vs 234 (± 72) (p = 0.012) [TX]. TAK-242 diminished significantly the severity of liver and kidney injury (TUNEL) in the CCl4 model. Hepatic TLR4 expression was upregulated in both models; TAK-242 modulated hepatic expression of genes in the TLR signaling (including TNFalpha, IL-6) (p < 0.05).
Conclusion: These data show for the first time an important role of TLR4 in the pathogenesis of ACLF. Inhibition of TLR4 signaling was associated with reduction in hepatic, renal and systemic inflammation, amelioration of organ injury in two ACLF rodent models and reduction in mortality providing a strong rationale for clinical evaluation.

PS-102

Circulating native albumin in patients with cirrhosis admitted to hospital for acute decompensation and acute-on-chronic liver failure: Relation to serum albumin levels, albumin function, and patient outcomes

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Background and aims: Serum albumin (SA) of patients with cirrhosis undergoes oxidative and non-oxidative damages, so that the molecules with a fully preserved structure, termed "native albumin" (NA), are substantially reduced. As the SA routinely measured in clinical practice includes both the NA and its altered isoforms, this study aimed to assess the relative changes of NA and SA in patients with cirrhosis and their relationships with albumin function and patient outcomes.
Method: 319 out of 516 patients with cirrhosis, enrolled in a prospective observational study on hospitalized patients for acute decompensation (AD) or acute-on-chronic liver failure (ACLF), were included in this analysis because of the availability of blood samples within 36 hours from admission. 18 outpatients with compensated cirrhosis were also enrolled as reference population. Serum NA concentration was derived from its relative abundance, as assessed by LC-ESI-MS analysis, and normalized on SA concentration. Albumin binding efficiency (BE) and detoxification efficiency (DTE) were determined by electron paramagnetic resonance analysis.
Results: NA concentration progressively declined from outpatients (2.1 mg/dl [1.6-2.3]) to AD (1.1 mg/dl [0.9-1.4]) and ACLF (0.9 mg/dl [0.6-1.2]) (p < 0.001). NA concentration was significantly correlated with SA levels (r_s: 0.649, p < 0.001) and MELD score (r_s: −0.430, p < 0.001). Covariance analysis showed that NA concentration significantly decline from outpatients to hospitalized patients with AD and ACLF independently from SA concentration (p < 0.001). BE and DTE were both significantly correlated with MELD score (r_s: −395, p < 0.001), NA (r_s: 0.516, p < 0.001) and SA (r_s: 0.524, p < 0.001). Multiple linear regression analysis showed that MELD score, NA and SA are independent predictors of dysfunctional BE and DTE. Finally, Cox regression analysis showed that NA, but not SA, was an independent predictor of ACLF (HR: 0.322, 95%CI 0.116-0.896, p = 0.030) and 90-day mortality (HR: 0.465, 95%CI 0.236-0.915, p = 0.027).
Conclusion: Both NA and SA are reduced in advanced cirrhosis. However, these data indicate that the decrease of NA is independent from and proportionally greater than that of the SA assessed by routine method. NA independently predicts albumin dysfunction, the onset of ACLF and short-term mortality. Whether albumin treatment should aim to increase not only SA, but also NA concentration is an attractive topic for future research.

PS-103

BTLA expression contributes to HBV-related acute-on-chronic liver failure morbidity and mortality by inducing CD4+ 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. B and T lymphocyte attenuator (BTLA) maintain T-cell immune tolerance and were increased on liver-infiltrating lymphocytes in HBV-ACLF patients. However, whether BTLA could lead to T cell immune exhaustion in patient with HBV-ACLF remains unknown.
Method: The blood samples were collected from 83 healthy subjects, 148 chronic hepatitis B (CHB) and 86 patients with HBV-ACLF admitted to Huashan hospital and the first hospital of Quanzhou; and liver tissues were collected from Huashan hospital. The expression of BTLA on peripheral blood mononuclear cells (PBMCs) and liver-infiltrating lymphocytes were detected by flow cytometry and immunohistochemistry. The gene expression profiles of $BTLA^+CD4^+$T cells and $BTLA^-CD4^+$T cells, as well as PBMCs treated or not with anti-BTLA were compared by RNA-seq. The plasma cytokines were detected by Luminex and ELISA. Recombinant cytokines or their inhibitors were used to identify specific cytokines that induce the up-regulation of BTLA. BTLA activator (anti-BTLA) or BTLA shRNA was used to determine whether BTLA could promote $CD4^+$T cell immune exhaustion.
Results: The expression of BTLA were significantly increased on Tem subtype, all subgroups of circulation $CD4^+$T cells and on intrahepatic $CD4^+$T cells in HBV-ACLF patients, but not on theirs $CD8^+$T cells. Moreover, $BTLA^+CD4^+$T cells were positively correlated with severity of disease, prognosis and infection complication. Compared to $BTLA^-CD4^+$T cells, $BTLA^+CD4^+$T cells manifest a more mature and more exhaustion phenotype. IL-6 and TNF-alpha could prompt the up-regulation of BTLA on $CD4^+$T cells and blocking IL-6 and TNF-alpha signalling pathways decrease BTLA expression. Cross-linked BTLA can inhibit the activation, proliferat0069on, cytokines production of $CD4^+$T cells, but promote the $CD4^+$T cells apoptosis. Knockdown of BTLA level can promote the activation, proliferation of $CD4^+$T cells. Cross-linked BTLA on one hand activates suppression signalling by phosphorylation of SHP1/2, and on the other hand, provides a pro-survival signal upon activating the PI3K-Akt-GSK-3bata signalling pathway.
Conclusion: Under the double whammy of SIRS and infection, BTLA was induced to deplete $CD4^+$T cells function and to weaken its ability of removing pathogen, and eventually contribute to secondary infection and aggravate HBV-ACLF patients' death. This study is helpful to elucidate the pathogenesis of HBV-ACLF and provide a new drug target.

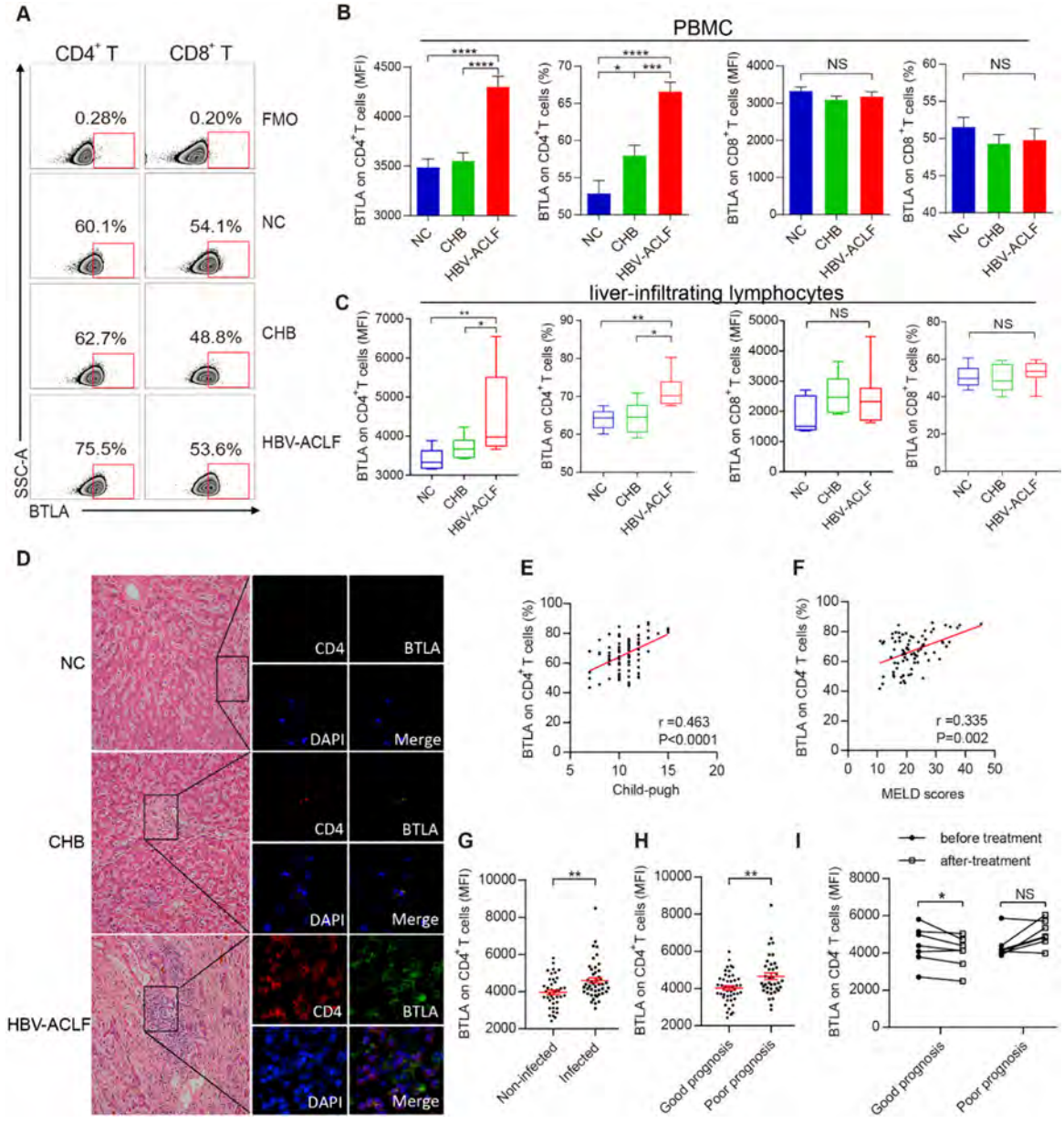

Figure: (abstract: PS-103)

PS-104

Prognosis assessment of acute-on-chronic liver failure in patients with hepatitis B virus-related cirrhosis requires specific criteria

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Background and aims: The most accepted diagnostic criteria of ACLF have been developed by the European CANONIC study in patients with acutely decompensated (AD) alcoholic or hepatitis C virus-related cirrhosis. We aimed to design diagnostic criteria of ACLF specific for patients with hepatitis B virus (HBV)-related cirrhosis.
Method: Prospective, observational study in 1, 402 patients with AD HBV-related cirrhosis admitted at 14 Chinese hospitals using an evidence-based methodology similar to that used for the European CANONIC study.
Results: We developed a new 5-variable organ failure (OF) score. Circulatory failure was excluded due to its low (0.9%) prevalence. Definitions of individual OFs (coagulation [INR ≥ 2], liver [bilirubin ≥ 22.0 mg/dL], kidney [creatinine ≥ 1.5 md/dL], respiratory [respiratory support], brain [overt encephalopathy]) and ACLF, based on associated mortality and number of OFs, respectively, differed from European definitions. The prevalence of ACLF, ACLF-1 (1 OF), ACLF-2 (2 OFs) and ACLF-3 (3-5 OFs) were 40.9%, 25.4%, 11.1%, and 4.4%, respectively. The 28-day transplant-free mortality were, respectively, 22.0%, 11.9%, 32.9% and 66.1%; it was 1.8% in patients without ACLF. The relative risk of 28-day mortality of ACLF-1 was 6.6, compared with no ACLF patients. Using either COSSH criteria (developed in HBV-related cirrhosis but largely based on the CANONIC Criteria) or European CANONIC criteria in our patients resulted in 37.2% and 65.8% false negative and 15.7% and 0.9% false positive diagnoses, respectively. Our criteria were validated in a cohort of 890.
Conclusion: ACLF in patients with AD HBV-related cirrhosis requires specific diagnostic criteria. The criteria developed in the European CANONIC study are inaccurate for ACLF diagnosis in these patients.
Registration number: NCT02457637.

NAFLD – Clinical Therapy

PS-105
Significant regression in fibrosis in paired liver biopsies following a 12-week aerobic exercise intervention in individuals with non-alcoholic fatty liver disease

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Background and aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is a rapidly growing health epidemic. Individuals with NAFLD often present with multiple comorbidities including; obesity, type 2 diabetes, metabolic syndrome and cardiovascular disease. In the absence of approved pharmacological treatments, lifestyle modifications are the first line of treatment. This study examined the benefits of a 12-week, aerobic exercise intervention (EI) on hepatic and extrahepatic outcomes in individuals with NAFLD and the sustainability of the benefits 12 weeks after completion.
Method: Individuals with biopsy proven NAFLD consented to take part in the EI. Pre-exercise assessments included review of liver biopsies by a single pathologist, baseline pre-exercise CAP and liver stiffness scores (Fibroscan, FS), cardiovascular fitness ($\dot{V}O_{2max}$), physical activity levels (PAL), anthropometry, blood profile and frailty measures. These measures were recorded before the EI (T0), immediately after the EI (T1) and three months after T1 (T2). The EI consisted of two supervised and three unsupervised aerobic exercise sessions per week with increasing intensity (45-75% heart rate reserve) and duration (24-45 minutes) for 12-weeks. Control participants completed only three physical assessments. A repeated measures ANOVA and Wilcoxon signed rank test were used to examine for significant differences in parametric and non-parametric measures, respectively.
Results: 25 individuals (16 exercise, 9 controls) completed the EI with 96% mean adherence. At T1, there was a significant regression of fibrosis ($p = 0.025$) in the exercise group which corresponded to a significant reduction in CAP ($p = 0.015$) and stiffness scores ($p = 0.025$) via FS. Additionally, there was a significant increase in $\dot{V}O_{2max}$ ($p = 0.034$), PAL ($p = 0.022$) and the number of individuals achieving WHO PAL guidelines ($p = 0.046$) at T1. There were significant reductions in BMI ($p = 0.01$), fat mass ($p = 0.001$), waist circumference (WC, $p < 0.0001$), HbA1c ($p = 0.047$) and in self-reported ($p = 0.034$) and test based ($p = 0.025$) frailty measures. At T2, CAP score ($p = 0.005$), BMI ($p = 0.04$) and WC ($p = 0.001$) remained significantly improved from T0. The remaining improvements at T1 were not sustained at T2.
Conclusion: This study demonstrates a significant regression in hepatic fibrosis in response to exercise therapy as assessed by paired liver biopsy and FS, with additional improvements in $\dot{V}O_{2max}$, anthropometry and frailty measures. That the benefits were not maintained at T2 indicates a need for strategies to integrate exercise and physical activity into a community-based setting to promote long term adherence to the therapy.

PS-106
An international, randomized, placebo-controlled phase 2 trial demonstrates novel effects of DGAT2 antisense inhibition in reducing steatosis without causing hypertriglyceridemia in T2DM patients

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Background and aims: DGAT2 catalyzes the terminal step in the synthesis of triacylglycerols from de novo synthesized fatty acids and newly formed diglycerides. We previously reported that specific inhibition of DGAT2 caused a marked improvement in hepatic steatosis (Hepatology 2005; 42: 362-371). In this clinical trial we examined the efficacy of a novel antisense inhibitor of DGAT2, IONIS-$DGAT2_{RX}$ versus placebo in T2DM patients with MRI-PDFF ≥ 10% in a double-blind placebo-controlled design.
Method: This international trial included 44 patients with NAFLD and T2DM, HbA1c, 8.1% BMI, 34.3 kg/m^2 and mean baseline MRI-PDFF of 18.8% who were randomized 2 :1 (Active: PBO) to either a once weekly subcutaneous injection of IONIS-$DGAT2_{RX}$ 250 mg or PBO (0.9% saline solution) for 13 weeks. MRI-PDFF was conducted prior to initiation of dosing and 2 weeks after the last dose. Primary end point was absolute reduction in liver fat content by MRI-PDFF.
Results: Treatment with IONIS-$DGAT2_{RX}$ resulted in a significant absolute reduction in liver fat of –5.37% (± 5.4) compared to –0.04% (± 5.8) in patients treated with placebo ($p = 0.003$). The relative percent reduction from baseline was also significantly higher –26.4% in ISIS-$DGAT2_{RX}$ treated patients compared to 1.0% in placebo treated patients ($p = 0.003$). Importantly, 50% (13/26) of the treated patients had at least a 30% relative reduction in liver fat ($p = 0.02$), Table 1; 30% or higher fat reduction has been associated with histologic

improvement in NASH in longer term studies. IONIS-DGAT2$_{RX}$ was well tolerated. There were no treatment related deaths or serious adverse events, no changes in hepatic or renal function and no thrombocytopenia. Liver fat reduction was not accompanied by hypertriglyceridemia or GI side effects and no elevations in serum transaminases, plasma glucose or body weight.

Table 1:

	Randomized Population (N = 44)	
	Placebo (N = 15)	ISIS DGAT2RX (N = 29)
Number of Patients who had Post-Treatment Liver Fat Percentage Assessment	15	26
Percent Reduction in Liver Fat Percentage ≥ 20%	2 (13.3%)	15 (57.7%)
p =		0.0052
Percent Reduction in Liver Fat Percentage ≥ 30%	2 (13.3%)	13 (50.0%)
p =		0.0188
Percent Reduction in Liver Fat Percentage ≥ 40%	1 (6.7%)	8 (30.8%)
p =		0.0804

Conclusion: These data suggest that DGAT2 inhibition may be a novel, safe and effective strategy for treatment of NAFLD and associated disorders. These data support further investigation of this agent's efficacy in biopsy-proven NASH.

PS-107

SGLT2 inhibition does not reduce hepatic steatosis in overweight, insulin resistant patients without type 2 diabetes

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the leading indication for liver transplant and is associated with increased cardiovascular and liver mortality, yet there are no licensed therapies. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are now widely used for their glucose lowering effects in patients with type 2 diabetes (T2D). Pre-clinical models have suggested a beneficial impact on NAFLD, but clinical data are limited and there are currently no data in patients without type 2 diabetes. We aimed to investigate the impact of SGLT2 inhibition on NAFLD in overweight, non-diabetic patients and establish the effect these agents may have on the processes that regulate hepatic steatosis *in vivo*.

Methods: We conducted an open-label, experimental medicine pilot study in insulin resistant overweight/obese individuals (n = 10), using gold-standard non-invasive assessments of NAFLD phenotype including hepatic magnetic resonance spectroscopy, 2-step hyperinsulinaemic euglycaemic clamps and stable isotope tracers to assess lipid and glucose metabolism. Investigations were performed before and after 12-weeks of treatment with the SGLT2 inhibitor, Dapagliflozin.

Results: Despite a body weight reduction of 4.4 kg, hepatic steatosis was unchanged following treatment. Hepatic glucose production rates increased and there was impairment of glucose disposal during the low-dose insulin infusion. Although circulating non-esterified fatty acid levels did not change, the ability of insulin to suppress lipolysis was reduced.

Conclusions: SGLT2 inhibition for 12 weeks does not improve hepatic steatosis in patients without T2D. Additional studies in patients with established T2D or impairments of fasting or post-prandial glucose homeostasis and needed to determine whether SGLT2 inhibition represents a viable therapeutic strategy for NAFLD.

PS-108

NGM313, a novel activator of beta-Klotho/FGFR1c: A single dose significantly reduces steatosis (liver fat by MRI-PDFF), inflammation (ALT, AST) and fibrogenic activity (Pro-C3) in NAFLD subjects

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Background and aims: NGM313 is a once-monthly humanized monoclonal antibody activator of β-klotho/FGFR1c. Insulin sensitizers have demonstrated decreases in hepatic steatosis, inflammation and fibrosis in patients with NASH, but pioglitazone (PIO) has limited use due to heart failure, weight gain, edema and fractures. This study compared the effects of a single dose of NGM313 *vs.* daily PIO on liver fat content (LFC), ALT, AST, Pro-C3, lipids, insulin sensitivity (HOMA-IR) and safety in insulin resistant patients with NAFLD.

Method: Twenty-five subjects were randomized 2:1 to either a single dose of NGM313 240 mg SC (n = 17) or PIO 45 mg PO QD (n = 8) for 36 days. Inclusion criteria included fasting glucose < 125 mg/dL, fasting

Table 1: (abstract: PS-108): Change from Baseline.

	Day 23[§] or 28[#]		Day 36	
	NGM313 240 mg × 1	PIO 45 mg QD	NGM313 240 mg × 1	PIO 45 mg QD
MRI-PDFF (Absolute) [§]	−5.1%***	−1.2%	−6.3%***	−4.0%**
% of pts with ≥ 5% ↓	38%	13%	63%	25%
MRI-PDFF (Relative) [§]	−30%***	−7%	−37%***	−25%**
% of pts with ≥ 30% ↓	50%	13%	63%	25%
Triglycerides (mg/dl) [#]	−72*	−21*	−49*	−38*
LDL (mg/dl) [#]	−15*	−8	−3	5
HDL (mg/dl) [#]	8*	5*	10*	10*
HbA1c (%)[#]	−0.14***	−0.10*	−0.22***	−0.14*
HOMA-IR (%)[#]	−2.6***	−3.1***	–	–
ALT (IU/L) [#]	−5.7***	−9.4***	−6.6**	−10.5***
AST (IU/L) [#]	−3.4***	−2.7**	−3.7*	1.4
Pro-C3 (ng/ml) [#]	−1.29*	1.23	–	–

*p < 0.05, **p < 0.01, ***p < 0.001

insulin > 10 mIU/ml, BMI > 30 kg/m^2 and NAFLD with ≥ 8% LFC by MRI-PDFF. MRI-PDFF was performed at Day 1, Day 23 and Day 36 and read centrally by a radiologist blinded to treatment sequence. Metabolic studies were performed at Day 1 and Day 28. One subject did not complete the Day 28 metabolic study.

Results: (Table 1) Significant reductions in absolute and relative LFC were seen. HOMA-IR and lipids improved with both treatments, consistent with insulin sensitizing activity. NGM313 and PIO improved HbA1c. ALT and AST were decreased significantly by both drugs. Pro-C3 was reduced with a single dose of NGM313 and not with PIO. The safety and tolerability profile was favorable for both drugs, with all AEs being mild and no safety signals observed. Mild increase in appetite was observed in two NGM313 subjects. Body weight increased by 1.6 kg with NGM313 *vs*. 2.4 kg with PIO.

Conclusion: A single dose of NGM313 demonstrated improvements in insulin sensitivity, FPG and lipids coupled with rapid and significant reductions in LFC, ALT, AST and Pro-C3. There were no identified safety or tolerability signals. These data support further evaluation of NGM313 in patients with biopsy-confirmed NASH.

PS-109

Partial inhibition of de novo lipogenesis with the acetyl-CoA carboxylase inhibitor PF-05221304 does not increase circulating triglycerides in humans and is sufficient to lower steatosis in rats

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Background and aims: Increased hepatic de novo lipogenesis (DNL) and reduced fatty acid oxidation are hypothesized to contribute to steatosis and lipotoxicity in non-alcoholic steatohepatitis (NASH). Acetyl-CoA carboxylase (ACC) catalyzes the first step in DNL, and modulates mitochondrial fatty acid oxidation. Inhibition of ACC by MK-4074 was shown to inhibit DNL and reduce steatosis in patients with NAFLD along with unexpected increases in circulating triglyceride (TG) levels (*Cell Metab.* 2017;26:576). That study evaluated a dose of MK-4074 which fully inhibited hepatic DNL. We sought to determine if partial inhibition of hepatic DNL with the liver-targeting ACC inhibitor PF-05221304 could decouple DNL inhibition from circulating TG elevations in rats and humans.

Method: The dose-response for hepatic DNL inhibition, circulating TG levels and steatosis was evaluated following administration of PF-05221304 for 4 weeks in Western-diet-fed rats. The dose response for hepatic DNL inhibition and serum TG levels was also evaluated in healthy adult humans administered oral PF-05221304 or matching-placebo for 14 days.

Results: Administration of PF-05221304 to healthy adult humans inhibited hepatic DNL in a dose-dependent manner, with a maximum average inhibition of 98%. At doses of PF-05221304 sufficient to inhibit DNL by > 90%, fasting and 24 hour serum TG levels were increased relative to baseline. However, increases in serum TG levels were not observed at doses which inhibited hepatic DNL by an average of ≤ 80%. To determine if doses which partially inhibit hepatic DNL are sufficient to reduce steatosis, studies were conducted in Western-diet-fed rats. Oral administration of PF-05221304 at 1, 3, and 10 mg/kg to Western-diet-fed rats inhibited hepatic DNL by 47%, 58% and 73% respectively relative to vehicle ($p < 0.001$). Mean reduction in steatosis of 60% ($p < 0.0001$) at the 2 higher doses were observed despite only partially inhibiting hepatic DNL.

Conclusion: Doses of PF-05221304 which only partially inhibit hepatic DNL (≤ 80% inhibition) did not elevate fasting or 24 hour serum TG levels in adult humans. Partial inhibition of hepatic DNL (58% and 73%) was sufficient to robustly lower steatosis in Western-diet-fed rats. Additional studies are needed to determine if these findings translate to patients with NASH.

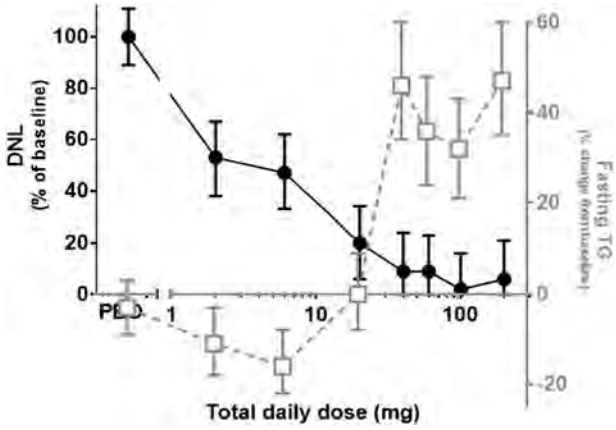

Figure 1: Dose-response relationship for hepatic DNL inhibition (% of baseline; mean ± 90% confidence interval) and % change from baseline (mean ± 80% confidence interval) in fasting serum triglyceride levels in healthy adult humans.

PS-110

Ketohexokinase inhibitor PF-06835919 administered for 6 weeks reduces whole liver fat as measured by magnetic resonance imaging-proton density fat fraction in subjects with non-alcoholic fatty liver disease

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Background and aims: Preclinical studies show that fructose rapidly enriches glycolytic metabolite pools, leading to activation of the Carbohydrate Response Element Binding Protein (ChREBP), a highly lipogenic transcription factor, that can promote steatosis and insulin resistance. Excessive fructose consumption has been shown to cause features of metabolic syndrome and NAFLD. KHK catalyzes phosphorylation of fructose to mediate its entry into the glycolytic pool. PF is a potent, reversible inhibitor of human KHK, and is expected to decrease hepatic de novo lipogenesis and steatosis, thereby ameliorating the pathogenesis of NAFLD. This clinical study was designed to test the hypothesis that KHK inhibition would lead to reduction in WLF.

Method: 53 subjects with NAFLD (> 6% WLF by MRI-PDFF) were randomized and 48 subjects completed the trial. Subjects were stratified by presence or absence of diabetes and baseline WLF. Participants received placebo (17), PF 75 mg (17) or PF 300 mg (14) once daily for 6 weeks.

	Week 6 Percent Change from Baseline [LS Mean (90%CI)]		
	Placebo	75 mg/day	300 mg/day
WLF PDFF	−7.78 (−17.72, 2.17)	3.67 (−6.32, 13.66)	−26.50 (−38.15, −14.86)*
Hs−CRP	8.33 (−9.82, 30.12)	−16.42 (−30.39, 0.36)	−31.01 (−44.00, −15.01)
Uric Acid #	6.52 (1.01, 12.03)	4.44 (−4.15, 13.04)	−11.53 (−16.48, −6.57)
Adiponectin	−14.25 (−25.12, −1.79)	18.29 (3.10, 35.73)	38.59 (18.63, 61.92)
HOMA-IR	0.13 (−0.43, 0.69)	−0.61 (−1.34, 0.12)	−0.53 (−1.16, 0.10)
IL−6	8.48 (−11.51, 32.98)	−0.72 (−19.43, 22.32)	−7.14 (−26.51, 17.34)

*$p < 0.0395$; #median (90% CI)

Results: Incidence of treatment emergent adverse events was low and similar across treatment groups. No SAEs were reported. Pharmacodynamic observations are summarized below.

Conclusion: PF administered for 6 weeks is well-tolerated with an acceptable safety profile in adults with NAFLD. PF 300 mg showed a statistically greater reduction from baseline compared to placebo in WLF. Dose-dependent percent changes from baseline were observed for hs-CRP (reductions), and adiponectin (increases) in PF treated groups. A trend for a dose-dependent decrease in insulin resistance (by HOMA-IR) was observed. Small numerical decreases in ALT, AST and GGT change from baseline were observed in the PF 300 mg group relative to placebo (not shown). No notable differences were found for changes from baseline in IL-6. These results suggest that additional studies are warranted to assess the potential of PF for the treatment of NAFLD/NASH.

PS-111

Six month interim results of MSDC-0602 K in a large phase 2b NASH study demonstrate significant improvement in liver enzymes and glycemic control (NCT02784444)

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Background and aims: MSDC-0602 K, a 2nd generation thiazolidinedione is designed to selectively modulate the mitochondrial pyruvate carrier relative to PPAR-γ, thus reducing PPAR-γ-induced adverse effects while mitigating deleterious effects of nutrient excess in NASH. The drug is being evaluated in the EMMINENCE Study, a 12-month, placebo-controlled trial in biopsy-confirmed NASH.
Method: 402 patients were enrolled from 57 US sites. Entry criteria included NAFLD Activity Score of ≥ 4 that included ballooning and inflammation ≥ 1, and fibrosis score F1-F3. Stratification required ≥ 50% F2/F3 and ≥ 50% type 2 diabetes. Randomization was 1:1:1:1 to daily oral doses of MSDC-0602 K (62.5, 125, and 250 mg) or placebo. An interim analysis of non-biopsy safety and efficacy was conducted in the first 328 patients completing 6 months of therapy.
Results: the 4 cohorts were well balanced with 58.8% female, median age 57 (range 20-82), 51.8% diabetic, mean NAS of 5.3 (SD 1.02), 39.9% F1, and 60.1% F2/F3. Baseline alanine transaminase was 56.4 U/L and placebo corrected change at 6 mos was 10.1%, 27.0% and 20.1% (p = 0.24, < 0.001, and = 0.004) for 62.5, 125, and 250 mg doses, respectively). Aspartate transaminase (baseline 43.8 U/L) decreased at 6 mos with placebo corrected reductions of 9.1, 21.3, and 11.4% (p = 0.36, = 0.012, and 0.2 for 62.5, 125, and 250 mg, respectively). Statistically significant reductions in bilirubin, alkaline phosphatase, and gamma glutamyl transferase were also seen at 6 months at the 125 mg dose. Markers of fibrosis APRI, CK-18, ELF, FIB-4, and FibroTest showed improvement with several reaching statistical significance at the 125 mg dose. In the diabetes cohort, baseline HbA1c (6.83-7.09%), decreased by 0.03, 0.49, 0.62, and 0.55% at 6 months for placebo, 62.5, 125, and 250 mg groups, respectively (p = 0.022, p = 0.001, and p = 0.006, respectively compared to placebo). Overall adverse event rates and rates of peripheral edema were similar across all 4 cohorts. As expected with an insulin sensitizing agent, there was a modest placebo-corrected dose-dependent increase in weight of up to 2% (significant for 125 and 250 mg doses).
Conclusion: The interim results from 328 of 402 NASH patients in the Phase 2b EMMINENCE study demonstrate significant positive effects on liver enzymes and glycemic control, suggesting that MSDC-0602 K may result in improvement of NASH and fibrosis on liver biopsy while also improving glycemic control in type 2 diabetes.

PS-112

Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycemic and lipid profiles in type 2 diabetes

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Background and aims: High fat/sugar diet leads to duodenal hyperplasia in rodent models. In the foregut of subjects with type 2 diabetes (T2D), abnormal entero-endocrine cell population and co-expression of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) has been described.
The present study was designed to investigate the effects of endoscopic Duodenal Mucosal Resurfacing (DMR) involving circumferential hydrothermal ablation of post-papillary duodenal mucosa on liver fat and key metabolic end points in T2D.
Method: Revita-2 (NCT02879383) is a multi-center, randomized, double-blind, sham controlled trial involving T2D subjects. In an open-label training cohort, liver fat content was estimated using local MRI facilities and proton density fat fraction (PDFF) acquisition protocols, before and 12 weeks following DMR.
Results: Among 24 subjects (28-75 years; 17/7 male/female; BMI 24-40 kg/m^2) with T2DM on oral antiglycemic agents (HbA1c: 7.5-10.0%), 17 (85%) had > 5% liver fat at baseline. Following DMR, mean (±SEM) weight fell (89.7 ± 1.9 vs 86.6 ± 2.0 kg, p < 0.001). Significant improvements were also observed in alanine transaminase (ALT) levels: 35.75 ± 4.08 vs 25.35 ± 1.67 U/L, p < 0.001; HbA1c 8.4 ± 0.2% vs 7.4 ± 0.2%, p = 0.001; fasting-C-peptide 3.22 ± 0.29 vs 2.66 ± 0.16 ng/ml, p = 0.01; HOMA-IR 5.96 ± 0.73 vs 4.14 ± 0.61, p = 0.01; ferritin 90.8 ± 16.6 vs 69.4 ± 15.5 ng/ml, p < 0.001 and TG/HDL ratio 5.44 ± 1.15 vs 3.92 ± 0.92U/L, p = 0.02.
Among the 17 subjects with > 5% liver fat at baseline, there was a marked reduction in absolute liver fat from 19 ± 2.0% to 12 ± 2.0%, (p < 0.001) and relative (−35.8 ± 7.8%, p < 0.001) liver fat at 12 weeks. No serious adverse events or unanticipated adverse device effects were observed.
Conclusion: Substantial reduction in liver fat and hepatic transaminase indicates therapeutic potential of DMR in non-alcoholic fatty liver disease. In addition, procedure improves insulin sensitivity, glycemic control and lipid profile in T2D.
Baseline (Left) and 12 week (Right) post treatment PDFF images from a single subject. Reduction in signal in the liver reflects a reduction in the PDFF following treatment.

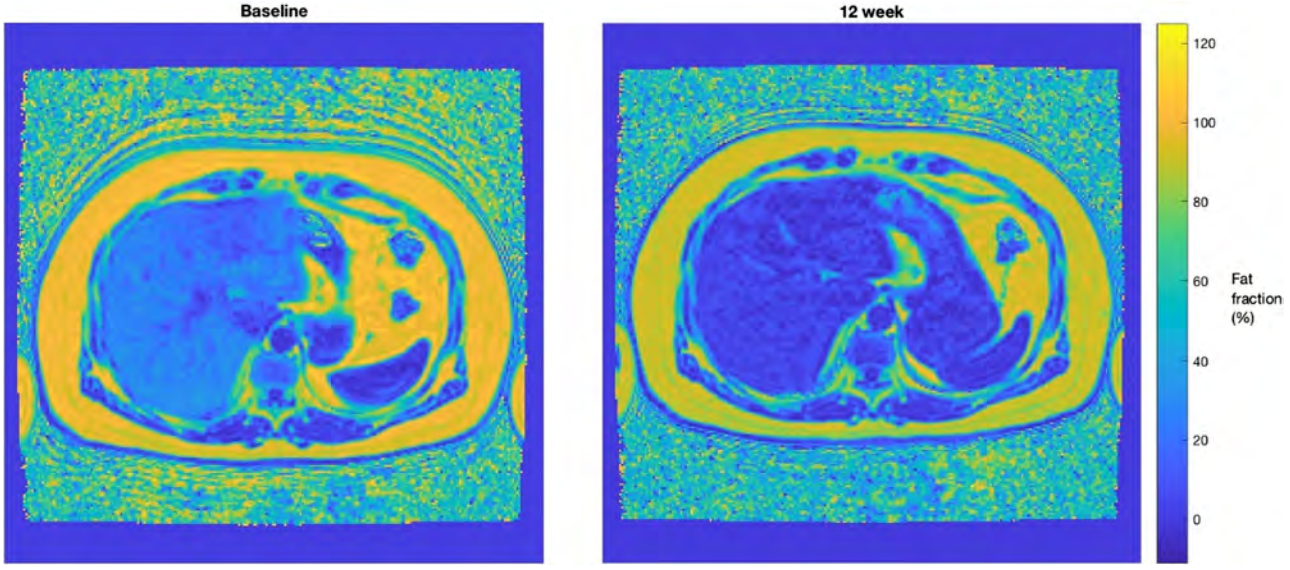

Figure: (abstract: PS-112) Liver MR Imaging (from a single subject) following DMR Procedure

Liver cancer – From Prognosis to locoregional treatments

PS-113

Analysis of the HSD17B13: TA allelic variant as a putative protective factor towards hepatocellular carcinoma in patients with and without chronic hepatitis C

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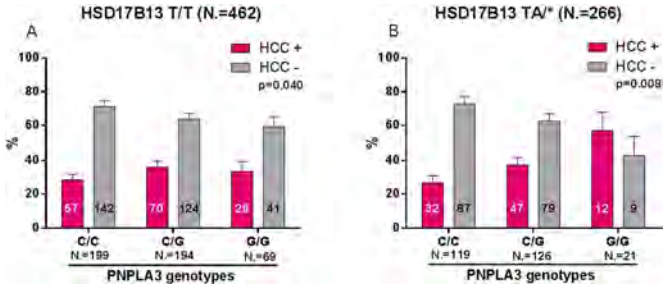
Background and aims: The PNPLA3 single nucleotide polymorphism rs738409 (C > G) is a major genetic factor for steatosis, fibrosis progression and hepatocellular carcinoma (HCC). In fact, carriers of the G allele with chronic liver disease are more likely to progress to cirrhosis and HCC, especially when affected by alcoholic or non-alcoholic fatty liver disease (NAFLD). However, these same patients have been shown to be relatively protected against developing cirrhosis by carriage of the HSD17B13:TA variant (rs72613567) (Abul-Husn NS et al. N Engl J Med. 2018;378:1096-106). Since cirrhosis is by far the strongest risk factor for HCC, it is conceivable that such protection might extend to HCC. We aimed to verify this hypothesis.
Method: The study population included N. = 728 patients, among whom N. = 246 had a diagnosis of HCC (Group 1; 135 with hepatitis C virus infection, HCV, 55%); N. = 180 HCV infected patients (Group 2) and 302 NAFLD (Group 3) patients had chronic liver disease with and without advanced fibrosis/cirrhosis, not complicated by HCC. Restriction fragment length polymorphism analysis was performed to determine the allelic variants frequency of PNPLA3 and HSD17B13.
Results: The PNPLA3:G frequencies were 0.40, 0.31 and 0.32 for Group 1, Group 2 and Group 3, respectively ($p = 0.004$). The HSD17B13:TA frequencies were 0.21, 0.28 and 0.16 for Group 1, Group 2 and Group 3, respectively ($p < 0.001$). The figure shows the distribution of PNPLA3 genotype frequencies, according to the presence or absence of HCC and HSD17B13 status. By considering only the subgroup of patients negative for HCV (N. = 416/728, 57%), similar results were observed: based on PNPLA3 genotype, patients with HCC were 22/118 (19%) vs. 10/55 (18%) (C/C), 35/131 (27%) vs. 21/55 (38%) (C/G), and 20/45 (44%) vs. 6/12 (50%) (G/G), among HSD17B13 wild-type ($p = 0.002$) vs. HSD17B13 variant carriers ($p = 0.006$), respectively.



Conclusion: The HSD17B13:TA allelic variant does not appear to decrease appreciably the risk of developing HCC conferred by carriage of the PNPLA3:G allele, neither among HCV positive nor among HCV-negative patients.

PS-114

Stabilization of UBQLN1 by circRNA_104797 mediates acquired sorafenib resistance in hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is the fifth most common tumor around the world. Sorafenib is a famous drug to treat HCC. However, sorafenib resistance commonly occurs within one year. The mechanism behind sorafenib resistance is still unveiled. Recently, some studies found that sorafenib may target mitochondrial electron transport chain complexes, resulting in ROS increase and cell death. How HCC cell develops to escape mitochondria damage is an interesting question.
Method: Sorafenib resistant (SR) cell lines were established by sustained treatment of small dose of sorafenib. Effects of sorafenib

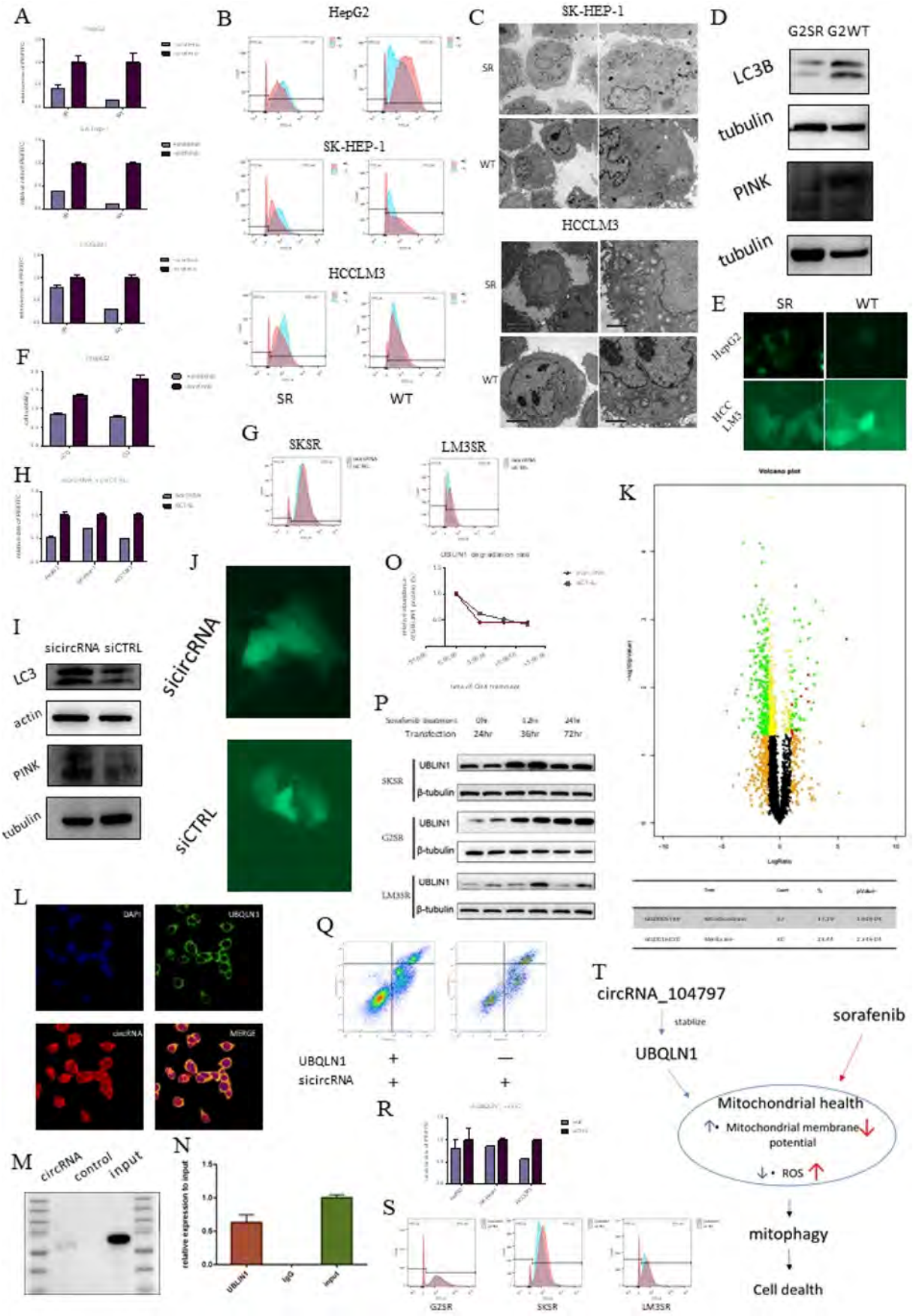

Figure: (abstract: PS-114)

was analyzed in cell viability by Cell Counting Kit-8 assay, ROS and mitochondrial transmembrane potential (MTP) by flow cytometry, cell morphology by transmission electron microscope (TEM). A CircRNA Array analysis and mass spectrum were carried out to detect possible interacting molecules.
Results: We established three pairs of SR cell lines. In accordance with variant cell growth inhibition rates, we found that ROS increased dramatically after sorafenib treatment in wild type HCC cell lines but decreased in SR cell lines. Correspondingly, MTP change was minor in SR cell lines. TEM also confirmed that mitochondria morphology was more integrated in SR cell lines after sorafenib treatment. We also observed that sorafenib induced less mitophagy in SR cell lines and autophagic inhibitor could partly reduce sorafenib induced cell death. Then an Arraystar Human CircRNA Array analysis showed that a circRNA named circRNA_104797 was upregulated in HepG2 SR cell line compared with WT cell line. Depletion of circRNA_104797 by siRNA transfection could increase cellular ROS, reduce MTP, and induce mitophagy. GO analysis of a mass spectrometric result revealed that mitochondria protein was enriched after siRNA transfection. Besides, comparing with the mass spectrometric result of circRNA_104797 pulldown protein, we found that UBQLN1 decreased after siRNA transfection. In consideration of UBQLN1's function, we supposed circRNA_104797 could mediate sorafenib resistance through binding to UBQLN1, which was confirmed by RNA immunoprecipitation, RNA pulldown and confocal fluorescence microscopy results. UBQLN1 degradation was accelerated after circRNA_104797 depletion. UBQLN1 depletion by siRNA transfection could also increase ROS and reduce MTP in SR cell lines. Furthermore, overexpression UBQLN1 could partly protect SR cell line from circRNA depletion induced cell death.
Conclusion: Our results uncovered a type of sorafenib resistance mechanism. In SR cell lines, circRNA_104797 increased to stabilize UBQLN1, while UBQLN1 can regulate MTP and ROS. Therefore, circRNA_104797 and UBQLN1 may offer to be potential targets to overcome sorafenib resistance.

PS-115
Evaluation of LI-RADS v2018 by magnetic resonance in US-detected nodules < 2 cm in cirrhotics
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Background and aims: Liver Imaging Reporting and Data System (LI-RADS) was developed to classify the observations in six categories from LR-1 (definitively benign) to LR-5 (definitively HCC), stratifying the probabilities of HCC diagnosis to assist the clinicians in the decision making. Since its implementation in 2011, LI-RADS has been updated according the results of several studies evaluating its diagnostic performance. In the last version in 2018, aimed to be implemented by AASLD, nodules between 10-19 mm displaying non-rim arterial phase hyperenhancement and non-peripheral washout were assigned as LR-5. The objective of this study was to evaluate the diagnostic accuracy of LI-RADS v2018 when using magnetic resonance imaging (MRI) for hepatic nodules ≤ 20 mm detected during ultrasound (US) surveillance in cirrhotic patients, with particular interest in those observations categorized as LI-RADS 3.
Method: Between November 2003 and February 2017 we included 262 cirrhotic patients with a newly US detected solitary ≤ 20 mm hepatic nodule who were prospectively examined by MRI and fine-needle biopsy (reference-standard) and followed-up with MRI every 6 months if initial definitive diagnosis was not achieved. A LI-RADS (LR) category according to v2018 was retrospectively assigned. The diagnostic accuracy for each LR category was described and the main MRI findings associated with HCC diagnosis were analyzed.
Results: Final diagnoses were: 197 HCC (75.2%), 5 intrahepatic cholangiocarcinoma (1.9%), 2 metastasis (0.8%) and 58 benign lesions (22.1%). 0/15 (0%) LR-1, 6/26 (23.1%) LR-2, 51/74 (68.9%) LR-3, 11/12 (91.7%) LR-4, 126/127 (99.2%) LR-5, and 3/8 (37.5%) OM were HCC. LR-5 category displayed a sensitivity of 64.5% (CI95%: 57.4–71.1), very similar to the sensitivity achieved by EASL criteria (62.9% [CI95%: 55.8–69.7]). Considering also LR-4 as diagnostic for HCC, the sensitivity slightly increased to 69.5% (CI95%:62.6–75.9) with minor impact on specificity (96.2%; CI95%:89.3–99.6). Regarding LR-3 observations, 51 out 74 were HCC, 2 were non-HCC malignancies, and twenty-one out 22 LR-3 nodules > 15 mm (95.5%) were finally categorized as HCC.
Conclusion: In cirrhotic patients with nodules ≤ 20 mm detected on US, distinction between LR-4 and LR-5 according to v2018 has minor impact. A relevant proportion of LR-2 and LR-3 lesions corresponded to an HCC and thus, an active diagnostic work-up including biopsy is recommended.

PS-116
Use of cyclooxygenase inhibitor and the risk of hepatocellular carcinoma in patients with chronic hepatitis B: A nested case-control study using a nationwide population-based data
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Background and aims: Recent studies showed the cyclooxygenase (COX) inhibitors are associated with reduced cancer development in various malignancies. This study aimed to investigate the relationship between the use of COX inhibitors and the risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB) using a nationwide population-based data.
Method: The nested case-control study was conducted using the National Health Insurance Service-National Sample Cohort (NHIS-NSC) from January 2003 to December 2013 in Korea. The use of COX inhibitors was measured using the cumulative defined daily dose (cDDD) which is the sum of prescribed dosages of drug in the exposed duration. All kinds of COX inhibitors that are available in Korea were included. We compared the use of COX inhibitors between HCC cases and the matched controls by categorizing 5 groups according to cDDD (< 28, 28–90, 91–180, 181–360, and > 360) adjusting the use of antiviral agents.
Results: A total of 4, 980 patients with CHB were analyzed as 996 HCC cases and 3, 984 matched controls. Matching variables were age at index date, sex, alcoholic liver disease, diabetes mellitus, liver cirrhosis, and follow-up duration. The number of COX inhibitor users (≥ 28 cDDD) was 358 patients (36%) and 1, 814 patients (45%) in HCC group and control group, respectively. The use of COX inhibitors was significantly associated with the decreased risk of HCC development compared to non-users (adjusted odds ratio [OR] 0.62, 95% confidence interval [CI] 0.52-0.73, $p < 0.001$). There was a dose-dependent inverse relationship between the use of COX inhibitors and the risk of HCC. The adjusted ORs were 0.75 (95% CI: 0.63–0.90), 0.41 (95% CI: 0.31–0.56), 0.38 (95% CI: 0.25–0.57), and 0.49 (95% CI: 0.31–0.79) in 28–90, 91–180, 181–360, and > 360 cDDD, respectively ($p < 0.001$).
Conclusion: The use of COX inhibitors was associated with reduced risk of HCC in CHB. COX-inhibitor may have a chemopreventive role in HCC development in patients with chronic liver disease.

PS-117

Multiplatform analysis of HCC tumors uncovered molecularly distinct subtypes

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Background and aims: While recent genomic profiling studies of HCC identified many genetic alterations, these studies are limited by a loose correlation between genetic alterations and their functional products such as proteins and metabolites. Reverse-phase protein array (RPPA) allows us to simultaneously measure multiple protein features, such as expression, modification of proteins, and interaction with ligands from the samples. To overcome current limitation of genomic studies, we generated genomic and proteomic data together from HCC tumors and performed integrated analysis of both data sets.
Methods: We generated gene expression profile data and proteomic data from 300 HCC tumors by using expression microarrays and RPPA platform. Supervised and unsupervised approaches were applied to analyze proteomic data and multiple genomic data such as somatic mutations, mRNA expression, miRNA expression, and copy number alterations were integrated with proteomic data to uncover most correlated genomic alterations with functional products. Clinical significance of identified key protein features were validated in multiple independent cohorts of HCC patients.
Results: Integrative analysis of genomic and proteomic data uncovered three subtypes of HCC with substantial difference in clinical outcomes. Interestingly, one of HCC subtype has strong mesenchymal characteristics as reflected in low expression of epithelial marker like CDH1 and CTNNB1. When assessed clinical relevance, the overall survival rate of patients in mesenchymal subtype was significantly worse than those in other two subtypes ($p = 0.001$). For validation of clinical association, we collected additional genomic and proteomic data from independent cohort of patient. Poor clinical outcomes of mesenchymal subtype is validated in multiple independent cohorts (in total of > 500 patients). Gene network analysis with integrated genomic and proteomic data further revealed association of subtypes with currently available treatments of HCC such as sorafenib and immunotherapy. In addition, multiple in-depth analysis of integrated data identified potential therapeutic target candidates for each subtype. Functional validation with cell lines demonstrated that some of candidates are essential for growth and survival of HCC cells.
Conclusion: HCC can be classified into distinct subtypes by analyzing integrated genomic and proteomic data. These analyses has identified potential therapeutic targets as well as biomarkers associated with therapeutic targets. Our study demonstrated merit of integrated analysis of proteomic data with genomic data to uncover potential driver genes of HCC development.

PS-118

HCV eradication before or following curative management of HCC in patients with cirrhosis allows optimal tumour management and improves survival: The French multicentre prospective ANRS CO12 CirVir cohort experience

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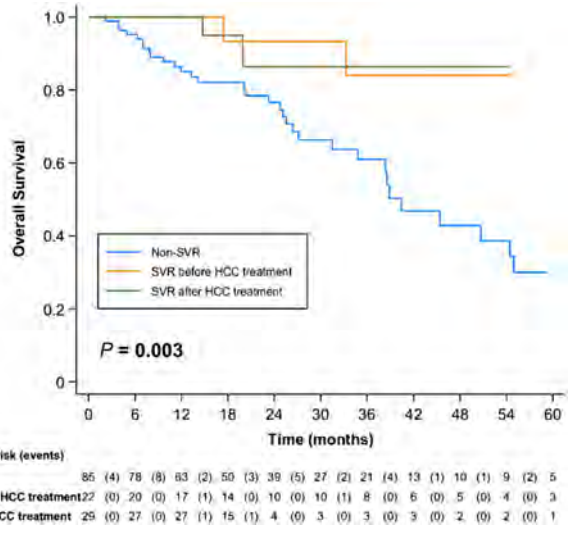
Background and aims: This study aimed to accurately assess the impact of HCV eradication on HCC recurrence, liver decompensation and overall survival in patients with compensated cirrhosis included in the French prospective multicentre ANRS CO12 CirVir cohort who were curatively treated for an incidental HCC.

Method: Data were collected from 1323 patients with compensated Child-Pugh A biopsy-proven HCV-cirrhosis recruited between 2006 and 2012 in 35 centres and prospectively followed-up, including achievement of a sustained virological response (SVR) and the occurrence of HCC during the study period. The primary outcomes for the present analysis were HCC recurrence, liver decompensation and overall survival measured from the time of HCC treatment.
Results: During a median follow-up (FU) of 67.5 months, 218 patients developed an HCC among whom 128 received a curative procedure [percutaneous ablation (n = 90) or a liver resection (n = 31]). At HCC diagnosis, patients were mostly males (58.7%), mean age was 63.9 yrs, Child-Pugh A status in 52.5%. HCC was mostly uninodular (75.7%), less than 20 mm in 66.7%, BCLC 0/A in 93.7%. 71 patients (52.9%) never achieved SVR, while 47 patients (38.8%) achieved SVR either before (n = 27; 20.7%) or after HCC occurrence (n = 23; 18.1%) [missing data = 7]. After a median FU of 27.1 months following HCC treatment, 55 (43.0%) experienced an HCC recurrence. SVR was not significantly associated with lower HCC recurrence risk, whether considering final SVR status (HR = 0.94 [0.51; 1.73], $P = 0.84$) or according to its time to achievement (before or after HCC emergence, global $P = 0.29$). During the same time-frame, 48 (37.6%) patients died (liver failure: 42%, HCC recurrence: 33%, extra-hepatic cause 25%). In univariate (Figure) and multivariate analysis, SVR was associated with an improved overall survival (HR = 0.19 [0.07; 0.48], $P = 0.001$), whether obtained before (HR = 0.24 [0.07; 0.79], $P = 0.018$) or after (HR = 0.14 [0.03; 0.58], $P = 0.007$) HCC diagnosis. Survival benefit was explained by a lower incidence of liver decompensation in case of SVR (HR = 0.26 [0.09; 0.75], $P = 0.013$) and higher rates of HCC recurrence re-treatment using sequential percutaneous ablation (83% vs 50% in non-SVR, $P = 0.01$). DAAs intake (n = 50, including 23 after HCC treatment) was not associated with a higher risk of HCC recurrence (HR = 0.56 [0.24; 1.30], $P = 0.18$) but with an improved overall survival (HR = 0.19 [0.04; 0.79], $P = 0.022$).



Conclusion: SVR achievement before or after HCC occurrence is not associated with a modified risk of tumour recurrence following implementation of a curative procedure in patients with cirrhosis. However, HCV eradication allows optimal HCC management by preventing potential deterioration of liver function and increasing rates of HCC recurrence re-treatment, leading to improvement of overall survival.

PS-119

Time-varying mHAP III is the most accurate score in predicting survival in patients wit hepatocellular carcinoma undergoing trans-arterial chemoembolization

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Background and aims: TACE is the most widely used treatment for patients with unresectable HCC. The prognosis of these patients is extremely variable due to differences in liver function, tumor burden and performance status and a median survival of around 40 months has been reported for well-selected candidates. Many prognostic scores have been proposed to identify those more likely to benefit from TACE. Moreover, albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (pALBI) grades have not been specifically evaluated in patients undergoing TACE.
An important confounding effect is that TACE is often repeated several times, but there are no studies evaluating prognostic scores as time-varying variables, i.e. recalculating the scores before each TACE procedure. The aim of this study was to compare different prognostic and staging systems in patients undergoing TACE in a large series of patients with HCC.
Methods: We retrospectively evaluated the accuracy of HAP, mHAP II, mHAP III, ALBI, and pALBI in estimating overall survival (OS) in patients with HCC undergoing TACE. We considered 1610 TACE performed in 1058 patients recorded in the Ita.Li.Ca database from 2008 trough 2016. Exclusion criteria were CPT score > 7 and/or refractory ascites. We carried out a time-dependent analysis to consider prognostic scores as time-varying variables, and calculated OS from the time of TACE to the time of the subsequent treatment. The total follow-up time for each patient was therefore split into several observations accounting for each TACE procedure, where appropriate. Values of the likelihood ratio test (LRT) and Akaike information criterion (AIC) were used to compare different systems.
Results: The median OS was 36 months. Comparing LRT and AIC values of the prognostic scores, mHAP III achieved the highest $\chi 2$ and lowest AIC values (39, 6 and 4638 respectively, $p < 0.0001$), indicating an improved predictive performance compared with HAP ($\chi 2$ 16.3, AIC 4665, $p = 0.0010$), mHAP ($\chi 2$ 19.9 AIC 4662, $p = 0.0003$), ALBI ($\chi 2$ 4.34, AIC 4673, $p = 0.0373$), whereas pALBI was not significantly different ($\chi 2$ 1.47, AIC 4676, $p = 0.2254$). The prognostic performance of mHAPIII was also superior to that of other HCC prognostic systems (BCLC, ITALICA, CLIP, MESH, MESIAH, JIS and HKLC). In time-varying multivariable Cox proportional hazards model, mHAP III maintained an independent effect on OS (hazard ratio 1.34, 95% CI 1.15-1.56). Other significant variables in the multivariable model resulted age, alcoholic etiology, radiologic response to TACE, and performing ablation or surgery after TACE.
Conclusion: In a large series of patients with HCC undergoing TACE, mHAP III was identified as the most accurate scoring system for predicting OS, using an innovative, time-dependent analysis of patients comprised in the Ita.Li.Ca. database.

PS-120

Post progression survival in patients with intermediate-stage hepatocellular carcinoma after receiving transarterial chemoembolization

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Background and aims: Correlations between progression patterns and post progression survival (PPS) in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib have been reported. These results are helpful for not only understanding the prognosis of patients who do not respond to sorafenib but also designing clinical trials. So far, several novel compounds have been developed in patients with HCC and some may be used in combination with transarterial chemoembolization (TACE) or compared with TACE. The aim of this study was to evaluate correlations between progression patterns and PPS in patients with intermediate-stage HCC after receiving TACE.
Method: From 2003 to 2016, 441 patients with intermediate-stage HCC, who received TACE as initial treatment at our institution, were enrolled in this study. Radiological responses were evaluated according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).
Results: The patient cohort was 77% male, a median age 71 years (range, 30-92 years). Concomitant conditions included hepatitis C virus (67%), alcohol abuse (16%), and hepatitis B virus (11%). The median overall survival was 27.2 months [95% confidence interval (CI); 23.6-30.8], and the median time to progression was 5.7 months (95% CI; 5.2–6.3). We observed progression in 378 patients (86%), intrahepatic growth in 187 patients (42%), new intrahepatic lesions (NIH) in 251 patients (57%) (with ≤ 3 lesions noted in 161 patients, 4–7 lesions in 34 patients, and with ≥ 8 lesions in 56 patients), and new extrahepatic lesions (NEH) in 47 patients (11%). In patients with ≥ 8 NIH lesions, PPS was significantly worse than that in 4–7 NIH lesions and ≤ 3 NIH lesions [≥ 8 lesions, 11.7 months (95% CI, 8.7–14.7 months), 4–7 lesions, 17.7 months (95% CI, 11.0–24.4), ≤ 3 lesions, 26.1 months (95% CI, 20.3–31.9), $p = 0.003$]. Similarly, PPS in patients with NEH lesions was significantly lesser than without NEH lesions [with NEH lesions, 7.7 months (95% CI, 4.9–10.5); without NEH lesions, 22.2 months (95% CI, 20.1–27.9 months); $p < 0.001$]. Following multivariate Cox hazard analysis, ≥ 8 NIH lesions and NEH lesions were independent prognostic factors of PPS in patients with intermediate-stage HCC after receiving TACE.
Conclusion: We indicated the strong positive correlations between progression pattern (≥ 8 NIH lesions and NEH) and PPS in patients with intermediate-stage HCC after receiving TACE as initial treatment. These results may be beneficial for designing future clinical trials related to TACE in patients with intermediate-state HCC.

Autoimmune and cholestasis II

PS-121

Obeticholic acid limits cholestasis induced cognitive decline by maintaining blood-brain barrier integrity and preserving neuronal health

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Background and aims: Primary Billiary Cholangitis (PBC) is an autoimmune disease of the bile duct and liver. Biliary epithelial cell injury causes cholestasis, fibrosis and systemic circulation of toxic bile acids. PBC patients often experience significant central fatigue with associated cognitive symptoms Including impaired short-term

memory and problems with concentration. Likened by patients to "brain fog" this under-recognised complex of central nervous system symptoms is a major contributor to poor quality of life and is currently untreatable.
The study aims to utilise the Bile Duct Ligation (BDL) model to investigate mechanisms of cholestasis-induced memory impairment in mice and explore the potential therapeutic benefit of the second-generation, FDA approved anti-cholestatic agent Obeticholic Acid (OCA).
Method: C57BL/6 mice underwent either BDL or sham surgery. A sub-group of BDL were treated prophylactically or therapeutically with OCA. Activity and cognitive function was evaluated by standardised behavioural tests. Fluorescence imaging and Transmission Electron Microscopy assessed hippocampal cell populations, cellular senescence and the Blood-Brain Barrier (BBB). Flow cytometry was used to measure FXR expression in the BBB. Gamma oscillation in the hippocampal slices were evoked by the cholinergic agonist Carbachol (10 uM).
Results: Spatial memory was significantly decreased in BDL mice. OCA therapy rescued the decline, returning cognitive function to near sham level. Astrocytes are key mediators of BBB integrity and neuronal function. Astrocyte coverage of the BBB was significantly reduced in BDL mice compared to sham controls, indicating damage to the BBB, likely mediated by bile acids. Neuronal senescence was increased in the hippocampus of BDL mice. OCA therapy restored astrocyte coverage of the BBB and reduced neuronal senescence, suggesting improved neuronal health. Hippocampal slices from BDL mice had impaired gamma frequency oscillations as only 20% had stable oscillations compared to 69% of slices from sham animals, indicative of deficit.
The Farnesoid X Receptor is expressed on microvascular endothelial cells of the BBB but decreased with BDL, suggesting that OCA, an FXR agonist could directly regulate BBB health during cholestasis.
Conclusion: OCA limits and reverses cholestasis induced cognitive decline through preserving BBB integrity and neuronal health. We propose that OCA may be an effective intervention for cognitive deficit in PBC patients if used early in the disease process.

PS-122
Seladelpar for the treatment of primary biliary cholangitis: Experience with 26 cirrhotic patients

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Background and aims: Primary biliary cholangitis (PBC) is a progressive liver disease that leads to cirrhosis. Seladelpar, a selective PPAR delta agonist, demonstrates potent anti-cholestatic and anti-inflammatory activity in PBC. We evaluated the efficacy and safety of seladelpar in PBC patients with clinically diagnosed compensated cirrhosis.
Method: PBC patients were enrolled into an ongoing, randomized, open-label Phase 2 study (EudraCT 2016-002996-91) and evaluated for the effect of oral seladelpar 5 and 10 mg. Eligible patients had inadequate response (alkaline phosphatase [AP] ≥ 1.67 × upper limit of normal (ULN)) or an intolerance to ursodiol and a total bilirubin ≤ 2 mg/dL. Cirrhosis was diagnosed using liver biopsy, imaging tests, or liver elastography. After 12 weeks, patients on 5 mg were dose-escalated to 10 mg when the AP threshold was not met (5/10 mg group). The primary outcome was AP % change from baseline. Secondary outcome measures included AP responder analyses (< 1.67xULN), changes in hepatic function, inflammatory markers, and pruritus using the visual analogue scale (VAS). Safety analysis included adverse events and laboratory parameters.
Results: 119 patients were exposed to at least one dose of seladelpar, 26 of whom had compensated cirrhosis (5/10 mg n = 15 and 10 mg n = 11). Analysis was performed with a July 2018 data cut. At this time 15 of 26 cirrhotic patients received seladelpar for 3 months, 13 of 26 for 6 months, and 8 of 26 for 1 year.
In cirrhotic patients, the baseline values for the 5/10 and 10 mg groups were: mean AP-277 U/L and 309 U/L, median total bilirubin-0.73 mg/dL and 0.80 mg/dL, median ALT-32 U/L and 50 U/L, and median VAS 20 and 37, respectively. Mean decreases in AP (%) were −25% and −39% at 3 months, −24% and −41% at 6 months, and −36% and −43% at 1 year in the 5/10 mg and 10 mg groups, respectively. After 1 year, all patients in 5/10 mg and 3 of 5 patients in 10 mg had Ap < 1.67 × ULN; the median decreases in ALT (%) were −31% and −50%, and the median absolute changes in pruritus VAS were 0 and −25 in 5/10 mg and 10 mg groups, respectively.
Three patients with cirrhosis experienced an SAE, all unrelated to seladelpar. Total bilirubin, platelets, albumin, and INR remained stable. No liver decompensation events were observed.
Conclusion: In PBC patients with compensated cirrhosis, seladelpar was shown to be safe and well tolerated and demonstrated anti-cholestatic and anti-inflammatory effects.

PS-123
Biliary tree stem/progenitor cells mediate the regeneration in biliary lining after injury

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Background and aims: In extrahepatic biliary tree (EHBT) are found the Peribiliary Glands (PBGs), these contain cells showing phenotype and biological properties of primitive endoderm called Biliary Tree Stem/Progenitor Cells (BTSCs). There are very few knowledges on the repair of injured biliary epithelium. Our aim was to evaluate *in vitro* and *in vivo* the BTSCs role in the regeneration of the biliary epithelium after injury and the pathways involved.
Method: Krt19CreTdTomato^{LSL} C57BL6/J mice were treated with 3, 5-Diethoxycarbonyl-1, 4-dihydrocollidine (DDC) for 14 days to induce biliary injury. Mice were sacrificed after 14 days of DDC treatment

(DDC) or after 14 of recovery after injury (DDC+14-R). EHBTs were collected and analyzed by immunohistochemistry (IHC) and immunoluorescence (IF). Human BTSCs (hBTSCs) were isolated from organ donors and were cultured in NOTCH, WNT or BMP pathway-inducing media using sDLL-1, RSPO-1 and Hegdehog respectively. Cell extracts were examined by RT-qPCR to analyze stem and mature cell gene expression. NICD, actived β-Catenin and Phospho-SMAD1/5 were quantify by Western Blot (WB).
Results: Significant increase of PBG area in DDC and DDC+14-R mice compared to and controls ($p < 0.05$; $N = 5$) was detected by IHC. Further, PBGs are still activated 2 weeks after DDC injury as demonstrated by $Ki67^+$ PBG cells. SOX9 was observed highly expressed in PBGs and biliary epithelium of DDC mice. Stimulation of NOTCH signaling by Jagged1 was observed in PBGs and biliary lining of DDC+14-R. Co-localization of Wnt3A/β Catenin were found in PBGs and biliary epithelium of DDC but not in control mice. Finally, very few $\alpha SMA^+/TdTom^+$ cells were detected in PBGs of DDC+14-R mice. *In vitro*, NOTCH pathway activation in hBTSC cultures induced a significative increase ($p < 0.01$; $N = 6$) of mature cholangiocyte genes expression while the endodermal stem cell genes expression was decreased. Instead, WNT pathway induction in hBTSC cultures enhanced SOX17 ($p < 0.05$; $N = 6$) and PCNA ($p < 0.01$; $N = 6$) gene expression. BMP pathway stimulation in hBTSCs cultures induced an increase ($p < 0.05$; $N = 6$) of gene expression of TWIST1, an EMT marker, compared to hBTSCs cultured in basal condition. *In vitro* pathway activations were confirmed by WB.
Conclusion: In conclusion, our results demonstrated that BTSCs have a key role in modulating the regeneration of biliary epithelium after injury and that NOTCH, WNT and BMP pathways are involved in the BTSCs activation.

PS-124
Cholestasis-induced kidney injury is ameliorated in Nlrp3 deficient mice
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Background and aims: Induction of cell death after cholestasis-induced hepatotoxicity caused by toxic bile acids starts in, but is not limited to, the liver. Another organ affected by cholestasis is the kidney, undergoing sever tubular epithelial injury and consecutive kidney injury and fibrosis. Since Nlrp3 inflammasome deficiency played a protective role after bile duct ligation (BDL) and BDL-associated kidney injury reflects bile cast nephropathy we studied the role of Nlrp3 inflammasome.
Method: We performed BDL on WT and NLRP3 knockout (Nlrp3-/-), as well as treatment with inflammasome inhibitor MCC950 5 days after BDL. Mice were sacrificed after acute (48 hours) or chronic (28 days) BDL injury. Livers and kidney were taken and inflammation, fibrosis and cell death were evaluated.
Results: Acute BDL induced liver injury was exacerbated in Nlrp3-/- mice compared to WT mice, as evidenced by liver injury markers such as serum transaminases as well as inflammatory markers. Remarkably, we found an increase in Cyp7a1 and Fxr in Nlrp3-/- mice compared to WT mice before BDL, in line with the increase of bile infarcts in Nlrp3-/- animals. After chronic BDL induced liver injury however, Nlrp3-/- as well as MCC950 treated mice showed a remarkable improvement with a decrease in liver injury as well as inflammation and fibrosis. Kidney injury however showed an improvement both after acute as well as chronic BDL-induced injury in Nlrp3-/- mice compared to WT mice. After acute kidney injury Nlrp3-/- kidneys showed reduced granulocyte infiltration and tubular damage marker KIM-1 and NGAL. Long-term impact of BDL on kidney injury showed full blown bile cast nephropathy with significantly less bile casts in Nlrp3-/- kidneys compared to WT mice, as well as a decrease in associated tubular damage as shown by KIM-1 and NGAL. Furthermore, F4/80 positive cells were significantly decreased in Nlrp3-/- kidneys. Finally, we also found reduced kidney fibrosis assessed by collagen accumulation in Nlrp3-/- kidneys compared to WT controls after BDL.
Conclusion: These results show that Nlrp3 is involved in triggering cholestasis induced kidney damage in the acute, but also in the chronic phase independent of ongoing liver injury and can be treated by an oral Nlrp3 inhibitor. A possible explanation of the difference between kidney and liver could be the increase of bile infarcts due to the higher bile acid synthesis in livers of Nlrp3-/- mice.

PS-125
Gut pathobionts underlie intestinal barrier dysfunction and liver Th17 immune response in primary sclerosing cholangitis
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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease and its frequent complication with ulcerative colitis (UC) highlights the pathogenic role of epithelial barrier dysfunction, yet its underlying mechanism remains unknown. Here, we aimed to identify the specific microbiota that contribute to the pathogenesis of PSC using humanized gnotobiotic mice.
Method: Patients with PSC/UC (n = 18), UC (n = 16), and healthy controls (HCs) were included in this study. 16s rRNA metagenome analysis and quantitative PCR to detect specific microbiota in human fecal samples were performed. We generated gnotobiotic mice by inoculating fecal samples from patients with PSC/UC (PSCUC mice), UC (UC mice), or Healthy controls (HCs) (HC mice). Gut barrier function, immunophenotyping, and the susceptibility to experimental hepatobiliary injury by DDC feeding in these mice were examined. To examine the interaction between bacteria and the intestinal epithelium, a monolayered human intestinal organoids were cultured with the specific bacteria in vitro.
Results: Metagenomic analyses revealed lower diversity and a distinct taxonomic trend with a higher prevalence of *Enterobacteriaceae* in the microbiota of PSC/UC patients. In contrast to germ-free (GF) or HC gnotobiotic mice, PSCUC mice demonstrated higher Th17 response in the liver and strong susceptibility to the experimental hepatobiliary inflammation, which was reversed by administration with RORgt inverse agonist. We identified three bacterial species, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus gallinarum from* the mesenteric lymph nodes of PSCUC mice by bacterial culture. Importantly, these pathobionts were specifically enriched in the feces of PSC/UC patients both in our cohort (*K. pneumoniae*, 17/18, *P. mirabilis*, 5/18, *E. gallinarum*, 12/18) and European validation cohort. The mono-inoculation of GF mice with PSC mice-derived *K. pneumoniae* caused mucosal invasion detected by fluorescence in situ hybridization with an EUB338 probe and the induction of $RORgt^+IL17^+CD4^+$ T cells in the liver, but was insufficient to induce a robust Th17 response, as was observed in mice inoculated with the three mixed strains. Using a mono-layered organoid culture system, we demonstrated that PSC/UC-derived *K. pneumoniae* unlike commercially available *K. pneumoniae* strains, directly induced epithelial-pore formation with apoptosis-related genes upregulation. Finally, we confirmed that antibiotic treatment targeting *K. pneumoniae* and *E. gallinarum* was effective in the reduction of pathogenic Th17 response in the liver in PSCUC mice.
Conclusion: Our results identified specific pathobionts in PSC/UC patients that collude in intestinal barrier disruption and subsequent Th17-priming in the liver, and provide insights into the implication of the gut microbiota in the pathogenesis of PSC.

PS-126

Fungi participate in the dysbiosis of gut microbiota in patients with primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, most often associated with inflammatory bowel disease (IBD). PSC patients have been shown to display a bacterial gut dysbiosis but fungal microbiota has never been studied in these patients. The aim of this study was to explore the fungal gut microbiota in PSC patients.
Method: We analyzed the fecal microbiota of: patients with PSC and concomitant IBD (n = 27), patients with PSC and no IBD (n = 22), patients with IBD and no PSC (n = 33) and healthy subjects (n = 30). Bacterial and fungal composition of the fecal microbiota was determined using 16S and ITS2 sequencing, respectively. To assess if microbiota features were associated with disease phenotype, a multivariate association test with linear models (MaAsLin) was used to override the effect of potential confounding factors such as age, gender, smoking or treatment.
Results: We found that patients with PSC exhibited bacterial dysbiosis characterized by a decreased biodiversity, an altered composition and a decreased correlation network density. These microbiota alterations were associated with PSC, independently of IBD status. For the first time, we showed that patients with PSC displayed a fungal gut dysbiosis, characterized by a relative increase in biodiversity and an altered composition. Notably, we observed an increased proportion of *Exophiala* and a decreased proportion of *Saccharomyces cerevisiae*. Compared to patients with IBD and healthy subjects, the gut microbiota of patients with PSC exhibited a strong disruption in bacteria-fungi correlation network suggesting an alteration in the inter kingdom crosstalk.
Conclusion: This study demonstrates that PSC is characterized by an altered fungal gut microbiota associated with an impaired fungi-bacteria correlation network. The implications of these findings remain to be defined but pave the way for the development of microbiota-based biomarkers and treatments in PSC.

PS-127

Analysis of liver infiltrating lymphocytes in primary sclerosing cholangitis by surface antigen and single cell RNAseq

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Background and aims: Little is known about the nature of liver infiltrating lymphocytes (LIL) in primary sclerosing cholangitis (PSC). Fine needle aspiration (FNA) of the liver has emerged as a safe, minimally invasive technique to obtain LILs for immunophenotyping. We evaluated whether FNA could be used to differentiate LIL in patients with PSC and other liver conditions (LC). and tested the hypothesis that cells expressing chemokine receptor CCR9 were preferentially enriched in PSC.
Methods: We obtained PBMC and LIL using FNA from patients with PSC and LC and performed multicolour flow cytometry, and single cell RNA sequencing on CD45+ sorted cells using the 10X Chromium Single Cell 3′ platform. We also performed immunohistochemistry (IHC) for CCR9 and CD3 on formalin fixed paraffin embedded (FFPE) liver biopsy sections from patients with PSC with and without inflammatory bowel disease (IBD), and LC.
Results: A median 12, 333 LIL were obtained from 31 patients (16 PSC, 15 LC). These displayed specific hepatic characteristics compared to PBMC including greater proportions of CD56+ NK cells, and more CD8+, CD69+, and CD161+ T-cells (respectively: 47.4%±3.4 vs. 37.3%±3.5; 37.5%±1.9 vs. 30.3%±2.3; 15.7%±2.0 vs. 4.5%±1.2; mean ±SEM, p < 0.0001 for all). There was no difference of CCR9 expression among CD4+ CD45RA- LIL between PSC/IBD and LC (4.6%±0.7 vs. 4.0% ±0.5, mean±SEM, p = ns).
IHC was performed on 36 FFPE liver biopsies (10 PSC/IBD, 12 PSC/no IBD, 14 LC). There was a trend towards higher mean CCR9 counts in

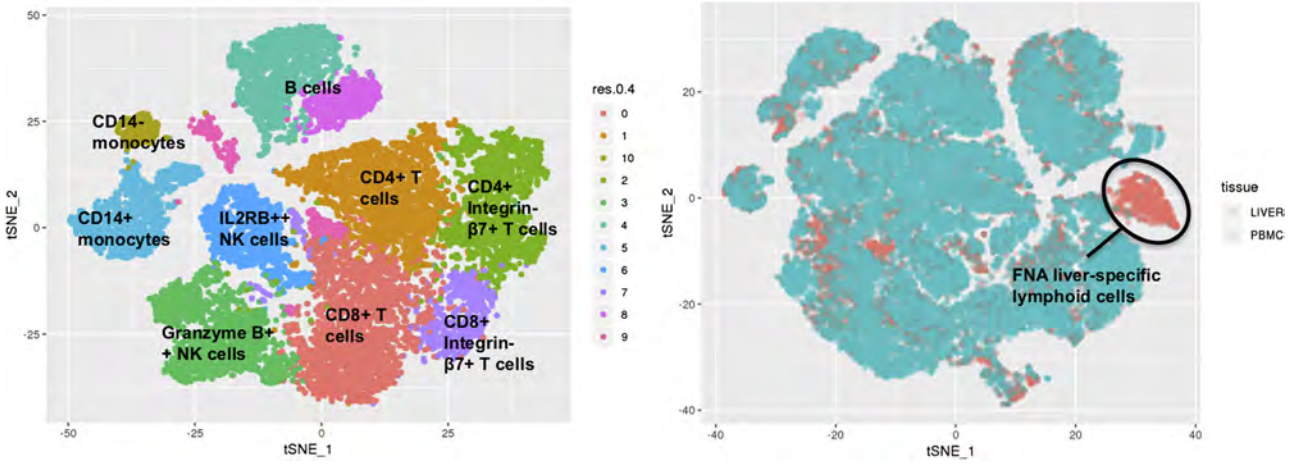

Figure 1: (abstract: PS-127): tSNE plots characterising and comparing FNA liver immune cells relative to PBMCs. Left panel: FNA liver immune cell types include CD8+ and CD4+ T cell, NK cell, B cell and myeloid cell populations (n = 4, 16, 867 cells analysed in total). Right panel: A lymphoid cell cluster (circled) is observable that is highly enriched in FNA liver (blue, n = 4) compared to matched PBMCs (red, n = 4).

PSC/IBD (3.4/5HPF [IQR 0.2-5.2]) vs. PSC/no IBD (0.5 [0.1-3.0], p = 0.334) vs. LC (2.0/5HPF [0.6-6.0], p = 0.92). CCR9+ T-cells were centred around the portal tracts.
On transcript analysis (n = 4;16, 867 liver immune cells), 11 clusters were identified including lymphoid and myeloid cell subsets displaying differential expression of cell adhesion molecules (e.g. ITGB7) and activation markers (e.g. granzyme B, CD69). One lymphoid population was highly enriched in LIL, expressing transcription factors such as IRF1 and FOXP1 and cell surface markers including CD2 and lymphotoxin β (see Fig 1).
Conclusion: FNA of the liver could isolate a liver-specific lymphoid cell population that is not found in PBMC. There was no clear difference in CCR9 expression between PSC and LC. Single cell RNAseq can also determine gene expression in LIL, and with refinement of the technique, could be used to ascertain if tissue-homing molecules such as CCR9, ITGB7, and CD161 are also differentially expressed in PSC.

PS-128

Risk of gall bladder cancer in patients with primary sclerosing cholangitis and gall bladder polyps: an opportunity to revisit the guidelines

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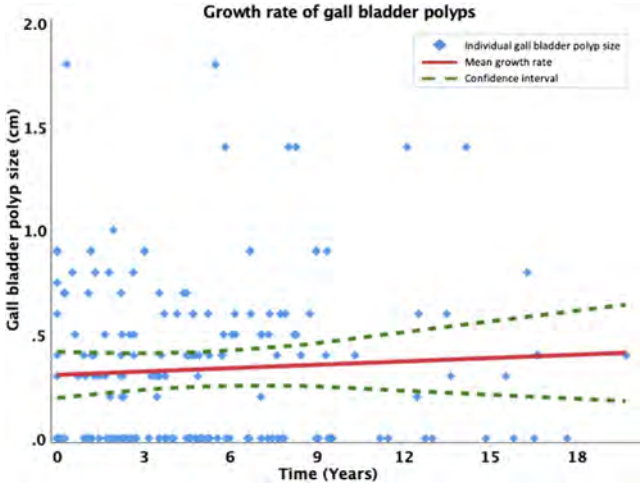
Background and aims: Primary sclerosing cholangitis (PSC) is a premalignant cholestatic liver disease associated with a risk of gall bladder cancer (GBC). International guidelines recommend cholecystectomy for gall bladder polyps of any size. We aimed to characterize the risk of GBC in PSC patients with gall bladder polyps.
Method: A retrospective review of patients with PSC followed at the Toronto Centre for Liver Disease between 2008–2018 was performed. All imaging and histology reports were reviewed for presence of gall bladder abnormalities. Descriptive statistics were used to characterize the cohort. The polyp growth as assessed by imaging was analyzed with repeated measurement methods using SAS.
Results: 366 PSC patients diagnosed between 1980 and 2017 were included. Mean age (SD) at diagnosis was 34 (± 15) years, 57% were male and 80% had large duct PSC. Mean follow-up time (SD) was 8.0 (± 5.9) years. Median number of imaging reports (IQR) per patient was 7 (4-13). A gall bladder polyp was seen in 17% (61/366) with median size (range) when first detected of 4 (2 –18) mm. At time of PSC diagnosis the median (IQR) ALT was 81 (35-135) U/l, AST 52 (32-73) U/l, ALP 231 (137-341) U/l, total bilirubin 12 (8-17) µmol/L and platelets 237 (180-279) × 10^9/L. Cholecystectomy was performed in 30% (18/61) of which pathology was available for 72% (13/18). Benign or no polyp was reported in 77% (10/13) and dysplasia or malignancy in 23% (3/13). In the 2 patients with adenocarcinoma, preoperative imaging described high risk features with an enlarging polyp or gall bladder mass. Low grade dysplasia was identified on explant in 1 patient with repeatedly stable 7-9mm polyp. Patients with gall bladder polyp who did not have cholecystectomy (43/62) were followed for median (IQR) 5 (2-9) years since the polyp was first detected. In this group 5% (2/43) had enlarging polyps (none greater than 8mm), 12% (5/43) stable or decreasing polyp size, and in 79% (34/43) the polyp was not reported on subsequent imaging. In 5% no subsequent imaging was available. In this cohort, gall bladder polyps did not show significant growth over time (Figure). After detection of a gall bladder polyp, the risk of developing GBC was 1.6 per 100 person years.



Conclusion: In the context of current screening recommendations, many gall bladder polyps in PSC patients are benign. Short term surveillance imaging may be considered prior to recommending immediate cholecystectomy in PSC patients without high risk imaging features.

EASL JOURNAL OF HEPATOLOGY

Saturday, 13 April 2019

General session III and award ceremony II

GS-13

Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in cwith PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection

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Background and aims: Myrcludex B/Bulevirtide (MyrB) is a first-in-class entry inhibitor to treat HBV/HDV infection. MyrB monotherapy resulted in HDV RNA decline and improvement of ALT levels (MYR 202). In a follow-up phase II study (MYR203) we reported end of treatment data in HBV/HDV infected patients receiving MyrB alone or combination with peg-interferon α 2a (PEG-IFNα) for 48 weeks (Wedemeyer et al. Hepatology 2018, DOI:10.1002/hep.30256). Here we present the 24-week (w) treatment-free follow-up data.

Method: 60 patients with HBV/HDV co-infection were randomized in 4 arms, receiving: 180 µg PEG-IFNα (A) or 2 mg MyrB plus PEG-IFNα (B), 5 mg MyrB plus PEG-IFNα (C), or 2 mg MyrB (D) for 48 w followed by a treatment-free period of 24 w. PEG-IFNα was given once weekly, and MyrB once daily, both as s.c. injection. The primary end point was undetectable serum HDV RNA at w72; secondary end points included ALT normalization, a combined treatment response (≥2log serum HDV RNA decline + normal ALT levels), and HBsAg reduction > $1\log_{10}$.
Results: *Safety:* MyrB was well tolerated with 155 drug-related AEs until w72 (mild n = 122, moderate n = 28, severe n = 5) primarily caused by an increase in total bile salts. Most AEs (n = 524) were related to PEG-IFNα. Two SAE (anal fistula and proctitis) occurred in one patient of arm B during follow-up, not-related to MyrB. All AEs resolved without sequelae; bile salts returned to baseline levels already at follow-up w50. *Efficacy:* Efficacy results are shown in the table below.
Conclusion: In contrast to PEG-IFNα monotherapy, a combination of MyrB with PEG-IFNα demonstrated high rates off-treatment HDV RNA suppression. HBsAg loss was achieved in a substantial proportion of patients, indicating a potential role of Myrcludex B in future HBV cure regimens.

Table: (abstract: GS-13)

Virological response	Time point	Arm A (n = 15) PEG-IFNα	Arm B (n = 15) 2 mg MyrB + PEG-IFNα	Arm C (n = 15) 5 mg MyrB + PEG-IFNα	Arm D (n = 15) 2 mg MyrB
Undetectable HDV RNA	w48	2/15	9/15	6/15	2/15
	w72	0/15	8/15	4/15	0/15
Median HDV RNA log reduction	w48	−1.14	−3.62	−4.48	−2.84
	w72	−0.26	−3.00	−1.38	−1.16
ALT normalization	w48	4/15	4/15	7/15	10/15
	w72	1/15	7/15	5/15	3/15
HBsAg: > 1log decline or undetectable	w48	0/15	7/15	2/15	0/15
	w72	0/15	6/15	2/15	0/15
Undetectable HBsAg	w48	0/15	3/15	0/15	0/15
	w72	0/15	4/15	0/15	0/15

GS-14

ENVISION, a phase 3 study to evaluate efficacy and safety of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1, in acute hepatic porphyria patients

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ELSEVIER

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Background and aims: Acute Hepatic Porphyrias (AHPs) are rare genetic diseases due to enzyme deficiencies involved in heme biosynthesis. AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP). Induction of aminolevulinic acid synthase 1 (ALAS1) can lead to accumulation of neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), resulting in potentially life-threatening, neurovisceral attacks and debilitating chronic symptoms. Givosiran is an investigational RNAi therapeutic targeting ALAS1 to reduce ALA and PBG levels in AHP patients and ameliorate disease manifestations.
Method: ENVISION (NCT03338816) is a Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trial in AHP patients to evaluate the effect of givosiran (2.5 mg/kg, given subcutaneously once-monthly) compared to placebo, on attack rate over six months. Eligible patients were aged ≥ 12 years with an AHP diagnosis and history of ≥ 2 attacks in the six months prior to enrollment. Patients also had to be willing to discontinue or not initiate hemin prophylaxis. The primary end point is annualized rate of attacks requiring hospitalization, urgent care, or home IV hemin. Secondary end points are safety/tolerability, ALA and PBG levels, hemin usage, symptoms, and quality of life measures.
Results: Study enrollment has been completed (N = 94, 18 countries, 36 sites). An interim analysis of safety and urinary ALA, a biomarker likely to predict clinical benefit, was conducted in 43 patients (41 AIP, 1 VP, 1 HCP; 23 randomized to givosiran, 20 to placebo) who were on study for at least three months. No deaths were reported. Serious adverse events were reported in 5/23 (22%) of patients on givosiran, and 2/20 (10%) on placebo. One patient on givosiran was discontinued due to > 8x ULN increase in liver transaminases (a protocol-stopping rule), which later resolved. Patients on givosiran showed a statistically significant urinary ALA reduction, compared to placebo group ($p < 0.001$). The study is ongoing, and results from the complete six-month double-blind period, including the primary end point of annualized attack rate, will be presented.
Conclusion: Givosiran is an investigational RNAi therapeutic under study for the treatment of AHP. An interim safety analysis of an ongoing Phase 3 study demonstrated a safety profile supportive of continued development and a significant reduction of the disease biomarker.

GS-15

Deficiency of the ABC transporter ABCC12/MRP9 is associated with chronic cholestasis syndromes and causes bile duct paucity in zebrafish and mouse model organisms

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Background and aims: Despite recent advances in understanding the genetic underpinning of progressive familial intrahepatic cholestasis (PFIC), the etiology for cholestasis remains unknown in many children. We surveyed the genome of children with chronic cholestasis for variants in genes not previously associated with PFIC and validated their biological relevance in zebrafish and murine models.
Method: Whole exome and candidate gene sequencing was performed in 38 children with normal GGT cholestasis without disease causing mutations in the genes *ABCB11, ATP8B1 or ABCB4*. Crispr/Cas9 gene editing was employed to induce truncating mutations in the candidate gene in C57BL/6 mice and zebrafish.
Results: A homozygous, truncating mutation (c.198del.Gly67Alafs*6) was detected in *ABCC12* encoding MRP9, a member of the superfamily of ATP-binding cassette (ABC) transporters, in a 1yo female patient with normal GGT cholestasis and bile duct paucity by liver histopathology. 3 more subjects were found to harbor compound heterozygous mutations in this gene. The biological functions of this transporter are largely undefined, and it has not been associated with liver disease before. Using IHC we found it to be expressed in bile duct epithelial cells (Fig 1a). Adult, male mice lacking *Abcc12* due to a 100 bp deletion in exon 3 displayed higher serum ALP (mean: 180 vs 86 IU/L, $p < 0.01$) and ALT levels (77 vs 37 IU/L, $p < 0.01$) compared with age matched WT controls. IHC for panCK revealed a higher percentage of bile ducts without lumen (36 vs 17%, $p < 0.05$). When younger mice were challenged by feeding

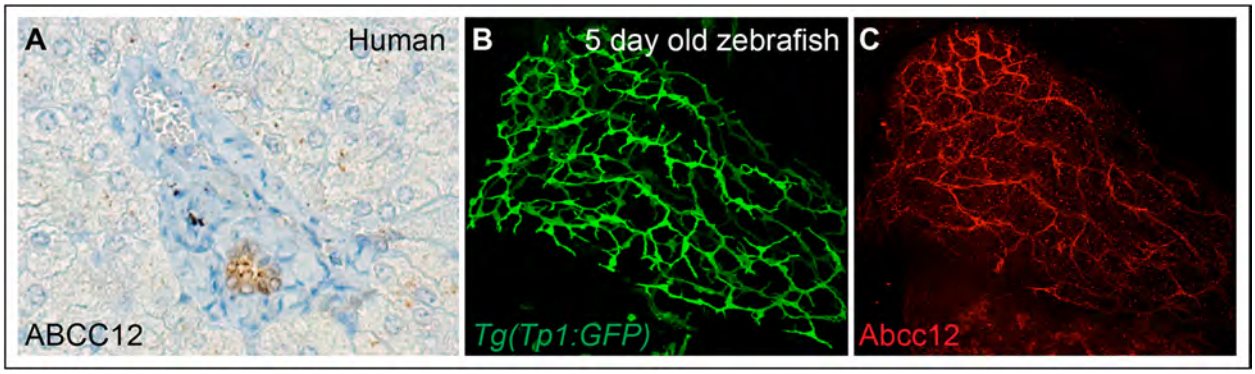

Figure: (abstract: GS-15) Liver tissue from an infant without liver disease (**A**), and 5-day-old zebrafish larvae expressing the transgene Tg (Tp1bglob:GFP) in biliary epithelial cells (**B**) were stained with an antibody against ABCC12 (**C**).

of 1% cholic acid admixed to the chow for 7 days, biliary injury was aggravated in Abcc12$^{-/-}$ mice compared with age/sex matched WT mice, as indicated by increased bile duct proliferation (area CK19+: 0.38 vs 0.32%, p < 0.05), higher serum total bilirubin levels, and more periportal fibrosis (Sirius Red stained area: 0.97 vs 0.72%, p = 0.05). In zebrafish, we detected conserved expression of the homolog of ABCC12 in cholangiocytes (Fig 1b/c). The zebrafish mutant harboring similar truncating mutations exhibits a significant reduction in cholangiocyte number compared to WT during juvenile stage and had elevated total bile acid and ALT levels at adult stage.

Conclusion: *Abcc12*/Mrp9 is a novel transporter expressed by cholangiocytes, and its loss is associated with bile duct paucity in humans, mice and zebrafish. The substrates for this transporter and mechanisms for cholangiocyte injury are under investigations.

GS-16

Safety and tolerability of liver-derived stem cells (HepaStem) infused in patients with acute-on-chronic liver failure or acute decompensation: a European phase I/IIa open-labelled study

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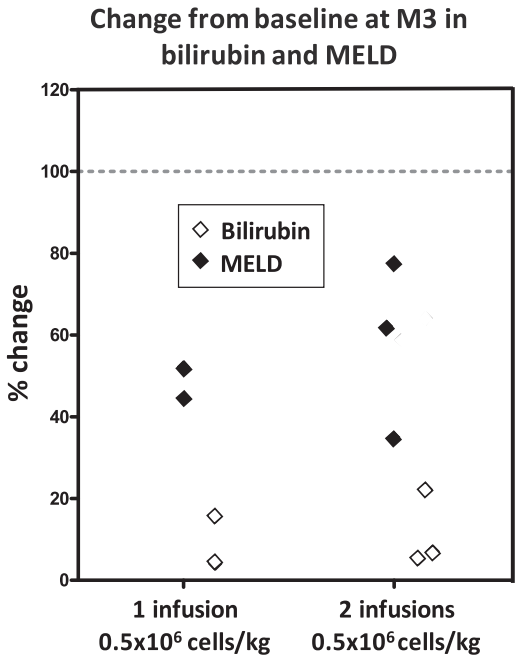
Background and aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation (AD) of cirrhosis associated with failure of one or more organs. HepaStem™ (Promethera) is a suspension of liver stem cells derived and expanded from the parenchymal fraction of collagenase-digested adult human liver. The immunomodulatory properties of HepaStem is expected to restore the immunological disturbances and functional impairment in patients with ACLF or AD. The main objective is the safety of single or double infusions of various doses in patients with ACLF or AD at risk of developing ACLF up to day (D)28 post treatment. Secondary objectives include safety and efficacy up to month (M)3.

Method: The study is composed of 6 dose-cohorts: 250 × 10^6 cells (n = 3); 0.25 × 10^6 cells/kg (1 dose, N = 3); 0.5 × 10^6 cells/kg (1 dose, N = 3; or 2 doses, N = 3); 1 × 10^6 cells/kg (1 dose, N = 3; or 2 doses, N = 3). Twelve patients were included in the first 4 cohorts and followed up to M3 after treatment.

Results: The 1st patient (ACLF) received no cells due to technical issue. The 2nd and 3rd patients (both ACLF) received 1 or 2 infusions of 250 × 10^6 cells (around 3.5 × 10^6 cells/kg/infusion). Nine patients (3 ACLF and 6 AD) received 1 infusion of 0.25 × 10^6 cells/kg, or 1 or 2 repeated infusions 1 week apart of 0.5 × 10^6 cells/kg. The 2nd and 3rd patients had severe epistaxis and one bled at the insertion side of the transjugular biopsy. They all suffered at baseline from severe coagulation disturbances. Both patients recovered; one of them had liver transplantation. After dose reduction in the subsequent cohorts, no serious events causally related to HepaStem were reported. Reported AEs were in line with those expected in regards underlying diseases and comorbidities. No drop in platelets, fibrinogen, or coagulation factors were observed. From the patients with transplant-free survival at M3, bilirubin and MELD decreased by respectively 80% and 50%.

Conclusion: At high HepaStem doses, 2 out of the 3 ACLF patients with severe coagulation disturbances experienced bleedings possibly related to study medication. HepaStem expresses tissue factor, which can activate the coagulation cascade and lead to consumption of coagulation factors; this effect is dose-dependent according to preclinical studies. Repeated infusions of 0.5 × 10^6 cells/kg were shown safe in this AD/ACLF patient population, and clinically significant MELD and bilirubin improvement is considered as an encouraging sign of efficacy.



GS-17

The integration of Hepatitis B virus into human genome is a common event in the setting of HBeAg negative disease: Implications for the treatment and management of CHB

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Background and aims: HBV Integration in the human genome is associated with hepatocarcinogenesis, a factor which should be considered in the initiation of treatment. We recently demonstrated HBV DNA integration in the early phases of HBV infection (*Mason et al., Gastroenterology 2012).* Here we analysed integration events in eAg negative disease with low to moderate levels of viraemia including those who currently do not meet treatment criteria.

Method: Liver tissue from 40 eAg negative CHB patients was studied. Patients were classified according to level of viraemia: group 1 (HBV DNA < 2, 000IU/ml; n = 8), group 2 (HBV DNA 2, 000-20, 000IU/ml; n = 14), group 3 (HBV DNA > 20, 000IU/ml; n = 18). cccDNA and pgRNA were evaluated by qPCR. HBV integration was identified by recognition of chimeric HBV human sequences by NGS [Illumina, median (IQR) coverage:114x (92x-138x)]. The threshold of parameters predicting HBV integration was defined by AUROC.

Results: Median (IQR) serum HBV DNA and HBsAg were 3.9logIU/ml (3.4-5.3) and 3980IU/ml (1260-10000) respectively. Patients in group 1 and 2 had comparable intrahepatic reservoirs of cccDNA and pgRNA. Conversely, compared to group 2, group 3 was characterised by higher cccDNA [median (IQR): 2.6 (2.3-2.7)] vs 2.0 (0.9-2.3) log copies/1000 cells, p = 0.01] and pgRNA [190 (7-775) vs 3.3 (1.5-12.2) copies/1000 cells, p = 0.02]. HBV integration was detected in all

3 groups with an overall prevalence of 32.5%: 50% in group 3, 14.3% in group 2 and 25% in group 1. Among the 15 recognised integration events; 10 involved the HBx-encoding region, followed by HBs (n = 3), core (n = 1) and pol (n = 1). HBV integration preferentially occurred within intronic regions (9/15), critical for RNA splicing and mRNA production. Notably, in 6 patients, HBV integration localised in human genes, regulating cell proliferation. Amongst them, NUP85, COL18A1, AGBL5 and ANKRD52 are specifically involved in hepatocarcinogenesis. Integrated HBV was also found in genes regulating lipid metabolism (CYP2UI, LMF-1) and the ISG, IFITM-1. By AUROC, HBsAg > 5, 000IU/ml identified the occurrence of HBV integration with the best diagnostic accuracy (86.5%), 100% sensitivity and 80% specificity.

Conclusion: HBV integration occurs across all patients with eAg negative disease including those with low HBV DNA (<2, 000IU/ml). Localisation of HBV integrants suggest that these events are not restricted to carcinogenesis, but also involved in mechanisms regulating hepatocyte metabolism and antiviral immunity.

GS-18

Preventive administration of ursodeoxycholic acid after liver transplantation for primary biliary cholangitis prevents disease recurrence and prolongs graft survival

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Background and aims: Primary biliary cholangitis (PBC) frequently recurs after liver transplantation (LT). Recent data have shown that PBC recurrence impairs graft and patient survival (1). Strategies to prevent PBC recurrence and its long-term impact are therefore needed. It has been suggested that ursodeoxycholic acid (UDCA) may prevent PBC recurrence after LT but data supporting this effect are limited (2). Our aim therefore was to assess in a large multicenter, international cohort the impact of UDCA administered preventively after LT on the incidence of PBC recurrence and long-term outcomes.

Method: Data from 941 patients (88% female; mean age: 54 years) who underwent LT for PBC over the past three decades among 16 centers and 9 countries were retrospectively analyzed. Among these patients, 211 (22%) have been treated with UDCA (10-15 mg/kg/d) continuously from the first 2 weeks post-LT (preventive UDCA). Recurrence of PBC was diagnosed based on liver histology. Adjusted Cox models, competing risk and restricted mean survival time analyses were used to study the factors associated with PBC recurrence and long-term outcomes.

Results: Over a mean follow-up period of 9.7 ± 7.7 years, 264 PBC recurrences, 111 graft losses, and 298 deaths occurred. Within the population of patients who had had at least 1 biopsy during follow-up (n = 667, 71%), the factors associated with PBC recurrence in a multivariate analysis included absence of preventive UDCA (p <.0001; Fig.1), younger age at LT (p <.0001), use of tacrolimus vs. cyclosporine regimen (p <.001), and use of protocol vs. clinically driven biopsies (p <.05). Preventive UDCA and cyclosporine use were the only 2 factors independently associated with survival without graft loss or PBC recurrence. Hazard ratios (95% CI) associated with preventive UDCA with respect to PBC recurrence, graft loss, and death were 0.42 (0.30-0.59), 0.44 (0.26-0.76), and 0.67 (0.51-0.89) respectively. Preventive UDCA was associated with a survival gain without graft loss or PBC recurrence of 21.1 months (95% CI: 12.6-29.5) at 12 years and 42.8 months (27.9-57.7) at 20 years.

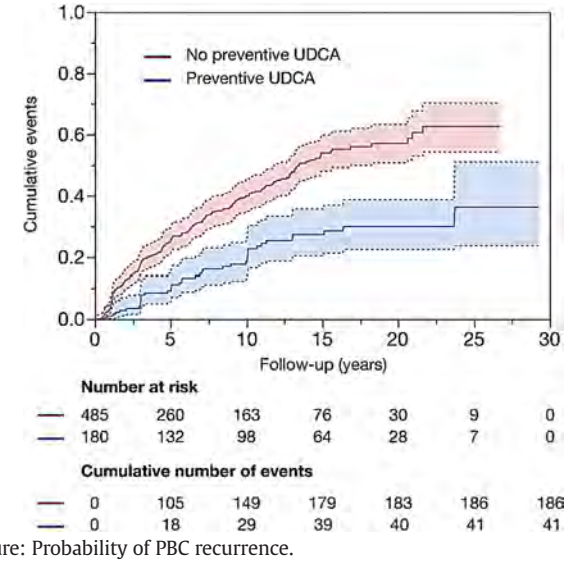

Figure: Probability of PBC recurrence.

Conclusion: Preventive administration of UDCA after LT for PBC prevents disease recurrence and prolongs graft survival.

(1) Montano-Loza et al. Gastroenterology 2018; (2) Bosch et al. J Hepatol 2015.

NAFLD – Preclinical pipeline

PS-129

The glucocorticoid antagonist ST001 prevents development of NASH and improves aspects of the metabolic syndrome in the DIAMOND (TM) mouse model

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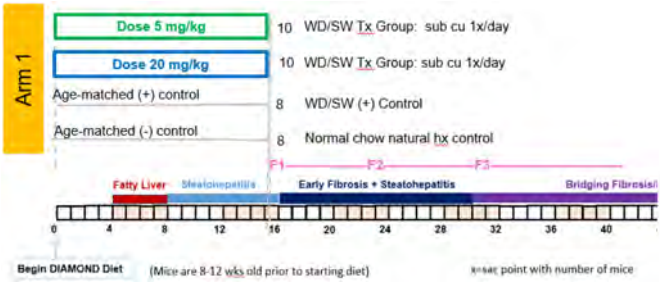
Background and aims: The steroid ST001 (fluasterone, SteroTherapeutics) is a strong in vivo antagonist to glucocorticoids

that retains beneficial immunosuppressive effects. It is being evaluated as a treatment for Cushing's Syndrome, in which most patients are insulin resistant and obese and 20% develop NASH. We aimed to determine if ST001 could prevent development of NASH in the DIAMOND™ mouse model.

Method: Mice were randomized into 4 groups: high dose (HD 20 mg/kg), low dose (LD 5 mg/kg), WDSW positive (PC) and NCNW negative (NC) natural history controls. Mice were raised for 16 weeks on diet, corresponding to a baseline NASH with mild fibrosis in all WDSW groups. Treatment groups were then injected once daily with aqueous vehicle or drug in vehicle for the 16 wks they were on-diet. Serum biomarkers of insulin sensitivity, LFTs, lipids, and liver histology (HandE and Sirius Red) were assessed.

Results: At necropsy, the body weight and liver weight of the mice in the HD group were significantly lower than the PC and LD groups. Interestingly, steatosis percentage was higher in the fluasterone-dosed groups compared to PC, but steatosis grade did not differ. Fasting blood glucose was higher in the treated groups, but ketones and serum triglycerides were lower compared to PC. No statistically significant differences in serum insulin or HOMA-IR were observed, although there was a strong trend to lower insulin in the HD group. Serum LFTs and cholesterol did not differ between the PC and treatment groups. Fluasterone had significant anti-fibrotic effects; NASH CRN fibrosis scores were significantly lower in both treatment groups compared to WDSW positive controls ($P \leq 0.001$) and perisinusoidal fibrosis was also significantly lower in both treatment groups ($P \leq 0.01$). While 66% of the 16-wk positive control mice progressed to NASH, none of the mice being treated with fluasterone progressed beyond simple steatosis, and this lack of progression was highly statistically significant ($P \leq 0.001$). Fluasterone eliminated ballooning in both dose groups compared to PC ($P \leq 0.0001$). Lobular inflammation and NAS score did not differ between groups but the SAF activity score was lower in both dose groups.



Conclusion: Fluasterone successfully met the primary study end point of preventing NASH development. While not an insulin sensitizer, it did improve some measures of insulin sensitivity and metabolic syndrome, suggesting that the development of NASH in this model may be partly driven by glucocorticoids as with Cushing's disease. These results support the biological rationale for further testing of anti-glucocorticoid compounds with immunosuppressive effects like fluasterone as NASH therapeutics.

PS-130

Preclinical pharmacology of CJ-14199, a new and potent ileum bile acid transporter inhibitor for non-alcoholic steatohepatitis

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Background and aims: CJ-14199 is a novel and highly selective ileum bile acid transporter (IBAT) inhibitor in preclinical development for the next-generation treatment of the chronic liver diseases such as non-alcoholic steatohepatitis (NASH). In the present study, we investigated the *in vitro* and *in vivo* pharmacological properties of CJ-14199 and the effect of CJ-14199 in a diet induced mouse NASH disease model.

Method: *In vitro* cell assay was performed using IBAT- or LBAT (Liver BAT)-overexpressing cell line. *In vivo* pharmacological properties of CJ-14199 in normal ICR mice were determined by the changes of fecal bile acid and plasma 7αC4. *In vivo* efficacy of CJ-14199 on NASH was evaluated by NAS (Non-alcoholic fatty liver disease Activity Score) and fibrosis area in the various diet-induced mouse NASH diseases model. Tissue distribution of CJ-14199 was investigated using quantitative whole-body autoradiography (QWBA) in rats.

Results: CJ-14199 selectively inhibited IBAT with IC_{50} of IBAT was 1.83~3.6nM, which was about 4000 times lower than IC_{50} of LBAT. Following oral administration of CJ-14199 to ICR mice, the concentration of fecal bile acid was increased with dose-dependent manner and the increase of plasma 7αC4 was observed. CJ-14199 significantly improved NAS and prevented progression of fibrosis in the various diet-induced mouse models of NAFLD/NASH. In a QWBA study in which [^{14}C]CJ-14199 was orally administered to SD rats, CJ-14199 was highly distributed in the gastrointestinal tract such as stomach, small intestine, and large intestine.

Conclusion: CJ-14199 is a highly selective IBAT inhibitor, and is locally distributed in target organ, the gastrointestinal tract. CJ-14199 showed not only the increase of fecal bile acid and plasma 7αC4, but also the improvement of NAS and fibrosis area in the diet-induced NASH model. Therefore, CJ-14199 has the potential as a new therapeutics for NASH.

PS-131

Elafibranor and nitazoxanide synergize to reduce fibrosis in a NASH model

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Background and aims: Drug combinations are increasingly required for the successful treatment of complex liver diseases. In NASH, drug combination has recently emerged as a new treatment paradigm to increase the proportion of patients that reach all treatment goals. The ideal NASH medication will both reverse NASH histology and stop the progression of fibrosis in patients at high risk of cirrhosis and complications.

Elafibranor (ELA), a PPARα/δ agonist can reverse NASH histology and decrease fibrosis, especially in patients with advanced disease (GOLDEN-505 phase 2b trial), and is currently being evaluated in the RESOLVE-IT phase 3 trial. We have recently identified nitazoxanide (NTZ), a phase-2 ready drug candidate with a good safety profile in man as a potent anti-fibrotic agent, by using an unbiased phenotypic screening approach.

The aim of this proof of concept study is to assess ELA/NTZ combination in a disease model of NASH to establish its potential value for treating human disease.

Method: Human primary stellate cells (HSC) were activated with TGFβ. The expression level of the profibrotic marker αSMA was measured by ELISA. A NASH phenotype was induced in C57Bl/6J mice by feeding a cholesterol-supplemented CDAA diet (CDAA/c) for 12 weeks. Animals received ELA alone (1 mg/kg/day), NTZ alone

(100 mg/kg/day) or ELA/NTZ combination for the entire study period of 12 weeks. Histological evaluation of NASH and fibrosis was performed in a blinded fashion.
Results: Nitazoxanide (NTZ) potently interfered with TGFβ-induced HSC activation in vitro. IPA analysis of transcriptional data showed that profibrotic signaling pathways (RhoA signaling, ILK signaling, Integrin signaling) were attenuated in HSC cells that received NTZ. At low doses, ELA and NTZ showed a modest inhibition (20–30%) of HSC activation, when used separately but this effect was doubled when both drugs were used as combination.
Histological examination *in vivo* revealed a severe NASH phenotype accompanied by perisinusoidal fibrosis. Liver fibrosis area was reduced by 41% and by 32% in mice treated with ELA and NTZ, respectively, whereas ELA/NTZ combination reduced the proportional fibrosis area by 60%. Transcriptomic analysis showed that ELA/NTZ combination created a synergistic beneficial action on multiple pathological mechanisms, involving liver cell death, inflammasone activation, immune cells recruitment and fibrosis.
Conclusion: Elafibranor and nitazoxanide synergize in vitro and in vivo to reduce liver fibrosis, opening interesting perspectives for further clinical development.

PS-132
The acetyl-CoA carboxylase inhibitor PF-05221304 exerts direct effects on hepatic inflammation and fibrosis independent of benefits on steatosis

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Background and aims: The molecular pathogenesis of non-alcoholic steatohepatitis (NASH) is complex, involving steatosis, lipotoxicity, hepatic inflammation and fibrosis. Acetyl-CoA carboxylase (ACC) regulates de novo lipogenesis (DNL) and fatty acid oxidation. ACC inhibitors reduce levels of steatosis in rodents and humans. In the present studies, the effects of a liver targeting, ACC1/ACC2 inhibitor (PF-05221304) on direct modulation of hepatic inflammation and fibrosis were evaluated in human-derived primary cells, and rat *in vivo* models, where improvements in steatosis do not contribute to efficacy.
Method: Effects of PF-05221304 on primary human T-cell and myofibroblast activation were assessed *ex vivo*. Effects of oral administration of PF-05221304 on markers of hepatic inflammation and fibrogenesis were evaluated in the diethylnitrosamine (DEN) chemical induced liver injury model and the choline deficient high fat fed rat model (CDAHFD).
Results: In primary human T-cells cultured under conditions to drive Th17 polarization, PF-05221304 inhibited DNL (EC_{50} 23 nM) and blocked polarization to Th17 pro-inflammatory cells (EC_{50} 151 nM) but not anti-inflammatory Treg cells. In primary human hepatic stellate cells treated with TGFβ1 to drive myofibroblast activation, PF-05221304 inhibited DNL (EC_{50} 31 nM) and attenuated myofibroblast activation as assessed by αSMA (EC_{50} 5 nM) and collagen (EC_{50} 23 nM) staining. In the rat DEN liver injury model, PF-05221304 administration reduced the %CD3 staining area, a marker of T-cell inflammation, by 33% ($p < 0.05$) and increased hepatic expression of the anti-inflammatory cytokine IL-10 ($p < 0.01$) without modulating steatosis, relative to vehicle. In the CDAHFD model, PF-05221304 administration reduced liver stiffness by 35% ($p < 0.001$), decreased αSMA staining area by 41% ($p < 0.01$) and Picro Sirius red staining by 26% ($p < 0.05$), without altering steatosis relative to vehicle treated rats. Additionally, hepatic expression of the activated myofibroblast marker gene αSMA and the fibrosis marker genes Col1A1 and Col3A1 were reduced by 46% ($p < 0.01$), 40% ($p < 0.01$) and 44% ($p < 0.05$), respectively, indicative of a reduction in hepatic inflammatory and fibrotic tone.
Conclusion: The liver targeting, ACC1/ACC2 inhibitor PF-05221304 produced direct improvements in markers of inflammation and fibrosis in both human-derived primary cells and rodent models, demonstrating that ACC inhibition has potential to address multiple dimensions of NASH pathogenesis.

PS-133
LXR inverse agonists reduce steatosis and fibrosis in the STAM mouse model but also improve insulin sensitivity in a high fat diet mouse clamp study

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Background: Nuclear receptors LXR alpha and beta are involved in the control of hepatic de novo lipogenesis and overall lipid and cholesterol homeostasis. We have developed potent, synthetic LXR inverse agonists (LXRias) which block transcriptional activity of both LXRs. The effects of PX-L788 and PX-L329 were tested in the STAM mouse model of progressive NASH and compared to a clinical stage ACC inhibitor (ACCi). Furthermore, we assessed the impact on glucose homeostasis and insulin signaling by LXR inverse agonist, PX-L665, in a mouse model of NAFLD as well as in a two-step euglycemic clamp study.
Methods: STAM model: C57BL/6 mouse pups were injected with streptozotocin 2 days after birth and were placed on high-fat diet at 4 weeks of age. From week 6 on, mice received PX-L788 (10 and 30 mg/kg), PX-L329 (1 and 5 mg/kg), ACC inhibitor (0, 3 and 10 mg/kg) or vehicle. HandE stained liver sections were assessed for NAS scoring, Sirius-red positive area (SRA) was analysed as a correlate of fibrosis. NAFLD Model: C57BL/6 mice (fed a high fat and cholesterol (1% by wt) diet for 6 wks) were dosed with PX-L665 (5 mg/kg) or vehicle for 3 wks and an oral glucose and pyruvate tolerance test (oGTT, PTT) were performed. Euglycemic clamp: C57BL/6 mice (fed a 60% high fat diet for 16 wks) were dosed with PX-L665 (5 mg/kg), Pioglitazone (30 mg/kg) or vehicle q.d. for 4 wks. During the two step euglycemic clamp (8 mU/kg/min and 18mU/kg/min insulin) the glucose infusion rate was recorded as a measure for insulin sensitivity.
Results: In the STAM mouse model all compound treatments reduced total NAS (NAS = 4.7; 3.9; 2.8; 3.0; 3.2; 3.0 for [cpd (dose in mg/kg)] vehicle, ´329 (1), ´329 (5), ´788 (10), ´788 (30), ACCi (10)) and resulted in reduced SRA (−41.15%, −42.56%, −18.36%, −48, 68%, −43.03% for ´329 (1), 329 (5), ´788 (10), ´788 (30), ACCi (10)). In the NAFLD model PX-L665 treatment reduced glucose production in a PTT (AUC blood glucose −21.5%) and decreased glucose-stimulated insulin secretion in an oGTT (AUC insulin: −34.7%) relative to vehicle. Clamp experiments revealed an improved insulin sensitivity, similar to Pioglitazone, upon PX-L665 treatment.
Conclusion: LXR inverse agonists demonstrate anti-steatotic and anti-fibrotic effects in the hypoinsulinemic STAM model, thus independent from insulin sensitisation. However, in HFD mice with elevated insulin resistance, an LXRia also substantially improved insulin sensitivity. Taken both effects together there is a strong biological rationale for the development of LXRias in NASH therapy

PS-134
Oral treatment with PBI-4547 promotes beta-oxidation and energy expenditure, and reverses liver damage and white adipose tissue fibrosis in high-fat diet and ob/ob mouse models of NAFLD.

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Background and aims: Obesity and its resulting metabolic disturbances are major health threats and the main cause of a host of diseases, including non-alcoholic fatty liver disease (NAFLD).

PBI-4547, a novel first-in-class orally active compound, has been shown to improve liver fibrosis resulting from CCl_4-induced liver injury. This study examined the effect of PBI-4547 in *ob/ob* and high-fat diet (HFD)-induced mouse models of NAFLD.
Method: Six-week old male *ob/ob* mice were treated with vehicle or PBI-4547 (10 or 50 mg/kg, oral once a day) from day 1 through 105. C57BL/6 mice were fed with either a standard or an HFD (Harlan, TD.06414) for 14 weeks. These mice were divided in three groups [Normal chow, HFD + Vehicle, and HFD + PBI-4547 (10 mg/kg, oral once a day)] and treated for an additional 6 weeks. Liver steatosis and ballooning as well as white adipose tissue (WAT) were assessed by hematoxylin and eosin (HandE) staining. Pro-inflammatory/profibrotic and fatty acid (FA) metabolism gene expression was measured in liver and WAT samples by qPCR. Blood glucose, serum triglyceride, and adiponectin levels were examined.
Results: Both *ob/ob* mice and HFD-mice displayed severe liver steatosis and ballooning, which was completely reversed with PBI-4547 treatment. PBI-4547 reduced collagen types I and III, MMP-2, and TIMP1 gene expression in liver of *ob/ob* mice and HFD-mice. Moreover, PBI-4547 treatment significantly reduced fibrosis and inflammatory cell infiltration in WAT for both animal models, and decreased profibrotic/inflammatory markers CTGF, MMP-2, Collagen I and MCP-1 in WAT of HFD-mice. To further characterize the activity of PBI-4547, quantitative RT-PCR analysis of the expression of FA transport, synthesis and oxidation markers was performed in liver and WAT of HFD-mice. In liver, PBI-4547 increased markers of mitochondrial FA transport and oxidation (ACOX-1, CD36, FABP4, CPT1β, PDK4) and FA synthesis (FASN). In WAT, PBI-4547 increased mitochondrial FA transport and oxidation markers CD36 and CPT1β, thermogenesis marker UCP-1 (by 16X, suggesting browning of adipose tissue) as well as glucose transporter GLUT4. Moreover, PBI-4547 completely inhibited Vaspin gene expression in WAT. Blood glucose and serum triglyceride levels were strongly reduced by PBI-4547 and serum level of adiponectin, which was reduced in *ob/ob* and HFD-mice, was significantly increased in PBI-4547-treated mice.
Conclusion: PBI-4547 is a potential novel therapy for NAFLD, obesity, and associated metabolic syndrome. PBI-4547 decreases liver and WAT profibrotic markers, and promotes β-oxidation and energy expenditure.

PS-135
MSDC-0602 K, a PPAR-gamma sparing modulator of the mitochondrial pyruvate carrier, improves NASH outcome in a diet-induced animal model of non-alcoholic steatohepatitis
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Background and aims: MSDC-0602 K, a second generation TZD, is currently being evaluated in a 52-week, phase 2b dose-ranging clinical trial in subjects with biopsy proven NASH (EMMINENCE, NCT02784444). MSDC-0602 K is optimized for the mitochondrial target of thiazolidinedione (TZD), the mitochondrial pyruvate carrier (MPC) complex, which is required to import pyruvate into the mitochondrial matrix from the cytosol. Modulating mitochondrial pyruvate metabolism through attenuation of the MPC produces insulin-sensitizing effects. Unlike the first generation TZDs pioglitazone and rosiglitazone, MSDC-0602 was designed not to bind PPARγ. We postulated that MSDC-0602 K treatment would improve clinical laboratory indices and pathophysiological aspects of NASH in the DIAMOND™ mouse model.
Method: Male DIAMOND™ mice received high fat sugar water diet (WDSW) or chow diet normal water (CDNW) for 24 wks. Mice on WDSW were randomized to MSDC-0602 K (30 mg/kg/day) and Vehicle (VC) gavaged QD for 16-24 wks (n = 10/group), and results were compared to baseline WDSW positive controls (baseline PC, n = 5) and 24-week CDNW negative natural history controls (NC, n = 5). The end points included measures of insulin sensitivity, lipids LFTs, and liver histology with HandE and Sirius Red staining to quantify NASH progression.
Results: MSDC-0602 K dramatically reduced HOMA-IR compared to VC and PC groups ($P \leq 0.002$ and 0.021, respectively); this was driven mostly by decreased fasting insulin compared to VC and PC groups ($P \leq 0.0006$ and 0.08, respectively). Remarkably, the HOMA-IR and fasting insulin values in the MSDC-0602 K treated mice were comparable to NC mice, even though their fasting glucose, ketones, triglycerides, body/liver weights, and hepatic steatosis (% and grade) did not differ from the VC group. Average serum AST and ALT in the MSDC-0602K-treated group was halved compared to the VC but did not reach statistical significance ($P \leq 0.07$ and 0.12 respectively). Relative to VC, treatment with MSDC-0602 K significantly decreased ballooning ($P \leq 0.024$; the SAF activity score was significantly lower in the MSDC-0602K-treated group compared to the VC ($P \leq 0.04$) and was reduced to the level of baseline controls. The NAFLD Activity Score (NAS) trended lower compared to VC in the MSDC-0602K-treated group ($P \leq 0.11$) The NASH CRN fibrosis score in the MSDC-0602K-treated group was 0; the MSDC-0602K-treated group was equivalent to the NC group. Significantly fewer MSDC-0602K-treated mice (3/10, 30%) progressed from simple steatosis to NASH compared to the VC group ($P \leq 0.023$).
Conclusion: MSDC-0602 K met the primary study goal of ameliorating and preventing progression of NASH. The drug treatment improved insulin resistance, LFTs, ballooning, and NASH outcome independently of weight and steatosis. These study results support the biological rationale for use of MPC modulators like MSDC-0602 K to treat NASH.

Liver cancer – Systemic treatment and immunotherapy

PS-136
Can lenvatinib meet clinical needs of patients with unresectable hepatocellular carcinoma? Multicenter analysis
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Background and aims: Although sorafenib (SOR) and regorafenib (REG) have been shown to contribute to improve survival of patients with unresectable hepatocellular carcinoma (u-HCC), effective therapeutic options for those patients, who show SOR intolerability or REG failure, have yet to be established. Recently, lenvatinib (LEN) was developed as a first-line tyrosine-kinase inhibitor (TKI) for treatment of u-HCC and made commercially available. Here, we examined the clinical efficacy of LEN in real-world practice.

Method: From March to August 2018, 109 u-HCC patients were treated with LEN at our hospitals. Following exclusion of those with a reduced dose at the start or with short the observation period (<2 weeks), 77 of 109 patients including those with an REG history (n = 11) were enrolled (72.0 ± 8.9 years old; 59 males, 18 females; HCV: HBV:alcohol:others = 38:14:12:13; dosage 8/12 mg = 49/28, TNM stage II/III/IVa/IVb = 8/28/4/37) and divided into 2 groups, TKI naïve (n = 33) and TKI experienced (n = 44). Therapeutic response was evaluated after 1, 2, and 3 months (M) using enhanced CT or MRI findings in accordance with modified RECIST guidelines, and the clinical therapeutic efficacy of LEN was retrospectively evaluated.
Results: The average observation period was 79.3 ± 40.7 days. The first evaluation of LEN therapeutic effect at 1 month was performed for 52 patients, which showed complete response (CR) in none, partial response (PR) in 20, stable disease (SD) in 22, and progressive disease (PD) in 10, for an overall response rate (ORR) of 38.5% and disease control rate (DCR) of 80.8%. Image findings of 37 patients at 3 months showed CR in 1, PR in 11, SD in 14, and PD in 11 (ORR 32.4%, DCR 70.3%). The 1- and 3-month progression free survival rates (PFSRs) were 90.1% and 80.1%, respectively, while 1- and 3-month overall survival rates (OSRs) were 98.6% and 93.4%, respectively. Hand-foot skin reaction was the most frequent adverse event in the present cohort [all grades, n = 31 (40.3%); grade 3, n = 7 (9.1%)], followed by general fatigue [grade 1/2, n = 26 (33.8%)], appetite loss [all grades, n = 22 (28.6%); grade 3, n = 5 (6.5%)], hoarseness [all grades, n = 17 (22.1%); grade 3, none], and hypothyroidism [all grades, n = 15 (19.5%); grade 3, none]. Although age was younger and TNM stage worse in the TKI experienced group (70.0 ± 5.9 vs. 75.6 ± 11.2 years, P = 0.040; II/III/IVa/IVb = 0/16/3/25 vs. 8/12/1/12, P = 0.006), there were no significant differences for Child-Pugh score (5/6/7/8 = 23/14/6/1 vs. 19/11/3/0, P = 0.512), PFSR (1-/3-month PFSR: 90.5%/80.1% vs. 89.7%/80.4%, P = 0.499), or OSR (1-/3-month OSR: 96.7%/96.7% vs. 100%/92.3%, P = 0.769).
Conclusion: Our results showed that early therapeutic response to LEN was favorable. LEN might be an important option for not only first-line but also second-/third-line therapy, thus helping to meet the present unmet need in regard to TKI treatment for u-HCC.

PS-137

A multicentric study on real-life impact of nivolumab in patients with hepatocellular carcinoma

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Background and aims: Nivolumab was granted accelerated approval by FDA for hepatocellular carcinoma (HCC) based on the results of the Checkmate 040 trial. We aim to describe the clinical/safety profile and outcomes of patients with HCC treated with nivolumab outside clinical trials (compassionate use).
Method: This is a retrospective, observational, multicentric study involving 10 healthcare centers with multidisciplinary teams led by hepatologists. Clinical and laboratorial data, previous treatments, adverse events (AE) and overall survival (OS) were recorded.
Results: 110 patients received nivolumab, of whom 74 in clinical trials and 36 outside clinical trials. Nivolumab was the first (1L), second (2L) and third-line (3L) treatment in 4 (11.1%), 18 (50%) and 14 (38.9%) patients, respectively. Sorafenib was the 1L in 100% of the patients who received nivolumab as 2L/3L and regorafenib was the 2L in 86% of the patients who received nivolumab as 3L. Regarding the 18 patients treated with nivolumab as 2L (61.1% Child-Pugh A; 38.9% Child-Pugh B and 100% PS0-1), 5 discontinued the 1L due to AE without radiologic progression and the remaining presented BCLCp-B (16.7%), BCLCp-C1 (27.8%) and BCLCp-C2 (27.8%). In the nivolumab-2L cohort, median follow-up and OS since the start of 1L was 12.5 months (IQR 7.7-28.9) and 28.5 months (95%CI 15.5-43.0) respectively. All, except 1 of 14 patients treated with nivolumab in the 3L (85.7% Child-Pugh A, 71.4% PS0 and 28.6% PS1) received nivolumab due to radiologic progression (BCLCp-B, C1 y C2: 7.1; 28.6 y 57.1%). In the nivolumab-3L cohort, median follow-up since 1L start was 21.3 months (IQR 15, 6-24, 4) and OS was not calculated owing to insufficient follow-up and number of events. Fifteen (46.8%) patients presented 25 AEs, of which 5 (20%) AEs were grade III-IV and 1 was grade V (rejection after liver transplantation). Corticosteroids were required for the management of AEs in 5 (15.6%) patients. There were 2 definitive discontinuations due to AEs (1 rejection after liver transplantation and 1 ascites).
Conclusion: The safety profile in this cohort is similar to that reported in clinical trials, despite the inclusion of patients in 2L and 3L. The heterogeneity in the patterns of progression before nivolumab and the fact that some patients started nivolumab due to intolerance to sorafenib/regorafenib without presenting radiologic progression highlights the need to consider these confounding factors when evaluating OS data.

PS-138

PD-1 targeted immunotherapy in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicenter real-world cohort

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Background and aims: Programmed cell death protein-1 (PD-1)-targeted immunotherapy has shown promising results in phase II studies of hepatocellular carcinoma (HCC). We report safety and efficacy data of an international, multicenter, real-world cohort of patients with advanced HCC treated with nivolumab or pembrolizumab.

Method: Sixty-five patients treated with nivolumab (n = 34) or pembrolizumab (n = 31) between July 10, 2015 and May 31, 2018 (data cut-off) across 6 centers in Austria and Germany were retrospectively analyzed.
Results: Child-Pugh class A/B/C was 32 (49%)/28 (43%)/5 (8%). Immunotherapy was used as systemic first-, second-, third-, or fourth-line treatment in 9 (14%), 27 (42%), 26 (40%), and 3 (5%) patients, respectively. Forty-six patients had at least one follow-up imaging and were therefore available for radiological response assessment. The overall response and disease control rates were 13% and 59%, respectively. Of 44 evaluable patients, four (9%) had hyperprogressive disease. Twenty-six (40%) patients had radiological disease progression and 21 (32%) participants died during follow-up. Median time to progression was 4.8 (95%CI, 1.7–7.9) months, median progression-free survival was 4.6 (95%CI, 1.9–7.4) months, and median overall survival was 11.0 (95%CI, 5.3–16.6) months. Most common adverse events were infections (n = 5), rash (n = 5), pruritus (n = 3), fatigue (n = 3), and hepatitis (n = 3). Efficacy and safety results were comparable between Child-Pugh A and B patients as well as between patients who received immunotherapy as first-/second-line and third-/fourth-line, respectively.
Conclusion: PD-1 targeted immunotherapy with nivolumab or pembrolizumab was safe in patient with advanced HCC, including subjects with Child-Pugh stage B and patients with intensive pretreatment. Efficacy was comparable to that reported in phase II studies.

PS-139
Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy
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Background and aims: Checkpoint inhibitors (CPi) are now standard of care in a variety of cancers. Various degrees of hepatic immune-related adverse events (LirAE) frequently occur, but diagnosis, clinical course and optimal management are poorly characterized. We sought to better understand causes of liver enzyme elevations (LEE) in patients treated with CPi, frequency of LirAE and impact on patient management.
Method: Patients enrolled in Phase I/II clinical trials within the Tumour Immunotherapy Program at Princess Margaret Cancer Centre from Aug 2012-Oct 2016 were included. Patients with a clinically significant LEE (ALT/AST > 3xULN and/or bilirubin > 1.5xULN) were identified and clinical records reviewed for cause, investigation, management and clinical outcomes.
Results: Of 338 patients treated with CPi, most (57.4%) received anti-PD-1 therapy whilst 17.4% received combination CPi. 74 (21.8%) had clinically significant LEE. Diagnostic evaluation included liver imaging in 52 (70.3%), HBV/HCV serologies in 13 (17.6%), autoimmune serologies in 6 (8.1%) and liver biopsy in 2 patients (2.7%). LEE was attributed to disease progression in 37 (50%), other drugs/toxins in 9 (12.2%), surgery in 5 (6.8%), other causes in 11 (14.9%) and to LirAE in 13 patients (18% of LEE and 3.8% of total cohort). LirAE was associated with prior CPi exposure (11.3% of patients with vs 2.4% of patients without prior CPi, p = 0.007) and other irAEs (occurring in 61.5% of patients with LirAE vs 19.8% of patients without, p = 0.002), but not with age, sex, primary malignancy, liver metastases or class or duration of CPi. Most patients with LirAE (12/13) received steroids with normalization of liver enzymes after a median of 37 days (range 7–102). 3 patients received further CPi with recurrent LirAE in 1 patient. During follow-up (median 8.2 months, range 0.6–51.8), 258 patients had disease progression and 100 patients died. Incidence of disease progression was lower in patients with LirAE (69.2% of patients with LirAE vs 92.9% of patients without, p = 0.015). No patient died of complications from LirAE.
Conclusion: LEE are common in patients receiving CPi and may be unrelated to cancer/CPi, requiring a full diagnostic evaluation. LirAE were more common in patients with previous CPi exposure and who had other irAEs. Those with LirAE had lower incidence of disease progression, possibly indicating more profound response to immunotherapy. Further work is required to identify risks for LirAE and optimize management.

PS-140
Association of gut microbiome with clinical response to nivolumab in advanced hepatocellular carcinoma: A pilot study
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Background and aims: Nivolumab (anti-programmed cell death-1, PD-1) is the first FDA-approved immune checkpoint inhibitor for advanced hepatocellular carcinoma (HCC). However, only ~20% of patients had an objective response to nivolumab; and the expression of PD-L1 could not predict the response. Gut microbiome was reported to modulate tumor response to checkpoint blockade immunotherapy in patients with melanoma. Whether the gut microbiome is also associated with clinical response to nivolumab in advanced HCC is unclear.
Method: From May 2017, 37 patients had received nivolumab treatment for advanced HCC in Taipei Veterans General Hospital. Among them, 20 patients were enrolled in this prospective study; and 12 of them completed fecal examination for gut microbiome analysis as well as already had radiographic assessment according to the RECIST criteria.
Results: The disease control rate was 50%, including three partial responses (25%) and three stable diseases (25%). The time to response was around 2 months (median interval 61 days, interquartile [IQR] 56–62). The median time to progression was 6.6 months (95% C.I. 0–15.5). Significant different composition of gut microbiome was observed between responders (R, n = 6) and non-responders (NR, n = 6). The responders had a relatively higher diversity in the fecal microbiome; and a significant clustering effect of the gut microbiome on response status was also observed in principal coordinate analysis according to either unweighted unifrac distance (p = 0.036) or Bray-Crutis distances (p = 0.019). Furthermore, the high dimensional class comparisons via linear discriminant analysis (LDA) of effect size also demonstrated differently abundant fecal bacteria between responders and non-responders to nivolumab therapy, with Aeromonadaceae enriched in NR and Burkholderiales enriched in R.
Conclusion: Gut microbiome has significant association with clinical response to nivolumab treatment in patients with advanced HCC. These findings highlight the therapeutic potential of modulating gut microbiome before immunotherapy.

PS-141
CyTOF-based immune monitoring of HBV-HCC patients receiving autologous anti-tumour T-cell therapy
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Background and aims: Short HBV-DNA fragments are frequently integrated in HBV-related hepatocellularcarcinoma (HBV-HCC).

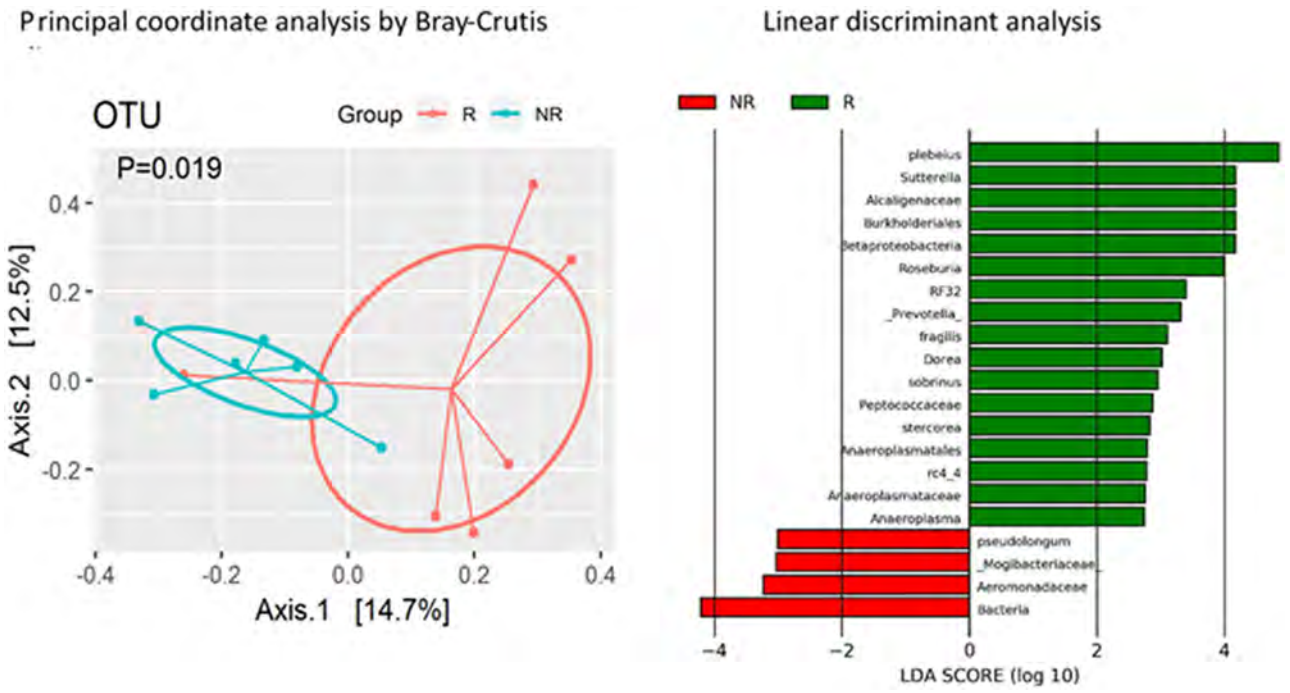

Figure: (abstract: PS-140)

These integrated HBV-DNA fragments can generate targetable CD8 T-cell viral epitopes allowing for the use of HBV-specific T-cells to eradicate HBV-HCC. Previously, we demonstrated how the analysis of HBV integrations in HBV-HCC tissues could be used to guide patient and HBV-specific TCR selection for use in HBV-HCC T-cell immunotherapy. Here, we focus on the immunological changes observed in patients during the course of the T-cell immunotherapy.

Method: HBV-HCC patients with metastases post liver transplantation were selected for T-cell immunotherapy. The metastases were analyzed for HBV integrations and the patients were treated with autologous mRNA electroporated T cells expressing HBV-specific TCRs. PBMCs from the patients were collected before and throughout the course of therapy consisting of multiple infusions of the transiently HBV-specific T-cells. Immune profiling of the PBMCs was performed by multi-parametric mass cytometry using 42 different markers.

Results: Despite the co-administration of immunosuppressive drugs due to the liver transplant, we detected a transient increase in the frequency of proliferating CD39+ CD8 T-cells within the first 5 days post T-cell infusion, which reached ~10% of total CD8 T-cells. This T-cell population was of effector memory phenotype (CD45AR-, CCR7-), co-expressing the activation markers Ki67, CD71, CD38 and HLA-DR, as well as the cytotoxic protease Granzyme A.

Conclusion: HBV-specific T-cell immunotherapy was able to induce detectable immunological changes in the peripheral blood of liver transplanted HBV-HCC patients under stable immunosuppression. Whether this is indicative of *in vivo* activation and proliferation of the infused HBV-specific T-cells, or a *de novo* induction of novel anti-tumour response warrants further monitoring and investigation.

PS-142

Analysis of sorafenib-regorafenib sequential therapy in patients with advanced hepatocellular carcinoma using baseline date of sorafenib

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Background and aims: Regorafenib is the second line drug after sorafenib in patients with advanced hepatocellular carcinoma (HCC), and has demonstrated a survival benefit compared to placebo in a Phase III trial (RESORCE trial). The RESORCE trial reported that median overall survival (OS) from the date of starting sorafenib for patients with the regorafenib arm to be over 26 months. However, the baseline clinical data at the time of starting sorafenib was not collected in the RESORCE trial. Therefore, the clinical benefit of sorafenib-regorafenib sequential therapy should be confirmed using data collected in field practice. This study aims to analyze the impact of sorafenib-regorafenib sequential therapy from the starting date of sorafenib in patients with advanced HCC.

Method: We retrospectively identified patients with advanced HCC who received sorafenib as the first line systemic therapy from June 2009 through December 2017. We excluded Child-Pugh B patients from this analysis.

Results: A total of 323 patients with Child-Pugh A liver function received sorafenib. Median age was 72 years, and the most frequent etiology was hepatitis C virus (n = 165, 50.3%), followed by hepatitis B virus (n = 45, 13.7%), and alcohol abuse (n = 43, 13.1%). A total of 94 (28.7%) patients had macrovascular invasion (MVI), and 142 (43.3%) had extrahepatic metastasis (EHM). The Majority of patients (89%) started a full dose of sorafenib (800 mg). The median OS for all patients was 13.7 months (95%CI, 11.8–14.2). During the observation

period, 29 patients were switched to regorafenib from sorafenib. The median OS in patients with sorafenib-regorafenib sequential therapy was 25.3 months (95%CI, 17.8–32.8) and which was higher than in patients who were treated with sorafenib therapy alone, i.e. they were unable to convert to regorafenib (median OS, 12.3 months; 95%CI, 10.4–14.2; P = 0.001). Not receiving regorafenib was an independent poor prognostic factor in the multivariate analysis with a cox hazard model, as well as for ECOG performance status, MVI, EHM, Child-Pugh score, and α-fetoprotein value.

Conclusion: Our results demonstrated the benefit of sorafenib-regorafenib sequential therapy in patients with advanced HCC using clinical data at the time of starting sorafenib. We recommend that it is necessary to increase the rate of conversion from sorafenib to regorafenib in patients with advanced HCC, although limited population of patients have switched sorafenib to regorafenib in the filed practice.

Cirrrhosis – Experimental aspects

PS-143

High-dimensional profiling of immune response in cirrhosis: Key role for activated CD8+ T-cells and relationship with prognosis

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Background and aims: Cirrhosis progression is associated with immune dysfunction. However, assessment of immune response in cirrhosis using high-resolution profiling has not yet been performed. The aim of the study was to use state-of-the art techniques for multiparametric characterization and unbiased analysis of immune phenotypes and functions across the entire spectrum of cirrhosis stages.

Method: single-cell mass cytometry profiling with 40 labels was performed on peripheral blood mononuclear cells from 30 patients with cirrhosis at different disease stages: compensated cirrhosis and decompensated cirrhosis (AD), with and without acute-on-chronic liver failure (ACLF). Unsupervised hierarchical clustering and regression analysis were performed to identify cell identities significantly different among disease stages. To further characterize the T cell compartment, single-cell T cell receptor (TCR) sequencing of activated CD8+ T cells was performed.

Results: mass cytometry data revealed that the only clusters of cells significantly different between patients with AD and those with compensated cirrhosis, regardless of the presence of ACLF, were clusters constricted to CD4+ and CD8+ T cells with activated phenotypes (CD69+ or CD38+HLA-DR+), that were significantly increased in AD. Patients with AD also showed significantly higher expression of PD1+ TIM3+ LAG3+ on CD8+ T cells and expansion of the CD4+CD25+CD127low Treg population, suggesting progression towards T cell exhaustion. Nonetheless, cytotoxic T cell activity (measured by in vitro IFNγ and IL-2 production) is preserved and significantly higher in AD compared to compensated patients. Analysis focused on patients with AD found that the only significant difference between patients with and without ACLF, was that those with ACLF had a markedly expanded monocyte population with significantly lower expression of HLA-DR and increase in PD-L1, compatible with a suppressor phenotype. TCR sequencing analysis showed that activated CD8+ T cells from patients with cirrhosis, independently of the disease stage, were markedly clonally expanded compared to healthy controls (48% vs 11% in cirrhosis vs controls; $p < 0.05$). We then analysed whether TCR sequences with common specificities were shared among different patients by clustering analysis. Among TCR sequences, we identified 13 clusters containing TCRs from multiple patients and from different disease stages, suggesting that T cell activation in cirrhosis may be driven by antigen recognition. Survival analysis showed that increase in activated CD8+ T cells and in CD8+TIM3+ T cells were associated with increased mortality.

Conclusion: high-dimensional profiling of immune responses in cirrhosis unveils a relevant role for CD8+ T cell activation in disease progression, that is associated with impaired outcomes.

PS-144

Autotaxin mediates lipid dysregulation in acute-on-chronic liver failure, promoting persistence of systemic inflammation via lysophosphatidic acid-mediated monocyte activation

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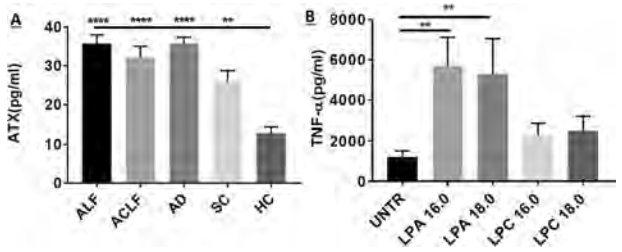
Background and aims: Acute-on-chronic liver failure (ACLF) is characterised by systemic inflammation and increased susceptibility to infection. Phenotypic and functional impairment in peripheral monocytes, with increased expression of regulatory Mer-tyrosine kinase (MERTK), has previously been demonstrated in ACLF. Lysophosphatidylcholines (LPCs) are immune-active lipids down-regulated in ACLF. The metabolic regulation of LPC and its role in monocyte function in ACLF is unknown.

Method: Patients with stable cirrhosis (SC, n = 18), acute decompensation (AD, n = 50) and ACLF (n = 60)) had admission and sequential plasma samples characterised by lipidomics (using ultra-performance liquid chromatography-mass spectrometry), cytokine and autotaxin (ATX) levels (by ELISA). Peripheral blood mononuclear cells (PBMCs) and isolated CD14+ monocytes were cultured in the presence of LPC or its ATX-derived product lysophosphatidic acid (LPA) with or without LPS stimulation. Monocytes were assessed for surface marker phenotype, cytokine production and phagocytic (E. coli pHrodo) capacity. Healthy volunteers (n = 40) and acute liver failure (ALF) patients (n = 30) served as controls.

Results: Patients with ACLF demonstrated significantly higher levels of TNF-alpha and IL-6 ($p < 0.001$) compared to SC, AD or HC, although TNF-alpha responses in ACLF were lower than ALF. ACLF plasma was depleted in multiple LPCs ($p < 0.001$) with up-regulated LPA levels ($p < 0.001$ cf controls). Patients who died or had sepsis had lower LPC levels than survivors (AUROC 0.94, $p < 0.001$). ATX was confirmed as the primary source of LPC-LPA conversion, with higher concentrations in patients with AD, ACLF and ALF (Fig A, $p < 0.001$), correlating with MELD and CLIF-SOFA scores (rho = 0.59, 0.65, $p < 0.01$ for both), and LPC and LPA concentrations. ATX levels rose dynamically over the first 48 hours of ACLF evolution ($p < 0.01$). ACLF patients had lower baseline HLA-DR, and higher CD163 and MERTK regulatory marker expression in CD14+ monocytes than controls; however, both CD163 and MERTK expression was markedly reduced in ACLF patients following 24-hour incubation with LPA ($p < 0.001$) but not LPC. LPA also induced significant up-regulation of

TNF-alpha production by CD14+ cells without improving phagocytic capacity (Fig B).



Conclusion: We show for the first time that phospholipid dysregulation in ACLF is dynamically mediated by ATX. Downstream LPA production inhibits resolution phenotypes in peripheral monocytes perpetuating inflammatory activation but not bacterial clearance. The therapeutic potential of the ATX-LPA axis requires further exploration.

PS-145

Albumin protects the liver from tumour necrosis factor alpha-induced cell death

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Background and aims: Albumin infusions reduce systemic inflammation and prevent organ failure (s) in patients with advanced chronic liver disease by mechanisms not completely defined. In the current study we performed *in vivo*, *ex vivo* and *in vitro* experiments to uncover the potential mechanisms implicated in the tissue protective actions of albumin.
Method: Double transgenic humanized neonatal Fc receptor (FcRn)/albumin mice were induced to stable cirrhosis by administration of carbon tetrachloride for 6 weeks and acute liver injury was provoked by injection of lipopolysaccharides (LPS) and D-galactosamine after receiving either placebo or two albumin dosages (1.5 g/kg). Hepatic F4/80 and caspase-3 immunostaining were assessed by immunohistochemistry and the population of peripheral blood Ly6C+Cd11b+ monocytes were measured by flow cytometry. *Ex vivo* and *in vitro* experiments were performed in precision-cut liver slices (PCLS) and hepatocytes, respectively, challenged with TNF-alpha in the presence or absence of albumin (15 mg/ml). Caspase-3 activity and cytosolic cathepsin B levels were measured by luminescence and fluorometric assays, respectively. The release of cytochrome C from the mitochondria to the cytosol was visualized by confocal microscopy and validated by Western blot. Gene expression was determined by real-time PCR.
Results: Transgenic humanized FcRn/albumin cirrhotic mice receiving albumin showed reduced levels of hepatic F4/80 and caspase-3 immunostaining. In addition, these mice showed an augmented number of patrolling and tissue repair $Ly6C^{Lo}$ monocytes and a reduced $Ly6C^{Hi}$ inflammatory subpopulation. In PCLS from wild-type mice, both preventive and therapeutic albumin administrations, significantly reduced TNF-alpha-induced caspase-3 activity and up-regulated the expression of tissue repair genes. Reduction of caspase-3 activity in hepatocytes incubated with albumin was associated with reduced release of the cysteine protease cathepsin B from lysosomes and a lower expression of the apoptotic transcription factor CHOP. Confocal microscopy experiments confirmed that albumin reduces the leaking of cytochrome C from mitochondria in hepatocytes.

Conclusion: Taken together, these findings uncover novel mechanisms by which albumin could protect organs from tissue damage, contributing to the understanding of why albumin infusions are useful in patients with advanced liver disease at risk of developing organ failures.

PS-146

Intestinal mucus and vascular barrier: FxR-modulated entry sites for pathological bacterial translocation in liver cirrhosis independent from portal hypertension and lymphatic route

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Background and aims: Pathological bacterial translocation (PBT) in liver cirrhosis (LC) is the pathophysiological hallmark for spontaneous bacterial infections increasing mortality. Factors known to contribute to PBT in LC are among others an increased intestinal permeability of which however, the mucus layer has not been addressed. A clear route of translocation for luminal intestinal bacteria is yet to be defined but we hypothesize that the recently described gut vascular barrier (GVB)[1] is impaired in cirrhosis leading to increased accessibility of the gut-liver-axis for bacteria.
Method: We applied partial portal vein ligation (PVL) or liver cirrhosis induced by carbon tetrachloride (CCl4) inhalation or bile duct ligation (BDL). Probe-based confocal endomicroscopy (pCLE) was utilized to evaluate the GVB by assessing extravasation of pre-defined sized FITC-dextrans. By dualband pCLE bacteria were visualized while crossing the muco-epithelial and vascular endothelial barrier.

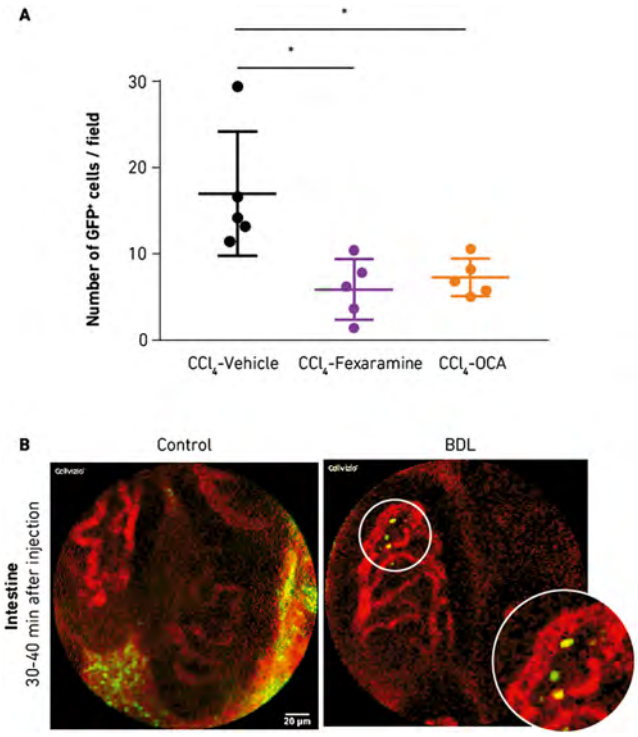

Figure: PBT from gut to liver of GFP-E.coli in CCl4-cirrhotic mice is reduced upon FXR agonists treatment (Fexaramine or obeticholic acid (OCA)) (A). GFP-E-coli crossed the muco-epithelial barrier and accessed the portal venous circulation in BDL but not in control mice.

Results: Healthy and pre-hepatic portal-hypertensive (PVL) mice lack translocation of FITC-dextran and GFP-E.coli from the small intestine to the liver whereas bile-duct-ligated (BDL) and CCl4-induced cirrhotic mice demonstrate PBT which is not altered by prior thoracic-duct ligation. Mucus layer is reduced in thickness with loss of goblet cells (GC) and *Muc2*-expression in cirrhotic but not PPVL-mice associating with a pathological translocation of GFP-E.coli through the ileal epithelium (Fig. 1B). GVB is profoundly altered in BDL and CCl4-mice with Ileal extravasation of large-sized 150 kDa-FITC-dextran but only minor in PPVL-animals. This pathological endothelial permeability and accessibility in cirrhotic mice associated with an augmented expression of PV1 in intestinal vessels. Pharmacological FXR-activation restores the normal GC density in CCl4-induced liver cirrhosis and improves GVB permeability ameliorating gut-liver-translocation of GFP-E.coli (Fig. 1A).
Conclusion: Liver cirrhosis but not portal hypertension per se grossly impairs the endothelial and muco-epithelial barrier promoting PBT to the portal-venous circulation. Both barriers appeared FXR-modulated with -agonists reducing PBT via the portal-venous route.

PS-147
Simvastatin-loaded nanoparticles are more effective and less toxic than conventional statins in a pre-clinical model of advanced chronic liver disease
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Background and aims: polymeric micelles (PM) are biodegradable, biocompatible and FDA-approved drug delivery systems (DDS), which are mainly directed to the liver and, due to its properties, can potentially load any type of molecule. Statins have demonstrated high potential to be considered a future treatment for chronic liver disease (CLD) but its side effects in patients with severely deteriorated hepatic function limit the administered dose and, thus, its effect. We aim at developing a drug delivery system based on PM to better target the liver sinusoidal endothelial cells (LSEC) and encapsulate simvastatin (PM-simva) in order to avoid muscular and hepatic toxicity and then improve the effectivity and safety of the drug.
Method: rats underwent bile duct ligation (BDL) and, 3 weeks after, cell isolation or in vivo treatment were performed. In cultured cells internalization was studied by flow cytometry after incubation with DTAF-labelled PM; to test its effect cells were treated for 16 h with empty PM, free simvastatin or PM-simv and gene expression was evaluated. In vivo, PM were i.v. administered once a day during one week and compared with vehicle or oral simvastatin treatments in haemodynamic studies.
Results: *In vitro*, LSEC derived from cirrhotic rats internalize PM-simva in similar way than healthy cells; after 10 min 50% of cells internalize PM and increased to 80% after 4 h. PM-simva have an effect increasing simvastatin target gene KLF2 in LSEC, Kupffer cells and hepatocytes. In LSEC this is associated with increased eNOS and reduced endothelin-1 expression. In KC and hepatocytes, KLF2 increased expression is associated with an increase in markers of cell phenotype maintenance.
In vivo, PM-simva biodistribution in BDL rats is mainly hepatic, 40% accumulate in the liver within 30minuts and importantly, have little muscular accumulation (2.4%). When administered for one week, hepatic toxicity is 70% in oral simvastatin vs. 0% in PM-simva and they reduce portal pressure (PP) from 16.8 in vehicle rats to 14.9 mmHg in PM-simva group ($p = 0.057$). PP in oral simvastatin treatment is 15.7 mmHg.
Conclusion: PM-simva show its effectiveness in improving liver cell phenotype in BDL-derived cells. Furthermore they cause less hepatic toxicity in this model and have greater effect in reducing portal hypertension being suitable DDS for treatments in CLD.

PS-148
Liver sinusoidal endothelial cells significantly cooperate in the phagocytic immune activities and activation of the adaptive T cell response in a model of experimental cirrhosis by CCl4
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Background and aims: Cells of the hepatic immune system play a fundamental role both in the detection and direct elimination of antigens, and in the activation of the adaptive response necessary for the maintenance of tissue homeostasis. Liver sinusoidal endothelial cells (LSECs) show functional capacity of antigenic presentation and activation of the adaptive T response. The objective was to determine the contribution of LSECs in hepatic immune function during experimental cirrhosis.
Method: Untreated Sprague-Dawley rats (Control group) and treated with intragastric CCl_4 for 12 weeks (CCl_4 group) were included. Perfused livers were collected, and Kupffer cells (KCs) and dendritic cells (DCs) were purified by beads. LSECs were isolated by differential centrifugation and adhesion on collagen pretreated plates. The phagocytic capacity was measured by internalization of LPS-FITC and posterior absorbance measurement (450 nm). For the evaluation of T lymphocytes activation, APCs were preactivated with bacterial LPS, and then co-incubated for 48 h with autologous CD4+ T lymphocytes isolated from spleen. The phenotypic expression of CD25 and CD71 on CD4+ T lymphocytes was analyzed.
Results: The innate immune response in controls is directed by the activity of LSEC cells. Its phagocytic capacity increases in cirrhosis and remains significantly above the phagocytic capacity of DCs and KCs in liver damage conditions (Table 1A). The expression of CD25 and CD71 as T cell activation markers is shown in Table 1B. The ability of induction of specific T cell responses increases in liver damage by all APCs. However, LSECs show an additional activation capacity in response to an acute stimulus in the pre-inflamed cirrhotic environment.
Conclusion: LSECs participate significantly in the regulation of the immune response in experimental cirrhosis by CCl_4.

PS-149
Recombinant glutamine synthetase: A novel strategy for the treatment of hyperammonemia and consequent hepatic encephalopathy in rodent model of cirrhosis and urea cycle enzyme deficiency
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Background and aims: In liver failure as well as UCD, there is an unmet clinical need for highly targeted, effective treatments for HA. When the urea cycle is compromised, alternative mechanisms of ammonia metabolism are triggered, such as the formation of glutamine by hepatic and muscle glutamine synthase (GS). However, the physiological upregulation of this enzyme is not sufficient to prevent HA. The aim of this study was therefore to

A)	PHAGOCYTOSIS *E.coli* abs 450 nm	
	Control	CCl_4
DCs	0,289±0,041	0,517±0,187 *
KCs	0,281±0,069	0,604±0,223 *
LSECs	0,416±0,015	0,920±0,820

B)	% cell membrane expression of CD25 in T cells	
	Control	CCl_4
DCs	15,81±10,73	24,74±6,70
DCs+LPS	14,69±7,37	24,44±7,49 *
KCs	16,55±7,14	24,45±7,96 *
KCs+LPS	16,05±8,27	24,20±7,94 *
LSECs	17,14±10,68	26,06±3,49
LSECs+LPS	17,26±11,23	35,64±7,84 *

	% cell membrane expression of CD71 in T cells	
	Control	CCl_4
DCs	1,02±0,14	3,37±1,08 *
DCs+LPS	2,06±1,63	3,90±0,76
KCs	1,47±0,17	4,08±0,92 *
KCs+LPS	2,78±1,33	3,60±0,72
LSECs	1,83±0,01	3,96±1,48 *
LSECs+LPS	0,92±0,34	9,36±7,00 *

A)
B)
C)

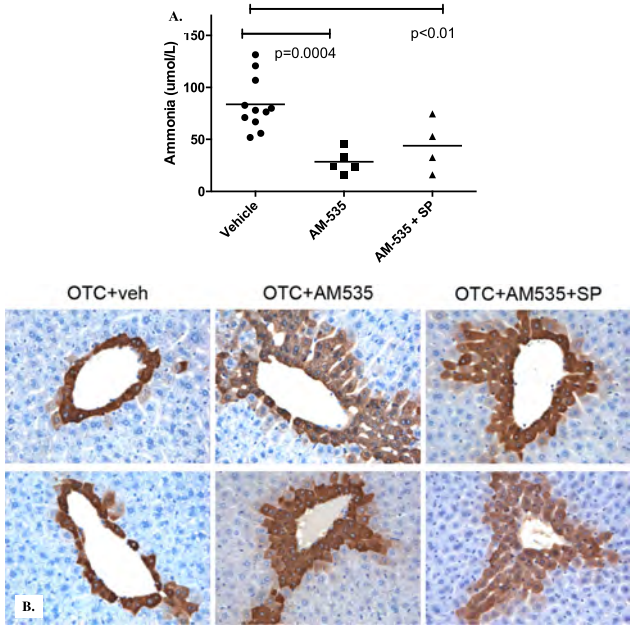
Figure 1. Phagocytic activity and T cell stimulation analysis. *A) E.coli phagocytosis by hepatic APCs (absorbance at 450 nm). B) Cell membrane CD25 and CD71 expression percentage in TCD4+ lymphocytes coincubated with the different hepatic APCs, preincubated or not with LPS for 18h.*

Figure: (abstract: PS-148)

assess recombinant GS (recGS; AM535; supplied by Ammun Ltd.) as a potential novel treatment for HA.

Method: *Study 1. GS in a bile duct ligated (BDL) rat model of cirrhosis:* 3 weeks after BDL, HA was induced by high ammonia diet for 5-days. Rats were treated with vehicle (n = 12) or AM-535 (20 mg/dl, ip. n = 11) on day 1 and 3. Plasma ammonia levels, brain water content and GS activity were assessed. *Study 2. GS in hemizygous ornithine transcarbamoylase-deficient mice ($OTC^{spf\text{-}ash}$)*: Mice were treated with vehicle (n = 11), AM-535 (20 mg/kg, n = 5) or AM-535+sodium phenylbutyrate (SP), an ammonia scavenger (0.3 g/kg, n = 4) for 6 days. Plasma ammonia levels were assessed and liver immunohistochemistry for GS was performed. *Study 3. In vivo localisation of AM-535:* AM-535 was labelled with a fluorescent probe and administered to CD-1 mice, which were imaged with an in vivo fluorescent imaging system for 14 days.

Results: *Study 1.* Rats treated with AM-535 had lower plasma ammonia [144 (+15) vs. 91 (+13) umol/L, $p < 0.01$], which was associated with less severe brain edema as reflected by brain water content [82 (+1.2) vs. 79 (+1.2)%, $p < 0.01$]. In addition, AM-535 treatment resulted in higher GS-activity in both plasma and liver as compared to the vehicle group ($p < 0.001$). *Study 2.* Plasma ammonia was significantly lower in the $OTC^{spf\text{-}ash}$ mice treated with AM-535 compared with vehicle. No additional effect of SP on plasma ammonia was seen in the AM-535+SP group [$p < 0.001$, **fig A**]. The administered AM-535 was localised in the pericentral regions in the liver, corresponding with usual zonation pattern of GS (**fig B**). *Study 3.* The in vivo imaging study with fluorescent AM-535 showed that the i. p. administered AM-535 was visible in high concentrations in the liver for 3-days.



Conclusion: The results of this study suggest that AM-535 is an effective therapy for HA in both cirrhosis and UCD. Given the safety and efficacy of enzyme replacement therapies, AM-535 should be developed further for clinical use.

Translational virology

PS-150

Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos (t)ide therapy with detectable but not quantifiable HBV DNA

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Background and aims: We previously reported that after 240 weeks of TDF or TDF/FTC treatment the majority of chronic hepatitis B (CHB) patients had detectable but not quantifiable (DNQ) HBV DNA (LLOQ ≤ 29 IU/ml). While these data suggest that viral suppression is not absolute with the current NUC therapies, it is not known whether the DNQ serum HBV DNA represents infectious virus. To determine if DNQ HBV DNA represents virus capable of infecting new hepatocytes, we utilized the PhoenixBio (PXB) uPA/SCID chimeric mouse model to assess the infectivity of serum from patients prior to and after long-term NUC therapy.

Method: Serum from nine CHB patients from clinical trial GS-US-203-0101 evaluating TDF or TDF/FTC was evaluated in the PXB mouse model. The nine patients had HBV genotype B or C infections, were HBeAg/HBsAg positive at baseline, and achieved viral suppression (≤29 IU/ml) at a median of 72 weeks. Baseline sera (mean viral load of 1.5×10^9 copies/ml) were inoculated into PXB mice (n = 2/sample) either undiluted or diluted such that the total amount of virus per mouse was 100, 10, 5 and 1 genome equivalents. A separate group of PXB mice were subsequently inoculated five times over a two week period with sera from patients taken 12-32 weeks after NUC treatment (HBV DNA ≤ 29 IU/ml) to determine if DNQ HBV DNA was infectious. Mouse sera were analyzed biweekly for HBV DNA by quantitative PCR and HBsAg/HBeAg by ELISA.

Results: Baseline patient sera were capable of establishing infections in PXB mice, reaching maximal viremia and antigen production at 30 days post-infection (average 5.5×10^8 copies/ml HBV DNA, 4.5×10^4 IU/ml HBsAg, 3.3×10^3 COI HBeAg). Dilution studies demonstrate that 1-5 genome equivalents are sufficient to result in infection. Mice that received multiple inoculations of sera from patients on NUC therapy with DNQ HBV DNA resulted in viremia for 9/31 (29%) samples at a median of 66 days post infection. No clinical or virologic features predicted infectivity of DNQ samples.

Conclusion: Sera from patients on long-term NUC therapy are capable of infecting naïve hepatocytes in the PXB mouse model, confirming NUC therapy does not fully suppress viral replication. Low levels of circulating virus may be sufficient to infect naïve hepatocytes to maintain chronic HBV infection in the liver in CHB patients on long-term NUC therapy. Reducing viral replication further may contribute to increased HBsAg loss among long-tern NUC treated patients.

PS-151

Hepatitis E virus infection induces mitochondrial fusion to facilitate viral replication through induction of autophagy

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Background and aims: Mitochondrial morphological dynamics play important roles in physiology and pathogenesis. This study aimed to understand mitochondrial morphological alteration in response to hepatitis E virus (HEV) infection and its implication.

Method: Liver biopsies of 17 patients with hepatitis E and 5 controls with hepatic hemangioma were reviewed for mitochondrial morphology by Immunofluorescence. Huh-7 cells inoculated with infectious HEV viral particle or transfected with *in vitro* generated HEV RNA were used to model HEV infection. Mitochondrial dynamics were observed by transmission electron microscope (TEM) and Immunofluorescence. Lentiviral mediated RNAi or lipofectamine delivered plasmids were applied to silence targeted genes. Viral replication was quantified by qPCR.

Results: Immunofluorescent staining of liver biopsies showed that 11 out of 17 (65%) HEV infected patients presented aggregated and fused mitochondria; whereas mitochondria in all 5 uninfected controls displayed uniform and spotty distribution. Ultrastructuralanalysis of HEV-infected Huh7 cells by TEM displayed elongated mitochondria (mitochondrial fusion) with obscure cristae (Fig. 1A). In contrast, mitochondria in uninfected cells displayed short and rod-like mitochondria with clear cristae. Consistently, immunofluorescent observation of HEV infected cells substantiated tubular mitochondria, in contrast to dispersive and fragmented mitochondria in uninfected cells (Fig. 1B). Mitochondrial fusion is modulated by proteins Optic atrophy 1 (OPA1) and Mitofusion 1 (Mfn1). Consistently, western blot analysis demonstrated an increase of both OPA1 and Mfn1 and a decrease of Fis 1 and Drp1 (regulators of mitochondrial fission) in HEV infected cells, compared with uninfected cells (Fig. 2A). Importantly, silencing of OPA1 or Mfn1, with a concomitant persistent fragmentation of mitochondria, resulted in a significant suppression of HEV replication, suggesting that HEV-induced mitochondrial fusion facilitates viral infection (Fig. 1C). Mechanistically, we found HEV infection can stimulate autophagy by inhibiting mTOR (Fig. 2B-C). While interference of mitochondrial fusion potently abrogated HEV induced autophagy by rescuing mTOR (Fig. 2B). Our previous study demonstrated that pharmacological or genetic activation of mTOR can facilitate HEV replication. Taken together, these results suggested that induction of autophagy could contribute to mitochondrial fusion mediated pro-HEV activity.

Conclusion: HEV infection induces mitochondrial fusion to facilitate HEV infection by induction of autophagy through suppressing mTOR. Mitochondrial dynamics represents a viable option for prevention and treatment for hepatitis E.

PS-152

Formation of semi-enveloped particles as a unique feature of a HBV deletion mutant

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Background and aims: In addition to virions, Hepatitis B virus (HBV)-infected cells release large amounts of subviral particles (SVPs) as spheres and filaments. SVPs are exclusively formed by HBV surface proteins (HBsAg). Virions and filaments contain all three surface proteins LHBs, MHBs and SHBs, while the spheres are composed almost exclusively of SHBs. LHBs encompasses the N-terminal PreS1-domain, followed by the PreS2- and the C-terminal S-domain. A deletion mutant lacking 15 amino acids (aa 25-39) in the PreS1-domain was isolated from a chronically infected patient.

Methods: HBV genomes were transiently expressed in HepG2 and Huh7 cells. Subcellular distribution of viral proteins was studied by confocal immunofluorescence microscopy and subcellular fractionation. Viral and subviral particles were isolated by density gradient centrifugation and analyzed by electron microscopy and western blot analysis.

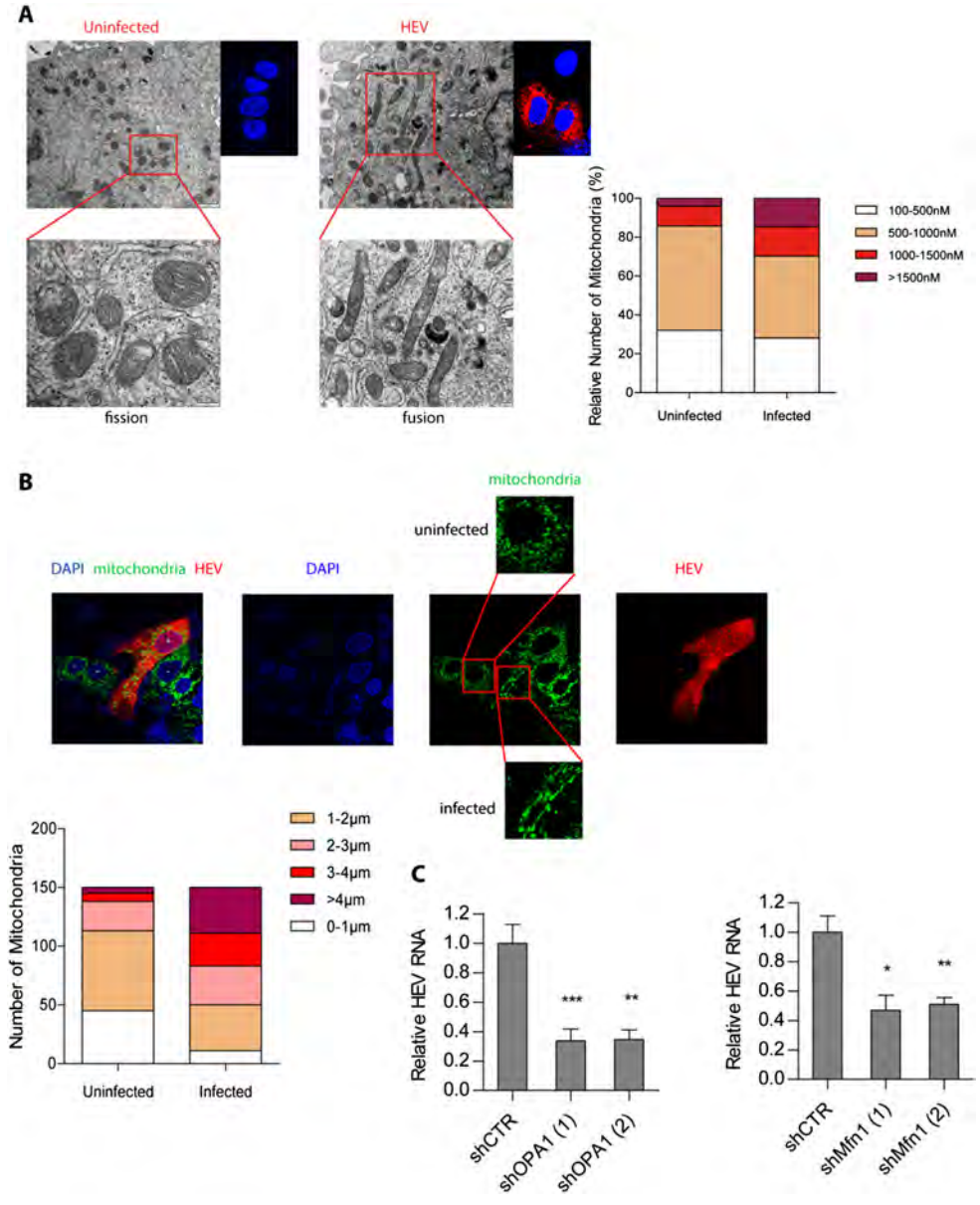

Figure 1: (abstract: PS-151)

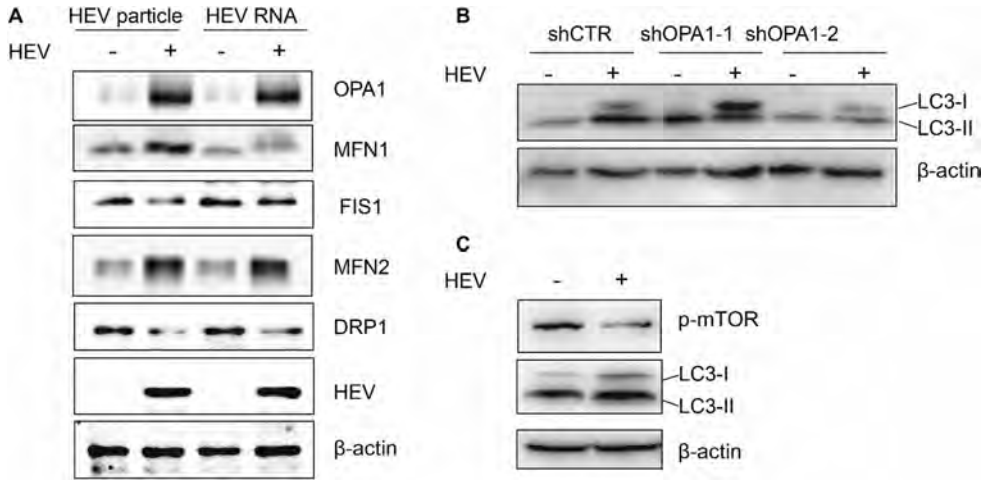

Figure 2: (abstract: PS-151)

Results: Expression of this mutant genome released higher amounts of LHBs in the form of shorter filaments as compared to the control. Morphology and release of spheres were not affected by this deletion. Most interestingly, a significant fraction of semi-enveloped virions was observed by electron microscopy that has been unprecedented so far. Stepwise insertion of aa 25-31, aa 32-39 and aa 25-39 increased the length of filaments. The rescue of aa 25-31 drastically decreased the fraction of semi-enveloped virions. Insertion of aa 32-39 had no effect on the rescue of the semi-enveloped virions, arguing against a simple spacer function of this region. Confocal immunofluorescence microscopy shows that deletion mutant and rescued mutants do not differ in subcellular HBsAg distribution and colocalization with ER, Golgi and MVB (multivesicular bodies) markers, arguing against differences in release pathways.
Conclusion: These data describe the first time formation of semi-enveloped HBV virions. In contrast to existing models, relevance of the N-terminal PreS1-domain (aa 25-31) for the morphogenesis and release of properly assembled virions and filaments is shown. As morphogenesis of virions (harbouring a nucleocapsid) and filaments (lacking a nucleocapsid) is affected by deletion of this region, it is concluded that this region triggers proper HBsAg-assembly independent of a direct interaction with the nucleocapsid.

PS-153

The pre-s2 deletion HBVmutants are responsible for the intracellular accumulation of the HBS protein, ER stress and mitochondria dysfunction

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Background and aims: Pre-S deletion HBV mutants are associated with HCC development and postoperative recurrence. Mitochondrial is related to lipid metabolism, liver diseases and HCC development. This study aimed to investigate the association of wild type and pre-S2 deletion HBV mutants with HBsAg retention, ER stress and mitochondrial dysfunction.
Methods: The HBV whole genome expression plasmids containing wild type or various pre-S2 deletion mutant sequences under the driving of HBV endogenous promoter or CMV promoter were transfected into Huh7 cells. The intracellular retention of HBsAg and the subsequent ER stress or mitochondria dysfunction were compared between Huh-7 cells transfected by plasmids expressing wild type HBV or various pre-S2 deletion mutants and hepatocytes of HBV infected FRG mice containing chimeric human hepatocytes.
Results: The ratio of intracellular to the HBsAg in culture medium were calculated. Intracellular HBsAg retention ratio was the lowest in the wild type, followed by the pre-S2 mutant with proline 142, and the highest in the HBV pre-S2 mutant without proline. The ER stress markers (pIRE1α, XBP1, CHOP) were significantly higher in Huh-7 cells transfected with plasmids of pre-S2 mutants by immunoblotting analysis. Colocalizations of HBsAg and an ER-marker calnexin were confirmed by confocal microscopy. In contrast to the diffuse and homogenous distribution of HBsAg expressed by wild type HBV, pre-S2 deleted HBsAg located over perinuclear area and aggregated into coarse granules or clumps in both transfected Huh-7 cells and HBV-infected human hepatocytes in FRG mice. Electron micrographs revealed that aberrant ER ultra-structures include ER dilation and fragmentation in HBV expressing cells. In addition, mitochondria fragmented with defects in cristae shape were also found in both wild type and pre-S2 mutants HBV expressing cells with different extents under transmission electron microscopy. Time lapse live imaging of mitochondria labeled with MitoTracker revealed that the mitochondria motility were impaired in wild type HBV expressing cells and even more severe in pre-S2 mutants-expressing cells. Using the human liver chimeric mouse model of Fah/Rag2/Il2rg (FRG), serum HBV DNA levels of FRG mice infected by the pre-S2 deletion HBV mutant were 2 logs lower than those infected by the wild type. The secretion of HBsAg in the serum of FRG mice infected with the pre-S2 deletion HBV mutant was also decreased.
Conclusion: Pre-S2 deletion HBV mutants are impaired in secretion which resulted in the retention of HBsAg inside the liver cells. The intracellular accumulation of HBsAg induces ER stress, mitochondria dysfunction which may subsequently impair lipid metabolism and contribute to HCC development.

PS-154

Dissecting the different roles of ORF3 in HEV spread and fecal shedding in a humanized mouse model

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Background and aims: Hepatitis E viruses (HEV) are an important enterically transmitted cause of viral hepatitis. The HEV RNA genome is single-stranded, positive-sensed RNA encoding 3 ORFs. Although ORF3 has a viroporin structure and is required for viral propagation in macaques, its exact role remains unclear. In the present study, we dissect ORF3's function via reverse genetics and infectivity studies, both in vitro as in the liver humanized mouse model.
Method: A genotype 3 HEV strain (Kernow C1, P6) was used as backbone to construct ORF3 mutant viruses. Virus stocks were produced by transfecting in vitro transcripts into Huh-7 (clone S10-3) cells followed by gradient ultracentrifugation to purify intracellular non-enveloped virions. uPA-NOG and TK-NOG mice (n = 15) were transplanted with human hepatocytes from a single donor and inoculated iv with ORF3 mutant viruses (6 log geq/mouse) upon establishment of a stable graft. Weekly feces and serum samples were obtained during the 6-weeks infection course, after which animals were sacrificed and liver and bile were collected for viral load determination by multiplex qPCR.
Results: Three ORF3 mutants were generated: an ORF3del mutant that contains a mutation in the start codon, a PSAP mutant that contains mutations in the C terminal late domain, and a CCC mutant that contains mutations in the N terminal cysteines 11–13 (a putative palmitoylation site). Replication and infectivity of all 3 mutants were comparable to the wild type (WT) HEV in vitro. WT ORF3 and the PSAP mutant predominantly localized to the apical membrane of HepG2 cells, whereas the CCC mutant was predominantly cytoplasmic. At sacrifice, HEV RNA was detectable in livers of 9/14 animals (1 mouse died at 4 weeks pi) with HEV RNA titers (4–7 log IU/gr tissue) comparable between WT (n = 4/4), PSAP (n = 4/4) and CCC (n = 1/2) inoculated mice. None of the ORF3del mutants proved infectious in vivo (n = 4/4). While all WT inoculated mice had detectable HEV RNA in bile (5-7 log IU/ml) and feces (3–6 log IU/gr), only 1/4 PSAP mutant inoculated mice showed quantifiable HEV RNA in bile and feces. The HEV CCC mutant was barely detectable in bile (< 3.75 log IU/ml) and negative in fecal samples (n = 3/3). Despite this, serum titers between WT-HEV PSAP and HEV CCC mutant viruses were comparable.
Conclusion: Overall this corroborates the importance of ORF3 in HEV propagation in vivo and suggests a role of a putative palmitoylation site at the N-terminus of ORF3 in secretion of HEV into the biliary canaliculi.

PS-155

HBV entry inhibition after interferon alpha treatment hinders HBV rebound in hepatocytes that became negative for all HBV markers during interferon treatment

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Background and aims: Treatment with interferon alpha (IFNα) can exert both immunomodulatory and antiviral effects, such as suppression of HBV transcription and cccDNA degradation. In this study, we aimed to investigate to which extent these antiviral effects take place in HBV-infected human hepatocytes in vivo and whether these effects can persist after treatment cessation. Moreover, we employed HBV entry inhibition to assess the role of new infection events in HBV rebound.
Methods: We treated HBV infected human liver chimeric mice with pegylated IFNα for 6 weeks (n = 13+5 untreated controls). Then, mice were either sacrificed (n = 5) or treatment was stopped to assess serological and intrahepatic viral changes for additional 6 weeks, either in the presence (n = 4) or absence of the entry inhibitor Myrcludex B (MyrB) (n = 4). MyrB treatment started 3 days before the last IFNα injection. HBV loads were analysed in serum and liver by qPCR. RNA in situ hybridization (RNA-ISH) and immunofluorescence were used to visualize both HBV transcription and the presence of SMC6, a component of the "structural maintenance of chromosomes complex" SMC5/6 which is degraded by the HBx protein, and hence may serve as a cellular marker of cccDNA suppression or clearance.
Results: Six weeks of IFNα treatment reduced median levels of viremia (1.2log), HBV transcripts (3.6fold) and cccDNA (4.3fold). As expected, SMC6 protein was degraded in most hepatocytes in the livers of HBV-infected control mice, but it was clearly detected in IFNα-treated mice. After stopping IFNα, HBV rebound occurred in 3 to 6 weeks and was accompanied by renewed SMC6 degradation in most human hepatocytes. Of note, we observed viremia increase also in MyrB-treated mice; however, entry inhibition blocked intrahepatic HBV rebound in a large proportion of human hepatocytes (>40%), which remained SMC6 positive and negative for HBcAg and HBV RNA (RNA-ISH). Interestingly, intrahepatic cccDNA levels in mice receiving MyrB during rebound remained as low as in mice sacrificed at the end of IFNα treatment.
Conclusion: Reappearance of the SMC5/6 complex in HBV-infected human hepatocytes in mice treated with IFNα did not hinder HBV reactivation after drug withdrawal in the setting of an established HBV infection. However, MyrB clearly maintained HBV negativity in a substantial proportion of human hepatocytes, suggesting that these cells had cleared cccDNA during IFNα treatment and that new infection events play a key role in HBV rebound post treatment.

PS-156

Antigen suppression effect of the core protein allosteric modulator RO7049389 in AAV-HBV mice is accompanied by transient upregulation of immune-cell gene signatures in the liver

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Background and aims: The hepatitis B virus (HBV) core protein plays critical roles in multiple steps of the HBV life cycle, representing an attractive target for anti-HBV therapeutics. We have previously demonstrated that oral administration of RO7049389, a small molecule HBV core protein allosteric modulator (CpAM) in Phase I clinical development, can result in sustained suppression of not only serum HBV DNA, but also HBsAg and HBeAg levels in a mouse model infected with recombinant adeno associated virus carrying HBV genome (AAV HBV). Here we report follow-up studies aimed at a better understanding of the mechanisms of RO7049389 beyond its direct antiviral effect.
Method: In vivo efficacy of RO7049389 was studied in AAV-HBV infected immunocompetent (C57BL/6) as well as immunodeficient (CB17 SCID) mice. RNA-seq based transcriptome analyses were applied to liver tissues collected from AAV-HBV infected or uninfected mice dosed with or without RO7049389. Time points for tissue collection were selected to cover the time window before, during, and after the decline phase of HBV antigens.
Results: Oral administration of RO7049389 (20 mg/kg once daily) in AAV-HBV infected C57BL/6 mice rapidly reduced serum HBV DNA level, reaching the lower limit of quantification (LLOQ, 4.3 Log_{10} copies/ml) within 14 days of treatment. In contrast, the onset of HBsAg and HBeAg decline was much delayed, occurred only after maximal DNA suppression was achieved. RNA-seq analysis of liver tissues revealed that RO7049389 induced temporal effects on host gene expression exclusively in the AAV-HBV infected mice. While few genes are modulated at both early (day 3) and late (day 35) time points, gene-set enrichment analysis indicated upregulation of gene signatures specific to multiple immune cell types in the liver around day 14 and day 21, which coincide with the onset of serum HBV antigens decline. When similar studies were conducted in AAV-HBV infected CB17 SCID mice lacking functional T and B cells, HBsAg and HBeAg were also reduced by RO7049389 treatment, though the effect was slightly delayed. Taken together, these data indicated that although on the gene-expression level both innate and adaptive immune responses were temporarily enhanced in RO7049389 treated AAV-HBV infected C57BL/6 mice, mature T and B cells are likely dispensable for the antigen suppression effect of RO7049389.
Conclusion: Our study indicates that the antigen suppression effect of RO7049389 in AAV-HBV mice is accompanied by transient upregulation of immune-cell gene signatures in the liver, but nevertheless does not depend on T and B cell functions. These effects clearly differentiate RO7049389 from other direct-acting antiviral drugs and will be further studied both in preclinical models and in the clinical setting.

Gut-Liver Axis

PS-157

Gut microbiome signature for cirrhosis due to non-alcoholoic fatty liver disease: A prospective twin and family study

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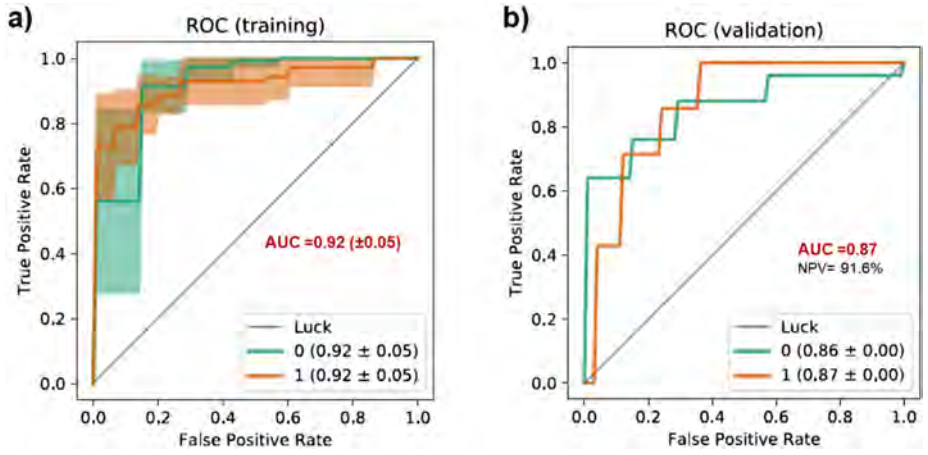

Figure 1: High diagnostic accuracy of a gut-microbiome signature for the detection of NAFLD-cirrhosis
AUROC to predict NAFLD-cirrhosis using Random Forest classification in (a) training (b) validation cohort.

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Background and aims: The presence of cirrhosis in non-alcoholic fatty liver disease (NAFLD) is the most important predictor of liver-related mortality. Moreover, we have demonstrated that first-degree relatives of probands with NAFLD-cirrhosis have a high risk of advanced fibrosis. The gut-liver axis has recently emerged as a pivotal component of NAFLD but limited data exist concerning the diagnostic accuracy of gut-microbiome-derived signatures for detecting NAFLD-cirrhosis. We aimed at examining the familial similarity of gut-microbiome composition and to test whether a non-invasive stool-microbiome-derived signature accurately detects NAFLD-cirrhosis.
Method: We characterized by 16S rRNA amplicon sequencing gut-microbiome compositions of 203 uniquely well-characterized participants from a prospective twin and family cohort, including 98 probands encompassing the entire spectrum of NAFLD (NAFLD-cirrhosis (n = 26), NAFLD without AF (n = 18), non-NAFLD controls (n = 54)) and their first-degree relatives (n = 105), assessed using advanced magnetic resonance (MR)-imaging proton density fat fraction (MRI-PDFF) for quantifying hepatic steatosis and MR-elastography (MRE) for quantifying liver fibrosis.
Results: We observed a significant correlation within biologically related pairs compared to random-unrelated pairs at the level of the phyla (p = 0.023) and 16S sequences of bacterial strains (p = 2.4E-41). In addition related individuals with shared-housing had a lower phylogenetic dissimilarity than those who did not share housing (p = 0.045). We identified a panel of 30 features, including 27 bacterial features and age, sex and body mass index, which were used to build a Random Forest classifier for detecting NAFLD-cirrhosis. In a *derivation* cohort of probands with NAFLD-cirrhosis and non-NAFLD controls, the model had a robust diagnostic accuracy (receiver operating characteristic curve (AUROC) of 0.92) for detecting NAFLD-cirrhosis **Fig. 1a**, confirmed in a *validation* cohort of first-degree relatives of proband with NAFLD-cirrhosis (AUROC of 0.87) **Fig. 1b.**
Conclusion: This study reports a strong familial correlation of gut-microbiome driven by shared-housing and provides evidence for a novel fecal-microbiome-derived signature to detect NAFLD-cirrhosis.

PS-158
Paneth cells drive microbial induced signals to promote angiogenesis and regulate portal hypertension

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Background and aims: The number of Paneth cells (PCs) is increased in portal hypertension and in the presence of bacteria, but the mechanisms by which these cells contribute to the regulation of splanchnic hemodynamics are unknown. We investigated their role in a model of conditional deletion of PCs in which we induced portal hypertension by partial portal vein ligation (PPVL).
Method: Math-1 Lox/LoxVillcreERT2 or control mice were injected three consecutive doses of tamoxifen before undergoing PPVL or sham surgery. Hemodynamic measurements were performed 14 days after PPVL. Intestinal and mesenteric angiogenesis was assessed by immunohistochemistry using CD-31 antibodies. Using a RT^2 profiler PCR array we quantified the expression of angiogenic genes in distal ileum. 3D enteroids from control and PC depleted mice were exposed to different bacterial derived products and E. *coli*. The conditioned media (CM) from these enteroids were co-cultured with endothelial cells (EC) to analyse tube formation activity on matrigel as well as wound healing responses. Proteomic analysis of CM was performed using MaxQuant v1.6.2.2.3 to quantify differentially regulated proteins.
Results: Portal hypertension was significantly attenuated in Paneth cell depleted mice compared to control mice and was associated with a decrease in portosystemic shunts (n = 8–11/group). Depletion of PCs also resulted in a significantly decreased density of blood vessels in ileum and mesentery. Tube formation and wound healing responses were significantly decreased in ECs treated with conditioned media from PC-depleted organoids. Proteomic results revealed that an important number of proteins associated with angiogenesis were downregulated in CM of enteroids lacking Paneth cells, confirming the data obtained from PCR arrays.

Conclusion: The in vivo and in vitro results presented here suggest that intestinal flora and microbial-derived factors activate Paneth cells to secrete proangiogenic signalling molecules to increase intestinal and mesenteric angiogenesis. These effects are abrogated in the absence of Paneth cells leading to a decrease in portal hypertension.

PS-159

Intestinal dysbiosis fuels liver disease progression via NLRP3 in the Mdr2$^{-/-}$ mouse model of primary sclerosing cholangitis

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Background and aims: There is a striking association between human cholestatic liver disease (CLD) and inflammatory bowel disease. However, the implications for intestinal microbiota and inflammasome mediated innate immune response in cholestatic liver disease remain imprecise. Here we investigated the functional role of gut-liver crosstalk for cholestatic liver disease in PSC patients and the murine PSC-model the Mdr2 knockout (*Mdr2*$^{-/-}$) mice.
Method: *Mdr2*$^{-/-}$, *Mdr2*$^{-/-}$ crossed with hepatocyte-specific deletion of capsase-8 (*Mdr2*$^{-/-}$/Casp8$^{\Delta hepa}$) and wildtype (WT) control mice to characterize the impact of Mdr2 deletion on liver and gut including comprehensive bile acid and microbiota profiling. To block caspase activation, a pan-caspase inhibitor (IDN-7314) was administered. Finally, the functional role of *Mdr2*$^{-/-}$ associated intestinal dysbiosis was studied by microbiota transfer (FMT) experiments.
Results: *Mdr2*$^{-/-}$ mice displayed an unfavorable intestinal microbiota signature and pronounced NLRP3 inflammasome activation within the gut-liver axis, as found by immunostaining and western blot analysis in the intestine as well as in the liver. In addition, significant NLRP3 inflammasome activation was found in livers of PSC patients. Intestinal dysbiosis in *Mdr2*$^{-/-}$ mice prompted intestinal barrier dysfunction evidenced by reduced colonic mucus layers, reduction of tight junction expression and increased permeability evidenced by an in-vivo FITC-dextran assay. Loss of intestinal barrier integrity and bacterial translocation triggered the hepatic NLRP3 mediated innate immune response and fueled liver disease progression. Strinkingly, *Mdr2*$^{-/-}$ microbiota was transmissible to healthy WT mice, urged intestinal barrier impairment and induced significant liver injury in recipient mice, which resembled the inflammatory *Mdr2*$^{-/-}$ phenotype characterized by NLRP3 activation within the gut-liver axis.
This phenotype could not be rescued by introducing *Mdr2*$^{-/-}$/*Casp8*$^{\Delta hepa}$ indicating that hepatocytic caspase-8 activation is a downstream consequence and dispensable for the inflammatory response. In contrast, caspase inhibition via IDN-7314 dampened inflammasome activation, improved barrier function, ameliorated liver injury, reversed serum bile acid profile and cholestasis associated microbiota signature.
Conclusion: CLD in *Mdr2*$^{-/-}$ mice triggers intestinal dysbiosis, which is transmissible to healthy WT mice. In turn, translocation of endotoxin into the portal vein and subsequent NLRP3 inflammasome activation as also found in PSC patients contribute to higher liver injury in *Mdr2*$^{-/-}$ mice. This process does not essentially depend on hepatocytic caspase-8, but can be blocked by IDN-7314, highlighting the causal role of intestinal dysbiosis and the subsequent innate immune response for disease progression in *Mdr2*$^{-/-}$ mice, which might also be relevant in humans.

PS-160

miRNA-21 signals through a gut-liver axis to regulate experimental cholestasis

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Background and aims: Gut microbiota plays an important role in gut-liver axis homeostasis. New evidence suggests that endogenous miRNAs, secreted into the intestinal lumen, may modulate gut microbiota function and abundance. For instance, loss of miR-21 alters gut microbiota composition in mice and protects against inflammatory bowel disease. Of note, we previously showed that miR-21 deletion ameliorates liver fibrosis in experimental cholestasis and improves adaptative response to bile acid dysregulation. Here, we aimed to characterize changes occurring in the gut microbiota of miR-21 knockout (miR-21KO) mice after bile duct ligation (BDL).
Methods: Three-month old C57BL/6 wild type (WT) and whole body miR-21KO mice were subjected to sham or BDL surgeries. After 3 days, the small intestine was collected for qRT-PCR analysis of intestinal permeability-related genes. Serum was also collected for biochemical analyses. Gut microbiota composition was evaluated by sequencing the 16S rRNA gene V3 region of bacterial DNA from the small intestinal lumen. In co-housing experiments, WT and miR-21KO animals were housed together for 1 month and then separated into different boxes for an additional month.
Results: Our results show that miR-21KO mice are protected against small intestinal dysbiosis induced by BDL. In particular, depletion of miR-21 in mice positively correlated with increased *Lactobacillus sp.* and diminished Proteobacteria. This effect is independent from the BDL, as miR-21KO co-housed mice display increased relative abundance of *Lactobacillus sp.* in the small intestine, compared with WT mice. Of note, separated miR-21KO animals showed higher amounts of *Lactobacillus sp.* when compared with co-housed miR-21KO. Further, mRNA expression of small intestinal tight junctions (ZO-1, JAM-A and Occludin-1) and stem cell markers (Lgr5 and Olfm4) are decreased in WT mice after BDL but remains unaltered in miR-21KO animals. Finally, miR-21 ablation also correlates with increased FXR mRNA expression in the small intestine, increased bile acid homeostasis and reduced liver injury.
Conclusion: Genetic ablation of miR-21 modulates small intestinal permeability and FXR expression, impacting on bile acid production and contributing for improved gut microbiota and host homeostasis. These results reinforce the importance of the gut-liver axis in protecting the liver after acute cholestasis.
Supported by PTDC/BIM-MEC/089572014 and SFRH/BPD/114924/2016 from FCT, Portugal.

PS-161

Lactobacillus rhamnosus GG culture supernatant improves energy expenditure and glucose tolerance in high-fat-high-fructose fed mice exposed to chronic intermittent hypoxia through regulation of intestinal microbiota and bile acid homeostasis

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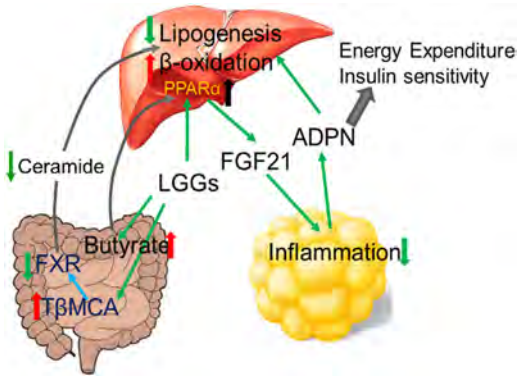
Background and aims: OSAS has been recently connected to metabolic disorders such as NAFLD and type 2 diabetes. Our previous studies have demonstrated that the probiotic *Lactobacillus rhamnosus* GG cultural supernatant (LGGs) prevents ALD and fructose-induced NAFLD. In the current study, we aimed to examine the effects the mechanism of LGGs on glucose metabolisms and body energy expenditure in mice fed a high-fat-high-fructose (HFHF) diet and exposed to chronic intermittent hypoxia in order to understand the underlying mechanisms.

Method: C57BL/6 mice were fed HFHF diet or normal liquid diet (NLD) respectively for 15 weeks. After 3 weeks feeding, two groups of mice were exposed to chronic intermittent hypoxia (CIH) for 12 weeks, and one of the groups was supplemented with LGGs at a dose equivalent to 10^9 CFU bacteria/day.

Results: HFHF diet feeding significantly increased body fat mass, hepatic steatosis, glucose tolerance, and liver injury, and decreased energy expenditure. These indices of metabolic disorders were worsened in mice exposed to CIH, indicating that CIH has an additive effect on HFHF diet feeding. The HFHF-fed mice supplemented with LGGs showed marked improvements in indices of metabolic disorder including fat mass, energy expenditure and glucose and insulin tolerance. LGGs treatment decreased hepatic fat content and adipocyte size. Adipose expression of HIF-1α, a marker of tissue hypoxia, was increased in HFHF-CIH mice, which was reduced by LGGs treatment. The reduction of adipose tissue hypoxia was associated with decreased inflammatory cytokines such as TNFα, IL-1β and IL-6. HFHF-CIH mice had a markedly reduced circulating adiponectin, and was significantly elevated by LGGs treatment. Metabolomics study showed that intestinal butyrate was significantly elevated by LGGs leading to hepatic PPARα activation and a robust elevation of FGF21 expression in the liver and in circulation. Importantly, depletion of FGF21 significantly attenuated the beneficial effect of LGGs. Furthermore, LGGs significantly changed hepatic and fecal bile acid composition. Fecal concentrations of TαMCA and TβMCA, which are known FXR antagonists, were decreased in HFHF-CIH mice but were significantly increased by LGGs treatment. Intestinal and circulation ceramide, which is regulated by FXR and contributes to NAFLD, was reduced by LGGs.



Conclusion: LGGs treatment prevents NAFLD and increases energy expenditure and insulin sensitivity induced by diet and hypoxia in HFHF-CIH mice. The beneficial effects of LGGs are mediated by multiple mechanisms. LGGs increases intestinal butyrate and hepatic PPARα expression leading to increased hepatic FGF21 expression and adipose adiponectin production. LGGs increases TβMCA which inhibits intestinal FXR and likely ceramide production. LGGs may be used as a potential treatment strategy in subjects with OSAS and metabolic syndrome.

PS-162

Gut microbiota is closely involved in the prognosis of HBV-related acute-on-chronic liver failure

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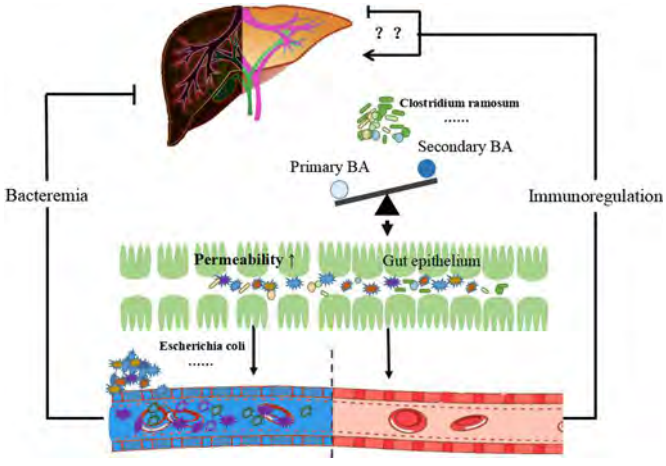
Background and aims: The characteristic of HBV-related acute-on-chronic liver failure (HBV-ACLF) is the rapid progression and frequently high mortality. However the specific influence factors that contributed to this remains to be clarified. Emerging evidence have highlighted the role of gut microbiota in liver disease. This study focused on defining the changes of the gut microbiota in fecal and blood of HBV-ACLF patients.

Method: We recruited 128 patients with HBV-ACLF and 20 health controls (NC). The two of the HBV-ACLF patients were collected three times approximately every week (7 ± 2days) according to the degree of disease progression: one case as regression, the other case as progression. The gut microbiota composition was determined using 16S rRNA gene sequencing of stool samples. Metagenome sequencing of fecal, blood, white blood cells of the two dynamic HBV-ACLF patients. The species composition was identified and pathway analysis of the predicted genes were performed using geeNOG, GO, KEGG database. The content of bile acids in fecal and blood was determined by liquid chromatography-mass spectrometry.



Results: The fecal microbiota diversity of HBV-ACLF group was significantly lower compared with that of NC. Among these gut microbiota, HBV-ACLF regression group showed higher abundance of Streptococcus, Megamonas, Clostridium, Ruminococcus and Dorea, while the progression group showed increased Veillonella and Enterococcus. Faecalibacterium, Roseburia, Lachnospiraceae, et al were significantly increased in the NC group. Metagenomic sequencing revealed Ruminococcus and Lachnospiraceae with different abundance have the same trend showed in 16 s rRNA gene sequencing. Further, correlation analysis of bile acids and gut microbiota showed only two types of bile acids, cholate and deoxycholate were detectable in the first week samples of HBV-ACLF. While on the second and third week samples, the types of bile

acids in the regression patients increased mainly secondary bile acids while such phenomenon was not observed in the progression group. Interestingly, we also observed that enterococcus-faecalis, escherichia-coli, veillonella-unclassified were co-existed in the fecal, blood and white blood cells simultaneously when clinical blood culture test was negative in the HBV-ACLF.

Conclusion: The abundance of different major gut microbiota, including Ruminococcus and Lachnospiraceae, may be a potential underlying mechanism of developing advanced HBV-ACLF. Bile acid metabolism indirectly influences the prognosis of HBV-ACLF through the regulation of intestinal flora. Besides, the co-exist of the several gut microbiota species in fecal and blood suggests that it may be very important to carry out antibiotic therapies ahead of the exactly evidences.

PS-163

Faecal microbiota transplantation with tenofovir is superior to tenofovir alone in improving clinical outcomes in acute-on-chronic liver failure due to hepatitis B: An open label randomized controlled trial (NCT02689245)

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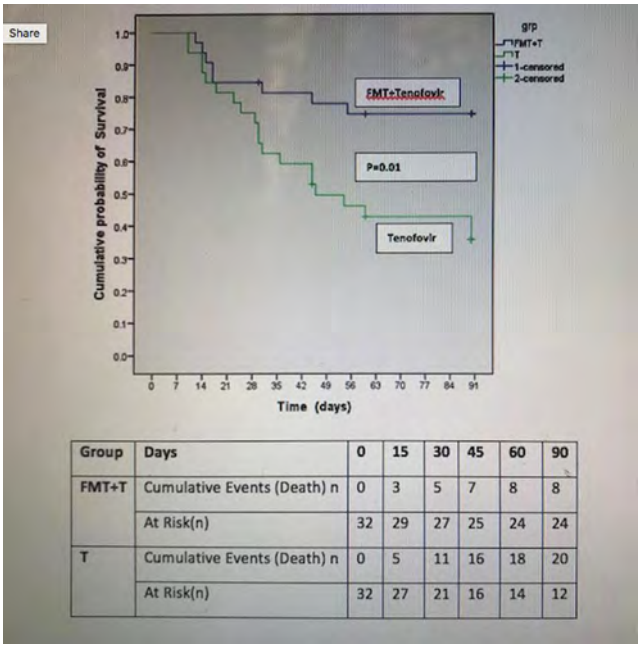
Background and aims: Acute-on-chronic liver failure due to reactivation of hepatitis B (ACLF-B) has a high mortality despite antiviral therapy, and urgent liver transplantation is often needed. Gut dysbiosis is an important contributor for development of infections and liver failure in ACLF. It is plausible that manipulation of gut microflora may favourably influence the course and outcome of this severe liver disease due to ACLF-B. **Aims:** We investigated the efficacy and safety of combining FMT with antiviral therapy compared to antiviral alone in improving transplant free survival at 3 months in ACLF-B.



Group	Days	0	15	30	45	60	90
FMT+T	Cumulative Events (Death) n	0	3	5	7	8	8
	At Risk(n)	32	29	27	25	24	24
T	Cumulative Events (Death) n	0	5	11	16	18	20
	At Risk(n)	32	27	21	16	14	12

Method: Patients with spontaneous reactivation of hepatitis B presenting as ACLF according to the APASL criteria having MELD > 18 with < 2 organ failures were randomised to receive either FMT+ Tenofovir (FMT-T) or Tenofovir alone. Liver and kidney parameters, APACHE and SOFA scores were assessed at baseline and at day 7, 15, 30 and 90. HBV DNA/HBsAg, changes in gut microbiome and serum levels of proinflammatory and anti-inflammatory cytokines and endotoxin levels were measured in both the groups [baseline, day 7, 30, 90].

Results: Sixty-four ACLF patients (52 male, 43.87 ± 8.55 years) completed the study; 32 in each arm. Baseline parameters were comparable in 2 groups. After 3 months transplant free survival was significantly (p = 0.01) superior in FMT+T Gr (24/32, 75.0%) then Tenofovir alone (12/32, 37.5%). Improvement in MELD at day 15, 30, 60 and 90 was significantly higher in FMT+T Gr than Tenofovir Gr (p = 0.02). Improvement in SOFA/APACHEII at day 15, 30, 60 and 90 was significantly higher in FMT+T then Tenofovir Gr (p = 0.01). The HBV DNA was reduced from 12.99 ± 2.52 IU/ml to 1.75 ± 0.59 in FMT + T group (p value = 0.03) and 12.77 ± 1.95 to 1.6 ± 0.43 (p value = 0.02) in Tenofovir group at 3 months, the differences were not significant (p value = 0.17). At day 15, > 2 log reduction in the HBV DNA level was associated with improved survival (p = 0.03). SIRS significantly improved (p = 0.02) at day 7, 15, 30, 60 and 90 in FMT+T than Tenofovir Gr. Infectious complication significantly lower in FMT+T Gr (p = 0.04).No adverse effects of FMT noted.

Conclusion: FMT along with tenofovir is well tolerated and is more effective than tenofovir alone in ameliorating liver failure, infectious complications and improving transplant free survival.

Liver transplantation I

PS-164

Patients with non-alcoholic steatohepatitis have inferior liver transplant outcomes

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Background and aims: Non-alcoholic steatohepatitis (NASH) is an increasing indication for liver transplantation (LT). Historically, patients with NASH are reported to have similar outcomes after LT compared to patients without NASH. The current study revisits this question. Post-transplant outcomes were evaluated among three major etiologies: NASH, hepatitis C (HCV), and alcoholic liver disease (ALD) to determine risks in LT associated with the NASH population.

Method: Data from the UNOS registry were analysed. Patients were divided into those with a diagnosis of NASH, HCV or ALD. Patients with overlapping diagnoses were excluded. LT was divided into four groups by era: Era 1: 2008–2010, Era 2: 2011–2013, Era 3: 2014–2015, Era 4: 2016–2017. Primary outcome was one year patient survival. Outcomes were compared among disease groups using Cox regression models adjusting for donor/recipient characteristics, except for recipient age, body mass index, and diabetes, which were considered NASH-associated characteristics. All patients had at least one year follow-up.

Results: There were 6, 344 patients with NASH, 17, 037 with HCV, and 9, 279 with ALD. The percent of patients with NASH and ALD rose significantly across eras from 14.0% to 27.9% and from 24.7% to 36.8%, respectively. The percent with HCV declined from 61.3% to 36.3%. In Era 1, the HCV group showed significantly worse one-year patient survival of 87.4% than the NASH and ALD groups at 90.3% (p = 0.007) and 90.6% (p < 0.001), respectively, whereas in Era 4, the NASH group showed significantly worse survival at 90.4% compared to 92.8% in the HCV (p = 0.004) and 93.5% in the ALD (p < 0.001) groups. The risk of one-year mortality in the NASH group became higher than the HCV and ALD groups in Era 4 with hazard ratios of 1.29 (p = 0.047) and 1.52; (p < 0.001). There was significant improvement in one-year

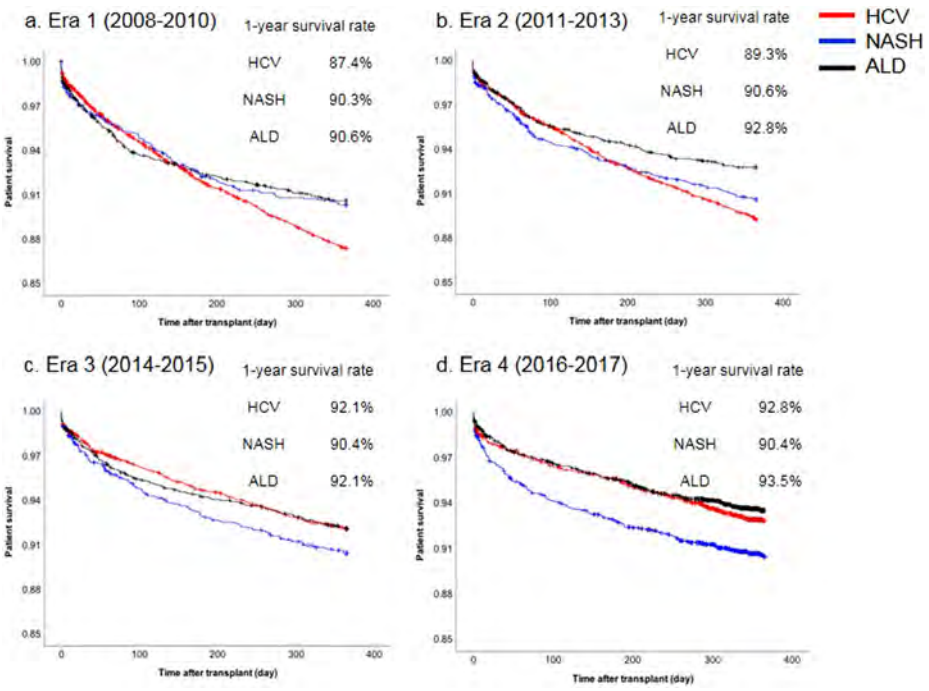

Figure: (abstract: PS-164) One year patient survival by diagnosis over eras.

patient survival over eras in the HCV (p < 0.001) and ALD groups (p = 0.001), whereas no improvement was seen in the NASH group.
The NASH group contained the fastest growing population of older patients. The annual number of patients over 65 years was largest in the HCV group in Era 1 at 144 per year compared to 103 in NASH and 94 in ALD. In Era 4, the NASH group has the largest number of patients over 65 at 422 per year compared to 369 in HCV and 227 in ALD. In addition, the effects of increasing age were most pronounced in the NASH group. Compared to patients < 50 years, the hazard of mortality in age 50-59, 60-64, 65-69 and ³70 years was 1.32 (p = 0.022), 1.64 (p < 0.001), 2.05 (p < 0.001), and 2.61 (p < 0.001). Mortality from cardiovascular/cerebrovascular disease was greatest in the NASH group accounting for 11.5% of deaths compared to 7.0% and 9.6% in HCV and ALD (p < 0.001).
Conclusion: The risk of LT in the NASH population has become higher than in HCV or ALD. This is likely to have profound implications in a time of shifting indications for LT.

PS-165

Handgrip strength adds more prognostic value to the MELD score than imaging-based measures of muscle mass in men awaiting liver transplantation

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Background and aims: Sarcopenia is associated with mortality in cirrhosis yet there is no gold standard for diagnosis. Little is known about the comparative utility of different diagnostic methods in predicting mortality. The aim of this study was to compare the relative prognostic impact of three commonly employed measures of sarcopenia in a single cohort of men awaiting liver transplantation.
Method: This single centre observational cohort study investigated outcomes in 145 men referred for liver transplant evaluation between 2005 and 2012. Baseline demographics included Model for End-stage Liver Disease (MELD) score. Muscle mass was estimated by handgrip strength, Dual Energy Xray Absorptiometry (DEXA) lean mass and muscle area on single slice CT scan at the 4th lumbar vertebra. Recorded outcomes included time-to-death or liver transplantation.
Results: The median age was 54 years [47; 59] and median MELD score 17 [14; 23]. Of the 145 men, 56 died, with a median time to death of 7.44 months [3.48, 14.16] and 79 were transplanted, with median time to transplant of 7.2 months [3.96, 12.84]. Muscle mass measurements correlated only modestly using different methods with the strongest correlation being observed between CT-measured muscle area and DEXA-measured appendicular lean mass (APLM) (tau 0.41, p < 0.001). For each modality, reduced muscle mass was associated with increased mortality, including CT-measured muscle (HR 0.94 [0.90; 0.98], p = 0.002), APLM (HR 0.99 [0.99; 0.99], p = 0.003) and handgrip strength (HR 0.94 [0.91; 0.98], p = 0.002) and these results retained significance independent of the MELD score. In predicting mortality, the handgrip strength-MELD bivariable Cox model was superior to a MELD-CT Cox muscle model (p < 0.001).
Conclusion: This study for the first time compares three commonly employed techniques to quantify sarcopenia in a cohort of men cirrhosis. There was only modest correlation between methods, but in a bivariable model incorporating MELD score, each of CT scan, DEXA and handgrip strength had similar prognostic value. Given the radiation, cost and access issues often related to CT and DEXA scans, we propose that handgrip strength is a simple alternative with comparable utility. The ability to perform handgrip strength serially has the additional benefit of allowing identification of deteriorating muscle strength in patients awaiting liver transplant.

PS-166

Repopulation of decellularized porcine bile ducts with human cholangiocyte organoids for the generation of human-sized bioengineered biliary tissue

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Background and aims: We have demonstrated proof-of-principle for the use of bioengineered ducts for biliary reconstruction in mice. However, clinical translation requires up-scaling of this technology to human dimensions. To address this challenge, we combined decellularized porcine bile ducts with human cholangiocyte organoids to generate bioengineered biliary tissue resembling the dimensions, micro-architecture and properties of the human bile duct.
Method: Primary Extrahepatic Cholangiocyte Organoids (ECOs) were isolated and propagated using our established protocol. Pig bile ducts were decellularized by intra-luminal perfusion using our established methodology and characterized using histology, DNA quantification and Scanning Electron Microscopy. Acellular bile ducts were anastomosed to pig common bile ducts, perfused with bile ex-vivo and monitored for leakage of bile. Nutrient diffusion was assessed using FITC-Dextran. Decellularized bile ducts were seeded with ECOs using our established protocols. Cell survival and growth were assessed using Presto Blue. Bile acid permeability was assessed using Cholyl-L-lysyl-fluorescein (CLF).
Results: Intra-luminal perfusion resulted in high decellularization efficiency, while preserving key architectural features, including the basal lamina, peribiliary glands and vascular plexus. Decellularized bile ducts can be surgically manipulated for biliary reconstruction ex vivo with no immediate complications. Nevertheless, perfusion with bile resulted in tissue degradation and bile leak. ECOs seeded on decellularized ducts rapidly expand to reach confluence and form an epithelial monolayer. These constructs survive long-term in culture and maintain key biliary features including marker expression (CK7, CK19, Sox9) and function, such as ALP and GGT activity. Importantly, the ECO monolayer prevents bile acid diffusion and provides an adequate barrier to bile which protects the scaffold from bile degradation. Furthermore, decellularized scaffolds allow passive nutrient diffusion, which is crucial for supporting the viability of the epithelial layer post transplantation.
Conclusion: ECOs can be combined with decellularized porcine bile ducts to generate constructs closely resembling the structural and functional properties of the human common bile duct. These findings provide proof-of-principle for the feasibility of human-sized hollow organ tissue engineering and pave the road for future studies in large animal models.

PS-167
Bile as a non-invasive source of cholangiocyte organoids for developing patient-specific disease modelling and personalized regenerative medicine

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Background and aims: Bile duct related diseases are the leading cause for pediatric liver transplantation and adult re-transplantation of a liver graft. Studying biliary diseases has long-term been hampered by the inability to culture bile duct lining cholangiocytes long-term. Recently was shown that Extra-hepatic Cholangiocyte Organoids (ECOs) that are derived from extra-hepatic bile duct (EHBD) tissue can be long-term expanded in culture. However, disease modeling or personalized regenerative medicine applications are limited since highly invasive bile duct biopsies are required to obtain these ECOs from individual patients. Therefore the aim of the current study is to investigate whether ECOs can be cultured from less invasively acquired bile fluid.
Methods. Bile-derived cholangiocyte organoids (BCOs) were cultured, according to the previous published protocol and collected from gallbladder bile obtained from donor livers for transplantation and from bile obtained by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography drain (PTCD) in patients. In addition, ECOs were initiated from three different patients and compared to BCOs on the genetic level (qrt-PCR), protein level (either immunohistochemistry, immunofluorescence or Western blotting) and functional level by testing the cholangiocyte specific transporter channels (ussing chamber and transport assay).
Results. Cultures were initiated from 1 ml of bile obtained from all different sources. Bile-derived cholangiocyte organoids could be effectively (8/9 attempts) expanded from all sources of bile from patients with a variety of diseases (primary sclerosing cholangitis, cholangiocarcinoma, bile stones and biliary stenosis after liver transplantation). BCOs expressed similar cholangiocyte markers on gene and protein level as tissue-derived ECOs and both lacked either stem cell- or hepatocyte markers. Furthermore, these cells expressed and responded similarly to stimulation and inhibition of different cholangiocyte ion-channels. Interestingly, cholangiocyte-organoids from a patient with cystic fibrosis (CF) clearly lacked CFTR channel activity, showing that cholangiocyte-organoids can be used as a disease model to study biliary diseases.
Conclusion. Our study showed that bile provides a novel minimally-invasive source of patient-specific cholangiocyte organoids. This creates new opportunities to study autologous bile duct regeneration and develop patient-specific disease models.

PS-168
Novel real time prediction of liver graft function during hypothermic oxygenated machine perfusion prior to liver transplantation

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Background and aims: *Ex situ* machine perfusion is a new method to potentially repair injured organs and assess organ function. In liver transplantation, however, no studies exist on reliable prediction of graft function during machine perfusion. We have developed a simple machine perfusion technique, hypothermic oxygenated perfusion (HOPE), which is applied after cold storage for 1-2 hours exclusively through the portal vein. The aim of this study was to analyze, whether liver graft function can be predicted during HOPE, besides optimizing of outcomes.
Method: We applied HOPE for DCD (donation after cardiac death) or extended criteria DBD (donation after brain death) human liver grafts in the past 5 years. Our entire series includes currently 100 HOPE treated liver transplanted patients with an overall tumor censored 5y graft survival of 89%. Based on recent reports on mitochondrial

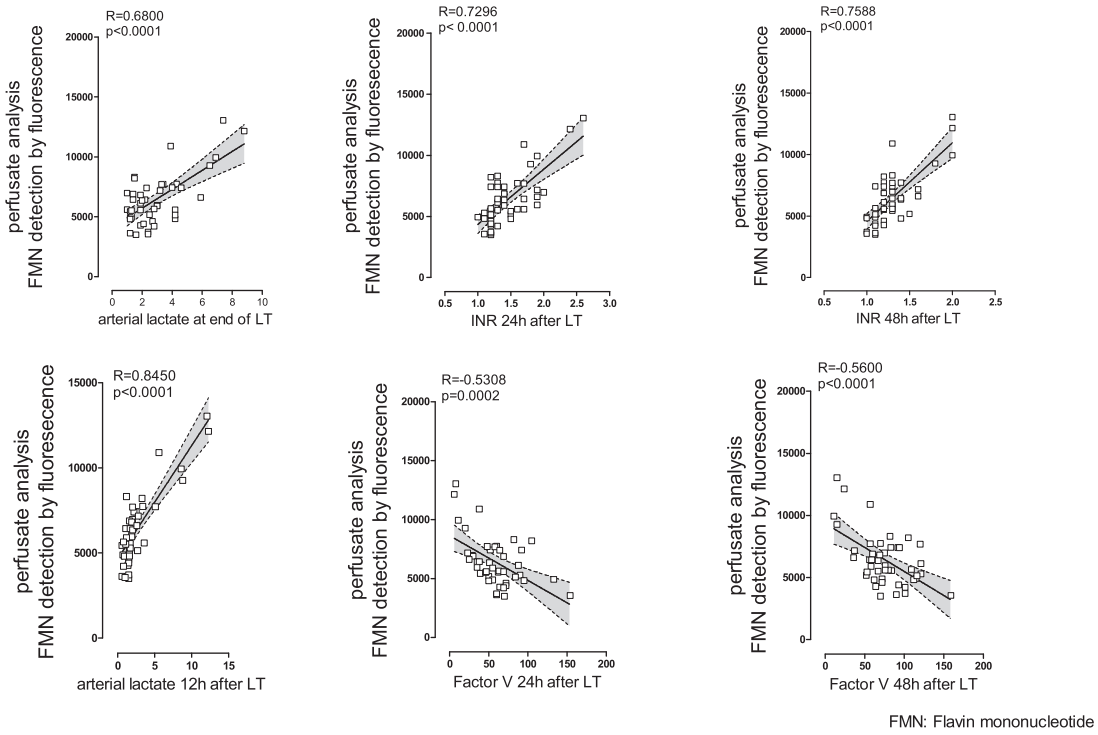

Figure: (abstract: PS-168) Prediction of graft function by machine perfusate analysis during HOPE.

metabolism, suggesting injury of mitochondrial complex I during re-oxygenation after ischemia, we monitored fifty livers during HOPE by fluometric analysis of released mitochondrial flavoproteins (flavin mononucleotide, FMN) in the machine perfusate. In detail, monochromal light with a wavelength of 450 nm was introduced to machine perfusate, and a spectroscopic detector quantified the proportion of fluorescent light, emitted at 90°. The peaks detected at a wavelength between 500 and 600 nm correspond to the emission spectrum of FMN, validated by additional NMR analysis. Perfusate measurements were correlated to liver graft function after transplantation, as determined by arterial lactate clearance, INR, factor V synthesis, and the L-GrAFT risk score (Agopian et al, 2018).
Correlation between fluometric perfusate analysis and liver graft function was calculated using Pearson's correlation coefficient. Reference values for strength of effect size were: "very weak" 0.00-0.19, "weak" 0.20-0.39, "moderate" 0.40-0.59, "strong" 0.60-0.79 and "very strong" 0.80-1.0.
Results: Real time optical measurement of mitochondrial FMN release in machine perfusates of fifty livers correlated strongly with lactate clearance and coagulation factors at day 1 and 2 after transplantation (Figure 1). Receiver operating characteristic curve analysis revealed an area under the curve (AUROC) of 0.80 (95% CI 0.67-0.93) for allograft dysfunction.
Conclusion: We demonstrate for the first time an accurate and fast prediction of liver graft function during ex situ machine perfusion before implantation, based on determining the level of mitochondrial complex I injury.
We expect a high clinical relevance of our results, as liver grafts from extended DBD or DCD donors potentially carry considerable risks for recipients. On-line estimation of outcome before implantation would therefore substantially increase safe utilization of liver grafts.

PS-169

Umbilical cords-derived mesenchymal stem cells ameliorated hepatocellular apoptosis mediated by PINK1-dependent mitophagy in liver ischemia/reperfusion injury dependent on AMPKα activation

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Background and aims: Hepatocyte apoptosis is a main pathophysiological process that underlies liver ischemia/reperfusion (I/R) injury. Mitochondrial abnormalities play a vital role in hepatocellular damage. It is well acknowledged the beneficial effects of umbilical cords-derived mesenchymal stem cells (UC-MSCs) on hepatocellular protection in response to liver I/R injury. However, the mechanism underlying these phenomena is still not fully clear.
Method: In the present study, a model of 70% liver I/R injury was used in vivo. UC-MSC (1×10^6 per mouse) was intravenously infused to the liver I/R injury mice. Hepatocellular anoxia/reoxygenation (A/R) model was established to mimic liver I/R injury and incubated with UC-MSCs conditioned medium (UC-MSCs-CM) for in vitro analyses.
Results: Mitochondrial dysfunctions of hepatocytes were observed in mice suffering from liver I/R injury, including mitochondrial reactive oxygen species (mtROS) overproduction, accumulation of mitochondrial fragmentation, lower ATP production and defective mitophagy. Meanwhile, along with reduced the protein expression of Parkin and PINK1, phosphorylated AMPKα (p-AMPKα) was dramatically downregulated. Loss of p-AMPKα was associated with ULK1 dephosphorylation and mTOR phosphorylation. These pathological changes were revered following a peripheral venous transfusion of UC-MSCs (1×10^6 per mouse). To validation, our results showed that the hepatocellular protective roles of UC-MSCs were abolished after added with 3-methyadenine (3-MA), an autophagy inhibitor, or

dorsomorphin, an AMPK antagonist, respectively. Furthermore, we used L02 hepatocyte line anoxia/reoxygenation (A/R) model to mimic liver I/R injury in vitro. UC-MSCs conditioned medium (UC-MSCs-CM) suppressed hepatocellular apoptosis and inhibited mtROS accumulation in the A/R environment. The reduced Parkin and PINK1 as well as suppressed PINK1-dependent mitophagy noted in L02 cells subjected to A/R condition were restored partially after L02 cultured with UC-MSCs-CM. And the effects of UC-MSCs-CM on cellular protection and induced mitophagy in L02 were weakened after L02 transfected with PINK1 siRNA or treated with dorsomorphin.

Conclusion: These results explored that UC-MSCs played beneficial effects on hepatocellular protection in liver I/R injury via PINK1-dependent mitophagy through activating AMPKα.

PS-170

A trend towards a lower patient survival is observed when either NAT+ve or NAT-ve donors with positive HCV Ab are transplanted into HCV negative recipients

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Background and aims: The proportion of HCV RNA positive cadaver organs has increased (~15%) due to the opioid crisis in the USA. Recently it has been suggested that HCV RNA positive organs could be safely transplanted into HCV RNA negative recipients because of the availability of safer and highly efficacious DAA regimens. The modeling studies have claimed benefits with this strategy, but the real life data are very limited. The objective of our study was to determine whether there were graft and patient survival when HCV negative patients received HCV RNA (NAT+ve) positive liver grafts.

Method: We queried UNOS data sets from 2015-2018 and stratfied recipients into 5 groups based on the status HCV anitbody and RNA of recipient and donors (donor HCV RNA status was determined by NAT and data collected since 2015). During the study period, 957 recipients received NAT positive liver grafts, but of these only 45 RNA negative recipients received NAT+ grafts. During the same period, 487 anibody positive but NAT -ve grafts were transplanted into 386 HCV positive and 101 HCV negative recipients.

Results: Important characterisitics of recipients and donor are shown in the table below. MELD scores were higher in HCV negative recipients who received grafts from HCV positive donors (NAT +ve or -ve). There were no differences (p = 0.33) in survival in HCV positive recipients whether they received NAT positive (n = 912) or HCVAb and NAT negative (n = 5310) grafts (Figure 1). There was a lower survvial (p = 0.011) when HCV negative recipients (n = 101) received HCV Ab +ve/NAT -ve grafts (Figure 2) as compared to HCV postive recipients (n = 4924) receiving HCVAb -ve/NAT -ve grafts. Survival was also lower (p = 0.002) when HCV negative recipients (n = 101) received HCV Ab +ve/NAT -ve grafts when compared to HCV positive patients (n = 386) receiving similar grafts (Ab +ve/NAT-ve) (Figure 3). Survival was also lower (p = 0.03) when HCV negative recipients (n = 45) received NAT positive grafts as compared to HCV positive patients (n = 912) receiving NAT positive grafts (Figure 4).

Variable	Donor NAT+ Recipient HCV+	Donor NAT+ Recipient HCV-	Donor Ab+ and NAT-v Recipient HCV+	Donor Ab+ and NAT-v Recipient HCV-	Donor Ab and NAT- Recipient HCV+
N	912	45	386	101	4924
Mean Age (SD)	59.0 (6.7)	52.4 (12.7)	59.5 (6.3)	56.5 (11.3)	59.1 (7.1)
Dialysis (%)	142 (15.6)	5 (11.6)	33 (8.6)	6 (5.9)	585 (11.9)
MELD (SD)	18.4 (7.9)	23.5 (8.4)	17.7 (7.5)	23.5 (8.2)	19.2 (11.1)
DRI (SD)	1.64 (0.39)	1.6 (0.28)	1.72 (0.42)	1.84 (0.46)	1.77 (0.43)

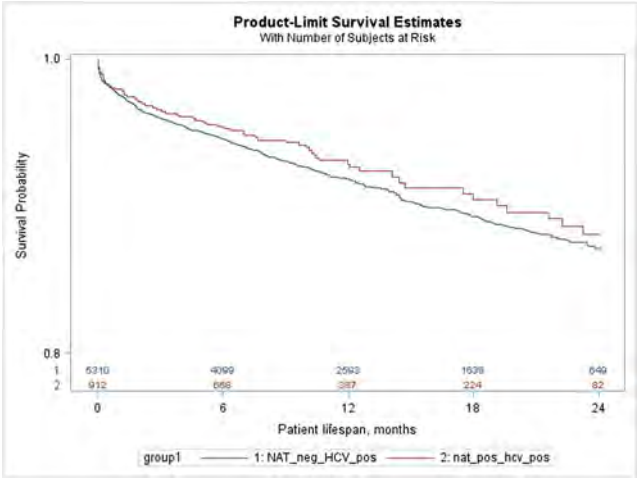

Figure 1

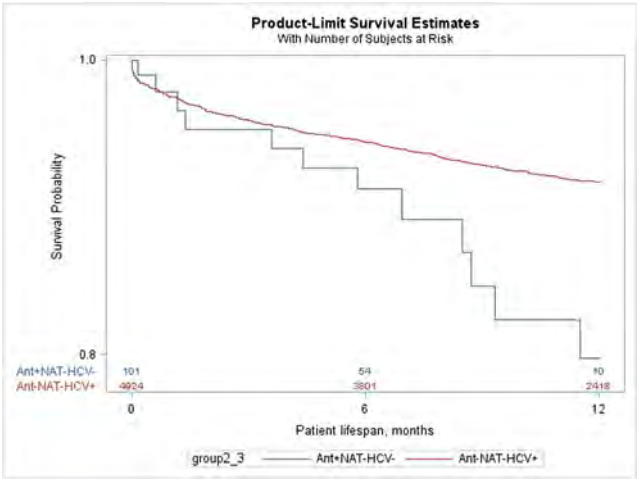

Figure 2

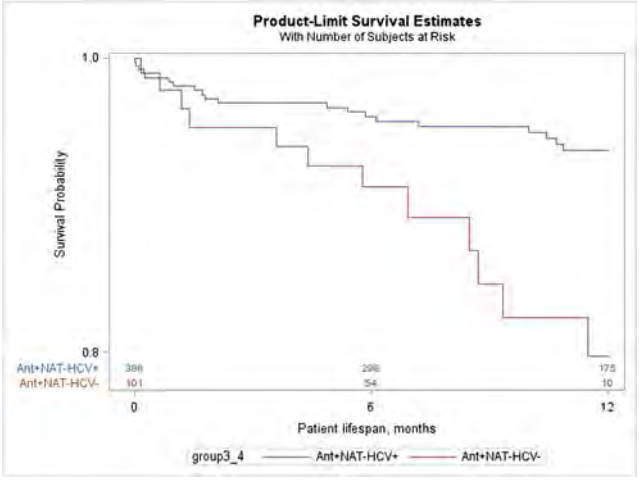

Figure 3

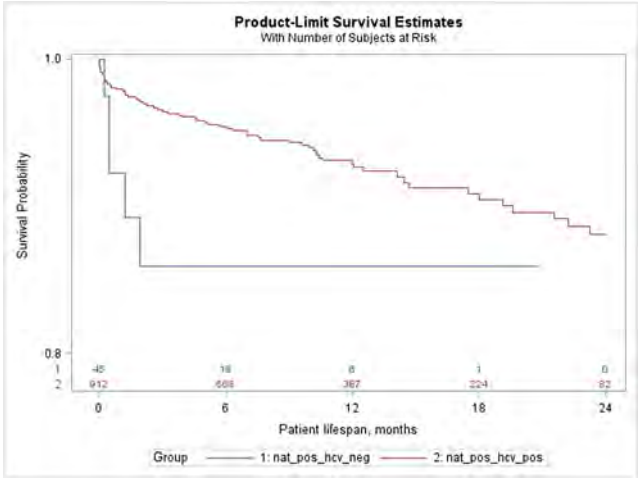

Figure 4

Conclusion: Early experience in HCV negative recipients receiving HCV positive liver grafts (antibody or NAT positive) suggests a trend towards a lower patient survival. This could be related to the higher risk profile of recipients, but caution should be exercised before routine transplant of liver grafts from HCV Ab +ve donors into HCV negative recipients.

Alcohol related liver disease

PS-171

Survival in a 10 year prospective cohort of heavy drinkers: Liver stiffness is the best long-term prognostic parameter

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Background and aims: Alcoholic liver disease (ALD) is the most common liver disease in the western world. Although measurement of liver stiffness (LS) by transient elastography has been well established for early diagnosis of fibrosis, no prospective long-term data on survival exist so far in patients with ALD. We here present first data on the prognostic impact of LS on long-term survival of Caucasian heavy drinkers in a 10 year, prospective single center trial.
Method: Information of survival status was obtained in 675 (71.6%) of 943 screened patients that had presented for alcohol detoxification (6.0 days) over a 10-year period from 2007 to 2017 with a mean daily consumption of alcohol of 178 g. Mean observation time was 3.7 years and mean duration of heavy drinking was 14.0 years. All patients had LS measurements by transient elastography and routine laboratory tests.
Results: During the observation time, 106 patients (15.7%) died. The cause of death could be clarified in 42 patients (39%) and it was liver-related in 16 (38%). Overall death was highest associated with LS (r = 0.291, P = 1.3E-14), followed by hemoglobin and alkaline phosphatase (AP). In a multivariate proportional hazard model, LS next to age, AP and serum albumin was the most significant independent predictor of survival with a hazard ratio of 1.013 (1.003 to 1.023, P < 0.05). Using ROC analysis, LS was the best predictor of death in general with an AUROC of 0.72 and a cutoff value of 14.0 kPa, followed by AP and albumin. Moreover, LS was the top predictor of death starting from 2 to 5 years. In contrast, LS was preceded by bilirubin and albumin in predicting one-year-survival. AUROCs to predict death for 1, 3 and 5 years were 0.76, 0.74 and 0.73, respectively, with corresponding cut-off values (Youden index) of 26.3, 14.0 and 6.4 kPa, respectively. When stratifying patients according to standard LS cut-off values < 6 kPa, 6 to 12.5 kPa and > 12.5 kPa, the survival curves were significantly different (p < 0.0001), 3-year survival rate was 94%, 88% and 74% and 5-year survival rate was 90%, 78% and 64%, respectively.
Conclusion: We here identify LS as the best long-term prognostic parameter in patients who heavily consume alcohol. LS measurements should become an important parameter for the screening of alcoholics.

PS-172

Acute adipocyte death preferentially induces liver injury and inflammation via the activation of CCR2+ macrophages and lipolysis

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Background and aims: Adipocyte death occurs under various physiopathological conditions, including obesity and alcohol drinking, and can trigger organ damage particularly in the liver, but the underlying mechanisms remain obscure. The aim of this study was to evaluate the pathological role of adipocyte death *in vivo* by using a model of acute adipocyte death in mice.
Method: To explore these mechanisms, we developed a mouse model of inducible adipocyte death by overexpressing the human CD59 (hCD59) on adipocytes (adipocyte-specific *hCD59* transgenic mice).
Results: Injection of these mice with intermedilysin (ILY), which rapidly lyses hCD59 expressing cells exclusively by binding to the hCD59 but not mouse CD59, resulted in the acute selective death of adipocytes, adipose macrophage infiltration, and elevation of serum free fatty acid (FFA) levels. ILY injection also resulted in the secondary damage to multiple organs with the strongest injury observed in the liver, with inflammation and hepatic macrophage activation. Mechanistically, acute adipocyte death elevated epinephrine and norepinephrine levels and activated lipolysis pathways in adipose tissue in a CCR2+ macrophage-dependent manner, which was followed by FFA release and lipotoxicity in the liver. Additionally, acute adipocyte death caused hepatic CCR2+ macrophage activation and infiltration, further exacerbating liver injury.
Conclusion: Acute and selective adipocyte death predominantly induces liver injury and inflammation, which is probably due to the superior sensitivity of hepatocytes to lipotoxicity and the abundance of macrophages in the liver.

PS-173

Differential contribution of RIP3-mediated cell death in alcohol and non-alcohol related liver disease

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Background and aims: Hepatocellular death is associated with the progression of both alcohol (ALD) and non-alcohol related liver

disease (NAFL/NASH); however, the pathogenic contributions of individual pathways of programmed cell death are not well understood. RIP3 kinase is a critical mediator of necroptosis, a regulated pathway of cell death. Recent data indicate that RIP3 kinase differentially contributes to liver injury in murine models of ALD and NAFL/NASH; *Rip3*-/- mice are protected from chronic ethanol-induced liver injury, but not high fat diet-induced liver injury. RIP3 contains two functional domains, a serine-threonine kinase domain and a RHIM domain that mediates interactions with other RHIM containing proteins; emerging evidence suggests that there are domain-specific functions for both the kinase and RHIM domain. Therefore, we tested the hypothesis that the kinase domain of RIP3 would differentially contribute to liver injury in murine models of ALD and NAFL/NASH.

Method: RIP3 kinase dead knock-in mice ($Rip3^{K51A/K51A}$) and wild-type controls were exposed to ethanol (chronic ethanol feeding or Gao-binge acute on chronic ethanol) or a diet high in fat, fructose and cholesterol (Western diet). All mice were on a C57BL/6J background.

Results: Interestingly, $Rip3^{K51A/K51A}$ mice were protected from Western diet-induced liver injury and inflammation, but not ethanol-induced liver injury. $Rip3^{K51A/K51A}$ on the Western diet gained weight at an equal rate to wild-type mice, but serum ALT and AST levels and hepatic triglycerides were reduced. Interestingly, inflammatory cytokine expression was still increased in the $Rip3^{K51A/K51A}$ mice in liver, but reduced in adipose tissue. In contrast, serum ALT/AST, hepatic triglycerides and inflammatory cytokine expression remained elevated in $Rip3^{K51A/K51A}$ on the ethanol diets.

Conclusion: Taken together, these data indicate that RIP3 plays a differential role in Western diet- versus ethanol-induced liver injury. In models of ALD, RIP3-mediated injury was independent of RIP3 kinase activity, while RIP3 kinase activity contribute to Western diet induced liver injury.

PS-174

Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis

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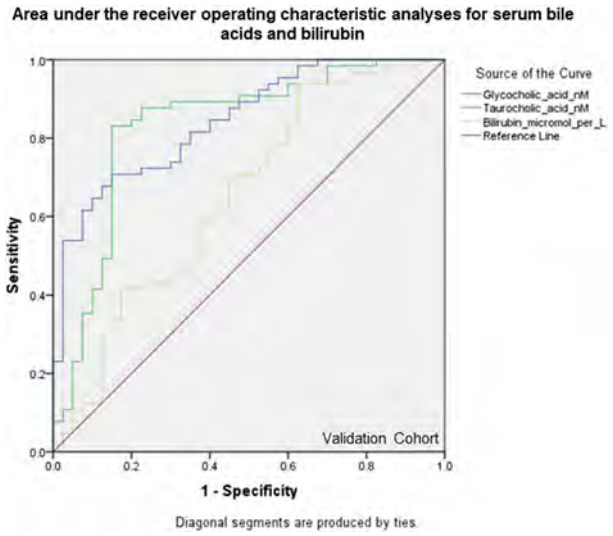
Background and aims: Alcoholic hepatitis (AH) is characterised by recent onset jaundice in patients with ongoing alcohol misuse. Distinguishing AH from decompensated alcohol-related cirrhosis (DC) guides rational use of prednisolone but can be challenging. Demonstration of steatohepatitis on liver biopsy remains the gold standard. Liver biopsy is not universally available and both biopsy and prednisolone are associated with complications. Differences in the serum bile acid (BA) profiles of patients with AH and DC have been reported. The aim of this study was to determine whether serum BAs can non-invasively discriminate between AH and DC.

Method: Serum BAs were measured by ultraperformance liquid chromatography-mass spectrometry in exploratory and validation cohorts. Patients with AH had a Maddrey's Discriminant Function (DF) > 32 and steatohepatitis on liver biopsy. The exploratory cohort comprised 68 patients with AH (median Model for End-stage Liver Disease score, MELD, 23) and 21 with DC (defined as MELD > 18; median 26); the validation cohort comprised 65 patients with AH (median MELD 25) and 40 with DC and jaundice (defined as bilirubin > 80 micromol/L and DF > 32; median MELD 30). Mean age was 49 years; 69% were male. Data was analysed by orthogonal projection to least squares discriminant analysis (OPLS-DA) and area under the receiver operating curve (AUROC) analysis.

Results: OPLS-DA accurately discriminated AH from DC in both exploratory and validation cohorts. The AUROC for the full BA profiles was 0.93 (95%CI 0.87-0.99) and 0.93 (95%CI 0.88-0.98) respectively. Model diagnostics identified glycocholic (GCA) and taurocholic (TCA) acid as dominant metabolites. The AUROC for serum GCA was 0.90 (95%CI 0.83-0.97) in the exploratory and 0.85 (95%CI 0.77-0.92) in the validation cohorts. The AUROCs for TCA were 0.87 (95%CI 0.77-0.97) and 0.83 (95%CI 0.74-0.92). Both performed better than bilirubin (AUROC 0.79 (95%CI 0.67-0.91) and 0.65 (95%CI 0.54-0.76) respectively). In the validation cohort, TCA concentration more than or equal to 8300 nM had a sensitivity and specificity for AH of 83% and 85%.



Conclusion: AH has a serum BA profile distinct from patients with DC and similar liver dysfunction and jaundice. The discriminatory performance of both the entire bile acid profile and individual bile acids (GCA and TCA) indicates that they are promising non-invasive biomarkers for severe AH and may reduce the need for liver biopsy.

PS-175

The burden of alcoholic cirrhosis is critically increasing in Canada: A population-based study

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Background and aims: Alcohol is one of the most common causes of cirrhosis. Over the last two decades, efforts to increase awareness of heavy drinking and improve access to care for alcoholic cirrhosis patients have been implemented. However, the impact of these efforts on the natural history of alcoholic cirrhosis have not been fully evaluated. Therefore, we undertook this study to evaluate changes in the epidemiology of alcoholic cirrhosis in Alberta, Canada.

Method: We used validated codes to identify alcoholic cirrhosis (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 571.2) in population-based administrative databases in Alberta, Canada (population ~4.3 million) from 2013-2017, with a washout period from 2009–2012. Multiple sources of data including inpatient, ambulatory care, and physician billing were linked. Annual prevalence and incidence were estimated using Poisson regression. Age/sex adjusted rate ratios were calculated. We used Kaplan-Meyer and Cox regression models to estimate all-cause mortality.

Results: During the study period, the overall annual age/sex adjusted alcoholic cirrhosis incidence was 38.9 cases per 100, 000 [23.2 (95%

CI: 22.4-24.1) and 55.6 (95%CI: 54.3-56.9) cases per 100, 000 for women and men, respectively], with a female to male incidence rate ratio (IRR) = 0.42 (95%CI: 0.37-0.48). The highest incidence rate was observed among men aged 40-59 (97.4 per 100, 000), with an IRR of 6.87 (95%: 6.78-6.96) compared to those aged ³ 80. While incidence rates remained stable across our study period (p = 0.37), prevalence rates increased significantly from 107.7 to 158.2 cases/100, 000 between 2013 and 2017 (p < 0.01). Prevalence rate was highest at 309.5 cases/100, 000 amongst men aged 60-79, with an IRR of 5.40 (95%: 5.31-5.49) compared to those aged ³ 80. During the study period we identified 5811 incident alcoholic cirrhosis cases, with a median age of 56 years (IQR 48-63) and 69.8% (n = 4053) were men. The age/sex standardized mortality rate was 13.1 per 100, 000 (95%CI: 12.5-13.7). Survival rates at 1, 3, and 5 years were 66.9% (95% CI: 65.6- 68.2), 60.7% (95%CI: 59.3-62.2), and 55.1% (95%CI:53.5-56.7) respectively, with 73% of our incident cohort presenting with decompensated cirrhosis at time of index diagnosis.

Conclusion: We report an increasing prevalence of alcoholic cirrhosis in this large representative Canadian population. Risk of developing alcoholic cirrhosis is highest among middle-age men, and the societal burden of alcoholic cirrhosis is significant with poor survival rates due to late diagnosis. Better surveillance, early detection of alcoholic liver disease patients, and the development of effective health care practices are warranted to facilitate preventative measures and avoid alcoholic liver disease and late diagnosis.

PS-176

Hyperoxidized albumin promotes platelet dysregulation to induce systemic inflammation in severe alcoholic hepatitis

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Background and aims: Hyperoxidized albumin promotes inflammation in severe alcoholic hepatitis (SAH). However its contribution in platelet activation, alteration of platelet phenotype and linked functions is yet not known.

Method: To explore 50 SAH patients, 20 alcoholic cirrhosis (AC) and 20 healthy controls (HC) were studied. Quantitative platelet proteomics in SAH was compared to HC (discovery), which led to the characterization of platelet phenotype (GO, KEGG, blood transcription modules-BTMs). Key dysregulated pathways were validated in a separate cohort of (n = 40) SAH patients. Platelets functions were correlated to severity of SAH. Causality of platelet activation/dysfunction was determined by in-vitro treatment of healthy platelets with patient plasma, purified albumin from the study groups or *ex-vivo* modified albumin (human mercaptalbumin-HMA, human nonmercaptalbumin-HNA1 and HNA2) in the presence or absence of CD36 (receptor for oxidised albumin) blockade.

Results: Quantitative platelet proteomics identified 202 proteins upregulated and linked to platelet activation, complement regulation, lipid transportation whereas 321 downregulated proteins related to platelet haemostasis and coagulation (FC ± 1.5, p < 0.01). Blood transcriptome module enrichment (BTM) showed inflammatory phenotype of SAH platelet. Validation studies confirmed increase in platelet-activation (PAC-1, P-selectin), intracellular-Ca^{2+} and aggregation in SAH (p < 0.05). Transcripts linked to platelet activation were increased and directly correlated (r2 > 0.3); whereas transcripts linked to granular secretions were decreased and inversely correlated (r2 > –0.3, p < 0.05) with severity. In-vitro stimulation of healthy platelets showed enhanced activation with patient plasma or purified albumin treatment, blocking of CD36 blunted this effect (p < 0.05). *Ex-vivo* modified albumin (mainly HNA2 – 1 mg/ml) showed markedly high activation/aggregation and intracellular ROS production in healthy platelets (p < 0.05), which significantly reduced after CD36 neutralization.

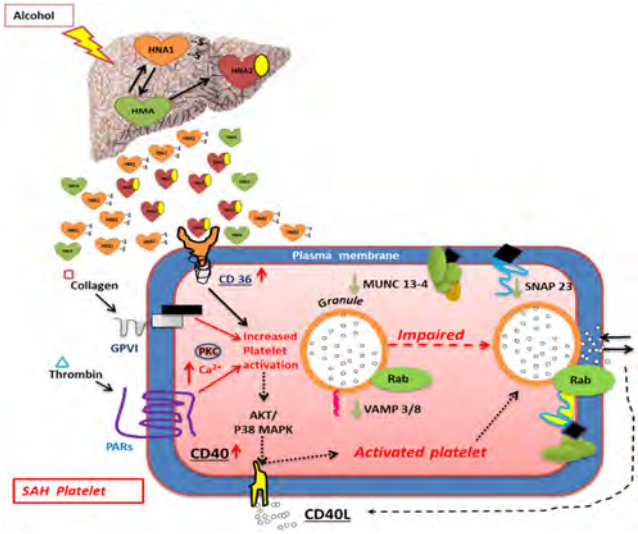

Figure: Proposed proinflammatory and prothrombotic platelet prototype in severe alcoholic hepatitis. Oxidised albumin majorly HNA2 over HNA1 promote platelet activation via scavenger receptor CD36. Platelet activation releases pro-inflammatory mediators, induces CD40L expression and ROS production in platelets per se to facilitate systemic inflammation in SAH.

Conclusion: Hyperoxidized albumin triggers platelet activation potentially through CD-36 receptor; promotes inflammation, oxidative-stress and may contribute to thrombotic events in SAH patients.

PS-177

HSD17B13 rs72613567 TA is associated with a reduced risk for developing hepatocellular carcinoma in patients with alcohol-related cirrhosis

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Background and aims: Host genetic factors play an important role in the development of alcohol-related cirrhosis. Hepatocellular carcinoma (HCC) complicates the course of this disorder in approximately 20% of affected persons Variant rs738409 in *patatin-like phospholipase domain containing-3* (*PNPLA3*) is an established risk factors for the development of alcohol-related cirrhosis and HCC. Recently, a loss-of-function splice variant rs72613567:TA in the gene coding for hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) was reported to be associated with a reduced risk for developing cirrhosis in individuals with alcohol use disorders and non-alcoholic fatty liver disease (NAFLD). The aim of this study was to undertake a case control study to determine if carriage of *HSD17B13* rs72613567:TA is associated with a lower risk for developing HCC in patients with alcohol-related cirrhosis and whether it modulates the risk conferred by carriage of *PNPLA3* rs738409.
Method: The total study population comprised of 2202 individuals with alcohol-related cirrhosis recruited from Germany, Switzerland, Italy and United Kingdom. Of these 840 had HCC and were designated as cases whilst the remaining 1362 had no evidence of HCC and were considered as controls. Genomic DNA was extracted from whole blood and genotyped for risk variants in *PNPLA3* and *HSD17B13*. The associations between genotypes and the risk of developing HCC were analysed using multivariate logistic regression. Adjusted allelic and genotypic odds ratios were calculated. Gene-gene interaction was evaluated by including interaction terms to the regression model.
Results: The presence of HCC was inversely associated with carriage of allele rs72613567:TA in *HSD17B13* (OR 0.72 [CI 0.61 – 0.85], p = 1.00×10^{-4}) and positively associated with rs738409 G allele in *PNPLA3* (OR 1.83 [CI 1.60 – 2.09], p = 1.62×10^{-18}) when examined using an additive model and controlling for sex, age and country. The risk reduction in the development of HCC was evident in both heterozygous (OR 0.75; 95% [CI 0.61 – 0.93], P = 0.008) and homozygous carriers of rs72613567:TA (OR 0.47; 95% [CI 0.30 – 0.74], P = 0.001). The rs72613567-rs738409 SNP-SNP interaction term was not significant P = 0.12.
Conclusion: In patients with alcohol-related cirrhosis, carriage of *HSD17B13* rs72613567:TA is associated with a lower risk for developing HCC, independently of the increased risk conferred by carriage of *PNPLA3* rs738409. The HCC risk conferred of carriage on *PNPLA3* rs738409 was not attenuated by *HSD17B13* rs72613567:TA in this sample.

Hepatitis C – Treatment and resistance

PS-178
Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir: the SMART-C study

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Background and aims: Direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection has high efficacy and limited toxicity. We hypothesised that efficacy and tolerability of an 8-week glecaprevir-pibrentasvir regimen for chronic HCV would be equivalent with a simplified and standard treatment monitoring schedule.
Method: In this open-label randomised controlled trial, treatment-naïve adults with chronic HCV without cirrhosis were randomly assigned (2:1) to receive glecaprevir-pibrentasvir 300/120 mg once daily for 8 weeks administered with a simplified or standard monitoring strategy. Following screening, study visits occurred at baseline and post-treatment week 12 in the simplified arm, and at baseline, week 4, week 8, and post-treatment week 12 in the standard arm. Study nurse phone contact was at week 4 and week 8. Patients considered to require additional treatment adherence support were not eligible, including those reporting injecting drug use in the past 6 months. The primary end point was SVR12, with a non-inferiority margin for difference of 6% (lower bound of 95% confidence interval [CI] -6.0%).
Results: In total, 380 patients with chronic HCV were randomized and treated with glecaprevir-pibrentasvir in the simplified (n = 253) and standard (n = 127) arms. Overall, 60% were male, 48% genotype 1, 32% genotype 3, 7% HIV positive, and 10% on opiate agonist therapy. By intention-to-treat, SVR12 was 91% (95% CI 88%, 95%) in the simplified and 94% (95%CI 91%, 99%) in the standard arm (difference between arms, -3.2% [95%CI -8.5%, 2.0%]; p = 0.27) (Table). In the per-protocol population, SVR12 was 97% (95%CI 95%, 99%) in the simplified and 98% (95%CI, 96%, 100%) in the standard arm (difference between arms, -1.0% [95%CI -4.0%, 2.1%]; p = 0.57).

	Standard monitoring N = 127	Simplified monitoring N = 253
Outcome, n (%)		
SVR12	120 (94%)	231 (91%)
Virologic failure	2 (2%)	6 (2%)
Failure for other reasons		1 (0.5%)
Death	0	2 (1%)
Discontinuation	0	13 (5%)
Loss to follow-up	5 (4%)	
Safety parameters, n (%)		
Discontinuation due to adverse event	0	1 (0.5%)
Death	0	1 (0.5%)
Treatment emergent serious adverse event	0	3 (1%)
Related to treatment	-	0

Conclusion: Among patients with chronic HCV infection without cirrhosis, treatment with glecaprevir-pibrentasvir provided favorable virological outcomes and tolerability with a simplified monitoring schedule. Clinical judgement will be required to select patients without additional adherence or follow-up support needs.

PS-179

Analysis of long-term persistence of HCV resistance-associated substitutions within NS3, NS5A and NS5B in genotype 1 and 3 after DAA treatment failure

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Background and aims: Treatment of chronic hepatitis C virus (HCV) infection direct acting antivirals (DAAs) is highly effective. Virologic failure is associated with the selection of HCV resistance-associated substitutions (RASs) in the majority of patients. Persisting RASs are largely unknown and have implications for a retreatment especially in countries without available multiple target retreatment options. This study investigated the long-term kinetics of RASs in genotypes (GT) 1 and 3 after a DAA-failure.

Method: Samples were obtained from the European Resistance Database containing samples of 1080 DAA failure patients. We analyzed a subgroup of 468 GT1- or GT3-infected patients with a documented sampling time after end of treatment (EOT), including sequential samples of 127 patients. NS3, NS5A and NSB5 genes were sequenced population based and RASs conferring a > 2-fold increased DAA susceptibility were analyzed.

Results: Patients have failed to grazoprevir/elbasvir (n = 10, 2%), simeprevir (SMV)/sofosbuvir (SOF) (n = 43, 9%), 3D (paritaprevir/ombitasvir/dasabuvir) (n = 73, 16%), ledipasvir (LDV)/SOF (n = 196, 42%), daclatasvir (DCV)/SOF (n = 97, 21%) or velpatasvir (VEL)/SOF (n = 49, 10%). At end-of-treatment (EOT), NS3 RASs were present in 69% of GT1-infected patients, however vanished fast until follow-up (FU) month (mth.) 12 and were only detectable in 30% of patients anymore. In SOF-experienced patients, NS5B nucleotide inhibitor RASs were rare and S282 T was observed in one individual with GT3 at FU3 and was not detectable anymore thereafter. NS5B non-nucleoside inhibitor RASs were detected in 72% of patients with GT1 at EOT and RASs declined to 59% in patients until FU12. NS5A inhibitor failures harbored high rates of RASs at EOT reaching frequencies of > 90% in GT1 and GT3. At FU12, the rates of RASs were stable with prevalences of 90% in subtype 1b and GT3, while in subtype 1a NS5A RASs already declined to frequencies of 76%. At FU24, RAS further declined to frequencies of 72% in subtype 1a and at this time point first signs of vanishing NS5A RAS were observed in GT3 as well, as RASs were detected in 78% of patients anymore. However, in subtype 1b the frequencies of NS5A RASs remained stable and were still detectable at FU24 in 90% of patients.

Conclusion: NS3 and NS5B RASs vanished fast during the first 12 months after EOT. High rates of persisting NS5A RASs were detected in subtype 1b 24 months after EOT, while they started to disappear in subtype 1a and GT3.

PS-180

ns5a resistance profile of genotype 1b virological failures that impacts outcome of re-treatment by glecaprevir/pibrentasvir: Nation-wide real world study

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Background and aims: Resistance-associated substitutions (RAS) are generated in chronic hepatitis C patients who failed direct-acting antiviral (DAA) treatment. Especially, RAS in NS5A may affect the efficacy of re-treatment since NS5A inhibitor is included in all available DAA regimens. This study examined the prevalence and specific pattern of NS5A RAS in patients who failed prior DAA and its impact on the efficacy of re-treatment by Glecaprevir (GLE)/Pibrentasvir (PIB) in the real-world.

Method: This nation-wide study involved 83 regional core centers for the treatment of liver disease and related hospitals. A total of 1, 420 genotype 1 patients who failed DAA treatment were registered, and RAS in NS3 and NS5A after virological failure was determined by population sequencing. The prevalence and patterns of NS5A RAS in these patients was compared to 1, 068 patients who are naïve to DAA. Association between RAS and sustained virologic response was analyzed in 545 patients who started re-treatment by GLE/PIB for 12 weeks.

Results: Among DAA failed patients, 83% of patients had failed 1 DAA regimen, 15% had failed 2 DAA regimens, and 2% had failed 3 DAA regimens. Daclatasvir (DCV)/Asunaprevir (ASV) was the most frequently used regimen (84%), followed by Ledipasvir (LDV)/Sofosbuvir (SOF) (13%) and Grazoprevir (GZR)/Elbasvir (EBR) (2%). The prevalence of NS3 RAS at positions 156 and 168, and NS5A RAS at positions 31, 32 and 93 was significantly high in DAA failed patients compared to DAA naïve patients. Dual RAS in NS3 plus NS5A was detected in 35% of DCV/ASV failed patients and in 20% of GZR/EBR failed patients. The prevalence of dual RAS in NS3 plus NS5A increased in parallel with the number of courses of prior DAA: 34% in 1 course of DAA failure, 55.3% in 2 courses of DAA failure and 86.7% in 3 courses of DAA failure. Among NS5A RAS, P32deletion was not found in any DAA naïve patient but was detected in 3.7%, 2.0%, and 4.3% of patients who failed prior DCV/ASV, LDV/SOF, and GZR/EBR, respectively. In 545 patients re-treated by GLE/PIB for 12 weeks, HCVRNA was negative at the end of treatment in 99.2% of patients (371/374), and SVR12 was 95.8% (227/237). The presence of any NS3 RAS or NS5A RAS at position 31 and 93 did not impact SVR. However, SVR was 25% in patients with P32deletion RAS compared to 97% in patients with wild type P32 ($p = 0.0002$).

Conclusion: This nation-wide study revealed highly complex nature of RAS after DAA failure. Re-treatment by GLE/PIB was highly effective except for patients having unique RAS P32deletion in NS5A.

PS-181

Unacceptably low SVR rates in African patients with unusual HCV sub-genotypes : Implications for global elimination

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Background and aims: Worldwide elimination of Hepatitis C (HCV) is attainable, but relies on efficacious first line therapy. Rare subtypes are underrepresented in clinical trials but exist as prevalent polymorphisms in some regions. We describe the genotype

distribution and antiviral treatment outcome in a south London cohort of African pts.
Methods: We identified all pts attending our service from 2015-2018 who were born in Africa. Information on HCV genotype, treatment regimen and outcome was obtained. Samples were analysed locally by VERSANT HCV Geno 2.0 Assay. Non-subtypeable samples were then analysed using Glasgow NimbleGen next-generation sequencing (NGS).
Results: Of 91 African pts, 47 (52%) had an unusual genotype, which includes non-subtypeable G1, non 1a/1b G1 or non 4a/4d G4. Of non-subtypeable samples that underwent NGS, 17 were classified as highly divergent G1a (div1a). These were closest in genetic sequence to G1a but the median p-distance was (sequence diverged by) 10.8%. 46/51 (90%) pts achieved SVR, however, SVR was only seen in 19/26 (73%) of those with unusual G1 subtypes, with failure in 4/16 div1a and 3/4 in G1L. SVR failure was associated with unusual G1 subtype and NS5a rather than PI based treatment. Following retreatment, 1 patient with divG1a has failed to achieve SVR after 16 weeks G/P. 2 patients with G1L have achieved SVR with G/P.

Age	54 (47, 64)	
Gender	42/91 (46%) female	
HIV +	8 (9%)	
Cirrhosis	20/91 (21.9%)	
Country of birth	n	Genotype
Cameroon	9	1, div1a, 1b, 2x1e, 1l, 2, 4, 4f
Congo	7	2, 4, 4c, 3x4k, 4r
Cote D'Ivoire	4	1a, 3xdiv1a
Egypt	3	2x1g, 4
Eritrea	3	1a, 4a, 5a
Ghana	6	1a, 2xdiv1a, 2a/c, 4, 6
Nigeria	26	2x1a, 4xun1, 3x1b, 1c, 2x1g, 1h, 3x1l, 5xdiv1a, 3a, 3x4a, 4f
Other African countries	33	8x1a, 3xdiv1a, un1, 3x1b, 1l, 1e, 1b/2k, 2k, 2a, 2x3h, 4x4a, 4r, 4x4e

Conclusion: In an unselected cohort of African pts the majority (52%) had an unusual genotype. The SVR rate of those with unusual genotype 1 was 19/26 (73%). This is unacceptably low in the current era. This was driven by 6 failures in pts taking sofosbuvir/ledipasvir, compared with only 1 failure on a PI based regimen and raises concerns about the roll out of first generation NS5a inhibitor based schemes across Africa. Depending on the chosen regimen, failure rates in African cohorts could be higher than in clinical trials, jeopardising HCV elimination agendas.

PS-182

Effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 1 infection who receive opioid agonist therapy: Treatment utilization and the impact of concomitant psychiatric medications

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Background and aims: Elbasvir/grazoprevir (EBR/GZR) for 12 weeks is an effective treatment for patients with hepatitis C virus (HCV) genotype (GT) 1 infection receiving opioid agonist therapy (OAT). This study assessed the real-world effectiveness of EBR/GZR in HCV GT1-infected patients receiving OAT.
Method: We conducted a nationwide retrospective observational cohort study of patients with chronic HCV infection in the US Department of Veterans Affairs who had received EBR/GZR for > 11 weeks between January 28, 2016, and August 31, 2017, and a diagnosis of opioid use disorder (ICD-10-CM code F11.x-) or ≥ 1 prescription for OAT (including methadone, buprenorphine, levomethadone, naloxone, and naltrexone) within 1 year prior to the index date through the end of treatment. Patients who had received buprenorphine transdermal patch, an undetermined HCV treatment regimen, or an NS5A inhibitor-containing regimen were excluded. SVR was defined as undetectable HCV RNA at ≥ 4 weeks after the end of treatment.
Results: 611 patients were included (male, 96%; black, 53%; mean age, 62 years), of whom 526 received EBR/GZR without ribavirin for 12 weeks and 85 received other EBR/GZR-based regimens. Forty-seven percent (n = 286) had GT1a and 50% (n = 303) had GT1b infection. Baseline viral load was < or ≥ 800, 000 IU/ml in 163 (27%) and 416 (68%) patients. Most patients were treatment-naive (n = 549, 90%), had chronic kidney disease stage 4–5 (n = 526, 86%), had received ≥ 1 OAT (59%; n = 363), had a history of alcohol abuse (77%; n = 471), had a history of drug abuse (90%; n = 548), or were receiving concomitant psychiatric medication (71%; n = 434). SVR was achieved by 586 of 611 patients (95.9% [95% confidence interval [CI], 94.0%, 97.3%), with high SVR rates in those who received EBR/GZR for 12 weeks (506/526, 96% [95% CI, 94.6%, 97.8%]). SVR in select subgroups is shown in the Figure.

SVR in select subgroups

Subgroup	n/N	SVR, % (95% CI)
Baseline viral load		
<800,000 IU/mL	156/163	96 (92.6, 98.8)
≥800,000 IU/mL	401/416	96 (94.6, 98.2)
HCV genotype		
GT1a	273/286	95 (93.0, 97.9)
GT1b	293/303	97 (94.7, 98.7)
Cirrhosis	205/216	95 (92.0, 97.8)
CKD stage 4–5	506/526	96 (94.6, 97.8)
History of alcohol abuse	455/471	97 (95.0, 98.2)
History of drug abuse	529/548	97 (95.0, 98.1)
Any concomitant psychiatric medication	417/434	96 (94.3, 97.9)
Benzodiazepines	60/61	98 (95.2, 100)
Mood stabilizer	184/192	96 (93.0, 98.7)
Antidepressant	327/342	96 (93.4, 97.8)
Antipsychotic	107/112	96 (91.7, 99.4)
Any OAT	343/363	94 (92.1, 96.8)

CKD, chronic kidney disease; GT, genotype; HCV, hepatitis C virus; OAT, opioid agonist therapy; SVR, sustained virologic response.

Conclusion: In this real-world population, EBR/GZR was highly effective in patients with HCV GT1 infection receiving OAT. SVR rates were consistently high regardless of baseline viral load, history of alcohol or drug abuse, or concomitant psychiatric medication.

PS-183

Association of patient-reported outcomes with cerebral metabolism in patients with chronic hepatitis C at baseline and post sustained virologic response

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Background: CHC patients experience significant impairment of emotional health and fatigue as assessed by PROs, which improves after SVR.
Aim: We assessed association of PROs and cerebral metabolites prior to treatment and after SVR in CHC patients treated with ledipasvir/sofosbuvir (LDV/SOF).
Method: CHC patients with genotype 1 without cirrhosis (N = 40, age: 45.3 ± 11.5, 48% male, 90% white) received 12 weeks of LDV/SOF. Clinical, laboratory, and PRO data were collected. The PROs included Short-Form (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) administered prior to treatment and after SVR-24. At the same time points, cerebral metabolism in the basal ganglia (BG) and frontal (FR) and dorsolateral prefrontal cortex (DL) was assessed using magnetic resonance spectroscopy (MRS). Metabolic markers measured included N-acetylaspartate (NAA), choline (Cho), and myoinositol (MI), in addition to Creatinine (Cr) as a control metabolite. Spearman's correlations between the PRO scores and the markers of cerebral metabolism were calculated.
Results: Of the entire cohort, 92% achieved SVR-24. Patients who achieved SVR experienced PRO improvement in 22 out of 26 calculated domains ($p < 0.05$). Prior to treatment, the ratio of MI in the BG was significantly and inversely correlated with Role Emotional of SF-36 ($r = -0.37$, $p = 0.02$). Similarly, the ratio of MI in the DL negatively correlated with Emotional Well-Being of FACIT-F ($r = -0.31$, $p = 0.05$). In contrast, post-SVR, the ratio of MI in the BG negatively correlated with different domains than at baseline, including Fatigue-FACIT-F and total CLDQ-HCV score ($r = -0.46$ and $r = -0.41$, both $p < 0.05$). Also, the ratio of MI in FR correlated with Emotional Well-Being-FACIT-F and Systemic Symptoms as measured by CLDQ-HCV ($r = -0.44$ and $r = -0.43$, both $p < 0.05$). Furthermore, post-SVR, the ratio of NAA in FR negatively correlated with Fatigue of FACIT-F, Emotional and total scores of CLDQ-HCV (r from -0.46 to -0.40, $p < 0.05$) while NAA in DL positively correlated with Bodily Pain-SF-36 ($r = 0.52$; $p < 0.01$). Lastly, choline metabolites in DL negatively correlated with Social Well-Being and total FACIT-F score ($r = -0.41$, $p < 0.05$).
Conclusion: Fatigue and emotional well-being PROs in CHC correlate with cerebral metabolites. This pattern changes after SVR, and may be related to viral clearance and changes in fatigue, pain and social well-being as assessed by PROs.

PS-184

Real-world effectiveness and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus infection: A meta-analysis

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Background and aims: Glecaprevir/pibrentasvir (G/P) is approved for adults infected with hepatitis C virus (HCV) genotypes 1-6. In clinical trials, G/P was associated with high rates of sustained virologic response at post-treatment Week 12 (SVR12) and was well tolerated. Currently, real-world evidence (RWE) regarding G/P use is being collected. A systematic review and meta-analysis of RWE reporting the effectiveness and safety of G/P were undertaken.
Method: Biosis, Derwent Drug File, Embase®, International Pharmaceutical Abstracts, Medline®, and SciSearch databases were searched using pre-defined terms for "G/P" and "RWE" to identify real-world prospective/retrospective studies (1 January 2017–15 October 2018) that reported SVR12 and/or safety parameters in HCV-infected adults ($N \geq 20$) treated with G/P. Congress presentations up to 12 November 2018 were included. Random effects meta-analysis was used to determine SVR12 and naïve pooling for adverse event (AE) rates. Intention-to-treat (ITT) SVR12 analyses included all patients dosed with G/P; modified ITT (mITT) excluded those who had non-virologic failure.
Results: 10, 048 adults treated with G/P in 16 studies were included; ITT SVR12 rates were reported in 14 studies and mITT SVR12 rates in 11 studies. SVR12 rates overall and by subgroups based on ITT and

Table: (abstract: PS-184)

	ITT-Patients, n (studies, n)	Meta-analysis ITT-SVR12, %; 95% CI	mITT-Patients, n (studies, n)	Meta-analysis mITT-SVR12, %; 95% CI
Overall	8279 (14)	96.6; 95.2–98.0	5995 (11)	98.1; 96.7–99.5
Cirrhosis				
Yes	629 (6)	97.8; 96.2–99.4	688 (7)	97.7; 96.1–99.3
No	3862 (5)	96.9; 94.2–99.6	4685 (6)	97.7; 95.3–100
HCV genotype				
1	1685 (6)	95.5; 92.5–98.4	2468 (4)	97.5; 93.9–100
2	375 (6)	96.4; 93.4–99.3	383 (4)	97.1; 94.5–99.8
3	1084 (6)	95.2; 92.0–98.4	700 (6)	95.8; 92.7–98.9
4	214 (4)	99.0; 97.6–100	165 (2)	98.5; 96.6–100
HCV treatment experience				
Treatment-naïve	NA	NA	3893 (4)	97.3; 94.0–100
Treatment-experienced (PRS or DAA)	181 (5)	97.7; 95.6–99.9	643 (5)	96.5; 93.4–99.7
Treatment duration				
8 weeks	1781 (4)	96.2; 92.7–99.7	3514 (6)	98.1; 95.6–100
12 weeks	603 (4)	95.7; 92.2–99.3	593 (3)	95.7; 91.8–99.6
16 weeks	NA	NA	NA	NA

DAA, direct-acting antiviral; NA, data available from < 2 studies; PRS, regimens containing interferon, peginterferon, ribavirin, and/or sofosbuvir

mITT populations are shown (Table). AEs were summarised in 6 studies and reported in 12.7% (724/5685) of patients. Treatment discontinuations due to AEs were summarised in 5 studies and reported in 0.5% (24/4508) of patients. The most frequent AEs were pruritus (4.7%; 126/2698), fatigue (4.4%; 146/3305), and headache (2.7%; 102/3759). SVR12 and safety data will be updated in the final presentation.

Conclusion: Consistent with results observed in clinical trials, RWE indicates that G/P is a well-tolerated and highly effective pangenotypic treatment option for a broad range of HCV-infected patients.

Non-invasive assessment of liver disease

PS-185

Magnetic resonance risk score and liver stiffness by transient elastography have complementary prognostic values in patients with primary sclerosing cholangitis

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Background and aims: Magnetic resonance (MR) risk scores and liver stiffness (LS) were previously shown to be associated with the clinical outcome in patients with primary sclerosing cholangitis (PSC)[1,2]. The aim of the current study was to assess the complementary value of the MR risk score without gadolinium[3] (Anali score without Gd) and LS to predict prognosis of PSC patients.

Method: Patients with large duct PSC from three European centers with three dimensional-MR cholangiography (3D-MRC) images available for central reviewing and a valid LS measurement assessed by Fibroscan performed within 6-month interval were included in a longitudinal retrospective study. Exclusion criteria consisted of decompensated cirrhosis, primary liver cancer, a history of acute cholangitis at study entry, PSC-autoimmune hepatitis variants. All 3D-MRC images were reviewed by two expert radiologists and the Anali score without Gd calculated according to the formula (1 × dilatation of intrahepatic bile ducts) + (2 × dysmorphy) + (1 × portal hypertension). The primary end point was survival without liver transplantation (LT) or cirrhosis decompensation. The prognostic value of LS and Anali score without Gd were assessed using Cox proportional hazard models.

Results: 162 patients were included. A total of 753 patient-years were available. Forty patients experienced an adverse outcome (4 LT, 6 liver-related deaths and 30 cirrhosis decompensations). LS and the Anali score without Gd were individually associated with the occurrence of an adverse outcome ($p < 0.001$ for both). Optimal prognostic thresholds were 10.5 kPa for LS and 2 for the Anali without Gd (Hazard Ratios: 2.07, $p = 0.03$ and 3.78, $p = 0.001$, respectively). The frequency of adverse outcomes according to the value of LS and Anali score without Gd was 8.3% in patients with LS ≤ 10.5 kPa and Anali ≤ 2, 24% in patients with LS > 10.5 kPa or Anali > 2 and 55% in patients with LS > 10.5 kPa and Anali > 2, respectively ($p = 0.001$). A significant difference in mean survival of these 3 subgroups of patients was observed (Log-Rank 26.8, $p < 0.001$) (Figure).

Conclusion: The combination of MR imaging and liver stiffness improves the stratification of PSC patients into groups with high, medium and low risk of developing adverse outcome.

References

1 Cazzagon N *et al. Hepatology* 2018;68 (Suppl.1):29A.
2 Corpechot C *et al. Gastroenterology* 2014;146:970–979.
3 Ruiz A *et al. Hepatology* 2014; 59:242–250.

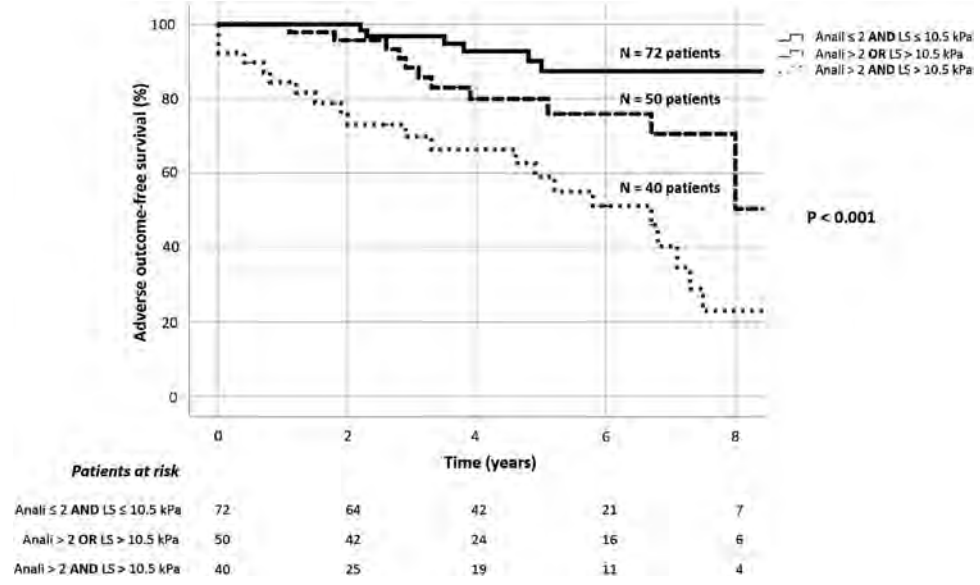

Figure: Kaplan-Meier curves for adverse outcome-free survival according to Anali score without Gd and LS used in combination.

PS-186

Functional liver imaging score derived from gadoxetic acid-enhanced MRI predicts outcomes in patients with advanced chronic liver disease

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Background and aims: Non-invasive methods for stratifying the risks of first hepatic decompensation and mortality in patients with compensated (cACLD) and decompensated (dACLD) advanced chronic liver disease, respectively, might facilitate individualized therapy. In contrast to other MRI-based methods, the Functional Liver Imaging Score (FLIS) derived from the hepatobiliary phase (HBP) of gadoxetic acid-enhanced MRI (GA-MRI) does neither require tedious measurements or calculations, nor specific hard- or software, and thus, is easily applicable in clinical routine.
We aimed to investigate the predictive value of FLIS for hepatic decompensation and transplant-free survival in a large series of patients with chronic liver disease (CLD).
Method: Our study comprised 262 consecutive patients with CLD but without malignancy who underwent a standardized GA-MRI protocol. Two radiologists blinded to the clinical data evaluated the FLIS components (0-2points each) in the HBP 20min after contrast administration: (1) contrast enhancement and (2) excretion as well as (3) portal vein sign.
Patients were stratified into three groups according to FIB-4 and the history/presence of hepatic decompensation: non-advanced CLD (FIB-4 ≤ 1.45), cACLD (FIB-4 > 1.45), and dACLD. Within these strata, patients with FLIS indicative of poor (0-3points) and good (4-6points) liver function were compared.
Results: Intra- (κ = 0.983, 95% confidence interval [95%CI]:0.971-0.991) and inter-observer (κ = 0.893, 95%CI:0.864-0.916) agreement for FLIS was excellent.
Patients with non-ACLD (n = 56;0-3points:25%), cACLD (n = 110;0-3points:15%), and dACLD (n = 99;0-3 points:46%) were followed for a median of 40.7, 40.6, and 13.7months, respectively. As expected, patients with non-advanced CLD had a negligible risk of clinical events. In cACLD patients, the FLIS was independently predictive of hepatic decompensation (0-3vs.4-6points;adjusted hazard ratio [aHR]:3.724, 95%CI:1.098-12.635;*P* = 0.035;panel A). Moreover, a FLIS score of 0-3points emerged as an independent risk factor for transplant-free mortality in both cACLD (aHR:7.437, 95% CI:2.742-20.17;*P* < 0.0001;panel B) and dACLD patients (aHR:2.869, 95%CI:1.311-6.281;*P* = 0.008;panel C).
Conclusion: The FLIS is an easy-to-use and highly reproducible imaging biomarker for the development of first hepatic decompensation and mortality in patients with ACLD. Implementation of the FLIS into GA-MRI reports might refine prognostication, and thus, facilitate personalized medicine.

PS-187

Transient elastography is the most reliable non-invasive predictor of advanced liver fibrosis in fontan-associated liver disease: The VALDIG FONLIVER study

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Background and aims: Fontan surgery (FS) is a palliative treatment in congenital heart diseases with single ventricle physiology. FS creates a hemodynamic system characterized by systemic venous congestion and low cardiac output, which leads to liver damage in the long-term. Assessment of liver fibrosis is controversial in this setting, since transient elastography (TE) can overestimate liver stiffness due to sinusoidal congestion, and liver biopsy can be risky, particularly in patients on anticoagulation. Aim: To evaluate the accuracy of TE to assess advanced liver fibrosis in patients with FS.
Method: International, multicenter, observational, prospective and analytical study. 19 FS patients were evaluated by blood test, Fibroscan®, Doppler US, MRI/CT, liver biopsy and HVPG. Inclusion period: 01/01/2015-01/11/2018. All liver biopsy specimens were analyzed by expert pathologists who, as the TE operators, were blinded to clinical information. Only liver biopsy specimens ≥1.5cm and with ≥5portal tracts were accepted. Portal and sinusoidal fibrosis, periportal inflammation and sinusoidal dilation were evaluated. METAVIR and Congestive Hepatic Fibrosis Score (CHFS) were used to stage liver disease.
Results: (Median, range). 19 patients were included. In 16/19 (84%) there was some degree of fibrosis, being advanced (CHFS 3-4) in 9/19 (47%). Although liver stiffness was > 10kPa in all patients, those

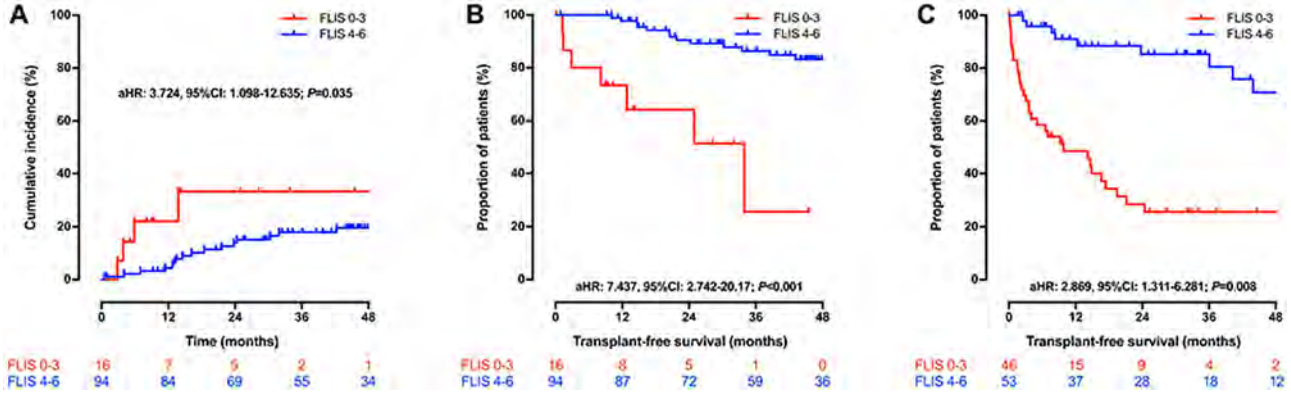
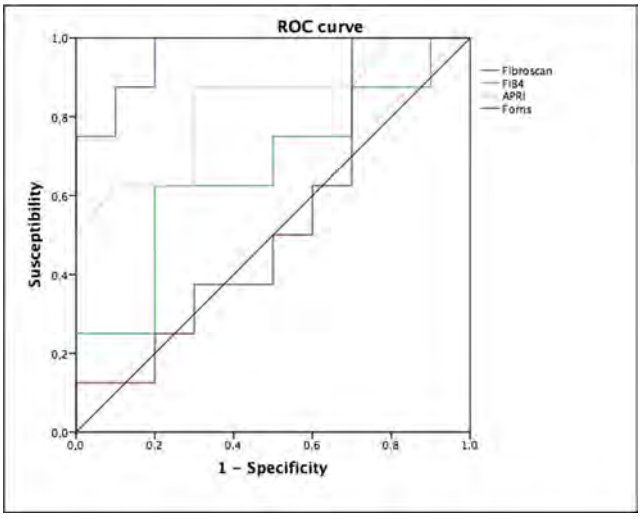


Figure: (abstract: PS-186)

with mild fibrosis (CHFS 0-2) had lower stiffness than those with advanced fibrosis [15.8 (11.6-28.4) vs 48.9 (27.3-70.6)kPa, p < 0.001]. Liver stiffness correlated with the degree of portal fibrosis (rho = 0.74, p < 0.001), sinusoidal fibrosis (rho = 0.63, p = 0.004), METAVIR score (rho = 0.74, p < 0.001) and CHFS (rho = 0.82, p < 0.001). Wedged hepatic venous (rho = 0.52, p = 0.03) and inferior vena cava (rho = 0.59, p = 0.01) pressures, but not HVPG, correlated with sinusoidal fibrosis. Portal inflammation was minimal in 2/19 (11%) and absent in 89%. The presence of a heterogeneous hepatic parenchyma on US/reticular enhancement on MRI/CT were not associated with greater histological liver damage, although a nodular surface was associated with advanced fibrosis according to CHFS (p = 0.04). TE accurately discriminated between patients with mild fibrosis (CHFS 0-2) and those with advanced fibrosis (CHFS 3-4), with AUROC 0.96 (0.73-1.0, p < 0.001). When the best cut-off of 26.4kPa was used, the sensitivity was 100% and the specificity 80%. Among the other non-invasive methods analyzed (FIB-4, APRI and Forns), only APRI correlated with the severity of fibrosis (rho = 0.57, p = 0.01).



Conclusion: TE is the most reliable non-invasive method for the diagnosis of advanced liver fibrosis in FALD, and the best cut-off seems to be higher than in other etiologies. Radiological features and serological methods commonly used for the diagnosis of advanced fibrosis in other etiologies are suboptimal in FALD.

PS-188

A novel non-invasive technology for liver fibrosis detection

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Background and aims: Liver fibrosis results from chronic liver damage and is a significant public health problem. Early stages of liver fibrosis are difficult to diagnose [1]. While it has been well accepted that progression of hepatic fibrosis is strongly correlated with increasing rigidity of liver tissue [2], how fibrosis modifies the mechanical properties of liver and how that in turn affect the blood flow dynamics in the liver is still not understood. We hypothesize that tissue rigidity can affect the dynamics of blood flow and that non-invasive blood flow measurements can be used to detect fibrosis. The aims of this study is the test this hypothesis and develop a novel non-invasive method for liver fibrosis detection.
Method: A computational model of blood flow in portal and hepatic veins was developed to demonstrate the quantifiable modifications of flow dynamics as a function of fibrosis progression. Ultrasound Doppler measurements as well as ELF (enhanced liver fibrosis using Fibroscan®) were collected with the corresponding biopsy data from 200 patients with F0-F4, F0 indicating healthy people. Physics-based machine learning analysis of the Ultrasound Doppler images were trained to classify F1-F4 based on clinical biopsy staging. Leave-one-out method was used as validation.
Results: Mathematical modeling suggest that blood flow dynamics showed quantifiable differences for different stages of fibrosis, which is confirmed by ultrasound Doppler data. Our classification of Stage F0-F5 showed clear discrimination of fibrosis of all stages (Figure 1). Comparing our technology with existing non-invasive technology, e.g. ELF (enhanced liver fibrosis using Fibroscan®), our technology showed better specificity in differentiate early stage fibrosis (Table 1).

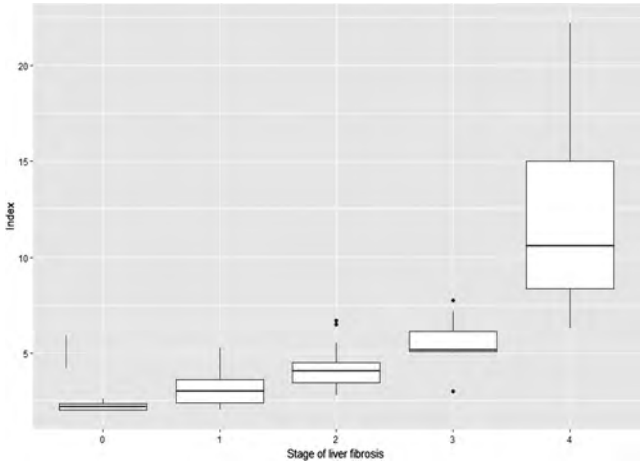

Figure 1. Stage liver fibrosis by Ultrasound Doppler measurement.

Health	Our Diagnostic Model	ELF(Fibroscan)
Sensitivity	94.12	92.7
Specificity	90.74	42.2
PPV	76.19	66.2
NPV	98	82.6

F1	Our Diagnostic Model	ELF(Fibroscan)
Sensitivity	68	62.3
Specificity	91.4	39.1
PPV	80.95	77.4
NPV	84.16	23.7

Table 1. Diagnostic performance for F0 and F1, very early stage fibrosis.

Conclusion: We have developed a series of mathematical models that showed the relationship between the liver stiffness and change in blood flow patterns in the hepatic veins. Analysis of clinical data from 200 patients confirmed that the blood flow patterns measured by the ultrasound Doppler Imaging can quantitatively reflect the fibrosis stage with high accuracy, even for early stage fibrosis.

PS-189

Toronto HCC risk index and albumin predict low risk of hepatocellular carcinoma after sustained virological response in hepatitis C infection

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Background and aims: Current guidelines recommend hepatocellular carcinoma surveillance for all F3/F4 after sustained virological response, however not all patients with advanced fibrosis are at

equally high risk of hepatocellular carcinoma. Hepatocellular carcinoma surveillance is unlikely to be cost effective if the incidence is below 1.3%/year. This study aimed to identify factors associated with a low enough risk of hepatocellular carcinoma post-treatment to forego hepatocellular carcinoma surveillance.

Method: Data were collected from the Toronto Centre for Liver Disease from 06/2006 to 10/2018 for all patients with advanced fibrosis (AST-to-platelet ratio index ≥ 1, FIB-4 ≥ 1.45, liver stiffness ≥ 9.5 kPa or biopsy ≥ F3) who achieved sustained virological response. Toronto HCC risk index combines age, sex, etiology, and platelet count to categorize patients with F4 as low (Toronto HCC risk index < 120), intermediate (Toronto HCC risk index = 120-240), or high hepatocellular carcinoma risk (Toronto HCC risk index > 240). Baseline patient data were collected at start of treatment and patients were followed from end of treatment until hepatocellular carcinoma occurrence, transplant, or death. Cox regression was used to identify factors associated with a low risk of hepatocellular carcinoma post-treatment.

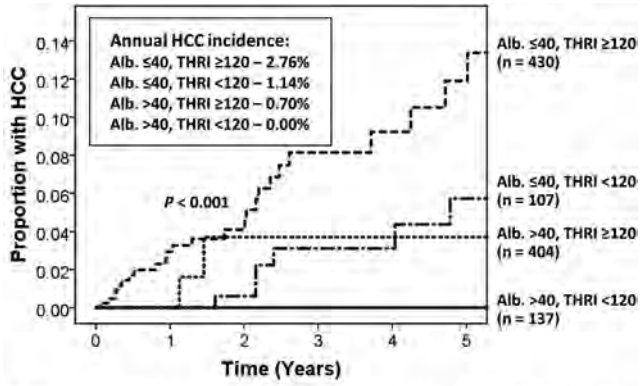

Figure 1. Albumin >40 g/L and Toronto HCC risk index (THRI) <120 independently predict low risk of hepatocellular carcinoma (HCC) after sustained virological response.

Results: Of 1, 093 F3/F4 patients who achieved sustained virological response, 397 (36.3%) received interferon-based and 696 (63.7%) received direct-acting antiviral therapy. Median age was 57.7 (IQR 52.1-63.1) years, 420 (38.4%) were female and 703 (64.3%) had cirrhosis. Patients were followed for median 1.4 (0.6-2.9) years: 4.1 (1.4-7.7) years for interferon patients and 1.0 (0.4-1.7) years for direct-acting antiviral patients. Forty-one (3.8%) patients developed hepatocellular carcinoma. By multivariable analysis, higher albumin and lower Toronto HCC risk index were associated with decreased hepatocellular carcinoma risk. Baseline albumin > 40 g/L (HR = 0.228 (0.101-0.516), P < 0.001) and Toronto HCC risk index < 120 (HR = 0.317 (0.098-1.029), P = 0.056) predicted a lower risk of hepatocellular carcinoma. Prognosis was improved in patients with albumin > 40 g/L or Toronto HCC risk index < 120, and best in patients with albumin > 40 g/L and Toronto HCC risk index < 120 (Fig. 1). Of 541 (49.5%) patients with albumin > 40 g/L, 7 (1.3%) developed hepatocellular carcinoma (incidence = 0.52% per person-year) and none of the 137 patients with albumin > 40 g/L and Toronto HCC risk index < 120 developed hepatocellular carcinoma.

Conclusion: Among hepatitis C patients with F3/F4 and sustained virological response, patients with baseline Toronto HCC risk index < 120 and albumin > 40 g/L have a very low risk of hepatocellular carcinoma. If confirmed with longer follow-up, hepatocellular carcinoma surveillance could be avoided in these individuals.

PS-190

Cirrhotic cardiomyopathy evaluated by myocardial deformation imaging and new diastolic dysfunction criteria: Prevalence and relationship with circulatory dysfunction

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Background and aims: The prevalence of CCM is not well known due to the lack of a specific diagnostic test. In addition, it may vary depending on diagnostic criteria used. Myocardial strain imaging with speckle-tracking echocardiography (STE) is a new method that has been believed to be a sensitive marker of early subclinical systolic

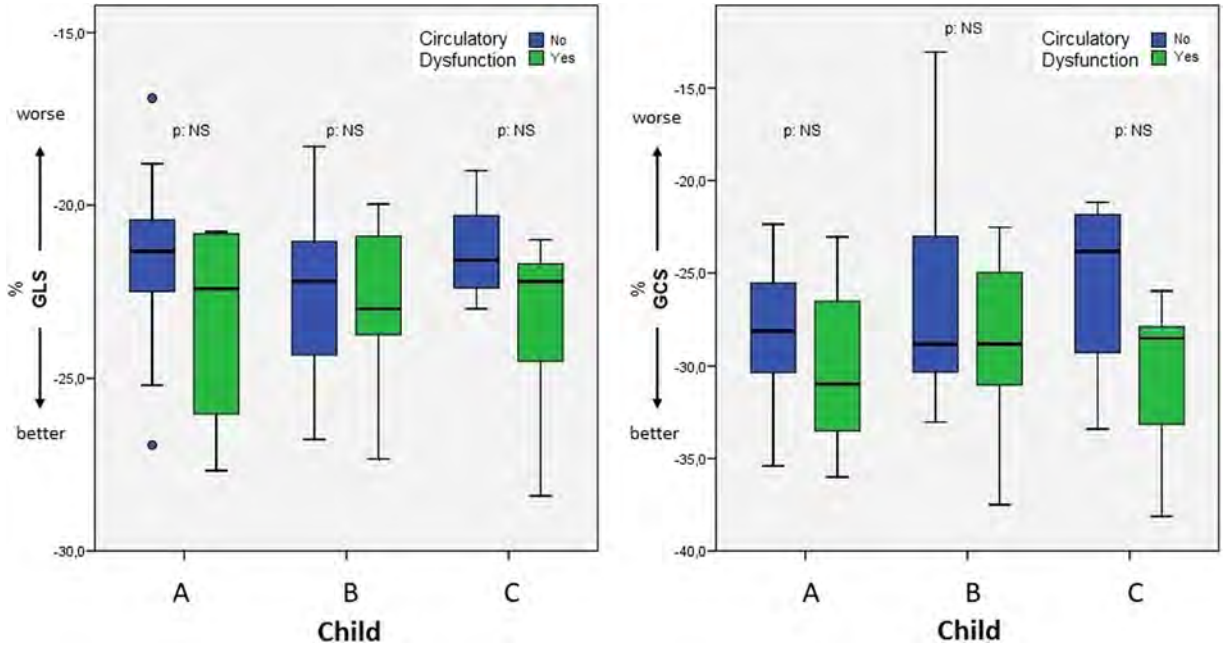

Figure: (abstract: PS-190)

impairment. However, studies are scarce and have shown variable results. The aim of this study was to investigate the prevalence of CCM evaluated by STE and its relationship with circulatory function.
Method: We conducted a prospective study enrolling patients with compensated and decompensated cirrhosis. Conventional and Tissue Doppler Imaging (TDI) echocardiography with myocardial deformation analysis (EPIQ7, QLAB v.10, Philips) were performed. Diastolic Dysfunction (DD) was assessed according to the latest defined criteria (Nagueh SF et al. 2016). Systolic function was estimate by STE with Global Longitudinal Strain (GLS, cut-off value: −20%) and Global Circumferential Strain (GCS, cut-off value: −22%). Plasma renin activity (PRA, cut-off value: > 4 ng/ml/hour) was determined as a surrogate of circulatory dysfunction (CD). Patients with structural heart disease and other cardiac conditions interfering with STE were excluded.
Results: A total of 88 subjects (male: 85%, age: 57, 5 ± 8, 2 years) were included. Child-Pugh class was distributed as follows: A, 31 (35.2%), B, 41 (46.6%) and C, 16 (18.2%). Alcoholic etiology was present in 58 cases (66.6%). Median MELD score was 13.4 ± 5.3. In ECG analysis, 11 (12.5%) subjects present QTc interval > 470ms. Regarding echocardiographic data, no patient was diagnosed of CCM by left ventricular (LV) ejection fraction, meanwhile, new criteria of DD identified 10 (11.3%) cases. GLS and GCS recognized CCM in 11 (12.5%) and 3 (3.4%) subjects, respectively. Prevalence of CCM did not differ between patients with or without decompensated cirrhosis (Child B-C: DD: 7/10 [70%] p:0, 17; GCS: 3/3 [100%] p:0, 19; GLS: 5/6[45, 5%] p:0, 15). Circulatory dysfunction was seen in 37 cases (42%), these patients showed better values of GLS and GCS but without statistical difference (Figure).
Conclusion: The prevalence of CCM is around 11-12% when the new diagnostic criteria are applied, lower than previously reported. STE did not show better diagnostic performance than DD. Circulatory dysfunction is likely to cause a compensatory increase of GLS and GCS, a hypothesis that requires further confirmation.

PS-191
External validation of an algorithm combining multi-analyte blood tests (FibroTest-LCR1-LCR2) for identifying subjects at risk of hepatocellular carcinoma among patients with chronic liver disease

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Background and aims: The early non-invasive detection and prediction of hepatocellular carcinoma (HCC) in patients (pts) with chronic liver disease, without or with cirrhosis is needed. We hypothesized that certain FibroTest (FT) components mediating hepatoprotection could be associated with the development of HCC. The algorithm FT-LCR1-LCR2 sequentially combining, FT and two multi-analyte-tests (LCR1-LCR2 patents pending) which increased the performance of AFP alone were constructed and internally validated in the prospective FibroFrance cohort (NCT01927133; *APT 2018*). The aim was to externally validate the sensitivity (Se) and the 5-yr prognostic value of FT-LCR1-LCR2.
Method: Pts of the ongoing prospective cohort of Bondy-Hospital, France, who had paired frozen serum with HCC prospectively detected (cases) were matched to controls who had not developed HCC during a similar follow-up (≥1 control for 1 HCC) using gender, age and Fibrotest fibrosis stages, blindly to LCR1-LCR2 results. The performance of FT-LCR1-LCR2 algorithm {high LCR2 (LCR2+) in pts with cirrhosis (F4+/LCR2+), or in pts without cirrhosis but with high LCR1 (FO123/LCR1+/LCR2+)}, was assessed and compared (Se and 5-yr survivals without HCC) with the standard AASLD surveillance (F4+/+-AFP). HCC diagnosis was either confirmed by biopsy, or suggested by non-invasive Barcelona criteria, or reported by death certificate.
Results: 159 pts were followed prospectively (median 5.1yr (IQR 2.5-7.1)), including 51 who had developed HCC (31 with cirrhosis and 20 without) and 108 controls (56 with cirrhosis and 52 without). The Se of FT-LCR1-LCR2 algorithm was higher *vs* standard surveillance: 78.4 vs 60.8 (p = 0.002) (Table), and the 5yr-survival without HCC was.90 (.81-.99) *vs*..77 (.67-.86; Logrank P = 0.003) according to FT-LCR1-LCR2 predetermined cutoff respectively. Similar results were observed in patients of 50 years of age or older (Table). In pts with HCC occurrence only 4/51 (7.8%) had disappearance of the algorithm signal vs 15/108 (13.9%) of controls when repeated in the same 159 pts, 1.5 yr (IQR 1.1-2.4) later, associated with an increase per year of LCR2, +0.014 (SE = 0.02) for cases vs 0.00 (0.01) for controls (Kruskal-Wallis P = 0.003).

Table: Performance of LCR1 in F0123, and sequential LCR1-LCR2 algorithm in all.

	ALL n (%)		50 years of age and older	
	HCC	Controls	HCC	Controls
LCR1 in F0123	**20**	**52**	**19**	**42**
LCR1 + inclusion	20 (100)	49 (94.2)	19 (100)	42 (100)
LCR1- inclusion	0 (0)	7 (5.8)	0 (0)	0 (0)
FT-LCR1-LCR2 algorithm all	**51**	**108**	**47**	**92**
FT-LCR1-LCR2 + inclusion	40 (78.4)	66 (61.1)	37 (78.7)	62 (67.4)
FT-LCR1-LCR2-inclusion	11 (21.6)	42 (38.9)	10 (21.3)	30 (32.6)
Standard AASLD algorithm all	**51**	**108**	**47**	**92**
Cirrhosis	31 (60.8)	56 (51.9)	28 (40.4)	50 (54.3)
No cirrhosis	20 (39.2)	42 (48.1)	19 (59.6)	42 (45.7)

Conclusion: The FT-LCR1-LCR2 algorithm was validated in an independent external cohort for the prediction of HCC.

Clinical developments in rare liver disease

PS-192
Lanreotide reduces liver growth in autosomal dominant polycystic kidney disease: Data from a 120-week randomized clinical trial

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Background and aims: Polycystic liver disease (PLD) is the most common extra-renal manifestation in autosomal dominant polycystic kidney disease (ADPKD). There is need for robust long-term evidence on the volume reducing effect of somatostatin analogues. Therefore we evaluated the effect of lanreotide on height adjusted liver volume (hTLV) and combined height adjusted liver- and kidney volume (hTLKV) in ADPKD patients with PLD.
Method: The DIPAK-1 study, a 120-week open label, randomized clinical trial, compared lanreotide versus standard care in 305 ADPKD patients to evaluate its renoprotective effect. For this analysis we studied the 175 patients with PLD, defined as hepatic cysts on MRI and a liver volume ≥ 2000ml. Of these, 93 were assigned to lanreotide (120 mg subcutaneously every 4 weeks) and 82 to standard care. Primary end point was percentage change in hTLV

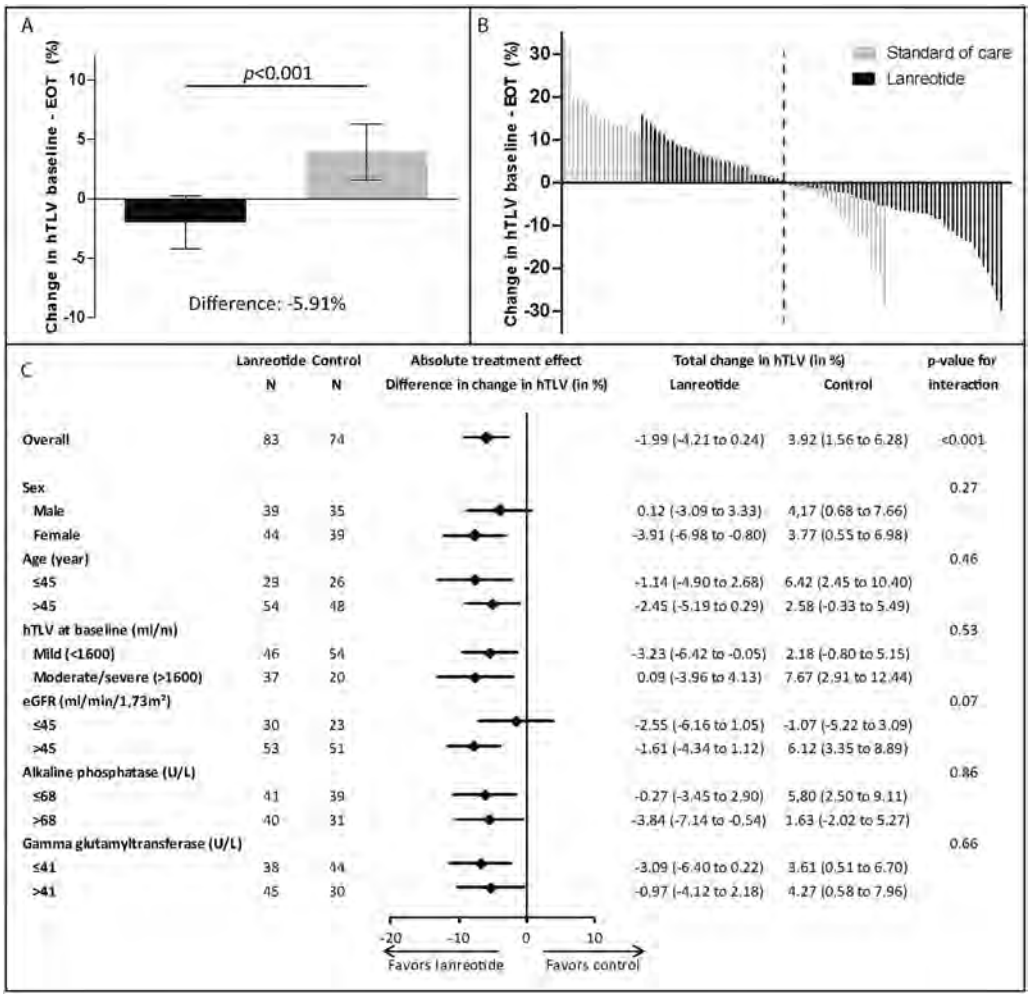

Figure: (abstract: PS-192): Change in hTLV between baseline and end of treatment A) Estimated percent change (mean ± 95% CI) in hTLV between baseline and end of treatment; B) percent change in hTLV, each bar represents 1 patient (dark bars-lanreotide, light bars-control group). All bars right from the scattered line represent decrease in hTLV, bars on the left represent increase in hTLV; C) subgroup analysis for the primary outcome.

between baseline and end of treatment (week 120). Secondary end point was change in hTLKV.

Results: At 120 weeks, hTLV decreased with 1.99% (CI −4.21 to 0.24) in the lanreotide group, whereas it increased by 3.92% (CI 1.56 to 6.28) in controls. Compared to controls, lanreotide reduced growth of hTLV by 5.91% (CI −9.18 to −2.63; p < 0.001). A beneficial treatment effect was still present 4 months after the last injection (−3.87%, CI −7.55 to −0.18; p = 0.04). Lanreotide resulted in an even stronger reduction in hTLKV compared to controls (−7.18%, CI −10.25 to −4.12; p < 0.001).

Conclusion: In patients with PLD due to ADPKD, lanreotide for 120 weeks reduced the growth of liver and combined liver- and kidney volume. This effect was still present four months after cessation of treatment; ClinicalTrials.gov number, NCT01616927

PS-193

Phase 2 open-label study with a placebo-controlled drug withdrawal period of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with Alagille Syndrome: 48-week interim efficacy analysis

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Background and Aims: Maralixibat (SHP625/LUM001) is a potent, selective and minimally absorbed ileal apical sodium-dependent bile acid transporter (ASBT) inhibitor, in development for the treatment of pruritus in patients with Alagille Syndrome (ALGS).

Method: This was a pre-specified 48-week interim analysis of a phase 2 study in children with ALGS. After an 18-week maralixibat run-in period (6 weeks ascending doses up to 400 µg/kg daily and 12

weeks of stable dosing), subjects were randomized to placebo or continued maralixibat treatment for 4 weeks. After this all subject were treated with maralixibat. Change in serum bile acid (sBA), caregiver and patient reported Itch Reported Outcome (ItchRO) scores, Clinician Xanthoma Severity Scale and Pediatric Quality of Life Inventory (PedsQL) were evaluated during the randomization period and through 48 weeks of treatment.

Results: The 31 enrolled participants' mean age was 5.4 years (1-15 years), 19 (61%) were males, 30 had JAGGED1 and 1 not identified mutation. Twenty-nine completed the withdrawal period and 25 the 48-weeks treatment. There was a 31% sBA reduction during the run-in period (mean [SD]: −87 [120] µmol/L, p < 0.001) in the overall group. During the randomization period, sBA levels returned to baseline (BL) in the placebo but continued to decrease in the maralixibat group (94 [133] vs. −17 [110] µmol/L, p = 0.038). At the end of the 48 weeks there was a 36% sBA reduction from BL in the overall group (−101 [170] µmol/L, p = 0.003). This coincided with a −1.7 [0.9] point mean reduction in weekly average morning ItchRO (Obs) score (0 = none, 4 = severe itching) at week 18, a 1.7 [1.0] vs. 0.3 [0.8] point increase in the placebo vs. maralixibat group during the randomization period (p = 0.008), and a −1.6 [1.3] point reduction at week 48 (Figure). A total of 72% of subjects experienced an ItchRO reduction from BL of ≥ 1.0 point. Clinician Xanthoma Severity scores decreased by 44% and PedsQL scores improved by 9.5 points over 48 weeks of treatment. Maralixibat was generally safe, the most frequent adverse events were diarrhea, abdominal pain, vomiting and upper respiratory infections. During the study a small ALT increase (18 [84] U/L) was observed, while total bilirubin did not change.

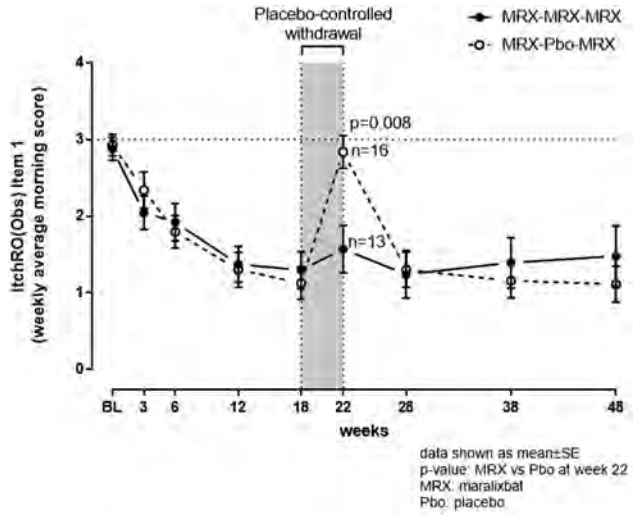

Figure: Pruritus change over time.

Conclusion: In cholestatic patients with ALGS, ASBT inhibition with maralixibat led to a significant reduction in sBA and improvement in pruritus compared to placebo and improvements in xanthoma severity and quality of life over 48 weeks of treatment.

PS-194

Effects of the ileal bile acid transport inhibitor A4250 on serum bile acids, pruritus and sleep in patients with Alagille syndrome: Phase 2 study results

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Background and aims: Alagille syndrome (ALGS) may include chronic cholestatic liver disease with intractable pruritus and progression to end-stage cirrhosis. Current treatments include invasive surgical biliary diversion and liver transplantation. The effects of A4250 (a potent, selective, reversible ileal bile acid transporter inhibitor that decreases bile acid reuptake with minimal systemic exposure) are reported in patients with ALGS.

Method: A phase 2, open-label, multi-centre study evaluating A4250 safety and tolerability in paediatric cholestatic liver diseases with pruritus (including ALGS) was conducted. Efficacy end points included change in serum bile acid levels and pruritus. Patients received oral A4250 10-200 µg/kg/day for 4 weeks.

Results: Six patients with ALGS were enrolled. All had elevated baseline serum bile acids (~2 to > 40×ULN). After 4 weeks of A4250 treatment, 5 patients had marked reductions in serum bile acids (range: −39% to −92%) and 1 patient assigned to the lowest A4250 dose (10 µg/kg/day) had a slight increase of 4%. Pruritus scores improved on 3 daily reported itch tools: a visual analogue scale (VAS; 0-10), Partial Patient-Oriented Scoring Atopic Dermatitis scale (PO-SCORAD; 0-10) and Whitington scale (0-4), as did PO-SCORAD sleep scores (Table). A4250 was generally well tolerated. Liver enzymes varied in ALGS patients and 2 patients in the 200 µg/kg/day group had elevated liver transaminases at baseline that increased further during treatment. Although the levels observed were within baseline variability, the DSMB halted dose escalation and the planned 300 µg/kg/day dose was not administered. No serious treatment-related adverse events, deaths or discontinuations were reported in ALGS patients.

Effects of A4250 on bile acids and pruritus in patients with Alagille syndrome

	Baseline	End of Treatment	Change
Bile acids, µmol/L	237.5 ± 79.7 (25.7, 563.8)	139.8 ± 64.4 (12.2, 352.7)	−46.3 ± 12.8% (−92, 4.3%)
VAS-Itch	5.5 ± 0.8 (3.5, 8.1)	3.2 ± 1.0 (0.2, 6.9)	−2.3 ± 1.0 (−6.1, 0.7)
Whitington-Itch	2.0 ± 0.24 (1.0, 2.6)	1.6 ± 0.4 (0.5, 3.0)	−0.5 ± 0.4 (−1.6, 0.8)
PO-SCORAD-Itch	5.0 ± 1.0 (1.8, 8.3)	2.8 ± 0.8 (0.1, 5.5)	−2.3 ± 1.0 (−6.7, 0.2)
PO-SCORAD-Sleep	3.8 ± 1.0 (0.8, 6.3)	2.4 ± 0.8 (0.8, 5.0)	−1.5 ± 1.0 (−5.4, 0.7)

Values represent mean ± standard error (min, max).

Conclusion: Orally administered A4250 was generally well tolerated, and observed reductions in serum bile acids and improved pruritus and sleep scores suggest that further investigation of A4250 in children with ALGS is warranted.

PS-195

Predicting long-term outcome after surgical biliary diversion in Bsep-deficiency patients: Results from the NAPPED consortium

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Background and aims: Progressive Familial Intrahepatic cholestasis type 2, or BSEP-deficiency (BSEP-def), results from mutations in the *ABCB11* gene. Mutations impair biliary bile salt secretion, leading to progressive liver disease. Symptoms do not always respond to medical therapy. Rather, patients are treated by surgical biliary diversion (SBD) and/or liver transplantation (LTx). We reported that SBD is associated with long-term native liver survival (NLS) in BSEP-def patients (Hepatol 2018, 68:S130). We now assessed if biochemical parameters after SBD could function as a reliable surrogate parameter for long-term NLS.

Method: From the global NAPPED database we analyzed patients with compound heterozygous or homozygous pathological mutations in *ABCB11*, who had undergone SBD (n = 51). Patients had mild (n = 34), moderate (n = 14) or severe (n = 3) mutations. For biochemistry analyses we used the most recent available sample pre-SBD and the first sample at > 2 months post-SBD. Continuous variables are expressed as medians and IQR. The association between serum bile acids (SBA), alanine aminotransferase (ALT) or total serum bilirubin (TSB), and NLS was analysed with cox-regression (corrected for sex and birthyear) and Receiver Operating Characteristic curve analysis.

Results: The major indication for SBD had been refractory, cholestatic pruritus (89%). SBD consisted of partial external biliary diversion (PEBD, n = 47), ileal exclusion (n = 3) or cholecystocolostomy (n = 1). Follow-up after SBD (at age 2.9 [1.3-6.0]yr) was 9.5 [2.5-12.5]yr. Pruritus was present in 94% pre- and in 41% post-SBD ($p < 0.001$). The diversion was closed in 6 patients (mild = 2, moderate = 3, severe = 1) at 2.0 [0.1-4.0]yr after SBD, followed by LTx in 5/6 patients at 6.3 [0.9-10.3]yr post-SBD. LTx was performed in 32% of all patients, 2.7[1.2-10.3]yr post-SBD. SBD was associated with a decrease in SBA (from 335 [195-459]μM pre-SBD to 44 [3-239]μM post-SBD; –91%, $p < 0.001$), ALT ($p < 0.0001$) and total serum bilirubin ($p < 0.0001$). Upon multivariate analyses, only SBA was significantly associated with NLS ($p < 0.001$). The figure shows NLS at the arbitrarily cut-off SBA level < or > 100μM ($p < 0.0001$) with an area under the ROC curve of 0.753 with an optimal cut-off point of 109μM with a sensitivity and specificity of 75%.

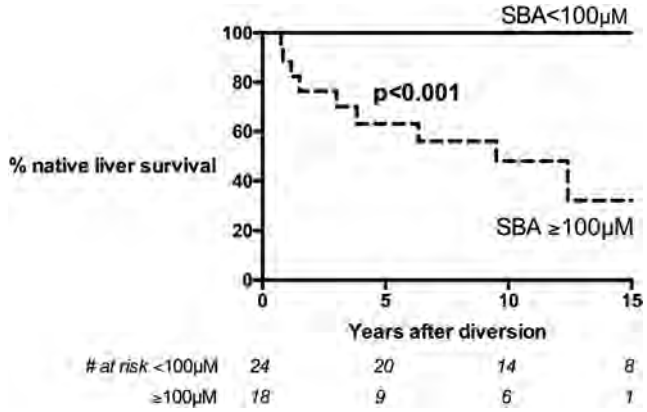

Figure: Native liver survival patients with BSEP-def with a post-SBD serum bile acid concentration below or equal to/above 100μM ($p < 0.001$). SBA: serum bile acid concentration.

Conclusion: SBD profoundly decreased SBAs in BSEP-def patients with mild or moderate genetic severity. Present data indicate that SBA levels below 100μM after surgical bile diversion predict a long-term NLS.

PS-196

Efficacy and safety of sebelipase alfa over 144 weeks in a diverse population of children and adults with lysosomal acid lipase deficiency

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Background and aims: Lysosomal acid lipase deficiency (LAL-D) is a rare, progressive disease characterized by accumulation of cholesteryl esters and triglycerides in the liver that leads to dyslipidemia, hepatomegaly, and liver cell damage. Sebelipase alfa (SA) is a recombinant human LAL indicated for the treatment of LAL-D. We report final results of LAL-CL06, a multicenter, open-label study designed to evaluate the safety and efficacy of SA.
Method: Eligible patients > 8 months of age with LAL-D were given SA 1.0 mg/kg by intravenous infusion every other week (qow). Dose escalation to 3.0 mg/kg qow and subsequently to 3.0 mg/kg weekly was allowed for patients who met protocol-defined criteria; dose reductions for tolerability were permitted to 0.35 mg/kg qow. No inferential statistical analyses were conducted.
Results: Of 31 patients enrolled and treated, 19 completed the 144-week study. At baseline, median age was 12 years (range, 3-55 y), 61% were male, 87% were white, and 55% were taking a lipid-modifying agent. Of 30 patients with a baseline liver biopsy, 20 had fibrosis and 8 had cirrhosis; of the remaining 2, 1 was < 4 years old and 1 had a prior liver transplant. Marked improvements in liver and lipid parameters and liver and spleen volumes were observed (Table). SA was generally well tolerated. Most adverse events (AEs) were mild to moderate in severity. Three patients (10%) experienced infusion-associated reactions that were mild (n = 1) or moderate (n = 2). One patient experienced anaphylactic reactions; the patient underwent desensitization and remained in the study through week 96. One patient discontinued due to a serious AE (liver transplant; unrelated to SA). Two patients (6%) tested positive for anti-drug antibodies (1 occasion each); neither developed neutralizing antibodies. No deaths occurred.

Parameter	Baseline (N = 31)	Week 144 (n = 19)	% Change From Baseline (n = 19)
ALT, U/L	63.5	38.0	−43.2
ALT ≤ 1.5 × ULN, n (%)	13 (42)	16 (84)	
AST, U/L	65.5	41.0	−32.7
AST ≤ 1.5 × ULN, n (%)	16 (52)	18 (95)	
GGT, U/L	31.5	16.0	−34.3
Liver volume, MN	1.4[a]	1.3[b]	−19.7[c]
Spleen volume, MN	2.6[a]	2.3[c]	−16.8[c]
Total cholesterol, mg/dL	233	193	−24.4
LDL-C, mg/dL	160[d]	121	−34.3
HDL-C, mg/dL	31	38	30.3
Triglycerides, mg/dL	159	112	−19.4

Data are medians. MN, multiples of normal.
[a]n = 27; [b]n = 13; [c]n = 12; [d]n = 30;

Conclusion: Long-term treatment with SA was well tolerated and resulted in sustained improvements in liver and lipid parameters in a broader patient population with LAL-D than was previously studied.

PS-197
Heterozygous alpha1-antitrypsin deficiency (Pi*MZ) is associated with increased liver stiffness and elevated liver enzymes in a multi-center European cohort

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Background and aims: Homozygous carriers of the alpha1-antitrypsin (AAT) 'Pi*Z' variant (Pi*ZZ genotype) are susceptible to develop liver cirrhosis, whereas the heterozygous Pi*Z carriage (Pi*MZ genotype) acts as a disease modifier in patients with alcohol abuse or non-alcoholic fatty liver disease. However, the relevance of Pi*MZ in subjects without another etiology of chronic liver disease (CLD) remains unknown. Therefore, we evaluated the extent of liver disease in non-carriers (Pi*MM genotype) as well as Pi*MZ/Pi*ZZ carriers without other CLDs.
Method: Overall, 235 Pi*ZZ individuals, 299 Pi*MZ subjects and 205 matched controls without AAT mutations (Pi*MM), were recruited as a part of our European, multi-center registry study. At recruitment, participants underwent routine lab tests and AAT genotyping as well as measurement of liver stiffness (LSM) and controlled attenuation parameter (CAP) via transient elastography. The coexistence of CLD was excluded by a standardized workup.
Results: Compared to Pi*MM, Pi*MZ carriers displayed higher AST, GGT and LSM values, but lower platelet counts. In particular, 9% of Pi*MZ carriers presented with LSM ≥ 7.1 kPa compared to 4% of Pi*MM controls. However, Pi*MZ individuals had significantly lower AST, ALT, GGT serum levels as well as lower LSM and CAP values than Pi*ZZ participants, while displaying significantly higher platelet counts and serum triglyceride levels.
Conclusion: Compared to Pi*MM and Pi*ZZ individuals, Pi*MZ carriers display intermediate phenotype in terms of liver injury and LSM. Unlike Pi*ZZ subjects, Pi*MZ patients do not present with liver steatosis and metabolic alterations.

PS-198
Fibroscan improves diagnosis of cystic fibrosis related liver disease

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Background and aims: Cystic Fibrosis related liver disease (CFLD) is the 3rd biggest cause of death in Cystic Fibrosis (CF). As a result of improved pulmonary therapy and increasing survival age it is becoming more prevalent. With no single reliable physical, biochemical or radiological screening tool available for the diagnosis of CFLD, it is thought the current guidelines underdiagnose the presence of liver fibrosis, particularly in its early stages. Newer criteria have recently been proposed (Koh, et al, Hepatology, 2017). With improving technology better techniques are required to screen for liver disease. Newer modalities for the assessment of fibrosis may provide a more accurate assessment. The aim of this project is to assess the use of FibroScan and novel platforms in the diagnosis of CFLD and compare to current best practice tools.

Table 1: (abstract: PS-197): Features of heterozygous Pi*MZ carriers compared to non-carriers (Pi*MM) and homozygous carriers (Pi*ZZ).

	Pi*MM *n* = 205	Pi*MZ *n* = 299	Pi*ZZ *n* = 235	*P* value *Pi*MZ vs. Pi*MM*	*P* value *Pi*MZ vs. Pi*ZZ*
Age (years)	45 ± 12	45 ± 16	45 ± 10	.714	.759
Sex (% female)	59%	59%	59%	.969	.912
BMI (kg/m^2)	25.8 ± 5.3	25.8 ± 4.6	25.8 ± 4.1	.989	.900
Diabetes (%)	2%	4%	4%	.099	.789
Mean alcohol consumption (g/d)	5 ± 4	3 ± 3	4 ± 6	.422	.147
AAT serum level (mg/dl)	140.3 ± 28.8	88.7 ± 21.2	25.7 ± 21.5*	**<.0001**	**<.0001**
LSM (kPa)	4.4 ± 1.3	5.6 ± 7.3	6.8 ± 6.6	**.034**	**.034**
LSM ≥ 7.1 kPa	4%	9%	22%	**.030**	**<.0001**
LSM ≥ 13 kPa	0%	1%	7%	.100	**.001**
CAP (dB/m)	238.7 ± 58.3	240.8 ± 63.7	265.6 ± 59.0	.708	**<.0001**
Triglycerides (mg/dL)	124.3 ± 75.5	124.3 ± 86.5	97.0 ± 47.5	.993	**<.0001**
ALT (% of ULN)	67.1 ± 31.6	73.6 ± 41.7	91.9 ± 81.2	.060	**.001**
AST (% of ULN)	62.0 ± 30.7	66.4 ± 32.3	78.6 ± 57.1	**.043**	**.002**
GGT (% of ULN)	50.1 ± 32.1	59.4 ± 44.8	64.8 ± 50.9	**.012**	**.017**
Platelets (G/L)	260.0 ± 70.4	255.5 ± 64.0	234.0 ± 65.9	**.032**	**<.0001**
Fib4	0.24 ± 0.16	0.35 ± 0.72	1.10 ± 0.55	.056	**<.0001**

Quantitative measures are expressed as mean ± standard deviation range or as relative frequency (%). Abbreviations: ULN, upper limit of normal (sex-specific); FIB-4; Fibrosis4-score.
*only levels in non-augmented patients were considered.

Method: A cohort (n = 102) of genetically confirmed, fully phenotyped patients from the Manchester Adult Cystic Fibrosis Centre, UK were identified at annual assessment. Demographic data including co-morbidity, *CFTR* genotyping, biochemistry and recent imaging were assessed to group patients into those with CFLD and CF controls. All patients underwent transient elastography (TE) with Fibroscan and assessment of currently available serum-based biomarker panels (ie FIB-4) and novel serum biomarkers.
Results: 10 of 102 patient classified as CFLD according to the European Cystic Fibrosis Society best practice guidelines (hereafter called Debray criteria) compared with 33 patients using newer proposed diagnostic guidelines, incorporating elastography (hereafter referred to as Koh criteria). In line with previous cohorts, no specific risk factor for development of CFLD was identified, although presence of diabetes mellitus correlated with CFLD using Koh criteria ($p = 0.047$). Liver function test appeared to be lower in those without liver disease compared to those with CLFD using both criteria, including aspirate aminotransferase (25 vs 36 ($p = 0.002$) vs 29 ($p = 0.456$)), alkaline phosphatase (117 vs 144.5 (Debray; $p = 0.004$) vs 138.5 (Koh; $p < 0.001$)) but not alanine aminotransferase (24 vs 50 (Debray; $p = 0.018$) vs 23 (Koh; $p = 0.605$)). Median platelet count is higher in those without CFLD (283 vs 229 (Debray; $p = 0.010$) vs 266 (Koh; $p = 0.046$)). Using both criteria, median elastography was significantly raised (4.6 vs 8.5 (Debray; $p < 0.001$) vs 6.75 (Koh; $p < 0.001$)). Moreover, median liver stiffness was greater in patients with radiological evidence of portal hypertension (4.3 vs 8.6; $p < 0.001$). Biomarker panels, including FIB-4 and APRI, did not accurately predict the presence of liver disease.
Conclusion: Here we present the largest cohort of CF patients assessed for the presence of liver fibrosis using TE based platforms. Our data compares currently available diagnostic criteria for CFLD, Fibroscan may have a role as an adjunct to increase diagnostic accuracy.

Flash abstract: HBV and Pregnancy

FA-01

Prevalence of mother-to-child transmission of hepatitis B virus: A systematic review and meta-analysis

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Background and aims: Prevention and control measures of hepatitis B virus (HBV) infection requires knowledge on the quantification of the burden of hepatitis B infection attributable to mother-to-infant transmission (MTCT).So far such data hasn't been comprehensively examined, we aim to estimate the exact risk and burden of MTCT of HBV.
Method: We systematiclly searched PubMed, Embase and the Cochrane Library from database inception to Oct 18, 2018, for primary data reporting MTCT of HBV among mothers (n≥10) with chronic HBV infection, in which definition of MTCT and measures against MTCT of HBV were descibebed. Search terms included strings pertaining to hepatitis B, mother, infant and vertical transmission. Two indenpent reviewers extracted data from eligible studies and assessed the quatity. We performed a meta-analysis with a DerSimonian-Laird random-effects model to calculate a pooled estimate of MTCT.
Results: Of the 118 studies inclued by our reserch, 1376 infants were diagnosed as MTCT from the total 28181 infants of chronic HBV infected mothers in 25 countries. The pooled MTCT rate of HBV in mother-infant pairs without any preventions was 29% (95% CI 13-49), ranged from 1% (0-6; Europe) to 34% (17-53; Asia), and HBeAg positive mothers showed significantly higher MTCT rate than HBeAg negative mothers (82% vs 4%). A significant deceasing in the pooled MTCT rate was shown in thoses infants received HBV vaccine soly (4% (95% CI 2-7)), including 8% (95% CI 4-10) in infants from HBeAg (+) mothers and 1% (95% CI 0-4) in infants from HBeAg (–) mothers. In

addition, the pooled MTCT rate in infants adopted combined immunoprophylaxis was 4% (95% CI 3-6), 6% (95% CI 6-9) in infants from HBeAg (+) mothers and 4% (95% CI 3-5) in infants from mothers unknown HBeAg status, what's more important, a pooled rate of 0% was observed in infants from HBeAg (−) mothers. Furthermore, the pooled MTCT rate were also 0% in infants with combined immuno-propgylaxis from mothers accepted antiviral intervention during pregnancy regardless HBeAg status of mothers and regions. 15 studies eligible for analysis of MTCT rate under various HBV DNA level, the pooled MTCT rate were 0%, 1% (95% CI 0-3), 1% (95% CI 0-3), 4% (95% CI 0-10), and 10% (95% CI 6-15) in infants from mothers with HBV DNA <4, 4-4.99, 5-5.99, 6-6.99, and 7-7.99 LogIU/ml, respectively.
Conclusion: This first global assessment revealed serious burden of MTCT of HBV, especially in high-endemic areas. Substantial variations between different regions, preventing measures, mothers with different HBeAg status, and HBV DNA level further highlighted the need of continued and individualizing prevention strategy against MTCT to achevie elimination of HBV infection in 2030.

FA-02

The efficacy of two different dosages hepatitis B immunoglobulin in interrupting mother-to-infant transmission of hepatitis B virus: a systematic review and meta-analysis

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Background and aims: Implementation of hepatitis B immuno-globulin (HBIG) combined with hepatitis B vaccine (HepB) has prevented mother-to-child transmission (MTCT) in a great degree, whereas, there is not consensus about the optimal dosage of HBIG for infants from chronic hepatitis B (CHB) infected mothers. Therefore, we did a systematic review and meta-analysis to compare the efficacy of two dosages of HBIG combined with HepB to interrupt mother-to-child transmission (MTCT) of CHB.
Method: We systematically searched MEDLINE, Embase, and Cochrane Library from database inception to Jan 16, 2019 for studies that infants accepted 100 or 200IU HBIG combined with HepB, while no intervention for their CHB mothers . We requested individual data from study authors and extracted primary data from published reports and online trial registries. The primary outcome was the rate of immonoprophylaxis failure, which was defined as HBsAg and/or HBV DNA positive of infants at 6-12 months old. Extracted data was caculated by random effects model
Results: 48 studies including 16121 infants were eligible for inclusion, 7478 infants in 100 IU group and 8643 infants in 200 IU group. No significant differences were found in the rates of immonoprophylaxis failure between 100 IU HBIG group (6%, 95% CI:4%–9%) and 200 IU HBIG group (7%, 95% CI :5%–8%). When further stratified according to HBeAg status and maternal HBV DNA load, comparable rates of immonoprophylaxis failure were shown in different HBIG dosage groups. In HBeAg (+) mothers, 7% (95% CI :4% −11%) infants became chronic HBV infection in 100 IU HBIG group compared to 8% (95% CI: 6%–10%) in 200 IU HBIG group. The rates were 1% in 100IU group (95% CI: 0%–2%) and 0% (95% CI 0%–0%)in 200IU group in infants born to HBeAg (−) mothers. Similarly in mothers with HBV DNA >106IU/ml, the rates were 8% (95% CI:5% −11%) versus 9% (95% CI :5%–14%) when accepted two different dosages of HBIG. Comparative analysis of 5 studies on two different dosages HBIG implicated consistent phenomenon (100IU vs 200IU: RR 1.16, 95% CI 0.82-1.64).
Conclusion: Our meta analysis highlighted that no significant difference was estimitated in the pure use of 100 and 200IU HBIG combined with HepB on blocking MTCT of HBV, regardless of maternal HBeAg status or viral load. It requires more large studies to examine whether100 IU HBIG should be recommended in preventing MTCT for infants born to CHB infected mothers.

FA-03

Caesarean section versus vaginal delivery to prevent mother-to-child transmission of hepatitis B virus: A meta-analysis

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Background and aims: Mother-to-child transmission (MTCT) is the predominant mode of HBV infection, which accounts for 35-50% of HBV infection in China. Despite to appropriate passive and active immunization, perinatal transmission of hepatitis B virus (HBV) through MTCT occurs up to 5-10% of infants born to women with HBV infection. It remains unclear whether parturition method affects MTCT of HBV. The aim of this meta-analysis is to assess whether cesarean section reduces the risk of MTCT of HBV, compared to vaginal delivery.
Method: Two investigators independently searched PubMed, Embase, Cochrane Library, China Biological Medicine Database, China National Knowledge Infrastructure, and Wanfang Data Library database for relevant studies published prior to January 2019. The terms hepatitis B, hep B, hepatitis B virus, HBV, HBsAg, HBeAg, cesarean section, vaginal delivery, natural labour, natural childbirth, delivery mode were combined using the Boolean operators AND or OR. Randomized trials, cohort and case-control studies assessing the effect of delivery mode on vertical transmission of HBV were included. The main outcome of was HBV MTCT according to delivery mode.
Results: A total of 1264 records were collected, and 23 were finally included. A total of 7735 mothers were included in the analysis with 4012 undergoing caesarean section (51.87%) and 3723 undergoing vaginal delivery (48.13%). The MTCT rate of HBV was 5.09% (394 of 7735) overall, with individual rates of 3.41% (137 of 4012) for mothers who underwent cesarean section and 6.90% (257 of 3723) for those who underwent vaginal delivery. The summary RR was 0.57 (95% CI:0.46-0.69, P < 0.01), indicating a statistically significant decrease in HBV vertical transmission with cesarean section, as compared to vaginal delivery. In the analysis of the maternal HBeAg status subgroups, similar results were observed in the HBeAg positive mothers (RR = 0.36, 95%CI:0.19-0.71, P < 0.01); but in the HBeAg negative group, we found no significant differences (RR = 0.97, 95% CI:0.10-9.91, p = 0.98). There was an obvious decrease in HBV vertical transmission with cesarean section when maternal HBV DNA≥6 $\log_{10}$ copies/ml (RR = 0.41, 95%CI:0.25-0.67, P < 0.001), however, when maternal HBV DNA<6 $\log_{10}$ copies/ml, no significant difference was observed among the two delivery modes (RR = 1.18, 95%CI:0.48-2.94, p = 0.71).
Conclusion: Cesarean section could reduce the risk of MTCT of HBV in comparison to vaginal delivery. Performing cesarean in highly viremic mothers with pre-delivery HBV-DNA levels ≥6 log10 copies/ml and/or HBeAg positive may be considered with caution. Moreover, future well-designed randomized control trials are needed to confirm our findings.

FA-04

Tenofovir disoproxil fumarate use during pregnancy and maternal bone health: The tenofovir in pregnancy (TiP) pilot study

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Background and aims: There is very limited information on bone mineral density (BMD) of women exposed to tenofovir during pregnancy. However, tenofovir is increasingly used among pregnant

women with HIV and hepatitis B virus (HBV) infection for their own health and for prevention of transmission of these viral infections to their offspring. We assessed the effect of tenofovir disoproxil fumarate (TDF) initiated during pregnancy among HIV-HBV coinfected women in a clinical trial in China.

Method: The Tenofovir in Pregnancy (TiP) study was a pilot phase II randomized controlled trial of the safety of a regimen containing vs. one not containing TDF, starting from 14 weeks gestation, in HIV/HBV co-infected pregnant women in Guangxi, China, who were antiretroviral drug-naive. The other antiretroviral agents were emtricitabine and lopinavir/ritonavir in both study arms. Maternal spinal and hip BMD were assessed by Dual X-ray absorptiometry (DXA) scans at delivery and at 6 months postpartum.

Results: Fifteen TDF-exposed and 16 TDF-unexposed women had evaluable BMD measurements at delivery. TDF-exposed women were similar at delivery to unexposed women on mean age (28.8 vs 27.8 years), gestational age at delivery (38.1 vs. 38.4 weeks), body mass index (21.2 vs 22.3 kg/m^2) and CD4+ T lymphocyte count (326.6 vs 393.3 cells/mm^3). The mean difference in BMD at lumbar spine between TDF-exposed and unexposed women was –0.01 g/cm^2 (95% confidence interval = –0.09, 0.08) at delivery and –0.01 g/cm^2 (95% confidence interval = –0.08, 0.07) at 6 months postpartum. The mean difference in BMD of femur neck at delivery and 6 months postpartum between TDF-exposed women and unexposed women was –0.07 g/cm^2 (95% CI = –0.15, 0.01) and –0.04 (95% CI, –0.14, 0.06), respectively. The mean change from delivery to 6 months postpartum in BMD at femur neck was 0 g/cm^2 in TDF-exposed women vs. –0.03 g/cm^2 in unexposed women (p = 0.12), adjusted for relevant covariates.

Conclusion: HIV/HBV coinfected women exposed to TDF during the second and third trimester of their pregnancy had slightly lower BMD at delivery and at 6 months postpartum, compared to women not exposed to TDF, but these changes were not statistically significant in this small sample size. There was no change in BMD from delivery to 6 months postpartum in the TDF-exposed group. The observed potential differences in BMD in women exposed to TDF are of uncertain clinical significance.

FA-05

Tenofovir disoproxil fumarate treatment is safe and efficacy for chronic hepatitis B mothers from early pregnancy

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Background and aims: Tenofovir Disoproxil Fumarate (TDF) is recommended to prevent hepatitis B virus (HBV) mother-to-child transmission (MTCT) from the second to the third trimester. Whereas, data about the safety and efficacy of TDF administration during the entire pregnancy was insufficient.

Method: Chronic hepatitis B infected pregnant women accepted TDF treatment either before pregnancy or from early pregnancy were enrolled, and followed up to 28 weeks after delivery. Adverse events were prospectively continuous recorded during follow-up, as well as HBV DNA and HBV serological markers.

Results: A total of 69 CHB mothers were enrolled, including 2 cases with spontaneous abortion, 1 case with premature labor, and 66 cases of full-term delivery, and among which 45 cases had finished postpartum 28 weeks follow-up. During pregnancy, the most common adverse events included hyperemesis gravidarum (7/67, 10.4%), gestational diabetes (5/67, 7.5%) and ALT flare (ALT >40IU/ml) (3/67, 4.5%). In addition, lower bone mass was observed in 6.7% (3/45). Furthermore, 25% mothers shown postpartum ALT flare and all were resolved spontaneously. Congenital abnormalities and neonatal growth were comparable to the normal population, while 1 infant reported laryngeal cartilage dysplasia and recovered without treatment. Bone mineral density was also evaluated, the median SOS z-score of the children was 0.3 (range: –0.6-2.0). None of the infants was positive for HBsAg or HBV DNA at 28 weeks old.

Conclusion: TDF treatment from early pregnancy was safety and efficacy for chronic HBV-infected pregnant mothers and their infants.

FA-06

Maternal nucleoside analogues treatment and infant immunoprophylaxis to prevent chronic hepatitis B in children: A prospective eight-year real-world study

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Background and aims: There has been an inconclusive debate about whether the use of nucleos (t)ide analogue during late pregnancy is necessary in pregnant women with high hepatitis B virus (HBV) DNA to prevent perinatal transmission in addition to immunoprophylaxis. In this eight-year study in real-world setting, we investigated the incidence of chronic HBV (CHB) infection in children born to CHB mothers and evaluated the efficacy of nucleos (t)ide analogue in the prevention of vertical transmission on long term follow-up.

Method: We prospectively enrolled pregnant CHB women in China. Women with HBV DNA level ≥2*10^6 IU/ml (highly viraemic) were recommended to receive telbivudine from week 28 of gestation until delivery and those with HBV DNA level <2*10^6 IU/ml (lowly viraemic) received standard care without nucleos (t)ide analogue. All infants received hepatitis B immune globulin and HBV vaccine within 24 hours postpartum. HBV serological markers and HBV DNA in umbilical cord blood were determined and children were followed up until December 2018.

Results: From January 2011 to December 2017, a total of 281 highly viraemic pregnant women presented to our hospital, of whom 161 agreed to receive telbivudine and 120 declined, while 105 lowly viraemic pregnant women were assigned to the control group. Among 233 completing the follow-up, 105 telbivudine-treated mothers, 61 untreated highly viraemic mothers and 67 lowly viraemic mothers gave birth to 111, 65 and 73 infants, respectively. Of these, 10 infants (4 born to telbivudine-treated mothers, 5 born to highly viraemic controls, 1 born to lowly viraemic controls) failed to receive HBV immunoprophylaxis owing to medical reasons and were excluded from the per-protocol analysis. HBV DNA levels declined significantly in the telbivudine treated mothers. In the intention-to-treat analysis, no children were infected in the telbivudine group or the lowly viraemic control group, as compared to nine children in the highly viraemic control group. The rate of CHB children were significantly higher in the highly viraemic control group than in the telbivudine-treated group and the lowly viraemic control group, both in the per-protocol analysis (6.7% [4/60] vs 0% [0/107], p = 0.016; 6.7% [4/60] vs 0% [0/72], p = 0.039) and the intention-to-treat analysis (13.8% [9/65] vs 0% [0/111], p < 0.001; 13.8% [9/65] vs 0% [0/73], p = 0.001). The proportion of the HBsAg-positive and the detectable level of HBV DNA in umbilical cord blood did not differ significantly between the telbivudine group and the highly viraemic control group. No hepatic flares were reported in the telbivudine-treated mothers after drug withdrawal.

Conclusion: The decline of HBV DNA levels after the use of telbivudine during late pregnancy was associated with lower incidence of CHB in children born to mothers with HBV DNA ≥2*10^6 IU/ml, probably by reducing the risk of perinatal transmission.

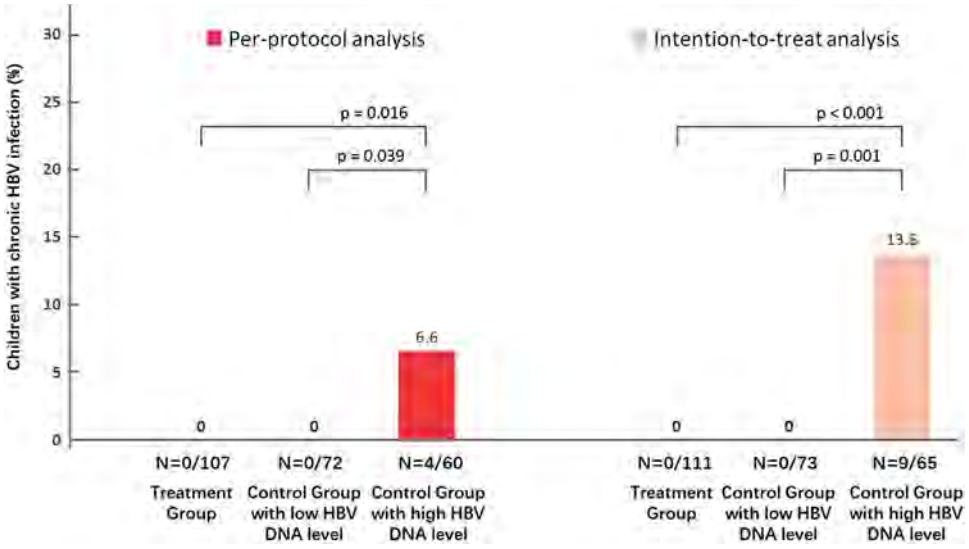

Figure: (abstract FA-06)

FA-07

A Bayesian network analysis of the efficacy and safety of antiviral therapy for chronic hepatitis B infection during diferent trimesters of pregnancy

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Background and aims: Mother-to-child transmisson remains the major risk of hepatitis B virus infection worldwide. Antiviral therapy to reduce maternal HBV DNA viral load at different trimesters of pregnancy has been employed to block mother-to-infant tranmission. This research aimed to demonstrate the efficacy and safety of antiviral therapy at different trimester of pregnancy to prevent mother-to-infant tranmission of hepatitis B virus.

Method: Controlled studies were included from PubMed, EMBASE and Cochrane databases inception through December 6th, 2019. Eligible studies included randomized controlled trial and observational studies of third trimester or/and before trimester antiviral treatment vs. controls for patients with hepatitis B virus infection. Extracted data were analysized by pairwised and network meta analysis.

Results: We included 23 studies (three randomized controlled trial and 19 non-randomized controlled studies) that enrolled 5335 pregnant women. By pairwise meta-analysis using non-antiviral treatment as the reference, antiviral treatment reduced MTCT, as defined by infant hepatitis B surface antigen sero-positive or HBV DNA sero-positive, after initiated before third trimester (RR = 0.07, 95%CI 0.03-0.14) or at third trimester (RR = 0.07, 95% CI0.32-0.50). Using network analysis, lower MTCT were seen with antiviral therapy before third trimester compared with treated at third trimester (OR = 0.019, 95% CI 0.00034-0.19). No significant differences were found in the congenital malformation rate (OR = 0.98, 95% CI 0.77-12), prematurity rate (OR = 1.0, 95% CI 0.42-2.6), and Apgar scores (OR = 0.79, 95% CI 0.10-6.4). Compared to treatment used at third trimester, no significant difference were found in improved maternal HBV DNA suppression at delivery and during 4-8 weeks' postpartum follow-up after beginning treatment before third trimester (OR = 4.7, 95% CI 0.072-2000). No significant differences were found in postpartum hemorrhage (OR = 1.1, 95% CI 0.56-2.3), cesarean section (OR = 1.2, 95% CI 0.83-1.6), and elevated creatininekinase rates (OR = 0.022, 95% CI 1.0e-20-3.8e+14) during different trimester.

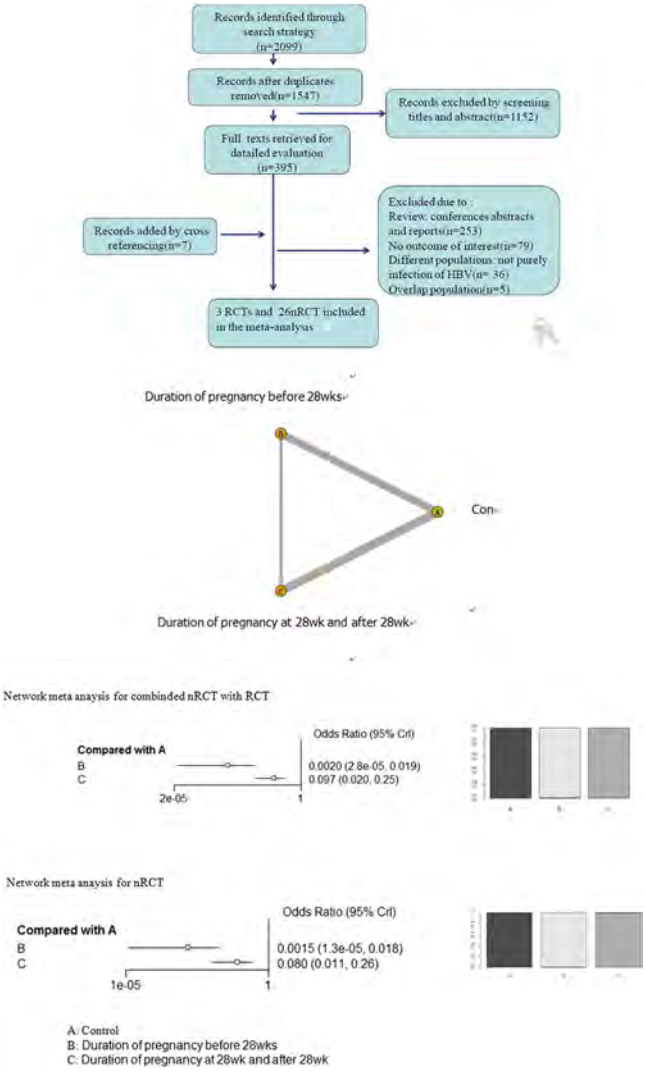

Figure: 1. The study selection process 2. Treatment networks 3. Forest plots and rank probabilities of infected infants for various interventions for perinatal hepatitis B virus transmission according network meta analysis.

Conclusion: Antiviral therapy improves HBV suppression and reduces MTCT in women with chronic HBV infection compared to the use of hepatitis B immunoglobulin and vaccination alone during different trimester of pregnancy. The earlier use of antiviral drug appears to be better to prevent MTCT of HBV in pregnancy without increased adverse maternal or fetal outcome.

FA-08

Hepatic flare after antiviral treatment withdraw in post-partum for pregnancy of chronic hepatitis B viral infection: A pairwise and Bayesian network meta-analysis

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Background and aims: Antepartum anti-viral therapy has been well established to break vertical transmission of hepatitis B virus. However, the optimum duration to extend anti-viral therapy remains uncertain. Therefore, we aim to demonstrate the hepatic flares after antiviral therapy withdrawal at different time of post-partum.
Method: Controlled studies were included from PubMed, EMBASE and Cochrane databases inception through December 6th, 2019. Eligible studies included randomized controlled trial and observational studies of post-partum flares that pregnant women with chronic HBV infection treated with antiviral therapy and discontinued the treatment after post-partum 0 week, 4 weeks and 12 weeks. Extracted data were analyzed by pair-wised and network meta-analysis.
Results: We included 12 studies (three randomized controlled trials and nine non-randomized controlled studies) that enrolled 2336 pregnant women. By pairwise meta-analysis using non-antiviral treatment as the reference, no significant difference was suggested in women withdrawal post-partum anti-viral treatment (risk ratio = 1.22, 95% CI 0.94-1.60). Similar results were seen in the subgroup analysis of discontinued therapy at post-partum 0 week (risk ratio = 1.29, 95%CI 0.57-2.96), 4 weeks (risk ratio = 1.39, 95% CI 0.82-2.38) and 12 weeks (risk ratio = 1.62, 95% CI 0.71-3.71) when compared with controlled group. Using network analysis, similar results were demonstrated in direct or indirect comparisons. Stopped treatment at post-partum 4 weeks showed no significant reduced hepatic flares compared with post-partum 0 week in only indirect comparison (risk ratio = 0.72, 95% CI 0.20-3.1). Withdrawal treatment at post-partum 12 weeks was not different from the treatment discontinued at post-partum 0 week (combined direct and indirect comparison, risk ratio = 0.82, 95% CI 0.22-3.6) and 4 weeks (indirect comparison, risk ratio = 1.2, 95% CI 0.26-3.47).
Conclusion: It appears that extending anti-viral therapy from 0 weeks to 4 weeks and 12 weeks after delivery does not protect against post-partum flares. Well designed studies are needed to confirm the optimal Withdrawal treatment time of post-partum.

Late breaker: Orals

LBO-01

Multicenter, double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension

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Background and aims: NASH is a leading cause of cirrhosis and liver transplant, and severe PH is a key driver of decompensation and worse clinical outcomes. Lowering hepatic venous pressure gradient (HVPG) has been associated with clinical benefit. Emricasan (oral pan-caspase inhibitor) decreased portal pressure and improved survival in cirrhosis models and in an open-label study reduced HVPG in cirrhosis patients with HVPG ≥12 mmHg. This study aimed to confirm these results.
Method: Patients with NASH cirrhosis and baseline HVPG ≥12 mmHg were randomized 1:1:1:1 to emricasan 5, 25, 50 mg or placebo (pbo) orally twice daily for 48 wks, with 1 follow-up HVPG at Wk 24 (primary end point) and all HVPG tracings evaluated by a central reader.

Table: Least Squares (LS) Mean Change* from Baseline at Wk 24

	Emricasan 5 mg N = 65	Emricasan 25 mg N = 65	Emricasan 50 mg N = 66	Pbo N = 67
HVPG (Overall)	−0.6 p = 0.96	−0.8 p = 0.79	−1.0 p = 0.65	−0.4
HVPG (Compensated)	−0.8 p = 0.10	−0.9 p = 0.09	−0.5 p = 0.27	+0.2
HVPG (Compensated HVPG ≥ 16 mmHg)§	−1.6 p = 0.01	−1.7 p < 0.01	−1.5 p = 0.02	+0.5
Caspase 3/7	−4% p = 0.90	−31% p < 0.01	−37% p < 0.01	−4%
cCK18	−27% p < 0.01	−32% p < 0.01	−34% p < 0.01	−13%
ALT	−8 p < 0.01	−8 p < 0.01	−6 p = 0.02	−3
AST	−6 p < 0.01	−7 p < 0.01	−3 p = 0.18	−1

p values (descriptive) for difference in LS mean vs. pbo
*Adjusting for baseline value, cirrhosis status, and/or NSBB use (multiple imputation for overall, observed case for rest)
§Post-hoc

Results: Of 263 subjects (59 US/EU sites) randomized, 13 discontinued prior to Wk 24 and 7 more had no or unevaluable Wk 24 HVPG. Treatment groups were generally balanced. Overall, mean (SD) age was 60.8 (8.8) years, 57% female, 91% Caucasian, 84% T2DM, BMI 35.3 (6.9) kg/m2, 76% compensated vs. 24% decompensated (only 1 prior event, stable on study entry), 88% Child Pugh A, MELD 9.0 (2.5), HVPG 17.0 (3.6) mmHg. HVPG was reduced in subsets of patients (Table). Treatment-emergent AEs were similar (81.6% combined emricasan vs. 82.1% pbo), with SAEs in 17.9% (emricasan) vs. 11.9% (pbo) and no imbalance in routine labs, vitals, ECGs.
Conclusion: Although the primary end point was not met, these data suggest that caspase inhibition with emricasan for 24 wks reduced portal pressure in compensated NASH cirrhosis patients with severe PH, especially those with higher baseline HVPG, and support further studies in these patients. Decreases in transaminases suggest an intrahepatic effect with reduction of liver injury. Potential effects on clinical outcomes and full safety data will be evaluated after completion of the 48-wk study.

LBO-02

Elafibranor, a peroxisome proliferator-activted receptor alpha and delta agonist demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid treatment

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Background and aims: Ursodeoxycholic acid (UDCA) is the established treatment for patients with primary biliary cholangitis (PBC). Up to 40% of UDCA-treated patients have suboptimal response and remain at high risk for disease progression. Elafibranor (Ela), a dual PPAR alpha and delta agonist, has potential as a new anti-cholestatic treatment for such patients.
Method: We evaluated the added anti-cholestatic effects of Ela in a 12-week double blind randomized placebo-controlled phase 2a trial of non cirrhotic patients with PBC and with inadequate response to UDCA defined as an alkaline phosphatase (ALP) >1.67x upper limit of normal (ULN). Patients were randomly assigned to Ela 80 mg/day, 120 mg/day or placebo (Pbo) (15 patients per group: 43 women and 2 men; mean age 59 years). UDCA was continued in all patients. The primary end point was ALP percentage change from baseline to week 12.
Results: Both Ela doses demonstrated a significant decrease in the mean ALP: −48% for 80 mg, −41% for 120 mg with a 3% increase for Pbo, producing a highly significant treatment effect versus Pbo: −52% (95% CI: [−62.5;−41.5]) ($p < 0.001$) for 80mg and −44% (95% CI: [−55.7;−32.1]) ($p < 0.001$) for 120 mg. The composite end point of ALP < 1.67xULN and ALP decrease >15% and total bilirubin < ULN, was achieved in 67% patients at 80 mg and 79% patients at 120 mg ($p = 0.002$ and $p < 0.001$ respectively) as compared to 6.7% patients on Pbo. Effect on gamma-glutamyl transferase was also highly significant as compared to Pbo: −39% for 80mg and −40% for 120mg ($p = 0.001$ and $p = 0.002$ respectively). Ela-treated patients showed improvement in lipid markers including total cholesterol, low-density lipoprotein and triglycerides, as well as reduction of anti-inflammatory markers (IgM, CRP, haptoglobin and fibrinogen); a decrease in C4, an intermediate of bile acid synthesis, was noted. By self-reported visual analogue scale (VAS) in patients with pruritus at baseline (10/group), the VAS median percentage change from baseline to week 12 was −24%, −49% and −7% in the 80mg, 120 mg and Pbo groups respectively. Both doses of Ela were globally well-tolerated.
Conclusion: A 12 week course of Ela demonstrated a substantial anticholestatic effect in patients with PBC and with inadequate response to UDCA. This was associated with anti-inflammatory and potential antipruritic effects which make it a promising novel treatment candidate.

LBO-03

Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir treatment in patients with chronic hepatitis B

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Background and aims: Both tenofovir disoproxil fumarate (TDF) and entecavir (ETV) have potent antiviral effect on hepatitis B virus, and are recommended as the first-line treatment for chronic hepatitis B (CHB). A recent study suggested that patients who received TDF treatment have lower risk of hepatocellular carcinoma (HCC) than those received ETV. We aimed to compare TDF and ETV on the risk of HCC in a territory-wide cohort of CHB patients.
Method: Consecutive adult CHB patients who initially treated by ETV or TDF for at least 6 months between January 2008 and December 2018 was identified using the Clinical Data Analysis and Reporting System that captures in-patient and out-patient data of all public hospitals and clinics in Hong Kong. Patients who had cancers or liver transplantation before or within the first 6 months of treatment were excluded. Missing data were replaced by multiple imputation (MI) by chained equations to create 20 complete data sets after 10 iterations. Propensity score (PS) weighting was used after MI to balance the baseline clinical characteristics between two treatment groups; PS included all covariates in the multivariable analysis (Table), serum creatinine, and renal replacement therapy. Fine-Gray model was used to adjust for competing risk of death.
Results: 29, 123 CHB patients were identified. Their mean age was 53.7 ± 13.3 years, 18, 492 (63.5%) were male; 1, 227 (4.2%) and 27, 896 (95.8%) first received TDF and ETV, respectively. At a median (interquartile range) follow-up of 3.3 (1.6-5.0) years, 9 (0.7%) TDF-treated and 1, 468 (5.3%) ETV-treated patients developed HCC. The 5-year cumulative incidence (95% confidence interval [CI]) of HCC in ETV and TDF-treated patients was 7.5% (7.1%−7.9%) and 1.3% (0.6% −2.6%), respectively (Figure). TDF use was associated with a lower risk of HCC than ETV use before (adjusted hazard ratio [aHR] 0.46, 95% CI 0.23-0.91, $p = 0.027$) and after multiple imputation, with (weighted HR 0.40, 95% CI 0.18-0.86, $p = 0.019$) and without (aHR 0.34, 95% CI 0.18-0.66, $p = 0.001$) PS weighting (Table).
Conclusion: TDF treatment is associated with a lower risk of HCC than ETV treatment in a territory-wide cohort of CHB patients.

Table:

Parameters	Univariate analysis			Multivariable analysis		
	HR	95% CI	*P* value	aHR	95% CI	*P* value
TDF *vs.* ETV	0.16	0.09-0.32	<0.001	0.34	0.18-0.66	0.001
Age	1.06	1.05-1.06	<0.001	1.05	1.04-1.05	<0.001
Male gender	2.30	2.02-2.62	<0.001	2.54	2.23-2.90	<0.001
Cirrhosis	5.05	4.56-5.60	<0.001	2.22	1.95-2.52	<0.001
Platelet*	0.37	0.33-0.41	<0.001	0.56	0.51-0.61	<0.001
Albumin	0.92	0.92-0.93	<0.001	0.98	0.97-0.99	<0.001
ALT*	0.78	0.75-0.81	<0.001	0.85	0.81-0.89	<0.001
Total bilirubin*	1.47	1.40-1.54	<0.001			
Positive HBeAg	0.76	0.67-0.87	<0.001	1.37	1.19-1.57	<0.001

* Platelet, ALT and total bilirubin were log-transformed in the model.

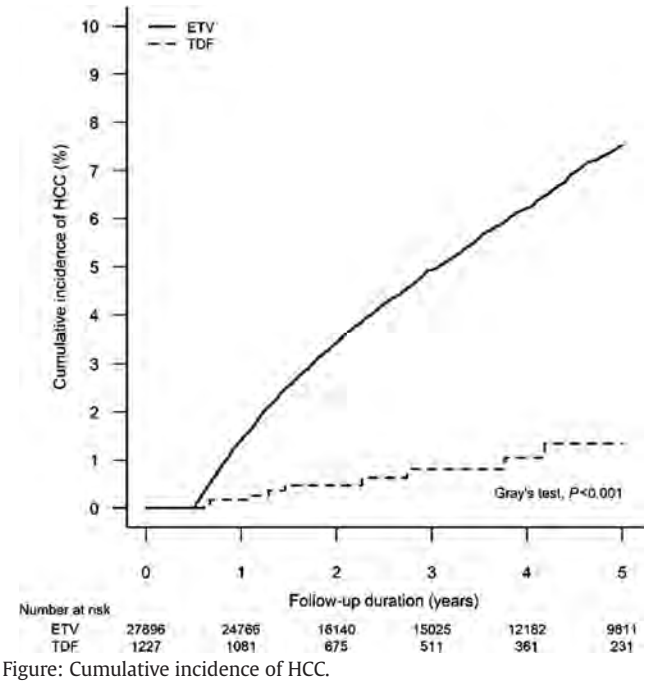

Figure: Cumulative incidence of HCC.

LBO-04

Efficacy and safety of sofosbuvir monotherapy in patients with chronic hepatitis E-The HepNet SofE pilot study

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Background and aims: Chronic hepatitis E virus infection (cHEV) is an emerging problem in immunocompromised patients. Treatment is limited to ribavirin (RBV) but many patients cannot be treated because of contraindications. Thus, there is an unmet need for new antiviral therapies. *In vitro* studies have shown that the HCV polymerase inhibitor sofosbuvir (SOF) inhibits the HEV replication, however case reports on the use of SOF in cHEV patients showed conflicting results.

Method: We performed an investigator-initiated, multicentre phase II pilot trial (NCT03282474) at 3 centers in Germany. Ten patients with confirmed cHEV who either failed prior RBV therapy or had contraindications for RBV received 400mg sofosbuvir daily for 24 weeks. The primary end point was undetectable HEV RNA at week 24. Secondary outcomes included analysis of antiviral efficacy defined by $\log_{10}$ decline of HEV RNA.

Results: Ten patients with cHEV entered the study but one patient was excluded from further analysis because of exclusion criteria. Mean age of the nine patients was 44 ± 14 years. Seven patients failed prior treatment with RBV (median 15 months (4-40)) and two patients were ineligible to receive RBV. Eight patients had a history of organ transplantation and one patient had common variable immunodeficiency. Two patients had cirrhosis. Median ALT before start of SOF treatment was 126 U/l (38-624). Baseline HEV RNA was 6E5 IU/ml (range 8E4-5E6 IU/ml). Overall 5/9 (56%) patients experienced a decline of HEV RNA of at least 1log10 IU/ml. The

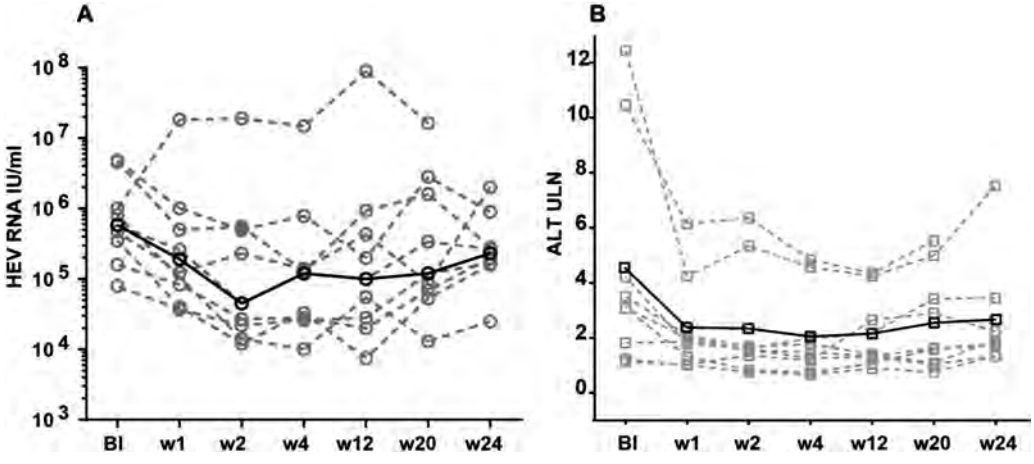

Figure: (abstract LB-04): A) Individual courses of HEV RNA in IU/ml of nine patients, black line represents median values B) Individual courses of ALT shown as upper limit of normal (ULN); black line represents mean values.

strongest median decline of HEV RNA was observed between baseline and week 2 (1.1 log10). However, no patient reached the primary end point and only two patients maintained a >1log10 reduction of HEV RNA at week 24. Importantly, ALT level showed a significant decline from 4.6 upper limit of normal (ULN) to 2.2 ULN at week 12 and 2.7 ULN at week 24. Treatment with SOF was well tolerated. Creatinine clearance was stable during therapy; all patients stayed above GFR 30 ml/min. Six serious adverse events were reported in three patients but only one (elevated lipase) was considered to be related to SOF. Sadly, this patient experienced a sepsis and died 4 weeks after SOF was stopped.
Conclusion: Sofosbuvir shows moderate antiviral efficacy but does not lead to cure of cHEV. HEV RNA decline was associated with ALT improvements. SOF should be further investigated in combination with RBV for the treatment of cHEV in immunocompromised patients.

LBO-05
Bezafibrate improves the effect of obeticholic acid on cholestasis in patients with primary biliary cholangitis
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Background and aims: Obeticholic acid (OCA) is the second line treatment for patients (pts) with primary biliary cholangitis (PBC) who have an inadequate response or are intolerant to ursodeoxycholic acid (UDCA) (1). Recently, bezafibrate treatment was also shown to improve biochemical responses in PBC pts (2). Here, we explored whether combining OCA and bezafibrate therapy normalised alkaline phosphatase (ALP) and bilirubin levels, since this is the strongest predictor of improved outcome.
Method: We included 16 pts of the POISE (PBC OCA International Study of Efficacy) study who received OCA (5 or 10 mg/d)±UCDA for 4-5 years (y). In 3 pts OCA treatment was terminated (pruritus n = 2). After 5 y, bezafibrate treatment (Eulitop 400 mg/d) in addition to OCA + UCDA was initiated in 11 pts (2 male, 9 female) with a mean age of 64 y and a median fibroscan value of 6.8 kPa (min: 4.7-max: 21.8). Due to myalgia, bezafibrate treatment was terminated in 2/11 pts. The effect on pruritus was assessed with the PBC-40 questionnaire. Our primary end point was a normalisation of ALP and bilirubin levels. p values were calculated per-protocol analysis.

Table 1: Biochemical parameters (Median [IQR])

	start OCA (n = 11)	6 m OCA (n = 11)	4-5 y OCA (n = 11)	6 m OCA + bezafibrate (n = 9)
ALP (U/L)	315.0 [275.0-408.4]	233.2 [194.4-259.4]	190.2 [157.4-252.0]	94.0 [90.0-143.5]
BILI (µMOL/L)	7.7 [6.8-20.9]	8.6 [5.8-18.0]	7.7 [6.8-14.7]	6.8 [5.0-10.5]
AST (U/L)	37.2 [27.9-67.9]	35.9 [23.8-69.0]	29.3 [26.3-47.8]	37.0 [27.5-48.5]
ALT (U/L)	45.6 [27.2-67.8]	29.3 [17.4-46.0]	21.9 [15.5-32.0]	27.0 [19.5-37.0]
GGT (U/L)	274.7 [97.3-397.7]	71.0 [52.1-189.9]	37.2 [27.6-87.8]	32.0 [26.5-103.0]

(1) Nevens F et al. N Engl J Med. 2016
(2) Corpechot C et al. N Engl J Med. 2018

Results: After 6 months (m) of OCA, ALP decreased in 73% ($p < 0.001$) and bilirubin in 64% ($p = 0.625$) of the pts. After 4-5 y of POISE, none of the pts reached the primary end point (normal ALP: 0/11 and normal bilirubin: 9/11) (see also Table 1). After 6 m of triple treatment, ALP further decreased in 100% ($p < 0.001$) and bilirubin in 67% ($p = 0.184$) of the pts. ALP was normal in 4/9 and bilirubin in 8/9 of the pts, reaching the primary end point in 44% of the pts. Itching decreased in 5/7 of the pts with bezafibrate therapy and their mean PBC-40 score decreased from 6.0 to 4.6 points ($p = 0.070$).
Conclusion: Combination therapy of OCA and bezafibrate in PBC pts had a strong additive effect on cholestasis and improved pruritus.

LBO-06
Interim safety and efficacy results of the ABI-H0731 phase 2a program exploring the combination of ABI-H0731 with Nuc therapy in treatment-naive and treatment-suppressed chronic hepatitis B patients
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Background and aims: Chronic Hepatitis B (CHB) infection is a major cause of morbidity and mortality worldwide. Nucleos (t)ide analogues (Nuc) are standard of care (SOC) but achieve low rates of sustained responses off therapy. The novel core inhibitor ABI-H0731 (731) exhibited potent anti-HBV activity over 28 days as monotherapy and is currently being tested in two phase 2a studies evaluating its potential benefit in combination with Nuc therapy.
Method: ABI-H0731-201 and ABI-H0731-202 are double blinded, placebo (pbo) controlled studies in F0-F2 fibrosis (or equivalent) CHB patients. In study 201, 47 HBeAg pos and 26 HBeAg neg subjects already suppressed on SOC Nuc randomized 3:2 for addition of 731 (300mg):Pbo to their SOC. In study 202, 25 treatment-naive HBeAg pos viremic subjects randomized 1:1 to Entecavir (ETV) + 300mg 731 or ETV + Pbo. Subjects randomized Day 1 and return to clinic weeks (wk) 2, 4 and then monthly up to wk 24 at which time they can enter an open-label long-term extension study of up to 1 additional year. Clinical labs, safety and PK are monitored, as well as HBV biomarkers including HBV DNA, HBV RNA, HBsAg and HBeAg. Primary efficacy end points are $\log_{10}$ decline in HBsAg/HBeAg at wk 24 (study 201), and $\log_{10}$ decline in HBV DNA at wks 12/24 (study 202).
Results: Enrolment is complete in both ongoing studies. 731 has been well tolerated; treatment emergent adverse events (AE) and

laboratory abnormalities have been few and generally mild or moderate. 3 subjects have had AE of rash (Grade (G)1 and G2) which did not limit 731 dosing: 2 self-resolved (G1) and 1 resolved on antihistamine (G2). No discontinuations due to AE or ALT flares have occurred. In study 201, 32 (suppressed) subjects have reached wk 12 and 2 subjects have reached wk 24. At wk 12, subjects on 731 + Nuc reduced HBV RNA levels by 2.6 $\log_{10}$ IU/ml vs an increase of + 0.2 $\log_{10}$ IU/ml in the Pbo + Nuc group. In study 202, 21 (naive) subjects have reached wk 12, and 4 subjects have reached wk 24. At wk 12 subjects on 731 + ETV reduced HBV DNA/RNA by 4.5/2.6 $\log_{10}$ IU/ml vs. 3.2/0.4 ($\log_{10}$ IU/ml) for the ETV + Pbo group. Individual subjects have shown decreases in HBeAg and HBsAg in both studies, but no meaningful conclusions can be drawn at this early timepoint.

Conclusion: Interim data suggest that ABI-H0731 + Nuc is well tolerated and provides early and enhanced antiviral benefit including HBV RNA reductions not seen on Nuc alone. Updated safety and efficacy data will be presented.

LBO-07

Effectiveness of therapy in 16, 567 directly-acting antiviral treated people in England: high response rates in genotype 3 hepatitis C infection regardless of degree of fibrosis, but ribavirin improves response in cirrhosis

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Background and aims: An estimated 100, 000 people in England have chronic hepatitis C (HCV) infection. Directly-acting antivirals (DAAs) are available, but drug choice is mandated centrally, based on national contracts, allowing comparison of regimens without confounding by clinician choice. A mandatory national registry monitors therapy. We examined sustained virological response at 12 weeks (SVR12) of different regimens.

Method: Anonymised data from 9 Jan 2019 was analysed using Stata 15. The null hypothesis was that there was no difference in SVR with different DAAs. Per protocol analyses assessed proportions with a valid outcome achieving SVR. Differences between SVR rates were statistically significant if $p < 0.05$ (Chi square or Fisher's exact tests).

Results: The registry lists 37, 693 people with HCV. 16, 756 DAA treated adults were due a 12-week post-treatment outcome eight weeks before this data extraction. 14, 603 patients had a per protocol outcome. Of these 13, 959 (95.59% [95% confidence interval (CI) 95.24% to 95.91%]) achieved an SVR12. Patients with some fibrosis had a significantly higher SVR12 (96.12% [95%CI 95.57% to 96.59%]), than those with compensated cirrhosis (94.21% [95%CI 93.45% to 94.89%]), or decompensated cirrhosis (90.02% [95%CI 87.16% to 92.29%]).

We focussed on genotype 3. For patients with moderate fibrosis, we compared SVR with 8 weeks Glecaprevir/Pibrentasvir (n = 92 (96.63% [95% CI 90.04% to 98.91%])) to 12 weeks Sofosbuvir/Velpatasvir (n = 214 (97.11% [95%CI 93.71% to 98.70%])) ($p = 0.793$). The SVR12 rate for patients with genotype 3 compensated cirrhosis given 12 weeks of Sofosbuvir/Velpatasvir and Ribavirin (n = 196 (97.96% [95%CI 94.67% to 99.23%])) was significantly higher than for those given Sofosbuvir/Velpatasvir (n = 218 (91.60% [95%CI 87.33% to 94.52%])) ($p = 0.005$), or Sofosbuvir/Daclatasvir and Ribavirin (n = 868 (92.17% [95%CI 90.18% to 93.78%])) ($p = 0.002$). 12 weeks of Glecaprevir/Pibrentasvir was not significantly different (n = 167 (96.41% [95%CI 92.23% to 98.38%])) to other regimens.

Conclusion: The English HCV treatment registry is a large, non-selective registry. SVR12 rates with Sofosbuvir/Velpatasvir and Ribavirin were higher than with Sofosbuvir/Velpatasvir or Sofosbuvir/Daclatasvir and Ribavirin in patients with genotype 3 HCV and compensated cirrhosis. No other significant differences were found.

LBO-08

Growth analysis in children with progressive familial intrahepatic cholestasis treated with the apical sodium-dependent bile acid transporter inhibitor maralixibat

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Background and aims: Maralixibat is a potent, selective and minimally absorbed ileal apical sodium-dependent bile acid transporter (ASBT) inhibitor. Pharmacological inhibition of enterohepatic circulation may offer an alternative to surgery in progressive familial intrahepatic cholestasis (PFIC). A pre-specified 48-week interim analysis of a phase 2 open-label study of maralixibat in PFIC demonstrated a therapeutic response in a subset of PFIC2 patients. We describe a 72-week post hoc analysis of growth parameters (NCT02057718).

Method: Maralixibat doses were escalated up to 280 µg/kg/day over 13 weeks and maintained for ≥72 weeks. Serum bile acid (sBA) change from baseline was the primary, alanine transaminase (ALT), total bilirubin levels (TB), caregiver-rated pruritus (ItchRO[Obs]; 0 = none; 4 = most severe itch) were secondary end points. Height and weight z-score changes from baseline were compared in patients meeting sBA and ItchRO treatment response criteria and those who didn't.

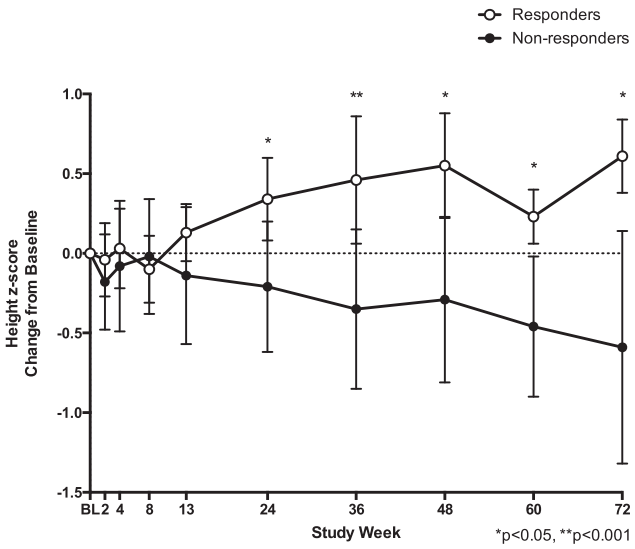

Figure: Height z-score change from baseline.

Results: Patients with PFIC2 (n = 25/33) were included; median age 4.0 years (range 1-13), 32% male. The primary end point of mean (SD) sBA reduction at week 13 was 29 (117) µmol/L; sBA reduction at week 48 was 59 (209) µmol/L. Six patients experienced sBA normalization (≤8.5 µmol/L) or reduction from baseline by ≥70% and ItchRO of 0 or

improvement ≥1.0 point (responders). Mean (SD) height and weight z-scores at baseline in responders/non- or partial responders were −1.33 (0.83)/−1.28 (1.23) and −0.63 (0.89)/−0.72 (1.07), respectively. After 48 and 72 weeks of treatment height z-score mean change from baseline was 0.55 (0.33) and 0.61 (0.23) in responders, compared to −0.29 (0.52) and −0.59 (0.73) in non- or partial responders ($p < 0.05$; Figure 1). Weight z-score mean change from baseline was 0.42 (0.29) and 0.32 (0.25) in responders and −0.29 (0.30) and −0.37 (0.51) in non-or partial responders ($p < 0.05$). Statistically significant differences were seen at 24 weeks of treatment and onwards. Treatment-emergent adverse events (TEAEs) were reported in all patients, 22 related to maralixibat, 15 had serious TEAEs, one led to discontinuation. The most frequent TEAEs were pyrexia, diarrhea, cough and abdominal pain.

Conclusion: Clinically relevant growth accelerations were observed in maralixibat treatment responders compared to non- or partial responders at 24 weeks and beyond, suggesting potential disease modification with ASBT inhibition.

EASL JOURNAL OF HEPATOLOGY

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NAFLD – Staging and prognosis

PS-199

sqFibrosis: A robust liver fibrosis scoring system for artificial intelligence telepathology

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Background and aims: Accurate assessment of liver fibrosis suffers from the data variations of the sampling error, staining and imaging heterogeneity in variable clinical lab settings. Experienced pathologists deal with such variations by comparing with other scoring samples in their memory to generate predictive decisions by selecting useful features and neglecting noises. Accordingly, we have developed fully a quantitative machine learning-aided algorithm (sqFibrosis) for liver fibrosis assessment using variable qualities/sizes of commonly available collagen-stains and imaging conditions of standard light microscopes from biopsy samples.
Method: A new staining index (sqFibrosis) for liver fibrosis evaluation was established as a combined index using 63 morphological features derived from tissue sections stained with conventional collagen dyes. Images acquired from 25 Thioacetamide-treated rat samples, 84 core biopsies of chronic hepatitis B (CHB), and 59-core biopsies with various etiologies (chronic hepatitis C (CHC), and autoimmune hepatitis (AIH)) were used to train and validate the index and to demonstrate its accuracy and reproducibility in the clinical settings.
Results: We showed that sqFibrosis reliably scores various fibrosis stages, as it can identify differences between all stages in animal samples and clinical biopsies ($p < 0.001$). Moreover, it is robust and unaffected by sampling error in image size, resolution and quality, allowing for sensitive scoring of fibrosis in animal samples (area under curve (AUC): 0.89–1.00 for fibrosis detection; 0.90–0.99 for significant fibrosis detection, 0.88–0.98 for advanced fibrosis detection, and 0.86–0.95 for cirrhosis detection) and can help elucidate the process of collagen deposition in fibrosis progression using different staining approaches. sqFibrosis could also address the staining quality and imaging platform variations (area under curve (AUC): 0.89–0.95 for significant fibrosis detection, 0.86–0.92 for advanced fibrosis detection, and 0.85–0.99 for cirrhosis detection) and has the ability to differentiate between Ishak stages 3, 4 and 5, 6 (AUC: 0.70) and P-I-R scores (AUC: 0.71), suggesting that it may be sensitive enough for monitoring intra-stage cirrhotic changes. Using patient samples, we further demonstrated that sqFibrosis also has the potential to stage liver fibrosis progression for other etiologies. Lastly, sqFibrosis demonstrates superior performance to CPA measurements on all counts.
Conclusion: Using only conventional collagen stained liver samples, sqFibrosis makes it possible to quantitatively score liver diseases in fully automated manner and partially correct the sampling error and variations.

PS-200

The combination of HEPAmet fibrosis score and transient elastography shows a high diagnostic accuracy in predicting advanced fibrosis in NAFLD

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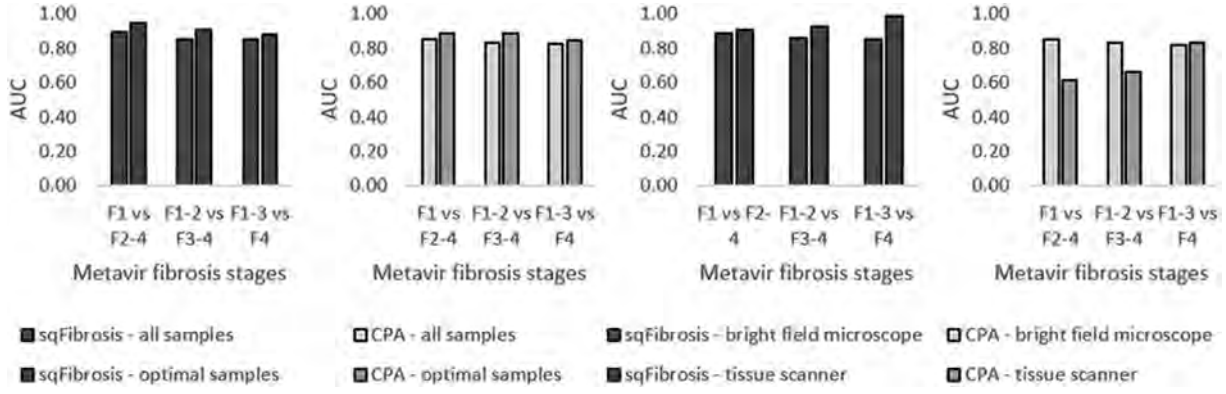

Figure: (abstract PS-199): Schematic illustration of sqFibrosis Index establishment

ELSEVIER

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Background and aims: A) To identify the baseline features of patients with hidden advanced fibrosis by transient elastography (TE); B) To assess the diagnostic accuracy of TE by using HEPAmet Fibrosis Score (HFS); C) To develop a stepwise algorithm between HFS and TE to improve the non-invasive detection of advanced fibrosis.
Method: International multicentre study including 885 biopsy-proven NAFLD patients (Spain n = 212, France n = 330, Italy n = 250, China n = 93). HFS (age, gender, DM, HOMA, albumin, AST, platelets), considering <0.12 and >0.47 as cut-offs, and TE were evaluated. Hidden advanced fibrosis was defined as TE <9.5 kPa when F3 was shown in liver biopsy.
Results: Fibrosis distribution was: F0 24% (215/885), F1 28% (244/885), F2 22% (192/885), F3 20% (174/885), F4 7% (60/885).
A) Factors related to hidden advanced fibrosis (21% (48/234) were: BMI (>9.5 kPa 32.5 ± 5 *vs.* <9.5 kPa 29.7 ± 4 kg/m^2; p = 0.001), GGT (>9.5 kPa 169 ± 229 *vs.* <9.5 kPa 90 ± 89 UI/L; p = 0.0001), HOMA (>9.5 kPa 9.6 ± 9.5 *vs.* <9.5 kPa 5.7 ± 3.4; p = 0.0001), platelets (>9.5 kPa 191 + 62 vs. <9.5 kPa 231 ± 66; p = 0.0001).
B) TE values were: F0 6.4 ± 2.8 kPa, F1 7.1 ± 2.9 kPa, F2 9.6 ± 4.7 kPa, F3 14.8 ± 8.6 kPa, F4 25.1 ± 15.9 kPa (p = 0.0001). kPa values according to fibrosis stage and HFS: F0 (HFS < 12: 6.2 ± 2.7 *vs.* HFS 0.12–0.47: 8.3 ± 2.8 *vs.* HFS >0.47: 7.6 ± 1.7; p = ns), F1 (HFS < 12: 6.9 ± 2.6 *vs.* HFS 0.12–0.47: 7.8 ± 3 *vs.* HFS >0.47: 6.2 ± 2; p = ns), F2 (HFS < 12: 8.7 ± 3.5 *vs.* HFS 0.12–0.47: 10.6 ± 5.1 *vs.* HFS >0.47: 11.6 ± 3.6; p = 0.002), F3 (HFS < 12: 11.2 ± 4.2 *vs.* HFS 0.12–0.47: 13.4 ± 6.5 *vs.* HFS >0.47: 20.5 ± 11.5; p = 0.0001), F4 (HFS < 12: 16.8 ± 13.3 *vs.* HFS 0.12–0.47: 25.2 ± 14 *vs.* HFS >0.47: 29.2 ± 17.1; p = 0.005) (Figure).
C) A stepwise algorithm based on HFS and TE distinguished a lowest and highest risk group of advanced fibrosis that included 45% of the total population: a) HFS >0.47 and TE >17.8 kPa: advanced fibrosis in 97.7% (43/44); Se. 18% Sp. 99.9%, PPV 97.7%, NPV 77.3%, LR + 119, LR- 0.82; b) HFS < 0.12 and TE < 6.7 kPa: advanced fibrosis in 2% (6/303); Se. 97.4% Sp. 45.7%, PPV 39.2%, NPV 98%, LR + 1.79, LR- 0.06.
Conclusion: Around 25% of patients with advanced fibrosis were not detected by TE, showing less insulin resistance and BMI and also better liver function. Besides, kPa values were different in patients with the same fibrosis stage when classified according to their HFS value. The stepwise algorithm combining HFS and TE allowed the detection of advanced fibrosis with a diagnostic accuracy higher than 98% in around 50% of NAFLD patients.

PS-201

External validation in NAFLD cohorts of the FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST to identify patients with active NASH (NAS ≥ 4) and significant fibrosis (F ≥ 2)

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Background and aims: Given the upcoming market release of drugs for at risk NASH patients, Echosens have developed a score to identify patients with active NASH (NAS ≥ 4) and significant fibrosis (F ≥ 2) combining FibroScan liver stiffness measurement (LSM), controlled attenuation parameter (CAP) and AST. The objective was to perform an external validation of this score in several independent cohorts of biopsy-proven NAFLD patients.
Method: Patients from three centers (Angers, Wenzhou, Hong-Kong) who underwent FibroScan (LSM and CAP) and a clinically indicated liver biopsy (LB) for suspected NAFLD were included. In each cohort, all LB were read by a single expert pathologist using the NASH CRN scoring system and the FLIP definition for NASH. FibroScan-based score performance to identify NASH + NAS ≥ 4 + F ≥ 2 was assessed using area under the receiver operating characteristics (AUC).

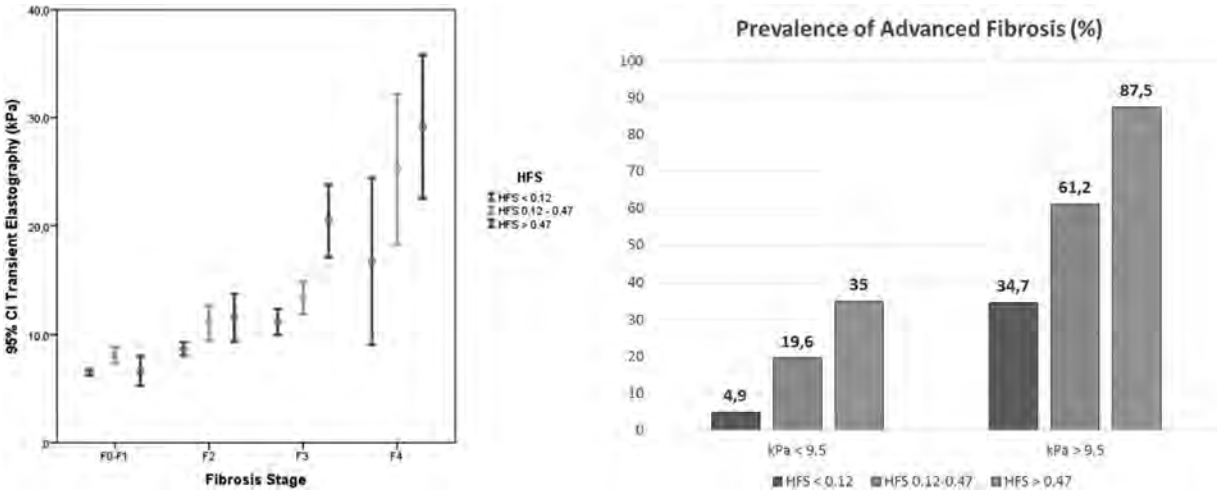

Figure: (abstract PS-200)

Table 1: (abstract: PS-201)

Cohort	Angers			Wenzhou			Hong-Kong			Pooled		
N	182			111			102			395		
Age (y)	58 [17]			40 [20]			55 [17]			53 [20]		
Female	36%			26%			47%			36%		
BMI (kg/m^2)	31.6 [8.6]			25.7 [4.3]			28.9 [5.3]			28.9 [6.9]		
AST (IU/L)	36 [22]			35 [28]			41 [31]			37 [26]		
ALT (IU/L)	48 [45]			51 [63]			68 [62]			53 [54]		
LSM (kPa)	7.9 [5.6]			5.9 [2.4]			9.2 [5.3]			7.4 [5.3]		
CAP (dB/m)	326 [72]			316 [50]			318 [61]			320 [62]		
Fibrosis F0F1	40%			85%			35%			51%		
F2	25%			9%			24%			20%		
F3	29%			5%			25%			21%		
F4	5%			0%			22%			8%		
NASH	67%			63%			60%			64%		
Fibrotic NASH	78 (43%)			12 (11%)			47 (46%)			137 (35%)		
Score LSM + CAP + AST	**0.80** (0.74–0.87)			**0.81** (0.69–0.93)			**0.86** (0.79–0.93)			**0.82** (0.78–0.87)		
AUC (95% CI)												
Performance	<0.40 N = 41% Se = 0.86 Sp = 0.61 NPV = 0.85	[0.40;0.76[N = 34%	>0.76 N = 26% Sp = 0.89 Se = 0.46 PPV = 0.77	<0.40 N = 58% Se = 0.75 Sp = 0.62 NPV = 0.95	[0.40;0.76[N = 28%	>0.76 N = 14% = 0.90 Se = 0.50 PPV = 0.38	<0.40 N = 31% Se = 0.96 Sp = 0.55 NPV = 0.94	[0.40;0.76[N = 38%	>0.76 N = 30% Sp = 0.89 Se = 0.53 PPV = 0.81	<0.40 N = 43% Se = 0.88 Sp = 0.60 NPV = 0.91	[0.40;0.76[N = 33%	>0.76 N = 24% Sp = 0.90 Se = 0.49 PPV = 0.71

Distribution: Median [IQR] or figure (%)

Diagnostic performance in each cohort were calculated using cutoffs determined in the score's derivation cohort: 0.40 for a sensitivity (Se) ≥ 0.90 and 0.76 for a specificity (Sp) ≥ 0.90.

Results: A total of 395 patients were analyzed. Characteristics of each cohort and pooled patients are given in Table 1 together with the score performances. Performance was good in each cohort with AUC above 0.80. Pooled AUC was 0.82 (0.78–0.87).

Conclusion: The simple score based on FibroScan LSM, CAP and AST showed good performance in all NAFLD cohorts. It could be used in liver units to efficiently screen patients with active NASH (NAS ≥ 4) and significant fibrosis (F ≥ 2) for drugs trials as well as identifying patients eligible for treatment when drugs will be on the market.

PS-202

Genome-wide association studies of abdominal MRI scans identifies loci associated with liver fat and liver iron in the UK Biobank

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Background and aims: Liver fat and iron accumulation (e.g. hereditary haemochromatosis (HH), dysmetabolic iron overload syndrome) have been implicated in liver disease pathogenesis, but little is known about the genetic factors influencing these heritable traits. Multiparametric MRI is a fast, non-invasive and accurate method of measuring intra-hepatic fat and iron content. Here we aim to find genetic variants influencing liver fat and liver iron, using data from the UK Biobank.

Method: Data was acquired from UK Biobank (application 9914). Liver phenotypes were calculated from MRI data by trained analysts using LiverMultiScanTM Discover. Genetic data (UK Biobank Axiom Array) in unrelated individuals of European Ancestry, (n = 6758) were extracted. GWAS was performed with PLINK v1.90 and GEMMA. Linear additive models were used, controlling for age, sex, BMI, genotyping array, and population structure.

Results: Significant associations were seen between liver iron and variants within the HFE gene (rs1800562 (C282Y), p = 2.2 * 10–66) and TMPRSS6. The product of both genes regulate the production of hepcidin, which is the "master" iron regulatory hormone which determines how much iron is absorbed from the diet. Liver fat associations were seen with variants in PNPLA3 (e.g., rs738409, p = 2 * 10–41), TM6SF2 (rs58542926, p = 4.3 * 10–40), APOE, GCKR, GPAM, and NCAN. The same alleles at these loci are also associated with other traits, e.g., GCKR (associated with type 2 diabetes, lipid traits and cardiovascular disease), TRIB1 (lipid traits and heart disease), GPAM (lipid traits), NCAN (type 2 diabetes and lipid traits), APOE (type 2 diabetes, lipid traits and heart disease) and PNPLA3 (lipid traits and non-alcoholic fatty liver disease).

Conclusion: This is the first GWAS using MRI determined liver fat and iron content to date, which provides insights into the biology of liver disease pathogenesis and its link to other metabolic diseases. The replication of known loci provides genetic validation of the utility of MRI for the non-invasive assessment of the above measures. As more imaging data becomes available (planned for 100, 000 individuals in UK Biobank), larger GWAS will allow detection of more susceptibility loci for both liver fat and iron.

PS-203

Dietary risk factors for non-alcoholic fatty liver disease by cirrhosis status: The US multiethnic cohort

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Background and aims: Epidemiological data on dietary risk factors for NAFLD from population-based studies are scarce. Here, we examined dietary factors in relation to NAFLD by cirrhosis status in African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites from the Multiethnic Cohort (MEC).

Method: A nested case-control analysis was conducted within the MEC, a large prospective study with >215, 000 participants in Hawaii and California. NAFLD cases were identified between 1999 and 2015 using Medicare claims. Controls were selected among participants without liver disease and individually matched to cases (10:1) by birth year, sex, ethnicity, and length of Medicare enrollment. Diet was assessed at baseline via a validated quantitative food frequency questionnaire. The association between dietary factors and NAFLD by cirrhosis status was quantified by odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable conditional logistic

regression stratified by matched sets and adjusted for body mass index, smoking status, and total calories.
Results: The study consisted of 2, 567 NAFLD cases (489 with cirrhosis; 2078 without cirrhosis) and 25, 579 controls. Men, African Americans, Latinos, and individuals who were obese or had diabetes were more likely to have NAFLD with cirrhosis than NAFLD without cirrhosis. Dietary factors associated with NAFLD-cirrhosis included: red meat (OR quartile 4 vs. quartile 1 = 1.36; 95% CI: 1.02–1.82), processed red meat (OR = 1.32; 95% CI: 1.00–1.74), saturated fat from meat and processed meat (OR = 1.43; 95% CI: 1.02–2.00), and cholesterol (OR = 1.59; 95% CI: 1.19–2.11). For NALFD without cirrhosis, carbohydrate (OR = 1.26; 95% CI: 1.01–1.57) and soda consumption (OR = 1.15; 95% CI: 1.00–1.32) were associated with risk.
Conclusion: Dietary risk factors for NAFLD seem to vary by cirrhosis status. Red meat, processed red meat, and cholesterol were associated with NAFLD with cirrhosis, while carbohydrates and soda intake were associated with NAFLD without cirrhosis.

PS-204
The relationship between FIB-4 progression and liver outcome among patients with type 2 diabetes mellitus: A population based hospital study
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Background and aims: The FIB-4 index is a simple non-invasive fibrosis test developed for the diagnosis of advanced fibrosis. We evaluated the risk of liver disease progression, a composite outcome of primary liver cancer and decompensated cirrhosis, at different FIB-4 cut-offs (1.45 and 3.25) in a large cohort of patients with type II diabetes.
Method: We conducted a retrospective cohort study among consecutive adult patients with at least one hospital stay at Cochin University Hospital (Paris, France) between 2010 and 2018 and with a ICD-10 diagnostic code for diabetes mellitus (N = 39, 700). We selected all patients with type 2 diabetes mellitus without cancer, connective tissue disorder, solid-organ or bone marrow transplantation, HIV infection and chronic liver disease other than alcohol and non-alcoholic steatohepatitis. All repeated measures of liver function tests, platelet levels and glycated haemoglobin were retrieved from the biological database of the institution and merged with the clinical dataset. Outcome measure was liver disease progression. We measured the risk associated with the onset of a FIB-4 index ≥ 1.45, > 1.45- < 3.25 and ≥ 3.25 with time-dependent cox models adjusted for sex, HbA1c level and the presence of alcohol use disorders.
Results: The cohort comprised 19, 547 (49.7%) patients totalling 63, 854 FIB-4 measurements in 14, 307 (73.7%) individuals. There was 11, 259 (57.6%) men. At cohort inception, median (IQR) age, FIB-4 index and HbA1c level were 68 (58–74), 1.8 (1.2–2.8) and 7.6 (6.5–9.2), respectively. A total of 3038 (15.5%) patients were recorded with alcohol use disorders during the study period. Overall, 281 (1.4%) patients developed a liver-related complication over a median 3.6 (1.2–5.6) years. A total of 8110 (56.7%) and 2573 (18.0%) patients reached the 1.45 and 3.25 FIB-4 threshold during the observational period. The adjusted hazard ratio (95% CI) for liver disease progression was 0.6 (0.5–0.8) and 0.3 (0.2–0.5) when patients remained under the 1.45 and 3.25 thresholds; it was 8.1 (6.3–10.6) over the 3.25 threshold. The adjusted hazard ratio for liver disease progression was 8.1 (6.2, 10.6), 8.2 (6.2, 10.8) and 7.0 (5.4–9.3) for patients with alcohol use disorders and a FIB-4 index that remained under the 1.45 and 3.25 thresholds; it was 7.0 (5.4–9.3) for patients who reached the 3.25 index.

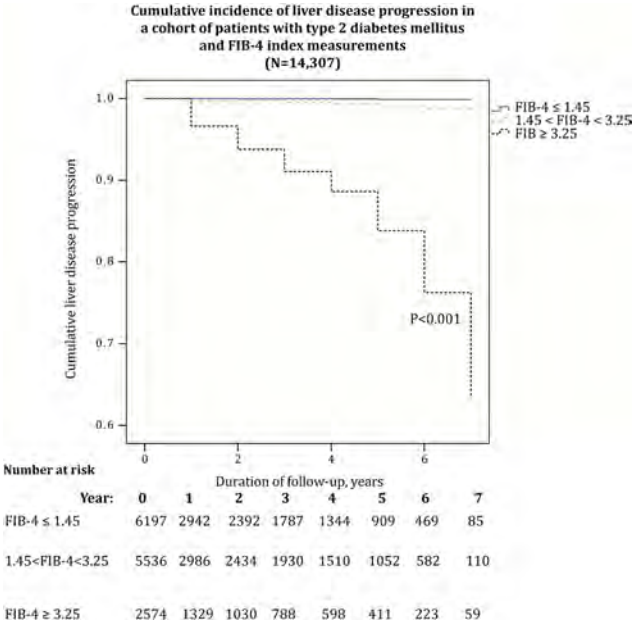

Figure: Cumulative incidence of liver disease progression in a cohort of patients with diabetes mellitus stratified on FIB-4 index (N = 19, 547).

Conclusion: The FIB-4 index progression to the 3.25 threshold is associated with chronic liver disease events among patients with type 2 diabetes mellitus. Alcohol use disorders are strongly associated with outcome.

PS-205
Longitudinal prognostic value of the most common algorithms for fibrosis in non-alcoholic fatty liver disease: An international study in non-cirrhotic, biopsy-proven patients
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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a global health concern since it may progress to Steatohepatitis (NASH) and ultimately cirrhosis. As fibrosis is the main determinant of progressive disease, an important unmet need is to establish a defined set of biomarkers that enable detection of fibrotic NASH and can predict liver-related morbidity and mortality. We aimed at validating the long-term prognostic value of the most currently used non-invasive fibrosis scores in a cohort of biopsy-proven NAFLD patients.

Method: 918 prospectively recruited patients underwent a liver biopsy for clinical suspicion of NAFLD in main referral tertiary centres in Italy (Turin, Milan, Rome, Palermo) and the United Kingdom (Newcastle). Clinical and biochemical data were collected at the time of biopsy and throughout the follow-up. The following non-invasive fibrosis scores were calculated: NAFLD Fibrosis Score (NFS), APRI, FIB-4, BAAT and BARD

Results: At baseline, 593 patients (65%) presented non-alcoholic steatohepatitis (NASH) and 220 (24%) had moderate or advanced fibrosis. After a median follow-up of 85 months (9–336), 75 patients developed liver-related events (ascites, oesophageal varices or hepatic encephalopathy), 15 patients developed hepatocellular carcinoma (HCC) while 91 patients presented cardiovascular events. Among the non-invasive scores, NFS and FIB4 had the highest potential to predict both liver events and HCC (AUROC Liver Events 0, 76 for both NFS and FIB4; AUROC HCC 0, 82 and 0, 80 for NFS and FIB4 respectively). Despite all the scores did not show a high impact on the prediction of the cardiologic outcome, patients with a BAAT of 4 or a BARD score ≥ 2 presented a higher risk of developing cardiovascular events (OR 8, 82 and 2, 175 respectively). The survival analysis demonstrated that patients who presented a NFS > 0, 675, a FIB4 > 2, 67, an APRI > 1 or a BARD score ≥ 2 reported a worse survival outcome (Log Rank <0, 001 for NFS, FIB4 and APRI; 0, 006 for BARD). No additional value was obtained when the different scores were combined together.

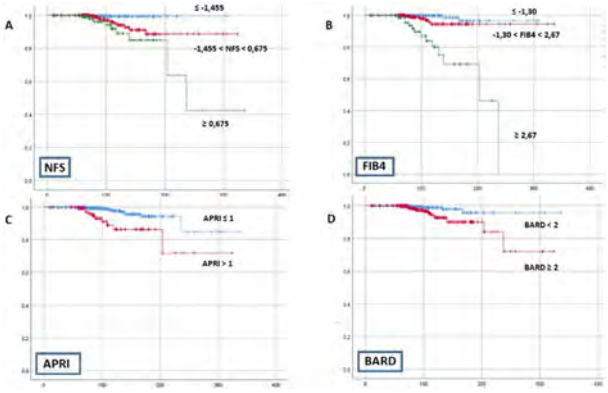

Figure: Survival curves of A) NFS B) FIB4 C) APRI D) BARD in our cohort

Conclusion: The lack of a prognostic biomarker for NAFLD and the ability of these algorithms to predict long-term NAFLD outcomes suggest the use of these scores in routine clinical practice may represent a tool to stratify patients at risk and to select patients for targeted therapies or pharmaceutical trials.

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Liver transplantation II

PS-206
Patterns and predictors of alcohol use after early liver transplant for alcoholic hepatitis

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Background and Aims: The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) is a multi-center consortium studying early liver transplant (LT) for alcoholic hepatitis (AH). To inform surveillance and intervention strategies for post-LT alcohol use, we sought to identify pre-LT factors associated with early versus later post-LT alcohol use, and if these patterns were associated with post-LT survival.

Method: In this multi-center longitudinal analysis, 11 US sites provided detailed pre-LT psychosocial, clinical, post-LT alcohol use, and survival data. Consecutive patients with clinically-diagnosed severe AH, no prior diagnosis of liver disease or AH, who received LT from 2006 to 2018, were included. Alcohol use post-LT was defined as *any* evidence of alcohol use post-LT: by clinical interview, biochemical testing, including ethyl glucuronide (ETG) and/or phosphotidylethanol (PEth). Alcohol use was categorized by date of first drink post-LT: none, early (≤1 year post-LT), later (>1 year post-LT) alcohol use. To evaluate factors associated with early vs. later post-LT alcohol use, Cox regression was performed, with LT recipients with no post-LT alcohol use as reference group, adjusting for center clustering.

Results: 140 LT recipients for AH survived to home discharge (69% male, median pre-LT abstinence 55 days, MELD-Na 39, Lille 0.79, 49% overt encephalopathy), with median post-LT follow-up of 2.5 years (IQR 1.5–4.4). Post-LT alcohol use was as follows: 91 (65%) none, 32 (23%) early use, 17 (12%) later use. The proportion with sustained alcohol use among early (11/32; 34%) versus later (4/17; 24%) alcohol use was similar (p = 0.43). Probability of any alcohol use post-LT at 1-, 3-, 5- years was 24% (95%CI: 18–32), 37% (95%CI: 29–46), 42% (95%CI: 33–53). In adjusted models, predictors of early alcohol use post-LT were younger age (HR 1.06, 95% CI 1.02–1.09, p < 0.001) and overt encephalopathy at LT (HR 1.75, 95% CI 1.05–2.91, p = 0.03), and of later alcohol use post-LT were female sex (HR 1.96, 95% CI 1.31–2.94, p = 0.001), >10 drinks/day pre-hospitalization (HR 2.45, 95% CI 1.05–5.73, p = 0.04) and prior failed rehabilitation attempt (HR 2.12, 95% CI 1.23–3.68, p = 0.007). After adjusting for MELD in separate bivariate models, both early (HR 6.36, 95% CI 2.18–18.5, p = 0.001) and later (HR 2.27, 95% CI 0.87–5.92, p = 0.09) alcohol use were associated with increased risk of post-LT death, though the association with later alcohol use did not reach statistical significance.

Conclusion: Pre-LT factors associated with early versus later post-LT alcohol use are different, which may inform surveillance strategies for post-LT alcohol use. Early (versus later) post-LT alcohol use appears to be more harmful as evidenced by the higher mortality risk. This highlights the first year post-LT as an especially important period to target interventions to prevent and treat alcohol use.

PS-207
Molecular classifier for T-cell-mediated and antibody-mediated rejection after liver transplantation

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Background and aims: Long-term management after liver transplantation (Ltx) is complicated by a low sensitivity of liver enzymes for detecting subclinical graft injuries, atypical histological features of T cell-mediated rejection (TCMR) and limited knowledge about antibody mediated rejection (AMR). Graft gene expression analysis has shown superiority over histopathological assessment in detecting graft injury after kidney transplantation. The aim of this study was to generate a molecular classifier for various rejection types after Ltx.
Method: Cryo-conserved liver biopsies were collected for RNA isolation since 2008. We performed next generation transcriptome sequencing (NGS) to identify molecular pattern of rejection. Therefore, three cohorts were used: A screening cohort of 71 biopsies with no histological rejection (NHR), subclinical (subTCMR) and clinical TCMR (cTCMR) or possible chronic AMR (pcAMR) for NGS. An identification cohort of 110 biopsies with the same entities was used for qPCR of candidates from NGS and designing and validation of the rejection classifier. An application cohort of 97 liver biopsies with ambiguous histological findings was used.
Results: For identification of the four entities 85 transcript candidates were identified with NGS in the screening cohort. Candidates were tested with qPCR in the identification cohort consisting of the same entities. A rejection classifier consisting of 40 transcripts (RC40) was designed and validated in this qPCR data set. RC40 reached low sensitivities, but moderate to high specificities and total accuracies for the identification of the four entities (Table 1). When applied in the cohort with ambiguous histological findings, RC40 identified 80% of subTCMR and cTCMR features within these ambiguous findings correctly. Graft hepatitis with elevated liver enzymes mostly had molecular phenotype of cTCMR (80%) or pcAMR (10%), while subclinical graft hepatitis mostly had a molecular phenotype of subTCMR (80%) or NHR (10%). The molecular phenotype of portal inflammation was mostly subTCMR or NHR.

Table 1: RC40 in identification cohort (n = 110; NHR = 31; subTCMR = 43; cTCMR = 18; cAMR = 18):

	NHR	subTCMR	cTCMR	pcAMR
Sensitivity	68%	65%	44%	39%
Specificity	86%	73%	90%	91%
Accuracy	81%	70%	83%	83%

Conclusion: This is the first approach to generate a gene expression classifier after Ltx incorporating more than TCMR. After further validation such a rejection classifier could help to retrieve more information from allograft biopsies and facilitate individualized immunosuppression.

PS-208
Impact of successful DAA therapy at 3 years of follow-up in liver transplant recipients with hepatitis C recurrence and moderate/severe fibrosis

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Background and aims: Data on the long-term impact of direct-acting antivirals (DAAs) in patients with moderate/severe hepatitis C virus (HCV) recurrence after liver transplant (LT) are still lacking. In 2014, we treated in our center a cohort of patients with post-LT hepatitis C recurrence and moderate/severe fibrosis, and we observed an improvement in clinical outcome and non-invasive markers of fibrosis at 1 year (y) after viral eradication. In the same group of patients, who were prospectively followed up in our center, we aimed to evaluate the impact of viral eradication on hepatic fibrosis and liver function tests at 2 and 3 y of follow-up.
Method: This prospective, monocentric study included 102 liver transplant recipients successfully treated with DAAs between June 2014 and December 2014. At the beginning of the treatment, 72 were affected by cirrhosis (Group A; F4 according to Metavir), 30 by moderate fibrosis (Group B, F3 according to Metavir) assessed by liver biopsy and/or transient elastography (TE). At 2 and 3 y after the end of DAAs, we evaluated liver function tests, AST to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) index and liver stiffness (LS) by TE.
Results: Patients were mostly male (77%) with a median age of 63 y; the median time between LT and viral eradication was 52 months (range 8–179). Three y after viral eradication the survival rate was 95% (97/102 patients).
Group A patients showed stable liver function tests at 2 and 3-y of follow-up (Child score A5 and MELD score 10) and platelet count significantly increased (from 112 × 10^9/L at 1-y to 131 × 10^9/L at 2-y to 135 × 10^9/L at 3-y, both $p < 0.001$). FIB-4 and APRI significantly decreased from the first to the second y (3.12 *vs* 2.86, p = 0.02; and 0.5 *vs* 0.4, p = 0.006 respectively). At the third y, these scores settled (2.69 and 0.4, respectively), compared with the second year (both p = 0.5) (Figure 1).
LS decreased from 14 Kilopascal (kPa) to 13 kPa at 2-y (p = 0.08), to 10.3 kPa at 3-y (p = 0.049) (Figure 1). One case of hepatocellular

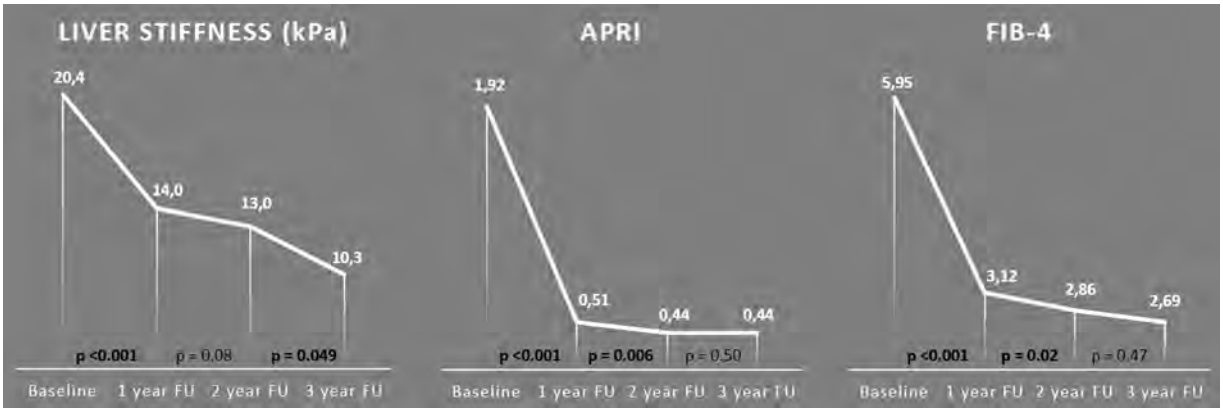

Figure: (abstract PS-208): Non-invasive markers of fibrosis after DAA therapy in cirrhotic patients.

carcinoma was observed in group A, 36 months after the end of DAAs. In group B we observed a trend in reduction of non-invasive markers of hepatic fibrosis (FIB-4, APRI and LS: at y-1: 2.08, 0.4, 7.8 kPa; at 2-y 1.76, 0.3, 7.1 kPa; at 3-y 1.78, 0.3, 6.7 kPa, respectively; no significant p values).
Conclusions: Viral eradication with DAAs contributed to stabilize liver function tests of our patients affected by post-LT hepatitis C with moderate/severe fibrosis. The improvement of platelet count and the progressive reduction of indirect markers of fibrosis in group A patients may reflect a favorable remodeling in the hepatic architecture and an initial reduction of portal hypertension.

PS-209
Whole Human liver decellularisation-recellularisation for future liver transplantation and extracorporeal device application
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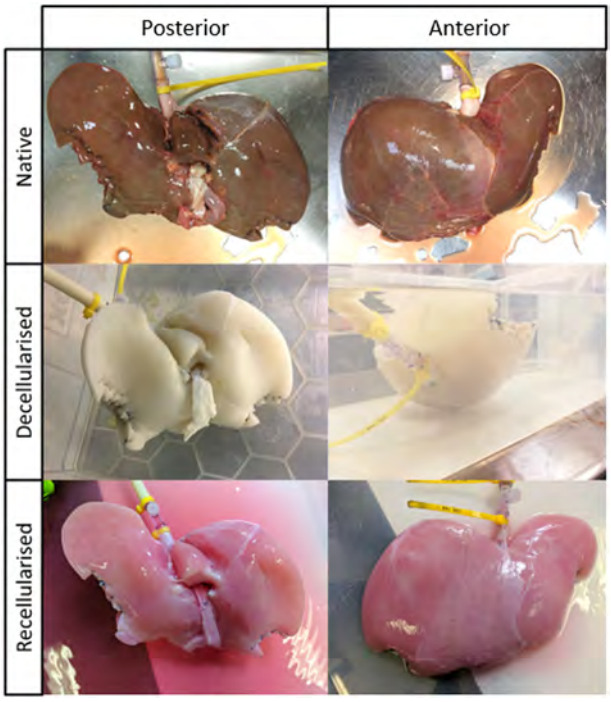
Background and aims: An estimated 29 million people in the European Union (EU) suffer from a chronic liver condition, with liver transplantation still remaining the only treatment for end-stage hepatic disease. Currently, there are approximately 6700 people awaiting liver transplantation in the EU. Considering that 15–25% of donated organs are discarded, whole human liver regeneration represents a novel approach to overcome current organ shortages. One possible approach is the use of native extracellular matrix (ECM) as a suitable environment for cells to restore tissue function. Therefore, the aim of this project was to demonstrate, for the first time, the recellularisation of a decellularised whole human liver for future transplantation and extracorporeal device applications.



Method: A paediatric human liver explant (840 g), diagnosed with Crigler-Najjar syndrome, was decellularised using a well-established method, previously characterized for cellular material elimination and preservation of ECM proteins and micro-architecture. Temperature, pH, oxygen and pressure sensors were incorporated into the Harvard Apparatus' ORCA system, as well as compressed air, O_2 and CO_2 reservoirs. The whole human liver scaffold was recellularised by retrograde IVC infusion with 2×10^9 HepG2 cells. The liver was maintained in 6 L of complete media with a flow-rate of 400 ml/min. The media was changed by replacing 3L of existing media with fresh complete media after 48 hours. Albumin secretion was measured using an ELISA kit at 0, 24 and 72 hours. The liver was fixed in 4% formaldehyde at 72 hours and sectioned into 21 parts to investigate repopulation by Haemotoxilin and Eosin (HandE) stating.
Results: Histological analysis using HandE staining showed that the infused cells have infiltrated all liver segments, excluding segment one. HepG2 cells were seen microscopically to have been migrating from the central vein towards the portal triad, including penetrating into the parenchymal space. Oxygen content in the media decreased from 20% to 10% during the course of three days. Additionally, pH was reduced by 0.4. Finally, albumin present in the media increased from 0 ng/ml on day 0, to 200 ng/ml on day 1, and to 1500 ng/ml on day 3.
Conclusion: This is the first report describing the recellularisation of a whole human liver ECM scaffold with a human hepatocyte cell line. This is a key advance in the development of a bioengineered human liver for future liver transplantation and extracorporeal device applications.

PS-210
Repeated hepatic regeneration stimuli promoted biliary decompression via formation of extrahepatic biliary collaterals
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Background and aims: Patients with tumour related biliary obstruction seem not to benefit from a modern therapy concept like "two-stage hepatectomy." Therefore we designed a novel "two-stage hepatectomy" model in rats with complete or selective biliary occlusion to investigate the postoperative course. Despite transsection of the common bile duct, we observed formation of biliary collaterals leading to complete biliary decompression in 3/5 animals after subjecting them to two consecutive regeneration stimuli (selective portal vein ligation, extented liver resection)
Method: We performed two experiments: In the first experiment, rats (n = 45) were randomised into three groups (each n = 15). Groups were defined by extent of biliary obstruction: no obstruction as control group with no transection of the bile duct (Sham), 70% biliary obstruction mimicking Klatskin III° by transecting the left bile duct (sBDT), 100% biliary obstruction mimicking Klatskin IV° by transecting the common bile duct (BDT). "Two-stage hepatectomy" consisted of selective left portal vein ligation (sPVL, 70% liver volume) at postoperative day (POD) 14 to enlarge the future liver remnant (FLR) followed by a 70% partial hepatectomy (70%PHx) at POD 21. Animals were sacrificed at POD 14, 21 and 28 to assess the severity of systemic cholestasis (bilirubin levels), hepatic injury (transaminases), synthetic function (albumin and prothrombin time) and the alterations of the hepatic architecture and proliferation index (HandE, BrdU). In experiment 2 another 25 animals were subjected to BDT, sPVL and 70%PHx to visualize biliary collateral formation by µCT-examination of the explanted liver.
Results: Despite the challenging sequence of three consecutive hepatobiliary procedures within three weeks, animals tolerated surgery well with a survival of 96.7% (68/70). Signs of complete biliary obstruction (bilirubin level, histological bile duct convolutes) decreased after sPVL, and even more after the subsequent 70%PHx

leading to the suspicion of biliary collateral formation. Upon injection of blue radiopaque silicon rubber compound we visualized collateral formation in totally 6 out of 25 (~24%) animals: in 2 out of 10 (20%) animals after BDT (n = 1 at POD 21 and 28) and in 1 out of 10 (10%) animals subjected to one regeneration stimulus (BDT+sPVL: n = 0 and BDT+70PHx: n = 1) and in 3 out of 5 (60%) animals subjected to "two-stage hepatectomy." 3D-reconstruction of the samples and histological work up revealed the formation of biliary collaterals.
Conclusion: The regenerative pressure due to two regeneration stimuli fostered biliary collateral formation after biliary transection in rats. This phenomenon was so far only observed in biliary obstruction model with bile duct ligation, but not in models with bile duct transection, calling for further investigation of extrahepatic bile duct remodelling.

PS-211
Liver transplantation for HCC: Applicability and performance of the AFP score in real life. The French organization for organ sharing (ABM) experience
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Background and aims: The composite AFP model was adopted in France in January 2013 as a nationwide selection tool for HCC pts candidates to LT. The aim of this study was to evaluate in the real life applicability and performance of this model in HCC patients listed during the 1rst year of implementation
Method: Adult patients listed and subsequently transplanted for HCC in 15 French transplant centers between March 1st, 2013 and March 1st, 2014 were studied.
Data prospectively collected in the national data base of the French OSO ABM were studied. Primary end point was 3-year recurrence rate. Secondary end points were % of transplanted patients within AFP criteria, 3-year survivals, overall and in subgroups meeting or not AFP criteria, and same end points in patients transplanted after down-staging within the AFP score ≤ 2.
Agreement for extracting the ABM-centralized data was obtained from each center. Data were extracted anonymously and quality-controlled for recurrence and death.
Statistical analysis were performed with cumulative incidence functions and competing risk analysis taking into account graft lost, death from non recurrence and recurrence as competing risks
Results: 341 patients consecutively listed for HCC were included (Milan in/out: 246/79 (75.7%/24.3%), MELD 10.4). 335 patients (95%) had assessment of AFP score at listing. Among those patients, 275 (80.7%), 11 (3.2%) and 24 (7%) were transplanted with a final AFP score of ≤ 2, > 2 or after down-staging, respectively. AFP score was not reassessed before LT in 31 pts (9.1%). 3-year recurrence rate was 10.88% (95%CI 7, 63–14, 78) overall, and 10.34% (95%CI 6.84–14.65), 27.27% and 20.00% in patients transplanted with AFP score ≤ 2, > 2 or after down-staging, respectively. Median time between downstaging and LT was 38 days (IQR [20–66]). 3-year overall survival was 79.74% [95%CI: 75.02–83.67].
Conclusion: In the real life, overall survival and recurrence rates in HCC patients transplanted with AFP score ≤ 2 were in strict agreement with those predicted by the AFP model. The higher incidence of recurrence in the down-staged patients prompted a quick revision of allocation rules, by introducing a test of time of 3 months and emphasized the importance of periodical assessment of new indication systems. Adherence of centres was good at listing but quaterly reassessment deserved a reinforced control. The new AFP score-based French indication system complies with EASL 2018 CPG on HCC and can be adopted as a new model to expand Milan criteria.

PS-212
Liver transplantation in patients with grade 3 acute-on-chronic liver failure: Pre-transplant risk factors of post-transplant mortality
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Background and aims: Liver transplantation (LT) in patients with cirrhosis and multiple organ failure (MOF) is a rare and controversial procedure given the ongoing organ shortage. The benefit of LT has been established for these patients in terms of individual survival but there have been diverging results concerning their post-LT outcomes as a group, which leaves uncertain the fairness of allocating organs to them in terms of collective utility. We report the post-LT results of a multicentre cohort and identify pre-LT criteria to help predict post-LT outcome.
Method: Patients who received LT with grade 3 acute-on-chronic liver failure (ACLF) between 2007 and 2017 in 5 transplant centres were retrospectively included and divided into a determination cohort (Strasbourg) and a validation cohort (Beaujon, Mondor, Tours and King's College). Immediate pre-LT one-year mortality risk factors were screened in the determination cohort and a multivariate logistic regression analysis was conducted. A predictive model was derived from these risk factors and evaluated in both cohorts by using the area under the receiver operating characteristic (AUROC) curve.
Results: One hundred and fifty-two patients met the inclusion criteria (76 in the determination cohort and 76 in the validation cohort). The overall one-year survival rate was 67.1%, with no significant difference between the two cohorts. In multivariate analysis, older age (OR = 1.092, 95% CI = 1.003–1.19, p = 0.0416), respiratory failure (not intubated vs. intubated vs. intubated with PaO_2/FiO_2 < 200mmHg: OR = 4.34, 95% CI = 1.02–18.49, p = 0.047), lactate levels > 4 mmol/l (OR = 8.04, 95% CI = 1.56–41.51, p = 0.0128) and lower leukocyte count prior to LT (OR = 0.86, CI 95% = 0.76–0.97, p = 0.014) were independent risk factors of one-year mortality. A predictive model derived from these factors was tested by comparing its AUROC curve in the determination and in the validation cohorts (0.87 vs. 0.80 respectively, p = 0.296). In addition, survival significantly differed according to the number of risk factors at the time of LT (p < 0.001).
Conclusion: We have identified four simple and clinically relevant factors that can be used to estimate the post-transplant outcome of cirrhotic patients with MOF and assist in the decision-making process with regards to the allocation of livers to such patients.

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Late breaker: Posters

LBP-01

In NAFLD, alcohol drinking habits and genetics predict progression to advanced liver disease: follow-up of population surveys

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in the population, but only a few patients progress to advanced liver disease. We analyzed risk factors for the development of such advanced liver disease in the general population with NAFLD.
Method: From several Finnish health-examination surveys (FINRISK 1992-2012 or Health 2000), we included individuals with NAFLD, defined as a fatty-liver index >30 and alcohol use <30 g/day for men and <20 g/day for women, with available genome-wide SNP data. Subjects with baseline clinical liver disease or viral hepatitis (baseline or follow-up) were excluded. Data were linked with national registers for liver-related admissions, mortality, and liver cancer until 2013, using ICD-codes reflecting liver cirrhosis or liver dysfunction. Age, sex, waist-hip ratio (/1SD), non-HDL and HDL cholesterol, triglycerides, diabetes, hypertension, alcohol use (g/day), wine fraction (percentage of total alcohol intake), binge drinking (5 drinks per occasion once/wk, once/month, or less often), PNPLA3 (rs738409), TM6SF2 (rs58542926), exercise (at least 2x/wk, 2-4x/month, or less often), smoking (current, former, never), and cigarettes/day were entered into backward stepwise Cox regression analysis with incident liver disease as the outcome.

	HR	95% CI	P
Age	**1.05**	**1.02-1.07**	**<0.001**
Waist-hip ratio (/1SD)	**1.80**	**1.32-2.44**	**<0.001**
HDL cholesterol	**2.09**	**1.08-4.04**	**0.03**
Alcohol use (10 g/day)	**1.43**	**1.12-1.82**	**0.004**
Binge drinking			
Less often	**Reference**		
Monthly	**2.69**	**1.27-5.69**	**0.01**
Weekly	**1.48**	**0.61-3.58**	**0.39**
TM6SF2 carrier	**2.18**	**1.12-4.24**	**0.02**
PNPLA3 carrier	**1.88**	**1.09-3.26**	**0.02**

Results: Complete data were available for 6462 NAFLD subjects (men 60%, mean age 53 yrs, diabetes 10%, lifetime abstainers 10%, mean alcohol intake 11 g/day). During 70401 person-years of follow-up, we observed 58 incident liver events. In the final Cox regression model, age, waist-hip ratio, HDL cholesterol, alcohol intake, binge drinking habits, PNPLA3, and TM6SF2 were significant independent predictors of liver events (Table). There was a 43% rise in the risk of liver events per each additional alcohol drink/day (1 drink = 10 g ethanol). We found no significant interaction effects between age or sex and the independent predictors.
Conclusion: Our findings highlight the role of alcohol drinking habits and genetics in the progression of NAFLD in the population. These data help identify patients at risk of developing complicated liver cirrhosis, in whom more intensive liver evaluation may be warranted.

LBP-02

Association between HBsAg loss and long-term clinical outcome in chronic hepatitis B: a systematic review and meta-analysis analysis

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Background and Aims: Seroclearance of HBsAg is the recommended primary treatment goal for chronic hepatitis B (CHB) virus infection according to the current guidelines. It is of great interest to assess whether HBsAg loss translates into improved patient outcomes. This could further inform drug development and regulatory decision-making. We report on a systematic literature review and metaanalysis evaluating the strength of association between HBsAg seroclearance and long-term clinical outcomes.
Method: A systematic literature review was conducted in PubMed, EMBASE, and Cochrane Library databases for articles published between January 1990 - November 2018. Included studies had > 50 CHB patients, measured for the presence of serum HBsAg at baseline and during follow-up, and reported data on the incidence of hepatocellular carcinoma (HCC), liver decompensation, liver transplantation (LT), and/or all-cause mortality. A meta-analysis of risk ratios (RR) using a random effects model was performed independently for each endpoint and for a composite endpoint where only the first clinical event reported was used. Reciprocal continuity correction factors were used for studies reporting 0 events. Sensitive analyses were conducted to determine the robustness of the results.
Results: Our initial search strategy identified 3503 articles, of which 92 were assessed for eligibility and 27 articles were included in the quantitative synthesis: 24 reporting data on HCC, 5 on liver decompensation, and 10 on LT and/or all-cause mortality. The meta-analysis of the clinical endpoints produced pooled RRs for the HBsAg seroclearance group equal to 0.34 (0.17 – 0.68, $p < 0.01$) for hepatic decompensation, 0.76 (0.58 – 1.01, $p = 0.019$) for LT and/or all-cause mortality, 0.39 (0.25 – 0.61, $p < 0.01$) for HCC, and 0.40 (0.26 – 0.59, $p < 0.01$) for the composite endpoint, indicating significantly improved clinical outcome following the loss of HBsAg. The composite event rates were 39/100,000 person-years for the HBsAg-loss group and 152/100,000 person-years for the HBsAgpersistent group. Sensitivity analyses through stratification of

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studies by treatment/natural history, HBV genotype, follow-up duration, and presence of coinfections showed that none of these factors significantly influence the RR for the composite endpoint ($p<0.05$).

Conclusion: The results of our analysis support the use of HBsAg seroclearance as a surrogate marker for improved clinical outcome in CHB patients.

LBP-03

LPCN 1144, an Androgen Receptor Agonist Targeted for NASH, Reduces Liver Fat and Key Serum Biomarkers

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Background and aims: Androgen receptor signaling has been shown to be involved in fibrosis, inflammation, and steatosis pathways in NASH. Here we report results from clinical trials with LPCN 1144, an orally bioavailable prodrug of testosterone, an androgen receptor agonist, on liver disease biomarkers in adult hypogonadal males.

Method: The Liver Fat Study (LFS) is a 16-week open-label, multi-center, single arm study with LPCN 1144 treatment in subjects (n = 36) with liver fat (LF) changes assessed by Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF).

The Study of Androgen Replacement (SOAR) trial was an active controlled randomized multicenter 52-week study with LPCN 1144.

Results: In the LFS, NAFLD (liver fat ≥5 %) prevalence was 58% at baseline (BL), with increased prevalence in obese males.

At the 8-week interim visit (16 week to be presented), subjects having BL liver fat ≥1 0% had mean absolute and relative liver fat reductions of 7.6% and 38%, respectively. Increasing BMI was associated with increased response (absolute liver fat change): BMI 30-40 kg/m2 (−5.2%); BMI ≥4 0 kg/m2 (−9.4%). The responder rate, based on absolute LF reduction of at least 4.1%, for subjects with LF BL ≥1 0% was 86%. 28% of NAFLD confirmed subjects experienced NAFLD resolution with LPCN 1144.

In the SOAR trial, subjects with elevated baseline ALT, GGT, TG, and Lp-PLA2 experienced significant reductions. Significant normalization rates for above-normal levels of liver enzymes (ALT = 52%, GGT = 31%) and lipids (TG = 34%, and LDL-C = 56%) were observed post LPCN 1144 therapy. ALT responder rate (ALT normalization with at least 30% reduction) as a potential indicator of liver histological improvement was 43%.

Additionally, improvements were observed with LPCN 1144 in sexual and mental domains.

LPCN 1144, with up to 52 weeks exposure, exhibited no adverse drug reaction in the Hepatobilliary System Organ Class (e.g., peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis and jaundice), no major adverse cardiac events (MACE), no signs of increased skeletal fragility or nephrotoxicity, and good gastrointestinal tolerability.

Conclusion: Our results indicate androgen deficiency is strongly associated with NAFLD/NASH in males. LPCN 1144 therapy meaningfully reduces liver fat in hypogonadal males, suggesting utility as a NAFLD/NASH therapy.

LBP-04

Investigation of synbiotic treatment in non-alcoholic fatty liver disease (NAFLD): Results of the INSYTE study

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Background and aims: Non-alcoholic fatty liver disease (NAFLD), is characterised by abnormal accumulation of triglycerides in the liver. Recent evidence suggests that altered gut microbiota can play a role in the pathogenesis of NAFLD. A synbiotic is a combination of a pro- and prebiotics. Our aim was to investigate the effect of synbiotic treatment on: a) liver fat; b) liver fibrosis bio-markers and c) gut microbiota in patients with NAFLD.

Method: In a phase 2 double-blind placebo-controlled trial (INSYTE-Investigation of synbiotic treatment in NAFLD), participants with NAFLD were randomised to 10-14 months intervention with either synbiotic (fructooligosaccharides; 4 g/day+*Bifidobacterium animalis* subsp. *lactis* BB-12) (n = 55) or placebo (n = 49). Liver fat was measured by magnetic resonance spectroscopy (MRS), and change in gut microbiota composition was measured by a 16S rRNA sequencing in stool samples. The effect of the synbiotic intervention was tested in regression models.

Results: Mean and standard deviation (SD) for age and BMI were 50.8 (12.6) years and 33.1 (5.2) kg/m^2 respectively. 65% were men and 37% of participants had diabetes. Mean and (SD) of baseline and end-of-study MRS liver fat percentage was 32.3 (24.8) and 28.5 (20.1) (synbiotic) and 31.3 (22) and 25.2 (17.2) (placebo). In the unadjusted intention to treat (ITT) analyses, there was no evidence of a difference between groups ($\beta = 2.8$; 95% CI: −2.2, 7.8; $p = 0.3$). In a fully adjusted model (adjusted for baseline measurement of the outcome plus age, sex, weight difference, baseline weight), weight loss was significantly associated with an improvement in MRS liver fat percentage at the end of the study ($\beta = 2.0$; 95% CI: 1.5, 2.6; $p = 0.03$). Synbiotic consumption fostered the growth of *Bifidobacterium* and *Faecalibacterium* at the expense of *Oscillibacter* and *Alistipes*.

Conclusion: Synbiotic treatment was effective in changing the gut microbiota in patients with NAFLD. However, this pro- and prebiotic combination was ineffective in modifying liver fat and fibrosis biomarkers.

LBP-05

classification and mutation prediction based on liver cancer hisopathological images using deep learning

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Background and aims: HCC is the most common subtype of liver cancer, and assessing its grade requires visual inspection by experienced pathologist. We aim to use HandE image to automatically classify them into well, moderate, poor or normal liver tissue, even predict the fifteen most commonly mutated genes in HCC using deep learning.

Method: We used 188 HCC whole-silde HandE Images with 16700 tiles at magnification of 60 X from the Genomic Data Commons databases to train a deep convolution neural network (inception v3, Easy DL) for classification and mutation prediction. The performance of this model, which is evaluated by receiver operating characteristic curve, is comparable to that of pathologists. Moreover, our models were validated on independent datasets of 94 whole-silde HandE images with 9400 tiles at magnification of 60 X from our center.

Results: Compared to pathologist, it demonstrated better accuracy (94.7%) and sensitivity (94.9%) for classifying its grade in the training cohort. The values of AUC in the internal and external validation cohorts were up to 0.95 and 0.93, respectively. Furthermore, we trained the network to predict the fifth most commonly mutated genes in HCC. We found that five of them, including TP53, CTNNB1, ALB, TERT and APOB, can be predicted from pathology images, with internal and external AUCs from 0.71 to 0.89.

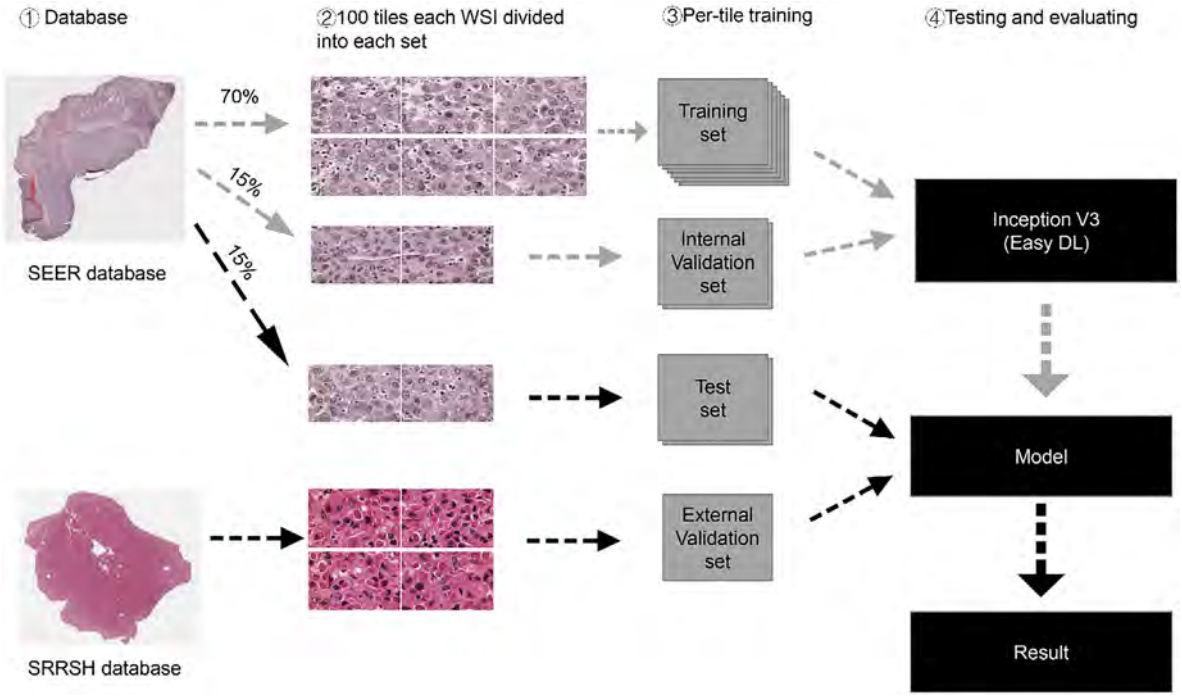

Figure (abstract: LBP-05): Strategy for training and validation.

Conclusion: Our novel models using deep learning can assist pathologists in the detection of liver cancer grade and gene mutations.

LBP-06

High Seroprotection Rates Achieved with Two Doses of Sci-B-Vac, a Third Generation Hepatitis B containing PreS1, PreS2 and S Antigens.

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Background and aims: Acute hepatitis B virus (HBV) infection may develop into a chronic disease, leading to a carrier state, chronic hepatitis, cirrhosis and liver cancer. Although licensed HBV vaccines are safe and effective in controlling HBV in healthy people younger than 40 years of age, vaccine efficacy decreases with age, in diabetics or smokers, in people with compromised immunity, or because of non-compliance with the required regimen. In both the US and Europe, there have been significant decreases in the incidence rates of acute HVB, however, the prevalence of chronic HBV and HBV carriers has actually remained constant or even increased. Europe, more so than the US, faces an increased risk of HBV due to the higher numbers of migrants and refugees. Thus, a more potent vaccine that is safe and protects faster or with fewer doses may address both public health and compliance needs. We tested the ability of SciBVac, a third generation HBV vaccine containing the Pre-S1, Pre-S2 and S components of HBV surface antigen (HBsAg) to elicit robust seroprotection after two or three immunizations.
Method: We analyzed the seroprotection rates (SPR or Anti-HBs of >10 IU/ml) after the second and third doses of Sci-B-Vac in three clinical studies, a phase 4 study conducted in Israel, a single arm open study (SciBVac n = 83) and two phase 3 studies; a single-blind comparative, controlled, randomized study conducted in Vietnam (SciBVac n = 120 and Engerix n = 117) and a comparative randomized study conducted in Russia (SciBVac n = 47 and Engerix n = 47). The three studies were conducted according to good clinical practice in healthy volunteers 18-45 years of age. Blood for Hepatitis B antibody testing was collected before and after each immunization. Standard diary cards were collected to determine vaccine reactogenicity and safety. Volunteers were followed for a total of 12 months.
Results: The SPR after two immunizations with SciBVac (day 180) was 98.8% (82/83) in the single arm Israeli study. The SPR after two immunizations with SciBVac or Engerix (day 180) was 98.3% (118/120) vs 81.2% (95/117, p = <0.001) in the Vietnamese study and 100% (47/47) vs 89% (42/47, p = 0.06), respectively in the Russian study. SPR post third immunization with SciBVac was 100% and 98% for Engerix in both phase 3 studies. Both vaccines had a similar reactogenicity and safety profile with no safety signals detected during volunteer follow-up.
Conclusion: Three separate SciBVac clinical studies demonstrate that the vaccine is well tolerated and that most individuals under the age of 45 achieve seroprotection with two doses of SciBVac.

LBP-07

Association of pharmacogenomics and pharmacokinetics with antiviral activity of Pradefovir for treatment of chronic hepatitis B infection

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Background and aims: Pradefovir, a liver-targeting oral prodrug of PMEA (active ingredient of adefovir), developed by using HepDirect TM patented technology, could be converted efficiently to PMEA by cytochrome P450 isozyme 3A4 (CYP3A4). The aim of this study was to evaluate the association of pharmacogenomics and pharmacokinetics with antiviral activity of pradefovir for treatment of chronic hepatitis B infection (CHB).

Method: 50 CHB patients were divided into five groups (10 for each group) and randomized within each group in the ratio 6:2:2 to receive an ascending dose of 30, 60, 75, 90, or 120 mg of pradefovir, adefovir dipivoxil 10 mg or tenofovir disoproxil 300 mg once a day for twenty eight days. The plasma pradefovir and PMEA concentrations were measured using LC-MS/MS, and pharmacokinetic parameters were determined by non-compartmental methods. Genetic analyses of absorption, distribution, metabolism and excretion were carried out by the Drug Metabolizing Enzymes and Transporter Affymetrix PharmacoScan Array.
Results: 50 patients (10 per group) were admitted and completed the study. Pradefovir has been well tolerated in CHB patients, and most of the adverse events (AEs) were mild, and there were no dose-limiting toxicities. AEs or laboratory abnormalities ≥G rade 2 were infrequent (40 times, 42% (21/50)), and 94% (47/50) patients experienced ≥1 AE on treatment. Pradefovir effectively inhibited HBV DNA for both HBeAg+ and HBeAg- patients. The mean decline in HBV DNA were −2.77 to −3.44IU/Ml at after pradefovir treatment, which were more than that at adefovir dipivoxil group, and the decline in HBV DNA of high dose group were also more than that at tenofovir disoproxil group. Tmax and t1/2 of pradefovir were obtained at about 0.25 to 1.5 hour and 1.91 to 2.95 h after administration. Conversion of pradefovir to PMEA was rapidly, the Tmax and t1/2 of PMEA were obtained at about 0.25 to 1.5 hour and 9.4 to 11.63 h after administration. Rs2517474 G, rs2517448 T or rs6457327 A allele were significantly associated with the higher exposure of pradefovir ($AUC_{0\text{-}24hour}$). However the relationship between the gene polymorphism with the decline in HBV DNA was not significant. Rs6939511 G allele was significantly associated with the higher exposure of PMEA ($AUC_{0\text{-}24hour}$), and the mean decline in HBV DNA was higher at G allele group after 28 days treatment (−3.37 and −3.06 IU/ml at A/G and A/A genotype, respectively).

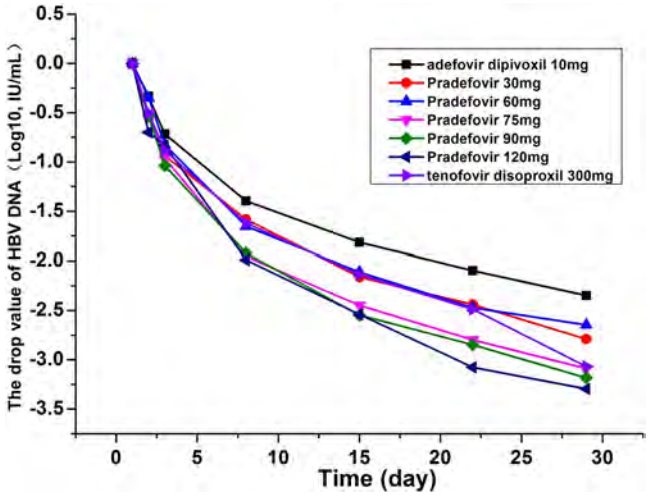

Figure 1: The drop value of HBV DNA (Log 10, IU/ml).

Conclusion: Pradefovir was found to be well tolerated and effectively inhibit hepatitis B virus in this study. Drug Metabolizing Enzymes and Transporter gene polymorphism was associated with the exposure of PMEA and antiviral effect. On the basis of these results, The gene polymorphism should be explored in phase II-III trials of treating CHB patients.

LBP-08

The World's Largest Hepatitis C Screening Program in Egypt

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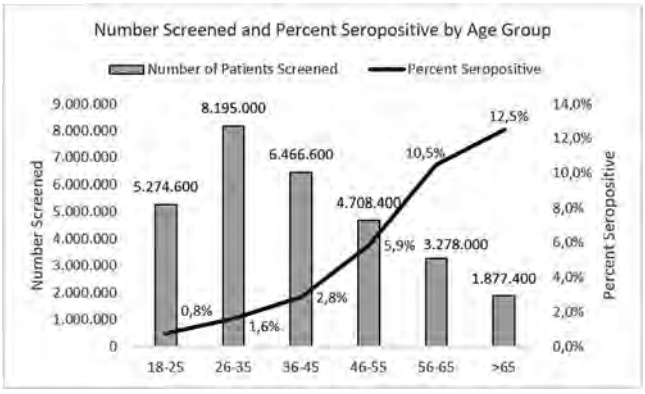
Background and aims: With the highest prevalence of HCV and 5.5 Million viremic patients, HCV elimination became a national health priority in Egypt. The national HCV treatment program with DAAs began in 2014, and by September 2018, about 2.5 million patients had been evaluated for and started treatment. These represented most patients who had been living with the diagnosis, and by mid 2018, the rate of patients registering for evaluation and treatment markedly decreased.
Methods: To augment treatment flow and meet disease elimination targets, a national population screening program was initiated in October 2018 aiming at screening all adults above the age of 18 (61 million), and all school children between the ages of 12 and 18 if their parents signed a letter of approval (15 million) within two years. The country was divided into three geographic sections of 17 to 23 million adults each, and the mass screening program is being implemented in three phases, with screening for adults lasting two to three months in each section, followed by screening school children. Screening is totally free and includes testing for anti-HCV, diabetes, hypertension and obesity. The cost of 12 weeks' treatment with locally produced generics was negotiated down to US$ 45. Preparation for each phase includes training ~1000 trainers who train more than 18, 000 healthcare workers (physicians, nurses, data entry personnel), and preparing screening sites in many Ministry of Health hospitals, rural health units, schools, sports facilities and youth centers. Each phase includes 5, 000 to 7, 000 screening sites, which work 12-hour days seven days a week. These screening sites are augmented by specially outfitted vehicles, which target crowds in mosques on Fridays, churches on Sundays, sports clubs, factories, and subway stations. Results are immediate, and data are transmitted instantaneously to a central database through handheld devices and cellular networks. Appointments are set for HCV seropositive individuals through the web-based registration system at a treatment center nearest to their residence, where further evaluation and treatment are free at the expense of the state.
Results: In the first 4.5 months of the program, turnout was massive, 29.8 Million persons were screened (78.5% of the target population in the areas where screening is still ongoing). Of these, 1.2 million were seropositive (4%), were referred for further evaluation, of whom 75% were viremic. Those who test positive and fail to show for their evaluation appointments are contacted to identify the cause of the "no show." The figure shows the number screened and percent seropositive in each age group.



Conclusion: With this screening program and the mass treatment effort that has been the largest in the world so far, Egypt is on a fast track to HCV elimination, and has the potential to be the first country to achieve the WHO disease elimination targets.

LBP-09

Liver humanization of Fah −/−/Rag2 −/−/Il2rg −/−andnbsp;NOD mice with human hepatocytes homozygous for M148I PNPLA3 allows the assessment of specific genotype contribution to NASH development in vivo.

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Background and aims: Current preclinical rodent models of NASH are inadequate and do not represent the full pathology of human NAFLD/NASH. This is reflected by the difficulties in the clinic, where observations from animal models failed to predict clinical trial outcomes.
Building on the liver humanized FRG KO model, we set out to establish an in vivo model, that recapitulates dyslipidemia/NAFLD/NASH with only high fat diet and without additional chemical inducers. To study hepatocytes from human donors with known genotypes of importance in the development of NAFLD and NASH, we assessed a PNPLA3 homozygous mutant donor in the model system.
Method: Fah −/−/Rag2 −/−/Il2rg −/− NOD (FRG KO/NOD) mice were transplanted with human hepatocytes from a donor homozygous for the G allele of rs738409 in PNPLA3. The M148I variant is significantly associated with high risk of NASH development. After near complete repopulation of the liver with human hepatocytes, the mice received either standard chow or a high fat diet (HFD) with fructose and cholesterol. The diets were 10% v 45% fat by kcal, respectively. Control murinized FRG KO/NOD animals (transplanted with murine NOD hepatocytes) were treated similarly (standard vs HFD chow). Animals from the four groups were bled every other week and sacrificed on weeks 8, 12, 16, and 20 after the start of the experiment.
Results: Lipidomics: Liver humanized mice on a regular diet show a lipid chemistry profile similar to humans (LDL/HDL ratio of ~1.5) whereas wildtype mice have low levels of circulating LDL (LDL/HDL ratio of ~0.3). After four weeks, the humanized animals on HFD had cholesterol levels 10-fold higher than control humanized animals. After eight weeks, the VLDL metabolic pathway started to fail, which is typical of a clinical NASH phenotype. Histology: By week sixteen, key NASH characteristics were detectable in the HFD group: hepatocyte ballooning, evidence of fibrosis, and a blood profile similar to that seen in patients with NASH. Liver histology of liver murinized mice did not exhibit similar features of human non-alcoholic fatty liver disease (NAFLD). Compared to animals transplanted with mouse hepatocytes, the liver humanized mice did not become obese, but did show an increase of liver to body weight ratio (control: 12% vs HFD: 15%).

Conclusion: The liver humanized FRG KO model adds significant human relevance to an animal model system and will be of high value in studying the efficacy of novel treatments against NAFLD and NASH in an in vivo setting. Moreover, the flexibility of transplanting human hepatocytes from different donors allows us to study the development of NASH in human hepatocytes with specific mutations like M148I PNPLA3. After successful transplantation, these mice can either be used for in vivo studies on drug metabolism and efficacy against liver disease, or the human hepatocytes can be plated fresh for use in high throughput in vitro studies.

LBP-10

A structurally engineered fatty acid, icosabutate, rapidly normalises elevated plasma ALT and gamma-glutamyl transferase (GGT) concentrations in a study population at high risk of NAFLD/NASH

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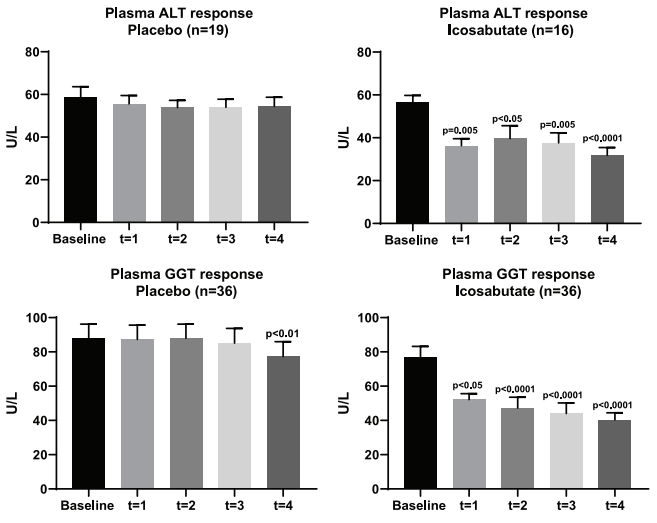
Background and aims: Excessive plasma and mitochondrial membrane polyunsaturated fatty acid peroxidation contributes to the pathology of steatohepatitis, making supplementation with cardioprotective omega-3 supplementation potentially counterproductive in NAFLD patients. We have recently shown that in contrast to eicosapentaenoic (EPA), icosabutate (structurally modified EPA that avoids membrane incorporation) markedly reduces hepatic oxidative stress and plasma alanine aminotransferase (ALT) in rodent models of NASH. As reductions in plasma ALT have shown to be predictive of histological responses to therapy in NASH, we assessed time-course changes in abnormal baseline ALT and gamma-glutamyltransferase (GGT) from clinical trials in 3 study populations with a high risk of NAFLD/NASH (hyperlipidemic, overweight/obese, high prevalence of diabetes) treated for up to 12 weeks with 600 mg/day oral icosabutate or placebo.
Method: Subjects with abnormal baseline ALT (>40 U/L) or GGT (>38 U/L females, >51 U/L males) from 3 clinical trials were identified. Plasma ALT and GGT were assessed over 5 time points: 0, 1, 2, 3 and 4 weeks (study end) in NCT02364635 (phase 1b) and 0, 2, 4, 8 and 12 weeks (study end) in NCT01893515 and NCT01972178 (both phase 2a studies). Sequential time points were characterized as baseline, t = 1, t = 2, t = 3 and t = 4 and differences versus baseline were assessed via Friedman's ANOVA with Dunn's correction.



Results: From a total of 115 icosabutate- and 106 placebo-treated subjects, 36 subjects in each group had abnormal baseline GGT whereas 16 and 19 had abnormal ALT respectively. Icosabutate induced a rapid (within 1-2 weeks) and significant 45% reduction in mean plasma ALT (56 baseline vs 31 U/L study end, $p < 0.0001$), with 14/16 (88%) subjects achieving a normal ALT at study-end. Plasma GGT was also rapidly reduced by icosabutate, achieving a 48% decrease vs. baseline (77 baseline vs 40 U/L study end, $p < 0.0001$). In the icosabutate treated arm 29/36 (81%) had normal GGT at study end (see Figure). Plasma ALP (subjects >70 U/L baseline) and AST (subjects >34 U/L baseline) were also significantly reduced at all time points in icosabutate treated, but not in placebo treated subjects.
Conclusion: Oral icosabutate (600 mg) rapidly reduces both plasma ALT and GGT within 1-2 weeks, with >80% of subjects achieving normal levels within 12 weeks. Absolute decreases are comparable/superior to those that have been associated with histological responses in NASH intervention trials. An upcoming phase 2b trial with icosabutate will confirm whether reductions in liver enzyme in a study population with a high prevalence of NAFLD/NASH are also predictive of decreases in patients with biopsy confirmed NASH.

LBP-11

Is it possible to successfully link migrants from low-income countries to HBV, HCV, and HIV services upon arrival in the European Union?

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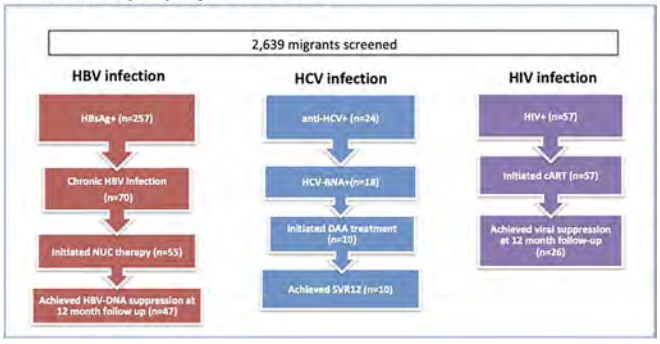
Background and aims: European Union/European Economic Area (EU/EEA) countries are not effectively addressing many public health challenges associated with the flow of migrants. We report HBV, HCV and HIV prevalence, risk factors and therapy outcomes in migrants crossing through Libya and arriving in Sicily.
Method: All migrants who arrived at 41 Immigrant Take Care Advocacy (ITaCA) centres in 2015-2017 were screened for HBsAg, anti-HCV Ab, and anti-HIV Ab within 6 weeks followed by confirmatory tests if positive. Patients with HBV and/or HCV infection were evaluated for liver fibrosis by transient elastography. HBV vaccination was offered to those negative. Patients with HBV, HCV and HIV infection received nucleos (t)ide analogs (NA), direct-acting antivirals (DAAs) and combination antiretroviral therapy (cART), respectively, from the regional healthcare system free of charge. Chi-square tests, odds ratios (OR) and adjusted odds ratios (aOR) were used for statistical analysis.
Results: 2, 639/2, 751 (96%) migrants (72% men) agreed to undergo viral screening. HBsAg was present in 257 (9.7%) migrants and 70 of these had chronic hepatitis. Of these latter, 55 (78.5%) started NA therapy and 47 (67.1%) achieved HBV-DNA suppression. Twenty-four (0.9%) were anti-HCV positive; 10 received DAAs and achieved SVR12. Fifty-seven (2.2%) had confirmed HIV infection and were offered cART. (Figure) The mean time crossing through Libya in 2015-16 was 10 weeks and 50 weeks in 2017. The probability of HBV and/or HIV infection was associated with having suffered sexual violence ($OR = 3.2$, $p < 0.001$ and $OR = 5.8$, $p < 0.001$) and was higher in women than men ($OR = 2.5$, $p < 0.001$ and $OR = 5.4$, $p < 0.001$). The prevalence of HIV infection was higher in men ($OR = 3.1$, $p = 0.01$) and women ($OR = 8.6$, $p < 0.001$) who had spent more time in Libya. Reported sexual violence ($aOR = 6.7$, $p < 0.001$) and a longer stay in Libya ($aOR = 4.7$, $p = 0.02$) were associated with higher risk for HIV infection in both genders and reported sexual violence ($aOR = 3.9$, $p < 0.001$) was associated with higher risk for HBV infection in women.

Figure. Proportion of migrants successfully retained in care in Italy 12 months after initiation of HBV, HCV, and/or HIV treatment



Conclusion: The Italian healthcare service is able to provide early screening for HBV, HCV, and HIV infection, linkage to care, and treatment in migrants arriving from Africa. Policy-makers should consider the ITaCA model in other European settings with large numbers of newly arrived migrants.

LBP-12

Phase 1a Study of the Safety, Tolerability and Pharmacokinetics of ABI-H2158, a Novel Second-Generation HBV Core Inhibitor, in Healthy Volunteers

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Background and aims: Chronic Hepatitis B (CHB) infection remains a major cause of morbidity and mortality worldwide. Standard of care (SOC) nucleos (t)ide HBV polymerase inhibitors can maintain profound on-treatment viral suppression, but this is rarely sustained following treatment withdrawal. ABI-H2158 (2158) is a novel 2nd generation core protein inhibitor with enhanced antiviral potency and pharmacokinetic (PK) properties in preclinical models (*in vitro* EC_{90} of 70 and 290 ng/ml against HBV replication and cccDNA establishment, respectively). Here we report Phase 1a results from the first-in-human Phase 1a/1b dose ranging study of 2158.
Method: Safety, tolerability and PK were assessed in 48 healthy volunteers, ages 19-50 (88% Male, 73% Caucasian). Five sequential single ascending dose cohorts of 8 subjects (6:2 active:placebo) received single doses of 2158 at 5, 25, 100, 300 and 500 mg orally (PO) under fasted conditions After washout, the 100 mg cohort subjects repeated a 100 mg dose following a high fat meal. A multiple dose cohort of 8 subjects (6:2 active:placebo) was given 300 mg once daily for 10 days. Safety evaluations included physical exams, adverse event (AE) monitoring, ECGs, and clinical safety labs. Intensive PK plasma sampling was conducted for all cohorts.
Results: 2158 was well tolerated. All patients completed dosing and evaluations. Treatment Emergent AEs (TEAE) were mild. Treatment emergent laboratory abnormalities were grade 1 or 2, infrequent, transient, and deemed not clinically significant. Single dose PK results demonstrated ABI-H2158 is rapidly absorbed, with an elimination half-life ranging from 10-18 hr. After single doses, area under the curve (AUC_{0-inf}) exposures and C_{24hr} values were dose proportional between 5 and 500 mg, with mean exposures ranging between 1, 610

to 146, 000 ng*hr/ml and 20 and 2, 420 ng/ml, respectively. Mean-maximum concentrations (C_{max}) were less than dose proportional, ranging from 174 to 6, 810 ng/ml. A high fat meal showed no significant food effect on either C_{max} or AUC. Multi-dose PK results will be presented.
Conclusion: Oral dosing of 2158 in healthy volunteers demonstrated favorable safety and PK properties supportive of PO QD dosing. Oral ABI-H2158 achieved systemic exposures that exceed those predicted to inhibit cccDNA establishment in CHB patients. ABI-H2158 is expected to enter Phase 1b studies in CHB patients.

LBP-13
Effect of treatment of hepatitis B patients with tenofovir disoproxil or entecavir on risk of hepatocellular cancer death in a U.S. Cohort
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Background and aims: Both entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are recommended as first-line treatment in patients with chronic hepatitis B (CHB). A recent study from Asia showed that treatment-naïve patients who started treatment with TDF had significantly lower risk of HCC compared to those who received treatment with ETV (HR = 0.61 and 95% confidence interval [CI] were 0.54-0.7). We used data from the longitudinal Chronic Hepatitis Cohort Study (CHeCS) to validate these findings in a US population that included both Asian and non-Asian patients.
Method: After excluding patients with liver transplant, HIV, or history of treatment with both ETV and TDF, we followed 822 CHB patients treated with either TDF (n = 407) or ETV (n = 415) for incidence of HCC and all-cause mortality. Cox regression was used to compare treatment effects and inverse probability treatment weighting (IPTW)—which included index age, sex, race, Fibrosis-4 score, and cirrhosis—was used to adjust for treatment selection bias. Death was considered a competing risk for HCC. The analysis was stratified by race (Asian or non-Asian). A subgroup analysis was conducted among previously treatment-naïve patients.
Results: Among 822 included CHB patients, 164 (20%) had previously received other antiviral treatment before starting TDF or ETV, 151 (18%) had cirrhosis, and 517 (63%) were Asian. Median follow-up was 3 years. The p value for race-by-treatment interaction was 0.17 for HCC and 0.30 for mortality. In the Asian group, the adjusted Hazard Ratios (aHR) for TDF versus ETV (95%CI) were 0.70 (0.29, 1.68) for HCC and 0.86 (0.48, 1.53) for mortality. In the non-Asian group, aHRs (95% CI) were 1.87 (0.60, 5.87) for HCC, and 1.25 (0.81, 1.92) for mortality. Results were similar in the treatment naïve patients (n = 677): among Asians, aHRs (95% CI) were 0.73, (0.29, 1.84) for HCC and 0.94 (0.51, 1.73) for mortality; in the non-Asian group, aHR (95% CI) were 1.21 (0.37, 3.98) for HCC and 1.17 (0.72, 1.90) for mortality.
Conclusion: We observed that risk of HCC among patients treated with TDF compared to those treated with ETV may vary by race group. Among Asian patients in our cohort, an adjusted hazard ratio = 0.70 (TDF vs. ETV) suggests a trend toward HCC risk reduction, consistent with the results published from Asia. There was no treatment-related difference in mortality risk between the two race groups. These findings need to be validated in a larger cohort.

LBP-14
Magnetic Resonance Biomarkers for Early Phase Steatohepatitis Clinical Trials: Short Term Evaluation in Adolescents, Transitoriness or Stability in Steatosis (STEATOSIS)
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Background and aims: Early-phase paediatric non-alcoholic fatty liver disease (NAFLD) clinical trials are designed with non-invasive parameters to assess potential efficacy. Increasingly, these parameters include MRI-derived proton density fat fraction (PDFF) and MR elastography (MRE)-derived shear stiffness as biomarkers of hepatic steatosis and fibrosis, respectively. Understanding fluctuations in these measures is essential for calculating trial sample sizes and interpreting study results. These are critical data needed by the European Medicines Agency and the USA Food and Drug Administration to plan clinical drug trials in children with NAFLD and the lack of such data in children comprises a critical knowledge gap. Therefore, the primary aim of this study was to assess whole-liver MRI-PDFF change in adolescents with non-alcoholic steatohepatitis (NASH) over 12 weeks. Secondary aims included assessing changes in hepatic MRE-shear stiffness, per-segment MRI-PDFF changes, serum aminotransferases activity, and anthropometrics.
Method: Adolescents 12-19 years with biopsy-proven paediatric NASH undergoing standard-of-care treatment were enrolled. Baseline and week-12 assessments of anthropometrics, AST, ALT, GGT, MRI-PDFF, and MRE-stiffness were obtained.
Results: Fifteen adolescents with NASH were included (mean age 15.7 [SD 2.9] years, mean BMI 34.6 [SD 4.6] kg/m^2). Hepatic MRI-PDFF was stable over 12 weeks (mean *absolute* change −0.8%, p = 0.24) (Figure 1). The correlation between individual baseline and week-12 values of MRI-PDFF was high (ρ = 0.97, 95% CI 0.90-0.99). Additionally, the MRE-stiffness was also stable (mean percentage change 2.7%, p = 0.44) with a moderate correlation between individual baseline and week 12 values (ρ = 0.50; 95% CI: −0.11, 0.84). The changes in weight (+0.97 kg) and BMI (+0.14 kg/m^2) were not significant (p = 0.45). Similarly, the changes in aminotransferases were not significant (ALT −18 U/L p = 0.19, AST −8 U/L p = 0.23, GGT −4 U/L p = 0.45).
Conclusion: In adolescents with NASH, fluctuations in hepatic MRI-PDFF and MRE-stiffness over 12 weeks of standard-of-care were small. These data on the natural fluctuation in quantitative imaging biomarkers can serve as a reference for interventional trials in paediatric NASH and inform the interpretation and planning of clinical trials.

LBP-15
Urinary Liver Fatty-Acid-Binding Protein (uL-FABP) improves accuracy of MELD score to predict short-term mortality in patients with decompensated cirrhosis
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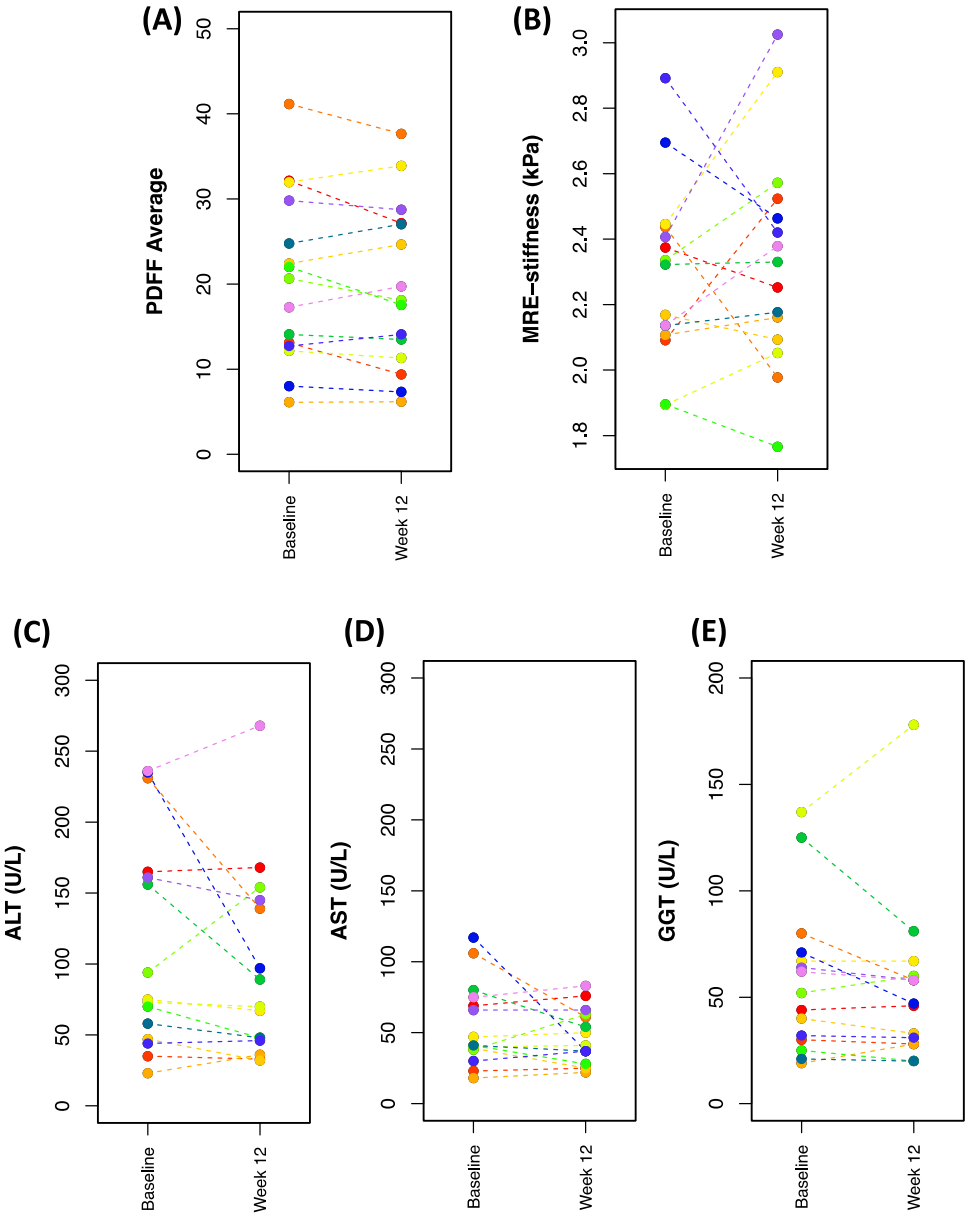

Figure: (abstract: LBP-14)

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Background and aims: Model for end-stage liver disease (MELD) is the best scoring system currently available to predict short-term prognosis in cirrhosis. However, it is known that MELD score has limitations and different attempts have been made to improve its prognostic accuracy with limited results. L-FABP is a small protein is highly expressed in the liver after tissue injury but is also expressed in other organs such as the kidney. We hypothesized that L-FABP could act as prognostic biomarker in patients with decompensated cirrhosis by reflecting multiorgan dysfunction. The aim was to investigate the usefulness of urinary L-FABP as a prognostic biomarker in patients with decompensated cirrhosis, and compare its accuracy to that of other biomarkers and MELD score.

Method: uL-FABP, urinary neutrophil gelatinase-associated lipocalin (uNGAL) and urinary kidney injury molecule 1 (uKIM1) were measured at the time of admission in a prospective cohort of patients with cirrhosis admitted to the hospital for complications of the disease. Clinical outcomes and survival were assessed over a 3-month period.

Results: a total of 310 patients were included (mean MELD score 20 ± 9). At the end of the 3-month follow-up, 207 (67%) patients were alive, 85 (27%) patients had died and 17 (5%) had been transplanted. Patients who died had significantly higher baseline levels of uL-FABP, uNGAL and uKIM1 compared to those who were alive: uL-FABP (median[IQR]) 52[24-107] vs 22[13-56]ug/gr creat, $p < 0.001$; uNGAL 84[37-265] vs 38[17-100]ug/gr creat, $p < 0.001$; and uKIM1 4.4[2.9-8.7] vs 3.6[2.0-6.6]ug/gr creat $p = 0.023$. Among all biomarkers, uL-FABP was the only one independently associated to 3-month mortality in the multivariate analysis, together with MELD score, serum sodium, leukocyte count and presence of hepatic encephalopathy. Predictive accuracy of uL-FABP was independent of the

presence of AKI or acute-on-chronic liver failure (ACLF) at admission. Interestingly, when patients were stratified according to median MELD score and median uL-FABP levels of the whole cohort, results showed that for the same MELD score value, those with high uL-FABP had significantly lower probability of 3-month survival compared to those with low uL-FABP levels (41% if MELD ≥ 20 and uL-FABp > 30 vs 62% if MELD ≥ 20 and uL-FABP < 30 vs; p < 0.001).
Conclusion: urinary L-FABP is an excellent biomarker to predict prognosis in patients with decompensated cirrhosis. Urinary L-FABP levels improve prognostic accuracy of MELD score to predict short-term mortality.

LBP-16
Phase II trial to evaluate immunogenicity and safety of a new adjuvanted HBAI20 Hepatitis B vaccine in non-responders: BE RESPONDER.
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Background and aims: Approximately 5-15% of the general adult population respond inadequately to the licensed recombinant hepatitis B vaccines. A new hepatitis B vaccine (HBAI20) was formulated wherein the adjuvant AI20, containing 20 µg recombinant human IL-2 attached to 20 µg aluminum hydroxide, was added to HBVaxPro©-10 µg.
Method: In a double-blind randomized controlled phase II trial, we compared the immunogenicity and safety of the new adjuvanted HBAI20 vaccine with that of the licensed recombinant HBVaxPro©-10 µg vaccine. Both vaccines were given in a 0, 1, 2 months schedule in 18-59 years old non-responders (hepatitis B surface antibody (anti-HBs) level <10 mIU/ml after three or more hepatitis B vaccinations).
Results: Out of 1, 076 persons invited, 133 adults were enrolled and randomized (3:1 ratio) to receive either HBAI20 or HBVaxPro©-10 µg vaccine. Two individuals withdrew informed consent and another 15 individuals were excluded from the per-protocol analysis. Eight weeks following the last vaccination, the seroprotection rate (≥1 0 mIU/ml) in the HBAI20 group (92.0%) was substantially higher than in the HBVaxPro©-10 µg group (79.3%), p = .087. In a sub-analysis for which the study was not powered, we observed a seroprotection rate of 83.1% and 68.8% among subjects 40 years or older, respectively (p = .318), and among individuals with more than one hepatitis B vaccination schedule this was 81.8% and 66.7%, respectively (p = .236). Rates of any adverse events were low and similar between the trial arms. There were two serious adverse events, both unrelated to the study vaccine.
Conclusion: In this group of hepatitis B vaccine non-responders, the HBAI20 vaccine demonstrated a higher seroprotection rate compared to the licensed recombinant HBVaxPro©-10 µg vaccine. The safety profile of HBAI20 vaccine was comparable to that of the licensed recombinant vaccine.

LBP-17
Robust Mucosal-associated invariant T (MAIT) cell activation in response to interactions with primary human liver cell subsets
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Background and aims: Mucosal-associated invariant T (MAIT) cells represent the most abundant T cell type in human liver. MAIT cells respond to bacterial metabolites presented by MHC-like molecule MR1 on antigen (Ag)-presenting cells (APCs). A metabolic study in mice suggested that the MAIT cell Ag precursor 5-amino-6-D-ribitylaminouracil (5-A-RU) is able to cross the intestinal barrier to reach both the circulation and the liver. In mouse models, activated liver MAIT cells were described as profibrogenic and, similarly, human MAIT cells from patients with liver cirrhosis show a pro-fibrogenic phenotype. It remains poorly understood which cells in the liver are involved in MAIT cell activation, and, consequently, how their profibrogenic function could be prevented.
Methods: We assessed Ag-presentation capacities of primary human liver cell subsets to human blood- and liver-derived MAIT cells. Responses were evaluated by defining activation markers and cytokine expression profiles of MAIT cells upon stimulation with synthetic Ag 5- (2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) or bacterial lysate from *E. coli*. To assess MR1-dependence and reversibility of the activation process, APCs were pretreated with MR1-blocking antibodies, and non-stimulatory MR1 ligands. To define tissue localization of MAIT cells, immunofluorescence staining was performed on cryopreserved human liver biopsies derived from healthy and diseased livers.
Results: Both parenchymal and non-parenchymal cells, including hepatocytes, hepatic myofibroblasts, sinusoidal endothelial cells and billary epithelial cells (BECs) were found to have the capacity to present Ag to MAIT cells. Presentation occurred in response to bacterial lysate and pure synthetic Ag. Importantly, human polyclonal liver-derived MAIT cells produced large amounts of IL-17, a cytokine with prominent profibrotic properties. MAIT cell activation was MR1-dependent and prevented by the presence of non-activating MR1 ligand 6-Formylpterin and acetylsalicylic acid derivative 5-formylsalicylic acid. The presentation capacities differed markedly among the investigated liver cell types, with BECs being the least efficient liver-derived APCs. Liver cells exposed to Ag precursor 5-A-RU had the capacity to generate active Ag endogenously. MAIT cells localized in the immediate proximity of specific liver cell subtypes when analysed *in situ*.
Conclusions: Our results provide new insights to the understanding of intrahepatic MAIT cell activation. By using both primary liver-derived APCs and liver-derived MAIT cells, and applying naturally occurring antigens as opposed to artificial T cell stimuli, we show the large *in vivo* interaction potential of this abundant intrahepatic cell type. Occupancy of MR1 with non-stimulatory ligands creates a therapeutic opportunity to prevent pro-fibrogenic properties of MAIT cells.

LBP-18
Effect of Obeticholic Acid on Liver Function in Patients with Fibrosis due to NASH
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Background and aims: Obeticholic acid (OCA), a potent and selective FXR agonist, has been shown to improve fibrosis in NASH patients in a pivotal Phase 3 study (REGENERATE). As part of the OCA development program, a study in patients (pts) with NASH evaluated the effect of OCA on liver function improvement using the HepQuant methodology. HepQuant measures the hepatic extraction of exogenously administered labeled cholate as a marker of liver function, which has been correlated to clinical outcomes using a Disease Severity Index

(DSI). Based on prior studies of the relationship of DSI to probability of varices, a 2-point decrease in DSI is considered clinically meaningful. The aim of this analysis was to measure liver function in NASH patients with fibrosis after 3 months of OCA treatment.

Method: 51 pts were randomized 1:2:2 to placebo, OCA 10 mg, or OCA 25 mg QD for 85 days. Labeled cholate was administered intravenously and orally on Day −1 (baseline), 8, and 85 for HepQuant assessment.

Results: 50 pts, primarily white with median age 55yrs and BMI 35 kg/m2 completed Day 85. 45 pts had a DSI at baseline (27% F1, 62% F2/3, 11% F4); 43 pts had both a baseline and Day 85 DSI assessment. The mean baseline DSI±SD (n) was for F1 16.4 ± 3.8 (n = 12), F2/3 19.0 ± 4.6 (n = 28), and F4 22.1 ± 6.7 (n = 5). The mean baseline DSI score for all pts (F1-F4) was consistent with an increased likelihood for varices based on previous results in NASH and HCV pts1. OCA treatment improved hepatic function as evidenced by the number of responders (>2-point decrease) and median decrease in DSI at Day 85 (Table). No unexpected safety findings were observed.

	Placebo	OCA 10 mg	OCA 25 mg
		F2/F3	
Responders	0% (0/5)	36% (4/11)	73% (8/11)
ΔDSI (Median)	-0.65	0.78	-3.81
		All (F1-F4)	
Responders	10% (1/10)	44% (7/16)	59% (10/17)
ΔDSI (Median)	-1.07	-1.17	-2.78

Conclusion: This is the first demonstration of OCA eliciting a dose-dependent clinically significant improvement in liver function in NASH. These results are consistent with the dose-dependent reversal of fibrosis observed in REGENERATE and further support the efficacy of OCA treatment in pts with fibrosis due to NASH.

Reference

1. Helmke S, *et al.* Presented at NASH Biomarkers. 2017 (Poster #15)

LBP-19

NGM282 Promotes HDL Biogenesis and Transhepatic Cholesterol Efflux to Prevent Atherosclerosis in Mice

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Background and aims: FGF19, an endocrine hormone produced in the gut, acts in the liver to control bile acid synthesis. NGM282, an engineered FGF19 analogue, reduces liver fat, liver injury, inflammation and fibrosis in patients with non-alcoholic steatohepatitis. However, NGM282 increases cholesterol levels, and the molecular mechanisms that integrate the FGF19 signaling with cholesterol metabolic pathways are incompletely understood. Here we investigate these mechanisms using a combination of pharmacological, bioinformatics, metabolomics and biochemical approaches.

Method: *db/db*, *Abca1*$^{fl/fl}$*Abcg1*$^{fl/fl}$, *Apoe*$^{-/-}$ and *Fgfr4*$^{-/-}$ mice received an intravenous injection of adeno-associated virus carrying FGF19, NGM282, caMEK1, caSTAT3 or GFP. Tissues were collected for transcriptome profiling, metabolomics and histological analysis. Serum levels of cholesterol, HDL-C and LDL-C were measured on a clinical analyzer. *Apoe*$^{-/-}$ mice were placed on a high-fat, high-cholesterol Western diet to induce atherosclerosis for *en face* analysis.

Results: Administration of FGF19 or NGM282 resulted in elevations in total cholesterol, HDL-C and LDL-C in *db/db* mice. Transcriptome profiling and pathway analysis revealed that FGF19 and NGM282 selectively modulate LXR signaling without causing steatosis. Metabolomics analysis uncovered an increase in intrahepatic hydroxysterols, natural ligands for LXR. FGF19 and NGM282 promote HDL biogenesis through the induction of *Abca1* and *Apoa1*, and cholesterol efflux from the liver by upregulating *Abcg5, Abcg8* and *Scarb1,* all LXR target genes. FGF19- or NGM282-associated cholesterol increases were blunted in mice deficient in ABCA1 or FGFR4. A constitutively active MEK1, but not a constitutively active STAT3, mimics the effect of FGF19 and NGM282 on cholesterol change. Furthermore, in dyslipidemic *Apoe*$^{-/-}$ mice fed a Western diet, treatment with NGM282 significantly reduced atherosclerotic lesion area in aortas (Figure 1).

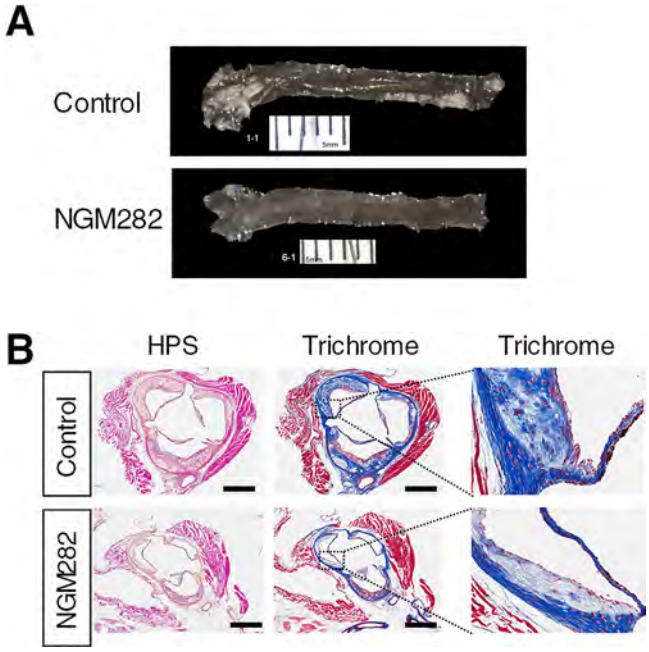

Figure 1: NGM282 protects against atherosclerosis in Apoe−/− mice.

Conclusion: The endocrine hormone FGF19 and its analogue NGM282 have a hitherto unsuspected intrinsic role in promoting transhepatic cholesterol efflux and HDL biogenesis through selectively activating LXR signaling, while ameliorating steatosis and atherosclerosis. Given that LXR agonists produce substantial increase in LDL-C in humans, the selective modulation of LXR by NGM282 may provide additional mechanism to the observed cholesterol increases in humans.

LBP-20

VK2809, a Novel Liver-Directed Thyroid Receptor Beta Agonist, Significantly Reduces Liver Fat with Both Low and High Doses in Patients with Non-Alcoholic Fatty Liver Disease: A Phase 2 Randomized, Placebo-Controlled Trial

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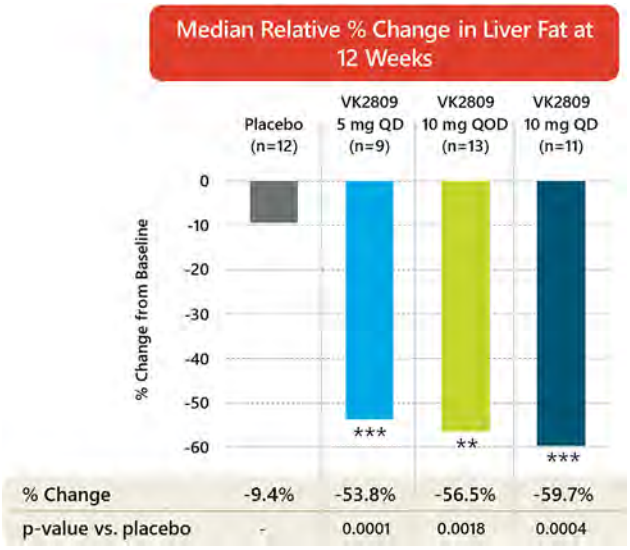
Background and aims: Thyroid hormone is an important regulator of lipid metabolism, particularly acting via the beta isoform of the hepatic T3 receptor. VK2809 is a small molecule prodrug of a potent thyroid beta receptor agonist. VK2809 is selectively cleaved in hepatic tissue by the action of cytochrome P450 isozyme 3A4, to release a pharmacologically active metabolite. We report herein new results

from a 12-week study of low-dose (5 mg) VK2809 in patients with NAFLD. The aim of this study was to examine the safety, tolerability and efficacy of oral VK2809 at three different doses (low-dose, 5 mg; high-dose, 10 mg; or 10 mg QOD) versus placebo in reducing liver fat content and LDL-C over a 12-week period in patients with NAFLD.
Method: This was a multi-center, randomized, double-blind, placebo-controlled, Phase 2a 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.
Results: Patients receiving VK2809 experienced statistically significant reductions in liver fat content by MRI-PDFF, relative to placebo. Mean absolute change from baseline in liver fat content was 8.7% for VK2809 5 mg QD (p = 0.0014), 8.9% for VK2809 10 mg QOD (p = 0.013), and 10.6% for VK2809 10 mg QD (p = 0.0030), vs. 1.1% for placebo. Median relative change from baseline in liver fat content was 53.8% for VK2809 5 mg QD (p = 0.0001), 56.5% for VK2809 10 mg QOD (p = 0.0018), and 59.7% for VK2809 10 mg QD (p = 0.0004), vs. 9.4% for placebo. The proportion of patients who had ≥3 0% reduction in MRI-PDFF was 100% for VK2809 5 mg QD (p = 0.0002), 76.9% for VK2809 10 mg QOD (p = 0.0048) and 90.9% for VK2809 10 mg QD (p = 0.0006), vs. 16.7% of placebo patients (see graphic). Among all patients receiving VK2809 therapy, 70% demonstrated a ≥5 0% reduction in MRI-PDFF (p = 0.014). VK2809 was shown to be well-tolerated in this study; no SAEs were reported in any cohort.



Conclusion: These novel data demonstrate that a 12-week treatment with low-dose VK2809 produced significant and robust improvements in liver fat content in patients with NAFLD that were similar to the high dose (10 mg). These data provide strong rationale for further development of VK2809 as well potential use of low-dose liver-targeted thyroid receptor beta agonist therapy as a treatment for patients with biopsy-proven NASH with fibrosis.

LBP-21

Effect of NGM282, an FGF19 Analogue, on Pruritus in Patients with Primary Sclerosing Cholangitis: Analysis of a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Background and aims: PSC is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical interventions. Approximately 50% of patients experience pruritus, a symptom that can reduce quality of life. NGM282 is a non-tumorigenic FGF19 analogue in development for chronic liver diseases in which bile acid dysregulation is involved in disease pathogenesis. We report here the effect of NGM282 on pruritus after 12 weeks of treatment.
Method: Sixty-two patients, with PSC by EASL criteria and an elevated ALp > 1.5xULN at Baseline (BL), were randomized to NGM282 1 mg, 3 mg or placebo (PBO) as a daily SC injection for 12 weeks. 5D-itch pruritus questionnaires (scores range from 5 to 25) were collected, and patients also recorded pruritus intensity on a numeric rating scale (NRS) ranging from 0 to 10. Higher numbers indicate more severe itch on both scales.
Results: At W12, changes from BL were +0.60, +0.30 and – 1.52 for 5D-itch score, +0.36, +0.01 and – 0.32 for pruritus NRS, in the PBO, 1 mg and 3 mg groups, respectively (Table 1). Pruritus was reported as a treatment emergent adverse event in 10% (PBO), 5% (1 mg) and 5% (3 mg) of patients. There were no discontinuations due to pruritus. Changes from BL to W12 in pruritus NRS correlate with changes in pruritus degree (r = 0.43, p < 0.01), direction (r = 0.43, p < 0.01), disability (r = 0.30, p < 0.05) and distribution (r = 0.33, p < 0.05), but not pruritus duration. Changes from BL to W12 in PIIINP correlate with changes in pruritus distribution (r = 0.42, p < 0.001), degree (r = 0.26, p < 0.05) and direction (r = 0.27, p < 0.05).

Table 1: Pruritus-Related PRO Measures

	PBO **(n = 20)**	NGM282 1mg **(n = 21)**	NGM282 3mg **(n = 21)**
5D-Itch Score (BL)	10.70 (4.60)	11.14 (3.79)	9.50 (3.87)
Δ 5D-Itch Score at W12, LS mean	**0.60**	**0.30**	**−1.52**
P value (W12 vs BL)	0.45	0.70	0.06
***NGM282 vs Placebo,** difference between means (95% CI)*		**−0.50 (−3.17 to 2.17)**	**−1.60 (−4.30 to 1.10)**
P value (NGM282 vs Placebo)		0.78	0.06
Pruritus NRS (BL)	1.50 (1.79)	2.29 (2.35)	0.90 (1.25)
Δ Pruritus NRS at W12, LS mean	**0.36**	**0.01**	**−0.32**
P value (W12 vs BL)	0.38	0.98	0.48
***NGM282 vs Placebo,** difference between means (95% CI)*		**−0.47 (−1.93 to 0.99)**	**−0.52 (−1.96 to 0.92)**
P value (NGM282 vs Placebo)		0.60	0.56

Conclusion: In this population of patients with PSC, treatment with NGM282 was not associated with drug-induced pruritus, but was associated with a trend of improvement in pruritus. These clinically relevant, patient-reported outcome measures should be evaluated in future trials.

LBP-22

Outcome of 119 cirrhotic patients with splanchnic thrombosis: a single center real-life experience

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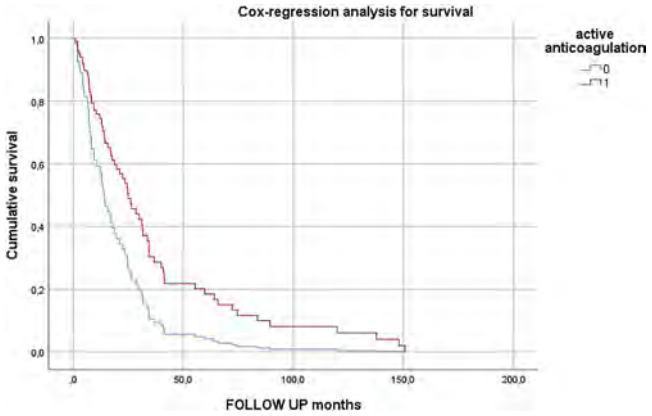
Background and aims: Splanchnic venous thrombosis (SVT) frequently affects patients with liver cirrhosis. Although being crucial for SVT, the benefit/risk ratio of anticoagulant treatment remains uncertain. Aims of this study were to evaluate the safety and efficacy of anticoagulant therapy (AT) in cirrhotic ST and to investigate outcomes.
Method: A cohort of 119 cirrhotic patients with ST, incidentally diagnosed during surveillance, were prospectively followed from 2000 to 2018 in our Hospital. Demographic, risk factors, clinical, laboratory, therapeutic and outcome data were collected. In patients with no active bleeding, a patient-tailored management with low-molecular-weight heparin (LMWH) or antivitamin-K (AVK) was started as soon as possible, associated to beta-blockers or endoscopic prophylactic treatments of variceal hemorrhages. The outcomes evaluated were major bleeding events (MB), recurrent thrombosis, recanalization and survival.
Results: Portal vein was the most common site of thrombosis (55%). Ninety-one patients (77%) had esophageal varices. Median Child Pugh Score was 8. Ninety-two patients (89%) were treated with AT: 69% with intermediate or full dose of LMWH and 23% with AVK. Twenty patients (22%) suspended AT due to clinical complications or decreased platelet counts. The median duration of therapy was 9 months, the median follow-up was 15 months. During AT, the incidence rates were 2.5 per 100 patient-years for major bleeding and 8.0 for all-cause mortality. Follow-up imaging, available for 91 patients, showed complete recanalization in 40 patients (44%), partial recanalization in 15 patients (16%), stable thrombosis in 27 patients (30%), progression or recurrent thrombosis in 9 patients (10%). Child Pugh score was improved in 27 patients (38%), stable in 31 patients (43%) and worsened in 14 patients (19%). At multivariate analysis, recanalization emerged as variable independently associated to Child Pugh improvement (Odds ratio 4.25; 1.3-14 95% CI; p = 0.02) while long-term AT resulted independently associated with a higher overall survival according to Cox-Regression analysis, adjusted for albumin levels, Child-Pugh score, HCC and recanalization (Odds ratio 1.88; 1.02-3.45, 95% CI; p = 0, 04).



Conclusion: AT appears to be safe and effective in our cohort of patients with cirrhosis affected by ST. Recanalization of ST is associated with improvement of liver function parameters. Moreover, long-term AT is correlated with higher overall survival.

LBP-23

Prognostic Impact of Peritumoral Neutrophil Infiltration on Hepatocellular Carcinoma Recurrence Following Liver Transplantation

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Background and aims: Peritumoral neutrophil (PMN) infiltration has been associated with poor clinical outcomes in various tumors; however, its role in hepatocellular carcinoma (HCC) remains understudied. Moreover, novel methods to analyze tumor microenvironments are needed in HCC, an immune responsive tumor. We sought to use quantitative multiplex immunofluorescence (qmIF) in HCC to better study the immune milieu and detect cellular predictors of clinical outcomes.
Method: Patients without hepatitis viral infection and with available clinical follow-up from a single center cohort of 634 consecutive patients who underwent liver transplantation (LT) for HCC between 1998 and 2018 were included in a pilot analysis. The expression of MPO (PMNs), CD3 (T cells), CD8 (CTL), CD68 (Macrophages), Hep-Par1 (Hepatocytes) and HLA-DR was assessed on each tissue sample using qmIF. Tumor sections were pre-selected by a pathologist and visualized using Vectra (Akoya). Using an artificial intelligence-capable software (Inform, Akoya) and RStudio, cell densities were calculated by dividing over the total number of nuclear cells as defined by DAPI staining (Nuclei).
Results: A preliminary cohort of 10 patient samples was stained and tissue integrity allowed for data to be interpreted in 8 patients, 3 of whom recurred at a median of 3.5 years while the other 5 remained recurrence-free at a median of 12 years post-LT. We found that MPO+ PMN densities are significantly higher in patients who suffered from post-LT HCC recurrence as compared to those who remain recurrence-free, and that this difference is primarily driven by PMNs located within the peritumoral stroma. (Median [IQR] 2.9 [2.1–3.1] vs 0.9 [0.7–1.9], p = 0.037). PMN infiltration within the tumor was not associated with outcome, densities were equal in tumors of patients who had recurrence and those who did not (Median [IQR] 1 [0.4–1.7] vs 1.1 [0.5–1.4], p = 0.882).
Conclusion: Higher densities of peritumoral PMNs are associated with post-LT HCC recurrence in this preliminary cohort of 8 patients. This work, the first reported application of qmIF in HCC, is ongoing and will be validated within a larger cohort of patients. Updated results will be presented at the conference.

LBP-24

Safety, tolerability and efficacy of volixibat, an apical sodium-dependent bile acid transporter inhibitor, in adults with non-alcoholic steatohepatitis: 24-week interim analysis results from a phase 2 study

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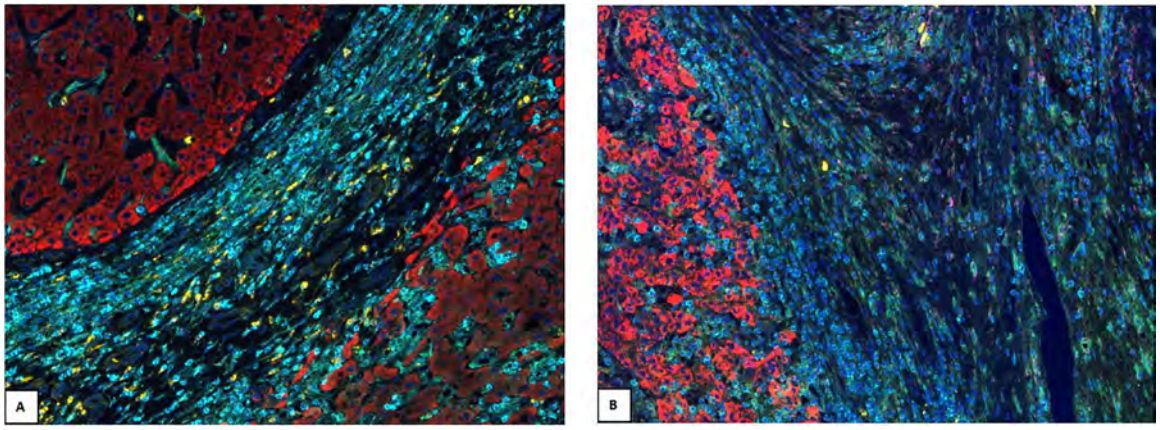

Figure: (abstract: LBP-23): Quantitative multiplex immunofluorescence images of HCC showing infiltration of PMNs in tumor and peritumoral stroma. A) High and B) Low PMN infiltration. HCC slides were stained for qmIF with Hep-Par1 (Red; Hepatocyte); MPO (Yellow; PMN); CD3 (Cyan); CD8 (Magenta); DAPI (Blue; Nucleus); CD68 (Green; Macrophage) and HLA-DR (Orange).

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Background and aims: Apical sodium-dependent bile acid transporter inhibitors (ASBTi) reduce serum low-density lipoprotein cholesterol, improve insulin resistance, change bile acid pool and decrease NAFLD activity score (NAS) in murine models of fatty liver disease. This study aimed to assess the safety, tolerability and efficacy of volixibat, a selective ASBTi, in adults with non-alcoholic steatohepatitis (NASH).
Method: In this double-blind, placebo-controlled, dose-finding study across 68 sites in the USA, UK and Canada, adults with NASH were randomized (1:1:1:1; stratified by presence of type 2 diabetes mellitus [T2DM] and baseline NAS) to treatment with once-daily volixibat (5 mg, 10 mg or 20 mg) or placebo (PBO) for 48 weeks. Primary outcome measure was a 2-point reduction in NAS without worsening in fibrosis from baseline to end-of-treatment. Analyses were done using intention-to-treat. An interim analysis (IA), based on absolute change in steatosis on MRI proton density fat fraction (PDFF) and percentage change of ALT, was planned after 80 participants received 24 weeks' treatment. ClinicalTrials.gov identifier NCT02787304.
Results: Between 24 October 2016 and 5 June 2018, 197 subjects were randomized to volixibat or PBO. Mean (SD) age of participants was 53.1 ± 12.8 years, 60.2% were women, 89.3% were Caucasian, mean BMI was 34.5 ± 6.3 kg/m^2 and 43.4% had T2DM. Mean baseline NAS was 5.2 ± 1.1 and MRI-PDFF was 18.5 ± 8.2%. At the IA, mean absolute change (±SEM) from baseline to week 24 in MRI-PDFF was not different for any volixibat dose (5 mg – 0.4 ± 1.3%, 10 mg – 0.2 ± 1.8% or 20 mg – 1.3 ± 1.1%) vs PBO (+0.2 ± 1.1%). Similarly, percentage changes in serum ALT were not different for any dose of volixibat (5 mg + 17.1 ± 10.6%, 10 mg + 14.1 ± 10.1% or 20 mg + 2.4 ± 9.2%) vs PBO (0.0 ± 5.6%). Subgroup analysis by sex, presence of T2DM, NAS and stage of fibrosis did not reveal any significant improvement with any volixibat dose. Review of 43 participants with paired liver biopsies did not reveal numerical differences in instances of a 2-point reduction in NAS or NASH resolution (both without worsening fibrosis) between PBO and volixibat dose groups. The most common adverse event was diarrhoea (volixibat 73.5%; placebo 20.4%). There were no deaths or serious adverse events related to volixibat.
Conclusion: Volixibat treatment for 24 weeks did not improve MRI-PDFF, serum ALT or histology in adults with NASH. (Funding: Shire, a Takeda company)

LBP-25

a phase 1 clinical trial of therapeutic vaccine t101 in chronic hepatitis b (chb) patients: a randomized, double-blind, placebo-controlled, single and multiple injections, dose escalation study

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Background and aims: Hepatitis B virus (HBV) infection is a worldwide health problem. It has been proved that the persistence of HBV is associated with the failure to stimulate an efficient HBV-specific immune response. T101, the Chinese counterpart of TG1050, is a replication-defective adenovirus serotype 5 (Ad5) expressing multiple HBV-specific antigens (polymerase, core and envelope) and it is used as a therapeutic vaccine for CHB patients. The application of T101 aims at inducing a broad HBV-specific T cell immune response and ultimately eliminating HBV infection.
Method: A total of 36 CHB patients with negative HBV DNA after NUC therapy were enrolled into the single dose (SD) cohorts and multiple dose (MD) cohorts. Patients were randomized to receive single subcutaneous injection of T101 (1.0E+9VP, 1.0E+10VP, 1.0E+11VP) or placebo at the ratio of 3:1, and 4 patients were enrolled for each dose in the SD cohort. For the MD cohort, patients were randomized to receive three weekly subcutaneous injections of T101 (1.0E+10VP, 1.0E +11VP) or placebo at the ratio of 3:1 and 12 patients were enrolled each dose. The aim of the trial is to evaluate the safety, immunogenicity and preliminary antiviral activity (the decrease of HBsAg level). T-cell responses were monitored by INFγ ELISPOT on PBMCs and the levels of anti-Ad5 neutralizing antibodies (NAd5) were also detected.
Results: T101 was well tolerated both in SD and MD cohorts. All of the adverse events were grade 1 or 2. No ALT flare, no SAE and no signs of immune-related AEs were observed. The most common AEs are

Flu-like symptoms and injection site reaction (induration, pain and pruritus), and most of them disappeared in 1~3 days after the administration. The administration of the T101 can rapidly induce HBV-specific (POL, Core or ENV) T cell immune response as early as 2 weeks after vaccination in CHB patients and last at least 12 weeks after vaccination. T101 can stimulate the body to produce NAD5 and reach peak concentration at 4th week after administration, and the titer decreased at the 12th weeks after administration. The preliminary antiviral effect was also observed. The HBsAg level had an average decrease about 22% at 1.0E+10VP dose group at the 4th weeks after administration and the maximal decrease reached 1.14 Log.

Conclusion: Subcutaneous injections of T101 are safe and tolerated in CHB patients. T101 can break the immune tolerance and stimulate HBV-specific (POL, Core or ENV) T cell immune response in CHB patients, at the same time the HBsAg level decreased. Data support future trials to explore the antiviral activity and safety of T101 in more CHB patients.

LBP-26

Magnetically controlled capsule endoscopy as a non-invasive tool for risk stratification of gastroesophageal varices in compensated cirrhosis (CHESS1801): A prospective multicenter study

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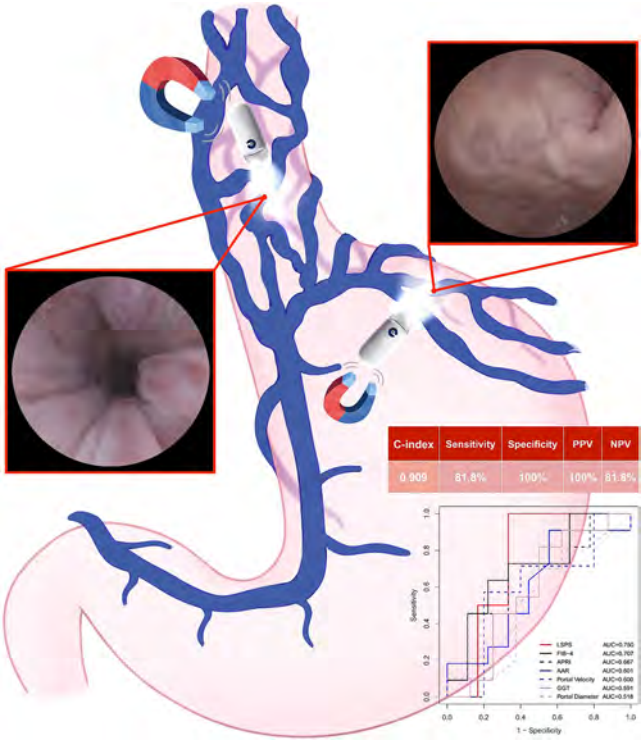
Background and aims: Variceal hemorrhage is a lethal complication in liver cirrhosis. The assessment of at-risk gastroesophageal varices (GOV) is of great therapeutic implications that once varices at risk for rupture are found, the primary prophylaxis of variceal hemorrhage is recommended. Therefore, an accurate non-invasive tool is needed to improve the risk stratification of GOV. The study aims to evaluate the performance of magnetically controlled capsule endoscopy (MCCE) for at-risk GOV in compensated cirrhosis.

Method: The prospective multicentre study (NCT03749954) was performed after local institutional review board approvals. Written informed consents were obtained. We recruited 20 well-characterized participants with compensated cirrhosis from 6 independent centres between November 2018 and January 2019. All participants were scheduled to receive both non-invasive MCCE (Ankon) and conventional endoscopy for assessing at-risk GOV. High-risk varices were defined as medium-large varices (>5 mm) or small varices (≤5 mm) with red wale sign and/or nipple sign. A thin and hollow detachable string was attached on the MCCE so that the technicians could observe the esophagus by controlling the string. The capsule was released from the string once it entered the stomach and then manually controlled by the guidance magnet robot as previously reported. Experienced physicians who were blinded to MCCE results performed conventional endoscopy as reference standard on the same day of capsule ingestion. All MCCE frames were uploaded to the cloud MCCE reading platform and evaluated by at least two independently experienced capsule endoscopists who were blinded to the endoscopy results. Prior to and after completing the MCCE and conventional endoscopy, participants were requested to complete a questionnaire regarding their perceptions and satisfaction.

Results: For the risk stratification of GOV, the C-index, sensitivity, specificity, positive predictive value, and negative predictive value of MCCE were 0.909, 81.8%, 100%, 100%, and 81.8%, respectively. The overall agreement on management decisions between MCCE and endoscopy was substantial at 90.0% with kappa score of 0.800. The diagnostic performance of MCCE for at-risk GOV was statistically higher than other non-invasive models including LSPS (liver stiffness × spleen size/platelet count score), FIB-4, APRI, AAR, portal velocity, GGT and portal diameter with the area under the curves of 0.750, 0.707, 0.667, 0.601, 0.600, 0.591, and 0.518, respectively. The preprocedure perception and postprocedure satisfaction score of MCCE was significantly higher than that of conventional endoscopy without sedation (11.2 vs. 4.2, $p < 0.001$).



Conclusion: MCCE could be used as a non-invasive screening tool for risk stratification of GOV with better preprocedure perception and postprocedure satisfaction in compensated cirrhosis.

LBP-27

Preliminary analysis of SuperDOT-C: A cluster randomised controlled trial of pharmacy-led versus conventional treatment for HCV positive patients receiving daily opioid substitution therapy-The Tayside sites

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Background and aims: The elimination of Hepatitis C (HCV) requires greater access to testing and treatment for at-risk groups. People prescribed Opioid Substitution Therapy (OST) are at high risk of HCV infection. Community pharmacists see this group frequently to provide OST. We report the interim results from 34 of 55 pharmacies undertaking this cluster randomised trial of a pharmacy-led test and treat pathway where pharmacists completed the assessment for treatment on-site.

Method: 34 community pharmacies from Tayside, Scotland took part in a cluster randomised trial providing either conventional or pharmacy-led care. Patients were recruited to the study if they were HCV PCR positive by dried blood spot test. For conventional care, pharmacists referred participants to a local centre for assessment. In the pharmacy-led arm, patients underwent one set of conventional bloods, based on this and patient history pharmacists assessed participants for treatment with Direct Acting Anti-Virals (DAAs) using a standard protocol, drug prescribing was by pharmacist prescribers (pharmacy-led arm). The study used sofosbuvir/ledipasvir to treat genotype 1 HCV infection and daclatasvir/sofosbuvir to treat genotype 3 infection. Treatment was delivered as daily modified directly observed therapy (DOT) in a pharmacy. The primary trial outcome was sustained viral response 12 weeks (SVR12) after treatment completion. The study is now closed and in follow-up.

Results: 251 HCV positive participants were recruited from a total pool of 1393 OST recipients attending the pharmacies. (99 conventional, 152 pharmacy-led $p < 0.01$). No significant differences were detected for gender, age or Fib-4 assessment between the groups. More genotype 3 participants were detected in the pharmacy-led arm ($p < 0.01$). A total of 187 new DBST were taken (88 conventional, 99 pharmacy led $p < 0.5$). From recruited participants, 138 commenced treatment with DAAs (45 conventional, 93 pharmacy-led ($p < 0.01$) and 113 achieved SVR 12 (35 conventional, 78 pharmacy-led $p < 0.01$). In the conventional arm, 2 participants failed at SVR12, 2 withdrew voluntarily and 7 were lost-to follow-up. In the pharmacy-led arm 3 participants failed SVR12, 1 withdrew voluntarily, 4 were lost-to-follow-up, 2 died prior to SVR12 and 2 participants had a rejected SVR12 sample.

Conclusion: Preliminary analysis suggests that the pharmacy-led treatment pathway increased both HCV testing and initiation of, treatment. The offer of testing, assessment and treatment with DAAs in a pharmacy increased HCV treatment uptake in people on OST. The delivery of treatment within the familiar setting of the community pharmacy was central to the success of the model.

LBP-29

BIO89–100, a novel PEG-FGF21 analogue, is efficacious following weekly and every 2-week subcutaneous dosing in spontaneous diabetic cynomolgus monkeys

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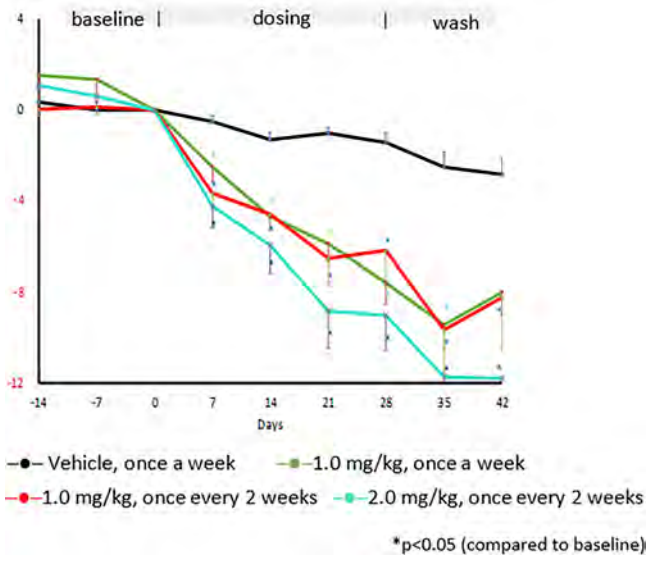
Background and aims: BIO89-100, a novel site-specific glycoPEGylated analogue of fibroblast growth factor 21 (FGF21), is under evaluation for the treatment of non-alcoholic steatohepatitis (NASH), a chronic fatty liver disease associated with obesity and type 2 diabetes mellitus. In previous study 89bio demonstrated efficacy of BIO89-100 (0, 0.1, 0.3 and 1 mg/kg) subcutaneous (sc) every week (qWk) in spontaneously diabetic cynomolgus monkeys. The objective of the current study was to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of BIO89-100 following qWk and every 2-week (q2Wk) sc administration of 1 mg/kg qWk and 1 or 2 mg/kg q2Wk in the same monkey model.

Method: Spontaneously diabetic cynomolgus monkeys (mean age 17 years, mean body weight 8.4 kg) were administered BIO89-100 sc at doses of 0, 1 mg/kg qWk, 1 mg/kg q2Wk or 2 mg/kg q2Wk over a 4-week period. Blood samples were collected for PK analysis on the first and last days of dosing. PD profiles were determined for each group during the pretreatment and treatment periods, and for 2 weeks following the last dose. PD parameters included body weight, food intake, clinical chemistry (triglycerides, total cholesterol, high-density-lipoprotein, low-density lipoprotein, alanine aminotransferase, glucose), serum insulin, HbA1c, oral glucose tolerance test (OGTT) and adiponectin.

Results: Half-life was approximately 50 hrs. The exposure profile of the qWk dose was similar to the q2Wk curve, except for a higher trough levels on Day 14 and Day 28 than with the qWk dose. Exposure to BIO89-100 (AUC and C_{max}) increased approximately in proportion to the increase in dose from 1 mg/kg q2Wk to 2 mg/kg q2Wk. Statistically significant reductions were observed in body weight (Figure 1), food intake, glucose, insulin, HbA1c, and serum lipids, along with increased adiponectin levels and improvement in oral glucose test results in all BIO89-100-treated groups vs. the vehicle group. The magnitude of the different effects varied somewhat between doses; however, the results were generally comparable among the dosing groups.

Figure1 - Body Weight Change (%)



Conclusion: The PK and PD profiles following qWk and q2Wk sc administration of BIO89-100 to diabetic cynomolgus monkeys demonstrate potential utility of this long-acting FGF21 analogue for patients with NASH. Clinical studies are underway to confirm the prolonged half-life and PD properties which may show potential utility of qWk and/or q2Wk dosing.

LBP-30

Changes in Serum Bile Acids Correlate with 7alpha-Hydroxy-4-Cholesten-One and Fibrogenesis Biomarker Pro-C3 with NGM282 Therapy in Patients with Non-alcoholic Steatohepatitis

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Background and aims: The presence and severity of NASH is associated with elevated circulating levels of bile acids (BA). NGM282, a non-tumorigenic FGF19 analogue, significantly reduced 7alpha-hydroxy-4-cholesten-3-one (C4, a marker of BA synthesis), ameliorated steatosis and improved hepatic inflammation and fibrosis in patients with NASH. To identify potential biomarkers of NGM282 therapy in NASH, we sought to evaluate the correlation of individual BA species with C4 and Pro-C3 (a marker of fibrogenesis) using pooled data from phase 2 trials.

Method: 157 subjects received NGM282 0.3 mg, 1 mg, 3 mg, 6 mg or placebo daily for 12 weeks. 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 by MRI-PDFF ≥8 %. Serum levels of C4 and BA species were determined by mass spectrometry (Mayo Clinic). Serum Pro-C3 was measured by an ELISA method (Nordic Bioscience). Correlation coefficients were calculated using Spearman's method.

Results: At W12, serum levels of C4 were significantly reduced in NGM282-treated patients (−51%, −77%, −93%, −79% and +43% from baseline in the 0.3 mg, 1 mg, 3 mg, 6 mg and the placebo groups, respectively). Individual BA, and those previously associated with histological features of NASH in particular, were decreased by NGM282 treatment. Ratios of primary to secondary BA were increased with NGM282 therapy. Reductions from baseline in both C4 and Pro-C3 were strongly associated with reductions in glyco-conjugated as well as unconjugated BA, but less strongly associated with tauro-conjugated BA (Table 1).

Table 1: Correlation of %Change in Individual BA with %Change in C4 and Pro-C3 at W12

	Δ C4%		Δ Pro-C3%	
	r	P	*r*	P
Conjugated primary BA				
Δ GCA%	0.48	<0.0001	0.34	<0.0001
Δ TCA%	0.08	0.29	0.18	0.020
Δ GCDCA%	0.34	<0.0001	0.31	<0.0001
Δ TCDCA%	−0.13	0.10	0.12	0.13
Conjugated secondary BA				
Δ GDCA%	0.38	<0.0001	0.38	<0.0001
Δ TDCA%	0.12	0.15	0.30	0.0001
Unconjugated primary BA				
Δ CA%	0.36	<0.0001	0.29	0.0002
Δ CDCA%	0.41	<0.0001	0.24	0.0025
Unconjugated secondary BA				
Δ DCA%	0.48	<0.0001	0.42	<0.0001
Total BA				
Δ TBA%	0.41	<0.0001	0.39	<0.0001

Conclusion: Changes in circulating levels of BA highly correlated with changes in Pro-C3 in NASH patients treated with NGM282, consistent the notion that BA may be a molecular trigger of hepatic fibrogenesis. NGM282 demonstrated significant and robust activity on lowering serum BA and Pro-C3, signifying potential disease-modifying activity in reversing fibrosis.

LBP-31

AXA1665, a novel composition of amino acids restores the dysregulated amino acid profile, lowers ammonia, and improves body composition and function in Child-Pugh class A and B subjects

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Background and aims: Sarcopenia has emerged as an independent risk factor for important clinical outcomes in cirrhosis, including hepatic encephalopathy (HE). It is closely linked to protein-malnutrition and perturbation in amino acid metabolism. A late evening snack (LES), considered part of routine care, appears to improve quality-of-life parameters in cirrhotic patients. While protein supplementation is advised, it carries the risk of worsening ammonia and HE in these patients. We designed a novel amino acid composition, AXA1665, to maximize anabolic activity and minimize ammoniagenesis to support liver health. We investigated its impact on safety, and markers of structure and function in a population of compensated, well-nourished Child-Pugh class (CPC) A and B subjects.

Method: Two amounts of AXA1665 were orally administered three times a day (TID) for 15d each to 16 CPC A-B subjects in a 2-period cross-over study. One group (n = 7) received only LES (control) in Period 1 followed by AXA1665 4.9 g TID (14.7 g/d) in Period 2; another group (n = 9) received AXA1665 14.7 g TID (44.1 g/d) in Period 1 followed by LES only (control) in Period 2. There was a 14d washout between periods. Subjects were domiciled in the research unit for the study duration; all meals/exercise were standardized. Plasma amino acids, albumin, body composition, and liver frailty index (LFI, composite marker of functional status as assessed by strength, speed, and balance) were measured on d1, d8, and d15 of each period. A standardized 35 g protein shake was provided 1 hour prior to the administration of AXA1665 or control on d1 and d15 of each period, and plasma ammonia levels were serially measured over the subsequent 5 hours to determine area under the curve ($AUC_{0\text{-}5h}$).

Results: AXA1665 was safe and well-tolerated at both doses. AXA1665 44.1 g/d, but not the 14.7 g/d or control groups, increased the fasted Fischer's ratio (FR; plasma branched chain to aromatic amino acid ratio) by 40.1% on both d8 and d15 vs. d1. Despite the provision of additional nitrogen via amino acids within AXA1665, the mean plasma ammonia $AUC_{0\text{-}5h}$ decreased by 12.8% and 24.5% on d15 compared to d1 in 44.1 g/d and 14.7 g/d AXA1665 groups, respectively. By contrast, the control group only had a 7.4% mean decrease in plasma ammonia $AUC_{0\text{-}5h}$ on d15 vs. d1. Plasma albumin trended upward in both AXA groups vs. control. By d15, the AXA1665 44.1 g/d, but not the 14.7 g/d or control groups, manifested a leaner phenotype (+2.8% mean increase in dry lean mass, -2.5% mean decrease in fat mass) with a 20.5% improvement in LFI vs. d1.

Conclusion: Within a 15d period, AXA1665 meaningfully improved the FR, lean mass and LFI, which are all surrogate markers of liver-related health and outcomes, while decreasing plasma ammonia. Future studies over longer durations are warranted to assess whether AXA1665 impacts cirrhosis-related sarcopenia and HE.

LBP-32

The Natural History of Ferroportin Disease-First Results of the International, Multicenter EASL non-HFE Registry

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Background and aims: Ferroportin (FPN) disease and hemochromatosis (HH) type 4 are phenotypically distinct diseases caused by mutations in *SLC40A1*. Both traits are characterized by high serum ferritin and hepatic iron overload. Transferrin saturation and splenic/macrophage iron overload distinguish FPN disease from HH type 4. Prognosis and management of patients with *SLC40A1* mutations has been inferred from HFE associated HH (type 1), despite distinct phenotypic presentation in patients with a FPN disease phenotype. The aim of the present study was to define the clinical and biochemical characteristics and management of patients with *SLC40A1* mutations in comparison to HFE HH.
Method: The EASL non-HFE registry study collect structured information on the clinical presentation, biochemistry, radiology, genetics and histology of patients with FPN disease. Data were compared with an age and sex matched cohort of patients diagnosed with HFE HH.

Table: Demographic and biochemical parameters of patients with FPN disease and HFE hemochromatosis.

	SLC40A1 mutation	HFE HH	p
N (females)	77 (41)	91 (47)	0.479
Age at diagnosis [years]	42.1 (±15.6)	40.5 (±13.5)	0.590
Serum iron [µg/dL]	74.2 (±46.1)	34.9 (±9.8)	<0.001
Ferritin [µg/L]	798 (505.6-1284)	427 (299.8-653)	<0.001
Transferrin [mg/dL]	216 (189-257)	167 (157.2-195)	<0.001
Transferrin saturation [%]	28 (21.5-37.5)	79 (60.5-84.5)	<0.001
Transferrin saturation >50%	11%	89%	<0.001
Liver iron content [µmol/g]	135.5 (±82.7)	123.2 (±107.1)	0.405
Median follow-up [years]	9.7 (±4.4)	7.6 (±5.6)	0.042
HCC incidence	1.3% (1/77)	1.1% (1/91)	1.000

Results: As of January 2019, 77 patients (41 female) with genetically confirmed FPN disease have been registered, representing the largest cohort of patients with disease-associated *SLC40A1* mutations. Seventeen different mutations were reported. Eleven percent of patients presented with a HH type 4 phenotype. Demographic and biochemical parameters are shown in the Table. Patients with FPN disease had significantly lower serum iron, ferritin, and transferrin saturation when compared with HFE HH patients. Hepatic iron concentration determined by MRI was 135.5 (±82.8) µmol/g in the FPN disease group as compared 123.2 (±107) µmol/g in the HFE HH group ($p = 0.405$). Five-year survival rate was 95.6% in HFE HH patients as compared to 100% in individuals with SLC40A1 mutations. In the FPN group 45% of patients received regular phlebotomies (mean treatment duration 9.2 years, 0.85 phlebotomies/month).
Conclusion: Although serum ferritin indicates more severe iron overload in patients with *SLC40A1* mutations than in HFE associated HH, both groups show comparable hepatic iron concentration. In contrast, lower serum iron and transferrin saturation are associated with better outcome in FPN disease, despite low rate of iron reduction therapy in patients with *SLC40A1* mutations.

LBP-33

Gelesis superabsorbent hydrogel prevents hepatic steatosis in a high fat diet-induced NAFLD pre-clinical model

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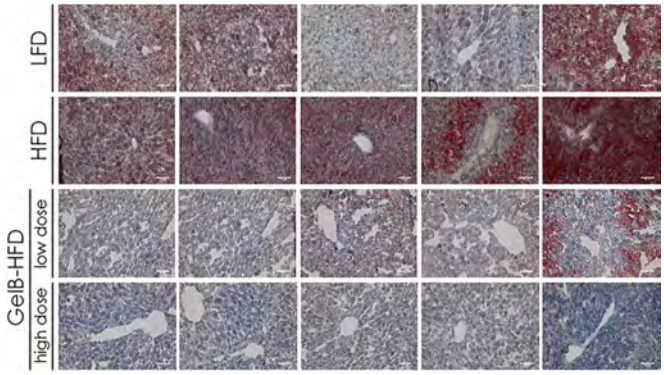
Background and aims: Obesity, insulin resistance and disrupted gut homeostasis are major contributors to the pathophysiology of NAFLD and its progression to NASH. The Gelesis novel hydrogel platform technology is based on crosslinked modified cellulose that can be orally administered. Based on previous preclinical work, Gel-B was designed to restore gut barrier function. Our aim was to evaluate whether Gel-B can prevent hepatic steatosis by repairing gut barrier function, reducing insulin resistance, affecting gut dysbiosis and weight loss, all mechanisms involved in NAFLD.
Method: C57BL/6J *wild type* male mice were fed with either isocaloric low fat diet (LFD: 10% lard) or HFD (45% lard), control groups, for 18 weeks. In parallel, 2 groups of mice were fed with the HFD supplemented with a low or high dose of Gel-B (GelB-HFD). Changes in body weight, glucose, insulin tolerance, GLP-1, and epididymal adipose tissue (EAT) were measured. Oil red O staining was performed to quantify triglyceride accumulation in the liver. Expression of zonula occludens-1 (ZO-1) and circulating levels of bacterial lipolysaccharides (LPS) were assessed to characterize the gut barrier function. Feces were collected and total genomic DNA was extracted. Bray-Curtis dissimilarity analysis was used to generate a principal coordinate analysis (PCoA).
Results: GelB-HFD significantly decreased EAT and blunted weight gain compared to HFD ($p < 0.05$); no difference in weight was observed in LFD alone. All mice on high dose (9/9) and (8/10) on low dose maintained healthy fat-free liver on HFD (Fig). In contrast, the LFD could not prevent hepatic steatosis while keeping the same weight range of GelB-HFD groups. A significant HOMA IR reduction was observed in the GelB-HFD (−18%; $p < 0.05$) compared to HFD, driven by reduction in fasting insulin ($p < 0.01$) and consistent with the improvement of glucose and insulin tolerance tests. Total GLP-1 increased in both GelB-HFD groups (low and high dose, $p < 0.05$, $p < 0.01$ compared to HFD and LFD). These findings in GelB-HFD were linked with improvement in gut barrier function by increasing ZO-1 and preventing an increase in LPS translocation. The PCoA revealed a clear and pronounced compositional separation of microbiomes after therapy with GelB.



Conclusion: These results support the role of GelB as a potential therapeutic option to target pathogenic mechanisms involved in NAFLD/NASH: excess weight, insulin resistance, gut barrier function and gut dysbiosis.

LBP-34

Effect of Resistance Associated Substitutions on Retreatment of HCV infected patients with prior failure to Direct Acting Antiviral Therapy

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Background and aims: 5-10% of HCV-infected patients are not cured with interferon free Direct Acting Antiviral (DAA) regimes. These patients are now being retreated with pan-genotypic regimes such as sofosbuvir, velpatasvir and voxilaprevir, (SOF/VEL/VOX), SOF/VEL with ribavirin (RBV), or glecaprevir and pibrentasvir (GLE/PIB). Here, we present the first real world re-treatment data from the UK.

Method: Blood samples were collected from 282 patients about to begin HCV retreatment. Next generation, deep, whole genome sequencing (WGS) was performed using target enrichment. HCV subtypes were assigned and NS3, NS5A and NS5B resistance associated substitutions (RAS) relevant to each genotype were identified (15% of reads cut off) using a bespoke pipeline developed for HCV-GLUE (hcv.glue.cvr.ac.uk).

Results: Pre-retreatment WGSs were generated from 260 patients. Of these, 87% had previously received an NS5A inhibitor, 30% a protease inhibitor and 50% sofosbuvir. 64% of patients had cirrhosis with 26% decompensated, 11% had hepatocellular carcinoma and 9% had previously received a liver transplant. Subtypes 1a (41%, n = 106) and 3a (39%, n = 102) were the most common; the remaining sequences included 19 subtypes within genotypes 1, 2, 3, 4 and 6. RAS to NS5A inhibitors were the most common polymorphisms, identified in 64% (n = 167) of patients. RAS to Protease Inhibitors were found in 30% (n = 78) and to NS5B Inhibitors in 5% (n = 14). Retreatment outcomes are currently available for 53 patients (the remaining outcomes will be available by April 2019). 53% (n = 28) of patients were retreated with SOF/VEL/VOX, 26% (n = 14) received GLE/PIB and 21% (n = 11) received SOF/VEL+RBV. The overall re-treatment SVR12 rate was 85% (45/53) ITT and 92% (49/53) PP; re-treatment failures included 1 non-responders and 3 relapsers

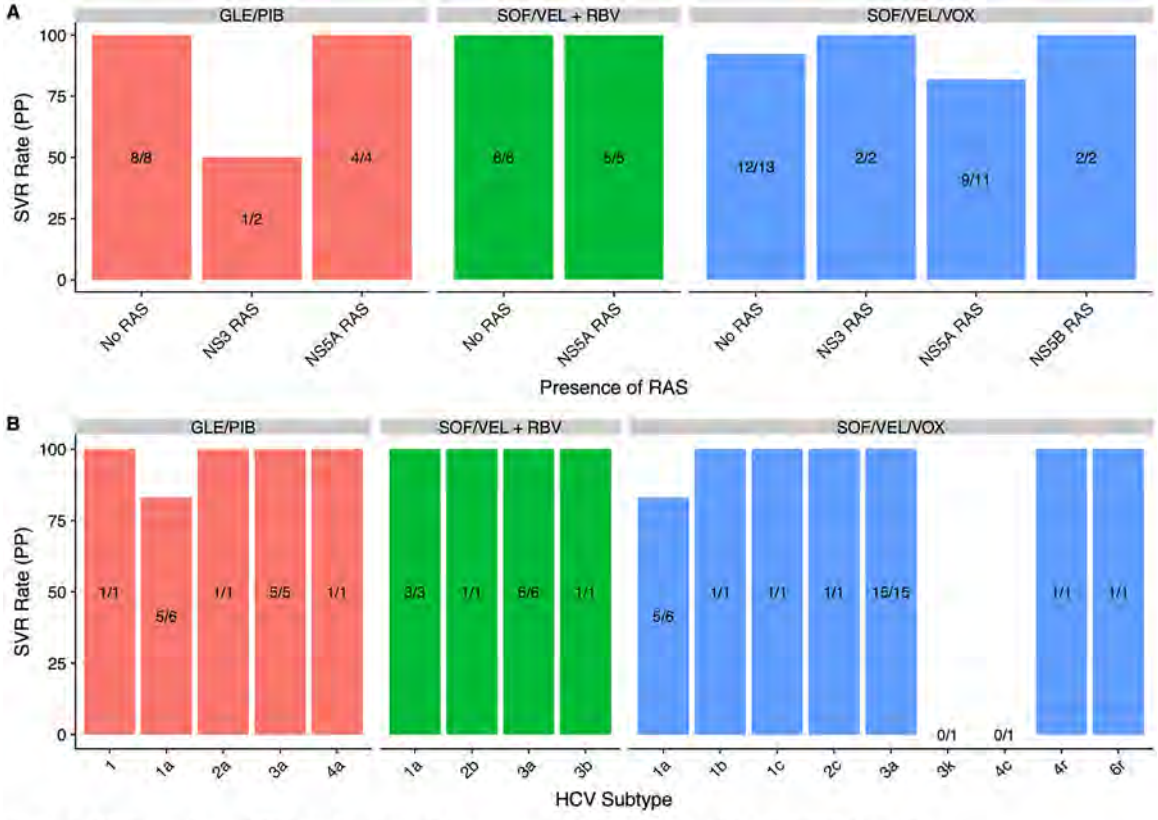

Figure 1: SVR12 rates for each DAA combination split by presence of RAS in each gene (A) or by HCV Subtype (B).

(4 cirrhotic, gt 1a, 3k, 4c), 2 patients lost to follow-up, 1 was re-infected, 1 discontinued. SVR rates by re-treatment regime, subtype and presence of RAS pre-retreatment is shown (Figure 1). At the time of retreatment initiation, 37% of patients had RAS to the NS5A inhibitor they received as retreatment, 8% had RAS to the NS3 Inhibitor and 4% had RAS to sofosbuvir. There was no association with the presence of RAS and outcome (p = 0.35).
Conclusion: The SVR rate for the retreatment of patients with prior DAA therapy failure is high. Pre retreatment RAS are common but do not associate with re-treatment outcomes. Interestingly the two SOF/VEL/VOX failures were subtypes rarely found in the UK (3k and 4c).

LBP-35
Kupffer cell development: A link between Notch signaling and LXRandalpha;
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Background and aims: Macrophages form a heterogeneous group of immune cells which contribute to tissue-homeostasis by performing functions fitting with the requirements of their specific tissue of residence. These tissue-specific functions are acquired through induction of transcription factors (TFs) which control the expression of a number of tissue-specific genes. Expression of these TFs is regulated by a combination of tissue-specific signals produced by the local environment of the macrophage or "macrophage niche." Using a Kupffer cell (KC) specific depletion model, we aim to investigate the signals produced by the KC niche and the TFs they induce which drive KC development.
Method: To study KC development and the KC niche, we used multi-parameter flow cytometry, (sc)RNA-seq, KC-specific mouse models, prediction algorithms and *in vitro* systems.
Results: To identify the distinct TFs required for KC development, we first performed transcriptomic analysis of developing KCs. This identified a set of KC-specific TFs, including LXRα, that are upregulated during the initial stages of KC development. Focussing on LXRa, we generated a KC-specific LXRα knockout mice. Upon loss of LXRα, KCs lose 30% of their identity genes and die within weeks. Having identified LXRα as a crucial TF for KC identity, we next sought to identify the signal (s) inducing expression of LXRα. To this end, we first cocultured bone-marrow monocytes with hepatic stellate cells, liver sinusoidal endothelial cells (LSECs) and hepatocytes, the cells we hypothesise to constitute the KC niche. Expression of LXRα was induced exclusively in the monocytes cocultured with LSECs. To narrow down the potential LSEC ligands inducing LXRα we profiled the transcriptome of LSECs. Using this information paired with the transcriptomic analysis performed on developing KCs, we employed an algorithm, called NicheNet, to predict intercellular communication by linking ligands with target genes. The top predicted interaction was between the notch ligand DLL4 produced by LSECs and NOTCH1/2, expressed by liver-infiltrating monocytes. To validate this prediction, we cocultured monocytes and DLL4 expressing OP9-cells. This induced expression of LXRα and KC-identity genes.
Conclusion: We have studied the development of monocytes into KCs and identified DLL4 expressed by LSECs as a tissue-derived signal inducing the expression of LXRα and KC-identity genes during KC development.

LBP-36
Inhibition of glutamine synthetase in monocytes from patients with Acute-on-Chronic Liver Failure resuscitates their antibacterial and inflammatory capacity
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Background and aims: Acute-on-chronic liver failure (ACLF) is associated with dysfunctional circulating monocytes whereby patients become highly susceptible to bacterial infections. Here we identify the pathways underlying monocyte dysfunction in ACLF and investigate whether metabolic rewiring reinstates their phagocytic and inflammatory capacity.
Method: Following phenotypic characterization, we performed RNA sequencing on $CD14^+CD16^-$ monocytes from ACLF and decompensated alcoholic cirrhosis patients. Additionally, an *in vitro* model mimicking ACLF patient-derived features was implemented to investigate the efficacy of metabolic regulators on monocyte function.
Results: Monocytes from ACLF patients featured elevated frequencies of IL-10-producing cells, reduced HLA-DR expression and, impaired phagocytic- and oxidative burst capacity. Transcriptional profiling of isolated $CD14^+CD16^-$ monocytes in ACLF revealed upregulation of an array of immunosuppressive parameters and compromised antibacterial- and antigen presentation machinery. In contrast, monocytes in decompensated cirrhosis showed intact capacity to respond to inflammatory triggers (1). Culturing healthy monocytes in ACLF plasma mimicked the immunosuppressive characteristics observed in patients, inducing a blunted phagocytic response and metabolic program associated with a tolerant state (1). Metabolic rewiring of the cells using a pharmacological inhibitor of glutamine synthetase, partially restored the phagocytic and inflammatory capacity of *in vitro*-generated- as well as ACLF patient-derived monocytes. Highlighting its biological relevance, the glutamine synthetase/glutaminase ratio of ACLF patient-derived monocytes positively correlated with disease severity scores (1).
Conclusion: In ACLF, monocytes feature a distinct transcriptional profile, polarized towards an immunotolerant state and altered metabolism. We demonstrated that metabolic rewiring of ACLF monocytes partially revives their function, opening up new options for therapeutic targeting in these patients.

Reference
1. Korf H, *et al. Gut* 2018;**0**:1–12. doi:10.1136/gutjnl-2018-316888

LBP-37
Evaluation of Hepatitis C Virus Rapid Diagnostic Test in HCV mono- and HCV/HIV co-infected patients from Low and Middle Income Countries
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Background and aims: Performance evaluations of Rapid Diagnostic Tests (RDT) for Hepatitis C Virus (HCV) antibody detection are mostly conducted in HCV-mono infected patients, often located in High

Income Countries. Although HIV is a commonly found co-infection in HCV-infected individuals, substantial data on RDT performance in HCV/HIV co-infected patients are lacking.
In the present study, we evaluated sensitivity and specificity of thirteen RDTs on 1'800 HCV mono- or HCV/HIV co-infected samples collected in different geographic regions, to fill the data gap in Low and Middle Income Countries (LMICs) and particularly the HIV-infected population.
Method: This is an observational, retrospective multicentre diagnostic accuracy study on archived EDTA plasma samples from Nigeria (42%), Cambodia (30%), Georgia (21%) and Belgium (7%).
Sensitivity and specificity were evaluated in each of 400 HCV mono- and HCV/HIV co-infected samples and each of 500 HCV-uninfected or HIV mono-infected samples. Results were compared to a composite reference standard combining two Enzyme Immuno Assays and a Line Immunoassay.
Each sample was tested on two lots per RDT and each result was read by three independent readers.
Results: Across all HCV RDTs and samples, the overall performance for sensitivity and specificity ranged from 91-99% and 90-100%, respectively. In the HCV-mono infected samples, both, sensitivity and specificity ranged from 98-100%. In the HCV/HIV co-infected samples, RDT performance was more variable, ranging from 80-99% for sensitivity and 88-100% for specificity.
False negative (FN) results were found across all genotypes, with a slightly higher proportion among genotype 4 and 6. For many samples there was no apparent relationship between CD4 counts and FN results in the HCV/HIV co-infected samples, though compromised immune status cannot be excluded as cause for FN results.
Conclusion: This is the first study assessing performance of frequently used HCV RDTs in a large sample set collected in diverse regions and with a focus on performance in the HIV infected population.
While RDT performance in the HCV-mono infected samples was overall good, it was variable in the presence of HIV infection, the reason for which could either be the immune-compromised status in HIV infection or the geographical origin of the HIV infected cohort.
Overall, these findings provide important insights for HCV RDT performance and should be taken into consideration when deciding on the most suitable RDT for screening in a particular setting or population.

LBP-38

Increasing Number of Metabolic Co-Morbidities are Associated with Higher Risk of Advanced Fibrosis in Patients with Non-alcoholic Steatohepatitis

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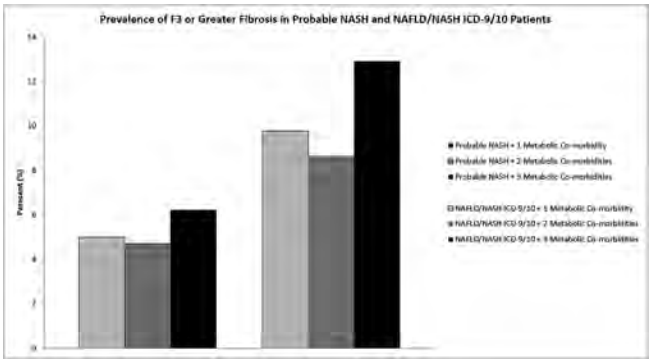
Background and aims: Accurate estimates of non-alcoholic steatohepatitis (NASH) prevalence are lacking, particularly the subset of patients with advanced fibrosis. We aim to evaluate prevalence and predictors of advanced fibrosis among patients with probable NASH using national clinical laboratory data.
Method: Clinical laboratory data from October 1, 2017-September 30, 2018 were collected using Quest Diagnostics database, which tests ~30% of U.S. adults annually. Adults with negative hepatitis B surface antigen, negative hepatitis C antibody, and elevated alanine aminotransferase (ALT) (>25 U/L women, >35 U/L men) were evaluated for prevalence of ≥F 3 fibrosis using fibrosis-4 score (FIB-4)>2.67. Patients were grouped by presence of one, two, or three concurrent metabolic co-morbidities (decreased high density lipoprotein (<40 mg/dL in men, <50 mg/dL in women), elevated triglycerides (≥1 50 mg/dL), or elevated hemoglobin A1C (≥6 .5%)). We further evaluated patients specifically with NAFLD/NASH ICD-9/10 codes from October 1, 2013-Septebmer 30, 2018 (n = 243, 050). Multivariate logistic regression models evaluated for predictors of ≥F 3 fibrosis.
Results: Among 20, 593, 077 patients (42.6% male, mean age 54.5), 9.4 million had available results to assess ALT and metabolic co-morbidities. Overall prevalence of ≥F 3 fibrosis was 3.34% (95% CI 3.33-3.34), which increased from 4.72% (95% CI 4.63-4.82) in patients with one metabolic co-morbidity to 6.24% (95% CI 6.06-6.42) in patients with three metabolic co-morbidities. Among patients with NAFLD/NASH ICD-9/10 codes, prevalence of ≥F 3 fibrosis was 9.07% (95% CI 8.95-9.18), which increased from 9.77% (95% CI 9.18-10.36) in patients with one metabolic co-morbidity to 12.91% (95% CI 11.79-14.03) in patients with three metabolic co-morbidities. On multivariate regression, significantly higher odds of ≥F 3 fibrosis was observed in men vs. women (OR 1.24, 95% CI 1.19-1.29), every 10-year increase in age (OR 2.02, 95% CI 1.99-2.06), and concurrent metabolic abnormalities (OR for three metabolic abnormalities vs. none: 1.31, 95% CI 1.23-1.40).



Conclusion: Among a large national sample of U.S. adults, estimated prevalence of ≥F 3 fibrosis among NASH patients ranged from 3.34-9.07%, representing 2.5-6.8 million individuals. Concurrent metabolic co-morbidities are associated with significantly higher odds of advanced fibrosis with estimated prevalence as high as 12.91% in patients with NASH and three metabolic co-morbidities.

LBP-40

Development of Oligonucleotide-Based miR-132 Antagonists for the Treatment of NASH

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Background and aims: MicroRNAs are small regulatory RNAs that play critical roles in animals and plants by regulating target gene expression at the post-transcription level. Many miRNAs are dysregulated in disease states including NASH, which indicates potential therapeutic targets for oligonucleotide-based drug development. Previous studies have shown that miR-132 is upregulated in livers of NASH patients and is involved in the development of NASH in rodent models. This study sought to validate miR-132 as a potential therapeutic target and to develop antagonists of miR-132 for the treatment of NASH
Method: Quantitative RT-PCR and Nanostring technologies were used to assess hepatic miR-132 levels from NASH patients as well as from several diet-induced mouse models of NASH. Over 250 oligonucleotide antagonists of miR-132 were synthesized and

analyzed for activity, safety and physicochemical properties. Efficacy of a lead compound was demonstrated in multiple mouse models of NASH. Global gene expression profiling was performed to unveil the underlying mechanisms of the lead compound.
Results: miR-132 was upregulated 2 to 4-fold in liver tissues of NASH patients compared to those of healthy donors. In several mouse models of NASH, treatment with a miR-132 antagonizing lead compound reduced liver triglyceride levels by up to 50%, neutralized serum liver enzyme levels (ALT and AST), enhanced glucose tolerance, and improved histopathological scores. Global gene expression profiling revealed significant increase in favorable metabolic genes and decrease inflammatory and fibrotic genes. The lead compound exhibited favorable pharmacological properties as only 2-4 weekly doses were sufficient to rescue NASH phenotypes. These therapeutics effects were sustained for up to 6 weeks following the final dose. The lead compound was well tolerated through intravenous and subcutaneous administration without any obvious drug-related adverse effects.
Conclusion: miR-132 is a promising therapeutic target for the treatment of NASH. Oligonucleotide-based antagonists of miR-132 exhibited excellent potency and pharmacological properties that warrant further development. Lead optimization is currently ongoing to generate drug candidate for first-in-human clinical studies.

Autoimmune and chronic cholestatic liver disease: Experimental and pathophysiology

THU-001
Identifying intrahepatic lymphocyte permutations in active untreated, resistant and treated autoimmune hepatitis

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Background and aims: Autoimmune Hepatitis (AIH) is an inflammatory disease associated with elevated transaminases, immunoglobulin G, autoantibodies (e.g. antinuclear antibody) presence and interface hepatitis with a lymphocytic infiltrate histologically. Standard of care is long term immunosuppression therapy and there is not a clear consensus for treatment withdrawal once biochemical and histological remission has been achieved.
We performed serial intrahepatic fine needle aspiration (FNA) on patients with AIH before and after establishing immunosuppression to investigate the intrahepatic immune response to successful therapy.
Method: 16 patients with AIH were recruited. 10 patients had active disease (5: new diagnosis, 5: refractory to treatment) and 6 were in remission. Biochemical remission was achieved in 5 patients with active disease by six months with prednisolone monotherapy. Peripheral blood mononuclear cells and intrahepatic aspirates were analysed using multicolour flow cytometry.
Results: Serial FNA was well tolerated and no complications were observed. Within the intrahepatic compartment, treated/controlled disease is associated with a significant increase in the proportion of CD4+ lymphocytes ($p = 0.045$), and with a reduction in both CD4+ end-stage effector frequency (CD45RA+, CCR7-) and CD8+ frequency ($p = 0.051$). A significant decrease in B cells are seen in both peripheral blood and the liver ($p = 0.043$ and $p = 0.002$ respectively) in those in remission.
Conclusion: Our data suggests that a distinct intrahepatic inflammatory pattern is present which then resolves with immunosuppression. Understanding key lymphocyte phenotypes may provide early biomarkers of successful therapy and even indicate patients in whom immunosuppression may be withdrawn.

THU-002
Macrophage activation marker neopterin predicts liver transplantation-free survival in primary sclerosing cholangitis

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Background and aims: Circulating biomarkers of fibrosis and inflammation may be of clinical utility in primary sclerosing cholangitis (PSC). Some of the biomarkers reflect macrophage activation, which has been linked to disease severity in experimental PSC models. Upon activation with interferon gamma, macrophages produce neopterin, which has been associated with disease activity and severity in several other conditions. In the present study we aimed to investigate the role of neopterin in two independent PSC cohorts.
Method: A discovery panel of 191 PSC patients (79% male, median 41 (range 16–72) years old) and 100 healthy controls from Norway (59% male, 40 (28–56) years), and a validation panel of 150 PSC patients (63% male, 43 (18–74) years) from Germany were included. Neopterin was analyzed using LC-MS/MS. Primary end point was liver transplantation or death. Survival from time of sampling was analyzed by Kaplan-Meier plots and Cox regression. Optimal cut-off was calculated using ROC-curve.
Results: Neopterin was elevated in PSC patients compared with controls in the discovery panel (median 11.9 vs. 10.6 nmol/L, $p < 0.001$), and higher in PSC patients reaching an end point (n = 87, 46%) than those who did not (median 13.6 vs 11.2, $p < 0.001$), with 11.8 as the optimal cut-off. Neopterin divided into quartiles strongly predicted liver transplantation-free survival with estimated mean survival ranging from 3.5 (highest quartile) to 6.6 years (lowest quartile) from time of sampling, $p < 0.001$. PSC patients with high neopterin (>11.8), showed a mean survival of 4.1 years, compared to 6.1 years in the low group ($p < 0.001$). PSC patients in the validation panel had less advanced disease (Mayo risk score mean 0.06 vs. 0.56, $p = 0.001$), and also here, patients reaching an end point during follow-up (n = 16, 11%) showed higher neopterin levels compared to patients without ($p = 0.006$). Neopterin > 11.8 was also associated with reduced liver transplantation-free survival in the validation panel ($p = 0.003$). When correcting for Mayo risk score, neopterin > 11.8 was independently associated with survival in the discovery panel ($p = 0.04$) but not in the validation panel ($p = 0.09$). A combined analysis of all patients including center and Mayo risk score as covariates yielded a hazard ratio of 1.8 (95% CI 1.1-2.7), $p = 0.01$ for high neopterin (>11.8).
Conclusion: Neopterin associates with liver transplantation-free survival in PSC, highlighting a possible role of this macrophage activity marker as a measure of prognosis and disease activity.

THU-003

European multicenter validation of autoantibodies against huntingtin-interacting protein 1-related protein for the diagnosis of autoimmune hepatitis in adults

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Background and aims: Autoantibodies are major components for the diagnosis of autoimmune hepatitis (AIH). Currently, common autoantibody testing is hampered by lack of either high specificity or sensitivity. We discovered antibodies against huntingtin-interacting protein 1-related protein (HIP1R) in AIH single center cohorts with a better overall accuracy and specificity compared to antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) (abstract PS-006; ILC 2018). We now validated anti-HIP1R antibody testing in a large European multicenter AIH cohort.
Method: IgG antibodies against HIP1R were measured via ELISA in cryo-conserved serum samples of 177 patients with untreated AIH, 57 patients with AIH on therapy and 303 patients with non-AIH liver diseases (100x PBC, 100x PSC, 13x toxic hepatitis, 4x genetic liver disease, 86x NAFLD/NASH).
Results: Anti-HIP1R antibody concentrations were elevated in serum samples of untreated AIH patients compared to non-AIH liver diseases ($p < 0.001$). Anti-HIP1R antibody concentrations declined under immunosuppressive treatment in AIH patients to values as seen in non-AIH liver diseases. Applying the same cut-off values as in our single center training cohort, anti-HIP1R antibodies were equally sensitive ($p = .075$), more specific ($p < .001$) and more accurate (95% confidence interval (CI): 68.7–76.8 (anti-HIP1R) vs. 52.9–62.1 (ANA)) to diagnose AIH compared to ANA (Table 1). SMA performed similar to anti-HIP1R antibodies in terms of specificity ($p = .477$) and sensitivity ($p = .728$) and trended towards lower overall accuracy (CI: 63.3–72.9) (Table 1). The majority of patients with untreated AIH but non-diagnostic ANA and SMA titers (12/177; 6.8% of patients with untreated AIH) had diagnostic anti-HIP1R antibody concentrations (8/12; 66.7%).

Table 1: Test criteria to diagnose untreated AIH.

	Anti-HIP1R	ANA	SMA
Sensitivity	63.3%	70.3%	72.4%
Specificity	78.5%	49.1%	63.6%
Accuracy	72.9%	57.6%	68.3%

Conclusion: This European multicenter study confirmed that anti-HIP1R antibody testing serves to distinguish AIH from other liver diseases with the highest overall diagnostic accuracy. Anti-HIP1R antibodies can help to facilitate the diagnosis of AIH even when ANA and SMA titers are low and non-diagnostic. Finally, anti-HIP1R antibodies can be determined much easier with a single ELISA compared to the conventional gold standard of autoantibody-diagnostic using immunofluorescence.

THU-004

Lactobacillus rhamnosus GG prevents liver fibrosis through intestinal FXR/FGF15-mediated inhibition of bile acid synthesis and the increase of bile acid excretion in mice

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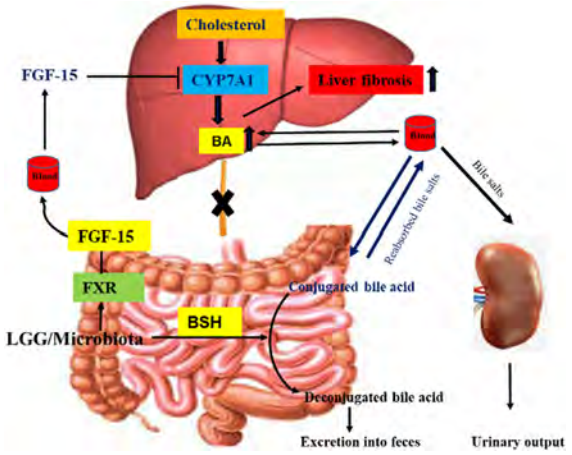
Background and aims: Gut microbiota play a critical role in liver disease. The purpose of this study is to examine the effect of probiotics *Lactobacillus rhamnosus* GG (LGG) in the prevention of liver injury and fibrosis induced by bile-duct ligation (BDL) and to understand the underlying mechanisms.
Method: Liver fibrosis was induced in mice by BDL for 11 days. LGG was given to mice by oral gavage at a dose of 109 CFU/day/mouse. Bile acid level and compositions of liver, serum, feces and serum were determined. Liver fibrosis and injury were assessed by histology analysis, liver fibrotic gene expression and serum biochemistry analysis. Intestinal microbiota were determined by pyrosequencing and gut lumen bile salt hydrolase (BSH) activity was determined. FXR activity was analyzed by a reporter system. Global and intestinal specific FXR inhibitors were used to dissect the role of FXR.
Results: LGG treatment significantly decreased hepatic total bile acid level, liver injury and fibrosis in BDL mice. Metabolomics profiling showed a distinct bile acid composition in serum, liver and feces among Sham, BDL and BDL-LGG groups. Hepatic concentration of T-βMCA, a FXR antagonist, were markedly elevated in BDL mice and reduced in LGG treated BDL mice. While CDCA, a FXR agonist, was decreased in BDL mice and normalized in LGG-treated mice. LGG significantly increased the expression of serum and ileum FGF-15 (19), which is a FXR target and suppressor of hepatic bile acid synthesis through gut-liver axis. As a result, hepatic expression of key enzymes in bile acid synthesis, CYP7A1 and CYP27A1 was significantly reduced by LGG. Fecal BSH activity was significantly increased by LGG in BDL mice, which was accompanied by increased gut BSH-producing bacteria population and de-conjugated bile acid content in feces. In addition, LGG treatment increases urine bile acid excretion. The beneficial effects of LGG were attenuated by global and intestinal FXR inhibition. Furthermore, we showed that LGG attenuate T-βMCA-suppressed FXR activity and FGF-19 (15) and SHP expression in intestinal epithelial cells.



Conclusion: LGG treatment prevents liver fibrosis in a mouse model of cholestatic liver disease. The beneficial effect of LGG is mediated by intestinal FXR/FGF-15 (19) signaling activation leading to an inhibition of liver bile acid synthesis and increasing of fecal and urine bile acid excretion. Probiotic LGG may be used to prevent/treat cholestatic liver disease.

THU-005

Activation regulators of peripheral blood and intrahepatic T effector cells in autoimmune hepatitis

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Background and aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease with unknown aetiology. T effector cells seem to play a crucial role in the pathogenesis of AIH by mediating the hepatic inflammation. Altered expression of activation regulators may account for enhanced T effector cell immune responses in AIH. We investigated regulators of T cell co- stimulation and co-inhibition in liver and blood of patients with AIH in comparison to healthy individuals and patients with other immune-mediated liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), and to immune-mediated drug- induced liver injuries (DILI).
Method: A total of 63 AIH patients (29 treatment-naïve and 34 under immunosuppressive treatment) were examined. Gene expression levels of *CBL-B, CTLA-4, GRAIL, ICOS, ITCH, NEDD4, OX40, PD-1, PKCϴ* and *TRAF6* were analysed by quantitative PCR of liver samples or isolated peripheral T cells of AIH patients and control subjects. Moreover, RNA in-situ hybridization with selected probes was performed on liver samples of AIH and DILI patients.
Results: Quantitative PCR screening revealed that peripheral blood T cells of AIH patients and healthy control subjects had similar gene expression levels of *CBL-B, CTLA-4, GRAIL, ICOS, ITCH, NEDD4, OX40, PD-1, PKCϴ* and *TRAF6*. In contrast, in livers of treatment-naïve AIH patients as compared to healthy control subjects, *CBL-B* (2-fold expr., $p = 0.009$), *PD-1* (10-fold expr., $p = 0.006$), *ICOS* (16-fold expr., $p < 0.001$) and *CTLA-4* (20-fold expr., $p < 0.001$) were significantly elevated. Intrahepatic expression of *CBL-B* and *ICOS* in AIH patients correlated positively with the modified hepatic activity index of these patients (mHAI, mean = 9; Spearmans R_s: 0.6, $p = 0.005$). RNA in-situ hybridization revealed that expression of *CBL-B* (57% positive cells in AIH vs. 20% positive cells in DILI; $p < 0.005$), *CTLA-4* (33% vs. 22%; $p < 0.02$) and *PD-1* (24% vs. 14%; $p = 0.03$) was elevated in liver-infiltrating cells (T cells and $CD3^-$ cells) in AIH patients as compared to DILI patients.
Conclusion: Expression of *CBL-B*, *CTLA-4*, *PD-1* and *ICOS* was significantly increased in livers of treatment-naïve AIH patients, whereas the expression levels in AIH patients under immunosuppressive treatment were not significantly different compared to healthy subjects. Therefore, altered expression of these activation regulators could be relevant for pro-inflammatory processes in AIH.

THU-006

Aberrant DNA methylation in bile accurately detects cholangiocarcinoma in patients with primary sclerosing cholangitis

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Background and aims: Patients with primary sclerosing cholangitis (PSC) have up to 20% lifetime risk of developing cholangiocarcinoma (CCA). Current strategies for identifying CCA in patients with PSC are suffering from low diagnostic accuracy. Consequently, the majority of patients are diagnosed at an incurable stage of disease, highlighting the need for novel early detection methods that could qualify more patients for curative treatment. We aimed at establishing robust DNA methylation biomarkers in bile for improved detection of CCA in PSC.
Method: By using highly sensitive droplet digital PCR (ddPCR) 100 µl of bile collected during endoscopic retrograde cholangiopancreatography or liver transplantation from 261 patients with PSC, CCA with and without PSC and other non-malignant liver diseases were analyzed for promoter methylation of *CDO1*, *CNRIP1*, *SEPT9* and *VIM*.
Results: Receiver operating characteristics (ROC) curve analyses revealed high area under the ROC curves (AUCs) for all four markers (0.87–0.97) for CCA detection. AUCs increased (0.92–0.98) when only CCA patients with underlying PSC were included. Combining the markers (≥1 of 4 markers positive for methylation) achieved both high sensitivity (100%) and specificity (94%) for CCA detection in patients both with and without PSC. In PSC patients who were diagnosed with CCA after bile sampling at least one marker was positive in all of the samples (100% sensitivity) taken up to 27 months prior to established CCA diagnosis.

	AUC (95% CI)	*P* value	Cutoff	Sensitivity %	Specificity %
CDO1	0.95 (0.88–1.02)	<0.0001	>1.545	88	97
CNRIP1	0.98 (0.95–1.00)	<0.0001	>0.455	100	93
SEPT9	0.98 (0.95–1.00)	<0.0001	>0.572	75	98
VIM	0.92 (0.77–1.06)	<0.0001	>0.399	75	97

AUCs, *P* values, cutoff value used for positive methylation, sensitivity and specificity values for the four individual DNA methylation biomarkers measured in bile in patients with CCA with underlying PSC (n = 8) vs. PSC controls (n = 210).

Conclusion: By using highly sensitive ddPCR to analyze robust epigenetic biomarkers CCA was accurately detected in small volumes of bile, even before standard detection modalities. These findings suggest that measurements of aberrant DNA methylation in bile may complement current detection methods and improve surveillance algorithms for CCA in PSC.

THU-007

Absence of BSEP (ABCB11) protects MDR2 (ABCB4) KO mice from cholestatic liver and bile duct injury through anti-inflammatory bile acid composition and signaling

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Background and aims: Bsep KO mice are protected from acquired cholestatic injury by metabolic preconditioning with a hydrophilic bile acid (BA) pool with formation of tetrahydroxylated bile acids (THBAs). We aimed to explore whether increased BA detoxification alters inflammatory signaling, thereby improving liver injury in the Mdr2 KO mouse.
Method: Cholestatic liver injury, hepatic inflammation and fibrosis in Mdr2/Bsep DKO and Mdr2 KO mice was studied for comparison. BDL WT and Mdr2 KO mice were treated with a THBA. Gene expression profile of inflammatory/fibrotic markers were investigated. RORγt+ and FOXP3+ T cells from liver were quantified by FACS. In vitro, the impact of THBA on chenodeoxycholic acid (CDCA) induced inflammatory signaling in IHH cells and RORγt as well as NFκB signaling in Jurcat cells (stably transfected with GFP -NFκB) were analyzed.
Results: In contrast to Mdr2 KO, DKO mice displayed increased BA hydroxylation and lacked histological features of sclerosing cholangitis. 67% of serum BAs in DKO mice were polyhydroxylated, (THBAs were most prominent), while Mdr2 KO mice had no such BAs. In contrast to profoundly increased gene expression of inflammatory/fibrotic markers (F4/80, Tnfα, Mcp1, Desmin, Col1a1; $p < 0, 05$) in Mdr2 KO, no increases were seen in DKO. Increased levels of PHBAs were associated with reduced RORγt+ (regulator of TH17 cell differentiation) cells but increased FOXP3+ (Treg differentiation) cell within the CD4 + CD3+ T cell population (50% RORγt+;5% FOXP3+ in Mdr2 KO vs 10% RORγt+;30% FOXP3+ cells in DKO). 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 also profoundly reduced by THBA. In IHH cells, THBA reduced CDCA induced mRNA expression of inflammatory markers (IL8, Icam, Cxcl2; $p < 0, 05$) and attenuated CDCA-induced NFκB activation in GFP-NFκB transfected Jurcat cells. Also in Jurcat cells, THBA attenuated RORγt signaling at mRNA levels (IL23 −55%, TGFβ-25%; TH17 related cytokines).
Conclusion: Increased formation of THBA (due to absence of Bsep) or THBA administration represses key pro-inflammatory signals such as NFκB and RORγt in hepatocytes and immune cells, protecting Mdr2 KO mice from cholestasis-associated inflammation and fibrosis. Therefore, THBA and their downstream targets may be a new potential treatment strategy for cholestatic liver diseases.

THU-008
Circulating fibroblast growth factor 21 regulates bile acids homeostasis in cholestatic patients

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Background and aims: Cholestatic disorders are a class of liver conditions where the production and/or flow of bile is impaired resulting in intracellular retention of toxic bile components, that in the long term leads to fibrosis, cirrhosis and liver failure.
To overcome the cholestatic toxic damage, there are protective compensatory pathways promoting bile acids (BA) transport into the systemic circulation and reducing liver BA production. Three mechanisms contribute to inhibit BA synthesis: i. BA activation of the Farnesoid×Receptor (FXR) that, by inducing the transcription of SHP (Small Heterodimer Partner), reduces the expression of *cyp7a1*, the rate-limiting enzyme in BA synthesis; ii. intestinal BA induction of the Fibroblast Growth Factor 19 (FGF19) that, after activating its receptor FGFR4, suppresses BA synthesis; iii. post-transcriptional reduction of CYP7A1 activity.
The growth factor FGF21, known to be a metabolic regulator, has been shown, in a rodent model, to diminish *cyp7a1* expression and therefore BA synthesis. However, FGF21 signaling pathway is specie-specific, being for instance FGF21 mRNA expressed in liver and adipose tissue in rodent, while apparently only in liver in humans. In this study we aimed at investigating whether in humans, FGF21 is involved in regulating BA homeostasis.
Method: 33 subjects undergoing abdominal surgery were investigated. Among them, 9 subjects were affected by obstructive cholestasis and 24 were non-cholestatic controls. Liver biopsies and serum samples were collected. Expression of the main nuclear receptors involved in transcriptional regulation of bile acid synthesis/transport and of biliary transporters was analysed by real time qRT-PCR. Circulating levels of FGF21, FGF19 were measure with commercial ELISA kit. Circulating total bile acids levels were assessed with HPLC.
Results: Circulating levels of FGF21 were significantly increased in cholestatic patients ($p < 0.05$) but no differences were detected regarding its hepatic mRNA expression. In the liver, expression of *cyp7a1* was significantly reduced during cholestasis, together with an increased mRNA expression ($p < 0.01$) of the short heterodimer partner (SHP). Expression of genes coding for canalicular biliary transporters, such as ABCB4 and ATP8B1 ($p < 0.05$) were also increased. Circulating levels of FGF21 directly correlated with hepatic FXR and SHP expression and inversely with CYP7A1 expression. Also, FGF21 serum levels positively correlated with FGF19 levels and circulating total bile acids.
Conclusion: In human obstructive cholestasis, circulating FGF21 is markedly increased and correlates with hepatic expression of nuclear receptors and hepatobiliary transporters involved in bile acids metabolism. Such findings provide insight into a cross talk FGF21/bile acids, suggesting FGF21 as possible circulating factor regulating bile acids homeostasis.

THU-009
High throughput RNA sequencing unravels pathways associated with cognitive deficit in primary billiary cholangitis

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Background and aims: Primary Billiary Cholangitis (PBC) is an autoimmune disease of the bile duct and liver. Biliary epithelial cell injury causes cholestasis, fibrosis and systemic circulation of toxic bile acids. PBC patients frequently experience significant central fatigue with associated cognitive symptoms Including impaired short-term memory and problems with concentration. Likened by patients to "brain fog" this under-recognised complex of CNS symptoms is a major contributor to poor quality of life and is currently untreatable. This study aims to investigate the mechanistic basis of cholestasis-induced memory impairment in mice and if these changes are ameliorated by the FDA approved drug Obeticholic Acid (OCA) using high-throughput RNA sequencing.
Method: C57BL/6 mice underwent either Bile Duct Ligation (BDL) or sham surgery. A sub-group of BDL were treated prophylactically with OCA. Animals were humanely killed at day 10 and brains removed for hippocampal biopsy. RNA was isolated from each biopsy sample and processed for RNA sequencing using an Illumina NextSeq 500 system. Differentially expressed genes were analysed using Qiagen's Ingenuity Pathway Analysis (IPA) software.
Results: 869 genes were differentially expressed (DE) comparing BDL with sham controls. Number of DE genes was decreased to 162 genes in BDL animals treated with OCA versus sham animals. Analysis of DE genes in the untreated BDL vs sham group displayed a decrease in gene expression related to synaptic long-term potentiation and cAMP signalling pathway (neuronal plasticity), a pathway whose inhibition is associated with memory impairment. S-adenosyl methionine (SAMe) biosynthesis, which has important implications in the liver

and in cholestatic fatigue, was also decreased. In addition, genes related to apoptosis signalling were upregulated.
In contrast, treatment of mice with OCA has restored all of the above deregulated pathways concurrently with up-regulation of neuronal differentiation and outgrowth genes (GATA3, Gli1, LEF1). Immunofluorescent analysis of the hippocampus revealed an increase in the protein expression of SOX2, a marker of neuronal proliferation. DE genes were further validated by RT-PCR.
Conclusion: Our results show that OCA treated animals have a hippocampal transcriptome similar to sham animals. Cholestasis correlates with reduced neuronal plasticity and SAMe biosynthesis, plus an increase apoptosis; which are reversed with OCA therapy.

THU-010
Shedding light on the X chromosome contribution to the genetic architecture of primary biliary cholangitis
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Background and aims: Genome-wide association studies (GWAS) in primary biliary cholangitis (PBC) failed to find X chromosome genetic variants associated with the disease. However, these studies analyzed the X chromosome applying methods designed for autosomes, without accounting for the analytical problems arising from X unique mode of inheritance. Aim of our study was to explore the contribution of the X chromosome to the genetic architecture of PBC, a highly sexually dimorphic complex disease with an autoimmune etiology, by performing a chromosome X-wide association study (XWAS).
Method: The study included data derived from 5 GWAS studies (cohorts from Italy, United Kingdom, Canada, China, Japan), for a total of 5, 244 cases and 11, 875 controls. Genotype data were quality checked, corrected for population stratification, and imputed using the IMPUTE2 software. A total of 110, 000 SNPs, common to all cohorts, were then used for association analyses. These were performed by using the PLINK-XWAS software by: 1) assuming uniform and complete X-inactivation in females and a similar effect size for males and females; and 2) considering separately males and females and then by combining p values (taking into account: differential effect-size/direction between males and females, and the weight of each study). A subsequent meta-analysis was performed using METAINTER.
Results: In the single-SNP association analysis we found 11 population-specific loci associated with PBC at a suggestive $p < 5*10^{-5}$, the most significant being a signal mapping within the OTUD5 gene ($p = 4.80*10^{-6}$; OR = 1.39 CI = 1.03–1.58; Japanese cohort). This gene codes for a protein that was demonstrated to suppress the type-I interferon-dependent innate immune response. The subsequent meta-analysis was performed separately for Caucasian and East Asian populations, and revealed a novel complex locus (containing GRIPAP1, PIM2, OTUD5, LL0XNC01, and KCND1 genes) below the threshold for genome-wide significance.
Finally, we performed a gene-ontology analysis, evidencing a significant enrichment for genes involved in immune system ($p = 8.4*10^{-11}$).
Conclusion: By applying a XWAS analysis, we were able to evidence novel association signals with PBC risk, shedding light on the genetic contribution of the "neglected" X chromosome to this immune-mediated disorder.

THU-011
Cholecystectomy causes worsening of primary sclerosing cholangitis features in Abcb4 knockout mice
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Background and aims: Patients with primary sclerosing cholangitis (PSC) commonly undergo cholecystectomy for gallbladder abnormalities. Experimental studies have provided evidence indicating that the gallbladder provides protection against hepatic bile acid overload. The aim of this study was to determine the consequences of cholecystectomy in Abcb4 knockout mice, a widely used model of PSC.
Method: Seven weeks old male and female *Abcb4* knockout mice underwent cholecystectomy or sham operation. Serum tests, immunohistochemical and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analyses of the liver tissue, were performed in all animals five weeks after surgery. Bile acid composition in the liver and plasma was analysed at that time, using high-performance liquid chromatography coupled to tandem mass spectrometry.
Results: Cholecystectomized *Abcb4* knockout male mice and to a lesser extent female mice had more severe fibrosis, assessed by sirius red staining, as compared to sham-operated animals of the same gender. Following cholecystectomy, males developed a significant increase in ductular reaction, ascertained by cytokeratin 19 immunostaining, and in total bile acid concentrations in the liver. They also displayed a significant decrease in the mRNA expression of sodium-coupled taurocholate transport protein (Ntcp) and a trend towards lower hepatic expression of cytochrome P450 Cyp7a1. Following cholecystectomy, females showed a significant increase in bilirubinemia, in hepatic concentration of the secondary bile acid taurohyodeoxycholic acid (THDCA) and in the hepatic expression of the organic solute transporter β (Ostβ).
Conclusion: Ablation of the gallbladder causes an aggravation of cholestatic and PSC features in *Abcb4* knockout male mice. Cholecystectomy also has a negative impact although less dramatic in *Abcb4* knockout female mice. These findings suggest that cholecystectomy may aggravate the liver status of patients with PSC and other cholestatic liver diseases.

THU-012
Prevalence of autoimmune liver disease related autoantibodies in various non autoimmune liver diseases
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Background and aims: The prevalence of autoimmune liver disease related autoantibodies has not been defined in patients with non autoimmune liver diseases and therefore need to be studied and the relevance defined. The aim of this study was to explore the prevalence of autoimmune liver disease related autoantibodies in various non autoimmune liver diseases.
Method: A total 8, 213 patients were enrolled, 351 were excluded due to autoimmune aetiology and hepatocellular carcinoma, 7862 patients with non autoimmune related liver diseases were analysed retrospectively, in hospital based study from 2012 to 2018. We aimed to investigate clinical profile, diagnosis, pattern of autoantibodies in various liver diseases.
Results: Mean age of the study population was 49.95 ± 14 years, with 78% being males. Age was also significant among the diseases ($p < 0.001$), with Wilsons diseases group being younger (34 ± 10.5 years)

as compared to others (44 ± 14.7 to 58 ± 10.1). Distribution of diseases group as per aetiology were as most common with alcohol liver diseases (ALD) 28.4%, followed by hepatitis B related (HBV)19.1%, hepatitis C related (HCV) 19%, non-alcoholic steatohepatitis (NASH) 17.1%, Drug-induced liver injury (DILI) 3.6%, Hepatitis E related (HEV) 5.9%, hepatitis A (HAV) 2%, and Wilson were least 0.8% common. The prevalence of antinuclear antibody (ANA) was 28.2%, Anti-smooth muscle antibody (ASMA) was 19.8%, perinuclear anti-neutrophil cytoplasmic antibodies (p ANCA)7.6%, anti-liver-kidney microsomal antibody (Anti-LKM) was 4.2%, Antimitochondrial antibodies (AMA) was 2.1%, Anti-soluble liver antigen (*SLA*) *a*ntibodies 1.8%. Average IgG level was 17.18 g/l and CRP was 8 mg/l and both were not found significant. ANA was predominately present in 38.9%, 36.5%, 25.3% and 15.1% in HBV, HCV, ALD, and NASH respectively. LKM −1 was present in 11.6% HCV patients as compared to others. pANCA was positive in 14.4% HCV patients, SLA was not found significant in any of the group. AMA was predominantly positive in DILI (5.8%) which was not significant. Gender wise, ANA was predominant in females in 44.8% as compared to males (5.9%) (p value < 0.001). Similarly, ASMA, LKM, pANCA, SLA, AMA were more prevalent in females in 34%, 11.5%, 23.7%, 3.6%, 5.6% respectively, all of which were clinically significant in females (p < 0.001). Acute-on-chronic liver failure (ACLF) was seen in 18.8% patients, male predominance was seen. Most common co-morbidity was hypothyroidism in 14.33% patients with female predominance.

Conclusion: All the autoimmune markers were more common in females. ANA was predominately present in HBV, HCV, ALD, and NASH respectively while AMA was common in patients with DILI. LKM −1 and pANCA were common in HCV patients while SLA was not found significant in any of the group. These findings suggest the need of further investigations to confirm or rule out the diagnosis of autoimmune liver diseases.

THU-013

Investigating the potential immunomodulatory role of mesenchymal stromal cells in primary sclerosing cholangitis

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Background and aims: Liver-infiltrating T lymphocytes and high levels of TNF are implicated in the destruction of bile ducts in primary sclerosing cholangitis (PSC). Mesenchymal stromal cells (MSC) possess immunomodulatory properties suggesting a potential therapeutic role in PSC. We studied the effect of MSC and MSC derived conditioned media (CM) on T cells from PSC patients.

Method: Peripheral blood mononuclear cells (PBMC) were isolated from PSC patients (n = 6) and healthy controls (n = 4). $CD4^+$ and $CD8^+$ T cells were purified using negative-bead selection kits from explant livers of PSC (n = 6) and primary biliary cholangitis (PBC) patients (n = 3). Cells were labelled with cell trace violet and co-cultured with MSC at ratios; 1:1, 1:4, 1:16, 1:64 1:256 (MSC:PBMC/T cells) in the presence of anti-CD3/CD28. MSC effect on $CD4^+$ and $CD8^+$ T cell proliferation and activation (TNF-alpha, IFN-gamma, IL2 expression) was studied by flow cytometry. Experiments were repeated using CM at concentrations; 100%, 90%, 80%, 70%, 60%, 50%.

Results: MSC suppressed the proliferation of circulating $CD4^+$ (28%, p = 0.0001) and $CD8^+$ (38%, p < 0.0001) T cells at ratios up to 1:16 compared to stimulated PBMC only (90% and 92% respectively). No significant differences in the MSC effect on suppression of T cell proliferation was seen between PSC patients and healthy controls. MSC reduced circulating $CD4^+$TNF-apha$^+$ (38%, p < 0.05) at 1:1 and $CD4^+$IFN-gamma$^+$ (2%, p < 0.05) expressing cells at ratios up to 1:4 compared to stimulated PBMC only (73% and 28% respectively) (n = 4 PSC). MSC suppressed intrahepatic $CD4^+$ (23%, p < 0.05) at ratios up to 1:16 and $CD8^+$ (20%, p < 0.01) T cell proliferation at 1:1 compared to stimulated $CD4^+$ and $CD8^+$ T cells only (83% and 85% respectively) (n = 6 PSC). MSC reduced intrahepatic $CD4^+$TNF-alpha$^+$ (38% vs 79%, p < 0.05), $CD4^+$IFN-gamma$^+$ (6% vs 29%, p < 0.01) and $CD4^+$IL2$^+$ (20% vs 61%, p < 0.01) expressing cells at ratios up to 1:16, 1:4, 1:4 respectively compared to stimulated $CD4^+$ T cells only (n = 5 PSC). Similarly, MSC suppressed intrahepatic $CD4^+$ (54%, p < 0.01) and $CD8^+$ (12%, p < 0.01) T cell proliferation compared to stimulated $CD4^+$ and $CD8^+$ T cells only (89% and 84% respectively) in PBC livers. Addition of up to 80% CM suppressed circulating $CD4^+$ (46% vs 84%, p < 0.01) and $CD8^+$ (50% vs 86%, p < 0.01) T cell proliferation compared to stimulated PBMC only (n = 8 PSC). Addition of 100% CM reduced circulating $CD4^+$IFN-gamma$^+$ (11% vs 29%, p < 0.01) expressing cells compared to stimulated PBMC only (n = 6 PSC).

Conclusion: MSC suppress the proliferation and activation of PSC patient derived circulating and intrahepatic T cells. MSC act directly and indirectly via release of soluble factors on circulating T cells. Our results support efforts to assess *in vivo* the immunomodulatory effects of MSC in PSC patients.

THU-014

Primary sclerosing cholangitis-associated biliary neoplasia demonstrates a high inter- and intratumour heterogeneity

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Background and aims: Tumour heterogeneity in primary sclerosing cholangitis (PSC)-associated cholangiocarcinoma (CCA) may attribute to the diagnostic limitations of cytology and fluorescence in situ hybridization of biliary brushes. In addition, these tumours are remarkably resistant to widely different chemotherapeutic drugs. A possible explanation may lie in that PSC-CCA is made up of divergent clones, each with their own genetic defence mechanisms to counteract therapeutic agents. We aimed to assess tumour heterogeneity through p53 and p16 protein expression analysis in PSC-associated biliary neoplasia.

Method: Formalin-fixed paraffin-embedded tissue samples from resection material of PSC patients with CCA and/or dysplasia were selected. Sections with CCA and foci with dysplasia were identified by two independent liver pathologists. Staining with p53 and p16 monoclonal antibodies was performed. Two investigators independently scored protein expression, p53 null mutation/wildtype/overexpression and p16 negative/heterogeneous/positive.

Results: A total of 18 resection specimens of PSC-CCA and 1 PSC-explant with dysplasia were included, and 37 tumour and 13 dysplasia sections were selected. P53 protein expression was classified as null mutation, wildtype and overexpression in 3/22/11 CCA and 2/7/3 dysplasia, respectively. In 5 patients, 7 CCA and 2 dysplasia samples showed null mutation or overexpression surrounded by neoplastic cells with wildtype expression. In one patient, 1 CCA and 1 dysplasia showed p53 overexpression with an abrupt transition to null mutation. Next generation sequencing (NGS) in this patient showed different patterns of genomic instability of *TP53* in overexpression compared to null mutation.

P16 protein expression was scored as negative, heterogeneous and positive in 13/18/6 CCA and 6/5/2 dysplasia, respectively. In four patients intratumour heterogeneity of the morphological aspect of p16 protein expression was observed.

Conclusion: PSC-associated biliary neoplasia is characterized by a high inter- and intratumour heterogeneity of p53 and p16 protein expression, indicating that such cancers consist of multiple clones

with substantially different genetic makeup. By using NGS genetic intratumour heterogeneity of *TP53* has been detected. These observations may explain the difficulty encountered to reliably diagnosis of PSC-CCA and provides a rational explanation for poor response to a large spectrum of chemotherapeutic agents.

THU-015

Mutational signatures during the neoplastic cascade towards cholangiocarcinoma in primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is associated with an increased risk of cholangiocarcinoma (CCA). Carcinogenesis and involved molecular processes are poorly understood. As PSC-related CCA (PSC-CCA) presumably follows the inflammation-dysplasia-carcinoma cascade, genetic aberrations might be detected at premalignant stage. We aimed to identify genetic alterations in PSC-related dysplasia and CCA by multiregional targeted sequencing.
Method: A total of 19 PSC-patients with biliary dysplasia and/or CCA after surgical resection were included. Resection specimens of 18 patients contained CCA±dysplasia, and one only dysplasia. DNA was extracted from sections of formalin-fixed paraffin-embedded tissue blocks. Targeted sequencing of a custom made cancer panel, consisting of 28 genes, was performed on 37 tumour and 6 dysplasia samples. Amplicons included in the gene panel were investigated in order to detect genomic imbalance of 13 genes of interest. In addition, copy number variations of *CDKN2A, EGFR, MCL1* and *MYC* were examined by fluorescence in situ hybridization (FISH).
Results: *TP53* mutations were the most common aberration observed in PSC-CCA (13 samples/8 patients), other mutations observed are in *KRAS* (7 samples), *GNAS* (3), *ERBB2* (2), *APC* (1) and *PIK3CA* (1). In addition, mutations in *TP53* (4) and *ERBB2* (3) were identified in four dysplasia samples. *CDKN2A* loss was seen in both tumour (7) and dysplasia (1), *SMAD4* and *TP53* loss only in tumour (10 and 1). Gain of *MYC, ERBB2, EGFR* and *PIK3CA* was found in 7/7/4/1 tumour and 3/2/1/1 dysplasia samples, respectively. Genomic imbalance assessment showed *MCL1*, *KRAS* and *FGFR3* amplification only in tumour samples (3/3/5). In one patient high level amplification of *EGFR* was found in dysplasia, while tumour did not show *EGFR* amplification. Strikingly, both loss and gain of *POLD1* were seen in tumour and dysplasia. We were able to confirm *CDKN2A* loss and gain of *MCL1, MYC* and *EGFR* in half of the samples by performing FISH. One or both of the analyses gave inconclusive results in the other half.
Conclusion: PSC-CCA exhibits multiple genetic alterations, including mutations and chromosomal imbalance. *TP53* mutations and genomic instability of *CDKN2A, MYC, ERBB2*, *EGFR* and *PIK3CA* seem to occur early in the multistep process since these alterations were observed at premalignant stage. These genetic alterations seem promising for development of sequencing guided diagnostic strategies of PSC strictures.

THU-016

Loss of signaling through the G-protein coupled bile acid receptor Tgr5 confers protection from fibrosis in the progressive cholangiopathy of Mdr2-/- mice

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Background and aims: Macrophages are chief cytokine producers in the liver under cholestatic conditions. They sense bile acids (BA) via the G-protein coupled receptor Tgr5 (Gbar1). Activation of Tgr5 has been associated with anti-inflammatory responses in models of acute cholestasis and in metabolic liver disease. Here we examine the role of Tgr5 in $Mdr2^{-/-}$ mice, in which biliary BA and cholesterol-microcrystals cause chronic inflammation and progressive fibrosis.
Method: Double knockout mice (DKO) were generated from $Mdr2^{-/-}$ and $Tgr5^{-/-}$ mice in C57BL/6 background and liver injury was characterized in 60-day-old male mice of both genotypes by determining serum liver biochemistries (colorimetric assays), percent area fibrosis on Sirius Red stained liver sections, and qPCR. Liver mononuclear cell (MNC) populations were enumerated by flow cytometry.
Results: Compared with $Mdr2^{-/-}$ mice, lack of Tgr5 activation in DKO mice reduced serum ALT (mean ± SEM: 197 ± 36 vs 359 ± 29 IU/L in DKO vs Mdr2-/-; $p < 0.01$) and ALP levels (70 ± 2 vs 83 ± 4 IU/L, $p = 0.01$). The liver-to-body weight ratios were significantly reduced in DKO ($p < 0.01$) and similar to wild type mice. Liver fibrosis was reduced (% area fibrosis: 4.2 ± 0.5 vs 6.3 ± 0.5%, $p < 0.05$) which was corroborated by downregulation of mRNA expression for Col1a2 ($p < 0.05$), and reduced number of periportal, desmin+ activated hepatic stellate cells in DKO mice. Serum BA concentrations were elevated and similar between both genotypes. Searching for mechanisms by which Tgr5 deletion conferred protection, we found that the pro-inflammatory cytokines TNFα and IL-1β were downregulated in whole liver ($p < 0.05$) and in hepatic MNC from DKO mice. While frequency of hepatic TNFα+ macrophages (MP) was reduced in DKO mice (%TNFa+/CD11b + F4/80+: 23 ± 3 vs 65 ± 3; $p < 0.01$), $Foxp3^{+}CD25^{+}$ regulatory T cells (Tregs) were expanded in these mice (%Tregs/CD4+: 4.4 ± 0.4 vs 2.7 ± 0.7; $p = 0.06$). When Tregs were cultured in media conditioned with supernatant collected from MP from WT or Tgr5-/- mice exposed to chenodeoxycholic acid, only the supernatant from WT mice repressed Foxp3 in Tregs.
Conclusion: In chronic cholestasis, bile acids induce pro-inflammatory cytokine production in hepatic MP in Tgr5-dependent manner which repress Treg responses and promote liver fibrosis. Whether the protective effects of Tgr5-deficiency in a genetic model can be reproduced in a pharmacological rescue approach in sclerosing cholangitis requires further investigations.

THU-017

Glucagon like peptide-2 treatment improves liver and bile duct injury in the Mdr2-/- mouse model of sclerosing cholangitis

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Background and aims: Glucagon like peptide (GLP)-1 has anti-apoptotic effects on cholangiocytes, thereby counteracting ductopenia and possibly cholestasis. GLP-2, deriving from the same precursor molecule proglucagon, exerts potent intestinotrophic endocrine and paracrine actions stimulating growth and repair of intestinal epithelium. However, its impact on liver, specifically on cholangiocytes, is poorly understood. Therefore, we aimed to test our hypothesis that the GLP2 analogue teduglutide has cholangioprotective and thereby anti-cholestastic effects in the Mdr2/Abcb4 KO mouse as a model of sclerosing cholangitis with profound hepatic inflammation and fibrosis
Method: Mdr2 (Abcb4) KO mice were injected daily for 2 weeks with a GLP-2 analogue (teduglutide). Liver RNA profiling was performed by RT-PCR. Liver histology/immunohistochemistry (IHC) and hepatobiliary bile flow were assessed.

Results: Inflammation was ameliorated as reflected by reduced mRNA levels of inflammatory markers (F4/80 (−35%), Mcp1 (−60%); iNos (−40%) $p \leq 0, 05$) in GLP-2 treated mice. Biliary fibrosis was improved by GLP-2 treatment as reflected by reduced Col1a2 mRNA expression (60%; $p \leq 0, 05$) and 3fold reduced ($p \leq 0, 05$) fibrotic areas in Sirius red stainings of GLP-2 treated Mdr2 KO mice. In addition, GLP-2 treatment reduced expression of profibrogenic and apoptotic markers Tgfβ (60%; $p = 0, 07$), Caspase3 (60%; $p \leq 0, 05$) as well as Chop (40%; $p \leq 0, 05$). CK19 mRNA and protein levels (IHC) showed a trend for an increase of about 1, 6fold at mRNA level ($p = 0, 06$) and 2fold at protein level ($p = 0, 6$) after GLP-2 treatment. In line, proliferation of cholangiocytes (and to lesser degree also hepatocytes) was increased in the GLP-2 treatment group reflected by increased KI67 protein levels ($p \leq 0, 05$, for both cell types). Despite elevated bile duct mass, expression of osteopontin (marker for reactive cholangiocyte phenotype, indicating a proinflammatory/profibrogenic status of cholangiocytes) was reduced 3fold ($p \leq 0, 05$) by GLP-2. Of note, this improvement of inflammatory and fibrotic markers by GLP2 was achieved without changes in bile flow, HCO3- output and serum biochemistry (ALT, AST, AP and bile acids) suggesting direct rather than indirect effects by improvement of cholestasis.
Conclusion: Our data show that GLP-2 treatment has a pro-regenerative, anti-inflammatory and anti-fibrotic effect on cholangiocytes in the Mdr2/Abcb4 KO mouse model of sclerosing cholangitis independent of cholestasis. Thus, targeting GLP-2 could be an interesting addition to the therapeutic armamentarium for cholangiopathies such as PSC and PBC.

THU-018

c-Jun N-terminal kinases act synergistically in hepatocytes to protect mice from cholestatic liver injury

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Background and aims: c-Jun N-terminal kinase 1 (JNK1) and JNK2 are predominantly expressed in all mammalian cells including liver cells. JNKs are activated in response to cholestatic liver injury (CLI). Our previous study showed that JNK1 is responsible for hepatic stellate cells (HSCs) activation in liver fibrosis. Moreover, we showed that JNK1 and JNK2 have combined effects in protecting mice from carbon tetrachloride (CCl4)- and acetaminophen-induced liver injury. However, the overlapping functions of both JNK genes during CLI is unknown. Here we aimed to define the overlapping function of JNKs in hepatocytes after bile duct ligation (BDL).
Method: Chronic liver injury was induced in $Jnk^{f/f}$ wildtype (WT), $Jnk2^{-/-}$ and $JNK^{\Delta hepa}$ (complete deletion of JNK1 and 2 in hepatocytes) mice via BDL. Liver injury as well as inflammatory parameters and cell infiltration were investigated. Fibrogenesis was assessed by immunoblotting, immunofluorescence and immunohistochemical analysis. Finally, bone marrow transplantation experiments were included.
Results: Combined JNK1 and JNK2 deletion in hepatocytes exacerbated liver damage markers-liver transaminases- and histological analysis exhibited increased hepatic injury and compensatory proliferation after BDL compared to $Jnk2^{-/-}$ and WT mice. TUNEL and cleaved caspase 3 staining indicated significantly increased apoptosis in hepatocytes of $JNK^{\Delta hepa}$ animals. Consequently, BDL significantly increased hepatic fibrosis in $JNK^{\Delta hepa}$ livers as assessed by Sirius Red staining as well as Collagen IA1, TIMP1 and MMP2 in WT mice. Concomitantly, immune cell infiltration and inflammatory cytokines measured by CD11b, F4/80, TNF, TGF β, IL-6, IL-1α/β were strongly up-regulated in WT mice but no alterations was evident between $Jnk2^{-/-}$ and $JNK^{\Delta hepa}$ BDL-treated livers. Moreover, BDL treated chimeric $JNK^{\Delta hepa}$ mice reconstituted either with WT BM (WT to $JNK^{\Delta hepa}$) or $JNK^{\Delta hepa}$ BM ($JNK^{\Delta hepa}$ to $JNK^{\Delta hepa}$) revealed significantly higher liver damage and liver fibrogenesis after BDL than WT mice reconstituted with either with WT BM (WT to WT) or $JNK^{\Delta hepa}$ BM ($JNK^{\Delta hepa}$ to WT)
Conclusion: Combined JNK function is protective in hepatocytes during cholestatic liver injury. This JNK-dependent effect is directly mediated by inhibiting caspase 8-dependent apoptosis during CLI.

THU-019

Impact of metabolic stress on the pathogenesis of autoimmune liver disease in subjects bearing missense variant of negative immune regulator Lnk/Sh2b3

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Background and aims: Lnk/Sh2b3 (Lnk) is an adaptor protein that negatively regulates cytokine signaling in immune cells and hematopoietic stem cells. GWAS has revealed that a missense variant of Lnk gene increases a risk for hepato-biliary autoimmune diseases, including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). However, the causal relationship between Lnk gene and the pathogenesis of liver autoimmunity is undisclosed. We sought to test the hypothesis that metabolic stress to the liver could enhance the risk of disease phenotypes in patients who possess genetic predisposition, by using Lnk deficient mice model.
Method: Recently we reported that Lnk deficient mice showed glucose intolerance and insulin resistance, which is accompanied by adipose inflammation with hyper-reactivity of IL-15 (Cell Reports, 2018). We examined Lnk deficient mice fed with high fat and high cholesterol diet (HF/HCD). In addition, we prepared Lnk deficient bone marrow chimeric mice and analyzed phenotypes of the liver.
Results: $Lnk^{-/-}$ chimeric mice showed no sign of liver inflammation with normal diet. However, AST and ALT levels from 6 week were significantly elevated with HF/HCD feedings in $Lnk^{-/-}$ chimeric mice. Histological analysis showed that accumulation of inflammatory immune cells is observed in $Lnk^{-/-}$ HF/HCD mice. In addition, analysis of intra-hepatic lymphocytes showed that $CD19^{+}$ $CD138^{+}$ plasmacytes were profoundly increased compared to the other type of cells. Moreover, overproduction of IgG and IgM and autoantibodies were detected from 6 week in serum of $Lnk^{-/-}$ chimeric mice.
Conclusion: Metabolic stress may be one of the triggers of pathogenesis of autoimmune liver diseases in subjects who have genetic predisposition to autoimmunity, or possessing Lnk/Sh2b3 variant.

THU-020

Postprandial changes in the hepatic bile acid transport in healthy human subjects measured by 11C-CSar PET/CT

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Background and aims: PET/CT with the tracer ^{11}C-CSar, a synthetic sarcosine conjugate of cholic acid, provides new possibilities for in

vivo studies of hepatic handling of conjugated bile acids, which are essential for digestion, excretion of metabolites and regulation of metabolism. We previously quantified hepatic uptake and secretion kinetics of ^{11}C-CSar in fasting healthy human subjects. It is unknown whether the postprandial changes in bile acids homeostasis leads to changes in the hepatic transport kinetics. The aim of the present study was therefore to quantify the postprandial changes in hepatic ^{11}C-CSar kinetics in healthy human subjects.

Method: Six healthy subjects underwent two subsequent 60-min dynamic liver ^{11}C-CSar PET/CT scans: one before (fasting) and one 15 minutes after ingestion of a standard liquid meal (4291 kJ; 33% protein, 32% fat, and 35% carbohydrates). Arterial and hepatic venous blood ^{11}C-CSar concentrations were measured during both scans as was hepatic blood flow using constant infusion of Indocyanine green/Fick's principle. Kinetic constants for exchange of ^{11}C-CSar between blood, hepatocytes and bile were calculated and are presented as mean (95% CI). Data were normally distributed and tested for statistically significance using a paired *t*-test.

Results: In the postprandial state, hepatic blood perfusion increased from 0.92 ml blood/min/ml liver tissue (0, 76; 1.07) to 1.23 ml blood/min/ml liver tissue (1.00; 1.45) ($p < 0.01$). In agreement with a high capacity for transport of ^{11}C-CSar from blood to hepatocytes, PS_{mem} was significantly higher than perfusion; mean fasting PS_{mem} was 3.72 ml blood/min/ml liver tissue (2.21; 5.22) and did not change ($p = 0.51$). Rate constant for backflux from hepatocyte to blood did not change ($p = 0.55$), whereas the rate constant for transport from hepatocytes to bile increased from 0.40 min^{-1} (0.25; 0.54) to 0.67 min^{-1} (0.36; 0.98) ($p < 0.05$) in agreement with an increase in the flow-independent intrinsic clearance from 1.82 ml blood/min/ml liver tissue (1.59; 2.05) to 2.13 ml blood/min/ml liver tissue (1.75; 2.50) ($p < 0.05$). Accordingly, mean hepatic residence time for ^{11}C-CSar decreased from 2.8 min (1.6; 4.0) to 1.9 min (0.6; 3.2) ($p < 0.05$). Rate constant for bile flow increased from 0.07 min^{-1} (0.05; 0.10) to 0.10 min^{-1} (0.08; 0.12) ($p < 0.05$).

Conclusion: Both the transport capacity from hepatocyte to bile and bile flow increased significantly in all subjects. Accordingly, the mean residence time in hepatocytes decreased in spite of increased influx of tracer from blood. The increased secretion could be due to recruitment of transporters at the apical membrane.

THU-021

Loss of bile salt export pump (Bsep/Abcb11) aggravates lipopolysaccharide induced hepatic inflammation in mice

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Background and aims: Bile salt export pump (Bsep) is the main canalicular transporter for biliary bile acid (BA) secretion. Although lack of BSEP causes severe cholestasis in human, Bsep KO mice are protected from acquired cholestasis because of metabolic preconditioning with a hydrophilic BA pool. This study aims to investigate whether presence of a hydrophilic BA pool may counteract development of hepatic inflammation.

Method: Wild-type (WT) and Bsep knockout (KO) mice were challenged with lipopolysaccharide (LPS) to induce hepatic inflammation. Serum biochemistry and liver histology were assessed. Hepatic markers of inflammation were analyzed by qPCR and Western blotting. Immunohistochemistry was used to determine inflammation.

Results: Bsep KO mice developed more severe LPS-induced liver inflammation than WT mice. LPS treatment increased serum levels of transaminases (ALT, AST) in Bsep KO mice compared to corresponding control group ($p \leq 0.05$), but remained unchanged in WT mice. AST, ALT and AP were elevated 6fold, 3fold, 3fold in LPS treated Bsep KO mice compared to challenged WT mice, respectively ($p \leq 0.05$). NF-kB, a main target of LPS-induced proinflammatory signaling, was significantly higher in LPS treated Bsep KO mice compared to WT mice at mRNA (1.7fold; $p \leq 0.05$) and protein level (1.8fold; $p = 0.052$). Increased inflammation was also reflected by elevated mRNA expression of proinflammatory cytokines Vcam (1.3fold), Icam (1.7fold), IL1b (2fold), Mcp1 (2.5fold), Tnfa (2.7fold), IL6 (3.2fold) and iNos (5fold) ($p \leq 0.05$). Immunohistochemistry of MAC2 showed increased immune cell number in livers of Bsep KO compared to those of WT mice. Ppara and Nrf2 (key regulators of inflammation) were both significantly reduced upon LPS challenge in Bsep KO mice at RNA level (60%; 40%, respectively; $p \leq 0.05$). Fxra, main regulator of BA metabolism and also known for its anti-inflammatory properties, was down-regulated in Bsep KO mice at mRNA level (53%; $p \leq 0.05$). Of note Cyp2b10, BA-detoxifying enzyme, was reduced by 53% ($p \leq 0.05$) in Bsep KO LPS treated mice compared to Bsep KO controls and by 40% compared to WT LPS challenged mice.

Conclusion: Absence of Bsep aggravates hepatic inflammation upon LPS stimulation, potentially by reduction of anti-inflammatory signaling via Fxra, Ppara and Nrf2 as well as by reduction of BA detoxification usually protecting these mice.

THU-022

CM-101- a Novel anti CCL24 monoclonal antibody reduces cholangiocytes proliferation in experimental cholestasis models

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Background and aims: Abnormal bile duct hyperplasia and cholangiocytes proliferation are two main features of primary sclerosing cholangitis (PSC). ChemomAb previous studies showed robust expression of CCL24 in cholangiocytes in liver biopsies from PSC patients. In this study we aimed to characterize the relevance of CCL24 in the abnormal cholangiocyte proliferation and to test the ability of CM-101, an anti CCL24 monoclonal antibody (mab), to reduce bile duct proliferation using two cholestatic animal models.

Method: Expression of CCL24 in mouse cholangiocytes was tested by immunohistochemistry in liver tissues. CM-101, a CCL24 blocking mab, was evaluated in two animal models: chronic α-naphthylisothiocyanate (ANIT) induced cholestasis in mice and bile duct ligation (BDL) in rats. In the chronic ANIT model mice were fed with ANIT diet (0.05%) for 4 weeks and treated with 5 mg/kg CM-101 or vehicle. In BDL model, rats were treated with either 10 mg/kg CM-101 or vehicle for two weeks following bile duct ligation. Cholangiocytes proliferation and hyperplasia were characterized using pan-CK, Ki67 and HandE staining.

Results: Similar to our previous observations in human liver biopsies, CCL24 was found to be expressed in mice cholangiocytes.

In the ANIT chronic treatment model, CM-101 treatment led to a significant improvement of several histopathological features. Significant reduction of fibrosis and complete abolishment of liver necrosis were observed in the CM-101 treated groups compared to vehicle treated group that was accompanied by reduction of bile acid serum levels. Biliary hyperplasia was decreased by 60%, together with reduction of Pan-CK staining further supporting a specific inhibition of cholangiocyte proliferation.

BDL induced massive cholangiocyte proliferation as seen by increased PAN-CK and Ki67 staining. Treatment with CM-101 decreased staining in the ductular area indicating a significant reduction of proliferation. Moreover, CM-101 led to down regulation of vascular endothelial growth factor (VEGF), a major regulator of cells proliferation in the liver.

Conclusion: Our finding reveals abundant expression of CCL24 in cholangiocytes implying its potential role in cholestatic diseases progression. Blocking of CCL24 by CM-101, led to significant reduction in cholangiocyte proliferation and bile duct hyperplasia, suggesting its potential therapeutic effect in PSC. CM-101 is therefore being tested in a Phase 2 clinical trial in PSC patients.

THU-023

Monoacylglycerol lipase inhibition protects from hepatic inflammation and fibrosis in mouse models of sclerosing cholangitis

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Background and aims: Lipid partitioning modulates cholestatic liver injury by providing ligands for nuclear receptors. Monoacylglycerol lipase (MGL) is the last enzymatic step in triglyceride degradation, hydrolyzing monoglycerides into glycerol and fatty acids (FA) and 2-arachidonoylglycerol into arachidonic acid (AA). We aimed to explore the role of MGL in the development of cholestatic liver and bile duct injury in mouse models of sclerosing cholangitis (SC).
Method: We analyzed the effects of 3, 5-diethoxycarbonyl-1, 4-dihydrocollidine (DDC) feeding in wild type (WT) and knock out ($MGL^{-/-}$) mice and pharmacological inhibition with JZL184 in the $Mdr2^{-/-}$mouse model of SC. Cholestatic liver injury and fibrosis were assessed by serum biochemistry, liver histology, and expression of bile acid (BA) synthesis/transport. FAs were measured by gas chromatography. Transfection and silencing were performed in vitro.
Results: $MGL^{-/-}$ mice were protected from liver injury with lower serum levels of ALT, AST (−50%), reduced ductular proliferation (CK19 −50% mRNA) and attenuated reactive cholangiocyte phenotype (OPN, VCAM). BA transporter protein and gene expression were increased for Mrp2/3, Ostα (+40%) and Mrp4 (+60%) without changes in Ntcp/Oatp1. Inflammation was suppressed as reflected by F4/80 IHC and Cox2 mRNA (−60%). Importantly fibrosis (Sirius red), hepatic hydroxyproline content (−50%), Col1a1/Col1a2 genes (−60%) were reduced. Intestinal gene expression revealed diminished inflammation (TNFα −70%, F4/80 −40%), while FXR target genes were reduced (FGF15, iBABP-50%) in line with increased BA synthesis (Cyp7a1 + 50%) in liver. Importantly, $Mdr2^{-/-}$ fed JZL184 showed reduced serum levels of ALT, AP and BA (−50%) as well as diminished fibrosis and Col1a1/Col1a2 genes (−60%). Ductular proliferation was attenuated (CK19 −40% mRNA) along with inflammation-F4/80 (−60%) and MCP1 (−50%) mRNA in liver and intestine (TNFα −70%, F4/80 −40%). Intestinal FXR target genes were again reduced (FGF15, iBABP-50%). Interestingly, FA analysis showed accumulation of AA in DDC-fed $MGL^{-/-}$ and in JZL184 treated $Mdr2^{-/-}$ mice. When MGL was silenced in Caco2, cells became unresponsive to FXR agonism by CDCA (iBABP −60%, FGF19 −50%). In vitro, retinoid X receptor (RXR) agonism induced by AA diminished FXRE luciferase activity (−70%).
Conclusion: Inhibition of MGL protects against hepatic inflammation and biliary fibrosis despite intestinal competition as a result of AA-mediated RXR agonism

THU-024

Methylation signatures in blood show accelerated epigenetic aging in patients with primary sclerosing cholangitis compared to healthy controls

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Background and aims: A DNA methylation (DNAm) signature derived from 353 CpG sites (the Horvath clock) has been proposed as an epigenetic measure of human chronological and biological age. This epigenetic signature is accelerated in diverse tissue types in various disorders, including non-alcoholic steatohepatitis (Loomba, et al. JCI Insight 2018), and is associated with mortality. Here, we assayed whole blood DNAm to explore epigenetic age acceleration (AA) in patients with primary sclerosing cholangitis (PSC).
Method: Using the MethylationEPIC BeadChip (850 K) array, DNAm signatures in whole blood were analyzed in 44 patients with PSC enrolled in a 96-week, Phase 2 trial of simtuzumab (Ishak F0-1, n = 22; F5-6, n = 22). AA, defined as the difference between DNAm age and the prediction based on a sex-adjusted linear model derived using a healthy reference population (n = 650), was calculated. Comparisons between patients with high and low AA (≥vs <median AA) were made using Mann-Whitney tests and Kaplan-Meier analysis was used evaluate the association between AA and PSC-related clinical events (e.g. decompensation, ascending cholangitis, cholangiocarcinoma, transplantation, death).
Results: The epigenetic model accurately predicted the chronological age of PSC patients (Spearman $\rho = 0.84$; $p = 9.7\times10^{-13}$) with a median difference of 4.4 years (IQR 5.25 years). Compared to healthy controls, significant AA was observed in PSC patients (median difference, 8.29 years; $p < 2.2\times10^{-16}$ [Figure A]). No significant differences in age, sex, race, BMI, use of UDCA, or presence of IBD were observed between PSC patients with low versus high AA. However, compared with patients with low AA, those with high AA had greater median serum ALP (193 vs 410 U/L; p = 0.007), GGT (221 vs 437 U/L, p = 0.05), ELF (9.1 vs 10.5, p = 0.007), and hepatic collagen content (4.3% vs 9.1%, p = 0.06) and α-SMA expression (3.9% vs 11.3%, p = 0.01). Cirrhosis (Ishak F5-6) was associated with significant AA (9.6 vs 6.9 years in F0-1; p = 0.015 [Figure A]) and PSC patients with high AA had a greater risk of PSC-related clinical events (log-rank p = 0.038 [Figure B]).

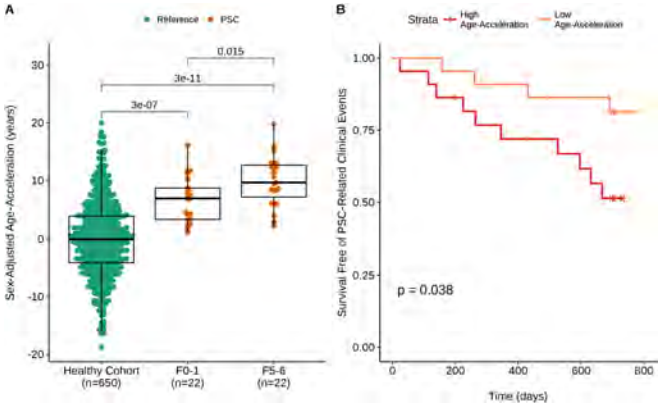

Figure: (A) Age acceleration in controls and PSC subjects according to fibrosis stage. (B) Survival free of PSC-related clinical events according to low versus high (relative to median) age acceleration.

Conclusion: This analysis of blood DNAm profiles suggests that compared with healthy controls, patients with PSC-particularly those with cirrhosis-exhibit significant acceleration of epigenetic age. Future studies are required to evaluate the effect of therapies on global methylation patterns and age acceleration in PSC.

THU-025

Pathway-analysis using datasets of GWAS and microarray identified IFNG as the most significant upstream-regulator in primary biliary cholangitis

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Background and aims: Genome-wide association studies (GWAS) in European descents and East Asian populations have identified more than 40 disease-susceptibility genes in primary biliary cholangitis (PBC). However, the disease-pathways and their upstream-regulators remain to be elucidated. The aim of this study is to objectively identify them in PBC by integrated analysis of GWAS and mRNA microarray in the Japanese population.

Method: We performed the analysis of disease-pathways and their upstream-regulators by Ingenuity Pathway Analysis (IPA) using the dataset 1 of GWAS (1920 PBC cases and 1770 controls) which included 261 annotated genes derived from 6760 SNPs ($p < 0.00001$), dataset 2 of mRNA microarray of liver biopsy specimens (15 PBC cases and 5 normal controls) which included 1506 genes with fold expression change >2 as compared to controls ($p < 0.05$), and dataset 3 of public mRNA microarray of peripheral blood mononuclear cells (PBMC) (2 PBC cases and 4 normal controls) which included 397 genes with fold expression change >2 as compared to controls ($p < 0.05$). Hierarchical cluster-analysis was performed using dataset 2 and the correlation of the genes with disease activity (AST, ALT and ALP levels) was analyzed.

Results: There were 34 genes (HLA, IKZF3, PRKCB, etc.) that were overlapped between the datasets 1 and 2, while there were 17 overlapped pathways (Th1, Th2 pathways, etc.) and 144 overlapped upstream regulators between the datasets 1 and 2. Among these 144 upstream regulators, 10 upstream-regulators showed fold expression change >2 in the micro array. Among these 10 upstream regulators, IFNG, CD40LG, SPIB, CD2, FASLG and B2M belonged to the cluster 1 which showed the strongest correlation with serum AST, ALT and ALP levels among 4 distinct clusters (cluster 1, 1-2, 2 and 2-2 containing 387, 308, 49 and 762 genes, respectively). PBC patients were also grouped into two distinct types, high and low disease-activity, by hierarchical clustering. Furthermore, the meta-analysis of upstream regulators using 3 datasets revealed that IFNG was the most significant upstream regulator associated with PBC ($p = 5.02E-49$).

Conclusion: Our hypothesis free integrated analysis using GWAS and microarray datasets predicted that IFNG is the most significant upstream-regulator in PBC. This is consistent with the previous reports demonstrating the importance of IFNG pathways in humans and mouse- model of PBC. Further studies focusing on IFNG -pathway are needed to identify the new molecular targets for PBC in humans.

THU-026

Natural killer T cells promote cholestatic liver disease in bile duct ligated mice

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Background and aims: Natural Killer T (NKT) cells are a subset of lymphocytes with immune regulatory properties. NKT cells consist of an invariant (iNKT) and a non-invariant subgroup both responding to lipid antigens presented by the non-classical MHC molecule CD1d. We have previously demonstrated that CD1d on cholangiocytes presents lipid antigens to NKT cells. In this project we investigated the role of NKT cells in the pathophysiology of cholestasis by ligating the common bile duct in CD1d knockout ($Cd1d^{-/-}$) and wild type (WT) mice.

Method: We performed bile duct ligation (BDL) of the common bile duct of $Cd1d^{-/-}$ and WT mice. Sham operated mice underwent an identical surgical procedure without BDL. Weight was monitored daily. The mice were sacrificed after 3 or 5 days, and serum, spleens and livers were collected. Isolated lymphocytes from liver and spleen were stained with monoclonal antibodies and analysed by flow cytometry. Serum was analysed for alkaline phosphatase (ALP) and bilirubin.

Results: WT mice undergoing BDL had a decreased hepatic NKT cell population indicating activation at day 5 (33% vs. 15%, $P = 0.02$), corroborated by increased CD69 expression at day 3 (median fluorescence intensity (MFI) 709 vs. 1458, $P < 0.001$) and day 5 (599 MFI vs. 1229 MFI, $P < 0.001$). In both liver and spleen there was no change in the percentage of the remaining $TCR\beta^+$ cells, nor did they have an activated phenotype. $Cd1d^{-/-}$ mice undergoing BDL were protected against disease compared to WT mice. This was demonstrated by reduced weight loss at day 1; (7% vs. 11%, $P = 0.002$), day 2; (8% vs. 16%, $P = 0.003$) and at day 3; (7% vs. 15%, $P = 0.0003$). $Cd1d^{-/-}$ mice also had lower serum levels of ALP; (345 U/L vs. 511 U/L, $P = 0.036$) and bilirubin; (115 μmol/L vs. 224 μmol/L, $P = 0.003$).

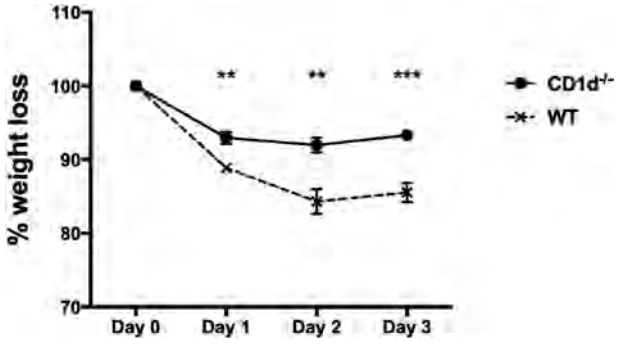

Figure: Daily percent weight for $Cd1d^{-/-}$ and WT mice after bile duct ligation.

Conclusion: We observed a clear activation of hepatic NKT cells in a mouse model of cholestasis. $Cd1d^{-/-}$ mice depleted of both invariant and non-invariant NKT cells were protected from cholestatic liver damage. Our findings contrast previous reports in $J\alpha18^{-/-}$ mice

lacking only iNKT cells. This suggests a potential detrimental role of the non-invariant NKT cells during cholestasis.

THU-027

The human apical sodium dependent bile salt transporter (ASBT) activates a bile salt-induced defense in human cholangiocytes

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Background and aims: We previously proposed the "biliary HCO_3^- umbrella" hypothesis as a protective mechanism of human cholangiocytes against potentially toxic hydrophobic bile salts present in human bile. This apical barrier of bicarbonate (HCO_3^-) might keep biliary bile salt monomers such as glycochenodeoxycholate (GCDC) in a deprotonated, negatively charged, membrane-impermeable state. Uptake of large amounts of hydrophobic bile salts by ASBT could be deleterious for human cholangiocytes. Therefore, we speculated that ASBT in human cholangiocytes may serve as mediator for the activation of defense mechanisms by trace amounts of biliary bile salts, but not as high capacity bile salt transporter. Here we studied ASBT-mediated uptake and signaling of bile salts in human and rodent cholangiocytes affecting cellular viability, apoptosis, and bile salt-sensitive defense mechanisms.
Method: Normal human (NHC) and mouse cholangiocytes (NMC) and ASBT-overexpressing human immortalized H69 cholangiocytes ($ASBT^+$-H69) were exposed to radiolabeled ^{3}H-taurocholate to determine functional bile salt uptake. Cholangiocyte apoptosis and viability were determined by caspase-3/-7 and WST assays. Intracellular signaling response to bile salts was analyzed mainly by RT-qPCR, WB and ELISA.
Results: NMC expressed *Asbt* mRNA at higher levels than NHC. Accordingly, taurocholate uptake was 100-fold higher in murine than human cholangiocytes. Overexpression of ASBT in H69 cholangiocytes increased Na^+-dependent bile salt uptake from 0.1 to 49.3 pmol/mg protein/min. Exposure to GCDC induced caspase-3/-7 activity in $ASBT^+$-H69 compared to controls, whereas TCDC had no effect. In NHC and $ASBT^+$-H69, both mRNA and protein expression of farnesoid x receptor (FXR) and fibroblast growth factor (FGF19) were positively correlated with ASBT-dependent bile salt uptake. In NHC, ASBT-dependent bile salt uptake led to increased membrane expression of anion exchanger 2 (AE2), cystic fibrosis transmembrane conductance regulator (CFTR) and transmembrane member 16a (TMEM16a), crucial for adequate apical Cl^-/HCO_3^- secretion.
Conclusion: Human compared to murine cholangiocytes have a markedly reduced capacity to take up conjugated biliary bile salts via ASBT. ASBT-mediated bile salt dependent intracellular defense mechanisms may stabilize the "biliary HCO_3^- umbrella" and, thereby, protect human cholangiocytes against uncontrolled ASBT-independent entry of potentially toxic human hydrophobic bile salts.

THU-028

Gut derived bacteria, presented by liver dendritic cells can activate liver MAIT cells in primary sclerosing cholangitis

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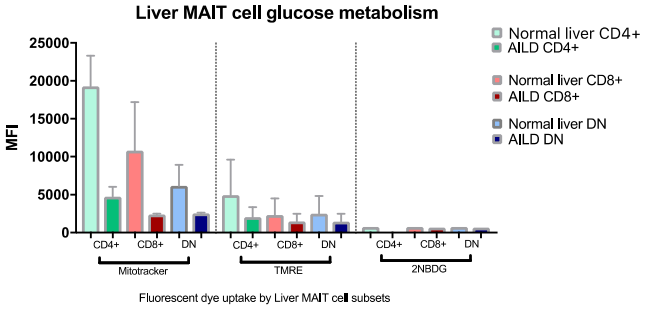
Background and aims: Mucosal-associated invariant T (MAIT) cells are the most abundant invariant T cell subset in the human liver. Their unique T cell receptor Vα7.2 is restricted by MR1, a MHC Class-1 like molecule. MAIT cell activation, via MR1 by microbial vitamin B metabolites or cytokines e.g. Interleukin 12 or 18, induces rapid release of Interferon gamma (IFNγ), Tumour necrosis factor alpha (TNFa), Granzymes and Perforin. Liver MAIT cells are emerging as significant players in autoimmune liver disease (AILD) but their biology is relatively unexplored. We aim to 1) investigate the functional profile of human liver MAIT cells activated by E.coli primed human liver dendritic cells (DCs) and 2) assess liver MAIT cell subset immunometabolism in AILD.
Method: 1) Cell Sorted liver DCs (HLADR+, CD123+, CD11c+) from human explanted PSC liver were stimulated with E.coli (200 E.coli/cell) or Control (Media with no E.coli) for 12hours, followed by addition of Cell Sorted CD3+ T cells from the same liver into this co-culture for 4hours. Expression of IFNy, TNFa and CD107a (degranulation marker) by MAIT cells (defined as CD3, Va7.2 TCR and CD161) were examined. 2) Glucose catabolism in MAIT cell subsets from AILD explants (n = 3, 1AIH, 1PSC, 1PBC) and normal liver (n = 2 donor livers) were explored using fluorescent dyes to assess a) Oxidative phosphorylation (mitochondrial mass (Mitotracker), mitochondrial membrane potential (TMRE, tetramethylrhodamine ethyl ester) and b) Glycolysis (2NBDG, 2- (*N*- (7-Nitrobenz-2-oxa-1, 3- diazol-4-yl) Amino)-2-Deoxyglucose) (n = 1 AIH, n = 1 donor liver). Co-culture and immunometabolism results were analysed with FlowJo V.10 and GraphPad Prism 6.
Results: 1) Functional assessment of liver derived MAIT cells activated by E.coli primed liver DCs revealed highest expression of IFNy 20.1% (TNFa 3.9%, CD107a 4.72%) compared to controls. 2) A marked difference in fluorescent dye Mitotracker uptake is seen between AILD and normal liver (Figure). Amongst AILD, slightly higher Mitotracker and TMRE (mitochondrial membrane potential) uptake was noted in CD4 compared to CD8 or DN MAIT cells. There was low 2NBDG uptake overall but none seen in CD4 MAIT cells.



Conclusion: We have shown for the first time that human liver MAIT cells can be activated by E.coli primed liver DCs in the PSC liver. Our preliminary data suggests CD4 liver MAIT cells in AILD and all normal liver MAIT cell subsets are metabolically quiescent compared to CD8 and DN liver MAIT cells in AILD, which may be utilizing Glycolysis or an alternative metabolic pathway.

THU-029

Interleukin 23 produced by hepatic monocyte-derived macrophages is essential for the development of primary biliary cholangitis

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Background and aims: Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease characterized by non-suppurative cholangitis resulting in progressive cholestasis. Mononuclear phagocytes (MNPs), comprise of monocyte, dendritic cells and macrophages, constitute major arm of the innate immune system and were shown to be involved in the pathogenesis of autoimmune disorders. Interleukin 23 (IL-23) is a pro-inflammatory cytokine belongs to

the IL-12 family. IL-23 positive cells were detected around bile ducts in patients with advanced stage of PBC and IL-23 serum levels were found to be in correlation with PBC disease severity. Our overall goal was to assess the involvement of IL-23 derived from MNPs in the pathogenesis of PBC, and specifically addresses the subset of cells responsible for IL-23 secretion in this pathology.

Method: We took advantage of transgenic mice systems enabling us to achieve MNPs restricted IL-23 deficiency ($CD11c^{cre}P19^{flox}$ and $CX3CR1^{cre}P19^{flox}$) and subjected them to inducible xenobiotic model of PBC by immunization with 2-octynoic acid conjugated to bovine serum albumin. In addition, specific hepatic MNPs populations were sorted from livers of affected animals and assessed for IL-23 expression. Analysis included histology assessment by HandE and Sirius red staining, anti mitochondrial (AMA) serum titers, flow cytometry for hepatic non-parenchymal cells, and hepatic cytokine expression profile by RT PCR.

Results: Both $CD11c^{cre}P19^{flox}$ and $CX3CR1^{cre}P19^{flox}$ mice exhibited significant amelioration of disease severity as manifested by reduced extent of portal inflammation and peri-portal collagen deposition assessed by liver histology, and decreased hepatic expression levels of the pro-inflammatory cytokines TNFα and IFNγ. In addition, Flow cytometry analysis revealed a decreased CD8/CD4 hepatic T cell ratio in MNPs restricted IL-23 deficient mice accompanied by a significant reduction in the incidence of hepatic IL-17A producing CD4+ T cells. No significant difference in AMA titers was observed. Real time PCR analysis done on sorted hepatic cells demonstrated unique high expression of IL-23 mRNA by monocyte-derived macrophages a specific MNPs population expressing both CD11c and CX3CR1.

Conclusion: Our results indicate a major role for IL-23 produced by hepatic monocyte-derived macrophages in the pathogenesis of PBC. These results may pave the road for the development of new immune-based and cell specific therapeutic modalities.

Cirrhosis: ACLF and Critical illness

THU-031

Hemorrhagic and thrombotic complications in critically patients with cirrhosis

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Background and aims: Altered haemostatic parameters are ubiquitous in patients with cirrhotic chronic liver disease (CLD), with changes in pro- and anti-coagulant processes that may result in haemorrhagic (HC) or thrombotic (TC) complications. In hospitalised patients with acutely decompensated (AD) CLD, indications are of increased risk of thrombotic complications, but that in acute on chronic liver failure (ACLF) is unknown. In a large cohort of critically ill patients with AD and ACLF we determined the prevalence and clinical associations of HC and TC.

Method: We studied consecutive patients with AD and ACLF admitted to a specialist Intensive Care Unit (ICU) 2009–2016. Demographics, clinical and standard laboratory findings and MELD and CLIF-C OF scores were determined. Using standard definitions, prevalence and timing of HC and TC were determined. Multi-variable analysis utilised logistic regression.

Results: The study cohort was 623 patients of median age 52 years, 61% male, 47% alcohol aetiology. Median MELD and CLIF-C OF scores were 26, and 11 respectively. 30% of patients had AD and 12%, 23%, and 35% had ACLF grades of 1, 2 and 3 respectively. 77 patients (12%) had hepatocellular carcinoma (HCC). Overall hospital mortality was 43%.

HC occurred in 332 (53%) patients, 67% with variceal bleeding. HC occurred on admission in 249 (40%) and as later episodes in 83 (13%) at median 9 (4–16) days later. Later HC were associated with greater ACLF severity ($p < 0.01$), prolonged APTR ($p < 0.01$) and increased mortality (Adjusted Odds Ratio 2.8 (95% CI 1.78–4.7) < 0.001).

TC occurred in 124 patients (20%), with 42 (7%) with pre-existing TC and 82 (13%) newly identified after ICU admission. New TC included 57 portal vein (PVT), 14 deep vein (DVT) 28 other venous and 5 arterial thromboses. Both pre-existing and new TC were independently associated with presence of hepatocellular carcinoma (AOR 3.7 (2.3–6.2), $p < 0.001$) but not coagulation status measures, ACLF severity or with administration of fresh frozen plasma, though new TC showed association with cryoprecipitate use ($p < 0.04$). TC on or after admission were not independently associated with increased hospital mortality.

Conclusion: In CLD patients admitted to ICU Haemorrhagic complications predominate and impact on mortality. Thrombotic complications are common and associated with concurrent HCC and may precipitate ACLF but are difficult to predict and do not show independent association with hospital mortality.

THU-032

Peritoneal CD206 links macrophage heterogeneity in decompensated cirrhosis with outcome of spontaneous bacterial peritonitis

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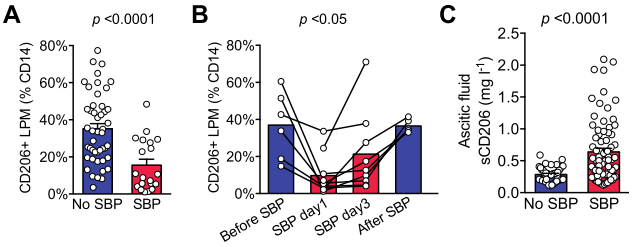
Background and aims: Peritoneal macrophages (PM) are thought to regulate peritoneal inflammation and control bacterial infections in decompensated cirrhosis. The aim of this study was to characterize human PM heterogeneity and to link PM activation with the outcome of spontaneous bacterial peritonitis (SBP).

Method: 186 patients with decompensated cirrhosis were included, of which 89 had SBP. Human PM were characterized by flow cytometry (n = 67), transcriptome-wide gene-level expression analysis (n = 4) and *ex vivo* experiments. The soluble form of the mannose receptor CD206 was determined in ascitic fluid by ELISA (n = 120).



Results: Employing CD206 surface expression, we identified subsets of human large (LPM) and small PM (SPM), which differed in granularity and maturation states. FACS-sorted LPM from patients with decompensated cirrhosis revealed discrete transcriptome clusters, comprising more than 4000 differentially regulated genes involved in cell cycle, metabolism, and immune signaling. In contrast to SPM, LPM displayed a resident inflammatory phenotype, released higher levels of TNF after stimulation and were more resistant to inducing LPS tolerance. CD206 expression and sCD206 release from LPM could be manipulated by incubating PM with TLR2/TLR6 and

TLR4 agonists *in vitro*. Serial clinical samples revealed a depletion of LPM in the early phase of SBP followed by a recovery after successful treatment (Figure 1A-B). Higher ascitic fluid concentrations of sCD206 identified patients with SBP (Figure 1C) and indicated poor survival after 90 days ($p < 0.003$, in log rank test).
Conclusion: CD206 expression indicates a sub set of mature, resident, inflammatory human PM. Ascitic fluid concentrations of its soluble form predicts poor outcome of SBP.

THU-033
Impact of early Hemodynamic correction of AKI in acute on chronic liver failure patients with large ascites
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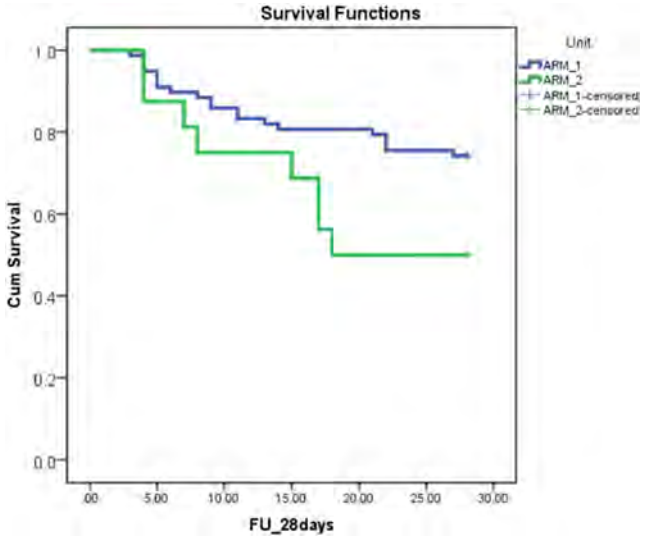
Background and aims: Renal failure is the most important predictor of mortality in patients with Acute on chronic liver failure (ACLF). Early initiation of therapy to correct hemodynamics, improves renal blood flow and may improve survival.
Aim of the study was to assess survival in ACLF patients with AKI (Creatinine >2) with continuous slow infusion of furosemide, albumin, with Terlipressin [SAFI (T)] administered according to a response-guided protocol as compared with Standard Medical Therapy (SMT) for Hepato-renal Syndrome (HRS).
Method: ACLF patients with AKI (defined by ICA-AKI Criteria) with Creatinine >2 and large ascites were included. Within 12 hrs of admission 2D-ECHO for cardiac indices and Systemic vascular resistence (SVR), Doppler for Renal artery resistive indices (RARI) and IVC diameter with respiratory variability and Urine sediments were examined to rule out pre-renal AKI and ATN respectively. Excluding pre-renal AKI and ATN, 78 patients in ARM 1 were managed with SAFI (T) and 16 patients in ARM 2, were managed with SMT. Patients in ARM 1 were given infusions of Furosemide at 2 mg/hr, albumin at 2gm/hr (20–40gm/d) and Terlipressin infusion at 2 mg/24 hrs. If 24-hr Urine Na persisted below 80meq, response guided increase in terlipressin (1 mg/24hrly) and Furosemide (2 mg/12hrly) was done after correcting anaemia (≥8 g/dl) and excluding cardiac conduction anomalies with baseline ECG (and repeated 12 hrly) till reduction/normalization of S. creatinine.
Results: Baseline Characteristics were comparable in both arms ARM1 [SAFI (T)] (N-78) v/s ARM2 [SMT] (N-16): CTP-12.3 ± 3.6 vs 12.3 ± 1.6, CLIF-SOFA- 10.9 ± 1.8 vs 11.5 ± 2.2, MELD- 33 ± 8.3 vs 34 ± 9.1, Creatinine- 2.8 ± 0.76 vs 3.3 ± 1.3, U Na day 0- 28.9 ± 21 vs 35.9 ± 6. Urinary Na improved to 126 ± 101 in ARM1 as compared to 86 ± 44 in ARM-2. Overall survival was 75% in ARM1 vs 50% in ARM-2. There was significant improvement in systemic hemodynamic parameters in ACLF patients in ARM 1.
Conclusion: Early correction of systemic hemodynamics with aggressive therapy leads to improved survival in ACLF patients with AKI.

Variable	Admission	End of therapy	p value
Heart rate (bpm)	97.2 ± 8.3	81.9 ± 8.9	.000
SV (ml/beat)	92.1 ± 25.1	72.5 ± 24.4	.000
SVI (ml/m^2/beat)	50.9 ± 13.9	43.4 ± 15.4	.001
Cardiac output (L/min)	8.9 ± 2.6	6.0 ± 2.3	.000
Cardiac index (L/min/m^2)	4.9 ± 1.4	3.6 ± 1.4	.000
MAP (mmHg)	81.6 ± 6.5	93.9 ± 4.9	.000
SVR (dynes-sec/cm^{-5})	668.8 ± 234.1	1299.5 ± 531.5	.000
SVRI (dynes-sec/cm^{-5}/m^2)	1206.8 ± 398.8	2192.7 ± 907.6	.000



THU-034
Serum metabolite profiling predicts survival in patients with hepatitis B virus related acute-on-chronic liver failure
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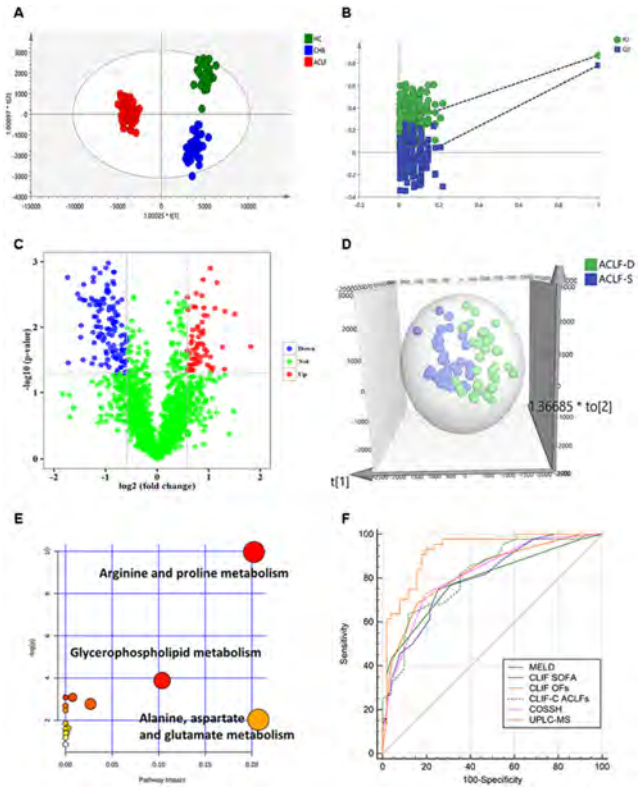
Background and aims: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is characterized by acute deterioration of liver function, organ failure and high short term-mortality. Predicting survival in these patients is meaningful to allocate resources for liver transplantation. The study was to investigate whether the metabolic profiling can predict the 28-day survival.
Method: 95 HBV-ACLF patients, who met the APASL ACLF criteria from December 2016 to January 2018, were recruited and followed for 28 day. 48 chronic hepatitis B patients (CHB) and 30 healthy controls (HC) with no history of liver disease were also enrolled. All serum aliquots were analyzed by Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) in both positive and negative mode. Multivariate analysis was performed by SIMCA P software.
Results: 51 subjects of the ACLF patients spontaneously survived. The age, hepatic encephalopathy grade, total bilirubin, blood urea nitrogen, international normalized ratio (INR), white blood cell count and platelet were associated with mortality. The non-survivors group show a higher Child-Pugh, MELD, CLIF-SOFA, CLIF-OFs, COSSH score ($p < 0.001$).The UPLC-MS metabolic profiling accurately discriminated not only ACLF patients from HC and CHB, but also survivors and non-survivors. Base on volcano plot and the VIP, 24 potential metabolites were selected. Elevated amino acid, bile acid, fatty acid and decreased phosphatidylcholines were found in non-survivors group. Metabolic pathways show these metabolites mainly contribute to the arginine and proline metabolism, glycerophospholipid metabolism and alanine, asparatate and glutamate metabolism. A new prognostic model based on the combination of lysophosphatidylcolines (16:0), argininic acid, blood urea nitrogen, INR and platelet can accurately predict survival. The area under the receiver operating curve (AUROC) for 28-day mortality was 0.923, which was significantly higher than that of the MELD, CLIF-SOFA, CLIF-OFs, CLIF-C ACLF, COSSH (all $p < 0.05$).
Conclusion: Serum metabolic differences could distinguish ACLF patients from CHB and HC. Amino acid dysregulation and lipid metabolism abnormality are associated with the severity of disease.

A new prognostic model combining metabolites with clinical indicators could predict mortality in HBV-ACLF patients but needs further validation.



THU-035

A shorter period of a subsequent episode of acute decompensation of cirrhosis predicts worse outcome: A single center experience

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Background and aims: Acute decompensation (AD) of liver cirrhosis is sometimes fatal and impairs quality of life. The dynamic change, e. g. recovery/deterioration of organ function, along with recurrent episodes of AD, is frequently encountered in clinical settings. The natural history of patients who survived without liver transplantation (LT) after their first episode of AD is still not elucidated.
Method: In this single liver transplant centre observation study approved by local institutional IRB, we retrospectively recruited 768 consecutive admissions to our liver unit from Apr 2015 to Apr 2018. After exclusion of admissions for planned procedures, 166 cases (254 admissions) with AD of cirrhosis were extracted. Patients with active HCC over Milan criteria, advanced malignancy of other organs, HIV, or patients undergo chronic dialysis were further excluded. Transplant-free survival (TFS, followed for at least 6 months) and various prognostic clinical parameters, including MELD and simplified CLIF-SOFA scores were evaluated. Acute-on-chronic liver failure (ACLF) was assessed according to the criteria suggested by EASL-CLIF Consortium.
Results: Totally, 120 cirrhotic patients (58% male; aged 63.5 ± 15 years) with 184 times of AD were analysed. Of the first episode of AD, 30% were of ACLF Gr 1–3. The TFS for 30 days was 85.8%. Patients who survived without LT for the first 30 days could be categorized as Group A: patients who recovered without a recurrent episode of AD (46%); Group B: patients who recovered once but with a subsequent episode (s) of AD (43%); Group C: patients who deteriorated without recovery (11%). Compared to Group A, patients in Group B were significantly older in age ($p = 0.03$), higher percentage of NASH and cirrhosis due to cholestasis, less active drinking. Group B patients were significantly more thrombocytopenic ($p < 0.01$), less leukocytic ($p < 0.01$), and of more frequent hypoalbuminemia ($p < 0.01$). However, patients of Group A and B didn't differ in Child-Pugh scores, MELD, simplified CLIF-SOFA scores, and percentage of higher grades of ACLF. Of patients of Group B who had shorter periods of subsequent ADs within 90 days, decreased 180-day ($p = 0.02$, log-rank) and 1-year ($p = 0.08$) TFS were noticed, compared to those beyond 90 days, even though MELD or CLIF-SOFA did not differ between the two groups.
Conclusion: The prognosis of transplant-free survivors within 30 days after the first episode of AD might be heterogeneous, and may not be predicted with widely used prognostic systems. Shorter periods of subsequent AD (within 90 days) might be prognostic for TFS in AD of liver cirrhosis.

THU-036

First description of the immune checkpoint receptor landscape in decompensated cirrhosis and ACLF

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Background and aims: Acute-on-chronic liver failure (ACLF) is characterised by a supra-inflammatory state that coexists with profound immune paralysis. Individual immunoregulatory check-point receptors (CR) can direct functional activation and/or inhibition of both innate and adaptive immunity. Neutralisation of inhibitory-CRs including PD1 (Nivolumab) and CTLA4 (Ipilimumab) has revolutionised cancer treatment via restoration of anti-tumour immunity. We have shown that bacterial translocation drives hyperexpression of inhibitory-CRs in Alcoholic Hepatitis but their role in ACLF is unknown.
Method: We measured serum levels of 15 known stimulatory and inhibitory CRs (including PD1, PDL1, CTLA4), bacterial translocation (D-lactate; DLac) and gut barrier integrity (Zonulin1; ZO1) by ELISA in 511 patients with decompensated cirrhosis included in the CANONIC Study; 334 with acute decompensation (AD) and 177 with ACLF at inclusion. Group comparisons, cut-off identification and survival analyses were performed in SPSS and R.
Results: Both soluble immune-activatory-CR CD40 ($p < 0.001$) and immunosuppressive-CR BTLA (B and T-cell Lymphocyte-Associated; $p = 0.004$) increased significantly with presence of ACLF and ACLF grade, but we saw no changes in PD1, PDL1 and CTLA4. Serum CD80, which can act as both inhibitory and stimulatory, also increased with ACLF grade ($p = 0.002$), in particular between ACLF1 and ACLF2 or 3 ($p < 0.02$). This was correlated with bacterial translocation; DLac ($p < 0.001$) and gut permeability; ZO1 ($p = 0.01$) across ACLF

grades, with DLac also discriminating between AD and ACLF ($p < 0.001$). Bacteremia during admission for all patients was also associated with increases in both DLac ($p = 0.005$) and ZO1 ($p = 0.009$). One-year transplant-free survival analysis demonstrated that increased survival was associated with lower serum BTLA (<862.31pg/ml; $p = 0.0002$), CD40 (<3.47pg/ml; $p < 0.0001$) and CD80 (<1654.28pg/ml; $p = 0.002$).

Conclusion: We demonstrate for the first time the association of both inhibitory and stimulatory immune checkpoints with the paradoxical "hyperinflammatory immunodeficient" state observed in ACLF reflecting the coexistence of a primed, hyper-activated, pro-inflammatory immunity whose antibacterial functions are switched off. Our analysis also reveals that intestinal permeability and bacterial translocation are related to ACLF severity and together with serum levels of checkpoint receptors may discriminate between clinical outcomes.

THU-037

Soluble MAdCAM-1 as a novel marker of hepatic endothelial dysfunction in acutely decompensated cirrhosis

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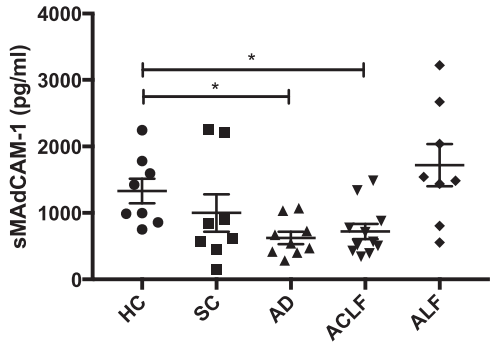
Background and aims: Mucosal addressin cellular adhesion molecule 1 (MAdCAM-1) is an endothelial adhesion molecule expressed on high endothelial venules of the gut lymphoid tissue, with aberrant expression observed on the hepatic endothelium in cirrhosis. Associations between response to therapy and soluble (s)MAdCAM-1 concentrations have been shown in patients with inflammatory bowel disease (IBD). *In vitro* data suggests Th1 inflammatory responses induce, whereas nitric oxide signalling can depress, MAdCAM-1 expression. However, the pattern of sMAdCAM-1 induction in syndromes where systemic inflammation and endothelial dysfunction coexist, such as acute-on-chronic liver failure (ACLF), are unknown.

Method: Plasma samples were obtained from patients with stable cirrhosis (SC, n = 8), acute decompensation (AD, n = 10), ACLF (n = 11), acute liver failure (ALF, n = 8), IBD (n = 4) in and healthy controls (HC, n = 8) with sequential samples taken at day 7 for ACLF patients (n = 9). sMAdCAM-1 was quantified using enzyme-linked immunosorbent assay (ELISA). Immunohistochemistry was conducted on cirrhotic explanted liver tissue (n = 21) and healthy donor tissue (n = 6) and stained with anti-MAdCAM-1 antibody.

Results: Liver histology of 17/21 (81%) patients with cirrhosis demonstrated positive MAdCAM-1 staining compared to 0/5 in the control group ($p = 0.001$), predominantly on the portal venous endothelium and peripheral lymphoid aggregates. sMAdCAM-1 was analysed in 19 patients diagnosed with alcoholic liver disease (ALD), 5 non-alcoholic steatohepatitis, 7 primary sclerosing cholangitis and 4 IBD. Compared with HC, ALD patients showed a significant reduction in sMAdCAM-1 (1330 vs 656 pg/ml, $p < 0.05$) with no differences observed when comparing other aetiologies to HC. Between AD and ACLF there was no difference in sMAdCAM-1 expression (700.8 vs 721.2 pg/ml), however, when comparing to HC both groups showed significantly lower concentrations (700.8 and 721.2 vs pg/ml 1330 pg/ml, $p < 0.05$). In contrast, for patients with ALF, sMAdCAM-1 concentration did not differ from HC (1729 vs 1330 pg/ml, $p = 0.99$). Furthermore, sMAdCAM-1 accurately predicted decompensated disease in this combined cohort (AUROC 0.845 95% CI 0.663-0.952, sensitivity 67%, specificity 100%, $p < 0.001$). Sequential ACLF samples revealed a trend towards recovery of sMAdCAM-1 concentration at day 7 compared to baseline (668.8 vs 890.1 pg/ml, $p = 0.054$).



Conclusion: MAdCAM-1 is a marker of endothelial activation in decompensated cirrhosis, independent of the presence of concurrent IBD. Soluble MAdCAM-1 expression is paradoxically depressed during the development of ACLF and strongly predicts decompensation and progression to multi-organ failure. This may represent the development of endothelial dysfunction. The role of MAdCAM-1 in promoting abnormal endothelial responses requires further investigation.

THU-038

Fungal pneumonia in critically ill cirrhotics: Spectrum and outcomes

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Background and aims: Liver cirrhosis causes immune dysregulation and increased susceptibility to fungal infections. We studied the epidemiology, spectrum, risk factors, and compared the rapid diagnostic methods and biomarkers for fungal pneumonia in critically ill cirrhotics admitted to intensive care unit (ICU).

Method: Single-center, prospective cohort study of 100 critically ill cirrhotics with fungal pneumonia between January to September 2018. Comparative analysis was done for culture, real time polymerase chain reaction (PCR) and biomarkers; bronchoalveolar lavage (BAL) and serum Galactomannan, and serum procalcitonin (PCT) measured on day 1, 3 7. Mortality within one month of diagnosis or discharge was analyzed.

Results: *Aspergillus flavus* was the most common species (70/100, 70%). Risk factors for fungal pneumonia included neutropenia (p 0.03), steroids prior to ICU admission (p 0.02), prolonged (>21 days) hospitalization ($p < 0.05$). Culture positivity was 80%. Culture was not inferior to real time PCR for diagnosis of fungal pneumonia. BAL Galactomannan was early prognostic marker with median rise >3.5 over the index value. Median PCT level was higher from day 1in the fungal pneumonia non-survivor than survivor group (3.29 vs. 0.8 ng/ml), with higher 30-day mortality (72%). Baseline PCT at admission to ICU was higher in non- survivors; levels on day 3 and day 7 were persistently higher. Higher PCT level was associated with bacterial co-infection (48%), antibiotic (74%) and antifungal therapy and renal failure and mortality.

Conclusion: Cirrhotics who are neutropenic, have prolonged hospitalization and exposed to steroids have a high risk of fungal pneumonia. High serum procalcitonin level is an independent prognostic biomarker of mortality risk in fungal pneumonia which reaches nearly 70%, high index of suspicion and early detetction is required in advanced cirrhosis.

THU-039

LPS-induced upregulation of RANTES in a new mouse model of bacterial infection related acute-on-chronic liver injury

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Background and aims: Bacterial infection (BI) is the second most common acute trigger leading to acute-on-chronic liver failure (ACLF) in humans. Here we aim to establish a novel BI-related ACLF model by intraperitoneal lipopolysaccharide injection to a knock-out mouse with well characterized chronic liver injury (*Abcb4*$^{-/-}$ mice) to mimic the disease conditions of ACLF and study the inflammatory events in this preclinical model.
Method: Fifteen week-old C57BL/6J (N = 16) (wild type, wt) or *Abcb4*$^{-/-}$ (N = 12) (knock-out, ko) were treated with IP injections of either LPS (4 mg/kg) or sterile saline solution (0.9% NaCl). Six hours after injection, mice were sacrificed, and plasma and liver tissue samples were collected. Liver-specific steady-state mRNA levels (relative to *Gapdh*) of interleukin-6 (*IL6*), C-reactive protein (*Crp*), Tumor necrosis factor-alpha (*Tnf-α*), regulated on activation, normal T cell expressed and secreted (*Rantes*, a.k.a. *Ccl5*), Toll like receptor 4 (*Tlr4*) and Monocyte chemoattractant protein-1 (*Mcp1*, a.k.a. *Ccl2*) were evaluated using the $2^{-\Delta\Delta Ct}$ method. Variables were evaluated with paired t-tests and $p < 0.05$ was considered as significant.
Results: LPS challenge resulted in rapid upregulation in hepatic expression of *Crp* (9-fold) and *Tlr4* (10-fold), while leading to a dramatic change in *IL6*, *Mcp1*, *Tnf-α* and *Rantes* mRNA levels with approximately 230-, 150-, 80- and 64-fold increases in wt control mice, respectively. Corresponding effects were also observed in the *Abcb4*$^{-/-}$ knock-out mice with no significant differences in terms of liver specific expressions of *IL6*, *Tnf-α*, *Tlr4* and *Mcp1* compared to wt mice. Of note, LPS resulted in a more profound upregulation of *Rantes* expression in *Abcb4*$^{-/-}$ mice with pre-existing liver injury (64-fold vs. 126-fold increase, $p = 0.037$), while *Mcp1* induction was comparable and *Crp* increase was more moderate (9-fold vs 4-fold, $p = 0.026$) in the knock-out mice compared with their wt counterparts.
Conclusion: In this dual hit model, high expression levels of hepatic cytokines and chemokines after intraperitoneal LPS injection suggest a novel promising approach to model BI-ACLI in Abcb4$^{-/-}$ mice. While excessive inflammatory responses might be dampened in this model after acute insult (LPS), we speculate that Rantes could specifically trigger inflammatory cascades with harmful consequences on further disease cause and prognosis.
This study was supported by BMBF LiSyM (031L0051).

THU-040

AARC score: A dynamic model to predict outcome in acute on chronic liver failure patients

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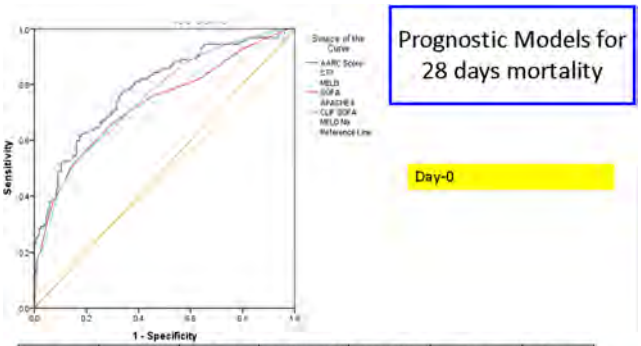
Background and aims: Acute on Chronic Liver Failure (ACLF) is a syndrome characterized by acute and severe hepatic abnormalities resulting from different types of insults, in patients with underlying chronic liver disease or cirrhosis with a high short-term mortality. Various score have been developed to determine severity of ACLF. APASL-AARC research consortium (AARC) have developed an AARC score to determine Prognosis of ACLF patient. In this study we tried to revalidate the score over a cohort of ACLF patients and evaluated the dynamicity of AARC score
Method: A total of 2324 ACLF patients, enrolled in the APASL-ACLF Research Consortium (AARC) with 90-day follow-up, were analyzed. AARC score (range 5–15) determined by 5 variables (Total bilirubin, Creatinine, Serum Lactate, Hepatic Encephalopathy and INR) was calculated and patients were divided into 3 grades- Grade A (score 5–7) Grade B (score –8–10) Grade C (score 11–15). Calculated AARC score was than validated over the entire cohort for goodness of fit and concordance by using Harrell's C and Somers D. It was also compared with other severity score like CTP, MELD and CLIF SOFA
Results: Mean age of patients was 47.35 years±13.35 years with 64.6% male.The overall survival of ACLF patients at 28 days was 40.6%, with a median of 29.7 days. The cumulative mortality in the first week in grade -A, B and C were 0, 11 and 45% respectively AARC-ACLF score (range 5–15) was found to be superior to MELD and CLIF SOFA scores in predicting mortality with an AUROC of 0.70.A score ≥ 11 at any time in 1st week was a predictor of mortality. The mortality risk could also be dynamicallyalculated as, with each unit increase in AARC-ACLF score above 10, the mortality risk increases by 20% whereas each unit increase in score within 7 days raises the 28 days mortality by 5.2%



Score	Area	CUT OFF	SENSITIVITY	SPECIFICITY	PPV	NPV
AARC Score	.78	10.5	64.1	75.9	70.7	70
MELD	.76	30	65.3	74.4	63.1	76.1
SOFA	.73	9.5	63.8	69.5	62.2	70.9
APACHE II	.70	15.5	57.9	68.8	56.8	69.8
CLIF SOFA	.69	11.5	52.2	74.9	66.8	61.9
CTP	.65	11.5	72.4	53	50.4	74.4

Conclusion: AARC-ACLF score is simple, easy and dynamic score to use in clinical practice which can reliably predict outcome in ACLF patient.

THU-041

Immune-metabolism disorder in progression of hepatitis B virus-related acute-on-chronic liver failure characterized by transcriptomics

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Background and aims: The pathophysiological etiology of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) remains

unclear. This study aims to characterize the molecular basis of HBV-ACLF using transcriptomics.
Method: Peripheral blood mononuclear cells (PBMCs) from patients with HBV-ACLF (n = 20) and acute-on-chronic hepatic dysfunction (ACHD), liver cirrhosis (LC), chronic hepatitis B (CHB) and heathy control groups (n = 15/group) were selected from a prospective multi-center cohort (Chinese Group on the Study of Severe Hepatitis B, COSSH-ACLF) for RNA-sequencing. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to confirm marker genes in the validation groups (n = 80 in ACLF group, n = 35/each other group).
Results: Principle component analysis (PCA) shows that HBV-ACLF patients with or without cirrhosis were positioned together, and clearly separated from the ACHD, LC and CHB patients, demonstrating the effectiveness of COSSH-ACLF criteria to diagnose HBV-ACLF. Functional synergy analysis of the differentially expressed genes identified 8 groups of biological processes (immune, inflammation, metabolism, virus, etc.) that contribute to HBV-ACLF progression, suggesting that excessive immune response triggered by HBV reactivation was a potential cause of progression from ACHD to ACLF grade 1. Subsequently, multiple organ failures induced by inflammation and metabolism disorder were developed in patients with ACLF grade 2/3. Comparison between the survived and deceased patients showed multiple physiological dysfunctions, e.g., metabolism disturbances of nitric oxide and ammonia, which consequently induced renal dysfunction and hepatic encephalopathy. Four differentially expressed genes, MERTK, PPARG, SEMA6B and THBS1 were functionally associated with those eight biological processes and showed increased expressions with the progression of CHB, LC, ACHD and ACLF. The qPCR validation within external patient groups confirmed their potential for use as HBV-ACLF biomarkers.
Conclusion: This study highlights immune-metabolism disorder as an important axis that drives HBV-ACLF progression, which differs from the systemic inflammatory response syndrome (SIRS) route in the patients with alcoholic liver disease-related ACLF in Western populations. This insight may help to develop more effective intensive treatment strategies to reduce the high mortality rate of HBV-ACLF.

THU-042
Hypoxia aggravates acute on chronic hepatitis through MIR-210 mediated macrophage autophagy impairment

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Background and aims: Patients with chronic hepatitis are prone to serious liver inflammation and contract Acute on Chronic Liver Failure (ACLF), when they are triggered by liver damage factors, but the mechanisms remain unclear. Different degrees of hypoxia exist in the liver tissue of chronic hepatitis, which contribute to poor prognosis. We aimed to study the role of hypoxia in mechanisms of ACLF.
Method: Expression of hypoxia inducible factor-1α (HIF-1α) in liver tissue of ACLF mouse was determined by Western Blot. Pretreating THP-1-derived macrophages (THP-M) in hypoxia condition and then exposing THP-M to LPS, the concentration of IL-1β in supernatant was measured by ELISA assay. The relative expression level of miR-210 was determined by qRT-PCR assay. The expression level of autophagy related molecules was detected by Western Blot.
Results: We found that HIF-1α was unregulated in liver tissue of ACLF mouse, indicating existence of hypoxia. Pretreating THP-M in hypoxia condition increased LPS-induced IL-1β secretion. Hypoxia increased miR-210 expression in macrophages apparently, and transfection of miR-210 agomir also increased LPS-induced IL-1β secretion. We further investigated the role of autophagy in hypoxia mediated excessive activation of macrophages. We found that hypoxia impaired macrophage autophagy, and upregulated miR-210 also impaired macrophage autophagy by targeting ATG7. Interference of miR-210 abrogated hypoxia-induced autophagy impairment and relieved hypoxia mediated excessive activation of macrophages.
Conclusion: Hypoxia impairs macrophage autophagy through miR-210, further leading to excessive activation and inflammatory cytokines secretion of macrophages in liver tissue of chronic hepatitis, which results in ACLF.

THU-043
Declining mortality of cirrhotic patients requiring admission to intensive care units for serious infections: A bi-national cohort study

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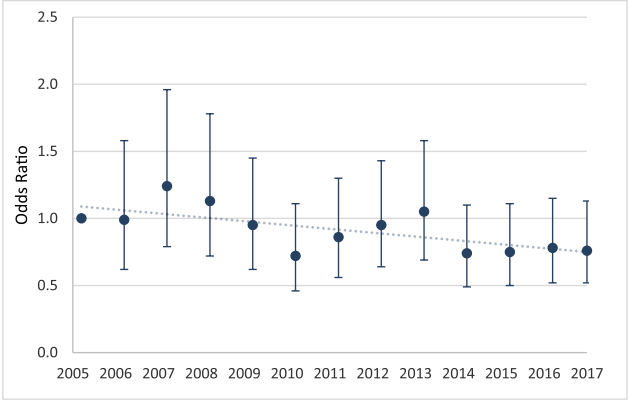
Background and aims: Epidemiological data on the outcomes of cirrhotic patients admitted to the intensive care unit (ICU) for serious infections are lacking. We aimed to describe changes over time in admissions and outcomes for such patients and to compare the results with the outcomes of those with and without cirrhosis admitted to ICU with other causes.
Method: We retrospectively analysed data from consecutive admissions of patients with cirrhosis to 183 ICUs between January 1st, 2005 and December 31st, 2017 as prospectively recorded by the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database.
Results: Admissions for cirrhotic patients with infections accounted for 4, 645 (0.6%) of all 813, 189 non-elective ICU admissions. The proportion of ICU admissions for cirrhotic patients with infections remained stable over the study period (0.6% per year). The median hospital and ICU stay were 12.1 (6.3–23.1) and 3.5 (1.7–7.2) days, respectively. Hospital mortality rate was significantly higher in patients with cirrhosis and infections compared to both cirrhotic patients admitted to ICU for other reasons and all other non-elective ICU admissions (35.5% vs 28.5 vs 15.2%, p < 0.0001). Mortality in cirrhotic patients with infections increased with the number of failing organs (15% in the absence of organ failure, 26% with one failing organ, 40% with two, 61% with three failing organs, 80% with four and 89% with five or more failing organs).



After adjustment for underlying severity of illness at admission to ICU, mortality in cirrhotic patients with infections decreased significantly over the study period (annual decline odds ratio, 0.97; 95% confidence interval; 0.95-0.99) (figure 1). The reduction in

mortality over time in the cirrhotic group with infections was comparable to cirrhotic patients with other indications for ICU admission (p value 1.0) and all other non-cirrhotic emergency ICU admissions (p value 0.14). There was no difference in the reduction in mortality over time in cirrhotic patients with infections admitted to ICUs between liver transplant and non-transplant centres (p = 0.12).
Conclusion: The mortality of cirrhotic patients admitted to ICU with infections is higher than for patients admitted with other indications but has declined over the past 13 years in line with a reduction in overall mortality of cirrhotic patients admitted to.

THU-044

Cystatin C as a predictive biomarker of ACLF development and mortality on the liver transplant waiting list

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Background and aims: Renal failure is the most common organ failure in patients with decompensated cirrhosis who develop acute-on-chronic liver failure (ACLF), and has a dreadful prognosis. The use of creatinine as an estimator of renal function has serious limitations in patients with cirrhosis. Cystatin C (CysC) is an early biomarker of renal dysfunction. However, its prognostic value in patients in the waiting list (WL) for liver transplantation (LT) has not been evaluated. We aimed to assess the capacity of CysC to predict both survival and development of ACLF in patients with cirrhosis in the WL.
Method: Retrospective cohort of patients with cirrhosis listed for LT at the Hospital Italiano from Buenos Aires (Argentina) between January 2014 and December 2017. Data was collected from the inclusion in the WL to death, LT or last date of follow-up. In all patients, CysC was measured at the time of pre-LT evaluation. The ability of liver-, kidney- and global status-related variables recorded at the time of WL inclusion to predict WL mortality and the development of ACLF (according to CLIF-SOFA definition) was evaluated with competing risk regression analysis (with LT as the competing risk of mortality in WL and LT or death as the competing risk of development of ACLF).
Results: A total of 180 patients with cirrhosis listed for LT were included: 40% female, median age 59 years, main etiologies of liver disease alcohol, HCV and NASH. The main indication of LT was decompensated cirrhosis (88%). The median values of MELD-Na, creatinine and CysC were 16 (13–21), 0.8 mg/dL (0.6–1.07) and 1.46 mg/L (1.13–2.05) respectively. The median follow-up for mortality and ACLF outcomes were 12.8 (6.59–24.55) months and 11.7 (4.45–22.62) months, respectively. During follow-up in the WL, 56 (31%) patients developed ACLF, 54 (30%) underwent LT and 35 (19%) died. After adjusting for possible confounders (MELD-Na, albumin, encephalopathy, gender and subjective global nutritional assessment) CysC ≥ 1.5 mg/L was an independent predictor of the development of ACLF (sHR 2.68; 95% CI 1.43–5.00; p = 0.002). Similarly, CysC ≥ 1.5 mg/L was an independent predictor of mortality in the WL (sHR 3.58; 95% CI 1.47–8.73; p = 0.005) after adjustment for MELD-Na, albumin and ACLF.
Conclusion: Higher levels of CysC are strongly associated with the development of ACLF and mortality in WL, regardless of MELD-Na, albumin or history of ACLF. CysC may help to identify patients at high risk of short-term mortality in the LT WT.

THU-045

Natural history of sepsis, organ failure and organ dysfunction in critically ill patients with acute on chronic liver failure

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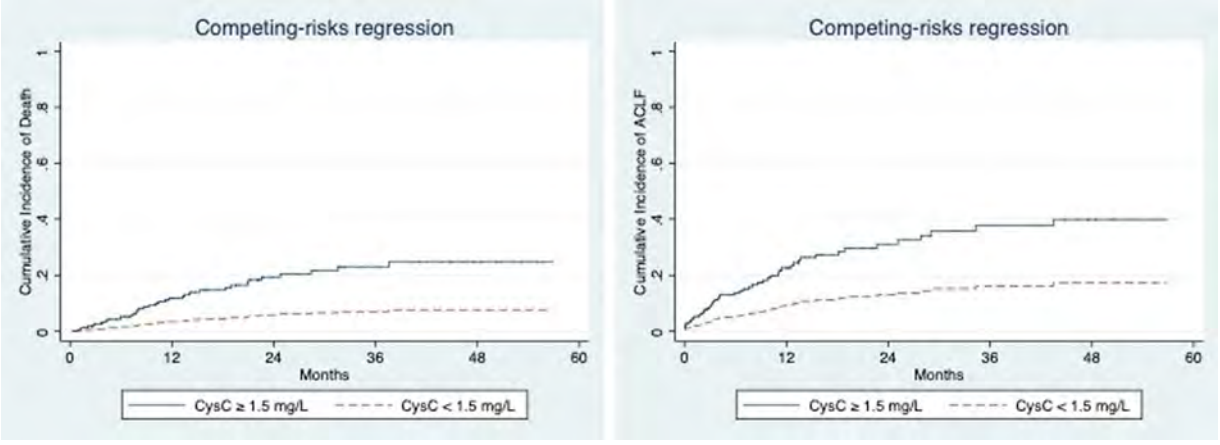

Figure: (abstract: THU-044)

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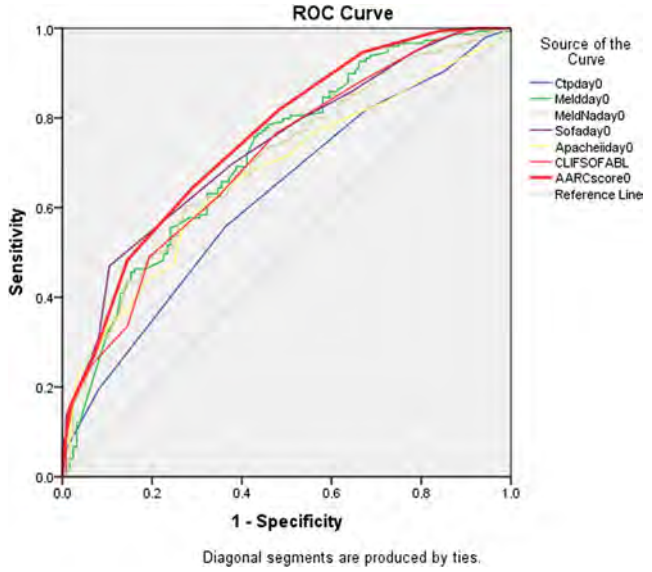
Background and aims: Acute on chronic liver failure (ACLF) is a serious clinical syndrome and carries a high overall mortality, especially those who are critically ill requiring intensive care unit (ICU) admission. We analyzed the natural history of sepsis and organ dysfunction or organ failure in patients with critically ill ACLF (CI-ACLF).
Method: Consecutive ACLF patients, fulfilling the APASL definition of ACLF and prospectively enrolled in the APASL-ACLF Research Consortium (AARC) were included. CI-ACLF patients requiring ICU admission at baseline or within 48 hours of hospitalisation were followed over next 30 days. Organ failure (OF) and organ dysfunction (OD) were defined as per AARC score for renal, coagulation and cerebral organs.
Results: A total of 632 patients with CI-ACLF were admitted to the ICU and complete 30 day data was available for 351 patients. Sepsis was seen in 47% of patients at baseline and in comparison to non-septic patients, carried a higher Day 7 (28.5% vs. 15.6%, p = 0.003) and Day 30 (57.6% vs. 40.3%, p = 0.001) mortality. New onset sepsis developed at day 4 and 7 in 30.3% and 38.7% respectively. Second-hit sepsis was seen in 37% of baseline septic patients. Patients with cerebral (No HE-No OF/Grade I and II HE-OD/Grade III and IV HE, OF- 35.8%/60.7%/75.6%, p = <0.001), renal failure (No OF/OD/OF-34.7%/45.1%/70.3%, p = <0.001) and circulatory failure (No OF/OD/OF-25.6%/60.5%/85.7%, p = <0.001) had significantly higher Day 30 mortality. Age, gender, total leukocytes count, platelet level, ammonia, creatinine, bilirubin, INR, lactate at baseline and presence of acute kidney injury (AKI) and hepatic encephalopathy (HE) were predictors of Day 30 mortality but on regression analysis age (HR, 95%CI-1.04, 1.02–1.06, p = <0.001), (log)INR (2.22, 1.25–3.95, p = 0.007), (log)Bilirubin (1.73, 1.11–2.70), lactate at baseline (1.24, 1.09–1.49, p = 0.001), HE at baseline (1.54, 1.10–1.75, 0.02) and AKI at baseline (2.11, 1.44–3.11, p < 0.001) were significant. AARC-ACLF score for CI-ACLF patients performed best with AUROC of 75% (Cut-off- 10.5, Sensitivity–64.4%, Specificity–71%, p < 0.001) for 30 day mortality.



Conclusion: Sepsis and organ failures as well as organ dysfunctions carry a high 30 day mortality in critically ill ACLF patients. AARC score is a useful tool for risk stratification in this sicker sub-group of ACLF patients.

THU-046

Implementation of acute kidney injury criteria to patients with acute-on-chronic liver failure: Characteristics of effect on outcomes

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Background and aims: The diagnostic criteria used to define acute-on-chronic liver failure (ACLF) uses serum creatinine as indicator of kidney failure. However, currently there is general consensus that assessment of acute impairment of kidney function in cirrhosis should be based on acute kidney injury (AKI) criteria and not on a single measurement of serum creatinine. Therefore, the relationship between kidney failure defined using AKI criteria and ACLF is not known. This study was aimed at investigating the characteristics of AKI in patients with and without ACLF and its relationship with outcomes.
Method: Prospective, single-center study of 639 consecutive admissions in 518 patients with decompensated cirrhosis. Patients were classified into 4 groups: 1)NoAKI-NoACLF (265 episodes); 2)NoAKI-ACLF (18); 3)AKI-NoACLF (142) and 4)AKI-ACLF (214). Demographic, clinical and analytical data as well as urinary biomarkers (NGAL, IL-18 and albumin) were assessed.
Results: AKI and ACLF occurred in 356 (55.7%) and 232 (36.3%) admissions, respectively. As expected, AKI stage 1A was more common in the AKI-NoACLF group compared to the AKI-ACLF group (53% vs 12%, p < 0.001) while AKI stage 3 was more common in the AKI-ACLF group (16% vs 1%, p < 0.001). With respect to the cause of AKI, acute tubular necrosis was more common in patients with ACLF compared to those without (13% vs 0%, p < 0.001). Interestingly, hepatorenal syndrome was more common in patients with AKI-NoACLF than in those with AKI-ACLF (32% vs 25%, p < 0.001). Resolution of AKI was observed in 89% of cases in AKI-NoACLF vs 54% in AKI-ACLF (p < 0.001). By contrast, progression of AKI occurred more frequently in AKI-ACLF (28% vs 4%, p < 0.001).
There was a striking difference in mortality between AKI-ACLF and AKI-NoACLF groups, both during hospitalization (38% vs 4%, p < 0.001, respectively) and at 3 months (49% vs 14%, p < 0.001). Mortality in AKI-NoACLF was slightly higher than that in NoAKI-NoACLF (14% vs 7%, p = 0.04).
Mortality was strongly associated with urinary biomarker levels, particularly NGAL. In multivariate analysis, presence of ACLF and urinary NGAL at day 3 were independent predictors of 3-month survival.
Conclusion: Characteristics and outcome of AKI are strongly dependent on the presence of associated ACLF. AKI without associated ACLF has good kidney and patient outcomes. Presence of ACLF and increased urinary levels of NGAL are associated with poor outcome.
Funded by FIS PI16/00043 and H20/20 731875 (LIVERHOPE).

THU-047

Recalbration of the CLIF-C ACLF score after weighting by organ and by the presence of TIPS in patients with acute-on-chronic liver failure

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Background and aims: Acute-over-chronic liver failure (ACLF) assciates a high short-term mortality. The most accurate prognostic score is CLIF-C ACLF score, which includes leukocytes blood count, age and organ failures according to CLIF-SOFA (semi-quantitative 1–3 points). The model equally scores each organ failure though they have different prognostic weights. Our study assesses, in a contemporary cohort of ACLF patients, whether CLIF-C ACLF score may be improved by weighting the type of organ failure and by incorporating other variables.
Method: Retrospective inclusion (2008-16) of 344 patients admitted to the ICU with ACLF. The coefficients of the CLIF-C ACLF score on day 3 were recalibrated by survival analysis at days 28 and 90 (transplantation as competitive event). Other variables not included in the original model were studied. Predictions of the original model were compared with predictions after recalibration: discrimination (AUR, Delong for comparison) and calibration (Hosmer-Lemeshow) were assessed.
Results: 25% of patients had grade 1 ACLF, 41% grade 2 and 34% grade 3. Alcohol was the predominant etiology of cirrhosis (66%), and sepsis (35%) and bleeding (21%) were the main precipitants of the ACLF. Recalibration of CLIF-C ACLF score showed different weights for each organ failure coefficient: liver 0, 529, coagulation 0, 515, circulation 0, 490, respiration 0, 417, kidney 0, 296 and brain 0, 295. At univariate analysis variables included in CLIF-C ACLF, serum sodium, ALT and the presence of TIPS were prognostic factors. At multivariate analysis, TIPS (HR 0.260, p = 0.001) remained in the model along with CLIF-C ACLF variables. Mean values of the new model were higher than original ones (60 ± 14 vs. 49 ± 12).
Discrimination of the original model was correct at 28 and 90 days: AUROC 0.831 and 0.804, respectively. The recalibrated model was superior with AUROC of 0.858 (28d) and 0.845 (90d) ($p < 0.05$). Calibration of both original and recalibrated models was correct (n.s. H-L test).
CLIF-C ACLF score ≥ 70 (proposed for futility) occurred in 21 patients, 20 of whom died at 28–90 days. At recalibrated model, values > 76 (49 patients) and >74 points (61 patients) had a 100% mortality at 28 and 90 days, respectively.
Conclusion: The type of organ failure has a differential prognostic weight in ACLF. Recalibration of CLIF-C ACLF score by weighting the type of organ failure and the presence of TIPS may improve its predictive capacity and limits to define futility.

THU-048

Intermittent high-flux albumin dialysis with continuous venovenous hemodialysis for acute-on-chronic liver failure and acute kidney injury

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Background and aims: AKI-HRS carries significant risk of morbidity and mortality due to lack of effective therapies. We report the results of a cohort, retrospective, single-center study to investigate the effects of continuous venovenous hemodialysis (CVVHD) coupled with intermittent high-flux single-pass albumin dialysis (SPAD) on survival and clinical and laboratory parameters in patients with ACLF and AKI-HRS.
Method: 16 patients (11 male), age 48 + 12 yrs, with severe decompensation of cirrhosis and AKI-HRS (n = 13) received extracorporeal therapy. The Ultraflux® Ci-Ca®CVVHD EMiC®2 kit (Fresenius MC) was used to improve middle molecule clearance. Each SPAD lasted 8 hrs and was followed by the CVVHD with no change of the dialyzer. Each subsequent SPAD/CVVHD was performed using a newly installed EMiC®2 kit. Fluid extraction rates ranged from 50 to 200 ml/h, depending on the urine output and fluid balance status. Data at the initiation of the first SPAD/CVVHD were compared with early morning data after termination of the treatment phase. Data are shown as mean + SD and were analyzed by ANOVA, Wilcoxon signed rank test, or binomial NPar Tests, where appropriate.
Results: All patients had markedly elevated plasma bilirubin levels and coagulopathy, 13 were oliguric or anuric, 14 had encephalopathy. All patients with alcoholic liver disease (n = 11) were actively drinking prior to admission. 5/16 patients were transplanted. Infection was a likely trigger of acute decompensation of cirrhosis in 4 pts. 37 SPAD/CVVHD treatments were performed [2.31 ± 1.40]; therapy was continued for 74.7 ± 51.8 hrs. Baseline MELD-Na score was 37.6 ± 6.6 and after SPAD/CVVHD treatment it was 33.4 ± 8.7 ($p < 0.001$). In parallel, the CLIF-C ACLF Grade, OFs, and estimated 1- and 3-mo mortality improved ($p = 0.003–0.032$). Clinically these changes were associated with improvement in AKI-HRS Stage and HE Grade ($p < 0.001$) and key blood tests (total bilirubin, NH_3, INR, creatinine). A 30-day and 90-day survival was 56.3%. Survival in the subgroup of AKI-HRS (n = 13) was 53.9%. Survival in patients after transplantation (n = 5) was 75.0%. Survival in patients not transplanted (n = 11) was 45.5%.
Conclusion: In this cohort of severely ill patients, SPAD/CVVHD improved a number of key clinical and laboratory parameters, including renal function, encephalopathy, blood coagulation indices, bilirubin and ammonia levels, MELD-Na, ACLF grade, CLIF-C OFs, and estimated 1- and 3-month survival. It is reasonable to postulate that survival may be further improved with earlier intervention (patients with lower MELD-Na score and ACLF Grade) and more SPAD treatments per patient.

THU-049

Impaired adaptive immunity is an early event in liver cirrhosis preceding acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is characterized by high levels of systemic inflammation and parallel suppression of the innate immune system. In contrast, little is known about changes of the adaptive immune system in ACLF. Therefore, we aimed to display an overview of prominent cell populations from both innate and adaptive immune system in order to find changes in

immune cell frequencies responsible for immunosuppression and susceptibility to infections in patients.
Method: Patients with compensated liver cirrhosis, decompensated liver cirrhosis, or ACLF were recruited from a prospective cohort study. Comprehensive immunophenotyping of relevant innate and adaptive immune cell populations was performed using high dimensional multicolour flow cytometry on peripheral blood mononuclear cells. In addition, replication of Torque teno (TT) virus as a marker of immunosuppression was quantified in serum.
Results: A high frequency of detectable TT virus was observed already in patients with compensated liver cirrhosis compared to healthy controls (>50% vs. 19%, p = 0.0003), suggesting early occurrence of immunosuppression in the course of liver cirrhosis. In line, profoundly impaired cellular immune responses were observed, deduced by reduced numbers of important cell populations of the adaptive and innate immune system like CD4+ T cells and CD8+ T cells-especially the naïve (CD45RA+ CD197+) subpopulations-, B cells, NK cells, and dendritic cells. Importantly, most of the observed changes were already evident in patients with compensated liver cirrhosis and were fully developed in patients with acutely decompensated liver cirrhosis, while ACLF was associated with only few additional changes in immune cell frequencies like a diminished compartment of Vdelta2 gamma-delta T cells. The frequency of T cells correlates inversely with the presence of TT virus displaying the contribution of reduced T cell numbers to the immunosuppression in patients.
Conclusion: Impaired innate and-in particular-adaptive cellular immunity occurs early in the pathogenesis of liver cirrhosis and precedes ACLF. This may contribute to the development of ACLF by increasing the risk of infections in patients with liver cirrhosis. This study also sheds light on the adaptive immune system as a potential distinct target of immunological therapy in liver cirrhosis and ACLF.

THU-050

Genetic variants of innate immunity receptors are associated with mortality but not with bacterial infections in liver cirrhosis

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Background and aims: Acute on chronic liver failure (ACLF) is characterized by the presence of acute decompensation of cirrhosis (AD), organ failure (s) and a high risk of short term mortality. Bacterial infections are among the most frequently observed precipitating events for development of ACLF. The lectin pathway of complement activation is crucial to the innate immune (IM) response to pathogens. Single-nucleotide polymorphisms (SNPs) in the lectin pathway genes determine their liver-derived protein level and/or functional activity. Multiple other components are also involved in IM signalling against pathogens, among which TLR2, TLR4, MYD88 and NOD2. The aim of the present study was to investigate whether SNPs in IM genes for pathogen recognition are associated with the occurrence of bacterial infections or mortality in patients with cirrhosis hospitalized for AD or ACLF.
Method: All patients hospitalized for AD or ACLF from the CANONIC study of whom we had DNA available were included. Twenty-one IM genes variants with known functional implications on protein level and/or functionality were genotyped in 826 patients. Associations between baseline characteristics of the patients, the occurrence of bacterial infections and survival rate at 90 days of follow-up in relation to the IM gene variants were analysed.
Results: None of the analysed SNPs was significantly associated with the occurrence of acute bacterial infections in general or spontaneous bacterial peritonitis (SBP) alone. However, in both univariate and multivariate logistic regression analyses the NOD2-G908R gene risk variant (OR 2.25, 95% CI 1.30–3.91, P = 0.004) was found to be a strong independent predictor of mortality along with age (OR 1.03, 95% CI 1.02–1.05, P < 0.001) and Model For End-stage Liver Disease (MELD) Score (OR 1.15, 1.12–1.17, P < 0.001). In a predefined subgroup analysis in patients with bacterial infections (n = 331) the same association with mortality was observed for NOD2-G908R (OR 2.78, 95% CI 1.74 –4.44, P < 0.001).
Conclusion: In patients with AD or ACLF, single nucleotide polymorphisms in the lectin complement pathway and innate immune signalling components for pathogen recognition were not associated with increased risk of bacterial infection or SBP alone. NOD2-G908R gene risk variant is independently associated with increased risk of short-term mortality in patients with AD or ACLF, particularly those with bacterial infections.

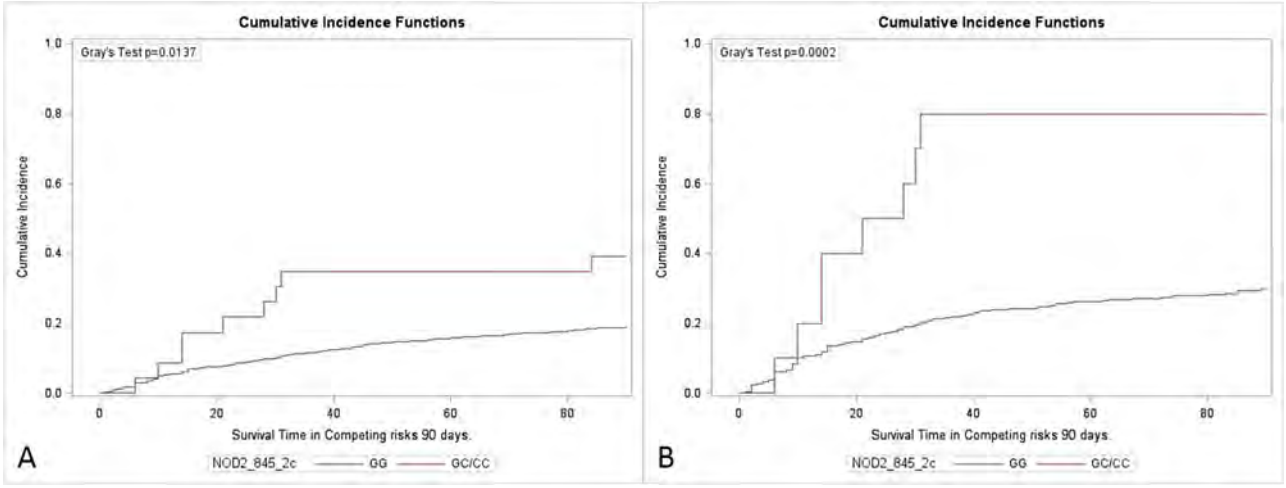

Figure 1A. Survival with competing risk analysis of NOD2-G908R gene risk variant in all patients at 90 days. Figure 1B. Survival with competing risk analysis of NOD2-G908R gene risk variant in patients with bacterial infections at 90 days.

THU-051

Establishment of a new animal model for the acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is a severe complication of liver cirrhosis characterized by hepatic and extrahepatic organ failures. Established precipitating events of ACLF include infections, excessive alcohol consumption, exposure to toxins and bleeding episodes. ACLF is associated with a very high mortality rate and targeted therapy options are not available yet. The aim of this study was to develop a new animal model for the evaluation of target-oriented therapy options for ACLF.
Method: C57BL/6 mice were infected with an Adenovirus expressing the major AIH autoantigen cytochrome P450 2D6 (hCYP2D6) and developed autoimmune hepatitis with resulting liver fibrosis 4 weeks after injection of the virus. On top of the chronic liver damage an acute trigger (paracetamol overdose for toxic liver damage or cecal slurry for induction of sepsis) for the development of ACLF was applied. As control groups served naïve C57BL/6 mice (control group 1) as well as C57BL/6 mice with chronic liver damage (CYP2D6 infected, control group 2) and C57BL/6 mice exposed to an acute trigger only (paracetamol or cecal slurry injection, control group 3). Serum and tissue samples were harvested at different points of time and lymphocytes were isolated. Serum parameters including IL-6 and ALT were analyzed and immunohistochemical stainings as well as FACS analyses were performed.
Results: C57BL/6 mice with ACLF showed significantly higher liver damage (e.g. ALT 12h: paracetamol vs. ACLF $p = 0.0046$; ALT 24h: sepsis vs. ACLF $p = 0.0009$; necrotic area: paracetamol vs. ACLF $p = 0.047$) as well as higher systemic inflammation (e.g. IL6 24h: sepsis vs. ACLF $p = 0.038$, paracetamol vs. ACLF $p = 0.2366$) when compared to mice of control groups. FACS analyses revealed significantly reduced CD4- ($p = 0.0095$) and CD8-T-cells ($p = 0.0095$) in mice with ACLF when compared to mice with chronic liver damage only (control group 2). Additionally kidneys of mice with ACLF showed a relevant damage of the distal tubule in histological staining which could not be detected in the control groups.
Conclusion: We present a new animal model for ACLF which is characterized by enhanced liver damage, significantly increased systemic inflammation as well as dysfunction of the immune system in comparison to control groups. Additionally ACLF mice develop kidney damage as a characteristic feature of extrahepatic organ involvement. Based on this model, targeted therapy options for ACLF can be evaluated.

THU-052

Immunometabolic profiling of ascites from patients with acute-on-chronic liver failure reveals increased MerTK+ immunosuppressive myeloid cells and cell death markers with preferential lipid metabolism compared to cirrhosis without organ failure

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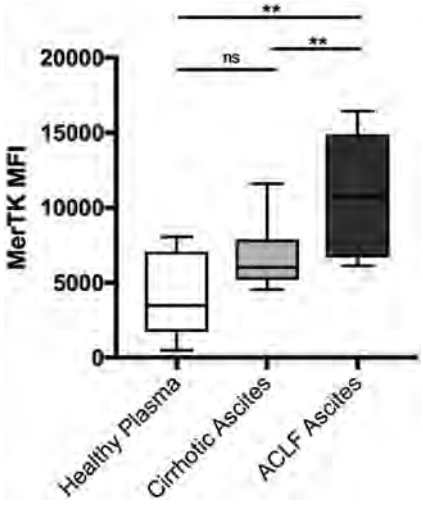
Background and aims: Acute-on-chronic liver failure (ACLF), characterized by rapid development of organ failure (OF) and high mortality, is associated with increased susceptibility to infection such as spontaneous bacterial peritonitis (SBP). Increased monocyte expression of pro-restorative marker Mer tyrosine kinase (MerTK) has been linked to dampened innate immune responses in ACLF. To investigate its potential role in SBP susceptibility, we sought to comprehensively phenotype the immunometabolic environment of ascites in patients with cirrhosis and ACLF.
Method: Plasma, ascites and ascitic cells (ACs) were obtained from cirrhotic patients on hospital admission. Healthy peripheral blood mononuclear cells (PBMCs) were cultured for 48hrs in 50% ascites derived from patients with and without ACLF. Healthy plasma was used as control. SBP cases were excluded. Monocyte immunophenotype (CD14, CD16, HLA-DR, MerTK) was determined by flow cytometry. Cell death markers (M30/M65) were measured using enzyme-linked immunosorbent assay, cytokines by multi-array immunoassay and metabonomic profile by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. LPS-stimulated *ex-vivo* AC TNF-α production was determined by intracellular staining. Transcriptomic profile of CD14+ ACs was analysed after FACS-sorting of MerTK+ vs. MerTK- subsets.
Results: MerTK expression (Median Fluorescence Intensity) was significantly increased in PBMCs exposed to ACLF ascites compared to cirrhosis without OF and healthy plasma ($p < 0.01$, figure 1). Ascitic M30 and M65 levels were greater than plasma ($p < 0.05$). In ACLF vs. cirrhosis, ascitic M30, M65 and TNF-α concentrations were elevated ($p < 0.05$). Ascitic M65 positively correlated with MerTK MFI and TNF-α ($p < 0.05$). However, LPS-stimulated TNF-α production of CD14+ ACs was attenuated compared to healthy PBMCs ($p < 0.05$). In ACLF, ^{1}H NMR revealed a markedly altered ascitic metabolic environment compared to cirrhosis without OF, with higher lactate, acetone, 3-hydroxybutyrate and lipid concentrations. In contrast, lipids in ACLF plasma were significantly depleted. Transcriptomic profiling revealed that CD14 + MerTK+ ACs upregulated the lipid-metabolic *ApoE* gene ($p < 0.05$), 40-fold change compared to CD14 + MerTK- ACs.



Conclusion: In ascites from ACLF patients profound immunometabolic disturbances are evident with upregulated MerTK expression, impaired pro-inflammatory responses to LPS, preferential lipid metabolism and evidence of epithelial cell death. The impact of these perturbations on bacterial clearance requires further exploration.

THU-053

Usefulness of lactate-free Asian Pacific Association for The Study of Liver acute-on-chronic liver failure research consortium ACLF score for predicting short-term mortality in patient with alcoholic liver disease

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Background and aims: Asian Pacific Association for the Study of Liver (APASL) acute-on-chronic liver failure (ACLF) Research Consortium (AARC) proposed new prognostic scoring system of ACLF including lactate. However, lactate is not routinely checked in clinical practice of patient with ACLF in Korea. Therefore, we aimed to investigate the predictive accuracy of lactate-free AARC-ACLF score for predicting short-term mortality in patients with alcoholic liver disease
Method: A total of 749 ALD patients who had liver failure (bilirubin ≥ 5 mg/dL and INR ≥ 1.5) in AARC database were investigated. Diagnostic performances for short-term mortality were compared according to the area under receiver operating characteristic (AUROC) curve. Predictive accuracy of lactate-free AARC-ACLF score were compared with other prognostic scores in 143 ALD patients with liver failure and 65 ALD patients with ACLF according to AARC definition in Korean ACLF cohort.
Results: Among 749 patients, 28-day and 90-day mortality were 40.3% and 51.5%. There were no significant differences in AUROC for predicting 28-day and 90-day mortality between AARC-ACLF score and lactate-free AARC-ACLF score (28-day mortality: 0.758 vs. 0.759, P = 0.938, 90-day mortality: 0.747 vs. 0.740, P = 0.383). In Korean ACLF cohort, the AUROCs of lactate-free AARC-ACLF score for predicting 28-day and 90-day mortality were 0.861 and 0.846 in ALD with liver failure, and 0.865 and 0.873 in ALD patients with ACLF according to AARC definition, respectively. In Korean ALD patients with liver failure and ACLF according to AARC definition, diagnostic performance of lactate-free AARC-ACLF score for predicting 28-day and 90-day mortality was comparable to those of Model for End-stage Liver Disease (MELD), MELD-Na, Chronic Liver Failure-Sequential Organ Failure Assessment score.
Conclusion: Lactate-free AARC-ACLF score is as excellent as AARC-ACLF score in predicting short-term mortality in ALD patients with liver failure of AARC database and Korean ACLF cohort.

THU-054

Acute variceal bleed leads to acute on chronic liver failure like syndrome in a small proportion of cirrhotic patients: an analysis of 3845 patients from AARC data base

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Background and aims: Acute on chronic liver failure patients have variable hemodynamic profiles, depending on the stage of underlying chronic liver diseases. These patients have high baseline hepatic venous pressure gradients (HVPG), which predisposes them to high risk of variceal bleed. However, it is not known, what proportion of patients with different Child's score develop post-bleed hepatic decompensation and ACLF like presentation. We investigated the spectrum, development of ACLF-like syndrome and mortality in patients with ACLF.
Method: Patients diagnosed to have chronic liver disease were recruited from Institute of liver and biliary sciences, New Delhi.This data was retrospectively collected on a predefined format from October 2009 to July 2018.A total of 3845 patients who had had the first episode of variceal bleed were analyzed. Of these, the patients who developed ACLF (APASL Definition) were also analysed.
Results: Out of the 3845 patients with first episode of Acute variceal bleed, Child A cirrhotics were 29.1% (n = 1118), Child B-30.1% (1172), Child -C-40.5% (1555).Males were 83.2% with mean age of 47.2 ± 11.25 years.Alcohol was the most common etiology in these patients. Among the Cirrhotics there was higher mortality in Child C Cirrhotics-35.7% (557) (p < 0.01). All Child A cirhotics with baseline bilirubin < 5/INR < 1.5/without encephalopathy/ascitis were then analysed for the development of ACLF post acute variceal bleed.A total of 1118 patients were analysed which showed the development of 3.6% (n = 39) of ACLF like syndrome
Conclusion: Variceal bleed can trigger ACLF like syndrome in a very small proportion (3.6%) of well compensated cirrhoticpatients. Prevention of acute variceal bleed should be incorporated even in well compensated cirrhotics to prevent development of ACLF.

THU-055

Improved stratification of liver failure syndromes using broad-panel bile acid LCMS phenotyping demonstrates novel pathways of dysregulation in tertiary bile acids in acute-on-chronic liver failure

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Background and aims: Acute and acute-on-chronic liver failure (ALF; ACLF) are characterised by hyperbilirubinemia, systemic inflammation and high mortality. Differential metabolism of bile acids (BA) in ALF and ACLF is poorly understood. We sought to comprehensively phenotype the BA profile in ALF and ACLF via a novel LCMS method including tertiary BAs, and compare with commercial assays.
Method: Plasma samples from 106 subjects (ACLF n = 27, acute decompensation (AD) n = 31, ALF n = 35, HC n = 9, stable cirrhotic (SC) n = 5) were profiled using both a commercially available fully quantified clinical assay of 15 BA and a novel broad panel (BP) semi-quantitative UPLC-MS method with extended coverage of secondary BA (including conjugated) and sulphated BAs (tertiary BAs). Data were analysed using principal components analysis (PCA) and partial least squares discriminant analysis (PLSDA) and correlated with clinical severity scores and outcome.
Results: 12 BAs were represented on both panels with high levels of agreement on correlation analysis for 10 of the 12 (average rho 0.75, average $p < 0.01$). The BP illustrated robust differences in BA metabolism between patient groups. BA profiles from the BP demonstrated variance in PCA models associated with total bilirubin and MELD but individual BA measurements did not correlate directly with these measures. 30-day mortality was associated with an increase in BA sulfation, and reduced secondary bile acids, implying a role of gut microbiota activity. Ursocholanic acid concentration discriminated ACLF from non-ACLF (AUROC = 0.79, $p < 0.01$). ACLF patients could only be distinguished from AD patients by increases in BAs from the BP, including glycoursodeoxycholic acid sulfate, conjugates of hyodeoxycholic acid and murocholic acid sulfate (PLS-DA: $R^2X = 0.449$, $R^2Y = 0.533$, $Q^2 = 0.428$). ALF patients exhibited increased conjugates and sulfates of deoxycholic acid, lithocholic acid, and 5-cholenic acid-3β-ol compared with ACLF patients (PLS-DA for overall model: $R^2X = 0.523$, $R^2Y = 0.292$, $Q^2 = 0.19$, robust to permutation testing).
Conclusion: Wider BA coverage of tertiary BAs give new insight into BA metabolism in liver failure, particularly the progression from AD to ACLF and differentiating ALF from ACLF. While likely to represent metabolic manifestations of gut dysbiosis and reduced renal clearance of sulphated BA, validation in larger cohorts with correlation to immunological phenotypes is required.

THU-056

Artificial liver support system improves short-term survival of patients with hepatitis B virus-related acute-on-chronic liver failure: A propensity-score matched analysis

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Background and aims: Acute-on-chronic liver failure (ACLF) is a complex syndrome with a high short-term mortality; in the meantime, liver transplantation is the only available treatment. This study aims to observe the effectiveness of the artificial liver support system (ALSS) as an alternative therapy on patients with hepatitis B virus-related ACLF (HBV-ACLF).
Method: The clinical data of 924 patients with HBV-ACLF receiving ALSS (n = 507) and standard medical treatment (SMT, n = 417) from Chinese Group on the Study of Severe Hepatitis B ACLF (COSSH-ACLF) open cohort from June 2013 to December 2017 were used in this study. The short-term (day 7, 14, 21, 28 and 90) mortality and cumulative survival rate were analyzed between ASSL and SMT groups. Propensity-score matched analysis was used to reduce bias in comparing these study outcomes.
Results: Among the patients assessed using the COSSH-ACLF criteria, the transplant-free mortality rate in ALSS patients' group at day 7, 14, 21 and 28 were significantly lower ($p < 0.001$) than those in SMT group (13.1-, 21.9-, 28.1-, 32.5% vs 22.1-, 33.9-, 41.7-, 45.2%, respectively), whereas the 90-day mortality rate has no significant difference ($p = 0.074$) between the two groups. Furthermore, the 7, 14, 21, 28 and 90-day cumulative survival rates were higher in ALSS patients' group compared to SMT group ($p < 0.001$). One-to-one paired cohorts were obtained following propensity-score matched analysis (172 pairs in ACLF-1, 101 pairs in ACLF-2 and 21 pairs in ACLF-3, totally 294 pairs). The 7, 14, 21, 28 and 90-day mortality rate were lower in ALSS group compared to SMT group ($p < 0.01$ at day 7, 14, 21, 28, $p = 0.055$ at day 90). The non-significance at day 90 might be associated with the limited patient cases. The cumulative survival rate of patients in ALSS group at day 7, 14, 21, 28, 90 were significantly higher than those in SMT group ($p < 0.01$). A lower mortality rate were observed in ACLF-1 ($p < 0.01$) and ACLF-2 ($p < 0.05$) in ALSS group compared to SMT group. Although several adverse events, including phlebothrombosis, plasma allergy response, bleeding from puncture site, hypotension and catheter-related infections were observed during ALSS therapy, they have no impact on patients' survival.

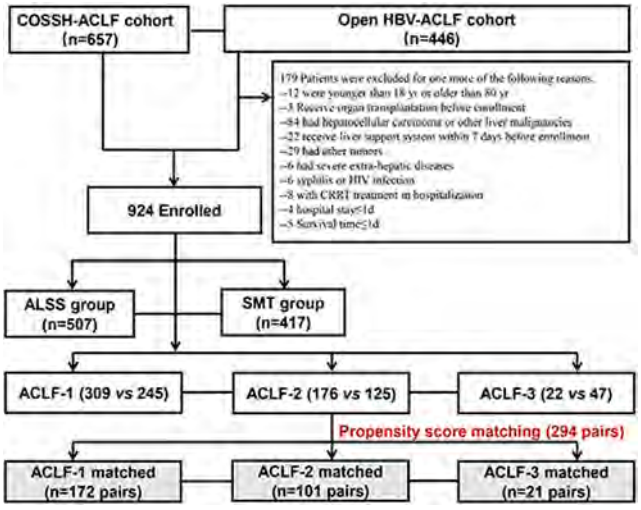

Figure: Patients select flow.

Conclusion: ALSS can improve short-term patients' survival in HBV-ACLF compared to SMT. Early application of ALSS helps to reduce short-term mortality rate especially in ACLF-1 and ACLF-2 grades.

THU-057

The homeostasis imbalance of autophagy in acute-on-chronic liver failure patients caused by acute exacerbation of chronic hepatitis B

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Background and aims: Although autophagy is critical in various liver diseases, its role in acute-on-chronic liver failure (ACLF) caused by acute exacerbation of chronic hepatitis B (CHB) is still elusive. The aims were to (1) analyze the changes in autophagic response in CHB

and ACLF and (2) correlate expression of autophagy pathways with liver histology.
Method: Normal liver tissues (n = 10), liver tissues of CHB (n = 15) and HBV-related ACLF patients (n = 22) are included. Electron microscopy of the ultrastructure of the autophagy was carried out on liver specimens. Messenger RNA (mRNA) and protein expression were measured by quantitative real-time PCR, Western blot, and immunofluorescent staining, respectively. We further analyzed the correlation between the expression levels of autophagy-related molecules and liver injury.
Results: Electron microscopy identified that, compared with normal subjects, the numbers of autophagy, ERphagy and mitophagy were increased in liver of CHB subjects and further increased in liver of ACLF subjects, which confirmed by measurement of immunofluorescence double staining. The results of RT-PCR showed that, compared with CHB patients, the ER-phagy receptors including SEC62, RTN3 and CCPG1 were upregulated and the mitophagy markers including PINK1, FUNDC1 and Nix were upregulated in liver of ACLF subjects. For autophagic markers, the genes and proteins of LC3, Atg-5, Atg-7, and Atg-12 were slightly up-regulated in liver of CHB subjects and significantly down-regulated in liver of ACLF subjects; furthermore, the expression of Lamp-1 was not increased in CHB or ACLF, but p62 was slightly increased in CHB and significantly increased in ACLF, showing a positive correlation with serum ALT, AST and TBIL; whereas the expression of Beclin-1 was gradually decreased from CHB to ACLF, showing a negative correlation with serum ALT, AST and TBIL. Importantly, the autophagic markers were gradually decreased from the early stage of ACLF to the later stage of ACLF.
Conclusion: The homeostasis imbalance of autophagy may play a complicated role in the pathogenesis of ACLF, and an autophagy response may predict the occurrence of ACLF caused by acute exacerbation of CHB.

THU-058

Gene profiling of toll-like recepter signaling pathways in patients with acute-on-chronic liver failure

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Background and aims: Toll-like receptors (TLRs) play a crucial role in detecting pathogen and organ/tissue injury. The aim of the study is to investigate the alteration of TLR signaling pathways in peripheral immune cells of patients with acute-on-chronic liver failure (ACLF).
Method: A total of 27 patients including 9 cases with compensated cirrhosis, 9 with de-compensated cirrhosis and 9 with ACLF, were enrolled in the study. Peripheral immune cells were isolated and alteration of TLR signaling pathways was evaluated using a RT² Profiler™ PCR Array. The fold change for each gene ($2^{(-\Delta\Delta CT)}$) was compared between the groups. Genes with fold change ratio ≥ 2 or ≤ 0.5 along with P value < 0.05 was considered to be differentially expressed.
Results: Neutrophils showed a broader gene adaptation than PBMCs in cirrhosis. A total of 17 genes were up-regulated in neutrophils from compensated cirrhosis, mainly distributing in adaptors, TLR interacting protein and downstream pathways. And 6 of 17 were seen in de-compensated cirrhosis. In contrast, no significant alteration of gene expression was found in PBMCs from cirrhosis. A trend towards down-regulation of the TLR signaling pathway was observed in both PBMCs and neutrophils from cirrhosis to ACLF. TLR3, IFNG, IL1B, TBK1, CCL2 and LTA were down-regulated in neutrophils, and TLR3, TLR9, TLR10, SIGIRR, IFNG, CCL2, CXCL10, PTGS2, IFNB1, LTA, IL2, IL12A and IRAK2 in PBMCs. On the other hand, CD14 and IL10 were up-regulated both in PBMCs and neutrophils of ACLF patients.
Conclusion: TLR signaling pathway genes is differentially regulated in PBMCs and neutrophils from cirrhosis to ACLF. A defective TLR3 and IFN expression, along with enhanced CD14 and IL10 expression, is a common hallmark of ACLF in peripheral immune cells.

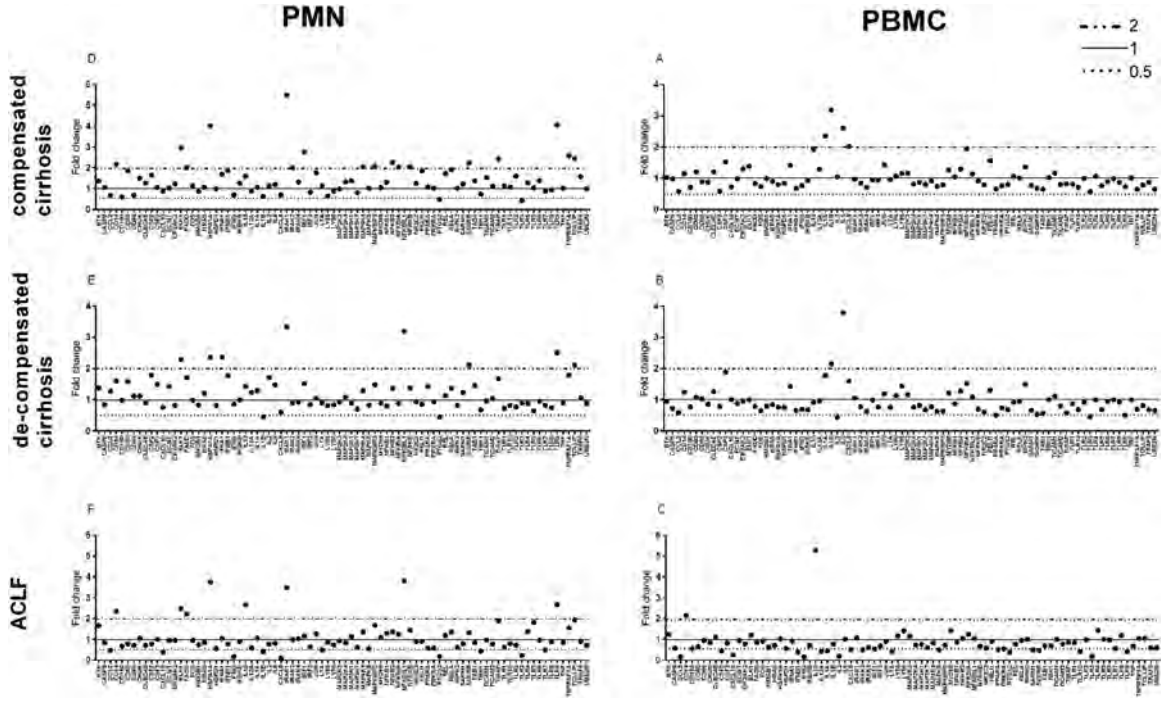

Figure: (abstract: THU-058)

Fibrosis

THU-061

Statins reduces liver fibrosis progression and promotes fibrosis regression in mice

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Background and aims: Statins impede cholesterol and isoprenoid synthesis and have many pleiotropic beneficial roles including antioxidant and anti-inflammatory effects. In the present study, we investigated the effects of statin treatment on liver inflammation, fibrosis and regression in a carbon-tetrachloride (CCl_4) model of chronic liver injury.
Method: Liver fibrosis was induced by CCl_4. Pitavastatin (3 and 10 mg/kg) were administered. Fibrosis was assessed by sirius red staining, alpha-smooth muscle actin (αSMA) and expression of fibrotic genes. Inflammatory genes and proteins were assessed. Phenotyping of subtypes of intrahepatic leukocytes was performed by flow cytometry. *In vitro* studies were performed using bone-marrow derived macrophages.
Results: C7BL/6J mice treated with pitavastatin demonstrated a resistance to fibrosis after a chronic treatment with CCl_4 as evidenced by decrease sirius red staining and α-SMA. Hepatic fibrogenic and IL-6 gene expression were decreased. Pitavastatin accelerated the regression of fibrosis 3 days after CCl_4 cessation, as evidenced by a lower expression of sirius red, α-SMA and fibrogenic genes in pitavastatin-treated mice. This enhanced regression was associated with a decreased influx of Ly-6C^{high} macrophages into the liver. Accordingly, LPS-treated macrophage displayed a significant reduction in IL-6 and TNFα.
Conclusion: Our results demonstrate that pitavastatin attenuates the development of liver fibrosis, and accelerates its regression. Additional experiments are required to decipher the mechanisms by which pitavastatin modulates both liver regression and fibrosis and to elucidate the role of macrophages.
Funding: This study is funded by the National Council for Scientific Research in Lebanon (AH, EH 01-10-17).

THU-062

Exploring the immune environment in chronic hepatitis C associated fibrosis by examining the portal vein

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Background and aims: Liver serves as an immunological barrier between portal and systemic circulation. Hepatitis C infection (HCV) results in immunological alterations in the setting of chronic inflammation and fibrosis in the liver. The aim was to assess the link between portal and peripheral immune markers and HCV associated fibrosis.
Method: 29 HCV patients underwent liver biopsy with portal vein cannulation. Portal and peripheral blood was obtained. Ishak fibrosis (IF) was used to score fibrosis. Flow cytometry and complete blood count assessed T, B- cells, and leukocytes, respectively. ELISA assessed cytokines grouped as proinflammatory (IL-6, IL-8, IL-18, TNF-α, TNF-β), type 1 helper T cell (Th1) cytokines (IFN-γ, IL-12p40, IL-12p70, CXCL9, CXCL10), and type 2 helper T cell (Th2) cytokines (IL-4, IL-5, IL-10, IL-13, CCL22, CCL11, CCL26). All reported correlations spearman $r > 0.35$, and $p < 0.05$.
Results: Portal and peripheral CD8+ T cells showed no correlation with fibrosis or cytokines. Among CD4+ T cells, higher portal (not peripheral) CD25+ and central memory CD4+ subsets were linked to fibrosis. Among proinflammatory cytokines, portal (not peripheral) IL-8 and TNF-α correlated positively with fibrosis and with portal CD4+ T and B cells. Among portal and peripheral Th1 cytokines, only IL-12p40 and IL-12p70 correlated with CD4+ T cells. In contrast, majority of the portal and peripheral Th2 cytokines i.e. IL-4, IL-5, IL-13, CCL22, and CCL26 correlated with CD4+ T cells. Portal CD4+ T cells were also linked to higher circulating eosinophils, cells of type 2 immunity. Similar to CD4 T cells, portal B cells were associated with Th2 cytokines IL-5, IL-13, and CCL22; and not with Th1 cytokines. Lastly, fibrosis and clinical markers of liver disease i.e. ALT, AST, ALP, AFP, and PT-INR, displayed associations with portal and peripheral sCD163, a type 2 polarized macrophage marker (M2).
Conclusion: Liver fibrosis showed associations with distinct CD4+ T cells and proinflammatory cytokines exclusively in the portal vein, which may be relevant to liver disease pathogenesis. Circulating immune cells displayed a predominant link to Th2 cytokines suggesting a possible shift in the type of immune responses in chronic HCV. The relationship of Th2 linked CD4+ T cells and M2 macrophage marker with increasing fibrosis and worsening liver disease suggests an importance of type 2 immunity in the pathogenesis of HCV associated fibrosis.

THU-063

Synergistic antifibrotic effect of rapamycin and zoledronic acid in advanced murine biliary fibrosis

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There is no effective antifibrotic therapy for biliary fibrosis. The *in vivo* microenvironment, especially profibrotic monocyte-macrophages, are central modulators of hepatic stellate cell/myofibroblast activation and represent a promising drugable target. We assessed the antifibrotic potential of a combination of two clinically used drugs, Zoledronic acid (ZA) and Rapamycin (RA) that affect macrophage polarization and their putative fibrogenic potential.
Methods: Mdr2-knockout (Mdr2KO) mice that had received one dose of diethylnitrosamine (DEN) at day 5 after birth were treated from month 5-6 (stage of advanced fibrosis with emerging HCC) with 1) ZA alone (100 µg/kg body weight i.p., three times per week), 2) RA alone (5 mg/kg body weight orally three times per week), 3) the combination of both drugs. A fourth group served as vehicle treated control. The degree of biliary fibrosis and extent of inflammation was quantified histologically using morphometry of HandE, Sirius Red, alpha-SMA, CK-19 and CD68 stained sections. Collagen deposition was confirmed by hydroxyproline determination. Real time PCR was performed to analyze hepatic expression of fibrosis-related (Col1a1, Col3a1, aSMA), macrophage-specific (TNFa, CCL2, TGFb1, HIF1a and several MMPs), and angiogenic (VEGF) genes.
Results: Compared to vehicle treated controls and to mice treated with the single drugs alone, Mdr2KO mice that received the ZA/RA combination at peak fibrosis and for only one month demonstrated a

twofold reduced collagen deposition, with elimination of bridging fibrosis ($p < 0.0001$). This was accompanied by a similar reduction of the cholangiocyte-specific marker CK19 and the HSC activation (aSMA) and a significant suppression of profibrogenic transcripts including Col1a1, Col3a1, aSMA, TNFa, and markers of M2-type macrophages, including HIF1a and MMP9. Moreover, the number of YM1+ (M2-type) relative to CD68+ (total) macrophages was significantly reduced by combination treatment vs all other groups.
Conclusions: The combination of RA and ZA, two agents with macrophage modulating activity, induces a remarkable regression of even advanced biliary fibrosis. This antifibrotic effect goes along with a marked reduction of HCC formation. Since both drugs are used in the clinic for other indications, with a reasonable safety profile, their clinical testing should be considered in patients with fibrotic and (pre) cancerous PSC and other liver diseases.

THU-064
Identification of new epigenetic targets in hepatic fibrosis

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Background and aims: Liver fibrosis is an essential component of chronic liver disease (CLD) and hepatocarcinogenesis. Hepatic cirrhosis, the most advanced stage of CLD, is becoming a worldwide health problem, with high mortality rates and no effective antifibrotic therapies available. Several molecular mechanisms implicated in the activation of hepatic extracellular matrix (ECM) producing cells have been identified. These include epigenetic mechanisms involving changes in DNA and histone methylation regulating the expression of key genes. Therefore, the enzymes responsible for these epigenetic events, such as DNA and histone-methyltransferases, would be attractive therapeutic targets. We have recently demonstrated that histone methyltransferase G9a and DNA methyltransferase DNMT1, forming a gene expression regulatory complex, play a key role in hepatocarcinogenesis. We have developed first-in-class dual inhibitors of these enzymes with therapeutic potential and significant antitumoral effects. The present study evaluates G9a as a possible therapeutic target in hepatic fibrosis and examines the antifibrotic potential of CM-272, our lead compound dual inhibitor of G9a/DNMT1.
Results: G9a is overexpressed in the fibrotic liver and is induced during the activation process of hepatic stellate cells (HSCs) in culture. We observed that G9a plays a very important role in the response of these cells to TGFβ, the main pro-fibrogenic cytokine, as G9a knockdown impaired TGFβ-mediated signaling and gene regulation. Treatment with CM-272 significantly modified the gene expression profile induced by TGFβ in human HSCs, prevented their profibrogenic response and the metabolic adaptation of these cells to hypoxia. We observed a potent antifibrotic effect of CM-272 in *ex vivo* models of precision-cut liver slices obtained from rats and patients subjected to profibrogenic stimuli (PDGF + TGFβ). Finally, the antifibrotic effect of CM-272 was corroborated in mouse models of hepatic fibrosis, such as the CCl_4 administration and bile duct ligation, where a very significant antifibrotic effect of CM-272 was observed without signs of hepatic or systemic toxicity.
Conclusion: G9a plays an important role in the activation of HSCs. We have demonstrated the antifibrotic potential of a dual G9a/DNMT1 inhibitory molecule, tested in *ex vivo* and *in vivo* models without apparent toxic effects. Our data suggest a new strategy for the development of effective therapies against fibrosis.

THU-065
Metformin reverses liver fibrosis via AMPK/PGC-1α mediated mitochondrial metabolic switch

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Background and aims: Liver fibrosis is pathological phenomena of dysfunctional repair response to chronic liver injury, which is characterized by the activation of hepatic stellate cells (HSCs). Cellular metabolic phenotype, which is regulated by a critical sensor AMPK, is closely related to cell fate. However, the roles of AMPK signaling pathway-mediated metabolic switch in liver fibrosis have not been well demonstrated.
Method: Immunofluorescence staining and q-PCR analysis were performed to identify the AMPK activity and the expression of metabolic genes in liver samples of patients with cirrhosis and mice following administration of CCl_4. Glucose uptake ability, oxygen consumption rate, lactate accumulation and ATP production, as well as HIF-1α activity, PGC-1α expression were measured in primary HSCs during transdifferentiation and after metformin administration, respectively. PGC-1α vectors were constructed and overexpressed in activated myofibroblasts to determine the effects of glycolytic and pro-fibrotic activities. Furthermore, mice with established liver fibrosis were administrated with metformin to measure the improvement of fibrotic status.
Results: We found that AMPK was inactivated in fibrotic regions in both patients with cirrhosis and mice following administration of CCl_4, which is associated with the increasing expression of pro-glycolytic proteins, such as Glut1, HK2, PKM2 and LDHA. Consistently, primary HSCs isolated from fibrotic models or myofibroblasts transdifferentiated from cultured, quiescent HSCs exhibited pro-glycolytic switch from oxidative phosphorylation, which could be rescued by activation of AMPK agonist, metformin. Mechanically, lower AMPK activity inhibited PGC-1α expression, an important transcription factor of mitochondrial biogenesis, but activated HIF-1α signaling. Enhancement of mitochondrial biogenesis and oxidative phosphorylation by overexpression of PGC-1α converted myofibroblasts to quiescent HSCs. In addition, metformin therapeutically alleviated CCl_4-induced liver fibrosis in an AMPK-dependent manner in mice.
Conclusion: This study clarified that AMPK activity-dependent pro-glycolytic switch drove the activation of HSCs and progress of liver fibrosis. AMPK agonist metformin might be expected to reverse established liver fibrosis by improvement of mitochondrial biogenesis.

THU-066
Association of apri index and elastography by shear wave elastography

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Background and aims: Dozens of non-invasive models composed of blood biochemical biomarkers have been proposed to detect liver fibrosis, including aspartate aminotransferase to platelets ratio index (APRI). The latest research has shown that ultrasound elastography can measure the hardness of liver tissue to determine the degree of

hepatic fibrosis with features of non-invasiveness, simplicity, speed and repeatability. Non-invasive methods including ultrasound elastography have emerged within the past decade and are increasingly replacing liver biopsy for liver fibrosis assessment, avoiding the risks and discomforts of this invasive method.
It is important to know the correlation that exists with two non-invasive methods of fibrosis. Determine if there is an association with the APRI and the measurement by hepatic elastography. Calculate the APRI for patients who underwent hepatic elastography by shear wave elastography.
Method: Cohort study, retrospective, analytical. The clinical records of the 2017–2018 period were reviewed of patients who attended the outpatient Gastroenterology and elastography was performed by shear wave. The liver test was analyzed and APRI was calculated, to later make a comparison with both. Patients who did not have data in the electronic file were excluded. Average and standard calculation were calculated for the continbes and association by means of Pearson. Statistical analysis was performed through the SPSS program, 19 version.
Results: One hundred and twenty-one shear wave elastography were performed in a year, the average age of the patients was 59.57 ± 12.64 years, predominant gender was the female 70 (57.8%), etiologies of liver diseases: PBC 4, Overlap syndrome (PBC + AIH) 2, NASH cirrhosis 16, cryptogenic cirrhosis 14, alcoholic cirrhosis 22, AIH cirrhosis 5, alcohol cirrhosis plus chronic hepatitis C, HVC cirrhosis 9, DILI 1, NAFLD 33, AIH 4, HVC 10. Of these patients, only patients with liver cirrhosis were 68 (56%), gender men 36 (52.9%) and women 32 (47.1%), we obtained the mean and standard deviation: APRI = 0.58 ± 0.59, Child Pugh = 5.5 ± 1.0, MELD = 10.5 ± 3.0, Elastography = 8.35 ± 3.83 Kpa, platelets = 142161 ± 76380, albumin = 3.67 ± 0.54. Sixteen (23.5%) patients presented with esophageal varices. Pearson's association coefficient with the variables of APRI and platelets was obtained obtaining p = 0.000, Elastography and platelets with p = 0.046. APRI and elastoscopy with p = 0.068.
Conclusion: There is no correlation with the rate of APRI and hepatic elastography, but liver elastography correlates with the number of platelets.

THU-067

Selective targeting of GLI1 suppresses the differentiation of hepatic progenitor cell towards fibrogentic cholangiocyte and fibrosis progression

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Background and aims: Although the role of canonical Hedgehog pathway has been well established in liver fibrosis, how Gli1 is regulated in a smoothened (SMO)-independent manner is still a puzzle. We studied the role of Gli1 in hepatic progenitor cell (HPC) differentiation and liver fibrosis progression.
Method: Liver samples of 144 chronic hepatitis B patients were obtained from biopsy. Masson staining and cytokeratin19 (CK19) immuno-staining were performed to observe the collagen deposition and ductular reaction. Fibrosis was induced in F-344 rats via subcutaneous injection of 30% carbon tetrachloride (CCl_4) twice a week for 6 weeks. Then, CCl_4 was administered in conjunction with intragastric 2-acetylaminofluorine (2-AAF) for 3 weeks to induce activation of HPCs *in vivo*, meanwhile, GANT61, a Gli1 inhibitor was intraperitoneal injected to investigate the therapeutic efficacy on ductular reaction and liver fibrosis progression. *In vitro* WB-F344 cells, the HPC line were treated with sodium butyrate (SB) to provide direct evidence for differentiation towards cholangiocytes, meanwhile with or without GANT61 or Gli1 siRNA.
Results: 144 Patients were divided into four groups (S1, S2, S3, S4) according to fibrosis stage. Interestingly, expression of CK19 was notably enhanced with the severity of liver fibrosis and closely correlated with the increase in the percent of positive area ratio of collagen ($r = 0.31$, $p < 0.001$). The results *in vivo* showed that expressions of OV6 and Epcam and ductual cell markers (CK19 and CK7) were increased significantly in CCl_4/2-AAF treated group compared to the CCl_4 only treated group. Double staining showed that OV6 was largely colocated with CK19 positive cells, and the number of OV6 (+)CK19 (+) cells was obviously increased after administration of 2-AAF. The hydroxyproline content, the positive area of collagen and expressions of α-smooth muscle action, collagen type I, collagen type IV, Ki67, Dhh and Gli1were significantly increased, While these datas were remarkably decreased in the GANT61 group compared to CCl_4/2-AAF treated group. These results suggested that a large number of HPC were activated and proliferated, and differentiated to cholangiocyte to promote the fibrosis progression after administration of 2-AAF, while inhibiting the Gli1 expression suppressed ductular reaction and fibrosis progression. *In vitro*, expressions of CK19, CK7, Ki67, Dhh and Gli1 were significantly increased after treatment with SB for 4 days. Interestingly, expressions of CK19, CK7, Ki67 and Gli1 were significantly down-regulated in the GANT61 group and Gli1 siRNA group.
Conclusion: Gli1 directs differentiation of HPC to fibrogenic cholangiocyte and promotes liver fibrosis progression, blocking Gli1 inhibits ductular reaction and accelerates fibrosis reversal, suggesting that Gli1 may be a potential treatment target to treat liver fibrosis.

THU-068

Alcoholic and non-alcoholic fatty liver disease and liver-related mortality: A cohort study

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Background and aims: We compared liver-related mortality by fibrosis severity between two types of fatty liver disease (FLD), non-alcoholic FLD (NAFLD) and alcoholic FLD (AFLD) in a large cohort of non-obese and obese individuals.
Method: A cohort study was performed with 437, 828 Korean adults who were followed for up to 14 years. Steatosis was diagnosed based on ultrasonography; fibrosis severity was determined by the fibrosis-4 score (FIB-4). Vital status and liver-related deaths were ascertained through linkage to National Death records.
Results: The prevalence of NAFLD and AFLD were 20.9%, and 4.0%, respectively. During 3, 145, 541.1 person-years of follow-up, 109 liver-related deaths were identified (incidence rate of 3.5 per 10^5 person-years). When changes in fatty liver status, FIB-4, and confounders during follow-up were updated as time-varying covariates, compared with the reference (absence of both excessive alcohol use and FLD), the multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) for liver-related mortality among those with low, intermediate, and high FIB-4 scores were 0.43 (0.19–0.94), 2.74 (1.23–6.06), and 84.66 (39.05–183.54), respectively, among patients with NAFLD, whereas, among patients with AFLD, the corresponding HRs (95% CIs) were 0.67 (0.20–2.25), 5.44 (2.19–13.49), and 59.73 (27.99–127.46), respectively. The associations were more evident in non-obese individuals than in obese individuals (P for interaction = 0.004).
Conclusion: In this large cohort of young and middle-aged individuals, NAFLD and AFLD with intermediate to high fibrosis scores wereassociated with an increased risk of liver-related mortality in a dose-dependent manner, especially among non-obese individuals.
Figure:
Figure 1. Flowchart of study participants.
Figure 2. Liver related mortality by fatty liver disease category and degree of fibrosis based on FIB-4.

THU-069

Human adipose derived stem cells exhibit enhanced liver regeneration in liver fibrosis model by controlled releasing hepatocyte growth factor

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Background and aims: Although mesenchymal stem cells (MSCs) provide effective therapy for liver fibrosis, there are conflicting data regarding their marginal therapeutic effects. This study aimed to enhance the potential of hepatocyte regeneration in human adipose mesenchymal stem cells (ASCs) and investigate whether they have robust therapeutic efficacy in experimental liver fibrosis.
Method: ASCs were cultured with four cytokines (ASC-C), the expression of hepatogenic factors was detected by microarray, and the effects of conditioned medium (CM) from ASC-C on the activation of hepatic stellate cells were analyzed. The therapeutic effects and mechanism of liver fibrosis induced by thioacetamide (TAA) were determined after cell transplantation. ASC-C exhibited high levels of hepatogenic (HGF, G-CSF), anti-apoptotic (IGFBP-2), and chemokine (IL-8) genes and increased expression of hepatocyte specific proteins.
Results: ASC-C CM inhibited the activation of hepatic stellate cells *in vitro*, and injection of ASC-C significantly delayed TAA-induced liver fibrosis and improved liver function and regeneration *in vivo*. In addition, human albumin-expressing ASC-C were observed in the livers of recipient animals. High levels of expression of HGF and its downstream signaling molecules, including p-38, were detected in the ASC-C-injected livers. Transplantation of ASC-C exerts anti-fibrotic effects and accelerates liver regeneration.
Conclusion: Thus, ASC-C may be a novel candidate for the enhanced treatment of liver cirrhosis in clinical settings.

THU-070

The nuclear factor TCF20 regulates the severity of liver fibrosis in mice

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Background and aims: Chronic liver diseases are related with the increase in collagen I production and deposition in the liver. This protein is synthesised in the endoplasmatic reticulum after the assembly of two peptides of procollagen alpha 1 (COL1A1) and one peptide of procollagen alpha 2 (COL1A2). The expression of both genes is regulated by different transcription factors such as SP1 and Ets. Accordingly, it has clinical interest to search for regulators of both transcription factors. In this context, the nuclear factor TCF20 acts as a co-activator of a variety of transcription factors, including SP1 and Ets. However, its function has not previously been studied in fibrogenic processes. Therefore, the objective of this study was to determine the role played by TCF20 in liver fibrosis through the generation of a mouse model of TCF20 gene deficiency.
Method: TCF20 knock-out mice were generated by microinjecting mouse embryonic stem cells $D09^{tm1\ (KOMP)Mbp}$ (KOMP Repository) to blastocytes C57Bl/6J.Ola.Hsd. Liver fibrosis was induced by the administration of carbon tetrachloride (CCl_4) three times a week during four weeks. The proteome from embryonic livers (E18.5) was analyzed by Label-free nLC MS/MS (Thermo Fisher Scientific). Mouse hepatic stellate cells (GRX) were transfected with plasmids that express a specific shRNA to silence TCF20 expression.
Results: TCF20 knock-out mice ($TCF20^{-/-}$) showed to be newborn-lethal. Liver proteomic analysis from $TCF20^{-/-}$ mice embryos (n = 5) revealed alterations in the aminoacid synthesis pathway and the oxidative phosphorilation. In contrast, heterozygous mice ($TCF20^{\pm}$) resulted to be viable without any apparent abnormality. After the CCl_4 treatment, $TCF20^{\pm}$ mice showed a significant increase in fibrotic area when compared to $TCF20^{+/+}$ (3.2 ± 0.1 vs 2.1 ± 0.1%, respectively; $p < 0.001$); as well as increased levels of ALT (2145 ± 1367.7 vs 690.4 ± 215.9 U/L, $p < 0.01$), AST (1413 ± 142.7 vs 562.4 ± 146.9 U/L, $p < 0.01$) and BUN (21 ± 2.5 vs 14.4 ± 1.0 mg/dL, $p < 0.05$). Seventy percent of TCF20 gene silencing in GRX cells was associated with an over-expression of COL1A1 when compared to control ($p < 0.05$).
Conclusion: TCF20 total deficiency is lethal in newborn mice. TCF20 partial deficiency is associated to increased fibrosis and liver injury *in vivo* and to an overexpression of collagen I in mouse HSC. Our results show a new function for TCF20 as a regulator of the severity of liver fibrosis after tissue damage.

THU-071

Matrix modulation in chronic liver injury and resolution

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Background and aims: A sexual dimorphism in liver inflammation and repair was previously demonstrated in a mouse model of acute liver injury. The aim of our study was to verify if hepatic matrix is differently modulated according to gender
Method: A chronic hepatic injury was established in Balb/cJ mice intra-peritoneally injected with CCl4 and sacrificed at week 2, 6, 12 and after 8 weeks of self-healing (recovery group). Fibrosis was evaluated. Collagen III and TIMP-1 were evaluated by Western Blot. The expression of MMP9 and MMP13 mRNAs was evaluated by qRT-PCR. The amount of Kupffer cells was investigated by flow-cytometry on liver single cell suspension.
Results: The amount of fibrosis in the recovery group was higher in females with respect to males (mean±ds females vs males: 4.48 ± 1.39 vs 2.46 ± 0.53 p = 0.032). Collagen III was found lower in females than in males at week 2, with a significant increase along the treatment, but only in female mice. TIMP-1 protein showed a progressive accumulation from week 2 to 12 only in females, with a significant decrease during the recovery period. The analysis of MMP9 revealed a down modulation (68%) of mRNA in males from week 6 to the end of the recovery period; moreover MMP9 mRNA was found higher (60%) in females than in males of the recovery group. MMP13 mRNA was found higher in males than in females at week 12 showing a progressive down modulation in females from week 6 to the end of the recovery period. Kupffer cells were abundant in both female and male mice in the early chronic liver damage and significantly decreased over time, albeit in the recovery group female mice showed a significant higher amount of this cell population, in comparison with males.
Conclusion: During fibrosis resolution, female livers failed to properly regenerate compared to males. An imbalance in MMPs-TIMP-1 homeostasis was apparent in chronically-injured female livers. Modulations of MMP9 mRNA are in line with fluctuations observed in fibrosis amount. MMP13 mRNA modulations agree with the observed flows of Kupffer cells but suggest that other cells than Kupffer are responsible for MMP13 mRNA variations.

THU-072

N-ras protects against experimental liver fibrosis by maintaining hepatocyte homeostasis

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Background and aims: The *Ras* genes (*H-ras*, *K-ras* and *N-ras*) encode for the RAS proteins with pivotal roles in the regulation of cell survival, differentiation, growth and apoptosis. Apart from their oncogenic properties, little is known on the context and cell-dependent phatophysiological roles of RAS proteins. In particular, N-RAS is critically involved in immune cell function. Hepatic fibrogenesis develops in response to inflammatory cytokines, cellular interactions with immune cells and morphogenic signals. In the present work, we hypothesized that N-RAS plays a pivotal role in the pathophysiology of liver fibrogenesis.
Method: N-ras deficient (*N-ras*$^{-/-}$) and wildtype (*N-ras*$^{+/+}$) mice bred in a C57BL/6 background were subjected either to perifibrilary or periportal fibrosis using 28 days (i) bile duct ligation (BDL) and (ii) CCl_4-induced liver fibrosis, respectively. Sham-operated and corn-oil-injected mice were included as controls. Histopathological examination of livers, immunofluorescence and immunohistochemistry, Western Blot and Real time (RT)-qPCR studies and gene array analysis were performed.
Results: Histopathological examination of *N-ras*$^{-/-}$ mice showed rupture increased presence of necrotic foci associated with significantly elevated markers of liver damage in serum compared with *N-ras*$^{+/+}$, 28 days after BDL and CCl_4. *N-ras*$^{-/-}$ livers exhibited increased cell death and compensatory cell proliferation markers such as PCNA and Ki-67. Futhermore, CD11b^{+}, F4-80^{+} and CD45^{+} cells were significantly increased in *N-ras*$^{-/-}$ compared with *N-ras*$^{+/+}$ animals, 28 days after treatment. Moreover, Collagen I and III deposition and α-smooth muscle actin (αsMA) mRNA and protein expression were significantly elevated. Mechanistically *N-ras*$^{-/-}$ livers showed activation of cleaved Caspase 8, RIPK1/3 and pMLKL together with decreased cleaved Caspase-3. Additionally, *N-ras* deficiency triggered overexpression of pAKT and pJNK1/2.
Conclusion: Our results indicate that N-ras plays a pivotal role in liver fibrogenesis. N-ras deficiency triggered cleaved Caspase 8, RIPK1/3 and pMLKL-dependent cell death, exacerbated compensatory proliferation, increased inflammation and immune cell infiltration and hepatic fibrogenesis. These findings suggest that N-RAS modulation could be a novel therapeutic approach for the treatment of chronic liver injury.

THU-073

The use of APRI and FIB-4 scores versus transient elastography for the assessment of liver fibrosis stage in patients with chronic hepatitis C: Is it possible to reduce the need for elastography?

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Background and aims: Liver fibrosis staging, based especially on liver stiffness measurement (LSM) with TE, represents an important step during the management of chronic hepatitis C (CHC). However, TE is not widely available and there is a need for less expensive and simpler non-invasive approaches especially in terms of the hepatitis C elimination strategy worldwide. In this context the use of scoring systems such as APRI and FIB-4 has been suggested but their validation in several populations is emerging. In this study the diagnostic performance of APRI and FIB-4 to detect significant fibrosis (F3) or cirrhosis (F4) compared to TE have been evaluated in a Greek CHC cohort.
Method: We retrospectively enrolled 589 patients admitted to our tertiary liver center with CHC who underwent TE [males: 370 (64.5%), mean age: 51.8 ± 12.2 years] between May 2014 and September 2018. The results of APRI and FIB-4 scores were compared to LSM.
Results: 117/589 (19.9%) patients had LSM values between 9–11.9 kPa and were classified as F3, while 249/589 (42.3%) were classified as F4. APRI (AUC = 0.735, p = 0.021) and FIB-4 (AUC = 0.769, p = 0.02) scores predicted F4 patients adequately. Cut-off values were determined as 0.66 (sensitivity 70%, specificity 66%) for APRI and 1.82 (sensitivity 72%, specificity 69%) for FIB-4. However, both scores were ineffective in predicting F3 patients. Cut-off values of 0.65 for APRI and 1.46 for FIB-4 predicted F3/F4 patients as one group of patients (sensitivity 65% and 74.5% respectively, specificity 75.5% and 70% respectively). Additionally, the use of APRI/FIB-4 as a combination marker with these cut-off values (0.65/1.46) adequately predicted F3/F4 patients (sensitivity 60%, specificity 83.5%, PPV 86%, NPV 55%). Furthermore, we determined that the same APRI/FIB-4 combination marker predicted adequately patients with low grade fibrosis F0-F2 (sensitivity 83.5%, specificity 60%, PPV 55%, NPV 86%) and could be used in order to reduce the need for LSM.
Conclusion: APRI and FIB-4 performed well in predicting advanced fibrosis. A proposed APRI/FIB-4 cut-off value of 0.65/1.46 as a combination marker could be used as a screening tool instead of LSM which is not widely available, especially in determining low grade fibrosis. Further prospective validation studies are required to confirm this finding.

THU-074

Anti-fibrotic effect of dimethyl fumarate on rat liver fibrosis induced by thioacetamide: Role of NF-kappa B, NLRP3, Nrf2 and autophagy

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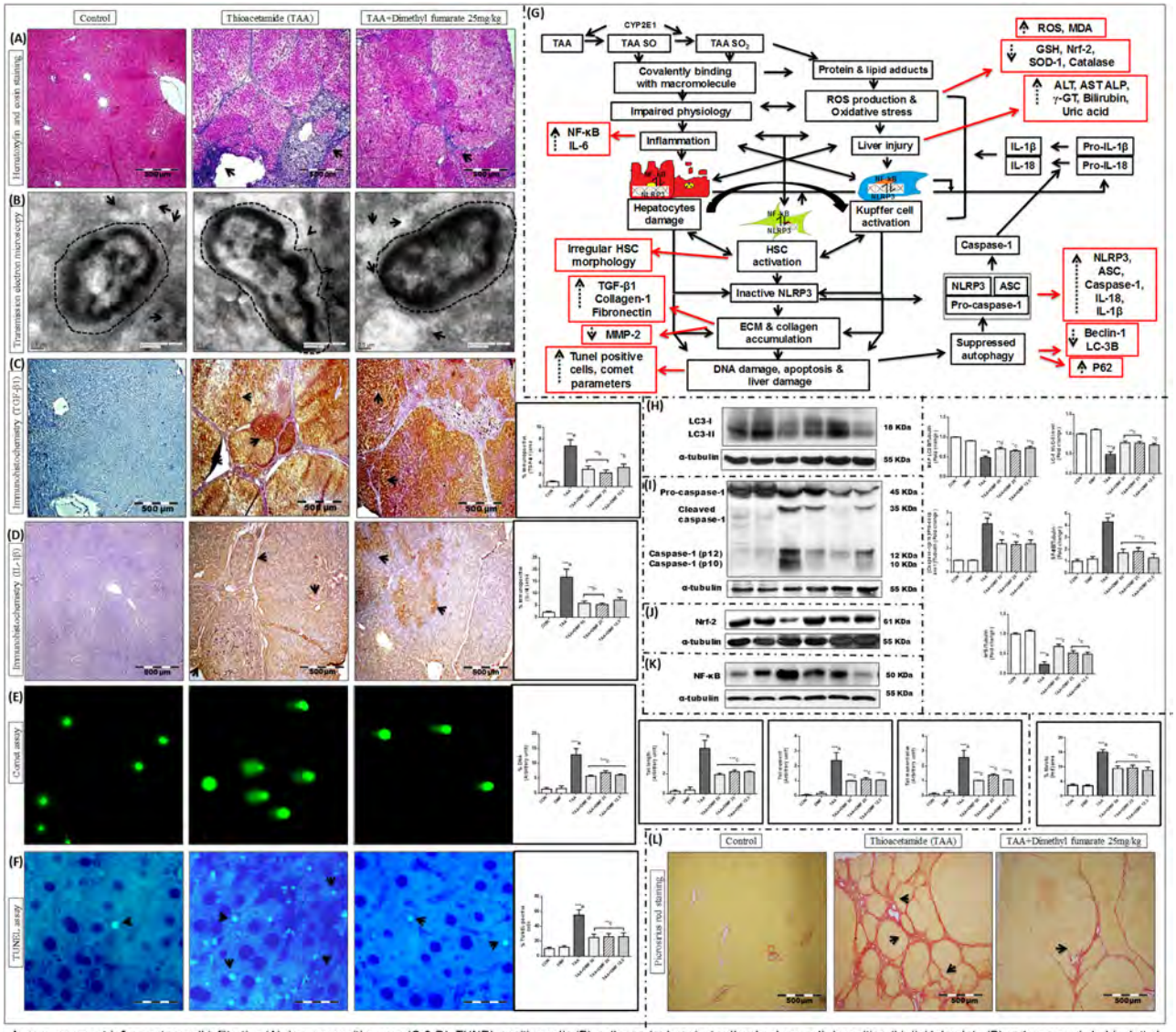
Background and aims: Fibrosis is the most common pathway involved in acute and chronic liver diseases, which ultimately leads to the end-stage liver cirrhosis. World Health Organisation in 2018 reported that cirrhosis is at 9th position in top 10 causes of death in lower-middle income countries. Liver injury activates hepatic stellate cell (HSC) that releases extracellular matrix proteins, facilitates the deposition of collagen at the site of injury and results fibrosis. Thioacetamide (TAA) is one of the most widely known hepatotoxicants, precisely mimics the initiation and progression of human liver damage in experimental animal models. Dimethyl fumarate (DMF) used for the treatment of multiple sclerosis and selected as a pharmacological intervention agent in the present investigation. The aim is to evaluate the hepatoprotective as well as anti-fibrotic potential of DMF against TAA-induced hepatic damage in rat.
Method: Male Wistar rats (250 ± 20 g) were exposed to TAA (normal saline) intraperitoneally at the dose of 200 mg/kg, twice weekly, while DMF (0.5% sodium CMC) was administered everyday by oral



Arrows represent inflammatory cell infiltration (A), immunopositive area (C & D), TUNEL positive cells (F), collagen (red against yellow background) deposition (L), lipid droplets (B) and area encircled in dotted lines showing HSCs (B). Comet assay (E). Immunoblots of selected targets (H, I, J &K). Schematic presentation of TAA-induced possible hepatic damage and subsequent protection with DMF at different targets. Dashed arrow represents either decrease or increase in respective expression/level in red boxes (G).

gavage at the doses of 12.5, 25 and 50 mg/kg for 6 consecutive weeks. Several parameters like biochemical, histopathological, transmission electron microscopy (TEM), immunohistochemical and immunoblotting were evaluated.

Results: TAA exposure significantly reduced the body weight, increased liver weight while DMF treatment did not restore the same. TAA-induced significant increase in the liver weight and profuse nodular appearance might be due to collagen deposition, new angiogenesis, and deposition of other fibrotic components. DMF intervention significantly ameliorated TAA-induced increase in AST, ALT, gamma GT, bilirubin, uric acid, MDA and decrease in reduced glutathione. TAA-induced significant increase in plasma transaminases (AST, ALT) level was might be due to damage of hepatocyte membrane results release of transaminases. Moreover, DMF treatment significantly normalised TAA-induced alterations in histopathological findings such as severe degree of lymphocyte infiltration, collagen deposition, necrosis, bridging fibrosis. Further, TAA exposure increased the TUNEL positive cells, %DNA, tail length, olive tail moment and activated HSCs, whereas DMF intervention normalised the same. Furthermore, DMF treatment significantly restored the TAA-induced alterations in inflammatory cascade (NLRP3, ASC, caspase-1, NF κappa B, IL-6), fibrogenic (TGF beta1, fibronectin, collagen1, MMP2), anti-oxidant (Nrf2, SOD-1, catalase), and autophagy markers (beclin-1, MAP LC-3B, p62).

Conclusion: Present investigation confirmed the anti-fibrotic effect of DMF as mediated by the restoration of TAA-induced oxidative stress, inflammatory cascade, DNA damage, histopathological changes, autophagy and anti-oxidant levels.

THU-075

2d- shear wave elastography for the spleen stiffness evaluation: A non-invasive marker for predicting high risk varices in patients with compensated liver cirrhosis

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Background and aims: Ultrasound based elastographic methods and biological markers can be used as non-invasive tools for predicting

the presence of high risk varices (HRV), defined as grade II, III esophageal and gastric varices, in patients with compensated liver cirrhosis. The **aim** of the study was to determinate the utility of spleen stiffness (SS) values measured by 2D-SWE as non-invasive marker for prediction of HRV, in patients with compensated liver cirrhosis.
Method: A prospective study was performed in 55 subjects with compensated liver cirrhosis, who underwent both spleen stiffness measurements (SSM) with a 2D-SWE technique (General Electric LOGIQ E9 XD clear 2.0) and upper endoscopy in the same admission. Spleen stiffness was performed with the patient in supine position and the SWE evaluation box was placed in the middle of the spleen, avoiding large vessels. Reliable SSM were defined as the median value of 10 measurements acquired in a homogenous area and an interquartile range/median (IQR/M) <0.30. Compensated liver cirrhosis was diagnosed based on clinical, biological and elastographic criteria (FibroScan > 12, 5 kPa)
Results: We obtained reliable SSM in 53/55 subjects (96.4%). 28/55 (51%) subjects had HRV. The mean SS values for patients with HRV were significantly higher as compared to those with first grade or no varices (18.6 ± 4.3 kPa vs. 15.7 ± 2.8 kPa with p = 0.0056). The best SS cut-off value measured with 2D-SWE-GE for predicting the presence of HRV in our study group was: 17.2 kPa (AUROC-0.80; sensitivity-67.8%; specificity-92%; PPV-91%; NPV-71, 9%).
Conclusion: Using the SS cut-off value > 17.2 kPa obtained by means of 2D-SWE we can rule in the presence of HRV, with a positive predictive value of 91%.

THU-076

SPP1 gene knockout in human hepatic stellate cells decreased profibrogenic cytokines and collagen gene expression

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Background and aims: Secreted phosphoprotein-1 (SPP1) is a stress sensitive multifunctional cytokine involved in innate immunity, cell proliferation, invasion, and metastasis. It was observed that SPP1 promotes activation and transformation of resting hepatic stellate cells into myofibroblast like cells and drives collagen synthesis. The purpose of the study was to evaluate the role of SPP1 on activation and transformation of human hepatic stellate cells and subsequent production of profibrogenic cytokines and collagen gene expression.
Method: Primary human hepatic stellate cells were isolated from pieces of surgically resected human liver tissue after pronase and collagenase digestion and purified using density gradient centrifugation. The isolated and purified stellate cells were cultured with appropriate medium for 48 h. The cultures were then divided into two sets and one set was treated with SPP1 CRISPR guide RNA sequences that efficiently knockout SPP1 gene without significant binding of Cas9 elsewhere in the genome. The second set of cultures without SPP1 CRISPR gRNA treatment served as control. The cultures were maintained for another 7–10 days. The cells were fixed and stained for α–smooth muscle actin (α–SMA) to examine the activation of stellate cells. Western blotting was carried out for SPP1, PDGF-B, TGF-β1, and collagens type I and type III. qPCR was performed to quantify mRNA of α-SMA, and collagens type I and type III.
Results: Immunocytochemical staining showed that the isolated quiescent stellate cells were positive for glial fibrillary acidic protein (GFAP) and negative for α-smooth muscle actin (α-SMA). Western blotting demonstrated complete knockout of SPP1 after treatment with CRISPR/Cas9 gRNA. Knockdown of SPP1 in primary hepatic stellate cells prevented activation and transformation of over 50% hepatic stellate cells into myofibroblast like cells and depicted marked decrease in the staining intensity of α-SMA. Western blotting for PDGF-B, TGF-β1, and collagens type I and type III showed significant decrease in the protein levels in SPP1 knockout cells. qPCR demonstrated marked reduction in the expression of α-SMA and collagens type I and type III mRNA indicating decreased activation of stellate cells and reduced synthesis of collagens after deletion of SPP1 gene.
Conclusion: The results of the present study demonstrated that SPP1 regulates profibrogenic cytokines and activation of stellate cells contributing to the pathogenesis of hepatic fibrosis. Furthermore, blocking of SPP1 has potential therapeutic implications to arrest hepatic fibrosis and related events.

THU-077

Fibro-protective molecular and cellular mechanisms emerge during resolution from thioacetamide-induced fibrosis

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Background and aims: The reported dynamic nature of hepatic stellate cells (HSCs) during fibrosis and resolution highlights that little is known of the fate of their co-migratory partner, liver progenitor cells (LPCs). Manipulating the known co-regulatory relationship between LPCs and HSCs during specific phases of fibrosis to alter their dynamic phenotypes may represent a new therapeutic target. Here we investigate thioacetamide (TAA) pre-treatment and recovery in mice, and the role and mechanism of resulting cell populations in the fibro-dynamic microenvironment of the liver after reintroduction of TAA.
Method: Tissue and sera were collected from C57BL/6 mice of two study groups (n = 5–9 per group): (a) pre-treated; 6-week TAA (300 mg/L drinking water), 4-week recovery, 6-week TAA and (b) naïve; 10-week control diet and 6-week TAA. Liver injury and fibrosis was characterized by extensive biochemical, histological and transcriptional analysis. Inflammatory, LPC and HSC subpopulations were identified by immunofluorescent staining. Primary isolated HSCs from healthy, fibrotic, and recovering mouse liver were co-cultured with the clonal bipotential murine oval liver (BMOL) LPC line prior to qPCR analysis of fibrotic transcriptional regulation.
Results: Phenotypically distinct inactivated desmin^{+}, aSMA^{-}, GFAP^{-} HSCs and CK19^{+} LPCs were confirmed in livers of pre-treated mice at d0, but not in naïve mice by immunofluorescence. TAA treatment induced early CD45^{+} inflammatory cell proliferation in naive mice typical to this model, which was notably absent in pre-treated mice. Elevated serum ALT levels and profibrogenic (aSMA, TGFb1, Col1A1 and TIMP1) transcription during early TAA treatment indicated a severe damage response in naïve mice. Incomplete resolution of fibrosis in pre-treated mice remained static throughout subsequent treatment, whereas naïve mice progressed to cirrhosis after 6 weeks of TAA. Primary HSCs isolated from fibrotic mice exhibit significantly reduced aSMA, Col1A1 and TGFb1 expression after co-culture with BMOL progenitor cells, suggesting anti-fibrotic regulation of HSCs through LPCs in this setting.
Conclusion: Contrary to the carbon tetrachloride model used in other recovery studies, TAA pre-treatment stimulates compensatory mechanisms, moderating the effects of a subsequent hepatic insult. As revealed through direct HSC-LPC coculture, LPCs may play a role in anti-fibrotic regulation of HSCs and could represent a mechanistic key to stabilising fibrosis for therapeutic benefit in patients with recurrent fibrotic pathology.

THU-078

PBI-4050 inhibits hepatic stellate cell activation, restores autophagy, and reduces CCl4-induced liver fibrosis

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Background and aims: Hepatic fibrosis is a major cause of morbidity and mortality for which there is currently no effective therapy. PBI-4050 is a dual GPR40 agonist/GPR84 antagonist with antifibrotic, anti-inflammatory and antiproliferative activities. We investigated the mechanism of action of PBI-4050 on human hepatic stellate cells (HSCs), the prominent cell type producing ECM and involved in liver fibrosis, and its antifibrotic activity in the CCl_4 mouse model.
Method: Primary human HSCs were stimulated with transforming growth factor (TGF)-β1 (10 ng/ml) or platelet-derived growth factor (PDGF)-BB (10 ng/ml) in the presence or absence of PBI-4050. Cell viability was assessed by the Resazurin fluorescence assay and cell cycle by flow cytometry. Phospho- and Total-AMPK, LKB1, mTOR, ULK1, and LC3A were detected by Western blot, and gene expression by qPCR. Liver fibrosis was induced in C57BL/6 mice by 10% CCl_4 in olive oil at 2 ml/kg, twice a week for 8 weeks, and mice were treated with PBI-4050 (200 mg/kg) or vehicle. The degree of fibrosis in the liver was evaluated by histopathology and gene expression analysis.
Results: Cell proliferation of HSCs treated 24 h with either TGF-β1 or PDGF-BB was inhibited by PBI-4050 without cytotoxicity. To confirm these results, cell cycle analysis was performed by flow cytometry on activated HSCs. PBI-4050 dose-dependently arrested HSC at the G0/G1 phase without inducing apoptosis. Subsequent analysis demonstrated that PBI-4050 decreased intracellular ATP concentration and signaled through the activation of LKB1/AMPK and the inhibition of mTOR phosphorylation. Furthermore, Ser555-ULK1 phosphorylation was increased and LC3A-II/LC3A-I ratio decreased suggesting a restoration of autophagy in these cells. In addition, we demonstrated reduced protein and mRNA levels of α-SMA and CTGF, and restoration of PPARγ mRNA expression. In CCl_4 mice, treatment with PBI-4050 reduced liver fibrosis as shown by a reduction of collagen (histological analysis and hydroxyproline content). PBI-4050 also significantly decreased gene expression of fibrosis, ECM remodeling, and epithelial to mesenchymal (EMT) markers (α-SMA, CTGF, MMP2, TIMP-1).
Conclusion: PBI-4050 inhibited HSC activation through reduction of intracellular ATP and the LKB1/AMPK/mTOR signaling pathway, resulting in restoration of PPARγ and autophagy. These results translate in reduction of liver fibrosis in the CCl_4 mouse model.

THU-079

Study of anti-fibrotic activity of human umbilical-cord tissue-derived mesenchymal stromal cells during fibrogenesis or resolution in murine models of liver fibrosis

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Background and aims: Substantial uncertainty exists from pre-clinical liver fibrosis models as to whether mesenchymal stromal cells (MSC) are anti-fibrotic, and yet clinically they have been proposed as a putative anti-fibrotic therapy for patients. Using two rigorous murine models, we aimed to determine the therapeutic effects of CD362-selected (S2+) umbilical-cord tissue-derived MSCs (UCT-MSC) on hepatic fibrogenesis and resolution.
Method: Peak fibrosis and resolution was delineated in C57Bl/6 mice using two models of chronic hepatic injury: 6 weeks of 2 µl/g body-weight intraperitoneal carbon tetrachloride (CCl_4), and 16 weeks of oral thioacetamide (600 mg/L) (TAA) in drinking fluid taken *ad libitum*. Intervention experiments were statistically powered to a 25% difference in picrosirius red (PSR) collagen proportional area (CPA) (N = 20/group). Human unselected or S2+ UCT-MSC from two donors were injected by tail vein (TV) ($2\times7.5\times10^5$ MSCs in each experiment) during either injury, or recovery in both models. Fibrosis outputs were PSR, hepatic hydroxyproline (HYP), quantitative polymerase chain reaction (qPCR) for collagen-1, -3, transforming growth factor-beta 1, matrix metalloproteinase-2, –9, and tissue inhibitor of metalloproteinase-1. Stellate cell activation was verified by qPCR and immunohistochemistry (IHC) for alpha-smooth muscle actin, inflammation by CD45, F4/80 IHC and flow cytometry. CryoViz of whole mice determined the bio-distribution and quantification of injected Q-Dot-labeled MSCs.
Results: Peak fibrosis was greater ($p < 0.05$) in the TAA (CPA 10.45% ± 1.62) than the CCl_4 (CPA 2.57% ± .51) model. Fibrosis persisted up to 21 days (CPA 1.48% ± .58) and 28 days (CPA 6.92% ± 2.29) after recovery respectively, albeit with a wide variance. MSCs injected during recovery or fibrogenesis in both models had no effect on fibrosis or hepatic stellate cell activation, compared to saline injection ($p > 0.05$ for all outputs). Use of unselected MSCs did not influence results ($p > 0.05$). CryoViz analysis in the CCl_4 model found 4.90% of TV injected cells in the liver after 24 hours and 0.78% after 8 days.
Conclusion: In two robust, adequately powered, murine models of liver injury and fibrosis, umbilical-cord-tissue-derived mesenchymal stromal cells, when given intravenously, were safe, had limited hepatic bioavailability, and no meaningful anti-fibrotic properties.

THU-080

Survivin aggravates fibrogenecity of hepatic stellate cells via mediating TGF-beta/PI3 K/Akt pathway

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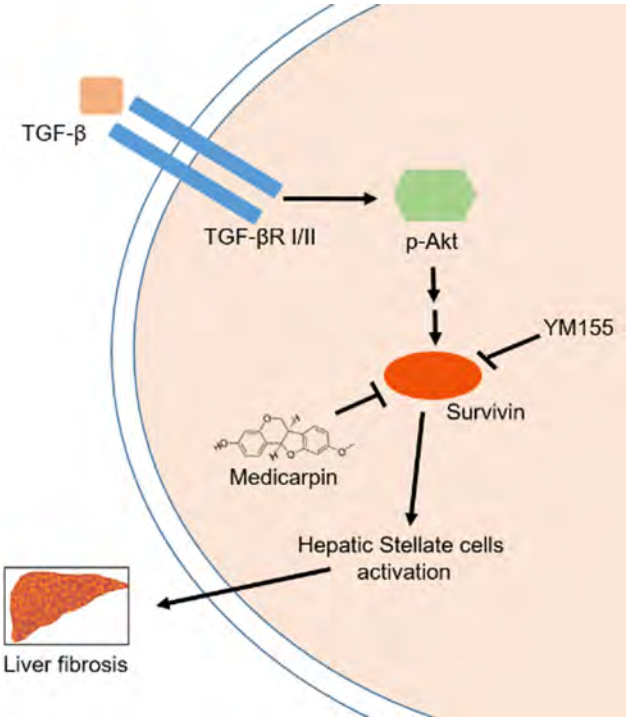
Background and aims: Liver fibrosis is scarring of hepatic parenchymal tissue due to excessive deposition of extracellular matrix (ECM) by activated myofibroblastic cells, predominantly hepatic stellate cells (HSCs). If the condition remains unmanaged, it leads to cirrhosis and liver cancer. Because the activation of HSCs is the principal mechanism leading to liver fibrosis, understanding the process of their activation could open new avenues to cure the condition. Survivin has a vital role in chronic liver diseases. However, its relationship in context to HSCs activation is unknown. Since surviving inhibitor YM155 has been shown to have moderate anticancer effects in clinical trials, therefore, we tried to position another molecule to target survivin. Previously we have reported that a small molecule medicarpin (phytoalexin) can reduce survivin in leukemia. In present study, we aim to evaluate survivin as potential therapeutic target for liver fibrosis.
Method: Wild-type C57BL/6 mice were fed with methionine choline deficient (MCD) diet (*ad libitum*) for eight weeks to induce biliary liver fibrosis. For non-biliary liver fibrosis model, C57BL/6 mice were

fed with high fat diet and administered 0.5 ml/kg dose of carbon tetra chloride (CCl4) for six weeks on every third day. Effects of survivin inhibitor YM155 and medicarpin were evaluated in TGF-β activated hepatic stellate cell line LX-2 for 48hrs. *In vivo* antifibrotic effects of medicarpin were assessed by treating CCl4 induced liver fibrotic mice with medicarpin for six weeks.

Results: Here we show that survivin is highly expressed in activated HSCs and correlates with the expression of p-Akt. Treatment of HSCs with survivin inhibitor YM155 abolishes HSCs activation, and TGF-β pathway inhibitor SB431542 in combination with YM155 potentiates this effect. Treatment of HSCs with medicarpin and observed a decrease in expression of survivin and activation of HSCs. Moreover, Administration of medicarpin (10 mg/kg), reduced the expression of HSCs activation markers αSMA, Col1a1.



Conclusion: Collectively these results indicate that survivin has an essential role in progression of liver fibrosis by regulating activation of hepatic stellate cells and molecules targeting survivin could be helpful in managing the liver fibrosis.

THU-081

Saracatinib, a Src family kinase inhibitor, decreases liver fibrosis

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Background and aims: The SRC family kinase belongs to a family of non-receptor tyrosine kinase and expressed ubiquitously in all cell types. When SRC phosphorylated, various membrane transcription receptor proteins, STAT3, AKT, and EGFR, are phosphorylated and activated to regulate various biological activities. Although inhibition of SRC activation has been reported to inhibit lung or renal fibrosis, little is known about the effet of inhibiting hepatic fibrosis. Here, we examined whether saracatinib, a SRC family kinase inhibitor, has the protective effect on liver fibrosis in vitro and in vivo.

Method: Liver fibrosis was induced by thioacetamide (TAA)-injection for 8 weeks in C57BL/6 mice and saracatinib was administered orally premixed with the pellet. We cultured AML12, LX2 and mouse primary hepatocytes. The effect of saracatinib on liver fibrosis was determined by Sirius red, immunohistorchemistry, real-time RT PCR and western blot analysis.

Results: Expression of SRC was upregulated at the mRNA and protein levels in liver of TAA-injected mice. In addition, we confirmed that phosphorylation of SRC was increased in TAA-injection mice. The SRC inhibitor saracatinib reduced TAA-induced collagen, αSMA and CTGF expression. In vitro studies also showed that TGF-β induces SRC phosphorylation and saracatinib inhibited TGF-β-stimulated CTGF and PAI-1 expression. In addition, saracatinib inhibited TGF-β-stimulated phospho-Smad3 and STAT3 expression.

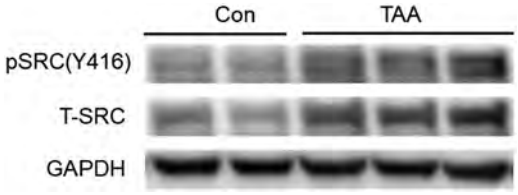

Figure 1: SRC is upregulated in TAA induced liver.

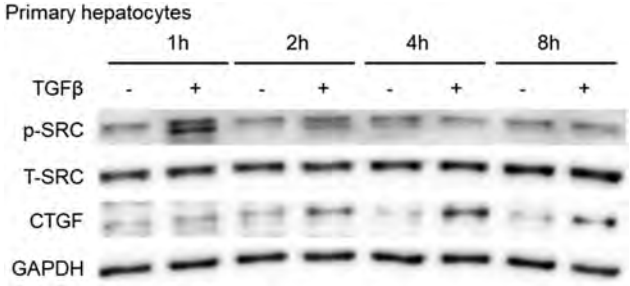

Figure 2: TGF-β increased SRC phosphorylation.

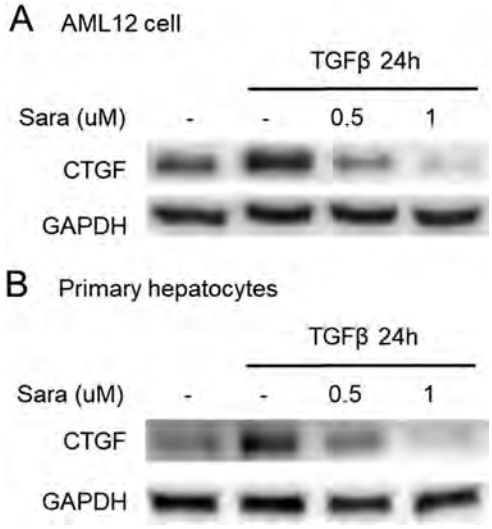

Figure 3: Saracatinib inhibits TGF-β induced CTGF expression.

Conclusion: The results of this study show that the SRC kinase is involved in TGF-β pathway and TAA-induced liver fibrosis. In addition, the SRC inhibitor saracatinib decreased TAA-induced collagen, αSMA and CTGF expression and inhibited TGF-β-stimulated CTGF expression. Furthermore, the inhibitory effect of saracatinib on liver fibrosis was associated with downregulation of TGF-β-stimulated phospho-Smad3 and STAT3.

THU-082

Thymosin beta 4 is a potential regulator of radiation-induced liver fibrosis

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Background and aims: Radiation-induced liver disease (RILD) is a major limitation of radiotherapy for the treatment of liver cancer. Activation of hepatic stellate cells (HSCs), the most prominent feature of liver fibrosis, is commonly observed in the livers of patients with RILD. Thymosin beta 4 (Tb4) is expressed by activated HSCs in fibrotic liver and regulates activation of HSCs via Hedgehog (Hh) signaling by modulating integrin linked kinase (ILK) and glycogen synthase kinase 3 beta (GSK-3b). Herein, we hypothesized that Tb4 might be associated with radiation-induced liver fibrosis.
Method: Male C57BL/6 wild-type (WT) and Tb4-overexpressing transgenic (Tb4-Tg) mice were exposed to hepatic irradiation (IR) with 6 Gy in five weekly fractions and sacrificed at one week after fifth IR. CRISPR/Cas9 system was employed to delete Tb4 gene in LX-2 cells, the activated human HSC line, and these cells were exposed to IR with 2 Gy and harvested at 48 hours after IR.
Results: Only 25% of Tb4-Tg mice survived after 5th IR, whereas all WT mice survived during IR. The ratio of liver weight to body weight (LW/BW) and the serum level of bilirubin were elevated in Tb4-Tg mice compared to WT mice after IR. Livers of Tb4-Tg mice had more Tb4-positive-HSC looking cells than livers of WT mice at baseline and after IR, as assessed by immunostaining. Protein levels of profibrotic markers, TGF-b, a-SMA, vimentin, desmin, col1a1, were significantly upregulated in Tb4-Tg compared with WT mice. Sirius red staining also supported more deposition of collagen fibrils in Tb4-Tg than WT mice. Furthermore, expression of ILK, GSK-3b, and Hh activators, smoothened and glioblastoma 2, increased in the irradiated livers of Tb4-Tg mice compared to WT mice. In addition, Tb4 deletion by CRISPR/Cas9 system induced downregulation of ILK, GSK-3b, smoothened, glioblastoma 2, and profibrotic genes in irradiated LX-2 cells.
Conclusion: Our findings demonstrate that Tb4 influences development of radiation-induced liver fibrosis, suggesting that Tb4 might be a potential regulator of radiation-induced liver fibrosis.

THU-083

Predicting advanced liver fibrosis using deep learning based biopsy image analysis

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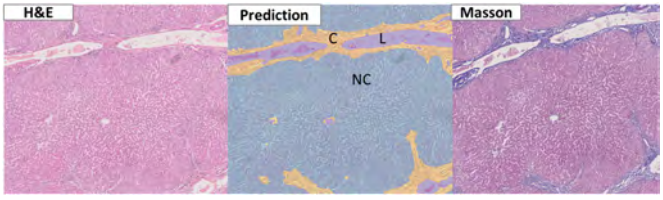
Background and aims: Liver fibrosis results from chronic liver damage and has been a strong clinical indication for liver health. Identifying the progression of liver fibrosis is vital for therapy recommendation and management. Liver fibrosis staging this analysis is often performed by expert pathologists using stains that target extracellular matrix components such as collagen; such analysis may be hindered by staining and interpretation variability. This study aimed to provide a more accurate and automated fibrosis classifier by machine learning analysis of features obtained from full slide HandE images.
Method: High-resolution, stage-annotated, HandE images (n = 115) were analyzed using a two-fold classification pipeline. First, a trained (through matched Masson's trichrome slides) pixel-based deep learning classifier (LinkNet) was used to perform sematic segmentation to annotate practical domains (collagen (C), lumen (L), non-collagen (NC)) (Fig. 1). Next, 58 full-slide features stemming from these annotations, which represented quantitative fibrotic descriptors such as fibrotic branching, envelopment, and fiber alignment, were developed and compared between patients with cirrhosis (S4) and all others (S0-S3). Finally, 10-fold cross-validated feature and machine learning algorithm selection was used to identify the optimal cirrhosis classifier, which was compared against the Masson trichrome stain's positive pixel count.
Results: On 51 million ground truth pixels, the pixel-based classifier leveled off at a prediction accuracy of over 99%. Individual full-slide features varied significantly in stage discrimination, with AUC's ranging between 0.70 and 0.93. Using only 3 whole slide HandE features, an optimized Support Vector Machine (SVM) model produced a cross validated sensitivity of over 95% and a 95% specificity for S4 (as compared to 52% and 96% respectively, using the trichrome stained positive pixel count) (Table 1).

Table 1: Performance Metrics for Stage 4 Prediction using the Proposed ML Model or the Trichrome Positive Pixel Count.

	Proposed Model	Trichrome Positive Predicted Pixels
Sensitivity	0.95	0.52
Specificity	0.95	0.96
Accuracy	0.98	0.88
AUC	0.98	0.83



Conclusion: Our novel, two-fold, HandE-based classification model provides an almost perfect degree of confidence in cirrhosis prediction for liver biopsies, showing superior prediction compared to Masson trichrome-based metrics. Thus, our model can be used to both supplement current pathological analysis and be used confidently for rapid biopsy staging where only HandE slides may be available.

THU-084

A comparative study of anti-Fibrotic therapeutics using aptamer-based quantitative proteomics in a rat model of non-alcoholic steatohepatitis cirrhosis

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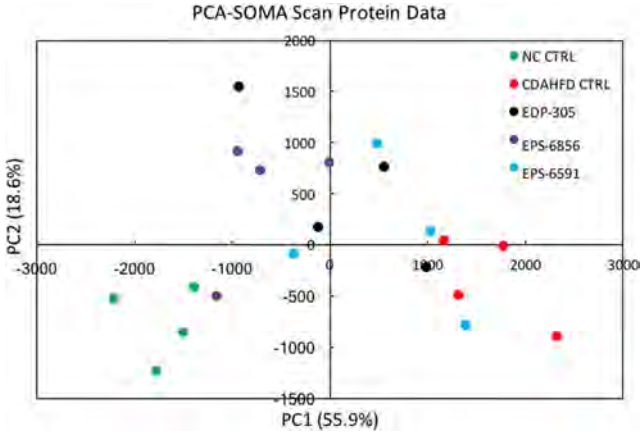
Background and aims: Cirrhosis is the common end point of all chronic liver diseases, including non-alcoholic steatohepatitis (NASH). Several therapeutics are currently under clinical investigation for the treatment of NASH cirrhosis and they target key features of the disease including lipogenesis, inflammation, and fibrogenesis. Effective biomarkers to assess the efficacy of these therapeutics are urgently needed and could also provide insights into shared mechanisms of action. Here, we investigate three anti-fibrotic therapeutics in a pre-clinical model of NASH cirrhosis: two ASK1 inhibitors, EP-026856 and selonsertib, and one FXR agonist, EDP-305.
Method: 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. Animals were randomized to receive daily oral gavage of either vehicle (0.5% methylcellulose (MC)), 30 mg/kg EDP-305, 30 mg/kg EP-026856, or 30 mg/kg selonsertib at the first signs of fibrosis (5 weeks, n = 8 per group). At 12 weeks, animals were sacrificed and serum samples, collected via cardiac puncture, were sent for proteomics analysis using SOMAScan.

Results: CDAHFD rats developed bridging fibrosis by 6 weeks that progressed to nodular cirrhosis by 12 weeks reminiscent of late-stage human disease. All three drugs were effective at inhibiting fibrosis as assessed by histological staining and hydroxyproline analysis (NC 208 ± 53 µg/g, MC 840 ± 269 µg/g, EDP-305 349 ± 112 µg/g, EP-026856 449 ± 212 µg/g, selonsertib 484 ± 197 µg/g). Utilizing SOMAscan, we quantitatively assessed 1305 proteins with high specificity. Principle component analysis (PCA) revealed highest similarity between normal chow rats and CDAHFD rats treated with EP-026856. These two groups separated across principle component 1 (PC1) from all other treatment groups. Utilizing ingenuity pathway analysis (IPA), we identified and placed discriminatory proteins along protein networks to visualize pathway enrichments in each of the animal groups. Pathway analysis revealed that the EP-026856 discriminatory proteins enriched the greatest number of distinct protein-protein interaction pathways. While only the ASK1 inhibitors enriched Akt, FoxO, and TGF-beta signaling pathways, EDP-305 uniquely enriched the ErbB signaling pathway.



Conclusion: By utilizing SOMAScan, we were able to identify non-invasive biomarkers of treatment response and potential pathways activated by different drugs currently in clinical trials. While all three drugs were effective in inhibiting fibrosis development in this rat model of NASH cirrhosis, PCA analysis identified EP-026856 has having the greatest effect on returning non-invasive serum markers back to baseline.

THU-085

Efficacy of enhanced liver fibrosis score and transient elastography for assessment of severity of fibrosis in chronic hepatitis C

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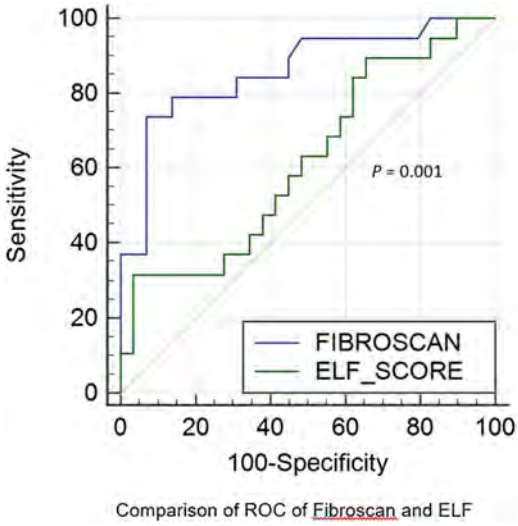
Background and aims: Chronic hepatitis C (CHC) patients with Genotype 3 infection having advanced fibrosis or cirrhosis need a longer duration of therapy and sustained virological response rate is lower with currently available directly acting antiviral therapy. Enhanced liver fibrosis (ELF) score and transient electrography (TE) are non-invasive methods for ruling out cirrhosis, have not been compared in Indian CHC patients. Aim is to compare TE and ELF for ruling out significant fibrosis (≥F2) CHC patients.

Method: Consecutive CHC patients who attended OPD at GIPMER from Sept. 2016 to May 2018 were included in the study. Patients with decompensated cirrhosis, BMI ≥ 30 kg/m2 or additional aetiology for liver disease were excluded. The liver biopsy was used as a gold standard; The METAVIR scoring system was used for grading fibrosis in liver biopsy. The TE by using fibroscan 430 mini and ELF were done on the same day in fasting state.

Results: Total of 50 patients were included, 30 were male and mean age was 35.02 ± 10.2 years. Genotype 1 and 3 found in 42 (84%) and 8 (16%) patients respectively. TE, ELF score calculation and liver biopsy was done in all patients. Median ELF score and TE score for patients were 9.46 and 5.95 kPa respectively. Significant fibrosis (≥F2) in biopsy, fibroscan and ELF score were 19 (38%), 14 (28%) and 47 (94%) patients respectively. The area under the receiver operator characteristic curve (AUROC) of TE was 0.860 [95% confidence interval (CI), 0.74-0.97], with the sensitivity and specificity of 79% and 86% for significant fibrosis and AUROC for ELF, was 0.619 [95% CI, 0.45-0.78], with the sensitivity and specificity of 74% and 42% respectively using liver biopsy as gold standard for diagnosing significant fibrosis. Using the proposed cut-offs, ELF overestimated fibrosis in 56% (28/50) of cases. We found statistically significant difference when comparing the AUROC of TE and ELF for diagnosing significant fibrosis (≥F2), ($p = 0.001$).



Comparison of ROC of Fibroscan and ELF

Conclusion: TE, as compared to ELF, is a better non-invasive method for diagnosing significant fibrosis (≥F2) in CHC patients. However, revised cut-off ELF score need to be established in CHC patients to improve its performance.

THU-086

Clinical study on plasma golgi protein 73 and the progression of viral hepatitis C-induced hepatic fibrosis

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Background and aims: To explore the correlation between plasma Golgi protein 73 (GP73)and the progression of Hepatitis C viral (HCV)-induced hepatic fibrosis.

Method: 232 cases of chronic hepatitis C (CHC) were included in our hospital from 2010.01 to 2018.09, which were diagnosed by serovirology and histopathological examination. And 31 healthy controls were enrolled. Clinical datas were collected. The plasma

GP73 level was detected by ELISA. Liver biopsy histopathological observation was based on liver inflammation grade (G1~3), fibrosis stage (S1~4) and "Beijing Classification" (P-I-R). The correlations were compared between GP73 and the stages of liver inflammation and fibrosis, disease progression and reversion. In addition, ROC of the subjects were performed to analyze the GP73 and APRI/FIB-4 in the diagnostic efficiency of fibrosis degrees and progression.

Results: The GP73 level of CHC patients was significantly higher than the healthy controls (94.82 ng/ml vs 172.90 ng/ml, $P < 0.0001$), and there were significant differences of the GP73 in mild and notable inflammation, 151.30 (113.70~174.75) and 172.15 (142.65~204.85) ng/ml in grade 1 and grade 2 to 3 respectively, $p = 0.004$). Particularly, GP73 levels were increasing with progression of liver fibrosis, these were in following: 151.30 (123.10~170.10), 157.90 (132.00~172.60), 181.70 (149.43~219.05), 208.50 (164.44~324.73) ng/ml in S1, S2, S3 and S4 respectively, and they are 189.16 (163.65~221.70) and 232.50 (174.60~335.65) ng/ml ($p = 0.023$) in the patients with compensated and decompensated liver cirrhosis. According to Beijing Classification, there was a significant difference of GP73 level in the Progression and Regressive/Indeterminate group, they are 177.08 (149.35~205.58) and 154.00 (121.95~178.05) ng/ml, $P = 0.004$. Furthermore, the AUC for the diagnosis in liver fibrosis of GP73, APRI and FIB-4 were 0.73, 0.78 and 0.81, respectively ($p < 0.0001$). And the AUC of GP73 for the diagnosis of Progressive fibrosis was 0.69 ($p = 0.011$), but ARRI and FIB-4 had no predictive significance.

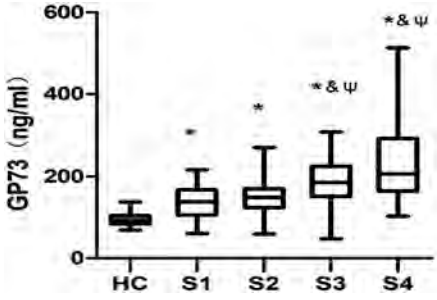

Figure 1: the GP73 levels in different statges. *:compared to HC, P<0.05; &:compared to S1, P<0.05; Ψ:compared to S2, P<0.05.

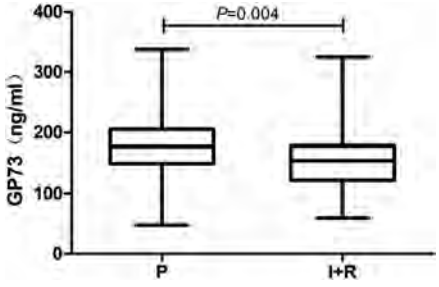

Figure 2: GP73 in P and I+R group.

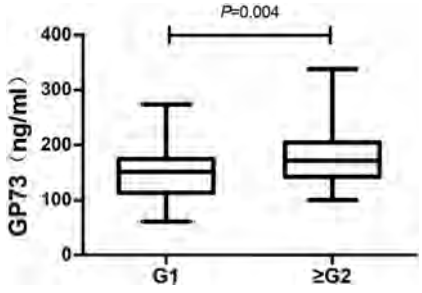

Figure 3: GP73 with different inflammation.

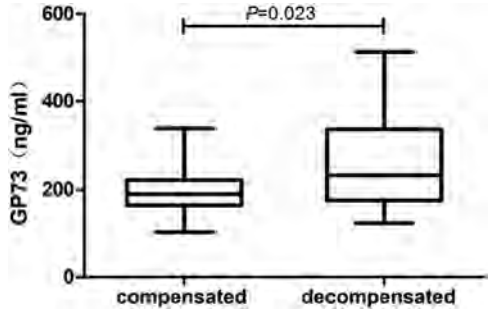

Figure 4: GP73 in different cirrhosis stages.

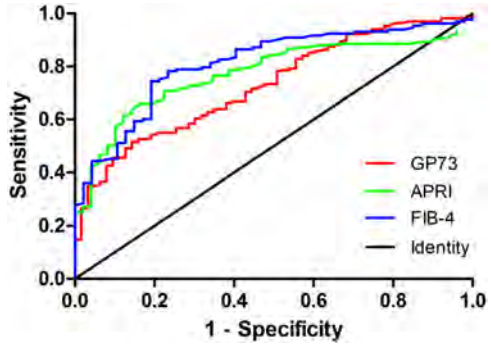

Figure 5: the ROC of GP73/APRI/FIB-4 in the diagnosis of fibrosis.

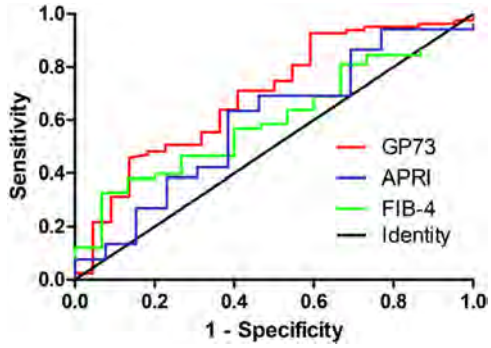

Figure 6: the ROC of GP73/APRI/FIB-4 in the diagnosis of "Beijing Classification"-P.

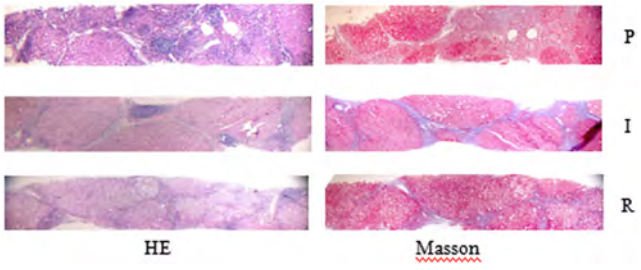

Figure 8: Beijing Classification "P-I-R".

Conclusion: The GP73 might be a potential biomarker for diagnosis of chronic HCV infection and the development of liver inflammation and liver fibrosis. Especially high level of the GP73 indicated progressive hepatic fibrosis.

Table 1: (abstract: THU-086): Analysis of basic data of patients with chronic hepatitis C in different fibrosis stages.

Variables	Fibrosis staging				F/X^2	P
	S1 (n=63)	S2 (n=50)	S3 (n=50)	S4 (n=69)		
Sax (M/F)	30/33	24/26	25/25	22/47	4.78	0.189
Age (Y)	48.00 (32.00 ~ 55.25)	51.00(47.50~ 56.50)	55.00(49.00 ~ 61.00)	59.00(52.00 ~ 65.50)	45.19	0.000
BMI (kg/m^2)	24.03 (22.04 ~ 26.37)	25.00(23.19~ 27.68)	25.56 (23.18 ~ 27.34)	25.10 (23.18 ~ 27.04)	3.39	0.335
ALB (g/L)	46.36±4.29	44.13±4.12	43.77±4.21	38.53±6.12	23.31	0.000
ALT (U/L)	22.00 (13.00 ~ 41.00)	41.00(19.50~ 71.50)	32.50 (18.25 ~ 67.00)	30.00 (18.00 ~ 48.25)	8.12	0.044
AST (U/L)	22.00 (18.50 ~ 28.50)	41.00(20.50~ 60.00)	29.50 (22.00 ~ 49.25)	36.50 (22.00 ~ 52.75)	15.62	0.001
GGT (U/L)	23.00 (16.00 ~ 34.00)	32.00(19.50~ 52.00)	40.00 (20.75 ~ 68.00)	42.00 (24.00 ~ 63.00)	8.30	0.040
PLT (10^9/L)	194.00 (153.50~232.50)	156.00 (120.00~189.00)	171.00 (128.50~225.75)	90.50(56.25~ 122.50)	65.46	0.000
GP73 (ng/ml)	151.30 (123.10~170.10)	157.90 (132.00~172.60)	181.70 (149.43~219.05)	208.50 (164.44~324.73)	54.70	0.000
APRI	0.30 (0.23 ~ 0.47)	0.64 (0.29 ~ 1.12)	0.49 (0.31 ~ 0.81)	0.96 (0.61 ~ 2.12)	61.99	0.000
FIB-4	1.01 (0.77 ~ 1.73)	1.95 (1.01 ~ 2.72)	1.95 (0.91 ~ 2.37)	4.06 (2.48 ~ 6.87)	75.12	0.000

THU-087

A 3-dimensional dynamic model to explore the immunomodulatory properties of the extracellular matrix and their implications in liver fibrosis

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Background and aims: The extracellular matrix (ECM) is a complex network of structural and functional proteins. It acts as an architectural scaffold with mechanical properties and is a reservoir for cell signaling molecules. In the liver, cross-talk between the liver cells, the ECM and the circulating immune system is involved in both maintaining homeostasis and driving disease. A better understanding of these complex interactions will allow us to explore the driving factors behind fibrosis, leading to the identification of novel therapeutic targets. Current culture and animal models do not accurately recapitulate the complexity of liver fibrosis. We used a tissue engineering approach to create a 3D-dynamic, humanized model of liver fibrosis incorporating the ECM, native liver cells and immune cells circulating in a custom-made perfusion bioreactor.
Method: Liver scaffolds were produced by decellularization of whole rat liver to remove cellular content, whilst maintaining overall organ architecture, ECM and vasculature intact. Hepatic stellate cells (HSC) were isolated from patient liver biopsy and peripheral blood mononuclear cells (PBMC) from matched patient whole blood or from healthy controls. Decellularised scaffolds were re-seeded with either PBMCs or HSCs and cultured in static or dynamic conditions. Scaffolds were analysed up to 7 days of culture by histology and immunofluorescence. PBMCs in dynamic culture were profiled by FACs to determine leukocyte subpopulations.
Results: Whole livers were successfully decellularized to remove native cells and DNA, while ECM and vasculature were conserved. In static culture conditions, scaffolds supported engraftment of certain PBMC subsets including specifically localised clusters of macrophages and CD3+ cells. The custom-made bioreactor was able to support PBMC viability in the dynamic system, allowing circulation of PBMCs in the vasculature of the decellularized scaffold. Bioreactor-guided serial seeding of HSCs produced re-populated liver scaffolds with cell-ECM interaction where fibrosis can be induced and PBMC can be continuously circulated through the system.
Conclusion: Decellularized whole liver scaffolds were repopulated with HSCs using a custom-made bioreactor. The bioreactor supports circulation of matched PBMCs and will allow us to explore ECM-HSC-immune cell interactions in the context of liver fibrosis.

THU-088

Serum markers of interstitial matrix formation (PRO-C3) and basement membrane remodeling (PRO-C4 and C4M) predict recurrence of fibrosis and survival in post-liver transplanted patients

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Background and aims: Following liver transplantation, 10–30% of patients rapidly progress to cirrhosis. There is an urgent need for predictive non-invasive markers of recurrent cirrhosis for a better risk management and for the monitoring of potential anti-fibrotic therapies. We therefore studied a panel of four defined serum biomarkers of interstitial matrix formation and basement membrane remodeling as predictors of recurrent cirrhosis after liver transplantation.
Method: Forty-seven liver transplatation patients were retrospectively divided into equally sized groups of fast, intermediate, or non-progressors towards recurrent cirrhosis according to the time from transplantation to cirrhosis; recurrent cirrhosis within 1 year, within 3–5 years, or no fibrosis within 5 years post liver transplantation, respectively. Fibrosis evolution was confirmed by liver biopsy. Markers of interstitial matrix type III and V collagen formation (PRO-C3 and PRO-C5), and basement membrane type IV collagen

formation (PRO-C4) and degradation (C4M) were assessed in serum samples using specific ELISAs. Blood samples were taken at 3, 6, and 12 months post-liver transplantation from all groups.
Results: PRO-C3, PRO-C4 and C4M were significantly elevated in fast progressors compared to non-progressors ($p < 0.05$-$p < 0.01$) at measurements taken three months after liver transplantation. Additionally, C4M and PRO-C4 differentiated between intermediate and fast progressors ($p < 0.001$ and $p < 0.05$, respectively). ROC curve analysis identified PRO-C4 and C4M as the best markers to discriminate fast progressors from non-progressors with AUROCs of 0.902 and 0.886, respectively. PRO-C3 was the best predictor post-liver transplantation survival with patients in the highest PRO-C3 tertile having significantly shorter post-liver transplantation survival compared to patients in the lowest tertile ($p < 0.01$) as well as predicting progressors towards cirrhosis with odds ratio of 28 ($p < 0.05$). When dividing the levels of C4M and PRO-C4 into tertiles, patients in the highest tertiles had an odds ratio of 21 or 85, respectively, of being progressors towards recurrent cirrhosis compared to patients in the lowest tertiles ($p < 0.05$-$p < 0.01$).
Conclusion: The study shows that elevated PRO-C3 levels are associated with both fibrosis progression and death, whereas markers of basement membrane remodeling is only associated with fibrosis progression. Thus, markers originating from different sites in the extracellular matrix may be used to monitor patients at risk of clinical events.

THU-089
Characterization of CDAA mouse model for non-alcoholic steatohepatitis at various time-points

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is defined by an increased storage of triglycerides and oxidation of fatty acids in hepatocytes. This can promote an elevated production of reactive oxygen species and necrosis leading to a severe hepatic inflammatory response and thereby progress to non-alcoholic steatohepatitis (NASH), which can result in fibrosis and ultimately cirrhosis. The pathologic onset and progression can be induced by a plethora of factors such as an imbalanced energy homeostasis, diabetes or obesity, whereas the impact of certain risk factors varies among patient groups depending on age, gender, genetic predispositions and lifestyle. The current treatment routine for NASH suggests diet and lifestyle adaptations, weight loss and -if indicated- diabetes therapy. Up until now there is no FDA approved drug to treat NASH and its consequences.
Method: Consequently, there is a high need for identification and development of specific therapeutic concepts, supported by a validated and disease-related animal model mimicking the pathologic onset and progression. Here, we analyze a mouse model based on a cholesterol-enriched, methionine-reduced, choline-deficient and amino acid defined diet (CDAA), leading to an attenuated VLDL production. The hereby promoted fat storage in hepatocytes leads to cellular damage, inflammation and fibrosis, while the animals do not suffer from reduced body weight as it is observed for classical methionine- and choline-deficient diets.
Results: Based on this diet composition we present an easy applicable model, which reveals the first symptoms of liver steatosis in a wild-type genetic background within two weeks of diet. In further detail, we characterize the time-dependent progression of pathological symptoms and plasma biomarker levels over 12 weeks in C57BL/6 mice upon cholesterol-enriched CDAA diet. Employing biomarkers such as TIMP1 and ProCollagen III, we are able to correlate their abundance in plasma samples with the severity and disease burden based on liver histology. Thereby document individual disease pro- or regression throughout the study and moreover minimize animal numbers.
Conclusion: In summary, we analyze a NASH mouse model showing a disease morphology that is comparable to patients -including steatosis, inflammation and fibrosis- within a relatively short period of time to further elucidate therapeutic concepts in NASH. Moreover the progression and therapeutic potential of various compounds can be monitored by defined biomarkers.

THU-090
Non-invasive fibrosis scores (APRI, FIB4 index, BARD): Useful tools for evaluating fatty liver disease

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Background and aims: Several non-invasive fibrosis assessment tests were developed in order to replace liver biopsy. Our goal was to assess the correlation between APRI, FIB 4 Index and BARD score with transient elastography (TE) in diabetic patients with fatty liver disease.
Method: We conducted a prospective study which included 469 diabetic patients out of which 454 with steatosis (mean age 61 ± 9.3 years, 55.1% females, 44.9% males) evaluated both by serum markers (TGO, TGP, platelets) as well as by TE-Fibroscan (Echosense, Paris, France, with incorporated CAP function). Based on specific formulas we calculated APRI, FIB 4 index and BARD score. Liver stiffness (LS) measurement was considered reliable only if 10 valid values were obtained, with an IQR < 30% and a success rate >60%. For differentiation between stages of liver fibrosis, the following cut-off values were used: F2-F3: 7–10.2kPa, F4 ≥ 10.3 kPa, and for steatosis we considered: S1 (mild)-232.5 db/m, S2 (moderate) –255 db/m, S3 (severe) –290 db/m.
Results: Severe steatosis according to CAP measurements prevailed: 69.5% of patients. Out of the 454 patients, 27.3% of them were overweight, whereas 62.5% were obese.
We tried to rule out cirrhosis by using APRI < 2 (98.5% patients) among which 368 patients (82.1%) had LS < 10.3 kPa, NPV = 82.6%. We found a moderate, but significant correlation between LS assessed by TE and LS predicted by APRI (Pearson r = 0.5, p = 0.001).
Regarding FIB 4 score, we found out that 94% patients had FIB4 < 2.6, thus ruling out advanced liver fibrosis (LS < 10.3kPa), NPV = 85%. The correlation between them was weak, but statistically extremely significant (r = 0.23, p = 0.0001). Patients with BARD score < 2 have a strong negative predictive value for advanced hepatic fibrosis, NPV = 86.1%. Among them, 97.5% had LS < 10.3 kPa
Conclusion: An APRI score < 2 and FIB 4 score < 2.6 can rule out advanced fibrosis when correlated with LS <10.3 kPa by TE. These two simple scores could be used as first line test to rule out patients without advanced fibrosis.

THU-091
Acalcemic vitamin D analogues show antifibrotic effects in vitro while paricalcitol prevents progression of established fibrosis in the CCl4 mouse-model

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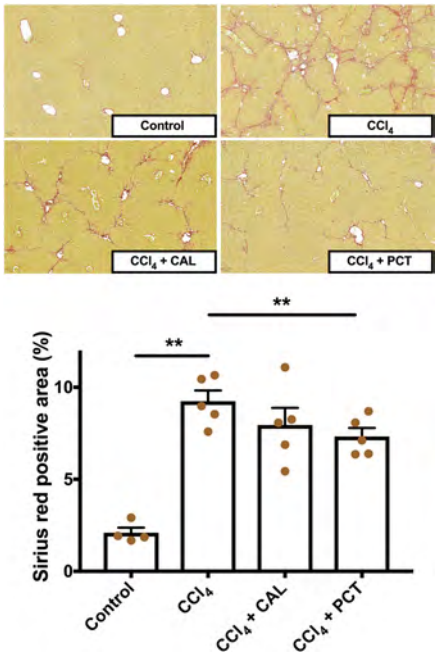
Background and aims: Liver fibrosis due to chronic liver diseases leading to liver cirrhosis is a highly prevalent life-threatening condition. So far, no cause independent antifibrotic agent has been established in clinical practice, despite of a high medical need. Vitamin D (VD) and its analogue calcipotriol demonstrated anti-fibrotic potency in preclinical models of liver fibrosis. Head to head comparison of calcitriol (CAL) to VD-analogues is pending. In this study we investigated the antifibrotic efficacy of clinically available VD-analogues in comparison to CAL *in vitro*. Paricalcitol (PCT), a systemically available VD-analogue approved for the treatment of secondary hyperparathyroidism, with a lower risk of hypercalcemia compared to CAL, demonstrated promising effects *in vitro*. We therefore analyzed the hepatoprotective effects of PCT in a head to head comparison with CAL in the CCl_4 mouse model.
Method: Murine hepatic stellate cells (HSC) and human LX-2 cells were treated with CAL and clinically available VD-analogues. HSC behavior was investigated using immunoblotting, collagen gel contraction assay, migration assay, real-time PCR, and immunofluorescence-microscopy. Proliferation was studied using a BrdU-assay. The CCl_4 mouse model was used to investigate effects *in vivo*. Therapy with CAL and the equipotent dosage of PCT in parallel to CCl_4 was initiated when a significant fibrosis (F2 to F3) was evident after 4 weeks. Efficacy was evaluated using serum-biochemistry, sirius-red staining and quantification of fibrosis with image analysis of sirius-red staining.
Results: Vitamin D agents reduced α-smooth muscle actin (α-SMA) protein-expression, an indicator for HSC activation, in murine HSC. Human LX-2 cells, when activated by tissue-growth-factor-β (TGF-β), showed a lower α-SMA protein- and ACTA2- and TGF-β mRNA-expression under PCT stimulation. TGF-β induced platelet-derived growth factor-receptor (PDGF-R) protein-expression and TGF-β mediated HSC contractility was reduced under stimulation with alfacalcidol. CAL and PCT showed hepatoprotective effects *in vivo* as indicated by reduced ALT levels compared to CCl_4 controls. PCT treated animals had significant lower calcium and bilirubin levels compared to the CAL group. The CAL group showed a pronounced weight loss. PCT but not CAL significantly inhibited the progression of established liver-fibrosis in CCl_4-model indicated by lower fibrotic area in image-analysis of sirius-red staining (Figure).



Conclusion: VD analogues show antifibrotic properties *in vitro*. PCT was superior to CAL in regard to prevention of hypercalcemia and side effects. PCT but not CAL significantly inhibited progression of established fibrosis in the CCl_4 mouse model. Acalcemic VD-analogues should be considered routinely in the investigation of VD for the treatment of liver fibrosis in future studies.

THU-092
Role of endothelial mitophagy during endothelial dysfunction and liver fibrosis
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Background and aims: Maintenance of healthy endothelial phenotype is essential to achieve an adequate cellular response against liver injury. The loss of liver sinusoidal endothelial cell (LSEC) phenotype known as endothelial dysfunction (ED) is a key event in the onset and progression of fibrosis since dysfunctional LSEC contribute to the activation of hepatic stellate cell (HSC). Defects in endothelial autophagy exacerbate ED and aggravate fibrosis due to, at least in part, an inefficient antioxidant response and accumulation of dysfunctional mitochondria worsening oxidative stress (OS). Mitophagy is a process that selectively removes damaged mitochondria (mainly oxidative damaged) and alleviates OS, however its role in ED and hepatic fibrosis is unknown. Our hypothesis is that mitophagy potentiation, would alleviate OS after injury by removing dysfunctional mitochondria, improving LSEC phenotype and consequently liver fibrosis.
Method: LSEC from control rats were cultured up to 48 hours to induce *in vitro* dysfunction. In addition, we isolated LSEC from CCl_4 treated rats (*in vivo* dysfunction). In dysfunctional LSECs, we evaluated mitophagy by markers of the PINK1/Parkin signaling pathway, the presence of dysfunctional mitochondria (Mitosox) and OS through the levels of reactive oxygen species (ROS). On the other hand, to evaluate the impact of OS on mitophagy, LSEC were treated with H_2O_2 and mitophagy levels were evaluated. Finally, in mouse LSEC (TSEC), autophagy was genetically inhibited (siAtg7) and potentiated with spermidine and evaluated their impact on OS, endothelial viability and mitophagic activity.
Results: Dysfunctional LSEC (*in vitro* and *in vivo*) showed an increase in ROS, an accumulation of dysfunctional mitochondria and a reduction in PINK1/Parkin signaling pathway. Exogenous OS caused mitochondrial damage that was accompanied by mitophagy upregulation. Autophagy inhibition in TSEC (siAtg7) was associated with accumulation of dysfunctional mitochondria and high levels of OS. Mitophagy enhancement using spermidine improved endothelial response to OS by increasing viability and reducing ROS, altogether contributing to an improvement of the endothelial phenotype.
Conclusion: Mitophagy potentiation improves endothelial response to oxidative stress by selectively removing damaged/dysfunctional mitochondria (mitophagy) and improves endothelial phenotype. Mitophagy enhancement could be a new antifibrotic strategy.

THU-093
The calpain inhibitor, BLD-2660, has robust anti-fibrotic activity in a rat model of non-alcoholic steatohepatitis
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Background and aims: Calpains are non-lysosomal Ca2+ dependent cysteine proteases, which modulate different cellular pathways and

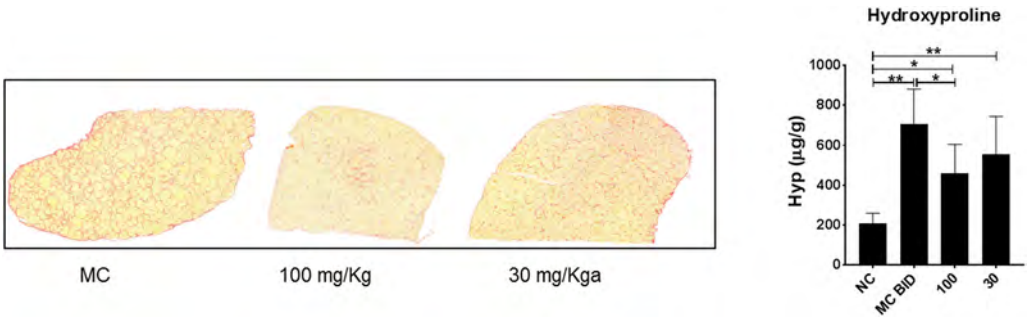

Figure: (abstract: THU-093)

have been involved in various inflammatory diseases. Calpains have also been shown to play a role in fibrosis development in mouse models of lung, skin, and myocardial fibrosis. Their role in liver fibrosis has yet to be explored. Here, we evaluated the effects of the small molecule inhibitor of calpain 1, 2, and 9, BLD-2660, provided by Blade Therapeutics Inc., in a rat model of non-alcoholic steatohepatitis (NASH).
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. After 5 weeks, rats were randomized to receive either vehicle control (0.5% methylcellulose (MC), 100 mg/kg BLD-2660, or 30 mg/kg BLD-2660 by BID gavage (n = 8 per group). At the end of the study, liver tissue and serum were collected for further analysis.
Results: Rats fed CDAHFD developed liver fibrosis (F3) after 5 weeks of CDAHFD diet, which progressed to cirrhosis (F4) by 12 weeks. Expression of Calpain1 and 2 increased in rats fed CDAHFD. Treatment with BLD-2660 significantly decreased fibrosis development as assessed by morphometric quantification of the collagen proportional area on Sirius red stained sections (NC 3.02 ± 1.98%, MC 13.2 ± 4.4%, 100 mg/kg BLD-2660 6.0 ± 1.6%$p < 0.001$, and 30 mg/kg BLD-2660 8.8 ± 6.6% $p < 0.05$). These results were verified by measuring liver hydroxyproline (NC 207.7 ± 52.77 µg/g, MC 702 ± 173 µg/g, 100 mg/kg BLD–2660 458.2 ± 146 µg/g $p < 0.05$, and 30 mg/kg BLD-2660 554.6 ± 190.3 µg/g).
Conclusion: In a rat model of NASH cirrhosis that more closely resembles the histology of human disease increased expression of calpain 1 and 2 was observed. Therapeutic treatment with BLD-2660 reduces fibrosis progression further supports that calpain inhibitors have broad anti-fibrotic effects.

THU-094
Simple prediction score to predict fibrosis in type 2 diabetes mellitus patients

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Background and aims: Non-alcoholic fatty liver disease is becoming the most common cause of chronic liver disease. The aim of this study was to identify factors associated with advanced liver disease in a cohort of type 2 diabetes patients and to make a prediction score.
Method: Patients were recruited prospectively in the study. Every first 6 patients who were referred to the Metabolic Disease Outpatient Clinic on a consultation day. Evaluation of liver fibrosis was made using Transient Elastography (FibroScan), performed in fasting conditions, with M and XL probes. Each patient was evaluated biologically for the presence of viral hepatitis (B and C) and an AUDIT-C score was performed to exclude alcohol abuse. Variables tested for the association with advanced liver fibrosis were: age, body mass index (BMI), abdominal circumference, hypertension, years after diagnosis of diabetes, glycemia, glycosylate hemoglobin, AST, ALT. Logistic regression was used for multivariate model to assess the association between advanced liver fibrosis and other variables. The cut-off value for advanced fibrosis was >8.4 kPa (Petta S et al. 2015).
Results: The total number of diabetics evaluated was 641. After the exclusion of others conditions, 468 patients with NAFLD were included. We randomly assign patients in the model development set-344 patients (mean age 60.1 ± 9.1, 54.4% females) and 123 in the validation set (mean age 60.6 ± 9.6, 54.3% women and 45.7% men). Advanced fibrosis was found in 28.7% (99/344) patients. To assess the advanced fibrosis predicting score, all clinical variables associated with advanced fibrosis, with $p < 0.05$ in the univariate analysis were considered in a multivariate regression model. Predicting score for advanced fibrosis was given by age, BMI, glycosylate hemoglobin and AST: 0.26*age (years) + 0.01*BMI (kg/m²) + 0.03* glycosylate hemoglobin (mmol/L) + 0.0004*AST (U/L)-0.9. The model gave us an accuracy of 92.1%, AUROC = 0.99, 95% CI (0.97-0.99). The best cut-off value for rule out advanced fibrosis was >16.4, Se = 100%, NPV = 100%. On the validation set we obtained an accuracy of 91.3%, Se = 92.1% and NPV = 87.5% for ruling out advanced fibrosis.
Conclusion: In our group, 28.7% of diabetic patients had advanced fibrosis. Body mass index (BMI), age, glycemia, glycosylate hemoglobin, AST, ALT were associated with advanced liver fibrosis. For ruling out advanced fibrosis, the new predicting score had 91.3% accuracy.

THU-095
Short and long-term evaluation of liver fibrosis and outcomes in patients with chronic hepatitis C after INF-free antiviral treatment

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Background and aims: The evolution of chronic hepatitis C into liver cirrhosis is correlated with an extensive accumulation of extracellular matrix, leading to the formation of large amounts of fibrotic tissue. The new direct-acting antiviral drugs (DAAs) can eradicate HCV infection in over 90% of patients. According to recent studies, the use of DAAs reduces the risk of complications even in advanced fibrosis. Therefore the aims of this study were to evaluate 1) changes in fibrosis during and after antiviral treatment; and 2) the incidence of hepatocellular carcinoma (HCC) and related mortality in various stages of fibrosis.
Method: This is a longitudinal monocentric prospective study. Laboratory and instrumental examinations were evaluated at baseline, at the end of therapy, and after 1 and 2 years following

treatment. The assessment of liver fibrosis was performed by transient elastography.
Results: Two hundred and ninety-six patients with chronic liver disease were enrolled, of whom 115 patients were treatment experienced, 181 naïve, including 2 with previous HCC. At baseline, the stiffness values were 13.46 ± 9.97 kPa. When the patients were divided by stiffness groups according to the fibrosis staging, the F0-F2 group and the F3-F4 one had stiffness of 6.07 kPa±1.68, and 17.93 ± 10.23, respectively. No statistically significant difference was found between stiffness values at baseline compared to end of treatment (EOT), while statistically significant differences were found between baseline and 1 year ($p = 0.05$) and the 2-year follow-up ($p < 0.01$). When the patients were divided into two groups (F0-F2 and F3-F4), no significant differences were found between the baseline and the EOT, or after 1 and 2 years from EOT in the F1-F2 group. On the contrary, statistically significant differences were found between the baseline and EOT, as well as 1 and 2 years after the end of treatment ($p < 0.001$) in the F3-F4 group. Five out of 67 patients with baseline cirrhosis developed HCC during post-treatment follow-up, 1 of whom died.
Conclusion: Non-invasive methods provide important prognostic information, particularly about regression of fibrosis or the occurrence of liver cirrhosis complications, despite the fibrosis regression after antiviral treatment. They may result very useful for the correct approach to patients with long life expectancies after direct-acting antiviral treatment.

THU-096
Development and validation of true serum biomarkers of liver fibrogenesis ans fibrolysis
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Background and aims: Better serum biomarkers to assess the progression of liver fibrosis and especially fibrosis reversal are urgently needed. We aimed to identify novel extracellular matrix derived serum biomarkers of fibrogenesis and fibrolysis using well defined cirrhotic sera and follow-up sera of patients post liver transplant (LTx) with rapid fibrosis progression (cirrhosis within 1–5 years) and of patients before and after highly effective antiviral therapy for chronic hepatitis C (CHC), with sustained viral response (SVR).
Method: Matricellular fibrosis markers A9, T2, T4, I7 and I3 were identified by SOMAScan proteomics of sera of patients with rapid fibrosis progression, and based on their mechanistic role in ECM remodeling. Follow-up sera of patients with well-defined course post LTx and cirrhosis and pre/post-antiviral therapy with SVR were used to confirm fibrosis marker plausibility. Sera of 40 healthy controls served as comparators. Serum concentrations of A9, T2, T4, I3 and I7 were measured via in-house developed sandwich ELISAs.
Results: Normal serum levels of A9, T2, T4 and I7 were in a narrow range (10 ± 6, 54 ± 20, 84 ± 23, 182 ± 30 ng/ml resp.). Serum levels of A9, T2, T4 and I7 were significantly higher (42 ± 37, 178 ± 77, 135 ± 44 and 303 ± 48 ng/ml resp.), in LTx and cirrhotic patients with rapid fibrosis progression compared to healthy or patients with mild fibrosis. Serum A9, T2, T4 and I7 differentiated between Child-Pugh groups. The AUC values of ROC curves to distinguish fibrosis F2-4 from F0-1 were >0.95 for T2 and I7, and >0.85 for T4 and A9. In patients with CHC before and after effective antiviral therapy, levels of A9, T2, T4 and I7 fell from 71 ± 58, 134 ± 68, 121 ± 55 and 147 ± 22 to 28 ± 31, 86 ± 31, 86 ± 32 and 141 ± 22 ng/ml after the antiviral therapy, whereas another marker, I3 increased significantly from 350 ± 179 to 407 ± 79. The underlying biochemistry as well as the results support a prominent role of A9, T2, T4 and I7 in liver fibrogenesis, and of I3 in liver fibrolysis. There was a significant correlation between the markers T2, T4 and I7.
Conclusion: We identified and validated 4 novel ECM derived serum marker of liver fibrogenesis and one putative marker of liver fibrolysis. Two fibrogenesis markers showed the currently highest predictive value for detecting significant fibrosis. Studies are ongoing to evaluate large prospective and follow-up cohorts of patients with NASH and other chronic liver diseases, including comparisons with current fibrosis markers.

THU-097
Serum infrared spectral profile is predictive of the degree of hepatic fibrosis in chronic hepatitis C patients
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Background and aims: Assessment of liver fibrosis is crucial to guide the therapeutic strategy in patients with chronic liver disease. In this study, we investigated the potential of serum Fourier transform infrared (FTIR) spectroscopy for assessing the degree of fibrosis in a series of patients with chronic hepatitis C (CHC).
Method: Serum samples from 94 CHC patients at different histological stages of fibrosis were selected : Metavir F0 (n = 20), F1 (n = 17), F2 (n = 20), F3 (n = 20) et F4 (n = 17). Infrared spectra (ten replicates per sample) were acquired in the transmission mode using an FTIR spectrometer (tensor 27, Bruker Optics GmbH, Ettlingen, Germany) coupled to a high-throughput system (HTS-XT, Bruker Optics GmbH). Each spectrum was recorded in the wavenumber range from 400 to 4, 000 cm^{-1}, at a nominal physical resolution of 4 cm^{-1} and averaged over 32 scans. Spectra that passed the quality test were converted to second derivatives using the Savitsky-Golay algorithm and *normalized* using the *SNV* procedure. Twenty wavelengths were selected by genetic algorithm according to their diagnostic performance as assessed by a PLS model with 5 components. The diagnostic performance was measured by the area under the ROC curve (AUROC) using a training set (n = 76) and a validation set (n = 18) to differentiate patients with fibrosis at stages F0F1F2 and those with fibrosis at stages F3F4 and then to differentiate patients with fibrosis at stages F0F1F2F3 and those with fibrosis at stage F4. To take into account the sample error, 1000 iterations were performed with the final set of 20 wavelengths in order to calculate the mean AUROC. Matlab-based algorithm was built for automatic spectral analysis and classification.
Results: After quality tests and spectral pre-processing, analysis was performed on the mean spectra (1849 variables per spectrum) from the 94 patients. The PLS model with 5 components allowed to differentiate F3F4 patients and F0F1F2 patients with AUROC of 0.89 ± 0.084 (mean±SD for 1000 iterations). Among the 1000 iterations, only 0.46% had AUROC < 0.70. For the comparison of stages F0F1F2F3 vs F4, the PLS model with 5 components also had a good diagnostic performance with AUROC of 0.90 ± 0.051. Only 0.34% of 1000 iterations had AUROC < 0.70.
Conclusion: Serum FTIR spectroscopy appears to have a strong potential of development as a new diagnostic tool in clinical practice for assessing the degree of fibrosis in patients with chronic liver disease. The algorithm developed in CHC patients is intended to be tested and validated in other chronic liver diseases. This innovative

technique enables data acquisition in a simple, rapid, reagent-free and high-throughput mode.
This study was funded by Société d'Accélération de Transfert de Technologie SATT Nord.

THU-098

Changes in liver stiffness measurements following DAA treatment among HIV/HCV-coinfected individuals: Does HIV contribute to liver disease after HCV cure?

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Background: HIV-coinfection is known to accelerate liver fibrosis progression in HCV-infected individuals. Treatment with direct-acting antivirals (DAA) has the potential to reverse liver fibrosis, but evidence of fibrosis regression among HIV/HCV-coinfected populations in the DAA era is limited. We aimed to assess changes in liver stiffness measurements (LSM) after HCV cure in HIV/HCV-coinfected individuals, and to determine the role of HIV disease and other predictors of liver fibrosis.
Method: Data from individuals participating in the co-EC study were used. The co-EC study is an ongoing (March 2016–) non-randomised trial of DAA therapy among HIV/HCV-coinfected individuals. LSM before and after treatment were obtained using transient elastography. To evaluate changes in LSM values following treatment, univariable and multivariable linear mixed regression models were used. Potential predictive factors of LSM were determined a priori. Subsequently, we tested the interactions between selected potential predictors and time since initial TE assessment. A p value of <0.05 was considered statistically significant.
Results: Of 200 included participants, 179 had at least one LSM available and 96 participants had two LSM results. Median time between pre- and post-DAA elastography assessments was 1.2 years [Interquartile range = 0.9–2.1]. In univariable analysis, successfully treated patients had a decrease of 0.95 kilopascal (kPa) (95%CI: −0.91, −0.99 kPa) in LSM value per year, becoming non-significant in multivariable analysis (LSM change −0.97 kPa; 95%CI: −0.92, 1.01). Longer duration of known HIV infection (1.01 kPa per year since HIV diagnosis; 95%CI: 1.00, 1.02) and a lower CD4 count (lowest v highest CD4 count tertile: 1.32 kPa; 95%CI: 1.04, 1.64) at initial elastography assessment were significantly associated with higher LSM. However, changes in LSM after HCV cure did not differ by CD4 count or HIV known duration. Hazardous alcohol consumption, HCV genotype and body mass index were not significantly associated with changes in LSM values in multivariable analysis.
Conclusion: Consistent with data on HCV-monoinfection, we observed a decrease in LSM following HCV cure among HIV/HCV-coinfected individuals. Markers of more advanced HIV infection did not seem to impact changes in LSM values after HCV cure. The finding that individuals with more advanced HIV have on average higher LSM needs longer follow-up to determine the clinical importance following DAA treatment.

THU-099

Collagen is not just collagen: Differential matrix expression induced by TgF-beta and PDGFs

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Background and aims: Accumulation of extracellular matrix (ECM) proteins is a hallmark of fibrosis. It leads to altered tissue homeostasis and ultimately organ failure. This occurs as fibroblasts are activated in interplay with many different cell types and growth factors that leads to increased synthesis and accumulation of extracellular matrix (ECM) proteins. We hypothesized that platelet-derived growth factor (PDGF)-AB, PDGF-BB and transforming growth factor (TGF)-β1 each induce synthesis profiles of different ECM proteins relevant for fibrogenesis.
Methods: The effect of PDGFs (AB and BB) and TGF-β1 on ECM protein synthesis was assessed in a "scar-in-a-jar" (SiaJ) cell model using primary human fibroblasts from a healthy donor. Cells were seeded in 48-well plates at the density of 30.000 cells/well and incubated for 24 h in DMEM + 10% FBS. This was followed by 24 h incubation in serum starvation media (DMEM + 0.4% FBS). Fresh culture media were then added (this day was referred to as day 0) consisting of starvation media in addition to 225/150 mg/ml Ficoll 70/400 and 1% ascorbic acid, and containing 0.04 nM TGF-β1, 4-, 0.4-, or 0.04 nM PDGF-AB or -BB or no stimulants (vehicle control). Culture media were changed and collected at day 3, 6, 10 and 13. Biomarkers of collagen type I (PRO-C1), III (PRO-C3), VI (PRO-C6) and fibronectin (FBN-C) formation were assessed by competitive ELISAS measured in the supernatants.
Results: TGF-β1 induced significant higher PRO-C1, PRO-C3 and FBN-C compared to PDGFs or the vehicle. Levels were 50-fold higher for PRO-C1 and FBN-C and 10-fold for PRO-C3 compared to vehicle. PDGFs resulted in higher concentrations of FBN-C and PRO-C1 but not PRO-C3 compared to the vehicle, and with lower potency than TGF-β1. PRO-C6 was inhibited by TGF-β1, but dose-dependently stimulated by PDGFs. FBN-C and PRO-C1 peaked after 6 days of TGF-β1 treatment. PRO-C3 peaked after 10 days of TGF-β1 or PDGF stimulation, respectively and PRO-C6 peaked after 10 days of stimulation of PDGF.
Conclusion: These data provide insight in the complex regulation of fibroblast induced ECM protein synthesis in response to different signalling molecules. The presented findings clearly indicate that different growth factors lead to different protein synthesis profiles. Thus, the SiaJ fibroblast model combined with biomarkers of ECM formation may be a useful tool for further investigation of the unique interplay between growth factors and fibroblasts.

THU-100

FGL2 regulates liverfibrosis progression and reversal by promoting profibrotic infiltrating macrophages maintenance

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Background and aims: Hepatic macrophages (HMs) are a heterogeneous population and hold central position in liver fibrosis progression and reversal. Fibrinogen-like protein 2 (Fgl2), expressed on macrophages in response to pathogens challenge, has been associated with severity of chronic hepatitis B. In this study, we aimed to investigate the role and the potential mechanisms of Fgl2 during liver fibrosis in vivo and in vitro.
Method: FGL2 levels were examined in patients of hepatitis B-related fibrosis. Murine model of liver fibrosis was established in wild type and *fgl2* mutant mice by intraperitoneal injection CCl_4. Liver fibrosis were detected by Sirius red or immunohistochemical staining against α-MSA. Resident and infiltrating macrophages were analysed by flow

cytometry. Cytokines of liver homogenate were assessed using ELISA. Pharmacological administration of muramyl dipeptide (MDP) by intraperitoneal injection was carried out to facilitate macrophage transition from profibrotic into restorative property. Bone marrow derived macrophages from wild type and *fgl2*$^{-/-}$ mice were co-cultured with were wild type hepatic stellate cells (HSC) to evaluate impact of Fgl2 expression on profibrotic macrophages.
Results: Fgl2 expression was associated with high grade of liver fibrosis in chronic Hepatitis B patients and experimental models in response to liver damage. Genetic ablation of the Fgl2 alleviated fibrosis in the chronically injured liver and promoted reversal during the resolution. Such effect was linked to a switch of macrophage from profibrotic into restorative phenotype in *fgl2*$^{-/-}$ mice in response to liver damage. Moreover, Pharmacological administration of MDP alleviated fibrosis in wild type mice and more profoundly in *fgl2*$^{-/-}$ mice. Such effect was associated with coordinated increased switch of infiltrating macrophages from Ly6C^{high} into Ly6C^{low} phenotype. On cellular levels, Fgl2 depletion in macrophages significantly dampened the activation of primary HSCs in response to macrophage-dependent stimulation.
Conclusion: Our data demonstrates that Fgl2 regulates liver fibrosis by maintaining profibrotic phenotype in resident and infiltrating macrophages. Target remodelling of infiltrating macrophages from proinflammatory Ly6C^{high} into restorative Ly6C^{low} ameliorates liver damage and fibrosis progression, thereby providing novel insights into therapeutic strategy for fibrosis treatment.

THU-101
Artery density in human liver: A valuable measure for staging of chronic liver disease

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Background and aims: Human chronic liver disease has classically been staged by density of collagen as estimated by the presence of collagen-containing septa (METAVIR, Ishak, Laennec systems) or by quantitative image analysis expressed as collagen proportionate area (sirius red or dual harmonic generation = qFibrosis). Recently, we have shown that severe cirrhosis is accompanied by 8-fold collapse of tissue revealed by increased portal tract number/mm^2, via duct density as well as artery density (AD). The present study demonstrates the value of AD as the basis of a new staging system.
Method: Preliminary measures of AD were performed on large excised liver specimens with variable etiology and stages (Laennec 0 to 4C, and regressed cirrhosis) to determine an optimal method. This method was applied to needle biopsies obtained in the course of a previously published therapeutic trial of entecavir in patients with chronic hepatitis B (Sun Y et al, Hepatology 2017;65:1438). 20 pairs of biopsies, obtained before and after 78 weeks of therapy, were evaluated by 3 methods. Stage was recorded blindly with the Laennec system. Collagen was quantified by qFibrosis (courtesy HistoIndex, Singapore). Artery profiles 12–20 microns diameter were counted on sections stained to identify smooth muscle actin.
Results: Artery density correlated closely with the other staging methods (qFibrosis vs AD, r = 0.60, p = 0.0002; Laennec vs AD, ANOVA F = 8.4, P = 0.0001) (Fig. 1). Laennec stage was improved at 78 weeks in 14 of the 20 pairs; those with an improved stage had a mean decrease in AD of 39% from baseline, consistent with repopulation of tissue with hepatocytes.

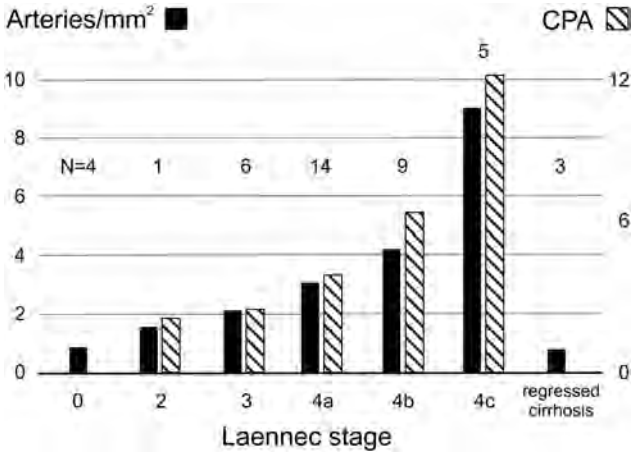

Figure: All data from needle biopsies in the hepatitis B trial, except stage 0 and regressed cirrhosis (hemochromatosis post-phlebotomy) tissue obtained at surgery. N = number of samples. Arteries 12–19.9 µm (solid bars). Collagen proportionate area (Total-CPA) by second harmonic generation (qFibrosis, hatched bars).

Conclusion: The close correlation among AD and other accepted staging systems indicates that this simple metric provides the basis for a new staging system. Minimal training is required to achieve less interobserver error compared to semiquantitative methods and does not require specialized equipment. The method can also be applied accurately to HandE slides if they are thin and well-prepared.
Artery density, as a measure of tissue collapse after disease-related hepatocyte loss, is fundamentally different from collagen measurement, providing insight into the pathogenesis of cirrhosis. Some increase of collagen density in cirrhosis is caused by collapse of preformed portal tract collagen. Comparison of these measures, standardized with appropriate controls, allows liver collagen to be subdivided into collapsed stroma and actively acquired collagen.

THU-103
HBEAG negative CHB patients is associated with more severe liver fibrosis than hbeag positive CHB patients: A propensity score matching analysis

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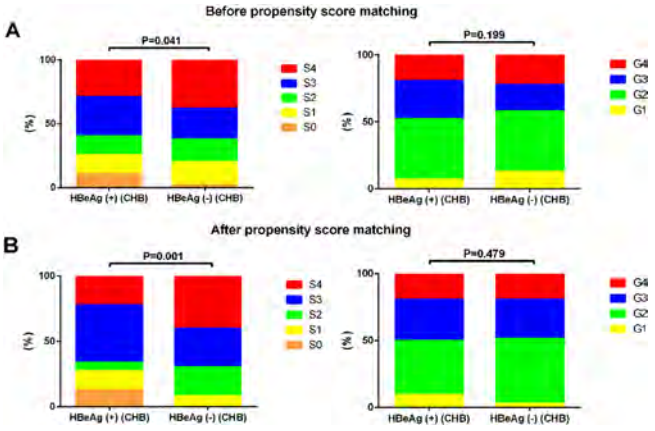
Background and aims: Serum hepatitis B e antigen (HBeAg) plays an important role in the progression and prognosis of hepatitis B virus (HBV) related liver diseases. However, few studies reported whether HBeAg status is related with the degree of liver injury in patients with chronic hepatitis B (CHB). We aimed to investigate the relationship between hepatitis HBeAg status and liver pathological stages in CHB patients using propensity score matching (PSM).
Method: A total of 286 treatment-naïve CHB patients with alanine aminotransferase (ALT) > upper limit of normal (ULN) who had undergone liver biopsy were enrolled in this study. PSM was performed to adjust for the imbalance of baseline confounders between HBeAg-positive CHB patients and HBeAg-negative CHB patients.
Results: Of these 286 CHB patients, 62 patients were included in each group after PSM. HBeAg-negative CHB patients (n = 100) exhibited a significantly severity of liver fibrosis than HBeAg-positive CHB patients (n = 186) before PSM (p = 0.041). However, there were no significant differences of the distribution of each inflammation grade

between HBeAg-positive CHB patients and HBeAg-negative CHB patients (p = 0.199). After propensity matching, CHB patients with HBeAg-negative (n = 62) still showed a significantly severity of liver fibrosis as compared with HBeAg-positive CHB patients (n = 62) (p = 0.001). Furthermore, the distribution of liver inflammation grade was comparable between HBeAg-positive CHB patients and HBeAg-negative CHB patients (p = 0.479).



Conclusion: HBeAg negative CHB patients may have more serious degree of liver fibrosis than HBeAg positive CHB patients in the propensity score matching (PSM) analysis.

THU-104

New fibroblast activation protein inhibitor, CPD60, attenuates fibrosis and chronic liver disease progresion in CCL4 induced liver fibrosis, but not in MDR2-/- mice

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Background and aims: Fibroblast activation protein (FAP) is a surface protein with prolyl endopeptidase activity expressed on activated (myo-) fibroblasts. Its functional role in liver fibrosis and desmoplastic cancer is limited. Targeting FAP in liver fibrosis could be a novel antifibrotic strategy in fibrogenesis, but there exist no studies on pharmacological FAP inhibition due to the lack of a specific, small molecule inhibitor. Cpd 60, a new FAP inhibitor based on a 4-quinolinoyl-Gly-cyanoPro scaffold, shows a potent and selective inhibition with a promising pharmacokinetic behavior. Here, we investigated the effects of this new FAP inhibitor in murine liver fibrosis models.
Method: 3 liver fibrosis models were employed and mice received Cpd60 at 15 or 50 mg/kg/day orally, or vehicle: 1) Parenchymal progression: C57BL/6-WT mice were subjected to 6 weeks of escalating doses of CCl4 by oral gavage and received Cpd60 or vehicle in the last 2 weeks; 2) parenchymal regression: fibrosis was induced by 6 weeks of CCl4 and allowed to reverse for 2 weeks with Cpd60 or vehicle; 3) Mdr2−/− mice or their FVB wildtype controls received Cpd60 or vehicle from week 5 to week 7 of age. Collagen determinations, histological studies, serum and enzyme activity determinations, and molecular biology techniques were carried out to assess liver fibrosis and inflammation.
Results: In CCl4 induced progression Cpd60 reduced Sirius red stained collagen area by 44% and 37% (15 and 50 mg/kg/day) (p < 0.05, compared to vehicle), total liver hydroxyproline by 33% and 22% (p < 0.01), aSMA+ myofibroblasts by 35% and 52% (p < 0.001) and YM1+ (M2-type) macrophages by 63% and 68% (p < 0.001). This was accompanied by a decrease of serum ALT and AST, as well as a significant downregulation of key transcripts related to fibrogenesis (acta2, col1a1, col3a1, timp1, spp1, pdgfrb, mmp2, mmp9 and mmp13) and inflammation (ccl2, ym1) transcripts. However, FAP inhibition was ineffective in decreasing these parameters in the regression model of CCl4 induced fibrosis and in the model of biliary fibrosis in Mdr2−/− mice. FAP inhibition regulated TGFb1 but not TGFb2 expression that is mainly produced by activated cholangiocytes.
Conclusion: We describe for the first time the effect of an oral FAP inhibitor (Cpd60) in 2 models of liver fibrosis progression and in one model of spontaneous regression. Pharmacological FAP inhibition suppresses parenchymal fibrogenesis, but does not affect fibrosis resolution or biliary fibrogenesis. Antifibrotic effects of FAP inhibition may be dependent on TGFb1 but not TGFb2. FAP inhibition may be useful in rapidly progressive liver fibrosis.

THU-105

Modulation of G protein alpha inhibiting activity polypeptide 2 in hepatocytes regulate liver fibrosis

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Background and aims: Fibrosis significantly contributes to the mortality due to end-stage chronic liver diseases. The cross-talk, between hepatocytes and hepatic stellate cells, is suggested to play a key role in fibrosis progression. While major efforts have been devoted to elucidate hepatic stellate cells' functions during liver fibrosis, the regulatory functions of hepatocytes remain elusive.
Method: We co-cultured primary hepatocytes with hepatic stellate cells and investigated the ability of hepatocytes to regulate fibrosis by modulating the expression of G protein alpha inhibiting activity polypeptide 2 (Gnai2). The in vivo functional analyses were performed in hepatocytes using adeno-associated virus in carbon-tetrachloride- and 3, 5-di diethoxycarbonyl-1, 4-dihydrocollidine-induced liver fibrosis.
Results: We found that overexpression of Gnai2 in hepatocytes suppresses expression of fibrogenic genes in co-cultured hepatic stellate cells. Further, we demonstrate that Gnai2 modulation regulate secretion of C-C motif chemokine ligand 2 (CCL2), a key molecular regulator of liver fibrosis.
Conclusion: Our findings revealed that molecular changes, which cause overexpression of Gnai2 in hepatocytes, leads to suppression of liver fibrosis via reduction in CCL2 levels. Hence, modulation of Gnai2 in hepatocyte, an easy-to-target cell type in the liver, may serve as a potential therapeutic approach for liver fibrosis.

Viral hepatitis C: Therapy and resistance

THU-111

High efficacy and safety of the combination HCV regimen elbasvir and grazoprevir for 8 weeks in treatment-naive non-severe fibrosis HCVGT1b-infected patients: Final results of the STREAGER study

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Background and aims: Genotype 1b is the most common HCV genotype globally, accounting for the largest proportion of infections in Europe, Latin America, Russia, Turkey, and East Asia. Reducing treatment duration can improve adherence and reduce drug exposure. L. Serfaty *et al.* have previously shown in a cohort of 56 patients that grazoprevir and elbasvir ± ribavirin for eight weeks can obtain an SVR12 higher than 90% (AASLD 2015). Accordingly, we evaluated the efficacy of eight weeks fixed dose single tablet combination of an NS5A inhibitor elbasvir 50 mg/d (EBR) and protease inhibitor grazoprevir 100 mg/d (GZR) in treatment-naïve patients, with non-severe fibrosis (F0-F2).
Method: Analysis included 112 treatment-naïve (TN), with non-severe fibrosis (Fibroscan® < 9.5 kPa and Fibrotest® < 0.59), HCV GT1b-mono-infected patients enrolled in the STREAGER trial, a study which included 117 patients. Historic labs were used for enrollment. Subsequent genotyping by sequencing during the course of the study identified five patients with non-1b genotype (2 GT1a, 1 GT1e, 1 GT1 h and 1 GT1 l). Thus, we will include in the final analysis 112 GT1b patients. The primary end point was the proportion of patients with HCV RNA below the lower limit of quantification (LLOQ) 12 weeks after treatment (SVR12).
Results: Mean age was 54 ± 13 years, 31% were male, viral load higher than 800.000 IU/ml: 70/112 (62.5%); ALT higher than the upper limit of normal: 51/112 (46%). Using Fibrotest® (FT), 69 had a F0-F1 fibrosis score (FT < 0.32); by Fibroscan® (FS) 100 had F0–1 fibrosis score (FS < 7.1 kPa). FIB-4 lower than 1.45 and APRI less than 1 was found in 74/112 (66%) and 107/112 (95.5%) patients respectively. By the end of treatment (EOT), 94.6% (106/112) of patients had HCV RNA < LLOQ. No adverse event grade III or IV related to treatment was observed. Relapse occurred in 3 patients. Viral loads before treatment of these 3 patients were as follows: 14, 16.4, 8.3 millions IU/ml. RAS (resistance associated substitutions) at relapse were respectively: Y93H; L31M, Y93H; L31M, Y93H. Then, mITT (modified intention-to-treat) SVR12 for patients with genotype 1b (after exclusion of the 5 patients with genotype non 1b) was 109/112 (97.3%). Two other patients relapsed 24 weeks after EOT (SVR24) despite reaching SVR12 and 1 patient is lost to follow-up. SVR24 results was 95.5% (106/111) in mITT. Further data related to the 112 patients will be available at the EASL meeting.
Conclusion: High SVR12 (109/112, 97.3%) was achieved in a TN non-severe fibrosis GT1b-infected patients treated for 8 weeks by the combination of elbasvir and grazoprevir.

THU-112

Real-world health care resource utilization and quality of life with G/P treatment: A pooled analysis from post-marketing observational studies

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Background and aims: To inform HCV treatment guidelines, it is important to understand healthcare resource utilization (HCRU) and treatment outcomes in routine clinical practice. As limited HCRU and quality of life data have been reported with direct acting antivirals, we present a pooled analysis across multiple countries of real-world HCRU and patient-reported outcomes (PROs) for patients receiving the pangenotypic regimen of glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor; co-formulated as G/P) in ongoing post-marketing observational studies (PMOS).
Method: Data were pooled from six countries (Austria, Belgium, France, Israel, Italy, and Switzerland) thus far participating in this prospective PMOS. Patients with chronic HCV genotypes 1-6 were eligible for the PMOS if they were receiving G/P at the treating physician's discretion according to local clinical practice, international recommendations and/or local label. HCRU was determined by the number of PMOS visits for patients within their local clinical setting. The study protocol recommended 5 visits per patient regardless of treatment duration. SF-36 and fatigue severity PROs and sustained virologic response at 12 weeks post-treatment (SVR12) were also assessed for patients with available data. The proportion of patients achieving significant improvement in PROs were reported for SF-36 and fatigue severity score (FSS) based on literature definitions of improvement.
Results: Among 238 patients, 227 (95%), 10 (4%), and 1 (<1%) received G/P for 8, 12, or 16 weeks, respectively. Overall, the number of HCRU visits (mean ± SD) was 4.2 ± 0.8. Percentages of patients attending each visit and achieving SVR12 are shown in the Table for subgroups of interest. In the PRO analyses at SVR12 visits, 54/159 (34%), 77/159 (48%) and 6/49 (12%) patients demonstrated significant improvement in their SF-36 physical (≥2.5 increase) and mental component scores (≥2.5 increase), and FSS (≥0.7 increase), respectively.

Subgroup, (%)	Baseline	During treatment	EOT	Post-treatment	SVR12 visit	SVR12 rate*
Cirrhotic (N = 10)	100	90	80	40	100	100
Non-cirrhotic (N = 228)	100	78	98	41	100	99
PWUD (-) (N = 164)	100	78	97	41	100	99
PWUD (+) (N = 68)	100	78	97	44	100	99
< 65 years (N = 171)	100	77	97	37	100	99
≥ 65 years (N = 67)	100	82	97	49	100	99

EOT, end of treatment; PWUD, person who uses drugs
*Among patients with follow-up in SVR12 window

Conclusion: G/P treatment demonstrated significant PRO improvement and high effectiveness, while the average number of HCRU visits was less than recommended in the protocol. Updated HCRU, PROs and SVR12 data will be presented at the Congress including all patients who reached SVR12 from these and additional countries as enrollment, treatment, and follow-up are currently ongoing.

THU-113

Comparison between safety and efficacy of two treatment regimens for pediatric patients with chronic hepatitis C virus: Sofosbuvir/ledipasvir versus sofosbuvir/daclatasvir regimen

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Background and aims: It is estimated that 11 million children under the age of 15 are infected by Hepatitis C virus (HCV), of whom 5 million are viremic. In the Egyptian children population (1- 14 years old), the prevalence of HCV antibody and HCV RNA are estimated to be 0.4% and 0.2% respectively, with genotype 4 being the most prevalent. Paucity of treatment options available for children with HCV infection fails to reflect the huge advances in adult's treatment regimens. The treatment regimen that is currently approved for children is a combination therapy of Ledipasvir/sofosbuvir (LDV/SOF) for genotype1, 4, 5 and 6, while genotype 2 or 3 can be treated cautiously with regimens approved for adults, as per European association for study of liver disease (EASL) guidelines. The aim of this study is to assess and compare the efficacy and safety of the standard regimen LDV/SOF against Daclatasvir/sofosbuvir (DCV/SOF) in Egyptian patients aged 10-17 years.
Method: Forty treatment naïve and experienced patients aged 10 to 17 years with PCR confirmed chronic HCV infection were enrolled and randomly assigned to two groups. Both groups were matched to age, sex and BMI. Inclusion criteria included subjects aged 10-17 years old, a positive PCR for HCV and Fibroscan result of F3 or less, while exclusion criteria included patients not meeting all inclusion criteria, those with hepatitis B virus, autoimmune hepatitis, and/or cirrhotic patients. Patients in group I received LDV/SOF 90 mg/400 mg once daily for 12 weeks while group II received DCV/SOF 60 mg/400 mg once daily for the same period. For patients in group I under 35 kg, and under 40 kg in group II, half the mentioned dose was given. Efficacy (in terms of a sustained virologic response-SVR) was assessed using PCR for HVC at week 4, week 12 (end of treatment) and 12 weeks after end of treatment (SVR 12) while safety was evaluated using close clinical follow-up and weekly laboratory investigations at three different intervals; weekly during the first month of treatment, monthly until end of treatment, and at 12 weeks from the last dose.
Results: All patient (n = 40) in our study achieved SVR 12 (100%). A significant decrease in ALT and AST was observed. No major side effects necessitating termination of treatment were observed in either group. The most common side effects were abdominal pain (40%) and fatigue (40%) in group I, and headache (45%) and abdominal pain (35%) in group II. There was no statistically significant difference between the two groups regarding the incidence or severity of side effects.
Conclusion: A 12-week regimen of LDV/SOF and DCV/SOF appear to achieve the same results in regards to efficacy and safety in the young population. More research should be targeted towards expanding treatment options of HCV for young patients to parallel those in the adult population, given the high prevalence of the disease among this age group.

THU-114

A comparison of currently available direct acting antiviral HCV therapy in Canada: On the path to elimination

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Background and aims: Over 300, 000 Canadians are living with HCV infection. Specific populations like people who use drugs (PWUD) are disproportionally affected by this epidemic. To meet the World Health Organization (WHO) goals for the elimination of HCV as a public health concern by 2030, special attention needs to be paid to these vulnerable populations. The most prescribed HCV treatment regimens in Canada include elbasvir/grazoprevir (EG), sofosbuvir/ledipasvir (SL), and sofosbuvir/velpatasvir (SV). While clinical trials have highlighted the efficacy of these regimens, real world data is required to confirm these results, especially among PWUD.
Method: A retrospective analysis was performed on all HCV-infected PWUD (positive urine drug screen in the previous 6 month) initiating HCV treatment (rx) at our centre between 06/15-10/18. All subjects were enrolled in a multidisciplinary model of care, addressing medical, psychologic, social and addiction-related needs. The primary outcome was achievement of SVR12 (undetectable HCV RNA 12 or more weeks after the completion of HCV therapy).
Results: A total of 216 individuals (58% heroin/62% cocaine) have initiated therapy with one of the regimens of interest. The EG cohort (n = 50) includes 7 HIV+, 34 on opiate substitution therapy (OST), 38 Rx naïve, and 4 cirrhotic. To date, 40 individuals are eligible for SVR12 evaluations (34/40 SVR12), with no virologic failures (6 LTFU). The SL cohort (n = 68) includes 12 HIV+, 22 on OST, 48 Rx naïve, and 19 cirrhotic. To date, 58 are eligible for analysis (53/58 SVR), with 4 LTFU and one unrelated opioid overdose death. The SV cohort (n = 98) includes 12 HIV+, 49 on OST, 85 Rx naïve, 20 cirrhotic. To date, 64 are eligible for SVR12 analysis (54/64 SVR, 8 LTFU, 2 relapse).
Conclusion: The currently available regimens for the treatment of HCV appear to be equally efficacious among PWUD populations. The main reason for not achieving SVR is LRFU, occurring in 8% of individuals. Our data provide support for expanded access to HCV treatment, even in the setting of active drug use. Focus must now be shifted to mitigate losses to follow-up and recurrent viremia. Given these results, health care providers have three excellent options to provide HCV treatment to PWUD engaged in care, in support of the WHO's global elimination targets.

THU-115

Effects of health-related quality of life of interferon-free antiviral therapy for chronic hepatitis C infection-Results from the GermanhHepatitis C-Registry (DHC-R)

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Background and aims: Only limited data are available so far, regarding the influence of interferon-free, DAA-mediated therapy on patient reported outcomes (PROs) and clinical symptoms in patients with chronic hepatitis C infection. Especially, the time course of measures of quality of life (QoL) associated with interferon-free antiviral therapy and potential predictors of QoL improvement have not been thoroughly investigated so far. Therefore, we longitudinally assessed Short-Form 36 (SF-36) scores in HCV patients antivirally treated in a real life setting and focused on the identification of subgroups especially profiting from DAA regimens with respect to self-reported QoL.
Method: The DHC-R (German Hepatitis C-Registry) is a national real-world cohort including about 14, 500 patients recruited by more than 250 centers (approx. 90% physicians in private practice). We

evaluated the influence of DAA medication on the time course of PROs (basically SF-36 scores) at the end of treatment (EOT) and at follow-up 12 to 24 weeks after EOT (FU12/24) compared to baseline (BL) levels. Antiviral treatment started on or after Feb 1, 2014, and data were analysed as of Feb 9, 2018. Potential predictors of QoL improvement were identified using multivariate linear regression models (considering predictor candidates such as age, comorbidities, use of ribavirin (RBV), pre-treatment status, aminotransferases, BL SF-36 scores).

Results: A total of 1, 180 patients with complete PRO-data were considered for this analyses (684 males, 496 females, mean age 53.4 years). In line with reports from registration trials, both SF-36 physical component summary scale (PCS) ($p < 0.001$) and mental component summary scale (MCS) ($p < 0.001$) increased significantly at EOT and FU12/24 when compared to BL levels. These increases were associated with SF-36 BL levels (BL PCS < 50: $P < 0.001$; BL mental summary score < 43: $P = 0.022$). Other potential factors (such as GPT, RBV, presence of cirrhosis, comorbidities) were not relevant in this context. Further sub-analyses demonstrated that the increase in the SF-36 subscale "social functioning" was associated with the absence of HIV infection ($p = 0.045$) and the absence of RBV containing treatment ($p = 0.002$). Of note, despite the overall improvement, worsening in SF-36 PCS was reported for 43.6 (EOT) and 38.0% (FU12/24) of the patients when compared to SF-36 BL level. SF-36 MCS worsened in 41.7 (EOT) and 31.9% (FU12/24) of the patients.

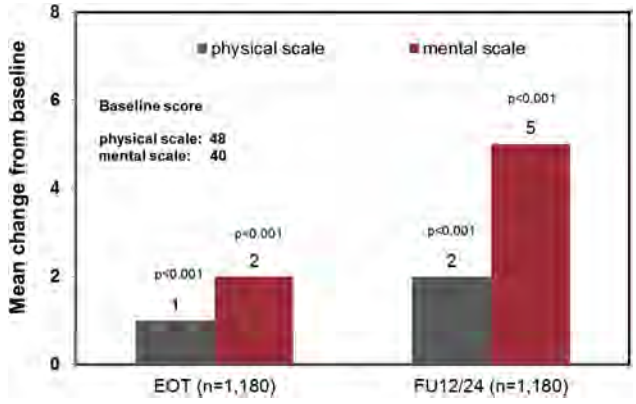

Figure: Mean change in physical and mental component summary score.

Conclusion: Hepatitis C patients undergoing DAA-based antiviral treatment significantly improve their self-reported QoL. The improvement in terms of increase in SF-36 scores is best predicted by BL levels of QoL. However, more than one third of patients do not improve in PCS and MCS. Longer follow-up is required to determine the extent of improvement in QoL after clearance of HCV infection.

THU-116

Effectiveness of the salvage therapy sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) in chronic hepatitis C: Clinical practice experience from the TRIO Network

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Background and aims: Although direct-acting antivirals (DAAs) failure is rare in clinical practice, SOF/VEL/VOX for 12-weeks is an FDA approved salvage therapy for patients that previously failed an NS5A inhibitor for any genotype (GT) or sofosbuvir without an NS5A inhibitor for GT1A or GT3. We report real world data from the TRIO network on the utilization and efficacy of SOF/VEL/VOX in US patients.

Method: Data from 196 patients who initiated SOF/VEL/VOX treatment between July 2017 to April 2018 were collected from providers and specialty pharmacies through Trio Health's disease management program. The primary outcome assessed was Per Protocol (PP) sustained virologic response at 12 weeks post treatment (SVR12). Comparisons were conducted using chi-square or Fisher Exact tests (categorical variables) or Student t test (continuous variables).

Results: 196 patients initiated SOF/VEL/VOX and although not indicated in the label, 4% (7/196) also received RBV. Intended duration was 12 weeks for 99% (195) with 1 patient receiving more than 12 weeks. By genotype: 78% (151) GT1, 3% (5) GT2, 16% (32) GT3, and 3% (6) GT4-6. Treatment status was reported for 194 of the 196 patients and only 21 (11%) were treatment naive (TN) indicating significant utilization for experienced patients. The top five prior therapies for the TE group included LDV/SOF ± RBV 53% (92/173), SOF/VEL ± RBV 12% (20/173), EBR/GZR ± RBV 11% (19/173), other SOF-based regimens 10% (17/173), and PrOD 6% (11/173). Physician-reported fibrosis score indicated cirrhosis for 42% (82) patients, consistent with baseline FIB-4 >3.25 for 40% (71/177) of patients with sufficient measures for calculation. Outcomes were: 0.5% (1/196) completed but were lost to follow-up, 4% (8/196) discontinued, 0.5% (1/196) died (cause unknown), 93% (183/196) achieved SVR12, and 2% (3/196) completed therapy but did not achieve SVR. Per protocol SVR12 rate was 98% (183/186) and the Intent-To-Treat SVR12 rate was 93% (183/196).

Conclusion: SOF/VEL/VOX in clinical practice is highly effective in prior treatment failures and treatment naïve patients with overall SVR12 rates of 98% (183/186) per protocol and 93% (183/196) in the Intent-To-Treat population.

THU-117

Evaluation of risk factors associated with failure to a first-line NS5A-containing regimen in HCV-infected patients naive to direct acting antivirals: Particular focus on natural resistance

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Background and aims: This study aimed to evaluate the presence of natural resistance-associated-substitutions (RASs) and other pre-treatment risk-factors for failure in a large group of HCV-infected patients (pts) naive to direct-acting-antivirals (DAA) with an available outcome after their first-line NS5A inhibitor-containing regimen in Italy.

Method: RASs in NS3/NS5A/NS5B (N = 1685/1497/1175) were analysed in 1947 DAA-naïve pts. Of them, 705 had an available outcome after a first-line NS5A-containing regimen recommended by the 2016/18 guidelines, with a baseline (BL) NS5A-test. HCV Sanger-sequencing was performed by home-made protocols. Potential differences between the sustained-virological-response (SVR) and virological-failure (VF) group were evaluated by Fisher's exact test. A multivariable logistic-regression analysis was performed to define risk-factors associated to treatment-response.

Results: Overall, 579/1947 (29.7%) pts showed at least one natural RASs, particularly NS5A-RAS was observed in 18.9% of pts. 705 pts (GT1a/b/g[200/214/1]-GT2a/c[84]-3a[141]-4a/d[65]) had an available outcome (656 with a SVR and 49 with a VF) after the following recommended NS5A-containing regimen: daclatasvir (DCV)/ledipasvir (LDV)/velpatasvir (VEL)+sofosbuvir (SOF) ± ribavirin (RBV) (N = 125/130/161), 3D/2D (paritaprevir/ritonavir+ombitasvir ± dasabuvir) ± RBV (N = 125/44), grazoprevir (GZR)+elbasvir (EBR) ± RBV (N = 70), glecaprevir+pibrentasvir (G/P) (N = 50). By analysing retrospectively the BL samples, a higher prevalence of natural NS5A-RASs was observed before treatment in DAA-failures (18/49, 36.7%) *vs* SVR-pts (94/656, 14.3%; P < 0.001). Notably, ≥ 2 risk factors for failure were more frequently observed at BL among pts who experienced a VF to a DAA treatment (37/49, 75.5%) compared to those achieving SVR (295/656, 45.0%, P < 0.001). By multivariable logistic-regression high HCV-RNA, natural RAS, cirrhosis, previous IFN-failure were negatively associated with SVR (see figure). Interestingly, all 32 GT1-3 pts treated with G/P achieved SVR, with the exception of 1 GT3, who had a breakthrough and had at BL the NS5A RAS A30 K and HCV-RNA >800.000 IU/ml. All others were without (or only 1) risk-factor: notably none of them showed BL RASs regimen-related.

Variables	Univariate		Multivariate	
	Adjusted odds ratio (95% C.I.)	P Value	Adjusted odds ratio (95% C.I.)	P Value
At least 1 RAS specific for regimen	0.312 (0.172-0.565)	<0.001	0.468 (0.231-0.949)	0.035
Baseline NS5A-RASs	0.289 (0.155-0.537)	<0.001	0.422 (0.199-0.892)	0.024
HCV-RNA >800,000 IU/ml	0.292 (0.136-0.627)	0.002	0.422 (0.199-0.892)	0.002
Previous IFN-treatment	0.386 (0.214-0.697)	0.002	0.391 (0.197-0.776)	0.007
Cirrhosis	0.440 (0.245-0.790)	0.006	0.432 (0.217-0.859)	0.017
HCV genotype				
1b*	1		1	
1a	0.997 (0.479-2.073)	0.993	0.990 (0.398-2.465)	0.983
1g	1.30*10^{8} (0)	1.000	6.3*10^{7}(0)	1.000
2a	1.30*10^{8} (0)	0.999	9.0*10^{7}(0)	0.999
2c	1.30*10^{8} (0)	0.997	5.8*10^{7}(0)	0.997
3a	0.733 (0.346-1.554)	0.418	0.518 (0.212-1.265)	0.149
4a	0.808 (0.173-3.770)	0.786	0.587 (0.066-5.224)	0.633
4d	1.657 (0.367-7.483)	0.512	0.883 (0.172-4.519)	0.881

Figure summarize a multivariable logistic-regression analysis adjusted for cirrhosis, previous IFN-treatment, baseline HCV-RNA, at least one RAS regimen-related, NS5A RASs regimen-related, and genotype (GT). IU: international unit, C.I: confidence interval, IFN: interferon *dummy

Conclusion: The presence of specific pre-treatment risk-factor, such as RAS regimen-related, BL HCV-RNA > 800.000 IU/ml, cirrhosis and previous IFN-failure were associated with virological failure for some specific regimens and GTs.

THU-118

Factors associated with hepatitis C treatment uptake among people who inject drugs in a population based data linkage study

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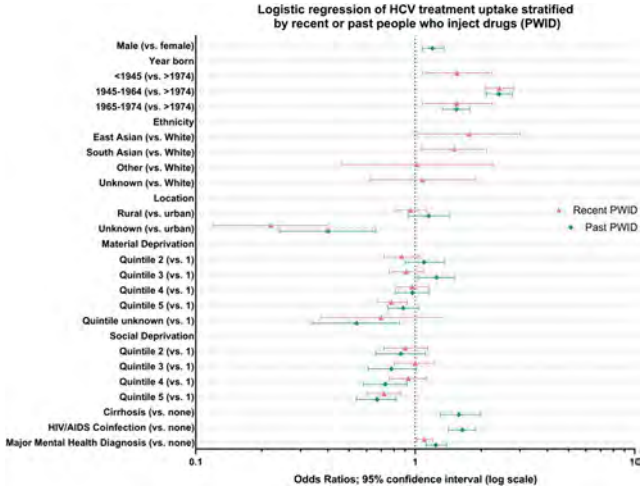
Background and aims: Previous studies showed lower hepatitis C virus (HCV) treatment uptake among people who inject drugs (PWID) compared to people with no injecting drug use (IDU). Identifying factors associated with PWID receiving HCV treatment could inform strategies to improve treatment uptake among this group. We identified factors associated with treatment uptake among HCV diagnosed people with recent or past IDU in British Columbia (BC), Canada.

Method: For these analyses, we used the BC Hep Testers Cohort (BC-HTC), which includes all individuals tested for HCV in BC since 1990, linked to all prescription drugs, medical visits, hospitalizations and mortality data. People diagnosed HCV RNA positive were stratified by history of IDU (recent PWID; IDU ≤ 3 years; past PWID, IDU > 3 years ago) and factors associated with treatment uptake (direct acting antiviral and interferon based) assessed using multiple logistic regression.

Results: Among 43, 266 individuals who were HCV RNA positive in BC from 1990-2015, 22% (9, 384/43, 266) were recent PWID and 16% (7, 084/43, 266) were past PWID. Among recent PWID, 34% (3, 181/9, 384) received treatment, compared to 31% (2, 198/7, 084) among past PWID, and 49% (13, 057/26, 798) among those with no history of IDU. Having a major mental health diagnosis and being born before 1974 was associated with increased treatment uptake among both recent and past PWID (Figure). For past PWID, male sex, HIV coinfection and cirrhosis were also associated with increased treatment uptake (Figure). Within both groups, factors associated with decreased treatment uptake included belonging to the most materially and most socially deprived quintiles, and those with unknown residential location (Figure).



Conclusion: The association between major mental health diagnosis and HIV infection, with increased treatment uptake among recent and past PWID may be due to improved engagement with social or health services among people with these diagnoses. The association between material and social deprivation and lower treatment uptake among recent and past PWID suggests additional support and services may be required to facilitate HCV treatment uptake among highly marginalized people. Further investigation in to the association between unknown residential location and lower treatment uptake among recent and past PWID should be undertaken to assess if this is related to homelessness or stigma related to marginalization.

THU-119

Direct-acting antiviral regimens without protease inhibitors may help maintain a healthy lipid profile after hepatitis C eradication

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Background and aims: Low VLDL- and LDL-cholesterol levels are characteristic of chronic HCV infection although this apparently healthy profile is associated with increased steatosis and augmented risk of cardiovascular disease (CVD). Additionally, HCV eradication with direct-acting anti-viral agents (DAAs) may result in increases in serum cholesterol and LDL, which might aggravate early CVD. Protease inhibitors (PI), now part of some DAA regimens, have previously shown a direct impact on lipid metabolism. It is, therefore, of paramount importance to determine to what extent these DAA-associated lipid changes are influenced by the eradication regimen chosen or by the underlying HCV disappearance.
Method: The study took place in the Hospital Universitario Miguel Servet (Zaragoza) from January/2018 to October/2018. All treatment-naive subjects with HCV were offered to join the study before DAA treatment. Exclusion criteria were the use of lipid lowering medications, HIV co-infection or decompensated cirrhosis. The lipoprotein and apolipoprotein (APO) profiles were studied prospectively by comparing pre and post-DAA regimens with and without PIs.
Results: HCV-infected DAA-naive subjects (n = 99, 52 women) were assigned to 4 different regimens according to clinical guidelines; sofosbuvir/ledipasvir (Harvoni, n = 5), sofosbuvir/velpatasvir (Epclusa, n = 40), glecaprevir/pibrentasvir (Maviret, n = 39), and grazoprevir/elbasvir (Zepatier, n = 15), being the last two PI-based therapies. All individuals had similar lipid profile at the baseline. HCV eradication regimen markedly increased their concentrations of APOB, as well as LDL and total cholesterol, irrespective of what treatment they were assigned. However, a PI-specific effect emerged in regards to subjects' high density lipoprotein (HDL) profile. Compared to PI-treated individuals, those upon non-PI regimens had at the end of the treatment an increased HDLc (mean[95% confidence interval: 61[56-66] *vs.* 50 mg/dl [46-53] for non-IP and IP, respectively, p = 0.001) and did not reduce their APOAI concentration (160 [150-170] *vs.* 140 mg/dl [130-150], for non-IP and IP, respectively, p < 0.001). This favorable effect on HDL concentration led to a decreased total cholesterol/HDL ratio (3.7 [3.4-4] *vs.* 4.2 [3.9-4.5], for non-IP and IP, respectively, p = 0.02), being lower ratios a surrogate of decreased risk of cardiovascular disease.
Conclusion: Our data suggest that the elimination of HCV with DAAs raises LDL-cholesterol and APOB. Those effects seem to be intrinsic to HCV eradication. However, this unfavorable lipid profile may be partially mitigated by using non-IP DAA therapy which increases HDL-cholesterol and prevents APOAI reduction. Given the many DAA-regimens available today, it is worth considering those which help maintain a healthy lipid profile, especially in those individuals with HCV and increased CDV-risk.

THU-120

Hepatitis C In children: Clinical profile and outcomes In the era of directly-acting antivirals in a tertiary centre in North India

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Background and aims: Hepatitis C is an important cause of chronic liver disease in adults with onset in pediatric age group. We analysed the profile and outcome of these children managed at our center, especially focusing on the treatment response with the newly available directly acting antiviral agents.
Method: A retrospective descriptive study was done to analyse the clinical profile and outcome of infants vertically exposed to hepatitis C (VE) and those with chronic hepatitis C (CHC), from year 2007 to 2018.
Results: Among the 52 subjects, 16 were vertically exposed (VE) infants and 36 were horizontally transmitted chronic hepatitis C (CHC).The mean age group of VE was 5.3 months (2 weeks-12 months) and that of CHC was 9.7 years (1-15 years).The possible route of transmission was hematogenous in 55% of CHC because of transfusion dependency (85% thalassemics, and 5% each sideroblastic anemia, immune thrombocytopenia and blood transfused for other cause). In 45% cases was because of unsafe injection practices. None was co infected with hepatitis B and none had extra hepatic manifestations. Follow-up was available in 9 (56%) of VE group and 26 (72%) of CHC group. All infants initially positive (N = 9) and followed up at 2 years age had either a negative HCV RNA or negative anti HCV antibody. Among the CHC group (N = 36), genotype was available in 21 patients with genotype 3 being most common (62%), followed by genotype 1 (28.5%) and 4 (9.5%).Follow-up was available in 26 patients. Spontaneous clearance was seen in 10 (38.4%) cases. Liver biopsy was done in 14 (87.5%) patients who were planned for treatment. Advanced fibrosis (F3 or more) was seen in 29% cases and 71% had early (F2 or less) or no fibrosis. 14 patients underwent anti HCV treatment. Peg IFN based regimen was used in 8 and among them 6 (75%) achieved an SVR. 2 (25%) non-responders had genotype 3 infection. In the DAA group (N = 6), mean age 8.8 years (5-11years), treated with Sofosbuvir + Daclatasavir or Ledipasvir or Ribavirin, all had achieved SVR (100%).Two patients are pursuing DAA therapy. No major drug related adverse effect was seen in treatment cohort.

Conclusion: CHC in children in India is mainly due to unsafe blood products and injection practices. Spontaneous clearance of chronic hepatitis C is seen in upto 1/3 children. Treatment with the newer DAA has 100% cure rate irrespective of genotype, is cost effective, more patient friendly and free of major adverse effects.

THU-121

Real world outcomes from NS5a treatment failures undergoing therapy with sofosbuvir/velpatasvir/voxilaprevir and sofosbuvir/glecaprevir/pibrentasvir

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Background and aims: Patients infrequently fail first line hepatitis C therapy. For those who do, second line therapy options include Sofosubuvir/Velapatasvir/Voxilaprevir (S/V/V) and Sofosbuvir/Glecaprevir/Pibrentasvir (S/G/P) (± ribavirin (RBV) for difficult-to-cure patients as per EASL 2018 treatment guidelines). We sought to examine the efficacy of treatment with these regimens in patients previously failing NS5a containing regimens.
Method: Patients commencing treatment with S/V/V or S/G/P were identified from the Scottish HCV database, and baseline data on age, sex, cirrhosis, genotype and prior treatments identified. Baseline resistance, where available, was recorded from laboratory records. Testing for NS5a resistance associated substitutions (RAS) was performed using in house population sequencing. Sustained Viral Response (SVR) was obtained from the database where available.
Results: 16 patients received 17 second line treatments (12 S/V/V, 5 S/G/P) post NS5a failure (see table). 6 were also Interferon (IFN) experienced, and 3 had failed a (non NS5a) Sofosbuvir based regimen. 4 were post transplant and 3 HIV co-infected. 11 had baseline RAS. To date 2 S/V/V patients have failed to achieve SVR, 1 following premature discontinuation due to side effects and 1 relapse in a post transplant GT1a patient with 3 prior treatment failures. The latter has initiated treatment with S/G/P/RBV for 24 weeks.3 S/V/V patients have achieved SVR12, the remainder of the cohort are pending SVR.
Conclusion: To date, 3/5 prior NS5a failures have achieved SVR with Sofosbuvir/Velpatasvir/Voxilaprevir, 3/4 excluding premature discontinuation. Further SVR data for this regimen and for Sofosbuvir/Glecaprevir/Pibrentasvir from this heavily pre treated cohort will be presented.

THU-122

Sofosbuvir/velpatasvir ± ribavirin for retreatment of patients with chronic hepatitis C virus infection and advanced fibrosis failing to a previous DAA combination regimen

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Background and aims: Failure to treatment of CHC virus infection with direct antiviral agents (DAA) occurs in about 2% of patients. Rescue therapy is still a cumbersome issue. We present data on retreatment with sofosbuvir+velpatasvir (SOF/VEL) ± ribavirin (RBV) in failures to DAA combination regimens.
Method: This was a multicenter study, based on an compassionate program for retreatment of patients with advanced liver disease who failed a previous treatment with DAA. SOF/VEL fixed dose ± weight based RBV was administered daily for 24 weeks. The end point was sustained virological response (SVR) at week 12 post-treatment. Resistance associated substitutions (RASs) were sought at baseline by Sanger method.
Results: The main characteristics of the patients are in Table 1. Thirty-four patients were enrolled and completed the follow-up (median age 56; 91% males; 73, 5% with cirrhosis; 26, 4% OLT recipients); most of the patients had RASs at NS5A and Y93H/C RAS was the the most

Figure: (abstract: THU-121)

Sex	Age	OLT	HIV	F4	GT	Regimen	RBV	Prior Failed Regimens			Ns5A RAS
								IFN	(S)ofosbuvir	NS5a	
M	52	N	N	N	1a	S/V/V	N	N	N	Graz/Elb/RBV	M28AV Q30R
M	58	N	N	N	1a	S/V/V	N	N	N	Graz/Elb	M28A Q30R
M	50	Y	N	N	3	S/V/V	N	Y	N	S/Vel	none
M	54	N	N	Y	3	S/V/V	Y	N	N	S/Graz/Elb/RBV	Y93H S62T
F	55	N	Y	Y	3	S/V/V	N	N	N	S/Dac/RBV	Y93H
M	46	N	Y	N	1a	S/V/V	N	N	S/IFN/RBV	PrOD/RBV	M28 T Q30R
M	58	N	N	Y	3	S/V/V	N	N	N	S/Dac/RBV	Y93H
M	50	N	N	N	3	S/V/V	N	Y	N	S/Vel/RBV	none
M	55	Y	N	N	1a	S/V/V	N	N	N	S/Led	L31M
M	51	N	N	Y	3	S/V/V	Y	Y	S/IFN/RBV	S/Vel/RBV	Y93H
M	39	N	N	N	3	S/V/V	N	N	N	S/Vel	A30K
M	56	Y	N	N	1a	S/V/V	N	Y	S/RBV	S/Led/RBV	none
M	56	N	N	N	1a	S/G/P	Y	N	N	Graz/Elb	M28A Q30R
F	29	N	Y	N	1a	S/G/P	N	N	N	S/Led	none
F	54	N	N	Y	1a	S/G/P	N	N	N	S/Led	None
M	44	N	N	N	1a	S/G/P	N	Y	N	PrOD	M28 V Q30H
M	56	Y	N	N	1a	S/G/P (24W)	Y	Y	N	S/Led/RBV S/V/V	none

frequent; 28/34 received RBV. Previous treatments (± RBV) were dasabuvir/ombitasvir/r-paritaprevir (2/5.9%); daclatasvir/sofosbuvir (19/55.8%); ledipasvir/sofosbuvir (12/35.4%); simeprevir/sofosbuvir (1/2.9%). Overall, 28 patients (82.3%) achieved SVR12. SVR by genotype were: 75%; 71%; 100%; 87.5%; 83.0%, respectively, for genotypes 1a; 1b; 2; 3; 4. SVR was achieved in 14/18 (77.8%) patients with Y93H/C RAS and in 6/8 (75%) in those with L31F/I/M RAS. Simultaneous presence of RAS at L31 and Y93 sites led to SVR in 2/4 (50%) patients. Among 9 patients with cirrhosis and ascites, 8 achieved SVR (88.9%); all had riceived RBV. All patients completed treatment with DAA; 1 patient stopped RBV due to anemia.
Conclusion: Rescue therapy with SOF/VEL ± RBV was safe and effective for patients who failed a previous DAA treatment, particularly in patients with genotype 3, even in the presence of RAS or decompensated cirrhosis.

THU-123

No effect of alcohol consumption or dependence on treatment outcome in chronic hepatitis C patients treated with Elbasvir/Grazoprevir in a real-world setting

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Background and aims: The efficacy and safety of direct acting antivirals have been evaluated in different real-world settings, however patient reported outcomes (PROs) evaluating alcohol consumption are scarce. The study aims to assess the association between alcohol consumption, and clinical outcomes, including sustained virological response (SVR12), using AUDIT-C, a validated PRO assessing alcohol habits.
Method: Zephyr is a French multi-center, prospective, observational study on Elbasvir/Grazoprevir (EBR/GZR) utilization in a real-world setting. PROs, including AUDIT-C, were collected in routine care. All the patients received the PROs and were free to fill them at the inclusion, end of therapy (EOT) and at follow-up week 12 and 48. This analysis is based on patients included between January and September 2018. Data will be updated by the time of the meeting.
Results: 183 patients with chronic hepatitis C were included. The mean age was 56.0 years old, with 52% of males and a BMI of 25.6 ± 5.0 kg/m². 162 (89%) were HCV treatment naïve. 26 (14%), 117 (64%) and 36 (20%) patients were infected by HCV Genotype 1a, 1b and 4, respectively. 132 (72%), 24 (13%) and 23 (13%) patients had fibrosis METAVIR stage F0-F2, F3 and F4, respectively. According to the investigators, 95 (52%), 67 (37%) and 19 (10%) patients were abstinent for alcohol consumption, consumed < 3 and ≥ 3 units/day, respectively. At inclusion, AUDIT-C was fully completed by 134 patients. Respectively, 92 (69%) and 43 (31%) patients consumed < 3 and ≥ 3 units/day. The mean value of AUDIT-C score was 2.4 (CI 95%: 2.0-2.9), 85 (63%) and 49 (37%) had an AUDIT-C score < 3 and ≥ 3. At the end of therapy, the AUDIT-C score was < 3 and ≥ 3 in 46/67 (69%) and 21/67 (31%). At the time of the abstract submission, 32/183 patients reached week 12 of follow-up and had available AUDIT-C score. The SVR12 rate was 95.4% (21/22) and 100% (10/10) in patients with an AUDIT-C score < 3 and ≥ 3, respectively. Final SVR12 results and PROs related to drug use, sexual behaviour, life habits (employment, housing and working conditions) will be added to the analysis at the time of the meeting.
Conclusion: The ZEPHYR study reports for the first time, in real world setting, efficacy and the effect of PROs following the use of EBR/GZR. In the set of 32 patients with available SVR12 and AUDIT-C score, alcohol consumption along with alcohol abuse or dependence does not impact EBR/GZR treatment efficacy.

THU-124

Efficacy and safety of glecaprevir/pibrentasvir for the pangenotypic treatment of chronic hepatitis C in former intravenous drug users: Subanalysis from a Spanish real-world cohort (Hepa-C)

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Background and aims: Glecaprevir and pibrentasvir (G/P) are direct-acting antiviral agents with pangenotypic activity against hepatitis C virus (HCV). Integrated analysis of nine clinical trials in patients with chronic hepatitis C (CHC) treated for 8 or 12 weeks showed sustained virological response (SVR12) of 98% and 99%, respectively[1]. Similarly, analysis of four clinical trials in patients with compensated cirrhosis treated for 12 or 16 weeks showed SVR of 96%[2]. Studies evaluating G/P in former i.v. drug users (IDUs) in clinical practice are scarce. **Aim:** To assess the efficacy and safety of G/P in a real-world cohort of former IDUs with CHC.
Method: Multicenter observational study from a Spanish real-life cohort including patients from 32 Spanish centers. Patients with CHC who received G/P for 8, 12 or 16 weeks (September 2017 to May 2018) were included and categorized according to the previous IDU. Primary end point was the rate of patients with undetectable HCV-RNA 12 weeks after end of treatment (RVS12, ITT). Patients lost during follow-up were excluded (mITT). Safety was assessed by collecting the reported adverse effects (AEs) (clinical and laboratory).

Quantitative variables are expressed as medians and 25th/75th percentiles. Qualitative variables are expressed as percentages.
Results: A total of 1, 581 patients were included, 294 (18.6%) with prior IDU. Median age was 50 (44-54) years, with BMI (kg/m2) of 25.3 (22-27.1). 84% were males, 97.8% Caucasians, and 85% naive. Compared to the remaining, IDUs were younger (50 vs. 55 years), had higher alcohol consumption (27.2% vs. 4.7%), were more frequently infected by genotype 1a, 3 or 4 (43.8%, 22.1% and 19.3% vs. 23%, 11.1% and 8.9%, respectively), and showed more advanced liver fibrosis by transient elastography (TE > 9.6 kPa) (23% vs. 11.6%) (all p < 0.001). Among IDUs, 199 (67.7%) have completed treatment and follow-up, and 190 (95.5%) achieved SVR12. Three (1.5%) were relapsers and 6 (3%) lost during follow-up. mITT SVR12 rates were 98.4% (190/193). No differences were observed in SVR12 comparing gender, genotype, fibrosis stage, or treatment duration. No significant adverse events were observed and no treatments discontinuations were needed.
Conclusion: Our preliminary real-world data confirm that G/P is an effective and save pangenotypic therapy for patients with chronic hepatitis C and prior IDU, similarly to the general population.

THU-125

High real-world effectiveness of elbasvir/grazoprevir in PWID on opioid substitution therapy with HCV genotype 1 infection: Results from the German hepatitis C registry (DHC-R)

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Background and aims: In most high-income countries, people who inject drugs (PWID) are the major population affected by chronic HCV infection with an estimated HCV prevalence of 60-80%. In clinical studies direct-acting antiviral (DAA) therapy has proven high efficacy in PWID on opioid substitution therapy (OST), even with ongoing drug use if treated with EBR/GZR. Until now, the effectiveness of EBR/GZR in PWID has not been investigated in detail in real-world. This was aimed by the present analysis of a large GT1 real-world cohort of the German Hepatitis C Registry.
Method: From September 2016 until July 2018, 992 patients (pts) with GT1 infection were treated at physician discretion's with EBR/GZR ± ribavirin (RBV) for 12 to 16 weeks in 130 medical practices and hospital outpatient departments. The present analysis was restricted to 613 pts who completed 12 or 24 weeks of follow-up or discontinued the treatment early; the demographic data are shown for this ITT population. Sustained virologic response (SVR) data were available and are shown for 599 pts (Per Protocol (PP) population).
Results: Demographics of 499 pts without former drug use (Non-OST/NDU) were compared with 67 PWID on OST therapy (OST) and 47 former/current drug users not receiving OST (Non-OST/DU): mean age was 56 vs. 45 vs. 47 years, male gender 54 vs. 81 vs. 72%, GT1a 23 vs. 74 vs. 70%, baseline viral load >800, 000 IU/ml 56 vs. 52 vs. 53%, cirrhosis 18 vs. 18 vs. 13%, HIV co-infection 3 vs. 6 vs. 19%, cardiovascular diseases 40 vs. 13 vs. 13% and psychiatric disorders 10 vs. 13 vs. 28%. NS5A RAS at baseline were tested in 15 vs. 37 vs. 34% while RAS were detectable in 12 vs. 0 vs. 13%. EBR/GZR treatment was used in 96 vs. 78 vs. 85% of pts and EBR/GZR+RBV in 4 vs. 22 vs. 15%. ITT and PP SVR rates were 96.2% and 98.6% in Non-OST/NDU pts, 89.6% and 98.4% in OST and 93.6% and 95.7% in Non-OST/DU pts (table). 7 reinfections occurred. 6 were observed in Non-OST/NDU and 1 in OST and were counted as therapy success in the PP analysis. Comparative statistics for the ITT and PP SVR results demonstrated a significant difference (p = 0.025) in SVR for Non-OST/NDU vs. OST in the ITT analysis, which was mainly due to LTFU.

	Non-OST/NDU	OST	Non-OST/DU
ITT SVR-n/N (%)			
Total	480/499 (96.2)	60/67 (89.6)	44/47 (93.6)
GT1a	107/115 (93)	45/49 (91.8)	31/33 (93.9)
GT1b	369/380 (97.1)	15/17 (88.2)	13/14 (92.9)
PP SVR-n/N (%)			
Total	484/491 (98.6)	61/62 (98.4)	44/46 (95.7)
GT1a	108/112 (96.4)	45/46 (97.8)	31/32 (96.9)
GT1b	372/375 (99.2)	16/16 (100)	13/14 (92.9)

Conclusion: Despite the controversy concerning HCV treatment in PWID, this analysis demonstrates a high real-world effectiveness of EBR/GZR treatment regimens in pts on OST as well as in Non-OST pts with a history of drug use. A significant difference among groups was only observed in ITT SVR for OST vs. Non-OST/NDU pts. Nevertheless, these findings suggest that reservations to initiate DAA therapy in these groups are unwarranted.

THU-126

HCV treatment outcomes among current and remote injection drug users: Real- life data

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Background and aims: A number of clinical trials (CO-STAR, D3FEAT, SIMPLIFY) have suggested that HCV treatment outcomes among active injection drug users (IDUs) is identical to that observed in other populations. It has been suggested that these data may not pertain to IDUs who would not be enrolled in such trials. Despite the recent publication of a meta-analysis on this subject, there is a need for more comparative data among current and remote IDUs treated for HCV under similar circumstances.
Method: A retrospective cohort analysis was performed on all HCV infected patients who were treated with Direct Acting Antivirals (DAAs) at our centre with a history of current or remote IDU between 04/14- 10/18. All participants had access to a multidisciplinary model of care addressing their medical, social, psychological, and addiction-related needs. The primary end point of this analysis was the achievement of SVR12 and its correlates, with a view to demonstrating whether active IDU was a correlate of treatment outcome when care was delivered to current and remote IDUs within the same setting.
Results: In this analysis, we compared 141 active and 88 remote IDUs who were evaluated at the SVR12 time point. Baseline demographic and disease characteristics for active and remote IDU, respectively: mean age 51.7/55.8 years, 78%/70% male, 53%/25% opiate substitution therapy, 36%/25% alcohol use, 22%/7% homelessness, 17%/16% cirrhotic, 14%/10% HIV co-infected. All oral HCV treatment for active and remote IDUs, respectively: 27%/18% SOF/VEL, 17%/23% SOF/LED, 13%/15% ELB/GRAZ and 23%/23% PrOD. Of the active IDUs that reached the SVR timepoint, 138/141 (98%) achieved SVR12 vs. 88/88 (100%) amongst remote IDUs by mITT analysis. Two active IDUs relapsed and one individual discontinued treatment due to medical complications unrelated to therapy. Four cases of reinfection have been identified, all amongst active IDUs at a rate of 1.6 per 100 person-years. Reinfection occurred at a mean of 50 weeks post SVR12 date.

Conclusion: Within a multidisciplinary care model, high SVR12 rates were achieved in both active and remote IDUs. Therapeutic failure and re-infection events occurred infrequently, but only among active IDUs. This supports the need to develop interventions to maintain these individuals in care during and after treatment to mitigate these risks and ensure that proper harm reduction interventions can be applied.

THU-127

Clinical Practice experience with pan genotypic therapies glecaprevir-pibrentasvir and sofosbuvir-velpatasvir in the TRIO Network

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Background and aims: In the continued evolution of DAA therapies, pan genotypic drugs GLE-PIB and SOF-VEL offer a simplification of HCV treatment. In this study we examine use of these agents to describe real-world use profiles and outcomes.
Method: Data specific to patients who initiated GLE-PIB (n = 1131) or SOF-VEL (n = 777) between Aug 2017 to April 2018 were collected from providers and specialty pharmacies through Trio Health's disease management program. Variable comparisons between treatment groups were conducted using chi-square, exact tests, or z-test for proportions. Multivariate analyses were performed using forward stepwise logistic regression (LR).
Results: In the TRIO data set, GLE-PIB patients had more 8-week therapy (75% v. 2%), were younger (29% v. 21% < 50), mostly GT1 (71% v. 22%), more CKD Stage 4-5 (7% v. 1%), and less cirrhosis (16% v. 27%) compared to SOF-VEL. Outcomes in the intent to treat (ITT) population receiving GLE-PIB were 93% (1049/1131) achieved SVR12, 2% (17/1131) completed therapy but did not achieve SVR12, 2% (21/1131) completed but were lost to follow-up (LTFU), 3% (38/1131) discontinued, and 1% (6/1131) died. ITT outcomes with SOF-VEL were 90% (701/777) achieved SVR12, 2% (15/777) completed therapy but did not achieve SVR12, 2% (14/777) LTFU, 5% (40/777) discontinued, and 1% (7/777) died. Nearly half of patients (45%) who discontinued SOF-VEL were with GT3 HCV compared to 5% for GLE-PIB. For GLE-PIB, 16% of patients who discontinued had severe renal impairment compared to 2% for SOF-VEL discontinues. Virologic failure with GLE-PIB was associated with treatment experience (TE) (OR: 0.14 (0.05-0.36), $p \leq 0.001$), cirrhosis (OR: 0.29 (0.11-0.80) p = 0.017), and VL > 6MM in GT3 (OR: 0.14 (0.03-0.60) p = 0.008). The presence of +RBV was significantly associated with virologic failure with SOF-VEL (0.16 (0.04-0.60) p = 0.007), likely representing a confounding factor not accounted in the LR. Per protocol (PP) SVR12 rates for subgroups defined by genotype, fibrosis, prior treatment experience, and baseline viral load were not significantly different by treatment except for cirrhotic GT3 which were 88% (22/25) for GLE-PIB and 98% (57/58) for SOF-VEL (p = 0.044).
Conclusion: 59% of study patients were treated with GLE/PIB ± RBV and 41% SOF/VEL ± RBV. In general, GLE-PIB treated patients were younger, had less fibrosis, and higher frequency of CKD Stage 4-5 compared to SOF-based regimens. Overall outcomes between regimens differed in ITT populations with a higher rate of discontinuations in patients receiving SOF/VEL (5% v 3% for GLE-PIB), possibly reflecting patients with more difficult to treat HCV. In the PP population, SVR12 rates for both therapies were 98%. Virologic failure in the GLE-PIB group was associated with TE, cirrhosis, and GT3*VL > 6MM. For SOF-VEL, virologic failure was associated with +RBV.

THU-128

Renal safety in 3, 264 HCV patients treated with DAA-based regimens: Results from a large Italian real-life study

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Background and aims: The use of Sofosbuvir (SOF)-based regimens has been associated with renal function worsening in hepatitis C virus (HCV) patients with impaired (≤45 ml/min/1.73 m^2) estimated glomerular filtration rate (eGFR), but it has never been further investigated. We therefore investigated renal safety of any direct-acting antivirals (DAA) in a large cohort of HCV patients, including patients with moderate to severe chronic kidney disease (CKD).
Method: All HCV patients treated with DAA in Lombardy between December 2014 and November 2017 with available kidney function tests at baseline, end of treatment (EOT) and 12 weeks after treatment completion (SVR) were included. Data were extracted from the NAVIGATORE-Lombardia web-based Platform. eGFR was estimated according to the MDRD formula, and CKD stage was defined according to the KDIGO classification.
Results: Among 3, 264 DAA treated patients included (65% were males, 67% cirrhotics, 61% HCV-1, 30% diabetics), median eGFR was 88 (9-264), and CKD stage was 4-5 in 23 (0.7%). SOF-based and RBV-containing regimens were used in 79% and 73% patients, respectively. During DAA treatment, eGFR values significantly declined in patients

with CKD-1 ($p < 0.0001$) and CKD-2 ($p = 0.0002$), with correspondent rates of CKD stage reduction of 25% and 8%, respectively. Rates of CKD improvement were 17% in CKD-2 patients. Conversely, DAA led to eGFR improvement in patients with eGFR < 60 ml/min/1.73 m2 ($p < 0.0001$ in CKD-3a, $p = 0.0007$ in CKD-3b and $p = 0.024$ in CKD-4/5). Among them, rates of CKD worsening were 8-17% (vs. improvement in 33-45%), at EOT. Changes in eGFR and CKD distribution remained stable at SVR. Predictors of worsening CKD at EOT were age > 75 years ($p = 0.05$), preserved baseline renal function ($p < 0.0001$) and diabetes ($p = 0.04$); predictors of worsening CKD at SVR were age > 75 years ($p = 0.005$), preserved baseline renal function ($p < 0.0001$), arterial hypertension ($p = 0.0006$) and on-treatment renal worsening ($p < 0.0001$).

Conclusion: In patients with preserved baseline renal function, DAA treatment led to statistically significant eGFR decline that was not reverted upon drug discontinuation. This detrimental effect was not observed in those with moderate to severe kidney dysfunction.

THU-129

New antiviral therapy and the quality of life in patients with HCV infection

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Background and aims: The effects of the infection with the hepatitis C virus (HCV) are not limited to the medical dimensions, but also apply to psychological and social areas. Our study aims to assess the influence of treatment with DAA-based therapies on the quality of life and on the level of stress perceived by the patients.

Method: The study was done on subjects diagnosed with HCV infection, F3-F4 METAVIR score, and detectable HCV-RNA viral load, treated with Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir for 12 weeks. All patients were clinically and biologically evaluated at the start of the treatment (SoT), at weeks 4, 8, 12 (end of treatment-EoT), respectively 12 weeks after therapy (sustained viral response-SVR). Quality of life (QHO-QOL Bref), level of perceived stress (PSS scale), and presence of depression and/or anxiety screening (HADS scale) were consecutively assessed at SoT, EoT and SVR. Statistical analysis was realized using SPSS software and Friedman test for consecutively data recorded.

Results: The study sample included 73 subjects (75.3% females, 50.7% urban area) with minor adverse events present in 30.37% of patients (asthenia, pruritus, insomnia), and none discontinued treatment. There were recorded: a high level of perceived stress in 20.5% (SoT), respectively moderate stress 78.1% (SoT), but during the treatment it was significantly improved ($\chi2\ (2) = 18.33$, $p < 0.0001$). Depression as assessed through HADS was present in 17.8% (SoT), and only in 1.4% at SVR ($\chi2\ (2) = 24.86$, $p < 0.0001$), similar situation being observed for anxiety: 45.2% (SoT), 9.6% (EoT), 5.5% (SVR) ($\chi2\ (2) = 33.95$, $p < 0.0001$). Patients under DAA therapy had statistically significant improvements in physical health ($\chi2\ (2) = 35.289$, $p < 0.0001$), psychological ($\chi2\ (2) = 39.42$, $p < 0.0001$), social relationships ($\chi2\ (2) = 54.10$, $p < 0.0001$), environment ($\chi2\ (2) = 41.52$, $p < 0.0001$).

Conclusion: DAA-based therapies lead to good outcomes not only related to the evolution of the liver disease, but also for the social functioning and quality of life of the affected individuals. Additionally, during the treatment and after it, the level of perceived stress, and the associated depression and anxiety with the medical condition were significantly reduced

THU-130

Management strategies for drug drug interactions between direct oral anticoagulants and hepatitis C directly acting agents: A multi-centre review

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Background and aims: Direct oral anticoagulants (DOACs) are increasingly prescribed as alternatives to warfarin. Predictable pharmacokinetics mean blood monitoring is not routinely required. However, risk of bleeding remains an important adverse drug reaction (ADR). DOACs, such as apixaban, rivaroxaban, edoxaban, and dabigatran, are substrates of CYP3A4 and/or P-glycoprotein making them susceptible to drug-drug interactions (DDIs) with Hepatitis C (HCV) Direct Acting Antivirals (DAAs). This may result in increased DOAC exposure and bleeding risk. Some DOAC/DAA combinations are contraindicated but the majority are classed as "amber" by University of Liverpool DDI website (www.hepdruginteractions.org) suggesting use with caution. Management of this DDI includes assessment of individual risk of bleeding, consideration of switching medicines to low molecular heparin (LMWH) or an alternative DAA, clinical monitoring for ADRs or, where available, plasma monitoring of anti-Xa activity. We gathered data from UK centres to describe the patient cohort and explore optimum strategies for management of this potentially serious DDI.

Method: A data collection form was sent to HCV pharmacists within the British Hepatology Pharmacy Group (BHPG) for patients co-prescribed DAAs and DOACs from June 17-May 18. Data on DAA and DOAC regimen prescribed, presence of cirrhosis, illicit drug use, treatment setting, and any ADRs reported was obtained. Management of the DDI was categorised as: clinical monitoring (CM), blood monitoring of anti-Xa activity (BM), switch to LMWH (SL), switch DAA (SD) or wait until DOAC completed (W) for short courses.

Results: 54 patients were identified. Baseline characteristics are outlined below. Management of DDIs was as follows: CM 24 (44.4%), BM 13 (24.1%), SL 9 (16.7%), SD 7 (13%), or W 1 (1.9%). Of 13 patients planned for BM, 6 had 0 or only 1 available result, 2 had increased levels and 5 had decreased levels on treatment. No treatment changes were made. 6/7 patients who switched DAAs were originally planned for a DAA which was contraindicated with the prescribed DOAC. ADRs were reported in 12 patients (22.2%); 1 mild bruising and 1 haemoglobin drop (patient with known varices). No serious bleeding ADRs were reported.

Baseline Characteristics	n = 54
Mean age (± SD)	46 (12.5)
Male (%)	43 (80)
Injecting drug use (within 3 months) (%)	13 (24.1%)
Genotype (%)	
1A	24 (44.4)
3	21 (38.9)
Other (1B, 2, 4)	9 (16.7)
Fibrosis Stage (%)	
F0-2	30 (55.6)
F3	5 (9.3)
F4 (CPA)	17 (31.5)
F4 (CPB/C)	2 (3.7)

Conclusion: Reassuringly, no serious ADRs were reported in this small cohort. However, only a third of patients were cirrhotic and further study is needed in this group with increased bleeding risk. BM was difficult to interpret in practice, in part due to sampling times. A case by case approach is needed in managing these patients with individual assessment of risk used to plan management of interaction.

THU-131

Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir for retreatment of chronic hepatitis C patients with a previous failure to direct-acting antivirals: A real-life study from the NAVIGATORE Lombardia and Veneto Networks

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Background and aims: Sofosbuvir/Velpatasivr/Voxilaprevir (SOF/VEL/VOX) is approved for retreatment of hepatitis C (HCV) patients with a previous failure to direct-acting antivirals (DAA), however real-life data are still limited. Aim of the study was to assess effectiveness and safety of SOF/VEL/VOX combination in an Italian real-life setting.

Methods: All consecutive HCV patients starting SOF/VEL/VOX treatment from 31 May 2018 in 27 centers were enrolled. Bridging fibrosis and cirrhosis were diagnosed by liver stiffness measurement (LSM): >10 kPa for F3 and >13 kPa for F4. Sustained virological response (SVR) was defined as undetectable HCV-RNA 4 (SVR4) or 12 (SVR12) weeks after the end of treatment (EOT).

Results: 179 patients were included in the analysis: median age was 56 (18-88) years, 73% males, BMI 24 (16-45), ALT 54 (13-387) U/L. Fibrosis stage was F0-F1 in 18%, F2 in 16%, F3 in 21%, F4 in 45%. 1% and 4% of patients were HBV or HIV coinfected, respectively. HCV genotype was 1 in 58% (1b 33%, 1a 25%), 2 in 10%, 3 in 24% and 4 in 8%. Median baseline HCV-RNA was 1, 012, 277 (482-25, 590, 000) IU/ml. Previous DAA ± ribavirin (RBV) treatments included combination of nNS5B + NS5A or NS3 inhibitor in 61%, NS3 + NS5A in 21%, NS3 + NS5A ± nnNS5B in 18%. First DAA course was optimal according to EASL recommendations in 88%. Testing for resistance associated substitutions (RAS) at DAA failure was available in 48% of patients. RAS were detected in the NS3 region in 26%, NS5A in 74% (Y93H in 61%) and NS5B in 20%; combined NS5A + NS5B or NS3 RAS were detected in 32%. Overall, patients received SOF/VEL/VOX for 12 weeks, and RBV was added in 21% of treatment schedules. Undetectable HCV-RNA at week 4 was achieved by 63% of patients, while EOT response by 91%. Rates of EOT response did not differ according to baseline HCV-RNA (<800, 000 vs. 800, 000-6, 000, 000 vs. >6, 000, 000: 85% vs. 88% vs. 80%, p = 0.8), fibrosis stage (F0-3 vs. F4: 82% vs. 94%, p = 0.1) or presence of RAS (yes vs. no: 78% vs. 88% p = 0.5). Treatment was discontinued in 2 (1%) patients, one due to virological failure at week 4 and the other for non-virological reasons. Most frequent adverse events were anemia, fatigue and nausea, reported in 3%, 5% and 2%, respectively. No severe adverse events were reported. Complete SVR data will be presented at the meeting.

Conclusion: SOF/VEL/VOX combination is an effective and safe retreatment for HCV patients failing a first DAA course in a real-life setting.

THU-132

Decentralised care with generic direct antivirals is effective in the management of patients with hepatitis C in a public health care setting: The Punjab model

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Background and aims: The prevalence of hepatitis C virus infection (HCV) infection in Punjab, India is 3.29%, with an estimated burden of around 650, 000 viremic chronic HCV (CHC) patients. The Mukh-Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) was launched in June 2016 to eliminate HCV from Punjab and provides no cost treatment to all CHC patients. We assessed the feasibility, safety and efficacy of decentralized care and treatment of CHC with12 or 24 weeks of sofosbuvir (SOF) + ledipasvir (LDV) or SOF + daclatasvir (DCV) ± ribavirin (RBV) in a public health care setting.

Method: ***Decentralized care:*** All patients were evaluated and treated at 3 University Hospitals (tertiary level healthcare) and 22 District Hospitals (secondary level); they were followed up to 12 weeks post-treatment to look for sustained viral response (SVR-12). ***Health care worker capacity building:*** All medical specialists were trained in a 4-hr course, followed by telehealth PGIMER-INASL-Punjab Extension for Community Healthcare Outcomes (ECHO) Clinics conducted fortnightly. 25 pharmacists from each of the 25 centres dispensed medicine. ***Data Management:*** 25 trained data entry operators and Clinton Health Access Initiative (CHAI) managed epidemiological data. ***Monitoring:*** Medical alerts were used for drug compliance

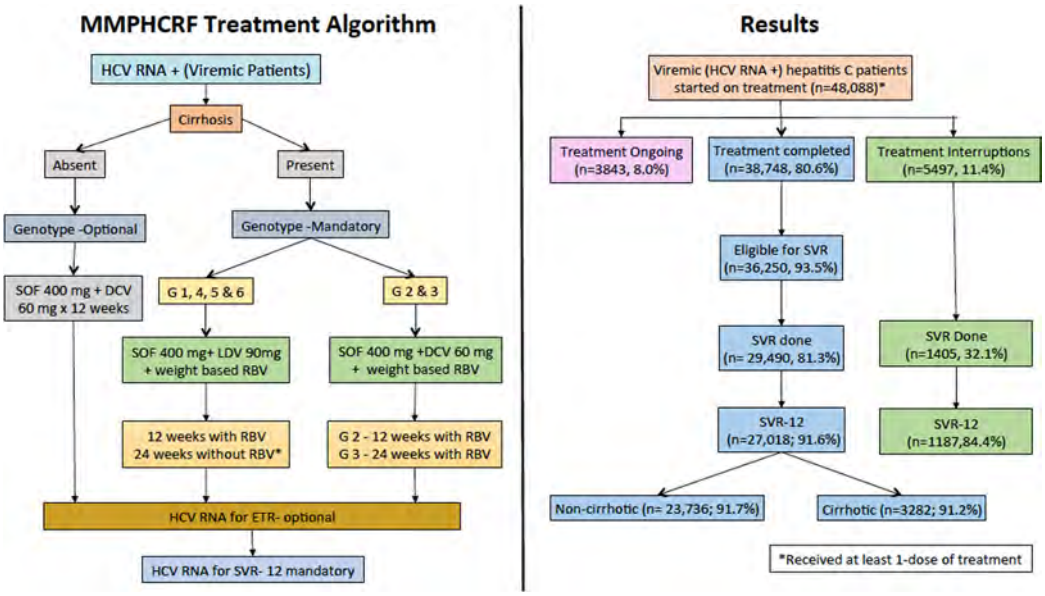

Figure: (abstract: THU-132)

monitoring. ***Study design:*** A cost-effective algorithm was developed using SOF-based regimens to treat all patients (Figure). The diagnosis of cirrhosis was based on clinical evidence, AST-to-platelet ratio index (≥ 2.0) or FIB-4 score (>3.25) or on liver stiffness measurement ≥ 12.5 kPa on fibroscan.
Results: We enrolled 48, 088 patients (63.9% male; mean age 42.1 years; 80.5% rural) during the period from 18thJune 2016 to 31stJuly2018; While 38, 748 (80.6%) patients completed the desired treatment, 5497 (11.4%) had treatment interruptions and 3843 (8.0%) patients are currently on-going treatment. SVR-12 was achieved in 91.6% of patients who had completed the treatment and in 84.4% of patients who had treatment interruptions (Figure). The predominant genotype (G) was G3 (69.9%) and 14.8% were cirrhotics. SVR-12 rates in cirrhotics versus non-cirrhotics and G3 versus non-G3 were comparable. Amongst 21, 753 patients who were interviewed for risk-factors, unsafe medical practices (11, 877; 54.6%), injection drug use (1640; 7.5%), unsafe dental practice (948; 4.3%), prior surgery (1420; 6.5%) and unprotected sex (112; 0.5%) were the main suspected modes of virus transmission. There were no major adverse events.
Conclusion: Decentralized care of HCV in Punjab India with generic all oral DAA regimens is a safe and effective regardless of genotype or presence of cirrhosis.
ClinicalTrials.gov number: NCT01110447.

THU-133

Resistance-guided retreatment of HCV infected patients with a previous failure to an NS5A inhibitor-containing regimen: Italian real life experience

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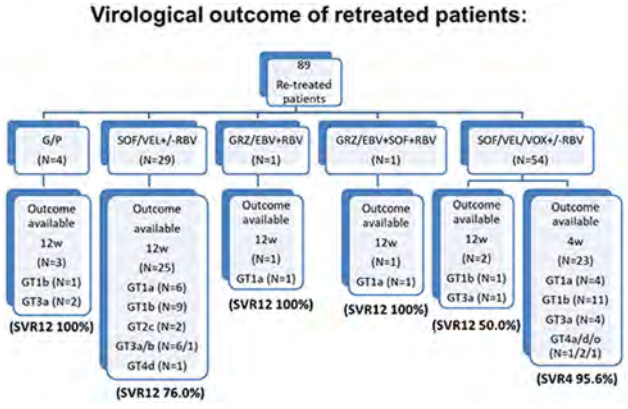
Background and aims: This study aimed to analyze Italian real-life data of patients (pts) who experienced a failure to a recommended NS5A inhibitor containing regimen and their retreatment.
Method: Within the Italian VIRONET-C network, 361 NS5A-failing pts infected with different HCV genotypes (GT) (GT1a/1b/2a-c/3a-b-g-h/4a-d-n-o-v = 84/118/17/106/36) were analyzed. Retreatment of 89 failures was investigated. HCV resistance test was performed by Sanger-sequencing.
Results: Failures following seven different NS5A containing regimens were studied: 3D/2D (paritaprevir/ombitasvir ± dasabuvir) ± ribavirin (RBV) (N = 69/4), daclatasvir/ledipasvir/velpatasvir (VEL) +sofosbuvir (SOF) ± RBV (N = 102/123/18), grazoprevir (GRZ)/elbasvir (EBV) ± RBV (N = 27), glecaprevir/pibrentasvir (G/P) (N = 18). Notably, 13.6% of NS5A-failing pts did not show any resistance associated substitutions (RAS), while 83.6% showed at least one NS5A-RAS and 46.6% at least one NS3-RAS, with multiclass-resistance in 37.7%. NS5A-RAS patterns were observed more frequently in G/P failures (GT1a 80%: Y93H+Q30H/D or +H58D; GT3a: 83.3% Y93H+A30 K/G or +L31I) compared to SOF/VEL (GT1a 20%: Y93H+Q30H, p = 0.2; GT3a 22.2%: Y93H/N+A30 K/T, p = 0.04).



To date, 89 failures have started a retreatment: SOF/VEL ± RBV (N = 29), SOF/VEL/voxilaprevir (VOX) ± RBV (N = 54), G/P (N = 4), GRZ/EBV ± SOF+RBV (N = 2) (see figure). The majority of pts were cirrhotic (56.2%) and relapser (87.6%). The overall prevalence of NS5A-RASs before retreatment was 86.5%, with multiclass resistance in 29.2% of pts. Among those completing post-retreatment follow-up, a sustained viral response at week 12 (SVR12) was observed in 25/32 (78.1%). Among those with ongoing follow-up, SVR4 was documented in 46/53 (86.8%).
SVR12 was 76% with SOF/VEL ± RBV (N = 25) and 100% with G/P for 8/12/16 wks (N = 3) or GRZ/EBV ± SOF+RBV for 12/24 wks (N = 2) despite the presence of NS5A RASs.
Until now, 54 pts have been started SOF/VEL/VOX ± RBV retreatment for 12 wks. 48/54 (88.8%) showed at least one baseline NS5A RAS, 21/54 (38.8%) multiple NS5A RASs, and 38/54 (70.3%) multiclass resistance. Of 23 pts with available outcome, 95.6% had SVR4. Only 1 GT1b infected patient failed as non-responder, but RASs were not detected before retreatment.
Conclusion: In this real-life setting, NS5A-RASs were frequently detected at failure, and multiclass resistance was close to 30%. SVR4 data with the recommended retreatment regimen SOF/VEL/VOX ± RBV was >95%. Our results show how HCV resistance test at failure may be useful to optimize retreatment strategies.

THU-134
Clinical and virological characteristics of patients with chronic hepatitis C and failure to voxilaprevir/velpatasvir/sofosbuvir treatment

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Background and aims: Failure to treatment of chronic hepatitis C virus (HCV) infection with direct acting antivirals (DAAs) is rare and is associated with the selection of resistance-associated substitutions (RASs). For a retreatment, a DAA combination regimen consisting of a second generation NS3 protease (voxilaprevir) and NS5A inhibitor (velpatasvir) plus sofosbuvir is approved. Only limited data is available of single VOX/VEL/SOF treatment failures from the approval studies. This study investigated the characteristics of VOX/VEL/SOF failure patients in real world.
Method: Samples were obtained from resistance databases in Germany, Spain and Italy containing samples of overall 2530 DAA failure patients. Population sequencing of NS3, NS5A and NSB5 was conducted and RASs conferring a >2-fold increased DAA susceptibility were analyzed. Limited clinical parameters were collected retrospectively.
Results: Altogether ten patients had a virologic treatment failure to VOX/VEL/SOF. Eight patients were male (80%) with a mean age of 60 years (54-70). The majority of patients was infected with genotype (GT) 3a (n = 5, 50%), while two individuals had GT1a and three were infected with GT1b. A cirrhosis was detected in five patients and another patient had a HCC and liver transplantation. Regarding the previous treatment, seven patients failed to one DAA combination

treatment, further two individuals had received two subsequent DAA treatments and an additional patient even failed to three DAA regimens. All patients had a history of at least one NS5A inhibitor regimen and NS5A RASs were common prior to VOX/VEL/SOF retreatment (89%, n = 8/9; thereof Y93 variants in n = 6/9 with available data), while NS3 D168 RASs were not observed. After virologic failure to VOX/VEL/SOF for 12 weeks, the NS5A resistance profile was identical compared to before retreatment in most of the patients (89%, n = 8/9 with available data). However, NS3 D168 RASs reached moderate frequencies only (33%, n = 3/9 with available data). Regarding NS5B SOF RASs, L159F was observed in one GT1b individual before and after VOX/VEL/SOF failure, other NS5B RASs were not detected. One patient had no NS3, NS5A or NS5B RASs, neither before nor after VOX/VEL/SOF failure.

Conclusion: Failure to VOX/VEL/SOF was mainly observed in patients infected with genotype 3a, but also in those infected with 1a and 1b. NS3 and NS5B RASs were uncommon, while NS5A RASs were frequent with a resistance profile maintained from previous treatments.

THU-135

Real-world HCV treatment in HCV-HIV coinfected population: Data from the TRIO network

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N (%)	All 1452	Rx 734 (51%)	No Rx 718 (49%)	Rx Fill 641 (87%)	Rx no Fill 93 (13%)
Mean (SD), p value					
Age	53.4 (10.9)	53.7 (10.4)	53.1 (11.4), 0.254	54.4 (10.0)	49.1 (11.8), < 0.001
CCI	0.7 (1.1)	1.0 (1.2)	0.5 (0.9), < 0.001	1.0 (1.2)	0.7 (1.1), 0.017
BMI	26.6 (5.8)	27.3 (5.8)	25.9 (5.8), < 0.001	27.3 (5.9)	27.4 (5.1), 0.938
CD4	552.3 (313.7)	569.6 (305.1)	534.5 (321.5), 0.038	572.2 (302.7)	548.3 (325.3), 0.538
Follow-up, months	25.6 (7.4)	26.2 (7.1)	24.9 (7.6), 0.001	26.8 (6.7)	22.1 (8.4), 0.001
N (%), p value					
Male	1062 (73)	555 (76)	507 (71), 0.103	489 (76)	66 (71), 0.020
Race			0.007		< 0.001
Black	815 (56)	382 (52)	433 (60)	350 (55)	32 (34)
White	584 (40)	323 (44)	261 (36)	263 (41)	60 (65)
Other	53 (4)	24 (3)	29 (4)	28 (4)	1 (1)
Fib-4 > 3.25	211 (15)	110 (15)	101 (14), 0.619	97 (15)	13 (14), 0.771
Alcohol	122 (8)	72 (10)	50 (7), 0.051	57 (9)	15 (16), 0.028
Smoking	563 (39)	307 (42)	256 (36), 0.016	271 (42)	36 (39), 0.514
Drug use	690 (48)	361 (49)	329 (46), 0.200	313 (49)	48 (52), 0.616
Homeless	11 (1)	8 (1)	3 (0), 0.140	8 (1)	0 (0), 0.279
Cirrhosis (ICD-10)	166 (11)	113 (15)	53 (7), < 0.001	103 (16)	10 (11), 0184
N (%)	All 1452	Rx 734 (51%)	No Rx 718 (49%)	Rx Fill 641 (87%)	Rx no Fill 93 (13%)
HCV viral load, VR > 6MM IU (ML	474 (33)	195 (27)	279 (39), < 0.001	166 (26)	29 (31), 0.281
HIV VR < 200 (ML	602 (41)	345 (47)	257 (36), < 0.001	307 (48)	38 (41), 0.204
CD4 < 200 (MCL	158 (11)	65 (9)	93 (13), 0.012	53 (8)	12 (13), 0.141
Hypogonadism	48 (3)	35 (5)	13 (2), 0.002	30 (5)	5 (5), 0.768
HBV	30 (2)	18 (2)	12 (2), 0.296	15 (2)	3 (3), 0.606
Hypertension	685 (47)	347 (47)	338 (47), 0.939	302 (47)	45 (48), 0.818
Hyperlipidaemia	137 (9)	79 (11)	58 (8), 0.080	71 (11)	8 (9), 0.472
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Figure: (abstract: THU-0135)

Background and aims: Per AASLD-IDSA guideline, HCV treatment should be prioritized in HCV-HIV coinfected patients (pts). We evaluated access to direct-acting antiviral agents (DAAs).
Method: Trio Health HIV network consists of 10 treatment centres providing care for 34, 000 HIV pts from 50 states, DC, and Puerto Rico in the US. We evaluated and verified Rx for pts with HCV-HIV on HIV regimens in Jan 1, 2016-Oct 31, 2018 at 5 sites. Pts with < 6 months follow-up or on clinical trials were excluded. Subgroups were compared using descriptive statistics, predictors of Rx and fill were evaluated via logistic regression.
Results: Of 1452 pts, 51% were prescribed DAAs, of those prescribed 87% filled Rx, therefore 44% of the pts ultimately received a DAAs. Differences were found in characteristics of Rx and Fill groups (Table). Rx were more likely to smoke, have higher BMI, Charlson comorbidity index (CCI), cirrhosis, less control of HIV, less likely to be black; Fill were less likely to use alcohol, had lower ALT values, and longer follow-up.
Conclusion: Despite guideline recommendations, less than half of HIV-HCV coinfected pts on HIV Rx were treated for HCV. Unlike HCV monoinfected pts, once prescribed, coinfected pts do not appear to face significant access barriers to DAAs from payers and the key care access issue is under prescribing.

THU-136
Ledipasvir/sofosbuvir for 8 weeks cures genotype 4 chronic hepatitis C in non-cirrhotic children and adolescents

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Background and aims: Globally, it is estimated that 6 million children may be HCV viremic with at least 100, 000 viremic adolescents in Egypt and limited access to treatment. Shortening of DAA therapy is cost-effective and may improve access and adherence of children and adolescents to HCV therapy. Ledipasvir/sofosbuvir (LDV/SOF) for 8 weeks in real world clinical settings achieved sustained virological response at 12 weeks (SVR12) in adults with hepatitis C viral (HCV) genotype 1 and 4 infections. We aimed to evaluate the efficacy, defined as SVR12, of 8 weeks LDV/SOF in HCV genotype 4 pediatric and adolescent population in a real-world setting.
Methods: Forty three (M:F 27:16; median age 12.5 yrs; range 10-17 yrs) children and adolescents >12 and < 18 years or ≥ 35 kg (median: 35.0 kg; range: 35-70.0 kg) with HCV-RNA positivity for at least 6 months and no evidence of cirrhosis were consecutively enrolled to receive ledipasvir 90 mg/sofosbuvir 400 mg fixed dose combination single tablet daily for 8 weeks. All patients had their laboratory and HCV-RNA tests assessed before DAA therapy (baseline) and at 4, 8 and 20 weeks (SVR12) after starting treatment. Fibroscan was assessed at baseline and at 20 weeks.
Results: The median baseline ALT and AST were 40.0 (interquartile range: 28.0-55.0) IU/L and 34.0 (interquartile range: 29.0-48.0) IU/L respectively and HCV viral load 297, 000 (interquartile range: 84519-1, 060, 000) IU/ml. All patients had an HCV-RNA below detection limit (<15 IU/ml) at week 4, 8 and 20 with 100% SVR12. Median percent change of fibroscan was −5.26% (interquartile range: −14.49% to −2.86%). Four patients had a CAP score of S1-S2 (steatosis >10%, to ≤ 30%); all had normal CAP (S0) at week 20. No serious adverse events were reported while all patients/legal guardians reported improved activity and sleeping pattern. Following therapy, one child exhibited at least 40% improvement in neuropsychiatric manifestations reported by his physician while another recovered from long term severe myalgia and bone aches starting week 4.
Conclusion: Shortened LDV/SOF 8 weeks' therapy cured 100% of non-cirrhotic children and adolescents in a real-world clinical setting and could offer a cost-effective therapy protocol to improve access to treatment in this special population.

THU-137
DAA therapy in women of child bearing age: Accidental conception during therapy and pregnancy outcome

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Background and aims: The prevalence of HCV antibody and HCV-RNA among Egyptian females aged 15-59 years is 8.1% and 5.5% respectively. Treatment of women of childbearing age (WoCBA) should be prioritized to minimize the risk of mother to child transmission (MTCT). Although pregnant females are excluded from DAAs treatment protocols, a minority may accidentally become pregnant while on treatment despite vigilant contraception. We aimed to assess the pregnancy outcome in WoCBA with chronic HCV who accidentally got pregnant while receiving DAA therapy.
Methods: This retrospective study included 58059 females in the childbearing period (18-45 years) enrolled to receive DAA therapy through the national treatment program between October 2014 and March 2016. Patients were included according to the approved standard inclusion and exclusion criteria. Demographic, clinical and laboratory baseline data were collected in addition to, ultrasound assessment of the liver. Pregnancy test was done for all WoCBA before starting therapy.
Results: The mean age of the studied group was (37.16 ± 6.31 years), 93.1% were treatment naiive and 10.7% were cirrhotic. Sofusbuvir and daclatasavir with or without ribavirin was the main treatment regimen in this group (80.6%) with 96.7% sustained virological response. We report 11 of the WoCBA who commenced DAAs and discontinued treatment for accidental pregnancy. Seven women could be contacted and 4 were unreachable. They were all naïve patients with median baseline HCV viremia of 441500 IU/ml and all were treated with SOF/DAC regimen for 12 weeks; 6 discontinued therapy at week 4 while one discontinued SOF/DAC at week 8. The later was HCV-RNA negative and sustained virological response. Six of those women reported full term non interventional deliveries of normal weight newborns with no congenital anomalies. One woman reported postpartum hemorrhage and received blood transfusion. All seven infants were tested for HCV antibodies at 18 months, only one was positive with low viremia. All those women were advised to check HCV-RNA and restart treatment if proved positive.
Conclusion: WoCBA with HCV infection should be prioritized in the cascade of care and treatment, while more data on the safety of DAAs during pregnancy is required to prevent MTCT.

THU-138
High efficacy and improvement in CPT class with sofosbuvir/velpatasvir plus ribavirin for 12 weeks in patients with CPT C decompensated cirrhosis

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Background and aims: The ASTRAL-4 study demonstrated the efficacy and safety of sofosbuvir/velpatasvir plus ribavirin (SOF/VEL+RBV) for 12 weeks in patients with CPT B decompensated cirrhosis. The current study is the first to evaluate the efficacy and safety of SOF/VEL+RBV for 12 weeks in patients with CPT C decompensated cirrhosis.

Method: This was an open-label, single-arm study conducted in France and the US. Patients had CPT score 10-12 at screening and infected with any HCV genotype. Patients with a portosystemic shunt, variceal bleeding in the 6 months prior to screening, HIV or HBV co-infection, or HCC were excluded. All subjects were treated with SOF/VEL (400 mg/100 mg) and RBV (starting dose of 600 mg/day regardless of weight) for 12 weeks. The primary efficacy end point was SVR12. Safety end points included tolerability of the regimen.

Results: Of the 32 patients enrolled, 26 (81%) were male and 28 (88%) were treatment naïve. The mean age (range) was 55 (39-77) years. Eighteen patients (56%) had genotype 1, 5 (16%) had genotype 2, and 7 (22%) had genotype 3. Genotype could not be determined for 2 patients. At baseline, CPT score ranged from 8-13, with 9 (28%) and 23 (72%) having CPT B and CPT C cirrhosis, respectively. MELD scores ranged from 10-25, with the majority (19 patients, 59%) having scores >15. SVR12 was achieved in 78% of patients (25/32), with no virologic failures. Among those who did not achieve SVR12, 1 discontinued study drugs on Day 17 due to coadministration of amiodarone for an SAE of ventricular tachycardia that was considered unrelated to study drugs, and 6 others died due to AEs expected in a population with advanced liver disease, including liver failure, sepsis, and variceal hemorrhage. Three patients received a liver transplant during the study. Among the 21 patients who achieved SVR12, who did not receive a liver transplant and who had CPT score evaluated, 48% (10/21) improved in CPT class from baseline to post-treatment Week 12. SOF/VEL+RBV was well-tolerated with no Grade 3-4, SAEs, or deaths considered related to study drugs.

Conclusion: This study demonstrates that treatment with SOF/VEL+RBV for 12 weeks was well tolerated and resulted in high rates of SVR12 that were associated with clinical benefit, as measured by improvement in CPT class. The high rates of mortality and liver transplant are consistent with the advanced liver disease of patients with CPT C cirrhosis.

THU-139

Real world experience of chronic hepatitis C retreatment with genotype specific regimens in non-responders to previous interferon-free therapy

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Background and aims: The development of interferon (IFN)-free all-oral regimens substantially improved efficacy of antiviral treatment for HCV, but despite excellent effectiveness the failures still occur. The aim of our study was to evaluate the efficacy of retreatment with genotype specific direct acting antivirals (DAA)-based regimens in non-responders to previous IFN-free therapy.

Method: Studied population consisted of 31 non-responders to IFN-free regimen, which received second IFN-free rescue therapy, selected from 6228 patients included in a large national database EpiTer-2.

Results: Age, gender and genotype distribution in the studied group were similar to the whole population, but patients included in this analysis demonstrated much more advanced fibrosis. Primary therapy was discontinued in 12 patients, which were recognized as non-virologic failures, whereas virologic failure was recognized in 19 patients which completed therapy. Overall SVR rate was 81% and 86% in intent-to-treat (ITT) and modified ITT analysis, respectively (74% and 78% in virologic failures, 92% and 100% in non-virologic failures). There were no significant differences in SVR rate after the rescue therapy related to the type of administered primary or rescue regimen. All non-responders to rescue therapy were cirrhotics resulting with SVR of 62% in virologic and 89% in non-virologic failures, whereas SVR rate in non-cirrhotics achieved 100%. Resistance associated substitutions (RAS) testing was carried out in 8 virologic non-responders and three of them had potential risk for failure of rescue therapy due to NS5A association, but two of them finally achieved SVR.

Conclusion: Rescue therapy with genotype specific regimens can be considered in non-cirrhotics if more potent regimens are not available, but should be avoided in cirrhotics. RAS testing does not seem to be helpful to select optimal rescue therapy among genotype specific therapeutic option.

THU-140

Characteristics of patients and effectiveness of chronic hepatitis C treatment during the initial 4 years of access to interferon-free therapy

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Background and aims: Aim was to follow the profile and effectiveness of treatment in patients with chronic hepatitis C in real world experience during 4 years of access to interferon-free therapy
Method: Study included 8737 patients treated in Poland between 2015–2018 from the EpiTer2 database. Analysis was carried-out as an comparison of three periods A: 2015-2016 (n = 2879) with data published recently (J.Viral.Hepat.2018;25:661), B: 2017 (n = 3349), C: 2018 (n = 2509).
Results: Gender distribution was similar in periods, but we observed significant reduction of age (A:55 ± 13, B:53 ± 15, C:50 ± 15 years), overweight (A:62%, B:55%, C:52%), accompanying diseases (A:69%, B:67%, C:40%), concomitant medications (A:65%, B:63%, C:23%). Genotype 1b was predominant, but decreased from 87% to 78%. Increasing proportion of treatment naïve (A:47%, B:66%, C:84%) and F0-F2 fibrosis (A:35%, B:53%, C:76%) was noticed. We observed reduced number of cirrhotics (A:44%, B;26%, C:15%), decompensation history (A:7.6%, B:1.6%, C:0.8%), Child-Pugh >A (A:6.0%, B:3.0%, C:1.1%), MELD >15 (A:4.4%, B:3.8%, C:2.2%), history of liver transplantation (A:3.5%, B:1.3%, C:0.1%). During B/C periods more HIV coinfected patients were treated (3.9% vs 1.4% in A). Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (OPrDR) was the most frequent regimen untill 2017 (A:64%, B:44%, C:23%), followed by ledipasvir/sofosbuvir ± ribavirin (LSR; A:27%, B:38%, C:33%), but in 2018 the leading became grazoprevir/elbasvir ± ribavirin (GER; A:0, B:12%, C:36%). SVR of OPrDR (n = 3905) was higher (97%) than LSR (95%; n = 2402) and GER (95%, n = 1266). SVR of 96% in 6222 non-cirrhotics was significantly higher than in 2382 cirrhotics (92%). Pangenotypic regimens became available in mid 2018, administered to 273 patients, data will be available for presentation at the meeting.
Conclusion: Patients treated currently for HCV are younger and demonstrate less advanced liver disease compared to the beginning of interferon-free era. Effectiveness of novel regimens in this large real world study reached up to 97%.

THU-141

Efficacy and safety of elbasvir/grazoprevir in a large real-life cohort of HCV-infected patients

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Background and aims: The efficacy and safety of Elbasvir/Grazoprevir (E/G) among patients with Hepatitis C Virus (HCV) chronic infection have been mainly investigated in clinical trials, and scarce real-life data are available yet. The aim of the study was to investigate efficacy and safety of Elbasvir/Grazoprevir in a large Italian real-life cohort.
Method: All HCV-infected patients consecutively treated with E/G within the Lombardia-Veneto web-based NAVIGATORE HCV Network were analysed. E/G was administered for 12 or 16 weeks, usually according to drug label. Fibrosis stage was determined histologically or non-invasively, through liver stiffness measurement (LSM). Sustained Virological Response 12 (SVR12) was defined as undetectable HCV-RNA 12 weeks after the end of treatment (EOT).
Results: Between 4/2017 and 7/2018, 1799 patients (47, 6% male, mean age 61 yrs) were treated with E/G. Genotype (G) 1a, 1b and 4 were 14% (n = 258), 77% (n = 1380), 9% (n = 161), respectively. HIV co-infection in 7, 8%. Mean GFR 92.9 ml/min, CDK stages: 48.1%CKD1, 37.0%CKD2, 11.8%CKD3, 1.0%CKD4 and 2.1%CKD5. Cirrhotic patients were 19% (n = 312). Mean LSM, MELD, APRI was 10 kpa, 7.5, 0.9, respectively. SVR12 rate in both cirrhotic and non-cirrhotic patients was independent on Genotype, treatment duration, albumin level, PLT count, MELD, APRI, LSM, HIV co-infection, CKD stage and gender. Only in non-cirrhotic patients, SVR12 was influenced by mean baseline HCV viral load (3.987.778 IU/ml in non-SVR vs 2.104.418 IU/ml in SVR, p = 0.011). No treatment-related discontinuation was reported. Adverse events were reported in 1.1% in non-cirrhotic vs 2.2% in cirrhotic patients (p = 0.14). Results of the 1260 patients who have currently reached SVR12 are reported in the table.

Results of the 1260 patients who reached SVR12

	GT 1a		GT 1b		GT 4	
Schedule	12w	16w	12w	16w	12w	16w
No cirrhosis						
SVR12 n (%)	81/81 (100%)	75/76 (98.7%)	724/744 (97.3%)	9/9 (100%)	57/58 (98.3%)	24/24 (100%)
Overall	99.4%		97.3%		98.8%	
Cirrhosis						
SVR12 n (%)	20/21 (95.2%)	16/17 (94.1%)	206/211 (97.6%)	1/2 (50%)	10/10 (100%)	7/7 (100%)
Overall	94.7%		97.2%		100%	

Conclusion: in a large real-life Italian cohort of patients with HCV infection, virological responses and safety profile of E/G 12 or 16 weeks were excellent across G 1a, 1b, 4, and liver fibrosis stages. The complete SVR data will be available for ILC2019.

THU-142

Sofosbuvir + velpatasvir + voxilaprevir in DAA failure patients with cirrhosis: Final results of the French compassionate use program

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Background and aims: The combination sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is approved for 12 weeks as a single tablet, once daily regimen, based on the phase 3 POLARIS studies for HCV patients who failed with DAA-containing regimens. Few data from real-world cohorts exist. We report the efficacy and safety of SOF/VEL/VOX ± RBV in DAA failure patients with cirrhosis included in the French compassionate use program.

Method: A total of 46 patients (33 males; mean age 58.7 years) were treated with SOF/VEL/VOX with RBV for 8 (n = 1) or 12 weeks (n = 9) or SOF/VEL/VOX for 12 weeks without RBV (n = 36). Patients were chronically infected with HCV genotype 1 (1a n = 10; 1b n = 3; 1e n = 2), 2 (n = 4), 3 (3a n = 17; 3b n = 1), 4 (n = 8), 5 (n = 1) and 41 had cirrhosis (Median FibroScan 16 kPa, [13.5-24.9]). Among the 46 patients, 3 were liver transplant recipients, and 5 were co-infected with HIV. Previous treatment was SOF/LDV (n = 16), SOF/DCV (n = 23), 2D/3D (n = 5), GZR/EBR (n = 2). Baseline resistance testing was performed in 39 (85%) patients and NS5A, NS3, and NS5B RASs were present in 34, 8, and 0 patients, respectively.

Results: All patients (n = 44) who achieved the end of treatment had undetectable HCV RNA. Among the 44 patients with available results at SVR4 and SVR12, SVR4 and SVR12 were observed in 43 (97.7%) patients and in 42 (95.5%) patients, respectively. Two patients (genotype 1a and 3a) experienced a relapse at SVR12. At baseline, Y93H was observed in the genotype 3a patient and, both NS3 and NS5A RASs were identified in the genotype 1a patient. Resistance testing at the time of the relapse is pending. To date, 3 serious adverse events were reported in 2 patients. One liver decompensation, and one HCC were reported in one patient with Child B8 score at the initiation of antiviral treatment. One HCC was observed in one patient classified Child A6 at baseline.

Conclusion: In a real-world cohort, the combination SOF/VEL/VOX ± RBV for 12 weeks is effective in patients with cirrhosis who failed with DAA combination containing 1st generation NS5A inhibitor and/or protease inhibitor. This strategy is safe in patients with compensated cirrhosis

THU-143

High effectiveness of elbasvir/grazoprevir treatment in patients with HCV genotype 1a infection in German real-world: Results from the German hepatitis C registry (DHC-R)

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Background and aims: For treatment of HCV GT1a infection with EBR/GZR German guidelines recommend a differentiated approach depending on baseline viral load (BVL). For low BVL ≤ 800, 000 IU/ml treatment with 12 weeks EBR/GZR should be considered, whereas for high BVL >800, 000 IU/ml a 12 weeks regimen of EBR/GZR is only recommended in the absence of NS5A RAS. In the presence of NS5A RAS or when RAS-testing is not available, treatment with EBR/GZR + ribavirin (RBV) for 16 weeks is preferred. Therefore, the present analysis investigated the adherence to these recommendations and the real-world effectiveness of EBR/GZR regimens in a large GT1a cohort of the German Hepatitis C Registry.

Method: From 09/2016 until 07/2018, 992 patients (pts) with GT1 infection were treated with EBR/GZR ± RBV for 12 to 16 weeks in 130 medical practices and hospital outpatient departments in Germany. The present analysis was restricted to 195 pts with GT1a infection who completed follow-up. The primary outcome was per protocol sustained virologic response at 12 or 24 weeks post treatment (SVR12 or SVR24).

Results: 88 pts (45%) with low baseline viral load (BVL) ≤ 800, 000 IU/ml and 107 pts (55%) with high BVL >800, 000 IU/ml showed comparable characteristics: mean age 49 vs. 51 years, female gender 30 vs. 33%, cirrhosis 22 vs. 17%, opioid substitution 26 vs. 24%, HIV co-infection 11 vs. 10% and treatment-naïve 74 vs. 70%. RAS at baseline were tested in 49% vs. 42% of pts with high/low BVL. 4 pts with high BVL (8%) and 2 pts with low BVL (5%) had NS5A RAS of which 50% were treated with EBR/GZR+RBV, respectively. In total, 65% of GT1a pts with high BVL and 94% of pts with low BVL were treated with EBR/GZR in the absence of RBV. Per protocol SVR rates stratified by low vs. high BVL were 85/86 (98.8%) vs. 97/102 (95.1%). All pts with NS5A RAS achieved SVR. When SVR rates were additionally stratified by age, pts with low BVL achieved high SVR rates across all age groups (table). Interestingly, in pts with high BVL younger than 50 years SVR was 100% but this rate decreased with higher age (table). A multivariate analysis will be presented to investigate the significance of these findings.

	SVR Rates, n/N (%)		
	Age < 50 years	Age 50-70 years	Age > 70 years
GT1a ≤ 800, 000 IU/ml	43/43 (100)	40/41 (97.6)	2/2 (100)
GT1a > 800, 000 IU/ml	46/46 (100)	46/49 (93.9)	5/7 (71.4)

Conclusion: In German real-world, 94% of GT1a infections with low BVL and 65% with high BVL are treated with EBR/GZR for 12 weeks. SVR rates are consistently high. While a decrease in SVR rates in pts with high BVL >800, 000 IU/ml can be observed, this seems to be limited to pts older than 50 years. Pts younger than 50 years achieve SVR rates of 100% independent of BVL.

THU-144

Ledipasvir/sofosbuvir for 8, 12, or 24 weeks is safe and effective in patients undergoing dialysis

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Background and aims: Approved HCV treatments for patients on dialysis are associated with complexities including drug-drug interactions, baseline resistance testing, use of ribavirin, and risk of hepatotoxicity. Despite higher concentrations of the primary circulating sofosbuvir (SOF) metabolite, GS-331007, in severe renal impairment, real-world case series demonstrated substantial use of SOF-based regimens in this population with no safety concerns identified. This study evaluated the safety, efficacy, and pharmacokinetics (PK) of ledipasvir (LDV)/SOF for 8, 12 or 24 weeks in patients with HCV infection on dialysis.

Method: Treatment-naïve or interferon-experienced patients, with or without compensated cirrhosis undergoing hemodialysis or peritoneal dialysis, were enrolled to receive open-label LDV/SOF (90 mg/400 mg daily) fixed-dose combination once daily. Eligible patients had HCV genotype 1, 2, 4, 5, or 6 infection. Treatment-naïve patients without cirrhosis infected with HCV genotype 1 received treatment for 8 weeks, patients with cirrhosis received treatment for 24 weeks, all other patients received 12 weeks of treatment. The primary efficacy end point was the proportion of patients with sustained virologic response 12 weeks after treatment (SVR12). The primary safety end point was the proportion of patients who discontinued therapy due to adverse events (AEs). Secondary end points included safety, viral resistance, and PK.

Results: 95 patients were enrolled at 21 sites in Taiwan, Italy, Germany, the USA, and Belgium. The median age was 61 years (range 32-84), 59% were male, 64% Asian, 22% treatment-experienced, and 20% had cirrhosis. Most patients had HCV genotype 1 (72%) or 2 (22%) infection. Most (92%) were on hemodialysis with a mean (range) dialysis duration of 11.5 years (0-43). Treatment was well tolerated; there were no discontinuations due to AEs. To date, 87/95 (92%) of patients achieved SVR12; with no virologic failures. Four (4%) patients died during therapy, two (2%) additional patients died during the posttreatment period after achieving SVR4, and two (2%) patients achieved SVR4 but have not yet attended their post-treatment week 12 visit. None of the deaths were considered related to LDV/SOF. The most frequent AEs were muscle spasms (13%), nasopharyngitis (12%), and headache (8%). Serious AEs (SAEs) occurred in 13% of patients, none was assessed as related to LDV/SOF.

Conclusion: Treatment with LDV/SOF single tablet regimen in patients with and without cirrhosis undergoing dialysis resulted in a 92% SVR12 rate with no virologic failures. The regimen was safe and well-tolerated with no treatment related discontinuations or treatment-related SAEs.

THU-145

High real-world effectiveness of elbasvir/grazoprevir in a HCV genotype 1 population with a migration background and predominant subtype 1b infection: Results from the German hepatitis C registry (DHC-R)

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Background and aims: Approximately 71 million individuals worldwide are chronically HCV-infected. Dependent on the geographical area stark differences regarding prevalence and genotype/subtype distribution can be observed. With an increasingly interconnected world due to migration, infectious diseases such as HCV do not remain geographically isolated. Therefore, the aim of the present study was to investigate the proportion of GT1 patients (pts) with a migration background undergoing treatment with EBR/GZR in a German real-world setting and to estimate its effectiveness in this patient population.

Method: From September 2016 until July 2018, 992 pts with GT1 infection were treated at the physiciańs discretion with EBR/GZR ± ribavirin (RBV) for 12 to 16 weeks in 130 medical practices and hospital outpatient departments. The present analysis was restricted to 613 pts who completed 12 or 24 weeks of follow-up or discontinued the treatment early; the demographic data are shown for this ITT population. Sustained virologic response (SVR) data were available and are shown for 599 patients (Per Protocol (PP) population).

Results: From the overall 613 pts, 360 (59%) were German natives and 253 (41%) had a migration background. Among the migrants, pts from the former Soviet Union (GUS countries) represented the largest population (51%). Demographics of native Germans, all migrants, and migrants from GUS countries differed markedly: mean age was 58 vs. 50 vs. 48 years, GT1b 58 vs. 81 vs. 91%, elevated gammaGT 59 vs. 49 vs. 45%, cirrhosis 19 vs. 16 vs. 12% and co-morbidities 90 vs. 84 vs. 78%, respectively. EBR/GZR treatment was used without RBV in 93 vs. 94 vs. 99% of pts and EBR/GZR+RBV in 7 vs. 6 vs. 1%, respectively. PP SVR was 97.7% in German natives, 99.2% in all migrants, and 99.2% in migrants from GUS countries. SVR rates according to GT1 subtypes and treatment regimens are summarized in the table.

	German natives	All Migrants	Migrants from GUS countries
PP SVR-n/N (%)			
Total	347/355 (97.7)	242/244 (99.2)	125/126 (99.2)
GT1a	141/147 (95.9)	43/43 (100)	11/11 (100)
GT1b	203/205 (99.0)	198/200 (99.0)	114/115 (99.1)
EBR/GZR	323/330 (97.9)	229/231 (99.1)	124/125 (99.2)
EBR/GZR + RBV	24/25 (96.0)	13/13 (100)	1/1 (100)

Conclusion: 41% of GT1 patients treated with EBR/GZR in a German real-world setting have a migration background. These patients show a much higher frequency of GT1b infections than German natives. In the migrant population treatment with EBR/GZR based regimens yields high SVR rates of 100% in GT1a and 99% in GT1b infected pts. These results are comparable to the high SVR rates achieved in German natives of 96% in GT1a and 99% in GT1b. This data strongly suggests that treatment adherence is excellent in HCV infected migrants.

THU-146

LDV/SOF/RBV is an effective first-line DAA regimen as well as re-treatment option for RF1_2k/1b patients within Georgian national hepatitis C elimination program

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Background and aims: HCV RF1_2k/1b patientsmake up to 76.0% among HCV genotype 2 patients receiving care at the Georgian national hepatitis C elimination program. These patients are treated with either Sofosbuvir/Ribavirin (SOF/RBV) or Ledipasvir/Sofosbuvir/Ribavirin (LDV/SOF/RBV) since 2015 within this program. Our aim was to evaluate baseline and retreatment outcomes among HCV genotype 2 patients receiving HCV care within national hepatitis C elimination program.
Method: Study included 401 adult patients with HCV genotype 2 as determined by 5'UTR/Core genotyping assay. NS5B sequencing was also performed for genotype clarification. Confirmation of breakpoint positions among selected RF1_2k/1b patients was performed by whole genome sequencing. Study patients were treated with either Sofosbuvir/Ribavirin (SOF/RBV) or Ledipasvir/Sofosbuvir/Ribavirin (LDV/SOF/RBV regimens) from September, 2015 to August, 2018. Re-treatment was done with LDV/SOF/RBV for 24 weeks.
Results: Of total 401 patients enrolled 305 (76.1%) had RF1_2k/1b strain and 96 (23.9%) had HCV 2a, 2k, or 2c subtypes. Of total patients, 354 (88.3%) were males with a median age of 49.9 years (IQR-42.1-55.5%), and 88 (21.9%) had liver cirrhosis. As of August 2018, sustained virologic response (SVR) was available for 304 individuals. SVR rate was 97.3% (72/74) among genotype 2 and 89.1% (205/230) among RF_2k/1b patients (p = 0.05), with an overall SVR rate of 91.1% (277/304). Highest SVR rate was observed among patients treated with LDV/SOF/RBV among both genotypes (99.5%). For patients with cirrhosis SVR was 94.1% (16/17) among genotype 2 compared to 83.7% (41/49) among RF1_2k/1b (p = 0.43) patients. Among non-cirrhotic patients, SVR was 98.2% [56/57] among genotype 2 as compared to RF1_2k/1b (SVR 90.6% [164/181]) (p = 0.08). Statistically significant difference was observed in response rates among patients treated with SOF/RBV (94.4% for genotype 2 vs. 64.6% for RF1_2k/1b, p = 0.02). Among patients with RF1_2k/1b LDV/SOF/RBV had higher SVR rate (100% [147/147%) vs. SOF/RBV (SVR 64.6% [42/65], p < 0.0001). All 27 failing patients were re-treated with LDV/SOF/RBV for 24 weeks yielding SVR rate of 100%.
Conclusion: LDV/SOF/RBV was found to be highly effective both as first-line regimen as well as retreating option for HCVRF1_2k/1b patients within Georgian national hepatitis C elimination program.

THU-147

Improvement of neutrophil function in hepatitis C patients under direct acting anti-viral treatment is associated with hemolysis parameters

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Background and aims: Hepatitis C (HCV) patients were shown to have impaired neutrophil function, which increases their risk of bacterial infections and worsen their prognosis. We showed before that direct-acting anti-viral (DAA) treatment improves neutrophil function in these patients and influences hemolysis. HCV infection is associated with increased hemolysis. Our aim is to study if there is a relationship between changes in neutrophil function and hemolysis parameters.
Method: Neutrophil function parameters (phagocytosis (phagocytic capacity (PC) and non-phagocyting cells (NPC)) and respiratory burst (burst without stimulus-resting burst (RB), burst after stimulation with fMLP-priming (P), burst after stimulation with E.Coli-full burst)) and hemolysis parameters (hemoglobin (Hb), bilirubin (Bili), hematocrit, haptoglobin (Hapto) and heme) were obtained from 85 HCV patients (mean age 57 ± 11 years, 40% female) before, after 12 weeks and 12 weeks after DAA treatment. To study the relationship between parameters Spearman correlation with Benjamini-Hochberg correction, simple linear regression (SLR), linear mixed model (LMM) with likelihood ratio test (LR) and ROC curve analysis were applied. Results of analysis were independent of liver function, ribavirin treatment, presence of sustained virologic response, age and sex. The analysis was performed using R and SPSS Statistics 23.
Results: There was a negative partial correlation between Hapto and RB (GMFI and %) and P (GMFI) and positive partial correlation between Hb and PC at baseline. SLR showed significant associations of Hb and PC. LMM showed that the increase in Hapto was associated with an increase in PC, a decrease in RB (GMFI) and a decrease in NPC. ROC curve analysis showed that the changes in Hapto over time were predictive for the changes in NPC, RB (GMFI) and P (GMFI). Changes in Bili over time were predictive for the changes in RB (%) (Table 1).

	Partial correlation	LMM (LR)	ROC curve
HaptoandRB (%)	R = -0.218 p = 0.046		
HaptoandRB (GMFI)	R = -0.243 p = 0.026	χ2 (1) = 4.66 p = 0.031	AUC = 0.652 p = 0.050
HaptoandP (GMFI)	R = -0.234 p = 0.032		AUC = 0.664 p = 0.023
HaptoandPC		χ2 (1) = 5.65 p = 0.017	
HaptoandNPC		χ2 (1) = 4.59 p = 0.032	AUC = 0.692 p = 0.013
HbandPC	R = 0.262 p = 0.016		
BiliandRB (%)			AUC = 0.635 p = 0.034

Conclusion: Improvement in neutrophil function in HCV patients after DAA treatment was significantly associated with decreased hemolysis. DAA therapy therefore has beneficial effects beyond viral clearance.

THU-148

Variability of selected extracellular matrix proteins concentrations in HCV infected patients treated with sofosbuvir and ledipasvir

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Background and aims: It is known that in most of patients with chronic hepatitis C (CHC) successfully treated with antiviral therapy, reduction in liver stiffness is observed. However, there is lack of data assessing treatment-related changes occurring in the concentration of direct fibrosis biomarkers. Therefore, our study aimed to assess the levels of laminin (LN), hyaluronic acid (HA) and collagen type IV (Col IV) and transient elastography (TE) in patients with chronic hepatitis C treated with direct acting antivirals (DAA).
Method: A total of 52 patients were enrolled to this study. 42 patients with CHC were treated with sofosbuvir and ledipasvir (all achieved

SVR), 10 healthy volunteers formed control group. In all patients TE was performed at baseline (BL) and SVR24, and serum concentrations of laminin, hyaluronic acid and type IV collagen were determinated by ELISA at BL, End of Treatment (EOT), SVR24.

Results: Baseline **c**oncentrations of HA and Col IV were significantly higher (p = 0, 012, p = 0, 002) in cirrhotics, and LN was notably lower in the control group than in HCV infected patients (p = 0, 003). A significant decrease of HA, LN and Col IV at SVR24 was observed in cirrhotics (p = 0.005, p = 0.009, p < 0.001). In patients without cirrhosis significant increase of LN, HA, Col IV was observed at EOT. However, at SVR24 HA and Col IV decreased to BL level, only LN remained significantly higher than at BL.

Conclusion: DAA treatment changes the concentrations of LN, HA, Col IV and its dynamics depends on the severity of liver disease. Assessment of direct fibrosis biomarkers and liver stiffness may have prognostic value in the course of liver disease after achieving SVR.

THU-149

Efficiency and safety of direct acting antivirals in chronic hepatitis C patients infected with genotype 2 and 3 in Turkey

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Background and aims: Genotypes 2 and 3 chronic hepatitis C (CHC) patients are less frequently seen than genotype 1 in Turkey. While these genotypes have had favorable treatment outcomes with interferon-based regimens, response rates are lower with direct acting antivirals (DAAs).

We aimed to evaluate efficiency and safety of DAAs in CHC patients infected with genotype 2 and 3.

Method: Between April 2017 and September 2018, 37 centers recorded 2230 patients. All patients >18 years with CHC under DAAs were enrolled in this observational study. Those infected with genotype 2 and 3 were analyzed for end of treatment response (EoTR) and response at week 12 (SVR12).

Results: Among 2230 patients recorded into the database; 267 (12%) were infected with genotype 2 or 3, 73 (27%) were female and mean age was 41.7 ± 17 years (range 18-84 years). The genotypes were 3 in 189 (71%) and 2 in 78 (29%). 25 (9.4%) had cirrhosis; 24 had compensated (Child-Pugh A) and 1 had decompensated (Child-Pugh B-C) cirrhosis.

Liver biopsy was available in 151 (57%, G3: 107, G2: 44) patients; mean histologic activity index (HAI) was 7.4 and fibrosis score was 2.4. HAI was mild (1-6) in 37%, moderate (7-12) in 59%, and severe (13-18) in 4%. Fibrosis was mild in 49% moderate in 47%, and advanced in 4%. While 200 (79%) patients were treatment-naïve, 57 (21%) were previously treated with pegylated interferon+ribavirin: 74% relapse and 26% non-responder. Baseline viral load was 5.3 x10^6 copies/ml. Ledipasvir + Sofosbuvir, Ledipasvir + Sofosbuvir + Ribavirin and Sofosbuvir + Ribavirin were given to 8, 15, and 154 patients, respectively. The drugs were tolerated well. Severe adverse events were not reported. SVR was evaluated in 134 patients, shown in Table 1. Response rate at week 4 was 119/147 (81%), EoTR 143/144 (% 99.3%) and SVR12 128/134 (95.5%).

Drugs	G3	SVR12	G2	SVR12
Ledipasvir + Sofosbuvir	4/4	100%	1/1	100%
Ledipasvir + Sofosbuvir + Ribavirin	11/12	91.7%	3/3	100%
Sofosbuvir + Ribavirin	67/69	97%	42/45	93, 3%
Overall	**82/85**	**96.5%**	**46/49**	**93.9%**

Table 1. Direct Acting Antivirals and Response Rates in Patients Infected with Genotype 2 and 3 Chronic Hepatitis C.

Conclusion: This study represents the largest study of genotypes 2 and 3 CHC in Turkey. Genotype 3 is much commoner than genotype 2 (71% vs 29%). Rate of male gender was higher (73%) and mean age was 42 years. Liver histology showed moderate to higher activity in more than half of the patients and fibrosis was moderate to severe in half. Sofosbuvir and ribavirin containing regimens provided a SVR of more than 90%. The response rate in genotype 2 (94%) was lower than that in genotype 3 (96.5%). DAAs containing sofosbuvir and ribavirin have found efficient and safe among genotype 2 and 3 CHC patients in Turkey.

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THU-150

Factors associated with treatment failure with SOF+RBV in patients with genotype 2 chronic hepatitis C and consideration of retreatment with GLE+PIB in patients not responding to SOF+RBV

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Background and aims: This study aims to elucidate factors associated with treatment failure with sofosbuvir (SOF) + ribavirin (RBV) in patients with genotype 2 (GT2) chronic hepatitis C and to examine the efficacy and safety of glecaprevir (GLE) + pibrentasvir (PIB) as a retreatment regimen in patients not responding to SOF + RBV.

Method: 915 patients with GT2 chronic hepatitis C were treated with SOF + RBV in 24 nationwide centers of Japanese Red Cross Hospitals. By comparing data of patients who achieved sustained viral response at post-treatment week 12 (SVR12) with those with unsuccessful responses to the therapy (non-SVR12), we investigated factors associated with treatment failure. Regarding the treatment failure cases, the presence of NS5B resistance-associated variants was also examined. Next, we investigated the rates of SVR and side effects in patients who received GLE + PIB as a retreatment regimen.

Results: Of the 915 patients administered SOF + RBV, 34 were non-SVR12. Multivariate analysis revealed that “a history of interferon (IFN) treatment” (odds ratio: 2.97, $p < 0.005$) and “a history of hepatocellular carcinoma (HCC) treatment” (odds ratio: 7.27, $p < 0.0001$) were associated with non-SVR12. In 19 of the non-SVR patients, we were able to investigate the presence of NS5B resistance-associated variants at the time of treatment failure, but S282 T mutation was not detected in any of these patients. The mean age of 29 patients who underwent GLE + PIB therapy as a retreatment regimen was 67.7 years. Of the 29 patients, 21 were men and 14 had

genotype 2a. Advanced liver fibrosis was noted in many; 20 patients had FIB-4 index of 3.25 or higher. The duration of therapy was 12 weeks in all patients. At week 4 of therapy, serum hepatitis C virus (HCV) RNA levels were below the limit of detection in all patients (26/26). At the completion of the therapy, a negative HCV RNA status was achieved in all patients (21/21). The SVR4 rate was 100% (20/20), and the SVR12 rate 100% (13/13). No patient has had a relapse, to date. The side effects noted included itchy skin in 5 patients and fatigue in 3, all of which were mild in severity. There were no discontinuations of the therapy.

Conclusion: A history of IFN treatment and HCC treatment were identified as factors associated with treatment failure with SOF + RBV therapy in patients with GT2 chronic hepatitis C. However, the involvement of NS5B resistance-associated variants was not observed. GLE + PIB therapy as a retreatment regimen in patients not responding to SOF + RBV was considered to be safe and highly effective.

THU-151

Real-world effectiveness and safety of glecaprevir plus pibrentasvir in HCV: A multi-country analysis of postmarketing observational studies

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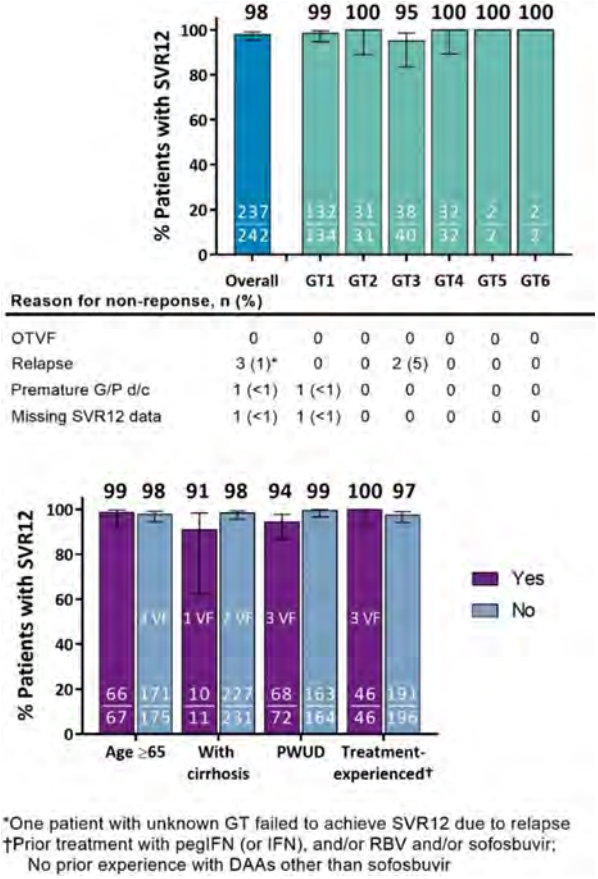
Background and aims: Across different countries, there is significant heterogeneity in DAA access and types of patients treated, thus real-world safety and effectiveness data in the era of pangenotypic regimens is crucial to better understand such treatment patterns. Here we report a pooled analysis across multiple countries of real-world effectiveness and safety from ongoing post-marketing observational studies (PMOS) using the recently approved, pangenotypic regimen of glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor; coformulated as G/P).

Method: Data were pooled from six countries (Austria, Belgium, France, Israel, Italy, and Switzerland) thus far participating in this prospective PMOS. Patients were receiving G/P at the treating physician's discretion according to local clinical practice, international recommendations and/or local label. Patients eligible for the PMOS had HCV GT1-6 infection, were HCV treatment-naïve or interferon, ribavirin and/or sofosbuvir-experienced, and either had compensated cirrhosis or were without cirrhosis. Cirrhosis status was most often assessed using transient elastography or non-invasive measures. Baseline characteristics and safety were summarized for all patients who received ≥ 1 dose of G/P. Effectiveness was assessed both overall and by subpopulations of interest as the percentage of patients achieving sustained virologic response (SVR) in all treated patients who have reached post-treatment week 12.

Results: Of 815 patients dosed, 89% were non-cirrhotic and 84% were treatment-naïve. As a result, most (86%) were assigned to 8-week G/P treatment, while 13% and 1% were assigned 12- or 16-weeks G/P treatment, respectively. Common prescribed and/or non-prescribed drugs included antithrombotic agents (9.2%), anxiolytics (8.3%), beta blocking agents (8.2%), antidepressants (8.0%), and drugs used in addictive disorders (7.2%). To date, for those reaching end of treatment and SVR12 visits, the SVR rates were 100% (546/546) and 97.9% (237/242; 3 virologic failures all due to relapse), respectively. SVR12 rates and reasons for non-response are reported both overall and by subpopulations of interest in the Figure. G/P was well-tolerated with no G/P-related serious adverse events (SAEs) and a low rate of AEs leading to premature G/P discontinuation (<1%). The most common AEs were fatigue (3%), asthenia (2%), headache (1%), and nausea (1%). Enrollment, treatment, and follow-up are currently ongoing.



*One patient with unknown GT failed to achieve SVR12 due to relapse
†Prior treatment with pegIFN (or IFN), and/or RBV and/or sofosbuvir; No prior experience with DAAs other than sofosbuvir

Conclusion: Effectiveness and safety of G/P in this study were consistent with that seen in registrational trials. Updated baseline characteristics, safety, and SVR data will be presented at the Congress to include all patients who have enrolled and reached SVR12 from these and additional enrolling countries.

THU-152

New in France: Universal access for HCV-treatment as demonstrated by a nationwide real-world cohort

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Background and aims: France is one of the first european countries engaged on HCV eradication. Since 2013, DAAs were initially prescribed to very severe patients (F3/F4, Liver transplant, HCV/HIV

co-infected), then extended to historically difficult to treat patients (GT3) and F2. In 2017 DAAs reimbursement was finally extended to all HCV-patients, including F0/F1.
HELIOS is a study cohort aimed to assess real-world effectiveness and safety of sofosbuvir-based therapy in patients with HCV chronic infection in France. Patients were recruited in two periods (Oct15-Jul16 and Oct17-Jul18). The analysis objective was to assess patient characteristics changes within 4 years and to put into perspectives therapeutic strategies as recommended by guidelines.
Method: 1020 HCV-patients who started SOF-based therapy were prospectively enrolled in a real-world cohort in 46 French centers. SVR12 was defined as HCV-RNA < 25 IU/ml 12 weeks after the end of treatment.
Results: Baseline characteristics were: mean age 55 ± 11 years, 60% male, 84% Caucasian, 23.1% F4, 23.4% F3, 11.5% HIV-HCV co-infected. 27.6% significant clinical medical history. SOF-based therapies distributed as follows: SOF/LDV ± RBV (n = 570), SOF+RBV (n = 22), SOF+DAC or SIM (49), SOF/VEL (379). The profile of HCV-patients treated in France between 2015 and 2018 has slightly evolved. HCV treatment experienced (39.2% to 22.7%), F0/F1 (39.5% to 55.6%), HIV-HCV co-infected (15.3% to 4.5%), extrahepatic manifestation (20.3% to 12.7%), illicit drug use (12.6% to 20.7%), excessive alcohol consumption (11.4% to 18.4%). Treatment discontinuation was reported on 6 patients: 2 lost of FU, 2 AEs not related, 2 AEs related to therapy (asthenia, general physical condition).On a per protocol analysis, total SVR12 was 98.5% (196/200 SOF/LDV, 140/140 SOF/VEL). No major safety issues were reported. The most common AE were asthenia (n = 71), headache (n = 49), nausea (n = 16), anemia (n = 14) and insomnia (n = 9). There was one treatment-emergent AE leading to death (hepatorenal syndrome).
Conclusion: This analysis demonstrates that the profile of HCV-patients treated in France has changed between 2015–2016 and 2017-2018 driven by treatment access recommendations. All patients have now access to potent pan-genotypic HCV-treatment. High SVR rates were reported with Sofosbuvir/Velpatasvir in this cohort. SVR were in accordance with clinical studies and other real-world cohorts. SOF-based therapy presented a favorable safety profile.

THU-153

Is sofosbuvir-based regimen safe and effective in hepatitis C virus-infected patients with stage 4-5 chronic kidney disease? A systematic review and meta-analysis

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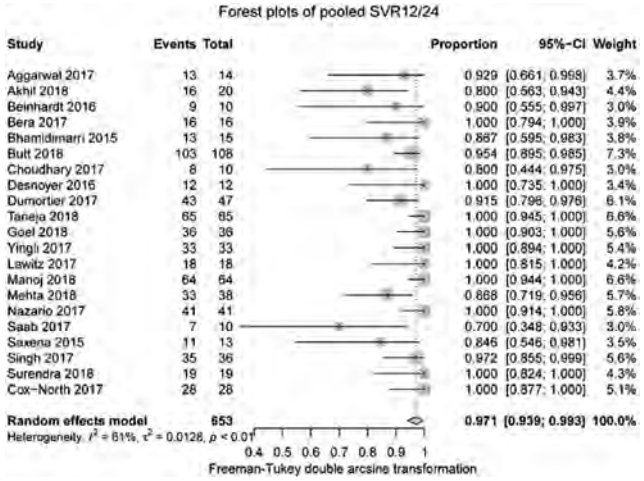
Background and aims: Whether sofosbuvir is suitable for hepatitis C virus (HCV) infected patients with severe renal impairment is inconclusive. The goal of the present study is to evaluate the safety and effectiveness of SOF-based regimen in the setting of stage 4 and 5 chronic kidney disease (CKD) by summarizing all available evidence.
Method: Two investigators independently searched PubMed, Web of Science, EMBASE and Google Scholar from inception through August 2018. Eligible studies were those that applied SOF-containing therapy to treat HCV infected patients living with comorbidity of stage 4 or 5 CKD (eGFR < 30 ml/min/1.73 m^2). SVR12/24 and SAE rate were aggregated via random effects model. The relative risk (RR) with 95% confidence interval (CI) was used to assess the impact of cirrhosis status to sustained virological response. Comparison was made between studies that adopted full dose and decreased dose of sofosbuvir in subgroup analysis.
Results: 21 studies with 717 patients (58.4% receiving dialysis) were included in the final meta-analysis. HCV genotypes ranged from GT1 to GT6 among these studies. GT1 was the predominant genotype (67%), followed by GT3 (20%) and GT2 (8%). 14 studies recruited cirrhotic patients, with varied proportion (11%-83%). SOF-based regimen included: SOF/LDV ± RBV, SOF+DCV ± RBV, SOF+SMV ± RBV, SOF+RBV, and SOF+PR, under different administration of sofosbuvir: 400 mg daily (full dose), 400 mg/48 h (decreased dose), 400 mg three times a week (decreased dose). Pooled SVR12/24 (per protocol) was 97.1% (95% CI 93.9%-99.3%, I^2 = 61%), and SAE rate was 4.8% (95% CI 2.1%-10.3%, I^2 = 60%). Patients with or without cirrhosis achieved comparable SVR12/24 (RR 0.93, 95% CI 0.85-1.02). There was no significant difference between studies applying full and decreased dose of sofosbuvir in terms of safety (SAE: 8.8% vs 2.9%, p = 0.13) and effectiveness (SVR12/24: 97.1% vs 96.2%, p = 0.72). 4 studies provided information about the kidney function before and after treatment. None of these studies reported significant change of eGFR/serum creatinine during treatment.



Conclusion: Our study suggests SOF-based regimen might be used safely and effectively in patients living with HCV infection/stage 4-5 CKD, with normal and reduced dose of sofosbuvir. Prospective and well-controlled trials are needed to confirm these findings.

THU-154

Low rate of hepatitis B reactivation among patients with chronic hepatitis C during direct acting antiviral therapy

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Background and aims: Hepatitis B Virus (HBV) reactivation has been reported in patients with chronic hepatitis C (CHC) with prior HBV exposure (HBsAg negative/anti-HBc positive) during direct acting antiviral (DAA) therapy. This led the US FDA to issue a black box warning on all DAA drug labels to recommend measuring HBV DNA and monitoring for HBV reactivation during and after treatment. Prior studies have looked at single time points either during or after treatment and may have underestimated HBV reactivation incidence. We aimed to conduct a more comprehensive evaluation of HBV reactivation with multiple time points during and after treatment.
Method: Patients with CHC from two North American sites were included who were treated with DAAs, had prior exposure to HBV (HBsAg negative/anti-HBc positive) and had sera from multiple time points pre-, during and post-treatment. Samples were tested for HBV DNA (Roche COBAS® Assay) and HBsAg at each time point. We defined HBV reactivation as detectable HBV DNA, if initially negative or quantifiable HBV DNA, if initially detectable (<20 IU/ml) ± HBsAg

seroreversion. We also evaluated the occurrence of ALT flares (≥2x ULN).

Results: Of 79 patients (44 at site 1; 35 at site 2), mean age was 62 years, 66% was male and 66% was Caucasian. Treatment regimens included LED/SOF ± RBV, SOF/VEL, SIM/SOF, SOF/RBV, PAR/RIT/OMB/DAS ± RBV for 12-24 weeks. Of 375 serum samples, 51 had insufficient volume to measure HBV DNA. Reactivation, observed in 8/79 (10%) patients, occurred in 6 at on-treatment week 4-8 and in 2 at off-treatment week 14/15 (Table). HBV DNA was detectable but < 20 IU/ml in 5 patients and quantifiable in 3, ranging from 33-184 IU/ml. An ALT flare or HBsAg seroreversion was not observed in patients with HBV reactivation. Detectable/quantifiable HBV DNA was transient in 4/8 while the duration could was unknown in 4/8 due to lack of follow-up samples but ALT flares did not occur in these patients.

Patient	HBV DNA (IU/ml)		
	Baseline	On-treatment	Off-treatment
1	Neg	Wk 4 < 20; Wk 12 < 20	Wk 14 < 20
2	Neg	Wk 4 Neg; Wk 8 Neg	Wk 15 33
3	Neg	Wk 4 < 20; Wk 8 Neg	Wk 13 Neg
4	Neg	Wk 4 Neg	Wk 1 Neg; Wk 14 < 20
5	Neg	Wk 4 52	Wk 2 Neg; Wk 17 Neg
6	Neg	Wk 4 < 20; Wk 8 184	
7	Neg	Wk 4 Neg; Wk 8 < 20	Wk 4 Neg; Wk 12 Neg
8	Neg	Wk 4 < 20; Wk 8 Neg	Wk 4 Neg; Wk 8 < 20; Wk 12 Neg

Figure HBV DNA results in patients with HBV reactivation.

Conclusion: The risk of HBV reactivation was low in CHC patients with recovered HBV. No ALT flares or HBsAg seroreversion was observed. These data suggest that monitoring for HBV reactivation among CHC patients undergoing DAA therapy is probably not warranted. We recommend only testing for HBV DNA in selected patients with ALT flares or failure of ALT normalization during DAA treatment.

THU-155

Polymeric, metallic nanoparticles, and curcumin as inhibitors of hepatitis C virus genotype 4a replication in vitro

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Background and aims: Despite the remarkable progress in treating HCV4a, there is still some serious concern on adverse side effects and viral resistance to treatment. Discovery of more effective and less toxic agents are still needed. In the current study, we evaluated the inhibitory effect of nanomaterials formulations and curcumin against replication of HCV4a in HCV-human hepatoblastoma cell line (huh7.5) harboring ED- 43/SG-Feo (VYG) replicon of HCV4a, both In *silico* and in vitro.

Method: Initial, *in-silico* screening using ligand-receptor docking against NS3 protease, NS5A and NS5B polymerase of HCV-4a with MolDock were done. The four materials with the highest antiviral activity; namely, chitosan, silver and gold nanoparticles (CNPs, AgNPs and AuNPs, respectively) as well as curcumin were used in the subsequent experiments. For the *in vitro* study, we treated the HCV Huh7.5 replicating system with the non toxic concentrations of all tested materials. The CC50 doses were determined using MTT assay and the efficacy concentrations (EC50) were also determined. The therapeutic index was calculated as CC50/EC50. Sofosbuvir (the polymerase inhibitor) was used as a positive control. Antiviral activity was evaluated by HCV real time RT-PCR and HCV core protein expression by western blot assay.

Results: MolDock showed binding affinity score with NS3 protease, NS5A and NS5B polymerase of −131.044, −149.498 and −133.494 for curcumin, −156.512, −131.875 and 154.603 for CSNPs, and −127.581, −167.192 and −131.535 for sofosbuvir, respectively. Chitosan nanoparticles were prepared with minor modifications (patent **1120-2018**) and was controlled to size of 29 nm and charges of 33 mV but AgNPs and AuNPs were controlled to sizes of 21.03 and 14.67 nm, with charges of −26.3 and −37.7 mV, respectively. Cytotoxicity assay by MTT revealed that CC50 concentrations were at 185 µg/ml, 50 µM, 300 µM for chitosan, silver, gold nanoparticles but was at 21.5 µg/ml and 50 µg/ml for curcumin and sofosbuvir compounds. We determined the EC50 of 15 µg/ml, 10.5 µM, 25 µM for chitosan, silver, gold nanoparticles respectively, but of 7 µg/ml and 5 µg/ml for curcumin and sofosbuvir respectively, as effective concentrations could dramatically inhibit HCV4a replication. HCV core protein expression ratio was at 0.79 ± 0.005, 0.87 ± 0.0042, and 1.16 ± 0.05 for CNPs, AgNPs and curcumin, respectively, but at 1.875 ± 0.04 for sofosbuvir versus positive infected cells of 5.66± 0.4. These data are the first description for CNPs and nanoparticles possessing antiHCV-4a activity.

Conclusion: Chitosan and silver nanoparticles showed desirable therapeutic index at 12.3 and 7 respectively that can be considered newly developed candidate for further drug delivery system and subjected to in vivo studies.

THU-156

Real world outcomes for Genotype 3 patients treated with glecaprevir/pibrentasvir: Real world outcomes from an unselected cohort

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Background and aims: Glecaprevir/Pibrentasvir (G/P) is a potent pan genotypic Direct Acting Antiviral (DAA). In registration trials SVR rates for GT3 were good, but did not match those of non-GT3 patients. Real world results are required to confirm efficacy amongst unselected patients, who may not meet rigorous clinical trial requirements. Clinician choice of DAA may introduce unexpected bias at a patient level in the context of other available GT3 regimens. In our treatment centres, in line with national guidelines, clinicians are restricted to prescribing a designated 1st line regimen unless there is an insurmountable drug -drug interaction (requiring independent review by a specialist pharmacist) eliminating physician choice as a confounder. In this context we sought to ascertain the real world outcomes of unselected genotype 3 patients receiving G/P.

Method: GT3 patients commencing G/P prior to 01/11/2018 in Glasgow treatment centres were identified from the Scottish HCV database. Data on age, gender, opiate replacement therapy (ORT) status, liver stiffness measurement (LSM)/fibrosis stage, prior treatment and HIV status were obtained along with treatment outcome. Fibrosis stage was defined by FIB-4 or LSM (F0-2), LSM (F3) and LSM, imaging or biopsy (F4) respectively.

Results: 382 patients met the inclusion criteria, 96 (25.1%) with advanced (F3/4) fibrosis, and 22 (5.8%) with prior treatment

(see figure for other baseline characteristics). Patients received 8/12/16 weeks of treatment in line with the license. To date, 270 (70.3%) have completed treatment, with low rates of premature discontinuation (2 (0.5%)). Of those reaching SVR12, 153/156 (98.0%) achieved SVR including 22 patients with cirrhosis (2 treatment experienced). Of the 3 not achieving SVR 2 relapsed and 1 died following completion of treatment. Further SVR data will be presented.

Baseline Characteristics	n = 382
Mean age (± SD)	45.7 (8.4)
Male (%)	269 (70.4)
HIV co-infected (%)	15 (3.9)
ORT (%)	200 (52.4)
Treatment experienced	22 (5.8) (19 IFN/RBV, 1 boceprevir/IFN/RBV, 1 Sof/Gras/Elb, 1 Sof/IFN/RBV
Fibrosis Stage	
F0-2	286 (74.9)
F3	24 (6.3)
F4	72 (18.8)
Mean LSM F0-3 (n = 298)	6.3 (1.9)
Mean LSM F4 (n = 70)	25.9 (15.4)

Conclusion: G/P is well tolerated in clinical practice, with low rates of premature discontinuation. Preliminary SVR results indicate a high efficacy amongst a GT3 cohort with significant rates of advanced fibrosis.

THU-157

Shortened duration pan-genotypic therapy with glecaprevir-pibrentasvir for six weeks among people with acute and recent HCV infection

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Background and aims: Glecaprevir-pibrentasvir for eight weeks is approved for treatment of chronic HCV infection in treatment-naïve individuals without cirrhosis. The aim of this study was to assess the efficacy of glecaprevir-pibrentasvir for six weeks in people with acute or recent HCV infection.
Method: In this open-label study conducted in Australia, New Zealand and England, adults with recent HCV (duration of infection < 12 months) received glecaprevir-pibrentasvir 300 mg/120 mg daily for six weeks. Primary infection was defined by first positive anti-HCV antibody (Ab) and/or HCV RNA within 6 months of enrolment and either acute clinical hepatitis within the past 12 months (symptomatic seroconversion illness or ALT >10x upper limit of normal [ULN]) or documented anti-HCV Ab seroconversion within 18 months. Reinfection was defined as new positive HCV RNA within 6 months of enrolment and evidence of prior clearance (positive anti-HCV Ab and negative HCV RNA on ≥ 2 occasions). The primary end point was sustained virologic response at 12 weeks post treatment (SVR12) with efficacy end points reported in the intention-to treat (ITT) and per-protocol (PP) populations.
Results: Thirty men (median age 43 years, 90% men-who-have-sex-with-men) received treatment, of whom 77% (n = 23) were HIV-positive, 33% (n = 10) had ever injected drugs and 13% (n = 4) had HCV reinfection. The majority were infected with HCV genotype 1 (80%, n = 24), followed by genotype 4 (10%, n = 3), 3 (7%, n = 2) and 2 (3%, n = 1). Median maximum ALT in the preceding 12 months was 381 U/L (range 26, 3087). Acute clinical hepatitis with ALT >10xULN was reported in 73%; five (17%) had jaundice. At end of treatment, HCV RNA was below the limit of quantitation in 97% (n = 29); one participant had quantifiable HCV RNA (21 IU/ml) and achieved SVR12. Of those who have reached post treatment week four (n = 28), SVR4 ITT and PP were 93% and 100%, respectively (loss to follow-up, n = 2). Of those who have reached post treatment week 12 (n = 24), SVR12 ITT and PP were 79% and 95%, respectively (detectable HCV RNA, n = 1; death after SVR4, n = 1; loss to follow-up, n = 3); sequencing is awaited to determine if recurrent viraemia represents relapse or reinfection. There were no treatment-emergent serious adverse events.
Conclusion: Shortened duration pan-genotypic therapy with glecaprevir-pibrentasvir for six weeks was highly effective among HIV-positive and HIV-negative individuals with acute and recent HCV infection.

THU-158

High efficacy of sofosbuvir and velpatasvir regardless of patients' clinical characteristics

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Background and aims: Second generation direct antiviral agents are characterized by very high SVR rates and good safety profiles. Real-life data are essential to further improve the care of the patients in our daily clinical practice.
Method: We conducted a prospective analysis of a representative Italian cohort involving untreated and previously treated patients with chronic HCV genotype 1, 2, 3, 4 or 5 infection, including those with compensated cirrhosis. The patient records were collected in the Department of Medical Science Gastroenterology Unit of the Molinette Hospital, University of Turin and we analysed the efficacy and safety of antiviral therapy under real-life conditions. All patients received the combination sofosbuvir (SOF) + velpatasvir (VEL) in a once-daily fixed-dose for 12 weeks. Of the 478 patients who received SOF+VEL treatment, 12.6% had HCV genotype 1a, 44.8% genotype 1b, 17.4% genotype 2, 17.2% genotype 3, 6.5% genotype 4 and 1% genotype 5. A total of 17.2% had cirrhosis, 31.4% had been previously treated for HCV and 78.5% had at least one comorbid condition.
Results: The primary end point was SVR at 12 weeks after the end of therapy. In 474 patients, we could document SVR12 data and found an overall SVR rate of 99.2% (470/474). All patients with HCV genotype 1a (61/61), genotype 4 (31/31) and genotype 5 (5/5) achieved SVR12. In HCV genotype 1b patients SVR rate was 99.5% (210/211), in genotype 3 and genotype 2 was 98.8% (79/80) and 97.6% (81/83), respectively. SVR12 rate was 97.5% in cirrhotic patients and 99.4% in non cirrhotic (p = 0.079). The great majority of patients (68.6%) was naive and they achieved SVR12 in 99.5% of the cases. The corresponding SVR rate in the subpopulation that had experienced a previous antiviral treatment was 98.6% (p = 0.416). SVR12 rates were not significantly different in patients with comorbidities (99.2%) and patients without any comorbid condition (99.0%, p = 0.873). Serious adverse events were reported in 10 patients (2.1%). No association between patients' characteristics and SVR was observed.
Conclusion: Treatment with SOF+VEL for 12 weeks provided high SVR rates in real-life conditions among both previously treated and untreated patients with HCV genotypes 1, 2, 3, 4, or 5, including those with cirrhosis or associated comorbidities.

THU-159

Real-world efficacy of elvasvir and grazoprevir for hepatitis C virus (genotype 1): A nationwide, multicenter study by the Japanese Red Cross Hospital Liver Study Group

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Background and aims: The purpose of this study is to determine the real-world efficacy and safety of the nonstructural protein (NS)5A inhibitor elbasvir (EBR) combined with NS3/4A protease inhibitor grazoprevir (GZR) in patients with hepatitis C virus (HCV) genotype 1 (GT1) infection in actual clinical practice.
Method: This study by the Japanese Red Cross Liver Study Group retrospectively evaluated the sustained viral response (SVR12) rate and safety of 12-week EBR/GZR treatment. This study also assessed factors associated with the SVR12 rate.
Results: Study patients included 159 men and 194 women with a median age of 72 years. Patient characteristics were as follows: 19.1% (67/351 patients) had a history of interferon therapy; 4.7% (16/342 patients) had a history of direct-acting antiviral (DAA) therapy; 20.5% (68/331 patients) had cirrhosis; 10.5% (37 patients) had a history of hepatocellular carcinoma treatment; 6.0% (18/297 patients) had an NS5A-L31 resistance-associated substitution (RAS) mutation; and 16.2% (48/297 patients) had an NS5A-Y93 RAS mutation. The overall SVR12 rate was 97.2% (343/353 patients). Treatment failure occurred in merely 2.9% (10/353 patients); however, eight of these patients had a history of DAA therapy, and the two other patients had NS5A-L31, -Y93 double RAS. The SVR rate was 50% (8/16 patients) in patients with a history of DAA therapy, and it was extremely poor, at 18.2% (2/11 patients), in patients with NS5A-L31, -Y93 double RAS. On multivariate logistic regression analysis, NS5A-Y93 RAS (odds ratio [OR] 19.6; 95% confidence interval [CI] 2.25-440.8; p = 0.0061) and NS5A-Y31 RAS (OR 114.8; 95% CI 14.74-2518.2; p < 0.0001) were identified as independent predictors of treatment failure. No serious adverse events were observed with EBR/GZR therapy, nine patients discontinued treatment due to complications such as liver disorders. Nonetheless, SVR was achieved in all patients who discontinued treatment.
Conclusion: The treatment outcomes of EBR/GZR were favorable in DAA-naïve patients, of whom 99.4% achieved SVR. However, the EBR/GZR response was poor in patients with a history of DAA therapy and NS5A-Y93, -L31 double RAS even when they were DAA-naïve. The SVR rate of EBR/GZR would have been 100% in patients with neither a history of DAA therapy nor a double RAS. This combination of drugs could also be given safely to patients and was, therefore, considered to be a highly useful first-line treatment for DAA-naïve patients with HCV.

THU-160

Outcomes of the national strategy on hepatitis C treatment with direct acting antivirals in a real-life setting: Results from a national survey in Slovenia

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Background and aims: Treatment of hepatitis C virus (HCV) infection with direct acting antivirals (DAAs) has proved excellent efficacy, as well in previously difficult to treat patients. In Slovenia, management of HCV infection has been organized systematically for over two decades with the second generation DAAs representing a standard of care since January 2015, at first restricted to patients with advanced liver disease and afterwards used with no restrictions. The aim of this study was to evaluate the strategy and efficacy of DAA treatment in a real-life setting at national level.
Method: All HCV-infected patients from Slovenia that started treatment with DAA combinations (simeprevir, sofosbuvir, paritaprevir/ombitasvir ± dasabuvir, sofosbuvir/ledipasvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir) between January 2015 and December 2017 were included prospectively on intention to treat (ITT) and modified ITT (mITT) analyses. Demographic, epidemiological, virological and clinical data were collected from all the hospitals performing HCV treatment in Slovenia and analysed.
Results: Overall, 383 patients were included, 67% were males, average age was 50 years. Among them, 45% reported intravenous drug use (IDU). Genotypes 1a, 1b, 1, 2, 3, and 4 were present in 34%, 32%, 2%, 3%, 26% and 3%, respectively. 18/383 (5%) were HIV coinfected. Fibrosis stage F3 was detected in 24% and F4 in 44%; 7% experienced Child-Pugh B or C decompensated cirrhosis and 8% presented hepatocellular carcinoma. 137/383 (36%) were interferon-based treatment experienced. Sustained virological response (SVR) rates were 90% (344/383) in ITT and 97% (344/354) in mITT analyses. In the latter, among those with no SVR, 9 patients experienced relapse and one was a complete non-responder; patients with genotypes 1, 1a, 2 and 4 presented 100% SVR, whereas those with genotypes 1b and 3 achieved 98% and 91% SVR, respectively; among patients with F3 and F4, SVR was reached in 99% and 97%, respectively; SVR was significantly more common in treatment naive (99%) compared to treatment experienced patients (94%) (CI = 99%, p = 0.0039); 97% of IDUs and 94% of HIV-positive patients gained SVR.
Conclusion: This study demonstrates excellent SVR rates of DAA treatment in a real-life setting in Slovenia achieved as a result of a national strategy and availability of new treatments which is in line with the global strategy towards viral hepatitis elimination.

THU-161

Baseline risk factors determine lack of biochemical response after SVR in chronic hepatitis C treated with DAAs: Results from the German hepatitis C registry (DHC-R)

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Background and aims: Elevated liver function tests (ALT, GGT) in chronic hepatitis C not always normalize after successful elimination of HCV by DAAs, indicating concomitant additional liver diseases. We analysed the factors determining biochemical response (normal ALT or GGT) of DAA therapy in a large real-world cohort.
Method: The DHC-R (German Hepatitis C-Registry) is a national multicenter real-world cohort including about 14, 500 patients recruited by more than 250 centers (approx. 90% physicians in private practice). Normal ALT (at 37°C) was defined as (i) ≤ 35 U/l for females and ≤ 50 U/l for males and or (ii) according to AASLD as ≤ 19 U/l for females and ≤ 30 U/l for males. Normal GGT (at 37°C) was defined as ≤ 40 U/l (female) and ≤ 60 U/l (male). Variables selected were HCV genotype (GT), sex, BMI, HIV coinfection, opioid substitution (OST), age, liver cirrhosis, alcohol, co-morbidities, co-medication, ethnicity, country of birth, HCV therapy. Statistical analysis was performed using univariate and multivariate logistic regression analysis.
Results: At baseline, we found elevated ALT in 3705/4946 (74.9%), elevated ALT (AASLD) in 4669/4946 (94.4%) and elevated GGT in 3018/4906 (61, 5%). 97% of patients achieved SVR12. At week 12 after end of therapy, we found elevated ALT in 451/4946 (9.1%) or ALT (AASLD) in 1906/4946 (38.5%) and GGT in 863/4879 (17.7%). A higher ALT at baseline was associated with HCV GT1 compared to GT3 (OR 2.42), male sex (OR 1.68), higher BMI (<18 vs 18-25 vs 25-30 vs >30; OR 2.04, 3.44, 3.25), liver cirrhosis (OR 1.90), being on OST (OR 2.13), being German vs. European or Russian (OR 1.46, 1.36). With the stricter ALT AASLD definition, liver cirrhosis and being of Russian origin dropped out and GT2 had a higher risk (OR 1.98). Higher GGT at baseline was associated with HCV GT3 and 2 compared to GT1 (OR 2.52, 1.37), higher BMI (<18 vs 25-30 vs >30, OR 1.84, 2.28), age >50 years (OR 1.28) and liver cirrhosis (OR 3.22).
At week 12 after end of therapy, a higher ALT was associated with higher BMI (<18 vs 18- < 25, 18- 25- < 30; OR 4.25, 2.91), age < 70 years (OR 1.54), liver cirrhosis (OR 2.55), alcohol consumption (OR 2.27) and non-SVR12 (OR 28.57). The same variables were selected using the AASLD criteria except age < 70 years, which fell out and a history of GT1a versus GT1b infection which was associated with a higher ALT (OR 2.56). Higher GGT at week 12 was associated with higher BMI, age > 70 years (OR 1.61), liver cirrhosis (OR 3.34), alcohol consumption (OR 3.83), non-SVR (OR 8.33). Co-medication, diabetes and HIV-coinfection were not identified as risk factors.
Conclusion: Successful HCV therapy can demask additional hepatic morbidities. In particular, risk factors already present at baseline like obesity, liver cirrhosis and alcohol consumption are associated with elevated liver function tests after SVR, indicating that these patients warrant further hepatological follow-up.

THU-162

The combination of sofosbuvir and daclatasvir is well tolerated and extremely effective in treating patients with hepatitis C with severe renal impairment including hemodialysis patinets

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Background and aims: Many of the treatments available for hepatitis C include sofosbuvir. Sofosbuvir has not been cleared for use in patients with eGFR under 30 ml/min leaving these group of patients with few options. Nevertheless, there are some reports in which patients with renal failure have been treated with sofosbuvir-containing regiments without any important adverse events. This study aims at determining the safety and effectiveness of a sofosbuvir-based treatment in patients with severe renal impairment.
Method: We enrolled subjects with severely impaired renal function infected with hepatitis C from 13 centers. Patients were treated for 12 weeks with a single daily pill containing 400 mg sofosbuvir and 60 mg daclatasvir (Sovodak, Rojan Pharma, Tehran, Iran). Patients with cirrhosis were treated for 24 weeks. Response to treatment was evaluated 12 weeks after end of treatment (SVR12).
Results: By the time of this report 79 patients had finished the follow-up period. 58 patients were on hemodialysis. 33 had cirrhosis, 8 decompensated. 40 were genotype 1 and 23 genotype 3. 22 patients had history of previous failed interferon-based treatment. Three patients died in which cause of death was not related to treatment. The remaining 76 patients all achieved SVR12.
Conclusion: The combination of sofosbuvir and daclatasvir is an extremely effective and safe treatment for patients infected with all genotypes of hepatitis C who have severely impaired renal function, including hemodialysis patients.

THU-163

Efficacy and safety of direct-acting antivirals for hepatitis C in elderly patients: a systematic review and meta-analysis

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Background and aims: Historically, age has been a major limitation of interferon-based antiviral therapy for hepatitis C. Since the introduction of direct-acting antivirals (DAAs) several studies have reported high efficacy and safety in elderly patients yet concerns were raised in some studies among different subgroups. Aim of this systematic review and meta-analysis was to assess and compare the efficacy and safety of DAA therapy among elderly (≥65 years or ≥ 75 years) and younger (<65 years or < 75 years) patients with chronic HCV infection.
Method: The PubMed MEDLINE and Embase databases were searched through July 2018. Two independent researchers extracted data and assessed quality and risk of bias. To account for different study populations between studies and heterogeneous study designs/protocols risk ratios for non-SVR (not mere SVR rates) were calculated and pooled using either fixed or random effects models, and group comparisons were performed. The primary outcome was efficacy of DAA therapy assessed by the RR for non-SVR among patients aged < 65 years vs. ≥ 65 years. This study was registered with PROSPERO (CRD42018104392).
Results: Overall, we identified 63 studies including 34, 082 patients treated with different DAAs. Risk for non-SVR was lower in patients ≥ 65 years of age (RR 0.91, 95% CI 0.83-0.99; p = 0.037) in the whole data set and in a subgroup analysis of cirrhotic patients (RR 0.54, 95% CI 0.36-0.82, p = 0.032). A trend towards a lower risk for non-SVR was observed in the elderly when applying age categories < 75 years vs. ≥ 75 years (RR 0.82, 95% CI 0.65-1.03; p = 0.086). Risk for non-SVR was

comparable between age groups in all other subgroup analyses including HCV genotype, treatment experience, therapy regimen or the additional use of ribavirin. Elderly patients (≥65 years) had a significantly increased risk of adverse events (RR 1.30, 95% CI 1.11-1.52, p = 0.001), but not for serious adverse events (p = 0.43) or treatment discontinuation (p = 0.15). Risk for anemia if treated with additional ribavirin was 2.84 (95% CI 1.73-4.66, p < 0.001) in elderly patients compared to patients < 65 years.

Conclusion: Our results show that DAAs are highly effective and safe in elderly patients. Ribavirin should be avoided in the elderly, as more AEs, and particularly anemia is observed. Further cost-effectiveness analyses are needed to evaluate the socio-economic benefit of treating elderly people without advanced liver disease.

THU-164

High cure rates of hepatitis C in a genotype 3 predominant Pakistani community using generic direct acting antivirals

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Background and aims: Pakistan Kidney and Liver Institute and Research Center (PKLIandRC) is running a 24-site Hepatitis Prevention and Treatment Program (HPTP) with government funding. The largest clinic in Lahore opened in March, 2017. Generic sofosbuvir (SOF) based regimens are used. Until daclatasvir (DCV) became available, Genotype (GT) 3, non-cirrhotics received SOF with ribavirin (RBV) for 24 weeks (w), while all GT-1 and only GT-3 cirrhotics were offered peg-interferon (peg)/SOF/RBV for 12w. GT testing was stopped with DCV availability. Patients are now treated with SOF/DCV ± RBV for 12w vs 24w depending on degree of fibrosis. Those with ≥ 3 months remaining on SOF/RBV were switched to SOF/DCV (cross over). We assessed rates of Sustained Virological Response (SVR) 12 and its predictors in HCV treated patients.

Method: All patients who received their last refill of SOF until April 30, 2018 were recruited from a single clinic. Those who either did not complete treatment or did not show up for SVR12 were excluded. A complete set analysis was run to assess SVR12 and factors potentially affecting it.

Results: SOF-based treatment was initiated on 5, 060 patients. 20% were cirrhotic (n = 1024) and 3% (n = 154) co-infected with hepatitis B. 80% (n = 4069) completed treatment and SVR12 was available on 73% (n = 3708). Among mono-infected patients, 26% (n = 913) received SOF/RBV, 45% (n = 1603) received SOF/DCV ± RBV and 2% (n = 84) received peg/SOF/RBV. 26% (n = 929) crossed over from SOF/RBV to SOF/DCV. The overall SVR12 was 97.5% with all regimens combined. SVR12 was higher in treatment naïve vs treatment experienced patients (98.1% vs 97.1%, p value 0.02) and in non-cirrhotics compared to cirrhotics (98.1% vs 95.2%, p value < 0.05). SVR12 for SOF/RBV, SOF/DCV and cross overs was 98.1%, 97% and 98.5% respectively. GT data was available in 1790 patients. SVR12 rates was not statistically significant based on GT, nor was it significant in those with and without GT data (GT-3 98.5% vs GT-1 97.6%, vs all others 100% p value >0.05, GT available 97.8% vs no GT 97.2%, p >0.05). Presence of DM lowered SVR12 rates (93.8% vs 97.9%, P value < 0.05), while age, HBV co-infection and HTN had no impact.

Conclusion: A large database of HCV patients, treated with generic SOF based regimen suggests high SVR12, even in the absence of GT testing at baseline when scaling up treatment, leading to cost-savings. Co-infection does not appear to impact cure rates.

THU-165

The risk of HBV reactivation among HBV/HCV co-infected patients treated with direct-acting antiviral agents: A single center experience

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Background and aims: As the number of reports of hepatitis B virus (HBV) reactivation increases in patients with HBV/HCV co-infection with direct-acting antiviral (DAA) agents, the US Food and Drug Administration has issued warnings about the potential risk of HBV reactivation in these patients. So far, there are very limited clinical data. We report the experience of DAA treatment in patients with HBV/HCV co-infection and factors affecting HBV reactivation during and after treatment with DAA.

Method: We conducted a retrospective observational study of 62 patients with HBV/HCV co-infection between January 2005 and April 2018 at the Pusan National University Hospital.

Results: Of the 62 patients, 25 patients were interferon (IFN) based therapy only, 15 patients were DAA alone, and 9 patients were DAA-treated after failure of IFN based treatment. SVR of IFN only treated group and DAA experienced group was 61.8% and 80.0%, respectively. The rate of HBV reactivation was higher in the patients with experience of DAA than the patients treated with IFN only (IFN only vs. DAA experienced 8.0% vs. 37.5%). In univariate analysis, HBV reactivation during or after anti-HCV treatment was more frequent in patients with experience of DAA (no vs. yes; 2 vs. 9, $p = 0.013$), in women (male vs. female; 3 vs. 8, $p = 0.037$) and in genotype 1b (1b vs. 2 vs. 3; 9 vs. 1 vs. 1, $p = 0.039$). The experience of DAA ($p = 0.016$) and women ($p = 0.020$) were significant predictors of HBV reactivation according to multivariate analysis. HBV reactivation was occurred at 50.5 weeks (range 4-173 weeks) from the start of anti-HCV treatment and time to HBV reactivation from the start of anti-HCV treatment was shorter in the DAA experienced group than IFN only treated group (157.5 ± 21.9 vs. 26.6 ± 27.7 weeks, $p = 0.036$). The mean peak elevation of ALT after HBV reactivation was 41.3 IU/L (range 11-113 IU/L), and the biochemical breakthrough did not occurred. At HBV reactivation, HBV DNA levels did not rise further and remained at similar levels or were not detected during 817 days.

Conclusion: HBV reactivation occurs more frequently in HBV/HCV co-infected patients who were treated with DAAs compared with IFN-based therapy. However, biochemical breakthrough was not occurred.

THU-166

Treatment of 320 genotype 3 cirrhotic patients with 12 weeks of sofosbuvir/velpatasvir with or without ribavirin: Real life experience from Italy

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Background and aims: Real life data on the treatment of HCV-related genotype 3 cirrhosis are needed to assess the efficacy of the combination Sofosbuvir and Velpatasvir (SOF/VEL). Indeed, the recent EASL recommendations define this combination as suboptimal in Genotype 3 patients with compensated (CPT A) cirrhosis. Starting from May 2017, 33 Prescribing-Centers Italy started to use SOF/VEL and collected data prospectively in a Network-database to explore the real life outcome of genotype 3pts with compensated cirrhosis treated with SOf/VEL+Riba.
Method: We retrospectively/prospectively analyzed the treatment outcome of **320 G3** patients, with compensated or decompensated cirrhosis.The pts were treated for 12weeks: 59, 8% with SOF/VEL and 40, 2% with SOF/VEL+RBV.

Figure

Baseline data

LSM (mean-SD)		APRI (mean-SD)		CTP=5		CTP>5	
RBV	No RBV	RBV	No RBV	RBV	No RBV	RBV	No RBV
24.0 (14.9)	19.9 (12.7)	2.7 (2.8)	2.0 (1.4)	59/121 (48.8)	62/121 (51.2%)	40/71 (56.3%)	31/71 (43.7%)

PLT <100.000		AGE (mean - SD)		Creatinina (mean - SD)		Albumin < 3,5 g/dl)	
35/71 (50.7%)	36/71 (49.3%)	52.6 (5.7)	53.9 (7.3)	0.78 (0.2)	0.88 (0.3)	15/29 (51.7%)	14/29 (48.3%)

Results of the 240 patients which have currently reached SVR 12

Schedule	Decompensation				CTP				Alb<3.5 & PLT<100.000					
	No		Yes		5		>5		no/no		yes/no		yes/yes	
	RBV	No RBV	RBV	No RBV	RBV	No RBV	RBV	No RBV	RBV	No RBV	RBV	No RBV	RBV	No RBV
SVR 12	62/66	63/64	10/11	6/6	47/51	58/58	32/34	20/23	7/7	7/9	18/18	19/20	50/56	57/60
p=	0.366		1.000		0.045		0.384		0.475		1.000		0.311	
SVR 12%*	93.9	98.4	90.9	100	92.2	100	94.1	87.0	100	77.8	100	95.0	89.3	95.0
Overall SVR	125/130 (96.1%)		16/17 (94.1%)		105/109 (96.3%)		52/57 (91.2%)		14/16 (87.5%)		37/38 (97.4%)		107/116 (92.2%)	
p=	0.528				0.277				0.333					

Results: Decompensated cirrhosis was present in 10, 2% of the pts (CHILD B). Baseline data are reported in table. No difference were observed between SOF/VEL and SOF/VEL+riba groups. 240 patients could be evaluated for SVR12. By ITT analysis, the overall SVR12 was 92, 4%. 5 pts discontinued for non liver-related causes; PP SVR is 96, 5%. No differences in SVR rates were observed by stratifying patients according to: platelets, albumin and creatinine. SVR 12 in CHILD > 5 pts (92.2%) were not statistically different from compensated patients (96, 3%) (p = 0.277) and among CPT > 5 pts were not statistically different from SOF/VEL (87%) and SOF/VEL+Riba (94.1%) (p = ns). Among CPT5 pts SVR 12 were statistically higher in SOF/VEL (100%) compared with SOF/VEL+Riba (92, 2%) (p = 0, 045).
Conclusion: In our cohort, the overall SVR12 in G3 patients with compensated cirrhosis is 96, 5% In patients with decompensated cirrhosis, the efficacy of SOF/VEL appears to be reduced in patients with both albumin < 3, 5 or PLT < 100.000. In these patients the use of ribavirin appears to improve the response rate but the size of the study population is too small to draw conclusions. Overall SOF/VEL is highly effective in genotype 3 patients with compensated cirrhosis.

THU-167

Prevalence, linkage to care and treatment of hepatitis C virus in person who inject drugs under opioid substitution therapy in a Spanish area

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Background and aims: PWIDs have high prevalence of HCV infection and limited access to health care, forming a risk group that explains most of transmissions. The treatment of PWIDs is a priority for the elimination of the HCV. Bitarte is the opioid substitution program that follows up all the methadone consumers in Guipuzcoa (Spain). The purpose of this project is to simplify the care circuit, approaching the resources to Bitarte, effectively treating the infection.
Method: All methadone consumers positive for HCV antibodies are monitored by the same psychiatrist. The hepatologist moves to the clinic, where a clinical assessment and a fibroscan are made. The antiviral therapy sent from the hospital pharmacy is dispensed together with the methadone by the nursery from de clinic, previously trained. We analyse prospectively the following outcomes: prevalence, genotype, viral load (VL), fibrosis degree, previous access to hepatologist, drug consumption, psychiatric comorbidity (before and after the treatment) and project effectivity (acceptance, efficacy, adherence and reinfections).
Results: Bitarte follows up 660 individuals in methadone program. 470 (71%) are HCV + antibodies. We excluded HIV coinfected (113) and individuals who lost contact with methadone programme in the last year (38). From the 319 HCV seropositive, 38.2% had never been examined by an hepatologist. Among those who had previously been examined, 68.1% failed in the follow-up. At current date, 146 have been treated and 1 refused treatment. 2 HCC have been diagnosed. The predominant genotype is GT1a (42%), followed by GT3 (29%). Regarding to fibrosis, 42% are F3 or F4. Before starting treatment, 38% have consumed heroine, 36% cocaine, 20% amphetamines and 50% cannabis in the last 6 months (measured in urine). We know the VL after treatment in 92 patients, all negative. 54 have reached the12th week after treatment with 1 relapser. Details of efficacy and adherence will be presented in the meeting.
Conclusion: 1) The HCV seroprevalence PWIDs in the north of Spain is 71%. 2) It is a population with a poor previous follow-up and advanced liver disease (F3-4). 3) The simplification of the care circuit

and the multidisciplinary team working is effective for the follow-up and treatment of this population.

THU-168

Real-life effectivness and safety of glecaprevir/pibrentasvir in HCV infected patients with chronic kidney disease

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Background and aims: Poor real-life data of Glecaprevir/Pibrentasvir (G/P) combination in the cure of HCV-infected patients with chronic kidney disease (CKD)are currently available. Aim of the present study was to evaluate the efficacy and safety of G/P in HCV-infected patients with CKD in a real-life scenario.
Method: Patients with compromised renal function (eGFR < 60 ml/min/1, 73m^2) were included. Sustained virologic response (SVR) was defined as an undetectable serum HCV-RNA after 12 weeks from end of therapy. An adverse event (AE) was defined as any unfavorable sign (including an abnormal laboratory finding) or symptom, during the drug administration and which does not necessarily have a causal relationship with treatment. If an AE caused death, hospitalization or therapy discontinuation, was defined as serious adverse event (SAE).
Results: Onehundredtwentytwo patients were enrolled: 30.3% had an end stage renal disease (ESRD), 46, 7% were male, median age 69 ± 13 yrs, 16, 4% were cirrhotics. Genotype 2 was the most frequent (53.3%), genotype 1b (33.6%), 3 (7.4%), 1a (4.1%), 4 (1.6%). Most of the patients (76.2%) were treated for 8 weeks. Currently107/109 reached a SVR (98.2%).There was no difference between ESRD patients and all the others (96.4% vs 98.8% p = 0.427). There were no virologic failures, 2 discontinuations for no drug-related SAEs. Thirteen pts reported pruritus as the most frequent AE and 3 SAE (death for car accident, jaundice and cryoglobulinemic syndrome) were reported. Full data will be shown at the EASL meeting.
Conclusion: Real-life G/P therapy confirms an excellent efficacy and safe profilein HCV-infected patients with CKD also in those with ESRD.

THU-169

Genotype 4 RAS patterns in a European hepatitis C cohort

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Background and aims: Worldwide approximately 20 million people are infected with a genotype (GT)4 hepatitis C virus (HCV). GT4 is highly variable, with 17 confirmed subtypes. It is the most common genotype in the middle east and norther-equatorial Africa, however, several cases have been observed in Europe. Although GT4 patients respond very well to direct-acting antivirals (DAA) in clinical trials, virological failure still occurs. Virological failure is often related to resistance associated substitutions (RAS). Due to the underrepresentation of GT4 in clinical trials and lack of real-life data, there is limited knowledge about RAS profiles. We used real-life GT4 data from the HepCare cohort (Hepatitis C antiviral therapy failure registry), to gather resistance data to assess the RAS at baseline and failure of European GT4 patients.
Method: We extracted data of patients with a GT4 confirmed HCV infection. Subtypes were provided by submitters and mostly based on in-house assays. As a quality control subtypes were re-assessed using the COMET tool. All sequences were aligned and trimmed to equal length with their reference strain using Aliview. We assessed RAS in the NS3, NS5A and NS5B at positions recommended by EASL guidelines and in addition identified all variation that occurred in paired (baseline -failure) sequences.
Results: We analysed sequences of 166 GT4 patients (80 baseline and 86 failures) of which five had paired baseline and failure samples. GT4 patients were submitted by five different European countries (Spain, Italy, Germany, Israel, and the Netherlands). The majority of the subtypes were *4d (77%)*, but also *4a (20%), k (1%), t (1%) and n (1%)* occurred in our cohort. NS3 baseline RAS are uncommon among all subtypes. However NS3-RASs at position 168 occurred in 22% of *4d* PI-failures. 80% of DAA failures have at least one NS5A RAS and 30% two or more (*4a/4d*). At baseline and failure, NS5A-polymorphisms at position 58 were frequent (56 and 58%, respectively) mostly in *4d*. In 5% of failures the E62Q/M RAS was detected, even though this RAS is not reported by EASL guidelines for GT4. In baseline NS5B sequences (n = 22) no RAS were detected, however, among failures the S282 T prevalence was 15% (n = 28).
Conclusion: GT4 has low numbers of baseline RAS, apart from polymorphisms at position 58. Almost all patients fail with at least one NS5A RAS, and potential new RAS at NS5A-position 62 was identified. Importantly, a high (15)% prevalence of the S282 T RAS at failure was detected among GT4 patients, which can challenge further retreatment with sofosbuvir.

THU-170

Real-world effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 4 infection: Results from a Veterans Affairs population

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Background and aims: Elbasvir/grazoprevir (EBR/GZR) administered for 12 weeks is a highly effective treatment option for patients with hepatitis C virus (HCV) genotype (GT) 4 infection, achieving sustained virologic response rates (SVR) of 96% in an integrated analysis of participants from phase 2 and 3 clinical trials. This study assessed the real-world effectiveness of EBR/GZR in patients with HCV GT4 infection.
Method: We conducted a nationwide retrospective observational cohort study of patients with chronic HCV GT4 infection in the US Department of Veterans Affairs. Patients were required to have received EBR/GZR with or without ribavirin (RBV) for ≥ 11 weeks, initiated between January 28, 2016, and August 31, 2017. Patients previously treated with an NS5A inhibitor-containing treatment regimen or undetermined regimens were excluded. SVR was defined as undetectable HCV RNA at ≥ 4 weeks after the end of treatment.
Results: A total of 125 patients were included, of whom 112 received EBR/GZR without RBV for 12 weeks and 13 received other EBR/GZR-based regimens. The majority were male (96.8%) and black (45.6%), and mean age was 62.4 years (SD, 5.2 years). Baseline viral load was < 800, 000 IU/ml in 51 (41%) patients, ≥ 800, 000 IU/ml in 67 (54%) patients, and unknown in 7 (6%) patients. The majority of patients (n = 119, 95%) were treatment-naive, of whom 62 (52%) had a

baseline viral load ≥ 800, 000 IU/ml and 9 (8%) had a baseline viral load ≥ 6, 000, 000 IU/ml. Overall, SVR was achieved by 123 of 125 patients (98%), with high SVR rates in the subgroups who received EBR/GZR without RBV for 12 weeks (110/112, 98%), who had diabetes (39/39, 100%), were receiving concomitant proton pump inhibitor therapy (38/38, 100%), with a baseline viral load ≥ 800, 000 IU/ml (66/67, 99%), or with cirrhosis (23/23, 100%). SVR rates among subgroups of patients with GT4 infection who received EBR/GZR without RBV for 12 weeks are shown in the Figure.

SVR rates in patients with GT4 infection

Baseline variable	EBR/GZR for 12 weeks N = 112	All patients N = 125
Treatment history, n/N (%)		
Treatment-experienced	2/2 (100)	6/6 (100)
Treatment-naive	108/110 (98)	117/119 (98)
Cirrhosis, n/N (%)	19/19 (100)	23/23 (100)
Baseline viral load, n/N (%)		
<800,000 IU/mL	48/49 (98)	50/51 (98)
≥800,000 IU/mL	56/57 (98)	66/67 (99)
<6,000,000 IU/mL	95/97 (98)	106/108 (98)
≥6,000,000 IU/mL	9/9 (100)	10/10 (100)
Unknown	6/6 (100)	7/7 (100)

EBR, elbasvir; GT, genotype; GZR, grazoprevir; SVR, sustained virologic response.

Conclusion: In this real-world population, EBR/GZR was highly effective in patients with HCV GT4 infection. SVR rates were consistently high regardless of treatment history, baseline viral load, advanced fibrosis, diabetes, or concomitant proton pump inhibitor therapy.

THU-171

Effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 1 infection receiving dialysis

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Background and aims: In the phase 3, placebo-controlled C-SURFER study, the combination of elbasvir and grazoprevir (EBR/GZR) was safe and highly effective in a population of participants with hepatitis C virus (HCV) genotype (GT) 1 infection and chronic kidney disease (CKD) stages 4-5, including those receiving dialysis. This study assessed the effectiveness of EBR/GZR in patients with HCV GT1 infection receiving dialysis in a large real-world clinical setting.
Method: We conducted a nationwide retrospective observational cohort study of patients with chronic HCV infection in the US Department of Veterans Affairs (VA). The study population included persons with chronic HCV GT1 infection who were receiving hemo- or peritoneal dialysis or with a diagnosis of end-stage renal disease identified by procedure and diagnosis codes in the VA Corporate Data Warehouse. Patients were required to have received EBR/GZR for ≥ 11 weeks, initiated between January 28, 2016, and August 31, 2017. Patients with acute kidney injury 1 year prior to treatment initiation or who had previously received an NS5A inhibitor-containing treatment regimen or kidney transplant were excluded. Sustained virologic response (SVR) was defined as undetectable HCV RNA at ≥ 4 weeks after the end of treatment.
Results: A total of 533 patients who received EBR/GZR for ≥ 11 weeks were included in the per-protocol population (cirrhosis, n = 239 [45%]; diabetes, n = 353 [66%]; depression, n = 294 [55%]; CKD 3, n = 16 [3%]; CKD 4-5, n = 486 [91%]). At baseline, the mean age was 64 years (SD, 4.99), and the mean estimated glomerular filtration rate was 16.4 ml/min/1.72 m^2 (SD, 59.7). Overall, SVR was achieved by 514 of 533 (96.4%) patients. SVR rates by GT1 subtype for various patient subgroups are shown in the Figure. Ninety percent of the patients received EBR/GZR without ribavirin for 12 weeks in this cohort. Of these patients, SVR rates were 281/290 (97%) in those with GT1a infection, 169/173 (98%) in those with GT1b infection, and 466/479 (97%) in those with any GT1 infection.

SVR rates in the per-protocol population

SVR	HCV genotype GT1a (n = 331)	GT1b (n = 182)	All (N = 533*)
All, n/N (%)	318/331 (96)	177/182 (97)	514/533 (96)
CKD stage 3	9/9 (100	7/7 (100)	16/16 (100)
CKD stage 4–5	293/305 (96)	57/162 (97)	468/486 (96)
History of alcohol abuse	151/158 (96)	91/93 (98)	261/270 (97)
History of drug abuse	157/163 (96)	85/88 (97)	253/263 (96)
Baseline viral load ≥800,000 IU/mL	179/186 (96)	82/86 (95)	270/282 (96)

CKD, chronic kidney disease; GT, genotype; HCV, hepatitis C virus; SVR, sustained virologic response.

*Includes 20 patients with unknown HCV GT1 subtype.

Conclusion: EBR/GZR was highly effective in patients with HCV GT1 infection receiving dialysis in the US VA population.

THU-172

It's the ribavarin, stupid: an analysis of >10, 000 hepatitis C treatment monitoring encounters and the factors associated with side-effects and non-adherence

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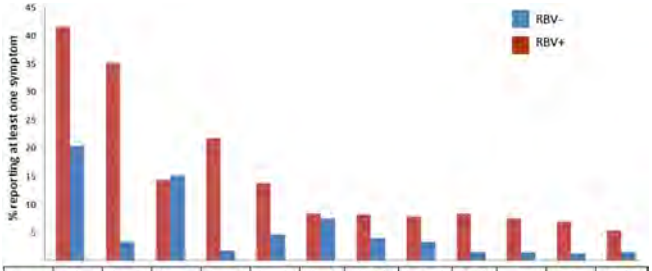
Background and aims: The England hepatitis C commissioning policy mandates selection of directly-acting antiviral (DAA) treatments for hepatitis C by lowest cost. This has pseudorandomised treatment such that the impact of different DAA regimens on side-effects and adherence between large, otherwise well-matched cohorts can be compared.
Method: We analysed 10273 treatment monitoring episodes in 1793 hepatitis C patients treated with DAAs at The Royal Free Hospital between July 2015 and July 2018. Reported side-effects were categorised into 58 symptoms and rated on severity. The frequency and severity of side-effects were compared across ribavarin (RBV)-containing and non-RBV DAA regimens. The impact of RBV, DAA regimen, age, gender, disease-stage, treatment-experience, daily dosage frequency and route of transmission was assessed on side-effects, adherence and treatment outcome by separate multivariate analyses (MVA).
Results: RBV-inclusive regimens were associated with between a 2 to 11-fold increased risk of 10 of the 12 most commonly reported side-effects (Figure 1). The addition of RBV to Sofosbuvir-based regimens also increased the mean severity score of symptoms (1.036 vs 1.523, p = 0.01). The use of RBV was the only parameter associated with both significant side-effects during treatment and non-adherence on MVA of the parameters above. The total frequency of side-effects during treatment was independently associated with non-adherence on MVA, as were the specific side-effects of insomnia and nausea. Importantly, we also found documented non-adherence was associated with an increased risk of failing to achieve SVR 12 (OR = 2.009, P = 0.0384). Significant differences in side-effect frequency were seen between RBV-free DAA regimens but these did not seem to impact on adherence.



Symptom	Fatigue	Anaemia	Headache	Dyspnoea	Insomnia	Nausea	Abdo Pain	Low mood	Dry Skin	Rash	Pruritus	Irritability
Relative Risk RBV+	2.05	10.28	0.94	11.7	2.846	1.121	2.069	2.299	All dermatological 5.113			3.473
P-value	<0.0001	<0.0001	ns	<0.0001	<0.0001	ns	0.0003	<0.0001	<0.0001			<0.0001

Conclusion: Adherence is of increasing importance as we treat increasing numbers of difficult-to-engage patients in community settings. These data clarify the markedly increased side-effect burden of RBV-inclusive compared with RBV-free regimens and show how this impacts significantly on adherence whilst controlling for multiple other factors.

THU-173

Sofosbuvir based anti-HCV therapy: Safe in hemodialysis

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Background and aims: The prevalence of hepatitis C among patients undergoing hemodialysis for end stage renal disease (ESRD) is much higher than the general population, ranging from 1-84.6%, with 38% being the figure for patients in Pakistan. It contributes to significant morbidity and mortality if left untreated. Sofosbuvir is an essential component of anti-HCV therapy available worldwide and assessing its safety in this population is vital.
Method: 23 patients undergoing regular hemodialysis for ESRD with HCV infection and not candidates for renal transplantation within the following 6 months, were included in the study. All patients received sofosbuvir 400 mg once daily, used in different combinations with daclatasvir, ledipasvir and ribavirin (ribavirin was used in fixed dose of 400 mg on alternate days). The duration of treatment was 12 to 24 weeks, depending on state of liver disease, previous treatment history and combination of DAAs used. All patients underwent check-up of viral response at end of treatment and 12 weeks after completion of therapy.
Results: 23 patients, 18 male and 5 female, average age 41.5 ± 14.5 years, were enrolled. All patients were undergoing hemodialysis two to three times per week. 21 (91.3%) were GT 3 and 2 (8.7%) GT 1. 8 (34.7%) patients had liver cirrhosis (5 Child A, 3 Child B). 3 (13%) were previous relapsers to sofosbuvir plus ribavirin and 1 (4.3%) was relapser to interferon therapy. 4 (17.3%) patients were treated with sofosbuvir plus ribavirin, 11 (47.8%) with sofosbuvir plus daclatasvir, 4 (17.3%) with sofosbuvir plus daclatasvir and ribavirin, 3 (13%) with sofosbuvir plus velpatasvir and one (4.3%) with sofosbuvir plus ledipasvir. 14 (61%) patients received antiviral therapy for 12 weeks and 9 (39%) for 24 weeks.
1 patient died during therapy due to myocardial infarction. 21 (91.3%) patients achieved viral clearance at end of therapy. 19 out of 22 (86.4%) patients showed sustained response at 12 weeks after end of therapy. 2 (8.7%) patients relapsed, evidenced by detectable viral RNA 3 months after ending therapy. No significant drug-related adverse effects were noted. Mild, occasionally reported, effects were slight lethargy, mild anorexia and dry cough.
Conclusion: Sofosbuvir is safe for use in HCV infected patients with end stage renal disease undergoing maintenance hemodialysis, with favourable viral response rates.

THU-174

Efficacy of L-Carnitine on the ribavirin induced hemolytic anemia for patients with HCV infection

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Background and aims: In the field of clinical practice, L-carnitine have been recently reported not only to alleviate hyperammonemia and reduce muscle cramps in patients with liver cirrhosis, but also improve anemia in patients with chronic hepatitis and renal dysfunction. Although chronic hepatitis C therapy has been dramatically changed with the recent appearance of direct acting antivirals (DAAs), some existing DAAs regimens using ribavirin has been mainly selected for patients with decompensated cirrhosis and who relapsed after prior DAAs monotherapy. In this study, we prospectively evaluated the preventing effect of L-carnitine supplementation during antiviral treatment using ribavirin on a hemolytic anemia in hepatitis C virus (HCV)-related chronic liver disease patients.
Method: This study, designed as a prospective and randomized clinical trial, was conducted at the third department of internal medicine in Nara Medical University Hostital between July 2015 and August 2016. A total of forty-one patients with chronic hepatitis was consecutively enrolled. Twenty-two patients received sofosbuvir plus ribavirin (group A) for three months, while nineteen patients were treated with sofosbuvir, ribavirin, and L-carnitine (group B). We analyzed the changes of hemoglobin concentration, the effects of antiviral treatment and the healthy status levels of patients assessed by the SF-8 questionnaires in the both groups.
Results: The decreased level of hemoglobin concentration in the group B was significantly smaller than that in the group A at every time point. Consistently, the serum lactate dehydrogenase (LDH) level of patients in the group A was significantly higher than that in the group B at both eight and twelve weeks after the beginning of treatment. Moreover, the prescribed dose intensity of ribavirin in the group B was higher than that of group A (100% vs 91.2%), resulting in that the ratio of sustained virological response (SVR) 24 in the group B was higher than the group A (100% vs 90.9%). Additionally, the physical functioning of patients in the group B was significantly better than that in the group A at the end of antiviral treatment.
Conclusion: O L-carnitine supplementation actually alleviates the ribavirin induced hemolytic anemia in patients with HCV and might relieve the physical burden of patients during the treatment of the ribavirin included regimen. These advantages would increase the opportunity of achieving SVR.

THU-175

Eligibility and feasibility of hepatitis C treatment in the era of direct-acting antiviral agents: Our experience in real-world practice

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Background and aims: In pre-DAAs era, some categories of patients (with HIV co-infection, intravenous drug users (IVDUs), psychiatric, with cirrhosis and elderly), were reported as "special" populations. This definition was based on limited feasibility and effectiveness of interferon-based HCV treatment, low compliance, potential drug-drug interactions and higher risk of adverse events. The aim of this study is to verify eligibility, feasibility and effectiveness of DAAs in "special" populations in our cohort.

Method: We studied 1278 pts who were referred to 1^ Department of Infectious Diseases of L. Sacco Hospital, Milan, Italy, for evaluation hepatitis C treatment, since 30/6/2013 to 31/12/2017.
Results: To date, out of 1278 pts, 1228 (95.5**%)** underwent DAAs treatment and completed follow-up of 12 weeks post-treatment. Among them, 348 pts were HIV co-infected, 262 IVDUs, 481 had diagnosis of cirrhosis, 35 pts were psychiatric, 372 elderly (>65 years old: 49 of them were >80 years old). Sustained virological response (SVR) was obtained as follows: 95.4% in HIV co-infected pts, 100% in IVDUs pts, 97.7% in cirrhotic pts, 100% in psychiatric pts, 97.5% and 100% in elderly (>65 and >80 years old respectively). Discontinuation for adverse events occurred only in 0.7% of 1228 pts: 4 HIV co-infected, 2 elderly and 3 pts with cirrhosis.
50 pts (3.9%) were excluded from treatment: 24/50 pts were HIV co-infected with active IVDU and poor compliance; whereas, in HCV mono-infected population, 16/26 pts refused therapy and 10/26 had serious co-morbidities.
Conclusion: In our experience, only a small number of patients (3.9%) resulted not eligible for DAAs treatment. SVR >95% was observed even in all "special" populations and only in a small percentage of cases (0.7%) therapy was discontinued for adverse events. These data confirm in real life the effectiveness, feasibility and safety of DAAs for all patients and the possibility to achieve HCV cure in almost all our patients.
In this setting, further efforts should be made by clinicians to reconsider also "difficult to treat" pts as suitable for therapy.

THU-176

Weight gain after interferon-free clearance of chronic hepatitis C: Results from the German hepatitis C registry (DHC-R)

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Background and aims: Hepatitis C Virus (HCV) infection can be associated with a variety of extrahepatic manifestations including metabolic alterations. Few single center studies reported substantial weight gain during and after interferon-free treatment of chronic hepatitis C which has been considered as a potential concern. The aim of this study was to investigate short- and long-term weight changes of patients followed in a large, real-world multicenter cohort.
Method: The DHC-R (German Hepatitis C-Registry) is a national multicenter real-world cohort including about 14, 500 patients recruited by more than 250 centers (approx. 90% physicians in private practice). Patients are treated at the discretion of the physician. Data are collected by a web-based system. Data quality is analyzed by plausibility checks and on site monitoring. This analysis is based on 5, 111 patients who were documented until July 15th 2018 and who were observed for up to 3 years after completion of antiviral treatment.
Results: At the end of antiviral treatment the proportion of patients with weight gain of at least 1 kilogram was 21.1% which constantly increased to 47.8% at 3 years after DAA treatment (Fig. 1). Mean weight change compared to baseline was −0.2 kg (SD 4.3) at end of treatment whereas weight increased significantly to 1.6 kg (SD 6.6) and 1.7 kg (SD 8.0) at follow-up year 2 and 3. Multivariate regression analysis at FU2 revealed body mass index and sex as significant predictors of weight change. Patients with BMI ≤ 30 had a mean weight gain of 1.9 kg whereas patients with BMI > 30 showed no significant weight changes (0.1 kg). Male patients had a mean weight gain of 1.9 kg which was higher than observed in female patients (1.1 kg, p = 0.014).

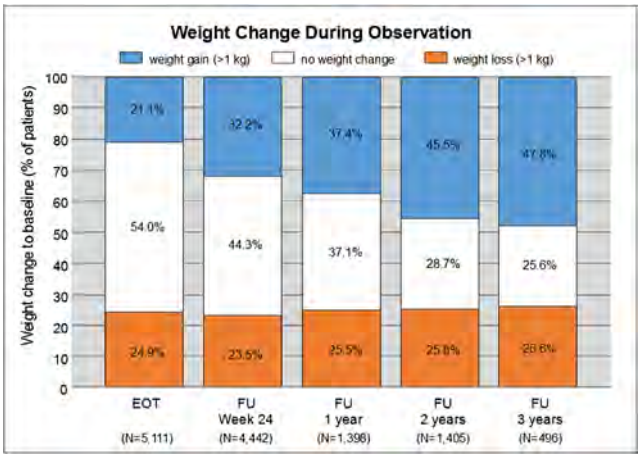

Figure: Weight change after interferon-free antiviral HCV treatment.

Conclusion: DAA treatment is followed by a substantial weight gain in almost half of the patients during long-term follow-up. Male patients were particularly vulnerable to weight gain. However, obese patients did not further gain weight which possibly could be explained by improved metabolic situation after HCV cure.

THU-177

Interim results of an ongoing project to eliminate chronic hepatitis C in people who inject drugs with ongoing intravenous drug use and a high risk of non-adherence to direct-acting antivirals in Vienna

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Background and aims: An important subgroup of people who inject drugs (PWID) receiving opioid agonist therapy (OAT), cannot be treated in the setting of a hepatologic center and would not regularly ingest their medication when handed to them for self-administration. Our hypothesis was that chronic hepatitis C in these patients could be ideally managed if care was provided at a low-threshold facility and direct-acting antivirals (DAA) were administered together with OAT under direct observation of a pharmacist, physician or nurse at a pharmacy or a low-threshold facility.
Method: 267 PWID on stable OAT with chronic hepatitis C and high risk for non-adherence to DAA-therapy (male/female: 203/64; mean age: 38.0 ± 8.3 years; genotype (GT) 1/2/3/4/: 158/3/97/6 (unknown: n = 3); HIV-coinfection: n = 17; liver cirrhosis: n = 53) started antiviral treatment. Patients received antiviral therapy together with OAT under direct observation of a pharmacist, physician or nurse at a pharmacy or low-threshold facility. The DAA-regimen was selected according to GT, fibrosis stage, pretreatment and current reimbursement policy of insurances.
Results: Following this concept of directly observed therapy, adherence to antiviral therapy was excellent: Only 0.15% of scheduled dates for ingestion of the antiviral therapy in combination with OAT were missed by the 267 patients. Till now, 190 patients have

completed treatment and a 12-week follow-up period. Virological cure of hepatitis C infection (sustained virologic response, SVR12) could be confirmed in 189/190 patients (SVR12 rate: 99.5%; 95% CI: 97.1-99.9). One patient died 8 weeks after end of therapy for reasons not related to treatment. During follow-up reinfections occured in 12/190 (6.3%) patients. The cumulative rate of reinfection 24 and 48 weeks after end of therapy was 5.5% and 9.9%, respectively.

Conclusion: Directly observed therapy of chronic hepatitis C at a pharmacy or a low-threshold facility is highly effective in PWID with ongoing intravenous drug use and a high risk for non-adherence to DAA. By this new concept, a group of difficult-to-treat patients can be cured, who could not have been treated in settings of studies published so far.

THU-178

Drug-drug interactions in HCV therapy: Still relevant for clinical practice?

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Background and aims: With direct-acting antivirals (DAA) drug-drug interactions (DDI) have emerged as a new challenge in the treatment of hepatitis C virus infection (HCV). In the present study we aim to i) assess if the frequency of DDI has changed over time, ii) identify patients with an increased risk for DDI and iii) identify drugs most commonly involved.

Method: All consecutive HCV patients treated at Hannover Medical School from January 2014 to July 2018 were evaluated for their concomitant medication and assessed for DDI with the prescribed antiviral regimen. DDI were classified as follows: 1) no interaction expected 2) potential weak interaction 3) potential significant interaction and 4) do not coadminister. The assessment was based on data from hep-druginteractions.org and in case of missing information an expert opinion of a pharmacist. To evaluate changing frequencies of DDI over time with various DAA regimens, periods were defined as follows: A) January 2014-November 2014, B) November 2014-August 2016 and C) August 2016-July 2018, based on new approval of key DAA.

Results: Overall, 670 patients were included in the study with a mean age of 55.5 years (18-85). 44.9% of patients were female, 42.2% had cirrhosis, 6.6% were older than 74 years. 350 different medications were used in the cohort. The median number of medications used per patient was 3 (0-19). Over time, the frequency of patients without interactions remained stable (A: 63.0%, B: 51.2%, C: 61.5%) but the frequency of contraindications doubled between period A and B and remained elevated in period C (A: 2.5%, B: 5.1%, C: 4.0%). On average, cirrhotic patients took significantly more medications with category 3 interactions (figure). Patients aged 65-74 were also more likely to suffer from category 3 interactions. Patients aged >74 years had similar risks for interactions as patients aged 65-74 (figure). The medications most frequently involved in category 3 and category 4 interactions with the modern DAA regimens sofosbuvir/velpatasvir, glecaprevir/pibrentasvir and elbasvir/grazoprevir were proton pump inhibitors, metamizole, statins and carvedilol.

Conclusion: DDI remain common and affect about 40% of patients treated with DAA. Cirrhotic patients and patients aged >64 years were identified to have an increased risk for DDI. The most common drugs involved in significant interactions in our cohort are proton pump inhibitors, metamizole, statins and carvedilol.

THU-179

Never too old to be direct acting antiviral treated for hepatitis C virus

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Background and aims: Elderly patients were seldom treated for HCV in the IFN era due to treatment side effects. IFN-free DAA therapy has minimal side effects making treatment feasible for many more patients, including the elderly. We report demographic and outcome data on all patients over 75 years of age who were treated for HCV with DAA therapy in 3 Canadian clinics.

Method: All HCV-infected patients greater than 75 years treated with DAAs without IFN were included. Information on demographics, treatment and outcomes were collected at 3 Canadian sites (Ottawa, Edmonton and Brampton). Fibrosis score was determined by transient elastography.

Results: 78 patients were included in the analysis. Patients were female (63%) with a mean age of 79 (SD 3.5, range 75-88 years; 36% were ≥ 80 years) and Caucasian (56%). 90% were treatment naïve. Genotypes included: G1a = 18%, G1b = 35%, G2 = 22%, G3 = 6%, and G4 = 9%. The mean METAVIR fibrosis score was 2.8 (SD 1.2) with 78% having fibrosis scores ≥ F2. 41% had cirrhosis. The main HCV treatments included: SOF/VEL = 33%, SOF/LDV = 32% and EBR/GZR = 17%. 13 of 78 (17%) received ribavirin (RBV) containing regimens with daily doses of 400 mg (n = 1), 600 mg (n = 1), 800 mg (n = 3), and

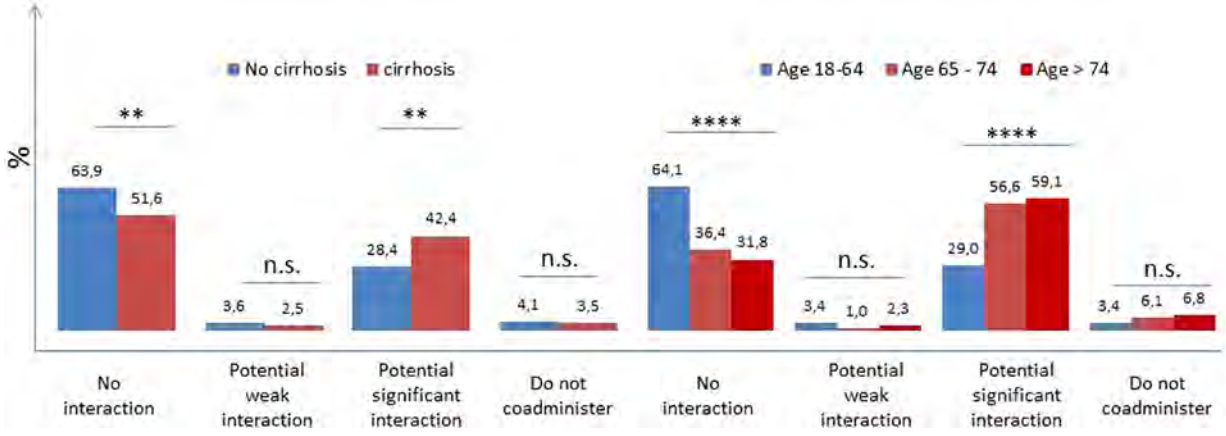

Figure: (abstract: THU-178): Drug-drug interactions in different subpopulations.

1000 mg (n = 8). 92% (57/62) with outcome results achieved SVR. No virologic failures occurred. SVR was 98% (n = 48/49) with non-RBV regimens and 69% (9/13) for RBV-recipients. Two deaths (ESLD, HCC), 1 discontinuation of all HCV medications at week 2, and 1 lost-to-follow-up occurred in RBV recipients. Mean on-treatment nadir hemoglobin in RBV recipients was 95 g/L (SD 22.1, range 57-128). RBV dose was reduced in 3 of 13 cases and was later discontinued in 2 of these 3 patients. Three received on-treatment PRBC transfusions.
Conclusion: Safety and efficacy of RBV-free DAA therapy is similar to that of younger adults. RBV-specific complications are frequent and without evidence of improved SVR in the elderly.

THU-180

Treatment of genotype 3 HCV infection in the large real-life "Navigatore Lombardia" multicentre cohort: Results from three different regimens

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Background and aims: In the direct acting antiviral (DAA) era, treatment of genotype 3 HCV (HCV-G3) is still challenging. The currently recommended treatment options are: sofosbuvir (SOF) + daclatasvir (DAC), SOF/velpatasvir (VEL), and glecaprevir/pibrentasvir (G/P). These recommendations are based on small, non-randomized trials or on comparisons with suboptimal and currently dismissed regimens, with HIV coinfection and cirrhosis being often under-represented. Direct comparisons of the 3 regimens are lacking, and real-life data are scarce on this issue. Temporal shifts in Italian prescription rules, alternating single regimens for HCV-G3, favour comparisons, reducing the risk of indication biases.
Method: All HCV-G3 patients consecutively treated within the Lombardia web-based Navigatore HCV Network were analysed. The primary end point was sustained virologic response 12 weeks after end of treatment (SVR12). Cirrhosis was defined by Fibroscan liver stiffness > 13 KPa. Uni- and multivariable logistic regression analyses were run to assess differences in SVR12 among regimens.
Results: Among 1535 patients treated for HCV-G3 with DAA, 271 were excluded from subsequent analyses as they had received suboptimal therapy (i.e. SOF+RBV ± pegylated interferon). Of the remaining 1264 patients, 27% were females, 53% cirrhotic and 31% had HIV coinfection; median (IQR) age was 53 (49-56) years, 41% had previous exposure to interferon. Overall, SVR12 was 95% (1202/1264): 94% (768/817) for SOF+DAC, 97% (319/327) for SOF/VEL, 96% (115/120) for G/P, P = 0.039, likely reflecting different prevalence of cirrhosis among the 3 groups (69%, 27%, 12%, respectively). At univariate analysis, treatment with SOF/VEL was associated with a higher likelihood of SVR12 (OR 2.54, 95%CI 1.19-5.43 P = 0.016). However, at multivariable analysis, when adjusted for gender, age, HIV status, presence of cirrhosis, baseline HCVRNA, the association lost statistical significance: OR 1.84 95%CI 0.78-4.35, P = 0.163. No other covariates were associated with treatment response.
Conclusion: In a large real-life setting of HCV-G3-infected patients with a high proportion of cirrhosis, the success rate was remarkable. The slight advantage of the SOF/VEL regimen was not confirmed at multivariable analysis, where adjustment for cirrhosis likely rebalanced the current shift of using novel regimens (i.e. SOF/VEL and G/P) for easier-to-treat patients in this era.

THU-181

Safety and efficacy of glecaprevir/pibrentasvir for the treatment of HCV genotype 1-6: Results of the HCV-TARGET study

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Background and aims: Glecaprevir/Pibrentasvir (G/P) is approved for treatment of chronic hepatitis C virus (HCV) genotypes (GT) 1-6 infection in treatment naïve (TN) and experienced (TE) non-cirrhotic as well as compensated cirrhotic patients. It is not recommended in patients with moderate hepatic impairment. We report real-world safety and efficacy of G/P in HCV-TARGET participants.
Method: Patients enrolled in HCV-TARGET were treated according to the local standards of care at academic (n = 45) and community

medical centers (n = 19) in North America (n = 60) and Europe (n = 4). Detailed information on demographics, clinical course, and adverse events was abstracted from medical records into a unique centralized data core. Independent data monitors systematically reviewed data for completeness and accuracy. This analysis includes patients who started G/P before August 1 2018.

Results: Of 660 patients treated with G/P 393 (60%) were male, 171 (26%) Black, 108 (16%) cirrhotic and 19 (3%) with history of decompensating events. Patients were predominantly treatment naïve (577, 87%); of whom, 312 (54%) completed an 8 week regimen. Overall, SVR12 for G/P is 344/359 (96%, 95% CI 93%-98%); GT1 225/234 (96%, 95% CI 93%-98%); GT2 49/54 (91%, 95% CI 80%-96%); GT3 50/51 (96%, 95% CI 90%-100%); Other GTs 20/20 (100%, 95% CI 84%-100%); TN 293/305 (96%, 95% CI 93%-98%), including 191/201 (95%, 95% CI 91%-97%) in those who completed 8 ± 1 weeks of treatment); and TE 51/54 (94%, 95% CI 85%-98%). Three hundred and one patients' virological outcomes are pending at this time. There were no virologic failures reported in 62 cirrhotics with available SVR data. On treatment adverse events (>90% mild in severity) occurred in 44% of patients. Common adverse events included fatigue (16%), headache (11%) and nausea (8%). Six patients experienced liver related events. Eighteen patients (3%) reported a total of 24 SAEs. Two patients died while on treatment: one of Lung cancer and second of unknown cause.

Category	N	%
All Patients Treated with G/P	**660**	**100.0%**
Male	393	60%
Black	171	26%
HCV genotype		
1	442	66%
1a	332	50%
Non-1a	110	17%
2	81	12%
3	88	13%
Other	49	7%
Cirrhosis	108	16%
Prior history of hepatic decompensation	19	3%
Prior DAA Treatment failure	23	4%
-NS5A experienced	16	2%
-PI experienced	1	0%
On-treatment Adverse Event (s)	288	44%
Disposition		
Completed Treatment	535	81%
D/C treatment early	33	5%
-AE	7	1%
-Lost to follow-up	22	3%
-Other reasons	4	< 1%
Still on Treatment	92	14%
SVR12 available	359	54%

Conclusion: G/P-based regimens in this real-world cohort show overall high efficacy with 96% SVR12 rate. This study cohort consisted of predominantly GT1 and treatment-naïve patients. Safety and efficacy results for all 660 patients will be presented.

THU-182

The PRIORITIZE study: A pragmatic, randomized study of oral regimens for hepatitis C- transforming decision-making for patients, providers, and stakeholders

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Background and aims: The PRIORITIZE Study was designed to evaluate the comparative effectiveness of recommended direct acting antiviral (DAA) treatment options for persons infected with HCV genotype 1 (GT1). The study also evaluated the multi-faceted outcomes that stakeholders identified as being most important to HCV treatment decisions. 1) rates of patients being cured and durability of cure, 2) drug side effects and other short and long-term treatment harms, and 3) patient-centered clinical benefits.

Method: This pragmatic, open-label, randomized trial of sofosbuvir/ledipasvir (SOF/LDV) (provided by commercial payer) vs elbasvir/grazoprevir (EBR/GZV) vs (paritaprevir/ritonavir-ombitasvir-dasabuvir (PrOD) (the latter 2 regimens provided via the study) enrolled GT1 DAA-naive participants. NS5a Resistance-Associated Substitutions (RAS) testing was offered prior to treatment initiations for all patients. Patient Reported Outcomes (PRO) surveys were collected at baseline, week 4, end of treatment (EOT), and year 1. Treatment duration and use of ribavirin was at the discretion of treating physician and patients were monitored per local standard of care. After the standard of care shifted in the U.S. (August 2017), randomization to PrOD was stopped and participants were randomized 1:1 to the remaining treatment arms. Comparison of outcomes with the PrOD regimen was restricted to participants enrolled prior to the amendment; the comparison of SOF/LDV and EBR/GZV was based on all participants. The primary outcome was SVR12 defined as HCV RNA < LLOQ at least 12 weeks after therapy completion.

Results: 1677 patients were screened, 1609 were randomized, and 1276 were dosed (429 of 726 randomized to SOF/LDV, 700 of 729 to EBV/GZR, 147 of 154 to PrOD). The primary reason for failure to dose after randomization was payer denial of SOF/LDV (n = 244). The enrolled population was 60% male, 42% Black, 68% noncirrhotic, 75% GT1a. The mean age was 55 years and 12% had confirmed baseline NS5A RASs. The most frequent adverse events (AEs) have been fatigue (25%), headache (15%) and nausea (20%). Serious AEs were reported by 46 participants; none was treatment-related. Overall, 111 participants (9%) discontinued treatment early due to: lost to follow-up, n = 61; AEs, n = 21; death, n = 6; non-adherence, n = 13; lack of efficacy, n = 1, withdrew consent, n = 4 and administrative, n = 5. Of these 111 participants, 25 had sufficient data to assess virologic outcome; 17 achieved SVR12. Of the remaining 1165 participants, 234 are pending SVR12 classification and 931 have final outcomes available; of whom 904 (97.1%) have achieved SVR12.

Conclusion: This pragmatic trial is the largest randomized study to evaluate the comparative effectiveness of recommended treatments for GT1 infection. Final SVR, safety and on-treatment PRO outcome data for this study will be presented.

THU-183

Prospective multicenter study of glecaprevir plus pibrentasvir combination therapy for patients with chronic hepatitis C

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Background and aims: The once-daily, ribavirin-free, pangenotypic, direct-acting antiviral (DAA) regimen glecaprevir + pibrentasvir has shown high and sustained virological response rates in phase 2 and 3 studies. We assessed the safety and efficacy of 8 and 12 weeks of this combination therapy for patients infected with hepatitis C virus (HCV) in real world.
Method: This single-arm, multicenter study involved eight centers in Japan. On October 31, 2018, 424 patients aged 26-89 years (n = 94 aged >75 years) infected with HCV genotype (GT) 1, 2, 3, or 4, of which 49 had undergone curative treatment for hepatocellular carcinoma (HCC), started the treatment. Oral glecaprevir (300 mg) + pibrentasvir (120 mg) was administered once daily for 8 weeks to 245 non-cirrhotic DAA-naïve patients with HCV GT-1 or –2, and for 12 weeks to 56 cirrhotic, 78 DAA-failure, 39 cirrhotic and DAA-failure, 6 GT-3, and 1 GT-4 patient. Anti-HCV efficacy was defined as a sustained virological response at 12 weeks post-treatment (SVR12) (HCV RNA < 15 IU/ml). The efficacy and safety analysis included all patients who received at least one dose of the study drugs (intention-to-treat population). This study is registered at UMIN (No. UMIN000030599).
Results: In all, 395 patients completed the treatment, including 225 (92%) of 245 patients on the 8-week regimen and 167 (93%) of 179 patients on the 12-week regimen. Three patients were dropped because they were given a different DAA regimen. SVR12 was evaluated in 288 patients (Table). All of the DAA-naïve patients with GT-1 achieved an SVR12. The 12-week regimen resulted in 100% SVR12 in patients with GT-2. Six patients did not achieve SVR12: one GT-2a patient, two GT-3b patients, and three GT-1b patients with past DAA failure. During treatment, severe adverse effects (SAE) occurred in five patients: esophageal varices rupture, cerebral bleeding, femur fracture, burn, and exacerbation of heart failure. Mild adverse effects were reported in 130 (33%) patients: itching was reported by 27 patients (6.8%), GI discomfort by 10 (2.5%), elevation of total bilirubin >2.0 mg/dL by 7 patients (1.8%), and hyperuricemia by 6 (1.5%), etc.

Table: SVR12 rate after DAA therapy for 8 and 12 weeks.

	8-Week Regimen	12-Week Regimen
Genotype 1	100% (77/77)	DAA naïve cirrhosis 100% (24/24) DAA retreatment 96% (68/71)
Genotype 2	99% (86/87)	DAA naïve cirrhosis 100% (15/15) DAA retreatment 100% (11/11)
Genotype 3	-	50% (2/4)

Conclusion: Glecaprevir + pibrentasvir for 8 or 12 weeks had a marked anti-HCV effect for GT-1 and GT-2 patients. The SVR rate was low in patients with GT-3. This combination therapy was reasonably safe, including in elderly patients.

THU-184
Correlates of unsuccessful hepatitis C virus therapy and recurrent viremia among active drug users: A mixed methods analysis

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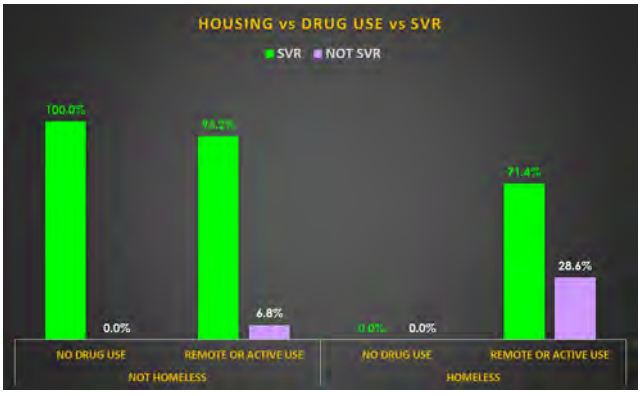
Background and aims: People who use drugs (PWUD) have been identified as a prioritized population to receive hepatitis C virus (HCV) therapy. Numerous clinical trials have now shown that high cure rates can be achieved in this population. Concerns remain about the risk of unsuccessful therapy due to non-adherence as well as the risk of HCV reinfection. This study was conducted to determine the frequency and correlates of the inability to achieve and/or maintain a sustained viral response (SVR) in a target population of active PWUD receiving care.
Method: We undertook a retrospective mixed-methods analysis of patients receiving Direct Acting Agents (DAA) HCV treatment at our centre between 03/14-12/17. Statistical analyses were carried out using Chi square and logistic regression models with SPSS V24. Additionally, two focus groups were held (04-05/18) with participants asked to identify key factors affecting engagement in care. Qualitative data analysis was done using the Framework Approach with NVivo 11 software.
Results: A total of 215 patients eligible were included (74% male (n = 160), 39% active drug users (n = 83), 88% lifetime drug users (n = 189)). SVR was achieved in 91.2% (196/215) cases. During 282.7 patient-years of follow-up, no cases of recurrent viremia post-SVR were detected. Homelessness was the most important independent correlate of an inability to achieve SVR [OR: 7.08; CI: 95% (2.07-24.25); p = 0.002]. Moreover, 100% of the patients who did not use drugs during HCV treatment and were not homeless (n = 26) reached SVR. In the focus groups, most participants identified housing as the key social issue that needs to be addressed to improve their quality of life. Also, a number of comments suggested an awareness of the risk of HCV reinfection and an understanding of strategies to avoid it.



Conclusion: Homelessness was the main predictor of non-SVR among HCV-treated PWUD and was identified as the key factor affecting their quality of life. Multidisciplinary programs to address HCV infection in this population must include strategies to address unstable housing to enhance their success and impact. To date, we have not observed any cases of HCV reinfection in patients continuing to be enrolled in our multidisciplinary program, suggesting that they may have acquired and implemented strategies to avoid it.

THU-185
Effectiveness and safety of DAA-based treatment of hepatitis C patients with severe and end stage chronic kidney diseases-EpiTer-2 database analysis

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Background and aims: The aim of this study was to analyze efficacy and safety of HCV treatment of patients with severe CKD, including HD and kidney transplants recipients, in Poland in years 2015-2017 and registered in real-world EpiTer-2 database.
Method: Among 6229 patients in EpiTer-2 database we identified 334 patients with any kidney disease. In 77 patients eGFR was < 30 ml/min/1.73 m^2, that included 53 patients on hemodialysis (HD). All patients underwent IFN-free, anti-HCV therapy.
Results: Among 77 patients with CKD stage 4 and 5 there were 35 females (45.5%) and 42 males (54.5%) with mean age 49.0 ± 12.08 and 49.4 ± 14.55 respectively. HCV genotype distribution analysis revealed dominance of genotype 1b-63 pts (82%), genotype 1a in 3 pts (4%), genotype 3 in 1 pt (1.3%) and genotype 4 in 10 pts (13%). Only 14 (18%) were cirrhotic, 4 had previous liver decompensation and 3 had esophageal varices. The most prevalent comorbidities were hypertension (56%) and diabetes (18%). Three patients had liver and 20 (29%) kidney transplantation. The majority of patients (74%) were treatment-naïve. The most frequent treatment was OBV/PTV/r ± DSV- in 39 patients (51%), GZR/EBR was used in 26 (34%), ASV/DCV in 4 (5%), GLE/PIB in 1 (1%). Seven patients (16%) were treated with LDV/SOF, contraindicated in patients with GFR < 30 ml/min/1.73m^2. The main reason for choosing LDV/SOF were DDIs and liver decompensation. There were no safety issue with LDV/SOF including renal function.
All patients, but 1 who was lost to follow-up, achieved SVR12, so ITT SVR12 was 99% and mITT SVR12 was 100%, that was even better than in the general cohort (ITT SVR12-95%; mITT SVR12-97%)
Adverse events were reported in 24 patients (31%) with 3 SAE (2 liver decompensations and 1 esophageal bleeding) that led to 1 treatment discontinuation.
All HD patients completed treatment, achieved SVR and there was 1 episode of ascites, 4 cases of anemia, 2 pruritus and 2 bilirubin level elevation. None of them led to therapy modification.
Conclusion: Extremely high efficacy and few side effects allowed to use DAAs in severe and end-stage kidney disease. In this real-world study we confirmed that patients are no longer difficult-to-treat population. but some of them may still require special attention due to decompensated liver cirrhosis when selecting regimen or establish follow-up procedures.

THU-186

Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015-August 2018

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Background and aims: In April 2015, Georgia with the support of U.S. CDC and Gilead Sciences, launched the world's first HCV elimination program. A key strategy is nationwide HCV screening, linkage to care, provision of treatment for all HCV persons and effective prevention interventions. A national serosurvey conducted in 2015 estimated 150, 000 persons with chronic HCV in the country. To achieve the elimination goal by 2020, a 90% reduction in prevalence of HCV, there are objectives including: diagnosing 90% of HCV-infected persons, treating 95% of those diagnosed and curing 95% of those treated. Progress towards the goal will be assessed by monitoring the HCV care continuum.
Method: A hepatitis C care cascade was constructed using data from the national HCV treatment program (Figure). The program collects data on all persons registered with the treatment program. Data on persons tested for chronic HCV infection through sustained virologic response (SVR) were extracted as of August 31, 2018. SVR rates were calculated using both per-protocol (PP) and intent-to-treat analysis (ITT).
Results: Among estimated 150, 000 adults living with chronic hepatitis C in Georgia, 61, 666 (41.1%) were diagnosed and registered with the treatment program. Among those registered in the program, 48, 871 (79.3%) have initiated treatment with either sofosbuvir or ledipasvir/sofosbuvir based regimens, of which 45, 088 (92.2%) have completed treatment. Among 41, 734 persons eligible for SVR assessment 32, 880 (78.8%) returned for final evaluation. In PP analysis SVR rate achieved was 98.2% (32, 297/32, 880) while 77.4% (32, 297/41, 734) of persons achieved SVR in ITT analysis. High cure rates were achieved for all HCV genotypes: 98.5% in genotype 1, 98.4% in genotype 2 and 97.7% in most challenging to treat genotype 3. Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 97.3% achieving SVR, and among patients with mild or no liver fibrosis (≤F2), SVR = 98.8%.

Figure: Hepatitis C care cascade as of August 31, 2018.

Conclusion: Georgia has made substantial progress towards eliminating hepatitis C, with over 40% of persons with HCV infection identified and registered for treatment. High cure rates have been achieved among those who received SVR testing. Efforts to identify and link to care persons with HCV infection, ensure SVR testing and implement prevention interventions are needed to achieve the elimination goals.

THU-187

Objective evidence of neurocognitive impairment associated with hepatitis C virus infection and of its regression after viral clearance with direct antivirals

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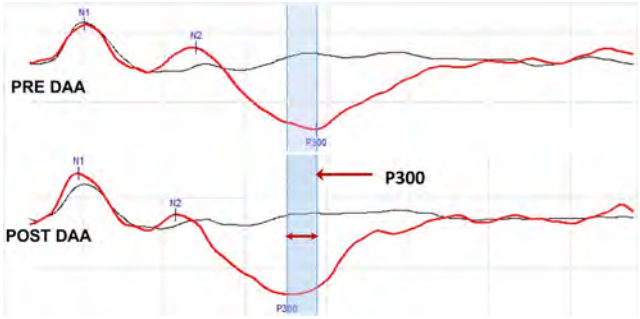
Background and aims: Neurocognitive impairment associated with Hepatitis C Virus (HCV) infection has a great impact on patients' quality of life. However, it is unclear whether it is due to viral infection per se (either directly for infection of brain cells or indirectly via neuroinflammation) or to other reasons, for example the mere awareness of having a chronic disease. This study was designed to investigate these issues.
Method: The study population included: N. = 23 HCV infected patients, N. = 15 patients with non-alcoholic fatty liver disease (NAFLD) and N. = 15 healthy controls. They were all matched for age, education and (limited to the 2 groups of patients) fibrotic stage. All subjects underwent a battery of 10 neuropsychological tests and measurement of the evoked potential P300. The 3 groups repeated testing six months apart; HCV patients were tested before and after therapy with Direct Antiviral Agents (DAA). For in vitro experiments, Human Brain Microvascular Endothelial Cells (HBMEC) were exposed to HCV strain JFH-1 cell cultured. The relative expression of intracellular viral RNA and inflammatory cytokines mRNA levels (Interleukin (IL)-1beta, IL-8, IL-18 and Transforming Growth Factor-beta) were then quantified.
Results: Only in the chronic HCV group a significant improvement was observed in the repeat examination in several cognitive fields, including verbal ability and logic thinking (Verbal judgments test $p < 0.001$), executive functions (phonological fluency $p = 0.001$), and P300 latency ($p = 0.003$) (Fig.1). Improvements occurred also in tests investigating episodic memory (Rey Auditory Verbal Learning Test immediate and differed tasks, $p < 0.001$ and $p = 0.001$ respectively), but being registered also in control groups were likely due to test-enhanced learning.
Moreover, at baseline patients showed significant deficits compared to both control groups in the tests mentioned above. *In vitro*, HMBEC exposed to viral inocula were negative for intracellular HCV RNA, however a striking rise in IL-1beta (8 fold $p < 0.0001$) and IL-8 (64 fold $p = 0.0005$) mRNAs was observed.



Conclusion: Neurocognitive deficits associated with HCV infection are demonstrable by neuropsychological tests and objective neurophysiologic tests, and regress after viral clearance. *In vitro* results suggest that the pathophysiological mechanism is more likely related to neuroinflammation induced by exposure to circulating virions, than to direct infection of brain cells.

THU-188

Retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C virus infection and prior DAA failure: An analysis from the German hepatitis C registry (DHC-R)

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Background and aims: Chronic hepatitis C virus (HCV) infection can be cured with all-oral direct-acting antivirals (DAAs) in >90% of patients. There are only few patients in whom DAA treatment fails. Re-treatment options for patients with DAA failure are limited. In Europe, the fixed dose combination of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) given for 12 weeks is the only approved DAA regimen for patients in whom HCV NS5A inhibitor-based therapy has failed. Aim of the present analysis was to evaluate the efficacy and tolerability of SOF/VEL/VOX under real-world conditions.
Method: The DHC-R (German Hepatitis C-Registry) is a national multicenter real-world cohort including about 14, 500 patients recruited by more than 250 centers (approx. 90% physicians in private practice). For the present analysis, all consecutive patients enrolled in the DHC-R who were retreated with SOF/VEL/VOX were analyzed (as of 9 Feb, 2018). SVR data were updated as of 4 Nov, 2018.
Results: Retreatment with VOX/VEL/SOF with or without ribavirin (RBV) was initiated in 86 patients with prior DAA failure. Patients were infected with HCV genotypes (GT) 1, 3, and 4 in 64%, 31% and 5%, respectively. Prior DAA regimens included: LDV/SOF ± RBV (n = 26), PrO ± D ± RBV (n = 27), VEL/SOF ± RBV (n = 12), GZR/EBR (n = 6), DCV/SOF ± RBV (n = 12), SMV/SOF+RBV (n = 1), and SOF+RBV (n = 2). The median age was 52.5 years (range, 26-79), 86% were male and 24% had compensated cirrhosis. Four patients had received RBV (GT1b, n = 2; GT3, n = 2) as part of their treatment. At the time of data analysis, 56/56 (100%) had achieved SVR. There were no virologic failures. SOF/VEL/VOX was well-tolerated. The most frequent adverse events included fatigue (16%) and headaches (10.5%). There were two severe adverse events (pneumonia, urothelial carcinoma) that were considered unrelated to HCV treatment.
Conclusion: Retreatment with SOF/VEL/VOX was highly effective and well-tolerated in this real-world cohort.

THU-189

Role of comorbidites in sofosbuvir-based treatment response: Clinical experience from an Italian real life cohort

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Background and aims: Chronic hepatitis C (CHC) can be complicated with comorbidities conditions that may impact the treatment eligibility and outcomes. The aim of this study was to assess sustained virological response (SVR) rates in a real-world cohort of patients with HCV infection treated with sofosbuvir-based regimens.
Method: All naive and prior interferon-treated patients with genotypes 1, 2, 3, 4 or 5 who started sofosbuvir-based treatment at the Gastroenterology unit of the Molinette Hospital, University of Turin from June 2014 trought May 2018 were included. All consecutive patients received Sofosbuvir (SOF) in association with: ledipasvir (LDV), daclatasvir (DCV), simeprevir (SMV) or velpatasvir (VEL) in a once-daily fixed-dose. The characteristics of the CHC population were evaluated-with specific focus upon use of medications and comorbidities. The primary end point was SVR at 12 weeks after the end of therapy by modified intention-to-treat analysis.
Results: Among a chronic HCV cohort of 1061 patients, at least one comorbidity condition was seen on the great majority of the patients (75.4%). The most common categories of comorbidities were: endocrine (37.4%), gastrointestinal (19.8%), haematological (19.1%), cardiovascular (15.4%) and neurological diseases (7.4%). The three most frequent comorbidities were hypertension (36.3%), diabetes (14.2%) and depression (12.1%). 1049 patients reached week 12 of follow-up post-treatment given that 4 patients died (2 of septic shock while receiving treatment and 2 of HCC during follow-up), 2 discontinued treatment (1 patient's decision and 1 adverse event) and 6 were lost to follow-up. Overall SVR rate was 98.2% (1030/1049). Unexpectedly SVR rates were lower in patients without comorbidites (96.9%) versus the ones that had them (98.6%, p = 0.068). All of the patients (100% 127/127) diagnosed with depression achieved SVR12, followed by the ones with high blood pressure (98.7% 377/382) and diabetes (98.0%, 147/150). All of the patients (100%, 63/63) with 5 or more comorbidities achieved SVR12, followed by the ones with 2 (99.9%, 206/208), 3 (98.8%, 162/164), 4 (98.0%, 100/102) and just 1 comorbid condition (97.7%, 211/216). Prior HCV treatment (p = 0.043) and cirrhosis (p = 0.013) were associated with SVR. HCV genotype 1b (OR = 7.105^{-8}, 95% CI 2.316^{-8}-2.180^{-7}, p = 0.000), genotype 2 (OR = 5.104^{-8}, 95% CI 8.185^{-8}-3.183^{-7}, p = 0.000), genotype 3 (OR = 2.965^{-7}, 95% CI 3.379^{-8}-2.601^{-6}, p = 0.000) and male gender (OR = 0.224, 95% CI 0.063-0.804, p = 0.022) were predictors of relapse.
Conclusion: Our real-life results validate the efficacy and safety of sofosbuvir-based regimens suggesting that, patients' comorbidities and the correlate therapies taken during antiviral treatment were not significantly associated with SVR rates. Male gender and HCV genotype 1b, 2 and 3 were predictors of relapse.

THU-190

Characteristics associated with sustained virologic response in chronic hepatitis C patients who received an abbreviated course of direct-acting antiviral therapy

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Background and aims: Treatment of chronic hepatitis C virus (HCV) with 8-12 weeks of direct-acting antivirals (DAA) results in sustained virologic response (SVR) rates > 95%. Limited data exists suggesting treatment durations of 3-6 weeks may also be curative. Shorter treatment durations can positively impact patient adherence and healthcare costs. Factors associated with SVR in patients receiving shorter courses include HCV viral load (VL) < 6 million copies/ml, absence of cirrhosis or resistance-associated substitutions (RAS), and HCV genotype. This project evaluated SVR rates in patients with chronic HCV who received abbreviated courses of DAA therapy and observed characteristics associated with SVR.
Method: A retrospective chart review was performed to identify all patients who received abbreviated courses of DAA-containing regimens for HCV from January 2014 to June 2018. Patients with incomplete documentation of treatment course or those treated with interferon, boceprevir, or telaprevir were excluded.
Results: A total of 2, 663 charts were reviewed and 87 patients met inclusion criteria. Fifty-three percent (n = 46) of patients achieved SVR. The median (interquartile range, IQR) percentage of treatment days completed was 66% (49-70%) for those who were cured vs. 17% (11-33%) for those who failed therapy. Median (IQR) baseline HCV VL was 1.2 million copies/ml (0.4-2.6 million copies/ml) vs. 2.2 million copies/ml (0.8-5.2 million copies/ml) for the SVR group and non-SVR group, respectively. More patients in the SVR group were genotype non-1a (50% vs. 27%, respectively), cirrhotic (28% vs. 20%, respectively), received an NS5B-contaning DAA regimen (76% vs. 68%, respectively), and had treatment interruptions (38% vs. 15%, respectively) when compared to the non-SVR group. Compared to the SVR group, more patients in the non-SVR group were HIV+ (4% vs. 10%, respectively), Hispanic (15% vs. 22%, respectively), and had RASs (2% vs. 17%, respectively).
Conclusion: Characteristics that appear to be associated with SVR in chronic HCV patients who received an abbreviated course of DAA therapy include genotype non-1a, therapy with an NS5B-containing regimen, and completion of at least 50% of the treatment course. Characteristics associated with treatment failure include HIV+ status, Hispanic ethnicity, and presence of RASs. Severity of liver disease, treatment interruption, and baseline HCV VL do not appear to impact the SVR rate in this patient population.

THU-191

The cost-effectiveness of an HCV outreach intervention for at-risk populations in London, UK

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Background and aims: Hepatitis C virus (HCV) disproportionately affects marginalised communities such as homeless populations and people who inject drugs (PWID), posing a challenge to traditional health services. The HepFriend initiative in London is a model of care utilising HCV outreach screening and peer support to link vulnerable individuals to HCV treatment in secondary care. The aim of the study is to assess the cost-effectiveness of the HepFriend initiative from a healthcare provider perspective, compared to standard-of-care pathways (consisting of testing in primary care and other static locations, including drug treatment centres, and linkage to secondary care).
Method: Cost-effectiveness analysis using a dynamic HCV transmission and disease progression model among PWID and those who have ceased injecting, including housing status and drug treatment service contact, parameterised using London specific surveillance and survey data, and primary intervention cost and effectiveness data (September 2015 to June 2018). Out of 461 individuals screened, 200

were identified as HCV RNA positive, 198 attended secondary care and 99 have commenced treatment to date. The incremental cost-effectiveness ratio (ICER) was determined using a 50-year time horizon.

Results: For a £20, 000 per quality adjusted life year (QALY) gained willingness-to-pay threshold, the HepFriend initiative was cost-effective, mean ICER of £8, 880 per QALY, and would become cost-saving at 45% (£17, 536 per treatment) of the current drug list price. Results are robust to variations in intervention costs and model assumptions.

Conclusion: New models of care that undertake active case-finding with enhanced peer-support to improve testing and treatment uptake amongst marginalised and vulnerable groups could be highly cost-effective and possibly cost-saving.

THU-192

All-oral, 12-week ravidasvir plus ritonavir-boosted danoprevir and ribavirin delivers 100% svr12 in treatment-naive non-cirrhotic hcv genotype 1 patients with resistance-associated substitutions of a phase 2/3 clinical trial in china

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Background and aims: Ravidasvir (RDV) is a pan-genotypic NS5A inhibitor with high barrier to resistance. As reported from phase 2 trial (NCT03020095), all-oral RDV and DNVr in combination with ribavirin achieved the SVR12 rate of 100% (38/38) in treatment-naïve non-cirrhotic patients with HCV GT1 infection in Taiwan. This s a subanalysis of phase 2/3 study of RDV and DNVr in combination with ribavirin regimen for treatment-naïve HCV genotype 1 (GT1) patients without cirrhosis in a large population in China Mainland.

Method: In this multi-center, randomized, double-blind, placebo-controlled phase 2/3 trial (NCT03362814), we enrolled 424 treatment-naïve, non-cirrhotic adult HCV GT1 patients from 42 sites in different provinces of China. These patients were randomized 3 : 1 to receive a combination of RDV 200 mg once daily plus DNVr 100 mg/100 mg twice daily and oral ribavirin 1000/1200 mg/day (body weight < 75/ ≥ 75 kg) (n = 318) or placebo (n = 106) for 12 weeks, then patients in the placebo group went on to receive 12 weeks' treatment with the above combination. The primary efficacy end point was the sustained virologic response rate 12 weeks after the end of treatment (SVR12) using the CAP/CTMHCV 2.0 assay (LLOQ = 15 IU/ml).

Results: Of the 424 patients (mean age 45yrs, range 21~73 yrs) enrolled, 47% were male, 82%(348/424) was IL-28B CC genotype, and most of the patients (305/424, 72%) had HCV RNA ≥ 800, 000 IU/ml at baseline. All patients had NS5A testing at baseline, with 76 patients (76/309, 25%, PPS) in the treatment group and 29 patients in the placebo group (29/101, 29%, PPS) having detectable RASs in the NS5A region. The most common NS5A RASs were R30Q (38/309, 12.3%), Y93H (21/309, 6.8%) and R30Q/Y93H (8/309, 2.6%) in the treatment group and R30Q (21/101, 20.8%), Y93H (6/101, 5.9%), R30Q/Y93H (1/101, 0.99%) in the placebo group. The overall SVR12 was 99.03% (306/309, 95%CI: 97.19%~99.80%, PPS)and 99.01% (100/101, 95%CI: 94.61%, 99.97%, PPS) respectively for the treatment group and the placebo group. All patients with baseline NS5A RAS from the treatment group (76/76, PPS) and the placebo group (29/29, PPS) achieved SVR12. 3 patients (3/309, 0.97%, PPS) in the treatment group experienced virologic breakthrough and 1 patient in the placebo group relapsed (1/101, 0.99%, PPS), none of them had RASs at baseline. No serious AE was assessed by the investigator as related to study drugs. Most of the abnormal laboratory tests of liver function were of mild or moderate severity (grade 1 and grade 2).

Conclusion: For Chinese treatment-naïve non-cirrhotic GT1 HCV adult patients, there was no significant impact of baseline NS5A RASs on SVR12 with 12-week ravidasvir plus ritonavir-boosted danoprevir and ribavirin.

THU-193

4 week treatment for hepatitis C: A randomized controlled trial (4RIBC)

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Background and aims: Since the introduction of Directing Acting Antivirals (DAA) the cure rate of chronic hepatitis C has been over 90% which even includes difficult to treat patients as cirrhotic and treatment experienced patients. Shortening treatment duration

could reduce overall treatment cost and probably improve adherence. If 4 weeks of treatment could be used in a large proportion of hepatitis C virus infected patients it will be much more feasible to implement in treatment of HCV infected drug users where adherence and lost to follow-up is a concern.

We have previously shown that 4 weeks of ledipasvir/sofosbuvir plus weight based ribavirin gave a cure rate of 92% in young and easy to treat patients. However Ribavirin adds to side effects but the addition might be defensible if treatment can be shortened.

We hypothesize that patients under the age of 50 with no or minimal liver fibrosis could be cured receiving only four weeks of glecaprevir/pibrentasvir and aim to investigate whether ribavirin is necessary in this population.

Method: The study consists of two phases. Phase 1: comparing glecaprevir/pibrentasvir ± ribavirin in a single center study and hereafter in phase 2 conduct a multicenter study with 168 patients. Here we present the preliminary results of phase 1. The trial was conducted at the outpatient clinic at infectious disease department at Odense University Hospital in Denmark.

Main inclusion criteria: Treatment naive patients with chronic hepatitis C (all genotypes), age < 50 years and liver stiffness measurement of < 8 kPa.

Patients were stratified according to genotype 3/non genotype 3. Thirty two patients were randomized 1:1 to either glecaprevir/pibrentasvir or glecaprevir/pibrentasvir + ribavirin for 4 weeks. Ribavirin was dosed 15 mg/kg q.d. with an upper limit of 1400 mg. The study was sponsored exclusively by the Danish Health Authorities.

Results: From May to August 2018, 32 patients initiated treatment: 31 patients have reached week 4 post treatment and 13 have reached 12 week post treatment.

SVR4 in the ribavirin containing arm was 86% (13/15) and SVR12 71% (5/7). In the ribavirin free arm SVR4 was 75% (12/16) and SVR12 50% (3/6).

Conclusion: These preliminary results suggest that ribavirin will be necessary for a 4 week regime with glecaprevir/pibrentasvir. Full SVR12 result for phase one will be presented at the conference as well as baseline and treatment resistance associated variants in patients not achieving SVR 12.

THU-194

Efficacy and safety of glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection: An integrated analysis of phase 2 and 3 studies

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Background and aims: The pangenotypic direct-acting antivirals (DAAs) glecaprevir (identified by AbbVie and Enanta) coformulated with pibrentasvir (G/P) are approved for the treatment of chronic HCV genotype (GT) 1-6 infection. However, the efficacy and safety data of G/P are limited in patients infected with HCV GT5 and GT6.

Method: The data analysis integrated data from 10 Phase 2b, 3a (registrational) and 3b (post-registrational) studies. The patient population comprised adults with chronic HCV GT5 or GT6 infection and compensated liver disease (with or without cirrhosis) who were treatment-naïve or experienced with regimens containing interferon (IFN) or pegylated IFN (pegIFN) ± ribavirin or sofosbuvir + ribavirin ± pegIFN. Patients received 8 or 12 weeks of G/P (300 mg/120 mg) depending on the design of the original study. Efficacy was evaluated as the rate of sustained virologic response (SVR) at post-treatment week (PTW) 12 (SVR12). HCV subtype was identified by phylogenetic analysis.

Results: Data from 181 patients were included in this integrated analysis, including 56 (30.9%) with HCV GT5 and 125 (69.1%) with HCV GT6 infection. Overall, 102 (56.4%) patients were treated for 8 weeks and 79 (43.6%) for 12 weeks, irrespective of the presence of cirrhosis. Most patients were male (54.1%), Asian (64.6%), < 65 years of age (72.4%), treatment-naïve (87.8%), with F0-F1 fibrosis (68%), and non-cirrhotic (non-F4, 84.5%). One GT5 subtype (5a) and 17 GT6 subtypes were included, with the majority of GT6 subtypes being 6a (35.2%) or 6e (24%). In patients with HCV GT5 infection, 95.7% (22/23) on 8-week treatment and 100% (33/33) on 12-week treatment achieved SVR12. In GT6, 98.7% (78/79) patients on 8-week treatment and 97.8% (45/46) on 12-week treatment achieved SVR12. Overall, 1% (1/102) of patients on 8-week treatment and no (0/76) patient on 12-week treatment experienced relapse. SVR12 rates by cirrhosis status and treatment duration are shown in Fig 1. Treatment-emergent adverse events (AEs) were mostly mild or moderate in severity (175/181, 96.7%). Most common AEs in at least 10% of patients were fatigue (29/181, 16%) and headache (27/181, 14.9%). Seven patients (3.9%) had treatment-emergent serious AEs, none of which were related to G/P or led to study drug discontinuation.

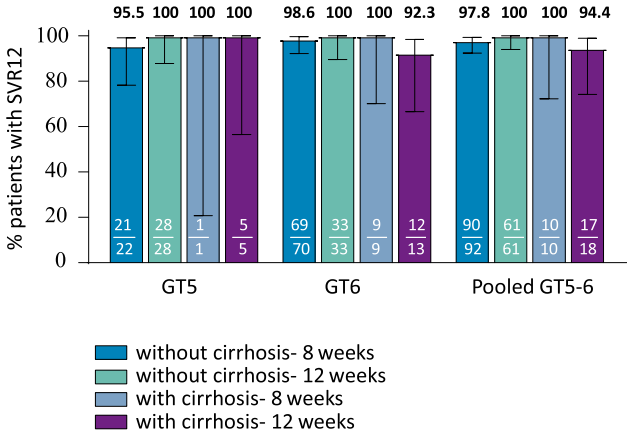

Figure 1: Efficacy with G/P in GT5/GT6 patients.

Conclusion: HCV GT5- and GT6-infected patients without cirrhosis or with compensated cirrhosis treated with G/P for 8 or 12 weeks achieved high rates of SVR12. There were no added efficacy benefits when treatment was extended from 8 to 12 weeks, even in patients with compensated cirrhosis. The G/P regimen was well-tolerated.

THU-195

An open-label, randomized, active control trial of 8 versus 12 weeks of elbasvir/grazoprevir for naive chronic hepatitis C genotype 1b patients with mild fibrosis (EGALITE): Impact of baseline viral loads and NS5A resitance-associated substitution

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Background and aims: Grazoprevir/elbasvir achieved a high sustained virological response (SVR) rate (>95%) for patients with genotype 1 or 4 (HCV-1/4) infection. The current study aimed to evaluate the efficacy of truncated treatment period of 8-week grazoprevir/elbasvir for naïve, HCV-1b patients with mild fibrosis.
Method: EGALITE (NCT03186365), a randomized, open-label, active controlled trial, enrolled 82 treatment-naive HCV-1b patients with fibroscan < 9.5 kPa from 11 centers in Taiwan to receive 8 (n = 41) or 12 (n = 41) weeks of elbasvir/grazoprevir, stratified by baseline viral loads (VL, cut-off: 800, 000 IU/ml) and interleukin-28B genotype. The primary end point was SVR12 (HCV RNA < 12 IU/ml at posttreatment week 12). Resistance-associated substitution (RAS) was determined by next-generation sequencing.

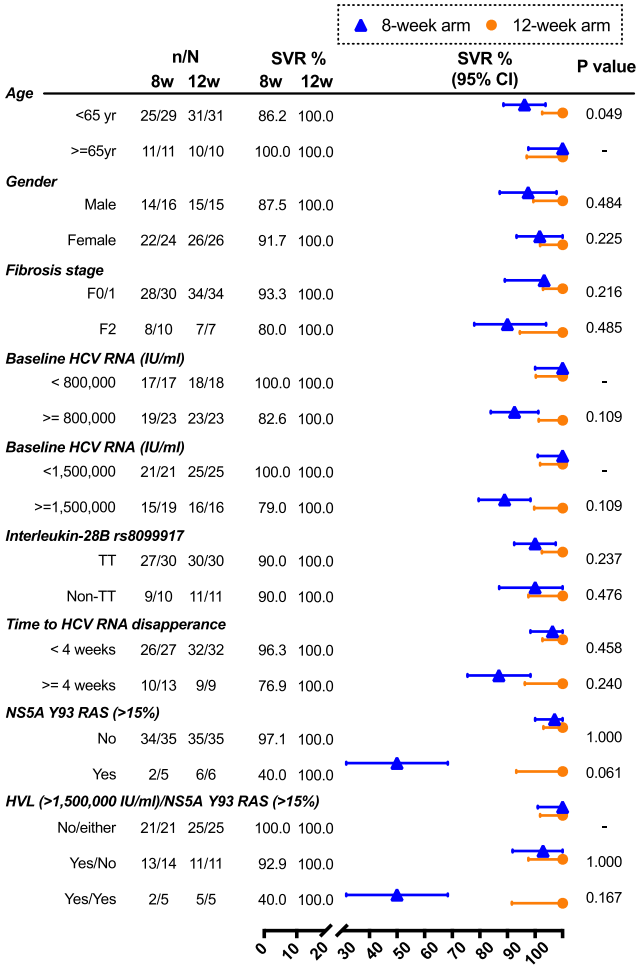

Figure 1: Rates of SVR12 stratified by subgroups between 8-week and 12-week arms among 81 naïve HCV genotype 1b patients with mild fibrosis.
Note: SVR, sustained virological response; CI, confidence interval; HCV, hepatitis C virus; NS5A, non-structural 5A protein; RAS, resistance-associated substitution; HVL, high viral loads.

Results: Overall, 50 (61%) were female; 46 (56.1%) with VL >800, 000 IU/ml and 22 (26.8%) interleukin-28B rs8099917 non-TT genotype. Both arms had comparable baseline characteristics/clinical features (Table 1). SVR12 was achieved by 87.8% (36/41, 95% confidence intervals [CI]: 81.4%-94.2%) and 100% (41/41, CI: 93.6%-100%) in full-analysis-set population and 90.0% (36/40, CI: 83.5%-96.5%) and 100% (41/41, CI: 93.6%-100%) in per-protocol population (excluding one HCV-6 patient) in 8-week and 12-week arms, respectively (both p = 0.055). In the 8-week arm, a significantly lower SVR12 rate was observed among patients with a high baseline VL (cut-off: 1, 500, 000 IU/ml, 79% [15/19] vs. 100% [21/21], p = 0.042) and those with baseline NS5A Y93H > 15% (40.0% [2/5] vs. 97.1% [34/35], p = 0.004). Between group analysis demonstrated patients with baseline VL > 1, 500, 000 IU/ml and NS5A RAS (Y93H > 15%) had a substantial lower SVR12 rate in 8-week (2/5 [40.0%, CI: 21.6%-58.4%]) than in 12-week arms (5/5 [100.0%, CI: 81.6%-100.0%] figure 1). All four HCV-1b relapsers in 8-week arm had NS5A RAS Y93H > 99% at posttreatment week 12. None experienced grade 3/4 adverse event, treatment-related serious adverse event and discontinuation.
Conclusion: Grazoprevir/elbasvir for 8-12 weeks was highly effective and safe in HCV-1b naïve patients with mild fibrosis, except for those with baseline high VL and significant NS5A RAS treated with 8-week regimen.

THU-196

Efficacy of 8 versus 12-weeks treatment with ledipasvir/sofosbuvir in chronic hepatitis C patients eligible for 8-weeks regimen in real world setting

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Background and aims: Non-cirrhotic treatment-naive hepatitis C patients infected with genotype 1 can be treated with Ledipasvir/Sofosbuvir (LDV/SOF) for 8 weeks according to Summary of Product Characteristics, but in real world practice this regimen is frequently extended up to 12 weeks. The aim of our study was efficacy comparison of 8 and 12-weeks regimens in patients eligible for 8 weeks therapy.
Method: Data of HCV genotype 1 infected patients treated with LDV/SOF between 2015 and 2017 and included into the EpiTer-2 database were analysed in respect to patients characteristics and length of treatment.
Results: Among total of 1718 patients treated with LDV/SOF, 679 were included in the analysis and 238 (35%) received 8-weeks regimen, whereas 441 patients were treated for 12-weeks although fulfilled criteria for a shorter LDV/SOF course. Majority of patients were infected with genotype 1b (89%) and demonstrated minimal fibrosis (55%). Twelve weeks regimen was assigned significantly more frequently to patients with comorbidities (71% vs 45%), concomitant medications (69% vs 39%), advanced liver fibrosis (32% vs 1%), HIV coinfected (7.9% vs 2.5%) and HBV coinfected (13.4% vs. 4.6%). Sustained virologic response rate was similar after 8 (98%) and 12 (97%) weeks of therapy according to intent-to-treat analysis and reached 99% in both groups after exclusion of patients lost to follow-up.
Conclusion: We confirmed high and the same efficacy of 8 and 12-weeks regimens of LDV/SOF in non-cirrhotic chronic hepatitis C patients infected with genotype 1 which fulfilled criteria for 8 weeks regimen according to current label and expert guidelines. This real-world study confirmed no need of 12-weeks therapy with LDV/SOF in this population.

THU-197

Comparative effectiveness of 8 versus 12 weeks of ombitasvir/paritaprevir/ritonavir and dasabuvir in treatment-naive patients infected with HCV genotype 1b with non-advanced hepatic fibrosis

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Background and aims: Since 2016 treatment-naïve patients with chronic hepatitis C virus genotype 1b infection with minimal or moderate fibrosis can be treated with ombitasvir/paritaprevir/ritonavir and dasabuvir (OprD) for 8 weeks according to Summary of Product Characteristics updated based on results of Garnet trial. The aim of our study was to assess the comparative efficacy of 8 and 12-week treatment duration of OPrD in patients with none, minimal or moderate fibrosis (F0-F2) treated in real-world setting.
Method: We analysed data of 3067 HCV genotype 1b infected patients treated with OPrD between 2015 and 2017 obtained from EpiTer-2 database.
Results: A total of 800 patients with non-advanced fibrosis were enrolled to the study, that included 223 (29%) treated for 8-weeks and 577 patients fulfilling criteria for shorter treatment but assigned to 12-weeks regimen. Majority of patients had no or minimal fibrosis, and they were more frequently treated for 8 weeks (82%) than 12 weeks (61%). Longer treatment duration was more often administered in patients with comorbidities (56% vs 31%), concomitant medications (45% vs 30%), HIV coinfected (0.7% vs 0%) and HBV coinfected (11.6% vs. 7.2%). SVR was achieved in 211 (95%) patients treated for 8 weeks and 561 (97%) for 12 weeks ($p = 0.09$). After exclusion of lost to follow-up patients, SVR rate reached 96% and 98%, respectively, and the difference was statistically significant according to the Fischer analysis ($p = 0.02$). All 10 non-responders from the 8 weeks group were naïve to DAA and demonstrated viral load below 6 million U/l. All except one demonstrated minimal fibrosis (F1) and 9 were males. We were not able to identify factors associated with non-response in this group.
Conclusion: We confirmed high effectiveness of 8 and 12-weeks regimens of OPrD in genotype 1b HCV infected patients with non-advanced fibrosis and supported no need of 12-weeks therapy in large majority of such patients. Further analysis of growing population treated for 8 weeks is necessary to identify possible factors responsible for non-response.

THU-198

Efficacy and safety of glecaprevir/pibrentasvir treatment for 8 weeks in treatment-naive patients with chronic hepatitis C virus infection without cirrhosis or with compensated cirrhosis: Analysis of data pooled from phase 2 and 3 studies

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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 to treat adults chronically infected with hepatitis C virus (HCV) genotypes (GT) 1-6. In HCV treatment-naïve patients, G/P is currently approved for 8 weeks in non-cirrhotic patients and 12 weeks in patients with compensated cirrhosis. A recent post-approval study of G/P for 8 weeks in treatment-naïve cirrhotic patients with HCV GT1, 2, 4–6 showed a high rate of sustained virologic response at post-treatment Week 12 (SVR12) that was similar to the rate with 12 weeks of treatment. This integrated analysis evaluated the efficacy and safety of G/P for 8 weeks in treatment-naïve patients without cirrhosis or with compensated cirrhosis.
Method: Data were pooled from treatment-naïve patients with HCV GT1, 2, 4–6 without cirrhosis or with compensated cirrhosis who received G/P for 8 weeks across 8 Phase 2 and 3 clinical trials.
Results: Of 1163 patients, 280 (24%) had cirrhosis. Most patients were white (79%) and had HCV GT1 (63%) or GT2 (22%); mean age was 53 years. Liver disease characteristics for non-cirrhotic vs cirrhotic patients were: platelets < 100 × 109/L, 1% vs 17%; aspartate amino-transferase-to-platelet ratio (APRI) ≥ 2, 2% vs 34%; FibroScan ≥ 20 kPa, 0% vs 51%; FibroTest ≥ 0.72, 7% vs 69%; FIB-4 ≥ 3.25, 4% vs 52%. The SVR12 rate (intention-to-treat, ITT) was 98% (1139/1163) overall, and was 98% in both non-cirrhotic (865/883) and cirrhotic (274/280) patients. Excluding non-virologic failures, the modified ITT (mITT) SVR12 rate was 99.9% (1139/1140); one non-cirrhotic patient had virologic relapse (<0.1%; 1/1145). SVR12 rates by baseline laboratory thresholds are shown (Table). Treatment-emergent adverse events (AEs) occurred in 57% (662/1163) of patients. The most frequent AEs (>5%) were headache (11%), fatigue (10%), and nausea (7%). Serious AEs were reported in 3% (30/1163) of patients. AEs led to study drug discontinuation in 0.3% (4/1163) of patients.

Table: mITT SVR12 rates by baseline laboratory thresholds.

	Below threshold, SVR12% (n/N)	Equal to or above threshold, SVR12% (n/N)
Platelets 100 × 10^9/L	100 (52/52)	99.9 (1087/1088)
APRI 2*	99.9 (1020/1021)	100 (107/107)
FibroTest 0.72†	100 (572/572)	100 (222/222)
FIB-4 3.25‡	99.9 (945/946)	100 (172/172)

Missing patients: *n = 12; †n = 346; ‡n = 22.

Conclusion: G/P for 8 weeks was highly efficacious and well tolerated regardless of cirrhosis status in treatment-naïve patients with HCV GT1, 2, 4–6 infection.

THU-199

Awake the dormants: Barriers to access to care and cure in patients with chronic HCV infection

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Background and aims: Despite improved safety and efficacy of HCV treatment, challenges remain in referral to care and access to treatment. Failure to treat and cure eligible-for-treatment patients may prevent achieving the goal of HCV elimination in Israel by 2030. AIM: To assess the number of "dormants" HCV patients (HCV-positive patients eligible for anti-viral treatment and were not referred to liver clinics) and to identify the patients'- and providers barriers to referral to care and to cure.
Method: Data were obtained from the computerized records and database of Haifa and Western Galilee District of Clalit Health Services (CHS) (the largest CHS district responsible for 800, 000 insured individuals) at years 2000-2012. The database contains information regarding demographic parameters, laboratory tests and pharmacy records, hospitalization and primary care physician records and death-related data. 3800 HCV-Ab positive patients were identified of whom 2895 were thoroughly investigated. 745 patients were HCV-Ab "low-positive" (PCR negative), 590 have been previously treated and cured, 259 left CHS, 81 died, 156 were active drug users, 136 had severe illness, mainly psychiatric, and 104 lost to follow-up. For the remaining 824 potentially eligible-for -treatment patients, a letter (e-mail) was sent to the primary care physician (PP) requesting completeness of the work-up including complete liver function tests, quantitative HCV RNA, HCV genotype and shear-wave elastography (logistics was assisted by the Carmel MC Liver Unit).
Results: Out of these 824 potentially eligible for treatment patients HCV-positive, only 208 patients were treated and achieved SVR and 108 are candidate to initiate treatment soon (28%). Overall barriers to referral or treatment among 1116 HCV patients were of the following reasons: providers'-related 317 (28%): no response from the PP (214), no work-up was performed (103), patients'-related 483 (43%): active IDU (156), severe illness, mainly psychiatric (136), logistic problems (128, of whom 106 are receiving OST), not interested in treatment (56) and financial reasons (7).
Conclusion: 40% of the barriers to cure are provider-related and 60% are patient-related. Ways to overcome these barriers and improve access to care and cure will be presented.

THU-200

The Real-Eorld Israeli experience of treating mild and severe chronic hepatitis C patients with elbasvir/grazoprevir: A large multi-center cohort study

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Background and aims: Elbasvir (EBR) and Grazoprevir (GZR) is a fixed dose combination regimen of Direct Antiviral Acting Agents (DAAs) that was approved in the USA and Europe for Chronic

Hepatitis C (CHC) patients with Genotype (GT) 1 and 4. In 2016, this regimen has been included in the Israeli Essential Drugs List (EDL) for F3-F4 CHC patients. F2 patients were included in 2017 EDL, and since January 2018 all CHC patients (F0-F4) are eligible for treatment. In this study we aim to characterize the real-world effectiveness and tolerability of EBR/GZR in CHC patients with all fibrosis stages.

Method: Data on demographics, clinical features, tolerability and virological response were collected from 15 centers in Israel in both hospitals and community clinics. Data would be presented for over 620 patients treated with EBR/GZR between June 2016 and March 2019.The primary efficacy end point was sustained virologic response at follow-up week 12 (SVR12); special attention was paid to co-morbidities, kidney function and drug-drug interactions (DDIs).

Results: This interim analysis includes 519 patients who were treated with EBR/GZR. Of the 519 patients, 46% had mild and 54% had advanced fibrosis (30% were cirrhotic patients). 52% of the patients were males. Mean age was 56.8 ± 14 years old. Patients with mild fibrosis were younger than patients with severe fibrosis (53 years old vs. 60 years old, P < 0.05). Most of the patients (84%) had GT1b. 12.7% (n = 51) of the patients had chronic kidney disease (CKD) stage 3-5 (stage 4/5- 6%), 14% (n = 74) had type 2 diabetes mellitus, 6% (n = 31) had HCV/HIV co-infection and 8 patients had symptomatic cryoglobulinemia. The most common concomitant medications included anti-hypertensive (31%), anti-acids (17%) and statins (13%).

Effectiveness: Interim analysis showed negative PCR at the end-of-treatment in 279 patients (99.3%) and SVR12 in 190/196 patients (97.4%). SVR12 was similar in patients with advanced- and with mild fibrosis (97.2% vs. 96.4%, respectively). Tolerability data which includes most common adverse events and SAEs will be presented.

Conclusion: CHC treatment with EBR/GZR in a real-world setting was associated with high SVR12 rates and good tolerability in both patients with mild as well as with advanced fibrosis.

Viral hepatitis B/D: Clinical aspects except therapy

THU-203

Hepatitis D infection and risk of hepatocellular carcinoma: A systematic review and meta-analysis of observational studies

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Background and aims: Hepatitis D virus (HDV) infection is the most severe form of chronic viral hepatitis, with a faster progression to cirrhosis and increased mortality compared with hepatitis B virus (HBV) monoinfection. However, the role of HDV in the development of hepatocellular carcinoma (HCC) remains debated.

We conducted a systematic review and meta-analysis of epidemiological studies to examine whether chronic HDV infection is associated with an increased risk of HCC compared to chronic HBV monoinfection.

Method: We searched Pubmed, Embase and Web of Science databases, with no date or language restriction. Search terms referred to chronic hepatitis D, liver disease progression and HCC.

We considered cohort, case-control and cross-sectional studies allowing the calculation of effect estimates for the association between chronic HDV infection and HCC, in comparison to chronic HBV infection, according to the definitions provided by the authors of each study.

Data extraction and quality evaluation were performed by two authors. Data were pooled using random-effects models and heterogeneity between studies was examined using the I^2 statistic.

Results: Eighty-eight studies (64 case-control studies including 20782 patients and 24 cohorts including 74822 patients), from 34 countries, were selected. Ten studies adjusted for confounders and 11 cohorts were prospective. The overall analysis showed a significantly increased risk of HCC in patients with chronic HDV infection (Figure),

	Studies (n)	Patients (n)	Pooled OR (95% CI)	p value	I2
Overall	88	95604	1.25 (1-1.56)	0.047	68.13
Cohort	24	74822	1.68 (1.23-2.22)	0.0009	64.31
Case-control	64	20782	1.08 (0.77-1.51)	0.6641	68.22
Quality					
High (NOS³5)	67	91565	1.27 (1-1.6)	0.0455	66.53
Low (<5)	21	4039	1.24 (0.62-2.49)	0.5503	73.28
Children					
Yes	1	96	NA	NA	NA
No	26	60851	2.11 (1.39-3.2)	0.0005	66.64
Unknown	61	34622	1.01 (0.76-1.34)	0.9636	65.68
HCV					
Yes	NA	NA	NA	NA	NA
No	22	19453	1.72 (1.01-2.92)	0.0439	69.04
Unknown	66	75862	1.18 (0.91-1.53)	0.2101	69.03
HIV					
Yes	4	997	7.13 (2.83-17.92)	<0.0001	0
No	11	19781	1.65 (1.01-2.7)	0.0468	56.73
Unknown	73	74826	1.12 (0.87-1.45)	0.3762	69.38
Sensitivity Analysis					
Studies with matching or adjustment	10	63555	2.41 (1.52-3.82)	0.0002	64.33
Prospective studies	11	7214	2.36 (1.34-4.14)	0.0029	31.37

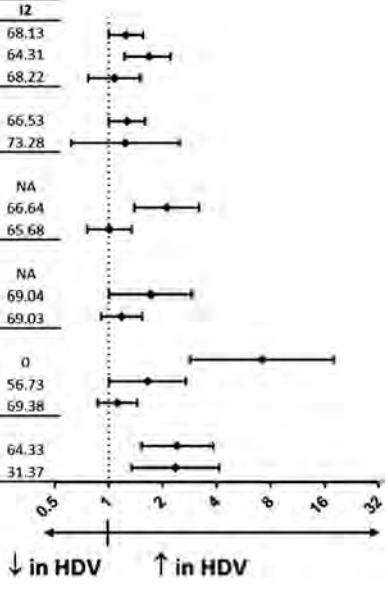

Figure: (abstract: THU-203)

despite the presence of substantial study heterogeneity (OR 1.25; 95% CI 1.00-1.56; p = 0, 047; I^2 = 68%). The effect was higher in cohort studies (OR 1.68; 95% CI 1.23-2.22; p = 0.0009; I^2 = 64.31%), particularly in those with a prospective design, with reduced heterogeneity (OR 2.36; 95% CI 1.34-4.14; p = 0.0029; I^2 = 31.37%) It was also confirmed in studies excluding children and patients infected with hepatitis C or human immunodeficiency virus (HIV) and was particularly strong in cohorts of HIV-infected patients.
Conclusion: To our knowledge, this is the first meta-analysis showing a significant risk increase for development of HCC in chronic HDV infection. Despite important study heterogeneity, this association was stronger with increasingly robust study design, in particular in prospective cohorts and in studies with adjustment for confounders. These data suggest a carcinogenic role for HDV and justify the need for strict HCC screening procedures in chronic hepatitis D.

THU-204

Analysis of interleukin 28B rs12979860 polymorphism relationship with spontaneous clearance of hepatitis D virus infection in Mongolian population

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Background and aims: Mongolia has the highest prevalence of hepatitis B (10.6%), C (11.1%) and D (7.2%) virus infections in the world that leads to highest mortality rate of the liver cancer.
Previous studies showed the single nucleotide polymorphism rs12979860 near the interleukin 28B (IL28B) is strongly associated with spontaneous clearance of hepatitis C virus and interferon treatment for this virus. But there is no adequate evidence of rs12979860 polymorphism near the 28B (IL28B) gene for spontaneous clearance of hepatitis D virus (HDV) using large number of statistically relevant samples.
The aim of our study is to investigate the association of rs12979860 polymorphism near the IL28B gene with spontaneous clearances of hepatitis D virus in Mongolian population.
Method: We have analyzed total of 374 participants (125 HDV spontaneously cleared people, 249 healthy people) for their rs12979860 polymorphism using restriction fragment length polymorphism (RFLP) assay and identified the association of spontaneously clearance of HDV and rs12979860 polymorphism. Randomly selected samples (96 samples) were Sanger sequenced for confirmation of RFLP results.
Results: The results of RFLP analysis showed that genotype frequencies of rs12979860 locus in healthy population (normal population) are following: 88.7% (221) for CC genotype, 11.245% (28) for CT genotype and 0.0 for TT genotype. In the HDV spontaneously cleared people group, the analysis showed that the genotype frequencies of rs12979860 locus are following: 84.8% (106) for CC genotype, 15.2% (19) for CT genotype and 0.0 for TT genotype. Statistical analysis by comparing the genotype frequencies of healthy group and HDV spontaneously cleared group showed that there is no significant difference between these two groups (p = 0.276, CI = 0.95).
Conclusion: There is no significant difference of genotype frequencies of rs12979860 locus near IL28B gene between the group of healthy population and group of HDV spontaneously cleared people.

THU-205

Evaluation of HBV outcomes after treatment discontinuation from 4 phase 3 studies

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Background and aims: Current international guidelines recommend stopping Nucleot (s)ide analogue (NA) therapy in a select group of patients with the aim of promoting sustained off treatment response. However, the durability and effectiveness of stopping NA therapy appears to be poor with results from several studies reporting virologic remission response rates of ~50%. Here we evaluate 4 large phase 3 studies for responses following treatment discontinuation.
Method: Patients from 4 phase 3 studies of TDF with or without Peg-IFN in HBeAg negative and positive patients were followed for up to 144 weeks after discontinuing treatment. Multivariate logistic regression modeling with stepwise selections were used to evaluate baseline (BL) and post-treatment discontinuation predictors of off-treatment responses, including; HBsAg loss and ALT < ULN with HBV DNA <2000 IU/ml, each in 3 separate models
Results: Of the 1423 enrolled in the parent studies, 660 HBsAg positive patients entered treatment free follow-up (TFFU) with a mean follow-up duration of 34 weeks. Demographic and disease characteristics of patients at the time of withdrawal are shown in Table. At the end of the TFFU, 2% had HBsAg loss and 17% of patients had ALT < ULN with DNA <2000 IU/ml. For the virologic outcomes, a lower BL HBV DNA level (Odds Ratio (OR): 0.748, p < 0.001), an increased duration of HBV DNA suppression (OR: 1.003, p < 0.0001), HBeAg negativity (OR: 2.821, p = 0.0013), a smaller increase in HBV DNA off treatment (OR: 0.505, p < 0.0001) and NA treatment (OR (NA vs Peg IFN): 8.285, p < 0.0001) at the time of withdrawal were significant predictors of patients who remain ALT <ULN with HBV DNA <2000 IU/ml at the end of follow-up. Predictors of patients with HBsAg loss include low BL HBV DNA levels (OR: 0.342, p < 0.001) and low HBsAg levels (OR: 0.445, p < 0.001) at the time of withdrawal.

		N = 660
Median Age, y (range)		37 (18-69)
Male, n (%)		449 (68)
Asian, n (%)		435 (67)
Genotype, n (%)	**A**	72 (11)
	B	161 (24)
	C	243 (37)
	D	171 (26)
Median BL ALT, U/L (Q1, Q3)		84 (56, 132)
Median BL HBV DNA, log10 IU/ml (Q1, Q3)		7 (5.6, 8)
Median BL HBsAg, log10 IU/ml (Q1, Q3)		3.9 (3.4, 4.4)
Treatment n (%)	**NUC**	275 (42)
	Peg IFN	161 (24)
	NUC + Peg IFN	324 (49)
Mean TFFU Duration, weeks (SD)		33.7 (37.29)
Median BL ALT at treatment withdrawal, U, L (Q1, Q3)		32 (23, 48)
Median BL HBV DNA at treatment withdrawal, log10 IU/ml (Q1, Q3)		1.30 (1.15, 1.52)
Median BL HBsAg at treatment withdrawal, log10 IU/ml (Q1, Q3)		3.47 (2.83, 3.97)
HBeAg positive at treatment withdrawal, n (%)		251 (38)

Conclusion: Treatment discontinuation results in the majority of patients having recurrence of HBV viremia with low rates of HBsAg loss or maintenance of inactive carrier state. Predicting outcomes in a diverse population will be required for safe and effective treatment discontinuation.

THU-206

HBV DNA relapse after stopping nucleoside analogue therapy in patients with HBsAg loss: Detectable pre-genomic HBV RNA is a better predictor of relapse than ultra-sensitive HBsAg- 'implications for HBV cure'

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Background and aims: Functional cure in chronic hepatitis B (CHB) is defined as a loss of HBsAg, undetectable HBV DNA and absence of ongoing liver damage. The EASL HBV guidelines recommend consolidation therapy with nucleos (t)ide analogue (NA) for at least 6 months after achieving HBsAg loss. HBV DNA or HBsAg re-activation is rare but markers predicting relapse are lacking. Serum pre-genomic (pg) HBV RNA reflects cccDNA transcriptional activity, and ultra-sensitive HBsAg assay (CLEIA HBsAgHQ Fujirebio) enables HBsAg detection at very low levels (0.5mIU/ml). We have evaluated the ability of pgHBV RNA, ultrasensitive HBsAg and anti-HBs antibody titre to predict HBV re-activation in patients who achieved HBsAg loss and stopped NA therapy
Methods: 19 CHB non-cirrhotic patients (61%males, median age 43.7 yrs) were treated for a median duration 8.5 yrs (1.6-12.2) with tenofovir (TDF) and achieved HBsAg loss after a median 7.5 yrs. Therapy with TDF was continued for median one year (0.5-2.7 yrs) after HBsAg loss. 12 weeks after TDF withdrawal 2 (11%) patients had detectable HBV DNA, but not HBsAg (qualitative). PgHBV RNA was measured by a novel real-time PCR research assay (Abbott Diagnostics [LLDQ 1.65 $\log_{10}$U/ml]), ultrasensitive HBsAg by CLEIA HBsAgHQ (Fujirebio) [LLDQ 0.5mIU/ml] and anti-HBs antibody titre on Abbott Architect [mIU/ml]. Levels were compared between patients according to re-activation status. In patients with re-activation TDF therapy was re-commenced and follow-up serum samples were available for test.
Results: Age, therapy duration overall and after achieving HBsAg loss, ALT activity and HBsAg levels by ultrasensitive test were similar at TDF withdrawal irrespective of re-activation. At the time of TDF withdrawal all patients had detected HBsAg by ultrasensitive test (median 1.23, range 0.6-190 mIU/ml). However, pgHBV RNA was exclusively detected in 2 patients with re-activation (median 2.12, range 2.01-2.23 $\log_{10}$U/ml, p = 0.02). Anti-HBs antibodies titres were lower in patients with re-activation (median 0.3 vs. 3.6 mIU/ml, p = 0.01). At the first visit after TDF withdrawal patients with re-activation had detectable HBV DNA (45600 and 12100 IU/ml), pgHBV RNA and HBsAg levels by ultra-sensitive assay increased from concentrations at therapy cessation. 12 weeks after re-commencing TDF, both HBV DNA and pgHBV RNA were not detected, HBsAg concentrations declined and anti-HBs antibodies levels increased.
Conclusion: Pre-genomic HBV RNA and anti-HBs antibodies are helpful makers to predict sustained loss of HBsAg without a HBV DNA increase after NA withdrawal in CHB patients who have achieved HBsAg loss on therapy. The HBsAg ultrasensitive assay provided a useful insight into dynamics of HBsAg changes after NA withdrawal but did not help to predict HBV re-activation. Larger studies assessing the utility of these markers to predict HBV re-activation after HBsAg loss are needed.

THU-207

A retrospective review of the incidence of hepatocellular carcinoma in patients with chronic hepatitis B attending the regional hepatitis clinic in Northern Ireland

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Background and aims: Hepatocellular Carcinoma (HCC) is a major concern in patients with Chronic Hepatitis B (CHB) and may develop, even when a patient is adequately treated. Incidence of HCC is reported as being higher in patients with co-factors including cirrhosis, high viral load, family history of HCC, male sex and alcohol excess.
In Northern Ireland all Hepatitis B cases are managed at a single regional centre.
The aim of this study was to ascertain the incidence of HCC in the CHB cohort attending the regional viral hepatitis clinic.
Method: Data was analysed using the regional liver unit Hepatitis B database. This information was cross-referenced with the CHB treatment database and Northern Ireland Electronic Care Record.
Co-infected patient were not included in this review.
Results: 1126 patients attended the Liver Unit for management of Hepatitis B between 2009 and 2018.
15 (1.3%) were diagnosed with HCC. 12 (80%) were male. 10 patients (67%) had established cirrhosis.
3 (20%) received transartertial chemoembolization (TACE), 2 (13%) were transplanted and 2 (13%) underwent resection, 1 (7%) received Sorafenib therapy, 1 (7%) underwent resection, TACE and Sorafenib therapy, 1 (7%) received ablation therapy. 5 (33%) were not suitable for intervention.
11 (73%) are now deceased.
10 patients (67.5%) were South East Asian in ethnicity, 1 (6.5%) was from Northern Ireland with 1 (6.5%) each from Portugal, Nigeria, Spain and Lithuania. 4 of the 5 patients who developed HCC without underlying cirrhosis were South East Asian men, the remaining patient was Portuguese.
7 patients (47%) had significant viraemia of >20, 000 at the time of diagnosis.
12 (80%) were treated with nucleotide/nucleoside analogues while the remaining 3 (19%) were referred at an advanced stage and not commenced on treatment. 9 (69%) of those receiving antiviral therapy achieved complete viral suppression at their last recorded HBV DNA PCR.
In total, 147 patients received antiviral therapy, of whom 49 (33%) had cirrhosis. The incidence of HCC in this high risk group was 12 (8%).
Conclusion: The incidence of HCC in patients with CHB attending the regional viral hepatitis clinic is 1.3% but is much higher in the subgroup that have received antiviral therapy (8%). Significant cofactors include male sex and South East Asian ethnicity, high viral load and established cirrhosis.

THU-208

Characterization of a novel chemiluminescent enzyme immunoassay for the quantitation of antibodies to hepatitis B core antigen class IgG and correlation with intrahepatic HBV covalently-closed-circular DNA

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Background and aims: Non-invasive biomarkers for the cure and the management of chronic hepatitis B (CHB) infection are an unmet need. Our aim was to characterize a novel HBV assay for the quantitation of anti-HBc IgG and to assess the correlation between

serum anti-HBc IgG and intrahepatic HBV cccDNA, in comparison to quantitative hepatitis B surface antigen (qHBsAg) and hepatitis B core-related antigen (HBcrAg) in patients with CHB infection.
Method: Serum samples and liver specimens were collected from 35 CHB patients (26M/9F; median age 52 [20-70] years; 25 chronic hepatitis and 10 cirrhosis). Intrahepatic HBV cccDNA was measured by digital-droplet PCR (Bio-Rad, USA) following total DNA digestion with plasmid safe ATP-dependent DNase. Serum qHBsAg and HBcrAg were measured by CLEIA on Lumipulse® G600 II analyzer (Fujirebio, Japan). qHBsAg limit of sensitivity was 0.005 IU/ml. The lower limit of detection (LLoD) and the measurement range of HBcrAg were 2 Log U/ml and 3-7 Log U/ml, respectively. The WHO 1st International Standard for anti-HBc (NIBSC code 95/522) was used for the calibration of anti-HBc IgG assay (Lumipulse® G HBcAb-N, Fujirebio).
Results: The new assay for anti-HBc IgG quantitation showed a linear dynamic range ($R2 = 0.997$, $p < 0.001$); lower limit of detection (LLoD) and quantitation (LLoQ) were estimated at 0.5 IU/ml and 0.8 IU/ml, respectively. The coefficient of variation (CV) for repeatability was 3.1% whereas the CV for reproducibility was 4.0%. In liver specimens, mean HBV cccDNA levels were 3.11 ± 1.14 Log copies/105 cells; in serum samples, mean qHBsAg, HBcrAg and anti-HBc IgG values were 3.13 ± 1.31 Log IU/ml, 3.8 ± 1.9 Log U/ml and 3.68 ± 0.83 Log IU/ml, respectively. In 18/35 (51%) patients, HBcrAg was below the measurement limit of the assay (<3 Log U/ml). HBV cccDNA correlated significantly with qHBsAg ($r = 0.624$, $p < 0.001$), HBcrAg ($r = 0.734$, $p < 0.001$) and anti-HBc IgG ($r = 0.553$, $p < 0.001$). In patients with HBcrAg values <3.0 Log U/ml, intrahepatic HBV cccDNA correlated significantly with anti-HBc IgG ($r = 0.752$, $p < 0.001$) but not with qHBsAg ($r = 0.384$, $p = 0.116$).
Conclusion: Anti-HBc IgG quantitation by CLEIA was a sensitive and accurate assay. Among the investigated biomarkers, HBcrAg was confirmed as reliable surrogate marker of intrahepatic HBV cccDNA. In patients with low HBcrAg levels (<3.0 log), anti-HBc IgG quantitation by CLEIA may be proposed as alternative marker for intrahepatic HBV cccDNA measurement.

THU-209

Dynamics of a transient elastography-based risk prediction model for hepatocellular carcinoma treated with antiviral therapy in chronic hepatitis B: A multi-center retrospective cohort study from the Korean Transient Elastography Study Group

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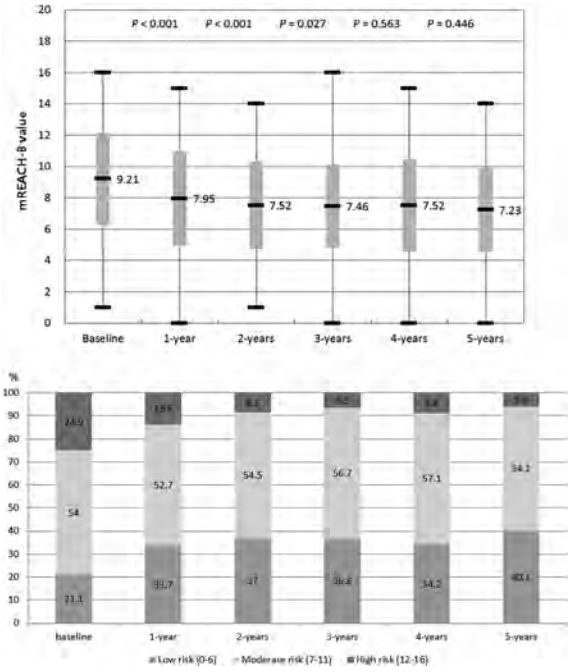
Background and aims: The transient elastography (TE)-based risk prediction models such as mREACH-B and LSM-HCC are used to predict the risk of hepatocellular carcinoma (HCC) development. However, the influence of antiviral therapy (AVT) on these TE-based risk prediction models in patients diagnosed with chronic hepatitis B (CHB) is unknown.
Method: In this retrospective study, Patients with CHB who initiated AVT using entecavir or tenofovir were recruited from 13 referral Korean tertiary academic institutes. Of the existing TE-based risk prediction models, the mREACH-B model was selected.
Results: Between 2007 and 2015, 1, 034 patients with CHB (545 non-cirrhotic, 489 cirrhotic) who initiated AVT using entecavir ($n = 729$) or tenofovir ($n = 305$) were recruited. The mean age of the study population was 46.8 years, and 61.8% ($n = 639$) of the patients were male. In subgroup analyses, patients with cirrhosis and those with HCC showed higher mREACH-B scores at baseline compared with those of the counterparts (8.2 *vs.* 10.3 and 9.1 *vs.* 11.6, respectively, all $P < 0.05$). The mean mREACH-B study population score was 9.21 at baseline, and it decreased significantly to 7.46 by 3 years of AVT (mean 7.95 at year 1, 7.52 at year 2, and 7.46 at year 3, all $P < 0.05$) and was maintained until 5 years of AVT (mean 7.52 at year 4 and 7.23 at year 5, all $P > 0.05$). The proportion of high-risk patients (mREACH-B score ≥12) was 24.9% at baseline, and it decreased significantly to 8.5% by year 2 of AVT (13.6% at year 1 and 8.5% at year 2; $P < 0.001$) and was maintained until year 5 of AVT (6.5% at year 3, 8.8% at year 4, and 5.9% at year 5, all $P > 0.05$). The mREACH-B scores at baseline, year 1 of AVT, and year 2 of AVT independently predicted HCC development (hazard ratio = 1.123-1.262), together with evidence of cirrhosis and platelet count (all $P < 0.05$). The cumulative incidence rate of HCC was significantly higher in high-risk patients than in low- (mREACH-B score 0-6) and moderate-risk patients (mREACH-B score 7-11) from the baseline (10.39% *vs.* 1.42% at year 5), year 1 AVT (11.95% *vs.* 2.51% at year 5), and year 2 AVT (14.03% *vs.* 2.91% at year 5) (all $P < 0.05$, log-rank tests). Similar results were obtained in the subgroups with and without cirrhosis.



Conclusion: The mREACH-B score was decreased significantly by AVT, up to 3 years. In addition, the mREACH-B score at baseline, year 1 AVT, and year 2 AVT significantly predicted HCC development. Thus, repeated assessment of the mREACH-B score is required to predict the changing risk of HCC development in patients with CHB undergoing AVT.

THU-210

HBcrAg levels at baseline are not predictive for HBsAg and HBeAg loss in patients treated with adefovir and PEG-interferon

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Background and aims: Various studies indicated that Hepatitis B core related antigen (HBcrAg) levels are correlated with intrahepatic covalently closed circular DNA (cccDNA) activity and serum HBV-DNA and HBV-RNA. The association with HBsAg levels is less clear. With various new HBV direct acting antiviral compounds under development, HBcrAg may be a valuable marker for HBV replication when HBV surface antigen (HBsAg) and HBV DNA are targeted and no longer reflect the viral intrahepatic HBV replication. However, HBcrAg as a predictor for response to treatment is not known. Here we aimed to identify the predictive value of HBcrAg for treatment outcome in CHB patients treated with a combination of adefovir and pegylated interferon alpha-2a (PEG-IFN).
Method: 92 CHB patients with high HBV-DNA levels were treated with adefovir and PEG-IFN for 48 weeks in a prospective study described previously. HBsAg loss was seen in 11% (5/44) of the HBeAg positive and 17% (8/48) of the HBeAg negative patients, two years after start of the study. HBcrAg was measured in stored serum samples from these patients at baseline (BL) using the Lumipulse chemiluminecence enzyme immunoassay analyser (Fujirebio Inc., Tokyo Japan) with a lower limit of detection of 3 $\log_{10}$ U/ml. Treatment outcomes were: HBsAg loss (functional cure), HBeAg loss and virological response (HBeAg negative and HBV DNA $\leq$ 2, 000 IU/ml). Treatment outcomes were established previously at: EOT, week 72 and week 144 after start of therapy. A multivariable logistic regression analysis adjusted for HBV genotype, age, ethnicity and gender was used to determine the association between HBcrAg levels at BL and treatment outcome, p values of <0.05 were defined significant.
Results: HBcrAg levels at BL varied significantly between HBeAg positive (median 8 $\log_{10}$ U/ml, IQR 6.6-8.4) and HBeAg negative (median 4.5 $\log_{10}$U/ml, IQR 3.9-5.6) patients ($p < 0.001$). BL levels of HBcrAg did not differ between patients who reached HBsAg loss (median 6.1, IQR 3.7-8.2) and who did not (median 5.8, IQR 4.6-8.0). The same was seen in patients with HBeAg loss (median HBcrAg 8, IQR 6.4-8.5) and without HBeAg loss (median HBcrAg 8, IQR 6.6-8.4). Also, in patients with a virological response after treatment, no statistical difference in HBcrAg levels at BL was observed.
Conclusion: HBcrAg concentration at baseline was not predictive for HBsAg or HBeAg loss in CHB patients treated for 48 weeks with adefovir and PEG-IFN.

THU-211

Evaluation of point shearwave elastography using acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in HBeAg-negative chronic HBV infection: A prospective longitudinal study

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Background and aims: Transient elastography (TE) and point shearwave elastography (pSWE) using acoustic radiation force impulse (ARFI) imaging have been widely validated for the non-invasive diagnosis of significant fibrosis ($F \geq 2$) and cirrhosis in patients with chronic liver disease. Patients with chronic HBe-antigen-negative HBV infection with persistently normal ALT and HBV-DNA levels <2000 IU/ml represent a large group of patients with mostly F0/F1 fibrosis who generally do not require antiviral treatment. However, follow-up of these patients is crucial to early detect fluctuating HBV-DNA and/or ALT levels and possible fibrosis progression. The aim of this study was to prospectively assess, whether pSWE represents a comparable diagnostic tool to TE for non-invasive assessment of liver fibrosis progression in a longitudinal cohort of untreated patients with HbeAg-negative chronic HBV infection.
Method: 922 consecutive patients (302 males, mean age 42 ± 12 years) with HbeAg-negative HBV infection were prospectively followed-up for 6 years. TE, pSWE as well as laboratory fibrosis markers FIB-4 and APRI were performed at study inclusion and at yearly intervals for 6 years. Patients were classified into the following 3 groups: nALTnHBV (ALT within normal range, HBV DNA <2000 IU/ml, n = 679), nALTeHBV (ALT within normal range, elevated HBV-DNA between 2000 and 10^5 IU/ml, n = 95) and eALTnHBV (elevated ALT, HBV-DNA <2000 IU/ml, n = 148).
Results: In the present study, pSWE results were significantly correlated with TE ($r = 0.292$, $p < 0.001$) and APRI values ($r = 0.197$, $p < 0.001$). Median ARFI values did not differ between eALTnHBV, nALTeHBV and nALTnHBV ($p = 0.43$, $p = 0.14$, $p = 0.05$). However, considering TE results, eALTnHBV had signficantly higher values despite low HBV compared to nALTnHBV and nALTeHBV ($p < 0.001$). In the 6 years of follow-up, median TE and pSWE values as well as FIB-4 and APRI values did not differ significantly from baseline values (median intra-patient changes at the end of follow-up relative to Baseline in nALTnHBV patients, TE: 0.75, $p = 0.62$; ARFI: 2.0, $p = 0.62$; APRI: 0.5, $p = 0.28$; FIB-4: 0.17, $p = 0.90$).
Conclusion: This study shows that pSWE using ARFI imaging is a reliable ultrasound-based method for the follow-up and the assessment of liver fibrosis in HbeAg-negative chronic HBV infection.

THU-212

Reactivation of occult HBV infection in HIV treated for HCV: A retrospective study

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Background and aims: Occult hepatitis B (OBI) reactivation is widely studied in immunocompromised subjects. A risk has also been described with anti-HCV direct-acting antivirals (DAAs). Aim of this retrospective study was to determine the risk of OBI reactivation in HCV-HIV patients not receiving dual active anti-HBV/HIV antiretroviral therapy (daART), treated with DAAs.
Method: We retrospectively studied HCV-HIV individuals with evidence of previous HBV exposure (HBsAg-, HBcAb+), treated with DAAs from Nov 2014 to Sep 2017, not receiving daART with tenofovir, lamivudine or emtricitabine and with undetectable baseline plasma HBV DNA. We defined HBV reactivation as an increase in both HBV DNA and serum aminotransferase, with or without clinical signs of liver decompensation.
Results: We enrolled 24 subjects. Figure shows patients' baseline characteristics. 2/24 (8.3%) developed HBV reactivation during the observation period. Both patients had AIDS history. Their CD4 nadir

was <50/mmc. At baseline they had good immunovirological control. *Case 1* was treated with SOF/VEL for 12 weeks and had HBV reactivation during follow-up, with an increase in transaminases and signs of liver decompensation. *Case 2* was treated with DCV+SOF +RBV for 24 weeks and had hypertransaminasemia at week 20, without clinical signs. Both patients showed a recurrence of HBV DNA and were switched to a daART with virological response.

Baseline Characteristics	n = 24	Case 1	Case 2
Age (year), median [IQR]	53 [50.5-58.3]	59	51
Male, n (%)	20 (83.3)	Male	Male
Prior Peg-IFN/RBV, n (%)	12 (50.0)	Naive	Naive
HCV RNA, log_{10}, median [IQR]	6.2 [5.8-6.5]	6.5	6.4
Stiffness (kPa), median [IQR]	16.1 [10.1-32.8]	7.2	46.4
HCV Genotype, n (%) 1 3 4	 11 (45.8) 10 (41.7) 3 (12.5)	4	1a
HCV Treatment, n (%) LDV/SOF ± RBV VEL/SOF ± RBV DCV/SOF ± RBV EBV/GRZ	 5 (20.8) 6 (25.0) 11 (45.8) 2 (8.4)	SOF/VEL	SOF/DCV+RBV
ALT, U/L median [IQR]	55 [38-72]	50	56
HIV RNA < 50, n (%) CD4+ count, median [IQR] CD4+ nadir	22 (91.4) 577 [346-754] 248 [111-338]	Undetectable 694 3	Undetectable 696 4
HIV Treatment, n (%) PI+INI INI+NNRTI No HAART	 19 (79.1) 2 (8.4) 3 (12.5)	RAL+DRV/r	RAL+DRV/r

Conclusion: This is the first study analyzing the risk for OBI reactivation in HCV-HIV population treated with DAAs. Our findings suggest history of AIDS and low CD4 nadir as potential risk factors for OBI reactivation. Despite small sample size, the remarkable rate of OBI reactivation (8.3%) observed could lead to hypothesize that subjects with OBI and HCV-HIV infection should receive daART during DAAs treatment or be closely monitored for OBI reactivation.

THU-213

Distinct features of hepatitis delta in a Mediterranean setting

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Background and aims: Hepatitis Delta is a rare but severe infectious disease caused by hepatitis D virus (HDV). Our aim was to establish the trend and profile of HDV-infected patients in a historically endemic mediterranean region and currently immigration receiving area.
Method: Retrospective evaluation of anti-HDV-IgG seroprevalence among HBV chronically infected patients followed in a reference Hepatology Unit. Demographic, clinical, analytic, serologic and virologic parameters were retrieved from chart review together with evolution events (cirrhosis, liver decompensation, liver transplantation and death).
Results: 70 HDV-HBV patients were included: 62, 9% were men and the median age was 52 years (interquartile range 12). Few were HBeAg positive at diagnosis (11.4%). Coinfection with other viruses (HIV 10%, HCV 11.4%), excessive alcohol consumption (34%) and overweight-obesity (50%) were common. Roughly 40% of patients were immigrants (table 1). Only 3., 4% had been treated with Interferon. Regarding HBV infection, 54.3% had received oral antiviral drugs, mostly tenofovir. Significant differences were found regarding the time between the diagnosis of infection and that of cirrhosis among patients diagnosed before and after 2000. Patients diagnosed after vs before the year 2000 were diagnosed within a median time frame of 2 vs 17 years, respectively, suggesting a late diagnosis in those recently diagnosed. The vast majority of patients developed cirrhosis (77.1%), liver decompensation (72.2%), need of transplantation (45.7%) and/5.7% patients died due to liver diseases.

Demographic parameters		*Total* *% (N)*	*Diagnosis pre- 2000* *57, 1% (N = 40)*	*Diagnosis post 2000* *42, 5% (N = 30)*
COUNTRY OF BIRTH BY REGION	*Spain*	67, 1% (47)	92, 5% (37)	33, 3% (10)
	Eastern Europe	24, 3% (17)	7, 5% (3)	46, 7% (14)
	Other	8, 6% (6)	0	20% (6)
DIABETES MELLITUS	*Non diabetic*	91, 4% (64)	97, 5% (39)	83, 3% (25)
	Diabetic	8, 6% (6)	2, 5% (1)	16, 7% (5)
ALCOHOL CONSUMPTION	*No alcohol use*	64, 3% (45)	70% (28)	58, 6% (17)
	Alcoholic	34, 3% (24)	30% (12)	41, 4% (12)
WEIGHT	*Underweight*	2, 9% (2)	2, 7% (1)	3, 8% (1)
	Normal weight	37, 1% (26)	32, 4% (12)	53, 8% (14)
	Overweight	32, 9 % (23)	37, 8% (14)	34, 6% (9)
	Obese	17, 1% (12)	27% (10)	7, 7% (2)
Serologic parameters				
HBe Antigen	*HBeAg +*	11, 4% (8)	20, 5% (8)	0
VIH	*VIH +*	10% (7)	17, 5% (7)	0
VHC	*VHC +*	11, 4% (8)	11, 4% (8)	0
Evolution events				
CIRRHOSIS PROGRESSION		77, 1% (54)	82, 5% (33)	72, 4% (21)
LIVER DECOMPENSATION		72, 2% (39)	77, 4% (24)	75, 0% (15)
TRASPLANTATION		45, 7% (32)	55, 0% (22)	33, 3% (10)
DEATH		5, 7% (4)	5% (2)	6, 7% (2)

Conclusion: Patients diagnosed in recent years are diagnosed late, possibly reflecting a late referral pattern among immigrants. We confirm a high rate of evolutive liver complications, probably related to HDV, although we cannot rule out the role of other etiologic agents such as alcohol, metabolic syndrome or hepatotropic virus coinfection.

THU-214

Annual average of integral FIB-4 index and HBV core-related antigen as an appropriate indicators for starting nucleoside analogues at an optimum timing

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Background and aims: Although nucleos (t)ide analogue (NA) has been reported to be useful for suppressing hepatocellular carcinoma (HCC) with hepatitis B patients, it is important not to miss an optimum timing of starting NA because not a few patients progress to HCC thereafter. Serum HBV core-related antigen (HBcrAg) is reported to correlate with intrahepatic cccDNA which may be related to viral activity and carcinogenic risk. In this study, we evaluated annual average of integral FIB-4 index (aaFIB-4) and serum HBcrAg for determining an adequate timing of NA and estimating the HCC risk during NA treatment.
Method: A total of 522 HBs antigen (HBsAg)-positive patients who did not have a history of HCC were followed from the start of NA [entecavir (ETV) 319, lamivudine (Lam) to ETV 76, Lam 28, Lam or ETV plus adefovir (ADV) 99 cases]. An aaFIB-4 was calculated from the integral value of each FIB-4 index during the same year. Serum levels of HBcrAg were measured by the Lumipulse® HBcrAg

Chemiluminescence Enzyme Immunoassay (Fujirebio, Tokyo, Japan). The dynamic range of the assay is 3.0 to 6.8 (log_{10} U/ml). Kaplan-Meier method was used to estimate the cumulative occurrence of HCC.

Results: During the median follow-up of 107 months, HCC was confirmed in 79 patients. Overall cumulative 5/10 year occurrence rate of HCC (5/10y-HCC rate) was 10.0/18.2%. The cut off value of aaFIB-4 and log_{10} HBsAg at the start of NA treatment for the occurrence of HCC during the treatment course was 3.00 and 3.2 (log_{10} IU/ml) by ROC analysis. 5y-HCC rate was 0/2.3/1.1/18.7/31.3 (%) for those whose pretreatment aaFIB-4 was <1.0/1.0-2.0/2.0-3.0/3.0-4.0/4.0 ≤ and 5.1/15.9/5.7 (%) for those whose pretreatment HBcrAg was <3.0/3.0-6.8/6.8 < .5/10y-HCC rate by the combined conditions is shown in Table. High aaFIB-4 was a significant predictive factor of HCC and high HBsAg/low HBcrAg indicated low risk of HCC. In cases of high aaFIB-4/low HBsAg, probability of HCC increased with increasing HBcrAg. 10y-HCC rate of cases whose HBcrAg remained <3.0 (Gr.1), decreased to <3.0 (Gr.2), remained ≥3.0 (Gr.3) was 5.1/11.9/17.8 (%). Among high aa FIB-4 cases, 5y-HCC risk of those whose aa FIB-4 declined below 3.00 during NA treatment was 17.2%, whereas those who did not show aaFIB-4 decrease was 29.5% (p = 0.04).

Table: 5y/10y-HCC rate (%) by the combined conditions of aaFIB-4 index, HBcrAg and HBsAg.

		Overall		aaFIB-4 <3.00		aaFIB-4 ≥3.00	
log_{10}HBsAg		<3.2	3.2 ≤	<3.2	3.2 ≤	<3.2	3.2 ≤
HBcrAg	<3.0	8.4/8.4	2.3/2.3	0/0	0/0	19.0/19.0	0/0
	3.0–6.8	17.6/30.2	11.9/19.6	5.0/14.7	2.4/5.1	22.9/48.0	24.6/39.2
	6.8 <	10.3/17.6	1.4/8.6	0/0	0/3.5	27.3/62.7	17.6/21.6

Conclusion: AaFIB-4 and HBcrAg at the start of NA treatment was correlated with occurrence of HCC afterwards. NA should be started before aaFIB-4 index reaches 3.00. The decrease of aaFIB-4 or HBcrAg after NA treatment may reduce the risk of HCC.

THU-215

Association between core mutations and annual decline rate of HBVDNA and HBsAg in chronic hepatitis B patients treated with nucleoside analogue

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Background and aims: We have reported that measurement of core I97L mutation in addition to HBVDNA and ALT levels would be useful to predict subsequent clinical course in chronic hepatitis B (CHB) patients. We investigated differences in annual decline rate of HBVDNA and HBsAg between patients who treated with nucleoside analogue therapy (NA) therapy (Group NA) and patients who were observed in the natural history of the disease (Group N). Hepatitis B core-related antigen (HBcrAg) may serve as useful marker for virus replication and reflect intrahepatic cccDNA.

Method: One hundred thirty-eight CHB patients who were determined core I97 were enrolled in this study. Median age of patients was 42 (male/female = 67/71, Group NA/Group N = 42/96, all patients had genotype C virus). Median observational period was 7.0 years. 1) In Group N (n = 96) annual decline rate of HBVDNA and HBsAg were compared according to presence of core I97L mutation. 2) Among Group NA (n = 42) annual decline rate of HBVDNA and HBsAg were compared according to presence of core I97L mutation before NA therapy. Moreover, HBcrAg at final visit was also compared according to presence of core I97L mutation.

Results: 1) In Group N annual decline rate of HBVDNA in patients with I97L was significantly higher than that in patients with I97 wild-type (0.23 log copies/ml/year, 0.05 log copies/ml/year, respectively, p = 0.036). On the other hand, annual decline rate of HBsAg in patients with I97L was significantly higher than that in patients with I97 wild (0.10 IU/ml/year, 0.05 IU/ml/year, respectively, p = 0.003). Furthermore, the rate of HBsAg loss in patients with I97L was significantly higher than that in the patients with I97 wild (24.3% vs. 3.6%, respectively, p = 0.002). 2) Among Group NA there was no significant difference in annual decline rate of HBVDNA and HBsAg. However, HBcrAg of the patient with I97L was significantly lower than that of the patients with I97I/Fwild (3.0 logU/ml vs. 3.7 logU/ml, respectively).

Conclusion: In CHB patients, patients with I97L had significantly higher annual decline rate of HBVDNA and HBsAg. Patients with I97L before NA treatment showed significantly lower HBcrAg at final visit. These results suggest HBcrAg levels would be low in patients who have I97L mutation before NA therapy.

THU-216

Rapid turnover of HBV cccDNA in nucleoside-treated chronic hepatitis B patients during drug resistance emergence and breakthrough

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Background and aims: Current low cure rates in patients chronically-infected with Hepatitis B Virus (HBV) using standard of care therapy are believed to be due to an inability to eliminate cccDNA reservoirs in patients. It remains unclear whether persistence is due to the longevity of cccDNA or its efficient replenishment by either *de novo* infection or intracellular amplification.

Method: Methodologies were optimized to enable analysis of distinct populations of cccDNA, pgRNA and viral DNA in both CHB patient sera and liver biopsies. Pan-genotypic primers were designed to amplify the HBV reverse transcriptase (RT) gene. HBV cccDNA from snap-frozen liver biopsies were extracted by a modified Hirt method, digested with T5 exonuclease, amplified by PCR. Intrahepatic rcDNA and HBV RNA were purified with QIAamp MinElute Virus kit from flow-through of Hirt extraction. HBV DNA and pgRNA were extracted from patient sera using a QIAamp MinElute Virus kit. Aliquots were digested by DNase I and used as a template for RT-PCR. Sanger sequencing results of PCR and RT-PCR fragments were analyzed using Sequencher™ software (Gene Codes) and the percentage of signature lamivudine/telbivudine resistance (Nuc^R) mutations was calculated by population sequencing or clone-based sequencing following TA-cloning.

Results: The emergence and disappearance of Nuc^R mutations was retrospectively monitored as a sensitive genetic marker of cccDNA turnover/evolution in a panel of patients with paired patient liver and serum samples from two clinical studies (EFFORT and ML18376). Critical to the success of this genetic approach, we found a strong relationship between the population sequences found in serum pgRNA, intrahepatic HBV RNA and cccDNA samples, validating serum RNA as a surrogate marker of cccDNA sequences at time points when liver biopsy samples were unavailable. The observed changes in Nuc^R viral variants (DNA) suggest the near complete turnover of wild-type pgRNA and cccDNA populations, with serum HBV DNA, pgRNA and cccDNA populations observed to switch between WT and Nuc^R populations in as little as 3-4 months in some patients. Compensatory mutations that affect fitness likely account for the range of timelines observed for complete viral genetic turnover in breakthrough patients. In all cases, turnover rates were measured in several months, not years, as previously predicted.

Conclusion: Serum pgRNA was validated as a surrogate genetic biomarker for cccDNA populations. Overall, cccDNA pools appear to

be dynamic, with rapid decay of existing populations and complete turnover in as little as 3-4 months. These findings support the potential for a finite treatment period for regimens that can fully suppress viral replication and inhibit regeneration of new cccDNA molecules.

THU-217

Low risk of HBV reactivation in a large European cohort of HBV/HCV coinfected patients treated with DAA

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Background and aims: Several cases of HBV reactivation during direct acting antivirals (DAA) for HCV were described in both HBsAg (+) and HBsAg (-)/anti-HBc IgG (+) patients. The exact rate of HBV-reactivation in HBV/HCV coinfection is poorly defined, especially in European cohorts. The aim of study was to characterize HBV/HCV coinfection and evaluate the prevalence HBV-reactivation during DAA.

Method: Analyzed population consisted of 6228 chronic hepatitis C patients (52% female, mean age 54yo, 82% HCV-GT1b, 34% with liver cirrhosis) receiving therapy with DAA in 2016-2017 included in a large national database EpiTer-2. DAA combinations consisted mainly of OBV/PTV/r±DSV±RBV (53%) and LDV/SOF±RBV (28%). Prior to the DAA all subjects had HBsAg testing and ALT-activity evaluated every 4 weeks during DAA. Anti-HBc IgG testing was available in 742 patients without HBsAg.

Results: 70 of 6228 patients (1.1%) had detectable HBsAg. HBV/HCV patients were significantly younger and more often infected with HCV-GT3 and 4 than HCV-group. They were also less often diagnosed with arterial hypertension (26% vs 38%, P = 0.04), diabetes (6% vs 15%, P = 0.03) and had lower BMI (24.5 vs 26.0, P <0.01). On the other hand, proportion of liver cirrhotics, ALT activity, MELD and Child-Pugh were comparable. Prior of DAA only 21 (30%) of HBV/HCV required NA-therapy.

In both groups DAA-therapy was continued according to plan in 96% (HBV/HCV) vs 95% (HCV) and number of adverse events was comparable. SVR rates were similar in HBV/HCV and HCV in overall group (mITT 97% vs 95%, P = 0.7) and for specific HCV-genotypes.

Importantly, in HBsAg (+) subjects only 3 (4.3%) HBV reactivations were observed, while none occurred in HBsAg (-)/anti-HBc IgG (+) group (n = 742). All 3 subjects with reactivation were HBeAg (-), infected with HCV-GT1 and had advanced liver disease (F3-F4). One reactivation was clinically significant with HBV-DNA increase (from 1.3 to 7.6 log10 IU/ml at wk5) and ALT-flare (1337 IU/m) requiring DAA discontinuation and NA therapy, while 2 remaining were subclinical with HBV-DNA increase form negative to 1.3 (wk12) and 3.2 log10 IU/ml (wk8). All subjects with HBV-reactivation reached SVR.

Conclusion: Data form a large European cohort suggest that the risk of HBV reactivation during therapy with DAA seems to be low in HBsAg (+) HBV/HCV subjects (<5%), while probably neglectable in HBsAg (-)/anti-HBc IgG (+). Interestingly, subjects with HBV/HCV coinfection seem to less often present symptoms and complication of metabolic syndrome.

THU-218

Immune reconstitution inflammatory syndrome and CD4 lymphocyte count as predictive factors for HBsAg seroclearance in HBV/HIV patients treated with antiretroviral therapy

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Background and aims: HIV infection has a great influence on the natural history of HBV infection, with enhanced risk of liver disease progression and increased liver-associated mortality compared with HBV mono-infection. Treatment of HBV infection in patients co-infected with HIV is commonly initiated with HBV-active antiretroviral therapy (ART), which includes two nucleoside/nucleotide reverse transcriptase inhibitors, usually either lamivudine or emtricitabine together with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). The main goal of HBV treatment is HBsAg seroclearance both in HBV mono-infected patients and in HBV/HIV coinfected patients. However, little is known about factors predicting HBsAg seroclearance. The aim of this study is to identify predictive factors for HBsAg seroclearance in HBV/HIV coinfected patients treated with ART.

Method: This is a retrospective study at our hospital in Osaka, Japan. A total of 43 patients coinfected with HBV/HIV who started TDF/TAF-based ART between December 2012 and December 2017 were analyzed with a mean follow-up period of 31.0 months. Immune reconstitution inflammatory syndrome (IRIS), which is a common complication of ART initiation and associated with an inflammatory response toward microbial antigens, was diagnosed according to Shelburne's criteria (J Antimicrob Chemother. 2006). Predictive factors for HBsAg seroclearance were assessed by univariate and multivariate logistic regression analysis.

Results: The baseline characteristics of all patients at therapy initiation were as follows (continuous variables are expressed as mean): age, 37.0 years old; sex (male/female), 43/0; HBV genotype (A/B/C/D/unknown), 31/0/3/0/9; HBV-DNA level, 7.4 logCP/ml; HIV-RNA level, 4.9 logCP/ml and CD4 lymphocyte count, 250/μL. All patients achieved sustained viral suppression. HBsAg seroclearnce

occurred in 13 patients with HBV genotype A and was not observed in patients with HBV genotype C. Seven out of the 13 patients showed liver enzyme elevation associated with IRIS within 3 months after antiretroviral therapy initiation. Both univariate and multivariate analysis showed that IRIS onset (odds ratio = 6.770, P = 0.0236) and initial CD4 lymphocyte count (odds ratio = 8.710, P = 0.0121) were found to be statistically significant predictive factors for HBsAg seroclearance following ART.
Conclusion: This study indicated that IRIS onset and initial CD4 lymphocyte count can be independent predictive factors for HBsAg seroclearance in HBV/HIV coinfected patients treated with ART.

THU-219

Long-term outcome in Caucasian patients with hepatitis B e antigen-negative chronic infection: An observational cohort study

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Background and aims: The long-term outcome and risk of hepatitis B virus (HBV) reactivation in the Caucasian population with hepatitis B e antigen (HBeAg)-negative chronic infection have rarely been studied before. In this study, we explored this issue by a long-term follow-up of patients with HBeAg-negative chronic infection.
Method: Out of 1, 081 patients with chronic HBV infection, we retrospectively identified 236 Caucasian patients with HBeAg-negative chronic infection who presented at the Outpatient Hepatology Department of University Hospitals KULeuven between 1 January 1968 and 31 July 2018. HBeAg-negative chronic infection was defined as low or undetectable HBV DNA (≤20, 000 IU/ml) and persistently normal alanine-aminotransferase levels (PNALT). Patients previously treated with HBV antiviral agents or corticosteroids were to be excluded as well as patients with cirrhosis at presentation and patients with co-existing chronic liver disease.

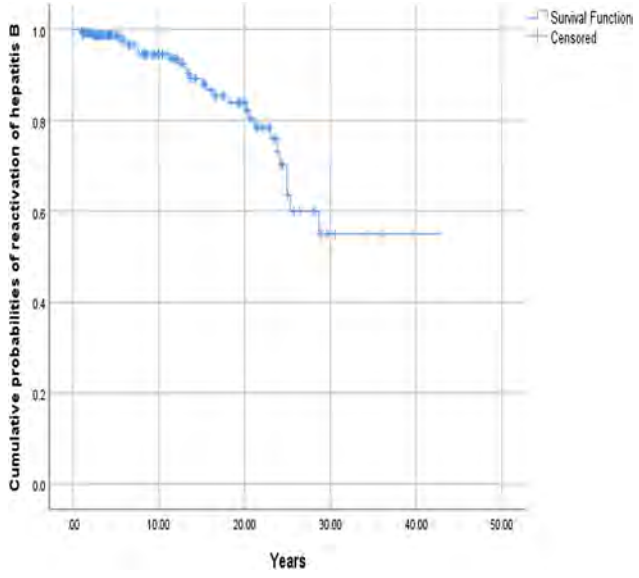

Figure 1: Cumulative probability of reactivation of hepatitis B in Caucasian patients with hepatitis B e antigen-negative chronic infection.
Results: During a median follow-up of 10 (interquartile range: 14.2) years, 208 (88%) of the 236 patients showed sustained remission, whereas the remaining 28 (12%) experienced reactivation of hepatitis B. The cumulative probabilities of reactivation of hepatitis B were 2% 8% and 27% at 5, 10 and 20 years follow-up, respectively (Fig. 1). In a multivariate analysis using Cox proportional hazards regression models, reactivation of hepatitis B was independently associated with advanced age at presentation (>40 years) (hazard ratio (HR) = 2.92; 95% confidence interval (CI) = 1.23-6.92; p = .015) and any HBV DNA level >2, 000 IU/ml (HR = 3.68; 95% CI = 1.53-8.82; p = .004). Significant fibrosis (liver stiffness >9 kPa) and cirrhosis developed in respectively 9/133 (7%) and 3/236 (1%) patients. Cox proportional hazard regression models showed that advanced age at presentation was the only factor significantly associated with a higher risk of significant fibrosis (HR = 4.90; 95% CI = 1.71-14.1; p = .003).
Conclusion: Antiviral treatment is not indicated in Caucasian patients with HBeAg-negative chronic infection since the prognosis of liver disease is favourable. However, the results from this study reinforce the need for clinical surveillance for the risk of HBV reactivation in patients older than 40 years and those with any HBV DNA level >2, 000 IU.

THU-220

Early steep decline of liver stiffness predicts histological reverse of fibrosis in chronic hepatitis B patients treated with entecavir

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Background and aims: Whether dynamic changes of liver stiffness measurement (LSM) could predict the reversibility of fibrosis remains unknown. Therefore, we evaluated the utility of LSM declining for predicting histological changes of fibrosis in patients with chronic hepatitis B (CHB) on antiviral therapy.
Method: In a prospective cohort of CHB patients treated with entecavir, virology, biochemistry and LSM were measured at baseline and every 6 months. Liver biopsies were conducted at both baseline and 18-month treatment. Fibrosis regression was defined by two criteria: (1) Ishak decreasing ≥1 stage, (2) Ishak decreasing ≥1 stage or predominantly regressive by posttreatment P-I-R classification. Piecewise linear mixed-effects model and ROC analysis were used to evaluate the dynamic changes of LSM and its predictive value for histological reversibility.
Results: We found that at month 18 of antiviral therapy, liver fibrosis was reserved in 86 patients of 212 (40.6%) CHB patients by Ishak reversal criterion. Overall, LSM declining was associated with attenuation of Ishak stage. The rate of LSM declining in the first 6 months was significantly faster in patients with fibrosis reverse (ΔLSM%Ishak = −2.19%/month, p = 0.0025; ΔLSM%Ishak/PIR = −2.56%/month, p = 0.0004). The predictive model based on baseline FIB-4 and Ishak stage as well as baseline LSM, PLT, ALB and their changes during the first 6 months could predict the histological reverse (AUROCIshak = 0.74, 95% CI: 0.67-0.80; AUROCIshak/PIR = 0.81, 95% CI: 0.74-0.87).
Conclusion: We concluded that dynamic changes of LSM during the first 6 months of entecavir therapy could predict histological reversibility of liver fibrosis in CHB patients.

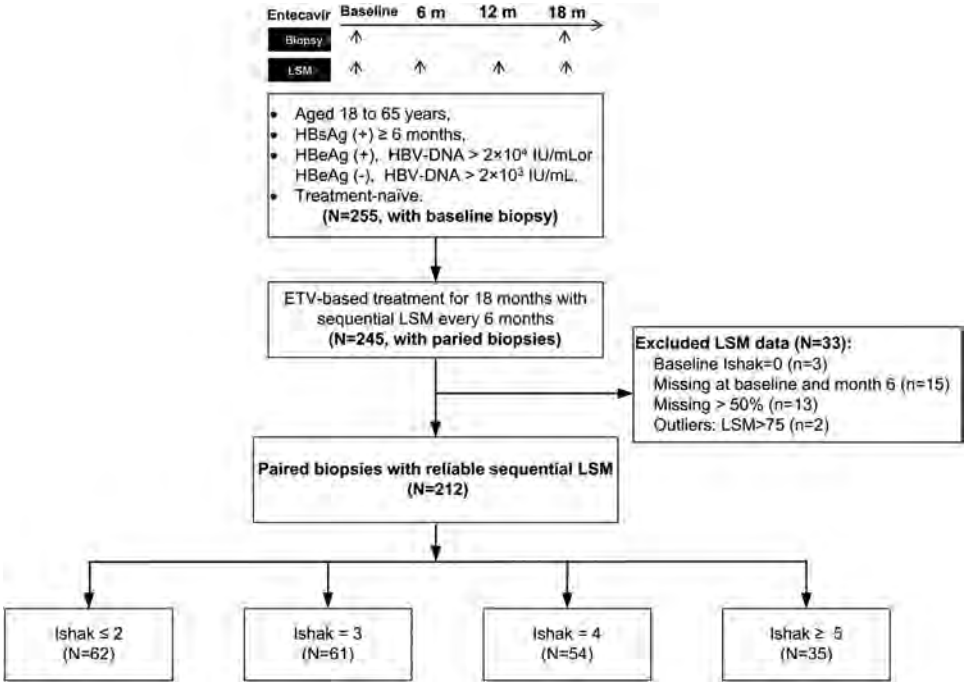

Figure 1: (abstract: THU-220): Flowchart of the selection of patients with paired liver biopsy and reliable sequential LSM.

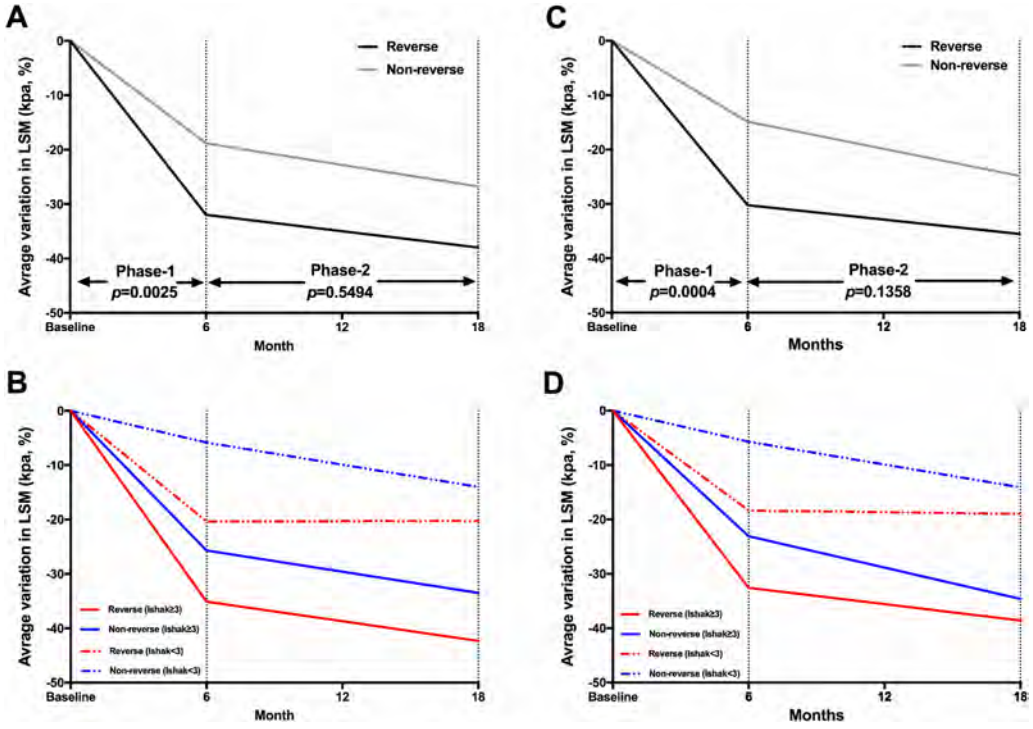

Figure 2: (abstract: THU-220): Biphasic pattern of LSM changes in CHB patients on antiviral therapy and LSM declining was associated with the fibrosis stage by the Ishak criterion (A and B) and by the Ishak/posttreatment P-I-R criterion (C and D). Under both criteria of fibrosis regression, dynamic changes of LSM consisted of a rapid phase of declining during the first 6 months of treatment and a slow phase of declining from month 6 to month 18. In patients with baseline Ishak stage ≥3, the first phase of LSM declining was significant faster in reverse group.

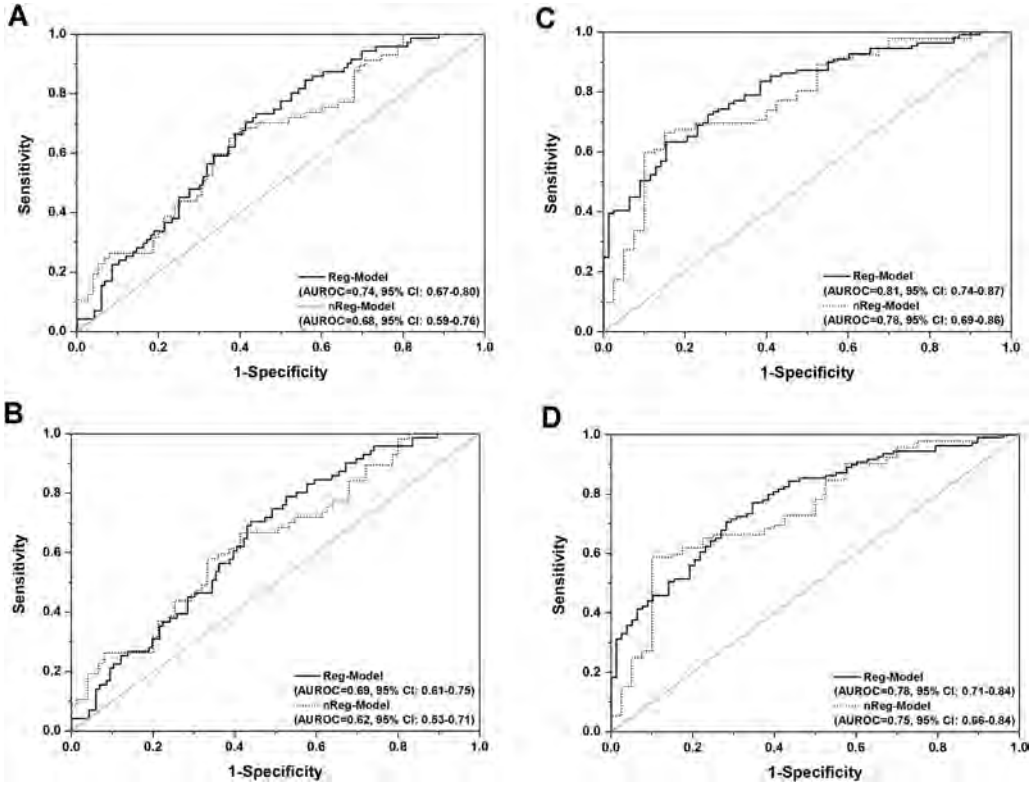

Figure 3: (abstract: THU-220): The performance of regression-predicting models for predicting histological reverse of liver fibrosis in patients with or without significant fibrosis in derivation set and validation set by the Ishak criterion (A and B) and by the Ishak/posttreatment P-I-R criterion (C and D). Reg-Models based on dynamic changes of LSM of first 6 months of treatment could predict histological reversibility of liver fibrosis in CHB patients. Reg-Model: prediction model in total CHB patients;nReg-Model: prediction model in CHB patients with significant fibrosis.

THU-221

Xpert HBV VL, simplifying HBV viral load testing and disease management

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Background and aims: Viral Load (VL) quantification plays a key role for the monitoring of patients affected by Hepatitis B virus. Recently Cepheid has developed a new cartridge-based HBV VL assay. The aim of this work was to compare the performance of the Cepheid Xpert HBV VL assay to the Abbott m2000 HBV VL assay, to assess the linearity, the inclusivity and the precision of Xpert HBV VL test. The workflow of the two assays has been evaluated.
Method: For the precision, 4 HBV specimen have been prepared by dilutions at different concentrations (0, 1.64, 6.09 and 7.92 log IU/ml) and tested on the Xpert HBV VL assay in duplicate for 10 runs over 10 days. For the method comparison (MC), 85 specimens from HBV infected patients were tested with both assays. Results were compared by a Passing Bablok and Bland-Altman analysis. The patient monitoring has been carried out on 80 serial plasma samples collected from 24 patients. Inclusivity has been assessed on 5 genotypes circulating in our region, genotype A, B, C, D and E. For linearity, one high viremic sample was diluted to several concentrations.The turn-around time (TAT), the hands on-time (HoT) have been determined on both assays.
Results: The MC showed a high correlation (R^2 = 0.99, slope = 1.04, intercept = –0.12, Passing Bablok) and a Mean Difference of –0.015 (CI 95% = –0.05-0.02 Bland Altman) between the assays. Linearity on the genotypes (A, B, C, D and E) shows an R^2 >0.95. Precision gave a standard deviation lower than 0.1 log IU/ml. Workflow has been analyzed on 1 week activity. Abbott method required 7h to process all the samples, Cepheid method provided all the results in 3h21min. The HoT required by Cepheid assay is significantly lower than the HoT for Abbott assay (36mn versus 54mn respectively). In our laboratory Abbott test is performed twice a week (two batches) and the mean TAT is 89h34mn. Cepheid assay showed a TAT of 3h21mn.
Conclusion: A good correlation was observed between both assays. Inclusivity and linearity showed very good performances with high R^2 values. The extraction, amplification and detection steps of Xpert HBV VL assay are all performed onto a single platform, GeneXpert system. It reduces consequently the complexity of the process and the labor time. Xpert HBV VL assay allows continuous loading of samples, which eliminates the need for batching, but it also allows urgent samples testing, leading to a significative improvement of our productivity.

THU-222

The application of novel HBV pgRNA assay to predict HBeAg clearance on long-term nucleos (t)ide analogues

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Background and aims: Nucleos (t)ide analogues (NAs) are associated with HBeAg loss in only approximately 40-50% of patients with prolonged therapy. The aim of the study is to identify the virological

profiles of patients who are unlikely to clear HBeAg with long term NA treatment so alternative therapy can be considered.
Method: HBeAg positive patients with baseline HBV DNA ≥ 5 $\log_{10}$ IU/ml on NAs for at least 20 months with available stored serial sera were included. HBV pgRNA was measured using the Abbott research assay [Sensitivity is 1.65 $\log_{10}$ U/ml with linearity from 2.5 to 7.5 $\log_{10}$ IU/ml (R^2 = 0.99)]. Clinical and virological parameters were compared between patients with and without HBeAg clearance on prolonged therapy.
Results: This predominantly Asian (86%) cohort included 17 and 11 patients with and without NA treatment-related HBeAg loss respectively. The duration of therapy, baseline HBV DNA, ALT levels were similar between the 2 groups [Table]. Patients with and without HBeAg loss achieved HBV DNA < 20 IU/ml at similar time line from start of therapy. Those with HBeAg loss, however, had significantly lower HBV pgRNA levels when HBV DNA became suppressed to < 20 IU/ml. With long term therapy more than 5 years, HBV RNA levels remained > 4 $\log_{10}$ IU/ml among those without HBeAg loss. Five of 17 (29%) patients with HBeAg loss had hepatitis flare (ALT > 100 U/L) associated with HBV RNA reduction (Mean 1.68 log) preceding HBeAg clearance. Their HBV pgRNA levels became <1.65 $\log_{10}$ IU/ml shortly after HBeAg loss. In contrast, 12 of 17 patients without hepatitis flare prior to HBeAg loss had significantly higher HBV pgRNA level (Average 3.12 $\log_{10}$ IU/ml) at time of HBeAg clearance. At last follow-up, the HBV pgRNA level was significantly lower among those with HBeAg loss [Table]. Ten of 17 (59%) patients with HBeAg clearance achieved HBV pgRNA < 1.65 $\log_{10}$ IU/ml.

[Mean, range]	HBeAg Loss (N = 17)	Without HBeAg Loss (N = 10)	P Value
Duration of therapy: Months	75 (22, 168)	84 (27, 184)	0.30
Baseline HBV DNA ($\log_{10}$ IU/ml)	7.2 (5.2, 8.2)	7.5 (5, 8.2)	0.28
Baseline ALT (U/L)	107 (18, 260)	84 (14, 268)	0.20
Time to HBV DNA <20 IU/ml (Months)	38.6 (10.6, 141)	46.9 (6, 159)	0.29
HBV pgRNA ($\log_{10}$ IU/ml) when HBV DNA <20 IU/ml	2.5 (*UD, 5.32)	5.6 (3.83, 6.72)	<0.00002
HBV pgRNA at last follow-up ($\log_{10}$ IU/ml)	1.62 (*UD, 3.33)	4.68 (3.29, 5.77)	<0.00001

*UD = undetectable

Conclusion: In this cohort, HBV pgRNA kinetics on therapy differentiated patients with and without HBeAg clearance on long term NA treatment. Those HBV pgRNA remained > 5.6 $\log_{10}$ IU/ml when HBV DNA was suppressed tended to have very gradual HBV pgRNA decline over prolonged therapy and were unlikely to achieve HBeAg loss. Hepatitis flare with ALT > 100 U/L was often associated with significant HBV pgRNA reduction and subsequent HBeAg clearance. These observations need to be carefully validated in a larger cohort of patients.

THU-223
Development of an optimized risk prediction model for hepatocellular carcinoma in chronic hepatitis B patients with well-controlled viremia by antivirals

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Background and aims: The risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B has been substantially decreased in the era of antiviral therapy. We aimed to develop an optimized risk prediction model for HCC in patients with well-controlled viremia by nucelos (t)ide analogues (NUCs).
Method: This study included patients who achieved virological response (VR; serum HBV-DNA < 2, 000 IU/ml on two consecutive assessments) by NUCs. Liver stiffness (LS) was assessed by transient elastography at the time of confirmed VR in all patients. Patients with decompensated liver cirrhosis or HCC at baseline were excluded. Multivariate Cox-proportional hazards model were used to determine potential factors for a risk prediction model.
Results: Among a total of 1511 patients, 143 (9.5%) patients developed HCC during follow-up. Age (adjusted hazard ratio [aHR] 1.04, 95% CI 1.02-1.06), LS ≥ 11 kPa (aHR 6.09, 95% CI 3.89-9.55), cirrhosis on ultrasonography (aHR 2.47, 95% CI 1.35-4.53), male gender (aHR 1.9, 95% CI 1.2-2.8), albumin <4.5 g/dL (aHR 1.77, 95% CI 1.21-2.59) and platelet < 135, 000/uL (aHR 1.57, 95% CI 1.07-2.32) were potential variables to make a risk prediction model for HCC development (all p < 0.05). These 6 parameters were weighted to develop a novel nomogram ranging from 0 to 271 points; a total point of 180 means the probability of 10% and 30% for HCC development at 5- and 10-years, respectively. The overall c-index was 0.876 (95% CI 0.845-0.902).
Conclusion: A novel nomogram enabled the more accurate prediction of HCC development among patients with well-controlled viremia by NUCs.

THU-224
Validation of modified PAGE B in patients with chronic hepatitis B undergoing antiviral treatment

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Background and aims: A new risk prediction model for development of hepatocellular carcinoma (HCC), that is, modified PAGE-B (mPAGE-B) which includes age, gender, platelet count and albumin level as constituent variables, has recently been proposed in Asian chronic hepatitis B (CHB) patients undergoing antiviral therapy. We aimed to externally validate mPAGE-B model and compared its predictive performance with that of conventional risk prediction models in the independent cohort.
Method: CHB patients undergoing oral antiviral therapy between November 2005 and December 2014 were consecutively recruited. The predictive performance of mPAGE-B and five conventional risk prediction models including the Chinese University-HCC (CU-HCC), the modified guide with age, gender, HBV DNA, and cirrhosis-HCC (GAG-HCC), the risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B), PAGE-B and Toronto HCC risk index (THRI) were assessed with comparisons.
Results: A total of 1330 chronic hepatitis B patients (821 men, 61.7%) who were treated with oral antivirals were finally analyzed. The mean age was 48.1 years. During the follow-up period (median, 65.8 months), 101 (7.6%) patients developed HCC. For the prediction of HCC development at 5-years, mPAGE-B showed the highest c-index (0.792, 95% confidence interval [CI] 0.759–0.826), followed by GAG-HCC (0.772, 95% CI 0.732–0.813; vs. mPAGE, p > 0.05), PAGE (0.769, 95% CI 0.731–0.807; vs. mPAGE, p > 0.05), REACH-B (0.714, 95% CI 0.663–0.764; vs. mPAGE, p < 0.05), CU-HCC (0.623, 95% CI 0.571–0.675; vs. mPAGE, p < 0.05), and THRI (0.542, 95% CI 0.516–0.599; vs. mPAGE, p < 0.05). The cumulative risk of HCC development at 3- and 5-years were 0% and 0% in the low-risk group (mPAGE score ≤ 8), 4.1% and 6.1% at 5-years in the intermediate-risk group (mPAGE score 8–12) and 10.8% and 19.7% in the high-risk group (mPAGE score ≥ 13), respectively (p < 0.001 by log-rank test; low- vs. intermediate-risk group, p < 0.001 and intermediate- vs. high-risk group, p < 0.001).

Conclusion: Our study demonstrated that mPAGE-B is applicable with acceptable predictive performance in Asian CHB patients receiving oral antiviral therapy. mPAGE-B showed the similar predictive performance to PAGE-B and GAG-HCC and the better performance than REACH-B, CU-HCC and THRI.

THU-225

Risk prediction model for hepatocellular carcinoma after hepatitis b e antigen seroclearance in patients treated with entecavir or tenofovir

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Background and aims: Only one risk prediction model for hepatocellular carcinoma (HCC) after hepatitis B e antigen (HBeAg) seroclearance has been available. Therefore, we established and validated a risk prediction model for HCC development after HBeAg seroclearance in patients with chronic hepatitis B (CHB) treated with either entecavir or tenofovir.
Method: We recruited patients with CHB who experienced HBeAg loss during either entecavir or tenofovir treatment between March 2006 and December 2016. Patients with significant alcohol abuse or decompensated cirrhosis were excluded.
Results: A total of 777 patients were evaluated. The mean age was 46.6 years old, and 59.3% were male. At the time of HBeAg seroclearance, 473 (60.9%), 296 (38.1%), and 8 (1.0%) of these patients received entecavir, tenofovir, or a combined use of entecavir and tenofovir, respectively. Ultrasonographic cirrhosis was identified in 321 (41.3%) patients. In multivariate analysis, male gender (hazard ratio [HR] = 2.236; 95% confidence interval [CI], 1.242-4.028; P = 0.007), ultrasonographic cirrhosis (HR = 6.076; 95% CI, 2.905-12.707; P < 0.001), and FIB-4 > 3.25 (HR = 2.145; 95% CI, 1.252-3.675; P = 0.005) were independent risk factors for HCC development after HBeAg seroclearance. Based on these independent predictors, a HBE-HCC model was developed (1x [male 1, female 0] + 3x (ultrasonographic cirrhosis 1, non-cirrhosis 0) + 1x (FIB-4 > 3.25 1, ≤ 3.25 0). The area under receiver operating characteristics to predict HCC development at 1-, 3-, 5-, and 10-years after HBeAg seroclearance was 0.775 (95% CI, 0.687-0.863), 0.791 (95% CI, 0.724-0.858), 0.771 (95% CI, 0.708-0.834), and 0.790 (95% CI, 0.745-0.845), respectively (all P < 0.05).
Conclusion: We established a new risk prediction model for HCC development, which we called the HBE-HCC model. This model is based on three independent risk factors (male gender, ultrasonographic cirrhosis, and FIB-4 > 3.25) in patients with CHB treated with entecavir or tenofovir and here we reported that the accuracy which can predict HCC development until 10 years was acceptable. This model might be helpful in risk stratification even with evidence of HBeAg seroclearance. However, external validation is required.

THU-226

Concomitant diabetes mellitus increases risk of liver fibrosis in treatment-naive chronic hepatitis B with low viral loads: Results from a matched case-control study

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Background and aims: >60% of the world's diabetic population are from Asia, and East Asia has a high prevalence of chronic hepatitis B (CHB). The presence of diabetes may affect disease outcomes in CHB, although this interaction is not well understood. We aim to determine the association between diabetes and CHB in terms of metabolic, virologic and transient elastography profiles.
Methods: We prospectively recruited CHB patients with concomitant type two diabetes mellitus, as defined by the International Diabetes Federation, for measurement of liver biochemistry, virologic profiles, metabolic parameters and transient elastography for liver stiffness (LS) and controlled attenuation parameter (CAP). This cohort was matched with non-diabetic CHB patients according to age, gender, nucleoside analogue treatment status and duration in a 1:1 ratio. Cirrhosis was defined following American Gastroenterological Association as LS ≥ 11.0kPa. Steatosis was defined as CAP ≥ 248 dB/m.
Results: 970 CHB patients, including 485 diabetic CHB (mean age 60.9 ± 8.4 years, 66.4% male, 68.2% treated with median treatment duration 79.1 months) and 485 non-diabetic CHB (mean age 60.5 ± 8.4 years, 66.4% male, 68.2% treated with median treatment duration 77.5 months) were recruited in this interim analysis. Among treatment-naïve patients, median HBV DNA level was 450 (IQR 56-6, 700) IU/ml and 67.2% had HBV DNA levels < 2, 000 IU/ml. Diabetic CHB patients, when compared to non-diabetic patients, had significantly higher median LS (6.7 vs 6.1 kPa, p = 0.001) and CAP (272 vs 240 dB/m, p < 0.001). Median LS measurements showed similar differences in treatment-naïve patients (6.3 vs 5.2 kPa, p < 0.001) but not in on-treatment patients (6.9 vs 6.9 kPa, p = 0.938). The prevalence of cirrhosis was also only significantly different in treatment-naïve patients (18.8% vs 5.8%, p = 0.001) but not in on-treatment patients (24.2% vs 23.3%, p = 0.784). By multivariate analysis, the presence of diabetes was independently associated with increased LS in treatment-naïve patients (OR 1.100, 95% CI 1.020-1.186, p = 0.013) but not in treated patients (p > 0.05).
Conclusion: With the concomitant presence of diabetes, the risk of liver fibrosis is increased in treatment-naïve CHB with low serum HBV DNA levels. Diabetic CHB patients, even when virological activity is quiescent, may need monitoring for cirrhosis-related complications.

THU-227

NTCP S267F variant associates with decreased susceptibility to HBV infection and decelerated progression of related liver diseases

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Background and aims: The sodium taurocholate co-transporting polypeptide (NTCP), encoded by the *SLC10A1* gene, is the entry receptor for the hepatitis B (HBV) and the hepatitis D (HDV) into hepatocytes. We aimed to determine potential associations of the rs2296651 variant (c.800C > T, S267F) with HBV infection as well as with the progression of related liver diseases
Method: The S267F variant was genotyped by DNA sequencing in 620 HBV-infected patients and 214 healthy controls (HCs). Among the patients, 450 individuals were tested for HDV by a nested PCR assay. Logistic regression was applied to examine the association.
Results: The S267F variant (genotypes rs2296651 CT and TT) was found more frequently among HCs (16%) compared to HBV-infected (6%) (HBV patients vs HC: OR = 0.32, 95% CI = 0.19-0.54, P = 0.00002). The T allele was found less frequent in HBV patients (3%) compared to HCs (OR = 0.34, 95%CI = 0.2-0.57, adjusted P = 0.00003). S267F variant (genotype CT) was also associated with decreased risk of the development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) (OR = 0.32, adjusted P = 0.013 and OR = 0.34, adjusted P = 0.002, respectively). In addition, patients with the genotype CT had lower levels of AST, ALT, total and direct bilirubin as well as higher platelet

NTCP rs2296651 S267F	CHB n = 176 (%)	LC n = 144 (%)	HCC n = 300 (%)	All HBV n = 620 (%)	HC n = 214 (%)	HBV vs. HC OR (95%CI); *P* value	CHB vs. HC. OR (95%CI), *P* value	LC vs. HC. OR (95%CI); *P* value	HCC vs. HC. OR (95%CI); *P* value
Genotype									
CC	165 (94)	137 (95)	281 (94)	583 (94)	179 (84)	Reference	Reference	Reference	Reference
CT+TT	11 (6)	7 (5)	19 (6)	37 (6)	35 (16)	0.32 (0.19-0.54); *P* = 0.00002	0.31 (0.15-0.64); *P* = 0.001	0.32 (0.13-0.79); *P* = 0.013	0.34 (0.17-0.68); *P* = 0.002
Allele									
C	341 (97)	281 (98)	581 (97)	1203 (97)	392 (92)	Reference	Reference	Reference	Reference
T	11 (3)	7 (2)	19 (3)	37 (3)	36 (8)	0.34 (0.2-0.57); P = 0.00004	0.32 (0.16-0.63); *P* = 0.001	0.32 (0.13-0.78); *P* = 0.012	0.33 (0.17-0.63); *P* = 0.001

Table: (abstract: THU-227): Association of NTCP S267F variant with HBV-related liver diseases. CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; HC, healthy controls; n, numbers individuals; OR, Odd ratio. *P* values were calculated using binary logistic regression model adjusted for age and gender.

counts, indicating an association with a more favorable clinical outcome.

Conclusion: The NTCP S267F variant of the *SLC10A1* gene exhibits protective effects against HBV infection and is associated with a reduced risk of progression to infection-related advanced liver diseases such as LC and HCC.

THU-228

HBV RNA can influence HBV viral load results depending on the test used

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Background and aims: The aim of HBV treatment with nucleot (s)ide analogs (NAs) is complete HBV DNA suppression and EASL guidelines recommend monitoring HBV DNA.
NAs therapy blocks the viral polymerase preventing the formation of HBV DNA from the pre-genomic RNA template that can be released in particles.
The detection and quantification of HBV RNA in plasma has been previously described.
The aim of the study was to compare different technologies for HBV DNA quantification (real time PCR and TMA) and evaluate potential impact of the type of test on clinical decision making.

Method: Remnant samples from a clinical study that evaluated treatment response in lamivudine-resistant chronic HBV patients were tested with the Roche **cobas**® HBV test (cobas) for the **cobas**® 6800/8800 Systems, the Hologic Aptima HBV test (Hologic) and with a modified version of the cobas HBV test adding a reverse-transcription step to the PCR profile, intended to amplify HBV RNA in addition to HBV DNA resulting in a total nucleic acid amplification test (cobas RT). The results from the three methods were compared to the reference test used in the trial. A sub-set of individual patients were analyzed with all methods over time (baseline, Weeks 12, 24, 48, 72, 84 and 96) and the mean viral load per time point was compared across tests.

Results: In total, 346 samples from 50 patients were included in the study. The means from all tests were concordant at baseline. At week 12 of therapy, the mean results were significantly different across tests. From week 24 up to week 96, the cobas mean results were comparable to the reference test while cobas RT and Hologic remained significantly different. cobas RT and Hologic mean results were comparable at all time points (figure).

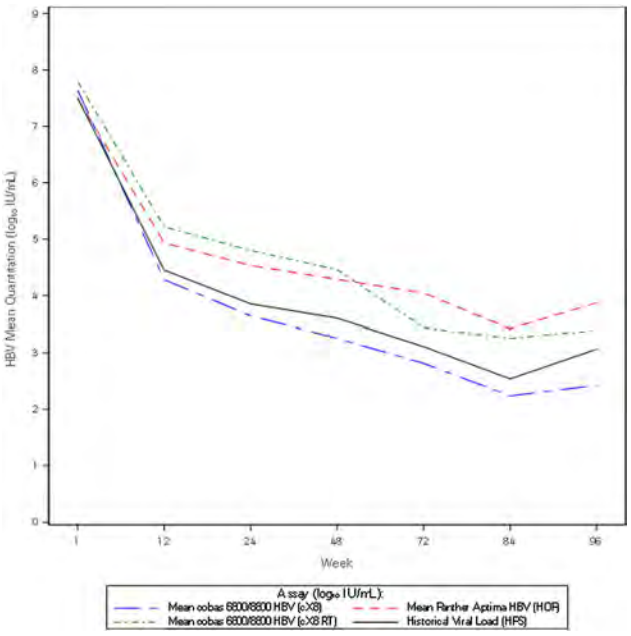

Figure: Longitudinal plot of mean viral load (across patients) from baseline to Week 96 for cobas HBV, Hologic HBV, cobas RT, and Historical HPS.

Conclusion: The presence of HBV RNA in plasma of subjects undergoing NAs treatment is suggested by the difference observed between viral load results of cobas vs cobas RT.
The results suggest cobas is specific for DNA, showing good correlation to the reference test while Hologic test results correlated

well with the cobas RT and were not comparable to the reference test during treatment with NAs suggesting lack of specificity for HBV DNA. The implications of RNA amplification can be misinterpretation of the clinical response and consequent additional interventions like adherence counseling, resistance testing and treatment modifications, all associated with incremental cost to the patient and health system which should be further evaluated.

THU-229

Increased gaps in hepatitis B pregnancy care identified among "low-risk" populations

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Background and aims: Although the United States (U.S.) is a low-endemic country with universal vaccination for the hepatitis B virus (HBV), about 1, 000 mothers still transmit HBV to their infants each year, making disease eradication difficult to attain. Pregnancy is a key time to intervene to decrease HBV transmission, as it is the only time for universal HBV screening in the U.S. However, recent studies demonstrate low rates of HBV DNA testing (<50%), initiation of antiviral therapy when indicated, and referral to specialty care (<60%) during pregnancy. These represent critical missed opportunities to prevent both vertical and horizontal transmission. We aimed to identify gaps in HBV pregnancy care and evaluate for predictors in an inner-city obstetrics care setting.
Method: We conducted a retrospective chart review of HBV-positive pregnant women at Mount Sinai Health System in NYC from 1/1/2015 to 6/30/2018. Adherence to care was defined as referral to specialist, HBV DNA testing, and antiviral initiation when indicated. Multivariable regression was performed to identify predictors of gaps in care. Causal inference analysis further delineated the causative impact of factors associated with adherence.
Results: 103 pregnancies in 96 patients were identified. Patients were 45.6% Asian, 31.1% African, and 7.8% White. 61 (59.2%) had private insurance and 42 (40.8%) had public (Medicaid) insurance. 14 (14%) were first diagnosed with HBV during the pregnancy. 86 (87%) had HBV DNA measured during pregnancy; of those, 46 (57%) had it checked at third trimester (weeks 25-30). 63 (69%) patients had not been following with a liver specialist prior to the pregnancy; of those, 46 (69%) were referred. Of the 15 who met criteria for antiviral therapy, 3 (20%) continued their pre-pregnancy treatment, 4 (27%) initiated therapy, and 8 (53%) were left untreated. Multivariable regression of insurance status, race, age, and provider type demonstrates a significant association between African ethnicity and increased adherence to care (OR = 3.28; 95% CI, 2.21-4.34). Causal inference demonstrates that having public (Medicaid) insurance causes increased adherence by an additional 16% from having private insurance.
Conclusion: Initiation of antiviral therapy when indicated during pregnancy remains low. Medicaid-insured and African-ethnic patients, considered underserved populations in the U.S., were more likely to receive the standard of care. Providers may selectively apply increased vigilance to certain "high-risk" groups, leaving others susceptible to gaps in care. As current efforts may be proportional to HBV prevalence, interventions (e.g., education and clinical decision support tools targeted to obstetrics care settings) in low endemic countries are necessary for global eradication of HBV.

THU-230

HBV and HDV confection trends in HIV+ patients in Vienna

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Background and aims: Despite vaccination recommendations, hepatitis B (HBV) coinfections are common in HIV+ patients. Recent immigration trends and high-risk behaviour among men who have sex with men (MSM) have likely impacted on the epidemiology of HBV and delta (HDV) coinfection among HIV+ patients in Europe.
Method: N = 1874 HIV+ patients attending our clinic between 2014-2016 were assessed at HIV diagnosis (baseline, BL) and at last visit (follow-up, FU). We assessed HBV immunization status (anti-HBs (+)) as well as HBV (HBsAg (+)/HBV-DNA (+)) and HDV (anti-HDV (+)) coinfection rates at BL and at FU.
Results: N = 68 (3.6%) patients were never tested for HBV. At BL, n = 89/1793 (5.0%) HIV+ patients had HBV coinfection, while only n = 51/89 (57.3%) were tested for HDV. However, n = 11/51 (21.6%) had anti-HDV (+) and n = 3/7 (42.9%) showed HDV-RNA-viremia.
At BL, n = 417 (23.3%) had HBV-clearance (HBsAg (-)/anti-HBc (+)/anti-HBs (+)) and n = 1081 (60.3%) were HBV-negative (HBsAg (-)/anti-HBc (-)), however, only n = 377 (34.9%) had received vaccination and showed anti-HBs (+).
After a median FU of 9.4 years, n = 136/704 (19.3%) had received HBV-vaccination. Importantly, n = 8/1081 (0.7%) had acquired new HBV-infection (including n = 1/377 of initially vaccinated patients)-resulting in an overall number of n = 59/1607 (3.7%) HBV/HIV coinfected patients at FU: n = 21 (35.6%) HBeAg (+), n = 11 (18.6%) HBeAg (-), and n = 27 (45.8%) with unknown HBeAg status. From BL to FU, n = 22/80 (27.5%) cleared their HBsAg (-) while on HBV-active ART.
Among the total n = 97/1793 (5.4%) patients with HBV-coinfection, n = 56 (57.7%) underwent HBV-DNA PCR during FU with n = 42 (75%) achieving HBV-DNA-suppression. HDV-testing was performed in n = 19/59 (32.2%) HBV-patients during FU and HBV/HDV-coinfection was found in n = 6/19 (31.6%) of tested HBV/HIV+ patients.
Under HBV-active ART, n = 13/27 (48.1%) patients achieved normalization of their ALT values at FU and only n = 2/72 (2.8%) had advanced liver fibrosis according to FIB4 score (>3.25) at FU.
Conclusion: While HBV-testing is regularly performed in HIV+ patients, HBV-vaccinations have not been sufficiently implemented. HDV-testing is not systematically performed-although about one third of HBV/HIV+ patients may have HDV-co/superinfection. Suppression of HBV replication was achieved in 72.3% of HIV+ patients and 31/82 (37.8%) lost their HBsAg from BL to FU.

THU-231

Risk of hepatocellular carcinoma in patients with immune-tolerant chronic hepatitis B

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Background and aims: Recent studies have suggested that patients with immune-tolerant chronic hepatitis B (CHB), characterized by hepatitis b e antigen (HBeAg) positive patients with high serum hepatitis B virus (HBV) DNA but normal alanine aminotransferase

(ALT), may develop hepatocellular carcinoma (HCC). However, it is unclear how to stratify HCC risk in these patients.
Method: A retrospective cohort of 651 HBeAg positive, adult patients with high serum HBV DNA levels (>7 log IU/ml) but normal or mildly elevated ALT levels (<80 U/L) were analyzed. Age and FIB-4 index were used to categorize patients, and assessed HCC incidence rate in each subgroups. Normal ALT was defined as <35 U/L for males and <25 U/L for females.
Results: During a median 5.2 years of follow-up (range: 1.0-17.8 years), 24 (3.7%) patients developed HCC. Age and FIB-4 index were independent factors associated with HCC development. When stratified, 5 and 10-year cumulative HCC incidence rates were 0% and 2.0% for patients aged <40 years plus FIB-4 index <1.45, and were 5.9% and 32.7% for patients aged ≥ 40 years plus FIB-4 index ≥ 1.45, respectively ($p < 0.001$). In patients with normal ALT levels (n = 301), 10-year HCC incidence rate was 0% for patients aged <40 years plus FIB-4 index <1.45, while 5 and 10-years HCC incidence rate was 4.5% and 27.1% for patients aged ≥ 40 years plus FIB-4 index ≥ 1.45, respectively ($p < 0.001$).
Conclusion: In patients with immune-tolerant CHB, HCC risk was considerably high for aged patients with elevated FIB-4 index while HCC risk was very low for young patients with low FIB-4 index. These two factors could effectively stratify HCC risk, indicating that they may guide management plan for this population.

THU-232

Hepatitis B vaccination is effective among HIV-infected adults in Uganda

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Background and aims: Coinfection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) is common in sub-Saharan Africa (SSA) and can lead to progression of liver disease, cirrhosis and hepatocellular carcinoma. Recent data demonstrate ongoing HBV transmission among HIV-infected adults in SSA, suggesting complications of HBV could be prevented with vaccination. Because HBV vaccine efficacy is poorly understood in HIV-infected persons in SSA, we sought to characterize the humoral response of HIV-positive Ugandan adults to the vaccine.
Method: We enrolled HIV-infected adults in Kampala, Uganda with no serologic evidence of prior exposure to HBV. Baseline socio-demographic variables, HBV and HIV history were obtained by participant interview and medical chart review. Three 20µg HBV vaccine doses were administered at intervals of 0, 1 and 6 months. Anti-HBs levels were measured at 4 weeks after the third vaccine dose. "Response" to the vaccine was defined as anti-HBs levels ≥ 10 IU/L and "high response" as ≥ 100 IU/L. Univariate and multivariate regression analysis were used to determine the predictors of vaccine response. **Results:** Of 251 HIV-positive adults screened, 132 (53%) had no prior HBV infection or vaccination and were enrolled. Most participants were women 89 (67%) and had a median (IQR) age of 32 years (27-41). 68 (52%) were on antiretroviral therapy >3 months. Median (IQR) CD4 count was 426 (261-583), and 64 (94%) of the 68 receiving ART had undetectable HIV RNA. Overall, 117 (92%) seroconverted to the vaccine (anti-HBs titres ≥10IU/L) with the majority 109 (86%) being high-level responders (anti-HBs ≥ 100IU/L). Eight (6.3%) were low-level responders (anti-HBs 10-100IU/L) and 10 (7.9%) non-responders (anti-HBs <10). In univariate analysis, only baseline CD4 >200 cells/mm3 was associated with both response (p = 0.02) and high-level response (p = 0.01). In multivariate analysis baseline CD4 was associated with "high response" with each unit increase in CD4 count corresponding to a 0.004 increase in vaccine response (p = 0.01, CI 0.001-0.008).
Conclusion: Half of the screened patients did not have immunity to HBV infection, suggesting a large "at risk" population for the infection among HIV-positive adults in Uganda. The vaccine was effective in eliciting a protective humoral immunologic response, particularly among those with higher CD4 counts. Our findings support routine HBV vaccination among HIV-positive adults at risk for HBV infection.

THU-233

Whole exome sequencing analysis of the role of rare human variation in chronic hepatitis B infection

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Background and aims: To examine the role of rare human genetic variation in CHB, we performed whole exome sequencing (WES) on 1438 patients with CHB and 18776 population controls to test for genetic associations with baseline CHB phenotypes.
Method: DNA was isolated from 1438 CHB patients (Table 1) enrolled in phase 3 clinical trials of tenofovir disoproxil fumarate or tenofovir alafenamide. WES data was generated to an average depth of 81x coverage using the Illumina HiSeq2500 or NovaSeq DNA sequencing platforms. Genetic associations were assessed using single-variant tests and gene-based collapsing to detect rare variant associations with CHB phenotypes, including risk of CHB persistence and baseline viral quantitative traits. Fisher's exact test (FET) and linear regression were used for binary and quantitative traits, respectively. All tests were Bonferroni-corrected to adjust for multiple testing.

Table 1:

		N = 1438
HBeAg positive, n (%)		776 (54)
Median ALT U/L (Q1, Q3)		74.0 (47, 116)
Median HBV DNA log10IU/ml (Q1, Q3)		7.17 (5.53, 8.28)
HBV Genotype, n (%)	A	118 (8.2)
	B	240 (16.7)
	C	626 (43.5)
	D	375 (26.1)
	Other	31 (2.3)
	Not available	48 (3.2)

Results: The role of MHC class II haplotypes in HBV persistence was confirmed with an exome-wide significant association centered at the rs2308930 SNP in *HLA-DPA1* (p = 1.249E-7, OR = 1.41; logistic regression of CHB cases and controls). No single variant or gene was found to reach statistical significance (p < 2.65E-6 for collapsing analysis), however, several biologically relevant findings were identified. In a collapsing analysis of hepatitis B viral load (VL), the top result was the charged multivesicular body protein 7 (*CHMP7*) gene (p = 1.08E-4, linear regression of VL), a member of the ESCRT-III pathway that plays a critical role in the maturation of viral particles. In addition, a depletion of rare functional variation in the interferon alpha 2 (*IFNA2*) gene among HBeAg positive patients was identified (p = 2.99E-4, FET of HBeAg status). The *IFNA2* collapsing signal was primarily driven by a depletion of the A120T allele. Variation in *CHMP7* and *IFNA2* was also correlated with reduced levels of HBsAg (p = 0.001 and 0.02, respectively).
Conclusion: Here we present the results of largest WES study of patients with CHB reported to date. The findings suggest that rare

variation in *CHMP7* and *IFNA2* may influence clinically relevant phenotypes in CHB, however, given that these did not achieve statistical significance, additional confirmation is required.

THU-234

High body-mass index is associated with increased risk of alanine aminotransferase elevation and hepatocellular carcinoma in chronic hepatitis B patients with sustained viral control

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Background and aims: Alanine aminotransferase (ALT) is a marker of liver damage that results from a range of etiologies. This study investigated whether high body-mass index (BMI) contributes to the risk of ALT elevation and hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients who achieved sustained viral control with antiviral treatment.
Method: This was a real-life, prospective cohort study which enrolled CHB patients receiving nucleos(t)ide analogues (NAs) treatment with sustained HBV DNA suppression (defined as HBV DNA undetectable on two consecutive visits 6 months apart). At study enrollment, logistic regression model was used to evaluate the association between high BMI (defined as BMI ≥ 25 kg/m^2) and the risk of ALT elevation (defined as ALT > 35 U/L in males and >25 U/L in females). Cox regression model was used to investigate the association between high BMI and the risk of HCC during follow-up. The impact of high BMI plus ALT elevation on the risk of HCC was also evaluated.
Results: A total of 2, 085 patients with sustained HBV DNA suppression were identified. At baseline, 494 (23.7%) patients had high BMI, the median ALT level was 23 U/L and ALT elevation was observed in 409 (19.6%) of patients. During a median follow-up of 2.27 years, 2011 patients finished at least two assessments of ALT, 578 (28.7%) patients had transient elevation of ALT (defined as ≥1 elevated ALT but some normal) and 139 (6.9%) patients had persistent elevation of ALT, 28 patients developed HCC with 3 years cumulative incidence of 1.85%. High BMI at baseline was associated with an increased risk of transient and persistent elevation of ALT (p < 0.001). The patients with high BMI at baseline had an increased risk of HCC, after adjustment by ALT, cirrhosis, age and sex [adjusted hazard ratio (aHR) and 95% CI: 2.40 (1.14-5.07), p = 0.021]. Compared to patients with BMI < 25 kg/m^2 and normal ALT at baseline, patients with BMI ≥25 kg/m^2 and ALT elevation were at the highest risk of HCC [aHR and 95% CI: 5.25 (1.87-14.73), p < 0.001].
Conclusion: High BMI is significantly associated with an increased risk of ALT elevation and HCC in CHB patients receiving NAs treatment with sustained viral control.

THU-235

Hepatitis B virus testing and cascade of care in a tertiary referral centre, Maastricht The Netherlands

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Background and aims: There are approximately 40, 000 people (0.2%) in the Netherlands chronically infected with the hepatitis B virus (HBV). Amongst this population, it is not clear how many have been linked to care and are still under follow-up in the hepatitis outpatient clinics. Therefore, in this study, we aimed to determine the cascade of care of all known chronic hepatitis B patients in our Maastricht UMC+.
Method: Based on laboratory and patient data, we retrospectively identified all people with a positive hepatitis B surface antigen (HBsAg) from 1st December 1996 to 30th September 2018. Demographic and viral factors (alanine-aminotransferase (ALT), HBV DNA and HBeAg status) were extracted within 6 months of a positive HBsAg, and it was identified if a specialist evaluation was conducted, from the hospital's database. Patients with a chronic HBV infection (positive HBsAg for >6 months) were observed until they started treatment or until their follow-up ended.
Results: In total, 644 HBsAg positive people with a median age of 35 years (interquartile range: 19) at the time of diagnosis were found. Out of 644 individuals with a positive HBsAg, 497/644 (77%) had ALT testing, 271/644 (42%) had testing for HBV DNA and 515/644 (80%) had HBeAg testing within six months after diagnosis. Overall, 75/644 (12%), 471/644 (73%) and 98/644 (15%) people were designated as acute hepatitis B, chronic hepatitis B and unknown cases respectively. A total of 421/471 people (89%) with a chronic HBV infection visited a specialist and 180/471 (38%) of them were eligible for antiviral treatment of whom 169/180 (94%) started treatment and 117/169 (69%) achieved HBV DNA suppression. At this moment, 79/169 (47%) chronic hepatitis B patients who started antiviral treatment are still under follow-up.

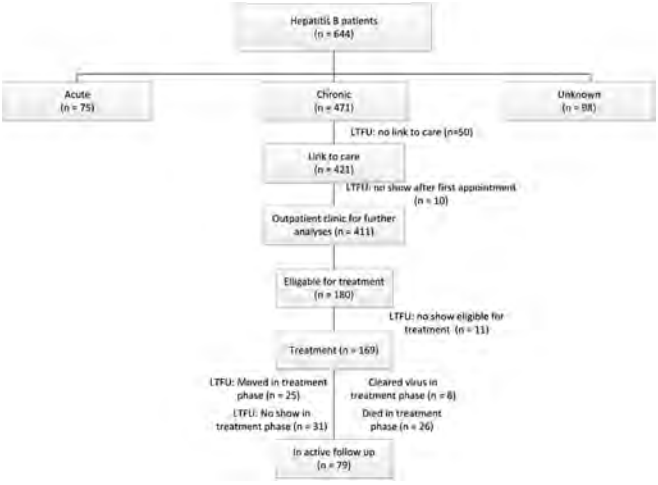

Figure 1: **Cascade of care for hepatitis B patients within the region of Maastricht, The Netherlands.** *LTFU, Loss to follow-up*

Conclusion: To a considerable amount of HBsAg positive individuals in the Maastricht region, the recommended laboratory testing and/or specialist evaluation is not given. Only half of the chronic hepatitis B patients who started antiviral treatment are still under follow-up. These results reinforce the need of continual public health efforts to re-evaluate chronic hepatitis B patients and to ensure adequate follow-up in order to eliminate viral hepatitis B by 2030.

THU-236

Integration of HBV DNA near cancer-related genes in HBsAg-negative hepatocellular carcinoma patients

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Background and aims: HBV DNA can integrate into host chromosomes, which may cause chromosomal instability and/or dysregulation of cancer-related genes, leading to HCC. We previously identified that HBsAg-negative HCC patients could have occult hepatitis B infection (OBI), based on their detectable HBV DNA in the liver tissues (Wong et al, J Hepatol. 2018;68:S474). In this study, we aimed to investigate the presence of HBV DNA integration in tumour and non-tumour tissues and identify the integration sites.
Method: Liver DNA was extracted from both tumour and non-tumour tissues of 62 HBsAg-negative HCC patients with OBI. HBV integration was detected by Alu-PCR sequencing, with one primer targeting to HBV (surface, core, polymerase, or X) and another primer targeting to the Alu-repeat regions in the human chromosomes.
Results: Of the 62 HCC patients with OBI, 43 (69%) were found to have HBV integration (35 found in tumour and 16 in non-tumour tissues, with 8 patients having integration in both tumour and non-tumour tissues). The majority (39/43; 91%) of OBI patients with HBV integration did not have histological evidence of cirrhosis. The common viral breakpoints of HBV integration were at the polymerase/preS1 region (18/35 tumour [51%] and 6/16 non-tumour [38%]) and the X/Enhancer II/precore region (15/35 tumour [43%] and 9/16 non-tumour [56%]). The most frequent identifiable integration sites in the tumour tissues were chromosome 5 (5 cases), chromosome 11 (3 cases) and chromosome 17 (4 cases), while the most frequent sites in the non-tumour tissues were chromosomes 3 and 4 (3 cases each). In the tumour tissues, integration near genes encoding the RING finger protein COP1 (negative regulator of p53), cyclin A2 (cell cycle-related), promoter region of TERT (regulator of telomerase activity) and lysine methyltransferase 2B (histone modification) were found. In the non-tumour tissues, integration near the coding regions of alpha-3-catenin (tumour suppressor in HCC) and CREB binding protein (transcription activator) were identified.
Conclusion: HBV integration was found in 69% of HBsAg-negative HCC patients with OBI. HBV integrations were identified mostly in the tumour tissues, but were also found in the non-tumour tissues. The majority of OBI patients with HBV integration did not have cirrhosis, suggesting that HBV integration, especially those near cancer-related genes, is a likely cause of HCC in OBI patients.

THU-237

Increasing prevalence of indications to choose bone/renal-friendly antiviral drug: A territory-wide study of 135, 414 patients from 2000 to 2017

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Background and aims: The latest clinical practice guideline from European Association for the Study of the Liver (EASL) published in 2017 advocate the use of entecavir or tenofovir alafenamide (TAF) over tenofovir disoproxil fumarate (TDF) according to age, bone disease and renal alteration. As patients with chronic hepatitis B (CHB) are aging with improved survival under better healthcare, more patients may fulfil these criteria. We aimed to determine the prevalence of these criteria in the territory-wide CHB cohort in Hong Kong over 18 years from year 2000 to 2017.

Method: CHB patients who have been under the care at primary, secondary and tertiary medical centers in the public sector in Hong Kong were identified through the Clinical Data Analysis and Reporting System of the Hospital Authority. The demographics and prevalence of relevant bone and renal co-morbidities, and relevant laboratory parameters were determined according to patients' first appearance in four time periods: 2000-2004, 2005-2009, 2010-2013 and 2014-2017.
Results: 136, 414 CHB patients were included. The prevalence of the above criteria increased over the four periods: age >60 years 11.6%, 20.4%, 27.6% and 35.4%; Steroid/medications that worsen bone density 57.2%, 50.5%, 56.0% and 61.8% respectively; albuminuria 0.2% 0.4% 0.7% and 1.1% respectively, and low phosphate (<2.5 mg/dl) 3.9%, 4.0%, 5.1% and 7.0% respectively (all $P < 0.001$; Figure).

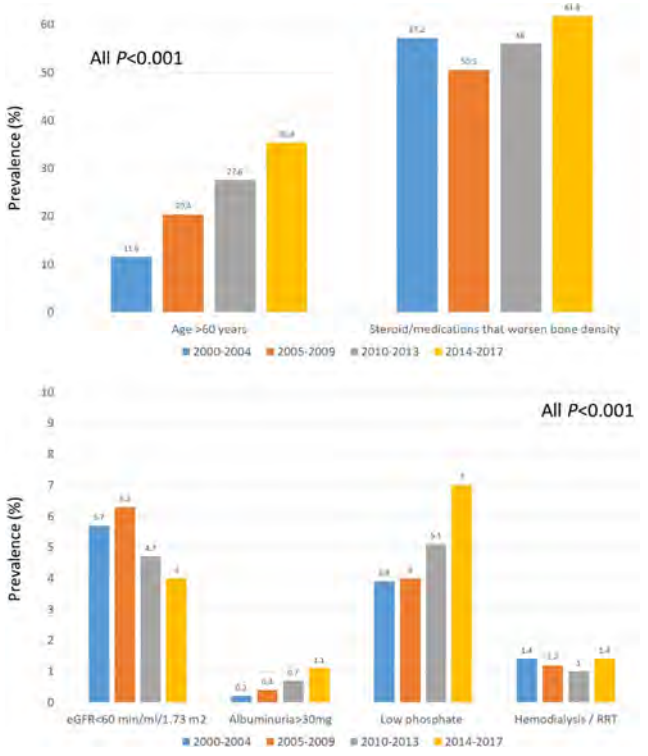

Figure: Prevalence of co-morbidities to choose entecavir or tenofovir alafenamide (TAF) over tenofovir disoproxil fumarate (TDF) over the four periods. eGFR = estimated glomerular filtration rate, RRT = renal replacement therapy.

Conclusion: CHB patients are getting older with increasing prevalence of indications to choose entecavir or TAF over TDF according to the latest EASL guidelines.
Funding: This work was supported by the Investigator Sponsored Research of Gilead Sciences (Reference: IN-US-988-5290).

THU-238

Low rates of antiviral therapy among treatment-eligible adults with chronic hepatitis B virus infection

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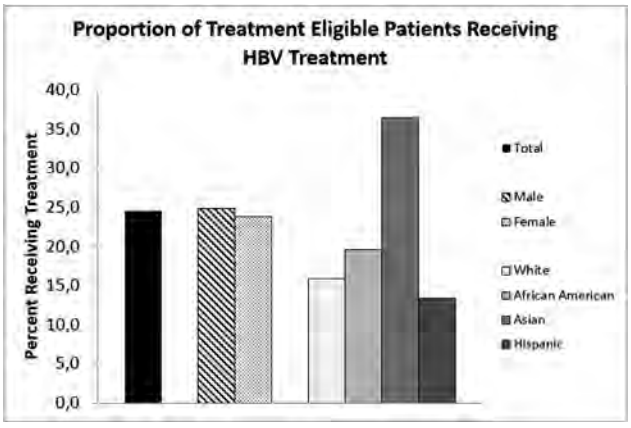
Background and aims: Timely initiation of hepatitis B virus (HBV) treatment among eligible patients contributes to viral suppression and reduces long term risk of disease progression to cirrhosis and hepatocellular carcinoma. However, overall HBV treatment rates are

sub-optimal, particularly among ethnic minority and immigrant populations, which are the highest risk groups for chronic HBV. We aim to evaluate treatment eligibility and treatment rates among a large ethnically diverse adult HBV population.

Method: We retrospectively evaluated adults with chronic HBV at two urban safety-net heath systems from January 1, 2010 to December 31, 2015, with a minimum of 2-years follow-up. Chronic HBV was identified with ICD-9/10 diagnosis coding and confirmed with laboratory data. HBV treatment eligibility was determined using American Association for the Study of Liver Diseases criteria, which included assessment of HBV E antigen (HBeAg) status, serum alanine aminotransferase (ALT), HBV viral load, and fibrosis stage. Comparison of HBV treatment eligibility and HBV treatment rates among eligible patients were performed using chi-square testing, and adjusted multivariate Cox proportional hazards models identified predictors of receiving HBV treatment among eligible patients. Statistical significance was met with $p < 0.05$.

Results: Among 2, 150 chronic HBV patients with available data to assess treatment eligibility (58.1% men, 25.8% white, 39.1% African American, 32.6% Asian, 12.4% Hispanic), 29.5% had cirrhosis, 5.3% had HCC. Overall, 28.4% were eligible for HBV treatment, with significantly higher rates of treatment eligibility among men compared to women (35.8% vs. 18.2%, $p < 0.01$) and similar eligibility across race/ethnicity groups. Among eligible patients, 24.5% received HBV treatment at any point during the study and only 8.0% received HBV treatment within 6 months of becoming eligible. While no sex-specific differences were observed, treatment-eligible Asians were significantly more likely to receive HBV treatment compared to whites (36.4% vs. 15.9%; HR 5.06, 95% CI 2.05-12.51, $p < 0.01$). Significantly higher likelihood of HBV treatment was also observed in patients with cirrhosis (24.9%; HR 1.81, 95% CI 1.07-3.09, $p < 0.03$).



Conclusion: Among an ethnically diverse cohort of HBV patients across 2 urban safety-net hospitals, only 24.5% of eligible patients received HBV treatment. While Asian HBV patients were significantly more likely to receive HBV treatment, over 60% of treatment-eligible Asian HBV patients did not did not receive treatment during the study period.

THU-239

Improving patient knowledge about hepatitis B virus leads to improvements in HBV disease monitoring

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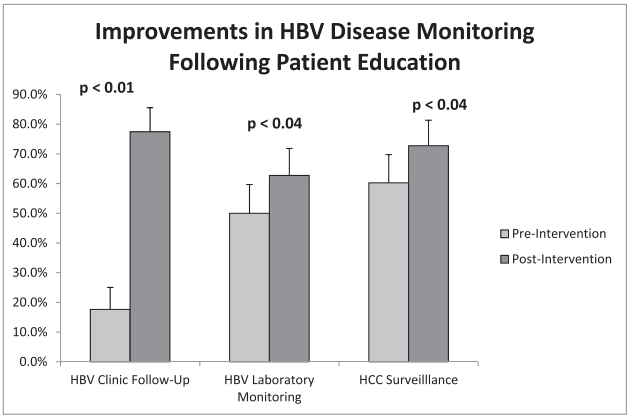
Background and aims: Suboptimal patient knowledge and awareness of hepatitis B virus (HBV) contributes to barriers in effective HBV monitoring. We aim to evaluate the impact of a HBV patient educational intervention on improving HBV disease monitoring, with a focus on clinic follow-up, laboratory monitoring, and HCC surveillance.

Method: Consecutive chronic HBV adults at a safety-net gastroenterology clinic were recruited from July 2017-May 2018. Surveys assessing HBV Knowledge were conducted before and after a formal language-concordant HBV education session. Appropriate HBV clinic follow-up (≥1 visit/year), laboratory monitoring (≥1 HBV viral load and alanine aminotransferase test/year), and HCC surveillance (≥1 HCC imaging test/year in eligible patients) were assessed before and after education. Improvements in these parameters of HBV monitoring were assessed using chi-square testing and adjusted multivariate logistic regression models.

Results: Among 102 HBV patients (54.9% men, mean age 52.0 ± 13.8, 83.3% Asian, 89.2% non-US born, 42.2% non-English speaking, 23.5% less than high school education, 37.3% unemployed), HBV Knowledge score improved from 7.0 out of total 13.0 points (95% CI 5.98-8.01), to 9.67 points (95% CI 9.41-9.93), representing 38.1% improvement. Following educational intervention, appropriate HBV clinic follow-up improved from 17.7% to 77.5% of patients ($p < 0.01$), HBV lab monitoring from 50.0% to 62.8% ($p < 0.04$), and HCC surveillance from 60.3% to 72.7% ($p < 0.04$). Post-education HBV Knowledge score was the only significant predictor of improvements in HBV disease monitoring. On multivariate regression, compared to patients with HBV Knowledge score <10, those who achieved HBV Knowledge score of ≥10 after the educational intervention were significantly more likely to have appropriate HBV clinic follow-up (OR 4.07, 95% CI 1.27-13.01, $p = 0.02$) and HCC surveillance (OR 9.20, 95% CI 1.48-57.14, $p < 0.02$), demonstrating the ability to improve HBV disease monitoring through increasing patients HBV awareness and knowledge.



Conclusion: HBV disease monitoring among safety-net populations, as measured by clinic follow-up, laboratory monitoring, and HCC surveillance was sub-optimal. A patient-centered language concordant educational intervention successfully improved patients HBV Knowledge, which translated into significant improvements in HBV disease monitoring.

This study is supported by an AASLD Foundation Clinical and Translational Research Award.

THU-240

Glial cell line-derived neurotrophic factor is associated with fibrosis in patients with chronic viral hepatitis B

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Background and aims: Liver biopsy is currently the most reliable way of evaluating liver fibrosis in patients. Its inherent risks limit its widespread use. Glial cell line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor superfamily, whereas its

content and expression in liver fibrosis was never studied. The aim of this study was to assess GDNF in human serum comparison with liver fibrotic F stages. Meanwhile, we detected the liver GDNF mRNA expression in liver biopsy and comparison with liver fibrotic F stages and biochemical parameters.
Method: There were 319 (F0 = 30, F1 = 71, F2 = 115, F3 = 67, F4 = 36) serum samples for GDNF detection using ELISA from patients with clinically diagnosed chronic liver disease who underwent liver biopsy. The expression of GDNF mRNA was also detected in 212 (F0 = 15, F1 = 38, F2 = 89, F3 = 46, F4 = 24) patients using real-time PCR analysis.
Results: The serum GDNF level in F4 stage were significantly higher compared with each F0-3 stage patients ($p < 0.001$). GDNF was associated with fibrosis stage (risk ratio [RR] 0.544, 95% confidence interval [CI]: 0.334-0.885). GDNF showed areas under the receiver operating characteristics curve (AUROC) of 0.77 (95% CI: 0.71-0.83) and 0.79 (95% CI: 0.71-0.88), for liver injury and F4 stage, respectively. Compared to existing fibrosis scores, GDNF was significantly superior to the aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis 4 score (FIB-4) for F4 stage. Liver fibrosis progression was associated with GDNF level using multiple logistic regression ([RR] 0.176, 95% [CI]: 0.061-0.509). GDNF mRNA from liver biopsy could reflect the liver G stage and validate the serum results in some extent.
Conclusion: GDNF levels are increased in patients with chronic viral hepatitis, reflecting HSC activation. Increased GDNF is associated with the severity of disease and predicts fibrosis. Non-invasive tests can accurately predict hepatic F4 stage and may reduce the need for liver biopsy in the majority of HBV-infected patients.

THU-241
Influence of HBV genotype on the risk of hepatocellular carcinoma: mediating roles of different phase of viral infection and epigenetic modifications

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Background and aims: Chronic hepatitis B (CHB) is a dynamic disease divided into several phases, depending on virus-host interaction. Duration of phases varies among CHB patients, and its association with hepatocellular carcinoma (HCC) remains inconclusive. HBV genotype is associated with timing of phase transition, but the underlying mechanisms are unclear. In vitro models suggest that HBV can alter host DNA methylation, affecting gene expression. We evaluated methylation status of leukocyte DNA to examine the significance of epigenetic variation in the interaction between virus and host immune system during phase transition and its associations with clinical outcomes.
Method: We used a case-cohort approach to investigate the long-term risks of HCC relating to phases of CHB and effect modification by HBV genotype in a longitudinal viral-load study of 1143 treatment-naive HBV carriers. We prioritized HCC-associated DNA methylation loci based on their correlation with viral replication and functional relevance with omics data and bioinformatics analysis. Mediating effects of distinct phases and epigenetic changes on genotype C-related HCC risk were assessed in 574 subjects using mediation analysis.
Results: Of 1116 subjects with ALT and viral markers data, 69 were immune-tolerant, 100 were immune-active (32 HBeAg positive), 505 were inactive, and 442 were phase indeterminate at baseline. The multivariate hazard ratios were 4.83 and 11.52, respectively, for the immune-tolerant and immune-active group, compared to the inactive group. HBV genotype modified this association. Integrative analysis of methylome with clinical data identified epigenetic changes associated with HCC and viral replication. We focused on methylation at CpGs in three immune genes (IFI44L, PRF1, and PRR5L) that demonstrated correlation with gene expression ($r = -0.34$–0.73; $p < 0.008$). IFI44L gene methylation was found to be strongly associated with immune-active phase ($p = 0.0015$) and genotype C infection ($p = 0.0190$). Mediation analysis indicated that prolonged immune-active phase accounted for 16.5% ($p = 0.0002$) of the effect of genotype C on HCC risk. IFI44L gene methylation was also identified as a mediator of the genotype C-related HCC risk through prolonged immune-active phase.
Conclusion: The association between HBV genotype and HCC was in part mediated through immune phases. We highlight a role of immune-specific gene methylation in phase transition and pathogenesis of virus-host interaction.

THU-242
Clinical non-invasive markers for hepatic inflammation and fibrosis assessment in chronic hepatitis B with normal alanine aminotransferase

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Background and aims: Liver biopsy is the reference method to assess hepatic inflammation and fibrosis and for antiviral therapy decision in chronic hepatitis B (CHB) with normal alanine aminotransferase (ALT). The study aims to explore non-invasive markers for assessing inflammation or fibrosis in CHB with normal ALT.
Method: 235 treatment naïve CHB patients with normal ALT underwent liver biopsy were analyzed in this prospective multi-center study. We analyzed data using univariate and multivariate analysis and receiver operating characteristic curve (ROC).

Table:

Variables	HAI < 5 and F < 3N = 119	HAI ≥ 5 or F ≥3N = 116	Univariate Analysis P value	Multivariate Analysis P value
Age, y	37.6 ± 10.7	41.9 ± 11.0	0.002	0.177
Male gender, n (%)	90(75.6)	75(64.7)	0.066	
PLT (10^9/L)	192 ± 54	158 ± 56	0.000	0.282
ALT (/ULN)	0.6 ± 0.2	0.7 ± 0.2	0.036	0.997
AST (/ULN)	0.6 ± 0.2	0.8 ± 0.4	0.000	0.031
ALP (/ULN)	0.6 ± 0.2	0.6 ± 0.2	0.148	
GGT (/ULN)	0.5 ± 0.8	0.9 ± 1.0	0.002	0.747
TBIL (umol/L)	14.7 ± 7.7	20.2 ± 37.9	0.121	
ALB (g/L)	45.5 ± 4.1	43.3 ± 4.8	0.000	0.155
GLB (g/L)	27.2 ± 3.9	28.7 ± 5.0	0.011	0.188
PTA (%)	101.2 ± 16.4	95.6 ± 20.3	0.027	0.667
AFP (ng/ml)	2.8 ± 1.6	12.9 ± 30.7	0.001	0.044
HA (ug/L)	92.3 ± 49.3	119.4 ± 78.1	0.002	0.393
PIIINP (ug/L)	3.0 ± 6.1	4.2 ± 4.2	0.099	
LN (ug/L)	32.8 ± 69.9	92.4 ± 172.3	0.001	0.465
C-IV (pg/ml)	736.1 ± 321.5	947.3 ± 460.5	0.000	0.398
LSM (KPa)	6.7 ± 7.3	11.5 ± 6.7	0.000	0.000
qHBsAg, $\log_{10}$ (IU/ml)	3.8 ± 1.0	3.4 ± 0.6	0.001	0.201
Anti-HBc, $\log_{10}$ (IU/ml)	3.8 ± 1.0	4.4 ± 0.6	0.000	0.001
HBV DNA, $\log_{10}$ (IU/ml)	5.8 ± 2.2	5.3 ± 2.0	0.054	
HBeAg, Positive, n (%)	63(52.9)	59(50.8)	0.750	

Results: 84 (35.7%) cases had moderate inflammation (Histology activity index, HAI ≥5) and alpha fetoprotein (AFP) ($p = 0.025$), anti-hepatitis B virus core antibody (anti-HBc) ($p = 0.001$) and liver stiffness measurement (LSM) ($p = 0.031$) were independent variables. 78 (33.2%) cases had significant fibrosis and platelet (PLT) ($p = 0.009$), albumin (ALB) ($p = 0.006$), anti-HBc ($p = 0.003$) and LSM ($p = 0.000$) were independent variables. Furthermore, 116 (49.4%)

cases had moderate inflammation or significant fibrosis who were recommended to receive antiviral therapy and aspartate aminotransferase (AST) (p = 0.031), AFP (p = 0.044), anti-HBc (p = 0.001) and LSM (p = 0.000) were independent variables. Our novel AAL index [AAL index = exp (Y)/[1+exp (Y), Y = 0.344*AFP (ng/ml) +1.643*$\log_{10}$Anti-HBc (IU/ml)+0.526*LSM (kPa)-12.119] showed good performance for diagnosing moderate inflammation or significant fibrosis with AUROC of 0.889. A high cutoff value (>0.64) with PPV of 96.2% was chosen to diagnose moderate inflammation or significant fibrosis and a low cutoff value (≤ 0.22) with NPV of 87.3% was chosen to exclude. Finally, 108 (46.0%) of 235 patients could avoid liver biopsy based on AAL index.

Conclusion: AST, AFP, anti-HBc and LSM are related to antiviral therapy decision among CHB patients with normal ALT. The novel AAL index is a more reliable non-invasive model.

THU-243

Occult hepatitis B virus infection after haploidentical haematopoietic stem cell transplantation patients: incidence and characterization of HBV pres/s gene mutations

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Background and aims: Occult hepatitis B virus (HBV) infection (OBI) is found in allogeneic haematopoietic stem cell transplantation (HSCT) patients. However, incidence and characterization of HBV preS/S gene mutations in patients with OBI infection receiving haploidentical HSCT (haplo-HSCT) has not been prospectively studied. OBI has been associated with an increased risk for the development of hepatocellular carcinoma and cirrhosis.

Method: We retrospectively evaluate the incidence and characterization of HBV preS/S gene mutantions in haplo-HSCT patients. From January 2014 to September 2018, 227 patients who received haplo-HSCT at Peking University Institute of Haematology were screened for hepatitis B surface antigen (HBsAg), antibodies to HBV core (anti-HBc). Serum samples negative for HBsAg and positive for anti-HBc were subjected to nucleic acid extraction and HBV DNA detection by real-time PCR. PreS/S gene mutants were analyzed by clonal sequencing in cases with occult HBV infection and 30 control chronic carriers.

Results: 189/227 patients were HBsAg-negative. The 15/189 (7.94%) HBsAg-negative patients with haplo-HSCT tested positive for HBV-DNA in serum. A total 13 OBI-patients and 30 control patients were analyzed for the the preS gene and S gene through sequencing simultaneously. 45 preS/S gene mutations were cloned from 13 OBI sequential serum samples, including 10 mutations that were not previously documented. 26 preS/S gene mutations significantly correlated with OBI. 11/13 OBI-patients (84.6%) carried in median 3 mutations in the three regions labelled here as preS1, preS2, and S were significantly higher in chronically-infected patients. Of 13 OBI sequences, 9 harboured MHR mutations. The populations of variants harbouring the D49V, W56T, L75M, I84T, A90V, P41Q, N51T, P/T78A, M120I, R135K, F141P and T168I mutations in the preS region and the T/I126M/N, P127I, Q129H and P142L mutations in the "a" determinant region were detected more frequently in the occult subjects than in the carriers.

Conclusion: This is the first report demonstrating OBI after haplo-HSCT confirmed by molecular analysis. We found a high prevalence (7.94%) of OBI in haplo-HSCT patients suggesting that routine screening for HBV-DNA should be considered in haplo-HSCT population in our region. Our data suggest that preS mutations and "a" determinant mutations are associated with OBI. This has implications for HBV diagnosis and vaccine improvement.

THU-244

Virological and clinical characteristics of chronic hepatitis delta patients of Mongolia

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Background and aims: Mongolia has the highest prevalence of chronic hepatitis B (HBV) and D (HDV) virus co-infection. HBV-HDV co-infection leads to rapid progression towards liver-related complications and is considered to be the most severe form of chronic viral hepatitis.

We here describe virological and clinical characteristics of chronic HDV patients in Mongolia.

Method: Data of 2303 HDV patients were collected for this retrospective study. We included individuals who tested positive for HBV surface antigen (HBsAg), HDV antibody (anti-HDV) and HDV-RNA any time between October 2015 to June 2018.

We summarized latest results for HDV-RNA, HBV-DNA, HBV envelope antigen (HBeAg), HBsAg, liver function tests, platelets (PLT) and fibroscan.

Patients were divided into groups according to HDV-RNA level (cleared (not detected), low (<10^4 IU/ml), medium (10^4 to 10^5 IU/ml) and high (>10^5 IU/ml)). Differences between this groups with respect to clinical markers and general biomarkers were analyzed by two-tailed t-test.

Results: Most individuals were HBeAg-negative (82.1%) and HDV-RNA positive (86.7%). 305 patients had cleared HDV-infection. Advanced liver fibrosis was found in 51.3% of the patients.

Table: (abstract: THU-244)

	patients tested	total n = 2303	cleared n = 305	low (<10^4IU/ml) n = 461	medium (10^4 to 10^5IU/ml) n = 336	high (>10^5IU/ml) n = 1201
mean age	2303	44.9	46	45.6	45.7	44.1
male%	2303	47.6	49.1	46.4	43.1	48.5
ALT±SDIU/L	897	71.2 ± 71.8	34.9 ± 27.8	49.5 ± 47.6	76.7 ± 81.7	86.4 ± 78.4
AST±SDIU/L	894	47.8 ± 41.5	27 ± 22.6	34.1 ± 24.4	51.5 ± 4.0	56.8 ± 46.7
ALB±SDmg/dL	891	42.2 ± 3.9	43.6 ± 3.9	43.5 ± 3.4	42.1 ± 4.3	41.4 ± 3.8
PLT±SD10^3/L	721	189.6 ± 56.9	202 ± 62.4	203.5 ± 64.0	176.3 ± 50.6	186.1 ± 53.4
HbeAg positive at serology%	712	17.9	7.2	7.4	8.5	26.1
HBV-DNA$\log_{10}$ IU/ml	1184	275-ND6.5 ± 7.6	6.9 ± 7.9	6.8 ± 7.7	5.3 ± 6.4	5.6 ± 6.6
HDV-RNA$\log_{10}$ IU/ml	2303	305-ND7.0 ± 8.1	0	3.2 ± 3.4	4.7 ± 4.4	6.9 ± 8.1
HBsAg$\log_{10}$ IU/ml	1228	3.9 ± 4.4	3.9 ± 4.8	3.7 ± 4.1	3.8 ± 3.8	4.0 ± 3.9
Fibroscan±SDkPa	720	10.9 ± 7.9	8.2 ± 6	10.1 ± 9.3	11.39 ± 7.19	11.5 ± 7.7

Fibroscan score was higher (p < 0.05) in patients with low, medium and high HDV-RNA levels versus patients who had cleared HDV-infection. We found no difference (p >0.05) between ALT and PLT levels in patients with low HDV-RNA versus patients with cleared infection. However, patients with medium and high HDV-RNA had elevated ALT and reduced PLT levels compared to patients who had cleared infection.

Conclusion: Mongolian chronic HDV patients are mostly young, HBeAg negative and have advanced liver fibrosis indicating rapid progression. Lower HDV-RNA level was indicative of less inflammation.

Alcoholic liver disease

THU-251

Metabolic risk factors for advanced liver disease among alcohol risk users in the general population

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Background and aims: 15–20% of alcohol risk users will develop liver cirrhosis. Metabolic factors may modify this risk for cirrhosis, but it remains unclear which metabolic factors are most important in alcohol risk users. We analyzed the role of several metabolic factors in predicting the development of advanced liver disease in alcohol risk users.

Method: Of 41243 participants in several Finnish health-examination surveys (FINRISK 1992-2012 or Health 2000), we included alcohol risk users, defined as weekly ethanol consumption > 210g for men and > 140g for women. Subjects with baseline clinical liver disease or viral hepatitis were excluded. Data were linked with national registers for liver-related admissions, mortality, and liver cancer until 2013. Metabolic factors (diabetes, body-mass index (BMI), waist circumference, waist-hip ratio, non-HDL and HDL cholesterol, triglycerides), hypertension, alcohol use, exercise, smoking, age and sex were analyzed for incident liver events by backward stepwise Cox regression analysis.

	HR	95% CI	P
Diabetes	3.42	2.07-5.63	< 0.001
Waist-hip ratio	241.0	14.9-3890	< 0.001
BMI	0.93	0.88-0.98	0.007
Hypertension	2.46	1.30–4.67	0.006
HDL cholesterol	2.09	1.34-3.24	0.001
Triglycerides	1.18	1.06-1.31	0.002
Exercise > once/wk	Reference		
Exercise 2-4x/month	0.99	0.64-1.54	0.96
Exercise less often	1.55	1.02-2.37	0.04
Alcohol use (g/wk)	1.001	1.00-1.001	0.003

Results: Among 2855 alcohol risk users with complete baseline and follow-up data (mean age 47 yrs, 70% male, mean alcohol use 370g/wk, diabetes 7%), there were 123 incident liver events. In the final backward Cox regression model (Table), diabetes, high waist-hip ratio, low BMI, HDL cholesterol, high triglyceride level and hypertension were independent metabolic predictors of incident advanced liver disease. Weekly alcohol use and inactive lifestyle were additional risk factors. Age and gender were non-significant, and adjustment for these in the final model did not alter results. There were no significant interactions between various metabolic factors and weekly alcohol use to the liver risk.

Conclusion: Diabetes, abdominal obesity, HDL cholesterol, triglycerides, and hypertension independently increased the risk for incident advanced liver disease among alcohol risk users in the general population. These findings may help to identify those alcohol risk users in whom more intensive interventions against metabolic factors are particularly important to prevent progression to advanced liver disease, and in whom more intensive liver evaluation may be warranted.

THU-252

Nursing staff volume is the most significant predictor of improved in-hospital mortality among alcoholic hepatitis patients admitted with ascites or hepatic encephalopathy: US nationwide population-based study

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Background and aims: Nursing care is associated with improved outcomes in many conditions. Alcoholic hepatitis (AH) patients have poor outcomes and require frequent monitoring during hospitalization. Therefore, our objective was to evaluate the association between nurse staffing and in-hospital mortality in patients with AH.

Method: We used the 2011 Nationwide Inpatient Sample (NIS) database to identify AH admissions in the United States. An AH admission was identified if the primary diagnosis was ICD-9: 571.1. Hospital-level nursing staff volume, which includes the volume of registered nurses, licensed practical nurses and nursing aids, was categorized into terciles (low [< 4.8], medium [4.8–6.4], and high-volume [> 6.4 nurse full-time equivalents per 1, 000 adjusted inpatient days]). Regression models assessed the impact of nursing volume on in-hospital mortality. We identified decompensated cirrhosis conditions based on validated ICD-9 codes. We adjusted for patient (e.g. demographics, insurance, and Elixhauser co-morbidities) and hospital characteristics, including hospital volume for cirrhosis-related admissions.

Results: We identified 2877 AH admission in 2011 corresponding to an estimated 31, 148 admissions in the United States. In our cohort, decompensated cirrhosis was prevalent (overall 37.6%; ascites = 28.4%; hepatic encephalopathy = 15.2%). Compared with patients admitted to hospitals with low nursing volume, patients hospitalized in high nursing volume centres were younger (median age: 46 vs. 48; P < 0.01) and more likely admitted to hospitals with high-volume of cirrhosis admissions (62.5% vs. 11.3%; P < 0.01). There was no difference between high and low nursing volume hospital admissions in relation to sex, insurance, or comorbidities. Although in-hospital mortality was similar across nursing volume groups (high vs. low: 3.3% vs. 4.2%; P = 0.52), patients with ascites or hepatic encephalopathy admitted to high nursing volume hospitals had lower mortality (high vs. low: 3.9% vs. 9.4%; P = 0.02). In our adjusted models, for AH patients without decompensated cirrhosis nursing volume was not a predictor of in-hospital mortality (high vs. low nursing volume: adjusted odds ratio aOR 3.76, 95% CI 0.82–17.21). However, among AH patients with decompensated cirrhosis, nursing volume was the only predictor of in-hospital mortality (high vs. low nursing volume: aOR 0.43, 95% CI 0.22–0.81).

Conclusion: High nursing staff volume significantly reduced in-hospital mortality among AH patients admitted with decompensated cirrhosis. Our findings suggest that altering admission pathways to

enhance nursing care for hospitalized decompensated AH cirrhotics may potentially improve in-hospital mortality.

THU-253

Equal efficacy of gastric and jejunal tube feeding in liver cirrhosis and/or alcoholic hepatitis: A randomised controlled trial

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Background and aims: Malnutrition is a frequent complication in decompensated liver cirrhosis (50%) and alcoholic hepatitis (almost 100%). Hospitalized patients who do not meet nutritional requirements are recommended to be enteral or parenteral feed (EASL eller ESPEN guidelines). No guidelines recommend a specific type of tube. However, jejunal feeding may result in the least discomfort and thus be more tolerable. We hypothesized that jejunal feeding, compared to gastric feeding, would be more efficacious in delivering the calculated amount of food and result in fewer accidental removals.
Method: 40 inpatients with liver cirrhosis and/or alcoholic hepatitis and a daily energy intake <75% of the calculated energy and protein demand was included consecutively. Patients were randomized 1:1 to nasogastric (NG)- or nasojejunal (NJ) tube feeding. All received Peptamen AF® as supplement to their oral intake. Participants were followed until discharge or death. The primary outcome was amount of food delivered. Secondary outcomes were number of tubes applied and bodyweight. Patients with HE 3 or 4 were excluded.
Results: 146 patients were screened, 40 were randomized (40% males, mean age 58 years, 70% cirrhosis, 10% alcoholic hepatitis, 20% both cirrhosis and alcoholic hepatitis. 30% were CP B, 70% CP C. A total of 33 fulfilled 7 days (6 discharged, 1 dead). Mean daily energy intake for 7 days were 6400kJ (NG) vs. 5900kJ (NJ) (p = 0.53). CP-B and NG: 6100kJ; CP-B and NJ: 5415kJ (p = 0.56); CP-C and NG: 5935kJ; CP-C and NJ: 5520kJ (p = 0.52).
The calculated caloric and protein requirement was not acquired in either of the groups. Mean deficit were 1650kJ for NG vs. 2322kJ for NJ. Tubes were accidently removed by the patients: once = 36; twice = 22; three times = 10, with, no differences between NG and NJ. There were no differences between group in the changes of bodyweight or albumin between baseline and day 7.
Conclusion: Jejunal feeding was not superior to gastric feeding in alcoholic hepatitis with or with out cirrhosis. In contrast, NG feeding tended to be more efficacious in patients with CP-B. Nutritional needs remained unmeet in both groups.

THU-254

Cumulative effects of western diet and alcohol abuse: A novel model of ASH/NASH-derived liver injury

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Background and aims: The life style in the prosperous parts of the world often include the overlapping of the Western diet (WD) (high fat and high sugar diet) with alcohol intake. Current clinical studies showed a strong causative link between dietary habits and the onset of chronic liver disease. However, the mechanisms by which WD and alcohol synergistically trigger liver damage still remain unclear. In the present work, we aimed to develop an innovative experimental model which resembles the compound effects of WD and alcohol as observed in patients with non-alcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH).
Method: Female C57BL/6 mice received 10% alcohol in the drinking water together with a WD for 10 weeks (*ASH/NASH model*). Mice receiving only WD or alcohol were used as controls. Serum markers of liver damage, blood lipids and glucose tolerance test (GTT), liver and epididymal white adipose tissue (eWAT) histology, hepatic triglyceride content (HTC) and hepatic expression of pro-inflammatory and pro-fibrotic genes were analysed.
Results: Our novel experimental *ASH/NASH diet* recapitulated the compound effect of WD and alcohol consumption in humans, leading to obesity, significant hepatomegaly and exacerbated glucose intolerance after GTT. The *ASH/NASH*-feeding resulted in hypercholesterolemia, high HTC, hepatic macrosteatosis and ballooning degeneration of hepatocytes. Significant liver damage was characterized by elevated plasma ALT and positive TUNEL staining. Notable, mice treated with the *ASH/NASH diet* exhibited significant hepatic inflammation and intrahepatic accumulation of $CD11b^+$ and $F4/80^+$-positive immune cells accompanied by upregulated mRNA expression of TNFα. Importantly the *ASH/NASH diet* diet also resulted in increased hepatic fibrosis and remarkable collagen accumulation in perisinusoidal areas. Furthermore, *ASH/NASH*-fed mice developed profound eWAT inflammation characterized by adipocyte hypertrophy, macrophage infiltration and a dramatic increase in crown-like structures.
Conclusion: The novel *ASH/NASH-diet* is an excellent novel model for the characterization of patients with signs of NASH/ASH. Importantly, the compound effects of WD and alcohol synergistically enhanced obesity, glucose intolerance, liver damage, triggered prominent steatohepatitis and hepatic fibrosis, as well as inflammation in the eWAT tissue. This diet therefore is a suitable tool in the search for new therapeutic avenues to combat chronic liver disease.

THU-255

Long term outcomes of alcoholic patients without clinical evidence of liver disease: A 15 years follow-up study

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Background and aims: Data considering the impact of alcoholic consumption and abstinence in alcoholic patients without liver disease are scarce. We aimed to investigate long-term outcomes of alcoholic patients without clinical evidence of chronic liver disease (CLD), and to identify risk factors for mortality and for the development of CLD.
Method: Alcoholic patients from a rehabilitation center were prospectively enrolled in a clinical protocol performed in 2002 and revaluated at 2011 and 2018. Demographic, clinical and alcoholic consumption data were collected, and available blood tests and abdominal ultrasounds were also analysed. We investigated long-term outcomes in 123 patients with no evidence of CLD at the first evaluation. Of those 22 patients were lost for follow-up.
Results: 101 patients with no CLD were included; 81.2% were male. At the first evaluation, the median duration and amount of alcoholic consumption was 24.5 ± 12.9 years (4–50) and 315 ± 207 g/day (47.5–1128.3 g/day), respectively; 59.4% were abstinent, for a period of 6 ± 30 months. At 15 years of follow-up, 45.5% have returned alcohol intake for a median duration and amount of 5.7 ± 7.7 years (0–15) and 98 ± 177 g/day (0–1072), respectively. Six (5.9%) patients developed CLD during follow-up; of whom, 60% presented as ascites. During follow-up 26.7% died, and causes of death were: cancer in 54.2%, cardiovascular in 29.2%, liver disease in 8.3%, infections and car accident both in 4.2%. Development of CLD on follow-up positively

associated with total years with consumption (47 ± 5 vs. 29 ± 1 years, p = 0.003) and binge drinking on follow-up (OR 13.5 [1.5–121.9], p = 0.015) and negatively with duration of abstinence on follow-up (2.3 ± 1.4 vs. 9.6 ± 0.8 years, p = 0.001). Type of alcoholic beverage, gender or ethnicity did not associate with the risk for CLD. Abstinence for longer than 3 years associated with higher CLD-free survival (15.8 ± 0.1 vs. 14.8 ± 0.1, p = 0.027). Patients that drank beer showed decreased overall survival (63.6 ± 2.1 vs. 75.8 ± 1.0, p < 0.001).
Conclusion: Long-term alcoholics with no evidence of liver disease can still progress to CLD in 6%, which associates with total years of consumption and negatively with time of abstinence on follow-up. Beer consumption seems to associate with higher overall mortality.

THU-256

Alpha-1 antitrypsin ameliorates experimental alcoholic liver disease and predicts patient outcome

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Background and aims: Alcoholic liver disease (ALD) is a substantial global health care problem, encompassing a broad spectrum of phenotypes including simple steatosis, steatohepatitis, liver fibrosis and cirrhosis or even HCC (hepatocellular carcinoma). Pro-inflammatory cytokines (TNF-α, IL-1β), gut-barrier dysfunction and toxicity of ethanol and its metabolites (namely acetaldehyde) have been suggested as critical factors in the development of ALD, resulting in hepatocyte damage and cellular infiltration of immune cells (e.g. neutrophils). Ultimately, these changes lead to liver fibrosis and cirrhosis. The acute-phase-protein Alpha-1 antitrypsin (A1AT) is a serin-proteinase inhibitor with anti-inflammatory properties (e.g. neutrophil elastase inhibition). In the present study we aimed to investigate the role of A1AT in ALD.
Method: In a cohort of 512 cirrhotic patients, biochemical and clinical parameters were compared between individuals with cirrhosis due to ALD and other etiologies, respectively. In a second step, the potential protective role of A1AT was evaluated in a murine binge-drinking model.
Results: Low A1AT serum concentrations (≤ 120 mg/dL) were significantly associated with poorer survival of cirrhotic ALD patients (p < 0.001), however, this finding could not be found in patients with liver disease of other etiologies (p = 0.18). Multivariate Cox-regression analysis revealed that low A1AT serum concentration (<120 mg/dL) was a NaMELD (Natrium model for end-stage liver disease)-independent predictor of transplantation/survival (HR = 2.17; 95% CI 1.20–3.92, p < 0.01). In a murine model of acute ALD a single ethanol gavage was associated with distinctive liver injury, inflammation and increased expression of hepatic *Serpina1* (p < 0.05). Moreover, simultaneous ethanol gavage and supplementation of A1AT ameliorated ethanol-induced hepatic injury exemplified by decreased *Tnfα* transcription (p < 0.05) and hepatic infiltration by MPO^+ cells (p < 0.001). Additionally, A1AT reduced hepatic microscopic steatosis (p < 0.05) upon acute ethanol exposure.
Conclusion: A1AT concentrations > 120 mg/dL are associated with increased survival in patients with alcoholic liver cirrhosis. A1AT supplementation might potentially serve as a novel therapeutic option in ALD.

THU-257

Fungal dysbiosis in alcoholic patients is associated with the severity of the liver injury

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Background and aims: Gut bacteria play an important role in alcoholic liver disease (ALD). Recently it has been showed that fungal dysbiosis is involved in disease severity in an animal model of ALD. The aim of this study was to characterize fungal dysbiosis in patients at different stages of ALD and its relationships with bacterial dysbiosis and clinical features.
Method: Gut bacterial/fungal profiles were analysed using 16s/ITS sequencing in healthy controls (HC) and alcoholic patients.
Results: A total of 133 patients were included: 28 HC and 105 alcoholic patients (with and without histologically proven alcoholic hepatitis). Alcoholic patients had an increase in Ascomycota and a decrease in Basidomycota phyla as compared to HC. Moreover, patients with severe alcoholic hepatitis (sAH) had a specific signature of fungal and bacterial dysbiosis as compared to cirrhotic patients without sAH. This dysbiosis included an increase in Candida and Xerochrysium levels in the mycobiota associated with an increase of the bacterial phyla, Proteobacteria, Fusobacteria and Actinobacteria. Candida levels were positively correlated to the sAH histological score. Also, the presence of serum anti-Saccharomyces cerevisiae IgG antibodies (ASCA), a marker of the immune response against fungi, was positively correlated to the fibrosis and alcohol hepatitis histological scores.
Conclusion: Overall, our study show that alcohol consumption induces a fungal dysbiosis that is correlated to ALD severity and to bacterial dysbiosis, supporting the role of fungal microbiota in ALD pathogenesis. Modifying fungal microbiota in patients with ALD could be a new therapeutic target in patients with ALD.

THU-258

Comparison of a fast corticosteroid tapering with the standard corticosteroid schedule in severe alcoholic hepatitis

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Background and aims: Corticosteroids reduce short-term mortality of patients with severe alcoholic hepatitis (AH). Prednisolone 40 mg/day for 28 days followed by tapering is the standard treatment. A shorter corticosteroid treatment could be useful to treat severe AH, reducing the risk for treatment-related complications. We aimed to compare the mortality between a fast corticosteroid tapering and the standard corticosteroid tapering schedule in patients with severe AH.
Method: We retrospectively reviewed a cohort of patients with severe AH (Maddrey score ≥ 32 and/or hepatic encephalopathy) who were responders based on Lille score, and treated with a fast corticosteroid tapering (prednisone 40 mg/day for 7 days followed by a reduction of 10 mg every week) between 2009 and 2017. Data were compared to an external cohort of patients from 3 other tertiary hospitals in the same area, treated with the standard schedule. We evaluated baseline characteristics, concomitant treatments, infection rate, and mortality.
Results: A total of 27 patients treated with the fast corticosteroid tapering and 52 with the standard schedule were included (mean MELD 22 ± 2 vs. 23 ± 2, respectively, p = 0.21). Corticosteroid treatment duration was significantly shorter in the first group (34 ± 9 vs. 45 ± 13 days, p < 0.001). Antibiotic prophylaxis was more frequent among patients treated with the fast corticosteroid tapering than in the standard schedule cohort (77.8% vs. 44.2%, p = 0.004). No significant differences were found in the use of nutritional

supplements, enteral nutrition or 180-day alcohol abstinence. The probability of death of patients treated with the fast corticosteroid tapering vs. the standard schedule was 0% vs. 3.8% at 30 days (p = 0.30), 0% vs. 7.8% at 90 days (p = 0.14), 7.4% vs. 11.8% at 180 days (p = 0.53), and 7.4% vs. 33% at one year (p = 0.02). We observed that 33.3% vs. 32.7% of patients, respectively, presented an infection at AH diagnosis (p = 0.95), and 29.6% vs. 40.4% developed infection after initiation of corticosteroids (p = 0.34). Multivariate analysis in the whole series showed that the fast corticosteroid tapering was a one-year independent predictive factor of survival, but antibiotic prophylaxis was not.
Conclusion: A fast corticosteroid tapering is not associated with a worse outcome than the standard schedule. This new regime could be a proper treatment strategy for severe alcoholic hepatitis, but randomized trials are needed to compare it to the standard schedule.

THU-259
The gene signature-MELD score and alcohol consumption determine long-term prognosis of patients with severe alcoholic hepatitis
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Background and aims: Accurate prediction of long-term prognosis of patients with severe alcoholic hepatitis (AH) is mandatory to guide therapeutic strategy. The gene signature-MELD (gs-MELD) score, a combination of a gene signature and the MELD score, has been proposed as a new prognostic tool and showed better diagnostic accuracy than all other prognostic scores for assessing the risk of death at 6 months (Trepo *et al*. Gastroenterology 2018;154:965–75).
Aim: To assess the long-term prognostic value of the gs-MELD score among patients with severe AH.
Method: Patients with severe AH (Maddrey Discriminant Function > 32) treated with methylprednisolone orally at a dose of 32 mg/day for a maximum of 28 days were followed for 5 years from the date of corticosteroid therapy initiation. The primary end point was survival at 5 years. The gs-MELD score was generated as described previously. Patients with a gs-MELD greater than 2.66 were considered to have a poor prognosis. Patients were considered abstinent if they had no alcohol consumption during follow-up.
Results: 48 consecutive patients with histologically proven severe AH from 4 European centers were included (median age: 52 years [95% CI: 48–56], median Maddrey Discriminant Function: 50 [95% IC: 45–58]). None had active infection at the start of corticosteroids. Median gs-MELD score was 2.6 (95% CI: 2.2–3.0). 14 (30%) were considered non-responders to corticosteroids at day 7 according to the Lille score. During follow-up, 19 patients (40%) were abstinent, 24 (55%) died and 4 (8%) underwent a liver transplantation. At 5 years, rates of survival without death or liver transplantation were 57% (95% CI: 36–78) and 14% (95% CI: 0–30) in patients with favorable and with poor gs-MELD score (p < 0.001), and 61% (95% CI: 35–86) and 22% (95% CI: 6–39) in abstainers and in consumers (p = 0.001), respectively. In time-dependent multivariable proportional hazards models, the gs-MELD score (hazard ratio: 5.78, 95% CI:2.17–15.38, p < 0.001) and alcohol consumption (hazard ratio: 12.18, 95% CI:3.16–46.95, p < 0.001) were independently associated with 5-year mortality.
Conclusion: While only the gs-MELD score determines prognosis at short-term, both gs-MELD score and alcohol consumption are independently associated with the risk of death at 5 years. Therapeutic strategies should target alcohol consumption to improve long-term prognosis.

THU-260
Alcoholic cirrhosis is associated with higher in-patient mortality compared to non-alcoholic cirrhosis
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Background and aims: Alcoholic liver disease represents a spectrum of alcohol related conditions that range from reversible steatosis to steatohepatitis, fibrosis, and cirrhosis. Alcohol is one of the most common causes of cirrhosis. Previous studies showed the high burden of alcoholic liver disease and higher rate of decompensation with alcoholic cirrhosis (AC), we aim to investigate mortality risk of AC among hospitalized patients with cirrhosis.
Method: We analyzed hospitalizations (age ≥ 18) with diagnostic ICD9 codes indicating cirrhosis in the National Inpatient Sample (NIS) 2014. An AC diagnosis was defined as a discrete AC diagnosis code or a non-alcohol related cirrhosis code plus either an alcohol use code or an alcohol related comorbidity (alcoholic hepatitis, alcoholic liver failure) code; all other cirrhosis codes excluding these criteria were defined as non-alcoholic cirrhosis (NAC). The primary outcome was the mortality odds ratio (OR) of AC vs NAC among all-cause hospitalizations with cirrhosis. Multivariate regression analysis was used to adjust for potential confounders.
Results: The total number of hospitalizations with AC included was 307, 215. The mean age was 55.8, 71.7% were male. Mortality among all-cause hospitalizations with AC was 6.6% (6.4%–6.8%) compared to 5.7% (5.5%–5.9%) with NAC (Table 1). AC was independently associated with higher mortality (OR 1.22; 1.15–1.29) compared to NAC among all-cause hospitalizations. Multivariate regression analysis was used to isolate variable including age, sex, race, insurance, hospital characteristics, disease complications, liver transplantation status, and Charlson Comorbidity Index. Among all-cause hospitalizations with cirrhosis, Hispanic race (0.89; 0.82–0.97), Medicare insured (0.83; 0.77–0.90) with primary insured as reference, urban hospital (0.86; 0.75–0.97), and liver transplantation during same hospitalization (0.32; 0.22–0.46) were associated with lower mortality; while older age (1.02; 1.018–1.024), uninsured (1.46; 1.31–1.62), higher Charlson Comorbidity Index (1.07; 1.06–1.09), and larger hospital bed sizes (medium/large with small as reference) were associated with higher mortality. All the comorbidities adjusted were associated with higher mortality (Table 2).

Table 1

Comparison of Alcoholic Cirrhosis vs. Non-alcoholic Cirrhosis

Characteristics	Alcoholic Cirrhosis	Non-alcoholic Cirrhosis
Total Number of Observations	307,215	314,600
Average Age (year)	55.8 (55.7-55.9)	63.0 (62.8-63.2)
Female (%)	28.3 (27.8-28.7)	50.4 (49.9-50.9)
HCV (%)	26.8 (26.2-27.4)	32.1 (31.4-32.8)
Ascites (%)	38.0 (37.4-38.6)	32.2 (31.5-32.8)
Spontaneous Bacterial Peritonitis (%)	3.7 (3.5-3.8)	2.6 (2.5-2.8)
Variceal Bleed (%)	7.0 (6.8-7.2)	3.8 (3.7-4.0)
Hepatic Encephalopathy (%)	21.8 (21.4-22.2)	15.0 (14.6-15.4)
Hepatocellular Carcinoma (%)	4.0 (3.8-4.3)	6.0 (5.6-6.4)
Septicemia (%)	10.7 (10.4-11.0)	11.1 (10.8-11.4)
Acute Kidney Failure (%)	24.1 (23.6-24.6)	25.9 (25.4-26.4)
Coagulopathy (%)	14.9 (14.4-15.5)	7.4 (7.0-7.8)
Liver transplant During Hospitalization (%)	0.5 (0.4-0.7)	1.0 (0.8-1.2)
In-hospital Mortality among All-cause Hospitalizations (%)	6.6 (6.4 -6.8)	5.7 (5.5-5 9)

Table 2

Mortality Risk Factors among Cirrhosis Patients

Factor	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI	p-value
Age	1.02	1.018	1.024	**<0.01**
Female Sex	0.96	0.91	1.01	0.13
Alcoholic Cirrhosis	1.22	1.15	1.29	**<0.01**
Race				
White	Reference			
Black	1.04	0.95	1.13	0.41
Hispanic	0.89	0.82	0.97	**0.01**
Asian and Pacific Islander	1.01	0.85	1.20	0.92
Native American	0.93	0.75	1.15	0.52
Other	1.05	0.91	1.22	0.50
Primary Insurance				
Private	Reference			
Medicaid	0.95	0.87	1.04	0.27
Medicare	0.83	0.77	0.90	**<0.01**
Uninsured	1.46	1.31	1.62	**<0.01**
Hospital Bed-size				
Small	Reference			
Medium	1.21	1.09	1.34	**<0.01**
Large	1.26	1.15	1.39	**<0.01**
Teaching Hospital	1.02	0.95	1.10	0.52
Urban Hospital	0.86	0.75	0.97	**0.02**
Charlson Comorbidity Index	1.07	1.06	1.09	**<0.01**
Liver Transplantation	0.32	0.22	0.46	**<0.01**
Hepatocellular Carcinoma	1.41	1.27	1.57	**<0.01**
Variceal Bleed	1.91	1.73	2.11	**<0.01**
Hepatic Encephalopathy	1.35	1.26	1.43	**<0.01**
Septicemia	7.04	6.63	7.47	**<0.01**
Acute Kidney Injury	3.50	3.29	3.71	**<0.01**
Ascites	1.20	1.13	1.26	**<0.01**
Coagulopathy	2.06	1.92	2.22	**<0.01**

Conclusion: AC was associated with higher inpatient mortality compared to NAC. The pathophysiology behind it is multifactorial: nutritional deficiency in AC can cause higher rate of coagulopathy; low thiamine and phosphate depletion in AC can contribute to hepatic encephalopathy; alcohol interferes with immune functions and can increase the risk for infection; thus causing higher rate of complications and worse outcome. Alcoholic cirrhosis requires more aggressive intervention and systemic approach in the inpatient setting.

THU-261

Validation of the pre-treatment neutrophil-to-lymphocyte ratio to predict response to corticosteroids in severe alcoholic hepatitis

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Background and aims: Previous analysis of the Neutrophil-to-Lymphocyte Ratio (NLR) in patients from the STOPAH trial identified patients with alcoholic hepatitis who have a survival benefit from corticosteroids. We aimed to validate this observation in an independent patient group.
Method: A validation group was derived from patients recruited from four United Kingdom centres (Leeds, Bristol, Brighton and Plymouth) treated for severe alcoholic hepatitis out with the STOPAH trial. All patients had a serum bilirubin greater than 80μmol/l and a discriminant function (DF) > 32. Treatment with prednisolone (40mg/day) and its continuation or discontinuation after 7 days was based on local clinical discretion. Kaplan-Meier analysis was used to assess survival. Log-Rank tests and *t*-tests were used for comparative analysis with 95% confidence intervals shown.
Results: There were 237 patients in the validation group, 138 of whom received prednisolone. The overall 90-day mortality was 26.3% *vs.* 32.6% for those treated and not treated with prednisolone respectively (p = 0.20; HR 0.73 (0.45, 1.19)). The mean NLR at baseline for all patients was 8.56 (7.23, 9.84). The NLR was greater in those who initially presented with AKI (10.22 *cf.* 7.37: p = 0.014; 0.57, 5.14) and infection (10.06 *cf.* 7.36: p = 0.023; 0.38, 5.01). There was no benefit with prednisolone treatment for those with NLR < 5 or > 8. There was an improvement in 28-day outcome with prednisolone if NLR 5–8 (Table). Those with a modified Glasgow Alcoholic Hepatitis Score (with incorporation of the NLR) ≥ 9 and NLR 5–8 had a reduction in 90-day mortality with Prednisolone treatment: 23.3% *vs.* 46.4%: p = 0.036; HR 0.268 (0.10, 0.71).

Table:

		NLR <5		NLR 5–8		NLR > 8	
		Untreatedn = 39	Treated n = 50	Untreated n = 35	Treated n = 37	Untreated n = 25	Treated n = 51
TOTAL n = 237	28 Day Mortality	5.1% P = 0.416 (0.44, 8.69)	10.0%	28.6% P = 0.0023 (0.026, 0.27)	2.7%	28.0% P = 0.469 (0.26, 1.91)	23.5%
	90 Day Mortality	18.4% P = 0.843 (0.32, 2.47)	16.3%	37.4% P = 0.097 (0.20, 1.14)	21.6%	48.0% P = 0.362 (0.34, 1.53)	39.2%

Conclusions: This real-life validation cohort confirms the observation that patients with severe alcoholic hepatitis and low (<5) or high (> 8) NLRs do not benefit from corticosteroids. Favourable outcome with corticosteroids is only seen in those with NLR 5–8.

THU-262

A modified Glasgow alcoholic hepatitis score incorporating the neutrophil-to-lymphocyte ratio is superior to other baseline scores of prognosis in alcoholic hepatitis

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Background and aims: The Neutrophil-to-Lymphocyte Ratio (NLR) has been shown to be prognostic in a variety of liver conditions. We assessed the role of NLR in the prognosis of alcoholic hepatitis and its performance when incorporated into the Glasgow Alcoholic Hepatitis Score (GAHS).
Method: The NLR was calculated from 789 patients who participated in the STOPAH trial. Area under the Receiver Operating Curve (AUC) analysis was performed. Kaplan-Meier analysis was used to assess survival. Log-Rank test was used for comparative analysis with 95% confidence intervals shown, and Pearson's correlation co-efficient (r) for correlations.
Results: The mean NLR at baseline for all patients was 6.51 (6.14, 6.88). Overall the baseline NLR had a modest discriminatory capacity with an AUC of 0.660 (0.626, 0.693) with an optimal cut-point of 5 (*J* = 0.247) for 90-day mortality. Mortality at Day 90 was 16.1% for those with a NLR < 5 and 33.6% for those with a NLR ≥ 5 (p < 0.0001; HR 2.39 (1.81, 3.15)). There was a strong correlation between the total white blood cell count (WCC) and NLR: r = 0.564 (0.52, 0.60); p < 0.0001. In view of this, the NLR was incorporated into the GAHS with an NLR threshold of 5 replacing the WCC threshold of 15, creating a modified GAHS (mGAHS). The AUCs for mGAHS for 28-day and 90-day outcomes were 0.783 (0.752, 0.812) and 0.739 (0.706, 0.770) respectively. For 28-day outcome the mGAHS AUC was superior to that of the DF (0.684: p < 0.0001; 0.05, 0.14), the original GAHS (0.763: p = 0.027; 0.002, 0.04) and the MELD (0.739: p = 0.0014; 0.009, 0.08). A mGAHS ≥ 9 was present in 460 patients (58.6%) with a

90-day mortality of 35.4% compared with a mortality of 10.8% for those with mGAHS < 9 (p < 0.0001 HR 3.91 (2.96, 5.17)).
Conclusion: The incorporation of the NLR into the GAHS improved the AUC and this mGAHS was superior to other baseline scores for predicting 28-day outcome.

THU-263

The demonstration of antibodies to histone 2B of the IgA-type helps to differentiate between alcoholic liver disease and non-alcoholic fatty liver disorder

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Background and aims: Re-analysing the clinical relevance of antibodies to histones for the serological diagnosis of systemic lupus erythematosus (SLE) we accidentally found that these antibodies-especially those to histone 2B-showed a strong association also with alcoholic liver disorders (ALD) when they were of the IgG-type and that IgA-antibodies were only found in ALD but not SLE. We, therefore, wanted to analyse the specificity and clinical relevance of abs to histone 2B of the IgA-type in more depth in order to see whether they occur also in patients with other chronic liver disorders.
Method: Sera from patients with clinically defined ALD (n = 58), non-alcoholic fatty liver disease (NAFLD; n = 52), drug-induced liver disease (n = 8), storage diseases (Wilson's disease, hemochromatosis; n = 9), and autoimmune liver disorders (AILD; autoimmune hepatitis [AIH] n = 353; primary biliary cholangitis [PBC] n = 255; primary sclerosing cholangitis [PSC] n = 41) as well as from 85 healthy individuals were analysed by ELISA using histone 2B as antigen. Peroxidase conjugated anti-human IgA-antibodies were used as secondary antibodies.
Results: Anti-histone 2B antibodies of the IgA-type were found in 62% of the patients with ALD and 38% of patients with drug-induced liver disorders but only 10% of patients with NAFLD, up to 14% of patients with AILD or storage diseases and 5% of healthy individuals (p < 0.001). Also antibody reactivity was significantly higher in patients with ALD than in the other groups of patients (p < 0.001).
Conclusion: These data indicate that antibodies to histone 2B of the IgA-type may be a helpful marker for the diagnosis of ALD and especially for its differentiation to NAFLD. Their presence in pts with drug-induced liver disorders indicates that the antibodies may be induced by a toxic process in general, not just alcohol. It still remains to be seen by which mechanism these antibodies are induced and whether gut barrier leaking may play a role.

THU-264

Transmission electron microscopy reveals dramatic hepatic zonal changes upon chronic alcohol feeding

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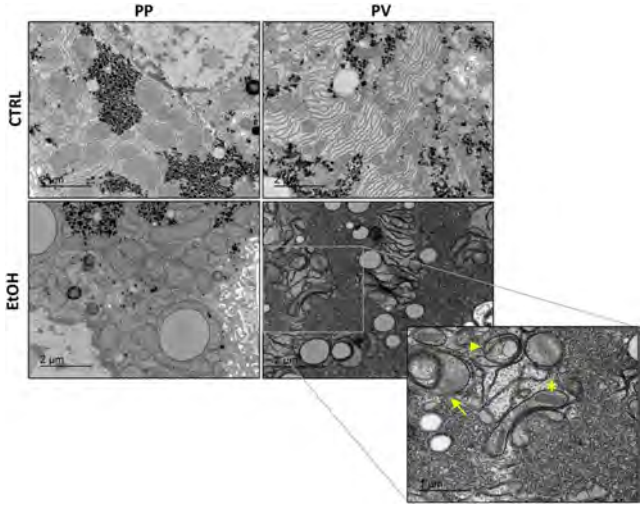
Background and aims: Alcoholic liver disease (ALD) is a leading cause of liver-related mortality. Ethanol (EtOH) induces changes in hepatocytes including lipid droplet (LD) accumulation, ER and oxidative stress, and mitochondrial dysfunction that can lead to cell death. Periportal (PP) and perivenous (PV) hepatocytes exhibit specialized metabolic functions due, in part, to exposure to different oxygen gradient and nutrients along the liver sinusoid. As the PV area is the most affected in ALD, we aimed to characterize the structural changes induced by ETOH in PP and PV hepatocytes using transmission electron microscopy (TEM).
Method: 8 week-old C57BL/6J male mice were fed a control (CTRL) or 5% EtOH Lieber-DeCarli diet (EtOH) for 30 days. Livers were washed via portal vein with Hanks I buffer and fixed with 3% glutaraldehyde in phosphate buffer. Semifine sections were observed with light microscopy to define PP and PV areas. Images from ultrathin sections containing both areas were taken using a TEM JEOL JEM-1010. Changes in mitochondrial number/length were estimated using Image J software.
Results: In CTRL diet both areas presented high glycogen content and few small LD. However, PV hepatocytes contained more RER and mitochondria than PP hepatocytes. Furthermore, PV mitochondria presented higher length/width ratio compared to PP mitochondria. Chronic EtOH intake induced a strong decrease in glycogen content in both areas, especially in the PV. EtOH increased LD number in both populations. While PP LD sizes ranged from small to very large, PV LD remained small. EtOH increased mitochondrial number and length in PP hepatocytes with the largest mitochondria surrounding LDs. In contrast, EtOH decreased mitochondrial size in PV areas while maintaining the high length/width ratio. The biggest effect of EtOH in PV area was a dramatic change in mitochondrial shape: concave forms with thick edges and a thin matrix in the center (arrowhead), and donut-like forms with bent shapes shrinking into a ring with a lumen containing cytoplasm (arrow). Some of these mitochondria presented unusual parallel cristae (*). Moreover, EtOH caused a shift from RER to SER in PV areas.



Conclusion: These data reveal that PP and PV areas are different in basal states. EtOH induces differential changes in both populations, pooling them further apart. ETOH predominantly induces structural changes in mitochondria from zone 3, which may account for the prevailing injury seen in this area in ALD.

THU-265

In severe alcoholic hepatitis, serum transferrin indicates impaired HNF4a signaling and predicts mortality independently of disease severity

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Background and aims: Severe alcoholic hepatitis (AH) confers substantial mortality but the underlying pathogenesis remains incompletely understood. Deranged iron parameters are common in liver disease patients and constitute attractive outcome predictors. Since alcohol suppresses the production of the iron-regulatory hormone hepcidin, we analysed the role of iron parameters in patients with severe AH.
Method: Ferritin, transferrin, iron, transferrin saturation (TSAT), non-transferrin bound iron (NTBI), soluble transferrin receptor (sTfR), and hepcidin were measured in sera from 828 patients with severe AH recruited prospectively via the STOPAH trial. Potential regulators of the established negative acute-phase protein (APP) transferrin were assessed in primary mouse hepatocytes.
Results: AH patients had diminished serum transferrin (median 93 mg/dl), but increased ferritin (median 625 ng/dl) and TSAT (median 70%). Among iron parameters, baseline transferrin was the best predictor of 28-day (AUROC 0.72, 95% CI 0.67–0.78) and 90-day survival (AUROC 0.65, 95% CI 0.61–0.70). Transferrin's predictive ability was comparable to the established scores MELD, GAHS, or DF and was independently associated in multivariable analysis. In contrast, NTBI and sTfR as the markers of excess unbound iron and functional iron deficiency, respectively, did not have an obvious prognostic importance. Hepatic transcriptome analysis revealed a strong positive relationship with the nuclear factor HNF4α and negative association with cytokines TGFß1, IL1ß, TNF or IL6. In primary hepatocytes, treatment with TGFβ1 or the HNF4α inhibitor BI6015 suppressed the production of the negative APP transferrin, while exposure to TNFα, IL1β, and IL6 had no effect.
Conclusion: Serum parameters of iron metabolism, particularly transferrin as a negative acute phase reactant, are strongly associated with outcome in severe AH. Accordingly, serum transferrin predicts 28- and 90-day mortality with a performance comparable to commonly used scoring systems. Transferrin′s decrease may reflect an impaired HNF4α axis.

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Comparison of clinical features and prognosis in different types of severe alcoholic hepatitis: Is it time to classify?

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Background and aims: Severe alcoholic hepatitis (SAH) is a clinical syndrome amongst people with with very poor prognosis. Various prognostic scores are available for predicting outcome in SAH.We evaluated the clinical characteristics of SAH with different underlying liver disease and compared the available prognostic models as predictors of outcome in patients with SAH.
Method: Patients which were diagnosed as alcoholic hepatitis with a Maddrey discriminant function (MDF) ≥ 32 were included. Enrolled patients were divided into 3 groups: type SAH-A (patients with underlying non-cirrhotic chronic liver disease), type SAH-B (patients with previous compensated cirrhosis) and type SAH-C (patients with previous decompensated cirrhosis). Biochemical parameters were collected at baseline. Complications and mortality were assessed during a 28-day follow-up period. The difference of 3 types of SAH upon survival was assessed by Kaplan-Meier analysis and tested using the log-rank test. MDF, age, model for end-stage liver disease (MELD), bilirubin, international normalized ratio (INR), and creatinine (ABIC), Glasgow alcoholic hepatitis score (GAHS), chronic liver failure-sequential organ failure assessment (CLIF-SOFA), were calculated 48 hours after admission and correlated with patient outcome after 28 days. Receiver operator characteristic (ROC) curves were plotted for all prognostic scores.
Results: 170 patients were included. 27 (15.9%) were defined as SAH-A, 52 (30.6%) as SAH-B, and 91 (53.5%) as SAH-C, respectively. Whereas age, prothrombin time, urea nitrogen, blood creatinine, INR, encephalopathy rate, infection rate, and 28-day death rate, were higher in patients with SAH-C ($p < 0.05$), and white blood cell, platelet count, albumin, γ-glutamyltransferase, total bilirubin, were higher in patients with SAH-A ($p < 0.05$). The Kaplan-Meier survival probability in patients with SAH-C (51.6%) was different from those with SAH-A (88.9%) and SAH-B (80.8%) ($p < 0.001$), Figure1. The CLIF-SOFA score, compared with other scores, most accurately predicted 28-day mortality, with an area under the ROC of 0.796 (MELD, 0.584, $p < 0.0001$; GAHS, 0.644, $p = 0.0035$; MDF, 0.681, $p = 0.0324$), Figure2. ABIC showed similar prediction level to CLIF-SOFA (0.745 VS. 0.791, $p = 0.2266$). The MELD score has poor sensitivity and specificity for early identification ($p = 0.073$).Underlying liver disease ($p = 0.002$) and CLIF-SOFA score ($p = 0.008$) were independent predictors of 28-day mortality.

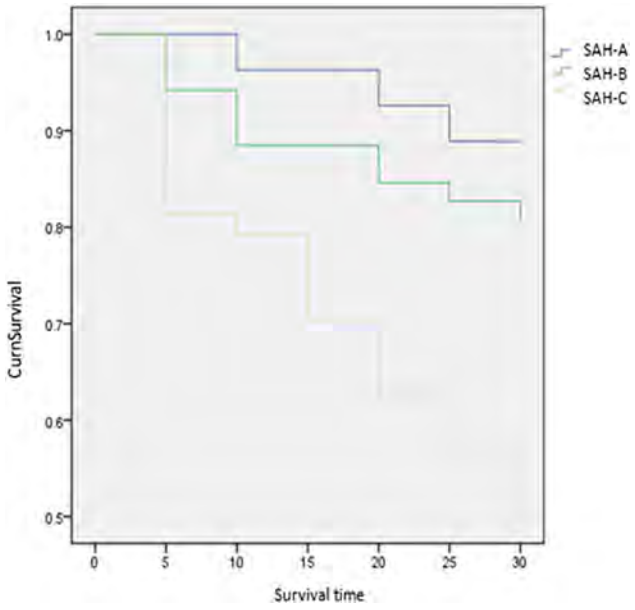

Figure 1: Kaplan-Meier survival probability for patients in 28 days

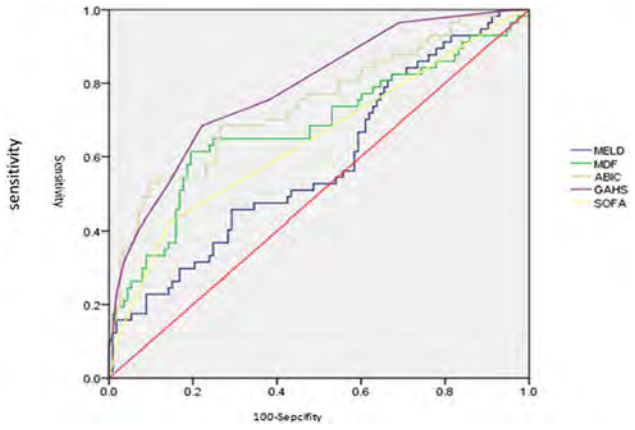

Figure 2: the receiver operator characteristic curves of various prognostic indicators for predicting 28-day mortality

Conclusion: There are significant differences in biochemical parameters, complication rates, and prognosis in SAH patients with different underlying liver disease. CLIF-SOFA is superior to the others in SAH.

THU-267

The increasing burden of alcohol related liver disease: A single tertiary centre experience

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Background and aims: Alcohol-related liver disease accounts for 60% of all liver disease and approx. 80% of liver-related deaths. In the UK, the high levels of alcohol-related health burden show no signs of subsiding, with over 10 million adults drinking excessively each week. Unless the trends are reversed, it is projected that over the next five years, £17 billion in costs to the NHS will be incurred.
Method: Data on all adult patients admitted with alcohol related liver disease were collected retrospectively over a 5 year period at a single tertiary centre hospital which serves a catchment of 800, 000 individuals.
Using the Trust database, the number of admissions, gender, diagnosis, number of deaths, length of stay and cost of admission were recorded. Comparative analyses were carried out to assess hospitalisation trends of major indicators over time.
Results: Data collection period was from 01/01/2013 to 31/12/2017 yielding 1196 patients with alcohol related liver disease, accounting for a total of 5859 admissions over 5 years. The average number of admissions per patient were 4.9 (± 2.3). The mean age was 61 years (±13), and 69% of the cohort were male. During the study period there was a 44% increase in admissions for alcohol related liver disease and a 75% increase in admissions for alcohol related cirrhosis. This was at an estimated total cost of admissions of £5.2 million in 2017, a 48% increase from 2013. Despite the increase in disease burden, the average length of stay (6.5 days vs 5.3 days) and inpatient mortality (23.4% vs 19.6%) fell during the study period.
Conclusion: This study demonstrates the increasingly detrimental impact of alcohol related liver disease on health services in the UK. Substantial increases in health care cost and utilisation among hospitalised patients were observed, while a possible improvement in disease management was noted. This highlights the urgent need to allocate resources so that effective prevention strategies can be implemented.

THU-268

Human microfibrillar-associated protein 4 expressed in the liver and serum in alcoholic liver disease predicts liver fibrosis severity with accuracy similar to transient elastography and enhanced liver fibrosis test

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Background and aims: Alcoholic liver disease (ALD) is a public health concern and responsible for half of all cirrhosis-related deaths. Early detection of fibrosis, ideally in the pre-cirrhotic stage, is a key strategy for improving ALD outcomes and for preventing progression to cirrhosis. We investigated the utility of human microfibrillar-associated protein 4 (MFAP4) as a serological biomarker for the early detection of alcoholic liver fibrosis.
Method: To evaluate the diagnostic accuracy of MFAP4 to detect ALD-induced fibrosis, we performed a prospective liver biopsy-controlled study involving 266 patients with prior or current alcohol overuse. All patients were evaluated with a) liver biopsy, b) transient elastography (TE), c) Enhanced Liver Fibrosis test (ELF) and d) serum MFAP4 level. All measurements and investigations were performed on the same day. Patients were split into a training (n = 153) and a validation (n = 113) cohort. Blood samples from 50 healthy gender- and aged-matched participants were used to determine the concentration of MFAP4 in healthy individuals. MFAP4 expression in liver biopsies was semiquantitatively evaluated by immunostaining of MFAP4 in 116 liver biopsies distributed across the full spectrum of Kleiner fibrosis stages. Patients with cirrhosis were followed until a hepatic decompensation episode developed.
Results: The distribution of Kleiner fibrosis stage in the cohort was F0 = 32; F1 = 93; F2 = 79; F3 = 17; F4 = 45. MFAP4 expression in liver tissue and serum MFAP4 levels increased with fibrosis stage until the development of advanced fibrosis (Spearman's $\rho = 0.66$, $p < .000$). The area under the receiver operating characteristic curve (AUROC) for detection of cirrhosis was 0.91 (95% CI 0.85–0.96) in the training cohort and 0.91 (95% CI 0.79–1.00) in the validation cohort. For detection of advanced fibrosis, the AUROC was 0.88 (95% CI 0.81–0.94) in the training cohort and 0.92 (95% CI 0.83–1.00) in the validation cohort. Sensitivity was 89% and specificity was 86% for detection of cirrhosis in the training cohort and respectively 59% and 99% in the validation cohort. The sensitivity was 76% and specificity was 90% for the detection of advanced fibrosis in the test cohort. Sensitivity was 55% and specificity was 100% for the detection of advanced fibrosis in the validation cohort. The diagnostic accuracy did not differ between MFAP4 and the ELF test or TE in an intention-to-diagnose analysis. The median follow-up was 452 days. MFAP4 did not predict hepatic decompensation in a time-to-decompensation analysis in the subgroup of 45 patients with cirrhosis.

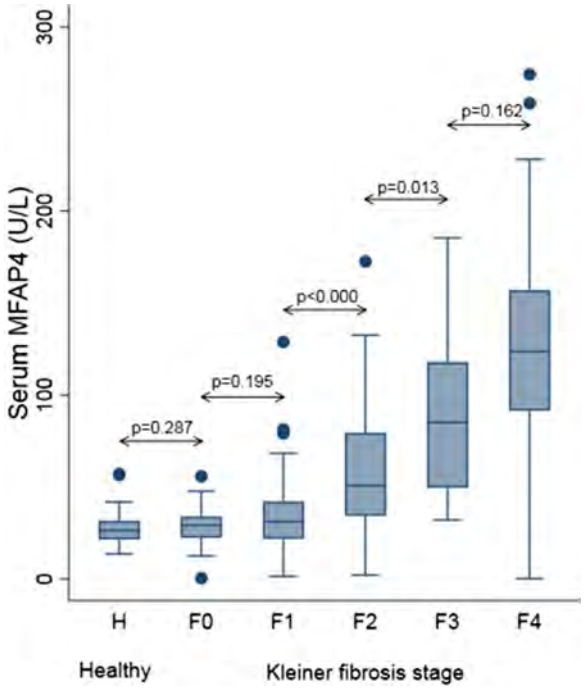

Figure: Boxplot of the serum concentration of MFAP4 in the healthy population group and in the cohort of patients with current or prior alcohol overuse distributed according to the Kleiner fibrosis stage.

Conclusion: MFAP4 is a novel serological biomarker that can detect ALD-related liver fibrosis with high accuracy.

THU-269

Abnormal lipoproteins in alcoholic hepatitis cause hepatocellular injury via inflammasome activation

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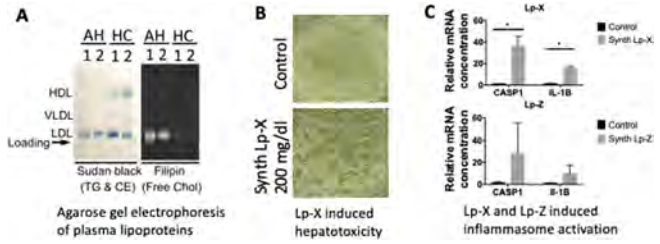
Background and aims: Alcoholic hepatitis (AH) is a severe acute manifestation of alcoholic liver disease with a mortality up to 30–50%. It has been shown that profound changes in circulating lipoproteins occur in severe alcoholic hepatitis. We aim to characterize the lipoprotein profile in AH and investigate the impact of abnormal lipoproteins on hepatocellular function.
Method: Patient samples were derived from an alcoholic hepatitis registry at Beth Israel Deaconess Medical Center. Human plasma was analyzed by agarose gel electrophoresis and stained by Sudan Black for neutral lipids and Filipin for free cholesterol. Serum lipoproteins were isolated by a Superose 12 10/300 GL size exclusion column and analyzed by negative stain electron microscopy. Synthetic Lp-X and Lp-Z were reconstituted using membrane extrusion *in vitro* and administered to HepG2 cells to evaluate cell viability and inflammasome activation.
Results: Lipoprotein profile in AH is characterized by the disappearance of normal circulating lipoproteins, including very low density lipoprotein (VLDL), high density lipoprotein (HDL), and a significant elevation of Lp-Z, a low density lipoprotein (LDL)-like particle that is enriched by free cholesterol and triglyceride, but deficient in cholesterol ester (A). Lp-X, a phospholipid and cholesterol-rich vesicle, is found in some patients. Reconstituted Lp-X- and Lp-Z-like emulsion particles were structurally similar to lipoproteins isolated from AH patients based on cholesterol content and electron microscopy images. Both Lp-X and Lp-Z-like emulsion particles demonstrate dose-dependent toxicity to HepG2 cells. Upon incubation with 200 mg/dl of Lp-X-like particles, HepG2 cells developed cellular swelling in 2 hours. Incubation with 200 mg/dl of Lp-X- and Lp-Z-like particles resulted in peak cell death at 2 hours and 6 hours, respectively (B). An increase in inflammasome gene expression, including CASP1 and IL-1β, was observed, a pattern that is consistent with changes associated with pyroptosis (C).



Conclusion: The accumulation of Lp-X and Lp-Z in the circulation is a characteristic disease feature in severe AH. These abnormal lipoproteins demonstrate hepatotoxicity through inflammasome activation *in vitro*. Our data suggest that Lp-X and Lp-Z are both biomarkers and potential therapeutic targets in severe AH.

THU-270

Severe alcoholic hepatitis has no influence on prognosis of variceal bleeding in patients with alcoholic cirrhosis

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Background and aims: Frequently, severe alcoholic hepatitis (AH) is manifested by portal hypertension related complications. Moreover, AH is associated with very high portal pressure, which is a risk factor for failure to control bleeding or low survival. The prognostic of variceal bleeding in these patients is not very well known.
The aim of the study was to evaluate the prognostic of patients with severe AH presenting with variceal bleeding.
Method: 128 patients with alcoholic cirrhosis and variceal bleeding recorded in our prospective variceal bleeding register (11.2013–03.2015 and 07.2017-present) were considered for inclusion. Among those with clinical criteria of severe AH (n = 51) transjugular liver biopsy was performed and confirmed the condition in 16 patients. Due to uncertain diagnosis of AH, the remaining patients with clinical criteria and no liver biopsy were excluded.
Results: Finally, 98 patients were included: 16 with severe AH and 77 with alcoholic cirrhosis. The median HVPG was 21 (14–30) mmHg in AH group (70% had > 20 mmHg). The age was significantly lower in AH group, 53 (35–65) vs. 59 (36–79), p = 0.004 and, as expected, bilirubin, AST and INR were significantly higher in AH. The AH and cirrhotic groups had similar outcomes regarding failure to control bleeding (12.5% vs. 9.1%, respectively, p = 0.48), the rate of infections during admission (20% vs. 17.8%, respectively, p = 1) or rebleeding within 42 days (0% vs. 10.8%, respectively, p = 0.594). However, the hospitalization length was longer in AH group in comparison with cirrhosis group, 14 (6–30) days vs. 9 (4–44) days, respectively (p = 0.006).
Mortality at 42 days was also not different: 3 (21.4%) patients in the AH, and 10 (14%) in the cirrhosis group, respectively (p = 0.44).
Conclusion: Patients with severe AH and variceal bleeding seems to have similar short-term prognosis with patients with alcoholic induced cirrhosis.

THU-271

Metabolic syndrome increases the risk of hepatic fibrosis in subjects with increased alcohol consumption: Results from a population-based cohort

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Background and aims: Increased alcohol consumption and metabolic syndrome (MS) are two of the most common etiologies of chronic liver diseases worldwide. There is very little information about the interaction between alcohol consumption and MS. Although MS may theoretically increase the intensity of alcohol-induced liver damage, there is no conclusive data to support this hypothesis. Therefore, the aim of the present study was to investigate the effect of MS on hepatic fibrosis in subjects with increased alcohol consumption from a large population-based cohort.
Method: 275 of the 3, 014 (9.1%) subjects in the cohort had increased alcohol consumption, defined as > 14 units per week in women and > 21 units per week in men (average 29 ± 14 units per week). Demographic, clinical and analytical variables, including various pro-inflammatory cytokines, were obtained in all the subjects included. Liver fibrosis was estimated by transient elastography (TE).
Results: The frequency of significant fibrosis (TE > 8kPa) in subjects with increased alcohol consumption was 10.2%, a value significantly higher than that of the remaining subjects of the cohort without increased alcohol consumption (5.3%, p < 0, 001). The existence of significant fibrosis was associated with the intensity of alcohol consumption as well as with several metabolic factors, particularly

body mass index, abdominal circumference, type 2 diabetes, MS, glycaemia and glycosylated hemoglobin. In a multivariate analysis, independent predictors of significant fibrosis were the intensity of alcohol consumption and MS (age- and sex-adjusted OR 3.5 (IQR 1.5–8.1)). In subjects with MS the frequency of fibrosis was 18.6%, compared with only 6.3% in subjects without MS ($p = 0.003$). Subjects with significant fibrosis had higher serum levels of interleukin-6 (IL-6) and soluble receptor II of TNFα (sTNFRII) with respect to subjects without significant fibrosis, suggestive of an increased systemic inflammatory activity (IL-6: 4.8 vs 2.1 pg/ml; sTNFRII: 5.6 vs 5.0 ng/ml; $p < 0.001$ and 0.013, respectively).
Conclusion: In patients with increased alcohol consumption, the existence of MS is associated with a markedly higher risk of significant hepatic fibrosis. This higher risk may be related to the systemic inflammatory activity characteristic of MS. This interaction between alcohol and MS should be taken into account especially for the implementation of measures to prevent chronic liver diseases among the general population.

THU-272

A study investigating the effect of extracorporeal cellular therapy with C3A cells on the survival of alcoholic hepatitis designed along the guidelines of the NIAAA

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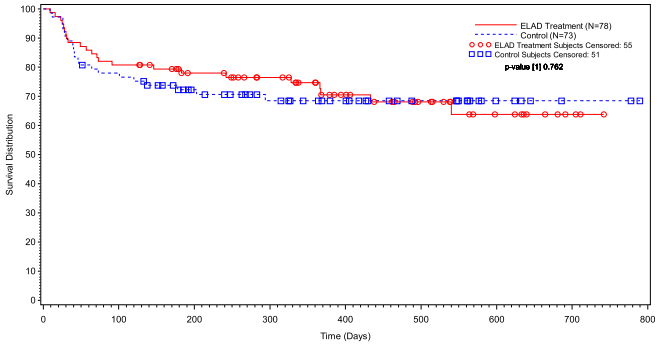
Background and aims: Alcoholic Hepatitis (AH) is a form of Acute on Chronic Liver Failure in Alcoholic Liver Disease (ALD). In 2016, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia published guidelines on the design of clinical studies investigating acute AH (Crabb DW et. Al. Gastroenterology 2016; 150:785–790).
Based on those guidelines and on a pre-specified group analysis of a phase II/III trial (Thompson et al. Liver Transplantation 2018 (24):380–393) enrolling 203 subjects, a sub-population was identified to be enrolled in the pivotal trial VTL 308 to investigate the efficacy and safety of extracorporeal C3A cellular therapy (ELAD) in AH.
Method: 151 subjects with AH, <50 yo, MELD < 30, INR < 2.5, creatinine <1.3 mg/dl, bilirubin > 16mg/dl were randomized 1:1 in 50 sites in the EU and the US to either SOC or SOC in combination with 5 days of ELAD therapy. The primary end point was survival.



Results: 78 subjects were randomized to ELAD and 73 to SOC. Mean (range) values for age was 39.3 (23–49), for MELD (25.14 (19-29), for Bilirubin 24.93 (16–44.7) mg/dl, for INR 1.82 (0.95-2.5), for creatinine 0.73 (0.3–1.27) mg/dl. There were no differences in age, ethnicity, sex, race, height, weight, MELD, time from hospital admission to randomization, ascites, liver volume, Child-Pugh Score, renal function, HE grade, coagulopathy, pulmonary function and CLIF SOFA at baseline.
The study failed its primary end point as depicted in figure 1.
There were 116 treatment emergent serious adverse events in 76 subjects receiving ELAD and 113 in 75 subjects receiving SOC (safety population), therefore treatment in this population appeared safe.
Conclusion: In its current version ELAD could not demonstrate a significant survival difference in this sample size.

THU-273

Role of PNPLA3 rs738409 and MBOAT7 rs626283 during alcohol detoxification: Indication of different mechanisms for fibrosis development

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Background and aims: The PNPLA3 rs738409 and MBOAT7 rs626283 polymorphisms have been identified as genetic risk factors for ALD progression; however, their molecular mechanisms are still poorly understood. We here study the impact of these two variants on various important clinical parameters in response to alcohol withdrawal.
Method: We prospectively enrolled heavy drinkers primarily presenting for alcohol withdrawal (n = 516). Mean alcohol intake was 184 g/day and the mean duration of detoxification was 6.3 days. All patients were genotyped for PNPLA3 rs738409 and MBOAT7 rs626283. In addition, inflammation, fibrosis and steatosis were non-invasively characterized in all patients using laboratory markers including M30 levels, CAP, LS and ultrasound before and after detoxification. In addition, in a subgroup of ALD patients (n = 105) liver biopsy was obtained and histologically analyzed.
Results: The PNPLA3 genotype frequencies were 41% 50% and 9% for CC, CG and GG and for MBOAT7 18% 52% and 30% for CC, CG and GG. Both genotypes (MBOAT7 CC and PNPLA3 GG) showed a strong and combined effect on fibrosis development in the overall cohort (ANOVA, $P < 0.05$). However, we observed striking differences between both genetic polymorphisms with regard to inflammation, fibrosis and steatosis in response to alcohol withdrawal. While inflammation showed no difference with a significant decrease during detoxification in all MBOAT7 genotypes, PNPLA3 GG showed significantly increased signs of liver injury after detoxification and a delayed resolution of inflammation (M30 and AST, $P < 0.001$). In contrast, inflammation resolved equally in all MBOAT7 genotypes (AST, $P < 0.001$) after detoxification. Finally, steatosis resolved in both polymorphisms and all genotypes to the same extent and no differences prior and after detoxification have been observed. In the histology cohort, PNPLA3 GG was significantly associated with inflammation (steatohepatitis, $P < 0.001$; ballooning, $P < 0.01$ and lobular inflammation, $P < 0.05$)), steatosis ($p < 0.05$) and microgranulomas ($p < 0.05$). Both variants were significantly associated with the presence of megamitochondria ($p < 0.001$).
Conclusion: While both variants showed a significant and combined effect on fibrosis progression, the response of steatosis and liver injury to alcohol withdrawal suggests important mechanistic differences. While PNPLA3 is primarily associated with liver injury and steatosis, MBOAT7 seems to sensitize directly for fibrosis development without affecting liver injury. Interestingly, both genetic polymorphisms did not affect the resolution of steatosis during alcohol withdrawal.

THU-274

Utility of quantitative CD64 expression on neutrophils in differentiating between bacterial Infection and inflammation in severe alcoholic hepatitis

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Background and aims: It is vital to differentiate infection from inflammation in patients with severe alcoholic hepatitis (SAH; MDF > 32: MELD > 20) since steroids may exacerbate sepsis. Fc receptor (FcγR1 or CD64) expression on neutrophils is a potential biomarker of bacterial infections.
Aim: To assess clinical usefulness of measuring quantitative CD64 expression on neutrophils in differentiating bacterial infection from inflammation in patients of SAH.
Method: In a cross sectional observational study from March 2016 to June 2018, neutrophil CD64 expression using flow cytometry and procalcitonin levels were studied in consecutive patients with SAH. CD64 expression on neutrophils was analyzed over 10, 000 counted cell on BD FACS Canto flow cytometer (BD biosciences). Full work up for infection was done in all patients including microbiological cultures twice in 72 hours, repeated at onset of new fever episodes. Patients were categorized into those with (SAH-I) and without infection (SAH). SAH-I included those with "definite" (pathogen isolated on culture) or "probable" infection (negative cultures but obvious symptoms eg. pus discharge or radiological findings eg. lung abscess on CT chest). Patients with bacterial infection (SAH-I; n = 63), without proven infection (SAH; n = 72), and healthy controls (n = 20) were included.
Results: The percentage of neutrophils with CD64 expression and their mean fluorescence intensity in patients with infection [76.2% (56.9–86.5) and 1431 (229–1828)] were significantly ($p < 0.05$) higher as compared to those without infection [16% (12.6-23.1), and 853 (20-968)] and in controls [7.05% (1.4–9.5) and 99.5 (54.7–140.7)]. Using a cut off value of 27%, sensitivity and specificity of CD64 expression on neutrophils to diagnose bacterial infection was 94% and 78% respectively. Sensitivity and specificity for procalcitonin was 83% and 72% at cut-off of 2.91ng/ml. Combining procalcitonin with CD64 increased the sensitivity to 98.3%.

Table 1: Descriptive Statistics

	Groups	N	Mean	Std. Deviation	P value
CD 64 (%)	Infection	63	76.66	22.60	< 0.001
	No Infection	72	16.02	18.96	
CRP mg/L	Infection	63	6.20	4.84	< 0.001
	No Infection	72	3.11	3.57	
Procalcitonin	Infection	63	4.38	2.40	< 0.001
	No Infection	72	1.85	1.28	
TLC	Infection	63	11108.19	6911.99	0.001
	No Infection	72	7402.50	4166.63	

Independent sample t test used, $p < 0.05$ significant

Conclusion: Quantitative measurement of CD64 on neutrophils can distinguish between systemic infection and inflammation in the setting of SAH.

THU-275

Blood transcript modules differentiate steroid responders from non-responders at baseline in severe alcoholic hepatitis

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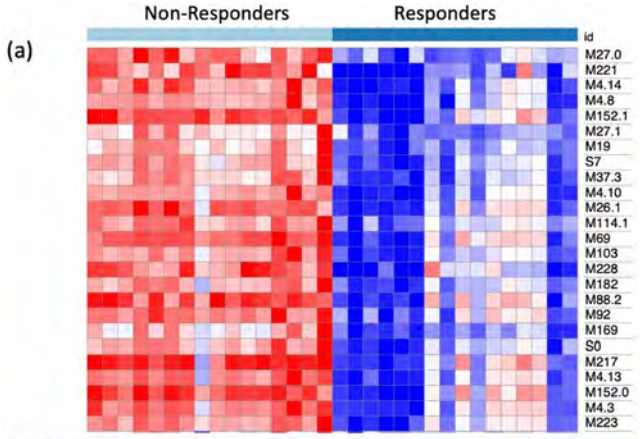
Background and aims: Steroid therapy is effective in severe alcoholic hepatitis (SAH) in about 60% of patients with high 1-month mortality. Baseline clinical and laboratory features do not differentiate responders from non-responders at baseline. We aimed to determine the variability in blood cells as a marker to identify non-responders at baseline.
Method: Baseline and day-7 blood samples were drawn from SAH patients (16 each responders and non-responders), total RNA from PBMCs isolated and subjected to whole blood transcriptome analysis by RNA-seq. Gene expression profiles were grouped into 346 blood transcription modules (BTM). Activity of each module was taken as mean of the expression of all genes in a BTM. The BTMs were further regressed and correlation networks drawn within each study group. These networks were used to compare between the groups to determine BTMs associated with immune cell types and their functions that could distinguish non-responders (Fig1: each node is a network of significantly regressed BTMs in a group).
Results: RNA-seq revealed a total of 19806 protein coding genes. 346 BTMs could be drawn from all these genes. Responders had unique BTMs at day-0 and day-7 (11 vs 43), whereas non-responders had 48 and 144 BTMs at same time points. There were 9 BTMs that persisted. Top 25 BTMs that differentiated the study groups at baseline are presented in the figure. Amongst these, BTMs related to T and B cell types were significantly ($p = 0.02$) over expressed (>2-fold) in non-responders at baseline. Other BTMs that could differentiate the study groups at baseline were NK and select chemokines (CCL1, 4, 5, 7, 8; CXCL10, 11, 12, 13; IL8) and receptors (CCR1 and 5).



(b)

BTM	FC(NR0/R0)	p-value	FDR(BH)	Module
M19	2.57	0.02	0.03	T cell differentiation (Th2)
M223	2.53	0.02	0.03	enriched in T cells (II)
S0	2.51	0.02	0.03	T cell surface signature
S7	2.75	0.02	0.03	CD4 T cell surface signature Th2-stimulated
M69	2.69	0.02	0.03	enriched in B cells (VI)
M152.0	2.73	0.02	0.03	TBA (source: B cells)
M152.1	3.02	0.02	0.03	TBA (source: naive B cells)
M217	2.76	0.02	0.03	TBA (source: B cells)
M61.1	5.28	0.02	0.03	enriched in NK cells (KIR cluster)
M27.0	2.18	0.02	0.03	chemokine cluster (I)
M27.1	2.62	0.02	0.03	chemokine cluster (II)

Figure: (a) Heatmap of top 25 differentiating BTMs, (b) Differentiating modules related to immune cells

Conclusion: Baseline blood transcriptome analysis can be used as an effective method for determining the underlying immune cell profile without going into detailed cell specific analysis.

THU-276

Women, Native Americans, and Asians experience the greatest increase in alcoholic hepatitis hospitalizations: An analysis of the 2008-2014 U.S. nationwide inpatient sample

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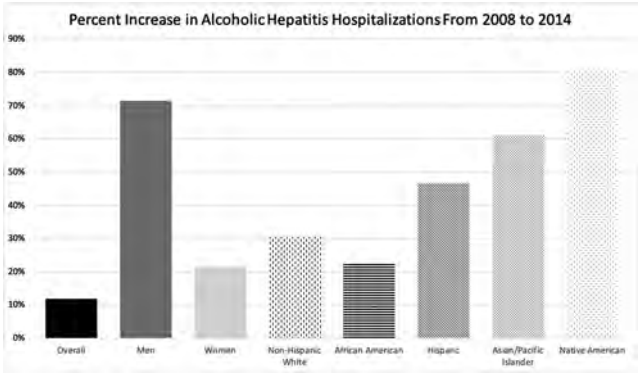
Background and aims: Excessive alcohol use remains a concerning issue contributing to significant morbidity and mortality, among which alcoholic hepatitis (AH) is one severe complication. To better understand the clinical and economic impact of AH, we aim to evaluate overall trends in AH-related hospitalizations and the increasing associated inpatient healthcare resource utilization.
Method: Using the 2008-2014 National Inpatient Sample, the largest all-payer inpatient database of hospital discharges in the U.S., AH-related hospitalizations among adults (age >18) were identified using ICD-9 codes. Survey-weighted annual hospitalization trends were stratified by sex, age, and race/ethnicity. Year-specific hospitalization rates were compared using chi-squared testing. Survey-weighted AH-related hospitalization charges were compared between years using adjusted Wald tests. Charges were inflation adjusted to 2014 U.S. dollars. Statistical significance was established with $p < 0.05$.
Results: Among 126, 268 AH-related hospitalizations representing a national estimate of 2.33 million hospitalizations (mean age 48.29 ± 11.3, 69.2% male, 64.5% non-Hispanic white, 10.3% African American, 9.7% Hispanic), 8.6% had concurrent hepatitis C, 16.1% ascites, 1.2% spontaneous bacterial peritonitis, and 11.0% hepatic encephalopathy at time of hospitalization. From 2008 to 2014, overall AH hospitalizations increased by 11.8% (16, 845 to 18, 837). During this same period, AH hospitalizations increased by 21.6% among women compared to 7.1% among men, $p < 0.01$. When stratified by race/ethnicity, the greatest proportional increases in AH hospitalizations were observed in Native Americans (+81%) and Asians (+61.3%), both significantly greater than African Americans (+22.8%, $p < 0.01$) and non-Hispanic whites (+30.6%, $p < 0.01$). When stratified by age, the greatest increase in AH hospitalizations was seen in those ages 60–69 years (+25.5%), whereas hospitalizations among patients <50 years decreased by 12% from 2008 to 2014. From 2008 to 2014, the estimated national economic burden of AH hospitalizations increased from $1.77 billion to $2.54 billion.



Conclusion: From 2008 to 2014, AH hospitalizations in the U.S. increased by nearly 12%, with the greatest increases seen among women, Native Americans, and Asians. Increasing healthcare resource utilization was also observed, and in 2014 total national AH-hospitalization related charges was $2.54 billion.

THU-277

Significant differences in alcoholic hepatitis related mortality in the United States by sex, race/ethnicity, and insurance: An analysis of the 2008-2014 nationwide inpatient sample

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Background and aims: Excessive alcohol consumption leading to alcoholic hepatitis (AH) is associated with significant morbidity and mortality. Whether certain populations affected by AH are at particularly higher risk of mortality is not well studied. We aim to evaluate disparities in in-hospital mortality among adults hospitalized for AH with a focus on sex, race/ethnicity and insurance-specific disparities.
Method: Using the 2008-2014 National Inpatient Sample, the largest all-payer inpatient database of hospital discharges in the U.S., AH-related hospitalizations among adults (age > 18) were identified. Survey-weighted in-hospital mortality rates were evaluated between groups using chi-square methods and adjusted multivariate logistic regression models that included age, sex, race/ethnicity, primary insurance, household income, hospital characteristics, liver-related complications, and All Patient-Refined Diagnosis Related Group (APR-DRG) risk of mortality score. P value <0.05 indicated statistical significance.
Results: Among 126, 268 AH hospitalizations representing a national estimate of 2.33 million hospitalizations (mean age 48.29 ± 11.3, 69.2% male, 64.5% were non-Hispanic white) 8.6% had concurrent hepatitis C, 16.1% ascites, 1.2% spontaneous bacterial peritonitis, 11.0% hepatic encephalopathy at time of hospitalization. Overall in-hospital mortality was 3.33%. Compared to women hospitalized for AH, men had significantly lower in-hospital mortality (OR 0.87 95% CI 0.80–0.94; $p < 0.001$). When stratified by race/ethnicity, Asian/Pacific Islanders had significantly higher in-hospital mortality compared to non-Hispanic whites (OR 1.70; 95% CI 1.18-2.43; $p = 0.004$). When evaluating insurance-specific mortality, compared to Medicare insured patients, those who were self-pay/uninsured had significantly higher in-hospital mortality (OR 1.25; 95% CI 1.08–1.44, $p = 0.002$), whereas there was a trend towards higher mortality in Medicaid patients (OR 1.13; 95% CI 0.99–1.29, $p = 0.069$).

Multivariate logistic regression evaluating predictors of in-hospital mortality

	Odds Ratio	95%CI	P value
Gender			
Female	1.000	Reference	
Male	0.867	0.80-0.94	.001
Race/Ethnicity			
Non-Hispanic White	1.000	Reference	
African American	0.943	0.82-1.09	.418
Hispanic	0.973	0.86-1.10	.678
Asian/Pacific Islander	1.700	1.18-2.43	.004
Native American	1.064	0.81-1.41	.661
Primary Insurance			
Medicare	1.000	Reference	
Medicaid	1.129	0.99-1.29	.069
Private/Commercial	1.017	0.90-1.16	.789
Self-pay/Uninsured	1.250	1.08-1.44	.002

Conclusion: Among adults hospitalized for AH in the U.S., overall in-hospital mortality was 3.33%. Significant sex, race/ethnicity and insurance-specific disparities in in-hospital mortality were observed, with the greatest in-hospital mortality observed in women, Asians, and patients who were uninsured or Medicaid insured.

THU-278

Increasing hospitalizations and resource utilization for alcohol associated liver disease and acute on chronic liver failure in young american adults

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Background and aims: Alcohol associated liver disease (AALD) is associated with significant morbidity, mortality and financial burden. Data are scanty examining trends on disease burden in young adults hospitalized with AALD. A proportion of these patients develop acute on chronic liver failure (ACLF) with multiorgan failure and high short-term mortality. Our aim is to assess trends in prevalence, in-hospital mortality, resource utilization associated with AALD and with ACLF in young adults.

Method: National Inpatient Sample (2006–2014) was queried for hospitalizations with discharge diagnosis of cirrhosis using ICD-09 codes. ACLF was defined with ≥ 2 organ failures (OF) and its severity stratified to 1, 2, 3 with 2, 3, and > 3 OF. Hospitalizations were stratified by age: young (≤ 35 yrs.) and old (> 35 yrs.).

Results: Of 447, 078 patients, admissions with discharge diagnosis of AALD between 2006 and 2014, 16, 114 (3.7%) were ≤ 35 years. The proportion of young patients with AALD increased from 3.4% in 2006 to 4.2% in 2014. A total of 29, 594 (6.6%) admissions developed ACLF, 1138 (7.1%) admissions in young. Young admissions compared to older had more severe ACLF (34 vs. 25% grade 2–3, P < 0.0001). Proportion of ACLF admissions in young increased from 2.8% in 2006 to 5.2% in 2014, P < 0.001 = 01. Compared to older, admissions in young were more female (35 vs. 29%), obese (11 vs. 7.6%), Hispanic (29 vs. 18%), and admitted with alcoholic hepatitis (41 vs. 17%) p < 0.0001 for all. Proportion of admissions with discharge diagnosis of AH increased in young from 24 to 42% from 2006 to 2014, P < 0.0001. Despite similar frequency of esophageal varices, young adults were more likely to have variceal bleeding (11 vs. 8%), hepatic encephalopathy (72.7 vs. 68.3%) and hepatorenal syndrome (28.5 vs. 19%), with increased use of mechanical ventilation (79 vs. 76%) and dialysis (31.9 vs. 27.9%), p < 0.001 for all. Compared to young, admissions in old had higher in-hospital mortality (7.4 vs. 5.5%, p < 0.0001). Similarly, ACLF admissions in young had longer hospitalizations (16.6 vs. 13.5 days) and higher hospital charges ($197, 199 vs. $154, 816), p < 0.0001. In-hospital mortality among admissions with AALD decreased from 9% in 2006 to 6.9% in 2014), but remained stable in young (5.9% to 5.8% respectively). Similarly trend on in-hospital mortality in ACLF admissions declined from 54 to 45% in young and from 52% to 43% in older patients. AH and non-AH related ACLF had similar in-hospital mortality (47.2 vs. 46.2%, P = 0.2).

Conclusion: AALD related hospitalizations are increasing in young adults in the US, and is mainly due to increasing frequency of AH. Further, this disease burden in young is increasing with higher frequency of admissions with more severe ACLF and is associated with consumption of hospital resources. Studies are needed to develop preventive strategies to reduce burden in young adults related to AALD and ACLF.

THU-279

The prognostic stratification using acute-on-chronic liver failure scoring systems for predicting short-term mortality in patients with alcoholic hepatitis

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Background and aims: To compare the existing various prognostic scoring models and newly proposed scores for acute-on-chronic liver failure (ACLF) and evaluate usefulness of stratification for the prediction of short-term morality in patients with alcoholic hepatitis (AH).

Method: A total of 705 clinical AH patients, enrolled in the APASL-ACLF Research Consortium (AARC) with 90-day follow-up, were analyzed. AARC-ACLF score, Maddrey discrimination function (DF) score, age, bilirubin, international normalized ratio and creatinine score (ABIC), Glasgow Alcoholic Hepatitis Score (GAHS), Child-Turcott-Pugh (CTP) score, model for end-stage liver disease (MELD), and MELD-Sodium (Na) scores were used to compare the performance for predicting 30-day and 90-day mortality. AARC-ACLF scores were categorized into three grades (Gr I: 5–7; II: 8–10; and III: 11–15 points) and survival curves by the Kaplan-Meier method were created and compared using log-rank test.

Results: Of 708 patients, 286 (40.4%) and 363 (51.3%) patients died within 30 days and 90 days, respectively. The area under receiver operating characteristics curve (AUC) of AARC-ACLF, DF, ABIC, GAHS, CTP, MELD, and MELD-Na was 0.752 (0.705–0.799), 0.630 (0.575–0.685), 0.658 (0.604–0.711), 0.577 (0.523–0.631), 0.641 (0.589–0.694), 0.705 (0.653–0.756), 0.703 (0.651–0.755), respectively, for 30-day mortality. The AUC of various prognostic scores for the prediction of 90-day mortality is similar. The performance of AARC-ACLF was superior to that of DF, ABIC, GAHS, CTP, while comparable to that of MELD and MELD-Na in predicting short-term mortality. According to AARC-ACLF grades, short-term cumulative survivals was statistically different (30-day, 82.4, 70.4, and 35.3% p < 0.001; 90-day, 76.9, 56.0, and 26.4% p < 0.001).

Conclusion: Compared to the previous AH prognostic scores, AARC-ACLF score and grades are simple and useful for predicting the short-term mortality in patients with AH. Further studies are needed to confirm these implications.

THU-280

Quantitative fibrosis assessment independently predicts outcome in alcoholic liver disease

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Background and aims: Semiquantitative assessment of hepatic fibrosis in conventional histopathology is prone to intra- and inter-observer variation. Digital image analysis provides an objective tool for quantitation of total fibrosis (TF) and, specifically, for discrimination of septal fibrosis (SF) and pericellular fibrosis (PCF). We have previously shown that conventional assessment of fibrosis stage and semiquantitative scoring of PCF has a differential impact on outcome in alcoholic liver disease (ALD), with stage F ³ 3 predicting worse outcome in compensated but presence of PCF predicting better outcome in decompensated ALD. The aim of the present study was to evaluate the prognostic value of quantitative assessment of TF, SF and PCF along with routine clinical and biochemical parameters in compensated and decompensated ALD.
Method: We investigated consecutive patients with ALD who underwent liver biopsy for staging or differential diagnosis. Clinical and biochemical parameters and date of liver-related death were collected. Median follow-up time was 4.3 years. After staining with sirius red, SF and PCF were manually segmented using digitized slides and collagen proportionate areas for TF, SF, and PCF were quantified using Definiens ™ software. Multivariable Cox regression was used to assess the prognostic value of clinical, biochemical and histological parameters for the prediction of 5-year liver-related mortality.
Results: Our cohort comprised 166 patients with ALD (compensated, n = 50; decompensated, n = 116). In compensated ALD, TF, ASH, ductular reaction, alcohol abstinence, INR, albumin, and platelet count were identified as prognostic variables; on multivariable analysis, TF (p = 0.002) and alcohol abstinence (p = 0.050) remained as independent predictors of outcome. In decompensated ALD, PCF/SF ratio, ASH, canalicular cholestasis, ductular cholestasis, sex, alcohol abstinence, bilirubin, INR, sodium, albumin, WBC, and platelet count were identified as prognostic variables; on multivariable analysis, PCF/SF ratio (p = 0.037), canalicular cholestasis (p = 0.014), bilirubin (p < 0.001), INR (p = 0.001), and sodium (p = 0.017) remained as independent predictors of outcome.
Conclusion: On multivariable analysis of clinical, biochemical and histological parameters, quantitative fibrosis types measured by digital image analysis showed independent prognostic value for 5-year survival in ALD.

THU-281

Single nucleotide polymorphisms associated with no interferon lambda 4 production are associated with reduced mortality in alcoholic hepatitis

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Background and aims: Single nucleotide polymorphisms (SNPs) in the genomic region encoding interferon lambdas (IFNλ) influence liver inflammation and fibrosis progression. This effect appears aetiology-independent as the association is observed in both chronic viral hepatitis and in non-alcoholic fatty liver disease. As alcoholic hepatitis shares many genetic risk factors and pathogenic features with non-alcoholic fatty liver disease, we investigated if *IFNL* genetic variants could influence severity and progression of alcoholic hepatitis.
Method: Fifty-eight patients with severe alcoholic hepatitis were genotyped for the *rs368234815* and *rs11768444 IFNL4* SNPs. SNP association with mortality, infection risk, inflammatory markers and IFN signalling were explored.
Results: Alcoholic hepatitis patients with a non-functional *IFNL4* gene have improved survival (p = 0.03) compared with those encoding the IFNλ4 protein. These patients also have lower plasma sCD163 (p = 0.05) and lower circulating monocyte counts (p = 0.01) and tend to have fewer infections at diagnosis (p = 0.15). We observe no differences in GAHS and MELD between the genotypes. The *IFNL4* genotype distribution between patients with alcoholic hepatitis and heathy controls is the same. However, patients with alcoholic hepatitis have a reduced expression of *IFNLR* in the liver (p = 0.01) and on circulating leukocytes and lower expression levels of IFN stimulated genes in circulating leukocytes than healthy controls. This however is not related to *IFNL4* genotype within patients with alcoholic hepatitis.
Conclusion: SNPs associated with no ability to express IFNλ4 seem to reduce mortality from alcoholic hepatitis, possible boosting infection resistance through effects on the monocyte/macrophage compartment.

THU-282

Augument of liver regeneration protects against ethanol-induced acute liver injury by promoting autophagy

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Background and aims: Alcoholic liver disease (ALD) is associated with high morbidity and mortality, and treatment options are very limited to date. Augmenter of liver regeneration (ALR) may protect against hepatic injury caused by chemical poisons, including ethanol (EtOH). Autophagy appears to positively influence survival in cases of liver dysfunction. Although ALR-mediated protection of mitochondrial morphology and function has been investigated extensively, the effects of ALR on mitophagy are less well understood to date. Our study is aiming to determine whether ALR-mediated protection against alcoholic liver injury is associated with changes in autophagy, particularly mitophagy.
Method: In this study, we investigated the impact of ALR-induced autophagy *in vitro* and *in vivo* in an ethanol-induced model of acute liver injury. ALT and AST and reduced histological lesions were measured to reveal the liver damage in mice overexpressing or knockdown *ALR*. The survival rates, improved maintenance of mitochondrial membrane potential and ATP levels were detected in *ALR*-transfected HepG2 cells following EtOH treatment. The expression of autophagy-markers including LC3-II, Beclin-1, and Atg5 were characterized by western blot and quantitative reverse transcription PCR. Liver transcriptome profile analysis was performed Ad-*ALR* (or $ALR^{\pm}$) and WT mice in response to EtOH treatment.
Results: Our study showed that hepatic overexpression of ALR alleviates EtOH-induced liver injury in mice, which is in line with its ability to protect the liver from a variety of other toxic insults. Furthermore, we could show that the protection conveyed by ALR expression may be mediated by promoting mitophagy and activating the mTOR signaling pathway. We confirmed an association of ALR overexpression with increased LC3II conversion and p62 degradation both *in vivo* and *in vitro*. Compared with control cells, ALR overexpression also upregulated Atg5 and beclin-1 expression, and increased Parkin translocation to mitochondria following ethanol stimulation. These results indicate that ALR induction enhances autophagy and mitophagy in response to EtOH-induced liver injury. In addition, SOD is decreased by ethanol intoxication and that is prevented by ALR. Our results showed that ALR promotes the mitochondrial SOD at transcriptional level to combat ethanol-induced hepatocyte injury.

Conclusion: ALR protected the liver from EtOH injury by enhancing autophagy, and the protection was mediated by mTOR signaling. Our results suggest the possibility that intravenous injection of ALR maybe a feasible clinical therapy to combat with ALD. The identifcation of ALR as a novel inducer of autophagy may not only serve as a new lead for developing new therapeutic agents for ALD, it may additionally serve as a novel molecular probe for studying the regulation of autophagy.

THU-283

FGF15 deficiency aggregates experimental alcoholic steatohepatitis in mice: A critical role for lipocalin 2 signaling

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Background and aims: Fibroblast growth factor (FGF) 15 (human homolog, FGF19) is a pivotal endocrine hormone largely expressed in the small intestine of rodents. Our group has previously demonstrated that ethanol administration to mice inhibits ileum Fgf15 synthesis, decreases circulating Fgf15, and causes hepatic dysfunctions.
Method: The present study assessed the causal role of Fgf15 and its hepatic signaling in development and progression of experimental alcoholic steatohepatitis by utilizing the Fgf15 knockout (FGF15KO) mouse model. Gender and age matched wild-type (WT) and FGF15KO mice were pair-fed with either an ethanol-containing diet or an ethanol-free diet (control) using a chronic-binge ethanol feeding protocol.
Results: Ethanol-administrated FGF15KO mice exhibited substantial hepatic triglyceride accumulation, exacerbated oxidative stress, and markedly augmented elevation of serum liver enzymes compared to ethanol-fed WT mice. Mechanistic studies revealed that removal of FGF15 in mice drastically augmented the ethanol-induced circulating level of lipocalin 2, a prominent regulator of lipid metabolism and inflammation in the pathogenesis of alcoholic liver disease. In cultured mouse AML-12 hepatocytes, treatment with recombinant FGF19 protein blocked the ability of ethanol or lipopolysaccharides (LPS) to induce lipocalin 2. Furthermore, knocking down FGFR4, a FGF15/19 receptor, abolished FGF19's ability to suppress lipocalin 2 levels in AML-12 hepatocytes exposed to either ethanol or LPS, indicating that FGF19 directly downregulates lipocalin 2.
Conclusion: Our present study illustrates a crucial role of FGF15/19-lipocalin 2 axis in alcoholic liver injury and suggests that ameliorating the FGF15/19-lipoalin 2 axis-mediated signaling could be of great value for the treatment of human alcoholic steatohepatitis.

THU-284

Hepatocyte-specific deletion of splicing factor SRSF3 exacerbates experimental alcoholic steatohepatitis in mice

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Background and aims: The RNA-binding protein Serine/arginine-rich splicing factor 3 (Srsf3) (also known as SRp20) plays critical roles for maintaining liver metabolic function. Liver-specific SRSF3 deficiency in mice caused spontaneous progressive liver damage, including steatohepatitis, fibrosis, and hepatocellular carcinoma (HCC) with aging, similar to the progression of human liver disease. Here, utilizing a hepatocyte-specific SRSF3 knockout mouse model (SRSF3HKO), we investigated the role of SRSF3 in the development and progression of alcoholic steatohepatitis.
Method: Gender and age matched SRSF3HKO mice and littermate loxP control (WT) mice were pair-fed with either an ethanol-containing diet or an ethanol-free diet (control) with the chronic-binge ethanol feeding protocol. Liver and serum samples were collected after 10 days of pair-feeding. We measured mRNA and protein expression levels of SRSF3 in the mouse samples as well as in liver samples from patients with alcoholic steatohepatitis and healthy individuals (controls).
Results: On the ethanol-containing diet, the SRSF3HKO mice displayed greater hepatic lipid accumulation, and augmented elevation of alanine aminotransferase and aspartate aminotransferase, markers of liver injury, compared with WT mice. Remarkably, the fatty livers of SRSF3HKO mice progressed to fibrotic liver in response to ethanol challenge. Accordingly, liver samples from patients with alcoholic steatohepatitis had significantly reduced SRSF3 gene and protein expression levels and displayed abnormality in pre-mRNA splicing of E-selectin, a pivotal neutrophil infiltration mediator, compared with healthy controls.
Conclusion: Our novel findings demonstrate that hepatocyte-specific SRSF3 deficiency in mice exacerbates the development and progression of alcoholic steatohepatitis in mice. Dysregulation of the hepatic SRSF3 and its signaling during ethanol exposure may represent an important mechanism that contributes to progression of human alcoholic steatohepatitis.

THU-285

Loss of X-Box Protein-1 in intestinal epithelial cells promotes the development of alcoholic liver disease in the liver

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Background and aims: In the context of alcoholic liver disease (ALD), the gut- liver axis has become a focus of major attention in the last few years. Increased gut permeability and intestinal flora alternation are increasingly recognized as major factors in ALD. Intestinal epithelial cells (IECs), play a pivotal role in maintaining gut permeability and intestinal microbiota homeostasis. The transcription factor *XBP1* is a key component of the endoplasmic reticulum (ER) stress response. In the present study, we hypothesized that deletion of *XBP1* in IECs might promote ALD development in the liver.
Method: Mice with specific deletion of *XBP1* in IECs ($XBP1^{\Delta IEC}$) and *XBP1*-floxed wildtype ($XBP1^{f/f}$) mice were subjected to acute ethanol (EtOH) intoxication and a diet model of ALD by performing either: (i) 3x PBS (3GP) or EtOH gavages (3GE) or (ii) Lieber-DeCarli control (LDC) and ethanol (LDE) diet for 4 weeks plus a single PBS or EtOH gavage, respectively. Upon sacrifice, organs were extracted, and markers of liver damage, histopathological examination and transmission electron microscopy (TEM) were performed.
Results: Serum markers of liver damage (e.g.: AST) were statistically increased in $XBP1^{\Delta IEC}$ compared with $XBP1^{f/f}$ after both models of

ALD: 3GE and LDE. Concomitantly, HandE staining of XBP1$^{\Delta IEC}$ livers displayed macrovesicular ballooning accompanied by significantly elevated inflammation and immune cell infiltration (CD45, F4/80) after LDE and to a lesser extent after 3GE. Furthermore, Oil Red O (ORO), Toluidine Blue staining and the content of intrahepatic triglycerides revealed significantly increased lipid deposition in XBP1$^{\Delta IEC}$ compared with XBP1$^{f/f}$ after LDE and 3GE feeding. Specifically, the TEM studies revealed lipid accumulation in hepatocytic cytoplasm, mitochondria and nuclei of XBP1$^{\Delta IEC}$, whilst XBP1$^{f/f}$ livers exhibited lipids in the cytosolic compartment. Since our mice had loss of XBP1 in IECs, we also evaluated the ileum of these mice. Importantly, presence of autophagic vacuoles, decreased lysozyme granules and dilation of the Golgi cisterns associated with loss of Paneth cells was characteristic of XBP1$^{\Delta IEC}$ compared with XBP1$^{f/f}$ ilea, after both models of EtOH intoxication.

Conclusion: Our results clearly suggest that loss of XBP1 in IECs triggers significant damage in the liver, opening a new avenue for research in the gut-liver axis in the context of ER stress and ALD, using two well-established models of EtOH intoxication.

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Activation of the NLRP3 inflammasome correlates with the severity of alcoholic liver disease

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Background and aims: Alcoholic liver disease (ALD) is a common liver disease in China but lack of definitive treatment. Aggravated inflammation with increased expression of proinflammatory cytokines is an important feature of ALD. Inflammasomes are cytosolic multi-protein complexes that are essential effectors for sterile inflammatory response, in which nucleotide-binding oligomerization domain-Like Receptor with a pyrin domain 3 (NLRP3) inflammasome is the most studied by far. NLRP3 inflammasome has been shown to be required for a wide range of liver diseases. However, the characteristic of NLRP3 inflammasome in human ALD remains unclear. The aim of our study is to investigate the characteristic of NLRP3 inflammasome during ALD.

Method: Blood samples were collected from healthy controls (HCs, n = 20) and ALD patients (n = 38) and the plasma levels of IL-1 beta were measured by enzyme-linked immunosorbent assay. The expression of NLRP3 inflammasome associated molecules in liver tissues from HCs (n = 4) and ALD patients (n = 5) were performed through qPCR and immunohistochemistry.

Results: As an indicator of activation of NLRP3 inflammasome, plasma levels of IL-1 beta were significantly elevated in ALD patients as compared to HCs ($p = 0.0075$), especially in patients with severe alcoholic hepatitis (Maddrey's DF > 32). The levels of NLRP3, ASC, Caspase-1 and IL-1 beta mRNA were significantly increased in ALD patients ($p = 0.0159$). Further Immunohistochemical staining showed that NLRP3 inflammasome was expressed in macrophages. Mechanically, mitochondrial DNA in microparticles of hepatocyte origin activated NLRP3 inflammasome in macrophages through TLR-9.

Conclusion: These data demonstrate that activation of the NLRP3 inflammasome increases significantly in ALD patients and closely associates with liver damage.

NAFLD: Clinical aspects except therapy

THU-291

Is non-alcoholic fatty liver disease a risk factor for chronic kidney disease?

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is thought to increase the risk of chronic kidney disease (CKD). This is because the risk factors for both conditions include obesity, diabetes, and hypertension. However, the evidence clarifying the independent role of NAFLD on CKD progression is lacking. Therefore, we investigated whether NAFLD is independently associated with CKD.

Method: In this study, 3, 725 Japanese individuals [1, 751 males, 1, 974 females; mean age, 53.4 ± 9.1 (17-89) years] who underwent medical examination at the Nara Health Promotion Center in 2012 were assessed. Patients with hepatitis B or C infection, other hepatobiliary diseases, or males and females consuming >30 and >20 g/day of alcohol, respectively, were excluded. Fatty liver was diagnosed based on abdominal ultrasonography (hepatorenal echo contrast and liver brightness); CKD was defined as an estimated glomerular filtration rate < 60 ml/min per 1.73 m^2. The prevalence of CKD was compared between participants with and without NAFLD in obese and non-obese subjects, subjects with and without hypertension or subjects with and without fasting hyperglycemia. Independent predictors of CKD were determined by logistic regression analysis.

Results: The prevalence of CKD was significantly higher in participants with NAFLD than in those without NAFLD. However, the prevalence of CKD in the participants with obesity was not significantly different between those with and without NAFLD. Similar results were obtained regarding the prevalence of CKD in participants with hypertension and those with fasting hyperglycemia. In non-obese participants, there was no difference in the prevalence of CKD between those with and without NAFLD. Similar results were obtained for participants without hypertension and those without fasting hyperglycemia. Logistic regression analysis demonstrated that obesity and hypertension were independent predictors of CKD but NAFLD was not independently associated with CKD.

Conclusion: The findings conclude that NAFLD is not an independent risk factor for CKD, but obesity and hypertension, which are complications of NAFLD, are independently associated with CKD.

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The natural history of NASH-induced advanced fibrosis in a large cohort of patients with type-2 diabetes

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Background and aims: Non-alcoholic steatohepatitis can lead to advanced fibrosis (AF) and cirrhosis especially in patients with type-2 diabetes (T2D). Large cohort studies on AF progression and regression in diabetics are lacking. The aim of this study was to assess the transition of AF in a large cohort of diabetics and define factors associated with worsening or improvement in fibrosis.

Methods: Using ICD-9 codes, all T2D with the diagnosis of fatty liver in a large U.S. healthcare system were identified. Baseline demographics, clinical characteristics, and laboratory data were collected. Non-invasive scores to assess AF were calculated at baseline (BL) and then recalculated using last follow-up (LF) laboratory values to assess for the transition using the following cutoffs (AST/ALT >1.4, APRI >1.5, FIB-4 >2.67, NFS >0.676). Patients were divided into 4 groups as follows: No AF either times (BL and LF), AF both times, transition from no AF at BL to AF at LF, transition from AF to no AF. A univariable and a multivariable logistic regression analysis were done to further assess which clinical factors are associated with transition in AF status. A p value < 0.05 was considered statistically significant.
Results: A total of 50, 695 patients were included. The mean age at BL was 51.2 ± 11.6 years and at LF was 59.6 ± 11.6 years with median duration between 1st and last available labs was 84.4 (24 –199) months. 55.3% were females, 71% were Caucasians, and 42.6% had family history of T2D. Baseline mean platelet count was 251 [208, 299] and mean HbA1c was 6.6[6.0, 7.9]. Interestingly, the prevalence of obesity, HTN, CKD, hyperlipidemia and CAD increased during this period (p < 0.001 for all). During this period, 25.8% of subjects transitioned from no evidence of AF to AF (progression), 6.4% transition from AF to no AF (regression) and, the rest stayed stable. Clinical factors associated with transition from no AF to AF (progression) were female gender, African-American race, and the presence of baseline obesity, CKD or CAD. In terms of T2D medications, the use of insulin was associated with progression to AF whereas the use of oral hypoglycemic agents was protective. Interestingly, the use of statins was associated with increased odds of AF regression (OR (95% CI) = 1.12 (1.00, 1.25), corrected p value of 0.045.
Conclusion: The natural history of AF transition in patients with T2D is bidirectional and certain baseline characteristics predict progression. The effects of commonly used medications in diabetics on AF progression need further analysis.

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Increased risk of advanced liver disease independently of classic metabolic risk factors or drug induced hepatotoxicity in patients with psoriasis

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Background and aims: Patients with psoriasis (Ps) frequently present with liver disease due to concomitant medication and/or coexistence of metabolic syndrome. However, the role that psoriasis plays as an immune-mediated disease, its phenotype, severity and treatment in the development of chronic liver disease, regardless of the presence of factors associated with the metabolic syndrome, are not well known.
Method: cross-sectional case-control study. Patients with Ps come from a consecutive cohort of patients with Ps in which other chronic liver diseases were discarded and variables associated with cardiovascular risk factors, metabolic syndrome, as well as those related to the severity, phenotype and treatment of the Ps were recorded. NAFLD was established by liver ultrasound and controlled attenuation parameter (CAP) measured with transient elastography (TE). Liver fibrosis was estimated by liver stiffness measurement (LSM) with TE. Controls come from a general population random sample and were matched by age, sex, BMI and presence of type 2 DM, hypertension and dyslipidemia, at a ratio of 1: 2.
Results: 57 cases of Ps were included (mean age 54.63 [12.06], 40 [70.2%] men) and 100 controls. It was detected a harmful consumption of OH in 10 patients (17.5%) and other causes of chronic liver disease were not identified. Fifteen patients were diabetic (26.3%), 25 had hypertension (43.9%) and 30 were dyslipemic (52.6%). The average PASI was 3.76 (± 3.27) and 36.8% of the cases were accompanied by joint involvement. 10 patients (17.5%) were receiving treatment with MTX, 17 with anti-TNF agents (29.8%) and 10 with other biological agents. Patients with Ps present an absolute value of TE and CAP significantly higher than controls (ET: 7.16 kPa [±3.25] vs 5.72 [±3.80], p < 0.0001) (CAP: 295.51 db/s [±65.17] vs 274.97 [±68.25], p = 0.042). In the univariate analysis, we found as predictor variables of fibrosis the diagnosis of Ps (crude OR 4, 01 [1, 961-8, 187], p < 0, 0001), obesity (1, 17 [1, 092-1, 268]; p < 0.0001), altered fasting blood glucose and alterations in liver function tests (GPT, GOT, GGT, albumin and platelets). We have not found differences according to treatment, phenotype or severity of Ps, the presence of metabolic syndrome components or OH consumption. In the multivariate analysis, Ps was found as an independent and the strongest predictor of fibrosis (3.94 [1.787-8.706]; p = 0.001), together with obesity (adjusted OR 1, 179 [95 CI: 1, 086-1, 280], p < 0.0001).
Conclusion: Ps patients have an increased risk of significant fibrosis. This risk appears independently of classical factors of metabolic syndrome or concomitant medication with potential hepatotoxicity. These data point to a possible role of the immune-mediated chronic inflammation underlying the cases of Ps and the existence of a dermo-hepatic axis.

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Non-invasive measures of liver fibrosis in NAFLD is associated with cardiovascular risk

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Background and aims: Many patients with non-alcoholic fatty liver disease (NAFLD) simultaneously suffer from cardiovascular diseases and often carry multiple cardiovascular risk factors. Several cardiovascular risk factors are known to drive the progression of fibrosis in NAFLD. It was the aim of this study to investigate whether established cardiovascular risk scores such as the Framingham risk score (FRS) and the Heart Score of the European Society of Cardiology (HS) are associated with the degree of fibrosis in NAFLD.
Method: We screened 2138 asymptomatic subjects (59.6 ± 10.2 years, 50% males, BMI 27.2 ± 4.6 kg/m²). The diagnosis of NAFLD was labeled if 1. (Areas of significant increased echogenicity in relation to the renal parenchyma present in right upper quadrant ultrasound) and 2. (Exclusion of viral, autoimmune, hereditary [Wilson`s disease, HFE-associated hereditary hemochromatosis, alpha-1 antitrypsin deficiency] liver disease and excess alcohol consumption evaluated by a questionnaire) was fulfilled. The FRS (estimates the ten-year risk of developing coronary heart disease) and HS (estimates ten-year risk of fatal cardiovascular disease) were calculated for each subject, as were NAFLD Fibrosis Score (NFS) and Fibrosis 4 Score (Fib4). Subsequently, NFS, Fib4, FRS and HS were correlated.
Results: Of 2138 subjects, 829 (38.7%) had NAFLD. Patients with NAFLD had a significantly higher cardiovascular risk: FRS: no NAFLD: 5.5 ± 5.2%; NAFLD: 8.8 ± 6.5% (p < 0.001); HS: no NAFLD: 2.9 ± 3.8%; NAFLD: 3.7 ± 4.1% (p = 0.002). Patients with NAFLD were grouped into three groups according their NFS: F0-F2 (n = 663); indifferent (n = 155); F3-F4 (n = 11). In patients with F0-F2 according to NFS, FRS was 8.0 ± 6.1%; with indifferent NFS, 10.8 ± 6.4%; and in F3-F4

(NFS): 11.5 ± 5.2%, respectively. HS showed a similar pattern: F0-F2 (NFS): 3.0 ± 3.4%; with indifferent NFS, 5.4 ± 4.5%, and in F3-F4 (NFS): 7.0 ± 5.7%, respectively. NFS correlated significantly with FRS ($r = 0.18$, $p < 0.001$) and HS ($r = 0.27$, $p < 0.001$). Likewise, patients with NAFLD were grouped into three groups according to their Fib4: F0-F1 (n = 589); indifferent Fib4 (n = 411); F3-F4 (n = 58). In patients with F0-F1 according to Fib4, FRS was 7.3 ± 5.8%; with indifferent Fib4, 11.1 ± 6.7%; and in F3-F4 (Fib4): 11.1 ± 6.9% respectively. HS did not change with respect to Fib4 estimated degree of fibrosis: F0-F1 (Fib4), 3.2 ± 3.6%; with indifferent Fib4, 3.3 ± 3.8%, and in F3-F4 (Fib4): 2.9 ± 3.9%, respectively. Fib4 correlated with FRS ($r = 0.25$, $p < 0.001$), but not with HS ($r = 0.02$, $p = 0.55$).

Conclusion: In this large asymptomatic screening cohort, subjects with non-invasive indicators of advanced stages of NAFLD had an increased risk of coronary heart disease and cardiovascular outcomes. A multidisciplinary approach including hepatologists and cardiologists is important to ensure optimal care for these patients at high risk of CVD and liver-related end points.

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Non-alcoholic fatty liver disease is associated with QTc lengthening in the general population

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Background and aims: Cardiovascular disease is the leading cause of mortality in the general population. Prolonged heart rate corrected QT (QTc) interval is a risk factor for cardiac death. We aimed to determine: (1) if underlying non-alcoholic fatty liver disease (NAFLD), a common disease in the population, is associated with QTc length and (2) if the histological severity of NAFLD is associated with more severe QTc prolongation.

Method: Two cohorts were studied: (1) The Multi-Ethnic Study of Atherosclerosis (MESA), a population-based prospective cohort study of 6814 adult men and women free of cardiovascular disease at enrollment, and (2) A biopsy-proven non-cirrhotic NAFLD cohort (n = 52) and age/gender matched non-NAFLD controls (n = 67) at Virginia Commonwealth University (VCU). NAFLD was identified by a Liver to spleen attenuation ratio (L/S) >1 on CT scan. Severity of NAFLD in the general population was graded as: no NAFLD (Hounsfield Units (HU) ≥ 55), mild NAFLD (HU 40-54) and moderate to severe NAFLD (HU < 40). Liver histology was scored by Non-alcoholic steatohepatitis Clinical Research Network (NASH CRN) criteria. Patients with alcohol consumption >2 units/day, viral hepatitis, cardiac arrhythmias, or patients taking antiarrhythmic medications or systemic steroids were excluded from the analyses. QTc was determined by Bazett formula using electrocardiograms performed at the time of initial enrollment. Data are presented as mean ± standard deviation (SD). The odds ratio (OR) with confidence interval (CI) of having a clinically significant QTc prolongation in NAFLD vs non-NAFLD individuals was determined.

Results: (1) MESA cohort: A subset of 3892 individuals met eligibility criteria; 666 individuals (17%) had NAFLD. Those with NAFLD had longer QTc than those without NAFLD (424 ± 22.7 ms vs 418 ± 21.2 ms; $p < 0.0001$). There was a step-wise increase in the mean QTc interval in association with NAFLD severity ($p < 0.0001$ for trend). Moreover, NAFLD was associated with higher likelihood of clinically significant QTc prolongation of >450 ms in men (OR 2.24; 95% CI 1.4 to 3.6) and >460 ms in women (OR 1.8; 95% CI 1.2 to 2.7) (2) VCU cohort: Mean QTc for grade 1, 2 and 3 steatosis was 422 ± 7 ms, 435 ± 8 ms, and 466 ± 19 ms, respectively; $p < 0.03$. Aside from steatosis, other histological features of NASH, NAFLD activity score and fibrosis stage were not significantly related to QTc.

Conclusion: The presence and severity of hepatic steatosis is associated with lengthening of the QTc interval.

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Hepatic and visceral adipose tissue expression of vitamin D receptor and vitamin D hydroxylases in relation to non-alcoholic fatty liver disease and adipose tissue inflammation

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic hepatic disease worldwide and associated with increased cardiovascular mortality. Visceral adipose tissue (VAT) inflammation is a leading cause of NAFLD and steatohepatitis (NASH) in obesity. Besides, adipose tissue (AT) represents the main site of vitamin D accumulation in humans and a major target of action of this hormone; similarly, a direct role of vitamin D (VD)/vitamin D receptor (VDR) axis has been demonstrated in liver pathophysiology. However, no data are available on the relationship between VDR expression and vitamin D metabolism in liver and VAT in metabolic disease. This study aimed at investigating the expression of VDR and VD hydroxylases in liver and VAT from obese patients in relation to the presence of NAFLD and VAT inflammation.

Method: Forty consecutive obese individuals candidate to bariatric surgery for clinical purposes (M/F: 11/29, mean ± SD age: 43.7 ± 9.6 years) were recruited at Sapienza University of Rome, Italy. Liver and omental biopsies were obtained intra-operatively and VDR, CYP27A1, CYP2R1 and CYP27B1 expression was evaluated by immunohystochemistry and real-time PCR in both tissues. Circulating 25 (OH)VD levels were measured on sera by colorimetry (DiaSorin, LAISON).

Results: Simple steatosis was diagnosed in 50% and NASH in 25% participants; hepatocyte VDR expression positively correlated with the presence of NAFLD, greater NAS steatosis ($p = 0.02$) and inflammation ($p = 0.002$) scores. Greater VDR expression in the liver was positively associated with VAT VDR expression ($p = 0.01$) and presence of VAT inflammation, as indicated by increased macrophage infiltration ($p = 0.008$) and expression of inflammatory markers such as IL-8 ($p = 0.01$), MIP1α ($p = 0.04$), MIP2 ($p = 0.002$) and DPP4 ($p = 0.01$). No association was found between circulating 25 (OH)VD and either hepatic or VAT VDR expression; similarly hepatic VDR expression did not correlated with VD hydroxylases expression in liver or VAT.

Conclusion: VDR is overexpressed in hepatocytes in the presence of NAFLD without showing further increase in more severe stages of the disease. VDR expression in hepatocytes may be likely induced by aberrant hepatic fat accumulation per se, representing a metabolic checkpoint in condition of chronic caloric excess and FFAs overload to the liver. The presence of a tight association between increased hepatic VDR expression, NAFLD and VAT inflammation, along with the novel finding of a correlation between VDR expression in liver and AT, point towards a central involvement of this receptor in metabolic disease, not necessarily mediated by its traditional ligand vitamin D.

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Prediction of NAFLD progression according to duration of exposure to obesity and diabetes: New approach to adapt therapeutic and research strategies

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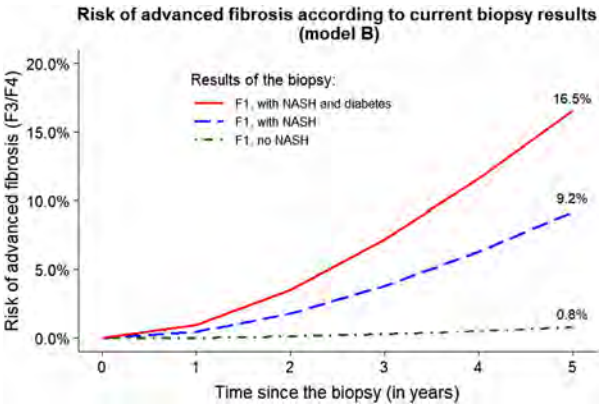
Background and aims: The identification of non-alcoholic fatty liver disease (NAFLD) patients with high-risk of disease progression is an unmet need. The "Atlas Biologique de l'Obésité sévère" (ABOS) database on severely obese patients, with available information on duration of exposure to disease progression cofactors, is a unique opportunity to develop a predictive tool. With such an approach, clinicians would be able to base their therapeutic decision according to the predicted risk of progression.
Method: 989 severely obese candidates to bariatric surgery, with systematic biopsy and reported history of obesity and diabetes, were prospectively included in the ABOS database.
Histological analysis was performed with Kleiner, NAFLD Activity and Brunt scores. From this data, two Markov models of NAFLD progression, based on the risk factors (sex, age, BMI at 20 years, presence of diabetes and its duration) and duration exposure to obesity, were developed assuming that all had normal liver (NL) at the onset of obesity: model A aims to assess the current risk of NASH or advanced fibrosis, knowing the duration of obesity; model B predicts disease progression over 5 years, in patients with histological data. Both models closely reproduced the observed dynamics of NAFLD (mean absolute error: 4.8% for model A, 5.3% for model B in the ABOS database; 9.9% and 9.2%, respectively, in an independent test cohort of 248 obese patients)
Results: Examples were provided to highlight the usefulness of the models.
Model A: a 50-years old woman, obese for 20 years, BMI 30 at 20 years-old, without diabetes, is predicted to have a 3.4% risk of being F3-F4 and 7.6% of having NASH. Patient with same risk factors but obese for 30 years would have 3.9% and 9.6% risks, respectively. The latter being diabetic for 10 years would have 9.1% and 16.6% risks, respectively.
Model B (Figure): a no-NASH F1, 50-years old woman, BMI 30 at 20 years-old, without diabetes, would have a 5-year risk of 0.8% to progress to F3-F4. This risk increases to 9.2% in a NASH F1 (without diabetes), and to 16.5% in a NASH F1 (with diabetes since 10 years), other cofactors being unchanged.



Conclusion: This work highlights the importance of exposure duration to obesity and diabetes to predict disease progression. It provides decision making tools that may be used for therapeutic strategy and help in the design of clinical studies by providing more accurate statistical hypothesis.

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Clinical characteristics of NAFLD/NASH patients from gastroenterology and endocrinology clinics

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) and its more aggressive form, non-alcoholic steatohepatitis (NASH), are closely linked to obesity, diabetes, hypertension, and hypothyroidism. Screening for NAFLD/NASH primarily occurs at gastroenterology/hepatology (GI/Hep) clinics, potentially limiting the screening of at-risk populations. The purpose of this study was to compare the prevalence of NAFLD/NASH and clinical characteristics between endocrinology (Endo) and GI/Hep clinics.
Method: Data was collected as part of the NASH Registry Study, in which participants are identified based on abnormal fibroscan (kPa ≥ 7.0, CAP ≥ 270), NAFLD fibrosis score (NFS) >−1.455, and/or biopsy-confirmed NASH. Information from consenting adults including demographics, recent lab results, and comorbidities was collected. Participants with excessive alcohol consumption or concomitant liver disease were excluded. Participants were grouped by the clinic in which they were recruited; either as a GI/Hep or Endo patient. Mean differences between groups were analyzed by t-test (continuous variables) or Chi-square (categorical).
Results: 561 adult subjects (mean age 55yrs) were prospectively enrolled and included in analyses, of which there were 356 GI/Hep and 205 Endo. Overall, participants tended to be Hispanic White and female, and no demographic differences were observed between groups. However, metabolic syndrome ($p < .001$), hypothyroidism ($p < 0.05$), pre-diabetes ($p < 0.01$) and type 2 diabetes ($p < 0.001$) were more prevalent in Endo patients, whereas colon polyps ($p < 0.001$) and NASH ($p < 0.05$) were more abundant in GI/Hep patients. GI/Hep patients also had a slightly higher incidence of hypertension, although not statistically different from Endo patients. BMI, waist and hip circumference, CAP, platelets, WBC and HbA1C were significantly higher, while age, kPa, ALT, AST and alkaline phosphatase were significantly lower in Endo vs GI/Hep patients. Clinical indices of fibrosis were also significantly higher in GI/Hep patients.
Conclusion: NASH prevalence was higher in participants from GI/Hep clinics. Endo patients present with significantly more risk factors for NASH, namely higher BMI, waist and hip circumference, and T2DM, while exhibiting lower indicators of fibrosis. Interestingly, almost all laboratory tests were more frequently collected at Endo vs GI/Hep clinics. These findings collectively highlight the importance of screening for NAFLD/NASH at Endo practices and enhancing NAFLD/NASH awareness among endocrinologists. Perhaps targeting these clinics is the first step in preventing the progression of disease often seen by specialists.

THU-299

Increased risk of mortality with liver disease progression in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients: An analysis of French national hospital care

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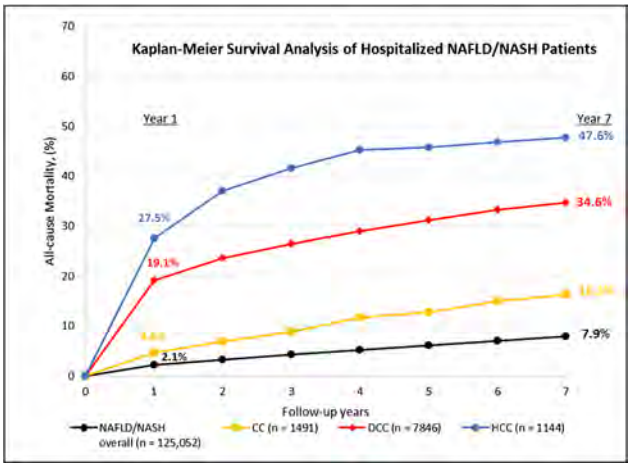
Background and aims: NAFLD/NASH can lead to compensated cirrhosis (CC), decompensated cirrhosis (DCC), and hepatocellular carcinoma (HCC), and is projected to be a major cause of liver-related mortality in the coming decades. However, limited data are available

on disease progression and mortality in French NAFLD/NASH patients. This study evaluated rates of disease progression and all-cause mortality in hospitalized NAFLD/NASH patients in France.
Method: Patients aged ≥ 18 years with NAFLD/NASH were identified from the French National Database on hospital care (PMSI) between 2009 and 2015, which captures all hospitalizations in France. Five study cohorts were identified via ICD-10-CM: (1) NAFLD/NASH overall, (2) CC, (3) DCC, and (4) HCC. Index date was defined as the earliest diagnosis date for each stage. Cohorts were not mutually exclusive. Survival analyses were performed via Kaplan-Meier curves for cumulative incidences of all-cause mortality occurring during hospitalization.
Results: Among 125, 052 NAFLD/NASH patients (mean age 55.9), 1, 491 (1.2%) were diagnosed with CC (1.2%), 7, 846 (6.3%) DCC, and 1, 144 (0.9%) HCC, with mean ages of 62.2, 65.0, and 70.1, respectively. The comorbidity burden was high for all cohorts: ≥ 43% had diabetes, ≥ 41% had cardiovascular disease, ≥ 21% had renal impairment, and ≥ 47% had hypertension. In 1 year of follow-up, 4-times as many NAFLD/NASH patients were diagnosed with DCC than CC (1200; 0.96% vs. 250; 0.20%), indicating under diagnosis of CC. In 7 years of follow-up, 5.6% of NAFLD/NASH patients progressed to more severe liver disease and 27.5% of diagnosed CC patients progressed to DCC. Mortality was high across cohorts and increased with liver disease progression: after 1 year mortality was 2-times higher in CC than NAFLD/NASH (4.6% vs. 2.1%) and almost 4-times higher DCC than CC patients (19.1% vs. 4.6%) (Figure). Overall mortality after 7 years in DCC was 34.6% CC, was 16.3%, and NAFLD/NASH was 7.9%.



Conclusion: Hospitalized NAFLD/NASH patients in France had high rates of comorbidities and high rates of liver disease progression (over 1 in 4 CC progressed to DCC). The overall NAFLD/NASH mortality rate of 7.9% was higher than the expected rate for the general similarly aged population of 4.6%, and increased with liver disease progression. Early identification and treatments to halt or reverse disease progression due to NAFLD/NASH may reduce the rate of mortality.

THU-300
Prevalence of NAFLD in patients with a first episode of stroke and impact on the mortality and severity at 3 months

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Background and aims: non-alcoholic fatty liver disease (NAFLD) is associated with a higher prevalence of cardiovascular events and subclinical atherosclerosis. Previous studies suggest that the presence of NAFLD and significant fibrosis could be associated with a higher severity and mortality in patients with a stroke. The aim of the study was to determine the prevalence of NAFLD in a prospective cohort of patients with a first episode of stroke and the relationship between NAFLD and severity and mortality at 3 months after stroke.
Method: retrospective analysis of a prospective cohort of patients admitted for a first episode of stroke. NAFLD was defined as the presence of a Fatty Liver Index (FLI) >60 and significant fibrosis according to the values of FIB4 adjusted for age (FIB4 >1.4 if age < 65 years and >2 if age >65 years). Patients with known liver cirrhosis were excluded. Mortality and severity of stroke were assessed with the Rankin scale (RS) at 3 months after stroke.
Results: from January 2016 to May 2018, 481 patients were evaluated with a first episode of stroke. 14 (2.9%) patients with a previous diagnose of cirrhosis and 65 (13%) for missing values to calculate the FLI were excluded. Finally, 402 patients were included, 58% men with a median age of 76 years and a BMI of 27Kg/m^2. The prevalence of hypertension, diabetes mellitus, dyslipidemia and atrial fibrillation was respectively: 71%, 32%, 52% and 32%. The etiology of the stroke was cardioembolic (31%), lacunar (19%), hemorrhagic (13%) and atherothrombotic (12%). The overall prevalence of NAFLD was 43.5% (n = 175), higher in men than in women (48% vs. 37% p = 0.03). 34% of the patients presented significant fibrosis. At 3 months after stroke, no significant differences were observed in patients with and without NAFLD in mortality (8.6% vs. 8.0%, p = 0.8) or in the severity of stroke (RS0: 20% vs.17%, RS1: 19% vs. 16%, RS2: 17% vs. 18%, RS3 25% vs. 20%, RS4 15% vs. 14%, RS5: 1% vs. 2%, p = 0.9).
Conclusion: in patients with a first episode of stroke, the prevalence of NAFLD is very high. NAFLD affects almost half of men. One third of patients are at risk of significant fibrosis. Even thought, the presence of NAFLD does not seem to condition a worse prognosis in our cohort

THU-301
Weight loss significantly reduces the risk of chronic kidney disease development in patients with non-alcoholic fatty liver disease

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Background and aims: Weight loss is regarded as a pivotal treatment strategy in non-alcoholic fatty liver disease (NAFLD). However, there is a lack of data evaluating whether weight loss affects long-term kidney function in this population. Therefore, we investigated the impact of weight changes on adverse kidney outcomes in NAFLD patients using a community-based, prospective cohort with a 12-year follow-up.
Method: Among 10, 030 participants from the Korean Genome Epidemiology Study, 1, 774 NAFLD patients were included in this study. Patients were categorized into four groups according to the quartiles of time-averaged percent weight change (TA-%weight change). Study outcomes were development of chronic kidney disease (CKD) and rapid decline of kidney function.
Results: The median value of TA-% weight change was −1.3% (interquartile range, − 4.2 to 1.1). During a mean follow-up of 108.7 ± 44.5 months, CKD developed in 510 patients (28.7%). Patients in the first quartile (TA-%weight change < −4.2%) had a significantly lower risk of CKD development (hazard ratio [HR] = 0.531, 95% confidence interval [CI] = 0.409-0.690) and rapid decline of kidney function (HR = 0.598, 95% CI = 0.458-0.782), compared with patients with minimal changes. Decreased risk of CKD development in patients of the first quartile remained significant in the overweight (HR = 0.528, 95% CI = 0.372-0.751) and obese (HR = 0.482, 95% CI = 0.307-0.755) groups.

Table 2: (abstract: THU-301): Uni- and multivariable Cox regression analyses of TA-%weight change categories for CKD development in patients with NAFLD

	n (%)	Crude		[a]Model 1		[b]Model 2		[c]Model 3	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
TA-%weight change quartiles									
Q1 (<−4.2%)	96 (21.6%)	0.583 (0.450-0.756)	<0.001	0.543 (0.418-0.705)	<0.001	0.542 (0.417-0.704)	<0.001	0.531 (0.409-0.690)	<0.001
Q2 (−4.2 to −1.3%)	124 (27.9%)	0.812 (0.638-1.033)	0.90	0.873 (0.685-1.112)	0.31	0.872 (0.684-1.111)	0.27	0.843 (0.660-1.075)	0.17
Q3 (−1.3 to < 1.1%)	141 (31.8%)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q4 (≥ 1.1%)	149 (33.6%)	1.043 (0.828-1.313)	0.72	1.079 (0.856-1.360)	0.52	1.079 (0.856-1.360)	0.52	1.132 (0.896-1.430)	0.30
TA-% weight change (per 1 SD increase)	510 (28.7%)	1.234 (1.133-1.343)	< 0.001	1.256 (1.155-11.367)	< 0.001	1.257 (1.155-1.368)	< 0.001	1.291 (1.185-1.407)	< 0.001

[a]Model 1: adjusted for age, sex, education, income, smoking status, history of CVD, mean arterial pressure, and metabolic syndrome.
[b]Model 2: model 1 + serum albumin and CRP.
[c]Model 3: model 2 + BMI and baseline eGFR.
* TA-%weight change, time-averaged percent weight change.

Conclusion: In conclusion, this study is the first to demonstrate that weight loss, above an average of 4.2%, was associated with significant risk reduction of CKD development and rapid decline in kidney function. It suggests that significant and sustained weight loss may improve long-term kidney outcomes in patients with NAFLD.

THU-302

Association between advanced fibrosis in fatty liver disease and overall mortality in terms of body size and body fat distribution

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Background and aims: Association between fatty liver disease and overall mortality have yielded inconsistent results, from a strong association to no association. This study aimed to determine the association between fatty liver disease and advanced fibrosis and overall morality according to body size and abdominal fat distribution as measured by computed tomography (CT).
Method: We performed a prospective cohort study of 38, 647 subjects (mean age, 51.3 years; 58.3% men) who underwent abdominal ultrasonography and fat CT from 2007. Fatty liver was diagnosed by ultrasonography and advanced fibrosis was defined as having high probability for advanced fibrosis using three non-invasive methods such as aspartate aminotransferase to platelet ratio index, non-alcoholic fatty liver disease fibrosis score, and FiB-4 score. Body size was categorized based on body mass index: obese (≥ 25 kg/m^2) or non-obese (<25 kg/m^2). Multivariate proportional Cox hazard regression analyses were performed to determine independent predictor of overall mortality.
Results: The prevalence of fatty liver disease was 32.6%, while the prevalence of advanced fibrosis in fatty liver disease was 1.8%. During the median follow-up of 88 months (range, 1.2-138), there were a total of 352 deaths. Fatty liver disease was not associated with higher overall mortality (multivariable-adjusted hazard ratio [HR]: 1.02, 95% confidence interval [CI]: 0.77-1.34), while an increased subcutaneous adiposity was associated with decreased mortality (HR 0.72 95% CI 0.60-0.80), more prominent in non-obese population. Subjects with advanced fibrosis had 3.5 fold increase in overall mortality (adjusted HR 3.52, 95% CI, 1.86 – 6.65, $p < 0.001$) after adjustment for other known risk factors of mortality. This significant increased risk of overall mortality in advanced fibrosis was more pronounced in non-obese population.
Conclusion: Fatty liver disease was not associated with increased overall mortality, while subcutaneous adiposity was associated with decreased overall mortality, more pronounced in non-obese population. Advanced fibrosis was associated with increased risk of overall mortality, more pronounced in the non-obese population.

THU-303

Report from the trenches: Real-life challenges to recruitment and enrollment in NAFLD clinical trials

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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, associated with both liver and all-cause mortality and projected to be the leading indication for liver transplantation. To date there are no effective pharmacological therapies and hence a race to drug development is critical. Despite its abundant prevalence, multiple challenges exist that hinder the recruitment and enrolment of participants in NAFLD clinical trials. The purpose of this study is to describe the real-world experience and screen failure reasons for recruitment into NAFLD clinical trials.
Method: Retrospective chart review of all patients referred for participation in a NAFLD clinical trial was performed from June 2016 to October 2018. Descriptive data were collected; the incidence of screen failure and the causative reasons for exclusion were investigated. Screen failure was defined as those participants who consented to participate in a study but were found to be ineligible based on inclusion and exclusion criteria.
Results: All screen failures (n = 40) were included for evaluation (Table 1). The most common cause of screen failure was a discordance in liver fibrosis stage between transient elastography and liver biopsy (19 cases, 48%). 53% (10/19) cases down-staged by 1 stage of fibrosis, 33% (6/19) down-staged by 2 stages of fibrosis, 11% (2/19) down-staged by 3 stages of fibrosis and 5% (1/19) cases were found to have cirrhosis excluding from a non-cirrhotic trial. 8 cases did not meet the criteria of NAS ≥ 4; 3 of the cases were being considered for cirrhotic trials but did not fulfil requirement of steatosis or inflammation.

Reason for Screening Failure	Number of Patients (n = 40)
1) Did Not Meet Minimum Inclusion Fibrosis Stage	19
2) Fibrosis score too low	18
3) Fibrosis score too high	1
NAS Score < 4	8
Consent Withdrawn	4
Refused Liver Biopsy	2
• Exclusion criteria	2
• Thrombocytopenia	1
• Change in anti-diabetic medication within screening period	1
• History of Hepatocellular carcinoma	1
• Hypertriglyceridemia	1
Fragmented Biopsy (Unable to Stage)	2

Conclusion: The screen failure rate for NAFLD trials remains high despite the abundance of disease. Most cases are due to a discordance between our non-invasive tools to assess fibrosis and assessment of liver fibrosis by the central reader compared to our local expertise. In clinical practice, we err on the side of caution and overestimate the degree of fibrosis while in clinical trials the degree of fibrosis is conservative, which is not reflective of the real-world. Efforts should be made to broaden inclusion criteria for NAFLD trials and/or discuss each case where there is a discrepancy and understand that features of NAS are lost as fibrosis progresses.

THU-304
Modeling NAFLD-related disease progression among the PITER SVR12 cohort

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is frequent among patients with chronic hepatitis C. The cured HCV population may be susceptible to worsening of NAFLD and development of non-alcoholic steatohepatitis (NASH), due to advancing age combined with high levels of obesity and metabolic risk factors. Modeling can help assess how continued liver disease progression due to NAFLD would alter the outcome of HCV cure.
Method: A model of NAFLD-related disease burden was applied to over 2, 000 participants in the Italian PITER cohort who achieved SVR12 to quantify disease progression and outcomes. Based on previously modeled prevalence among the general Italian population by age group and gender, 670 cohort participants during 2014-2018 were estimated to have NAFLD. This cohort entered the model by disease stage and data year and were followed over time. Over 80% of the cohort entered the model at fibrosis stage ≥ F2 and 65% were classified as F4. Progression through fibrosis stages varied by age group and gender. Disease burden and mortality were estimated through 2030.
Results: NAFLD cases peaked at 640 cases in 2017, declining 40% to 380 cases by 2030. In 2018, 86% of cases were classified as ≥ F2 fibrosis (530 cases), 77% as ≥ F3 fibrosis (480 cases) and 64% as F4 fibrosis (400 cases), reflecting the high burden of disease attributable to previous viral infection. By 2030, the proportion of cases classified as ≥ F2 fibrosis declined to 78% (300 cases) of total prevalent NAFLD, due to lower mortality among participants with no/mild fibrosis. Likewise, the proportion of cases estimated as ≥ F3 declined to 70% and F4 cases declined to 56% of the total. There were an estimated 140 incident decompensated cirrhosis and 15 incident liver cancer cases from 2014-2030. Median age was estimated at 66 years in 2018, increasing to 74 years by 2030. Half of the cohort was lost to mortality by 2030 (330 total deaths). Nearly half of deaths were classified as NAFLD-related (160 liver deaths).
Conclusion: In the presence of NAFLD, disease progression will continue among a portion of the cured HCV population. The post-SVR population will experience high rates of chronic disease and remain susceptible to liver morbidity and mortality. Additional research and improved diagnostic technologies are needed to quantify the probability of NASH and related disease progression among post-SVR cases with advanced fibrosis and metabolic risk factors.

THU-305
Comparing perceptions of illness among patients with chronic liver disease

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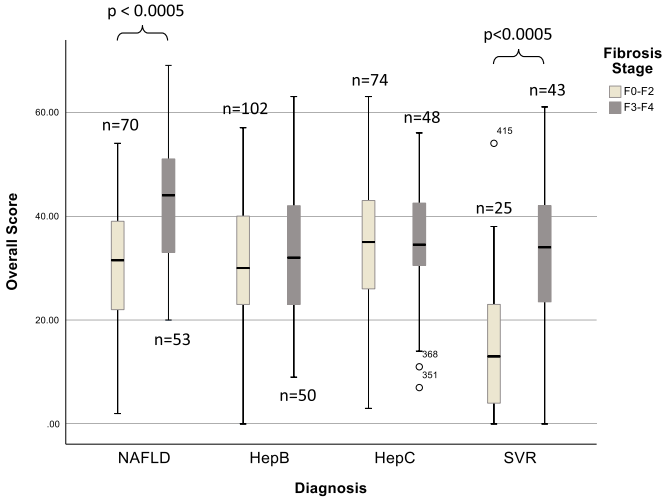
Background and aims: When patients are diagnosed with a chronic disease, their understanding of the illness and its severity may influence the goals they set and the steps they take towards its management. Perception of disease severity may be particularly challenging in chronic liver disease due to its relative lack of attributable symptoms. In this study, we examined the relationship between disease perception and disease severity (as measured by degree of liver fibrosis) among patients with various chronic liver diseases.
Method: We administered the Brief Illness Perception Questionnaire (Brief IPQ) to patients at the Toronto Centre for Liver Disease who had been diagnosed with or were receiving treatment for non-alcoholic fatty liver disease (NAFLD), hepatitis B infection (HBV) or hepatitis C infection (HCV) including patients who had achieved sustained virological response (HCV-SVR). Patients were categorized by fibrosis stage as early (F0-2) versus late (F3-4). Increasing IPQ scores indicate perception of more severe illness. Individuals with HIV, liver cancer, decompensated cirrhosis or severe comorbidities were excluded.



Results: A total of 465 participants completed the Brief IPQ. Scores were higher in those with advanced compared to mild fibrosis in only NAFLD and SVR patients (Figure). Among low fibrosis patients, the

mean score for SVR patients was significantly lower when compared to mean scores for all other groups (30.64 for HBV, 33.91 for HCV, and 30.37 for NAFLD; $p < 0.0005$ for all three comparisons). As well, among high fibrosis patients, the mean score for NAFLD patients was significantly higher than mean scores for all other groups (33.18 and $p = 0.001$ for HBV, 35.04 and $p = 0.017$ for HCV, and 32.07 and $p < 0.0005$ for SVR). Lastly, for the question assessing how much patients perceived treatment to help their illness, both the high and low fibrosis NAFLD groups had significantly greater mean scores compared to all other high ($p = 0.002$ for HBV, $p < 0.0005$ for HCV and SVR) and low fibrosis groups ($p = 0.057$ for HBV and $p < 0.0005$ for HCV and SVR) respectively.

Conclusion: Patients with chronic liver disease seen generally have accurate perception of their disease severity and the efficacy of treatment. The Brief IPQ proved to be a useful and reliable test for assessing disease perception, which may have value for assessing individuals' understanding of and engagement in their disease management.

THU-306

Liver function tests in NAFLD: Changes in upper normal limits, does it really matter?

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Background and aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is the commonest cause of abnormal liver function tests (LFTs). The current Upper Normal of Limit (UNL) of LFTs was derived from an apparently "healthy" population, where a high rate of undiagnosed NAFLD and chronic viral hepatitis may be suspected. We aimed to evaluate potential implications of changes in UNL of ALT in patients with NAFLD.

Method: We retrospectively assessed consecutive first referrals with a clinical or histological diagnosis of NAFLD from 2010 to 2017. The high UNL of ALT was set at 45 IU/L for men and 34 IU/L for women, while the low UNL of ALT was set at 30 IU/L for men and 19 IU/L for women. The UNL of AST was 40 IU/L for both men and women. Liver biopsies were scored according to the NASH CRN Scoring System. All patients underwent Liver Stiffness Measurement (LSM).

Results: 436 patients were enrolled; of these, 288 underwent liver biopsy. Lowering the UNL of ALT reduced the percentage of patients who had liver fibrosis or NASH despite normal ALT from 10% to 4% and from 28% to 4% respectively. However, the percentage of those with increased ALT and no evidence of liver fibrosis or NASH increased from 27% to 33% and from 3% to 19% respectively. There were no differences in terms of demographic, anthropometric and metabolic features.

Conclusion: Liver function tests might both under- and overestimate NASH-related liver disease. Reducing the UNL might not beneficial and lead to an increase in overall healthcare burden. Risk stratification in NAFLD should rely on a combination of risk factors, not on LFTs alone.

THU-307

Whipple procedure increases the risk for non-alcoholic fatty liver disease

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Background and aims: Asian studies report an increased incidence of non-alcoholic fatty liver disease (NAFLD) post pancreaticoduodenectomy (PD), ranging from 7.8% to 40.0%. We sought to investigate the incidence and predictors of NAFLD after PD in an ethnically diverse population in the United States.

Method: We conducted a retrospective study of patients who underwent PD between 12/2010 and 12/2016, as well as patients who underwent a cholecystectomy (CH) or distal pancreatectomy (DP) serving as controls. Various imaging modalities were used to detect NAFLD with CT scans comprising 97.3%. Using Hounsfield units (HU), NAFLD was defined as a liver:spleen ratio < 0.9, or in patients who had a splenectomy, an absolute value of < 40 HU. We abstracted information on demographics, comorbidities, type and indication of surgery, post-operative use of pancrelipase and insulin, and use of chemotherapy. Patients who had NAFLD prior to surgery and those without post-operative imaging were excluded. Chi-square test was used to evaluate for associations, with a p value < 0.05 considered significant. Nominal logistic regression was used for multivariate analysis.

Results: A total of 123 patients were included: 66 controls (29 CH + 37 DP) and 57 PD. Sixty-one (49.6%) were male, 95 (80.5%) Caucasian, 57 (47.1%) Hispanic, median age at the time of surgery of 64 years and average BMI of 26.2 kg/m^2. Median follow-up time was 2.2 years. The proportion of patients developing NAFLD within the first 3 years post CH and DP versus PD was 30.3%, and 70.2%, respectively. Race, ethnicity, age, BMI, hypertension, diabetes, use of pancrelipase or insulin post-operatively, or use of chemotherapy were not associated with increased frequency of NAFLD post-operatively. After adjusting for age, gender, ethnicity, BMI, surgery indication and comorbidities, the type of surgery was the only independent predictor of NAFLD.

Table 1: Preoperative and postoperative variables associated with the development of NAFLD

	NAFLD present (N = 60)	NAFLD not present (N = 63)	P value
Age, median (range)	62 (18-87)	64 (35-89)	1.00
Female, n (%)	32 (53.3)	30 (47.6)	0.59
BMI >30, n (%)	13 (24.1)	14 (25.0)	1.00
Hispanic, n (%)	28 (46.7)	29 (47.5)	1.00
Type 2 diabetes, n (%)	17 (28.3)	15 (23.8)	0.68
Hypertension, n (%)	26 (43.3)	34 (54.0)	0.28
Hyperlipidemia, n (%)	15 (25.0)	14 (22.2)	0.83
Type of surgery (N = 123)			< 0.0001
Control group (Cholecystectomy + Distal Pancreatectomy), n (%)	20 (33.3)	46 (73.0)	
Pancreaticoduodenectomy, n (%)	40 (66.7)	17 (27.0)	
Diagnosis (n = 123)			0.11
Malignancy (n = 73), n (%)	39 (65.0)	34 (54.0)	
Benign (n = 36), n (%)	10 (16.7)	26 (41.3)	
Neuroendocrine tumor (n = 14), n (%)	11 (18.3)	3 (4.8)	

Conclusion: Patients who undergo a pancreaticoduodenectomy are at increased risk for the development of NAFLD post-operatively. The natural history of this post-op NAFLD is unclear and additional studies are warranted.

THU-308

More than 4 times higher healthcare costs for end-stage liver disease patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

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Background and aims: NAFLD/NASH patients who progress to advanced liver disease (AdvLD) [compensated cirrhosis (CC)/ decompensated cirrhosis (DCC)/liver transplant (LT)/hepatocellular

carcinoma (HCC)], have significantly higher healthcare resource utilization and costs as compared to NAFLD/NASH patients who do not progress. However, previous studies have not comprehensively adjusted for baseline patient and disease characteristics. This study evaluated adjusted costs associated with progression among NAFLD/NASH patients using a large generalizable US claims database.

Method: NAFLD/NASH patients aged ≥ 18 years from 2006-2016 were identified retrospectively from the IBM Watson Health MarketScan® Commercial healthcare claims database using ICD-9/10-CM codes. Following the initial NAFLD/NASH diagnosis, development of CC, DCC, LT or HCC was identified using their first diagnosis date for each severity stage (index date). Annual healthcare costs for each liver severity stage were obtained from per patient per month estimates, adjusted for baseline demographics and comorbidities through generalized linear models.

Results: Of the total 153, 323, 509 individuals in the database, 468, 017 NAFLD/NASH patients who met inclusion/exclusion criteria were identified. Among this NAFLD/NASH cohort, 96.9% (453, 564) were without AdvLD, 1.6% (7, 665) had CC, 3.4% (15, 833) had DCC, 0.1% (696) had LT and 0.1% (428) had HCC. Patients across all liver stages had a mean age of 48-52 years and >50% females. The comorbidity burden was high across all liver stages with more than 57% patients having ≥ 1 co-morbidity, including hypertension, hyperlipidemia, cardiovascular disease, type-2 diabetes (T2DM) and renal impairment. The adjusted annual healthcare costs increased significantly as patients progressed through liver severity stages. As compared to NAFLD/NASH without AdvLD (adjusted costs: $23, 860), the cost of CC, DCC, LT and HCC was 1.22, 5.64, 8.27 and 4.09 times higher respectively, with adjusted costs being $29, 078, $134, 448, $197, 392 and $97, 563 respectively (p < 0.001)[Figure]

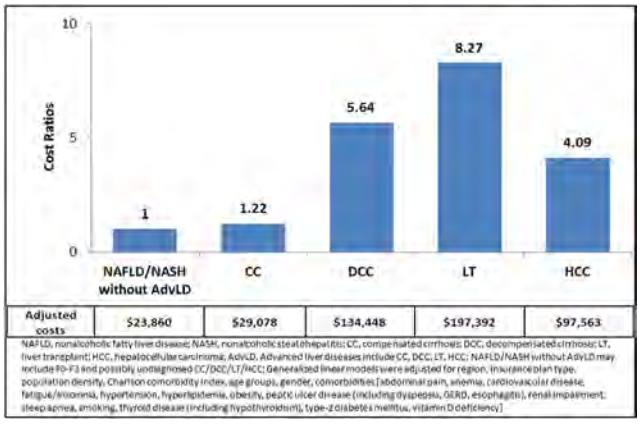

Figure: Generalized Linear Models for Adjusted Annual Healthcare Costs among NAFLD/NASH Patients with AdvLD

Conclusion: Amongst a large cohort of commercially insured NAFLD/NASH patients in the US, adjusted healthcare costs for NAFLD/NASH patients who progress to DCC/LT/HCC were 4-8 times higher than in patients who do not progress. Halting or reversing fibrosis to prevent progression to DCC/LT/HCC in CC patients due to NAFLD/NASH is imperative to limit the increasing healthcare costs.

THU-309

Cardiovascular risk assessment and management improves outcomes in a specialist multidisciplinary non-alcoholic fatty liver disease clinic

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the developed world and is predicted to become the leading indication for liver transplantation by 2030.

Patients with NAFLD usually have features of the metabolic syndrome as well as myriad of other cardiovascular risk factors. The majority of deaths among the NAFLD population are attributable to cardiovascular events such as myocardial infarction and cerebral vascular events.

Therefore, it is imperative that patients diagnosed with NAFLD undergo cardiovascular risk assessment and that where found, these risk factors should be managed proactively.

Here we assess the effectiveness of cardiovascular risk assessment and management as part of a Specialist Multidisciplinary NAFLD clinic.

Method: Data from 120 patients whom underwent a cardiovascular risk assessment as part of their routine care in a multidisciplinary NAFLD clinic were included. We assessed the impact of this service by assessing changes in LDL cholesterol, HbA1c and QRISK-3 score.

Results: Baseline data, mean age was 55.7 (9.3) years with mean weight of 90.7 kg and mean BMI of 32.3 kg/m^2. 17.5% were current smokers. Rates of known pre-existing comorbidities including hyperlipidaemia, hypertension and diabetes were 65.8%, 59.1% and 21.7%, respectively. Those with established cardiovascular disease (CVD) equated to 10%.

The 10-year QRISK-3 score for CVD in 17.6% of the patients was >20%; 53.7% had a score between 10 and 20% and 28.7% had a score of < 10% (Figure 1).

Hyperlipidaemia management was suboptimal in 67% of patients at baseline. Lipid lowering treatment was altered or commenced in 44% of patients. For primary prevention 68.3% achieved the LDL reduction of < 3 mmol/L. For secondary prevention, 75% reached the LDL target of < 2 mmol/L.

An additional 13 patients with undiagnosed type 2 diabetes were detected. The mean HbA1c prior to intervention was 77.6 mmol/mol. Diabetes treatment was commenced or altered in 34/39 (87.2%) patients in total. The mean HbA1c post intervention were 62.3 mmol/mol, representing a mean improvement of 15.3 mmol/mol.

Overall, the mean reduction for 10-year QRISK-3 score for CVD was 5.2% with a mean gain in CVD free years of 2.1 years (Figure 1).

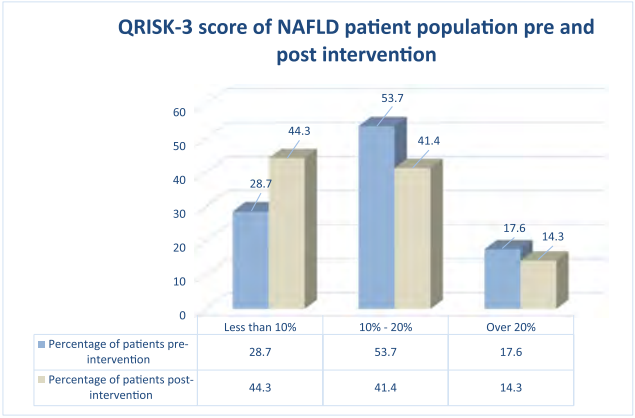

Figure 1: The QRISK-3 score for 10-year CVD risk of NAFLD patient population, pre and post intervention.

Conclusion: Cardiovascular risk assessment in the multidisciplinary NAFLD clinic aides the detection and treatment of conditions such as hyperlipidaemia and type 2 diabetes mellitus, creating an opportunity to optimise the management of these comorbidities and hence reducing the cardiovascular risk profile in the NAFLD population.

THU-310

Non-alcoholic steatohepatitis is associated with a higher risk of advanced colorectal neoplasm

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is known to increase the risk of adenomatous colonic polyps. However, the role of screening colonoscopy in patients with biopsy-proven NAFLD in detecting advanced colorectal neoplasm is not clearly evidence-based. Therefore, we investigated whether the histological severity of NAFLD is associated with advanced colorectal neoplasm.
Method: This study included patients >18 years old who underwent routine colonoscopy between 2013 and 2018 within a biopsy-evaluated prospective NAFLD cohort. Advanced colorectal neoplasm was defined as an adenomatous polyp greater than 10 mm in diameter and/or with villous histology and/or with high-grade dysplasia or adenocarcinoma.
Results: Among the 476 subjects with biopsy-proven NAFLD (n = 379) and healthy controls without any evidence of NAFLD (n = 97) who underwent colonoscopy, the prevalence of advanced colorectal neoplasm was 11.1% (n = 53). Patients with advanced colorectal neoplasm had higher grade of steatosis (p = 0.004) and higher stage of hepatic fibrosis (p = 0.044) than those with normal colonoscopic findings or low-grade adenomatous polyp. Multivariable logistic regression analysis revealed that the presence of non-alcoholic steatohepatitis (NASH) was an independent risk factor for both colorectal polyp (odds ratio [OR], 2.08; 95% confidential interval [CI], 1.12-3.86; p = 0.020) and advanced colorectal neoplasm (OR, 2.81; 95% CI, 1.01 –7.87; p = 0.049).
Conclusion: The presence of biopsy-proven NASH was significantly associated with an increased risk of advanced colorectal neoplasm among patients with NAFLD. This finding may alert physicians to conduct screening colonoscopy in patients with NASH to detect advanced colorectal neoplasm early.

THU-311

Liver enzymes cut offs in patients with advanced non-alcoholic fatty liver disease: A multi-center study

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Background and aims: Primary care physicians rely on liver enzymes to assess non-alcoholic fatty liver disease (NAFLD) severity however the reliability of abnormal enzymes for determining this is uncertain. The prevalence of normal and abnormal liver enzymes and their cut offs with advanced NAFLD are not well determined. Aim is to assess the prevalence of abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in patients with advanced NAFLD.
Method: In this multi-center cross-sectional study, we calculated the percentage of abnormal ALT, AST and ALP based on lab references and AASLD recommended references (normal ALT and AST ≤ 35 U/L for males and £ 25 U/L for females) in NAFLD patients with MR elastography (MRE) ≥ 2.5 kPa (possibly correlated with NASH), those with MRE ≥ 3.62 kPa (advanced fibrosis) and those with MRE ≥ 4.7 kPa (correlated with cirrhosis). Fisher's exact test was used for testing association strength.
Results: The cohort included 245 patients: 53% female; 47% DM or pre DM; mean BMI 32 (3.7) kg/m^2, ALT 43 (22.5) U/L, AST 32 (14.8) U/L, and ALP 78 (20) U/L). Normal ALT, AST and ALP were found in 49%, 51%, and 81% of patients with MRE ≥ 2.5 kPa, in 40%, 43%, and 78% of patients with MRE ≥ 3.62, and in 40%, 53%, 77% of patients with MRE ≥ 4.7 kPa, respectively. We analyzed associations of abnormal ALT, AST, ALP and patients with MRE ≥ 2.5, ≥ 3.62 and ≥ 4.7 kPa respectively based on lab references or AASLD recommended references as shown in table. AUC of ALT to detect advanced fibrosis was 0.55 and 0.68 respectively when we used local lab references. Using AASLD references, AUC of increased to 0.59 for ALT and 0.72 for AST respectively.

Table:

	Local labs reference range			AASLD reference range		
	MRE ≥ 2.5 (%)	MRE < 2.5 (%)	P vale	MRE ≥ 2.5 (%)	MRE < 2.5 (%)	P vale
Abn ALT	51	43	0.32	74	64	0.16
N ALT	49	57		26	36	
Ab AST	49	23	**0.0001**	64	47	**0.016**
N AST	51	77		36	53	
Abn ALP	19	6	**0.009**	N/A		
N ALP	81	94				
	MRE ≥ 3.62	MRE < 3.62		MRE ≥ 3.62	MRE < 3.62	
Abn ALT	60	44	**0.0247**	76	68	0.27
N ALT	40	56		24	32	
Abn AST	57	32	**0.0006**	69	53	**0.03**
N AST	43	68		31	47	
Abn ALP	22	11	0.05	N/A		
N ALP	78	89				
	MRE ≥ 4.7	MRE < 4.7		MRE ≥ 4.7	MRE < 4.7	
Abn ALT	60	45	**0.05**	73	69	0.64
N ALT	40	55		27	31	
Abn AST	47	36	0.15	60	56	0.66
N AST	53	64		40	44	
Abn ALP	23	12	0.06	N/A		
N ALP	77	88				

Conclusion: Significant number of patients with normal liver enzymes based on local lab references had NASH (~50%) and/or advanced fibrosis (~40%). Lower cut offs such as the AASLD reference range need to be used in NAFLD/NASH.

THU-312

Physician-recommended lifestyle interventions and associated effects among non-alcoholic steatohepatitis patients with and without cardiovascular-metabolic related comorbidities: A European real-world study

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Background and aims: Patients who have non-alcoholic steatohepatitis (NASH) should receive the same degree of lifestyle management from their physicians regardless of whether they have additional comorbidities. This analysis aims to establish if additional cardiovascular-metabolic (CVM) related comorbidities affect the way NASH patients are managed in a real-world setting.
Method: Data were derived from the 2018 5EU Adelphi NASH Disease Specific Programme, a real-world, cross-sectional survey. Physicians completed questionnaires describing five consecutive NASH patients. These same five patients were asked to provide additional

information. Physicians reported comorbidities and clinical values. Patients reported weight/lifestyle-related factors. Patients were classified by absence versus presence of CVM comorbidities (type 2 diabetes, hypertension, dyslipidaemia, myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease).
Results: 270 physicians (48% hepatologists, 52% gastroenterologists) provided data on 1, 353 NASH patients. Of these, 238 had both physician and patient responses available comprising of NASH+CVM (45%) and NASH-only (55%). NASH+CVM had higher mean BMI vs. NASH-only (33.5 vs 29.4 kg/m^2), with physicians more likely to advise weight-loss (86% vs 75%). Whilst NASH+CVM patients reported higher physician-recommended weight maintenance (71% vs 52%), increased exercise (75% vs 54%) and dietician visits (49% vs 33%), they are less likely to be happy with their weight progress (10% vs 35%). NASH+CVM patients felt lifestyle changes had helped improve their overall health (58% vs 46%), control blood sugar (25% vs 13%) and lose weight (41% vs 29%). Conversely, NASH-only patients were more likely to self-report no perceived benefit via lifestyle changes compared to NASH+CVM patients (20% vs 6%).
Conclusion: The EASL-EASD-EASO Clinical Practice Guidelines advocate lifestyle change in all patients with NAFLD/NASH. Real-world evidence suggests this is most frequently implemented amongst NASH+CVM, not NASH-only patients. NASH+CVM patients self-report more benefit from implemented changes complementing the notion that NASH-only patients warrant additional targeted lifestyle management. Additionally, this may highlight differences in lifestyle management approaches between specialist groups, with non-diabetologist influence and infrastructure less likely to advocate and support lifestyle change.

THU-313
Differences between non-alcoholic steatohepatitis patient characterisation and management approaches: A multinational real-world study

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Background and aims: Whilst global Non-Alcoholic Steatohepatitis (NASH) prevalence is currently unknown, differing healthcare systems, physician and patient factors equally pose regional challenges when managing NASH. This analysis aims to describe the characteristics of consulting NASH patients across Europe (EU), Canada (CAN) and the Middle East (ME) and establish any differences in current management approaches.
Method: Data were derived from the 2018 Adelphi NASH Disease Specific Programme, a real-world, cross-sectional survey. Physicians completed questionnaires describing five EU/CAN and ten ME consecutive NASH patients alongside completing an attitudinal physician survey. Diagnosis was via liver biopsy (LB) or non-invasive test (NIT) assessment, with physicians reporting diagnostic tests, clinical values and associated management.
Results: 444 physicians (35% hepatologists, 43% gastroenterologists, 22% diabetologists) provided data on 2, 267 NASH patients. ME patients are younger (47.3 vs 55.7/EU vs 55.3/CAN) with a higher proportion unemployed (13% vs 5%/EU vs 3%/CAN). Staging via LB is most likely in EU (48% vs 35%/CAN vs 20%/ME), via Fibroscan in ME (72% vs 60%/EU vs 44%/CAN). Diagnostic "liver screens" to exclude other diagnoses were more consistently completed in CAN, e.g. testing serum ferritin/transferrin saturation (85% vs 61%/EU vs 10%/ME). ME is least likely to assess levels of alcohol intake at diagnosis (9% vs 70%/EU vs. 89%/CAN). ME perform the greatest variety of tests to monitor NASH (10.0 tests vs 5.8/EU vs 5.3/CAN) and were most likely to prescribe off-label Vitamin E as NASH therapy (49% vs 19%/EU vs 12%/CAN). ME physicians more frequently reported treating the underlying cause of disease via other related comorbidities (76% vs 54%/EU vs 35%/CAN). EU physicians target NASH via weight-loss approach (GLP-1: 25% vs 6%/CAN vs 6%/ME). CAN physicians likely to address NASH via referral to nutritionist (65% vs 45%/EU vs 55% ME). All results $p \leq 0.05$.
Conclusion: NASH management approaches vary across EU, CAN and ME. Despite standard LB diagnostic recommendation, in a real-world setting LBs more likely in EU, Fibroscans more likely in ME with similar application of both in CAN. ME physicians monitor NASH more regularly and attempt off-label treatment approaches targeting underlying causes of disease, CAN physicians more likely to rely on lifestyle changes. Regional differences may be influenced by healthcare systems and culture and need to be accounted for across geographies.

THU-314
Serum Zinc levels as a prognostic factor for extra-hepatic carcinogenesis in Japanese patients with non-alcoholic liver disease

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Background and aims: Chronic liver diseases are associated with zinc (Zn) deficiency. However, no previous studies have examined the relationship between serum Zn levels and the incidence of hepatic and extra-hepatic malignancies in patients with non-alcoholic fatty liver disease (NAFLD). The aim of this study was to investigate the prognosis based on serum Zn levels in biopsy-proven NAFLD patients.
Method: A total of 179 NAFLD patients who underwent liver biopsy were enrolled. Firstly, we identified laboratory markers and pathological findings associated with serum Zn levels. Secondary, we assessed the factors, including serum Zn levels, associated with the incidence of hepatocellular carcinoma (HCC) and extra-hepatic malignancies.
Results: Zn level significantly decreased along with progression of hepatic fibrosis ($p = 0.012$), but there were no significant differences among inflammatory grades. Zn levels were most strongly correlated with albumin levels ($r = 0.432$, $P < 0.001$). In addition, Zn levels were significantly correlated with homeostasis model assessment of insulin resistance (HOMA-IR) ($r = -0.300$, $P < 0.001$) and branched chain amino acid/tyrosine molar ratio (BTR) ($r = 0.337$, $P < 0.001$). On the other hand, HCC and extra-hepatic malignancies developed in 7 (3.9%) and 10 (5.6%) during follow-up period (median 7.9 years), respectively. When Zn deficiency was defined as serum level < 70 μg/dL, 39 of our patients (21.8%) were classified as Zn-deficient. Patients with Zn deficiency had significantly higher incidental rate of extra-hepatic malignancies ($p = 0.026$). The majority of extrahepatic malignancies in this patients' population were breast cancer and digestive malignancies. Conversely, serum Zn levels were not able to predict hepatocarcinogenesis ($p = 0.141$). Multiple logistic regression analyses revealed the following risk factors associated with the incidence of extra-hepatic malignancies: serum Zn level < 70 μg/dL (hazard ratio [HR] 3.504, 95% confidence interval [CI] 1.010-12.157, $P = 0.048$) and liver inflammation (A2-3) (HR 3.445, 95% CI 0.886-13.395, $P = 0.074$).
Conclusion: The progression of liver fibrosis was associated with lower serum Zn levels, and serum Zn levels were correlated with nutrition markers and insulin resistance in biopsy-proven NAFLD patients. Importantly, Zn deficiency was an independent risk factor of extra-hepatic carcinogenesis in NAFLD.

THU-315

Non-cirrhotic patients with non-alcoholic fatty liver disease have impaired quality of life: Independently predicted by body mass index, diabetes and liver stiffness

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Background and aims: Patient related outcome measures are important determinants of cost-effectiveness of therapies. Quality of life is significantly impaired in patients with non-alcoholic fatty liver disease (NAFLD) and cirrhosis. However, the extent to which it is impaired before the development of cirrhosis and the factors that contribute to impairment have been less well studied.
Method: In a prospective study, set in a secondary care specialist clinic, we assessed quality of life (QOL) using the SF-36v2 questionnaire in 142 patients with NAFLD (n = 50 female, n = 92 male) and 9 healthy controls diagnosed by ultrasound and fibroscan. In a subset of patients, NASH was diagnosed histologically and staged according to the NASH CRN. Patients with cirrhosis were excluded from this study. QOL data was analysed with stepwise multiple regression models to identify factors independently affecting QOL scales.
Results: Non-cirrhotic patients with NAFLD had significantly reduced physical health QOL (mean 35.72) compared to healthy controls (mean 47.21, p = 0.016) and the normative UK population (n = 7984, mean 50, p < 0.001) (1). Patients with liver stiffness >7.9kPa (n = 53) had reduced physical health QOL compared to those with liver stiffness ≤ 7.9kPa (n = 80) (mean rank 56.3 vs 74.1, p = 0.009). However, we did not see differences in QOL domains when comparing results from patients with biopsy-proven NASH (n = 49) with patients who did not have NASH on biopsy (n = 18) or those whose non-invasive scores were too mild to warrant biopsy (n = 75). Moreover, there was no significant difference in QOL scales when comparing patients with biopsy-proven F3 or F2 fibrosis (n = 31) with those with F0 or F1 fibrosis (n = 36) or when comparing F3 fibrosis (n = 20) to F0, F1 and F2 fibrosis (n = 47). The factors independently associated with impaired physical health-related QOL in non-cirrhotic patients with NAFLD were age (B = – 6.082, p < 0.001) and high BMI (B = – 3.848, p = 0.008), whereas type 2 diabetes mellitus (B = – 9.356, p = 0.019), fibroscan score >7.9kPa (B = – 9.635, p = 0.013) and female gender (B = –9.813, p = 0.014) were associated with reduced general health QOL.
Conclusion: QOL is an important patient-related outcome measure in liver disease. Even before the onset of cirrhosis, NAFLD significantly reduces QOL. Understanding the independent predictors of impaired QOL may target existing and future therapies to those who are most likely to benefit.

1. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. 1999;53 (1):46-50.

THU-316

Cognitive impairment or hepatic encephalopathy? A prospective cross-sectional study in patients with non-alcoholic fatty liver disease

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Background and aims: Recently, we are facing major changes in the landscape of liver cirrhosis. HCV with predominant liver damage is replaced by non-alcoholic fatty liver disease (NAFLD) with inherent multi-organ involvement due to metabolic syndrome (MS). We hypothesized that diagnosing hepatic encephalopathy (HE), may be challenging in the presence of cognitive dysfunction secondary to increasing age, diabetes mellitus (DM), hypertension (HTN), obstructive sleep apnea (OSA) and other MS associated conditions.
Method: a prospective cross-sectional study. Patients with NAFLD diagnosed by US were asked to report 5 HE related complaints (confusion, sleep-wake disturbance, day time somnolence, lack of concentration or energy) and underwent laboratory tests, transient elastography and HE testing by pen-and-paper tests, Stroop test, inhibitory control test and critical flicker frequency. Patients with a history of overt HE were excluded.
Results: Sixty eight patients were included. Mean age was 54.3 ± 13.6, 38 (56%) were female. Advanced fibrosis level (F3-F4) was found in 28 (41%) patients. MS, HTN, DM and diabetic microvascular complications were found in 49 (72.1%), 32 (47%), 26 (38%) and 8 (12%) patients, respectively. Six (9%) patients had OSA.
Diagnosis of MHE was considered when at least two HE tests were abnormal-found in 12 (17.6%) patients. In addition to fibrosis level, having HTN, duration of DM and age were associated with abnormal MHE tests (Table). In multivariate analysis, only age was independently associated with 2 abnormal HE tests.
Two thirds of patients had at least one HE complaint, while 33 (49%) had 2, and 19 (28%) had 3 or more complaints. Having 3 and more HE complaints was not associated with parameters of severity of liver disease: advanced fibrosis, steatosis, ALT level or platelet count. However, hypercholesterolemia and diabetic microvascular complications were predictive of having 3 HE complaints (Table). Frequency of OSA was higher in patients with 3 and more HE complaints:4 (21%) vs 2 (4%) p = 0.059.

Table:

	Logistic regression OR [95% CI]	Adjusted for age
Predictors of 2 MHE tests		
Fibrosis level	2.0 [1.2-3.5]	NS
HTN	7.7 [1.5-38.6]	NS
Duration of DM	1.17 [1.06-1.3]	NS
Age (per year)	1.15 [1.04-1.26]	1.2 [1.05-1.4]
Predictors for having 3 HE complaints		
F3-4	1.16 [0.39-3.45]	
Steatosis	0.4 [0.1-1.7]	
ALT	1 [0.98-1.02]	
Platelets	1 [0.99-1.01]	
Hypercholesterolemia	3.6 [1.1-12.7]	
Diabetic microvascular complications	5.5 [1.3-25.8]	

Having 2 abnormal MHE tests was more common in patients with 3 HE complaints compared to those with less (37% and 10% p = 0.028), but still, 12/19 patients with HE complaints did not have 2 abnormal MHE tests.
Conclusion: In patients with NAFLD clinical symptoms of HE and even specialized tests of MHE may be less specific due to related comorbidities affecting cognitive status and alertness. Further studies for optimal MHE tests in NAFLD are needed.

THU-317

The prescribing patterns and use of statins in patients with non-alcoholic fatty liver disease

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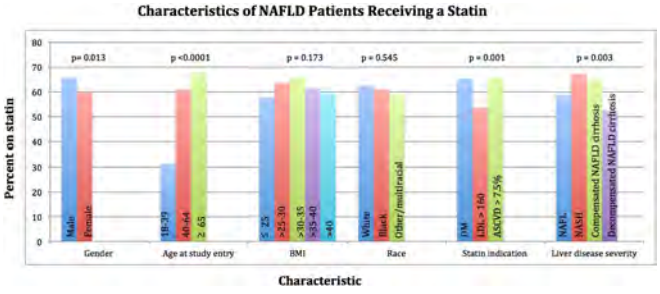
Background and aims: NAFLD, often encountered in the background of metabolic syndrome, represents a spectrum of progressive liver disease. Among NAFLD patients with metabolic syndrome, the most common cause of death is arteriosclerotic cardiovascular disease (ASCVD). Although statins are considered safe in liver disease, and even potentially beneficial in patients with cirrhosis, many patients are not prescribed a statin or other lipid-lowering agent despite one being indicated because of concerns about hepatic enzyme elevations. We aim to determine whether statins are underprescribed in NAFLD patients with indications for lipid-lowering agents, and whether this effect is magnified in patients with cirrhosis.
Method: TARGET-NASH, a longitudinal observational study of participants followed at 55 sites (41 academic/14 community) in the US, includes patients across the entire spectrum of NAFLD as defined by pragmatic case definitions. Data from medical records are centrally abstracted and monitored for completeness and accuracy. A cross-sectional analysis was performed to measure indications and prescriptions for lipid-lowering agents in patients with NASH, NAFL, compensated NAFLD cirrhosis and decompensated NAFLD cirrhosis.
Results: A total of 3, 284 adult participants (1279 NAFLD cirrhosis, 1317 NASH, and 688 NAFL) were studied. 1923 (58.6%) had one or more of the following indications for lipid lowering therapy: diabetes, LDL ≥ 160, or ASCVD score ≥ 7.5%. 62.1% of patients with an indication were prescribed a lipid lowering medication (58.6% with NAFL, 67.1% with NASH, 64.9% with compensated cirrhosis and 52.5% with decompensated cirrhosis). Men (65.6% vs 59.9%), patients ≥ 40 (64.0% vs 31.3%), those with any CV disease history (74.4% vs. 59.3%) and those with a CV event (79.7% vs. 59.4%) were more likely to be prescribed a statin. Similar proportions of patients managed in academic and community centers, 62.4% and 61.5%, of those with indications were prescribed a statin. Statins were used in 65% of those prescribed lipid lowering therapy.



Conclusion: Statins and other lipid-lowering agents are underprescribed in adult patients with NAFLD despite clear indications, particularly those with decompensated cirrhosis. Underprescribing is more common among women and younger patients. A shift in treatment paradigm is essential to ensure optimal use of statins and other lipid lowering agents in patients with NAFLD to reduce cardiovascular outcomes.

THU-318

Elevated urinary bisphenol A levels are associated with non-alcoholic fatty liver disease among adults in the United States

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Background and aims: The relationship between bisphenol A (BPA) and non-alcoholic fatty liver disease (NAFLD) is undefined. We studied the impact of BPA on NAFLD.
Method: We performed a cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2005-2014 among adults in the United States (US). NAFLD was diagnosed using the hepatic steatosis index (HSI) and the US fatty liver index (USFLI) in the absence of other causes of chronic liver diseases. The first sample using HSI consisted of 7, 605 adults. The second sample using USFLI consisted of 3, 631 participants with availability of fasting data.
Results: Of the first 7, 605 participants (mean age 47 years, 48.4% male), the prevalence of NAFLD and abnormally elevated alanine aminotransferase (ALT) levels was correlated with urinary BPA levels ($p < 0.05$). Compared to the reference group with lowest quartile of urinary BPA levels, those with 3rd quartile and 4th quartile were 81% and 53% more likely to develop NAFLD defined by HSI. In a multivariate model, the ORs for NAFLD in 3rd quartile and 4th quartile were 1.69 (95% CI 1.39-2.04) and 1.44 (95% CI 1.19-1.76), respectively (*P* for trend < 0.001). In the second sample using USFLI, high BPA levels (4th quartile) remained an independent predictor of NAFLD (OR 1.44 95% CI 1.05-1.98, *P* for trend = 0.012).
Conclusion: High levels of urinary BPA were associated with NAFLD in a nationally representative sample of adults in the US. The pathophysiology remains unclear and warrants further investigation.

THU-319

Association between body size-metabolic phenotype and non-alcoholic steatohepatitis and significant fibrosis

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Background and aims: Body size-metabolic phenotype may help predict whether or not individuals with non-alcoholic fatty liver disease (NAFLD) develop advanced liver disease. We studied the association of body size-metabolic phenotype and non-alcoholic steatohepatitis (NASH) and significant fibrosis.
Method: Our cross-sectional study included 559 subjects (mean age of 53 years; women 51%) with biopsy-proven NAFLD. Clinical, genetic, and histological characteristic features of NAFLD were evaluated. The metabolically unhealthy phenotype was defined by the presence of two or more metabolic components, while body size was categorized based on body mass index: obese (≥ 25 kg/m^2) or non-obese (<25 kg/m^2). Body sizemetabolic phenotypes were divided into four study groups: (1) metabolically-healthy/non-obese (MHNO), (2) metabolically-unhealthy/nonobese (MUNO), (3) metabolically-healthy/obese (MHO), and (4) metabolically-unhealthy/obese (MUO).
Results: MHO and MUNO groups demonstrated comparable levels of insulin resistance, adipose tissue insulin resistance indexes, and visceral adipose tissue (VAT) areas. The VAT area was significantly higher in the MUO group versus MHO group. However, the VAT to subcutaneous adipose tissue (SAT) ratio was highest in the MUNO group. There was no difference in histology between the MUNO, MHO, and MUO groups. Multivariate analyses adjusted for age, sex, smoking status, PNPLA3, TM6SF2, and VAT/SAT areas demonstrated an independent and dose-dependent relationship between the body size-metabolic phenotype and NASH or significant fibrosis. After excluding MHNO, re-analysis did not demonstrate a significant difference between the MHO, MUO, and MUNO groups in terms of increased risk for NASH and significant fibrosis.

Conclusion: The MUNO group displayed similar degree of hepatic histological severity compared to their MHO counterparts. Metabolic milieu beyond obesity may play a pathogenic role in MUNO individuals who develop NASH with significant hepatic fibrosis.

THU-320

Evaluation of atherosclerosis and coronary artery stenosis of non-alcoholic fatty liver disease

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Background and aims: Cardiovascular disease (CVD) is the most common cause of death of non-alcoholic fatty liver disease (NAFLD) patients. CVD surveillance should be important in the management of NAFLD whereas it has not been well established. Moreover, association between the pathogenesis of CVD and NAFLD remains unclear. We evaluated carotid atherosclerosis and coronary artery stenosis (CAS) and tested utility of carotid ultrasonography for the surveillance of CAS in NAFLD.
Method: A total of 100 patients (56 females and 44males; median age, 60 years old: median body mass index, 28.2 kg/m^2) with liver biopsy-proven NAFLD were enrolled in this study. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were examined with FibroScan® in all patients. Maximum intima-media thickness including plaque (max IMT) was measured using ultrasonography. Coronary CT angiography was performed to detect CAS if max IMT >1.0 mm. Association between pathogenesis of NAFLD and atherosclerosis/CAS was evaluated.
Results: Median of max IMT was 1.3 mm, and 60 patients showed max IMT >1.0 mm and 39 patients showed max IMT >1.5 mm. Max IMT significantly correlated with age ($r = 0.39$, $p < 0.001$). Max IMT of patients with advanced liver fibrosis (Kleiner fibrosis stage ≥ 2) was thicker than those with liver fibrosis ≤ 1 (1.62 mm vs. 1.13 mm, $p < 0.05$). Multivariate analysis indicated that age, sex and LSM were significant factors associated with max IMT. In the patients with max IMT ≥ 1.0 mm, 38.9% patients showed significant (75% stenosis or severe) CAS in coronary CT angiography. All patients with significant CAS showed max IMT ≥ 1.5 mm, and median max IMT of the patients with significant CAS was thicker than those without significant CAS (2.16 mm vs. 1.79 mm, $p < 0.05$) and liver fibrosis tended to be advanced in the patients with CAS (LSM, 16.3 kPa vs. 10.5 kPa: Fibrosis stage ≥ 2, 22.7% vs. 8.3%) whereas there were no differences in CAP (265 dB/m vs. 261 dB/m). In the multivariate analysis, max IMT was risk of significant CAS independent to diabetes.
Conclusion: Prevalence of advanced carotid atherosclerosis is surprisingly high and carotid atherosclerosis and CAS relate to liver fibrosis in NAFLD. Surveillance of NAFLD with advanced liver fibrosis is important and carotid ultrasound could be useful to identify the patients with high risk of CAS and CVD.

THU-321

Fluorodeoxyglucose perfusion and uptake in abdominal organs is associated with hepatic disease state in patients with non-alcoholic fatty liver disease

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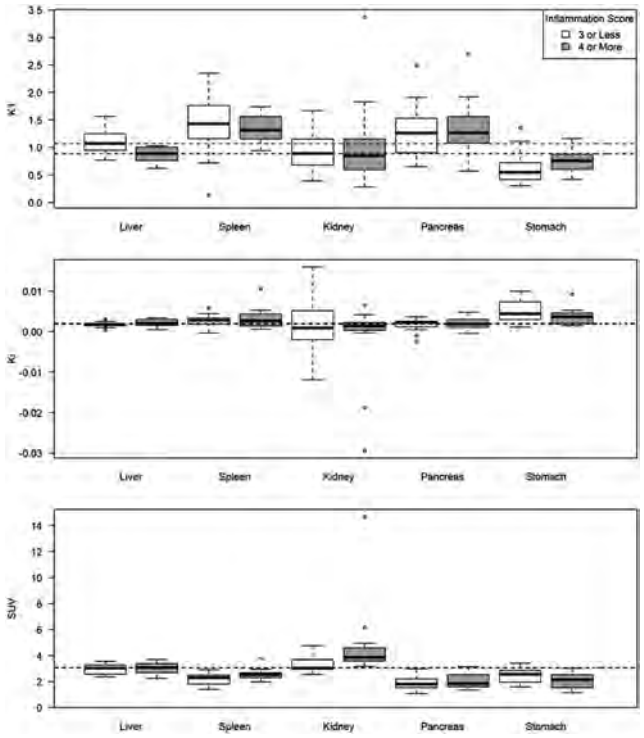
Background and aims: The effect of hepatic steatosis, inflammation and fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) on extra-hepatic pathologies is appreciated yet poorly understood. Characterizing the metabolic interactions between liver and related organs in patients with NAFLD may define risk factors for liver inflammation and fibrosis. The aim of this study is to explore the relationship between glucose uptake and metabolic activity in the liver and other abdominal organs as they relate to the state of NAFLD, utilizing dynamic ^{18}F-fluorodeoxyglucose (FDG)-PET.
Method: Patients with biopsy-proven NAFLD underwent FDG-PET in a fasting state. Imaging parameters were measured using established 3-compartment model of hepatic FDG kinetics. Due to limited field of view of current PET scanners, we were able to extract kinetic data from surrounding abdominal organs- kidney, stomach, pancreas, and spleen. The FDG parameters were compared using linear mixed effect models. These were also compared with histologic parameters within and between organs. Spearman correlations amongst parameters were calculated.
Results: Of the 30 patients, 67% were female, mean age 55 years, BMI 32.9 kg/m^2, Hgb A1c 5.8% and pre-PET blood glucose 113 mg/dL. Eight patients had advanced fibrosis (fibrosis score ≥ 3) and 67% having steatohepatitis (NAFLD activity score >4). Compared to the liver, the fold change of FDG influx rate (K_i) was relatively similar across the organs other than stomach (0.0025, $p = 0.008$) and kidney (−0.0024, $p = 0.009$). The surrogate for perfusion, characterized by rate of FDG uptake to the tissue from blood, K_1 was significantly higher in the spleen ($p = 0.022$) and pancreas ($p = 0.042$) but lower in the stomach ($p < 0.001$). Metabolic activity, characterized by standardized uptake value (SUV), was lower in all organs except the kidney, when compared to the liver. SUV of the kidney and spleen showed weak positive correlation with liver inflammation ($r = 0.41$, $p = 0.038$) and NAS score ($r = 0.4$, $p = 0.036$), respectively. Patients with high inflammation had a greater difference in SUV between the liver and kidney than those with low inflammation ($p < 0.001$; Fig 1).



Conclusion: Here we present FDG kinetic data of extra-hepatic abdominal organs in relation to NAFLD disease state. Although our data is limited by its small size and lack of comparison to healthy subjects, it shows that FDG uptake and perfusion rates are differential in the abdominal organs, which may be driven by hepatic inflammation and fibrosis.

THU-322

Statin use on development and progression of non-alcoholic fatty liver disease: A nationwide cohort study

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Background and aims: Use of statins in non-alcoholic fatty liver disease (NAFLD) subjects may reduce cardiovascular morbidity, whereas evidences lack to show benefits of statins on development and progression of NAFLD. We aimed to investigate role of statins on development of significant liver fibrosis in NAFLD subjects and on occurrence of NAFLD among non-NAFLD population.
Method: From the nationwide cohort, this study included 176, 387 subjects that entered the National Health Insurance Service Physical Examination Cohort of the Republic of Korea in 2006 and followed up for 10 years. NAFLD was diagnosed by calculating hepatic steatosis index (HIS), and significant liver fibrosis was evaluated using BARD score.
Results: The subjects with HSI >36.0 and without previous statin use were selected as NAFLD cohort (n = 22, 337). The subjects that were exposed to statins during the 10-year follow-up (n = 6, 817) were age and sex matched with those that never had statin treatment (n = 15, 520). The NAFLD subjects that underwent statin therapy had significantly increased risk of advanced liver fibrosis (AHR [adjusted hazard ratio] 1.36; 95% CI [confidence interval] 1.18-1.58) independent of accompanying diabetes mellitus (DM) (AHR 1.40; 95% CI 1.12-1.74 with DM) (AHR 1.32; 95% CI 1.08-1.611 without DM). The subjects with HSI < 30.0 were included in non-NAFLD cohort (n = 41, 241). Among them, 5, 053 subjects eventually experienced statin treatment, and 36, 188 subjects never had statin therapy. Non-NAFLD subjects that experienced statin treatment had increased risk of developing NAFLD (AHR 1.36; 95% CI 1.18-1.58).
Conclusion: This nationwide population based study suggests that beneficial effects cannot be expected in NAFLD subjects regarding progression of liver fibrosis with statins. For those without evident NAFLD, correcting dyslipidemia with statin would not prevent NAFLD development.

THU-323

Impact of genetic polymorphisms associated with NAFLD on hepatic and vascular complications in diabetes

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Background and aims: Type 2 Diabetes (T2DM) and NAFLD share common metabolic risk factors. NAFLD is influenced by genetic polymorphisms, namely PNPLA3 and MBOAT7. The impact of these polymorphisms in the diabetic population is not fully explored, therefore we aimed at investigating their role with regard to liver and vascular complications in a T2DM multi-centric cohort.
Method: Three-hundred nineteen patients attending the diabetes clinic were enrolled. Genotyping for rs738409 C > G (I148M in PNPLA3) and rs641738 C > T (TMC4 in MBOAT7) polymorphisms was performed in all patients, as well as FibroScan® using liver stiffness measurement (LSM) ≥ 7.0 for M probe and 5.7 kPa for XL to define fibrosis ≥ 2, and ultrasound examination to assess steatosis.
Results: Mean age was 69 ± 9 years and 49% patients were males. Steatosis was present in 89%, hypertension in 78%, dyslipidemia in 84% (78% of whom on statins), obesity in 32%. The 64% of the cohort was on antidiabetic therapy, while the 36% on diet only (mean HbA1c 7 ± 1.1%); 85% of patients presented at least one vascular complication, 80% a macrovascular one (66% carotid plaques; 71% intima-media thickness (IMT) >0.9 mm; 18% coronary artery disease) and 29% a microvascular one (16% nephropathy; 14% microalbuminuria; 11% retinopathy; 3% neuropathy); LSM ≥ 7/5.7 kPa was present in 47 (15%) patients, PNPLA3 mutated allele (G) in 47% and 7% in heterozygous and homozygous state and MBOAT7 mutated allele (T) in 46% and 18% in heterozygous and homozygous state. Prevalence of at least one microvascular complication and of LSM ≥ 7/5.7 kPa (M/XL probe) was significantly higher in patients homozygous for PNPLA 3 G allele, and this association remained in multivariate analysis adjusted for age, sex, glycaemic control, duration of T2DM, smoke, hypertension, BMI, statins, ACE/ARBs and the other polymorphism studied (OR 3.6; 95% CI 1.2-10.4; p = 0.02; OR 3.7; 95% CI 1.4-9.7; p = 0.008); conversely prevalence of at least one macrovascular complications was significantly lower in patients homozygous for MBOAT7 T allele and this association remained in multivariate analysis adjusted for the same variables (OR 0.4; 95% CI 0.2-0.9; p = 0.03).
Conclusion: NAFLD genetic polymorphisms have an impact not only on liver fibrosis but also on vascular complications in T2DM.

THU-324

Non-alcoholic fatty liver disease causes dissociated changes in metabolic liver functions

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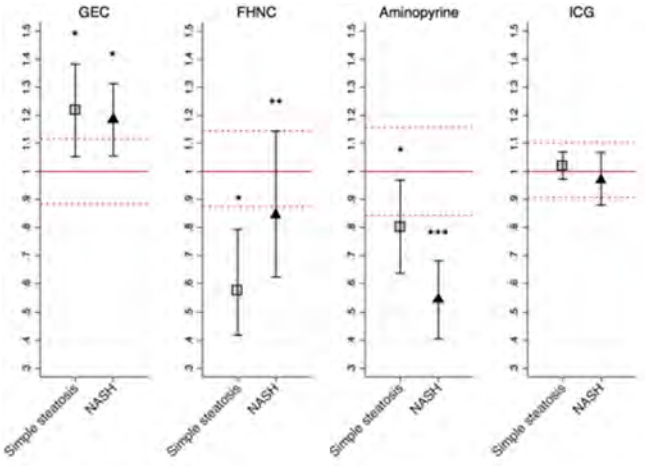
Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a major health concern affecting 25% of the world's population. It is generally held that a fatty liver does not influence liver function, but quantitative measurements of metabolic liver functions have not been systematically performed. We aimed to study selected hepatocellular metabolic functions in patients with different stages of NAFLD.
Method: Twenty-five non-diabetic, biopsy-proven NAFLD patients [12 with simple steatosis and 13 with non-alcoholic steatohepatitis (NASH)] and ten healthy controls were included in a cross-sectional study. Hepatocyte cytosolic function was assessed by the galactose elimination capacity (GEC), mitochondrial-cytosolic metabolic capacity by the functional hepatic nitrogen clearance (FHNC), microsomal function by the aminopyrine breath test, and excretory liver function by the indocyanine green (ICG) elimination test.
Results: GEC was 20% higher in NAFLD than in controls [3.15 mmol/min (2.9-3.41) vs. 2.62 (2.32-2.93); p = 0.02]. FHNC was 30% lower in NAFLD [23.3 l/h (18.7-28.9) vs. 33.1 (28.9-37.9); p = 0.04], more so in simple steatosis [19.1 l/h (13.9-26.2); p = 0.003] and non-significantly in NASH [27.9 l/h (20.6-37.8); p = 0.19]. Aminopyrine metabolism measured as the 2-hour cumulative percentage dose recovery was 25% lower in simple steatosis [8.9% (7.0-10.7)] and 50% lower in

NASH [6.0% (4.5-7.5)] than in controls [11.9% (9.3-12.8)] (p < 0.001). ICG elimination was intact.



Metabolic liver functions – normalised to healthy controls
Means with their 95% confidence interval shown.
■: Simple steatosis, ▲: NASH, red lines: healthy controls.
*: significantly different from controls, **: significantly different from simple steatosis,
***: significantly different from controls and simple steatosis.

Conclusion: The hepatocellular metabolic functions were altered in a manner that was dissociated both by different effects on different liver functions and by different effects of different stages of NAFLD. Our results revealed a reduced mitochondrial and microsomal function and coexisting intact cytosolic and excretory function. This is compatible with the present pathophysiological understanding of the disease that some sub-hepatocellular compartments are more damage-prone to NAFLD than others. Our findings emphasise that even simple steatosis and early NASH are indeed hepatic diseases with organ function consequences, and do not simply represent innocuous fat accumulation in hepatocytes.

THU-325

Regional liver function investigated by galactose positron emission tomography is reduced in patients with non-alcoholic steatohepatitis

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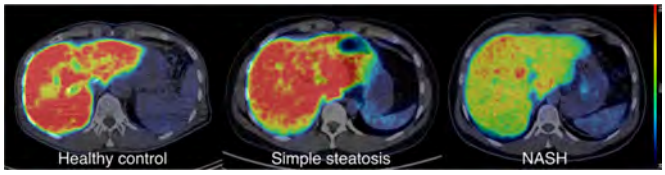
Background and aims: Little is known about how the structural changes of non-alcoholic fatty liver disease (NAFLD) affect liver function. We investigated in vivo effects of hepatic fat fraction and morphological changes on regional (2-[^{18}F]fluoro-2-deoxy-D-galactose (^{18}F-FDGal) positron emission tomography (PET)) and global (galactose elimination capacity (GEC)) metabolic liver function in patients with non-alcoholic steatohepatitis (NASH), simple steatosis, and healthy controls.
Method: Twenty-five biopsy-proven, non-diabetic NAFLD patients (13 NASH, 12 simple steatosis) underwent ^{18}F-FDGal PET, GEC, and magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF). Nine healthy controls were included.
Results: Mean hepatic ^{18}F-FDGal metabolism expressed as standardized uptake value (SUV), was 13.5 (95% CI, 12.1-14.9) in NASH, 16.0 (14.9-17.1) in simple steatosis, and 16.9 (15.8-17.9) in controls (p < 0.001) (Figure). Each 5 percentage point increment in liver fat fraction was associated with a 0.7 reduction in SUV (0.3-1.0; p < 0.001). The reduction of SUV in NASH was not attributable to fat alone as mean liver fat fraction was the same in NASH and simple steatosis (~30%; p = 0.5) and results remained unchanged after correction for the effect of fat (p = 0.008). The mean fat-free liver volume was larger in NASH than in simple steatosis and controls (p = 0.15) and exhibited a high functional heterogeneity with the coefficient of variation for SUV being 19% higher than in simple steatosis (p = 0.05) and 35% higher than in controls (p = 0.004), with no significant difference between simple steatosis and controls (p = 0.13) (Figure). GEC was unaffected by NAFLD (p = 0.9) while GEC per fat-free liver volume was reduced in NASH to 1.71 mmol/min/ml (1.58-1.84) vs. 1.95 (1.82-2.09) in simple steatosis and 1.91 (1.67-2.14) in controls (p = 0.05).



Conclusion: In NASH, while total capacity for galactose metabolism was maintained by an increased fat-free liver volume, regional metabolic capacity was markedly reduced with high functional heterogeneity that was not observed in the simple steatosis patients or the healthy controls. This was due not only to fat infiltration but also to other disease specific features of NASH such as ballooning and fibrosis. Thus, NASH, as opposed to simple steatosis, disturbs the uniform metabolic function of the liver.

THU-326

Relative fat mass: A new definition of obesity and NAFLD

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of adiposopathy. Recently, a new score was developed to estimate body fat percentage (relative fat mass, RFM). We aimed to evaluate the performance of RFM, as compared to other anthropometric measurements, in predicting the presence and severity of NAFLD.
Method: RFM, body mass index (BMI) and other anthropometric measurements were evaluated in two cohort of subjects: a cohort from a Portuguese prospective epidemiological study (e_Cor), and morbidly obese patients with biopsy-proven NAFLD. Associations were studied between RFM and BMI, and liver disease assessed by non-invasive tools in the first cohort and by liver histology in morbidly obese.
Results: In the general population cohort, 744 subjects (48% male) were enrolled. BMI-defined obesity was present in 23% and RFM-defined obesity in 86%. Insulin resistance (IR) associated with BMI-defined obesity (OR 4.37 [2.16-8.84]) and weight (OR 1.05 [1.02-1.08]) in men, and waist circumference (WC) (OR 1.07 [1.03-1.11]) in women. Dyslipidemia and hypertension associated with RFM-defined obesity in men (OR 2.96 [1.36-6.47] and OR 5.37 [1.31-22.06], respectively). Ultrasound-diagnosed NAFLD in 33%, associated with weight in men (OR 1.03 [1.003-1.06] and WC in women (OR 1.06 [1.02-1.10]). ALT elevation associated with weight in men (OR 1.04 [1.02-1.07]) and NAFLD Fibrosis Score-estimated advanced fibrosis with BMI-defined obesity in women (OR 42.43 [3.61-498.13]). In the

morbidly obese cohort, 152 subjects were enrolled, of whom 84% were female, 29% had steatohepatitis and 9.4% advanced fibrosis. Adiponectin associated inversely and leptin positively with RFM, in men. The severity of steatosis increased linearly with BMI and WC in women. Higher BMI associated with steatohepatitis in women and advanced fibrosis in men.
Conclusion: RFM-defined obesity better predicted dyslipidemia and hypertension (though not IR) and adipokines imbalance, however, it did not add value to BMI-defined obesity, in predicting NAFLD or liver injury.

THU-327
Lifestyle modification leads to a significant decline in aminotrasnsferase activity even without weight reduction in children with non-alcoholic fatty liver disease
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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is currently one of the most common health concerns due to a sedentary lifestyle and improper eating habits. Children develop fatty liver along with insulin resistance and metabolic syndrome.
Method: The study group consisted of 35 boys and 15 girls, age range 3-16 years (mean 10, 51 ± 3, 18 years), with the diagnosed non-alcoholic fatty liver disease. Differential diagnosis of the liver steatosis was performed to exclude underlying liver diseases. All patients underwent weight and height measurements, physical examination and blood collection for hematologic and biochemical parameters. APRI and PNFS were calculated basing on established formulas. Patients received lifestyle modification advice regarding diet and physical exercises. All children were followed during control visits for 2, 45 ± 1, 45 years. End point parameters were weight reduction and a decline in aminotransferase activity.
Results: 40/50 children were overweight, 7 had normal BMI. Weight loss was obtained in 22/50 children; 28 children gained weight after the follow-up period. ALT decline was observed in 36/50 children. Children with ALT reduction had lower BMI at the end of follow-up period (27, 29 ± 4, 84 vs 31, 01 ± 4, 93 kg/m$^{2;}$ p = 0, 035). Moreover, higher initial APRI value (0, 45 ± 0, 28 vs 0, 27 ± 0, 15; p = 0, 003) and more significant reduction of this parameter (− 0, 15 ± 0, 24 vs 0, 07 ± 0, 12) was observed in this group of patients. Decline in ALT activity was negatively related to PNFS (r = – 0, 61; p < 0, 05), APRI (r = – 0, 45; p < 0, 05), GTP activity (r = – 0, 41; p < 0, 05).
Conclusion: Although the decline in aminotransferase activity is related to lower BMI, it can be obtained due to lifestyle modification even without weight reduction in children with NAFLD. Higher initial markers of liver injury do not exclude an improvement in liver parameters after lifestyle modification.

THU-328
The prevalence of NAFLD in morbidly obese subjects revisited
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Background and aims: The global obesity epidemic is a driver for obesity-related complications such as non-alcoholic fatty liver disease (NAFLD). The active "hepatitic" subtype of NAFLD is non-alcoholic steatohepatitis (NASH) and potentially leads to liver fibrosis and cirrhosis. It is estimated that the prevalence of NAFLD in the general population is approximately 25% but increases to over 90% in morbidly obese subjects. It is important to validate the alarmingly high prevalence of NAFLD, including the occurrence of NASH, since these numbers are based on studies that differ in set-up (i.e. diagnostic tool, histological staging system). The aim of this study was to determine the prevalence of NAFLD in a cohort of morbidly obese subjects scheduled for bariatric surgery.
Method: In this prospective cohort study, 149 morbidly obese subjects scheduled for bariatric surgery were included. A standard metabolic work-up was performed and body composition was assessed using bioelectrical impedance analysis. Liver biopsies were obtained perioperatively and were evaluated by a panel of liver pathologists. Histological diagnosis was based on Steatosis Activity Fibrosis (SAF) score. NAFLD was categorized into simple steatosis when steatosis was present in >5% of hepatocytes without ballooning or NASH if ballooning and inflammation were both present in the biopsy.
Results: No NALFD was seen in 43.6%, simple steatosis in 47.7% and NASH in 8.7% of subjects. Subjects with NAFLD were older than subjects without NAFLD (48.7 ± 10.3 y. vs 42.7 ± 10.8 y; p < 0.001), had higher prevalence of hypertension (38.0% vs 18.5%; p = .012), type 2 diabetes (32.4% vs 10.8%; p = .002) and dyslipidemia (29.6% vs 12.3%; p = .014. Median (IQ range) BMI did not differ significantly: 38.0 (35.2-40.5) vs 38.4 (35.1-40.0) vs 38.5 (37.1-40.9) in subjects with healthy liver, NAFLD and NASH, respectively. Subjects with NAFLD had a lower percentage of total body fat (44.7 ± 5.5% vs 47.8 ± 4.8%; p = .005), and a higher fat-free mass (55.9 ± 5.5% vs 52.6 ± 5.4%; p = .002), than patients with a healthy liver. Of interest, preoperative weight loss was equal in subjects with healthy liver, NAFLD and NASH.
Conclusion: In sharp contrast to previous studies and to the general dogma that the prevalence of respectively NAFLD and NASH is 90% and 20% in subjects with (morbid) obesity, data from our large prospective cohort indicates that this prevalence is much lower in Dutch subjects.

THU-329
Opioid use is common in patients with non-alcoholic fatty liver disease and associated with severity of liver disease, hepatic encephalopathy and psychiatric comorbidities
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Background and aims: Pain control is difficult in patients with non-alcoholic fatty liver disease (NAFLD) and particularly those with cirrhosis. Painful comorbidities are common in NAFLD and are often treated with opioids. We aimed to determine the prevalence of opioid use and associated characteristics in a real-world cohort of NAFLD patients.
Methods: TARGET-NASH, a longitudinal observational study at 55 sites in the United States, includes patients with NAFLD defined by pragmatic case definitions. Opioid use was defined as opioid use in the year prior to cohort enrollment. We compared opioid users and non-users by demographic factors, comorbidities and liver disease severity using univariate analyses and developed a stepwise logistic regression model of opioid use.
Results: The cohort included 3284 patients with NAFLD, including 1317 with non-alcoholic steatohepatitis (NASH) and 1279 with NAFLD cirrhosis. Opioid use was reported in 17.8% and was more common with females (20.2% vs 14.3%) and patients with advanced liver disease (10.3% NAFL, 17.5% NASH, 22.1% NAFLD cirrhosis), BMI ≥ 32 kg/m^2 (22.2% vs 13.0%), diabetes (21.9% vs 13.7%), depression (30.2% vs 10.2%), rheumatologic disease (34.5% vs 16.6%),

osteoarthritis (33.3% vs 16.1%) and fibromyalgia (47.1% vs 16.0%) ($p < 0.001$ for all). Among patients with cirrhosis, MELD was similar among opioid recipients and non-recipients (mean 10.1 vs 9.8, $p = 0.370$). Opioid use was more common among those with hepatic encephalopathy (30.6% vs 19.8%, $p < 0.001$) and ascites (27.0% vs 20.0%, $p = 0.006$). In a logistic regression model, liver disease severity, BMI ≥ 32 kg/m^2, diabetes, osteoarthritis, depression and rheumatologic disease were associated with opioid use. Age and race were not associated with opioid use.

Patient Characteristic	Odds Ratio (95% CI)
NAFL vs NAFLD Cirrhosis	0.64 (0.47, 0.87)
NASH vs NAFLD Cirrhosis	0.89 (0.72, 1.10)
BMI (≥ 32 vs < 32 kg/m^2)*	1.49 (1.22, 1.82)
Diabetes	1.21 (0.99, 1.49)
Osteoarthritis	1.93 (1.47, 2.52)
Depression	3.05 (2.51, 3.71)
Rheumatologic disease	2.11 (1.54, 2.88)

*Median BMI for cohort = 32 kg/m^2

Conclusion: Nearly 1/5 of NAFLD patients reported opioid use and, in patients with cirrhosis, usage was twice that of those with NAFL. Opioid use was associated with depression and presence of hepatic encephalopathy. Given safety concerns of opioids, alternative pain control options and treatment of mental health comorbidities should be pursued for patients with NAFLD.

THU-330
Biochemical liver tests reflect the genetic risk for fatty liver disease with increasing body weight but not with alcohol consumption

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Background and aims: Liver tests are commonly used as surrogates for liver health. We aimed to examine whether liver biochemistries are related to the genetic risk for fatty liver, conferred by PNPLA3 and TM6SF2 risk alleles, in groups stratified by weight and alcohol consumption on the population level.
Method: PNPLA3 and TM6SF2 genotypes were determined in 1814 Caucasian subjects from a colonoscopy screening program. Clinical and biochemical data were obtained by standard methods. Subjects were grouped according to BMI, alcohol consumption and genotypes.
Results: Carriers of the PNPLA3 or the TM6SF2 risk allele had a higher risk for fatty liver compared to wild type (PNPLA3: OR 1.252, TM6SF2: OR 1.586). Adiposity amplified the effects of the PNPLA3 risk allele on serum GGT and ALT levels on the population level. Liver biochemistries were not related to the genetic risk for fatty liver in groups stratified by alcohol consumption. Body weight and HOMA-IR are the determinants of GGT ($R = 0.250$, $p < 0.0001$ for women, $R = 0.196$, $p < 0.001$ for men) and ALT ($R = 0.318$, $p < 0.001$ for women, $R = 0.255$, $p < 0.001$ for men) independent of the underlying genetic risk.
Conclusion: This study confirmed that carriers of the PNPLA3 variant and the TM6SF2 variant exhibit an increased risk for developing fatty liver. The commonly used liver biochemistries are related to the underlying genetic risk for hepatic steatosis in the obese study cohort. However, liver biochemistries do neither reflect the genetic risk in the lean nor overweight group, nor with alcohol consumption. BMI and HOMA-IR are the determinants of liver tests, however, this relationship is independent from the underlying genetic risk.

THU-331
Derivation and validation of a cardiovascular risk score for prediction of major acute cardiovascular events in non-alcoholic fatty liver disease: The importance of an elevated mean platelet volume

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Background and aims: Cardiovascular disease is a key cause of morbidity in non-alcoholic fatty liver disease (NAFLD) but appropriate means to predict major acute cardiovascular events (MACE) are lacking. We aimed to design a bespoke cardiovascular risk score in NAFLD.
Method: A retrospective derivation (2008-2016, 356 patients) and prospective validation (2016- 2017, 111 patients) NAFLD cohort study was performed. Clinical and biochemical data were recorded at enrolment and mean platelet volume (MPV), Qrisk2 and Framingham scores were recorded one year prior to MACE (Cardiovascular death, myocardial infarction, stroke, and transient ischaemic attack).
Results: The derivation and validation cohorts were well matched with MACE prevalence 12.6% and 12% respectively. On univariate analysis, age, diabetes, advanced fibrosis, collagen proportionate area >5%, MPV and liver stiffness were associated with MACE. After multivariate analysis, age, diabetes and MPV remained independently predictive. The "NAFLD CV-risk score" was generated using binary logistic regression: **0.06* (Age) + 1.2* (MPV) + 0.135* (DM[1])-19.46** [1] ***Diabetes mellitus: 0: absent; 1: present.***
(AUROC 0.882). A cut-off of < –3.2 gave a Sensitivity 98%, Specificity 63%, PPV 26%, NPV 99%. An MPV alone of >10.05 gave a sensitivity 97%, specificity 59%, PPV 24% and NPV 97% (AUROC 0.85). Validation cohort AUROCs were comparable at 0.75 (NAFLD CV-risk) and 0.72 (MPV). In the full cohort, the NAFLD CV-risk score and MPV outperformed both Qrisk2 and Framingham scores.

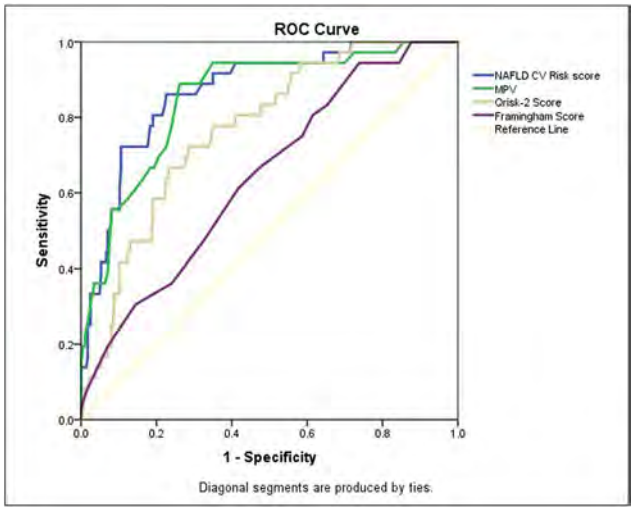

Figure: Diagnostic performance of NAFLD CV risk score and MPV vs traditional scores.

Conclusion: The NAFLD CV risk score and MPV accurately predict 1-year risk of MACE thereby allowing better identification of patients that require optimisation of their cardiovascular risk profile.

THU-332

Healthcare resource utilisation, demographics, and comorbidities by diagnosis codes and histological stage in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in a large integrated healthcare delivery system in the U.S

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Background and aims: The increasing prevalence of non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH) portends a large clinical and economic burden. However, there are limited data analysing Healthcare Resource Utilisation (HCRU) by diagnosis code and disease severity as determined by liver histopathology. Aims: 1) Describe prevalence, demographics, and comorbidities of NAFLD/NASH within Kaiser Permanente Southern California (KPSC); 2) Determine HCRU as quantified by stage of disease.

Methods: Retrospective cohort study of KPSC patients with diagnosis codes for NAFLD/NASH Jan 2006-Dec 2016. Exclusions: non-NAFLD/NASH liver disease diagnoses. Disease progression was determined by codes and procedures indicative of cirrhosis and portal hypertension. Comorbidities were determined by diagnosis codes and lab values. Liver biopsy reports were reviewed for steatosis, inflammation, ballooning and stage of fibrosis. HCRU was calculated over one-year post-index date including laboratory studies, office visits, hospitalisations, prescriptions dispensed, email and telephone encounters, and expressed as mean counts/person per/year. SAS EG 9.3 was used for statistical analyses.

Results: N = 103, 036 patients were included. Demographics, comorbidities, and HCRU are shown in the table. HCRU increases with progression of NAFLD/NASH to cirrhosis and decompensated cirrhosis with largest impact for hospitalisations (4-fold increase). Additionally, 505 biopsies were reviewed showing: Stage 0: 137 (27.1%), stage 1-2: 202 (40%), stage 3: 47 (9.3%), stage 4: 119 (23.6%). HCRU was significantly increased for labs, office visits, prescriptions, and telephone encounters in patients with cirrhosis vs non-cirrhosis.

	NAFLD, No cirrhosis	Compensated cirrhosis	Cirrhosis w/ portal hypertension	Decomp Cirrhosis
N	94716	1527	881	5912
Age	52.7	64.4	66.3	63.5
BMI >30 (%)	55.5	48.5	48.5	37.0
Diabetes (%)	33.6	47.9	56.3	39.3
Dyslipidaemia (%)	45.7	63.3	62.8	51.9
Hypertension (%)	70.6	78.0	70.1	79.1
Cardiovasc Dis (%)	41.0	57.8	59.6	47.4
Labs, mean (SD)	20.4 (35.6)	43.9 (63.7)	51.8 (72.2)	93.9 (153.1)
Office visits, mean (SD)	8.6 (9.4)	13.5 (12.5)	14.4 (12.0)	16.7 (15.0)
Hosp, mean (SD)	0.2 (0.5)	0.3 (0.8)	0.3 (0.8)	0.8 (1.5)
Rx, mean (SD)	7.3 (6.1)	10.9 (7.3)	11.0 (6.6)	13.5 (8.5)
Emails, mean (SD)	0.4 (1.2)	0.5 (1.4)	0.5 (1.3)	0.6 (1.7)
Tel enc, mean (SD)	1.3 (2, 4)	2.5 (3.6)	2.6 (3.6)	3.2 (4.8)

Conclusion: HCRU increases with progression to cirrhosis. This highlights the importance of identification and treatment at early stages of fibrosis to reduce the economical and clinical burden of this disease.

THU-333

The HSD17B13:TA (rs72613567) splice variant protects against severity of non-alcoholic fatty liver disease but not fibrosis

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Background and aims: Recently, the splice variant rs72613567:TA in the *17β-hydroxysteroid dehydrogenase 13* (*HSD17B13*) gene has been shown to be associated with a reduced risk for alcoholic liver disease, non-alcoholic liver disease (NAFLD) and of progression from steatosis to steatohepatitis. Aim of our study was to investigate the effects of rs72613567:TA carriage in a well-defined group of patients with biopsy-proven NAFLD.

Methods: Patients with NAFLD in a prospective registry study who underwent liver biopsy were genotyped for the *HSD17B13*- (minor allele:TA) and the *PNPLA3*-gene (minor allele: G). Furthermore, standard laboratory tests were measured. The NAFLD-activity score (NAS) was used to grade all liver biopsy samples.

Results: 239 patients with biopsy proven NAFLD were included in the study:Age 49 ± 13, 143 male (59.8%), BMI 33 (Median; range 28-41), NAS: ≤ 4:124 (51.9%); 5-8: 115 (48.1%); fibrosis: F0-2: 180 (75.3%); F3-4:59 (24.7%). 78 (32.6%) patients underwent bariatric surgery. 81 (33.9%) patients were rs72613567:TA heterozygotes and 17 (7.1%) homozygotes (overall allele frequency: 24.1%).NAS scores ≥ 5 in TA-allele carriers were less frequent than in T/T carriers (T/T: 77 [54.6%] vs. all TA carriers: 38[38.8%], p = 0.016; vs. TA/T:32 [39.5%] or TA/TA 6 [35.3%], p = 0.039). In PNPLA3 G-allele carriers NAS scores ≥ 5 were significantly more frequent than in C/C carriers (C/C 42[36.8%] vs. C/G 47[54.7%] vs. G/G 26[66.7%], p = 0.002]. The protective effect of the TA-allele was only observed in *PNPLA3* C/C homozygotes (NAS ≥ 5: TA-carriers 11 [23.4%] vs. T/T 31 [46.3%], p = 0.013)but not G-allele carriers (NAS ≥ 5: TA-carriers 27 [52.9%] vs. T/T 46[62.2%], p = 0.304). rs72613567 was not associated with more advanced fibrosis (F ≥ 3/4: TA-carriers 23[23.7%] vs. T/T 36[25.5%], p = 0.749). In a multivariate regression analysis (Table 1) harboring at least one TA-allele was associated with a reduced risk for NAS ≥ 5 independent of *PNPLA3* G-allele carriage, serum triglyceride-levels and fibrosis-stage. Diabetes mellitus and older age were independent markers of advanced fibrosis (F3/4).

Table 1:

	Univariate HR	95%CI	p value	Multivariate HR	95%CI	p value
Age	0.992	0.97-1.01	0.397			
Sex	0.822	0.49-1.38	0.459			
BMI	0.983	0.95-1.01	0.280			
HSD17B13 T/T vs. TA	0.526	0.31-0.89	0.016	0.43	0.24-0.76	0.004
PNPLA3 C/C vs. C/G	2.06	1.17-3.65	0.013	2.23	1.20-4.15	0.011
G/G	3.43	1.59-7.38	0.002	4.13	1.78-9.58	0.001
Fibrosis. Per Grade (0-4)	1.39	1.11-1.74	0.004	1.35	1.06-1.71	0.015
Diabetes	1.34	0.76-2.36	0.302			
Arterial Hypertension	1.53	0.89-2.62	0.127			
Total Cholesterol	0.999	0.993-1.004	0.640			
Triglycerides	1.004	1.001-1.007	0.011	1.006	1.002-1.009	0.001

Conclusion: In biopsy proven NAFLD patients the loss-of-function rs72613567 T >TA variant in the *HSD17B13*-gene is associated with significantly less severe fatty liver disease, irrespective of *PNPLA3* genotype and metabolic risk factors.

THU-334

PNPLA3 rs738409 C >G variant predicts liver-related events and death in non-alcoholic fatty liver

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Background and aims: Patients with non-alcoholic fatty liver disease (NAFLD) are at higher risk of developing liver-related complications -hepatic decompensation (HD) and hepatocellular carcinoma (HCC)- including death, the severity of liver fibrosis and metabolic comorbidities being the main risk factors. Emerging evidences reported that a single nucleotide polymorphism in PNPLA3 gene is associated with a higher prevalence of liver damage and HCC, but prospective date are not available. We aimed to assess whether the common rs738409 variant in PNPLA3 gene can predict the occurrence of liver-related events and death in a large cohort of NAFLD patients.

Method: We considered 469 consecutive Italian individuals with histological diagnosis of NAFLD or with clinical diagnosis of compensated cirrhosis due to NAFLD, prospectively followed for at least 6 months. Hepatic events (HD and HCC) and death were recorded. The rs738409 G >C polymorphisms was genotyped by TaqMan assay.

Results: NAFLD patients had a mean age of 50 years with a higher prevalence of male gender (62.2%). Thirty-three percent were diabetic, and 35.6% had advanced fibrosis/compensated cirrhosis. During a median follow-up of 65 months (range 6.8-171 months) 27 HD, 12 HCC and 15 deaths (11 liver-related) were recorded. PNPLA3 C >G variant was associated with a higher risk of HD (HR 1.97, 95%C.I 1.14-3.41, p = 0.01) (Figure 1), this picture being confirmed (HR 1.82, 95%C.I 1.05-3.14, p = 0.02) after adjusting for age >50 years and diabetes, but being lost when including in the model the presence of advanced fibrosis/compensated cirrhosis (HR 1.55, 95%C.I 0.88-2.74, p = 0.12). A nonsignificant trend was also observed for the link between PNPLA3 variant and both HCC occurrence (HR 2.13, 95%C.I 0.92-4.92, p = 0.07) (Figure 2) and liver-related death (HR 2.18, 95%C.I 0.94-5.07, p = 0.06) (Figure 3), the strength of these associations being maintained after adjusting for age >50 years and diabetes (HCC || HR 2.6, 95%C.I 0.88-4.77, p = 0.9; Liver-related death || HR 1.95, 95% C.I 0.84-4.52, p = 0.1).

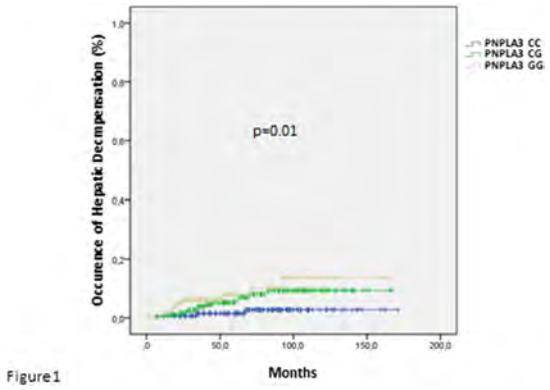

Figure1

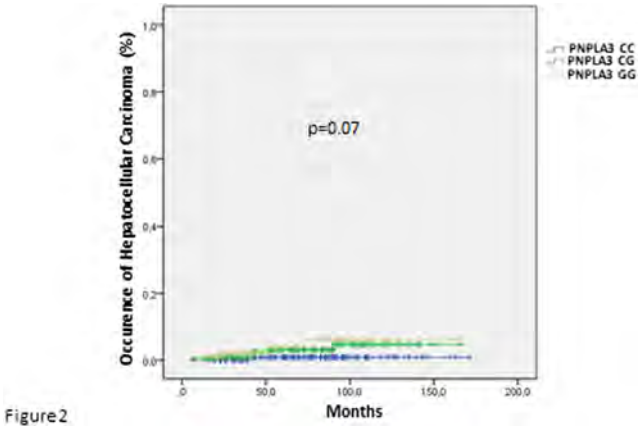

Figure2

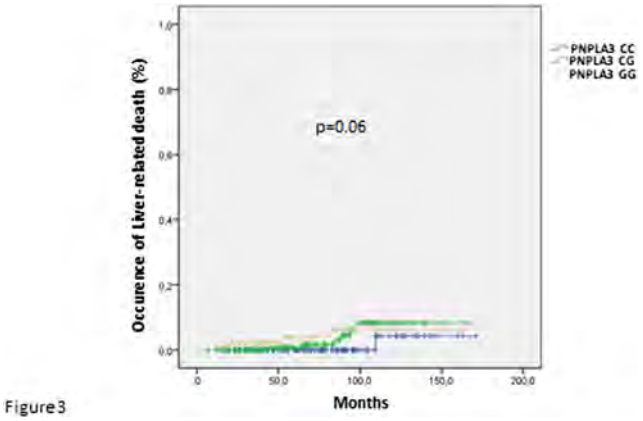

Figure3

Conclusion: Patients carrying PNPLA3 rs variant are at higher risk of liver-related events and death, this picture being mostly driven by developing advanced fibrosis/cirrhosis.

THU-335

FXR rs35724 C >G variant modulates cholesterol levels, carotid atherosclerosis and liver damage in non-alcoholic fatty liver

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Background and aims: Farnesoid X receptor (FXR) plays a key role in biliary acid and lipid homeostasis, and experimental evidence suggest that it can modulate atherosclerosis and liver damage due to non-alcoholic fatty liver disease (NAFLD). We examined the impact of FXR rs35724 variant on circulating cholesterol, carotid atherosclerosis and liver damage in a large cohort of patients at risk of non-alcoholic steatohepatitis (NASH).

Method: We considered 1, 447 consecutive Italian individuals at risk of NASH with liver histology. Common carotid arteries intima-media thickness (CC-IMT) was evaluated using ultrasonography in a subgroup (n = 703). The rs35724 G >C polymorphisms was genotyped by TaqMan assay. Gene expression was evaluated by RNASeq in a subset of patients (n = 124).

Results: Patients carrying FXR rs35724 variant had significantly higher hepatic mRNA levels of FXR, these last being associated with higher hepatic FGFR4 and Cyp39 in turn involved in bile acids synthesis. In the entire cohort of NAFLD patients, FXR rs35724 variant was independently associated with higher total circulating cholesterol (p = 0.01), while an inverse independent association was found for CC-IMT (p = 0.02). In patients with high circulating cholesterol (>200 mg/dl), FXR rs35724 was protective against NASH (OR 0.78, 95%C.I.0.61-0.99;p = 0.04) and severity of fibrosis (OR 0.81, 95%C. I.0.66-0.99;p = 0.04), these results being confirmed after adjusting for clinico-metabolic and genetic confounders.
Conclusion: Genetically induced increased FXR due to the rs35724 variant, while being linked to higher serum cholesterol, may not invariably results in more severe carotid atherosclerosis but may protect against NASH and hepatic fibrosis in patients with high cholesterol. The translational relevance of these results in terms of risk stratification and FXR-based target therapy is worthy of further investigation.

THU-336
Possible ways of concomitant hypothyroidism effect on the course of non-alcoholic fatty liver disease

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Background and aims: Hypothyroidism is one of the common concurrent diseases in non-alcoholic fatty liver disease (NAFLD) patients. Moreover, hypothyroidism, even in subclinical form, is found to be associated with an increased risk of NAFLD development. The mechanisms of such dependence remain unclear. The aim of the study was to investigate influence of hypothyroidism on insulin resistance, adipokine profile and lipid metabolism in NAFLD patients.
Method: The study involved 188 NAFLD patients (average age 53.6 ± 12.34 years), including 20 NAFLD patients with subclinical hypothyroidism and 24 NAFLD patients with manifest hypothyroidism. 144 NAFLD patients with normal functional activity of the thyroid gland formed a comparison group. The control group consisted of 45 healthy individuals. Biochemical parameters, lipid profile, insulin, leptin, adiponectin blood levels were investigated.
Results: The study of lipid profile showed higher total cholesterol level in the blood by 10.7% (p = 0.04) and 12.5% (p = 0.02) as well as increased low density lipoprotein cholesterol concentration by 15.2% (p = 0.04) and 14.5% (p = 0.04) in NAFLD patients with both subclinical and manifested hypothyroidism as compared to NAFLD patients without thyroid dysfunction. NAFLD patients were shown to develop insulin resistance, which became more severe in case of concomitant subclinical or manifest hypothyroidism. In NAFLD patients with subclinical and manifested hypothyroidism J.F. Caro index was in 4.15 times (p < 0.001) and 3.38 times (p < 0.001) lower as compared to NAFLD patients without hypothyroidism. In NAFLD patients with manifested hypothyroidism HOMA IR index was at 67.7% (p = 0.04) higher in comparison with patients having normal thyroid activity. The patients with subclinical and manifested hypothyroidism were found to have a higher leptin level at 35.7% (p = 0.04) and 72.1% (p = 0.009), and those with NAFLD and manifested hypothyroidism also in 2.1 time (p = 0.004) lower adiponectin content in the blood as compared to patients without hypothyroidism. Our study shows that NAFLD patients with concomitant hypothyroidism are characterized by more pronounced changes of insulin resistance, adipokine and lipid profiles. Further investigations are required to examine the mechanisms of these findings.
Conclusion: Insulin resistance syndrome, adipokine imbalance and dyslipidemia can be aggravating factors of the course of NAFLD in patients with concomitant hypothyroidism.

THU-337
Cardiovascular risk factors and fibrosis severity in NAFLD: is there a link?

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Background and Aims It is well documented that patients with NAFLD have an increased cardiovascular risk due to the presence of metabolic comorbidities. However, it is not clear whether cardiovascular risk is associated with an increased risk of liver disease in patients with NAFLD. Carotid artery intima media thickness (CCA IMT) can be used as a predictor of increased cardiovascular risk. Therefore, we evaluated if IMT correlates with the presence of NASH and fibrosis severity in such patients.
Method: We included consecutive patients with NAFLD. Transient elastography (TE) with FibroScan (Echosens) was performed in all patients and significant fibrosis was defined as a liver stiffness (LS) value ≥ 7.5 kPa. Abdominal fat thicknesses [(subcutaneous minimum and maximum (SCmin, SCmax), pre-peritoneal (PP), peri-renal (PR), visceral (VF) and abdominal fat index (AFI = PP/SCmin)], spleen size (SS) and CCAs IMT were measured using Affiniti 70G ultrasound (Philips). A right CCA IMT ≥ 75th percentile was considered as significant predictor of cardiovascular disease as per published data.
Results: 395 patients with NAFLD, mean age 55 ± 13y, 60% male, BMI 31.6 ± 5.8 kg/m^2, waist circumference (WC) 107 ± 15 cm, 43% with diabetes, 55% hypertension, 77% hyperlipidaemia.
Predictors of a right CCA IMT >75 percentile were increasing age (OR 1.088, 95%CI 1.058-1.188, p < 0.001) and male gender (OR 1.736, 95% CI 1.004-3.002, p = 0.048). In the subset of 126 patients with available liver biopsy, the presence of NASH or significant fibrosis was not associated with an increased CCA IMT.
Conversely, on univariate analysis, a LS value ≥ 7.5 kPa was associated with diabetes, hypertension, right CCA IMT ≥ 75th percentile, age, BMI, WC, VF, SS, total cholesterol, platelets, AFI, ALT and Hb1Ac. On multivariate analysis predictors of significant fibrosis were diabetes (OR 3.186, 95%CI 1.770-5.735, p = < 0. 001), AFI (OR 0.588, 95%CI 0.393-0.880, p = 0.010), SS (OR 1.370, 95% CI 1.173-1.600, p < 0.001) and ALT (OR 1.011, 95% CI 1.004 –1.017, p = 0.003).
Conclusion: Significant liver fibrosis is independent from increased cardiovascular risk in patients with NAFLD and is mainly associated with presence of diabetes, increasing ALT and reducing AFI. Targeted interventions for components of the metabolic syndrome should be offered to all NAFLD patients irrespective of the severity of the underlying liver disease.

THU-338

Prevalence and dynamics of NAFLD-associated fibrosis among HIV+ from first presentation to last follow-up

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has been reported to be highly prevalent in HIV+ individuals and if progressing to steatohepatitis (NASH) may induce liver fibrosis/cirrhosis. Additionally, some ART-regimens are known to cause metabolic alterations and thereby cause hepatic steatosis. Thus, we aimed to analyze epidemiological trends in the prevalence and severity of NAFLD in our Vienna HIV+ cohort.
Method: N = 1874 HIV+ patients attending our clinic between 2014 and 2016 were included. Epidemiological, clinical and laboratory parameters as well as ART regimens were retrospectively assessed at HIV-diagnosis (baseline) and at last contact. Patients with viral hepatitis or other chronic liver diseases were excluded. The prevalence of liver fibrosis according to NAFLD fibrosis scores (NFS) at first and at last visit were analyzed.
Results: After excluding n = 405/1874 (21.6%) due to viral hepatitis, NFS was available in n = 1283 (87.3%). At baseline, dyslipidemia and diabetes were diagnosed in 413 (32.2%) and 19 (1.5%) patients, respectively. 1074 (83.7%) patients showed NFS < −1.455 (absence of advanced fibrosis) and n = 17 (1.3%) showed NFS ≥ 0.676 (indicating F3/F4 NAFLD-fibrosis) at baseline, while n = 192 (15.0%) had intermediate NFS. Among patients with NFS-F3/F4 fibrosis, 1 (5.9%) had diabetes, 4 (23.5%) had dyslipidemia, and 5 (29.4%) were on HIV protease inhibitors (PI).
After a median follow-up of 5.9 years, 45/1469 (3.1%) patients had acquired viral hepatitis coinfection. Overall, 421 (31.8%) had dyslipidemia, 63 (4.8%) had diabetes and 188 (14.2%) were on PI-ART at follow-up. Data for NFS-calculation was available in 1325/1424 (93.0%) patients at last follow-up: n = 22 (1.7%) had NFS-F3/F4 fibrosis at last follow-up, including 10 (45.5%) with diabetes, 4 (18.2%) with dyslipidemia, and 9 (40.9%) on PI-containing ART.
Conclusion: Although dyslipidemia, diabetes and PI-containing ART were common in HIV+ patients without viral hepatitis coinfection, only 1.3 to 1.7% had suspected NAFLD-F3/F4 fibrosis. The study is limited by its retrospective design and lack of systematic imaging/elastography assessments. Thus, the true rate of NASH/NAFLD-fibrosis within the HIV+ patients remains to be established-especially for HIV+ patients with indetermined NFS scores.

THU-339

The relationship between the PNPLA3, TLL1 polymorphism combination and advanced fibrosis in Japanese patients with non-alcoholic fatty liver disease

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Background and aims: Hepatic fibrosis is an independent risk factor for mortality and liver-related events in patients with non-alcoholic fatty liver disease (NAFLD). PNPLA3 rs738409 has been associated with fibrosis in viral and nonviral hepatitis. TLL1 rs17047200 also has been associated with developing hepatocellular carcinoma probably via hepatic fibrogenesis. We estimated the impact of these genetic polymorphisms on hepatic fibrosis in Japanese patients with NAFLD.
Method: We analyzed the association between these genetic variants and the backgrounds of 817 individuals who received health checkups (health check cohort) from 2012 to 2014. Then, we investigated the relationship between genetic variants and liver histology in 258 consecutive patients with biopsy-proven NAFLD in Japan (NAFLD cohort) from 2012 to 2017.
Results: The prevalence of PNPLA3 CG/GG in the NAFLD cohort was higher than that in the health check cohort (p\0.001). The prevalence of patients with advanced fibrosis (stages 3-4) was higher for PNPLA3 genotype CG/GG than CC (p = 0.048) and for TLL1 genotype AT/TT than AA (p = 0.044). The high-risk group which had at least two risk alleles of these variants was more likely to have advanced fibrosis (p = 0.004). Multivariate analysis identified body mass index [odds ratio (OR) 1.123, serum AST (OR 1.037, p = 0.004], serum albumin (OR 0.247, p = 0.032), and genetic high risk (OR 2.632, p = 0.026) as predictors of advanced fibrosis.

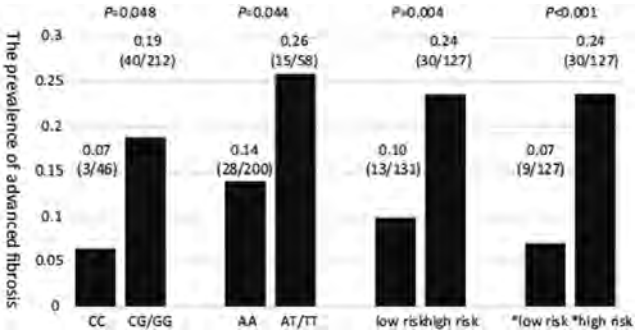

Figure: Prevalence of advanced fibrosis according to PNPLA3, TLL1 genotypes, genetic risk (low risk, \2; high risk, C2), and *genetic risk adjusted for sex and age

Conclusion: In Japanese patients with NAFLD, individuals with risk alleles of PNPLA3 and TLL1 may have a risk of advanced fibrosis.

THU-340

Epidemiology of NAFLD and advanced fibrosis in the French general population: A population-based cohort study in 118, 664 subjects (NASH-CO study)

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Background and aims: Assessment of the prevalence of NAFLD and NASH in the French general population is an important issue to quantify the disease burden. The aim of this study was to assess the prevalence and risk factors of NAFLD and associated liver fibrosis in a large French population-based cohort by using non-invasive markers.
Method: The study population consisted of 118, 664 participants from a sample drawn from the nationwide CONSTANCES cohort designed to be representative for age, gender and socioeconomic status of the French adult population. After exclusion of subjects with excessive alcohol consumption, viral hepatitis and other causes of liver diseases, 102, 344 subjects were analyzed. Non-invasive diagnosis of NAFLD and advanced fibrosis were performed using the Fatty Liver Index and Forns Index (FI). We used FI because in a previous work we observed it was as efficient as FIB4 for the detection of advanced fibrosis (AUC 0.8). Subjects with FLI >60 were considered as having NAFLD and those with FI >6.9 as having advanced fibrosis (NASH-CRN F ≥ 3).
Results: The global prevalence of NAFLD in the study population was 16.7% (CI95% 16.5-16.9), 24.6 and 10.1% among male and female

subjects, increased from 5.2% in subjects aged 18-28 yrs to 26.8% in subjects aged 68-78 yrs and reached 79.7% and 63% in obese and type 2 diabetic subjects, respectively. In the overall sample population, NAFLD was significantly associated (all $p < 0.001$) with older age (52.9 ± 11.7 vs 47.2 ± 13.6 yrs), male sex (66.8 vs 45.4%), obesity (58.2 vs 12.3%), diabetes (13.6 vs 3.7%), metabolic syndrome (59.8 vs 15.4%), high blood pressure (HBP) (28.6 vs 11.6%), hypertriglyceridemia (44.9 vs 12.3%) and ALT above normal threshold (33.9 vs 11.1%). In multivariate analysis, all factors remained significantly associated with NAFLD. Advanced fibrosis was only observed in NAFLD patients with a prevalence of 2.6% (IC95% 2.4-2.8), and a prevalence of 7.6% (IC95% 6.5-8.7) in NAFLD patients with diabetes. In multivariate analysis, independent risk factors of advanced fibrosis in NAFLD patients were age (OR = 4.1), male sex (OR = 7), obesity (OR = 1.4), diabetes (OR = 2.4), HBP (OR = 1.7) and elevated ALT (OR = 3.2).
Conclusion: NAFLD affects 1/6 of a large French population-based cohort with no excessive alcohol consumption or viral hepatitis. Advanced fibrosis is observed in 2.6% of NAFLD subjects, and in 7.6% of NAFLD subjects with diabetes. Age, male sex and metabolic disorders are independent risk factors of both NAFLD and advanced fibrosis.

THU-341
Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load

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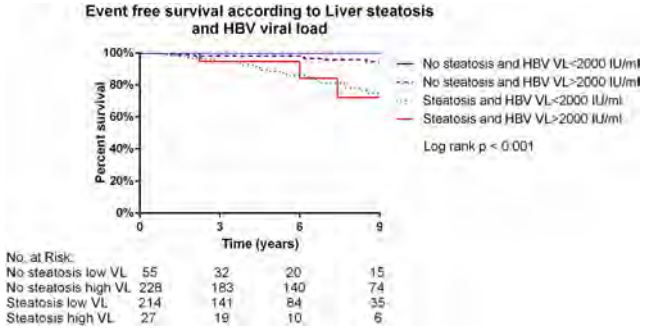
Background and aims: Chronic hepatitis B (CHB) may co-occur with liver steatosis (LS) in up to 30% of patients. Both LS and HBV viral load (VL) are associated with poor outcomes in CHB patients. The present study was designed to investigate the association between LS and HBV viral load (VL) and their effects on a composite outcome of all-cause mortality and the development of cancer.
Method: This is a retrospective study of 524 CHB treatment naïve patients, who attended to the liver clinic of a tertiary hospital from January 2007 to December 2017. Mean follow-up of six years. LS was validated by at least 3 ultrasonographic (US) examinations in all patients. Liver biopsy was available for 170 patients. The primary end point of the study was the composite end point of all-cause mortality and development of cancer. Secondary end points included all-cause mortality, malignancy of any type, and the development of HCC. Kaplan-Meier survival estimate and Cox proportional hazards regression analysis were used to analyze the incidence of the primary end point.
Results: Out of 524 CHB patients, 241 (46%) had LS with a strong correlation between the degree of LS as assessed by US or by liver biopsy ($r = 0.9$, $p < 0.001$). Patients with LS were significantly older than patients without LS and had higher BMI. In addition, type 2 DM and hypertension were significantly more common in the LS population ($p < 0.05$ for all). Multivariate analysis showed that LS was associated with a significant 3-fold increased risk of all-cause mortality and the development of cancer (HR 3.18, 95% CI 1.64-6.16, $p < 0.001$), whereas baseline HBV VL was not significantly associated with this composite outcome (HR 1.44, $p = 0.33$). In addition, an inverse association between the degree of LS, assessed either by US or liver biopsy, and HBV VL was found.
Conclusion: CHB patients with LS have an increased risk for all-cause mortality and the development of cancer compared to CHB patients without LS, regardless of their baseline HBV VL. Although tending to have a lower baseline viral load, CHB patients with LS should be closely monitored irrespective of VL level.



THU-342
Development of a model to predict survival in recipients of liver transplant for non-alcoholic steatohepatitis

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Background and aims: Non-alcoholic steatohepatitis (NASH) is projected to become the leading reason for liver transplantation (LT) in the near future. It is imperative to better understand the risk-benefit profile in an individual patient, so that we offer transplant to patients where there is a clear benefit as opposed to potential harm. The aim of our study was to develop a model to predict survival in recipients of LT for NASH.
Method: Liver transplant recipients whose primary indication was NASH were identified from the Scientific Registry of Transplant Recipients (SRTR) database (n = 11326, from 1987-2017). Patients with cryptogenic cirrhosis with a Body Mass Index (BMI) greater than 30 were also included. We excluded patients with hepatocellular carcinoma or those less than 18 years of age. Only recipient-specific factors were analysed. Data was analysed using univariate and multivariate Cox Proportional Hazard models. Through a series of covariate selection steps, a parsimonious set of independent predictors of survival were identified.
Results: Patient survival post liver transplantation for patients with NASH at 7 days, 30 days, 1 year, 3 year and at 5 years were 98%, 95%, 86%, 80% and 74% respectively. After univariate and multivariate analysis, the recipient factors found to be associated with the patient survival are shown in Table 1. Age and Serum Creatinine are analysed as continuous variables and other parameters are considered in binary. The model was internally validated and calibrated, giving Bootstrap-corrected errors of 0.0036, 0.0008, 0.0151, 0.0097 and 0.0048, for the survival probabilities for 7, 30 days, 1, 3 and 5 years respectively.

Survival Predictors	p value	Hazard Ratio (95% CI)
History of Diabetes	< 0.001	1.17 (1.08, 1.27)
History of Angina	0.051	1.17 (1, 1.36)
Recipient Age (at transplant)	< 0.001	1.02 (1.02, 1.02)
Portal vein thrombosis	0.034	1.12 (1.01, 1.24)
Mechanical ventilation at time of transplant	< 0.001	1.37 (1.19, 1.57)
Non hospitalised recipients	< 0.001	0.77 (0.71, 0.83)
Serum Creatinine before transplant	0.038	1.04 (1, 1.07)
History of TIPS procedure prior to transplant	0.028	1.13 (1.01, 1.26)

Figure: Table-1: Independent Predictors of Patient survival

Conclusion: We have developed and validated a Cox model that is able to accurately predict patient survival post liver transplantation using recipient factors. Derivation of a practically useable risk calculator, along with validation in a local cohort at the University Health Network will further help in delineating risk assessment in an individual candidate for transplant.

THU-343

Systematic review: Patient reported quality of life outcomes in non-alcoholic fatty liver disease: Effect of disease severity and duration

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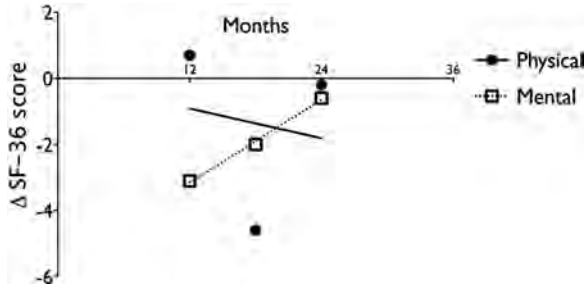
Background and aims: The objective of this review was to assess the impact of NAFLD on health related quality of life (HRQL) in both static (single time point) and dynamic (repeated over time) measures in patients with NAFLD.
Method: A systematic search was conducted in PubMed (1948-present). Primary articles were screened based on pre-specified inclusion criteria and papers with the highest relevancy were selected based on their abstracts. HRQL data was then extracted from relevant articles into a pre-prepared spreadsheet.
Results: A total of 553 papers were identified, of which 11 papers were included in the review. These studies included a total of 4495 patients had NAFLD (mean age 51, % male 44), of which 1127 subjects had biopsy-confirmed NASH. Seven studies were cross sectional, and four were longitudinal of which 3 were randomised control trials (RCT). HRQL was measured using 36-Item Short Form Survey (SF-36) in seven studies and the Chronic Liver Disease Questionnaire (CLDQ) in 3 studies and one study used the HRQOL-4 questionnaire. Scores were compared to normative US healthy population control data in six studies. Four studies reported dynamic outcomes whilst seven reported static outcomes. NAFLD was associated with reduced HRQL compared to control populations. When compared to non-alcoholic fatty liver (NAFL), HRQL in NASH or advanced fibrosis (AF) scores was significantly lower with the greatest impairment seen in domains concerning physical function (mean SF36 47.1 vs 44.4 vs 30.4 vs 44.4 vs 47.1 for NAFL, NASH and AF respectively, $p < 0.05$ for each comparison). Studies with repeated measures of HRQL over time showed improvement over time in mental aspects of HRQL in both treatment and placebo arms of therapeutic studies, whereas physical aspects showed no significant improvement.



Conclusion: NAFLD is associated with poorer HRQL, especially in domains relating to physical function. Mental HRQL was seen to improve over time in prospective studies, regardless of treatment arm. This may show that a diagnosis of NAFLD may cause initial distress which eases over time, or that repeated contact with liver services can ease patients' concerns without necessarily changing physical function. Further data is needed to be able to draw any firm conclusions.

THU-344

The influence of non-alcoholic fatty liver disease on a two year prognosis of the patients with stable coronary heart disease depending on SYNTAX score II

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Background and aims: To evaluate the contribution of non-alcoholic fatty liver disease (NAFLD) in predicting risk of major cardiovascular events by cumulative proportion surviving depending on the SYNTAX score (SS) II in pts with stable coronary heart disease (CHD) who underwent coronary artery stenting.
Method: 150 pts (aged: 53.7 ± 3.5 years) with stable CHD who have had an acute coronary syndrome with an indication of coronary artery stenting more than 3 months ago were examined. Pts were categorized into 2 groups according to the SS II value: Group I-SS II value less than 29 (n = 97); Group II-SS II value more than 29 (n = 53). In each group, pts without NAFLD (subgroup A), with non-alcoholic steatosis (subgroup B), with non-alcoholic steatohepatitis (NASH) (subgroup C) were identified. General clinical examination, ECG, EchoCG, liver elastography, liver ultrasound, evaluation of the liver functional state were performed to all pts. Each coronary lesion based on angiogram at the time of acute coronary event was scored to SS I, than to SS II which were calculated by online calculators. Survival analysis based on Kaplan-Meier curves was evaluated by a two-year cumulative proportion surviving (%), the difference between groups was determined by Cox's F and Gehan's Wilcoxon tests.
Results: A two-year cumulative proportion surviving was the highest in pts without NAFLD: by reoccurring myocardial infarction (MI)-100.0% (Group IA) vs. 100.0% (Group IIA); by ischemic stroke-93.5% (Group IA) vs. 85.4% (Group IIA) ($p > 0.05$); by death from cardiovascular causes-96.8% (Group IA) vs. 88.9% (Group IIA) ($p < 0.05$); by re-revascularization-98.4% (Group IA) vs. 85.8% (Group IIA) ($p < 0.05$). In pts with non-alcoholic steatosis a two-year cumulative proportion surviving was significantly lower: by reoccurring MI-100.0% (Group IB) vs. 96.1% (Group IIB); by ischemic stroke-73.7% (Group IB) vs. 49.5% (Group IIB) ($p < 0.05$); by death from cardiovascular causes-74.1% (Group IB) vs. 49.5% (Group IIB) ($p < 0.05$); by re-revascularization-82.4 (Group IB) vs. 58.8% (Group IIB) ($p < 0.05$). The lowest a two-year cumulative proportion surviving in pts with NASH was observed: by reoccurring MI-78.6% (Group IC) vs. 60.0% (Group IIC) ($p < 0.05$); by ischemic stroke-54.5% (Group IC) vs. 33.3% (Group IIC) ($p < 0.05$); by death from cardiovascular causes-58.6% (Group IC) vs. 33.3% (Group IIC) ($p < 0.05$); by re-revascularization-71.8% (Group IC) vs. 31.8% (Group IIC) ($p < 0.05$).
Conclusion: The course of stable CHD in pts who underwent coronary artery stenting depends on the NAFLD presence and its severity and is the most prognostically unfavorable in pts with NASH. The severe course of NAFLD forms a high risk of major cardiovascular events by SS II values and causes a significant decrease of a two-year cumulative proportion surviving in pts with stable CHD who underwent coronary artery stenting combined with NAFLD.

THU-345

Lean NAFLD patients have lower prevalence of cardiovascular, metabolic and severe liver disease compared to overweight or obese patients with NAFLD

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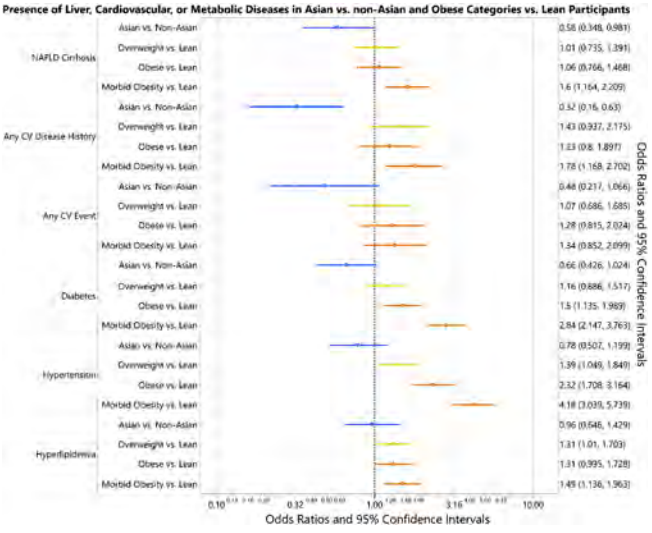
Background/Aim: Although non-alcoholic fatty liver disease (NAFLD) is associated with obesity, it is also seen in patients with

normal BMI (lean NAFLD). TARGET-NASH includes a large cohort of racially diverse patients including many with normal BMI, providing a unique opportunity to compare prevalence of NAFLD cirrhosis, cardiovascular (CV) and metabolic abnormalities among those with normal vs. high BMI.

Methods: TARGET-NASH, a longitudinal observational study of participants at 54 sites (39 academic/15 community) in the U.S, includes patients across the entire spectrum of NAFLD as defined by pragmatic case definitions. Data from medical records are centrally abstracted and monitored for completeness and accuracy. An analysis was performed to compare CV and metabolic abnormalities and severity of liver disease across BMI categories: Lean (>18.5-25, n = 436), Overweight (>25-30, n = 874), Obese (>30-35, n = 849), and Morbid Obesity (>35, n = 1069); and race (Asians vs non-Asians). Odds ratios and confidence intervals were adjusted by age, sex, center type (academic vs. community); site was included in models as a random effect.

Results: 436/3228 (13.5%) participants were lean. There was a clear decreasing trend ($p < 0.0001$) in the proportion of Asian patients (n = 401) across BMI categories: Lean (46%), Overweight (19%), Obese (5%) and Morbidly Obese (1%). Independent of BMI categories, Asian NAFLD had a significantly lower prevalence of cirrhosis (12% vs. 44%) and CV history (4% vs. 16%), and numerically less CV events (5% vs. 12%), diabetes (28% vs. 55%), hypertension (51% vs. 75%) or hyperlipidemia (48% vs. 63%) compared to non-Asians. Similar or more marked differences were observed when BMI cut-off of 23.5 was used to define lean Asians. Independent of race, lean participants had a significantly lower prevalence of hypertension (55% vs 66%) and hyperlipidemia (52% vs 62%), and numerically less NAFLD cirrhosis (24% vs. 36%), CV history (8% vs 15%), CV events (7% vs 10%), and diabetes (34% vs 43%) compared to overweight participants.



Conclusion: Lean NAFLD comprised 13.5% of our cohort and was significantly more prevalent among Asians. Across BMI categories, Asians had a significantly lower prevalence of cirrhosis and numerically lower prevalence of CV and metabolic abnormalities than their non-Asian counterparts. Longitudinal follow-up is ongoing to determine if lean NAFLD have slower progression of liver disease, in particular among lean Asians.

THU-346

Plasma ApoE levels are associated with non-alcoholic fatty liver disease: the PREVEND cohort study

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is featured by increased plasma triglycerides, consequently to very low density lipoproteins (VLDL) elevations, but the extent to which plasma apolipoprotein E (ApoE) is elevated in NAFLD is unclear. Here we determined the relationship of plasma ApoE and its genotype with NAFLD.

Method: Plasma ApoE and genotypes were determined in 6, 762 participants of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort. Fatty Liver Index (FLI) $\geq$ 60 was used as a proxy of NAFLD.

Results: In total 1, 834 participants had a FLI $\geq$ 60, which coincided with increased prevalence of type 2 diabetes mellitus, metabolic syndrome, (central) obesity, elevated triglycerides, higher non-high density lipoprotein cholesterol and apolipoprotein B (all $p < 0.001$). ApoE was increased in subjects with an elevated FLI compared with subjects with a normal FLI (0.048 vs. 0.036 mmol/L, $p < 0.001$). In multivariable linear regression analysis, plasma ApoE levels were positively associated with an elevated FLI when taking account of ApoE genotypes and other clinical and laboratory covariates (fully adjusted model: beta = 0.201, $p < 0.001$). In a sensitivity analysis (n = 4, 730), which excluded subjects with positive cardiovascular history, impaired estimated glomerular filtration rate, elevated urinary albumin excretion and drug use, plasma ApoE was also independently associated with elevated FLI (beta = 0.221, $p < 0.001$). Stratified analysis for ApoE genotypes (ApoE ε3ε3 homozygotes, ApoE ε2 carriers, and ApoE ε3ε4 and ε4ε4 carriers combined), showed independent positive associations of plasma ApoE levels with an elevated FLI (all $p < 0.001$).

Conclusion: Increased plasma ApoE levels are associated with NAFLD, even when taking account of different ApoE genotypes. Increased plasma ApoE may contribute to altered VLDL metabolism in NAFLD.

THU-347

Economic and clinical burden of non-alcoholic steatohepatitis in patients with type II diabetes in the United States

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Background and aims: NASH is the progressive form of non-alcoholic fatty liver disease (NAFLD) and is strongly associated with T2DM. Patients with both T2DM and NAFLD/NASH have increased risk for adverse clinical outcomes leading to higher risk for mortality and morbidity. Aim: To assess the economic burden of NASH and T2DM in the US.

Method: We built a Markov model with 1-year cycles and lifetime horizon to estimate the economic burden of NASH with T2DM in the adult US population from the health system perspective. Cohort size was determined by population size, prevalence of T2DM, and the prevalence and incidence of NASH in the US for 2017. Model includes 11 health states-NAFL, NASH-fibrosis stages 0, 1, 2, 3, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), one-year post-LT (1yPLT), post-LT (PLT), and 3 death states -liver-related (LRM), cardiovascular (CVM), and background mortality (BM). Transition probabilities (TPs) were

calculated from our meta-analyses and literature. TPs to LT and BM were age-related. Annual costs for NASH and diabetes were taken from literature or micro-costed using 2017 current procedural terminology (CPT) codes. Costs were discounted at 3% annually. Annual incidence rate of NASH in T2DM were assumed to be 5 times higher than the general population.

Results: We estimated that there were 17 million people in the US living with T2DM and NAFLD in the US, of which 3.9 million had both T2DM and NASH. Lifetime costs specifically related to NASH in these patients were $58.2 billion. Over the next 50 years, NASH with T2DM accounted for a large number of transplants, deaths (CV-related and liver related deaths), and cirrhosis complications (Table 1).

Table 1: Economic Burden of NASH with Type II Diabetes in the US in 2017

	T2DM and NASH
Lifetime Costs Associated with NASH	$58,176,567,817
Liver Transplants (N)	207,724
Liver-Related Deaths (N)	757,499
Cardiovascular Deaths (N)	1,340,158
DCC Person-Years (N)	1,011,764
HCC Person-Years (N)	271,221

Conclusion: Our model predicts an enormous clinical and economic burden due to NASH with T2DM over the next 50 years. It is highly likely that interventions that reduce morbidity and mortality in NASH with T2DM could potentially reduce this projected clinical and economic burden. In fact, these benefits may be greater since we assumed conservative inputs for our model and did not increase medical costs or the incidence of T2DM or NASH over time.

THU-348

Patients with non-alcoholic steatohepatitis experience severe impairment of health related quality of life

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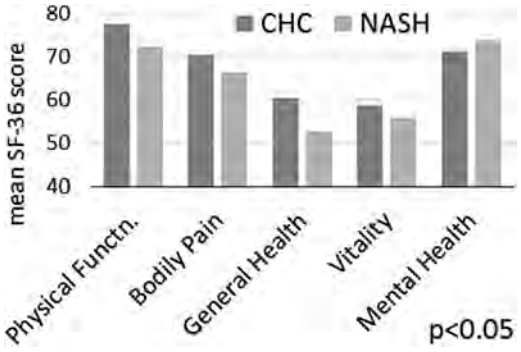
Background and aims: Chronic hepatitis C (CHC) and NASH are common causes of chronic liver disease. Although there is substantial evidence suggesting poor HRQL in CHC patients, similar data in NASH is lacking. AIM: Compare HRQL scores in patients with advanced fibrosis due to CHC to NASH.

Method: Patients with advanced fibrosis (bridging fibrosis and compensated cirrhosis) due to CHC and NASH were included. Prior to treatment, all patients had completed Short Form-36 (SF-36, score range 0-100), a disease-specific version of Chronic Liver Disease Questionnaire (CLDQ, range 1-7), Work Productivity and Activity (WPAI) (range 1-0), and extensive clinical data. Patients were matched 1:1 according to their age, gender, race, country of origin, and presence cirrhosis. The HRQL scores of matched CHC and NASH subjects were compared using a non-parametric Mann-Whitney test.

Results: We included 1338 patients with NASH with advanced fibrosis (mean age 57.2 years, 47% male, 76% white, 60% enrolled in the U.S., 55% with cirrhosis) and 1338 matched patients with CHC with advanced fibrosis. Patients with CHC and NASH had similar rates of psychiatric disorders (40 vs. 41%) and reported similar employment rates (52 vs. 54%) (both $p > 0.05$). As expected, patients with NASH had higher BMI (mean 33.7 vs. 27.6) and more type 2 diabetes (74% vs. 16%) (all $p < 0.01$). Patients with NASH had significantly lower HRQL scores related to physical health than CHC: Physical Functioning, Bodily Pain, General Health, Vitality, and Physical Summary of SF-36, and Fatigue of CLDQ (all $p < 0.02$). In contrast, patients with CHC had lower Mental Health score of SF-36 and Emotional score of CLDQ than NASH, and reported greater impairment in their daily activities as measured by WPAI (all $p < 0.002$). In multivariate regression analysis, after adjustment for demographic parameters, cirrhosis, and history of psychiatric disorders, having NASH was independently associated with lower physical HRQL scores (beta – 2.5 to – 7.5 for SF-36 domains, – 0.21 for Fatigue of CLDQ) and higher mental health-related scores (beta +2.7 for Mental Health of SF-36, +0.25 for Emotional of CLDQ) (all $p < 0.005$).



Conclusion: Patients with NASH and advanced fibrosis have more impairment of their physical health-related scores than patients with CHC and advanced fibrosis. These data should dispel the misconception that NASH is an asymptomatic disease with little negative impact on patient experience and well-being.

Imaging and drug targeting

THU-363

Lipid nanoparticle pre-treatment improves adeno-associated virus diffusion in the primate liver and enables an increase of therapeutic transgene expression

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Background and aims: AAV vectors have been successfully used in preclinical studies and in clinical trials to express therapeutic proteins in the liver. Transduction of a limited percentage of hepatocytes can be sufficient for expression of secreted proteins. However, most hepatic metabolic monogenic disorders caused by the deficiency of an intracellular enzyme or membrane transporter would require a high percentage of hepatocytes to be transduced to achieve a therapeutic effect. This can be routinely achieved in rodents, but has proven to be a significant hurdle in large animals hampering the feasibility of such liver directed AAV based gene therapies

The liver has a very high capacity to remove particles from the circulation. The cells from the reticuloendothelial system (RES) play a central role in this clearance process. Those cells can ingest and destroy foreign material and therefore constitute the first cellular barrier between the blood flow and the liver tissue. The saturation of

the hepatic reticuloendothelial cells by nanoparticles or lipids has been shown to block uptake of particles from the circulation. We hypothesized that saturation of the RES could increase AAV-vector transduction and distribution in the liver, subsequently improving transgene expression, in large animals. Therefore, we explored the potential of pre-treatment with Intralipid, an FDA approved emulsion of soy bean oil, egg phospholipids and glycerin in non-human primates.

Method: Non-human primates (NHPs, n = 2) were injected intravenously with Intralipid one hour before intravenous administration of AAV5-hFIX. A control group (n = 2) was injected with AAV5-hFIX at the same dose after prior treatment with PBS. The levels of hFIX were measured in plasma. AAV vector DNA and transgene RNA copies numbers were assessed in the liver by QPCR and fluorescent in situ hybridization (FISH).

Results: After Intralipid pre-treatment, an increase in the levels of hFIX transgene expression was observed in the animals injected with AAV5-hFIX when compare to the control group (average of 3.5-fold). A similar increase was observed at the hFIX mRNA levels. Accordingly, the vector DNA copies numbers were higher in the liver tissues of the animals treated with Intralipid than in the control group (average of 2.6-fold). Remarkably, Intralipid pre-treatment resulted in an enhanced diffusion of AAV5 vector through the liver tissue. The percentage of transduced hepatocytes was up to 4-fold higher when Intralipid was used.

No adverse effect of Intralipid on the immunity against AAV5 capsid proteins or the transgene was observed.

Conclusion: Pre-treatment with a lipid emulsion prior to AAV5 administration improves significantly the efficacy of AAV vector delivery to the liver and enables a broader hepatic cell targeting throughout the tissue. This approach represents a valuable tool for liver-targeted gene therapies application.

THU-364

Liver cT1 predicts clinical outcomes in patients with chronic liver disease

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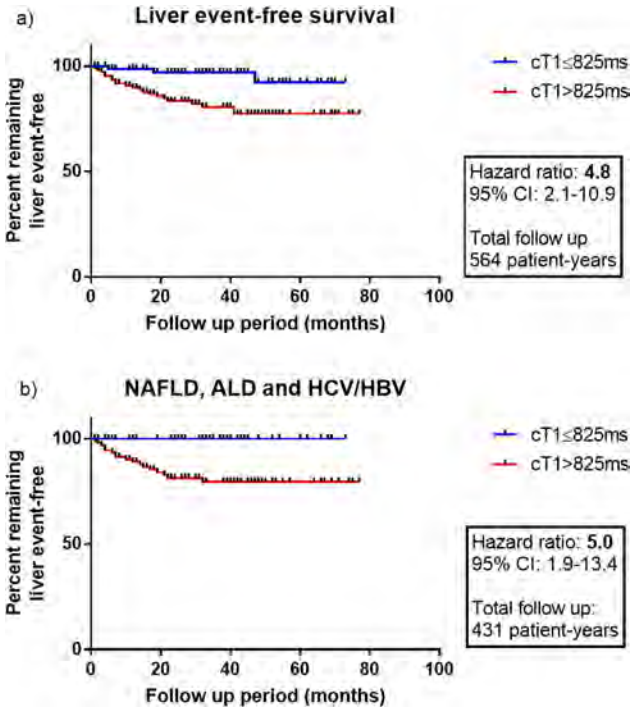
Background and aims: The magnetic resonance imaging (MRI) parameter T1, when corrected for iron content (cT1) can quantify extracellular water content, which rises with fibrosis and inflammation. We have shown liver cT1 correlates with histological fibrosis and ballooning. Here we examine liver cT1 as a prognostic biomarker to predict clinical outcomes. Patients with varying liver disease aetiologies underwent multiparametric imaging (T1, T2* mapping (iron) and MR spectroscopy (fat)). Liver*MultiScan*™ software was used to obtain cT_1 liver maps and calculate the mean cT1 value from 3 regions of interest (ROIs) placed in the liver parenchyma.

Method: Patients were followed up for development of clinical outcomes by review of their medical records blinded to the imaging results. All-cause mortality, liver mortality, liver transplantation and liver-related events (ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma) were considered as clinical end points. Analysis was carried out for mortality and liver event-free survival. Patients who developed multiple end points were censored at the index event for liver event-free survival analysis.

Results: 190 patients were followed up for 564 patient-years (median (IQR) 35 (19–51) months). 119 (72%) patients were male; mean age (± SD) was 52 (± 13) years. Liver biopsy was performed in 165 patients. Histologic fibrosis assessment by Ishak staging was none/mild (F0-2) in 85 (52%), moderate (F3-4) in 25 (15%) and severe (F5-6) in 55 (33%) patients. Main diagnoses were viral hepatitis (n = 54, 28%), NAFLD (70, 37%) and alcohol related liver disease (26, 14%). 24 new liver events occurred during follow-up, including 15 deaths. Using the equivalent cut-off (Pavlides et al, 2016), cT1 could significantly differentiate between all-cause mortality ($p = 0.021$), liver-related mortality ($p = 0.010$) and liver event-free survival ($p = 0.005$; Fig 1a). For prediction of liver events, cT1 > 825ms had a hazard ratio (HR) of 4.8 and correctly classified 21/24 (84%) liver events; liver iron and fat did not predict clinical outcomes. In NAFLD/ALD/HCV/HBV patients (n = 150), cT1 > 825ms correctly classified 17/17 liver events ($p = 0.001$; Fig 1b). ISHAK F5-6 predicted liver event-free survival ($p < 0.001$, HR: 19) correctly classifying 18/21 (89%) events.



Conclusion: We provide further evidence that liver cT1 can predict clinical outcomes in a larger cohort of patients with chronic liver disease of mixed aetiologies and particularly well in NAFLD, ALD and HCV/HBV patients.

THU-365

Adeno-associated virus-serotype-specific transduction patterns in mice and non-human primates liver tissue: Implications for therapeutic efficacy

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Background and aims: AAV-based liver gene therapy has proven efficacious in mouse models of inherited disorders, but little is known about the transduction pattern of various AAV serotypes in the primate or human liver. To address this question, we assessed the AAV distribution pattern in the liver tissue of mice and non-human primates (NHPs) injected with either AAV serotype 1 or 5. The overall percentage of cells positive for the presence of AAV vector DNA/hFIX transgene RNA as well as the intensity and area of the positive signal were assessed. Additionally, AAV vector spatial distribution throughout the liver tissue was determined.

Method: Mice were injected intravenously (IV) with either AAV1-hFIX (human factor IX), AAV5^{ch}-hFIX or PBS, while NHPs were injected with either AAV1-hFIX, AAV5^{ch}-hFIX at dose or PBS. Liver tissues were collected post mortem and analyzed by fluorescent in situ hybridization (FISH) using probes specific for AAV vector DNA

and hFIX transgene mRNA. Hepatocytes were characterized based on Albumin RNA in mice and Serpina1 RNA in NHPs (FISH) while central veins were localized by Glutamine Synthetase (GS) protein detection by immunohistochemistry (IHC). Images were acquired with a slide scanner and analyzed with the use of an image analysis software (HALO, indica labs). For FISH image analysis, cells were scored from weak positive **(1+)** to strong positive **(4+)** based on combination of average positive signal area [μm^2] and average intensity of positive signal within cell [RFU].

Results: In mice, percentage of liver cells positive for the presence of AAV vector DNA/hFIX mRNA was similar for AAV1 and AAV5. However, liver cells positive for AAV5 vector DNA/hFIX RNA displayed a higher signal score than liver cells positive for AAV1 vector DNA/hFIX RNA suggesting more efficient transduction per cell by the AAV5 vector. Most cells transduced by AAV1 or AAV5 expressed Albumin and therefore were characterized as hepatocytes. Interestingly, spatial distribution of AAV vector DNA/hFIX RNA positive signal within the liver tissue was different for the two serotypes: AAV5 vector DNA/transgene RNA was more localized around the central veins whereas AAV1 was more homogenously distributed throughout the liver tissue.

In NHPs, the percentage of liver cells positive for AAV vector DNA/hFIX RNA was higher for $AAV5^{ch}$ than for AAV1, and like mice, AAV5 resulted in a higher AAV vector DNA/hFIX RNA probe signal score indicating a more efficient transduction per cell with AAV5 than with AAV1 in injected NHPs. Yet, in NHPs, unlike in mice, not only AAV1 but also AAV5 vector DNA/transgene RNA was homogenously distributed throughout the liver tissue.

Conclusion: These results indicate that mouse models may have a limited value to predict the efficacy of liver-targeted AAV-based gene therapy, in particular in the context of development of therapies for metabolic disorders.

THU-367

Linking diabetic cardiovascular disease with non-alcoholic fatty liver disease through L-carnitine: A hyperpolarized MRS study

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Background: Diabetes increases the incidence of non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD).

NAFLD can progress to NASH and into cirrhosis. NAFLD has been shown to be associated with CVD and insulin resistance. However, the underlying mechanisms linking NAFLD and CVD in the context of diabetes need to be elucidated in order to improve quality of life for patients. Studies have shown that L-carnitine levels are decreased in diabetic patients, and that L-carnitine supplementation protects cardiac as well as liver function.

Method: Male Wistar rats were treated with streptozotocin (STZ, 55mg/kg; n = 20) to induce diabetes or act as controls by injecting citrate buffer (CTR; n = 20). Daily intra-peritoneal injections of either saline or L-carnitine (3 g/kg/day) were initiated and continued for three weeks. Following treatment, cardiac function was assessed with MRI and metabolism with hyperpolarized magnetic resonance spectroscopy (MRS) respectively. Liver tissue was extracted for metabolomics analysis.

Results: L-carnitine treated control and diabetic animals had reduced blood TAG levels (**Fig.1A**). L-carnitine resulted in higher liver choline (**Fig.1B**) and decreased glutamate levels, the latter only in the diabetic group (**Fig.1C**). Cardiac function was depressed in the diabetic group and L-carnitine improved diastolic function through elevation of end-diastolic lumen, EDL (**Fig.1D**). This functional improvement was accompanied by increased flux through pyruvate dehydrogenase (PDH) in the diabetic heart, while L-carnitine reduced PDH-flux in the control group (**Fig.1E**).

Conclusion: We show a linkage between diabetic heart and the liver. Metabolism in both the heart and liver was modulated by L-carnitine. The liver is critical for choline metabolism, and studies have shown that NASH is associated with lower choline concentrations. This study

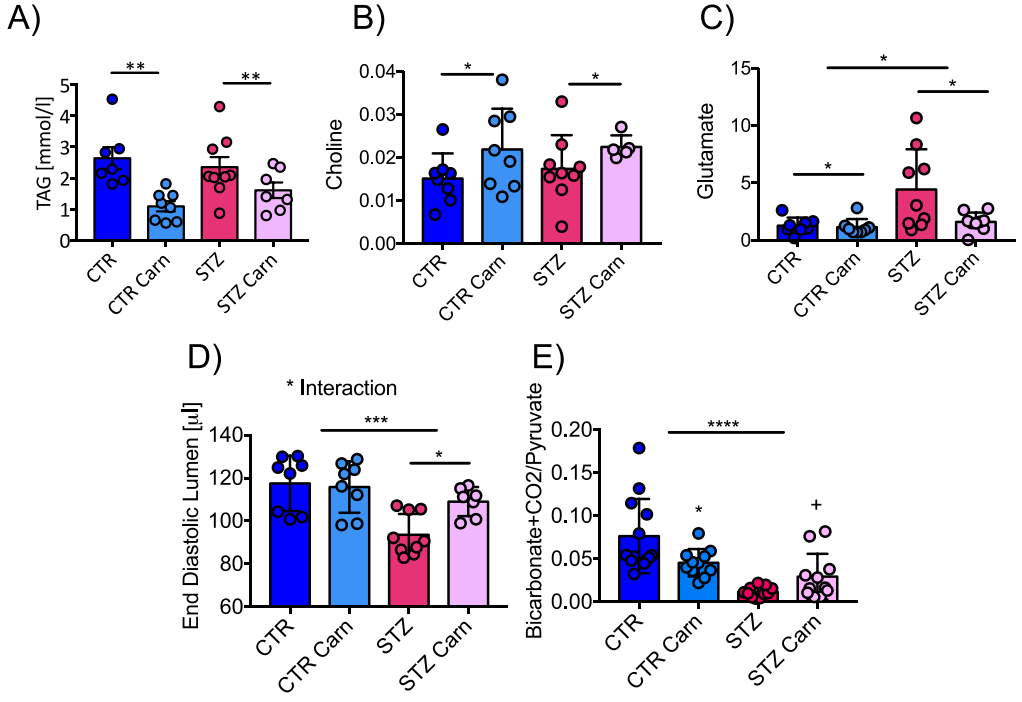

Figure: (abstract: THU-367): A)Serum triglycerides (TAG) levels in fasted state BC)Liver metabolites. D)End diastolic lumen (EDL) obtained from CINE MRI. E)Pyruvate dehydrogenase flux (Bicorbonate+CO2/pyruvate ratio) obtained from hyperpoalrized MRI.

demonstrates that some of the beneficial effects of L-carnitine could be mediated through increased liver choline levels, in addition to improving cardiac function and metabolism. Investigating cardiac function and metabolism in patients with NAFLD could provide an understanding of the interactions between the liver and heart and provide insights into novel therapeutics.

THU-368
Multimodal pre-clinical imaging of liver inflammation and fibrosis

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Background and aims: Formation and remodeling of the extracellular matrix (ECM) is critical during wound healing and scar formation but excessive connective tissue formation, as seen in fibrosis, can be detrimental and lead to organ failure. Besides massive ECM accumulation, fibrosis also involves the formation of new vessels and the establishment of abnormal angio-architecture of the liver.
We have recently developed a spontaneous animal model, the NIF mouse, that recapitulates the process of persistent inflammation leading to tissue remodeling and fibrosis that is commonly observed in human fibrotic disorders. Liver fibrosis is a slow progressing disease requiring large and long costly clinical trials. Current non-invasive clinical and pre-clinical imaging systems are unable to access the spatial resolution domain to reliably detect fibrosis in its early stages. Thus, there is great potential and need for developing time efficient new approaches that can accurately diagnose the early-stages of liver fibrosis and in combination with a relevant preclinical *in vivo* model will identify the most promising drugs at an early stage of disease.
Method: Here we apply magnetic resonance imaging (MRI), optical projection tomography and synchrotron radiation imaging in a multimodal imaging approach that exploits the different strengths of these modalities to establish a method for longitudinal, high resolution, and global evaluation of the inflammatory and fibrosis component of the disease phenotype spontaneously developing in the N-IF mouse model.
Results: Eight-week-old NIF and control mouse liver samples revealed the potential of using SWI MRI for identifying fibrotic liver tissue. Liver fibrosis and cirrhosis involves the accumulation of scar tissue, which impedes blood circulation in the liver, leading to portal hypertension and as consequence the formation of new vessels (also called angiogenesis) and the establishment of abnormal angio-architecture of the liver that can be visualized by OPT, obtaining quantitative 3-D images of total organ fibrosis. Further, we have performed synchrotron radiation micro-CT on 8-week old NIF liver tissue. In comparison to healthy liver tissue we could detect a changed microstructure with less and disrupted sinusoids which can be distinguished in 3D images of the hepatic vessel network. This could give an Implication for the impaired exchange between sinusoids and hepatocytes in fibrotic livers.
Conclusion: This data will serve as baseline observation for determining the impact of therapeutic regimes targeting inflammation and/or fibrosis. Advances in the elucidation of the biology of fibrosis, combined with improved technologies for assessment will provide a comprehensive framework for design of antifibrotics and their analysis in well-designed clinical trials.

THU-369
Efficacy and safety of endoscopic ultrasound-guided liver biopsies in parenchymal liver diseases: A systematic review and meta-analysis

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Background and aims: Percutaneous and trans-jugular biopsies are the primary methods of obtaining liver tissue. While the utility of endoscopic ultrasound (EUS) guided liver biopsies for focal liver lesions is established, the role of EUS-guided random liver biopsies in the diagnosis of parenchymal liver diseases is of interest. We conducted a systematic review and meta-analysis to determine the efficacy and safety of EUS-guided liver biopsy in patients with suspected parenchymal liver diseases.
Method: Multiple databases were searched from 1988 through January 2008 incorporating retrospective chart reviews, prospective trials (randomized and non-randomized), and case series. The primary study outcomes were procedural success, determined by number of complete portal tracts (CPTs) and total specimen length (TSL). Secondary outcomes assessed safety of EUS-LB, including complications of pain, bleeding, peritonitis and death. Estimates were pooled across studies using the random effects model.
Results: A comprehensive search of the literature identified 1, 578 potential studies. Twenty studies with a total of 885 adult patients who underwent EUS-LB were included in the analysis. The most common indication for EUS-LB was elevated liver function tests (LFTs) without biliary obstruction. No studies included patients with thrombocytopenia (defined by platelets < 50, 000), coagulopathy (INR > 1.5), decompensated liver disease or pregnant subjects. The mean number of CPTs ranged between 3.5–38.4 with a pooled mean of 15.2 (95% CI = 11.5–18.9). The mean TSL ranged between 10.5 mm-77.0 mm with a pooled mean of 41.4 mm (95% CI = 30.2–52.6). Complication rates were low, including: bleeding 0.6%–5.0% (pooled 2.2%; 95% CI = 1.3%–3.8%) and pain 0.9%–33.3% (pooled 4.0%; 95% CI = 2.6%–6.2%). There were no reported adverse events of peritonitis or death.
Conclusion: EUS-guided liver biopsy is an effective alternative to percutaneous liver biopsy that meets the standard specifications for an optimal liver biopsy as defined by the European Association for the Study of the Liver (25 mm TSL) and the American Association for the Study of Liver Diseases (20 mm TSL and > 11 CPTs). This meta-analysis concludes that EUS-guided liver biopsies can provide evaluable samples with low complication rates. Additional studies evaluating various types of biopsy needles may provide further support for the use of EUS-guided liver biopsies.

THU-370
Quantification of hepatic metal overload by laser ablation inductively coupled plasma mass spectrometry imaging (LA-ICP-MSI)

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Background and aims: Metal overload plays an important role in the development of liver diseases. Wilson's disease (WD) and hereditary hemochromatosis (HH) are good examples how metal buildups lead to organ damage and liver failure. They induce oxidative stress, severe dysfunction of mitochondrial energy production, and alterations in sterol metabolism resulting in severe molecular impairments. Precise metal quantitation and the identification of metal accumulates is still challenging. We have established novel LA-ICP-MSI protocols that allow quantitating various metals and metalloids in liver specimens of experimental metal overload models and in clinical samples obtained from patients suffering from WD or HH.

Method: All human samples have been collected in the course of routine clinical care and were obtained by a standardized protocol. WD and HH genotyping was carried out using validated TaqMan allelic discrimination assays and LightCycler technology. Liver samples were cryo-cut into 30 µm thick slices with a CM3050S cryomicrotome (Leica Biosystems) on −18°C cryo-chamber temperature and −16°C object area temperature, and thaw-mounted onto adhesive StarFrost® microscope slides (Knittel Glass). For the LA-ICP-MSI, we used a quadrupole-based inductively coupled plasma mass spectrometer (ICP-MS, XSeries 2, Thermo Scientific) coupled to a laser ablation system (NWR 213, New Wave Research). 30 µm thick tissue sections were ablated by a focused Nd:YAG laser beam in the scanning mode (wavelength 213 nm, repetition frequency 20 Hz, laser spot diameter 60 µm, scanning speed 60 µm/s).
Results: We demonstrate that LA-ICP-MSI technique allows precise measurement and visualization of copper and iron deposits with high spatial resolution, sensitivity, quantification ability, and exceptional reproducibility in liver tissue. Moreover, our measurements revealed that hepatic iron and copper overload are associated with large variations in other trace metals.
Conclusion: LA-ICP-MSI has multi-element capability suitable to simultaneously measure and quantify a large variety of different metals and metalloids within liver tissue. Therefore, this method is an important diagnostic option in hepatology. The established workflow is straightforward and creates metal maps that are easy to interpret. Furthermore, the simultaneous measurement of various metals offers unique opportunities for a deeper understanding of the biology and changes in metal fluxes during metal-associated liver diseases.

Liver development, physiology and regeneration

THU-371

Modulation of H3K27 methylation by EZH2 and UTX/JMJD3 small molecules inhibitors impacts on proliferation and differentiation of hepatic progenitor cells and differentiated hepatocytes plasticity

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Background and aims: Histones methylation at specific lysine and arginine residues is dynamically regulated by different histone methyltransferases and demethylases and plays a critical role in many biological processes. The methyltransferase EZH2, as part of the Polycomb Repressive Complex 2 (PRC2), controls the di-trimethylation of H3K27 (H3K27me2/3) and triggers gene suppression, whereas the lysine demethylases Jumonji D3 (JMJD3, KDM6B) and the UTX (KDM6A) demethylate H3K27me2/3, leading to transcriptional activation. An increased expression of Ezh2 is frequently detected in HCC tissues. It correlates with aggressiveness and/or poor prognosis of HCCs and may help to discriminate between liver pre-neoplastic/dysplastic lesions from cancer. Here, we investigate the impact of the pharmacological modulation of H3K27 methylation on hepatic cells proliferation, differentiation and plasticity using the human bipotent progenitor cell line HepaRG.
Method: Proliferating HepaRG (pHepaRG), DMSO/low serum-differentiated HepaRG cells (dHepaRG) and primary human hepatocytes (PHHs) were treated with the epigenetic drugs GSK-126 (EZH2 inhibitor) and GSK-J4 (JMJD3/UTX inhibitor). RNA-Seq libraries were prepared using the TruSeq® Stranded RNA HT (w/Ribo-Zero™) and sequenced (75×2 cycles) on an Illumina HiSeq platform.
Results: EZH2 methyltransferase and JMJD3/UTX demethylases are differentially regulated in dHepaRG cells, resulting in a strong reduction of H3K27 methylation levels. RNA-seq analysis of GSK-J4 treated dHepaRG cells showed that the inhibition of JMJD3/UTX demethylase activity strongly downregulated several metabolic and differentiation pathways, whereas cell cycle and DNA replication pathways were upregulated. RT-PCR analysis confirmed that GSK-J4 treatment induces a drastic decrease of hepatic differentiation markers, such as Albumin and Cyp3A, 4 and a significant increase of proliferation markers, such as Ki67 and CCNB1. The inhibition of JMJD3 and UTX demethylase activity in human primary hepatocytes induced their partial de-differentiation with a reduction in albumin expression and secretion and Cyp3A4 activity. GSK-J4 treatment of dHepaRG cells and PHHs induced cell cycle re-entry and increased cell mobility in scratch wound assays. Conversely, the inhibition of EZH2 methyltransferase activity with GSK-126 decreased cell proliferation and upregulated several hepatic markers in pHepaRG cells.
Conclusion: Our results indicate that the balance of EZH2 and JMJD3/UTX activities plays an important role in the control of cell proliferation and differentiation in hepatic progenitor cells and that the pharmacological modulation of H3K27 methylation using small molecule inhibitors of EZH2 and JMJD3/UTX activity may be exploited to induce hepatic progenitor cells differentiation and differentiated hepatocytes plasticity and proliferation.

THU-372

Exosomes from human umbilical cord mesenchymal stem cells promote liver regeneration in aged mice after major hepatectomy via activating sirtuin1 pathway

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Background and aims: Aging is known to negatively influence liver regeneration, which restrict the extent of hepatectomy in the elderly population. Exosomes are small double-membrane vesicles participating in intercellular communication. Previous studies have shown the ability of exosomes from umbilical cord-derived mesenchymal stem cells (UC-MSC-Exo) to promote hepatocyte proliferation. However, little is known about their biological function on aging liver. Thus, we aim to determine whether UC-MSC-Exo contribute to liver regeneration in aging mice after major hepatectomy.
Method: Exosomes from human umbilical cords-derived mesenchymal stem cell were isolated and characterized. In vivo study, we used model of 70% partial hepatectomy to evaluate whether UC-MSC-Exo promote hepatocyte proliferation and liver regeneration in aging C57BL/6 mice. In addition, primary hepatocytes were isolated and cultured to determine whether UC-MSC-Exo enhanced proliferation of senescent hepatocytes in vitro.
Results: Compared with young (8–10 weeks) mice, old (> 16 months) mice were more susceptible to oxidative stress and showed decreased hepatocytes regeneration after major hepatectomy. In addition, hepatic expression of sirtuin 1 (SIRT1) was significantly reduced in old mice compared with that in young mice. UC-MSC- Exo exhibit dose-dependent ability to promote proliferation of aging hepatocyte in vitro and in vivo. Mechanistically, UC-MSC-Exo fuse with the hepatocytes directly and increase synthesis of SIRT1. Finally, ablation of SIRT1 expression within aging hepatocytes abolished the proliferative effect of UC-MSC-Exo.
Conclusion: Exosomes from umbilical cord-derived mesenchymal stem cells could deliver the synthetic component to stimulate SIRT1 expression in senescent hepatocytes, resulting in their proliferation

and liver regeneration after major hepatectomy. These results represent a potentially new contributing mechanism of MSC-Exo in liver regeneration and have important indications for novel therapeutic approaches in age-related diseases.

THU-373

IL-6 trans-sginaling controls liver regeneration after partial hepatectomy

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Background and aims: Interleukin-6 (IL-6) is critically involved in liver regeneration after partial hepatectomy (PHX). PHX-induced generation of the soluble IL-6R by ADAM proteases strengthens IL-6 trans-signaling in which IL-6 forms an agonistic complex with the soluble IL-6 receptor (sIL-6R) to activate all cells expressing the signal-transducing receptor chain gp130. In contrast, without activation of ADAM proteases, IL-6 in complex with membrane-bound IL-6R and gp130 activates classic signaling. It has been suggested that IL-6 trans-signaling *via* the soluble IL-6/IL-6R complex is involved in liver regeneration. However, long-term contribution of IL-6 trans-signaling for liver regeneration after PHX is unknown. In this study we try to investigate the long term contribution and the importance of IL-6 trans-signaling for liver regeneration after PHX by using novel IL-6 trans-signaling mice. We survey the long-term consequences of global IL-6 signaling inhibition versus IL-6 trans-signaling selective blockade after partial hepatectomy on liver regeneration by IL-6 monoclonal antibodies and sgp130Fc, respectively. For first time we studied the importance of IL-6/IL-6R in the liver regeneration after partial hepatectomy by using IL-6R knockout mice.
Method: We generated novel IL-6 trans-signaling mice, which were genetically engineered to only execute IL-6 trans-signaling and abrogated classic signaling by *genetic* conversion of all membrane-bound IL-6R into sIL-6R proteins. The compensatory role of IL-6 trans-signaling in liver regeneration was then identified by monitoring stat-3 phosphorylation and hepatocyte proliferation.
Results: In this study we could show whereas IL-6R deficient mice were strongly affected by PHX, survival and regeneration of IL-6 trans-signaling mice was indistinguishable from control mice. Both global IL-6 blockade and selective inhibition of IL-6 trans-signaling results in strong decrease of overall survival after PHX, accompanied by decreased STAT3 phosphorylation and proliferation of hepatocytes. We could also show that IL-6 trans-signaling induces hepatocyte growth factor (HGF) production by hepatic stellate cells (HSC).
Conclusion: By using two independent strategies we demonstrate that IL-6 trans-signaling fully compensates for the loss of IL-6 classic signaling in liver regeneration after PHX.
In addition expression of HGF by hepatic stellate cells (HSCs) is under the control of IL-6 trans-signaling after PHX.

THU-374

The INCRNA H19-dervied MIR-675 promotes liver necroptosis by targeting fadd

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Chronic inflammation is closely linked to cancer formation. Many molecular pathways are involved in the inflammatory response and some of these including microRNAs, have been connected to liver cancer development. The H19 derived microRNA-675 (miR-675) has been implicated as both tumor promoter and tumor suppressor and also plays a role in liver inflammation, which is not yet fully understood. We found that miR-675 promotes cell death in human hepatocellular carcinoma (HCC) cell lines. We show that FADD, a mediator of apoptotic signaling, is a miR-675 target and is down regulated by this miRNA. Importantly, we found a negative correlation between miR-675 and FADD expression in mouse models of HCC as well as in human samples. We demonstrate in a mouse model of liver inflammation that over expression of miR-675 represses FADD expression and promotes necrosis. We confirm both *in vitro* and *in vivo* that this necrotic cell death is necroptosis which can be inhibited by the necroptosis specific inhibitor Nec-1/Nec-1 s. We also show that necroptosis induced by miR-675 expression, is mediated by p-MLKL (Mixed Lineage Kinase Domain Like Pseudokinase) in a lipopolysaccharide (LPS) induced liver inflammation. Furthermore, miR-675 enhanced MLKL binding to RIP3 (receptor-interacting protein 3) a key signaling molecule in necroptosis. In conclusion, down regulation of FADD by miR-675 promotes liver necroptosis in response to inflammatory signals. We propose that this regulation cascade could stimulate and enhance the inflammatory response in the liver, making miR-675 an important regulator in liver inflammation and potentially also in HCC.

THU-375

Transcription factor TRIM33 controls liver progenitor cell towards hepatocyte differentiation through synergizing with SMAD2/3 following massive parenchymal loss

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Background and aims: In liver disease with severe parenchymal loss, e.g. acute-on-chronic liver failure (ACLF), liver progenitor cells (LPC), the local stem cells, are the main cell source to replenish lost hepatocytes through cell reprogramming. The molecular mechanisms underlying LPC towards hepatocytes differentiation in ACLF largely remain unknown to date. Tripartite motif protein (TRIM) 33 is a crucial transcription factor for differentiation of embryonic stem cells through the formation of transcription factor complexes with p-Smad2/3, the downstream substrates of activated TGF-β signaling. This transcription factor complex opens binding sites at promoters of master regulators of differentiation, e.g. goosecoid (GSC), for the additional transcription factor complexes, such as Smad4-pSmad2/3-FoxH1. The current study investigated the role of TRIM33 in LPC differentiation towards hepatocytes.
Method: We enrolled 113 liver tissue specimens from patients with compensated cirrhosis, 20 ACLF with liver transplantation and 3 ACLF spontaneously recovered. Expression of TRIM33, FoxH1, GSC and presence of p-Smad2 was measured by immunohistochemistry. *In vitro*, BMOL cells, a murine LPC line, were used as an LPC towards hepatocyte differentiation model.
Results: Given that more than 70% hepatocyte buds derive from LPC in cirrhotic liver, patients with cirrhosis are ideal candidates to observe successful LPC differentiation towards hepatocytes. In 90 HBV-associated compensated cirrhotic patients, most buds showed

strong immune positivity for p-Smad2, TRIM33, FoxH1 and GSC in the same hepatocytes. However, in 20 ACLF patients, who received liver transplantation, expression of TRIM33, FoxH1 and GSC were undetectable. In contrast to these patients, 3 spontaneously recovered ACLF patients showed strong nuclear FoxH1 and p-Smad2 staining in LPC and hepatocyte-like cells. *In vitro*, BMOL cells differentiated into hepatocyte-like cells, expressing hepatocyte specific proteins, e.g. albumin and transferrin, synthesizing glycogen, and losing cholangiocyte phenotype as evident from reduced CK19 and SOX9 expression over time. In this transdifferentiation process, phosphorylation of Smad2 and Smad3, and expression of TRIM33 and FoxH1 were induced and maintained at high levels. Immunoprecipitation analysis revealed the presence of TRIM33/p-Smad2/3 complexes. Knockdown of Smad2, Smad3, TRIM33 or FoxH1 significantly reduced expression of albumin and transferrin. TRIM33 expression was upregulated by EGF, whereas blocking the EGF receptor reduced expression of TRIM33, albumin and transferrin.
Conclusion: Transcription factor complexes TRIM33/Smad2/3, which are driven by EGF and TGF-β signaling, mediate differentiation of LPC towards hepatocyte in severe liver disease with massive parenchymal loss, e.g. liver cirrhosis and ACLF.

THU-376
A viral mediated liver repopulation assay without the use of transgenic animals

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Background and aims: Animal models of liver repopulation assay is the ''gold standard'' to determine the functionality of transplanted cells. Most liver repopulation assays require genetic modifications to the recipients to provide selective advantage for the donor cells to outcompete the host cells during regeneration. Currently, the generation of these assays involve extensive breeding of transgenic animals, such as the urokinase plasminogen activator (uPA) mice, the fumaryl acetoacetate hydrolase (FAH) deficient mice, and the $Mdm2^{fl/fl}$ mice. Here, we developed an alternative strategy using a viral mediated method to inhibit hepatocyte proliferation in wild type mice as recipients for liver repopulation assay. This method reduces the number of transgenic animals required, time and cost for conducting therapeutic liver repopulation assay.
Method: We packaged a partial coding region of p21 into an Adeno-Associated Virus Serotype 8 (AAV8-p21) Vector under the control of the hepatocyte specific Thyroxine binding globulin (TBG) promoter. Due to the hepatotropism of the AAV8 and the hepato-specificity of the TBG promoter, this will confine the p21 overexpression in hepatocytes specifically. Recipient wild type C57Bl6 mice were administrated with AAV8-p21 or AAV8-Ctrl by tail vein injection at a concentration of 2.5×10^{11} GC/ml. Mice were then given a dose 1.5 mg/kg of Carbon Tetrachloride (CCl4) through intraperitoneal injection 7 days after the AAV8-p21 injection to induce hepatocyte damage. 10^6 freshly isolated TdTomato (tdTom) hepatocytes were transplanted into the recipient mice 2 days after the CCl4 injection. Recipient mice received weekly injection of 1.5 mg/kg CCl4 after transplantation and tissue were analysed one month after transplantation.
Results: p21 protein expression was observed in mice received AAV8-p21 injection and the lack of hepatocyte proliferation was observed after CCl4 injection. Similar engraftment of donor cells was observed 1-week post-transplantation in the AAV8-p21 injected mice compared to controls. When repetitive CCl4 was administrated weekly up to a month, transplanted hepatocytes repopulated 10 times better in the AAV8-p21 injected group than the controls and reconstitute around 30 percent of the liver. Transplanted cells are functional from the expression of CYP2D enzymes and HNF4a expression. The donor cells repopulate the liver uniformly without zonal preference and picrosirius red staining shows similar level of scar deposition in both groups suggesting the injury and regenerative mechanism is unaltered in the AAV8-p21 mediated liver repopulated model.
Conclusion: Here, we report a novel and rapid method to investigate the liver repopulating capacity of cells without using genetic modified animals.

THU-377
Systemic blood pressure is not associated with hepatic perfusion and metabolic activity by 18F-FDG PET in patients with NAFLD

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Background and aims: ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) has the potential to quantitatively characterize fatty liver disease states. However, the effect of change in systemic hemodynamics on hepatic and splenic FDG-PET parameters in humans is not yet well understood. In the present study, we aim to examine the relationship between systemic blood pressure with perfusion and metabolism of the liver and spleen in non-alcoholic fatty liver disease (NAFLD) patients by FDG PET.
Method: Systolic (SBP), diastolic (DBP) blood pressures, and mean arterial pressure (MAP) were measured from biopsy-proven NAFLD patients. FDG PET was performed on all fasting patients and analyzed using 3-compartment modeling. Regions of interests (ROIs) were placed on eight individual liver segments and the spleen to obtain the surrogate of perfusion as characterized by the FDG blood-to-tissue rate K_1 and the overall metabolic activity as characterized by standardized uptake value (SUV). Associations between the FDG parameters and systemic blood pressure were determined by linear regression, adjusting for body mass index (BMI), age, gender, and use of beta and calcium channel blockers.
Results: 30 NAFLD patients were enrolled (67% female). Mean age 55 years, SBP 125 mm Hg, DBP 76 mm Hg, and MAP 70.5 mm Hg. 27% of the patients had advanced fibrosis (Kleiner Fibrosis ≥ 3). There was no association between blood pressure (s) and FDG K_1 and SUV in the liver and the spleen. Similarly, blood pressure (s) did not associate with the K_1 of each segment of the liver. Significant effect of SBP and DBP was observed only in a single segment with change in fibrosis. Among those with advanced fibrosis (> stage 3), K_1 in segment 5 increased with increasing SBP (p = 0035) and decreased marginally

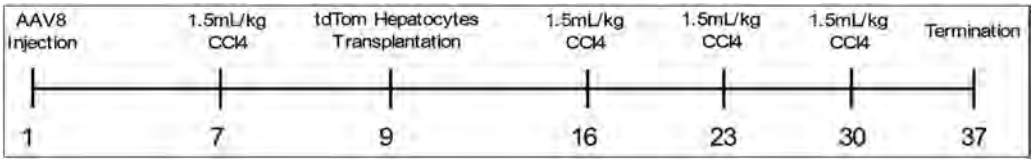

Figure 1: (abstract: THU-376): Schematic illustration showing the experimental setup

with increasing DBP (p = 0.049). However, no association between systemic blood pressure with other segments of the liver and the spleen for K_1 and SUV were observed among subjects with early or advanced fibrosis.
Conclusion: Although our study is limited by the number of patients, it provides preliminary data on the effect of changes in blood pressure on liver/spleen perfusion and glucose metabolism. We present data to show that systemic blood pressure did not appreciably affect either hepatic perfusion or overall metabolic activity in NAFLD patients. Future analysis in larger cohorts are needed to further define the effect in individual liver segments and relation to disease state.

THU-378
Messenger RNA transcriptome profiling reveals a distinct phenotype of human bone marrow mesenchymal stem cell-derived hepatocytes
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Background and aims: The hepatocytes differentiated from stem cells are promising alternatives of primary human hepatocytes (PHHs) to treat liver disease. However, the differentiation mechanism is still unclear, and the in vitro differentiated immature hepatocytes limit the further clinical translation. In this study, we aimed to clarify the transcriptome characteristics of hepatocytes differentiated from human bone marrow mesenchymal stem cells (hBMSCs) for future clinical application.
Method: Human BMSCs were isolated from bone marrow of health volunteers, and differentiated into hepatocytes. After 20 days differentiation, hBMSC differentiated hepatocytes (hBMSC-Hep) were harvested for mRNA sequencing (mRNA-seq), using hBMSCs and PHHs as controls. The significantly differentially expressed genes (DEGs) were identified via bioinformatics analysis, and validated in hBMSC transplanted fulminant hepatic failure (FHF) pigs.
Results: hBMSC-Heps exhibited a polygonal morphology, and were positive for albumin staining and glycogen accumulation. The transcriptome profiling of hBMSC-Hep showed specific hepatic functional pathways. Comparing with hBMSCs, 630 DEGs were identified to be significantly upregulated in hBMSC-Heps and PHHs, while 1082 DEGs were downregulated. Functional annotation clustering analysis showed that the upregulated DEGs were involved in hepatic functions, such as sterol metabolism, lipid transport, oxidation reduction, inflammatory and immune responses,. And the downregulated DEGs were related with stem cell characteristics, such as multipotent differentiation, cell cycle regulation and cytoskeleton reorganization. Total 18 DEGs (9 up- and 9 down-regulated) with > 5 fold changes were confirmed by quantitative real-time PCR in three independently experiments, which showed a similar results of mRNA-seq. Further validation of hBMSCs transplantation with FHF model in pigs showed that the implanted hBMSCs completely differentiated into hepatocytes within 7 days, and the 5/9 upregulated DEGs (*TDO2*, *HP*, *SERPINA3*, *LBP* and *SAA1*) exhibited a same expressed trend. Such 5 DEGs with > 150-fold change of increase were mostly contributed to the liver metabolism and inflammation, which imply a differentiation ability of mature hepatocytes.
Conclusion: The mRNA transcriptome profiling demonstrated a mechanical direction of hBMSC differentiation into hepatocytes, and five DEGs may contribute to improving strategies of hBMSC-derived hepatocytes.

THU-379
Deficiency of apoptosis-stimulating protein two of p53 promotes liver regeneration in mice by activating mammalian target of rapamycine
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Background and aims: Although liver regeneration has been intensively studied in various ways, the mechanisms underlying liver regeneration remain elusive. Apoptosis-stimulating protein two of p53 (ASPP2) was discovered as a binding partner of p53 and plays an important role in regulating cell apoptosis and growth. However, the role of ASPP2 in hepatocyte proliferation and liver regeneration has not been reported.
Method: The expression profile of ASPP2 was measured in a mouse model with 70% partial hepatectomy (PH_X). Liver regeneration and hepatocyte proliferation were detected in wild-type ($ASPP2^{+/+}$) and ASPP2 haploinsufficient ($ASPP2^{\pm}$) mice with PH_X. The mammalian target of rapamycin (mTOR) and autophagy pathways were analyzed in the $ASPP2^{+/+}$ and $ASPP2^{\pm}$ mice with PH_X. After rapamycin or 3-methyladenine (3-MA) treatment, hepatocyte proliferation and liver regeneration were analyzed in the $ASPP2^{+/+}$ and $ASPP2^{\pm}$ mice with PH_X.
Results: ASPP2 expression was shown to be upregulated at the early stage and downregulated at the late stage. Compared to the $ASPP2^{+/+}$ mice, liver regeneration was enhanced in $ASPP2^{\pm}$ mice with 70% PH_X. In addition, compared to the $ASPP2^{+/+}$ mice, the mTORC1 pathway was significantly upregulated and the autophagic pathway was downregulated in $ASPP2^{\pm}$ mice with 70% PH_X. Inhibition of the mTORC1 pathway significantly suppressed liver regeneration in $ASPP2^{\pm}$ mice with 70% PH_X. In contrast, disruption of the autophagic pathway further enhanced liver regeneration in $ASPP2^{\pm}$ mice with 70% PH_X.
Conclusion: ASPP2 deficiency can promote liver regeneration through activating the mTORC1 pathway, which further regulates downstream molecules, such as those related to autophagy and p70S6 K expression in mouse model post-PH_X.

THU-380
DLL4 restores damaged liver by protecting hepatocytes and enhancing cholangiocyte differentiation
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Background and aims: Hepatocyte necrosis and intrahepatic cholangiolar injury are the main pathological mechanisms of fulminant hepatic failure (FHF). Delta-like ligand 4 (DLL4)-mediated Notch activation contributes to reversing hepatic and biliary injury. However, its detailed mechanism is still unclear. This study aimed to clarify the role of DLL4 in restoring damaged liver by protecting hepatocytes and enhancing cholangiocyte differentiation.
Method: The efficacy of DLL4 was evaluated in a rat model of FHF by determining the survival rate, observing the liver structure and examining the biochemical index. The human hepatocyte line QSG-7701 was transfected with pcDNA-DLL4 and si-DLL4 to evaluate the protective effects of DLL4. The potency of DLL4 in inducing cholangiocyte differentiation from human bone marrow mesenchymal stem cells (hBMSCs) was assessed by measuring the expression of cholangiocyte-specific genes and proteins.
Results: DLL4 treatment significantly prolonged the survival of rats with FHF (p < 0.05). Liver tissue structure and biochemical functions were significantly improved in rats in the DLL4 treatment group. The hepatocyte-specific markers albumin (ALB), alpha fetoprotein (AFP), cytokeratin 18 (CK18), hepatocyte nuclear factor 4 alpha (HNF4

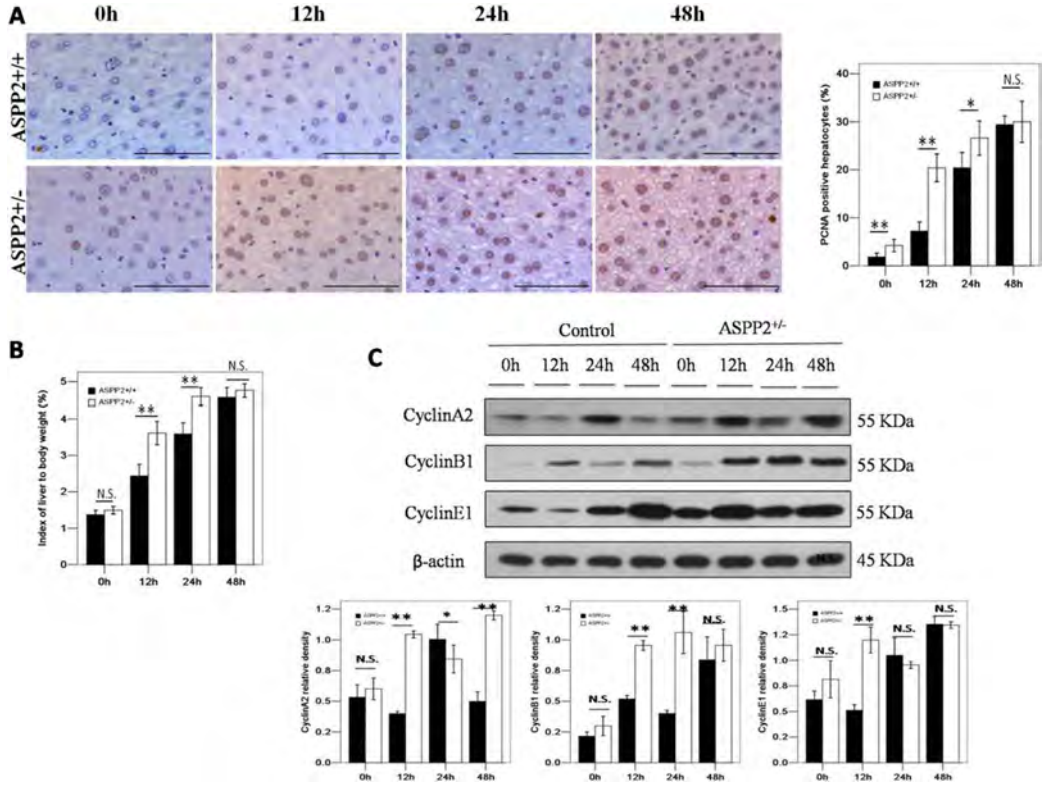

Figure1: (abstract: THU-379): Enhanced liver regeneration in ASPP2 ± mice after 70% PHX.

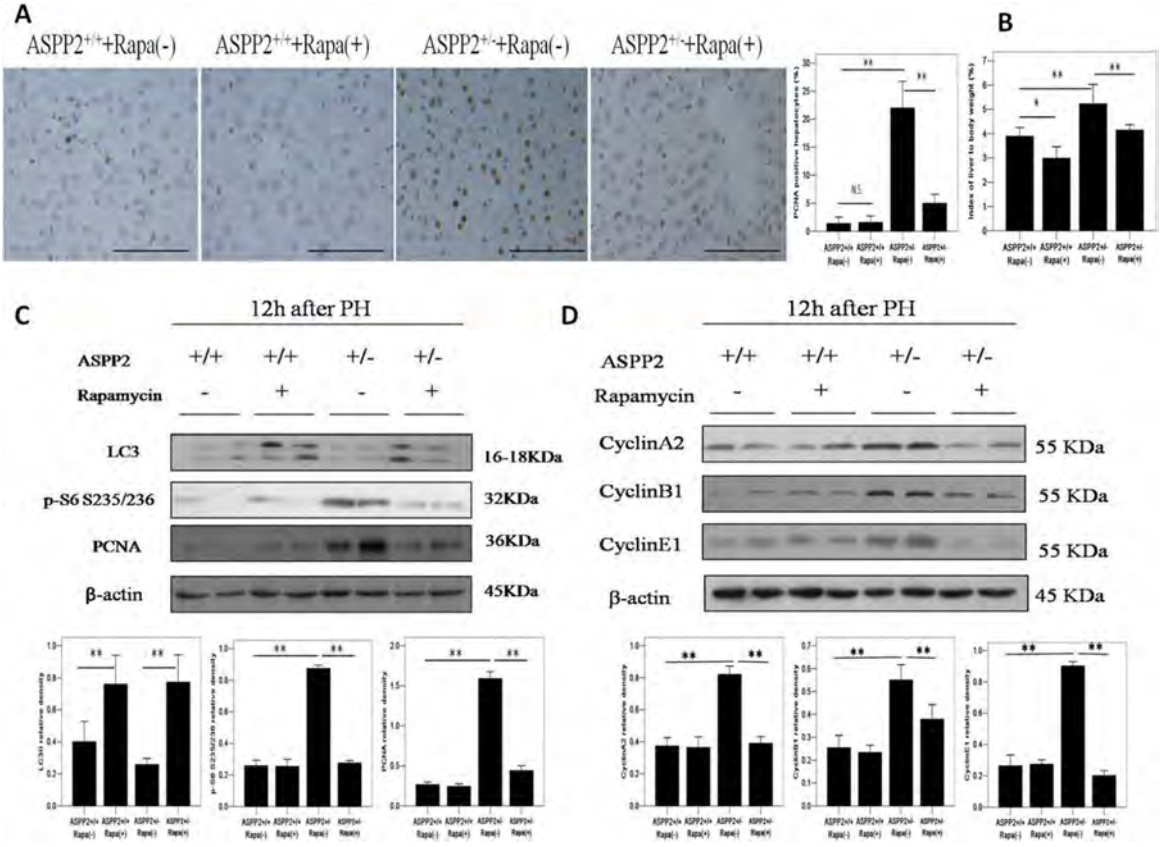

Figure 2: (abstract: THU-379): Inhibition of the mTORC1 pathway significantly suppresses liver regeneration in ASPP2 ± mice.

alpha) and cytochrome P-450 (CYP450) were upregulated by *DLL4* overexpression and downregulated by *DLL4* knockdown in cultured QSG-7701 hepatocytes. Furthermore, hBMSC-derived cholangiocyte-like cells induced by DLL4 showed a specific increase in the expression of cholangiocyte-specific genes (e.g., *CK19*, SRY-BOX 9 [*Sox9*] and cystic fibrosis transmembrane conductance regulator [*CFTR*]).
Conclusion: DLL4 restores damaged liver by protecting hepatocytes and enhancing cholangiocyte differentiation from hBMSCs, and DLL4 has the potential to be used in future clinical therapeutic applications.

THU-381
Characterization of regeneration in chronic hepatitis B before and after entecavir treatment in 20 patients
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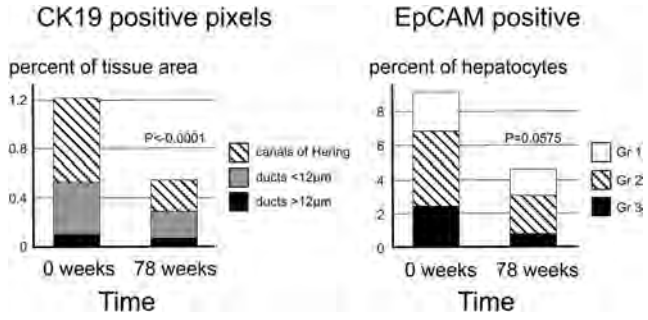
Background and aims: Human chronic liver disease is characterized by regions of collapsed parenchyma resulting in septa composed of approximated tissue structures and associated fibrosis. After cessation of primary injury, progenitor activity causes repopulation of these septa with bud-derived hepatocytes. Although the natural history of buds has been studied with various markers (Stueck A, Hepatology 2015), the timing of hepatocyte repopulation and maturation is unknown. The present study clarifies timing by examination of biopsies obtained during the course of a therapeutic trial of entecavir in chronic hepatitis B (Sun Y et al, Hepatology 2017;65:1438).
Method: Liver biopsies were obtained before (0 weeks) and after viral eradication had been achieved (78 weeks). 20 pairs of biopsies were stained for CK19 and EpCAM. CK19 positive pixels were counted with ImageJ software (NIH). Positive pixels were subclassified by location in large tubular ducts (> 12 µm), small tubular ducts (< 12 µm), and non-tubular structures (canals of Hering = COH). EpCAM positivity in hepatocytes were graded 0-3 and expressed as percent of total hepatocyte area.
Results: CK19+ pixels in COH decreased 62% with time ($p < 0.0001$). EpCAM expression was found in 8.7% of hepatocytes at 0W and 3.9% at 78W ($p = 0.0575$) (Figure 1). EpCAM correlated with CK19 in COH ($p = 0.0022$). EpCAM expression was less intense after therapy with adjacent domains of various intensities present concurrently. At 78 weeks, both markers remained at higher than normal levels.



Conclusion: The progenitor-derived budding process is easily observed with CK19 and EpCAM expression in most biopsies with active chronic hepatitis B. The process has largely subsided at 78 weeks, especially where damaged foci have regained near-normal parenchymal appearance. Hepatocyte division continues for a time after bud initiation so that cytoplasmic CK19 and EpCAM are diluted (or degraded) after new synthesis of the markers has ceased. The marked change in COH number with time confirms that many are transient structures in regions of incompletely healed injury. As such, they are likely residual tags of distal ducts resulting from the budding process. EpCAM expression related to regeneration may be distinguished from pre-neoplastic expression by the gradients of intensity (fading) with eincreasing distance from the duct centers. We expect to further clarify the time course of healing as 5-year biopsies from this trial become available in coming months.

Public Health

THU-382
Use of facility-based provider initiated testing and counselling approach to ascertain viral hepatitis C status in high burden populations in Nigeria
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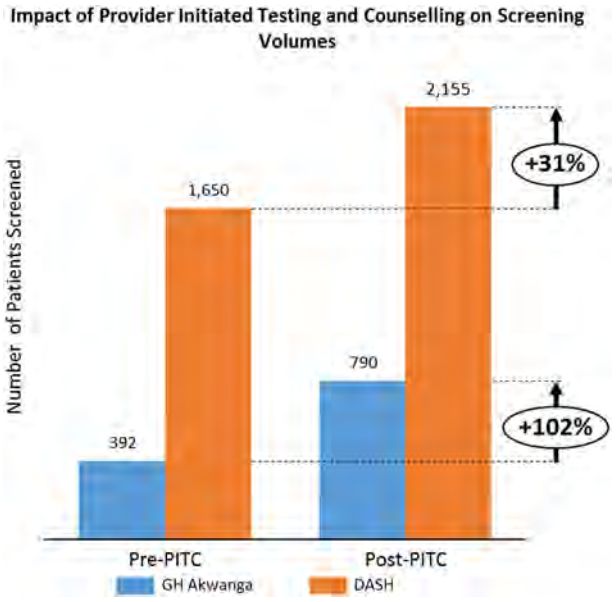
Background and aims: In Nigeria, an estimated 24 million persons chronically infected with HBV and/or HCV could proceed to develop advanced liver diseases, and pose a risk of disease transmission if untreated. Despite the high burden of the disease and opportunities available for treatment, approximately 95% of people infected with HCV are unaware of their status. To improve case identification, Provider Initiated Testing and Counselling (PITC) used in the HIV program and approved/recognized by the World Health Organisation was employed across two facilities in Nasarawa State, to drive HCV case detection. Using this approach, patients visiting the facility outpatient clinics were offered screening for HCV to ascertain their status. This analysis aimed to highlight the impact of PITC at these pilot facilities in Nasarawa as a model to improve case identification in high burden environments.
Method: This analysis utilized retrospective data from facilities to determine access to and volume of HCV screenings successfully conducted using Rapid Test Kits (RTKs). Two facilities, Dalhatu Araf Specialist Hospital (DASH) and General Hospital (GH) Akwanga in Nasarawa were selected as initial pilot sites to demonstrate impact with two different health facility tiers. While healthcare worker trainings were conducted for physicians on HCV management during this timeframe, all other relevant facility-level factors including human resource capacity, laboratory and clinic workflow remained the same. Six months of retrospective data on adult HCV screening through outpatient departments (OPD) were compared pre- and post-PITC intervention and screening volumes and seropositivity were assessed. Pre-PITC data was collected from January to July 2017 for DASH and July to December, 2017 for GH Akwanga. Post-PITC data was collected from October 2017 to March 2018 for DASH and March to August 2018 for GH Akwanga.
Results: Six months retrospective data were compared across two facilities pre- and post-PITC intervention (2017-2018). At DASH, 1650 individuals (mean:275/month) were screened pre-PITC with 14% HCV seropositive while post-PITC, 2155 individuals (mean:359/month) were screened with 15% HCV seropositive. In GH Akwanga 392 persons (mean:65/month) were screened pre-PITC with 17% seropositive while post-PITC, 790 persons (mean:132/month) were screened with 16% seropositive.
Conclusion: Implementation of PITC led to a 31% and 103% increase in patients referred for HCV screening services from the OPD clinics at DASH and GH Akwanga respectively. Sero-positivity remained relatively stable across timeframe, implying a net increase in the volume of positive patients identified and referred for confirmatory

testing. Outcomes of the study shows that the PITC model may be critical to expanding access to early diagnosis to enable persons ascertain HCV status in high burden environments.



THU-383

Dried blood spots: A useful tool for virologically caracterising the hepatitis C virus epidemic

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Background and aims: Incident hepatitis C virus (HCV) cases identified in Europe occur mostly among people who inject drugs (PWID). The identification and characterization of recent infections is necessary for understanding mechanisms of current HCV transmission in this population. Dried blood spot (DBS) samples have demonstrated their usefulness in facilitating the HCV diagnosis and could help to characterize the local epidemic among PWID. Thus, we aimed to (i) establish the validity of DBS to assess HCV genetic variability by next-generation sequencing (NGS), (ii) identify acute infections through genetic variability estimates, and (iii) identify transmission clusters.
Method: HepCdetect II is a cross-sectional study of 410 active PWID in four harm reduction settings in Barcelona. DBS were collected from all participants, and plasma was additionally collected in 300 cases. DBS were qualitatively tested for HCV RNA [Saludes V, J Viral Hep 2018], and viral loads were quantified from plasma (Abbott). For positive samples, a 389-bp region of the HCV NS5B gene was amplified. Sequence libraries were indexed and subjected to Illumina paired-end sequencing (2x250 cycles, MiSeq). Inter and intra-host HCV genetic variability estimates and cluster analysis based on patristic distances were performed from NGS data [Montoya V, Infect Genet Evol 2016]. NGS was performed from plasma when available or from DBS when not; for 16 participants both plasma and DBS were sequenced.
Results: Excluding samples with viral loads <10, 000 UI/ml, 98.8% of 173 plasmas and 89.8% of 59 DBS were successfully characterized by NGS. The major circulating subtypes were 1a (39.3%) and 3a (33.3%), followed by 1b (16.4%) and 4d (6.8%). Two mixed infections were identified. The genetic variability estimates (Shannon entropy and single nucleotide variants) were not significantly different between plasma-DBS pairs. Based on Shannon entropy measures observed in acute and chronic infection controls, 34 (14.6%) cases were identified as acute, and 27 (79.4%) of them were identified as part of a transmission cluster.
Conclusion: DBS represent a valuable tool for facilitating HCV diagnosis, and also for characterising and monitoring HCV epidemics, since they can be successfully used to identify acute HCV infections and transmission clusters. HCV preventive strategies directly targeted to PWID populations currently experiencing ongoing HCV transmission could inform public health interventions.

THU-384

Clinical Performance of determine TM HBsAg 2 rapid test for hepatitis B detection

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Background and aims: Hepatitis B virus (HBV) infection is estimated to affect 292 million people worldwide. Approximately two thirds of chronically infected patients in the EU and 90% of patients worldwide are unaware of their hepatitis B status. There is a major need for a reliable near patient test to help enhance diagnostic rates globally. DetermineTM HBsAg 2 is a rapid test for the detection of HBsAg, since it is capable of detecting the 0.1 IU/ml WHO International Standard for HBsAg (NIBSC code 12/226), giving results in 15 minutes. The aim of this study is the evaluation of the clinical performance of DetermineTM HBsAg 2 rapid test for hepatitis B detection.
Method: We conducted a prospective, multi-centre study to establish the clinical performance of the DetermineTM HBsAg 2 rapid test in venous whole blood, plasma and serum as well as fingerstick whole blood. The DetermineTM HBsAg 2 test (Alere Medical Japan, Tokyo, Japan (now Abbott), Chiba, Japan) is an in-vitro, visually read, qualitative, immunochromatographic assay for the detection of HBsAg in 50 µL sample. The reference method for the study was the Abbott ARCHITECT® quantitative HBsAg assay. This study enrolled 351 evaluable subjects, 145 of these subjects were HBsAg-positive (age ranging 2-86 years) across 5 clinical sites in the UK and 1 clinical site in Spain.

Results: The sensitivity and specificity were 97.2% and 98.5% for fingerstick whole blood at 15 minutes when using the reference assay cut-off 0.05 IU/ml, and the sensitivity increased to 97.9% when using the pre-specified cut-off 0.13 IU/ml, which is required by the European regulations. At the 15-minute reading, the sensitivity was 97.2%, 97.9% and 98.6% and the specificity was 99%, 99.5% and 100% for venous whole blood, serum and plasma, respectively. An algorithm following up a positive fingerstick test result with a Determine™ HBsAg 2 plasma or serum test demonstrates 100% specificity.
Conclusion: The Determine™ HBsAg 2 test gives a result with high sensitivity and specificity at 15 minutes, making it an ideal tool for point-of-care testing in HBV screening programmes. The Determine™ HBsAg 2 test has the potential to enable large-scale population-wide screening, to reach the WHO target of 90% of HBV patients diagnosed by 2030.
Disclosures: Alere Medical Japan, (now Abbott), provided materials and expenses to perform the study.

THU-385
Targeted screening for hepatitis C and predictors of advanced liver disease in the birth cohort in a tertiary primary care clinic

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Background and aims: : Hepatitis C virus (HCV) associated complications have been decreasing since the advent of highly effective antiviral medications and the recommendation of universal screening by the CDC (8/2012) and USPSTF (6/2013) for the 1945-1965 birth cohort (BC). NASH is now increasing in prevalence and as the etiology of complications of liver disease. The aim of our study is to determine the impact of HCV screening and risk factors for advanced fibrosis in the BC in a tertiary primary care practice.
Method: Data was extracted from the electronic medical record of all BC patients panelled to a primary care provider who underwent HCV screening between 9/8/2010 and 03/05/2018. If more than one HCV Ab screen was performed, only data associated with first testing was collected. Fib4 and APRI scores were calculated to screen for advanced fibrosis.
Results: 7097 BC pts were screened during the study period, 3462 (48.8%) male, 6435 (92.0%) white, 1028 (14.5%) had Diabetes, 2389 (34.1%) had BMI ≥30. From 2011 to 2017 there was a marked increase in the number of patients screened [188 (2.6% of screened) vs. 2009 (28.3%) of screened)]. 6876 (96.9%) were screened on or after 2012. Of the patients screened, 124 (1.7%) were HCV Ab+, of those 33 (26.6%) were HCV RNA +. ALT was available in 5578 patients. ALT was ≤ 30 U/L in 3544 (63.5%), between 30-60 U/L in 1499 (26.9%) and >60 U/L in 535 (9.6%). There was a correlation between ALT level and RNA + (TABLE). 3 out of the 4 patients with HCV RNA and ALT ≤ 30 had risk factors for HCV. Risk for intermediate or advanced fibrosis determined by APRI using multivariate analysis were HCV RNA + OR (95% CI) as 8.27 (3.30, 20.7) with p < 0.0001), Diabetes OR (95%CI) as 1.61 (1.29, 2.02) with p < 0.0001, ALT > 30 (OR (95%CI) as 13.0 (10.3, 16.4) with p < 0.0001) but not BMI ≥ 30 OR (95%CI) as 0.86 (0.71, 1.05) with p = 0.1342). BMI ≥ 30 was significant on univariate but not multivariate analysis. Fib4 score (not included) correlated with APRI (Pearson Correlation as 0.77, p < 0.0001).

HCV RNA detection/quant PCR	ALT (≤ 30, (30, 60], > 60)				
	ALT ≤ 30	30 < ALT ≤ 60	ALT > 60	Total	P Value
Positive	4 (0.11%)	13 (0.87%)	16 (2.99%)	33	< 0.0001
Negative	3540 (99.89%)	1486 (99.13%)	519 (97.01%)	5545	
Total	3544	1499	535	5578	

Figure: Association between HCV RNA and ALT.

Conclusion: The number of BC patients screened for HCV in primary care clinics increased following the CDC and USPSTF recommendations. EMR risk based assessment to determine screening for HCV in patients with an ALT ≤ 30 U/L could decrease the cost of HCV screening. Screening for advanced fibrosis in patients with DM or elevated ALT within the BC should be considered. Confirmation in other large primary care clinic data sets will be needed.

THU-386
Interim results of hepatitis prevention, control and elimination program in Ulaanbaatar, Mongolia

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Background and aims: Mongolia has the world's highest rate of liver cancer mortality—nearly 12 times the global average. Prevalences of chronic hepatitis B, C, and D in Mongolia are at an endemic level and constitute the main cause for Mongolia's world-leading liver cancer mortality rate. Cirrhosis and liver cancer mortalities currently account for 15% of total annual mortalities in Mongolia. The Onom Foundation and partners initiated the Hepatitis Prevention, Control, and Elimination (HPCE) Program on September 8, 2014. The Parliament of Mongolia officially adopted the HPCE Program into the 2016-2020 Action Plan of the Government of Mongolia (GoM) on September 9, 2016. HPCE Program of Mongolia aims to eliminate HCV in Mongolia by 2020 and to significantly reduce hepatitis-induced liver cirrhosis and HCC mortalities. Within the program, free general population hepatitis screening, two free-of-charge HCV viral load testing and no-out-of-pocket-cost HCV treatment campaigns have been initiated nationwide. This study aimed to evaluate the progress of the program by comparing the HCV prevalence of 2013 and 2018 among the apparently healthy population of Ulaanbaatar, Mongolia.
Method: A cross-sectional study design was used to randomly select 552 participants aged 20 years and older from Ulaanbaatar city population of Mongolia. Anti-HCV screening was performed by rapid test (OraQuick, USA). Anti-HCV positive samples were further tested for HCV-RNA using RT-PCR (Cepheid GeneXpert, USA).
Results: In this study, total of 552 subjects were enrolled including 296 (53.6%) men and 256 (46.4%) female. HCV prevalence and detectable HCV-RNA percentage are shown in Table 1. In addition, results of 2013 Ulaanbaatar population HCV prevalence study are shown (Dashtseren et al). The overall prevalence of anti-HCV was 7.4% in 2018, while it was 9.9% in 2013. Furthermore, percentage of detectable HCV-RNA was 46.3% (19) in 2018 and it was almost 2 times higher (87.7%) in 2013 before started using DAA treatment in Mongolia. A number of treated people in 2018 were 10 (24.4%).

Table 1: Comparison of HCV prevalence and detectable HCV-RNA in 2013 and 2018

Years	2013	2018
Total number of samples	573	552
Anti-HCV prevalence % (n)	9.9 (57)	7.4 (41)
Percentage of detectable HCV-RNA (n)	87.7 (50)	46.3 (19)
Percentage of spontaneously cleared HCV-RNA	12.2 (7)	24.4 (10)
Percentage of treated people with DAA	0	24.4 (10)

Conclusion: This study clearly shows successful implementation of HPCE Program. It also shows that in order to reach the target to eliminate HCV by 2020 Mongolia has to accelerate the implementation progress.

THU-387

Eliminating viral hepatitis C in Belgium: A mathematical model of the micro-elimination approach

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Background and aims: The hepatitis C virus is one of the leading causes of chronic liver disease and liver-related deaths worldwide, prompting the World Health Organization to define targets for eliminating it by 2030. Belgium has had a 'Hepatitis C Plan' since 2014, yet elimination efforts remain unclear. The estimated prevalence is low in the general population (0.57%), though higher in several subgroups. This study sets out to employ the best available data to construct a micro-elimination model to guide national efforts.
Method: A constrained optimization modelling approach was applied for developing the "HepC Countdown" model in Excel with the objective to demonstrate how many patients need to be treated to reach elimination of hepatitis C by 2030, based on reported or estimated prevalence, incidence and reinfection rates (just for PWID) and current versus alternative treatment rates. Six subgroups with increased risk of hepatitis C were studied: people living with HIV, haemodialysis patients, migrants, patients with advanced liver disease, people who inject drugs and prisoners.
Results: According to the model, none of the subgroups would achieve hepatitis C elimination by 2030 at current treatment rates (Table 1). With the current rate of 3%, hepatitis C elimination would be reached by 2057 at the earliest in all subgroups with the exception of PWID (2314). For Belgium to meet the WHO targets, the average percentage of patients to treat per year out of the total pool of patients to be treated needs to be fixed at 8% of the current patient pool.

Table 1.: Mathematical modelling results based on current Belgian hepatitis C situation

	CURRENT SITUATION					
	Patients to treat at 80% of the reported/ estimated patient pool in 2030	Patients treated by 2030	Patients left untreated by 2030	Patients not treated (%)	Average number of patients treated per year (2018-2030)	Year of elimination
PEOPLE LIVING WITH HIV*	282	92	190	67%	7.0	2057
HAEMODIALYSIS PATIENTS*	238	78	160	67%	6.0	2056
MIGRANTS**	14, 969	4, 882	10, 087	67%	375	2056
PATIENTS WITH ADVANCED LIVER DISEASE**	17, 500	5, 722	11, 778	67%	440	2057
PEOPLE WHO INJECT DRUGS**	3656	996	2, 660	73%	77	2314
PRISONERS**	1, 422	465	957	67%	36	2056

*Reported.
**Estimated.

Conclusion: In order to reach the WHO elimination targets much greater efforts are required in Belgium, including removing hepatitis C treatment reimbursement restrictions. Improving surveillance and prevention would further facilitate efforts.

THU-388

Annual healthcare costs double for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients who progress to advanced liver disease: A multivariable analysis of German real-world data

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Background and aims: Healthcare resource utilization (HCRU) and costs significantly increase among NAFLD/NASH patients who progress to compensated cirrhosis (CC). This study evaluated comorbidities, HCRU and associated costs among NAFLD/NASH patients who progress to advanced liver disease (including CC, decompensated cirrhosis [DCC], liver transplantation [LT], hepatocellular carcinoma [HCC]) in Germany.
Method: Adult patients with NAFLD/NASH (ICD-10-GM) were identified retrospectively from 2011-2016 in the InGef database containing claims data of >4 million individuals. Patients with other causes of liver diseases were excluded. Following the prevalent NAFLD/NASH diagnosis, patients were identified with liver severity stages (NAFLD/NASH non-progressors (NN/NP), CC, DCC, LT, HCC) using their first diagnosis date (index date). Per patient per quarter values were annualized. A generalized estimating equation model was used to derive adjusted costs. Patients were censored at disease progression, end of continuous enrolment, death, or end of follow-up.
Results: Of 4, 580, 434 individuals in the database, the study identified 215, 655 (5%) prevalent NAFLD/NASH patients. During the follow-up, 100, 644 incident events of different liver severity stages were reported (NN/NP [79, 245 (78.7%)], CC [411 (0.4%)], DCC [20, 614 (20.5%)], LT [11 (0.01%)] and HCC [363 (0.4%)]). Comorbid burden was high, with 33-67% patients across liver severity stages having ≥3 conditions of hypertension, hyperlipidemia, type-2 diabetes, renal disease and cardiovascular disease. Mean annual hospitalizations were significantly higher for NAFLD/NASH patients with advanced liver disease [CC (2.51), DCC (3.49), LT (2.38), HCC (4.95)] than NN/NP (1.75) ($p < 0.05$ except for LT). Additionally, mean annual costs among

NAFLD/NASH patients with advanced liver disease were significantly higher than NN/NP [€10, 291 (CC), €22, 561 (DCC), €34, 089 (LT), €35, 910 (HCC) vs. €3, 818 (NN/NP)] ($p < 0.05$ except for LT); inpatient costs were the primary driver. Multivariable analyses adjusted for demographics and comorbidities confirmed this trend.

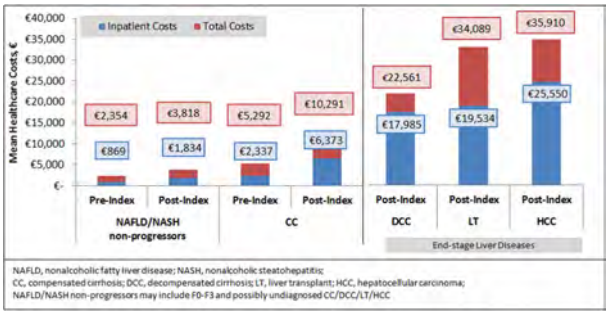

Figure: Annual Mean Healthcare costs for NAFLD/NASH patients with Advanced Liver Disease

Conclusion: Underdiagnosis of CC was apparent among NAFLD/NASH patients. Those who progress to advanced liver disease have high comorbidity burden with costs increasing by over 800% when compared to NN/NP. Early identification and effective treatment options to halt or reverse fibrosis are needed to prevent disease progression and the associated long-term costs.

THU-389

Assessment of hepatitis C screening strategies in different community settings in a Canadian metropolitan area

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Background and aims: It is estimated that over 45% of individuals with chronic hepatitis C virus (HCV) infection in Canada remain undiagnosed. Understanding current rates of HCV diagnosis and linkage to care in different community settings is critical information for developing future screening strategies.
To evaluate HCV screening strategies in three different community settings: emergency department (ED), medical walk-in clinic (MC) and community outreach (CO).
Methods: We implemented birth cohort (1945-1975) HCV testing in the ED and MC, and universal testing during CO. Blood samples in the ED were collected by finger prick on Dried Blood Spot (DBS) collection cards and tested for anti-HCV with reflex to HCV RNA. In the MC and CO, we used anti-HCV point-of-care testing followed by HCV RNA on DBS card. Patients with positive HCV RNA were linked to care.
Results: 5, 144 individuals were tested during 1.5 years; 142 (2.8%) were HCV reactive (Table). Seropositivity varied among all three groups: 1.8% (95%CI 1.2%-2.4%) in the ED, 0.4% (95%CI 0.1%-0.7%) in the MC and 5.3% (95%CI 4.3%-6.3%) in the CO. Of Ab positives, 117 (82.4%) underwent HCV RNA testing. 61 (82.4%) out of 74 HCV RNA positives were linked to care. Compared to the general population the HCV prevalence was significantly higher in the CO (5.3% vs. 0.7%; $p < 0.0001$), and in the ED (1.8% vs. 0.7%; $p < 0.0001$). The MC group exhibited similar seropositivity as the general population (0.4% vs. 0.7%; $p = 0.12$).

Characteristics	HCV Ab tests				p value
	Total N = 5114	ED N = 1639 (32.0%)	MC N = 1452 (28.4%)	CO N = 2023 (39.6%)	
Age (median, range)	56 (15-97)	58 (35-74)	51 (15-97)	54 (16-97)	<0.0001
Male n (%)	2354 (46.0)	850 (51.9)	591 (40.7)	913 (45.2)	<0.0001
HCV Ab Positives n (%)	142 (2.8)	29 (1.8)	6 (0.4)	107 (5.3)	<0.0001
HCV RNA Tests n/HCV Ab positives (%)	117/142 (82.4)	26/29 (89.7)	5/6 (83.3)	86/107 (80.4)	0.531
HCV RNA Positives n/HCV RNA tests (%)	74/117 (63.2)	18/26 (69.2)	4/5 (80.0)	52/86 (60.5)	0.443
Linkage to Care n/HCV RNA positives (%)	61/74 (82.4)	14/18 (77.8)	3/4 (75.0)	44/52 (84.6)	0.474

Conclusions: The HCV prevalence in the CO and ED was significantly higher than the general Canadian population. Using DBS for HCV testing ensured high HCV RNA test uptake. Screening efforts in populations with higher prevalence, such as the ED and outreach programs, were higher yield and still resulted in good linkage to care.

THU-390

Results of a birth cohort hepatitis C screening program in an academic emergency department in Canada

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Background and aims: Epidemiologic and modeling studies suggest that between 45 and 70% of individuals with chronic hepatitis C virus (HCV) infection in Canada remain undiagnosed. The Canadian Association for the Study of the Liver (CASL) recommends one-time screening of baby boomers (1945-1975), based on data showing HCV prevalence is highest in this cohort and screening is cost-effective. Screening programs in the US have shown a very high prevalence of previously undiagnosed HCV among patients seen in the Emergency department (ED). The utility of ED screening has not been evaluated in Canada.
To assess the feasibility of implementing a targeted birth-cohort HCV screening program in the ED setting.
Method: Patients born from 1945 to 1975 presenting to the ED of a tertiary care hospital were offered HCV testing. Patients with life-threatening conditions and unable to provide verbal consent in English were excluded. Blood samples were collected by finger prick on Dried Blood Spot (DBS) collection cards and tested for anti-HCV with reflex to HCV RNA. Patients with positive HCV RNA were referred to a liver specialist.
Results: During a 14-month period, 6, 613 patients in the birth cohort presented to the ED during daytime hours. 77% (5, 117) met the eligibility criteria, 52% (2, 817) were offered testing: 269 (11%) were previously tested, 487 (20%) declined. 1639 (66%) individuals

underwent testing: median age 58.2 (35-74), 850 male (51.9%). Of these, 29 patients (1.8%; 95%CI 1.2%-2.4%) were anti-HCV positive: 18 (69.2%) were HCV RNA positive, 7 (26.9%) negative and 3 not done due to inadequate DBS sample. Screening was successfully done by non-medical staff (mean 8/day, median spots on DBS 3). 14 patients (78%) were linked to care and 4 lost to follow-up. The HCV prevalence in the ED was significantly higher than the general Canadian population (1.8% vs 0.7%; $p < 0.0001$) but much lower than reported rates in American EDs (1.8% vs 10.3%; $p < 0.0001$).

Conclusion: Acceptance of HCV screening in the ED birth cohort was high and easily performed using DBS to ensure the majority of positive samples were tested for HCV RNA. Challenges with implementation limited the number of people tested. HCV prevalence among this ED birth cohort was higher than the general population but lower than seen in the ED in the US. This may in part be due to exclusion of individuals with more severe medical issues or possibly due to population and healthcare system differences between countries.

THU-391

Impact of early screening and treatment of hepatitis C virus and improvements in risk reduction on HCV transmission among HIV-infected men who have sex with men in France: A modeling approach

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Background and aims: Hepatitis C virus (HCV) incidence has increased recently among HIV-positive men who have sex with men (MSM) in France. This epidemic is associated with high-risk sexual behaviours, notably chemsex (the use of psychoactive substances during sexual encounters). We assessed the impact of alternative strategies to prevent HCV transmission-including screening, immediate treatment with direct acting antivirals (DAAs) and risk reduction-among HIV-positive MSM in France.

Method: We developed a deterministic dynamic compartmental model to simulate HCV transmission among HIV+ MSM, accounting for HIV and HCV care cascade, natural history and low- and high-risk groups (no versus chemsex practices). The model was calibrated to an initial HCV incidence of 0.92 per 100 person-years (PY) among French HIV+ MSM in 2016 (Dat'AIDS cohort). We assessed the impact of 8 strategies on HCV incidence and prevalence over a 10-year period starting in 2019, including: current practices (S0), current recommendations (S1), more frequent HCV screening with treatment at diagnosis (S2-S3), reduction in high-risk sexual behaviours (S4), and combined strategies (S5-S7; see Table).

Results: Current practices (S0) produced HCV prevalence of 0.94% and incidence of 0.298/100 PY in 2029. Strategies aimed solely at expanding screening and treatment (S1-S3) all yielded ~30% reductions in both HCV prevalence and incidence. Greater reductions in both prevalence/incidence (~40% and ~54%, respectively) were obtained via risk reduction (S4). Strategies combining screening, treatment, and risk reduction (S5-S7) produced the greatest possible reductions in both prevalence (53%) and incidence (65%).

Strategies	Prevalence (%) in 2029	Incidence/100 PY in 2029
S0 (Baseline) Current practices of HCV screening (annual) and treatment initiation (3 months after diagnosis)	0.94	0.298
S1 HCV screening every 6 months and immediate treatment initiation at diagnosis (current recommendations)	0.68	0.216
S2 HCV screening every 3 months for high-risk group* and immediate treatment initiation at diagnosis Keeping S1 for low-risk group	0.64	0.202
S3 S2 for all HIV+ MSM	0.62	0.196
S4 50% decrease of high-risk behaviours by 2022 S0+S4	0.57	0.136
S5 S1+S4	0.45	0.108
S6 S2+S4	0.44	0.104
S7 S3+S4	0.42	0.101

*High-risk group corresponds to individuals with "chemsex" practices

Conclusion: Implementing the current HCV screening and treatment recommendations among HIV+ MSM in France would have a marked impact on HCV transmission. Combining these recommendations with interventions to decrease high-risk sexual behaviours would make it possible to reach very low levels of HCV prevalence and incidence. These findings underscore the relevance of combining both approaches to eliminate HCV in this population.

THU-392

Building capacity within a hepatitis C treatment model. the validation process for a hepatitis C pre-treatment pharmacist assessment complex intervention toolkit

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Background and aims: Knowledge relating to use of direct-acting antivirals is confined to specialist centres in Ireland. The pre-treatment pharmacist assessment is a novel complex intervention toolkit which has been designed and optimised with the aim of supporting devolvement of Hepatitis C treatment to primary care providers including pharmacists, nurses and clinicians. It combines all aspects of pre-treatment assessment (E.g. fibrosis staging, drug-drug interactions) into a user-friendly proforma to ensure optimum Hepatitis C treatment selection. Feasibility and acceptability of the toolkit has been assessed using survey methodology. Healthcare interventions which facilitate devolved Hepatitis C care must ensure that optimum clinical outcomes are maintained for patients and that evidence of their effectiveness is determined through robust research studies. This study describes the validation process for this toolkit for pharmacist use.

Method: Pharmacists were invited to participate in this matched cohort study to review Hepatitis C case vignettes using the toolkit or standard of care. Participants were divided into two groups using a concealed randomisation method. A random sample of anonymised test cases were selected from the Irish Hepatitis C treatment registry using selected co-variates (E.g. fibrosis stage). A sample size of 58 cases per group was calculated with 7 participants per group to complete 8 cases each. Group A utilised the toolkit and group B

completed the cases as per standard of care. The primary end point was selection of an optimum treatment regimen as per national guidelines. Secondary end points included time to completion, detection of drug-drug interactions and identification of patient interventions. T-test analysis was completed to assess variation in results between groups.

Results: A total of 56 cases were completed per group. Use of the toolkit was associated with selection of an optimum treatment regimen in 92.9% of cases as compared with 60.7% of cases in group B ($p < 0.05$). Drug-drug interaction detection rates were significantly higher with toolkit use (75% vs 47%;$p < 0.05$). Participants utilising the toolkit suggested an average of 3.4 interventions per case versus 2 per case in Group B. The toolkit was associated with a longer median time to completion (20 versus 15 minutes), however this was not found to be statistically significant (p:0.060).

Conclusion: Study findings confirm the effectiveness of the toolkit in aiding pharmacists in selecting the optimum Hepatitis C treatment regimen. The potential for pharmacists working in all practice environments in Ireland, including community, to make a robust contribution to treatment of Hepatitis C, is something that can be supported using this toolkit. This type of capacity building within our limited healthcare resources is key to upscaling the model of care in Ireland to achieve elimination targets.

THU-393

HCV infection in Canadian immigrants: Characteristics and treatment outcomes of the CANUHC cohort

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Background and aims: HCV-infected patients from endemic regions of the world immigrate to Canada and are subsequently referred to viral hepatitis clinics for management. Cultural differences and language barriers are potential obstacles to receiving HCV treatment. We set out to describe the diversity of the Canadian HCV-infected immigrant population and assess HCV DAA therapy outcomes.

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. Information on immigration history, country of origin and race is collected. Characteristics and outcomes (SVR) were compared by immigration status and race using Chi square, Student's t test and median test at significance levels of $p < 0.05$.

Results: Between January 2016 and May 2018, 725 HCV-infected patients initiating DAA therapy were enrolled in CANUHC (overall mean age: 53 (SD 12.7); 66% male; 78% white, 3% black, 4% South East Asian, 4% East Indian, 5% Indigenous). 19% were born outside of Canada (17% South East Asia and Indian Subcontinent, 7% Sub-Saharan Africa). Mean age was similar [54 (SD 13.9) years in immigrants versus 52 (SD 12.4) years in Canadian-born, $p = 0.09$]. A greater proportion of DAA treated immigrants were female. HIV co-infection was less common in immigrants (1% vs 6%, $p = 0.04$). The genotype distribution mirrored the country of origin/regional genotype distribution prevalence. The overall median baseline fibrosis stage (F2) was similar among Canadian and foreign-born patients. Fibrosis stage remained similar by groups when stratified by sex (male, $p = 0.68$; female, $p = 0.53$). SVR rates of 91% and 93% were similar in immigrants and Canadian-born patients respectively ($p = 0.80$) and did not differ by race ($p = 0.67$).

Variable	Immigrant to Canada (n = 134) n (%)	Canadian-Born (n = 591) n (%)	P Value
Male Sex	70 (52)	406 (69)	< 0.001
Race			
White	53 (40)	460 (88)	< 0.001
Black	10 (8)	11 (2)	
South East Asian	24 (18)	5 (1)	
East Indian	26 (20)	3 (1)	
Indigenous	1 (1)	32 (6)	
Other	18 (14)	11 (2)	
Genotype			
1a	24 (19)	311 (55)	< 0.001
1b	38 (30)	53 (9)	
1 (ab or unknown)	4 (3)	9 (2)	
2	13 (10)	59 (10)	
3	32 (25)	134 (24)	
4	13 (10)	2 (< 1)	
6	5 (4)	2 (< 1)	
Mixed	---	1 (< 1)	
Fibrosis Stage			
F1	49 (41)	209 (40)	0.59
F2	20 (17)	117 (22)	
F3	18 (15)	71 (14)	
F4	32 (27)	126 (24)	
Treatment Naive	40/69 (58)	244/345 (71)	0.04
Achieved SVR	32/35 (91)	140/151 (93)	0.80

Conclusion: Despite a diverse immigrant population in Canada access to and success with DAA therapy appear to be equitable.

THU-394

Cancer risk among people with HIV, HBV, and/or HCV infections

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Background and aims: HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections each are associated with increased cancer risk. However, data on viral co-infection's synergistic effects on cancer incidence are limited. In this study we assessed the effect of co-occurrence of HIV, HBV and HCV on all cancers, anal cancer, non-Hodgkin Lymphoma (NHL) and liver cancer.

Method: The British Columbia Hepatitis Testers Cohort includes all individuals (~1.7 million) tested for HCV or HIV, or diagnosed with HCV, HIV, or HBV linked with data on medical visits, hospitalizations, cancers, prescription drugs and vital statistics. We included individuals tested for all three infections since 1990 and followed them from the date of their last test until the first cancer diagnosis, death, or 12/31/2015. Diagnostic codes from the population-based BC Cancer Registry were used to ascertain cancer occurrence. We utilized the Fine and Gray competing risks regression model to estimate adjusted sub-distributional hazard ratios (aHRs) for all cancers, anal cancer, NHL, and liver cancer, with death as a competing risk.

Results: Among 514, 501 individuals tested for all infections, 12, 586 (2.45%) had any cancer, 100 (0.02%) had anal cancer, 552 (0.11%) had NHL and 1, 081 (0.21%) had liver cancer during a median follow-up of 4.19 years (interquartile range: 2.11, 8.47). Compared to individuals with no infection, aHR for all cancers was highest for HIV/HBV co-infections (aHR 2.55, 95% CI: 1.91–3.42), followed by triple infections (aHR 2.29, 95% CI: 1.80-2.89) (Figure). The risk of anal cancer was

higher among individuals with HIV (e.g. triple infection aHR 22.61, 95% CI: 7.27-70.33), while risk of liver cancer was higher among those with HBV or HCV mono or co-infections and triple infections (aHR 41.40, 95% CI: 21.95-78.05). The risk of NHL was the highest among HIV/HBV co-infections followed by triple infection and hazard remained elevated in all infection groups (Figure).

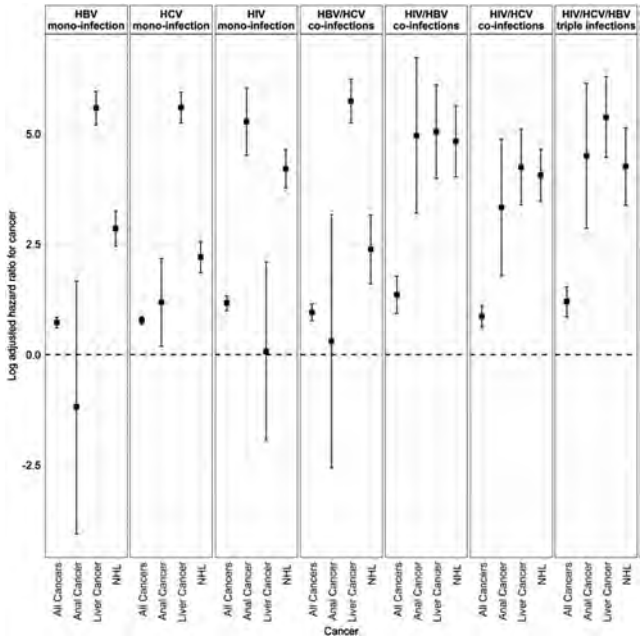

Figure: Log of adjusted hazard ratios for association of infections with cancers.

Conclusion: HIV, HBV and HCV infections are associated with an overall higher risk of cancer. The highest risks for anal cancer and NHL were among those living with HIV infection and the highest risk for liver cancer was among HBV/HCV co-infected individuals. The observed association between HCV and anal cancer, which may be due to the presence of human papillomavirus and/or residual confounding, requires further investigation.

THU-395

Hepatitis C elimination by enhancing care and treatment among HIV co-infected individuals (the co-EC study): Real world evidence of decreasing HCV incidence and prevalence

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Background and aims: Gay and bisexual men are the key population affected by HIV and hepatitis C (HCV) coinfection in Australia. The co-EC Study supports general practitioners to initiate treatment in primary care settings, aiming to provide proof-of-concept that treatment scale-up could eliminate HIV/HCV coinfection among gay and bisexual. This analysis describes the co-EC cohort and reports on HCV treatment outcomes in primary and tertiary care sites, and the population impact (incidence and prevalence) of HCV over time.
Method: A nurse-led, clinician-directed trial of HCV directly acting antiviral treatment among people with HCV/HIV co-infection was performed in Melbourne, Australia. At six key primary and tertiary care sites for HIV clinical care, providing care for 75% of people with HIV in our jurisdiction, all HCV/HIV coinfected people meeting standard prescribing guidelines were eligible for treatment. Primary HCV incidence and prevalence among the primary care population was measured using a state-wide surveillance system that electronically collects HCV and HIV testing data from 2012 to present. Poisson regression was used to determine change in incidence.
Results: 200 participants were recruited, 55% reporting recent injecting drug use and 76% condomless sex, of whom 177 initiated treatment in the study period 2016-2018. SVR12+ (SVR at or after 12 weeks post treatment) per protocol among people treated using any regimen in primary care was 97.1% (95% CI: 91.4-99.1%), which was not significantly different to tertiary care, SVR12 100% (95% CI: 92.1-100%). Twenty-six percent (46/177) required specialist referral for HCV prescribing, primarily for advanced liver disease or other non-HIV co-morbidities.
Over 9100 HCV tests were performed in primary care among gay and bisexual men living with HIV in Victoria since 2012; between 50 and 60% were tested annually. At the population level, HCV RNA prevalence among people with detectable HIV and HCV antibodies was 57% in 2016, which declined to 8% (an 86% reduction) in 2018 ($p < 0.01$). HCV incidence significantly decreased by a factor of 0.79 (95%CI = 0.69-0.92, p = 0.002) (a 21% reduction) each year.
Conclusion: HCV treatment in primary and tertiary care was highly effective in this real-world cohort of HIV/HCV coinfected men, many who have high-risk sexual and drug-use behaviour. This study provides proof of concept that expanding HCV treatment access is feasible and can lead to rapid HCV elimination among gay and bisexual men.

THU-396

Hepatitis C screening among the population of Georgia within the national elimination program

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Background and aims: Georgia is high hepatitis C (HCV) prevalence country. According to the latest nationwide seroprevalence study conducted in 2015, 7.7% of the population is anti-HCV antibody

positive and 5.4% has chronic hepatitis C infection. Since the launch of the National HCV Elimination Program in 2015, the country of Georgia has stepped up its efforts to achieve the goals of the National HCV Strategy and identify 90% of the HCV infected population by 2020. Therefore, screening campaigns became massive and rigorous in the country, with the active involvement from public and private organizations. Over 800 sites provide HCV screening across the country free-of-charge, following the National HCV Screening Protocol approved by the Ministry of Health. Full coverage is achieved among blood donors, pregnant women, hospitalized patients and military recruits.

Method: This analysis was prepared based on the data from the unified electronic HCV screening database, which is being used by all screening provider sites. The database is administered by the National Center for Disease Control and Public Health and it captures information of each HCV screening performed in the country. We looked at the numbers of screened individuals by different populations, as well as positivity rates among them.

Results: Since the launch of the Elimination Program in April 2015 through April 2018, more than 1.2 million individuals have been screened on HCV, with the overall positivity rate-9%. Positivity rates vary through the population groups, with the lowest rate among pregnant women (0.5%) to the highest prevalence in state opioid-substitution therapy beneficiaries (91.3%) (See the figure). Infection is also highly prevalent in people with hemophilia (62.5%) and people living with HIV (39.7%).

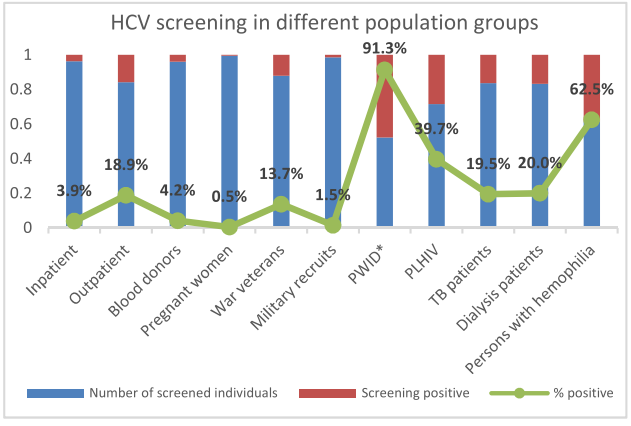

Figure: HCV screening in different population groups (April 2015-April 2018) * State Opioid-Substitution Program beneficiaries screened on HCV

Conclusion: More than one third of the adult population has been screened in Georgia and about half of estimated number of anti-HCV positive adult population were identified. Although, to reach the national strategy goals, it is required to increase screening coverage and reach the people who have never been tested, as well as raise awareness among population and improve infection control in medical and non-medical facilities to prevent transmission and reduce the number of new infections.

THU-397

Screening strategies for hepatitis C virus elimination in Italy

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Background and aims: Hepatitis C virus (HCV) elimination could be achieved in Italy by newly linking 36, 400 patients to care and treating 38, 000 patients annually by 2025. However, cost-effective screening strategies are needed to make elimination a reality. HCV is more prevalent in the older Italian population, so our objective was to determine if birth cohort-based screening could be cost-effective in Italy.

Method: A Markov disease burden model was populated with Italian data to quantify the annual HCV-infected population by liver disease stage, sex, and age. An economic impact module was added to quantify medical costs (costs of screening, antiviral treatment, including assessment and monitoring, and liver-related complications) and health effects, denominated in quality-adjusted life years (QALYs), associated with HCV infection. Prevalence of undiagnosed, asymptomatic HCV infection was used to calculate the number of HCV antibody screens needed annually. The cost-effectiveness threshold was set at €25, 000 as commonly accepted in the Italian guidelines. Modeled outcomes for disease burden, medical costs, and health effects of HCV infection were assessed under the status quo and as well as a scenario to achieve the World Health Organization's Global Health Sector Strategy targets for eliminating HCV by 2030 under four screening strategies. The screening strategies included universal or targeted screening by birth cohort: the 1948-78 cohort, the 1958-78 cohort, and graduated birth cohort screening (birth years 1958-78 over 2021-23, 1948-78 over 2024-27, and 1948-84 over 2028-30).

Results: All screening scenarios were found to be highly cost-effective (less than €3, 000 per QALY gained) compared with the status quo. The 1948-78 birth cohort screening scenario was the least costly, with €5.5 billion in total medical costs by 2031. This was €24.7 million less than screening in the 1958-78 birth cohort, €37.6 million less than universal screening, and €55.3 million less than graduated screening. Screening the 1948-78 birth cohort would gain approximately 140, 000 QALYs by 2031, compared to 134, 000, 127, 000, and 123, 000 QALYs for the universal, 1958-78 birth cohort, and graduated birth cohort, respectively.

Conclusion: In Italy, implementing screening in the 1948-78 birth cohort was the most cost-effective option, and showed the greatest reductions in overall disease burden by 2030. This strategy should be considered to sustain Italy's momentum towards achieving HCV elimination goals.

THU-398

Circulating HCV resistant strains may result in long-term challenges to HCV elimination: A modeling study

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Background and aims: Significant developments in antiviral treatment of hepatitis C virus (HCV) have improved the management of the infection, making HCV curable. Cohorts of real-life patients treated with direct-acting antivirals (DAAs) have reported sustained virologic response rates (SVR) exceeding 95%. However, the retreatment of the ~5% that have failed to the first course of DAA treatment may be challenging, as treatment failure is associated with selection of resistant associated substitutions in the viral genome. The aim of the study is to assess the risk of potential rebound of a resistant HCV among people who inject drugs (PWID).

Method: A dynamic stochastic model was developed to simulate HCV transmission, incorporating the effect of treatment and harm reduction (HR) strategies. Two chronic hepatitis C (CHC) prevalence settings (45% and 60%) were considered, with population of 10.000 PWID and baseline HR coverage of 40%. We defined PWID with resistance infection as those who have two consecutive failures both in first DAA treatment (SVR 95%) and in retreatment with first-line or PI regimens (SVR ~85%) or in retreatment with SOF/VEL/VOX (SVR 90-95%). The time horizon of the analysis was 25 years (2018-2043).

Results: Our results highlighted that a potential rebound of resistant HCV is likely to occur under a first-line or PI-based regiments retreatment strategy, primarily in settings with high baseline prevalence in long-term. Specifically, under this strategy, the model anticipates that only patients with resistant virus would remain after 2029 (Figure a). Annual HCV incidence would exceed the levels of the elimination target after 2036 (Figure b). Under a SOF/VEL/VOX retreatment strategy, annual HCV incidence would be barely above elimination targets by 2043. Expanding harm reduction coverage from 40% to 75% by 2030 would be sufficient to maintain the results of elimination and control the spread of resistant virus.

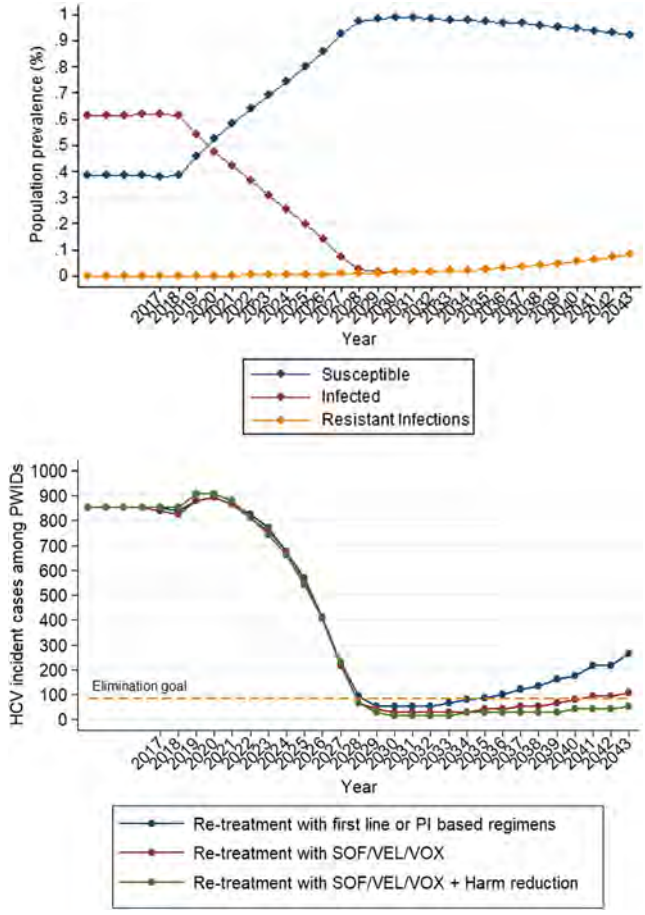

Figure: Model predictions concerning a 60% baseline chronic HCV prevalence under various re-treatments options. A. Distribution of the population under retreatment with first-line or PI regimens, B. Incident cases

Conclusion: A potential rebound of resistant HCV is likely, beyond 2035 and mainly, in high baseline prevalence settings. To prevent the emergence of resistant virus, retreatment of people with multiple DAAs failures should be optimized and harm reduction measures should be implemented to control the spread of resistant HCV.

THU-399

First Belgian hepatitis E seroprevalence study shows low stable birth-cohort specific seroprevalence until 2014, with recent 2016-2018 increase in single centre estimates

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Background and aims: Recent studies have shown rising seroprevalence of hepatitis E virus (HEV) in younger age cohorts in Europe, but substantial regional differences are found. We aimed to evaluate trends in time in birth cohort-specific HEV seroprevalence and regional differences in Belgium.
Method: Firstly, we performed a retrospective analysis of HEV IgG seroprevalence on two national serum banks obtained from sentinel laboratories in 2006 and 2014. Five to ten-year age cohorts held equal amounts of samples and were equally distributed in sex and regional origin. Secondly, a prospective, single centre HEV IgG evaluation was performed of 1200 patients visiting the Hepatology department between 2016 and 2018. Wantai anti-HEV IgG ELISA assays were performed. Results equal or above 1.1 OD/cutoff were considered positive, below 1.1 as negative. Statistical analysis with R included a one-sided power analysis to specifically estimate required sampling for birth cohort-specific seroprevalence evaluation (1604 and 2087 samples respectively). Chi-square analysis or Fisher's Exact Test was performed in SPSS 25 to compare sex, region and birth cohort proportions.

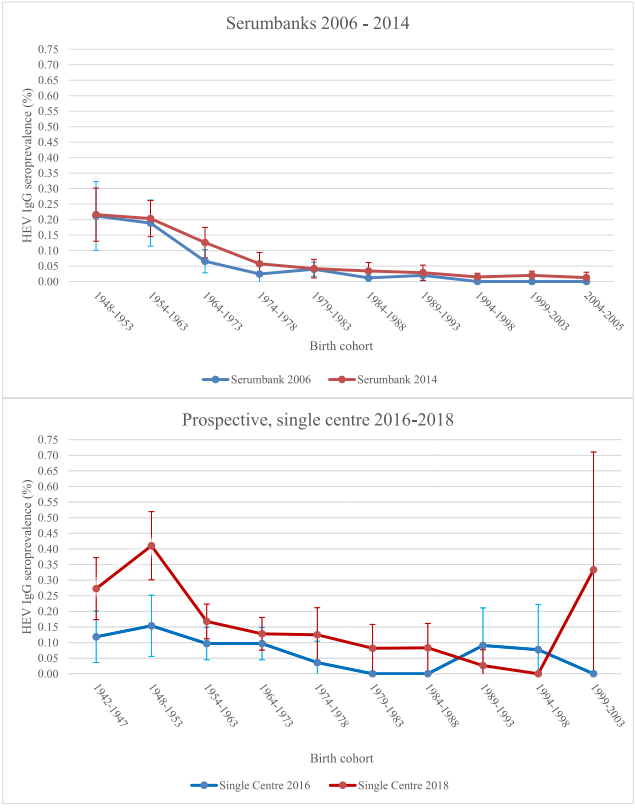

Figure: HEV IgG birth cohort-specific seroprevalence in Belgium, between 2006 and 2014 and 2016 and 2018

Results: Overall HEV IgG seroprevalences were 4.7% (76/1604, CI 3.2-6.3) and 5.8% (121/2087, CI 4.5-7.1) in 2006 and 2014 ($p = 0.161$), respectively. In the single centre analysis, HEV IgG seroprevalences were 8.6% (43/499, CI 6.2-11.1) and 17.1% (120/701, CI 14.3-19.9) in 2016 and 2018 ($p < 0.001$), respectively. No significant differences between sexes were found for any of the years ($p = 0.603$, $p = 0.942$, $p = 0.944$, $p = 0.657$). Significant regional differences were found in

2014 (p = 0.021) with a significant rise between 2006 and 2014 in two provinces: Hainaut (1.5% to 6.0%, p = 0.043) and Namur (3.7% to 14.7%, p = 0.037). We found no significant birth cohort-specific differences between 2006 and 2014, but in the single centre analysis we found a significant increase between 2016 and 2018 in the two oldest birth cohorts (born 1942-1947: 11.9% to 27.3%, p = 0.028 and born 1948-1953: 15.4% to 41%, p = 0.002).
Conclusion: Compared to reported seroprevalences in surrounding countries, initial analysis of Belgian nationwide HEV IgG seroprevalence shows stable and rather low rates. No birth cohort-specific increase in seroprevalence is seen between 2006 and 2014. A regional increase of seroprevalence was however found in two south-western provinces. In addition, single centre analysis between 2016 and 2018 suggests a recent rising seroprevalence, especially in older birth cohorts.

THU-400
Alanine-aminotransferase and 20-year risk of liver disease, cancer, ischemic heart disease, and diabetes in a Danish general population sample aged 30-49 years

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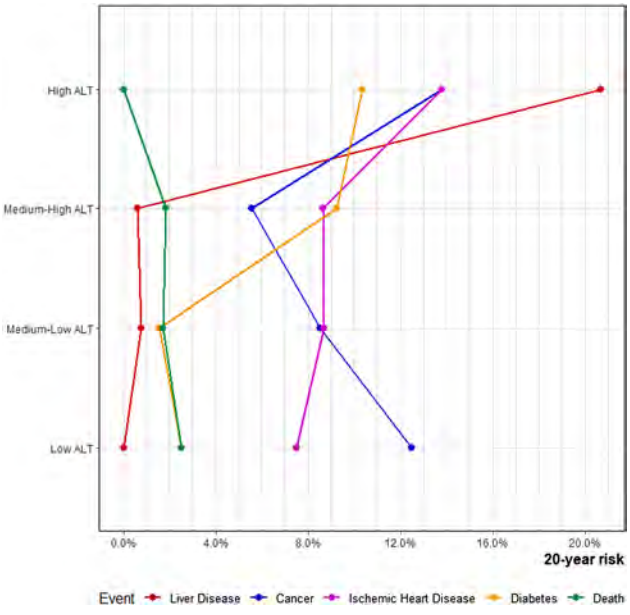
Background and aims: Alanine-aminotransferase (ALT) is an enzyme chiefly found in the liver, and serum ALT is the most frequently used marker of liver cell injury. We examined the association between ALT levels and long-term risk of liver disease, cancer, ischemic heart disease, diabetes, and death in a general population sample of persons aged 30-49.



Method: We obtained the data from the Ebeltoft Health Promotion Project, a randomized controlled trial examining the value of health examinations in the general population aged 30-49 years. We used Danish healthcare registries to follow the 905 trial participants for up to 20 years. We divided the participants into four ALT categories based on their baseline values: low (ALT ≤ 10 U/l), medium-low (ALT 11-34 U/l for men, 11-22 U/l for women), medium-high (ALT 35-69 U/l for men, 23-44 U/l for women), and high (≥ 70 U/l for men, ≥ 45 U/l for women). We calculated the absolute risks of each event by ALT category using the cumulative incidence function, with the other events considered as competing risks. We also calculated all-cause mortality using the Kaplan-Meier estimator.
Results: For men and women with "high ALT," the 20-year risk of a hospital diagnosed liver disease was 20.7% (95% CI: 8.4-36.7). Patients with a lower ALT had a 20-year risk of 0.8% or less. Risk of cancer was highest for participants with "low ALT" or "high ALT" (20-year risk: 12.5% [CI: 4.6-24.6] and 13.8% [CI: 4.3-28.6], respectively). The 20-year risk of ischemic heart disease was highest in the "high ALT" group, with a risk of 13.8% (CI: 4.3-28.6). Risk of diabetes was highest for patients with "medium-high ALT" or "high ALT" (20-year risk: 9.3% [CI: 5.4-14.3] and 10.3% [CI: 2.6-24.3], respectively). The probability of being alive after 20 years without having developed liver disease, cancer, ischemic heart disease, or diabetes was highest in the "low ALT" (75.0% [CI: 58.5-85.7]), "medium-low ALT" (78.7% [CI: 75.3-81.7]), and "medium-high ALT" (74.1% [CI: 66.6-80.1]) groups, compared to participants with "high ALT" (41.4% [CI: 23.7-58.3]).
Conclusion: Members of the general population with a high ALT value at age 30-49 years had an increased 20-year risk of liver disease, cancer, ischemic heart disease, and diabetes. Those with a low ALT had a high risk of cancer. These findings may be valuable for patient counselling in the general practice or outpatient settings.

THU-401
Changes in mortality due to chronic liver diseases in Spain during the period 2002-2016

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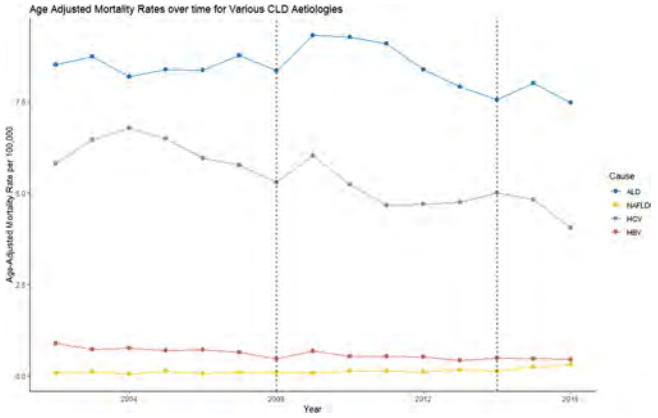
Background and aims: Chronic liver disease (CLD) is responsible for a significant burden of disease worldwide. The objective of the present study was to estimate the burden of disease in terms of mortality by each of the 4 most common aetiologies of CLD, alcoholic-liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), hepatitis C virus (HCV) and hepatitis B virus infections (HBV) in Spain from 2002 to 2016.
Method: We collected data from the Spanish Institute for Statistics (INE) 2002-2016 mortality records and selected individuals with a primary cause of death of ALD, NAFLD, HCV and HBV using ICD-10 codes. We obtained temporal age-adjusted mortality rates using trend analysis. Deaths with unspecified aetiology of chronic liver disease were proportionally distributed among the 4 aetiologies.



Results: A total of 91, 664 deaths were included in the analysis, yielding an aggregated age-standardized yearly mortality of 14.5 per 100, 000 for the 2002-2016 period. ALD mortality remained stable at

8.4 deaths per 100, 000 persons from 2002 to 2008, increased an average 3% yearly from 2009 to 2011 to 9.0/100, 000p, and steadily decreased to 7.5 deaths per 100, 000 persons up to 2016. HCV-related mortality peaked at 2004 at a 6.8 per 100, 000 persons and slowly decreased at a 2.6% yearly average rate till 2014 to 5.0/100, 000p. From 2014 to 2016, HCV related mortality has had a reduction to 4.04/100, 000p, which represent a decrease in mortality of 19.2%. HBV-related mortality has reduced 50% from 0.89 to 0.44 per 100, 000. Although still low in comparison with other aetiologies, NAFLD-related mortality has increased from 0.07 to 0.3 per 100, 000p representing a 297% increase from 2002 to 2016.

Conclusion: In our population analysis of CLD mortality in Spain, we find three relevant time-frames that coincide with the economic expansion of 2000-2008, the financial crisis and the 2014 introduction of novel HCV therapies. ALD remains the main cause of death for CLD, NAFLD has increased and both HBV and HCV-related mortality have decreased. Accuracy of death certificates based upon ICD-10 codes is subject to misreporting and misclassification.

THU-402

Tailored message interventions using social marketing approach versus traditional message for increasing participation in viral hepatitis screening for Japanese workers

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Background and aims: Although 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, and the prevalence of hepatitis virus infections at work sites remains unknown. In Japan Health Insurance Association, which is belonged to about 37 million Japanese who are working in Medium and Small Sized Companies, the attendance rates of hepatitis screening was less than 2% of workers even the cost of only $ 5. The aim of this study was to examine whether the effectiveness of a tailored message intervention based on a social marketing approach increased viral hepatitis screening.

Method: A leaflet which was a tailored message condition for the screening was individually sent to 398, 636 Japanese workers of Japan Health Insurance Association who wish to get annual general check-up in 2017. For control subjects, we simultaneously enrolled about 338, 145 workers with a non-tailored message condition. In addition, we sent the leaflet which mentioned having the screening for free of charge to some workers. A thorough examination of the participants who screened positive was encouraged by forwarding to them a referral letter by Japan Health Insurance Association to specialized medical institutions. The main outcome measure was attendance rates in HBV and HCV screening.

Results: There was a significant difference in viral hepatitis screening attendance rates at follow-up assessments between the tailored matched-message condition (n = 54, 052, 16.0%) and the control (n = 4,794, 1.2%; $p < 0.001$). In cost free subjects, the rates significantly increased (49.3%; $p < 0.001$) compared with the message condition and control group. Six hundred two workers (1.1%) were positive for HBV (n = 382, 0.7%) and HCV (n = 222, 0.4%), respectably. Among them, two hundred fifty-six (42.6%) were confirmed to medicate within 6 mounts after the screening by medical bill checking system of Japan Health Insurance Association.

Conclusion: 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 by using social marketing approach may help detect carriers who are unaware of their infection and require treatment.

THU-403

The consensus hepatitis C cascade of care: Methodology and initial findings from three countries

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Background and aims: The World Health Organization (WHO) has called for the elimination of hepatitis C virus (HCV) as a public health threat by 2030. Efforts to monitor progress toward HCV elimination are hampered by the lack of a unified approach to defining HCV cascade stages, data sources and methodologies. The aims of this study were to develop a cascade of care for use in national and sub-national monitoring worldwide with well-defined stages, and to pilot the new instrument. The ultimate goal was to support strategic decision-making aimed at maximising the progression of HCV-infected individuals from diagnosis to cure.

Method: Leading clinical and public health experts reviewed the published literature on existing HCV cascade of care methodologies, as well as relevant information about cascade monitoring in the HIV field. Key methodological issues were discussed and agreed by consensus, and cascade stages and definitions formulated. Experts on the epidemiology of HCV in Denmark, Norway and Sweden applied the resulting HCV cascade of care instrument to national and-in the case of Denmark-sub-national data to report on progress toward HCV elimination in these countries.

Results: The proposed consensus cascade is comprised of four stages: infected, diagnosed, treated and cured. The four stages were defined in relation to an annual period beginning 1 January. Definitions took into account spontaneous clearance and the time lag between treatment initiation and sustained viral response. Norway and Sweden completed the cascade using national data and estimates for the three years of interest, 2015-2017, while Denmark reported using subnational data from three of its five regions. The cascades from all three settings showed high levels of fall-off from the diagnosed to the treated stage; an estimated 3%-18% of those diagnosed in 2017 received treatment (Figure 1). Large proportions of the estimated HCV-infected populations in Norway and Sweden

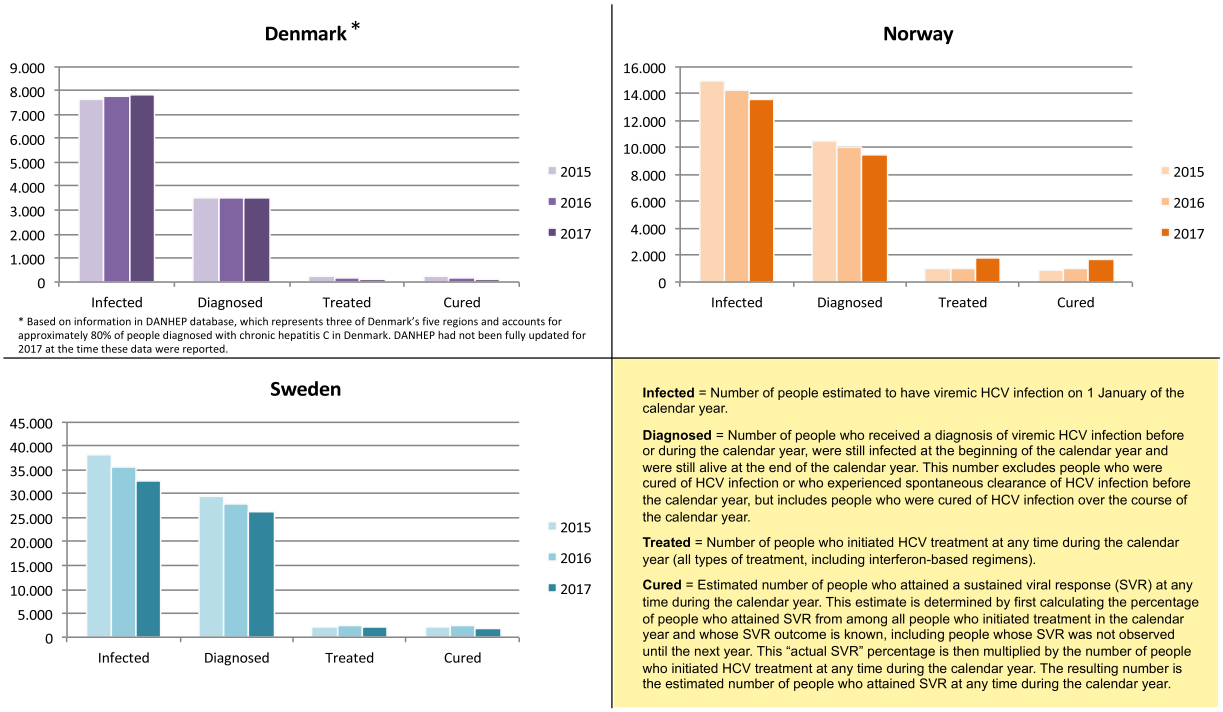

Figure 1: (abstract: THU-403): Estimated hepatitis C cascades of care for Denmark, Norway and Sweden, 2015–2017

are diagnosed-70% and 80%, respectively-while fewer are diagnosed in the Danish regions represented.
Conclusion: The Consensus HCV Cascade of Care is an effective instrument for monitoring progress toward WHO elimination targets and we recommend its use for national and subnational reporting. Reporting entities should describe any assumptions that informed the estimates reported for each cascade stage.

THU-405
Complications of chronic hepatitis B: Prevalence and disparities in a US health system cohort 2006-2016

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Background and aims: There are no recent reports of longitudinal trends in chronic hepatitis B (CHB)-related complications among routine clinical care patients in the US. Using data from the Chronic Hepatitis Cohort Study (CHeCS), we analyzed longitudinal rates of cirrhosis, decompensated cirrhosis, and all-cause mortality as well as disparities by age, sex, and race.
Method: Join-point and Poisson regression (univariate and multivariate) were used to estimate the annual percent change (APC) in each outcome from 2006 to 2016.
Results: A total of 5528 unique CHB patients were included. Prevalence of cirrhosis (including decompensated cirrhosis) doubled from 6.7% in 2006 to 13.7% in 2016. Rates among female patients were roughly half that of male patients (Rate ratio [RR] 0.47; $p < 0.001$). Cirrhosis rates were lowest among the youngest patients and highest among the oldest; rates increased over time in all age groups (adjusted APC (aAPC) 3.8-10.8; $p < 0.001$). Overall prevalence of decompensated cirrhosis increased from 2.3% to 5%; as with cirrhosis, rates were lowest among the youngest patients and highest among the oldest. aAPC increased (aAPC = +6.2%; $p < 0.001$) but did not differ by sex, age, or race. Incidence of all-cause mortality remained flat across the study period (1.4% to 1.7%), but varied by sex (female vs male RR = 0.61; $p < 0.001$) and age. APC increased among African Americans (aAPC = +6.2%; $p = 0.01$) but remained flat among Asian American/Pacific Islander (AAPI) and White patients ($p > 0.70$).

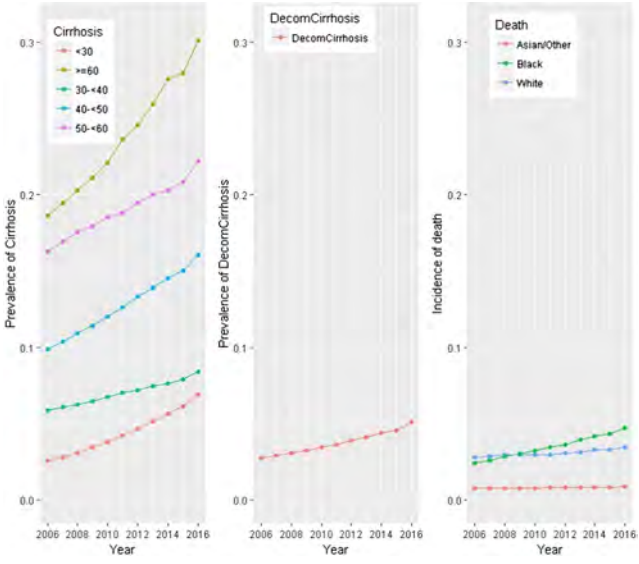

Figure: Rates of cirrhosis and decompensated cirrhosis, and incidence of mortality among patients with chronic hepatitis B.

Conclusion: From 2006 to 2016, prevalence of cirrhosis among CHB patients doubled; rates were highest among older, male, and African American patients. Rates of decompensated cirrhosis also doubled

over the study period. Incidence of all-cause mortality was steady in both AAPI and White patients, but increased among African Americans.

THU-406

Cost-effectiveness analysis of "treat all" guidelines for chronic hepatitis C in Brazil

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Background and aims: Home to over 1 million HCV-infected individuals, the Brazilian public health system incorporated direct-acting antivirals (DAAs) in 2015 for advanced liver disease. By 2017, DAAs had been delivered to about 65, 000 people. Recently, the Ministry of Health (MoH) decided to expand treatment to all patients regardless of liver damage. Our aim was to evaluate the cost-effectiveness of universal treatment for chronic hepatitis C in Brazil, which remains lacking.
Method: A Markov model simulated natural disease progression and treatment intervention for adult HCV mono-infected patients, from diagnosis to death, with characteristics drawn from a public hospital cohort (Hospital de Base, Brasilia). Costs and outcomes were compared for 3 scenarios: treat from Metavir fibrosis stage F3 (S1), treat from F2 (S2) or treat all patients (S3). Rates for background and liver disease-related mortality, disease progression, sustained virologic response (SVR) and quality-adjusted life years (QALYs) were based on official data and literature review. Direct costs, including ambulatory and hospital fees, and drug prices (US$ 6, 212.64 per 12-week therapy) were estimated from public payer perspective, considering MoH guidelines and databases. Discount rate was 5% for costs and outcomes. Incremental cost-effectiveness ratios (ICERs) were interpreted according to GDP per capita (US$ 9, 821). Extensive sensitivity analysis was performed.
Results: At baseline, 80% of patient population was in stages F3 or F4. S3 was the most effective strategy with mean gain of 0.01 and 0.03 QALYs compared to S2 and S1, respectively. However, due to cost, S3 was not cost-effective against S2 (US$ 16, 980/QALY), nor was S2 against S1 (US$ 12, 352/QALY). Varying the gender's distribution, fibrosis stage and age distribution at diagnosis, probabilities of progression, ambulatory and hospital costs and probabilities of svr did not hold much impact on ICERs. By contrast, results were highly sensitive to QALY and drug price variation. At US$ 1506, 75 per 12-week therapy, according to new prices under negotiation at the MoH, S1 became dominated and S3 highly cost-effective against S2 (US$ 429/QALY).
Conclusion: At current drug prices, expanding hepatitis C treatment eligibility is not cost-effective. However, universal treatment can be highly cost-effective or even cost-saving, compared to delaying treatment till F2 or F3 stages, once therapy costs are considerably reduced. Efforts to lower DAA prices are key to put Brazil on track with World Health Organisation targets to eliminate HCV infection by 2030.

THU-407

Implementation of a hepatitis C testing and linkage to care program in the Philadelphia jail system

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Background and aims: Hepatitis C (HCV) infection disproportionately affects those in correctional institutions. The HCV seroprevalence n incarcerated populations ranges from 17.4%-23.1% and in Philadelphia jails is estimated to be 17%. HCV-associated liver disease is a frequent cause of inmate death and has recently surpassed HIV deaths. International societies recommend that all incarcerated persons undergo HCV testing. HCV testing is not universally performed in this setting and treatment is provided only to those with advanced liver disease who meet sobriety and behavioural criteria.
Method: In October 2017 the Philadelphia Department of Prisons (PDP) partnered with Philadelphia FIGHT Community Health Centres to develop an HCV testing and linkage to care program for sentenced inmates. PDP leadership requested a staged roll out of the program due to concerns about the downstream costs of treatment. The first six months of the project consisted of providing HCV education and protocol training for PDP medical staff, securing necessary contracts, and hiring one FIGHT linkage coordinator. The following six months required an iterative process of developing inclusion criteria and modifying protocols.
Results: On 2 April 2018 a list of the 14 inmates expected to be released within six weeks was provided for testing. The PDP medical staff requested the FIGHT linkage staff to be present at the time of testing to provide patient education. On 1 May 2018 the PDP expanded eligibility to include all inmates who were expected to be released within six months (n = 246).

	eligible for testing	released before testing	refused testing	available for testing	tested within the month of eligibility	tested within 1 month of being declared eligible	total number tested between 1.4.18-15.11.18
April	14	4 (29%)	3 (21%)	7 (50%)	6 (43%)	6 (43%)	7 (50%)
May	112	32 (29%)	11 (10%)	69 (62%)	54 (48%)	63 (56%)	69 (62%)
June	80	35 (44%)	5 (6%)	40 (50%)	11 (14%)	38 (48%)	40 (50%)
July	56	18 (32%)	1 (2%)	37 (66%)	24 (43%)	37 (66%)	37 (66%)
August	914	324 (35%)	44 (5%)	546 (60%)	175 (19%)	304 (33%)	433 (47%)
September	201	85 (42%)	3 (1%)	113 (56%)	12 (6%)	68 (35%)	78 (39%)
October	218	68 (31%)	6 (3%)	144 (66%)	56 (26%)	68 (31%)	68 (31%)
Total	**1595**	**566 (35%)**	**73 (5%)**	**956 (60%)**	**338 (21%)**	**584 (37%)**	**732 (46%)**

Conclusion: To achieve the WHO HCV elimination targets by 2030 we must be testing for and treating HCV in correctional settings. Building an HCV testing program in correctional settings in the US is feasible but can be challenging and is influenced by concerns regarding the downstream cost of medication. Ideally all correctional settings should provide routine opt-out testing to all individuals upon intake.

THU-408

Screening for viral immunity prior to immunosuppressive or biologic therapy

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Background and aims: Immunosuppressive therapies and biologic agents are increasingly used as first-line treatments for inflammatory conditions across multiple specialties. Patients on these therapies are particularly susceptible to viral infections, while live vaccines may be contraindicated or rendered less effective. Major society guidelines recommend reviewing immunization history prior to initiation of immunosuppressive or biologic agents, in addition to screening for latent hepatitis B virus and tuberculosis. Routine pre-treatment screening for measles, mumps, and rubella immunity has been recommended but is not well-established. The purpose of this study

was to assess current pre-treatment screening practices, with the goal of better informing the standard of care.
Method: A retrospective review of patients on immunosuppressive or biologic agents was conducted within a single multi-hospital health system over a seven-year period (2011–2017, inclusive). Each treated patient was screened for selected laboratory values recorded at any point prior to treatment. These values included rubella IgG, measles IgG, mumps IgG, varicella zoster IgG, hepatitis B serology, and interferon-gamma release assay for tuberculosis.
Results: A total of 771 patients were included, representing 838 unique initiations of infliximab (54.5%), azathioprine (37.5%), adalimumab (6.8%), ustekinumab (0.6%), etanercept (0.2%), certolizumab (0.2%), and apremilast (0.2%). Screening rates were highest for hepatitis B surface antibody and antigen (80–100%), and lowest for varicella zoster IgG (10–40%), interferon-gamma release assay (0–20%), measles IgG (0–30%), mumps IgG (0–30%), and rubella IgG (0–30%). Screening rates were similar across all drugs surveyed.

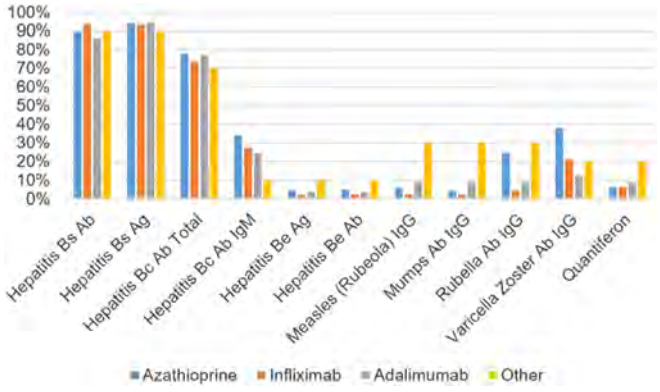

Figure: Rates of laboratory assays conducted for patients on immunosuppressive or biologic agents.

Conclusion: Among patients treated with immunosuppressive or biologic agents in a multi-hospital health system over a seven-year period, screening compliance was relatively high for hepatitis B serology, however was considerably lower for assessment of measles, mumps, rubella, and varicella immunity. These results are in agreement with our previous analyses of survey data, and highlight the need for improved pre-treatment screening guidelines.

THU-409

Progress on scaling up testing and treatment for hepatitis C elimination in Punjab, Pakistan: Hepatitis prevention and treatment program

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Background and aims: The province of Punjab, Pakistan has one of the highest burdens of hepatitis C (HCV) in the world. 90% remain undiagnosed. Punjab government funded Hepatitis Prevention and Treatment Program (HPTP), by Pakistan Kidney and Liver Institute and Research Center (PKLIandRC), to scale-up testing and treatment. Between March 2017 and October 2018, 24 community clinics for viral hepatitis care were opened across Punjab, Pakistan. Two doctors without specialty training, supported by a nurse, laboratory technician and a pharmacist formulate the core team at a clinic. Guidance is provided by hepatologists at the central hub in Lahore. On the first visit, testing for HCV antibody (anti-HCV) and hepatitis B surface antigen, is done by rapid testing. Results are reported in 20 minutes. Positive cases are counselled for further testing. For HCV, blood samples are taken for HCV PCR, blood picture, liver and renal function, to confirm and stage disease. AST to Platelet Ratio Index and Fibrosis-4 Index is used for staging. Pakistan is Genotype (GT) 3 predominant region (>85%), hence GT is not performed. At follow-up, treatment is initiated with Sofosbuvir (SOF) and daclatasvir (DCV) using standard protocols. All steps are recorded in centralized electronic medical records. This paper describes overall program and its initial progress.
Method: We constructed a care cascade by performing an analysis on screening, confirmation testing and uptake of treatment up to November 10, 2018. Treatment completion rates were assessed for those who received their last refill on April 30, 2018.
Results: As of November 10, 2018, a total of 224, 687 patients had sought care across the 24 centers. 47.4% male and 52.6% female. 82% (n = 183, 370) were tested for anti-HCV, 37% (n = 84, 067) were found positive. 23% (n = 51, 778) were found to have chronic HCV. 16% (n = 36, 663) were enrolled in SOF based treatment. As of May 31, 2018, 7, 659 people have completed treatment. Sustained Virolgical Response (SVR) 12 was available in 63% of those that completed treatment (n = 4841). SVR12 for the overall program was 97.3% in those with SVR 12 data. (Figure 1).

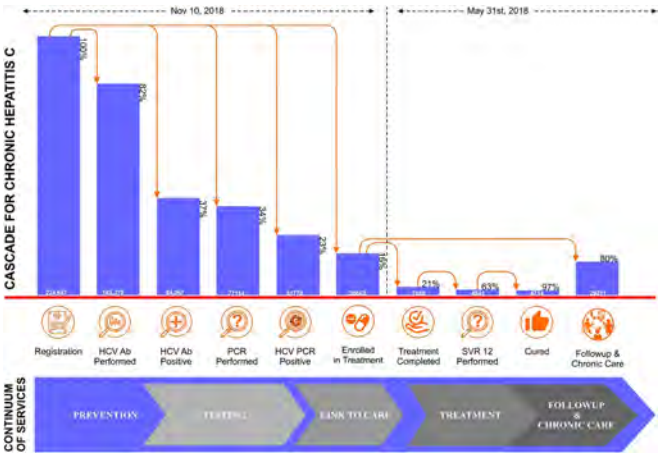

Figure 1: Treatment cascade for care, of patients presenting to Hepatitis Prevention and Treatment Program, Pakistan.

Conclusion: This program highlights community-based scale up of testing and treatment to achieve WHO elimination goals in high burden setting. Lessons learnt could be used for scale-up in other settings.

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Hepatitis B prevention of mother to child transmission integrated into antenatal care services in Mozambique

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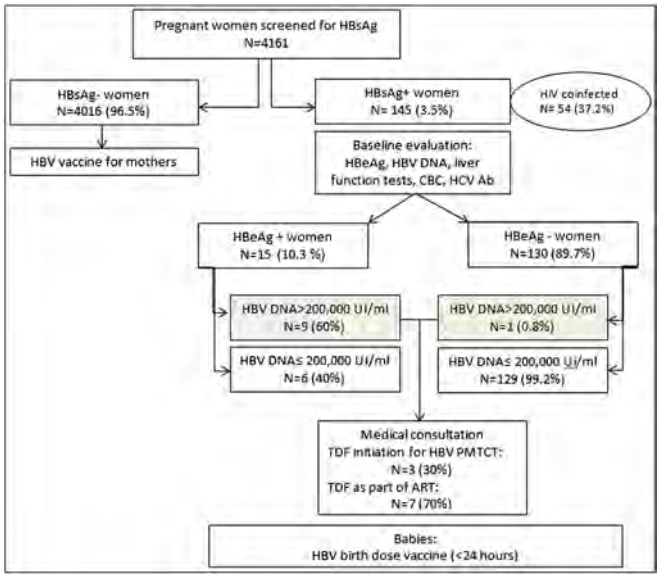
Background and aims: Hepatitis B (HBV) is mostly transmitted in endemic areas during peripartum and early childhood.

Implementing strategies to prevent mother-to-child transmission (PMTCT) is important to achieve WHO HBV elimination goals by 2030. Currently, neither HBV screening during pregnancy nor birth vaccination are available in Mozambique. The Ministry of Health (MOH) is developing national hepatitis guidelines which will include a PMTCT component. In response, Médecins Sans Frontières (MSF) and MOH have piloted a Hepatitis B prevention strategy in a maternity unit of Maputo to establish a sustainable model of care.

Method: In an existing MOH maternity unit, we implemented systematic point-of-care HBV screening (Alere Determine®) by nurses at initial antenatal visits, in addition to standard-of-care HIV and syphilis testing. Women testing positive for HBsAg were further tested for HBV viral load (VL), HBeAg, HCV Antibodies (SD Bioline®), liver function, creatinine and full blood count. Tenofovir (TDF) was prescribed for women who: a) were co-infected with HIV, b) had high HBV VL (>200, 000 IU/ml) for PMTCT or c) met WHO treatment criteria. Midwives provided HBV birth dose vaccine within 24 hours for all exposed babies. Women who underwent testing between Novembers, 2017-18 were included in this analysis.

Results: 4161 pregnant women were screened for HBV. Of these, 145 (3.5%) were HBsAg positive, and their median age was 27.4 years (IQR 23.1-32.6). Of these, 54 (37.2%) were co-infected with HIV, and none with HCV. The median APRI score was 0.3 (IQR 0.2-0.4); only 3 women had APRI >1. Among HBsAg positive women, 15 (10.3%) were HBeAg positive. Of these, 9 (60%) had high HBV VL (>200 000 IU/ml); only one HBeAg negative woman had high VL. Among the ten patients with high VL, seven were receiving TDF as part of a regular ART (antiretroviral therapy) regimen, and three were initiated as HBV PMTCT.



Conclusion: The prevalence of HBV in our cohort (3.5%) exceeds the WHO threshold (2%) recommended for systematic HBV screening during antenatal care. In this high HIV endemic context, most women in need of HBV PMTCT were already receiving TDF. This intervention highlights the feasibility of incorporating HBV screening and care into existing MOH maternity services, including birth dose vaccination. Future analysis, including HBV testing of infants, will be conducted to evaluate outcomes and propose interventions in resource-limited settings.

THU-411

Effectiveness of direct: Acting antivirals for the treatment of viral hepatitis C in Rwanda

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Background and aims: Direct-acting antivirals were first introduced in Rwanda in November 2015 replacing interferon-based therapies. Clinical trials conducted mainly in high-income settings have reported up to 95% of sustained virological response 12 weeks post treatment (SVR12). However, little is known about the real-world effectiveness of these drugs for treating chronic Hepatitis C (HCV) in resource-constrained settings. The aim of this study was to evaluate the effectiveness of DAAs recently implemented in Rwanda. In addition, factors associated with virological failure and non-virological due to premature treatment discontinuation are presented.

Method: De-identified demographic, clinical and HCV treatment data were extracted from national HCV program monitoring database. Data for all patients who initiated DAA-based treatment between November 2015 and March 2017 were included. Our primary outcomes consisted of patients who achieved SVR12 and those who were classified as non-virologicial failure. Univariable and multivariable logistic regression models were fit to estimate the relationship between patients' clinical and demographic characteristics and virological outcome.

Results: 894 patients initiated treatment during the study period and 590 completed the full treatment sequence. In our analysis, 91.5% (540/590; 95% CI = 88.9-93.6) of patients achieved SRV12. In an intention-to-treat analysis, 60.4% of patients achieved SVR12 (540/894; 95% CI = 57.1-63.6), 50 patients (5.6%; 95% CI = 4.2-7.4) experienced virological failure and 304 patients (34.0%; 95% CI = 30.9-37.2) were considered as discontinuing treatment prematurely. Having a pre-treatment viral load above the median split (800.000 copies/cml was associated with virological failure (aOR = 2.6; 95% CI = 1.3-5.1; $p < 0.01$). Patients residing in Western Province were more likely to discontinue care (aOR = 1.8; 95% CI = 1.14-2.98; $p = 0.01$) compared to those in Kigali, and the association between paying out-of-pocket and earlier discontinuation was trending towards statistical significance (OR = 1.6; 95% CI = 0.9-2.8; $p = 0.05$).

Conclusion: DAAs treatment was found to be effective when implemented through Rwanda's national health system. Decentralization and enhanced financing efforts are underway in Rwanda, which could improve access to treatment and clinical follow-up as the country embarks on its journey towards HCV elimination.

THU-412

Iceland may already have reached the WHO 2030 targets for diagnosis and treatment of hepatitis C virus infection: Results from the treatment as prevention for hepatitis C (Trap HepC) program

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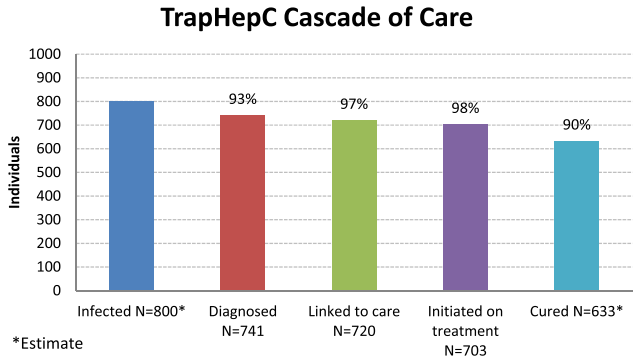
Background and aims: To achieve elimination of hepatitis C virus (HCV) as a major health threat, the World Health Organization (WHO) has set treatment service coverage targets of 90% diagnosis and treatment of 80% of eligible patients by the year 2030. Injection drug use (IDU) accounts for 90% of existing and almost all new HCV infections in Iceland. Most people who inject drugs (PWID) are routinely tested for HCV. Therefore, it is estimated that a small number of patients remain undiagnosed. Reporting to a national HCV registry is mandatory.
Method: Starting in 01/2016 with the TraP HepC program, all patients in Iceland infected with HCV are offered direct acting antivirals (DAAs), aiming for elimination of domestic transmission of HCV. PWID and prisoners are prioritized and various strategies are employed to enhance testing, linkage to care, and harm reduction. Untreated patients are identified and linked to care by cross-referencing several data sources including The HCV registry and Vogur Addiction Hospital database.
Results: In 2016, a total of 1287 HCV antibody positive individuals were identified in the HCV registry with additional 161 cases until 6/2018 for a total of 1448. When accounting for PCR negative, including previously treated and excluding temporary visitors, a total of 741 HCV PCR positive individuals currently living in Iceland were identified. The number of HCV tests increased from 5500 in 2015 to 8700 in 2017. No new infections were identified by outreach point-of-care testing among risk groups. Testing revealed a 30% infection rate among prison inmates, however, all had been diagnosed previously. As of November 2018, 720 patients (97% of those diagnosed) were linked to care. DAAs were initiated for 703 patients (98% of linked to care). Among 558 patients treated during the first 24 months, overall cure rate with first treatment attempt was 89%. Recent IDU was reported by 189 (34%). The majority of patients not achieving cure were retreated. On the basis of extensive screening among risk groups it is likely that >90% of domestic HCV infection have been diagnosed.



Conclusion: A major scale-up in testing and treatment for HCV in Iceland has resulted in a high rate of engagement and treatment. Iceland may already have reached the 2030 WHO service coverage targets of 90% diagnosis and treatment of 80% of eligible patients. Hopefully these results will translate into the elimination of HCV as a major health threat in Iceland.

THU-413

Service delivery for hepatitis C care: A systematic review and meta-analysis

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Background and aims: Worldwide, only a small proportion of those HCV infected persons have been diagnosed and treated. Increasing access to care in low-middle income countries (LMICs) will require adoption of simplified service delivery models such as decentralization and task shifting to non-specialists, and integrated testing and treatment at harm reduction sites. We conducted a systematic review and meta-analysis to establish their effectiveness on outcomes across the continuum of HCV care in different populations
Method: Bibliographic databases and conference abstracts were searched for clinical trials or observational studies published between 01/2008 to 02/2018 that evaluated interventions and outcomes along the HCV care cascade in PWID, prisoners (Pris), PLHIV, and general population (GenPop). Decentralisation was defined as either full (**FD**)-testing and treatment at same site, or partial (**PD**)- testing and referral for treatment**,** and task-shifting as HCV treatment by non-specialist physicians or nurses. Data was pooled using random effects meta-analysis
Results: 85 eligible studies from 19 countries (9 from LMICs) were included. 36 were in PWID, 12 in Pris, 2 in PLHIV, and 35 in the GenPop. 21 (25%) reported outcomes across the continuum of care, 21 (25%) the pre-treatment cascade only, and 43 (50%) treatment only. There was considerable heterogeneity in outcomes- Testing uptake (n = 18) 72% (95%CI 35-100) in PWID; 39% (95% CI 3-75) in GenPop; 40% (95%CI 21-59) in Pris. Linkage to care (n = 31) 58% (95%CI 41-75) in PWID; 72% (95% CI 58-86) in GenPop; 62% (95% CI 36-88) in Pris. Treatment uptake (n = 33) 69% (95%CI 46-72) in PWIDs; 52% (95%CI 36-67) in GenPop; and 71% (95%CI 60-80) in Pris. Among PWID, FD compared to PD had higher testing uptake: 88% (95%CI 78-98) vs. 47% (95%CI 4-99), and linkage to care: 80% (95%CI 62-98) vs. 53% (95%CI 30-76), but similar SVR rates: FD 93% (95%CI 89-97) vs PD 88% (95% CI 84-93). Results were similar for FD and PD in the GenPop. Task-shifting achieved similar SVR in both PWID 92% (95%CI 88-97) vs. 92% (95%CI 85-99) and GenPop 92% (95%CI 87-96) vs. 91% (95%CI 87-95)
Conclusion: Integration of testing and treatment with harm reduction for PWID achieved high levels of testing uptake and linkage to care. Decentralization and task-shifting achieved high levels of HCV cure in all populations. There is a need for more studies from LMICs and a more systematic approach to reporting outcomes across the continuum of care.

THU-414

Low rate of treatment uptake amongst recently released prisoners with active HCV infection

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Background and aims: There is high prevalence and incidence of HCV amongst prisoners. Prison treatment programs therefore provide an excellent opportunity to treat a marginalised population at high risk for transmission. However, short prison sentences mean that not all prisoners can be treated even in the context of comprehensive prison management programs (McDonald, J Hepatol, 2017; 66 (1) : S70 (PS-126)). There are no data about the rate of successful linkage to HCV care amongst recently released prisoners, a group who face many social challenges. We aimed to

determine the proportion commencing HCV therapy in the community amongst a group of recently released prisoners.
Method: Prisoners with HCV infection, who had been assessed as suitable for DAA therapy by our prison hepatitis program, but released prior to starting therapy, were included. Prior to release, prisoners were assessed by a hepatitis nurse; tests included HCV RNA and transient elastography. On release, all prisoners were referred to a local healthcare service for HCV treatment. All Australians are eligible for reimbursed HCV treatment, which can be dispensed in the community by primary care physicians. The primary outcome of this analysis was dispensing of HCV therapy within 6 months of release from prison, confirmed by the national medication prescribing database.
Results: Seventy-five HCV RNA positive prisoners were followed for 6 months post release. The mean age was 40 yrs, 66 (88%) were male, and 11 (15%) had cirrhosis. 59 (78%) prisoners identified as a person who injects drugs in the month prior to incarceration. 27 (36%) received opioid substitution therapy (OST) while incarcerated and psychiatric comorbidity was self-reported by 56 (75%). Only 19 (25%) were prescribed HCV therapy within 6 months of release. Of these, 7/19 (37%) were prescribed treatment on reincarceration. Predictors of treatment commencement were reincarceration ($p = 0.02$) and absence of cirrhosis ($p = 0.01$), but was not associated with OST, injecting drug use in the month prior to incarceration or psychiatric comorbidity.
Conclusion: The rate of HCV treatment post-release was low, despite all prisoners having been assessed as suitable for HCV treatment in prison, and HCV treatment being freely available in the community. The most important predictor of HCV treatment was reincarceration. These data emphasize the importance of maximizing treatment uptake during the period of incarceration. New models of care to improve linkage to community HCV treatment among recently released prisoners are required.

THU-415

Changing patterns of liver disease in Wales: First results from the Wales liver disease registry

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Background and aims: Liver disease is the third most common cause of premature death in the UK. At present major epidemiological studies have been based upon mortality data limiting our understanding of the true burden of liver disease and potential targets for service improvement. The Wales Liver Registry has been created as part of the Liver Disease Delivery Plan for Wales 2015-2020 to inform the effective provision of hepatology services within Wales.
Method: The Registry is populated by ICD10 code diagnoses from ONS mortality data and Patient Episode Database for Wales (PEDW) capturing all coded diagnoses of liver disease of inpatient and day case activity in Wales between 2001 and 2016. Data is pseudo anonymised with linking of recorded diagnoses, epidemiological and mortality data.
Results: Between 2001 and 2016 the number of new diagnoses of liver disease in Wales, based on relevant ICD10 coding, increased from 3354 in 2001 to 8115 in 2016. The incidence of each individual liver disease diagnosis increased during this period. Between the first 3 years (2001-3) and the final 3 years (2014-16) of the registry there was a 6-fold increase in fatty liver disease, 1.23 fold increase in alcohol related liver disease and 1.7 fold increase in viral hepatitis. Diagnoses of cirrhosis and portal hypertension, decompensated cirrhosis and primary liver cancer increased 2.1-, 1.7- and 2-fold respectively during this period.
Overall mortality of patients with liver disease remained static in Wales between 2001 and 2016 (mean = 1522 deaths per annum). Between 2001-3 and 2014-6 deaths in patients with fatty liver disease and liver cancer increased by 2.3 fold and 1.75 fold respectively. In contrast there was a decrease in deaths in those with alcohol related liver disease (30.2% reduction) and viral hepatitis (21.6% reduction) during this period.
Conclusion: Early analysis of the Wales Liver Disease Registry demonstrates a 2.5 fold increase in the number of new diagnoses of liver disease since 2006. There was a shift to fatty liver disease as the most common diagnosis within the defined groupings used for this analysis. Strikingly in spite of this increase in liver disease mortality rates have been static with improvements in mortality in individuals with alcohol related liver disease and viral hepatitis. We aim to further develop the Wales Liver Disease Registry with prospective data collection, incorporating all Wales primary care data and developing time to event analyses to identify opportunities for health interventions.

THU-416

Use of telemedicine as a cost-effective program to achieve microelimination of hepatitis C virus infection among patients in a public healt care system in a low-income country

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Background and aims: Direct antiviral agents (DAAs) are highly effective and safe; them have simplified the treatment of patients with hepatitis C virus infection (HCV). The use of communication technology allows avoiding the displacement of patients from remote places, reducing costs in health-care. *The Medical Services of Mexican Petroleum* (PEMEX) have 700, 000 health-care insured beneficiaries located throughout the country; the institution counts with 30 medical units divided into 8 regions throughout the country, including primary-care, regional centers, and specialty-care hospitals. Moving all the patients of the different regions of the country to Mexico City to receive antiviral treatment and follow-up by the gastroenterologist would be extremely expensive.
Aim: To evaluate the cost-effectiveness of a telemedicine as a part of an hepatitis C microelimination program among the Mexican insured population of PEMEX.
Method: A coordinator of the program in Mexico City, with experience on DAAs therapy was in charge to train through telemedicine using an internet platform, all primary-care physicians (PCP) responsible for treating HCV in the 8 different regions of the country. They were instructed on the criteria for selecting patients and how to prescribe the DAAs and their follow-up.
All patients diagnosed with HCV and susceptible to receive DAA therapy were included. They were prescribed: sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, elbasvir/grazoprevir.
All of them were studied, treated and followed-up in their own region for their PCP with support of the coordinator of the program by telemedicine, all the decisions made by the PCP were supervised throughout the internet platform, phone-call or chat by the coordinator of the program and a group of specialists in Mexico City.
Results: We included for the analysis 116 patients, 83 F, 33 M, mean age 61.3 ± 11.40. Genotype 1 = 73, genotype 2 = 42, Genotype 3 = 1. 43 patients without significant fibrosis, and 73 cirrhotic: Child Pugh A = 63, B = 9, C = 1. All the viral loads at the end of treatment were reported negative (100% response), all patients were treated in a minimum of 4 visits in place of adscription through telemedicine, which saved $ 2400 per patient (includes the payment of per diem,

transportation, and disability) that makes a total of 324 800 dollars in total only by way of transfer to the capital. There were no serious side effects, so no treatment should be discontinued

Conclusion: It was possible to cure all patients (100%), there were no serious side effects. It stands out that 41 (35%) did not have significant fibrosis in such a way that they did not develop cirrhosis saved in the medium and long term economic and human resources for not developing this complication, as well as an excellent prognosis for all these patients. The use of telemedicine also generated significant savings because patients were not invested in their transfer.

THU-417

CURE-IT Program-Introducing equity, removing barriers and treating patients hepatitis C close to home: The Queensland experience

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Background and aims: Background and aims: Healthcare delivery in Queensland has geographical challenges including distance, transport and distribution of specialists and services. HCV affects approximately 230 000 people in Australia. In 2016, the Pharmaceutical Benefits Scheme facilitated primary care prescribing of the new DAA's. Traditional HCV treatment occurred in tertiary hospitals, requiring patient travel, multiple attendances and missed appointments.

The "CURE IT Program" facilitates a shared model of care between community prescribers, hospital specialists, whilst providing clinical, financial and a best practice governance encouraging appropriate treatments. The "CURE IT" Program is "echo-lite," utilising a clinical nurse and hospital consultant offering daily advice to municipal, regional and remote communities, needle exchange workers and hospital prescribers. All patient treatments are facilitated by the treating GP close to home. Patients with advanced liver disease were referred pre or after treatments.

Method: From March 2016 all referrals to The Prince Charles Hospital were reviewed for suitability for CURE-IT. Simultaneously, community providers were engaged and provided with written and verbal education regarding HCV treatment and the "CURE IT" Program. Completed proforma's containing relevant information (patient demographics, medical history, ultrasound and laboratory results) were returned to the specialist, whereupon, following review patients were commenced on treatment in 1-2 business days. The average time taken for the specialist to review each request was 5-7 minutes.

Results: Between March 2016 and November 2018, 380 remote treatment requests were assessed:

371/380 (97.6%) patients approved for community based treatment.	350/380 (92.10%) patients GP commenced DAA therapy.	371/380 (97.63%) avoid hospital visits
9/380 (0.02%) patients referred for specialist review.	220/350 (62.85%) patients completed therapy.	218/220 (99%) achieving SVR
38/380 (10%) lived 70 –647km from Brisbane	>1200-1600 outpatient appointments avoided	>44, 000 kms of travel avoided

Conclusion: CURE-IT has redefined specialist healthcare delivery achieving SVR in 99% of patients, not one of whom have attended hospital. PROM's- Other end points have resulted in a "patient centred, patient focused program" factors most important to patients-treatment closer to home, treatment by a trusted GP, reduction of hospital visits, reduction in time lost from work, reduction in financial loss for patients, distance travelled by patients and this may all be doubled if partners also attended. The "CURE IT" Program has also had unintentional network gains including: dynamic collaborative relationships with primary care, increased awareness of HCV, liver disease, cirrhosis liver cancer and treatments, leading to upskilling of regional and rural healthcare workers.

THU-418

Community-based screening for significant liver fibrosis among apparently asymptomatic adults in Delhi

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Background and aims: Community-based screening for liver fibrosis using non-invasive methods like Transient Elastography (TE) can play a major role in enabling early diagnosis of Chronic Liver Diseases (CLD). This study aims to find out (i) the proportion of subjects with significant liver fibrosis and its predictors, (ii) the number needed to screen (NNS) to detect one subject with significant fibrosis among apparently asymptomatic adults in the community.

Method: A cross-sectional study was done among asymptomatic adult volunteers (age ≥ 18 years) from the catchment areas of 72 randomly chosen "*Mohalla clinics*" (Primary healthcare clinics in Delhi), using a mobile screening van. A pre-tested questionnaire was used to collect demographic data and past and personal history of the subjects. Post the interview; a trained research team performed TE to obtain liver stiffness measurement (LSM), HBsAg, Anti-HCV and a venous blood sample was collected to test for alanine aminotransferase (ALT) and Total Cholesterol (TC). LSM ≥ 8.0 kPa and >13.0 kPa were taken as cutoffs suggesting clinically relevant/significant liver fibrosis and cirrhosis, respectively. Data were entered in Microsoft Excel and analysed using STATA ver. 14.

Table 1: Predictors of significant liver fibrosis among study subjects using multivariable logistic regression

Predictor	Reference	Adjusted Odds Ratio with 95% Confidence Intervals (CI)	p value
Age		1.02 (1.01-1.03)	< 0.001*
Gender			
Male	Reference		
Female		0.43 (0.35-0.51)	< 0.001*
ALT levels			
Normal	Reference		
Raised ALT		3.28 (2.71-3.97)	< 0.001
BMI			
18.5-22.9 (Normal)	Reference		
< 18.5 (Underweight)		2.22 (1.24-3.97)	0.007*
23-24.9 (Overweight)		1.21 (0.80-1.84)	0.36
25-29.9 (Obese)		1.87 (1.34-2.61)	< 0.001*
≥ 30 (Morbidly obese)		4.06 (2.95-5.60)	< 0.001*
History of DM and/or HTN			
No	Reference		< 0.001*
Yes		1.85 (1.52-2.26)	
Anti-HCV			
Non-Reactive	Reference		
Reactive		2.96 (1.18-7.38)	0.02*

*significant; Model R^2: 13.3%.

Results: A total of 4928 subjects were screened; 54.6% were men and the median age of subjects was 41 years. Significant liver fibrosis was seen among 13.9% of the study subjects and 3.4% had cirrhosis. The NNS to detect one subject with significant fibrosis was 7.1. Table 1 describes the independent predictors for significant liver fibrosis.
Conclusion: Almost 14% of asymptomatic adults were found to have significant liver fibrosis in New Delhi, indicating the urgent need for mass screening campaigns to detect asymptomatic patients.

THU-419

Prevalence of hepatitis B and C virus infections in Mongolian children and adolescents

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Background and aims: Since decades Mongolia ranks among the countries with highest prevalence of hepatitis B (HBV) and C (HCV) virus infection. In 2013 HBV and HCV prevalence among the general adult population was estimated to be 11.1 and 8.5%, respectively. To tackle the burden of disease the Mongolian government took several measures. An HBV vaccination program for newborns was already introduced in 1991 and has been further improved since then. In 2016 the Parliament of Mongolia officially adopted the Hepatitis Prevention, Control, and Elimination (HPCE) Program into the 2016-2020 Action Plan aiming to eliminate viral hepatitis by 2020. Free hepatitis screening for the population aged 15 years and older as well as two treatment campaigns providing access to affordable HCV treatment were initiated.
We determined the current HBV and HCV prevalence among Mongolian children and adolescents, to assess whether there is need for further action specifically targeting this age group.
Method: A total of 3403 randomly selected children and adolescents (aged 0 to 24 years) from 17 Mongolian provinces were enrolled in a cross-sectional study. HBV surface antigen (HBsAg) and HCV antibody (anti-HCV) was tested on site using rapid diagnostic tests (CTK Biotech) on finger stick blood.
Results: Among a total of 3403 individuals aged 0 to 24 years we found 64 HBsAg- and 44 anti-HCV-positives, which were distributed unevenly between different age groups (**Table**).

Table: HBsAg and anti-HCV prevalence among Mongolian children and adolescent.

Age group	0-4n = 715	5-9n = 720	10-14n = 700	15-19n = 672	20-24n = 596	totaln = 3403
HBsAgn, (%)	6 (0.73)	7 (1.0)	11 (1.6)	4 (0.6)	36 (6.0)	64 (1.9)
anti-HCVn, (%)	7 (1.0)	3 (0.4)	8 (1.1)	10 (1.5)	16 (2.7)	44 (1.3)

Prevalence of HBsAg among the four age groups of individuals aged 0 to 19 years was low. While HBsAg-prevalence was comparable between these age groups, it was higher in individuals aged 20 to 24. This might be explained by lower quality and technique of vaccination 20 years ago. Anti-HCV-prevalence was generally low and tendentially increasing with age.
Conclusion: Overall HBsAg- and anti-HCV-prevalence within Mongolian children and adolescent was relatively low.
We therefore see no urgent need for further improvement of the HBV vaccination program or the inclusion of individuals below 15 years of age group in the population-wide hepatitis screening.

THU-420

Examination of patient and provider perceptions of hepatitis C care in Rwanda

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Background and aims: In Rwanda, estimates suggest that hepatitis C seroprevalence ranges between 3.1% to 4.1% in the general population and 4.5%-4.7% among people living with HIV. Direct-acting antivirals (DAAs) were introduced in Rwanda in November 2015 with four specialist physicians prescribing DAAs at four tertiary hospitals, one specialized laboratory for viral load testing, and one pharmacy supplying DAAs. The current study aimed to explore patients and healthcare providers' perceptions and experiences of the barriers and facilitators to DAA-based treatment in Rwanda in the early days of this major shift in service delivery.
Method: Semi-structured, face-to-face interviews were conducted with 39 patients treated with DAAs and 10 healthcare providers who managed HCV treatment from November 2015 to March 2017. Patients within each treatment outcome classification (achieved SVR12, virological failure and treatment discontinuation) were assigned a randomly generated number in Microsoft excel, stratified by hospital. Interview transcripts were translated into English and analysis was guided by a general inductive approach.
Results: According to patients**,** the availability of DAAs in Rwanda was in itself a motivator patients were grateful that they could access these drugs. The positive relationship patients shared with health-care providers and the support received from family and friends were reported as the main facilitators to treatment. From the perspective of healthcare providers, the lack of stigma around HCV, a motivated healthcare staff and mild side effect profile of DAAs increased patients' adherence to treatment. Barriers reported by patients included limited knowledge around liver health and HCV, difficulties in accessing testing and treatment services due to financial hardship and the centralized nature of treatment services. Healthcare providers reported heavy workloads, need for additional HCV-specific training for nurses and occasional communication break-downs with the central-level as barriers.
Conclusion: To our knowledge, this is the first study to identify barriers and facilitators to DAA-based treatment from the perspectives of patients and healthcare providers in sub-Saharan Africa. We found a suite of interrelated factors that enabled and impeded care at both the individual-and system-level. There was a high-degree of consistency between patient's and healthcare providers, suggesting that these factors were represented widely in the healthcare system. Results from this study can be used to design and enact evidence-informed interventions to help maximize the impact of DAAs as Rwanda moves towards HCV elimination.

THU-421

Lower alcohol taxes are associated with increased liver transplant listing

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Background and aims: Alcoholic liver disease (ALD) is a leading indication for liver transplantation worldwide with rising prevalence. Whether relationships exist between transplant listing for ALD and changes in state alcohol tax rates or alcohol consumption has not been explored.
Method: State-level alcohol per capita consumption of spirit, wine, and beer was determined from published United States 2003-2015 data. Excise and ad valorem on- and off-premise tax rates of spirit, wine, and beer were calculated following standard practices. Using the United Network for Organ Sharing (UNOS) database, we analyzed 2003-2015 state-wide patient-level data to determine if transplant listing for ALD was associated directly with alcohol consumption per capita and inversely with alcohol taxes. Univariate and multivariate regression was performed with clustering at the state level controlling for the pre-specified variables age, sex, race, education, employment, and insurance.
Results: Of 137, 440 patients listed for liver transplant, 21.2% (29, 161) were for ALD, with increasing prevalence over time, up to 25.0% in 2015. Compared to all other patients, patients listed for ALD were more likely to be older, men, of White, Hispanic, or American Indian/Alaska Native race/ethnicity, unemployed, and with less education and private insurance ($p < .01$). Multivariate analysis indicated increased listing for ALD was associated with increased consumption of spirit (OR 1.67, 95% CI 1.12-2.49, $p = .01$); for each additional gallon of ethanol per capita of spirit consumed, patients were more likely to be listed for liver transplant for ALD. Multivariate analysis including consumption and taxation did not significantly affect consumption findings, and suggested a significant inverse relationship of spirit excise tax on-premise (OR.85, 95% CI.72-1.00, $p = .05$) and off-premise (OR.85, 95% CI.72-.99, $p = .04$) (Table 1); i.e. as spirit excise tax decreased, listing for ALD increased.

Table 1: Multivariate regression for liver transplant listing for Alcoholic Liver Disease (ALD) by alcohol consumption and tax, controlling for age, sex, race, education, employment, and insurance

	On-premise			Off-premise		
	OR	95% CI	p	OR	95% CI	p
Spirit						
Consumption	1.73	1.14, 2.62	.01	1.71	1.11, 2.64	.02
Tax, excise	.85	.72, 1.00	.05	.85	.72,.99	.04
Wine						
Consumption	1.52	.96, 2.41	.08	1.50	.99, 2.27	.06
Tax, excise	.43	.11, 1.64	.22	.44	.13, 1.42	.17
Beer						
Consumption	1.29	.79, 2.11	.30	1.27	.80, 2.03	.32
Tax, excise	.04	.00, 1.44	.08	.04	.00, 1.44	.08

Conclusion: Listing for liver transplantation for ALD was directly associated with alcohol per capita consumption and inversely associated with spirit excise taxes. These findings suggest a possible public health benefit of increasing spirit taxes.

THU-422

Referral, treatment uptake and self-reported barriers in drug users diagnosed with active hepatitis C attending a low-threshold methadone program in Lisbon

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Background and aims: A previous study conducted between June 2015 and May 2016 on 825 drug users attending a mobile low-threshold methadone program (LTMP) in Lisbon, revealed that 68.4% of individuals with antibodies to HCV had active hepatitis C (n = 307) and among them, 30.0% had advanced liver fibrosis (*Eur J Gastroenterol Hepatol 2017*). At that time, a referral to conventional medical care for all participants with active hepatitis C was performed. After two years' time passed, the aim of the study is to evaluate the referral and treatment uptake of those HCV infected patients and to characterize possible barriers to treatment.
Method: Cross-sectional rollover study in previously selected drug-users with active hepatitis C (n = 307) performed during October 2018 and implemented by a self-completion of a questionnaire. The Ethics Committee of the National Institute of Health approved the study.
Results: Of the 307 individuals with hepatitis C diagnosed in the previous study, 191 were still attending the LTMP and of those, 150 individuals agreed to participate in this evaluation.
Among patients with advanced liver fibrosis in 2015-2016 assessment, 62.0% (26/42) reported to remember having mild liver disease or not to remember their liver disease stage.
Since the previous diagnosis and referral, only 67.1% (n = 100) were evaluated at least once in a hospital consultation due to hepatitis C, 45.0% (n = 67) initiated treatment and 27.5% (n = 41) were successfully treated, while 15.4% (n = 23) wait for assessment of treatment response.
The most frequent barriers to referral and treatment reported by treatment-naïve patients not followed-up in hospital consultations (38.3%; n = 57) were: costs of transport to hospital (53.8%; n = 28); long wait for consultation (50.0%; n = 26); costs of consultation fees (48.1%; n = 25) and perception that hepatitis C is not a severe medical problem (35.8%; n = 19).
Additionally, 73.7% (n = 42) of these untreated and unfollowed patients would prefer to be treated for hepatitis C at the low-threshold program rather than on a hospital-basis.
Conclusion: More than 2 years after confirmed diagnosis of hepatitis C and referral to conventional health care, a significant proportion of the patients did not access specialized care and therefore were not treated for hepatitis C, mainly due to economic and social barriers. Individualized medical-social strategies are needed to timely treat these individuals at their specific contexts.

THU-423

Patient group monitoring of implementation of WHO viral hepatitis C recommendations: Identifying the gaps between policy and practice in Europe

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Background and aims: The viral hepatitis C continuum of care (CoC) was adopted by WHO in 2016 to define the major steps in comprehensive care for viral hepatitis: prevention, testing, linkage

to care, treatment, and chronic care. This study aims to determine patient perspectives on the discrepancies between policy and practice to support efforts to eliminate viral hepatitis as a public health threat.

Method: Twenty-five organisations from the European Liver Patients' Association, each representing one country, were engaged in a survey in October 2018 to monitor implementation of national viral hepatitis policies. The cross-sectional survey was disseminated electronically via REDCap. Respondents received questions based on validated data sources that confirmed the existence of that policy in their country or, where unavailable, based on specific WHO policy recommendations. Participants were queried using a 5-point Likert scale on the degree to which the policies were functioning or implemented in practice. Questions were distributed between four components of the HCV CoC: 4 prevention questions (n = 61 total responses), 2 testing (n = 28), 23 linkage to care (n = 575), and 5 treatment (n = 52). Results were analysed descriptively using R.

Results: Among policies pertaining to the four domains (Fig 1) of the viral hepatitis CoC, patient groups reported the highest level of positive implementation for HCV treatment policies (67.3%), followed by prevention (54.1%), linkage to care (53.4%), and testing (46.5%). Linkage to care received the largest share of strong negative responses (12.5%) compared to testing (10.7%), treatment (3.8%), and prevention (3.3%). Data from individual questions in the linkage to care component revealed that patient groups reported the highest negative response on targeting of viral hepatitis services for transgender people (64%), and for migrants and sex workers (56%); while integration of HCV care within existing services was reported to be negative, "not at all" or "slightly" integrated, in the case of migrant health services (60%), alcohol use (52%), and non-communicable disease services (48%) (data not shown).

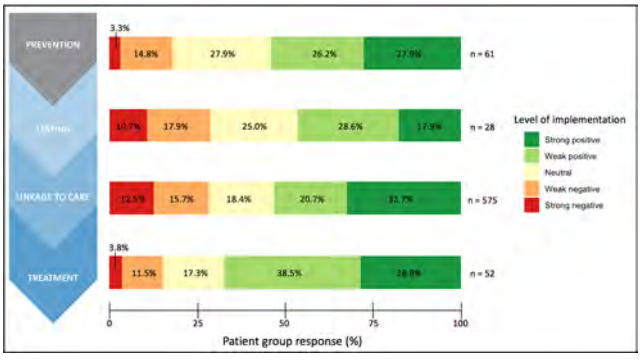

Figure 1: Level of implementation of policies across the viral hepatitis continuum of care in 25 European countries

Conclusion: Patient group respondents in 25 countries reported that the level of implementation of HCV policies and recommendations in practice in Europe remains incomplete across the continuum of care, especially in areas of linkage to care, testing, and services for vulnerable populations.

THU-424

HCV care cascade of PWIDs reached within the Global Fund needle and syringe program in Georgia

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Background and aims: Within the Global Fund HIV Program HCV screening is integrated in the PWID comprehensive service package to support Georgian hepatitis C elimination program. HCV AB screening positive PWIDs were followed across the HCV care to develop PWID HCV care cascade for 2018.

Method: HCV AB rapid test screening is provided by nurses at the Needle and Syringe Program (NSP) Drop-in centers (16 sites) and mobile ambulatories (6 units) as well as by peer PWIDs countrywide in Georgia. PWIDs who agree to provide personal ID are registered in the National hepatitis C elimination database, others are registered in the HIV prevention program database with 15 digit unique identifier number.

All HCV AB positive PWIDs are referred for HCV RNA testing to HCV treatment sites or collected samples for core-Ag confirmatory testing are sent to the National Reference Laboratory (Lugar Center). The National Hepatitis C Elimination Database allows tracking of those PWIDs who are registered by personal ID across full continuum of HCV care.

Results: During 10 months of 2019 total 23914 PWIDs were reached within the NSP program out of which 13, 836 were screened on HCV AB with 3324 (24%) positive results. 1221 PWIDs agreed to provide personal ID for registration in hepatitis C elimination database, out of which 865 (70.8%) were HCV AB positive and were enrolled in the HCV care cascade analysis. HCV RNA testing was performed for 608 (70.2%) PWIDs with 84% (511) positivity rate. 255 (49.9%) PWIDs were enrolled in HCV treatment with a mean of 59.7 (± 54) days of led time from confirmation to treatment. Mean time from HCV AB testing to RNA testing was 16.7 days (± 37.8 days). Mean time for full HCV care cascade of PWIDs from screening to enrollment in treatment program was 74 days (± 51.1 days), with the minimum the same day enrollment and the maximum of 298 days prior initiation of treatment.

Conclusion: Despite the continues efforts to support hepatitis C elimination program through the Global Fund Needle and Syringe Program in Georgia, the number of PWIDs enrolled in HCV treatment remains small. Due to criminalization of drug use PWIDs are reluctant to provide personal information that complicates the monitoring of PWIDs across HCV care. More community based peer accompanied referral interventions and/or NSP integrated HCV treatment programs are necessary to increase the number of PWIDs enrolled in the treatment as well as to decrease the time from HCV AB screening to HCV treatment initiation.

THU-425

Questioning the concept of cure: The morbidity and mortality of a homeless population following HCV treatment

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Background and aims: Underserved populations such as the homeless have high rates of both hepatitis C (HCV) and alcohol use. Difficulties in accessing specialist care services means that they have a high risk of liver disease. Treating homeless populations for HCV is possible if services reach-out into the community however morbidity and mortality can remain disproportionately high compared with the general population. We studied the morbidity and mortality rates of homeless and underserved individuals infected with HCV.

Methods: The HepCare project, co-funded by the European Commission, aims to outreach HCV screening to at-risk underserved populations. In London, we worked alongside the FindandTreat team's mobile health unit, using HCV point-of-care tests and a portable Fibroscan to determine liver fibrosis, to individuals accessing homeless and drug services. Chronically infected HCV

individuals and those with severe fibrosis or cirrhosis were referred and supported into specialist care. Peer support workers were trained alongside the clinical team to screen individuals and improve linkage to care. Information was gathered on demographics and risk factors, plus linkage to care, treatment outcomes, SVR and all-cause mortality
Results: Over 20 months 461 individuals attending homeless or drug services in London were screened, the majority (78.7%) were male; the median age was 45.7 years (IQR 39-52); most were UK born (76.6%) and a total of 197 people (42.7%) were found to be chronically infected with HCV. Drug use was common with 329 (71.4%) having ever injected and 125 (27.1%) currently injecting. Problem alcohol use was high with a third (33.6%) consuming more than 50 units per week. Fibroscan was carried out on 283 individuals and over 1 in 4 (22.7%) had advanced fibrosis or liver cirrhosis (>F3). We found that the age-standardised all-cause mortality rate for our cohort was much higher than the general population (SMR 3.8, 95% CI 1.8-8).
Conclusions: There is a high burden of morbidity and mortality in this group compared with the general population. It is also likely that the above estimate is conservative, given that deaths were only recorded for those who were identified as being chronically infected, and not the entire screened cohort. This population clearly has a high burden of disease and will need specialist strategies to improve the cascade of care, integration with other services and will require a re-appraisal of the concept of cure.

THU-426
Further validation of a liver "traffic light" test as a prediction model for survival and development of serious liver-related events

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Background and aims: Deaths from liver disease are continuing to rise despite huge advances in healthcare. Many non-invasive methods for liver fibrosis detection have been created, including the Southampton Liver Traffic Light (SLTL) test. However, few are sufficiently validated, especially in predicting serious liver-related events (SLE) or effectiveness in the community; the SLTL aims to achieve this.
Method: Clinical data from 4854 patients (community and secondary-care) with suspected liver disease were prospectively analysed over a mean follow-up period of 54 months (range 1-181 months). The SLTL is an algorithm incorporating hyaluronic acid, procollagen-3 N-peptide (P3NP), and platelet count results. It ultimately grades patients for liver fibrosis: green (low risk), amber (intermediate risk), red (high risk). AUROC analysis and survival graphs were established for predicting mortality and development of SLE, including varices and ascites.
Results: More deaths were observed within the red group of patients 280/1585 (17.7%) compared to amber 31/873 (3.6%) and green 49/2396 (2%) groups. A higher proportion of SLE was observed within the red group (29.5%) compared to amber (5.6%) and green (2%) groups. Survival plots demonstrated significantly increased mortality and development of SLEs in the red group compared with green and amber groups (Mantel-Cox, $p < 0.001$), with a further finding of significant increase in development of SLE in the amber group compared to green (Mantel-Cox, $p < 0.001$). Additionally, patients whose grade remained red over the follow-up period had lower survival than those who improved to amber (Mantel-Cox, $p < 0.001$) or green (Mantel-Cox, $p = 0.001$). AUROC analysis of the graded and continuous SLTL test results achieved prognostic values of 0.75 and 0.82 for mortality, respectively, and 0.80 and 0.87 for development of SLE, respectively. SLTL further demonstrated the ability to rule out risk of death and development of SLE based on achieving NPVs of 98% and 97%, respectively.
Conclusion: The SLTL test has been validated for predicting survival and development of SLE in the community. It could aid primary care decisions for risk management and referrals to specialists in the overall hope to detect liver disease earlier in the general population.

THU-427
A community-based fast-track seek-test-treat program to enhance diagnosis and linkage to care for hepatitis C infection among people who inject drugs in Athens, Greece (ARISTOTLE HCV-HIV program)

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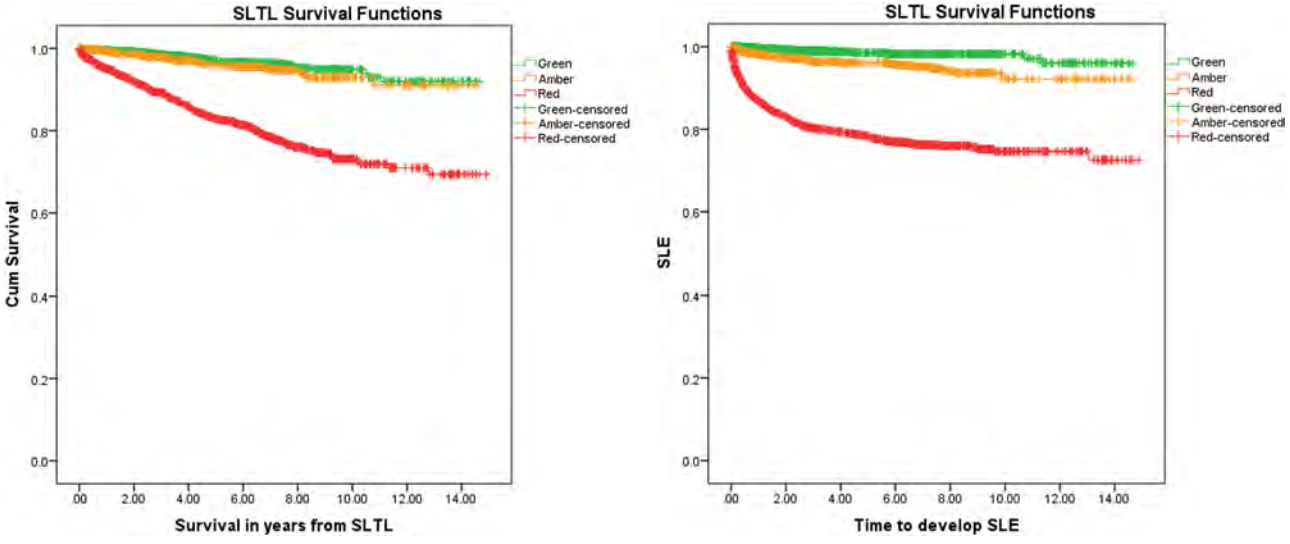

Figure: (abstract: THU-426)

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Background and aims: Approximately 80% of PWID who seek opioid substitution treatment (OST) in Athens are anti-HCV (+). It is estimated that annual treatment rates with DAAs of 4%-8% would reduce HCV prevalence in this population by 46%-90% in 2030. However, diagnosis and treatment rates remain low. We aim to describe a program designed to increase diagnosis and linkage to HCV care among active PWID in Athens.
Method: ARISTOTLE HCV-HIV is a "seek-test-treat" community-based program where PWID are recruited using chain-referral sampling with monetary incentives. Participation includes interviewing, fibroscan evaluation, blood testing (anti-HCV/HBsAg/anti-HIV, genotype in case of HCV/HIV coinfection or fibroscan ≥ 7.0 kPa, i.e. fibrosis ≥ F2, biochemical evaluation), counseling and linkage to care. PWID eligible for DAAs with available social security number are entered to the national HCV treatment registry to obtain treatment approval. A network of collaborating clinicians was set up and a peer-navigator accompanies patients to their first appointment with them. We present data until September 2018, i.e. before fibrosis-based treatment restrictions were removed in Greece.
Results: In a period of 5 months (April 2018-September 2018), 1, 088 PWID were recruited; 75.6% were active injectors (injecting in the past month) and 22.4% were on OST. Prevalence of anti-HCV and of HCV/HIV coinfection was 78.1% and 16.6%, respectively. At baseline, only 2.4% of anti-HCV (+) reported DAAs treatment. Out of 1088 PWID, 159 (14.6%) fulfilled treatment criteria due to HCV/HIV coinfection. In the remaining 665 PWID with HCV monoinfection, 37.9% had chronic hepatitis C/fibroscan ≥ 7.0 kPa whereas a substantial proportion (56.7%) had fibroscan < 7.0 kPa and, thus, were not eligible for treatment. Genotypes 1, 3 and 4 were identified in 34.0%, 53.6% and 11.4% of patients, respectively. Out of those with HCV monoinfection, 70.6% had available social security number and were entered to the treatment registry.
Conclusion: Community-based peer-driven chain referral allowed to reach rapidly a large number of active PWID not linked to OST. In the presence of treatment restrictions, approximately 4 out of 10 PWID with HCV monoinfection were eligible for DAAs; this would increase to 9 out of 10 if restrictions were removed. The majority of patients fulfilling treatment criteria were entered in the national treatment registry and efforts to issue social security numbers for the remaining is ongoing.

THU-428

Routine point of care antenatal screening of hepatitis B virus in windhoek, Namibia: Feasibility of implementation

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Background and aims: Elimination of mother-to-child transmission (MTCT) of hepatitis B virus (HBV) infection in sub-Saharan Africa is achievable. Identifying pregnant women at high risk of transmitting the infection to their infants is a key step in implementing prophylaxis. Currently, hepatitis B surface antigen (HBsAg) screening for pregnant women in Namibia is performed using a laboratory-based immunoassay. This study aimed to determine the feasibility and costs associated with implementing rapid test-based screening for HBV in pregnant women in Namibia.
Method: Consented pregnant women were counselled and screened for HBsAg by trained healthcare workers at participating antenatal clinics in Windhoek, using the Determine™ HBsAg rapid test. Venous blood was collected from all positive patients and a subset of negative patients for confirmatory laboratory-based HBsAg testing on the ARCHITECT i2000SR analyser to infer the diagnostic performance of the rapid test. Acceptance and usability of the rapid test from the perspective of the healthcare workers were assessed through a user-appraisal questionnaire. All resources including consumables, health-care workers' time, building space and facilities (and their quantity) were measured and valued to determine the costs of providing HBsAg screening at the clinics, in comparison to laboratory testing.
Results: A total of 515 pregnant women participated in the study; 28 (5.4%) tested HBsAg-positive. All 28 positive and 268 out of 487 negative results were laboratory-confirmed to be true, giving a sensitivity and specificity of 100%. All six healthcare workers involved in the study found the test simple to use. They showed preference for rapid testing over laboratory testing for routine antenatal screening of HBV; believing that this method would improve the care of pregnant women. The full cost of rapid testing was approximately US$6 in comparison to US$18 for the HBsAg test at the laboratory.
Conclusion: Screening using rapid testing is a cost-effective and feasible alternative for detecting HBV infection in pregnant women. The rapid test used in this study showed acceptable performance, and its roll-out was supported by the healthcare workers participating in the study. Implementation of this intervention, as part of the strategy for eliminating MTCT of HBV infection, is therefore feasible in a low resource setting like Namibia.

THU-429

Serial testing with the enhanced liver fibrosis test and liver stiffness is cost-effective for detection of advanced alcoholic liver disease in primary care

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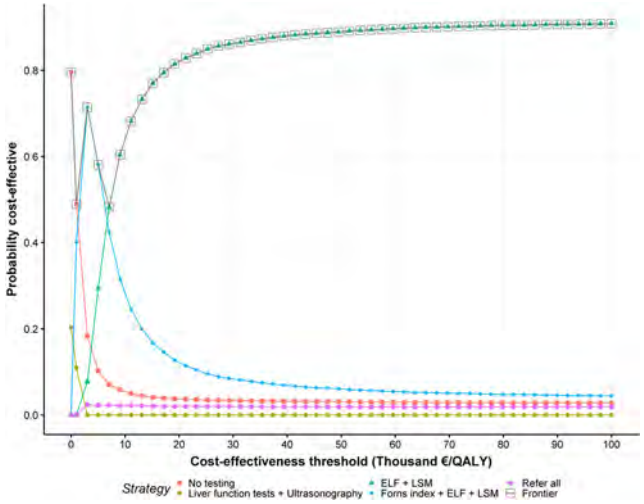
Background and aims: Alcoholic liver fibrosis is a preventable disease that is largely asymptomatic until decompensated cirrhosis occurs. Primary care based screening of individuals with excessive alcohol consumption could reveal those with progression to advanced fibrosis earlier. We therefore aimed to evaluate the cost-effectiveness of screening for advanced fibrosis in primary care patients with an excessive alcohol consumption, using the Danish health care sector as examplar.
Method: The target population was 45-year olds with a history of excess drinking for at least one year. We evaluated screening with three strategies: 1) standard-of-care using routine liver function tests applied in parallel with follow-up ultrasonography for test-positives, 2) the enhanced liver fibrosis (ELF test) serum marker, with follow-up liver stiffness measurement (LSM) for positives above 10.5, and 3) three-tier strategy using the indirect marker Forns Index to control before strategy two. We compared the screening strategies to no testing and direct referral of all to outpatient FibroScan. We used a decision model of linked decision trees and Markov state-transition models informed by extracted data from published literature. The primary outcomes were lifetime quality-adjusted life-years (QALYs) and direct health care costs.
Results: The optimal screening strategy was ELF test and LSM follow-up, which correctly identified the true disease status of 97.9%. At an incremental cost-effectiveness ratio of €5, 707 per QALY gained, the strategy had an 80% chance of being cost-effective. This result was

robust to probabilistic sensitivity analysis. The Forns-index followed by ELF and LSM had the best positive predictive value and the lowest incremental cost-effectiveness ratio (€1, 005 per QALY gained), but a lower negative predictive value and resulted in worse patient outcomes over the lifetime according to our model. The strategy of referring all to LSM had the best negative predicted value, but lower effectiveness and higher costs. Standard-of-care had lower effectiveness and higher incremental cost-effectiveness ratio.



Conclusion: Primary care based screening for advanced alcoholic fibrosis is likely a cost-effective intervention. The optimal strategy was serial testing with the ELF test, followed by liver stiffness measurement if positives, while the cheapest strategy included adding Forns test first in the sequence.

THU-430

Changing prevalence of aetiological factors among Australians hospitalized for cirrhosis

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Background and aims: Cirrhosis is a major global public health problem, due largely to obesity-related non-alcoholic fatty liver disease (NAFLD), hazardous alcohol consumption and chronic viral hepatitis B (HBV) and C (HCV). In the past two decades, important preventive and treatment strategies have been put in place in many countries to halt transmission HBV and HCV. However, decreases in the number of new cases of cirrhosis due to these causes may be offset by increasing levels of obesity and its metabolic complications, and sustained alcohol consumption in many countries. In a population-based study of patients with cirrhosis, we examined changes in aetiology of liver disease leading to hospital admission over the 9-year period.
Method: Hospital data on all patient admissions during 2008-2016 in the state of Queensland were obtained. We identified 30, 327 hospital admissions for cirrhosis in 10, 254 adult patients.
Results: The commonest aetiology was alcohol-related cirrhosis (49.5%), followed by cryptogenic cirrhosis (28.5%), HCV (14.6%), NAFLD/NASH (4.8%) and HBV (3.3%). Males were most commonly admitted than females apart from in NAFLD/NASH cirrhosis (55.9%). Whilst the prevalence of alcohol-related cirrhosis remained stable over the 9-year period ($p = 0.410$), there were increases in the prevalence of HCV, HBV, NAFLD/NASH and cryptogenic for men and women (see Figure for men), and the proportion of patients allocated two or more aetiological factors increased from 17.1% in 2008-2010 to 30.0% in 2014-2016 ($p < 0.001$). The average prevalence of chronic HCV nearly doubled between 2008 and 2010 (11.2%) and 2014-2016 (21.4%; $p < 0.001$), that of cryptogenic was 26% higher in 2014-2016 (25.8% vs. 32.6%, $p < 0.001$) and the prevalence of chronic HBV and NAFLD/NASH were about 60% higher (2.6% vs. 4.1% for HBV, $p = 0.003$ and 3.8% vs.6.0% for NAFLD/NASH, $p < 0.001$). The prevalence of patients not allocated to any aetiology decreased during this time-period (21.3% vs 16.3%, $p < 0.001$).

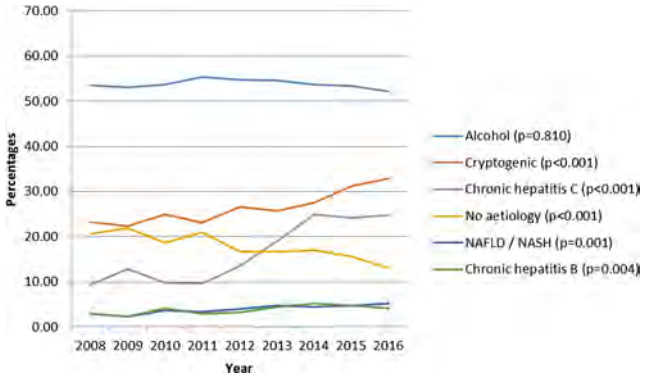

Figure: Trends in prevalence of selected aetiology among men

Conclusion: Our data highlights the increasing importance of HCV and cryptogenic/NASH/NAFLD, and to a lesser extent HBV, as contributing factor for cirrhosis. Strategies to prevent cirrhosis should be a major public health priority. The large number of cryptogenic cirrhosis suggests that more diagnostic support and specialist input may be important to help refine diagnosis for patients and to better understand the epidemiology of liver disease.

THU-431

The burgeoning growth in cirrhosis-related hospitalization in Australia, 2008-2016

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Background and aims: While chronic liver disease is a major global public health problem, it has not been recognized as a National Health Priority Area in Australia. A population-based study using hospital admission data for cirrhosis in the large state of Queensland, Australia during 2008-2016 was performed.
Method: Hospital data on all patient admissions (public and private) and deaths during 2008-2016 in the state of Queensland were obtained. Queensland is a large state in the north-east of Australia with a population of 4.9 million. We identified all hospital admissions for cirrhosis for patients aged 20 years or older. We reported age-standardized hospitalization rates/10, 000 person-years by gender and per calendar year, in-hospital case fatality rate among these admissions (n = 30, 327) and examined the factors associated with hospital deaths.

Results: Age-adjusted hospitalization rates increased by 32% between 2008 and 2016, from 8.50/10, 000 (95%CI 8.18-8.82) to 11.21/10, 000 (95%CI 10.87-11.54). Admission rates peaked in men at 34.03/10, 000 in 55-59 year-olds. The age-standardized admission rate for Indigenous Australians was 32.79/10, 000 (95%CI 31.28-34.31). Alcohol misuse was a contributing factor in over half (55.1%) of all admissions, and in 26.8% of admissions patients resided in most socio-economically disadvantaged areas. The overall in-hospital case fatality rate was 9.7% for males and 9.3% for females, and decreased significantly in males from 10.25% in 2008 to 8.32% in 2016 ($p < 0.001$). Admissions associated with hepatorenal syndrome (AOR = 7.24, 95%CI 5.99-8.75), HCC (AOR = 2.53, 95%CI 2.20-2.91), hepatic encephalopathy (AOR = 1.94, 95%CI 1.61-2.34), acute peritonitis (AOR = 1.93, 95%CI 1.61-2.33), jaundice (AOR = 1.82, 95%CI 1.20-2.75) and age ≥ 70 years (AOR = 1.63, 95%CI 1.38-1.92) were significantly associated with in-hospital mortality. A higher Charlson comorbidity index ($p = 0.021$), longer length of hospitalization ($p < 0.001$) and residence outside of a "major city" ($p < 0.001$) were also significantly associated with in-hospital mortality.

Conclusion: Our data highlights the increasing healthcare use by Australians with cirrhosis and this has major resource and economic implications. Greater awareness and emphasis on preventive care is needed to reduce the increasing prevalence of cirrhosis and the personal, social and economic burden of its complications.

THU-432

Viral sustained response in chronic hepatitis C did not reduce short term heatlh expediture

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Background and aims: Viral sustained response in chronic hepatitis C virus seems to reduce the health expenditure by diminishing the hepatic and extrahepatic complications. The aim of our study was to analyse health-expenditure of these patients before and after antiviral treatment.

Method: The health expenditure of patients treated from 2015 to 2017 in Catalonia (an area of Spain) with direct-acting antiviral agents was analysed comparing the period pre-treatment (until the end of treatment) and post-treatment period. Data source: Registry of Patients and Treatments (RPT) and Registry of Morbidity and Use of Health Services of Catalonia (MUSSCAT).

Results: 12, 683 patients were treated in Catalonia for chronic hepatitis C by direct antiviral agents (2, 740 in 2015, 5, 782 in 2, 016, 4, 161 in 2017). Of these, 11.9% did not have fibrosis (F0-F1), 25.2% moderate fibrosis (F2), 59.6% significant fibrosis or cirrhosis (F3-F4) and 3.3% fibrosis not determined (ND). The median time of follow-up after treatment was 16.5 ± 8.5 months. Service's use (rates per 100 patients/year) before and after treatment was as follows: hospital admissions: 30.2 vs 36.4; Hospital admissions due to complications of cirrhosis: 2.9 vs 2.7; hospital days: 172.8 vs 183.3; visits to Primary Care: 1, 112.0 vs 1, 220.3, visits as outpatient's hospital: 743.6 vs 694.1; medications dispensed: 436.6 vs 580.1. When stratified by fibrosis-degree, a significant decrease of 12.2% in the number of admissions due to complications of cirrhosis is observed. A decrease in outpatient visits is also observed in F2 (11.9%), F3-F4 (8.9%) and ND (19.5%); and days of hospitalization in the F0-F1 (10.1%) and in the F2 (27.1%).

Conclusion: Antiviral treatment of chronic hepatitis C virus does not reduce the use of short-term health resources, except for the number of admissions due to complications of cirrhosis, number of out-patient's visits for patients with advanced liver fibrosis, and hospitalization's days for patients with a milder degree of fibrosis

THU-433

Availability of information in drug labels for appropriate prescribing in patients with hepatic impairment

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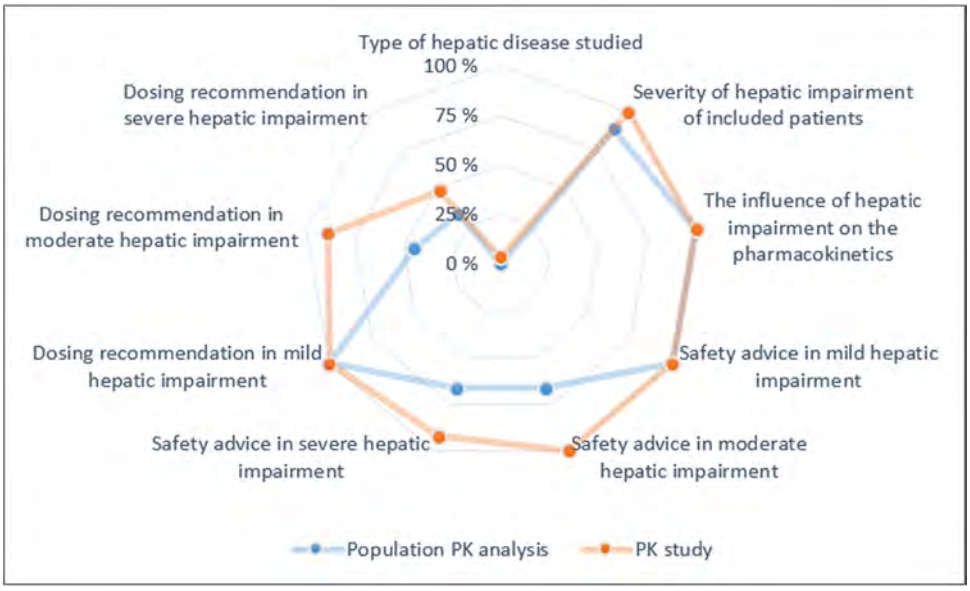

Figure: (abstract: THU-433): Available information in drug labels on use in hepatically impaired patients, based on PK study (n = 27) or population PK analysis (n = 9), expressed in percentage of available information.

Background and aims: Before new drugs are authorized, the influence of hepatic impairment on the pharmacokinetics (PK) needs to be determined. In Europe, these PK studies are performed and described in the label, i.e. the Summary of Product Characteristics (SmPC) according to the European Medicines Agency (EMA) guideline from 2005. We aim to evaluate the availability of information on hepatic impairment in drug labeling and the relevance of this information for clinical practice.
Method: We reviewed the information on patients with hepatic impairment included in SmPCs of new medicines authorized by the EMA between 2015 and 2017. We evaluated the completeness and clarity based on nine required information items described in the EMA guideline. This evaluation resulted in an availability and an applicability score.
Results: The SmPCs of 51 medicines were analysed. A PK study in patients with hepatic impairment was conducted in 27 (53%), the impact of hepatic impairment was evaluated using population PK analysis in nine (18%) and for 15 (29%) medicines no study was conducted. The SmPCs contained 81% (range 67-100%) of required information for medicines with a dedicated PK study, and 67% (range 44-89%) for those using population PK analyses (Figure 1). For these 36 medicines with PK data, 59% of the information was conclusive, 16% ambiguous and 25% was not available. Low scoring items were: "definition of hepatic impairment" (no conclusive SmPC) and "safety advice in severe hepatic impairment" (14 conclusive SmPC). This safety advice was often ambiguously described as "use with caution" or "not recommended to use."
Conclusion: While the labels score well in terms of completeness of information, the definition and description of the patients with hepatic impairment is often unclear and inconsistent. This can negatively influence the practical use by healthcare professionals.

THU-434

Poorly chosen upper limits of normal for alanine aminotransferase may burden the patient and health system unnecessarily

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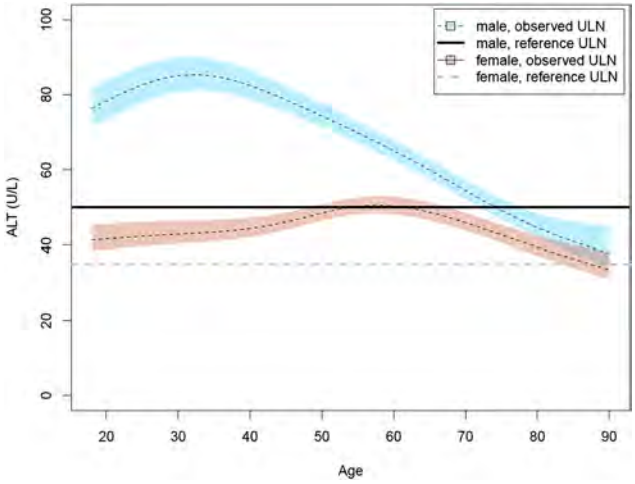
Background and aims: Upper levels of normal (ULN) for alanine aminotransferase (ALT) generally take sex into account, but not age. This simplification may lead to misclassification in a relevant proportion of the population and may burden the patient and health system unnecessarily.
Method: Consecutive blood samples from 2015-2017 were analysed from a large laboratory (LADR Geesthacht) servicing medical practices. All blood samples were considered in which ALT, AST, or GGT were measured. The definition "upper limit of normal" of a laboratory value often corresponds to the 95th percentile of a healthy population. In our analysis, the ULN for ALT is 35 U/L for women and 50 U/L for men. Sensitivity analyses included healthy subsets (excluding patients with hepatitis B (HBsAg or anti-HBc positive) or at risk for non-alcoholic fatty liver disease (NAFLD) presenting with either elevated GGT, triglycerides, cholesterol, HbA1c, or glucose (according to Prati, Ann Intern Med 2002) and one random sample per patient). A subset of healthy subjects was considered that was being checked up because of occupational regulations and not for health reasons. Age was categorized in decades (18-24, 25-34, 35-44, etc.).
Results: A total of 1, 369, 162 blood samples were available from 601, 780 adult patients (51% female, mean age 58). ALT was measured in 1, 000, 486 of these blood samples. There is an extreme age dependence in ALT values for men: Elevated values were seen in 20.0% (95% CI 19.5% to 20.4%) of patients between the ages of 25 and 34, but only 6.7% (95% CI 6.4% to 7.0%) between the ages of 65 and 74. The 95th percentile reaches values above 80 U/L instead of 50 U/L at the age of 35 and falls to below 50 U/L by the age of 75 (Figure 1). Results do not change if one sample per patient is considered. The sub-population of healthy individuals showed similar qualitative results. Here, elevated ALT values were seen in 11.5% (95% CI 11.1% to 12.0%) of patients between the ages of 25 and 34 and 2.7% (95% CI 2.4% to 3.0%) between the ages of 65 and 74. These results were very similar in the healthy "occupational" subset.
There is only a weak age dependence in women in contrast to men (Figure 1).



Conclusion: Currently used reference values for ALT imply that subsequent diagnostics are needed for a large proportion of young men. Our data beg the question whether age-adapted reference values for ALT are needed.

THU-435

A threshold analysis for the cost-effectiveness of hepatitis B and hepatitis C testing in emergency departments in the UK

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Background and aims: The prevalence of blood borne viruses (BBVs) is higher in emergency department (ED) attendees compared to the general population, due to higher attendance of marginalised populations. Studies have suggested prevalence up to 2% and 2.9% for hepatitis B (HBV) and hepatitis C (HCV) in EDs in England, although this varies considerably across regions. HIV testing in EDs in the UK is recommended in high prevalence areas (prevalence of 0.2% or higher), but there is no defined threshold for hepatitis testing. Hepatitis testing for those already receiving blood tests in EDs could provide an efficient setting to diagnose and treat those living with hepatitis.
Method: A Markov model was developed to analyse the impact of opt-out hepatitis C (HCV) and hepatitis B (HBV) testing in EDs in the UK. The model used data from studies of ED testing in the UK to

parameterise test costs and intervention effects (contact rates and linkage to care). For HCV we used an antibody test cost of £3.64 and RNA test cost of £68.38, and assumed a direct acting antiviral treatment cost of £10, 000. For HBV, we used a HBsAg test cost of £3.51 and annual treatment costs of £3, 672 for pegylated interferon-alpha and £578 for tenofovir disoproxil fumarate. We considered what prevalence of HCV (RNA-positive) and HBV (HBsAg) would be required to make ED testing cost-effective at a threshold of £20, 000 willingness to pay (WTP) per quality adjusted life year (QALY) gained. The model used a lifetime time horizon.

Results: The prevalence required for ED testing to be cost-effective was 0.3% HCV RNA prevalence, and 0.2% HBsAg prevalence, under our base case parameters (Figure). The prevalence thresholds were sensitive to the cost of the diagnostic tests and the linkage to care achieved (proportion of patients contacted with diagnosis, attend referral and receive treatment).

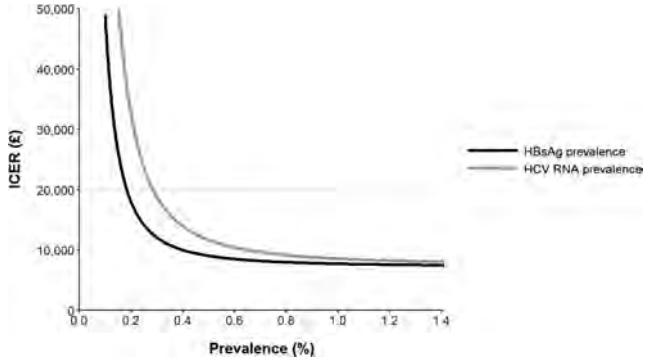

Figure: Incremental cost-effectiveness ratio (ICER) by HCV Ag and HBsAg prevalence

Conclusion: Early evidence suggests that ED testing and ED based linkage to care for HCV and HBV is likely to be cost-effective in many geographical areas across the UK, based on current studies of prevalence amongst ED attendees. Additional studies are required to evaluate ED testing across regions, using epidemiological, linkage to care and cost data specific to each region. This can help provide robust estimates to inform public health guidelines in the UK.

THU-436

The cost-effectiveness of one-time birth cohort screening for hepatitis C as part of the National Health Service health check programme for 40 to 74 year olds in England

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Background and aims: Hepatitis C (HCV) birth cohort screening has been implemented in the US, but there is little evidence of its cost-effectiveness in England. The national health service (NHS) offers a health check for 40 to 74 years olds in primary care in England every five years, to assess and reduce a person's risk of heart disease, diabetes, kidney disease and stroke. This health check could provide a platform for HCV testing.

Method: A Markov model was developed to estimate the cost-effectiveness of adding HCV testing to the NHS health check, for individuals in birth cohorts between 1950 and 1979. The model also aimed to identify areas of uncertainty in the model and the key drivers of cost-effectiveness. Prevalence estimates were derived from a population based model of HCV burden in England (0.1% to 0.27% amongst attendees). We assumed the intervention costs were a HCV antibody test and nurse time. Due to uncertainty, two data sources were used for disease transition probabilities; published estimates used in other economic evaluations, and transition probabilities estimated from the population based model. We assumed direct acting antiviral (DAA) treatment costs of £10, 000. Results are presented as incremental cost-effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained, with a £20, 000 per QALY willingness to pay threshold. We estimated the value of information (VoI), representing the maximum value for future research to reduce all uncertainty in the model.

Results: Base case ICERs ranged from £7, 394 to £24, 388 and £17, 517 to £45, 803 across birth cohorts for the two sources of HCV transition probabilities, respectively (Figure). The intervention is most likely to be cost-effective for those born in the 1970's, with lowest ICERs in this birth cohort. The model was most sensitive to the HCV transition probabilities, the probability of referral and receiving treatment, and the prevalence of HCV. The maximum VoI across all birth cohorts was £10.5 million, with the highest value for future research in the probability of referral and receiving treatment, HCV transition probabilities, and the utility associated with achieving a sustained virological response.

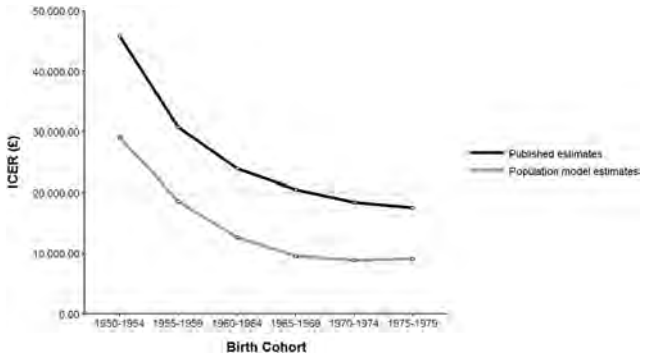

Figure: Cost-effectiveness of birth cohort screening across birth cohorts, by source of transition probability

Conclusion: There is considerable uncertainty in the cost-effectiveness of birth cohort screening for HCV as part of the NHS health check in England. We show further studies are warranted to reduce uncertainty in cost-effectiveness estimates, particularly for younger birth cohorts (1970s) in which the intervention is most likely to be cost-effective.

THU-437

The Global Epidemiology on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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Background and aims: Although NAFLD and NASH are closely associated with T2DM, the global prevalence of T2DM and NAFLD is

not well described. Aim: To assess the global prevalence of NAFLD in patients with T2DM.
Method: PubMed, Ovid-Medline, EMBASE and Web of Science were searched from January 1989 to September 2018 for terms involving NAFLD, NASH and T2DM. Strict exclusion criteria was applied. Review articles, abstracts, population including pediatric, bariatric surgery, type 1 diabetics, and non-English articles were excluded. Pooled NAFLD prevalence was calculated using random-effects models. Prevalence rates for NAFLD were stratified according to geographic region. Potential sources of heterogeneity were investigated using sub-group analyses and meta-regression.
Results: Of the 1685 studies, 99 met criteria (N = 222, 816 subjects with T2DM) from 25 countries. Pooled overall global NAFLD prevalence among diabetics was 61.1% (95% CI: 57.2 to 64.8, I2 = 99.5%). The predicted rate of T2DM+NAFLD was 5, 185 per 100, 000 global population. Meta-regression models showed that region, age and diagnostic method ($p < .05$) were associated with NAFLD prevalence and jointly accounted for 75.9% of heterogeneity. Among T2DM, South America (73.8% [52.4-87.8]) had the highest prevalence of NAFLD, followed by Europe (70.0% [65.7-73.9]), Oceania (70.3% [59.0-80.0]), South Asia (61.1% [53.0-68.6]), West Asia (59.1% [33.8-80.4]), East Asia (55.3% [51.2-59.3]), United States (53.1% [26.1-78.4]), and Africa (32.0% [10.6-65.0]). Over a follow-up of 5-10.9 years, pooled all-cause, CVD, and liver-related mortalities among T2DM+NAFLD patients were 11.9% (95% CI: 2.7 to 40.2, I2 = 95.2%), 2.1% (95% CI: 0.4 to 9.7, I2 = 73.8%), and 1.6% (95% CI: 0.2 to 13.8, I2 = 78.0%). A total of 808 biopsies (9 studies) documented a pooled overall NASH prevalence of 64.0% (95% CI: 53.4-73.4, I2 = 86.3%) in NAFLD patients with T2DM. This NASH prevalence rates were 56.8% (95% CI: 40.7-71.6) for United States, 61.1% (95% CI: 36.3-81.2) for South America, 56.4% (95% CI: 46.2-66.0) for East Asia, 66.9% (95% CI: 49.1-80.9) for South Asia, and 93.8% (95% CI: 66.5-99.1) for Oceania. Also, in this group, advanced fibrosis (stages F3-F4) was reported in 10 articles comprising 1, 250 subjects with the pooled overall prevalence of 10.4% (95% CI: 5.2-19.9, I2 = 92.6).
Conclusion: This study provides global prevalence rates for NAFLD, NASH and fibrosis in T2DM that can inform models to estimate its clinical and economic burden.

THU-438

The presence of type 2 diabetes is independently associated with impairment of patient-reported outcomes in patients with non-alcoholic steatohepatitis

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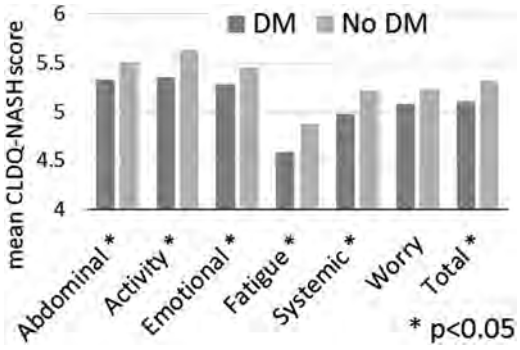
Background and aims: Non-alcoholic steatohepatitis (NASH) is highly prevalent in patients with type 2 diabetes (T2DM). Patients with NASH and T2DM experience higher rates of adverse clinical outcomes. Aim: To assess the impact of T2DM on Patient-Reported Outcomes (PROs) of patients with NASH.
Method: Patients with NASH and bridging fibrosis or compensated cirrhosis were enrolled in the phase 3 STELLAR trials of selonsertib. PROs were assessed using Short Form-36 (SF-36), Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH), EQ-5D, and Work Productivity and Activity Index (WPAI) prior to treatment initiation and compared between NASH patients with and without T2DM using Mann-Whitney test.
Results: There were 1667 NASH patients with PRO data (age: 58 ± 9 years, 40% male, 73% white, 52% cirrhotics, and 74% with T2DM). Patients NASH and T2DM were older (mean 58.4 vs. 56.3 years), had greater BMI (mean 33.7 vs. 32.7), had more cirrhosis (54.5% vs. 45.5%), higher haptoglobin, C-reactive protein, GGT, and greater liver stiffness by Fibroscan, but lower MELD score (mean 7.0 vs. 7.3) as well as lower AST, bilirubin, hemoglobin, and apolipoprotein B (all $p < 0.05$). Out of 23 calculated PRO scores from the 4 instruments, 12 scores were lower in NASH with T2DM: Physical Functioning, Bodily Pain, General Health, Vitality, and Physical Summary of SF-36, 5 out of 6 domains of CLDQ-NASH (Figure), and EQ-5D utility score (all $p < 0.03$). The average magnitude of impairment was from −2.6% to −6.3% of a PRO range size. In multiple regression analysis with adjustment for demographics, location of enrollment site, smoking, BMI, cirrhosis, and history of comorbidities, the presence of T2DM was independently associated with a significant impairment in 11 PRO scores (betas ranging from −1.9% to −6.1% of a PRO range size; $p < 0.05$).



Conclusion: In patients with NASH, T2DM is independently associated with PRO impairment. This suggests that NASH with T2DM is not only associated with substantial clinical burden, but also PRO and potentially economic burden.

THU-439

Variability in liver function test results and the risk of heart disease and mortality: A nationwide population-based study

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Background and aims: Variability in metabolic parameters such as fasting glucose levels, blood pressure, and body weight can affect health outcomes. In this study, we investigated the association between variability in liver function test results and the risk of mortality and cardiovascular outcomes in the general population.
Method: Using nationally representative data from the Korean National Health Insurance System, 8, 376, 860 people who were free of chronic liver disease, malignancy, congestive heart failure (CHF), myocardial infarction (MI), atrial fibrillation (AF), heavy drinking and who underwent ≥ 3 health examinations between 2009 and 2012 were followed to the end of 2017. Variability in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) was measured using the average real variability, standard deviation (SD), and variability independent of the mean (VIM). High variability was defined as the highest quartile of variability. Cox proportional hazards models adjusting for age, sex, body mass index (BMI), smoking, alcohol, regular **exercise, income, presence of comorbidities, and respective liver enzyme level were used.**

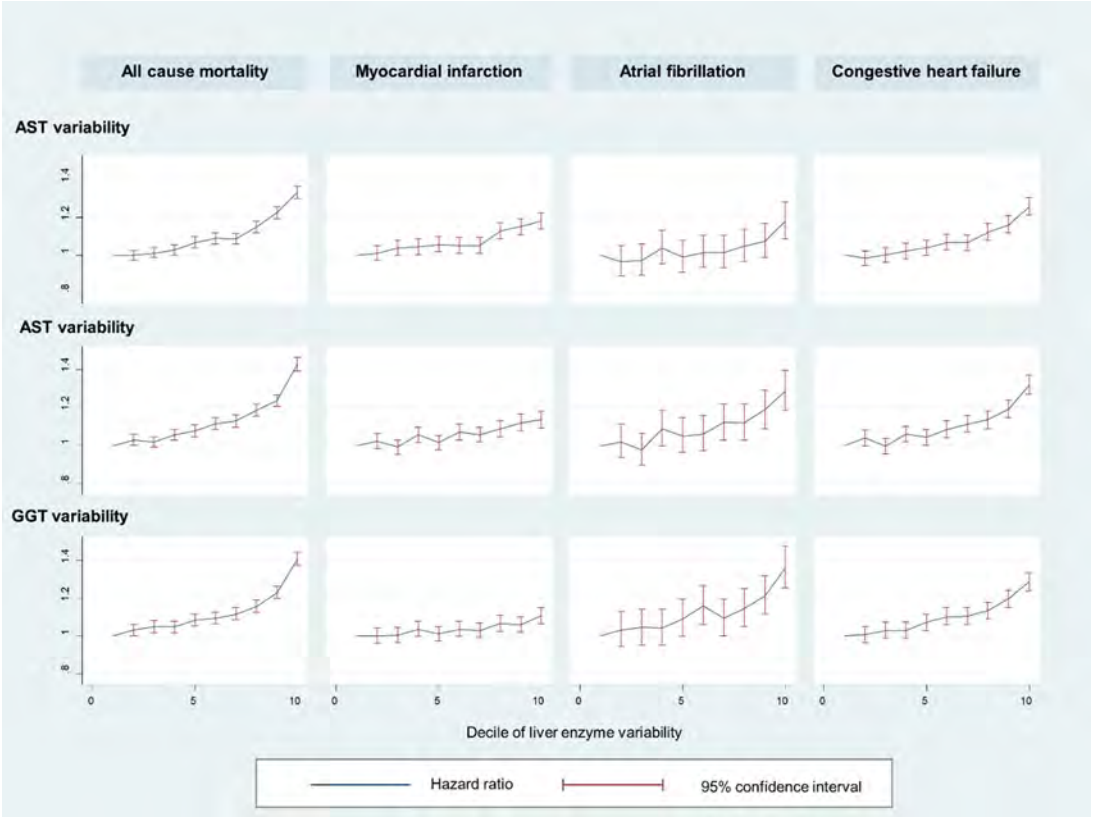

Figure 1: (abstract: THU-439): Risk of mortality and heart disease by deciles of liver enzymes variability

Results: There were 134, 345 deaths (1.5%), 64, 753 CHFs (0.7%), 67, 370 MIs (0.8%), and 81, 914 AFs (0.9%) during a median follow-up of 5.4 years. In the multivariable analysis, there was increasing trends of the association between liver enzyme variability and all study outcomes. The degrees of association were largest for GGT variability which were more marked in subjects with lower BMI and non-drinkers: all-cause mortality [HR (95% CI): Q2, 1.05 (1.03-1.07); Q3, 1.11 (1.09-1.13); Q4, 1.27 (1.25-1.29)]; CHF [Q2, 1.04 (1.02-1.07); Q3, 1.12 (1.09-1.15); Q4, 1.20 (1.18-1.23)]; MI [Q2, 1.03 (1.01-1.06); Q3, 1.07 (1.04-1.09); Q4, 1.10 (1.07-1.12)]; and AF [Q2, 1.07 (1.01-1.13); Q3, 1.16

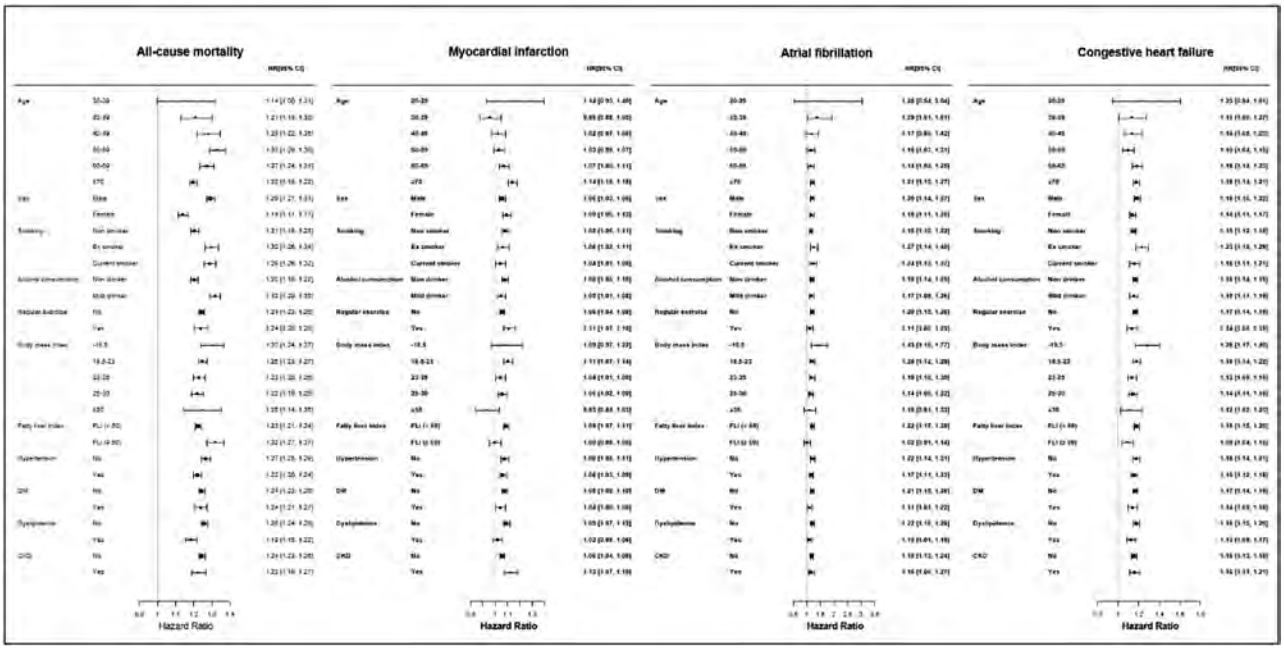

Figure 2: (abstract: THU-439): Risk of mortality and heart disease by level of liver enzymes variability with stratification by baseline characteristics

(1.11-1.23); Q4, 1.26 (1.20-1.32)]. Similar results were obtained when modeling the variability using the SD and VIM, and in various sensitivity analyses.
Conclusion: Higher visit-to-visit variability of liver enzyme was an independent predictor of all-cause mortality and cardiovascular events.

THU-440
Changing incidence of reported hepatitis B and its different trends amongest age groups in china from 2004-2016
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Background and aims: To provide a detailed national-level description of the reported incidence of hepatitis B in China during 2004–2016, and analysis the changing trend difference among age groups.
Method: Data were obtained from China's National Notifiable Disease Report System, reported trends were estimated by Joinpoint regression analysis.
Results: Overall, there were 13, 543, 137 new cases of hepatitis B reported in China from 2004 to 2016, among the new reported cases of viral hepatitis in total, the majority (80%) was ascribed to hepatitis B infections. The reported incidence of hepatitis B rose from 2004 (67.96/100, 000) to 2009 (88.82/100, 000), and then decreased in 2016 (68.74/100, 000). From 2004 to 2007, APC of hepatitis B reported incidence was 10.3% (95% CI 4.1 to 16.9, $P < 0.05$), indicating an increased trend, while, from 2007 to 2016, APC was –3.5% (95% CI –4.5 to –2.5, $P < 0.05$), indicating a significant decrease, overall, the AAPC of hepatitis B was –0.2% (95% CI –1.6 to 1.2, P = 0.8), indicating a stable trend. Age distribution in the first decade of this period was analyzed, average reported incidence of HBV was highest in the 20~29 age group, the lowest reported incidence was in age group between 1 and 9 years old. The reported incidence changing trend of "Age < 1," "30-39," "40-49" age groups kept stable, the "1~9," "10-19," "20-29"age groups showed a significant descending trend, all of the age groups of people more than 50 years old showed increased trend from 2004 to 2013. Generally, most of the age groups showed significant decreased or stable trend after 2007 or 2008, however, for the "50-59" age group, the changing trend kept increasing in all stages.
Conclusion: This study indicates that hepatitis B infections continue to constitute the majority of viral hepatitis cases in China, the changing trend of hepatitis B was kept stable nin recent years. For the young (Age < 19 years old), HBV reported incidence showed a significant descending trend, which consistent with the application of HBV vaccine. For the elders (Age >50 years old), the incidence changing trend showed increasing, which indicated that for the elders, the risk for infecting with hepatitis B is still high, after successfully vaccination for children, to decrease the prevalence of hepatitis B, vaccination among adults should also be conducted.
(APC: Annual percentage change; AAPC: average annual percentage change)

Liver tumours: Experimental and pathophysiology

THU-441
Site-specific structural N-glycan alterations limit CD73 nucleotidase activity in human hepatocellular carcinoma
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Background and aims: Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, is a leading cause of

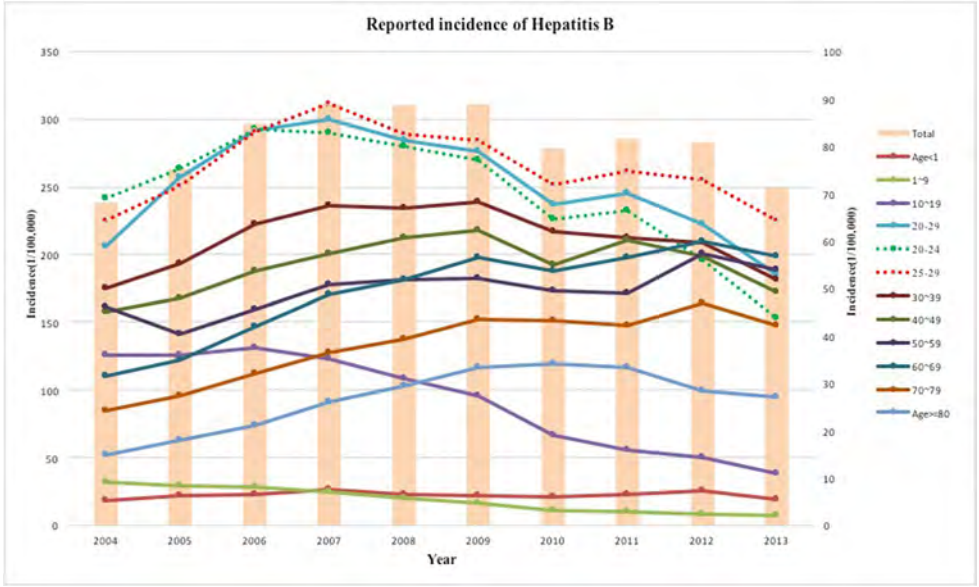
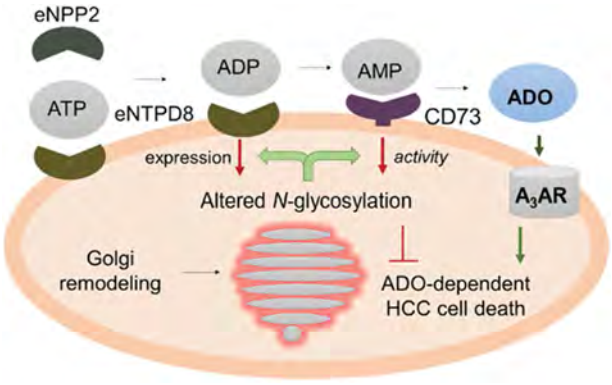


Figure: (abstract: THU-440): Age distribution of reported incidence of hepatitis B from 2003-2013

cancer-related deaths globally. Adenosine-3 receptor (A3R) activation blocks HCC progression in rodents, and small molecule A3R agonists are undergoing clinical development for HCC patients. Here, we examined the regulation of *ecto*-5´-nucleotidase (CD73), a novel target of cancer immunotherapy that produces extracellular adenosine, in human HCC.

Methods: We analyzed CD73 expression and correlation with tumor characteristics and patient outcomes using The Cancer Genome Atlas (TCGA). In addition, we extracted CD73 from paired surgical specimens of HCC tumor and non-tumor adjacent liver tissues and normal control liver tissues collected under approved protocols, and performed glycopeptide mass spectrometry analysis. RNAseq analysis was performed to compare the expression of glycoprotein-encoding genes in addition to molecular, biochemical, and cell biological assays using multiple human HCC cell lines.

Results: High expression of the CD73-encoding gene (*NT5E*) correlated with poor survival in HCC patients ($N = 365$; $p = 0.012$) but did not correlate with a specific HCC immune subtype, based on TCGA data. We show using analysis of surgical specimens from HCC and adjacent liver tissues similar CD73 protein levels between normal and tumor hepatocytes. However, tumor-associated CD73 was primarily intracellular and exhibited altered *N*-linked glycosylation, independently of HCC etiology or fibrosis presence. The altered CD73 glycosylation correlated with a 2.7-fold decrease in tumor associated 5´-nucleotidase activity ($p < 0.0001$), which was otherwise necessary to induce cell death in HCC cultured cells. Mass spectrometry profiling of CD73 from tumors demonstrated a significant increase in high-mannose CD73 glycans on residues N311/N333. Blocking CD73 N311/N333 glycosylation caused intracellular CD73 accumulation and decreased 5´-nucleotidase activity *in vitro*, similar to the phenotypes observed in the primary human HCC tumors. Aberrant Golgi function was implicated as a potential mechanism, based on altered tumor expression and organization of the structural protein GM130 and genes encoding other *N*-linked glycoproteins, as determined by RNAseq analysis.



Conclusion: Our results reveal a novel glycosylation mechanism for regulating endogenous purinergic signaling in HCC tumors.

THU-442

Role of drug transporters in the chemoresistance of hepatoblastoma

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Background and aims: Hepatoblastoma (HB) is the predominant form of liver cancer in childhood. Although 80% of HB patients respond to standard neoadjuvant preoperative chemotherapy based on doxorubicin and cisplatin, in the remaining 20% the response is very poor and the prognosis is bad. The lack of response can be due to the presence of mechanisms of chemoresistance (MOCs), including the reduction of intracellular content of drugs as a result of changes in uptake/efflux proteins involved in the transport of drugs. We have investigated the role in HB chemoresistance of the so-called "transportome," i.e., the set of plasma membrane transporters expressed at a given time by tumour cells.

Method: Genes involved in drug transport were analyzed by RNA-sequencing in 18 HB specimens and their matched non-tumour (NT) tissues and results were confirmed by RT-QPCR. Selected genes were studied by RT-QPCR, western blot and immunofluorescence in HB-derived HepG2 and HuH6 cell lines in basal conditions and after 72 h of exposure to cisplatin and doxorubicin. Drug sensitivity of HB cell lines was determined by Sulforhodamine B test. Transport activity of ABC efflux pumps was analyzed by flow cytometry using specific substrates and inhibitors.

Results: Significant changes in the expression of drug transporters in HB as compared with surrounding NT tissue were found. SLCO1B1/3 (OATP1B1/3) and SLC22A1 (OCT1) genes were markedly down-regulated in tumours, and lower levels correlated with worse prognosis. Regarding ABC pumps, several ABCC transporters were highly expressed in HB. Interestingly, ABCC4 (MRP4) was up-regulated in tumours of patients with more aggressive phenotype (C2 vs C1). The expression levels of uptake (SLCO1B1, SLCO1B3, SLC22A1, SLC22A3, SLC31A1) and efflux (ABCB1, ABCC1–5, ABCG2) transporters found in cell lines suggested that both HuH6 and HepG2 cells presented a multidrug resistant phenotype, since they had very low expression levels of uptake transporters together with high or very high expression levels of export pumps. Moreover, the exposure of cells to 0.1 µM doxorubicin or 5 µM cisplatin for 72 h increased the resistant-phenotype of HB-derived cells, mainly by up-regulation of ABCG2 in HuH6 and ABCC3 in HepG2 cells.

Conclusion: Drug transportome can play an important role in HB chemoresistance and several transport proteins have been selected as potential candidates for HB prognosis and to develop novel therapies to overcome chemoresistance.

THU-443

Unexpected pro-tumorigenic effect of the chemokine Cxcl10 by modulation of tumor stroma in a murine model of HCC

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Background and aims: HCC progression is linked to the dynamic crosstalk between tumor cells and the surrounding tumor stroma. Tumor stroma is a complex, modifiable composition of fibroblast, extracellular matrix, immune cells and vasculature. The pro-inflammatory chemokine Cxcl10 is implicated in the crosstalk between parenchymal as well as non-parenchymal cells e.g. infiltrating immune cells and plays a key role during acute and chronic liver injury. Here we aimed to investigate the role of Cxcl10 in HCC progression.

Method: Hepatocellular carcinoma (HCC) was induced in *Cxcl10*$^{-/-}$ and wild-type (WT) mice via a single i.p. injection of N-Diethylnitrosamin (DEN, day 14) and weekly i.p. injections of low dose carbon tetrachloride (CCl_4, week 4–26). Liver tissue was characterized by histologically staining for proliferation (Ki67),

apoptosis (cleaved caspase 3) and vascularization (VEGF-R2). The HCC-related immune response was analyzed by comprehensive multicolor flow cytometry and immunofluorescence (IF)/-histological (IHC) staining with specific focus on tumor associated T cells (e.g. CD3, CD4, CD8). *In vitro,* the HCC cell line Hepa1–6 was stimulated with Cxcl10 and proliferation was assessed by BrdU incorporation.

Results: Treatment of WT mice with DEN/CCl_4 showed an enhancement of Cxcl10 expression in tumor tissue as compared to control tissue (qRT-PCR, $P < 0.05$). The deletion of *Cxcl10* in a HCC model led to a decreased tumor burden (number + size, $P < 0.05$) compared to WT mice, which was linked to a slight reduction of proliferative tumor cells ($p < 0.07$). *In vitro,* the stimulation of a Hepa1–6 with Cxcl10 did not alter cell proliferation implicating no direct effects of Cxcl10 on tumor cell proliferation. As CXC chemokines are implicated in cancer hallmarks e.g. angiogenesis and immune cell recruitment, we hypothesized that Cxcl10 exert its pro-tumorigenic effects. Indeed, *Cxcl10*$^{-/-}$ tumors showed a lower amount of microvessel density ($p < 0.05$). By flow cytometry analysis and IHC staining, we revealed significant differences in stromal $CD3^+$ T cell accumulation ($p < 0.001$) with an enhancement of $CD4^+$ T helper cell ($p < 0.01$) as well as $CD8^+$ cytotoxic T cell ($p < 0.05$) subsets in DEN/CCl_4 treated *Cxcl10*$^{-/-}$ mice in comparison to treated WT mice. Of note, the boost of T cells and the improvement of HCC phenotype was not associated with a compensational enhancement of Cxcl9-the other ligand of the Cxcl10 receptor Cxcr3.

Conclusion: Interestingly, our results revealed an unexpected pro-tumorigenic function of Cxcl10 in a murine HCC model. Cxcl10 stimulates tumor neovascularization and suppresses the accumulation of T cells with potential anti-tumoral properties. Hence, these data implicate CXCL10-directed stroma modification as novel target for HCC treatment.

THU-444

Alteration of miRNAs expression in patients with HCV-related cirrhosis who developed HCC after therapy with DAAs

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Background and aims: Hepatitis C virus (HCV) is still one of the causes of hepatocellular carcinoma (HCC) related to liver disease. The treatment of HCV infection has radically changed by the new direct acting antiviral drugs (DAAs) that have shown to be effective and well tolerated. The impact of DAA on the risk of HCC development in cirrhotic patients is still controversial. Several studies have shown a correlation between serum and tissue levels of specific miRNAs and the development of HCC in patients with chronic hepatitis C; therefore they have been suggested as biohumoral markers for early and non-invasive diagnosis of HCC.

Our aim is to report miRNAs differentially regulated in HCV+ patients with or without de novo HCC after DAA treatment

Method: We enrolled a total of 80 patients with HCV+ cirrhosis treated with DAAs. Of these, 40 patients developed HCC (HCC group) in the six months after the end of therapy and 40 didńt (non-HCC group). Plasma and serum were recorded at the start (baseline) and the end of therapy. 8 patients of each group were selected for a screening phase, where 172 miRNAs were detected in the baseline samples in microarray plates. The miRNAs with significantly different expression between the 2 groups were selected and validated in the whole cohort, in samples at baseline and at the end of therapy by RT-q-PCR.

Results: In screening phase, 10 miRNAs with significantly different expression between HCC and non-HCC group at baseline were selected: miR-382-5p, miR-132-3p, miR-584-5p, miR-221-3p, miR-28-5p, miR-324-3p, miR-133b, miR-122-5p, miR-130b-3p, miR-27a-3p. Validation of results in the whole groups showed that: miR-382-5p, miR-132-3p, miR-584-5p and miR-221-3p were more expressed in HCC group compare to non-HCC group at baseline. Instead, in samples at the end of therapy, only miR-382-5p was more expressed in HCC group compare to non-HCC group.

Furthermore, within non-HCC group the expression of miR-324-3p, miR-133b and miR-122-5p was significantly decreased at the end of therapy compared to baseline. The same differences were obtained in HCC group in addition to a decreased expression of miR-132-3p and miR-221-3p in patients at baseline vs end of therapy (all $p < 0.05$).

Conclusion: These are preliminary results that should be refined according to the baseline characteristics of patients and the evolutionary confounding factors.

THU-445

Beta-catenin signaling controls NKG2D ligands expression in liver tumorigenesis

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Background and aims: Hepatocellular carcinoma (HCC) has emerged as the second leading cause of cancer-related death worldwide. Due to the advanced stages of HCC at the time of diagnosis, conventional treatments for solid tumors frequently end with treatment failure, recurrence, or poor survival. However, due to the impressive role of the immune microenvironment during tumorigenesis, approaches targeting immune effectors represents an exciting prospect for therapeutic.

In these lines, our goal is to understand immunosurveillance mechanisms taking place during HCC using both murine models and human samples.

These mechanisms are based on the expression of ligands for example after oncogenic stress on epithelial cells that are recognized by the receptor on immune cells. We focused to study NKG2D system described as very efficient anti-tumoral process in several tumors.

Method and Results: First, we monitored the expression of NKG2D ligands in a vast cohort of HCC patients ranged according to HCC classification groups. Genomic functional studies helped to define two major HCC tumor groups based on chromosomal stability: G1/G2/G3 groups associated with high chromosomal instability, inflammation and poor prognosis (*TP53* mutated); G4/G5/G6 groups associated with low chromosomal instability and good prognosis (G5/G6 *CTNNB1* mutated)

We showed that NKG2D ligands mRNA expression was higher in HCC tumors harboring chromosomal instability (G1/G2/G3) compared to G4/G5/G6 groups suggesting that NKG2D ligands expression associates with chromosomal instability.

Accordingly, we validated these results in our murine HCC models, one mimicking G1/G2/G3 groups of aggressive tumors (DEN induced HCC model) and the other harboring *ctnnb1* mutated HCC tumors mimicking G5/G6 groups.

Moreover, we observed a strong downregulation of NKG2D ligands both at the mRNA and the protein level in our *ctnnb1* mutated HCC. In addition, we observed the same behavior in other β-catenin activated context e.g. in the Apc KO mouse model that recapitulates a drastic activation of β-catenin signaling and β-catenin mutated αML cell line by CRISPR-Cas 9 technology. These results evidenced that β-catenin signaling controls negatively NKG2D ligands expression.
To get into the mechanism, we identified by ChIP-seq immunoprecipitation that β-catenin directly controls NKG2D ligands.
Conclusion: Collectively, these results identified β-catenin as a strong regulator of NKG2D ligands expression in the liver.
We are currently investigating whether the reintroduction of NKG2D ligands expression in *ctnnb1* dependent liver tumorigenesis will worsen the course of tumorigenesis in terms of inflammation, proliferation and grade of tumors.

THU-446

AMPK/PGC-1α-mediated metabolic reprogramming of hepatic stellate cells promote stemness of hepatocellular carcinoma via metabolite lactate shuttle

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Background and aims: Hepatic stellate cells (HSCs), as important interstitial cells in liver cancer microenvironment, play an important role in the malignant process of liver cancer. We previously found that the metabolic shifts of mitochondria drove the malignant transformation of tumors, suggesting that the mitochondrial metabolism mode might affect the cell fates in the tumor microenvironment. However, the role of HSCs in hepatocellular carcinoma (HCC) stem cell pool and its regulatory mechanism is not fully demonstrated.
Method: Glucose uptake ability, oxygen consumption rate, lactate accumulation and ATP production, as well as AMPK activity, PGC-1α expression of HSCs were measured in a co-culture system with HCC cells. The expression of MCT1, the abilities of side population, sphere formation and tumor incidence and metastasis were detected to explore the stemness of HCC cells after co-culture. The glycolytic phenotype and pro-fibrotic capacity of HSCs, as well as stemness of HCC cells, were determined using AMPK agonists metformin or inhibitors of lactate accumulation.
Results: We found that after co-culture with HCC cells, HSCs were activated with the metabolic phenotype switch from oxidative phosphorylation to glycolysis mediated by the AMPK/PGC-1α signaling inactivation, characterized by increased glucose uptake, oxygen consumption rate and lactate production. Interestingly, the metabolic intermediate lactate transferred to and took up by HCC cells via the lactate transporter MCT1, promoted the stemness of HCC cells. AMPK agonists metformin or inhibitors of lactate accumulation administrated in HSCs not only converted myofibroblasts to quiescent HSCs, but also reduced the side population, sphere formation and inhibited tumor incidence and metastasis of HCC in an *in vivo* tumor model. In agreement, pharmacologic inhibition of MCT1-mediated lactate upload dramatically affected tumor outgrowth of HCC.
Conclusion: In this study, we explored the mechanisms of AMPK/PGC-1α signaling pathway in HSCs mitochondrial metabolic shifts and demonstrated a reciprocal metabolic interplay between HSCs and cancer cells through metabolite lactate shuttle in HCC microenvironment, providing a novel cue of metabolism-based approaches to enhance the efficacy of cancer therapy.

THU-447

DNA damage response CHK2 activates senescence cellular program and supports oxidative metabolism to drive hepatocellular carcinoma development

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Background and aims: Hepatocellular carcinoma (HCC) arises in most cases in a context of chronic hepatic inflammation. The causes for the underlying liver disease are diverse and comprise chronic viral infection, alcohol toxicity or non-alcoholic steatohepatitis. In these conditions, senescence constitutes a cellular response triggered by insults associated with DNA damage, oxidative stress and telomere attrition. It has been described that DNA damage response triggers senescence as a response to suppress transformed cells, but this phenomenon remains obscure. Aim of the study was to elucidate the mechanisms linking DNA damage response proteins such as CHK2 to cellular program of senescence and its role in HCC development.
Method: Human hepatocytes immortalized with hTERT (HuS), and p53 mutated HCC cell line Huh7 were used in biochemical studies. A transgenic TG (ALB1HBV)44BRI/J and a metabolic (STAM) HCC mouse model were employed. Finally, microparticles were isolated from blood of cirrhotic patients and normal subjects to evaluate CHK2 mRNA expression levels.
Results: Liver of 15–18 month old TG mice and 16 week old STAM mice showed expression of proteins CHK2, γ-H2AX, both markers of DNA damage response and $p21^{CIP1}$a marker of senescence. These findings coincided with de novo expression of glycolytic enzymes hexokinase I and pyruvate kinase M2 (PKM2). In vitro, CHK2 and γ-H2AX negative Huh7 cells expressed low levels of hexokinase I, PKM2, and phosphoglycerate kinase 1 (PGK1). Conversely, CHK2 and γ-H2AX positive HuS cells overexpressed hexokinase I, PKM2, and PGK1 and the glycolytic enzymes paralleled the markers of senescence SA-β-gal and $p21^{CIP1}$. Furthermore, measurements of oxygen consumption and metabolomic analysis by NMR spectroscopy revealed that overexpression of CHK2 increased mitochondrial oxidation of tricarbossylic acid cycle intermediates and stimulated elevated mitochondrial reactive oxygen species (ROS) production. Knockdown of CHK2 expression blocked mitochondrial ROS production, re-established ATP synthesis and reduced the expression of DNA damage marker γ-H2AX. CHK2 mRNA significantly increased in a cohort of cirrhotic patients in comparison to normal subjects.
Conclusion: The metabolic alterations that occur upon activation of DNA damage response lead CHK2 to repurpose mitochondria from ATP synthesis into ROS production. Together, these findings identified a dysfunction of senescence as a factor fueling HCC development.

THU-448

Multicentric prospettive study of validation of angiogenesis-related gene polymorphisms in hepatocellular carcinoma patients treated with sorafenib: Interim analysis of INNOVATE study

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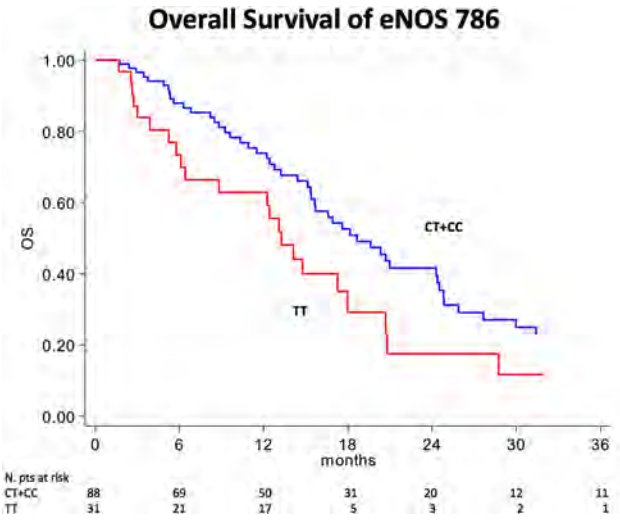
Background and aims: Although sorafenib is the upfront standard care of treatment for advanced hepatocellular carcinoma (HCC), molecular predictors of efficacy have not been identified yet. In the ePHAS study we analyzed three *eNOS* polymorphisms and at univariate analysis, patients with *eNOS*-786 (rs2070744) TT genotype had significantly shorter median Progression Free Survival (PFS) and Overall Survival (OS) compared to those with other genotypes. In the ALICE-1 and ALICE-2 studies, *VEGF-A*, *VEGF-C*, *VEGFR* and *HIF-1α* polymorphisms resulted independent prognostic factors for PFS and OS at multivariate analyses. On the basis of these preliminary results, our aim is to validate in a prospective study these data in patients with HCC treated with sorafenib (NCT02786342).
Method: This is a prospective Italian multicenter study, that includes 160 HCC patients receiving sorafenib. For this interim analysis we analyzed *eNOS-786* polymorphism on 119 patients. *eNOS*-786 T > C was analyzed by Real Time PCR in relation to the primary end point (OS). Event-time distributions were estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test.
Results: 119 HCC patients (102 males and 17 females), prospectively treated with sorafenib from May 2015 to September 2018 were included. Median age was 69 years (range 28–88 years). 95 patients had Child-Pugh A and 23 had Child-Pugh B7. 42 had BCLC-B and 77 patients had BCLC-C.



At univariate analysis, we confirmed that *eNOS*-786 TT genotype were significantly associated with a lower median OS than the other genotypes (13.3 vs 18.7 months respectively $p = 0.021$, HR 1.96, 95% CI 1.08–2.94 $p = 0.023$). Moreover, patients carrying a TT genotype for *eNOS*-786 showed a lover percentage of Disease Control Rate at the first CT re-evaluation than those carrying other genotypes (50.5% vs. 25%).
Conclusion: This preliminary date confirms the prognostic role of *eNOS*-786 in advanced HCC patients treated with sorafenib. Previous studies have suggested that DNA variant at the *eNOS* gene can quantitatively regulate eNOS expression. The point variation at nucleotide −786 bp was associated with a significant reduction in the *eNOS* gene promoter activity resulting in lower levels of eNOS mRNA, eNOS protein and enzyme activity.
In conclusion, our data show that *eNOS* polymorphisms may identify patients who are more likely to benefit from sorafenib treatment.

THU-449

Nuclear orphan receptor COUP-TF2 increases the resistence to anoikis and induces amoeboid movment and metastatic potential in hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is the second cause of cancer-related death worldwide. In the last few years, the role of nuclear receptors in hepatocarcinogenesis has received great attention. The orphan nuclear receptor COUP-TF2 regulates important biological processes such as glucose and lipid metabolic homeostasis. Recent studies indicate that COUP-TF2 is a pro-oncogenic factor but its role in HCC is still controversial. Aim of this study was to evaluate the role of COUP-TF2 in HCC.
Method: COUP-TFII expression on primary HCC samples was evaluated by immunohistochemistry. Overexpressing COUP-TFII HCC cells lines were created through stable transfection with pcR3.1/COUP-TF2 (Hepa1–6/COUP-TF2, HuH7/COUP-TF2, HepG2/COUP-TF2). The migration and the ability to colonize sites at a distance from the growth front were evaluated by Time-Laps microscopy. Finally, we studied the role of COUP-TFII in an in vivo models of mouse carcinogenesis (TgN (Alb1HBV)44Bri) realizing a triple transgenic animal where the liver-specific Cre expression deletes COUP-TF2 in hepatocytes and in xenograft model where mice were inoculated with human smmc7721 hepatocarcinoma cells stable transfected with COUP-TF2 or silenced by specific short hairpin.
Results: COUP-TFII is over-expressed in primary HCC samples and Kaplan-Meier and Cox regression analysis show that it may be an independent prognostic factor of worst outcome. Overexpression of COUP-TF2 has no significant effects on cell proliferation, but Live cell imaging experiments showed that COUP-TF2 induces a pro-metastatic phenotype characterized by an increased resistance to anoikis and amoeboid migration. Moreover, we found that several proteins involved in the organization of the cytoskeleton, cell-cell or cell-substrate adhesion (i.e. FAK, P-FAK, T-cadherin, β-catenin, αV-integrin, VCAM and α-tubulin), were differently modulated in COUP-TF2 overexpressing *vs* control cells. Finally, COUP-TF2 deletion in hepatocytes of HBV-transgenic mice (Tg[HBV]CreKOCOUP-TF2) reduces tumour growth and in xenograft model reduces pulmonary metastasis compared to control animals.
Conclusion: Our study uncovers COUP-TFII as a critical new player in hepatocarcinogenesis and HCC progression. The evidence that COUP-TFII deletion has a little impact in adult physiological functions and its transcriptional activity could be potentially regulated by ligands, indicates that this nuclear receptor is a promising target for HCC therapy.

THU-450

RFX5 promotes hepatocellular carcinoma progression via transcriptional activation of YWHAQ

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Background and aims: We previously identified that RFX5, a classical transcription regulator of MHC II genes, was significantly upregulated in hepatocellular carcinoma (HCC) tumors and cell lines. This study aims to reveal its biological significance and the underlying mechanism in HCC.
Method: The role of RFX5 in HCC was investigated by monitoring the colony forming and subcutaneous tumor growth ability of HCC cells after knocking down RFX5 with lentiviral CRISPR/Cas9 system. The transcriptional target of RFX5 in HCC cells was determined by ChIP-seq analysis in HepG2 and then validated with ChIP-PCR and luciferase assay in a set of HCC cell lines. The involvement of RFX5 transcriptional activated genes in HCC development was further determined by colony formation rescue experiment.
Results: We found that overexpression of RFX5 promoted HCC cell proliferation and colony formation, while knocking down RFX5 greatly inhibited the colony formation and subcutaneous tumor growth of several HCC cell lines. Moreover, we identified a group of transcriptional target genes of RFX5. Among these genes, YWHAQ, a member of the 14-3-3-protein family, was closely regulated by RFX5 both in HCC tissues and cell lines. Some study has been proved YWHAQ could interact with many signaling pathways that are critical for apoptosis and cell proliferation, mainly through binding phosphoserine/threonine motifs. We found that RFX5 could directly bind to the promoter of YWHAQ by ChIP-seq and ChIP-PCR assay in HCC cell lines. We also found that RFX5 could enhance the transcriptional activity of YWHAQ promoter by luciferase assay. Modulating the expression of RFX5 in HCC cell lines could subsequently alter the expression level of YWHAQ. Most importantly, the mRNA expression level of YWHAQ was elevated in HCC and tightly correlated with that of RFX5, and linked to the bad prognosis of HCC patients. Notably, YWHAQ overexpression largely rescued the growth inhibitory effects of RFX5 depletion in HCC cells, indicating that YWHAQ is a downstream effector of RFX5.

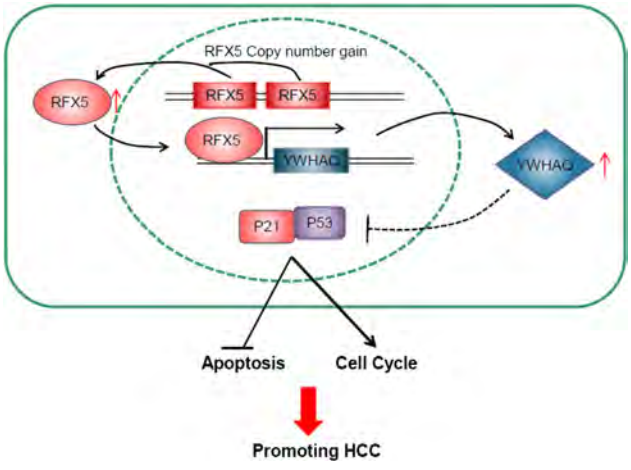

Figure: Graphical Abstract

Conclusion: RFX5 could promote hepatocellular carcinoma progression via transcriptional activation of YWHAQ.

THU-451

Characterization of cholangiocarcinoma primary, circulating and metastatic stem-like cells

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Background and aims: Cholangiocarcinoma (CCA) is an extremely heterogeneous adenocarcinoma arising from malignant transformation of biliary tree. Cancer Stem Cells (CSCs) are a subset of tumor cells responsible for tumor initiation, recurrence and metastasis. Spread of stem-like Circulating Tumor Cells (CTCs) in the blood plays a major role in tumor recurrence, metastasis initiation and drug unresponsiveness. Thus, we hypothesized the existence of CCA stem-like relapse-initiating cells. The present study aimed to explore the evolution of stemness features during CCA progression.
Method: Enrichment of CCA stem-like subset by sphere culture (SPH) in established CCA cell lines (HUCCT1) and primary CCA cell culture (MTCHC-01). Adherent monolayer (MON) cells as control. *Mouse:* set up of CCA orthotopic mouse model by using Luciferase-GFP (Luc-GFP) transfected SPH and MON HUCCT1/MTCHC-01 cells. Isolation of GFP+ tumor cells from primary and metastatic tumors by FACS sorting. Molecular characterization by qRT-PCR. *Human:* spiking experiments with low concentrations of GFP+ MTCHC-01 added to healthy peripheral blood mononuclear cells (PBMC). Identification of MTCHC-01 cells by FACS, after CD45 depletion. Same CTC-isolation setting used on 1 CCA and 1 hepatocellular carcinoma (HCC) patient blood sample. Isolated CCA-CTCs characterized by qRT-PCR.
Results: *Mouse:* CCA SPH-primary tumor derived GFP+ cells showed CSC and EMT-related gene enrichment compared to MON-primary tumors. In accordance, SPH cells were responsible for enhanced tumor spread in secondary organs (lungs, spleen, mesenteric lymph nodes) and bloodstream. Notably, SPH-disseminated cells showed up-regulation of almost all tested CSC- and EMT-related gene compared to SPH-primary tumor cells. *Human:* set of the better CTC isolation conditions with spiking experiments. HCC-CTCs identified by FACS as CD45-CD34- cells. Interestingly, 79 CD133+ CTCs were identified in HCC sample. In accordance with these results, CCA-CTCs revealed up-regulation of selected CSC-like genes.
Conclusion: These findings suggest that CCA SPH cells are enriched in stem-like disseminating tumor cells responsible for metastasis formation. Moreover, very preliminary results obtained in human samples indicate the possible presence of CTCs with stem-like traits in liver cancer patients.

THU-452

TFOX, a novel TGF-beta target gene, switches TGF-beta activity toward EMT during tumor progression of human hepatocellular carcinoma

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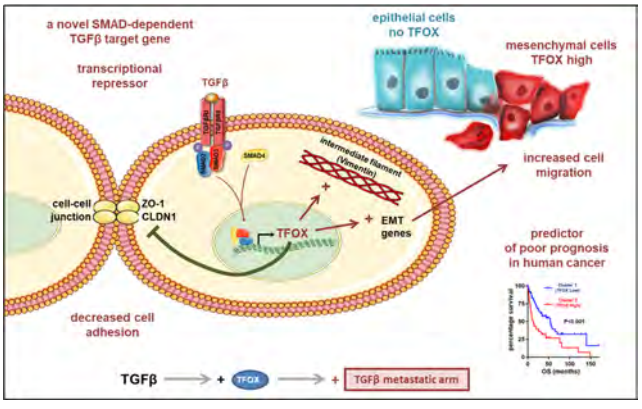
Background and aims: Transforming Growth Factor beta (TGFb) is a pleiotropic cytokine which controls fundamental cellular processes

associated with tumor onset and progression (e.g. proliferation, migration). In hepatocellular carcinoma (HCC), we previously highlighted TGFb signatures to discriminate patients with good and poor prognosis (Coulouarn, Hepatology, 2008), suggesting that TGFb may represent a relevant therapeutic target. However, targeting TGFb in cancer is complex given that it exhibits onco-suppressive or pro-tumorigenic properties, depending on the tumor stage. At an early stage TGFb induces cytostasis but at an advanced stage TGFb promotes metastasis, as a potent inducer of epithelial-mesenchymal transition (EMT). So far, the molecular mechanisms switching the actions of TGFb during tumor progression are not fully understood. The aim of our study was to characterize TFOX, a predicted transcriptional factor that we hypothesize to be involved in the functional duality of TGFb in cancer.

Method: Gene expression profiling was used to identify TFOX as a novel TGFb target gene in 8 HCC cell lines. Transient and stable TFOX gain and loss of function (lentivirus, siRNA, Crispr/Cas9) combined with functional assays (e.g. cell adhesion, migration) were used to determine the function of TFOX. Expression of EMT markers was determined by western blot and immunofluorescence. Clinical relevance of TFOX in human cancer was performed by integrative genomics.

Results: We show that i) TFOX is a novel canonical SMAD-dependent target of TGFb; ii) TFOX expression correlates with a mesenchymal phenotype, as exemplified by the expression of epithelial (e.g. CDH1/E-Cadherin) and mesenchymal (e.g. VIM/Vimentin) markers; iii) TFOX acts as a transcriptional repressor, as demonstrated by the endogenous TFOX loss of function gene signature made of 87% up-regulated genes; iv) TFOX mediates pro-metastatic properties of TGFb, by reducing cell adhesion, increasing cell migration and inducing EMT markers (e.g. VIM); v) TFOX correlates with VIM expression in human HCC (2 independent datasets: n = 81 and n = 193 HCC); and vi) TFOX expression predicts a poor prognosis (e.g. reduced patient survival), not only in liver cancer, but also in colon, stomach and kidney cancer. In HCC, TFOX is highly expressed in poor prognosis G1 subtype (Boyault, Hepatology, 2007) associated with a poor differentiation but is lowly expressed in good prognosis G5–6 subtypes associated with *CTNNB1* mutations.



Conclusion: Altogether, TFOX is identified as a novel effector of TGFb and its deregulation in cancer is clinically relevant being associated with the pro-tumorigenic properties of TGFb in poor prognosis tumors. Determining the expression of TFOX in advanced tumors in which the pro-metastatic arm of TGFb is activated could help to identify patients who may benefit from targeted therapies using TGFb inhibitors.

THU-453

Dissecting the landscape of (epi-)genetic alterations during sequential evolution of liver cancer

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Background and aims: Development of primary liver cancer is a multi-stage process. Pre-neoplastic dysplastic lesions emerge on the basis of chronic liver damage and evolve into early hepatocellular carcinoma (eHCC) and, subsequently, progressed HCC (pHCC). Detailed molecular characterization and prediction of pre-neoplastic lesions at high risk for malignant transformation would significantly advance our diagnostic and therapeutic approaches. We here utilized integrative molecular analyses to characterize the sequential evolution of liver cancer and aimed to define key epigenetic drivers and biomarkers of HCC development and progression.

Method: Methylation 450k-beadchip analyses were performed on cirrhotic liver (n = 7), low- (n = 4) and high-grade (n = 9) dysplastic lesions, eHCC (n = 5) and pHCC (n = 3) from 8 HCC patients with chronic hepatitis B infection. Differentially methylated gene regions (DMGR) were identified in comparison to non-cirrhotic and non-infected liver (n = 9). Potential epi-drivers and biomarkers were identified by integrative analyses of transcriptomic changes and validated in an independent cohort from the TCGA database.

Results: The proportion of hypermethylated DMGR progressively increased from cirrhosis over dysplastic- to HCC and peaked in eHCC lesions. Early epigenetic alterations involved signaling pathways related to cell death, apoptosis and immune regulation, while late changes centered on cell survival, growth and migration. A common regulation of stem cell-associated pathways including Wnt/b-catenin signaling was revealed in dysplastic as well as eHCC potentially predisposing tumor progression. Moreover, we identified 101 genes with significant methylom changes in dysplastic and cancerous lesions with concomitant progressive gene expression alterations in cancer tissue. We further defined an epi-panel of early epigenetic marks in dysplastic lesions including selected CpG-sites with confirmed differential methylation in cancer tissue and consequential transcriptional alterations of the target genes using an independent cohort of 362 HCC and 49 surrounding liver samples. Unsupervised hierarchical clustering confirmed a robust classification in malignant and non-malignant lesions.

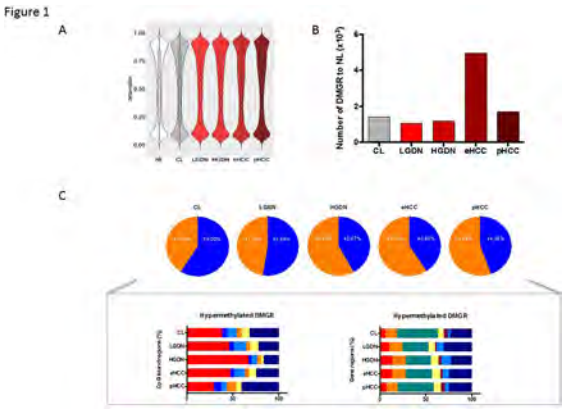

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Figure 2

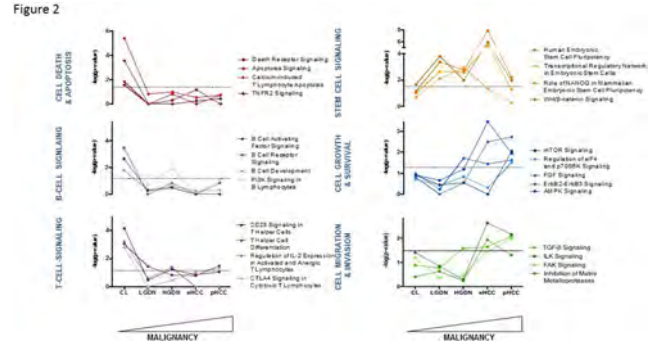
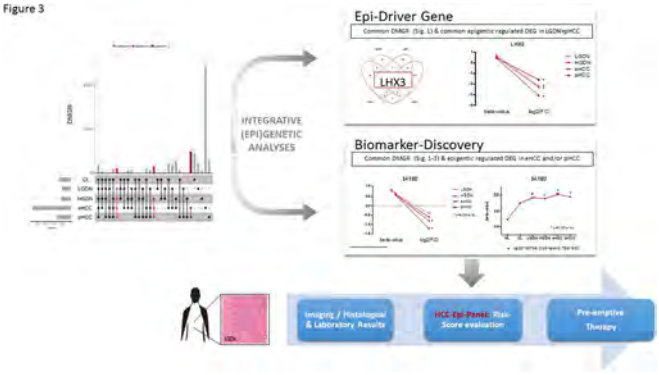


Figure 3



Conclusion: Our results confirm that epigenetic changes occur early during hepatocarcinogenesis. Epigenetic modifications, therefore, might be of high diagnostic/predictive utility for the identification of dysplastic lesions at risk for cancer progression. The identified (epi-) panel of oncogenic epigenetic marks might be useful to complement phenotypic classifications and facilitate selection of lesions amenable to early therapeutic interventions.

THU-454

Dual CCR2/CCR5 antagonism as macrophage targeted therapy in experimental hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is an inflammation-associated cancer and characterized by specific tumor-associated macrophages (TAMs) which sustain tumor development. The chemokine-receptors CCR2 and CCR5 are involved in attraction and polarization of TAMs. The possibility to target monocyte infiltration and/or their pro-tumoural polarization was investigated by using Cenicriviroc (CVC), a selective dual CCR2/CCR5 antagonist.
Method: HCC was induced in 5-week-old male sv129 mice by weekly diethylnitrosamine (DEN)-injections for 20 weeks. Mice were treated with CVC 100 mg/kg or vehicle by daily oral gavage for 5 weeks (25–30 weeks of age). Liver damage and HCC development were analyzed by liver histology and qPCR, multiplex and flow cytometry analyses on serum and liver tissue. Life CD45+Ly6G-CD11b+F4/80+Ly6C+ infiltrated monocytes, CD45+Ly6G-CD11b+F4/80+Ly6C-Tim4- monocyte-derived macrophages and CD45+Ly6G-CD11bintF4/80+Ly6C-Tim4+ Kupffer cells (KC) were isolated from the liver by fluorescence activated cell sorting (FACS) and analysed for inflammatory and pro-tumorigenic markers by qPCR. The effect of CVC was further investigated in vitro on bone-marrow derived macrophages (BMDM).
Results: CVC treatment was well tolerated and mice showed reduced weight loss compared to vehicle treated mice. Treatment efficacy was confirmed by elevated serum CCL2 levels in CVC treated mice. CVC treatment did not result in a better survival rate or reduced tumor load. However, CVC treated mice showed a tendency to reduced fibrosis, evaluated on sirius red staining, with significant lower expression of MMP9 and MMP12 and the cytokines TNFalpha and IL-10. Flow cytometric analyses did not reveal significant differences between liver monocyte/macrophage populations between CVC and control treated mice while FACS-isolated KCs from CVC-treated mice showed reduced expression of TNFalpha and IL6 and an increased anti-tumoural CD86/CD206 balance compared to KCs from vehicle treated mice. The latter was confirmed in vitro on BMDM were CVC resulted in reduced expression of CD206, Arg-1, iNOS and CCR2.
Conclusion: CVC treatment in DEN-induced HCC did not result in better survival rate or reduced tumor load although the therapy influenced the tumoural micro-environment and might shifted liver KCs towards an anti-tumoural phenotype. Further research with combination therapy seems mandatory.

THU-455

Metabolomic analysis by 1H-nuclear magnetic resonance spectroscopy suggest that there are 2 phenotypes of human hepatocellular carcinoma developed in non-alcoholic fatty liver disease according to fibrosis level (F0F1 vs F3F4)

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Background and aims: There is a rising incidence of Non-alcoholic Fatty Liver Disease (NAFLD) as well as of the frequency of Hepatocellular Carcinoma (HCC) associated with NAFLD which occurs in 40% of cases in the absence of cirrhosis. There is no study reporting the impact of fibrosis on metabolic profile of HCC developed in NAFLD. The aim of this study is to highlight new biomarkers and propose metabolic pathways of HCC according to fibrosis stages (F0F1 *versus* F3F4).
Method: A non-targeted metabolomics strategy was applied. The analysis included 52 pairs of human liver tumoral tissue (HCC) and non tumoral tissue collected from the French Liver biobank. Among the 52 HCC, 26 were developed in severe fibrosis or cirrhosis (F3F4) and 26 no or mild fibrosis (F0F1). Tissue extracts (aqueous and lipid) were analyzed by ^{1}H-Nuclear Magnetic Resonance spectroscopy at 400 MHz. An optimization evolutionary method (genetic algorithm, Linear Discriminant Analysis and cross-validation) has been used to identify metabolites associated to HCC *vs* non tumoral tissue (NTT).
Results: We compared each group of HCC tissue with their own NTT. The metabolomic analysis revealed in HCC-F0F1, an increase in the level of derivatives of choline (phosphocholine and glycerophosphocholine) and a decrease in phosphoethanolamine corresponding to an alteration of phospholipid membranes synthesis, increased levels of glutamine suggesting the activation of glutamine synthetase. Lipids extracts analysis indicated a decreased of fatty acids suggesting an up-regulation of beta oxidation of fatty acids into Krebs cycle. In contrast, HCC-F3F4 is characterized by an accumulation of branched amino acids (Valine, Leucine and Isoleucine) suggesting an activation of the mTOR pathway as well as an increase in creatine and sarcosine which may reflect methylation disorders involving up-regulation of Glycine N Methyl Transferase (GNMT). Moreover, lipids analysis indicated an increase in free and total cholesterol content as

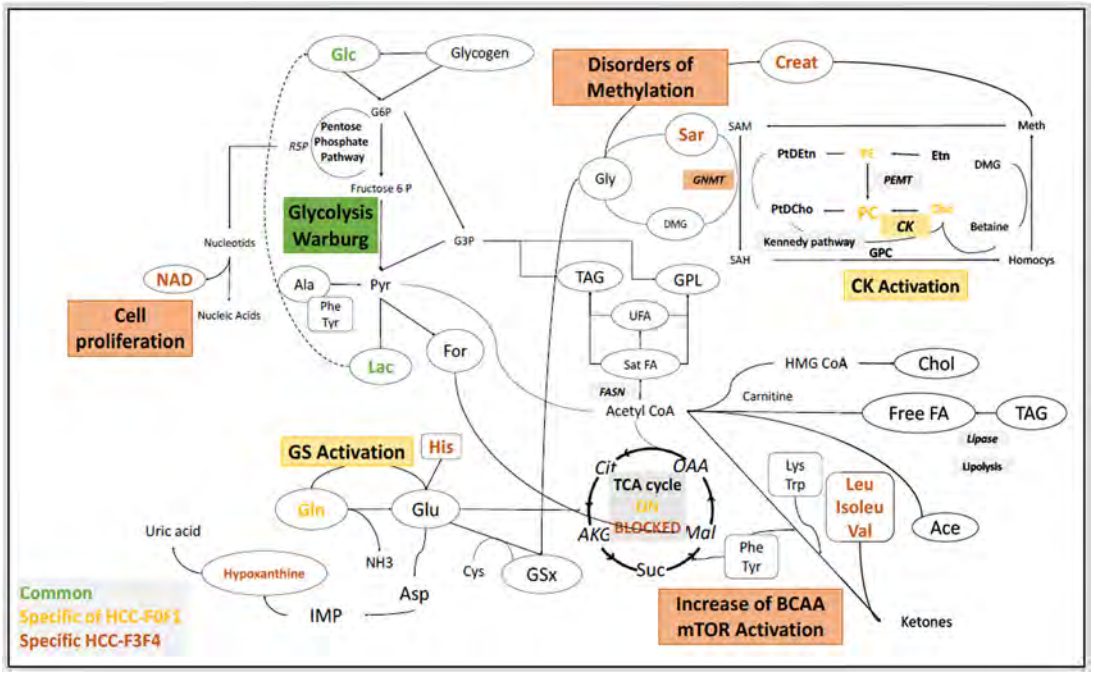

Figure: (abstract: THU-455): Hypothetic mechanistic pathways of HCC-NAFLD according to fibrosis severity.

well as an increase of saturated fatty acid levels suggesting an up-regulation of fatty acid synthase activity (FASN) which may contribute to tumor growth and proliferation.

Conclusion: In conclusion, metabolomic analysis of aqueous and lipid extracts allow us to suggest for the first time that there are two phenotypes of HCC developed in NAFLD according to the fibrosis level. This study highlights the impact of underlying pathology on metabolic reprogramming of the tumor.

THU-456

Polyploidy spectrum: a new marker of molecular HCC tumour classification

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Background and aims: Polyploidy is a fascinating characteristic of liver parenchyma. Hepatocytes polyploidy depends on the DNA content of each nucleus (nuclear ploidy) plus the number of nuclei per cell (cellular ploidy). Which role can be assigned to polyploidy during human HCC development is still an open question. Here, we investigated whether a specific ploidy spectrum is associated with clinical and molecular features of HCC.

Method: Ploidy spectra were determined on a total of 85 paired (tumor/adjacent) surgically resected tissues from HCC patients as well as 5 tissues from healthy control. To define ploidy profiles, quantitative and qualitative *in situ* imaging approach was used on paraffin tissue liver sections.

Results: We first demonstrated that polyploid hepatocytes are major components of human liver parenchyma, polyploidy being mainly cellular (binuclear hepatocytes). Across liver lobules, polyploid hepatocytes do not exhibit specific zonation pattern. During liver tumorigenesis, cellular ploidy is drastically reduced; binuclear polyploid hepatocytes being barely present in in HCC tumors. Remarkably, nuclear ploidy is specifically amplified in HCC tumors. In fact, nuclear ploidy is more amplified in HCCs harboring low grade of differentiation and related to p53 mutations. Our results finally demonstrated that highly polyploid tumors are associated with poor prognosis and higher proliferation rate.

Conclusion: Our results underscore the importance of quantification of cellular and nuclear ploidy spectrums as an accurate diagnostic test for HCC tumorigenesis.

THU-457

DoubleCortin/Like Kinase 1 (DCLK1) expression characterized specific cancer stem cell subpopulations of human cholangiocarcinoma primary cell cultures where its inhibition exerts anti-neoplastic effects

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Background and aims: Cholangiocarcinoma (CCA) is a very aggressive cancer with high chemoresistance. We demonstrated that CCA is enriched of Cancer Stem Cells (CSCs); this feature is associated with aggressiveness and drug resistance. Recently, DCLK1 was validated as a CSC marker in different gastrointestinal tumors.
Our aims were to evaluate: i) DCLK1 expression and biological function in primary cell cultures of CCA subtypes iCCA (intrahepatic) and pCCA (perihilar) and; ii) DCLK1 expression in human CCA samples *in situ* and its serum concentration.
Method: Primary cell cultures were prepared from surgical specimens of human iCCA and pCCA and CSCs were immunosorted for specific markers (LGR5, CD13, CD90, EpCAM, CD133). hBTSC and hHPSC physiological primary stem cell cultures were used as controls of iCCA and pCCA respectively. DCLK1 expression was analysed by RT-qPCR, western blot and immunofluorescence. In functional studies, the effects of a selective DCLK1 inhibitor (LRRK2-IN-1, 72hrs of treatment) on cell proliferation (MTS Assay, population doubling time-PDT), apoptosis (AnnessinV-FITC/PI) and colony formation capacity were evaluated. DCLK1 gene expression in surgical resected CCA and healthy samples was evaluated by RT-qPCR. DCLK1 serum concentration was measured in CCA, HCC, cirrhotic and healthy patients by ELISA.
Results: For the first time, we demonstrated DCLK1 mRNA and protein expression in iCCA and pCCA. An increased expression of DCLK1 in CCA was evidenced in association with other CSC markers and its highest expression was observed in specific subpopulations of CCA-CSCs (i.e. $pCCA^{LGR5+}$ and $iCCA^{CD133+}$). DCLK1 showed cytoplasmic localization in $pCCA^{LGR5+}$, $iCCA^{CD133+}$, unsorted pCCA and iCCA cell cultures. LRRK2-IN-1 (5 μM) added to CCA cultures increased PDT, decreased proliferation, colony formation capacity and colony size, and induced apoptosis in both iCCA and pCCA compared with controls ($p < 0.01$). LRRK2-IN-1 showed a dose-dependent anti-proliferative effect (2.5μM-20 μM) by MTS assay with an IC_{50} of 9.61 μM in unsorted pCCA, 14.72 μM in unsorted iCCA, 4.51 μM in $pCCA^{LGR5+}$ and 9.61 μM in $iCCA^{CD133+}$ cells. Furthermore, LRRK2-IN-1 did not influence hBTSC and hHPSC primary cell cultures viability. DCLK1 gene expression was lower in healthy tissues than in specimens of iCCA and pCCA ($p < 0.01$). Interestingly, DCLK1 was detected in serum samples of iCCA and pCCA patients. DCLK1 serum levels were lower in cirrhotic and HCC patients compared to CCA patients ($p < 0.05$), but we have never observed DCLK1 protein into serum samples of healthy controls.
Conclusion: In conclusion, DCLK1 expression characterizes specific CCA-CSC subpopulations and could represent a serum biomarker for CCA. DCLK1 inhibition exerts anti-neoplastic effects in primary CCA cell cultures.

THU-458

Identification of relevant oncogenes in RAS-activated primary liver cancer using a targeted screening approach

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Background and aims: Gene mutations within the RAS signaling pathway occur with a frequency of 15–20% in human hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Activation of RAS signaling is associated with a poor prognosis. However, it remains unclear if specific targeted therapies could be beneficial in this subgroup of patients. In the RPK mouse model, liver-specific expression of oncogenic *Kras* and genetic inactivation of the tumor suppressors *Rb* and p53 mimics genetic changes found in a subgroup of human primary liver cancers. Hepatic tumors in this model resemble human HCC and ICC, as well as tumors of mixed HCC/ICC differentiation. We used a targeted *in vitro*-screening approach to identify relevant oncogenes in our model, followed by *in vivo*-transfection of mouse hepatocytes with transposon-based shRNA constructs.
Method: RNA and protein from microdissected liver tumors of $Rb^{lox/lox};p53^{lox/lox};Kras^{LSL-G12D/+}$ (*RPK*) mice and liver tissue of age matched control mice were analyzed by mRNA microarray, qPCR and western blot. Gene knock-down in primary cell lines from RPK tumors was achieved using lentiviral *shRNA* constructs. Proliferation and clonogenic assays were used to test for the functional relevance of target genes. Transposon *CreER*-constructs harboring inducible *shRNAs* were injected by hydrodynamic tail vein injection to achieve target gene knock-down *in vivo*.
Results: Highly upregulated genes in *RPK* tumors were identified by mRNA microarray analysis. Of all genes tested, only shRNA constructs against *Dmbt1* significantly decreased cell proliferation and clonogenic capacity. Knock-down of *Dmbt1* was verified by mRNA and protein analysis. *In vivo* experiments using *CreER-shDmbt1* transposon constructs showed a significantly longer survival of RPK mice in comparison to controls injected with a random shRNA construct.
Conclusion: Activation of RAS signaling is found in up to one in five patients with primary liver cancer and is associated with a poor prognosis. Using a targeted screening approach in a mouse model with RAS-dependent liver tumors, we identified *Dmbt1* as a relevant oncogene. Of note, DMBT1 functions as a tumor suppressor in other cancers probably through suppression of anti-cancer immunity. Here, we identified a novel oncogenic role of *Dmbt1* in the liver cancer. Interestingly, *DMBT1* is upregulated in a subset of human HCC and many ICC, where it could present a possible target for cancer therapy.

THU-459

Non-parenchymal TREM2 halts hepatocarcinogenesis through the inhibition of liver inflammation and hepatocyte proliferation

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Background and aims: Hepatocellular carcinoma (HCC) is a prevalent and aggressive cancer that usually arises on a background of chronic liver injury where liver regenerative and inflammatory processes are involved. The triggering receptor expressed on myeloid cells 2 (TREM2) is predominantly expressed in hepatic non-parenchymal cells and inhibits Toll-like receptor (TLR)-derived signalling, protecting the liver from various types of hepatotoxic injury. However, its role in liver cancer is unknown. Here, the role of

TREM2 in hepatocarcinogenesis and liver regeneration was investigated.
Methods: TREM2 expression was analysed in liver tissue samples of 2 independent cohorts of HCC patients compared to control individuals. Experimental models of HCC and liver regeneration in wild type (WT) and *Trem2*$^{-/-}$ mice, and *in vitro* studies with hepatic stellate cells (HSCs) and HCC spheroids were conducted.
Results: *TREM2* expression was induced in human HCC tissue compared to normal liver tissue. In addition, *Trem2* expression was upregulated in the livers of DEN-induced carcinogenic liver injury mouse model as well as during liver regeneration after partial hepatectomy (PHx). *Trem2*$^{-/-}$ mice developed more liver tumours irrespective of size after diethylnitrosamine (DEN) administration, displayed exacerbated liver damage, inflammation, oxidative stress and hepatocyte proliferation. Notably, administration of an anti-inflammatory diet blocked DEN-induced hepatocarcinogenesis in *Trem2*$^{-/-}$ mice. Moreover, *Trem2*$^{-/-}$ livers showed increased hepatocyte proliferation and inflammation after partial hepatectomy (PHx). Supernatant from human hepatic stellate cells that overexpress TREM2 inhibits human HCC spheroid growth *in vitro*.
Conclusion: *TREM2* expression in non-parenchymal cells protects the liver from inflammatory-related hepatocarcinogenesis, representing a novel therapeutic target.

THU-460
Longitudinal monitoring of cell-free DNA predicts for transarterial chemo-embolization failure in hepatocellular carcinoma
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Background and aims: Level 1 evidence supports the use of transarterial chemo-embolization (TACE) in intermediate stage hepatocellular carcinoma (HCC), however survival outcomes are heterogeneous. Alpha-fetoprotein (AFP) is a well-established and widely used biomarker for HCC, however the sensitivity of AFP as a diagnostic and prognostic tool is limited by the existence of non-AFP-secreting tumours. Plasma derived cell-free DNA (cfDNA) is a compelling novel biomarker for monitoring cancer outcomes in both the curative and palliative setting. Here, we describe our preliminary experience of cfDNA monitoring in hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolisation (TACE).
Method: A total of 54 patients with HCC who received TACE were identified within the PRECISION biobank at Imperial College Healthcare NHS Trust. Of these, 18 patients had matched plasma samples taken at baseline, post-TACE and on subsequent progression, with matched full demographic information available. Relevant plasma samples were retrieved, and cfDNA was extracted and quantified at all three time points. Mutational load by next generation sequencing (NGS) was carried out.
Results: Of the 18 patients identified, 72% were male and 28% female. 50% had Childs Pugh B disease (7–9), and 50% Childs Pugh A (5–6). 10 patients (55%) secreted AFP, defined as a value above the normal range. 72% of our cohort had documented cirrhosis. Across all 18 patients, there was a reduction in cfDNA levels following TACE, which increased subsequently on progression (median cfDNA levels of 921 (185.9–4804) ng/ml at baseline, 845 (251–2300) ng/ml following TACE and 1084.5 (80.3–72155) ng/ml on progression. Patients whose post-TACE cfDNA levels were higher than their baseline levels (31%) had a poorer overall survival (OS), with a median OS of 47.1 months compared to 116.8 months for those who saw any reduction in their cfDNA titre following treatment (Figure 1). Of note, in AFP non-secretors (n = 8), cfDNA had an obvious added utility in monitoring response to treatment, with a baseline median cfDNA of 1011.9 (185.9–2250) ng/ml; post-TACE median cfDNA of 843 (251–2300) ng/ml and on-progression median cfDNA of 1165 (369.6–3341) ng/ml, compared to AFP values of 2.5 (1–9) ng/ml; 5 (1–8) ng/ml and 3 (2–7) ng/ml respectively. NGS results will also be reported.

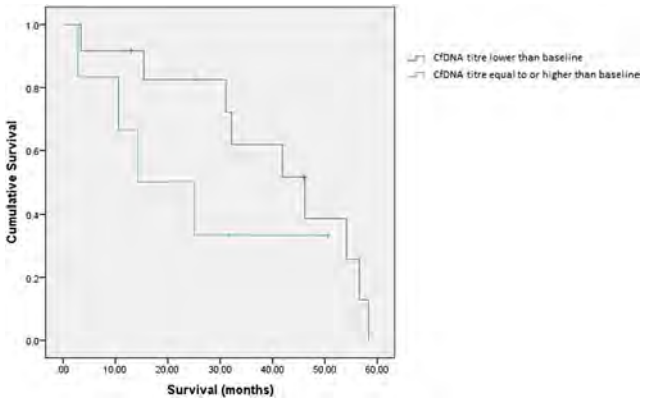

Figure 1: Overall survival in patients undergoing treatment with TACE, stratified by cfDNA response.

Conclusion: Plasma cfDNA analysis represents a potential strategy to monitor disease progression in HCC patients treated with TACE, particularly in those who do not secrete AFP. This technology can easily be applied to the clinic.

THU-461
A diet-induced lean non-alcoholic steatohepatitis-associated hepatocellular carcinoma mouse model
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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has 24% prevalence globally. Its progressive form (non-alcoholic steatohepatitis; NASH) can lead to hepatocellular carcinoma (HCC) development. Interestingly, NAFLD can develop in the absence of obesity and diabetes, with a prevalence of 7% in lean individuals in the US and 25–30% in some Asian countries as a result of a diet high in fructose/fat/cholesterol and genetic predisposition affecting lipid export from the liver. Currently, there is limited understanding of lean NAFLD/NASH HCC pathogenesis, necessitating the development of mouse models for this disease. The aim of this work is to develop a diet-induced lean NASH-HCC mouse model.
Method: Thirty-five mice were fed a choline deficient, high trans-fat, sucrose, cholesterol (CD-HFSC) diet and fifteen mice were fed an isocaloric control low fat diet starting at 4 weeks of age. Choline deficiency is associated with triglyceride accumulation in the liver similar to genetically susceptible human NAFLD patients. Mice were weighed weekly, plasma liver enzymes and lipids were assessed at 17 and 26 weeks of age and glucose tolerance tests were performed at 8, 20, 32, and 44 weeks. Liver tissue was analyzed post mortem to assess nodule development and liver histology in order to determine the development of NAFLD, NASH, fibrosis and HCC.
Results: Mice fed the CD-HFSC diet developed HCC as early as 46 weeks of age with high penetrance (60.7%) at 56 weeks in the absence of obesity. 92.9% of these mice developed hyperplastic nodules and 89.3% had dysplastic nodules. 100% of the mice fed the CD-HFSC diet developed NASH and 51.8% had fibrosis stage 2–3. Mice fed the CD-HFSC diet experienced liver damage as evidenced by the significantly higher plasma ALT and AST levels ($p < 0.05$). Mice fed the CD-HFSC diet had lower plasma cholesterol and triglyceride levels compared to

mice fed the control diet, suggestive of retention of these lipids in the liver. Glucose tolerance was similar in both diet groups. Interestingly, nodule size at the end point was positively correlated with higher plasma liver enzyme (AST) and glucose levels at earlier time points.
Conclusion: Mice fed a diet deficient in choline and high in trans-fat, sucrose, and cholesterol experience liver damage and develop lean NASH-HCC in the absence of cirrhosis by 56 weeks of age. This mouse model is expected to aid in further understanding the pathogenesis of lean NASH-HCC.

THU-462

StARD1 is induced in human HCC and its overexpression aggravates cholesterol-mediated hepatocarcinogenesis in vivo

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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide and the end-stage of chronic liver disease. Hypercholesterolemia is also a growing health concern and a critical factor in the progression of fatty liver disease. StARD1, which transports cholesterol to mitochondria, has a role in the transition from steatosis to steatohepatitis which can progress to HCC. Obesity and hepatic steatosis promotes tumorigenesis, but the role of cholesterol and StARD1 overexpression in HCC progression has not been elucidated yet. **Aim**: To examine the homeostasis of StARD1 in human HCC and to study the role of cholesterol and StARD1 in chemically-induced HCC and the therapeutic effect of ezetimibe *in vivo*.
Method: 14 days-old wild type mice were injected i.p. with a single dose of the carcinogen diethylnitrosamine (DEN). Mice were fed high fat diet (60%) containing cholesterol (0.5%) (HFHC) supplemented or not with ezetimibe (Ez) for 32 weeks. In some cases, DEN-treated mice fed HFHC were injected with adenovirus to overexpress StARD1. Liver samples were analyzed for inflammation, fibrosis and tumor markers by WB, IHC and qRT-PCR. StARD1 expression was examined in samples from HCC patients.
Results: Liver cholesterol levels were higher in the HFHC fed group compared to HFHC+Ez group. Moreover, inflammation (IL-6, Ly6D, Ly6c), proliferation (PCNA, Ki-67) and fibrosis (collagen 1A1, αsma, TGFβ) markers were elevated in the HFHC group compared to HFHC+Ez group. In addition, tumour markers (AFP, CK-19, GP-73, Birc5) induced by DEN were elevated in mice fed the HFHC, and ezetimibe reversed this increase. Interestingly, adenovirus-mediated StARD1 overexpression (5–10 fold) 3–4 months after DEN treatment doubled the multiplicity and area of tumors in mice fed HFHC and increased the expression of tumor, fibrosis and inflammation markers. These findings were accompanied by increased activation of HIF-1α-mediated gene expression. Finally, liver biopsies from patients with HCC exhibit increased levels of StARD1 and HMGCR, which catalyzes the rate-limiting step in the synthesis of cholesterol, compared to samples from control subjects.
Conclusion: Cholesterol aggravates HCC and ezetimibe reversed this effect. StARD1 overexpression increases hepatocarcinogenesis, in part by stimulating HIF signaling. As patients with HCC exhibit increased StARD1 expression, these findings suggest that targeting StARD1 may be of potential relevance in HCC.

THU-463

Role of natural killer cells receptors on the development and progression of hepatocellular carcinoma

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Background and aims: NK cells play a crucial role in tumour immunosurveillance. Killer immunoglobulin-like receptors (KIRs) are key regulators of NK-mediated immune responses and their expression, which is genetically determined, is highly heterogeneous and regulated by different aplotypes. In this study we assessed the genetic pattern of KIRs and their human leukocyte antigen (HLA) ligands in liver transplanted patients with and without hepatocarcinoma (HCC) in order to identify a potential correlation between the frequency of inhibitory/activating KIRs and development/progression of the tumour.
Method: We analysed a single centre cohort of transplanted cirrhotic patients with and without HCC. Clinical data were collected along with the histological features of the explanted livers. The immunogenetic profile of the patients were compared to those of healthy individuals. High resolution (4 digits) typing of HLA A, B, C and 14 KIRs gene loci was performed. Subjects were divided into 2 groups according to homozygosity for KIR haplotype A (AA), heterozygosity (AB) or homozygosity for KIR haplotype B (Bx). They were also stratified according to the numbers of activating/inhibitory KIRs, the type of KIRs related HLA-ligands and the combinations with their receptors.
Results: 87 patients were included: 52 (60%) had HCC. HCV infection was the primary cause of liver disease (82.8%). No significant difference was observed in the frequency of HLA alleles and activating/inhibitory KIR genes and KIR aplotypes between patients and controls. The frequency of KIR2DS4, the only activating KIR gene of aplotype A, was similar between HCC and non-HCC group. However, homozygosis for the deletion variant of KIR2DS4 was more common in HCC group (23% vs 3% p = 0.009), indicating that a higher proportion of HCC patients with KIR haplotype A did not express any activating KIR genes compared to only 1 non-HCC patient. In contrast, HCC patients outside Milan criteria or with microvascular invasion showed a higher prevalence of the activating KIR gene 2DS2 (100% vs 30%; p = 0.003) and a lower frequency of the inhibitory KIR gene 2DL1 (40% vs 83%; p = 0.039).
Conclusion: Loss of activating KIR2DS4 was more frequently observed among HCC patients, suggesting a decreased cytotoxic function of NK cells and therefore a negative impact on tumour immunosurveillance. However, the higher frequency of activating KIR2DS2 observed in patients with a more aggressive tumour suggest that NK could play a potential dual role in HCC development and progression.

THU-464

NASH-related liver carcinogenesis is critically affected by hypoxia-inducible factor 2 alpha

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Background and aims: Hypoxia and hypoxia inducible factors (HIFs) are believed to significantly affect the progression of chronic liver diseases (CLD). Recently, we showed that hepatocyte HIF-2α activation is a key feature in both human and experimental NAFLD and significantly contributes to disease progression in both experimental animals and human patients. In the present study, we investigated the contribution of hepatocyte HIF-2α in promoting the

development of NAFLD/NASH-associated hepatocellular carcinoma (HCC).
Method: The role of HIF-2α was investigated: a) in human HCC liver specimens from NAFLD/NASH patients, b) in mice carrying hepatocyte-specific deletion of HIF-2α (HIF-2α fl/fl/Alb-Cre mice) receiving diethyl-nitrosamine (DEN) administration plus choline-deficient L-amino acid refined (CDAA) diet (DEN/CDAA protocol); c) in HepG2 stably transfected to overexpress HIF-2α vs cells transfected with the empty vector.
Results: HIF-2α as detected by immunohistochemistry (IHC), was expressed in HCC specimens from NAFLD/NASH patients, with higher expression in patients experiencing early tumour recurrence. Following the treatment with the DEN/CDAA protocol, mice carrying hepatocyte specific deletion of HIF-2α showed a significant decrease in the volume and number of neoplastic liver tumour masses in transgenic mice vs control littermates. Liver tumours in HIF-2α transgenic mice were also characterized by a significant decrease in: a) transcripts levels of tumour associated macrophages and fibroblasts/myofibroblasts markers (including F4/80 and α-smooth muscle actin); b) transcript levels for critical and HIF2α-related target genes, including EPO, c-Myc and CXCR4. In vitro data indicate that HIF-2α is also able to significantly induce cell proliferation, a process that seems to be impaired in the HIF-2α fl/fl/Alb-Cre mice compared to the control littermates.
Conclusion: These results indicate that the activation of HIF-2α in hepatocytes has a critical role in the development of experimental liver carcinogenesis in a dietary NAFLD/NASH-related environment.

THU-465
Variation of different histone deacetylases and the functional effects of HDAC inhibitors in hepatocellular carcinoma
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Background and aims: Histone deacetylases (HDACs) comprise in humans currently 18 members divided in 4 classes. HDAC inhibitors (HDACi) appear as promising therapeutic strategy for cancer treatment. The aim of this study was to comprehensively analyze HDAC expression and to functionally analyze the effect of HDACi in HCC.
Method: HDAC expression levels were analyzed in primary human hepatocytes (pHH) and HCC cell lines (Hep3B, HepG2, PLC and Huh7) with qRT-PCR. HDAC activity was measured with fluorometric activity assay (Biocat). HDAC inhibitors SAHA, TSA and TPX were purchased from Sigma. Cytotoxicity was measured with LDH Assay (Roche). Migration was measured with Trevigen Migration assay. Clonogenic assay was performed by seeding at low density, and colony counting after 7 days treatment. Apoptosis was measured with FACS with ANNEXIN V-FITC Kit (Invitrogen).
Results: qRT-PCR analysis revealed significantly increased expression of HDAC 1/2/3/8 (class I); HDAC 4/5/7/9 (class IIa); HDAC 6/10 (class IIb) and HDAC 11 (class IV) in 4 human HCC cell lines and 11 human HCC tissues compared to pHH. Biochemical analysis showed significantly higher HDAC-activity in HCC cells compared to PHH. In human HCC samples, expression levels of individual HDACs varied significantly but particularly HDACs of classes IIa showed significant correlations, i.e. it appeared that there are “high” and “low” HDAC-expressers. TCGA (The Cancer Genome Atlas) data set analysis of 377 HCC patients revealed that high HDAC1/2/8, (Class I), HDAC4/7/9 (Class IIa) or HDAC6 (Class IIb) correlated with poor patient survival. Next, we analyzed the effects of 3 different HDACi: SAHA (irreversible inhibitor of predominantly Class-I), trichostatin A (TSA; reversible inhibitor of foremost Class-IIb; less effective against Class-I, with the exception of HDAC5), and trapoxin (TPX; irreversible pan-inhibitor acting at nanomolar concentrations). All 3 HDACi caused dose-dependent toxicity in HCC cells, while the same doses did not exhibit any toxicity in PHH. Functional analysis of HDACi in sub-toxic doses showed a dose-dependent reduction of proliferation, with TSA and TPX inducing a complete growth arrest, while SAHA inhibited proliferation only approximately 50%. Furthermore, all 3 HDACi reduced the migratory potential and clonogenicity of HCC cells but also this with different efficacy. Moreover, combination with HDACi enhanced the efficacy of sorafenib in killing sorafenib susceptible cells. Furthermore, treatment with HDACi reestablished sorafenib sensitivity in resistant HCC cells.
Conclusion: HDACs promote different facets of tumorigenicity of HCC cells and HDACi showed qualitatively similar but quantitatively different inhibitory effects on HCC cells, which may be exploit to develop therapeutic approaches. HDACi and sorafenib combination appears as novel approach to break sorafenib resistance of HCC cells.

THU-466
Epigenetic regulation of gene expression in a HCC-NASH murine model
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Background and aims: Epigenetics play an important role in the progression from non-alcoholic fatty liver disease (NAFLD) to hepatocellular carcinoma (HCC). The aim of our study was to unravel how the interaction between genes and miRNAs expression could affect the development of HCC in a murine model.
Method: Twenty-five male six-weeks mice C57BL/6J were fed a HFHCC diet (40% Kcal fat, 1% cholesterol and 42 g/L glucose/fructose in drinking water) for 52 weeks. Anatomorphological features, histological, biochemical and metabolic parameters were measured. Total RNA from liver tumors and surrounding non-tumorous areas (n = 3) was extracted and the transcriptomic and epigenetic profile were studied by ClarionS and miRNA4.0 arrays including > 22, 000 transcripts and > 3, 000 miRNAs (mature and pre-miRNA) (ThermoFisher, CA, USA). The interaction was evaluated by using TAC software (ThermoFisher, CA, USA).
Results: HFHCC diet induced NASH in mice, characterized by macro-microvesicular steatosis, inflammatory foci at lobular, portal and periductal levels, followed by presence of hepatocyte degeneration (ballooning) and moderate fibrosis. The model also showed a progressive increase in the hepatic, lipidic and glucidic parameters. Besides, we also detected several foci of cellular alterations in > 40% animals and nodules in >20%, which were classified into adenomas or well-differenciated HCC Gpc3+. The transcriptomic analysis of HCC showed up to 20 genes differentially expressed ($p < 1 \times 10^{-9}$; fold ± 2; FDR < 0.05) compared to the surrounding areas. Similarly, the epigenetic profile revealed 32 miRNAs with differences ($p < 0.01$; fold ± 2;FDR < 0.05). Finally, by analyzing the target gene prediction of miRNAs we could confirm the interactions miRNA-genes (miRNAome).
Conclusion: miRNAs modulate the expression a great number of genes at the time that one gene could be differentially expressed by the combined action of several miRNAs. Here, we associated the expression of potential markers such as Spink1 or Gpc3 to HCC, and hypothesize that both genes (Tstd1, Adck4) and miRNAs (miR-21a, miR-27a) could play a role in its development. By deciphering miRNAome in NAFLD-HCC patients new biomarkers and therapeutic target could be developed and detected.

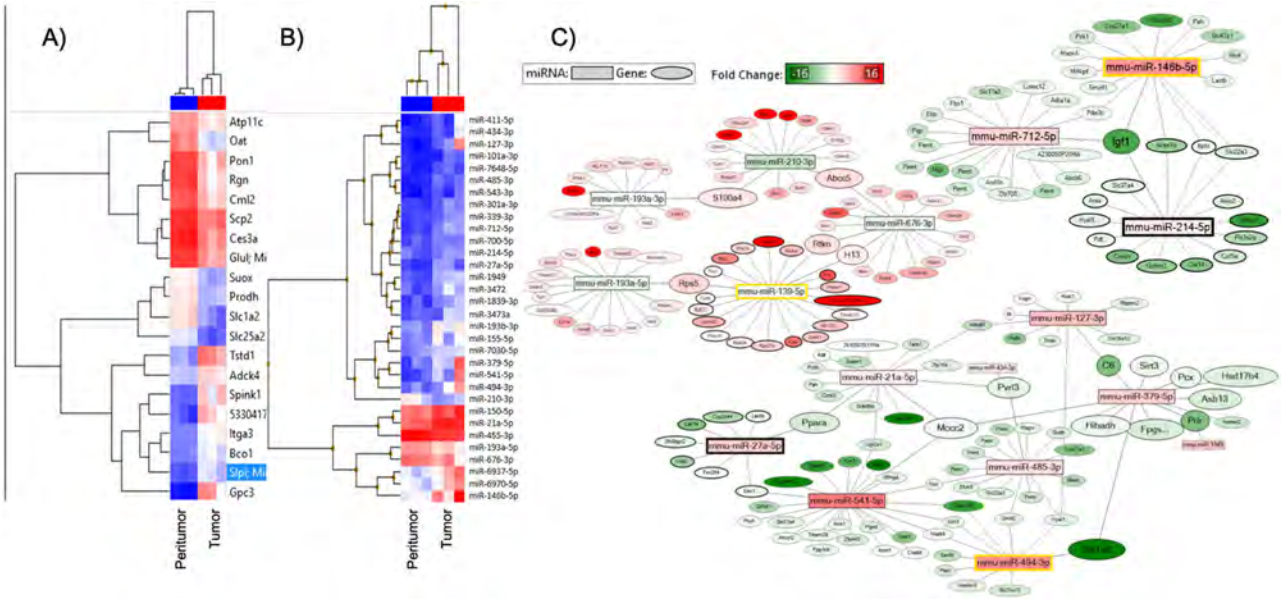

Figure: (abstract: THU-466)

THU-467

Comparison of the immune tumour microenvironment between primary and metastatic hepatocellular carcinoma: Implication for biomarker research of immunotherapy

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Background and aims: Biomarker research of immunotherapy for HCC is often hindered by availability of tumor samples and concerns of quality of archival samples. TME of different anatomical sites may differ in composition of immune cells or expression of immune-related genes and confound the analysis.
Method: Archival formalin-fixed paraffin embedded tumor samples were obtained from (1) HCC patients who underwent surgery for both the primary HCC and metastatic HCC to lungs; and (2) HCC patients who received anti-program cell death-1 (anti-PD1)-based immunotherapy for advanced/metastatic diseases. Expression of immune-related genes were measured by the Cancer Immune Panel (Nanostring). Composition of immune cells in TME was evaluated by multiplex immunofluorescence staining (OPAL 7, Perkin Elmer). The response to immunotherapy was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and a clinical benefit response (CBR) was defined as complete (CR) or partial response (PR) according to RECIST 1.1 or stable disease (SD) lasting for > 16 weeks.
Results: For the 31 patients who had adequate paired tumor samples for analysis (median age 50.5 years, male/female 27/4, duration between liver and lung tumor resection 0–80.9 months), the median Pearson's correlation coefficient of the immune gene expressions between the primary liver and metastatic lung tumors was 0.87 (range 0.39–0.96), suggesting that TME between liver and lung tumors was similar in most patients. The proportion of CD4+FoxP3+ T cells was significantly higher in lung (metastatic) vs. liver (primary) HCC (1.2 ± 1.9% vs. 0.3 ± 0.8%, p = 5.4e-5), whereas the proportions of other tumor-infiltrating immune cells were similar. For the 27 patients who received antiPD1-based immunotherapy (0 CR, 8 PR, 11 SD, 8 progressive disease), patients with CBR (n = 16) had significantly higher proportion of tumor infiltrating CD8 T cells (24.2 ± 16.4% vs. 7.9 ± 8.1%, p = 0.02) and a 2.3-fold increase in the expression score defined by genes associated with CD8 T cell exhaustion (LAG3, CD244, EOMES, PTGER4).
Conclusion: Archival tumor tissue may be used to identify CD8 T cell exhaustion in TME that may be associated with better efficacy of antiPD1-based immunotherapy in HCC. The similarity of TME between primary liver and metastatic lung HCC suggested that anatomical site may not be a critical confounding factor in biomarker exploration for HCC immunotherapy.

THU-468

SLU7 controls genome integrity: New role of truncated SRSF3 proteins

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Background and aims: The metabolic capacities of hepatocytes are maintained by the expression of a complement of genes that support hepatocellular differentiation and quiescence. However, the liver is endowed with an unparalleled regenerative capacity which entails hepatocellular proliferation while maintaining life-supporting metabolic functions. We previously identified the splicing regulator SLU7 as an essential gene in the maintenance of the quiescent, differentiated and metabolically functional liver. Importantly, SLU7 expression is reduced in the chronically injured human liver, and in hepatocellular carcinoma (HCC) cells and tissues. However, we also found that SLU7 expression was essential for the survival of HCC cells and this survival dependency on SLU7 was not observed in non-transformed hepatocytes. One major difference between transformed and normal cells is their proliferative activity, we have now further characterized the role of SLU7 in HCC cell cycle progression.

Method: Cell cycle analysis, detection of DNA:RNA hybrids (R-loops), sister chromatid cohesion analysis (SCC), RT-PCR, Western blot, IHQ, RNA-pull down, partial hepatectomy (PH).
Results: We found that SLU7 prevents the formation of R-loops and the generation of DNA damage and is required for the maintenance of SCC and progression through mitosis. We provide direct evidence demonstrating that SLU7 regulates the splicing and expression of sororin (CDC5A), a key gene in proper chromosome segregation. Mechanistically, these activities involve SLU7-mediated regulation of miR-17–92 and SRSF3 splicing to prevent the generation of aberrant truncated isoforms of SRSF3 (SRSF3-TR). In vivo we found that hepatocyte-specific knockdown of *Slu7* expression in mouse livers resulted in enhanced DNA damage and in impaired liver regeneration after PH. Importantly, SRSF3-TR isoforms are detected in the cirrhotic liver and in HCC.
Conclusion: We have gathered *in vitro* and *in vivo* evidence showing that SLU7 is essential for the preservation of chromosomal stability and DNA integrity during cell proliferation, as well as for mitotic progression. Our findings on reduced SLU7 expression in liver disease may contribute to understand the mechanisms of chromosomal instability, which is an early event in carcinogenesis. However, our findings also identify this splicing regulator as a new molecular target for HCC therapy, given its herein demonstrated key function in the mitotic progression of cancer cells.

THU-469

Nanoparticular bisphosphonate to selectively target and repolarize liver macrophages for efficient anti-tumour response

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Background and aims: Bisphosphonates, such as Alendronate (AL) or Zoledronate, were developed as anti-osteoporotic drugs that inhibit osteoclasts, a specialized population of macrophages. Prior studies suggested macrophage repolarizing and thus antitumor activity of zoledronate in rat hepatocellular carcinoma [J Transl Med. 2011, Zhou DY et al]. However, after oral or iv application, bisphosphonates rapidly bind to bone or are excreted by the kidneys. Therefore, we aimed to develop biodegradable and nontoxic nanogel particles (NP) with covalently linked Alendronate (AL-NP) that primarily home to the liver.
Method: NP with diameters below 100 nm were synthesized by controlled-radical polymerization combined with polymer-induced self-assembly and post-polymerization modification. Alendronate was efficiently incorporated by coupling its nonfunctional primary amine group to a squaric acid group of the NP to generate AL-NP.
Results: In M1/M2-polarized murine macrophages, unloaded NP did not show cytotoxicity even at high concentrations, while AL-NP induced a 50% reduction of cell viability at 1 mM AL loading, equal to free AL. Low concentrations of AL-NP (30, 60 µM Alendronate) repolarized putative profibrotic and cancer promoting M2-polarized bone-marrow derived macrophages towards anti-fibrotic and anti-tumorous M1 macrophages, increasing their expression of TNF-a and Interferon-g and decreasing CD206 (mannose receptor), as determined on the transcript and protein level via qPCR and FACS analysis. AL-NP repolarized macrophages more efficiently as equal doses of free AL, while NP alone had no effect. After intravenous injection in healthy Balb/c mice, more than 80% of near-infrared fluorescence labeled CS800-AL-NP rapidly accumulated in the liver, whereas CS800 labeled AL was readily cleared via the kidneys. CS800-AL-NP were effectively taken up by CD45+ F4/80+ CD11b+ liver macrophages (>90%), CD31+ endothelial cells (>40%), albumin+ hepatocytes (>40%), CD90+/TH1 portal myofibroblasts (>40%), NK1.1+ NKT cells (>90%), CD11c+ dendritic cells (>40%) and to a minor degree in CD3+ T-cells (< 10%), as determined by flow cytometry. CS800-AL-NP were well tolerated and showed no toxicity at high concentrations up to

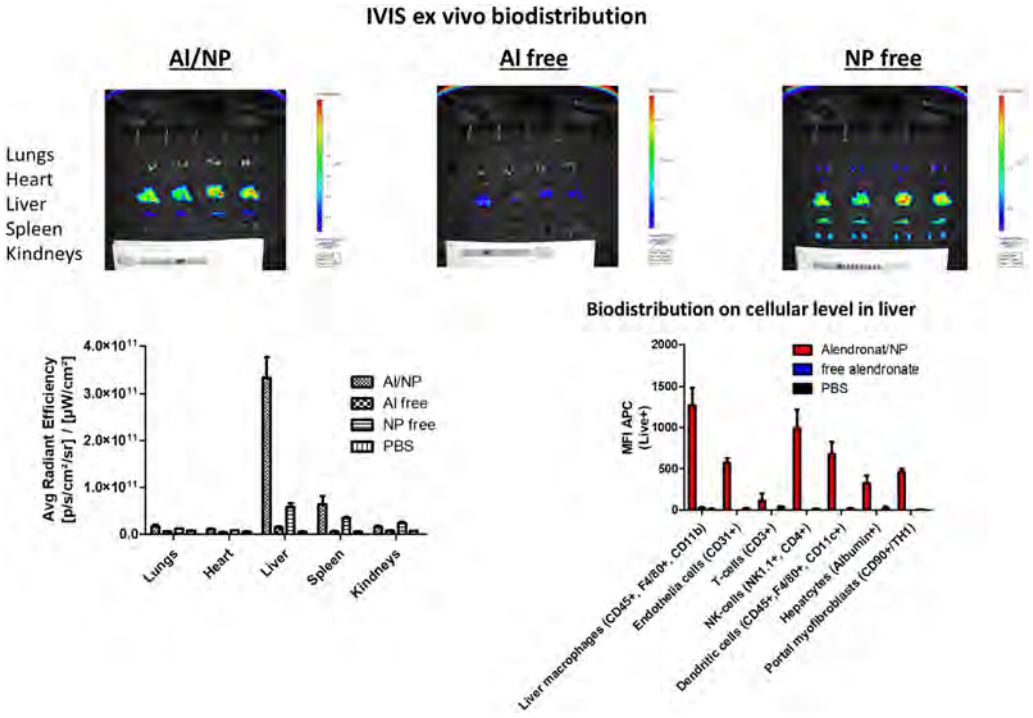

Figure: (abstract: THU-469): Biodistribution of AL/NP on macroscopic and cellular level

12.5 mg/kg AL as assessed-histology and by routine blood tests for liver/renal toxicity.
Conclusion: We have designed AL-NP as novel biocompatible nanocarriers for the bisphosphonate AL. Nanocarrier-coupled AL was almost exclusively sequestered by the liver and showed promising repolarizing effects on M2-type primary macrophages, shifting their cytokine levels towards a putative anti-fibrotic and anti-tumor M1 phenotype. CS800-AL-NP were efficiently taken up by liver macrophages, endothelial, fibroblastic and parenchymal cells, NKT cells, dendritic cells but not by T cells.

THU-470

The mRNA-binding protein tristetraprolin promotes hepatocarcinogenesis but inhibits tumour progression in liver cancer

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Background and aims: The RNA-binding protein (RBP) tristetraprolin (TTP/*ZFP36*) has been shown to be downregulated in several cancer types but has also been described to promote metabolic disturbances. Since HCC frequently develops within metabolically disturbed livers, we aimed to elucidate the effect of TTP on liver carcinogenesis and tumor progression. Using a liver-specific *Ttp* knockout mouse model (ls*Ttp*-KO) and *in vitro* TTP overexpression, tumour initiation and progression were analysed in order to elucidate the mechanistic role of TTP in HCC.
Methods: TTP expression was analysed in three large human data sets (TCGA and GEO) comprising almost 400 samples. Effects tumour initiation, inflammation, and hepatic lipids were determined in ls*Ttp*-KO mice *via* HE staining, flow cytometry, and GC-MS. Effects of TTP overexpression was analysed *via* MTT-assay (chemosensitivity), scratch assay (migration), flow cytometry (proliferation), and qPCR (TTP target identification) in HepG2, PLC/PRF/5, and Huh7 cells.
Results: *ZFP36* expression was downregulated in tumour samples compared to non-tumour or cirrhotic tissue in all three of the analysed large human data sets. ls*Ttp*-KO mice had a significantly decreased tumour burden upon treatment with the carcinogen diethylnitrosamine (DEN). No difference was observed between wild-type and ls*Ttp*-KO animals regarding DEN-induced changes in hepatic leukocyte numbers ($CD45^+$). DEN short-term treatment led to an increase of hepatic fatty acids, which was almost abrogated in the DEN-treated ls*Ttp*-KO mice. In the long-term DEN model no difference between the genotypes was observed in the DEN-treated group, but within the control group ls*Ttp*-KO showed elevated levels of saturated and monounsaturated fatty acids. Regarding chemosensitivity only a minor effect of TTP overexpression was observed in Huh7 cells. However, TTP overexpression distinctly decreased migration ability in PLC/PRF/5 and Huh7 cells, and proliferation in HepG2, PLC/PRF/5, and Huh7. Several oncogenes were downregulated in TTP-overexpressing HCC cells, e.g. B-cell lymphoma 2 (*BCL2*), c-Myc (*MYC*), and vascular endothelial growth factor A (*VEGFA*).
Conclusion: Our data suggest that hepatocytic TTP promotes hepatocarcinogenesis, while it shows tumour-suppressive actions in hepatic tumour progression.

THU-471

Establishment of a short-termed orthotopic transplantation model in C57/B6 mice that recapitulates characteristic features of human intrahepatic cholangiocarcinoma

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Background and aims: Intrahepatic cholangiocarcinoma (ICC) is a highly aggressive cancer ranking the second most common liver cancer worldwide and is associated with very poor prognosis and limited treatment options. To identify and understand molecular mechanisms of the rise and progression of cholangiocarcinoma animal models that recapitulate human disease are needed. Until today only few allograft or xenograft transplant ICC models that claim challenging operative techniques or longer time periods for tumor development are available. Here we present a murine orthotopic transplant model on B6 background resulting in ICCs with high molecular homology to human ICC within two to four weeks.
Method: 6–8 weeks old C57/B6 male mice were injected with $2^{*}10^{6}$ Hep55.1C cells in the left liver lobe and tumor growth was followed by weekly ultrasound. Mice were sacrificed after two and four weeks after cell injection. Immunohistological liver stainings were performed to determine protein expression of cholangiocyte and hepatocyte markers. mRNA sequencing and qPCR was performed to analyze gene expression of tumor and surrounding tissue. Intrahepatic as well as systemic immune response was characterized by flow cytometry analysis.
Results: Mice developed liver tumors after two or four weeks of Hep55.1C cell transplantation with a 100% incidence. Tumors had a size of 0.6cm² or 1cm² on average and showed features of highly differentiated biliary adenocarcinomas with tubular structures. Immunohistological stainings revealed a ubiquitous signal for pan-cytokeratin within tumor tissue with a loss of HNF4α expressing highlighting the ICC phenotype of the tumors. Supportively, real-time PCR analysis showed high expression of cholangiocyte markers (CK7, CK19, SOX9) but not of hepatocyte (HNF4 α, transthyretin) or hepatocellular carcinoma markers (α-Fetoprotein, albumin) in tumor tissue. Characterization of intrahepatic cell composition by flow cytometry displayed an induction of both innate and adaptive immune response as reflected by an increase of neutrophils, B-cells, and myeloid cells in the tumor tissue after two weeks. Surprisingly, this effect was partially reversed after four weeks following transplantation. Moreover, comparing transcriptomic analysis following RNA sequencing of tumor tissue from our mouse model with published data sets from human ICC tissue using gene set enrichment analysis, we were able to identify high similarities between our model and human ICC.
Conclusion: Here we present a highly reproducible ICC mouse model characterized by two advantages from the experimental point of view: 100% success rate of tumor induction with fast progression and

characteristic molecular features of human ICC. Our model is therefore most suitable to define and evaluate interventional therapies in ICC.

THU-472

Pharmacological inhibition of PIM1 suppresses tumor progression and enhances chemosensitivity in hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is a common and aggressive malignancy worldwide. Targeted therapies provide new strategic treatment options for HCC. PIM1, a serine/threonine kinase, is upregulated in the hypoxic microenvironment of HCC and promotes tumor progression through regulating glycolysis. In the current study, we will evaluate the preclinical efficacy of targeting PIM1 by specific inhibitor in vitro and in vivo.
Method: PIM kinase inhibitor 1SGI-1776 was used to treat HCC cell lines including MHCC97L and Huh7. Altered expression of downstream targets of PIM 1 was confirmed by western blotting. IC50 was determined by MTT assay. Cell proliferation, cell motility and matrigel invasion assays were employed to study the effects of proliferation and metastasis upon altered PIM1 functions. Glucose uptake assay and apoptosis assay with Annexin V/PI staining were carried out to examine the effects of glucose uptake and chemosensitivity, respectively. In vivo tumor growth was investigated by a subcutaneous injection model using MHCC97L cells coupled with inhibitor treatment by oral lavage.
Results: Treatment of HCC cells with SGI-1776 resulted in a concentration-dependent reduction in cell proliferation, migration and invasion. SGI-1776 treatment also sensitized HCC cells to cisplatin and suppressed PKM2 and glucose uptake in vitro. In vivo tumor growth was suppressed upon administration of SGI-1776.
Conclusion: Targeting PIM1 by PIM inhibitor demonstrates efficacy in suppressing HCC progression, hampering glucose metabolism, and enhancing chemosensitivity of HCC cells. It is a potential targeted therapy for HCC.

THU-473

Role of intracellular lysyl oxidase in progression of primary liver cancer

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Background and aims: Lysyl oxidases (LOX) are a family of extracellular proteins involved in collagen and elastin crosslinking causing stiffening and modulation of the extracellular matrix (ECM). LOX genes have been shown to play both tumour promoting and suppressive roles, but function of intracellular LOX in primary liver cancer (PLC) is largely unknown.
Method: To evaluate the expression of LOX, we have analysed the transcriptomes from 158 intrahepatic cholangiocarcinoma (iCCA), 53 hepatocellular carcinoma (HCC) and 197 matched surrounding liver (SL) tissues. Data was confirmed using TCGA (CHOL and LIHC) and correlated with clinical features. Microdissection of intra-tumour stroma and epithelium compartments in CCA (n = 23) and HCC (n = 8) was used to generate a stromal signature and in cellular deconvolution with CIBERSORT. LOX gene and protein expression was measured in tumours, primary and established cell lines (HCC = 17, iCCA = 11), hepatic stellate cells (HSC), and cancer associated fibroblasts (CAFs). Functional analysis was performed on cells exposed to recombinant LOX (rLOX), CAF and HSC conditioned media (CM) and LOX inhibitor (BAPN). LOX immunoprecipitation (IP) followed by mass-spectrometry (MS) was used to identify novel interaction partners.
Results: LOX is significantly overexpressed in PLCs compared to SL (HCC; $P = 0.005$, iCCA; $P < 0.0001$) and high expression of LOX is associated with poor survival (HCC; $P = 0.035$, iCCA; $P = 0.017$). Analysis of tumour stromal and epithelial compartments showed a significant correlation of LOX expression with stroma in both iCCA ($p < 0.0001$, $r = 0.5$) and HCC ($p < 0.0001$, $r = 0.75$). In normal murine liver, LOX is predominantly expressed by HPCs compared to hepatocytes, cholangiocytes and Kupffer cells ($p < 0.0001$). Similar, human hepatic CAFs and HPCs express significantly higher levels of LOX compared to PLC cells ($p < 0.0001$). Immunohistochemical staining of LOX in tumour tissue showed high abundance in cancer cells contrary to mRNA expression in cell lines, suggesting it can have extracellular origin. LOX-negative cells challenged by CM or rLOX showed an intracellular location (including in the nucleus), suggesting its functional role beyond ECM organization. LOX IP followed by MS identified LOX binding partners in both nuclear and cytoplasmic components in rLOX-treated cancer cells. Using BAPN to inhibit LOX resulted in a reduced stromal cells proliferation.
Conclusion: We have shown in PLC that increased expression of LOX is driven by CAFs and associated with diminished survival. Nuclear location of tumour-specific LOX can be mimicked by exposing primary cancer cells with CM or rLOX, suggesting LOX may play important roles in tumour progression beyond collagen crosslinking. LOX may present a putative target in treating PLC.

THU-474

Existence of intratumoral teriary lymphoid structures predicts better prognosis in Barcelona clinic of liver cancer stage 0-a hepatocellular carcinoma

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Background and aims: Tumor-associated tertiary lymphoid structures (TLS) are associated with favorable clinical outcomes in various solid tumors. However, their prognostic value in hepatocellular carcinoma (HCC) remain controversial. This study aimed to investigate clinical relevance of intratumoral TLS in HCC patients treated by surgical resection.
Method: Tissue arrays and immunohistochemistry were used to evaluate the existence and degree of TLS in specimens from a total of 303 HCC patients. Clinical relevance of intratumoral TLS was investigated in patients with Barcelona Clinic of Liver Cancer stage 0-A HCC. The results were verified in a public data set and an independent cohort of 149 patients with early stage HCC.
Results: TLS were identified in 102 (33.7%) cases after pathological reviewing, among which 83 (27.4%) and 19 (6.3%) cases were lymphoid aggregated and lymphoid follicles, respectively. No correlation was detected between existence of intratumoral TLS and overall survival ($p = 0.088$) as well as late tumor recurrence ($p = 0.308$), whereas a significant positive association was found between TLS and early relapse ($p = 0.004$). Univariate and multivariate

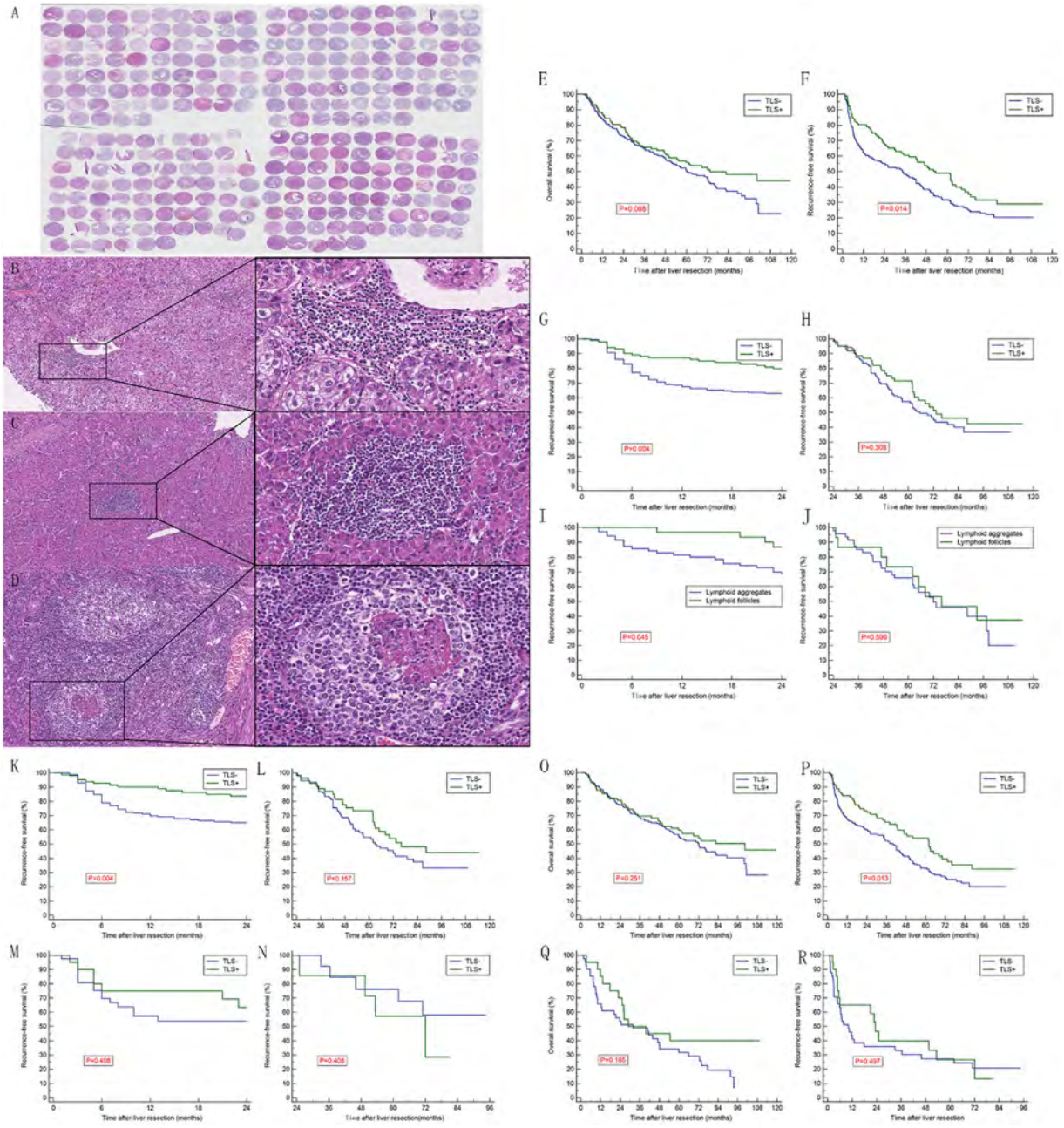

Figure: (abstract: THU-474): Characterization of tertiary lymphoid structures within hepatocellular carcinoma (A-D); Clinical relevance of intratumoral tertiary lymphoid structures in 303 patients with hepatocellular carcinoma (E-F); Association between intratumoral tertiary lymphoid structures and tumor relapse (G-J); Association between intratumoral tertiary lymphoid structures and tumor relapse for HCC patients with different tumor stages (K-N); Association between intratumoral tertiary lymphoid structures and tumor relapse for HCC patients with different tumor stages (O-R).

analyses identified TLS as a favorable factor for early tumor relapse (hazard ratio, HR = 0.501, P = 0.005). Patients with more mature TLS were associated with better clinical outcomes (p = 0.045). Importantly, the prognostic value of TLS was limited to BCLC stage 0-A HCC (p = 0.004), other than more advanced tumor (p = 0.408).
Conclusion: Our study suggested that the existence of intratumoral TLS was associated with a decreased risk of early tumor relapse for patients with BCLC stage 0-A HCC. TLS-targeted immune-modulating therapies might be potential strategies for effective immune-mediated tumor control.

THU-475

CENPF translocation for autoantigen presentation and autoimmune activation in hepatocellular carcinoma

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Background and aims: Tumor-associated antigen autoantibodies have advantages in early diagnosis of tumor. We have screened out CENPF autoantibody with high sensitivity and specificity in early hepatocellular carcinoma (HCC) diagnosis, but the mechanism of CENPF induced autoimmune activation and autoantibody production

is unclear. We found it might be associated with abnormal expression and localization of CENPF and cell apoptosis. We undertook this study to reveal the mechanism of CENPF antigen exposure and autoantibody production.

Method: The expression levels of CENPF in HCC cell lines, normal liver cell, tumor tissue and adjacent normal tissue were analyzed by real-time PCR and Western blot. The autoantibody level induced by HCC cells with different CENPF expression was assayed in tumor mouse model. The cellular localization of CENPF in HCC cells and normal liver cell was analyzed using confocal microscopy. By ELISA method, we assayed the secretion of CENPF into intercellular space in tumor tissue and adjacent normal tissue. After cell apoptosis induction, we studied the translocation and localization of CENPF by confocal microscopy and flow cytometry. The phagocytosis of apoptotic bodies and blebs by DC cells was analyzed by confocal microscopy.

Results: CENPF was overexpressed in HCC as compared with non-tumor cell or tissue. Highly expressed CENPF induced more autoantibody production in tumor mouse. Overexpressed expressed CENPF distributed in both nucleus and cytoplasm of HCC cells, whereas in normal liver cell CENPF mainly localized in the nucleus of dividing cell. In tumor tissue and adjacent normal tissue, no significant difference was seen in secretion of CENPF into intercellular space. The cell membrane expression level of CENPF was in direct proportion to cell apoptosis rate and was independent with cell necrosis. During apoptosis, apoptotic blebs were formed and CENPF was translocated from apoptotic cell bodies to apoptotic blebs. Apoptotic blebs and bodies seemed to be a preferred target of DC phagocytosis.

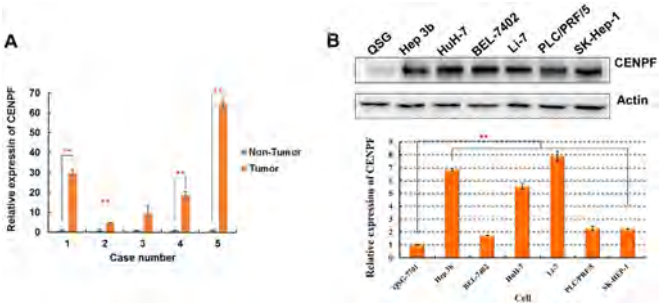

Figure 1: CENPF was overexpressed in HCC as compared with non-tumor tissue (A) or cells (B).

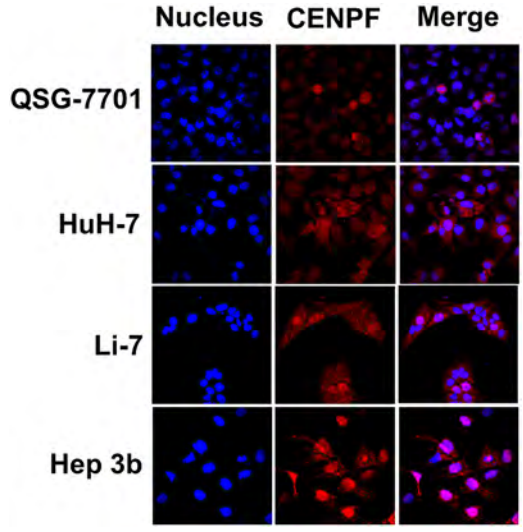

Figure 2: The distribution of CENPF in HCC cells HuH-7, Li-7, Hep 3b, and normal liver cell QSG-7701.

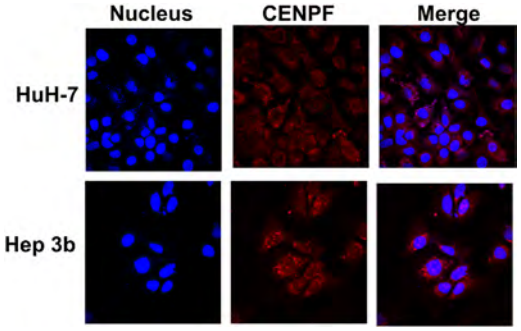

Figure 3: apoptotic blebs were formed and CENPF was translocated from apoptotic cell bodies to apoptotic blebs.

Conclusion: The overexpressed and abnormal localization of CENPF in HCC were key factors in autoantibody generation. Cell apoptosis induced the subcellular translocation and surface exposure of CENPF antigen, thus might result in antigen capture and autoantibody production.

THU-476

Modeling cancer stem cell and differentiated cancer cell phenotypes in liver cancer organoids

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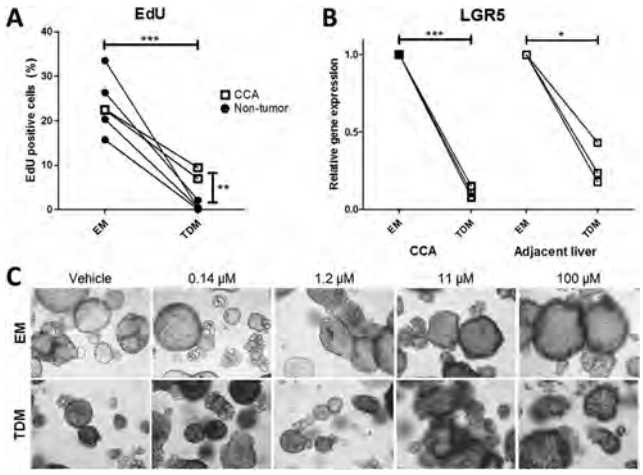
Background and aims: Cholangiocarcinoma (CCA) is a biliary-type liver tumor with a dismal prognosis, due to late diagnosis, high chemo-resistance and tumor heterogeneity. Recently, we established long-term 3D CCA organoids which retain the histological architecture, gene expression profile and genomic landscape of the original tumor and are amenable to drug screening approaches. Due to the stem cell characteristics of organoids, CCA organoids represent a cancer stem cell (CSC)-like phenotype. CSC's are known to be resistant to chemo- and radiation therapy. However, the bulk of cancer cells in a tumor have a differentiated (non-stem cell) phenotype and are more therapy-sensitive. The aim of our study is to establish a model to study both the CSC and differentiated cancer cell phenotypes in CCA organoids and apply this in drug sensitivity screening.

Method: Organoids from CCA, non-tumorous adjacent liver and healthy liver tissue (all n = 3–6) were differentiated by blocking cancer stem cell signaling pathways. At day 5, cell viability, proliferation, cell death and differentiation potential was tested on gene expression (qPCR) and protein (immunohistochemistry) level and compared to CSC-like organoids. Drug sensitivity of differentiated and CSC-like CCA organoids was tested with sorafenib.

Results: Live/dead staining revealed that the level of cell death in differentiated organoids was similar to CSC-type cultures. Differentiated CCA organoids had a reduced proliferative rate, as demonstrated by reduced EdU incorporation (fig. A) and down-regulation of Ki67 gene expression ($p < 0.001$). Even though proliferation is inhibited, metabolic activity was stable, indicating a higher metabolic activity per differentiated cell. Gene expression analysis showed that known CSC markers LGR5 (fig. B), CD44 ($p = 0.01$) and CD133 ($p < 0.01$) were downregulated upon differentiation. Preliminary results from a drug sensitivity assay suggested that differentiation of CCA organoids increased their sensitivity to sorafenib (fig. C).



Conclusion: This study shows that it is feasible to differentiate liver tumor-derived organoids from a CSC-like phenotype towards a differentiated cancer cell phenotype. Differentiated CCA organoids are less proliferative, downregulate CSC markers and are more sensitive to sorafenib. More elaborate drug screenings are ongoing in order to more accurately identify effective compounds to treat CCA.

THU-477

Sumoylation/acetylation drives forward oncogenic role of LKB1 in Liver

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Background and aims: In contrast with the commonly accepted model that describes Liver kinase B1 (LKB1) as a tumor suppressor in a wide variety of tissues, our group and also others have reported its oncogenic role in the liver. Indeed, LKB1 aberrant expression is associated with low survival in hepatocellular carcinoma (HCC) by unknown mechanisms.
SUMOylation is a reversible post-translational modification (PTM) with a crucial role on the control of nucleocytoplasmic signaling and transport of its target proteins. Even though loss-of-function mutations in components of the SUMO pathway are rare due to the fact that SUMOylation is an essential process to cells, expression of the SUMO E2 conjugating enzyme (UBC9) and other E3 SUMO-protein ligases are found to be upregulated and related to poor prognosis in HCC. In this work, we have explored the mechanism underlying the oncogenic behavior of LKB1 in HCC. New insights of SUMOylation/acetylation in LKB1 regulation are discussed in the context of tumor driver *vs* tumor suppressor in the liver.
Method: To address this, we have overexpressed LKB1 in human hepatoma cells and by using histidine pull-down assay we have investigated the role of the hypoxia-related SUMOylation/acetylation in the regulation of LKB1 oncogenic role. High affinity SUMO binding entities-based technology has been used to validate our findings in an in vivo pre-clinical mouse model and in liver cancer patients. Finally, we have performed a molecular modeling between SUMOylated LKB1 and its formal interactors STe20-Related ADaptor (STRADα) cofactor involved in the regulation of LKB1 nucleocytoplasmic shuttling and its activity.
Results: In human hepatoma cells under hypoxic stress, LKB1 overexpression induces deregulated cell growth and changes in its cellular localization. By using site-directed mutagenesis, we have shown that SUMO-2 LKB1 at Lys178 is the responsible to hamper LKB1 nucleocytoplasmic shuttling and fuel hepatoma cell growth. Importantly, we have identified that acetylation at Lys48 is required by LKB1 SUMOylation. Molecular modelling of SUMO modified LKB1 further confirmed steric impedance between SUMOylated LKB1 and the STe20-Related ADaptor cofactor, involved in LKB1 export from the nucleus. Finally, we provide evidence that endogenous LKB1 is modified by SUMO/acetylation in preclinical mouse models of HCC, complemented with clinical HCC biopsies.
Conclusion: In conclusion, we have shown that SUMO-2 modifications of LKB1 at Lys178 after its acetylation at Lys48 occur in human hepatoma cells and HCC, thus inhibiting the binding of LKB1 to STRADα and hampering its nucleocytoplasmic shuttling. The nuclear localization of LKB1 by SUMO modification is the main and differential driver of its oncogenic role in liver.

THU-478

CXCL5 induced by transforming growth factor-beta and Axl signalling causes neutrophil extracellular trap formation in hepatocellular carcinoma

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Background and aims: Transforming growth factor (TGF)-beta and the receptor tyrosine kinase Axl that is activated by its ligand Gas6 are crucially involved in the development of hepatocellular carcinoma (HCC). Gas6/Axl interacts with 14-3-3-zeta to aberrantly activate TGF-beta/Smad3 linker region at serine 213 via c-Jun N-terminal kinase, causing the activation of pro-metastatic genes and autocrine TGF-beta signaling. In addition, the synergy of TGF-beta and Gas6/Axl induces the expression and secretion of CXCL5. Notably, CXCL5 is almost exclusively expressed in TGF-beta-positive HCC patients, correlating with neutrophil infiltration into the HCC microenvironment and poor patient survival. In this study, we aimed at investigating the TGF-beta/Axl/CXCL5-dependent attraction and activation of neutrophils.
Method: We employed human HCC models upregulating CXCL5 in response to long-term TGF-beta exposure. TCGA datasets of HCC patients (n = 400) were analyzed in tumor-, stroma- and immune-compartments by in silico microdissection. Formation of neutrophil extracellular traps (NETs) was studied by confocal immunofluorescence analysis and enzyme-linked immunosorbent assays by detecting citrullinated histone 3 (cit-H3) and neutrophil-specific enzymes. Inhibition of Axl and TGF-beta signaling in HCC cells was performed by pharmacological intervention, CRISPR/Cas9 genomic editing and RNA interference.
Results: The analysis of novel TCGA datasets revealed upregulation of CXCL5 in a large HCC patient cohort expressing Axl and TGF-beta. Loss of either Axl or TGF-beta signaling in human HCC cells abrogated CXCL5-dependent migration and attraction of neutrophils. Co-cultivation of CXCL5-secreting HCC cells with neutrophils induced NET formation as detected by the release of DNA associated with cit-H3 and neutrophil elastase as well as by the release of neutrophil DNA linked to myeloperoxidase. NET formation induced by the exposure of neutrophils to supernatants of CXCL5-positive HCC cells was

diminished by treatment with neutralizing CXCL5 antibody. Pharmacological or genetic inhibition of either TGF-beta/Smad or Axl signaling reduced NET formation, suggesting that Axl/TGF-beta is essentially involved in regulating the immunophenotype. In HCC patient samples Axl, TGF-beta and CXCL5 expression correlated with neutrophil infiltration and NET formation.
Conclusion: The molecular collaboration between TGF-beta and Axl induces the CXCL5-dependent NET formation in HCC. Disruption of TGF-beta/Axl/CXCL5 signaling provides a promising therapeutic strategy to interfere with HCC progression in TGF-beta-positive patients.

THU-479
The hepatocyte specific role of the NRF2/KEAP1 axis for HCC Progression during chronic liver disease

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Background and aims: Hepatocellular carcinoma (HCC) occurs as a consequence of malignant transformation of hepatocytes frequently triggered during chronic inflammation and consecutive liver fibrosis. Oxidative stress has been considered as a conjoint pathological mechanism, and it contributes to initiation and progression of liver injury. The KEAP1 (Kelch-like ECH-associated protein-1)/NRF2 (erythroid 2-related factor 2) axis is a major regulator system of cellular redox balance. We investigated whether activation of the NRF2 pathway, by inactivation of the negative regulator KEAP1, affects the development of liver injury, fibrogenesis and HCC development.
Method: Hepatocyte specific NEMO ($NEMO^{\Delta hepa}$) knockout- mice were crossed with hepatocyte specific KEAP1 ($KEAP1^{\Delta hepa}$) knock-out mice to generate $NEMO^{\Delta hepa}$/$KEAP1^{\Delta hepa}$ mice. Primary hepatocytes as well as liver were subjected to microarray analysis. Furthermore, liver injury, DNA damage, proliferation as well as liver fibrogenesis and HCC development were analysed.
Results: Microarray analysis of primary hepatocytes of $NEMO^{\Delta hepa}$ and $NEMO^{\Delta hepa}$/$KEAP1^{\Delta hepa}$ and their controls revealed that particularly two signalling pathways were differentially regulated. Hepatocyte specific KEAP1 deletion upregulated genes involved in glutathione metabolism and xenobiotic stress (e.g. HO-2, Nqo1). Secondary, genes involved in cell cycle regulation and DNA replication were dramatically downregulated in $NEMO^{\Delta hepa}$/$KEAP1^{\Delta hepa}$ compared to $NEMO^{\Delta hepa}$ primary hepatocytes.
Accordingly, 8-week old $NEMO^{\Delta hepa}$/$KEAP1^{\Delta hepa}$ mice showed significantly elevated hepatic GSH levels and genes involved in the oxidative stress response compared to $NEMO^{\Delta hepa}$ mice. Furthermore, deletion of KEAP1 in $NEMO^{\Delta hepa}$ mice resulted in reduced apoptosis, proliferation and DNA damage. Subsequently, $NEMO^{\Delta hepa}$/$KEAP1^{\Delta hepa}$ mice displayed decreased fibrogenesis and in late disease stage a lower tumour incidence, a reduced tumour number and decreased tumour size.
Conclusion: Hepatocyte specific inactivation of KEAP1 in $NEMO^{\Delta hepa}$ livers attenuated apoptosis, DNA damage and hepatic fibrosis progression. Consequently, deletion of KEAP1 in $NEMO^{\Delta hepa}$ mice ameliorated HCC progression. Hence, KEAP1 is an attractive target to treat chronic liver disease.

THU-480
Imaging mechanical stiffness and molecular landscapes of cancer stem cell niches in human hepatocellular carcinomas

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Background and aims: Hepatocellular carcinoma (HCC) is the 3rd cause of cancer death worldwide and its heterogeneity challenges patient management. HCC heterogeneity distributes across a continuum of decreasing tumour differentiation and increasing proliferation. Proliferative-type HCCs exhibit a rich extracellular matrix (ECM) network, cancer cell plasticity and clinically aggressive stem/progenitor cells. These features are histologically observed as ECM-rich hotspots embedding cancer stem/progenitor cells. They are called "fibrous nests." The aim of this work is to image and model the plasticity of ECM and cancer cells and to obtain a dynamic picture of the mechanical forces in tumour tissues. In fibrous nests, cancer cells may be arranged as "Indian files" aligned along collagen fibres and myofibroblasts. This alignment may involve ECM-cell interactions and mechanical forces affecting cell fate through 3-dimensional ordering of collagen fibrils.
Method: we applied second harmonic generation (SHG), which is very performant for imaging human liver fibrosis, and two-photon-excited fluorescence microscopy (TPM), which combines SHG with fluorescence immunodetection. By Polarization-dependence SHG, the geometric organization of collagen fibrils can be studied and correlated to ECM stiffness. Then, we *in vitro* modelled fibre alignment in Huh-7 human liver cancer cells cultured in collagen matrices of varying mechanical properties.
Results: CD44, HAPLN1 and LGR5 (+) cancer stem/progenitor cells and ACTA2 (+) myofibroblasts were aligned along collagen fibres in human HCCs. By SHG combined with TPM, we co-localized collagen fibres with CD44 (+) cancer stem/progenitor cells and ACTA2 (+) myofibroblasts. The number of collagen pixels and the rates of fibre alignment were higher in high-grade than in low-grade fibrous nests. Fibre alignment rates related to ECM stiffness were then modelled *in vitro* in Huh-7 human liver cancer cells cultured in collagen matrices of varying mechanical properties. In these in vitro models, TPM and SHG showed that the longitudinal axis of tumour cells aligned parallel to collagen fibres, reproducing "Indian files."
Conclusion: cancer cell invasion along oriented collagen fibres seems to be a general mechanism whereby tumour cells make up the trails along which they infiltrate. These tools will allow further studies on the molecular landscapes and signalling pathways underlying mechanical forces in human HCC fibrous nests.

THU-481
Classification of intrahepatic cholangiocarcinoma microenvironment based on immune cell and tumor stromal features

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Background and aims: Intrahepatic cholangiocarcinoma (ICC) is characterized by an abundant stroma. Different components of the tumor microenvironment (TME) have been correlated with poor outcomes of patients. However, there are no systemic histological classifications for ICC stroma applied in daily practice. Here we classified stroma of ICC into four histological subtypes (early, activated, mature or inflammatory stroma) using formalin-fixed and paraffin-embedded samples and correlated with its pathology features.
Method: A total of 60 primary mass forming ICCs treated by resection were collected. Components of tumor microenvironment including tumor-infiltrating lymphocytes (TILs), cancer-associated fibroblasts

(CAFs, classified as normal or activated) and tumor fibrosis were evaluated, based mainly on routine staining methods. Immunohistochemistry stains detecting alpha-smooth muscle actin (α SMA), CD3 and CD276 were performed to support histological evaluation. Areas of the stromal subtypes in each tumor were separately evaluated and the prominent component (≥ 50% stroma area) was considered as the final stromal type of each case. The number of CD3 positive lymphocytes were counted and TILs were analysed at the invasive margin (IM) and tumor center (TC) using standardized assessment methods.

Results: ICC cases with activated, early, mature and inflammatory stroma accounted for 53.3%, 23.3%, 18.3%, and 5%, respectively. The early subtype was characterized by a loose stroma with low fibrotic and CAFs densities; activated stroma had a high number of activated CAFs; mature stroma consisted of high collagen density and low number of CAFs while inflammatory stroma contained prominent and diffuse lymphocyte infiltration. ICCs with activated stroma were associated with higher frequency of vascular invasion (29/32 cases), compared to those with early stroma (7/14 cases), mature stroma (6/11 cases), and inflammatory stroma (1/3 case) ($p = 0.004$). However, ICC showed widely intratumoral stromal diversity including differences in the numbers, distribution, and components of inflammatory infiltration. The infiltration of lymphocytes was mainly found at the invasive margin of ICCs with mature or activated stroma. The mean percentages of TILs (40%, 12%, 8%, and 5%) and mean number of CD3 positive lymphocytes (122, 40, 28 and 6 cells/mm^2) at the TC, but not at IM, showed significant difference among stromal subtypes (inflammatory, activated, early and mature stroma, respectively, $p = 0.02$). Furthermore, activated stroma was associated with large bile duct histological type. CD276 expression was found on activated stroma of 20/27 (74%) ICC cases, but not on background liver.

Conclusion: We have identified four stromal subtypes of ICC correlated with histological subtypes, tumor invasion and tumor immune features, which may be useful to predict patient outcomes.

THU-482

A human anti-MICA/B antibody boost NK cell responses in hepatocellular carcinoma

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Background and Aims. Natural Killer (NK) cells play a key role in tumor immunity, their function being tightly regulated by NK receptors and their ligands. Current evidence indicates that hepatocellular carcinoma (HCC) cells express several NKG2D ligands, including major histocompatibility complex class I chain-related protein A and B (MICA/B). We investigated whether a human anti-MICA/B monoclonal antibody (mAb) and *in vitro* treatment with drugs able to enhance MICA/B expression on tumor cells could boost NK cell responses toward HCC cells.

Method: Peripheral blood mononuclear cells (PBMC) were obtained from healthy donors (HD) or HCC patients. Liver-infiltrating lymphocytes were simultaneously obtained from tumorous (TIL) and surrounding non-tumorous (LIL) tissue by mechanical and enzymatic treatment. NK cell degranulation was assayed after coculture of unstimulated or IL15-stimulated PBMC, LIL or TIL with Huh7.5 or primary HCC cells. MICA/B expression on target cells was examined before and after bortezomib or gemcitabine treatment. Antibody-dependent cellular cytotoxicity (ADCC) was assayed by 7-aminoactinomycin D (7-AAD) release from target cells in the presence of a humanized MICA/B-specific mAb.

Results: Anti-MICA/B mAb significantly enhanced degranulation of circulating NK cells toward Huh7.5 cells in HD. Similar results were obtained when Huh7.5 cells were treated with gemcitabine or bortezomib that were shown to induce MICA/B expression. Similar findings were observed with circulating NK cells from HD and HCC subjects using primary HCC cells as target. Interestingly, TIL, but not LIL, showed increased degranulation for autologous untreated HCC cells. However, when anti-MICA/B was tested for its ability to mediate ADCC toward primary HCC cells, significantly increased 7-AAD release was found in HD only, in agreement with reduced CD16 receptor expression on patients' circulating and intra-hepatic NK cells.

Conclusion: A MICA/B-specific mAb significantly increased peripheral and tumor-infiltrating NK cell degranulation in HCC patients. Moreover, the same mAb was able to promote significant ADCC by HD NK cells for primary HCC cells, suggesting a possible use in immunotherapy for primary liver cancer based on allogeneic NK cell infusion.

THU-483

Blood based weighted gene co-expression network analysis identifies miRNA prognostic biomarkers for HCC

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Background and aims: Hepatocellular Carcinoma (HCC) ranks fifth as most common cause of cancer related death worldwide. Although treatment options have improved in the past 30 years, prognosis remains unsatisfactory. The lack of effective outcome prediction models prevent the opportunity for individualized treatment protocols. The potential role of microRNAs (miRNA) as prognostic biomarker has witnessed an increasing interest, owing to the non-invasive nature of miRNA-based screening assays. In this study, we used the weighted miRNA co-expression network analysis (WGCNA) to identify circulating miRNA clusters and miRNA candidates as predictive biomarkers for therapy response and overall survival.

Methods: Twenty patients with early/intermediated stage HCC were enrolled and treated according to the EASL/AASLD practice guidelines. Patients were staged at time 0 and 1, 6, 12 month from therapy with CT scan and/or MR; the longest follow-up was 48 month. Blood samples were collected at the admission time and the whole blood miRNome was analysed thought miRNA 3.0 gene array (Affymetrix). Expression data were used for the WGCNA. Network modules associated with clinical parameters were identified and Hub miRNAs were selected as biomarker candidates. Biomarkers were internally validated through a bagging out of bag predictive model with a bootstrap sampling.

Results: Six miRNA modules were identified and associated with clinical data such as treatment response, recurrence time, survival. Two modules were associated with treatment response, and one to survival. Within these modules, five hub miRNAs have a significant association with treatment response and survival ($p < 0.01$ and Module Membership > 70%), miR-194-5p, miR-3150b-3p, miR-4526, miR-574-5p, miR-4462. The selected miRNA were included in a

bagging out of bag predictive modelling procedure with bootstrap sampling of 1000 cycles. When considering the model including miR-3150b-3p, miR-4526 and miR-4462 as predictor for therapy response the AUC was 0.84 with a specificity and Sensibility of 85.7% and 83.3%, respectively.
Conclusions: WGCNA identified several key circulating miRNAs that may be used as potential biomarkers to predict therapy response in HCC patients.
Funding: The study was supported by the project surface-enhanced Raman microRNA for cancer (SERMI4CANCER) POR FESR 2014 2020 Friuli Venezia Giulia, decree no.3028 05/05/2017 and no. 4526 16/06/2017.

THU-484

Mass spectrometric analysis of serum haptoglobin fucolysation in patients stratified according to fibrosis stages, and the presence of hepatocellular carcinoma

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Background and aims: Serum haptoglobin (Hp) is a reporter molecule for aberrant glycosylation in liver disease. Bifucosylated tetra-antennary haptoglobin glycan (fHp), has been used as a potential marker for primary liver cancer (HCC), but its specificity according to severity of fibrosis has never been assessed.
The aim was to assess if fHp was associated with HCC independently of the fibrosis stage and could increase the performance of the standard test (AFP), and not-standard tests (AFPL3, PIVKA).
Methods: From a prospective cohort, we retrospectively selected patients (Pts) with available frozen serum, 110 with contemporaneous HCC for assessing the sensitivity, and for assessing the specificity in versus 140 controls without HCC, including 81 with non-cirrhotic stages (F0 to F3) and 59 Pts with cirrhosis with the 3 classes of severity (F4.1, F4.2, F4.3), according to FibroTest cutoffs (JHepatol 2008). Applicability was defined as Hp ≥0.3 mg/L enabling the identification of fHp. LCR3- Algorithms (patent pending) were constructed (logistic regression) combining fHp, total Hp, GGT, apoA1, alpha-2-macroglobulin, with and without AFP-AFPL3-PIVKA, adjusted for age and gender. AFP and AFP-L3 were measured on a μTASi30 analyzer (Wako) and PIVKA by Lumipulse® G120 analyzer (Fujirebio). The presence of fHp was assessed by MALDI-TOF analysis of Hp purified using an anti-Hp antibody immobilized HPLC column. The N-glycans were released with PNGaseF, desialylated with neuraminidase, purified and permethylated prior to MALDI-TOF-TOF MS analysis.
Results: (Table)

Conclusion: Hp-F was strongly associated with the presence of HCC and permitted to improve the performances of current HCC biomarkers.

THU-485

Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma

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Background and aims: Modulation of adaptive immunity is postulated to underscore the efficacy of TACE. We evaluated the influence of TACE on T-cell function by assessing the phenotypic characteristics of lymphocyte populations from archival liver explants of patients who underwent orthotopic liver transplantation (OLT) with (T^+) or without (T^-) prior-TACE treatment using multi-parameter immunohistochemistry and targeted transcriptomics.
Method: We profiled tumoural and non-tumoural cirrhotic background tissue to evaluate regulatory $CD4^+/FOXP3^+$ (T-reg) and immune-exhausted $CD8^+/PD1^+$ T-cells in relationship with the expression of actionable drivers of anti-cancer immunity including PD-L1, IDO-1, CTLA-4, Lag-3, Tim-3 and CD163. Expression of candidate biomarkers was compared across T^+ and T^- patients and correlated with clinico-pathologic characteristics. We utilised Nanostring PanCancer Immune profiling to broadly characterise the differential enrichment of 770 immune-related transcripts across T^+ versus T^-.
Results: We analysed archival samples from 20 OLT recipients (T^+ n = 11, T^- n = 9), 80% males, 75% with HCV-cirrhosis. Median tumour size was 2.3 cm, 75% of patients had T1-T2 tumours, 85% were within Milan criteria, 70% grade 2 with micro-vascular invasion in 35%. Median percentage of necrosis post TACE was 30% (range 0–90%). T^+ and T^- groups were similar by size, stage, grade, etiology of cirrhosis and MVI ($p > 0.05$). T^+ specimens had evidence of significantly lower density of $CD8^+/PD1^+$ immune-exhausted T-cells within the tumour (9 versus 21 cells/mm^2, p = 0.03) but higher $CD4^+/FOXP3^+$ density of T-regs in cirrhosis (7.5 versus 0 cells/mm^2, p = 0.01). We found no significant difference in the expression of a number of drivers of T-cell

Table 1: (abstract: THU-484): Applicability, sensitivity (Se), specificity (Sp) of FfHp according to fibrosis stage, age and gender

Fibrosis stage	HCC n	fHp+ True positive NA (%)/n (% = Se)	Age ≥ 50 yr (%)	Male (%)	controls n	fHp+ False positive NA %/n (% = 1-Sp)	Age ≥ 50 yr (%)	Male (%)
F0	2	0 (0)/1 (50)	1 (50)	1 (50)	27	0 (0)/0 (0)	12 (44)	12 (44)
F1	4	0 (0)/3 (75)	4 (100)	4 (100)	14	0 (0)/1 (7)	5 (36)	5 (36)
F2	5	0 (0)/4 (80)	2 (5)	2 (40)	21	0 (0)/0 (0)	12 (57)	12 (57)
F3	10	0 (0)/7 (70)	9 (90)	9 (90)	19	1 (5)/1 (5)	11 (58)	11 (58)
F4.1	21	2 (12)/13 (62)	16 (21)	16 (76)	19	4 (21)/4 (21)	16 (84)	16 (84)
F4.2	36	11 (31)/18 (50)	31 (86)	31 (86)	19	8 (42)/2 (11)	17 (90)	17 (90)
F4.3	24	11 (46)/11 (46)	22 (24)	22 (92)	21	7 (33)/7 (33)	14 (67)	21 (68)
Total	**102**	**24 (14)/58 (57)**	**91 (89)[2]**	**85 (83) [1]**	**140**	**20 (14)/15 (11)**	**87 (62)**	**87 (62)**

NA: not applicable [1]P < 0.001 between HCC and controls [2] P = 0.005 between HCC and controls
FfHp alone had in intention to diagnose Se = .57, Sp = .89 and per protocol Se = .74, Sp = .88
Among these fibrosis-adjusted Pts the best AUROC (95%CI) was obtained by LCR3 algorithm with fHp-AFPL3-PIVK (.92;.86-.95) vs.82 (.75–0.87;P = .006) for standard AFP,.84 (.77-.89;P = 0.02) for AFPL3 and.85 (.78-.90;P = 0.04) for PIVKA. The false positive rate was 33% among Pts with severe cirrhosis.

exhaustion including PD-L1, IDO-1, Lag-3, Tim-3 or CD163 across T+ versus T- samples. Targeted transcriptomic profiling revealed differential regulation of genes reflective of adaptive and innate anti-cancer immune responses across T^+ versus T^-.
Conclusion: Pre-treatment with TACE is associated by lower density of immune-exhausted intra-tumoural T-cells and stronger T-reg infiltration in the peri-tumoural infiltrate. This highlights the pleiotropic effects of TACE in modulating the tumour microenvironment and strengthens the rationale for developing immunotherapy alongside TACE to improve clinical outcomes of patients with HCC.

THU-486

A pro-regenerative environment triggers premalignant to malignant transformation and pinpoints new therapeutic targets

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Background and aims: Aging, chronic tissue damage and inflammation are main risk factors and contributors to cancer. We investigated the interactive relationship of premalignant senescent hepatocytes, a regenerative environment and the influence of secreted factors for liver tumorigenesis in a mouse model.
Method: Through hydrodynamic tail vine injection of transposon based constructs for the expression of oncogenic NRasG12 V we triggered oncogene induced senescence in 5–10% hepatocytes of C57Bl6/j mice. In wt mice these senescent cells are eliminated by immunosurveillance. We then performed 2/3 partial hepatectomy (PH) as well as thioacetamide treatment to induce acute liver regeneration or chronic liver damage/regeneration respectively. We further applied transcriptomic and proteomic analysis to identify mechanisms of premalignant to malignant transition and for its suppression. Results were also validated in oxidative stress induced senescence and human cells.
Results: Interestingly, senescent hepatocytes are attenuating the regenerative process, indicated by less proliferation and a higher amount of cell cycle arrested cells. However, under regenerative pressure immunosurveillance is aborted. Even a single acute damage by PH is sufficient, leading to expansion of premalignant senescent hepatocytes already 40 days post PH and finally liver tumor development. Immune surveillance is not reinitiated after tissue regeneration finished, but liver tumor development still takes time, as first mice succumb to cancer around 150 days post tissue damage. The same situation we saw in case of chronic liver damage. Through investigating the transcriptomic signature we identified TFF3 as a potential player and could show that TFF3 knockdown abrogates the transformation of premalignant hepatocytes upon liver damage. The animals which still got a tumor showed no knockdown in the tumor tissue for TFF3. Through further transcriptomic as well as proteomic analysis we identified IGFBP5 as a mediator of tumor suppression. Tff3 knockdown leads to a strong upregulation of IGFBP5 which then suppresses IGFR1 signalling and blocks pro-oncogenic downstream pathways. The relation of Tff3 knockdown and IGFBP5 upregulation is conserved in humans and also suppresses human cancer cell proliferation.
Conclusion: We showed that liver damage triggers premalignant to malignant transformation of hepatocytes, immunosurveillance escape and liver tumor formation. This can be suppressed by inhibiting TFF3, leading to a strong upregulation of IGFBP5. Furthermore this mechanism is conserved in humans and represents a therapeutic target.

THU-487

Circulating MIR-4492 as a biomarker to predict therapy response and disease free survival in hepatocellular carcinoma

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Background and aims: One of the most crucial strategies to improve prognosis of patients with Hepatocellular Carcinoma (HCC) involves the discovery of predictive non-invasive biomarkers. This study aimed to investigate the potential role of serum miR-4492 as a prognostic biomarker in the cohort of patients with HCC.
Method: A total of 100 HCC patients were enrolled and treated according to the ESSL/AASLD practice guidelines. Serum samples were collected at the admission time. Twenty serum samples (discovery cohort) were profiled through miRNA 3.0 gene array (Affymetrix). miRNAs associated to therapy response and disease-free survival (DFS) were further validated in 80 HCC serum samples (validation cohort). miRNAs were profiled by qRT-PCR. Relative quantification (fold of change) was determined using the $2^{(-\Delta\Delta Ct)}$ method. MiR-1280 was used as an internal control. Statistical analysis was performed by using NCSS software for non-parametric test (Whitney-Mann).
The receiver operating characteristic (ROC) curves were plotted to estimate the prognostic value of the miRNA.
Results: Among the miRNA selected from the discovery phase, miR-4492 was significantly associated to therapy response and DFS. Mir-4492 showed a decreased expression in patients with no or partial response to treatments ($p = 0.006$) and with a DFS lower than 24 months ($p = 0.035$). The significance level improves in patients treated with transarterial chemoembolization (TACE) ($p = 0.002$). The receiving operating curve (AUC of serum miR-4492 for therapy response) was 0.68 (0.54–0.78 95%CI), with a 70.0% sensitivity and 64% specificity. The AUC for therapy response improves to 0.81 (0.54–0.94 95% CI) with a 83% sensitivity and 73% specificity when considering the TACE-treated patients. When considering the predictive value of serum miR-4492 of DFS longer than 24 month the AUC was 0.67 (0.47–0.79 95%CI) with a 63% sensitivity and 72% specificity.
Conclusion: Serum miR-4492 is as a novel biomarker for predicting treatment response and DFS in HCC patients.
Fundings:
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THU-488

Acquisition of stem-like features in cholangiocarcinoma is associated with an oxidative metabolism

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Background and aims: Compared to tumor-bulk, cancer stem cells (CSC) are resistant to drugs and responsible for tumor initiation as well as relapse. However, mechanisms underlying CSC state in cholangiocarcinoma (CCA) remain largely unknown. Growing evidence indicated that deregulated cellular metabolism is linked to acquisition of tumor stem-like properties as well as drug resistance. The present study aimed to explore alterations of glucose metabolism in CCA stem-scenery.

Method: Stem-like compartment was enriched by sphere culture (SPH) in established human intrahepatic CCA cells (HUCCT1, CCLP1, SG231). CCA-SPH extracellular flux analysis was examined by seahorse technology. CCA-SPH expression of hexokinase II (HKII), pyruvate kinase M1 (PKM1), PKM2 and Peroxisome proliferator activated receptor gamma coactivator 1-α (PGC-1α) was investigated by western bottling. Metformin effect on survival was examined by MTT. Glucose uptake was quantified by incorporated (U-14C) deoxy-D-glucose.

Results: In contrast to parental cells grown as adherent monolayers (MON), metabolic analyses by seahorse technology revealed that CCA-SPH have a more efficient respiratory phenotype by mitochondrial oxidative phosphorylation (OXPHOS). In agreement, CCA-SPH cells showed down-regulation of the glycolytic marker HKII, indicating adaptation toward mitochondrial respiration. Also, PKM1 overexpression and PKM2 repression in CCA-SPH cells correlated with decrease of glucose uptake as well as with reduction of GLUT-1 expression. Finally, over-expression of PGC-1α in CCA-SPH indicated that mitochondrial biogenesis and respiration was functionally relevant in CCA stem-like cells. These data were corroborated by FACS analysis showing in CCA-SPH a higher mitochondrial membrane potential (MitoTracker Red) as well as elevated mitochondrial mass (MitoTracker Green). Consequently, CCA-SPH survival was impaired after targeting mitochondrial complex I (by administration of metformin, phenformin, rotenone), complex III (antimycin) or ATP sintase (oligomycin). More importantly, metformin drastically affected expression of CSC-like (CD13, CD133, EpCAM) and pluripotency genes (KLF4, NANOG, BMI1) as well as epithelial mesenchymal transition (EMT)-signaling (E-cadherin, Vimentin, ZEB1, ZEB2, Slug, Snail), suggesting its possible contribution to the CCA-stem subset. In an in vivo xenograft model, metformin limited the growth of CCA-SPH-derived tumors in immunocompromised mice, confirming the OXPHOS-associated phenotype of CCA-stem-like subset. Analysis of published microrarray-based data in 59 CCA vs. surrounding liver confirmed significant (FDR q-val < 0.2) signals of stemness and OXPHOS.

Conclusion: Our findings indicate that CCA stem-like cells undergo a metabolic reprogramming resulting in OXPHOS addiction to meet energy demands.

THU-489

Mixed HCC-ICC liver cancer derives from hepatic progenitor cells: A lineage tracing investigation in a mouse liver inflammation model

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Background and aims: Primary liver cancer is the second leading cause of cancer-related death worldwide. Primary liver cancers include: Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and Mixed HCC-ICC tumor. Preceding the development of primary liver cancer, there is usually cirrhosis which results from a prolonged period of chronic inflammation. It has been proposed that hepatic progenitor cells (HPCs) could contribute to hepatocarcinogenesis. However, this has not yet been proven. These cells proliferate in response to injury and chronic inflammation in the liver. In this study, we aimed to determine whether HPCs contribute to liver cancer development in the MDR2 KO mouse model of inflammation-induced HCC.

Method: In order to enable tracing of progenitor cells, we generated a transgenic mouse based on the MDR2 KO that harbours a YFP reporter gene driven by the Foxl1 promoter, the promoter of a liver progenitor specific marker. These mice (MDR2 KO$^{Foxl1CRE;\ RosaYFP}$) develop chronic inflammation by the age of 1 month and HCCs by the age of 16 months followed by Mixed HCC-ICC tumors at the age of 18 months.

Results: At the age of 3 months, upon severe inflammation, YFP positive HPCs proliferate and differentiate, giving rise to both cholangiocytes and hepatocytes. In addition, at the age of a year and later, HPCs are present in the chronically inflamed livers and within dysplastic nodules (DN). Within the livers of 16-month old MDR2 KO$^{Foxl1CRE;RosaYFP}$ only a minority of DNs were positive for YFP expression. Furthermore, the HCC tumors that have developed, were YFP negative, but contained scattered YFP-positive HPCs. At later stages (18-month) these mice developed Mixed HCC-ICC tumors and very few ICC. Interestingly, the Mixed tumors were YFP positive, implying that they were derived from HPCs. These HCC-ICC YFP positive tumors accounted for 45% of the total tumors observed and they also express stem cells markers including Epcam, Cd24a, Cd133 and Krt19. These findings recapitulate the characteristics of human Mixed ICC-HCC tumors which also shown to have stem cell-like features. Next generation sequencing (NGS) analysis of human and mouse Mixed ICC-HCC tumors, revealed the presence of HPCs gene signature, implying that they originate from Foxl1 HPCs cells. In addition, RNA seq analysis revealed that both, human and mouse Mixed HCC-ICC tumors have a very similar pro-survival pathway signature. Most significantly, IL6 signalling was found to be up-regulated in these Mixed tumors at the RNA and protein levels.

Conclusion: Taken together, our results suggest that mixed HCC-ICC but not HCC tumors, originate from HPCs in the inflammation induced liver cancer model, and that the driver of this process involves the IL6 signalling pathway.

THU-490

Liver NK cells from NLG4 KO mice inhibit progressions of hepatocellular carcinoma of C57BL/6 mice model through decrease in p53 and AKT expressions

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Background and aims: Cirrhosis is a main risk factor for hepatocellular-carcinoma (HCC) development. However, direct role of NK cell in HCC-progression is not fully understood. Therefore, we aimed to study the role of neuroligin-4 (NLG4) receptor of NK cells in models of HCC in C57BL/6 mice.

Method: HCC cell-line (Hep3B) secreted high levels of alpha-fetoprotein (αFP) were injected in the back of irradiated C57BL/6 (sub-lethal dose) and liver NK cells from both WT and homozygous NLG4$^{-/-}$ (KO) mice were transplanted at day 5 following HCC injections. Hepatic tumor sizes and serum αFP were then assessed from day 6 till day 14. Liver P53 and AKT expressions by RT were tested at day of sacrifice.

Results: Tumor mass increase in animals with HCC injections and was associated with elevated αFP serum levels in all tested time intervals. Mice receiving the liver NKs from the NLG4$^{-/-}$ animals showed a significant decrease in tumor at days 10, 12 and 14. Liver NKs from the WT animals did not alter tumor progressions. At the day of sacrifice, serum αFP levels maintained were almost not significant in all tested groups as the WT mice showed an elevations in their αFP levels and ended to similar levels of the groups probably attributed to lost effects of irradiations. Liver p53 showed to be significantly high (1.5 fold increase) in the mice groups with HCC alone while almost decreased in mice receiving liver NKs from the NLG4$^{-/-}$ to levels similar to the animals with no HCC. These results were associated with decrease in AKT only in animals receiving liver NKs from the NLG4$^{-/-}$ ($p = 0.001$).

Conclusion: p53 is a more sensitive marker for HCC tumorigenesis than αFP in C57BL/6 mice in advanced stages of tumor. The

mechanism of p53-mediated repression of αFP levels may be active during hepatic differentiation and lost in the process of tumorigenesis. NK from NLG4$^{-/-}$ mice showed to decrease tumor through p53 inhibitions and decrease in AKT indicating its associations with pathways decreasing proliferations of HCC and reinforces the importance of NLG4 modulation as a therapeutic target for HCC.

THU-491

The role of alanine glyoxylate aminotransferase in hepatocellular carcinoma

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Background and aims: The high mortality rate associated with hepatocellular carcinoma (HCC) is mainly due to lack of effective markers for early detection of the disease. In the Western world, metabolic syndromes and the causal rearrangements are increasingly associated with HCC. However, we have limited understanding on how these aberrations contribute to liver tumorigenesis. The aim of this study is to characterize novel metabolic pathways inducing HCC onset and progression.
Method: We have analyzed the transcriptomes of HCCs obtained from a murine model of liver cancer (*Mdr2* knock out), followed by exposure to the carcinogen DEN. We analyzed the transcriptomes of 458 HCC patients and performed immunohistochemical staining and metabolic analysis on 164 HCC patients. Furthermore, we analyzed the methylation status of *AGXT*. To understand the role of *AGXT* on HCC progression, we genetically modified HCC cells by knocking out (KO) *AGXT* by CRISPR/Cas9 and also restored its expression by knock-in. On these HCC clones, we performed transcriptomics, metabolomics and functional assays.
Results: The transcriptomic analysis of *Mdr2*$^{-/-}$/DEN model showed *AGXT* among the top scored differential expressed genes. In 458 HCCs, *AGXT* was shown to be significantly downregulated in a subset of patients. Analysis of the clinical variables revealed a correlation between low *AGXT* and poor overall survival as well as high grade tumors. Moreover, impaired *AGXT* expression inversely correlated with the methylation status of its promoter. Association between the level of *AGXT* expression and tumor grading was confirmed at protein level by immunohistochemical staining of 95 HCC tissues, showing a pericentral location of the protein. Importantly, *AGXT* KO cells had a higher rate of proliferation, migration and colony formation compared to the parental cells, and KO phenotypes were normalized in *AGXT* restored cells. Integration of transcriptomics and metabolomics between *AGXT*-defined subsets of patients showed a dysregulation of key components in fatty acid, amino acids and energy metabolism. Also, this relationship of *AGXT* level and metabolic rearrangements was seen in the transcriptomic analysis of *AGXT* KO cells.
Conclusion: *AGXT* is a key enzyme in the glyoxylate cycle. However, here we show that depletion in HCC cells cause a significant reduction of lipids and rearrangement of the amino acid metabolism. Thus, this study contributes to unravel additional roles for *AGXT* and advance our understanding of how metabolic imbalances can affect HCC tumorigenesis.

THU-492

Role of regulatory T cells and checkpoint inhibition in hepatocellular carcinoma

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Background and aims: Immune checkpoint inhibition suggests promissing progress for treatment of advanced hepatocellular carcinoma (HCC). However, the underlying cellular mechanisms remain unclear because liver cancer cells apparently do not upregulate inhibitory checkpoint molecules. Here, we analysed whether CD4$^+$ regulatory T cells (Tregs) can alternatively trigger checkpoint inhibition pathways in HCC.
Method: Using flowcytometry we analysed expression of checkpoint molecules (PD-1, PD-L1, CTLA-4, GITR, Tim-3) on peripheral CD4$^+$CD25$^+$Foxp3$^+$ Tregs as well as their secretion of inhibitory mediators (IL-10, IL-35, TGF-beta, galectin-9) in 108 individuals (50 patients with HCC, 41 non-tumour bearing liver disease controls, 17 healthy controls). Functional activity of Tregs on T effector cells (IFN-gamma production, cytotoxicity) was characterized *in vitro* using a lectin-dependent cellular cytotoxicity (LDCC) assay against checkpoint inhibitor-negative P815 target cells.
Results: Unlike liver patients without malignancy and healthy controls, the frequency of checkpoint inhibitor-positive Tregs in the blood inversely correlated to age of patients with HCC (PD-L1, $p = 0.0080$; CTLA-4, $p = 0.0029$) and corresponded to enhanced numbers of Tregs producing IL-10 and IL-35 ($p < 0.05$ each). Tregs inhibited IFN-gamma secretion and cytotoxicity of CD8$^+$ T cells when added to LDCC against P815 cells. Treg-induced inhibition of IFN-gamma secretion could be partially blocked by neutralizing PD-1 and PD-L1 antibodies specifically in the patients with HCC.
Conclusion: In HCC peripheral Tregs upregulate checkpoint inhibitors and contribute to systemic immune dysfunction and antitumoural activity by several inhibitory pathways, presumeably facilitating tumour development at young age. Blocking PD-L1/PD-1 interactions *in vitro* selectively interfered with inhibitory Treg-T effector cell interactions in the patients with HCC and resulted in improved antitumoural activity also against checkpoint inhibitor-negative tumour cells.

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Reciprocal changes in ARID1A and EZH2 are associated with cholangiocarcinoma development in a mouse model of caroli disease with high Yap expression

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Background and aims: Congenital Hepatic Fibrosis (CHF) and Caroli disease (CD) are genetic cholangiopathies caused by mutations in the

PKHD1 gene. In about 15% of patients, CD may progress to Cholangiocarcinoma (CCA). *ARID1A* is a component of the SWI/SNF complex that blocks YAP regulators (i.e E2F1 or AKT) and EZH2, the catalytic subunit of polycomb repressive complex 2; EZH2 it has been shown to be overexpressed in several malignancies. We aimed to investigate if these epigenetic regulators are involved in the development of CCA in *Pkhd1*$^{del4/del4}$ mouse, an orthologous model of CD.

Method: Mucous production was examined by Alcian blue staining. EZH2, YAP and ARID1A protein expression was evaluated by immunohistochemistry and western blot. The DNA aneuploidy was examined by FACS. *Arid1a, Pik3pi, Sca-1, Nanog, Ctgf, Cdk1* gene expression levels were evaluated by RT-PCR. Silencing of ARID1A was performed using siRNA. Thioacetamide (TAA) was administrated in the drinking water (300 mg/L).

Results: *Pkhd1*$^{del4/del4}$ mice but not their WT controls, display an age-dependent increase of mucous production and nuclear YAP expression. DNA aneuploidy and EZH2 protein expression were detected only in aged (9- 12-months-old) *Pkhd1*$^{del4/del4}$ mice. *Pkhd1*$^{del4/del4}$ mice treated with TAA developed high grade dysplasia after 4 months and CCA after 7 months, whereas WT controls showed only ductular reaction and fibrosis. Gene expression of EZH2 and of YAP target genes increased in TAA treated *Pkhd1*$^{del4/del4}$ mice as respects to untreated *Pkhd1*$^{del4/del4}$ mice. Gene expression of *Arid1a* and its target gene *Pik3pi* decreased in the liver of TAA treated *Pkhd1*$^{del4/del4}$ mice, compared to TAA treated WT mice. ARID1A silencing in *Pkhd1*$^{del4/del4}$ cholangiocytes *in vitro* increased nuclear levels of YAP and the expression of YAP target genes (*Nanog, Sca-1, Cdk-1*).

Conclusion: Cholangiocytes of aged *Pkhd1*$^{del4/del4}$ mice show pre-malignant features of dysplasia. Treatment with TAA accelerated the progression to CAA in *Pkhd1*$^{del4/del4}$ but not in WT mice, indicating that *Pkhd1*$^{del4/del4}$ mice are prone to develop CCA. The progression from low grade dysplasia to CCA is accompanied by an increase in EZH2 expression and YAP transcriptional activity and by a concomitant decrease of *Arid1a* gene expression. Interestingly, the latter is known to be frequently mutated in human CCA.

THU-494

MicroRNA-96 in non-B non-C hepatocellular carcinoma

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Background and aims: We have shown by genome-wide DNA methylation analysis that regions corresponding to microRNA clusters including the miR-183/96/182 cluster were hypomethylated in non-B non-C hepatocellular carcinoma (NBNC-HCC) tissues samples compared to their adjacent liver tissues. The aim of this study is to investigate the roles of the miR-183/96/182 cluster in NBNC-HCC development.

Method: We collected frozen or paraffin-embedded 122 pairs of tumor and adjacent background samples obtained from patients undergoing surgery. We quantified the expression levels of miRNA-96, miRNA-182 and miRNA-183 in tumor and background tissues and compared with clinical data. We then transfected these miRNAs into Hep G2 cells, and their effects on cell proliferation, invasion capacity, and apoptosis were determined.

Results: We found that the expression of miR-96, miR-182, and miR-183 was upregulated in tumor tissues compared to background tissues ($p = 0.0241$, $p = 0.0011$, and $p = 0.0035$ respectively). Surprisingly, when NBNC-HCC patients were divided into two groups according to the level of miR-96 expression in tumor tissues, those with relatively high level of miR-96 expression exhibited longer disease-free survival compared with the others ($p = 0.0321$). Transfection of miR-96 in Hep G2 cells resulted in the suppression of cell growth and invasion capacity. We also found that the apoptotic cells were increased in miR-96-treated Hep G2 cells. Microarray and quantitative PCR analyses showed that some genes related to invasion such as GPC3, ZEB1, SNAI1, and those related to negative regulation of apoptosis such as NPM1 were decreased in miR-96-treated cells.

Conclusion: Elevated expression of antitumor miR-96 in tumor tissues were significantly associated with disease-free survival in NBNC-HCC patients.

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Real-time, intravital imaging of diethylnitrosamine-induced hepatocellular carcinoma

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Background and aims: The role of the microenvironment in hepatocarcinogenesis is complex, comprising interactions between immune, angiogenic and cancer-associated fibroblasts. Intravital microscopy (IVM) techniques allow direct visualisation of tumour cells interacting with their microenvironment. This can provide insights into the ability of tumour cells to migrate, metastasize, and induce angiogenesis. In the liver, IVM cancer models to date have been confined to studying colorectal cancer metastasis, or hepatocellular carcinoma (HCC) by imaging inoculated cancer cell lines. These models have obvious limitations in terms of studying the true tumour microenvironment. We previously developed an IVM protocol for directly imaging mouse liver in real-time, using a range of imaging modalities including multiphoton (MP) and Coherent Anti-Stokes Raman Scattering (CARS) microscopy. We hypothesized that a similar approach could be used in the setting of hepatocarcinogenesis.

Method: The diethylnitrosamine (DEN) model of HCC is well established. We have combined this model with a novel IVM approach, allowing sequential, real-time imaging of the liver via a surgically implanted titanium abdominal imaging window (AIW). This technique, in conjunction with MP microscopy and other label-free imaging modalities, allows us to image DEN-induced HCC in fluorescent reporter mice, at cellular and subcellular resolution.

Results: We show for the first time, that DEN-induced HCC can be directly imaged under terminal anaesthesia. We present data using the Albumin Cre$^{\pm}$;Confetti mouse, in which hepatocytes express one of four different fluorescent reporters. An AIW can be surgically

implanted on an area of HCC, to allow live imaging. Use of CARS microscopy demonstrates that this technique could be used to analyse blood flow and angiogenesis within HCCs and the surrounding tumour niche.

Conclusion: To the best of our knowledge, mature tumours from the DEN-induced murine HCC model have not previously been imaged in real-time *in vivo*. This provides a novel opportunity to undertake experiments designed to interrogate subtle differences in tumour biology and blood flow, which might only be detectable using an IVM system. This could also facilitate in-depth study of the efficacy of novel chemotherapeutic agents, allowing both assessment of topography of intra-tumoural drug delivery, and also the relative efficacy of targeting specific cell lineages within the setting of HCC.

THU-497

Molecular fingerprint of hepatocellular carcinoma in patients with non-alcoholic steatohepatitis

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Background and aims: Non-alcoholic steatohepatitis (NASH) is emerging as one of the leading risk factors for hepatocellular carcinoma (HCC), but its molecular pathogenesis is still ill-defined. This study aims to identify unique molecular traits that differentiate NASH-HCC from other aetiologies through an integrative molecular characterization.

Method: A total of 225 tissue samples were collected, including samples from 125 biopsied/transplanted NASH patients; and 100 resected/transplanted NASH-HCC patients. Molecular characterization of FFPE samples, comprised expression array (n = 53 NASH-HCC; n = 74 NASH), whole exome sequencing (n = 50 NASH-HCC), and SNP array (n = 44 NASH-HCC).

Results: NASH-HCC patients compared to NASH non-HCC patients were prevalently males (82% vs 42%, $p < 0.001$), with older age (67 years vs 54, $p < 0.01$), higher diabetes incidence (72% vs 50%, $p = 0.004$), hypertension (80% vs 52%, $p < 0.01$) and cirrhosis (69% vs 29%, $p < 0.001$). When exploring the transcriptome of non-tumour tissues, NASH cases showed enrichment of liver metabolism pathways, whereas NASH-HCC cases were enriched in hallmarks of inflammation (TNFα-NFkβ, IL6, STAT3), epithelial-mesenchymal transition (TGFβ1), proliferation (AKT, mTOR), as well as poor-prognosis liver signatures ($p < 0.05$). Regarding NASH-HCC neoplastic tissues, gene expression profiles demonstrated that they can be classified in proliferation (50%) and non-proliferation (50%) molecular classes. Mutational analysis identified genes with mutations in ≥ 10% of NASH-HCC tumours: *TERT* (52%), *CTNNB1* (28%), *TP53* (18%) and the TGFβ-receptor *ACVR2A* (10%). Unsupervised clustering of mutational signatures showed that NASH-HCC tumours are clustered in 2 groups, enriched in liver-cancer signatures #16 (44%) and #5 (22), respectively; and that a third cluster (15%) was enriched in signature #3, which is novel in liver cancer. When conducting signature clustering in 42 viral/alcohol-related HCCs, signature #3 cluster emerged as specific of NASH-HCC.

Conclusion: Non-tumour liver tissue of NASH-HCC patients is characterized by a cancer-field enriched in inflammatory, epithelial-to-mesenchymal transition and proliferation signalling pathways. NASH-HCC tumours showed high frequency of *TERT*, *CTNNB1*, *TP53* and *ACVR2A* mutations; and a novel liver-cancer mutational signature (#3, 15%), suggesting genotoxic factors specifically associated to this entity.

THU-498

Mass-spectrometric analysis of deregulated proteins in gallbladder carcinoma

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Background and aims: This study focuses on gallbladder carcinoma (GBC) which is a rare and understudied cancer entity. The main risk factors are female gender, age, ethnicity, obesity, cholelithiasis and chronic gallbladder inflammation. GBC treatment options are very limited and 2-year survival rates of unresectable GBC is less than 10%. Radical surgery is the only potentially curative treatment option but due to late diagnosis few patients are eligible. Therefore, the development of new treatment options, including targeted therapy for GBC is required to improve patient outcome.

Method: We performed quantitative LC-MS-based proteomics of a total of 18 FFPE tumors, 5 healthy gallbladder and 5 tumor stroma specimens from a German GBC cohort. The quantitative proteomic analysis was performed in three sets: healthy vs tumor, tumor vs stroma and long vs short survival. The analysis revealed differentially expressed proteins in the distinct groups, which were further subjected to pathway analysis. Candidate genes representing potential tumor suppressors were selected.The role of these candidate genes in proliferation, migration and clonogenicity was investigated in GBC cell lines to evaluate their specific function.

Results: We detected approximately 5, 000 proteins. Between long and short surviving patients 611 proteins with a significant difference (adj. p value < 0.05) were found. Among the enriched pathways in patients with worse survival are the cellular defense response and regulated exocytosis. Downregulated pathways are the ECM organization and cell/biological adhesion.

We also found 1766 proteins to be differentially expressed between healthy gallbladder and GBC (adj. p value < 0.05). Interestingly, pathways for RNA processing and inflammatory response were upregulated, whereas, cytoskeleton organization and biological/cell adhesion were downregulated.

In order to identify potential tumor suppressor candidates, we selected genes of the significantly downregulated pathways with at least 4-fold decrease in tumors. This led to the identification of FHL1 and ANK3. Both proteins were strongly downregulated in the 5 tumor samples, compared to the 5 healthy gallbladder samples. FHL1: fold difference: 8.6, $p < 0.001$, FDR = 0.008 and ANK3: fold difference: 4.5, $p < 0.001$, FDR = 0.0002. Based on intermediate to low endogenous expression of the respective genes, cell lines were selected to induce stable overexpression to study the biological functions of the genes. FHL1 overexpression in NOZ and G-415 cells significantly reduced the velocity of wound closure and the ability to form colonies, supporting a tumor suppressive role in GBC.

Conclusion: Proteomic profiling of a well-characterized German GBC cohort identified many differentially expressed proteins and tumor-relevant downregulated pathways. Functional validation confirmed the tumor suppressive function of FHL1.

THU-499

Angiotensin receptor blockade attenuates cholangiocarcinoma cell growth by inhibiting the oncogenic activity of Yes-associated protein

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Background and aims: Cholangiocarcinoma (CCA) is a destructive malignancy with limited responsiveness to conventional chemotherapy. Yes-associated protein (YAP), a transcriptional co-activator, is a critical oncogene in several cancers. It has been shown that oncogenic YAP occurs in both human CCA cell lines and patient specimens, with nuclear YAP showing potential for use as an independent prognostic marker of overall survival in CCA. Moreover, recent evidence has also shown that it is regulated by angiotensin II (AT-II). Thus, this study aimed to elucidate the effect of angiotensin receptor blocker (ARB) on human CCA cell growth.
Method: WST-1 and TUNEL assays were performed to examine the effects of AT-II and/or ARB, losartan, on *in vitro* human CCA cells (KKU-M213 and HuCCT-1) proliferation and apoptosis, respectively. To create a xenograft model, we injected 1×10^6 of human CCA cells into the flanks of BALB/c nude mice. After the tumor was established, losartan was administrated at dose of 30 mg/kg per day. Immunohistochemistry was performed for analysis of intracellular cell proliferation, YAP activation and angiogenesis. Western blotting was carried out to evaluate the phosphorylation of YAP. Quantitative real-time PCR was also performed to assess the mRNA levels of YAP transcriptional genes and selected genes related to epithelial-mesenchymal transition (EMT), differentiation, and stemness. Immunohistochemistry was performed for analysis of intratumor cell proliferation, YAP activation and angiogenesis. Additionally, we investigated the effects of AT-II and/or losartan *in vitro* endothelial tubular formation.
Results: Losartan not only suppressed CCA cell proliferation stimulated by AT-II in a dose-dependent manner but also induced apoptosis, decreased phosphorylation of YAP (Ser127), and down-regulated YAP target genes (i.e., *CTGF*, *CYR61*, *ANKRD1*, and *MFAP5*). However, losartan did not affect EMT, differentiation, or stemness in the CCA cells. A xenograft tumor growth assay showed that oral administration of losartan at a low clinical dose significantly reduced subcutaneous tumor burden and attenuated intratumor vascularization in CCA cell-derived xenograft tumors in BALB/c nude mice. Furthermore, losartan inhibited AT-II-stimulated *in vitro* endothelial tubular formation.
Conclusion: These results indicate that ARB therapy could offer a potential novel strategy for the treatment of CCA.

THU-500

EGFR is a preventative target for NASH-induced liver cancer

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Background and aims: Non-alcoholic steatohepatitis (NASH) has become a serious health problem with the increase of metabolic syndrome. NASH is one of the major causes of liver cancer, however, the mechanism how NASH develops hepatocellular carcinoma (HCC) remains unclear. In addition, genetic analyses have not proposed any treatment or prevention so far, because there are no targetable driver mutations found in HCC.
In the background liver which is chronically injured, typically cirrhotic, gene alterations accumulate for 20–30 years, and hepatocytes demand anti-stress and regenerative responses to survive under stressed-condition. One of the key molecules is p62, a multifunctional adaptor protein. Previously, we reported that p62 accumulates in a variety of chronic liver diseases and activate Nrf2 and mTORC1 to adapt pre-cancerous cells to stress (Cancer Cell 2016, PMID: 27211490). These responses necessary for survival in chronic liver injury may drive hepatocarcinogenesis, so that we are focusing on the NASH-background liver.
Method: Using a genetic mouse model in which high fat diet induces HCC highly relevant to human NASH-HCC (Cancer Cell 2014, PMID: 25132496), we searched genes altered in the background liver by RNA sequence analysis, then examined the protein expression of the genes. Finally, we tested whether a natural product could reduce the incidence of HCC in this animal model.
Results: From results of RNA sequence and immunoblotting analyses, we found that EGFR signaling was hyperactivated in the mouse NASH liver. For liver cancer, the use of EGFR inhibitors has not been successful so far. For example, a phase III trial of sorafenib plus a major EGFR inhibitor erlotinib for the treatment of advanced-HCC did not show clear benefits compared with the sorafenib plus placebo arm (J Clin Oncol 2015, PMID: 25547503). However, the preventative effect of EGFR inhibition has not been explored yet. In this mouse study, we found that inhibition of EGFR signaling by a natural compound drastically attenuated NASH-HCC incidence. Mechanistically, this treatment induced EGFR degradation, not its dephosphorylation, leading to robust tumor suppression.
Conclusion: We show that EGFR inhibition significantly suppressed HCC induction in the mouse NASH-HCC model. EGFR signaling may be highly active in pre-cancerous cells which form dysplastic nodules and this signaling may facilitate these cells develop into liver cancer. Our results support the concept that EGFR signaling is a driver of liver carcinogenesis and is a suitable target for NASH-HCC prevention.
This is the first report showing that EGFR inhibition could prevent NASH-induced HCC and a natural compound could be a potential drug candidate.

THU-501

Myeloid-specific IRE1 alpha deletion reduces tumour development in a non-alcoholic steatohepatitis-induced hepatocellular carcinoma mouse model

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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. Macrophage inositol-requiring enzyme 1 alpha (IRE1a), an ER-stress protein, has shown to be involved in macrophage cytokine production and myeloid-specific IRE1a knock-out (KO) mice showed reduced weight gain during high fat diet feeding. However, the effect on NASH and subsequent HCC development has not been examined. Here, we investigated the effect of myeloid-specific IRE1a deletion on experimental NASH-HCC development.
Method: Mice with non-functional myeloid IRE1a were created by crossing IRE1a floxed mice with LysM-Cre mice. Two-day old KO and wild type (WT) mice were subcutaneously injected with streptozotocin (STZ) and male mice were fed a high-fat, -sucrose, -cholesterol diet (shortly called HFD) from the age of 4 weeks till 21 weeks. Control KO and WT mice received a PBS injection and matched

control diet. Mice were evaluated for obesity, diabetes, NASH and HCC by analyses of serum, fat and liver samples.
Results: STZ injection resulted in lower body weights at the age of 4 weeks (start of HFD) compared to control mice and resulted in elevated fasting glucose levels in STZ-WT mice, which was not observed in STZ-KO mice. HFD feeding resulted in more fat accumulation (p = 0.009) and a higher body weight (p = 0.05) but attenuated glucose intolerance (p = 0.01 at peak glucose levels) in STZ-KO mice compared to STZ-WT mice. While no difference was observed in the NAFLD activity score between STZ-KO and STZ-WT mice after HFD feeding, STZ-KO mice presented with significant lower tumour loads (p = 0.009) and reduced alpha fetoprotein gene expression both in tumour and surrounding tissue compared to STZ-WT mice. Liver monocyte infiltration was significantly higher (p = 0.01) and pro-inflammatory cytokine induction tended to be more pronounced in STZ-KO mice compared to STZ-WT mice after HFD feeding whereas the control KO mice showed a tendency to lower levels of pro-inflammatory markers and liver monocytes compared to control WT mice under homeostatic conditions.
Conclusion: Our results indicate that myeloid-specific IRE1a deletion attenuates diabetes induction and results in reduced NASH-induced HCC without significant influence on HFD-induced NASH development.

THU-502

ZEB1 expression in myofibroblasts regulates their interaction with cholangiocarcinoma cells promoting tumour progression

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Background and aims: Cholangiocarcinoma (CCA) is characterized by a prominent fibrous stroma which gene signature has been associated with a poor prognosis. CCA stroma is mainly composed of myofibroblasts (MF) thought to be derived from hepatic stellate cells (HSC). This activation is a well-orchestrated process controlled by epithelial-mesenchymal transition-inducing transcription factors (EMT-TF). The role of ZEB1 in MF function is largely unknown. Therefore, the main objective of this study was to elucidate the role of ZEB1 expressed by MF in the progression of CCA.
Method: Immortal activated human HSC, generated by ectopic telomerase expression, were used as MF model. Knockdown of ZEB1 was performed by lentivirus infection of shRNA-ZEB1 (MF-shZEB1) (and the corresponding shRNA-Control (MF-shCtr)). EGI-1 and HuCCT1 cell lines were used as CCA cell models. Conditioned media (CM), obtained from either MF or CCA cells, was used to mimic tumor-stroma crosstalk communication. *In vivo* experiments were performed using a xenograft tumor model in immunodeficient mice.
Results: ZEB1 knockdown in MF caused a downregulation of fibrotic markers (α-SMA, COL4A1 and vimentin) and soluble factors, including growth factors (TGF-β, IGF2, EGF, HB-EGF, PDGFB and osteopontin) and pro-inflammatory cytokines (IL-6 and IL-8), as compared to MF-shCtr. On the contrary, TNF-α and IL-1B, involved in cell death promotion, were upregulated in MF-shZEB1. Upon TGF-β stimulation fibrotic markers were upregulated both in MF-shCtr and MF-shZEB1 cells, while the expression of soluble factors was increased only in MF-shCtr cells, and remained unchanged in ZEB1-depleted MF. Moreover, MF-shCtr cells were more resistant to the toxic effect of gemcitabine than MF-shZEB1. Crosstalk communication experiments showed that CM from CCA cells increased cell viability of MF-shCtr but induced cell death of MF-shZEB1 cells, along with an increase of p53 and p21 protein expression. The inverse experiment showed that CM from MF-shCtr caused an increase in viability and STAT3 phosphorylation of CCA cells, as compared to CM from MF-shZEB1. *In vivo*, subcutaneous injection of EGI-1+MF-shCtr to immunodeficient mice led to generation of larger tumors than EGI-1+MF-shZEB1 or EGI-1 alone.
Conclusion: ZEB1 expression in MF plays a key role in CCA progression by inducing proliferative and survival signaling both in CCA tumor cells and MF, which may impact effectiveness of current therapy regimens with gemcitabine.

THU-503

Macrophage migration inhibitory factor shows a pro-proliferative and anti-apoptotic effect on hepatoma cells in vitro and promotes tumour growth in vivo

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Background and aims: Macrophage Migration Inhibitory Factor (MIF) is a proinflammatory cytokine and has been characterized in different chronic diseases as well as solid tumors. Here, MIF reflects a carcinogenic role as it drives neo-angiogenesis and metastasis but inhibits apoptosis. Referring to the MIF receptors, CD74 was identified as an important target of MIF in malignant diseases. In this study we first analyze the role of MIF and its receptor CD74 in murine hepatoma cells *in vitro*. Next we apply a toxic model of murine hepatocellular carcinoma (HCC) to study the role of MIF and CD74 in HCC *in vivo*.
Method: BrdU assay was performed to analyze the influence of recombinant mMif on the proliferative capacity of Hepa 1–6 cells. Next, the role of mMif in sorafenib-induced apoptosis of Hepa 1–6 cells was investigated by an Annexin V-assay as well as TUNEL-staining. In both assays, an anti-CD74 antibody was used to investigate a dependence on CD74 signalling. To examine the role of MIF in murine HCC the DEN/CCl_4 model was applied to mice with a hepatocyte-specific *Mif* depletion (*AlfpCre*$^{+}$*Mif*$^{flox/flox}$ mice, *Mif*^{1hep}), *CD74* deficient mice and respective control mice. Tumor size and number were analysed. Next, qPCR of *Mif* and *CD74* was executed in dissected liver and tumor tissue of control mice whereas qPCR of proliferation markers was conducted in control as well as *Mif*^{1hep} and *CD74* deficient mice. Immunohistochemical staining of Mif and Ki67 was complemented.
Results: mMif promotes the proliferation of Hepa 1–6 cells in a dose-dependent manner. Moreover, mMif inhibits sorafenib-induced cell death of Hepa 1–6 cells as evidenced by decreased Annexin V- and TUNEL-staining. Both effects can be reversed using a CD74 neutralizing antibody. In WT mice, qPCR and immunohistochemical staining of dissected liver tissue showed an increased expression of Mif and CD74 in tumor tissue as compared to fibrotic liver tissue. DEN/CCl_4 treatment of *Mif*^{1hep} as well as *CD74* deficient mice results in a decreased number and size of tumors compared to respective controls. Furthermore, tissue of *CD74*$^{-/-}$ mice showed a reduced proliferation rate in the Ki67 staining replicating the *in vitro* results *in vivo*.
Conclusion: In this study we present first data on MIF´s pro-proliferative and anti-apoptotic impact on hepatoma cells and identify CD74 as a possible partner of MIF in murine HCC *in vivo*. As a conclusion, the inhibition of the MIF/CD74 axis could present a promising target for the improvement of HCC directed therapies.

THU-504

lncRNA HOTAIR promotes cancer stem cell properties in hepatocellular carcinoma via the STAT3/NANOG pathway

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Background and aims: lncRNA HOTAIR has been proved to play an essential oncogenic role in tumor initiation and progression, including hepatocellular carcinoma (HCC). However, the regulatory role of HOTAIR in liver cancer stem cells (LCSCs) properties remains largely elusive. The aim of this study was to investigate whether HOTAIR could modulate LCSCs properties in HCC.
Method: CD133 (+) LCSCs were purified from HCC cell lines Huh7 and HepG2 by FACS analysis. pHOTAIR or shHOTAIR were employed to ectopically increase or decrease HOTAIR expression. Then cell proliferation, colony formation, migration, and self-renewal capacity of LCSCs, as well as expression of NANOG, OCT4, SOX2 and STAT3 were analyzed. ChIP was used to detect the interaction of STAT3 on its target gene.
Results: Here we showed that lncRNA HOTAIR was highly expressed in LCSCs. Knockdown of HOTAIR markedly repressed the proliferation, colony formation, migration, and self-renewal capacity of LCSCs, whereas ectopic expression of HOTAIR dramatically promoted LCSCs properties. Furthermore, HOTAIR upregulated a panel of stemness genes, in which NANOG was found to be among the most significant one. Mechanically, HOTAIR activated STAT3 signaling via EZH2, leading to activation of NANOG expression and maintenance of LCSCs properties. Moreover, Treatment with STAT3 inhibitor abolished the effects of HOTAIR on the processes of LCSCs, as well as the expression of NANOG. In addition, phosphorylated-STAT3 directly binds to the NANOG promoter and regulates its expression.
Conclusion: Collectively, our findings suggest that lncRNA HOTAIR might play a critical role in the maintenance of LCSCs properties by activating the STAT3/NANOG signaling. Targeting HOTAIR would provide a novel therapeutic strategy for HCC.

Posters Friday, 12 April 2019

Autoimmune and chronic cholestatic liver disease: Clinical aspects

FRI-001

The PBC-10: A validated short clinic symptom screening tool for primary biliary cholangitis

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Background and aims: The impact of symptoms in PBC is increasingly appreciated and the recent EASL guidelines recommend annual symptom assessment. At present, however, there are no validated short assessment tools. The existing tools such as the PBC-40 being research tools which are too cumbersome for normal clinic use. Therefore we need a valid, short and practical Quality of life (QoL) measure and symptom screening tool for use in patients with PBC at the point of care. The aim of this study was to develop a short version of the PBC-40 QoL measure that can be easily used in clinical practice.
Methods: We analysed a total of 4721 completed PBC-40 QoL questionnaires from the UK-PBC cohort database. We used a dataset of completed PBC-40 questionnaires in 2013 (n = 2219) to derive the short PBC-QoL and carry out the initial validation. We then confirmed the validation of the short PBC-QoL on a second cohort of patients with PBC who returned the PBC-40 questionnaire in 2017 (n = 2502). We carried out stepwise regression psychometric analysis to identify the items for the short version of PBC-QoL. We selected those items that contributed 95% of the variation in the scores. We assessed the internal consistency, item-total correlation, frequency of endorsement, principal component analysis (PCA) and construct validity for the short PBC-QoL questionnaire.
Results: We identified the 10 most important questions to derive the short form PBC-QoL questionnaire (PBC-10). Further testing showed that PBC-10 had good internal consistency (Cronbach's Alpha of 0.905), item-total correlations between 0.2–0.8 (Table 1), good construct validity (r = 0.5583). Principal component analysis showed that the 10 questions provided good representation of 6 different QoL aspects of patients with PBC: fatigue, psychological, cognitive, physical, skin and eating or drinking domains. Further validation on the second cohort of patients with PBC (n = 2502), confirmed the validity and reliability of PBC-10. There were no ceiling effects and skewness values of all 10 items ranged were acceptable between –1 to 1.

Table: PBC-10 items and their psychometric properties.

	PBC-10 items	% cumulative variance	Item total correlations
1	Fatigue interfered with my daily routine	.688	0.803
2	Because of PBC, I found it difficult to concentrate on anything	.816	0.779
3	PBC has reduced the quality of my life	.868	0.791
4	I have felt embarrassed because of the itching	.903	0.542
5	I feel guilty that I can't do what I used to do because of having PBC	.921	0.792
6	I had to force myself to do the things I needed to do	.936	0.804
7	My mouth was very dry	.945	0.574
8	My social life has almost stopped	.951	
9	I ate or drank only a small amount and still felt bloated	.958	0.571
10	If I was busy one day I needed at least another day to recover	.963	0.802

Conclusion: PBC-10 is a new short and valid quality of life measure that has the potential to be used in usual clinical practice for patients with PBC.

FRI-002

Sustained remission after treatment withdrawal in autoimmune hepatitis: A multicenter retrospective study

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Background and aims: In patients with autoimmune hepatitis (AIH), relapse rates up to 90% after treatment withdrawal have been reported. The main objective of this study was to assess in AIH patients with prolonged complete biochemical response the relapse rate after treatment discontinuation and to identify the factors associated with relapse. Secondary objectives were to identify the predictive factors of histological remission and to evaluate the evolution of hepatic fibrosis.
Method: Data from patients with AIH followed between 1988 and 2018 in 7 centers from France were reviewed retrospectively. Patients

who had reached sustained biochemical remission on first-line immunosuppressive treatment were included. Relapse was defined as any elevation of aminotransferases or gammaglobulins/immunoglobulins G after treatment withdrawal. The relapse rate was analyzed using Kaplan Meier analysis. The predictive factors of histologic remission were analyzed by univariate and multivariate logistic regression analysis.

Results: Sixty-two AIH patients (47 female, median age: 44 years) were included. Thirty-nine stopped therapy after a median treatment duration of 64 months (25–265) and a median biochemical response of 47 months (13–155), among which 24 had a biopsy before withdrawal: 21 had a Metavir score A0 and three A1. During follow-up, 7 relapsed with a median time of 9.4 months. The cumulative rate of relapse was 12% at 12 months and 25% at 64 months. Only one patient with Metavir score A0 at treatment withdrawal relapsed, Other relapsers were 2 patients Metavir A1 and 4 without biopsy before treatment withdrawal. In univariate analysis, the only significant difference was a higher prevalence of anti smooth muscle antibodies in relapsers than in sustained responders (100% vs 50%, p = 0.005). Among the 62 included patients, 47 had a biopsy after a median treatment duration of 65 months (20–265) and a median biochemical response of 48 months (9–149). Twenty-five (53%) were Metavir A0 and 22 (47%) ≥ A1. Multivariate analysis showed that independent predictors of histological remission were older age (OR1.11 CI95% (1.03;1.2) P = 0.007), mild to moderate fibrosis at diagnosis (OR = 8.06 CI95% (1.4;47.6) p = 0.02) and AST level < 0.6 × ULN at the time of control biopsy (OR = 7.05 CI95% (1.3;36.7) p = 0.02). Regarding the course of fibrosis after a median time of 48 months of biochemical remission, there was a significant improvement in the stage of fibrosis (p = 0.007).

Conclusion: This retrospective study indicates that the relapse rate after treatment withdrawal in AIH patients is limited (25% at 64 months) when the treatment is stopped after a prolonged period of biochemical remission and a complete histological response. Older age, mild to moderate fibrosis at diagnosis and lower serum concentration of transaminases AST at the time of control biopsy are independent predictors of histological response.

FRI-003

Early response to corticosteroid treatment supports differentiation of drug-induced liver injury and autoimmune hepatitis

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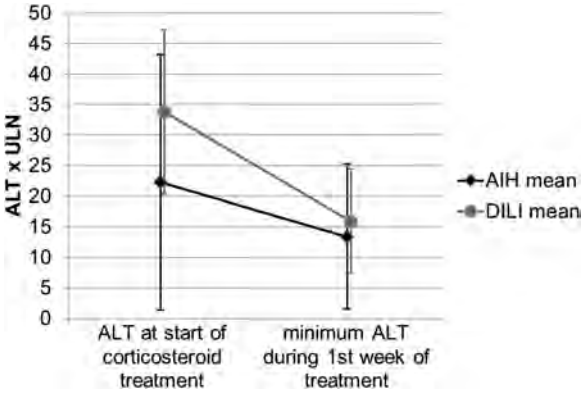
Background and aims: Drug-induced liver injury (DILI) and idiopathic autoimmune hepatitis (AIH) are competing diagnoses in patients with acute liver injury and drug intake. In absence of markers unequivocally identifying DILI or AIH, scores like RUCAM and the AIH score are used to distinguish both entities at initial presentation. However, in some cases the diagnosis remains ambiguous. Consequently some DILI patients unnecessarily receive longterm corticosteroid treatment. Our aim was investigate a simple parameter to discriminate DILI and AIH shortly after starting steroid treatment.

Method: For the present analysis, 43 patients with acute liver injury who took at least one drug and who received corticosteroids were included and comprised 22 DILI and 21 AIH cases. AIH score and RUCAM were calculated at initial presentation, the final diagnosis was made from analyzing the course of disease. Changes in the serum alanine aminotransferase (ALT) concentrations after starting corticosteroid treatment were determined and compared between the DILI and AIH groups.

Results: While 58% of patients (n = 25) were correctly classified at presentation by AIH score and RUCAM, respectively, in nearly one third (n = 13) of the 43 patients results were inconclusive. Five other patients were misclassified by the scores. The decrease in ALT levels one week after the initiation of steroid therapy was significantly more pronounced in patients with the final diagnosis of DILI than in AIH patients (accuracy 81%). This difference was also observed in the 18 patients misclassified or with inconclusive results at initial presentation (accuracy 94%).



Conclusion: Short-term response of ALT to steroid therapy helps to differentiate DILI and AIH. This may be helpful to determine the duration of corticosteroid treatment, particularly in patients with inconclusive diagnostic scores.

FRI-004

Cirrhosis status at diagnosis, non-Caucasian descent, treatment response and age determine long term survival in autoimmune hepatitis

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Background and aims: Treated autoimmune hepatitis (AIH) has a ten year survival between 80 and 96%. Conflicting reports exist on predictors of long term survival. The aim of this study was to evaluate the influence of baseline parameters and treatment response on long term survival in AIH patients.

Method: In this retrospective cohort study patients with AIH were included in 4 university hospitals in the Netherlands. Baseline and survival data were collected by chart review. Survival was defined as survival free of liver transplantation or liver-related death. For the influence of treatment response on survival a landmark analysis was used in which follow-up started 12 months after start of treatment. Uni- and multivariate Cox regression and Kaplan-Meier and logrank analysis were performed.

Results: In total 396 AIH patients with median follow-up of 110 months (range: 1–560 months) were included. Cirrhosis was present in 124 (31%) of which 39 (10%) were decompensated at diagnosis. During follow-up 18 patients received a liver transplantation and 18 patients died from liver related causes. Univariately higher age, non-Caucasian descent, low ALAT, low albumin and low platelets were correlated to worse survival (p = 0.027; p = 0.004; p = 0.017; p < 0.001 and p < 0.001 respectively), and ten year survival was worse in compensated vs decompensated cirrhotic patients vs non-cirrhotic patients (84% vs 51% vs 98%; p < 0.001). Patients reaching complete biochemical remission in the first 12 months of treatment had a better survival compared to patients who did not (p = 0.002).

In multivariate analysis age, non-Caucasian descent and cirrhosis status at diagnosis remained significant predictors for survival. If treatment response after 12 months was added this, cirrhosis status and non-Caucasian descent remained significant, but age was not significant anymore.
Conclusion: At diagnosis presence of (de)compensated cirrhosis, non-Caucasian descent and age predict long term survival in autoimmune hepatitis. Reaching biochemical remission within 12 months after diagnosis replaces age as significant factor in landmark analysis. This is the only identified modifiable factor and should be a treatment goal to prevent progression of disease and improve long term survival.

FRI-005

Characteristics and outcome of autoimmune hepatitis-primary biliary cholangitis and autoimmune hepatitis-primary sclerosing cholangitis overlap patients compared to autoimmune hepatitis patients

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Background and aims: In 10% of the autoimmune hepatitis (AIH) patients features of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) are present, called overlap or variant syndromes. The aim of this study was to characterize AIH-PBC and AIH-PSC patients and compare outcome to AIH patients.
Method: In a retrospective cohort study all patients with AIH-PBC and AIH-PSC were included in 3 university hospitals. AIH-PBC patients had to fulfil the strict Paris criteria. AIH-PSC patients needed a definite diagnosis of AIH according to the simplified criteria and signs of PSC on ERCP, MRCP or onion ring fibrosis on liver biopsy. Characteristics and outcome were compared to AIH in a case-control design matched on age and cirrhosis.
Results: Twelve AIH-PBC, 25 AIH-PSC and 74 AIH patients were included. AIH-PSC patients were more often males compared to AIH patients (56% vs 28%; $p = 0.007$) and had large duct PSC in 92%. AIH-PBC patients had higher AF and GGT ($p < 0.001$ and $p = 0.006$) and presence of AMA antibodies in 75%. AIH-PSC and AIH-PBC had lower ALAT than AIH at diagnosis ($p = 0.014$) but IgG levels and SMA antibodies did not differ ($p = 0.79$ and $p = 0.58$).
Treatment with prednisone, azathioprine and ursodeoxycholic acid (UDCA) was started in all AIH-PBC and AIH-PSC patients, except UDCA in 2 patients. Complete AIH remission was obtained in 8 (67%), 16 (64%) and 61 (82%) of the AIH-PBC, AIH-PSC and AIH patients ($p = 0.12$).
The median GLOBE score in AIH-PBC patients was −0.41 (range: −1.57–2.91) resulting in an expected median 10 year survival of 89% (range: 4–97%). The median Amsterdam Oxford score was 2.45 (range: 0.95–3.75) in AIH-PSC patients resulting in an expected median 10 year survival of 59% (range: 14–88%).
At the end of median follow-up of 107 months (range: 1–353) 4 (33%) AIH-PBC, 8 (32%) AIH-PSC and 8 (11%) AIH patients had progressed to liver transplantation or liver related death ($p = 0.023$). Four (16%) AIH-PSC developed a cholangiocarcinoma.
Conclusion: In 12 AIH-PBC patients and 25 AIH-PSC patients using strict criteria no difference was found regarding IgG, SMA antibodies and response to therapy compared to AIH patients. Survival was worse in AIH-PSC and AIH-PBC patients than AIH patients. Survival of AIH-PBC patients was worse than expected according to the GLOBE score and survival of AIH-PSC patients was better than expected according to the Amsterdam Oxford score although AIH-PSC patients are at risk for developing cholangiocarcinoma.

FRI-006

Soluble CD163 and mannose receptor as markers of liver disease severity and long term prognosis in patients with primary biliary cholangitis

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Background and aims: In primary biliary cholangitis (PBC) activated macrophages are involved in liver inflammation and fibrosis. The macrophage activation markers soluble (s)CD163 and sMR are associated with liver disease severity and prognosis in other chronic liver diseases. However, sCD163 and sMR have never been investigated in PBC patients.
Method: We included 202 patients with PBC from the Italian PBC Study Group cohort. Blood samples from study inclusion were used to estimate correlation between the macrophage activation markers and ALP, ALT and bilirubin. Further, the patients were followed from enrolment until they experienced an event or censoring at the last known hospital visit. Events were defined as follows: (1) death from a liver-related cause, meaning liver failure, variceal haemorrhage, or hepatocellular carcinoma (HCC); or (2) LT for PBC.
Results: Ninety-three percent were women and median age was 62 (IQR 53–71) at enrolment. Median sCD163 was 3.43 mg/L (IQR 2.48–5.35) and median sMR was 0.35 mg/L (IQR 0.28–0.45). There was a significant increase in sCD163 and sMR with increasing baseline ALP, but not with increasing ALT or bilirubin. sCD163 and sMR was lower in patients with treatment response to UDCA compared to the non-responders (3.25 vs. 4.37). The 179 patients in the follow-up analysis were followed for a median of 8.6 years, and sCD163 and sMR predicted long-term risk of LT or liver related death. Finally we showed an increasing in the prediction accuracy of poor outcome gained by adding sCD163 to the UK-PBC risk score.
Conclusion: The macrophage activation markers correlate with ALP in PBC patients and are prognostic markers of liver related death or LT.

FRI-007

Serum markers of macrophage activation CD163 and Mannose receptor predict transplant-free survival in primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a progressive and remarkably variable liver disease characterized by bile duct inflammation and fibrosis. Biomarkers predicting outcome are currently not established. Soluble (s)CD163, a macrophage specific activation marker, and mannose receptor (sMR) is associated with disease severity and outcome in other liver diseases but has not

been investigated in PSC. *Aim:* To evaluate the prognostic utility of sCD163 and sMR in patients with PSC.
Method: Plasma samples were available from 138 large-duct PSC patients (102 [74%] also had inflammatory bowel disease) recruited 2008–2012. The median follow-up time was 2.2 (range 0–4.3) years. Macrophage activation markers sCD163 and sMR were assessed by ELISA. The Enhanced Liver Fibrosis (ELF) Test as well as the Mayo score were assessed for comparison.
Results: Both markers showed incremental elevation in groups of PSC patients with increasing disease severity as defined by either Mayo score or ELF test ($p < 0.001$). Patients with high baseline plasma levels of sCD163 or sMR had shorter survival compared to patients with low baseline plasma levels whether divided into groups defined by tertiles, established upper limit of normal, or optimal cut-off value defined by Youden ($p < 0.001$). Both sCD163 and sMR were associated with transplant-free survival in univariate Cox-regression analyses but not in multivariate analyses.
Conclusion: Specific markers of macrophage activation are elevated according to disease severity in PSC patients. Furthermore, sCD163 was identified as a potent prognostic marker and predictor of transplant-free survival in PSC.

FRI-008
Incidence, prevalence and mortality of primary sclerosing cholangitis in Italy: A population-based study
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Background and aims: Studies on primary sclerosing cholangitis (PSC) are mainly based on tertiary referral, retrospective case series with relevant selection bias, and population-based epidemiologic studies are scarce. To estimate prevalence, incidence and mortality rates of PSC in Italy, using population-based data sources.
Method: Two data sources were used: i) the National Rare Diseases Registry (RNMR) run by the National Center for Rare Diseases of the Italian National Institute of Health (ISS); ii) the National Mortality Database (NMD), run by the Unit of Statistics of ISS, based on official data from the Italian National Institute of Statistics. In the period 2001–2014, all PSC cases (defined according to RNMR criteria) were selected. A deterministic linkage between RNMR and NMD was performed to evaluate the vital status and causes of death of the selected cases. Given that PSC does not have a specific code in ICD-10, the larger group "cholangitis" (code K83.0) was investigated.

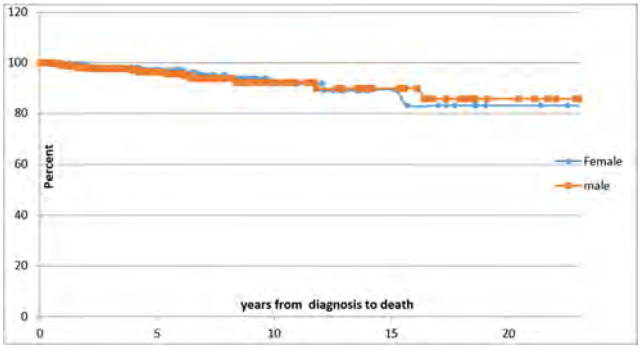

Figure: Survival time in years from diagnosis using Kaplan Meier estimator

Results: In the study period 502 PSC cases were identified (40% females). Since the RNMR reached full national coverage in 2011, PSC patients registered before where excluded; the mean number of new PSC patients registered in 2012–2014 was 61/year with a mean crude annual incidence of 0, 10 per 100.000 persons. The estimated crude prevalence of PSC was 0.78 per 100.00. Mean age at disease onset and at diagnosis were 33 and 37 years, respectively, highlighting a mean diagnostic delay of 4 years. We reported interregional mobility with overall 12% of patients moving in other regions. Ten-year survival was 92%; in 52% of deaths, the cause was PSC-related.
Conclusion: This is the first description of epidemiology of PSC in Italy. For rare conditions such as PSC, population-based cohorts studies are of paramount importance. Incidence and prevalence rates of PSC in Italy, using a population-based study design, are markedly lower and survival much longer than the ones reported from tertiary, single-centre series. Moreover, the diagnostic delay and the patient interregional mobility highlights the need for increasing awareness on the disease and for resource reallocation among regions within the National Health Service system.

FRI-009
Bezafibrate add-on therapy in high-risk primary biliary cholangitis is associated with prolonged predicted survival even in patients with incomplete biochemical improvements
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Background and aims: Data from the BEZURSO trial showed that bezafibrate therapy in addition to ursodeoxycholic acid (UDCA) increased the rate of complete biochemical response in patients with high-risk primary biliary cholangitis (PBC). However, not all patients from this trial equally responded to bezafibrate add-on and the efficacy of this treatment in incomplete responders remains uncertain. This post-hoc analysis of the BEZURSO trial aimed to characterize the factors predictive of, and the predicted outcomes associated with, an incomplete response to bezafibrate add-on therapy in high-risk PBC patients.
Method: The study population included 100 patients with an incomplete response to UDCA (Paris-2 criteria) who were randomly assigned to bezafibrate 400 mg/d ($n = 50$) or placebo ($n = 50$), in addition to continued UDCA, for 24 months. Incomplete response to bezafibrate was defined at the end of study (EOS) based on Paris-2 criteria. The predictive factors of incomplete response to bezafibrate were studied using a logistic regression model. The Globe and UK-PBC risk scores were used to estimate the predicted mortality or need for liver transplantation (LT) in complete and incomplete responders from each treatment group. The Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner tests were used for the comparison of groups.
Results: The rate of incomplete Paris-2 response to bezafibrate was 30%. At baseline, the factors individually associated with an incomplete response to bezafibrate included significant pruritus (VAS > 3), portal hypertension (PH), and high values of liver stiffness, total bilirubin, ALP, or AST. In multivariate analysis, PH and high ALP levels (> 2.53 xULN) were independent predictors of incomplete response to bezafibrate. At EOS, median levels of ALP in bezafibrate complete responders (BCR), bezafibrate incomplete responders (BIR), and placebo patients (PP) were 0.90 xULN, 1.52 xULN, and 2.62 xULN, respectively. Median (IQR) changes from baseline to EOS in 15-year predicted mortality or need for LT of BCR, BIR, and PP were –45% (–58%; –25%), –16% (–41%; –3%), and 14% (–1%; 47%), respectively with the Globe score and –43% (–61%; –16%), –13% (–32%; 13%), and

22% (7%; 50%), respectively with the UK-PBC score ($p < 0.001$ for both models; Figure). The predicted mortality or need for LT was significantly reduced in BIR as compared to PP ($p < 0.01$ and $p < 0.05$ for Globe and UK-PBC models, respectively).

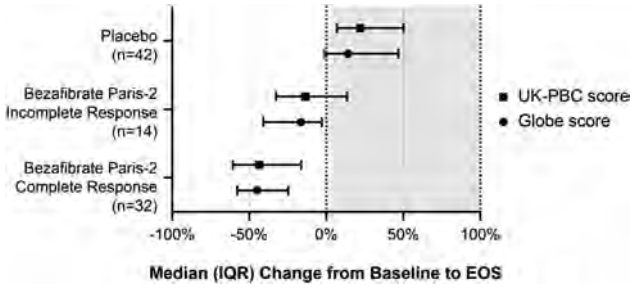

Figure: Predicted changes in 15-year mortality or need for LT

Conclusion: A third of PBC patients with an incomplete UDCA Paris-2 response still exhibits an incomplete biochemical response after 24 months of bezafibrate add-on therapy. These patients present more frequently at baseline with PH or ALP levels > 2.53 xULN. Their predicted mortality or need for LT is lower than that of UDCA plus placebo-treated patients suggesting that bezafibrate therapy should be continued in those patients.

FRI-010

Bezafibrate add-on therapy in high-risk primary biliary cholangitis is associated with an improvement of fibrometer and fibrometer-VCTE, two high-accuracy non-invasive fibrosis tests extensively validated in frequent chronic liver diseases

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Background and aims: Data from the BEZURSO trial showed that 2 years of bezafibrate therapy in addition to ursodeoxycholic acid (UDCA) improved the measures of vibration-controlled transient elastography (VCTE) and of enhanced liver fibrosis (ELF) score in patients with high-risk primary biliary cholangitis (PBC). The number of sequential liver biopsies, however, was too limited to show an effect on histology. The present post-hoc analysis aimed to assess the effect of bezafibrate add-on therapy on the measures of Fibrometer and Fibrometer-VCTE, two high-accuracy non-invasive fibrosis tests, [1, 2] and of Inflameter, a necro-inflammatory activity score.
Methods: The study population included 100 patients with an incomplete response to UDCA (Paris-2 criteria) who were randomly assigned to bezafibrate 400 mg/d (n = 50) or placebo (n = 50), in addition to continued UDCA, for 24 months. Fibrometer^{2G}, Fibrometer^{2G}-VCTE, and Inflameter were measured at baseline, 12 months, and end of study (EOS). Associations with histological fibrosis stage or hepatitis activity grade (METAVIR classification) were evaluated using the Kruskal-Wallis test. The performance for the diagnosis of cirrhosis was determined using the C-statistic. Longitudinal changes were analyzed in each treatment group using linear mixed models.
Results: A total of 235, 210, and 235 measures of Fibrometer^{2G}, Fibrometer^{2G}-VCTE, and Inflameter were analyzed in 82, 75, and 82 patients, respectively. Concordance analysis was made based on 105 liver biopsies collected in 82 patients. Fibrometer^{2G} and Fibrometer^{2G}-VCTE were significantly associated with histological fibrosis stage ($p < 0.001$ for both) but not with hepatitis activity grade. Inflameter was associated with high hepatitis activity grade ($p = 0.07$). The diagnostic performance of Fibrometer^{2G} and Fibrometer^{2G}-VCTE for cirrhosis was 0.83 and 0.92, respectively. Longitudinal analysis showed a significant reduction in the slope of Fibrometer^{2G}, Fibrometer^{2G}-VCTE, and Inflameter in the bezafibrate group as compared to the placebo group ($p < 0.001$ for all). The median differences (95% CI) between bezafibrate and placebo groups in percent changes from baseline to EOS in Fibrometer^{2G}, Fibrometer^{2G}-VCTE, and Inflameter were −42% (−69%; −14%), −37% (−83%; 8%), and −35% (−52%; −17%), respectively.
Conclusion: Two years of bezafibrate add-on therapy in high-risk primary biliary cholangitis is associated with a significant improvement of Inflameter, Fibrometer, and Fibrometer-VCTE, thus supporting a long-term beneficial effect on both hepatic inflammation and fibrosis.

1. Cales P et al. Clin Biochem 2010;43:1315–1322.
2. Boursier J et al. Am J Gastroenterol 2011;106:1255–1263.

FRI-011

Ductular reaction, intermediate hepatocites and fibrosis extension correlate with prediction of treatment failure to ursodeoxycholic acid in primary biliary cholangitis

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Background and aims: We recently derived and validated a model including alkaline phosphatase (ALP), bilirubin, aminotransferase, age at diagnosis, and waiting time before receiving ursodeoxycholic acid (UDCA), i.e. the *UDCA-response score* (*URS*). This score predicts future response to UDCA prior to initiation of therapy in patients with primary biliary cholangitis (PBC) and enables pre-treatment selection of high-risk PBC patients for second-line therapy earlier in the disease course, hence delivering effective care. Aim of this study was to validate the correlation of the predictive model *URS* with histological features in PBC patients.
Method: We evaluated formalin-fixed, paraffin-embedded liver biopsies from treatment-naive PBC patients, performed at diagnosis. Biopsies with fewer than nine complete portal tracts were excluded. Sections were stained with hematoxylin-eosin and Sirius red. We used the Ishak system to grade portal inflammation, interface hepatitis, lobular inflammation. Sirius Red stain was used for

quantitative assessment of fibrosis using an image analysis algorithm. Cytokeratin 7 (K7) immunoreactivity was used to evaluate ductular reaction (DR) and intermediate ($K7^+$) hepatocytes (IH). The area occupied by $K7^+$ DR was quantified by an image analysis algorithm. IH were defined as hepatocytes positive by immunofluorescence for K7 and albumin. Histological evaluation was done independently by two authors blinded to the clinical data.

Results: In 46 liver biopsy samples from treatment-naive PBC patients, the *URS* was associated with DR ($r = -0.830$, $p < 0.0001$, **figure 1**), IH ($r = -0.544$, $p < 0.0001$) and fibrosis extension ($r = -0.707$, $p < 0.0001$). Moreover, there was correlation between the extent of DR and ALP at diagnosis ($r = -0.514$, $p < 0.0001$), interface hepatitis ($r = -0.554$, $p < 0.0001$), and fibrosis extension ($r = -0.609$, $p = 0.0060$). No statistically significant correlation was found between the *URS* and interface hepatitis, portal and lobular inflammation.

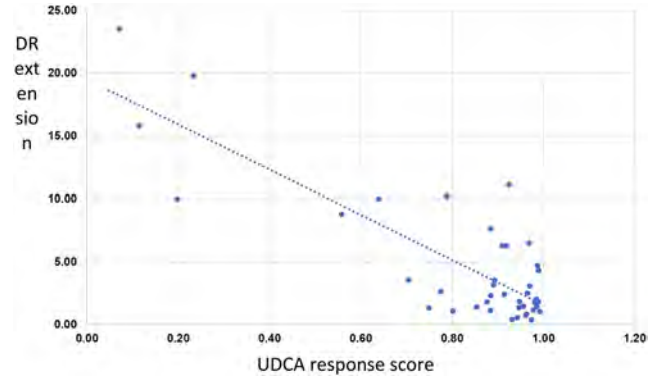

Figure 1: Correlation of estimated probabilities of response to UDCA based on the UDCA Response Score with the extent of ductular reaction expressed as volume fraction of liver parenchyma.

Conclusion: We identified that ductular reaction, intermediate ($K7^+$) hepatocytes and fibrosis extension correlate with prediction of treatment failure to UDCA in PBC. Ductular reaction and intermediate hepatocytes are a hallmark of severe biliary injury. This emphasizes the value of liver biochemistry at diagnosis as accurate surrogate biomarker for biliary injury in PBC and suggests that the severity of biliary injury and fibrosis are major determinants of treatment failure to choleretic treatment.

FRI-012

Analysis of clinical and histological factors to differentiate autoimmune hepatitis of drug induced liver injury

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Background and aims: The differential diagnosis between AIH and DILI is a clinical challenge due the lack of specific diagnostic tests. Our aim was to investigate clinical and/or histological factors which may facilitate the differential diagnosis of these entities.

Method: Retrospective observational study of histologic registers of AIH and DILI in our institution (2007–17), reviewed by an expert pathologist. Diagnosis was based in AIH diagnostic scores, CIOMS-RUCAM and evolution parameters. Comparative analysis was made by Chi-Square and non-parametric tests, Odd ratio (CI 95%).

Results: Forty-six patients (50% men):20 DILI, 26 HAI, mean age: 53.8 ± 14, 6. Hepatocellular biochemical pattern, IgG elevation and a chronic course were associated with AIH. Presence of autoantibodies was associated with AIH, but 38% of these patients had a negative immunological study. DILI was associated with cholestasic syndrome, fever and hypersensibility, and with a higher phosphatase alkaline, bilirubin and leucocytes serum levels. In the histological study, the presence of interface hepatitis and linfoplasmocitary infiltrate were the best predictive factors of AIH while cholestasis was of DILI. There weren't differences in neutrophilic infiltrate, hepatic russets, necrosis nor endothelitis.

Conclusion: In our study histological features were the ones which determine more accurately the diagnosis of AIH, because a relevant percentage of these patients had a negative autoantibody study. Biopsy remains the most important diagnosis test in the differential diagnosis between both entities.

Figure 1: (abstract: FRI-012): Independent factors of AIH.

Variables	DILI (n = 20)	HAI (n = 26)	p (< 0, 05)	OR (IC 95%)
Cholestasic syndrome	**19/20 (95%)**	15/26 (57, 69%)	0, 0059	**0, 072 [0, 008–0, 62]**
Fever	**6/20 (30%)**	1/26 (3, 85%)	0, 0326	**0, 093 [0, 01–0, 86]**
Hypersensibility	**7/20 (35%)**	0/26 (0%)	0, 0014	*Not calculable*
Hepatocellular biochemical pattern	12/20 (60%)	**23 (88, 46%)**	0, 0376	**5 [1, 14–22, 89]**
Phosphatase alkaline (U/L)	**283, 20 ± 179, 28**	173, 23 ± 149, 60	0, 0282	0, 995 [0, 991–0, 999]
Total bilirrubin (mg/dl)	**13, 26 ± 8, 62**	7, 78 ± 8, 66	0, 0051	**0, 929 [0, 86–0, 999]**
Leucocytes (x1000/μl)	**9, 14 ± 3, 71**	6, 49 ± 1, 79	0, 0050	**0, 620 [0, 43–0, 89]**
Neutrophils (x1000/μl)	**5, 94 ± 4, 06**	3, 73 ± 1, 31	0, 0056	**0, 523 [0, 28–0, 96]**
IgG (mg/dl)	1334, 31 ± 487	**2127, 76 ± 1116, 34**	0, 0175	**1, 002 [1, 001–1, 003]**
Autoantibodies	2/20 (10%)	**16/26 (61, 54%)**	0, 0006	**14 [2, 74–75, 78]**
Clinical evolution:	1/20 (5%)	**8/26 (30, 77%)**	0, 0406	*Chronicity vs Remission*
Chronicity	17/20 (85%)	13/26 (50%)		**10, 46 [1, 16–94, 48]**
Remission	2/20 (10%)	5/26 (19, 23%)		
Flares				
Cirrhosis on follow-up	2/20 (10%)	**11 (42, 31%)**	0, 0217	**6, 6 [1, 2–34, 53]**
Interface Hepatitis	5/20 (25%)	**22/26 (84, 62%)**	< 0, 0001	**16, 49 [3, 79–71, 72]**
Linfoplasmocitary or plasmocitary portal infiltrate	2/20 (10%)	**12/26 (46, 15%)**	0, 0210	**6, 86 [1, 3–36, 04]**
Histological cholestasis	**11/20 (55%)**	5/26 (19, 23%)	0, 0153	**0, 195 [0, 052–0, 725]**

FRI-013

A combined blood and MR imaging risk score for monitoring liver inflammation in paediatric AIH

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Background and aims: Management of autoimmune hepatitis (AIH) is highly variable in practice, with lack of consensus on optimal follow-up strategies for patients, including the utility of on-treatment liver biopsy. Patient preference does not support serial biopsies, and blood based measures alone lack the sensitivity to subtle inflammation.
Liver*MultiScan*™ is a multiparametric MRI method which measures iron-corrected T1 (cT1). This has been shown to correlate with the key histological features of liver disease (ballooning, inflammation and fibrosis), and to predict clinical outcomes. Here, we evaluate the utility of cT1 in AIH, in combination with circulating biomarkers, for the stratification patients experiencing flares of liver inflammation.
Method: Forty-six AIH patients (19 male; mean age 13.8 [6–18yrs]; underwent Liver*MultiScan*™, with comparison to liver biopsy and liver enzymes (ALT, AST, GGT and bilirubin). Correlation with the imaging and blood biomarkers against biopsy was explored using Spearman's Rho. The ability of these biomarkers to identify individuals with histologically confirmed portal inflammation was evaluated using AUROC analysis, with step-wise logistic regression used to combine biomarkers into a risk score.
Results: All biomarkers correlated with Ishak fibrosis (Table 1-top) and all except total bilirubin correlated with portal inflammation (Table 1-bottom). Pairwise comparisons identified different patterns for cT1 compared to blood biomarkers, with stronger separation between Ishak scare 2–3 and 5–6 ($p < .001$) and equally a more stepwise pattern with portal inflammation.
Independently, both cT1 and ALT were the best predictors of portal inflammation ≥ 2 (cT1 AUROC: 0.70 (0.55–0.85, se: 39%, sp: 100%, NPV:61%, PPV: 100%)); ALT AUROC 0.73 (ci: 0.58–0.88), se: 61%, sp: 77%, NPV: 56%, PPV: 81%). Interestingly, the superior model with the strongest predictor of those with current portal inflammation ≥ 2 was a risk score combining cT1, total bilirubin and AST, (AUROC of 0.84 (0.7–0.94)) that was able rule-in those currently experiencing a "flare" with 100% specificity (PPV 100%, NPV 57%, Sensitivity 50%).

Table 1:

	cT1	ALT	AST	GGT	Bilirubin
Ishak Fibrosis	Rho = 0.43 p = 0.003	Rho = 0.43 p = 0.001	Rho = 0.45 p = 0.001	Rho = 0.43 p = 0.003	Rho = 0.52 p = 0.000
Portal Inflammation	Rho = 0.34 p = 0.022	Rho = 0.47 p = 0.001	Rho = 0.39, p = 0.081	Rho = 0.38 p = 0.001	Rho = 0.04 p = 0.785

Conclusion: Both ALT and cT1 are effective biomarkers for identifying portal inflammation. This performance for identifying low level inflammation however is further enhanced when cT1 is used in composite with AST and total bilirubin, highlighting the potential of multiparametric MRI when used in conjunction with circulating markers of disease for monitoring paediatric patients with AIH. Further research is warranted.

FRI-014

Diagnostic criteria for autoimmune hepatitis: what is a normal "IgG"?

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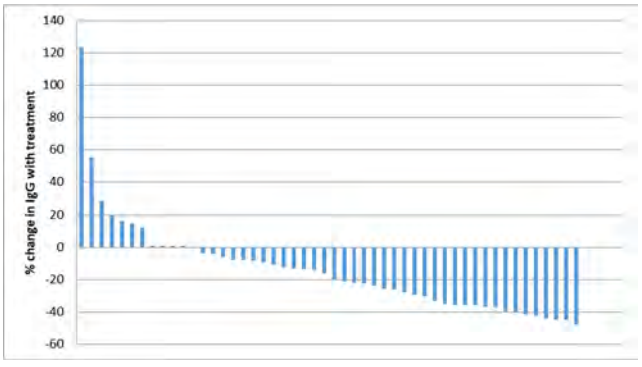
Background and aims: Simplified diagnostic criteria for autoimmune hepatitis (AIH) have been established by the International Autoimmune Hepatitis Group (IAIHG). These comprise autoantibodies, IgG level, histological parameters and the absence of viral hepatitis. "Probable" AIH is defined as a score ≥ 6 and "definite" AIH as a score of ≥ 7. Previous work has shown these criteria to have high sensitivity and specificity but a false negative diagnosis rate of 11%. The aim of this study was to apply the simplified IAIHG criteria to a cohort of AIH patients in a well-defined region of North-East England and North Cumbria to establish the false negative rate of diagnosis and examine the individual parameters in more detail.
Method: Clinical data was collected on 490 patients with an *a priori* clinical diagnosis of AIH. Information included demographic details, antibody status, IgG levels at diagnosis and follow-up and treatment response.
Results: The median age at diagnosis was 52 (4–87) years with 389 (79%) females. The majority (361 patients, 82%) were anti-nuclear or smooth muscle antibody positive, consistent with Type 1 AIH. 96% of patients had a diagnostic liver biopsy confirming AIH.
There were 62/335 (19%) patients with complete data available who did not meet the simplified IAIHG criteria for "probable" or "definite" AIH. IgG at diagnosis was available in 369 patients (median 22.3g/L (5.6–64.8), normal range 5.8–15.4) but 55 patients had normal IgG (15%), 24 (6%) had elevated IgG < 1.1xULN and 290 (79%) had elevated IgG > 1.1xULN. IgG at diagnosis and post-treatment were available for 277 patients, of whom 50 (18%) had normal IgG at the time of diagnosis (13.0g/L (5.6–15.4)). These patients would not have accrued "points" for IgG using the current criteria. However, IgG values at follow-up were significantly lower; median 10.1 (6–22) ($p = 0.0002$) (Figure).



Conclusion: Nearly a fifth of patients in this cohort had normal or sub-normal IgG values at the time of diagnosis with AIH. After treatment, 78% had experienced a decrease in their IgG. This suggests that the upper limit of normal being used currently may be too high and that delta change in IgG with therapy (rather than absolute values) is important. Patients are at risk of not being diagnosed in a timely manner with delayed treatment and potential under-treatment which are known to lead to higher morbidity and mortality in patients with AIH. Larger studies are needed to redefine the "normal" ranges for IgG.

FRI-015

Environmental triggering in primary biliary cholangitis: Disease risk relates to coal mining activity

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Background and aims: Primary biliary cholangitis (PBC) has a complex aetiology with the interplay of genetic and environmental factors. Spatial disease clustering suggests there may be an environmental trigger but its nature remains elusive. This study explored the role of putative environmental risk factors in a comprehensive cohort of PBC patients in the North-East of England and North Cumbria, using primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) as comparator autoimmune liver diseases. The aims were to see if disease clustering was associated with environmental factors local to the cases and if there were differences between PBC, PSC and AIH.
Method: All patients with PBC (n = 2150), PSC (n = 472) and AIH (n = 963) 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 (RR) in postcode districts. The null model examined for areas of high and low disease prevalence and models were then fitted with single spatial covariates. These were selected based on data from previous studies regarding triggering of autoimmunity: urban-ness, traffic, landfill sites, coal/lead mines, sandstone/limestone quarries, social deprivation scores and heavy metals. Deviance Information Criterion (DIC) was used to compare the fits of models.
Results: Different postcode districts with high and low prevalence were identified for each disease (Figure). When spatial covariates were added to the null model, coal mining was strongly associated with a higher prevalence of PBC (change in DIC 9.885). In contrast, high prevalence of PSC was seen in more rural and less socioeconomically deprived areas (change in DIC 2.308 and 2.784, respectively). No associations were found in AIH.
Conclusion: This work confirms that high and low prevalence areas are seen in PBC, PSC and AIH but with different postcode districts being "high risk" in each disease. The associated environmental risk factors for PBC and PSC were strikingly different. No associations with the putative risk factors were seen in AIH. The relationship between coal mining and PBC suggests that exposure to environmental entities through mining activity (due to specific use in the mining industry or altered exposure through micro-environment disruption) is linked to disease development. Further assessment is needed to investigate potentially modifiable pathological mechanisms or triggers for autoimmune liver diseases.

FRI-016

Validation of the PREsTo machine learning algorithm for the prediction of disease progression in patients with primary sclerosing cholangitis

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Background and aims: PREsTo is a machine learning-based algorithm that accurately predicted the risk of hepatic decompensation in patients with non-advanced PSC. Our objective was to prospectively validate the PREsTo algorithm for the prediction of disease progression in a randomized trial of PSC patients.
Method: We included 234 adults with large-duct PSC enrolled in a phase 2b, placebo-controlled trial of simtuzumab (SIM). Since SIM was ineffective in this 96-week study, treatment groups were combined for this analysis. The estimated risk of hepatic decompensation at 2 years was calculated according to the PREsTo algorithm using baseline (BL) age, alkaline phosphatase (ALP), AST, bilirubin, albumin, sodium, hemoglobin, platelets, and PSC duration. Liver fibrosis was staged according to the Ishak classification at BL, week 48, and week 96. Discrimination of PREsTo for hepatic decompensation, PSC-related clinical events (i.e. decompensation, ascending cholangitis, cholangiocarcinoma, transplantation), and progression to cirrhosis was determined using c-statistics. Model calibration was evaluated according to tertiles of predicted risk using the Hosmer and Lemeshow goodness-of-fit statistic.
Results: The median age was 45 years, 64% were male, 48% had UC, 62% were on UDCA, 51% had bridging fibrosis or cirrhosis, and the median (IQR) serum ALP and bilirubin at BL were 260 U/L (129–401) and 0.7 mg/dL (0.5–1.1), respectively. Over a median follow-up of 23.0 months (range, 2.8, 27.8), 10 subjects (4.3%) developed hepatic decompensation (ascites [n = 6], encephalopathy [n = 2], variceal hemorrhage [n = 2]), 47 subjects (20%) developed a PSC-related clinical event (first events of ascending cholangitis [n = 27], decompensation [n = 6], cholangiocarcinoma [n = 3], and other [n = 11]), and 36 of 209 (17%) non-cirrhotic subjects progressed to cirrhosis. PREsTo accurately predicted hepatic decompensation (c-statistic, 0.87 [95% CI

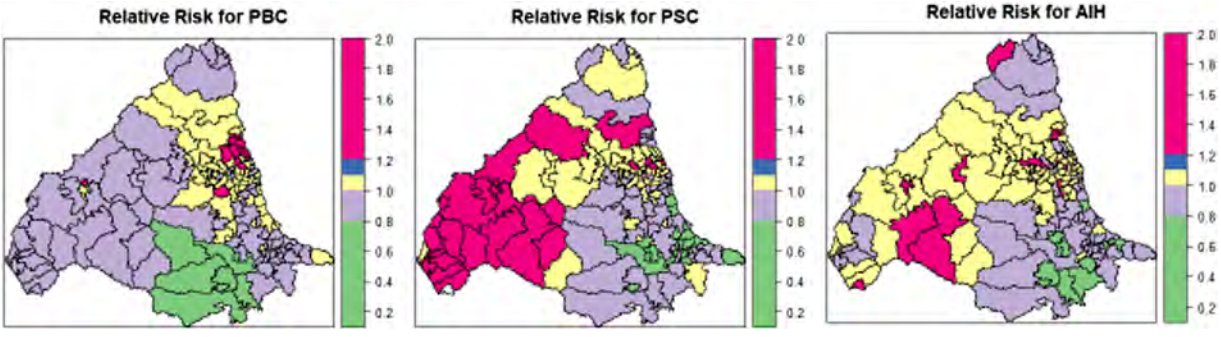

Figure: (abstract: FRI-015)

0.79–0.96]), but discrimination was lower for PSC-related clinical events (0.74 [95% CI 0.67–0.82]) and progression to cirrhosis (0.62 [95% CI 0.52-0.73]). Calibration of PREsTo for hepatic decompensation was good (observed vs expected events: low-risk: 0 vs 0.8; medium-risk: 1 vs 1.0; high-risk: 9 vs 8.4; p = 0.36).
Conclusion: In this prospective clinical trial of patients with PSC, the PREsTo algorithm accurately predicted the risk of hepatic decompensation, but had reduced performance for other PSC-related complications including progression to cirrhosis.

FRI-017
High prevalence of possible PSC recurrence post transplant evaluated by protocol biopsies
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Background and aims: Primary sclerosing cholangitis (PSC) is one of the leading indications for liver transplantation (LTX) in the Nordic countries. Recurrent PSC (rPSC) is estimated to affect at least 20-30% and is associated with reduced graft survival. The diagnosis is challenging and true prevalence figures are so far not available. We therefore aimed to evaluate the incidence and impact of rPSC on graft- and patient-survival using protocol biopsies.
Method: We evaluated all transplanted PSC patients with protocol liver biopsies in the time period 2008–2017. Clinical routine histology reports were classified as possible rPSC or no rPSC. Prevalence was calculated at 1, 3 and 5 years following LTX. Patient and graft survival were estimated by Kaplan-Meier plots, and the log rank test was used for comparison.
Results: Two hundred and fifty-one PSC patients receiving a liver allograft were evaluated for inclusion. Fifteen patients (6%) were excluded due to treated hepatic artery stenosis/thrombosis or early biliary strictures/anastomotic strictures. Out of the remaining 236 patients 48, 56 and 70 patients had liver biopsies at 1, 3 and 5-years post-LTX respectively. Histology was classified as possible rPSC in 27 (56.3%) 29 (51.8%), and 44 (62.9%) at 1, 3- and 5 years. In time-to-event analyses from the time of liver biopsy, there were no differences in re-transplantation-free survival between patients with possible rPSC and no rPSC at histology.
Conclusion: The prevalence of possible rPSC based on routine pathological evaluation of liver biopsies was above 50% at all time points, but this did not affect outcome in terms of graft and patient survival in a 5 years perspective. A structured approach to classification of rPSC in terms of histology and MRI is warranted in order to further evaluate the role of these modalities in predicting outcome.

FRI-018
High risk of no response and poor prognosis of immunosuppressive therapy in patients of pbc-aih overlap syndrome
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Background and aims: The aim of this study was to elucidate the clinical and histological features, response to corticosteroid therapy and long-term outcome of PBC-AIH overlap syndrome.
Methods: A cohort study was performed to evaluate the usefulness of immunosuppressive therapy and UDCA combination in this unique group. This cohort study was performed prospectively between October 2013 and May 2018 and included 96 biopsy-proven patients diagnosed according to strict criteria. The primary end points were biochemical response and outcome. Logistic regression analysis was performed to identify factors significantly associated with biochemical response.
Results: 49.0% of patients did not respond to treatment. The baseline values of total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, IgG, and presentation of cirrhosis differed significantly between the responders and non-responders ($p < 0.05$). The presence of cirrhosis ($p = 0.013$; odds ratio = 0.280) and IgG values ($p = 0.003$; odds ratio = 0.871) were associated with lack of response to the combination of UDCA and immunosuppression. Adverse event-free survival differed significantly between the two groups, according to the Kaplan-Meier estimate. Second-line immunosuppressive agents (mycophenolate mofetil and tacrolimus) led to biochemical remission in 33.3% of patients who did not respond to initial immunosuppression. Liver transplants were given to 2 patients with PBC-AIH. Eleven patients died from liver-related causes during follow-up.
Conclusions: There is a high risk of no-response and bad prognosis of PBC-AIH overlap syndrome in Asians. Early identification of no-response may allow timely intervention to prevent clinical deterioration. Second-line immunosuppressive agents only lead to 33.3% of response.

FRI-019
Readmission in hospitalized patients with autoimmune hepatitis in nationwide inpatient setting
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Background and aims: Autoimmune hepatitis (AIH) is an autoantibody mediated chronic inflammatory disease of the liver with a variety of different clinical phenotypes. AIH presentation can vary from asymptomatic elevations of liver enzymes, to nonspecific symptoms associated with chronic liver disease, to acute liver injury including rarely, fulminant liver failure. While typically managed in the outpatient setting, we aimed to study risk factors in hospital readmission among AIH.
Method: This is a retrospective cohort study using the 2014 NRD. We included non-elective hospitalizations with a diagnosis of AIH. Hospitalizations with age less than 18, or liver transplantation performed during same hospitalization were excluded, transfers to other hospitals and patients who left against medical advice were excluded as well. We also identified hospitalizations with cirrhosis, which was defined as hospitalizations with a diagnostic code of cirrhosis or any complications of cirrhosis (table 1). Readmission was defined as the first admission to hospital for any non-trauma cause within 90 days of the index admission. The primary outcome was the 90-day readmission rate. Secondary outcomes included mortality rate, causes for readmission, and readmission risk factors.
Results: The total number of admissions with AIH was 9, 153. The mean age was 57.7 (56.8-58.5), 77.8% were female, 43.9% had coexisting cirrhosis, and 10.6% underwent liver biopsy during hospitalization. The in-hospital mortality rate was 3.7%. The all-cause 90-day readmission rate was 25.2%. The in-hospital mortality rate for readmitted patients was 4.7%. The top causes for readmission were (1-5): hepatic encephalopathy, AIH, unspecified septicemia, non-alcohol-related cirrhosis, acute kidney failure. AIH with cirrhosis population had an in-hospital mortality rate of 6.1% and 90-day readmission rate of 31.1%. Various risk factors were tested using univariate and multivariate regression analysis. The odds ratios (ORs)

and p values were calculated using multivariable logistic regression and independent factors for readmission were identified: Medicaid (OR 2.24; 1.53-3.26) and Medicare (1.54; 1.20-1.98) with private insurance as reference, cirrhosis (1.42; 1.18-1.71), and higher Charlson Comorbidity Index (1.13; 1.08-1.19) were associated with higher odds of readmission, while liver biopsy (0.69; 0.51-0.94) was associated with lower odds of readmission after adjusting for multiple factors (table 2).

Table 1: Supplement

	Diagnostic/Procedure Codes (ICD 9)
Autoimmune Hepatitis	571.42
Liver Transplantation	50.51, 50.59
Liver Biopsy	50.11, 50.13
Cirrhosis	571.2, 571.5, 571.6
Esophageal Varices	456.1, 456.21
Variceal Bleed	456.20, 456.0
Hepatocellular Carcinoma	155.0
Portal Hypertension	572.3
Hepatic Encephalopathy	572.2
Hepatorenal Syndrome	572.4
Hepatopulmonary Syndrome	573.5
Ascites	789.59
Spontaneous Bacterial Peritonitis	567.23

Table 2: Independent Predictors of Readmission

Factor	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI	p-value
Age	0.99	0.99	1.00	0.06
Female Sex	1.00	0.82	1.22	0.99
Cirrhosis	1.42	1.18	1.71	**<0.01**
Charlson Comorbidity Index	1.13	1.08	1.19	**<0.01**
Liver biopsy	0.69	0.51	0.94	**0.02**
Prolonged Length of Stay (>10 days)	1.08	0.85	1.38	0.53
Primary Insurance				
Private	Reference			
Medicaid	2.24	1.53	3.26	**<0.01**
Medicare	1.54	1.20	1.98	**<0.01**
Uninsured	1.20	0.76	1.86	0.41
Median Household Income in Patient's Zip Code				
1st Quartile ($1-39,999)	Reference			
2nd Quartile ($40,000-50,999)	0.89	0.71	1.11	0.30
3rd Quartile ($51,000-65,999)	0.86	0.68	1.07	0.17
4th Quartile (≥$66,000)	1.00	0.80	1.26	0.97
Hospital Quintile (low-high)				
1st Quartile (1-20%)	Reference			
2nd Quartile (21-40%)	0.88	0.56	1.39	0.58
3rd Quartile (41-60%)	1.08	0.72	1.61	0.72
4th Quartile (61-80%)	0.99	0.67	1.45	0.95
5th Quartile (81-100%)	1.09	0.76	1.56	0.64

Conclusion: A quarter of AIH hospitalizations cause readmissions within 90 days. Readmissions were mostly for AIH, cirrhosis, and related comorbidities. The decreased readmission rate associated with liver biopsy may suggest that in the appropriate clinical setting, earlier utilization of tissue diagnosis prompts appropriate and effective therapy.

FRI-020

Identification of risk factors for histological progression with sequential liver biopsies in primary cholangitis patients

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Background and aims: Clinical outcomes of primary biliary cholangitis (PBC) remain vague despite improvements in the understanding of its natural history and prognosis. We previously reported that biochemical response to ursodeoxycholic acid (UDCA) according to the Nara criteria predicted the histological progression of PBC. The aim of this study was to determine factors associated with histologic progression in PBC patients using sequential liver biopsies.

Method: Thirty-five patients with PBC who received UDCA treatment underwent sequential liver biopsies. UDCA was administered in all patients after the initial liver biopsy. Accordingly, the patients were categorized into those demonstrating histological progression (progression group, PG) and those lacking histological progression (non-progression group, NPG). Pathologic staging was performed according to the Scheuer (SC) and Nakanuma (NA) systems. The NA system included grading of liver fibrosis (fibrosis score) and bile duct loss (BDL score). Univariate and multivariate analyses were conducted to assess factors distinguishing the PG and the NPG.

Results: Average patient age at the initial liver biopsy was 53.5 years, and patients were female. A mean of 2.7 liver biopsies per patient were obtained over a mean follow-up period of 6.7 year. There were 6, 12, 17, and 0 patients with SC stages 1, 2, 3, and 4, respectively, whereas 0, 7, 24, and 4 patients were categorized into NA stages 1, 2, 3, and 4, respectively. According to the SC system, 13 patients had histological progression, whereas 22 patients did not exhibit histological progression. According to the NA system, 9 and 26 patients were in the PG and NPG, respectively. The fibrosis and BDL scores progressed in 13 and 8 patients, respectively, whereas 22 and 27 patients did not exhibit progression, respectively. In univariate analysis, gamma-glutamyl transpeptidase (γ-GTP) level at two year after UDCA treatment initiation and pretreatment alanine aminotransferase (ALT) level were identified as risk factors for SC and NA stage progression, respectively. Univariate analysis also identified pretreatment γ-GTP level as significant factor associated with the increase in fibrosis score and ALT level at one and two year and aspartate aminotransferase level at two year after UDCA treatment initiation as significant factors associated with the increase in BDL score. However, in the multivariate analysis, there were no significant differences between PG and NPG for the serum liver enzymes. Multivariable logistic regression analysis showed that the rates of change in the γ-GTP levels after one year of UDCA treatment was an independent factor associated with the increase in NA stage progression.

Conclusion: The rates of change in the γ-GTP levels after one year of UDCA treatment is a significant factor for the increase in NA stage progression in PBC patients with sequential liver biopsies.

FRI-021

Comparing the predictive performance of the Mayo risk score and the GLOBE score in a large cohort of patients with primary biliary cholangitis

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Background and aims: The Mayo Risk Score (MRS) is the traditional risk prediction model in patients with primary biliary cholangitis (PBC), but its utility in clinical practice may be hampered by the use of peripheral edema as a subjective parameter. In contrast, the GLOBE score only includes readily available objective parameters. We aimed to assess and compare predictive performance of the MRS and GLOBE score in a large international cohort of patients with PBC.
Method: This study included patients of 7 centers of the GLOBAL PBC Study Group. By retrospective chart review, additional data were collected on diuretic use, peripheral edema and prothrombin time (PT), enabling calculation of the MRS. A combined end point of death or liver transplantation (LT) was used. Discriminatory performance of the MRS and GLOBE score was assessed with C-statistic at yearly intervals up to 5 years of UDCA therapy. Prediction accuracy of both models was assessed by comparing predicted survival with the actual observed survival in Kaplan-Meier analyses.
Results: A total of 1100 UDCA-treated PBC patients were included, with a mean (sd) age of 53.6 (12.0) years, of whom 1003 (91%) were females. During a median follow-up of 7.6 (IQR 4.1-11.7) years 169 patients reached an end point: 42 patients underwent LT and 127 patients died. At 1 year of UDCA treatment, the C-statistic for the MRS was 0.77 (95% confidence interval [CI] 0.73-0.81) and for the GLOBE score 0.80 (95% CI 0.76-0.84) ($p > 0.05$). The C-statistics was similar for both scores when recalculated from 2 to 5 years following initiation of UDCA. For the MRS the observed minus the predicted 5-year transplant-free survival in the < 20th, 20th –80th and > 80th percentile was +0.3%, +3.9%, and +13.2%, respectively. For the GLOBE score these differences were +0.3%, +1.8% and –0.8%, respectively. In patients with abnormal bilirubin ($n = 124$), the C-statistic was 0.73 (95% CI 0.66-0.80) for the MRS and 0.75 (95% CI 0.67-0.82) for the GLOBE score. Within this subgroup the observed minus the predicted transplant-free survival at 3 years and 5 years of follow-up was –6.3% and –9.6% for the MRS, and –3.4% and –2.7% for the GLOBE, respectively.
Conclusion: In this large cohort of patients with PBC, the MRS and GLOBE score had comparable discriminating performance for LT or death. However, the GLOBE score showed better prediction accuracy and may therefore be better applicable in daily clinical practice for optimal management of individual patients.

FRI-022

Characteristics of autoimmune hepatitis with acute presentation

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Background and aims: Autoimmune hepatitis (AIH) is a heterogeneous disease with a broad clinical spectrum. The aim of this study was to analyze the characteristics of patients with AIH with acute presentation in our area.
Method: 179 patients diagnosed of AIH from 1995 to 2018 were included; 113, prospectively recorded, had acute presentation (AP) and 66, retrospectively recorded, other patterns of presentation (non-AP). AIH diagnosis was based on Simplified Criteria or clinical judgment. A liver biopsy was obtained in 143/179 patients (79.8%; 81.4% AP, 77.2% non-AP). AP was defined by ALT > 10xULN, severe acute hepatitis (SAH) by prothrombin < 50% and acute liver failure (ALF) when encephalopathy was added to the previous findings.
Results: Among 113 patients with AP, 10 (9%) were diagnosed in the period 1995-2002, 43 (38%) in 2003-2010 and 60 (53%) in 2011-2018. 25 of them (22.1%) had SAH and 10 (8.8%) ALF; no differences were found in the proportion of SAH or ALF in the three periods of time (20%/25.5%/36.6%; $p = 0.35$). Comparing patients with AP and non-AP there were no differences in sex (female 71.6% vs 80.3%; $p = 0.20$) or age [55 (45-65) vs 53.5 (36.7-64.5); $p = 0.28$)]. Features of other autoimmune diseases were more frequent in non-AP than in AP patients, but without statistical significance (37.8% vs 25.6%; $p = 0.086$). AP were more frequently seronegative (18.6% vs 7.2%; $p = 0.007$) while IgG levels were similar in AP and non-AP (19 vs. 18 g/L; $p = 0$, 44). The proportion of patients with atypical histology was higher in AP than in non-AP (31.5% vs. 7.8%; $p = 0.001$). Simplified Criteria score was ≥ 6 in 60% in AP and 69% in non-AP ($p = 0.31$). Although there were no differences in the proportion of patients with ≥ 1 acute exacerbation during follow-up (39.8% in AP vs 28.7% in non-AP; $p = 0.13$), patients with AP needed more frequently second line treatment (15.9% vs 4.5%; $p = 0.022$). During a median follow-up of 77 months (26-131), 15 patients were transplanted and 30 died. Free transplant survival at 5, 10, 15 and 20 years was 78.4%, 75.4%, 69.1% and 49.1% in patients with AP and 90.8%, 84.8%, 74.2% and 66.8% in those with non-AP ($p = 0.090$).
Conclusion: In our area, acute presentation of AIH is increasing. Nearly one third of AIH with AP develop severe acute hepatitis or acute liver failure. Patients with AP are frequently seronegative and with atypical histology, which makes diagnosis difficult. Response to standard treatment and free transplant survival are lower in patients with HAI with AP than in the rest.

FRI-023

Inadequate response to UDCA among PBC patients under routine care in the US: Rising serum bilirubin even in the normal range is a risk factor and subsequent clinical follow-up differs based on treatment response

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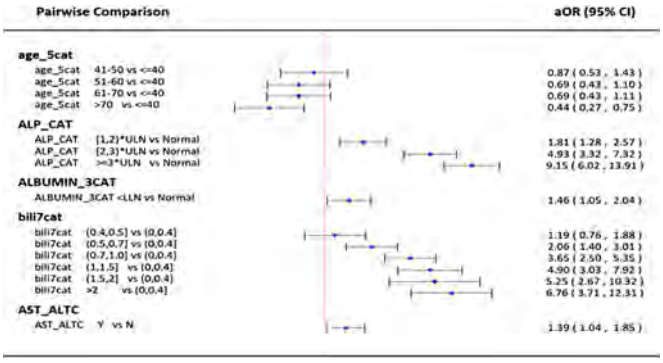
Background and aims: Ursodeoxycholic acid (UDCA) is a first line treatment in patients with primary biliary cholangitis (PBC) that is often followed by second-line therapy if there is inadequate response (IR). Previous analyses by the Fibrotic Liver Disease Consortium showed that pre-treatment total bilirubin, even within the normal range, is associated with increased risk of mortality. In the present

study, we analyzed the effect of pre-treatment bilirubin and other covariates associated with the risk of IR, and compared follow-up care between patients with/without IR.
Method: Baseline data were collected for PBC patients at time of UDCA initiation between 2006 and 2015. Total bilirubin was categorized as > 2, 2 > 1.5, 1.5 > 1.0, 1.0 > 0.7, 0.7 > 0.4, and ≤ 0.4 mg/dL. IR was defined using Paris II criteria 12 months after UDCA initiation. Logistic regression was used to estimate the adjusted risk for IR; model accuracy was assessed using area under the receiver operator characteristic curve (AUROC). Z-statistic was used to compare rates of follow-up care and treatment modification per person-year (PPY) between IR and non-IR patients.
Results: Among 1578 UDCA treated patients (13% men; 8% African American, 9% Asian American/American Indian/Pacific Islander (ASINPI); 25% Hispanic), 706 (45%) had IR to UDCA at 12 months post-baseline. The multivariate model (AUROC = 0.79) showed that younger age, increasing alkaline phosphatase (ALP), low albumin, and a ratio of aspartate to alanine aminotransferase (AST/ALT) > 1.1 were independently associated with an increased risk of IR. Bilirubin—even in the high-normal (1.0 > 0.7) and mid-normal (0.7 > 0.4 mg/dL) ranges—was also significantly associated with increased risk of IR compared to low-normal levels (≤ 0.4 mg/dL; Figure). A sensitivity analysis that defined IR as ALp > 1.67xULN yielded similar results. Compared to responders, patients with IR were more likely to: discontinue UDCA (0.08 vs 0.04 PPY; p < 0.01); add obeticholic acid (0.023 vs 0.004 PPY; p < 0.01); and were more likely to see a specialist (5.12 vs 3.16 visits PPY; p < 0.01), undergo liver imaging (1.23 vs 0.56 tests PPY; p < 0.01), have liver-related laboratory testing (18.4 vs 10.2 tests PPY; p < 0.01), be hospitalized (0.11 vs 0.07 PPY; p < 0.01), and seek emergency care (0.13 vs 0.08 PPY; p < 0.01).



Conclusion: Almost half of PBC patients (45%) in a routine clinical care cohort showed IR to UDCA. Baseline bilirubin > 0.4 mg/dL is associated with increasing risk of IR. Patients with IR had higher rates of specialist follow-up and health care utilization.

FRI-024

Incidence and prevalence of autoimmune hepatitis in England 1997-2015. A population-based cohort study

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Background and aims: There are few population-based studies of the incidence of autoimmune hepatitis over long time periods. The burden of the disease and how it has changed over time has therefore not been fully explored. We conducted a population-based cohort study on the incidence of autoimmune hepatitis in England, 1997-2015.
Method: From the Clinical Practice Research Datalink, we included 882 patients diagnosed with autoimmune hepatitis in primary or secondary care in England between 1997 and 2015. We followed the patients through 2015 and calculated the sex- and age- standardised incidence and prevalence of autoimmune hepatitis. We examined variations in incidence by sex, age, calendar year, geographical region, and socioeconomic status. We calculated incidence rate ratios with Poisson regression.
Results: The overall standardised incidence rate of autoimmune hepatitis was 2.08 (95% confidence interval 1.94-2.22) per 100, 000 population per year, higher in women than in men, higher in older age, and independent of region of residence and socioeconomic status. The incidence doubled from 1.27 (95% confidence interval 0.51-2.02) per 100, 000 in 1997 to 2.56 (95% confidence interval 1.79-3.33) per 100, 000 population per year in 2015. The standardised point prevalence on 31 December 2015 was 19.24 (95% confidence interval 18.08-20.41) per 100, 000 population.
Conclusion: This population-based study showed a high incidence of autoimmune hepatitis which has doubled over an eighteen-year period. The incidence in England was particularly high in older women and was similar across all regions of England and independent of socioeconomic status.

FRI-025

Long-term outcome in autoimmune hepatitis: The second twenty years

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Background and aims: Liver disease can progress in AIH despite treatment, but follow-up data beyond 20 years are sparse. Here, we aimed to assess outcomes over the 2nd twenty years of follow-up and to compare these with outcomes in patients followed up from initial diagnosis.
Method: Survival analysis and standardised mortality ratio (SMR), considering liver transplant as death; group comparisons using Kaplan-Meier and Cox regression analysis.
Results: 65 consecutive patients (diagnosed 1971-96), who had already been followed up for 20 years were followed up for a further (median (range)) 6.1 (0.3-26) years. Age at start of year 21 was 63 years (mean). Six patients were untreated (one had inactive cirrhosis; later transplanted, when AIH was confirmed; 5 had mild disease). Two patients had previously discontinued immunosuppressive treatment (IST) and a third did so after 27 years.
Two patients moved away after 28 and 39 years and were censored, 13 were discharged to primary care and remained alive until the end of follow-up. Of these, five were on IST, four were not and data were unavailable in four. The other 41 patients remained on IST until end of follow-up.
Of the 65 patients, 34 had cirrhosis by year 20 (22 at initial diagnosis) and 5 more developed cirrhosis after 20 years. Five patients (four on IST) suffered their first relapse after 20 years.
At end of follow-up (31/12/16), 42 of the 65 patients were alive, 3 had undergone liver transplantation, and 20 had died: 3 from liver disease (one hepatocellular carcinoma) and 17 from extra-hepatic causes (7 malignancy, 6 infection, 4 other causes). Survival from all-cause

death or transplant was lower in these 65 patients during the 2nd 20 years than in 327 consecutive patients followed from initial diagnosis (1987-2016); age at diagnosis 54 years): 68+7% (SEM) vs. 76+3% after 10 years and 38+10% vs. 47+4% after 20 years. However this was due to the older age of the 2nd 20-year cohort at start of follow-up (63 v 54 years), as the survival difference disappeared when adjusted for age. Survival from liver-related death/transplant was similar in the two cohorts (figure). SMR over the second 20 years was 1.45 (0.84-2.65) not significantly different from SMR in the 327 patients followed from diagnosis: 1.60 (1.21-1.91).

Figure: Survival from liver related death or transplant during the 2nd 20 yr of follow-up (n = 65) compared to those followed up from diagnosis (n = 327)

Conclusion: During the 2nd 20 years of follow-up, patients with AIH continue to have disease relapse and to develop cirrhosis. They have similar survival to patients followed from initial diagnosis.
Survival from liver related death or transplant during the 2nd 20 yr of follow-up (n = 65) compared to those followed up from diagnosis (n = 327)

FRI-026

Long-term assessment of the effects of obeticholic acid in patients with primary biliary cholangitis on immune and inflammatory markers

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Background and aims: Obeticholic Acid (OCA) is a potent and selective farnesoid X receptor agonist approved for the treatment of primary biliary cholangitis (PBC). PBC is a chronic liver disease characterized by the immune mediated destruction of bile ducts resulting in cholestasis, cirrhosis and liver failure. The POISE study was a randomized, placebo-controlled phase 3 study investigating daily OCA 5-10 mg in PBC patients with an ongoing open label extension (OLE). The purpose of this analysis was to assess the long-term effects of OCA on key markers of liver damage and inflammation.

Method: Patients enrolled in the double-blind phase had an inadequate response to UDCA or were intolerant of UDCA. Upon completion of the 12-month double-blind phase, 198 patients enrolled in the OLE and received OCA. For this analysis, patients were pooled and assessed from the time of first dose of OCA. Data are shown through 48 months of OCA exposure, for patients randomized to placebo in the double-blind phase, only 36 months of data are included.

Results: At baseline (N = 198), patients were 92% female, mean age was 55 years, PBC disease duration was 9 years, and 93% received UDCA (mean dose: 16 mg/kg/day). As observed in the Table, there were sustained and significant reductions in immunoglobulins (Ig) A, G and M throughout 48 months of OCA treatment. In addition, significant reductions were observed in tumor necrosis factor (TNF)-α, c-reactive protein (CRP), and cleaved cytokeratin (CK)-18 throughout the duration of the OLE. No clinically meaningful changes were observed with transforming growth factor (TGF)-β and interleukin (IL)-12, both remained within the normal range.

Median (Q1, Q3)	Baseline	Δ From Baseline to 36 Months OCA (N = 161)	Δ From Baseline to 48 Months OCA (N = 120)
CRP mg/L	3 (2, 7)	−0.7*** (−2, 0.3)	−0.6** (−2, 0.5)
TNF-α pg/m)	11 (9, 14)	−3*** (−4, −1)	−2*** (−3, −0.4)
TGF-β ng/ml	25 (19, 35)	2 (−7, 11)	0 (−5, 7)
Ck-18 U/L	124 (83, 201)	−28*** (−78, 15)	−3 (−52, 40)
IL-12 pg/ml	138 (94, 198)	9 (−21, 28)	21** (−6, 43)
IgA g/L	2 (2, 3)	−0.2*** (−0.5, −0.1)	−0.3*** (−1, −0.1)
IgG g/L	13 (11, 15)	−1*** (−2, −0.03)	−1*** (−2, 0.2)
IgM g/L	4 (2, 6)	−1*** (−2, −0.4)	−1*** (−2, −0.4)

*p < 0.05; **p < 0.01; ***p < 0.0001. p values for the comparisons to baseline were obtained using a Wilcoxon signed rank test. Normal ranges: CRP 0-3 mg/L, TNF-α 8.1 pg/ml, TGF-β 18.3-63.4 ng/ml, Ck-18 80 U/L, IL-12 34-246 pg/ml, IgA 0.7-4 g/L, IgG 7-16 g/L, IgM 0.4-2.3 g/L

Conclusion: These results demonstrate that OCA has a durable anti-inflammatory effect in patients with PBC as observed by reductions on key markers of apoptosis (TNF-α and CK-18) and inflammation (CRP). Furthermore, a sustained reduction is observed in IgM, which is classically elevated in PBC patients. The clinical significance of OCA mediated reductions in IgA and IgG continues to remain unknown.

FRI-027

Serum bile acids significantly associate with the fibrogenesis biomarker Pro-C3: analysis of a randomized, placebo-controlled trial of NGM282 in patients with primary sclerosing cholangitis

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Background and aims: PSC is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical interventions. NGM282, a non-tumorigenic FGF19 analogue, reduces levels of 7alpha-hydroxy-4-cholesten-3-one (C4, a marker of bile acid synthesis) and fibrosis biomarkers, including Pro-C3, in patients with PSC and NASH. To assess the impact of NGM282 on bile acid (BA) species which may be implicated in fibrosis, we evaluated the correlation of individual BAs with C4 and Pro-C3 (a marker of fibrogenesis) using our placebo-controlled trial data from patients with PSC treated with either NGM282 or placebo.

Method: As previously reported, sixty-two patients, with PSC by EASL criteria and an elevated ALP > 1.5xULN at baseline (BL), were randomized to NGM282 1mg, 3mg or placebo for 12 weeks (W12). Serum concentrations of BA species and C4 were determined by mass spectrometry (Mayo Clinic). Serum Pro-C3 was measured by an ELISA method (Nordic Bioscience). Correlation coefficients were calculated using Spearman's method.

Results: Serum concentrations of individual BAs significantly correlated with Pro-C3, but not C4, at W12 (Table 1). Placebo-adjusted reductions from BL to W12 were observed in hydrophobic (toxic) BAs, including DCA ($p < 0.001$ for both NGM282 1mg and 3mg groups), GDCA ($p = 0.003$ for 1mg, $P < 0.001$ for 3mg) and TDCA ($p = 0.03$ for 3mg). At W12, relative changes in Pro-C3 from BL were – 21% ($p = 0.008$) and – 27% ($p < 0.001$) with NGM282 1mg and 3mg, respectively, versus +11% ($p = 0.08$) with placebo.

Figure: Table 1: Correlation of individual bile acids with Pro-C3 and C4 concentrations at week 12

	Pro-C3		C4	
	P value	P value	r value	P value
Conjugated primary bile acids				
GCA	0.62	< 0.0001	–0.03	0.83
TCA	0.52	< 0.0001	–0.12	0.37
GCDCA	0.55	< 0.0001	–0.25	0.06
TCDCA	0.46	0.0003	–0.28	0.032
Conjugated secondary bile acids				
GDCA	0.31	0.020	0.27	0.038
TDCA	0.28	0.038	0.22	0.09
Unconjugated primary bile acids				
CA	–0.18	0.18	0.09	0.49
CDCA	–0.21	0.12	–0.01	0.92
Unconjugated secondary bile acids				
DCA	–0.06	0.65	0.52	< 0.0001

Conclusion: Circulating concentrations of the major hydrophobic BAs strongly correlate with the fibrosis marker Pro-C3 in PSC patients treated with NGM282. Both serum BAs and Pro-C3 are lowered by NGM282 suggesting that the effects of NGM282 on bile acid synthesis may be pathophysiologically linked to its anti-fibrotic effects in PSC. Our data confirm the need for further consideration of using markers such as BAs and Pro-C3 in the determination of efficacy of new therapies for patients with PSC.

FRI-028

Spleen stiffness and liver stiffness measurements as surrogate markers of liver fibrosis in patients with autoimmune hepatitis: prospective, single-center study

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Background and aims: Shear-wave elastography allows reliable measurements of LSM and SSM in patients with AIH, and they both are of help in identifying patients with cirrhosis. For fibrosis staging, SSM results seem to be however less biased by hepatic inflammation as compared to LSM rendering SSM potentially a more reliable tool in patients with AIH.

Method: We analysed two cohorts of patients with AIH: 34 patients (24 women, mean age 40.5 years) who had SWE done within 1.6 months from liver biopsy (19 with cirrhosis) and 91 consecutive, treated AIH patients (74 women, mean age 38.4 years) without flare. LSM and SSM measurements were done with SuperSonic Imagine Aixplorer®. Serum CD163, a macrophage activity marker, was measured by ELISA to assess the impact of liver inflammation on SSM.

Results: The optimal cut-off for detecting liver cirrhosis for LSM was 16.1 kPa (AUROC 0.9, 95% CI 0.79-1.01, $p < 0.01$, sensitivity 89% and specificity 87%). The optimal SSM cut-off for cirrhosis was 30.4 kPa (AUROC 0.98, 95% CI 0.93-1.04, $p = 0.02$) and had 92% sensitivity and 100% specificity. In the treated group without flare, a total of 26 (29%) had cirrhosis, applying the LSM cut-off ≥ 16.1 kPa. Comparison of patients with and without cirrhosis showed robust differences in fibrosis indices (FIB-4, FibroQ), markers of portal hypertension (platelet count, spleen diameter, esophageal varices) and liver injury surrogates (MELD) between both groups (all $p < 0.001$). Notably, LSM showed a significant correlation with all inflammatory markers: ALT and IgG (both $p < 0.01$) and CD163 ($p < 0.001$). In contrast, SSM correlated with CD163 ($p < 0.01$), but not with the other markers of hepatic inflammation.

Conclusion: Shear-wave elastography allows reliable measurements of LSM and SSM in patients with AIH, and they both are of help in identifying patients with cirrhosis. For fibrosis staging, SSM results seem to be however less biased by hepatic inflammation as compared to LSM rendering SSM potentially a more reliable tool in patients with AIH.

FRI-029

Non-alcoholic fatty liver disease and steatohepatitis in autoimmune hepatitis: important player or innocent bystander?

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) affect 17-46% of western countries population, making coexistence with other liver diseases inevitable. Our aim was to investigate the prevalence and clinical significance of NAFLD/NASH in patients with autoimmune hepatitis (AIH), in a multicentric large cohort.

Method: Prospectively collected data from patients with well-established AIH from 6 academic centers (Greece, Canada, Japan, Germany and Spain) were evaluated retrospectively. The presence of NAFLD and NASH in liver biopsy reports was recorded in detail in order to compare the clinical and laboratory data as well as the outcome between AIH patients with and without NAFLD/NASH.

Results: 580 patients (433 females, 74.7%; age at AIH diagnosis 46 ± 18 years; 175 from Greece, 309 from Canada, 44 from Japan, 29 from Germany, 13 from Spain; follow-up 103 ± 86 months) were included. NAFLD was present in 123/580 (21.2%) baseline biopsies. In more detail, 107/580 (18.4%) had NAFLD (64/107 steatosis only; 43/107 steatosis and lobular inflammation) and 16/580 (2.7%) NASH. Patients

with AIH-NAFLD/NASH were older at AIH diagnosis (p = 0.004), had higher BMI (p < 0.001), lower AST, ALT, ALP and bilirubin (p < 0.05 for each), but higher albumin (p < 0.001), triglycerides (p = 0.05) and lower simplified score (p = 0.02) compared to those without NAFLD/NASH. AIH-NAFLD/NASH patients suffered more frequently from hypertension, diabetes and obesity (p < 0.001 for each). AIH-NAFLD/NASH patients were less likely to be anti-SLA/LP positive (p = 0.005), but more likely to be anti-LKM positive (p = 0.02). Although progression to cirrhosis was not associated with NAFLD/NASH presence, AIH-NAFLD/NASH cirrhotic patients (39/197) were more likely to decompensate during follow-up (p = 0.01). The presence of NAFLD/NASH did not affect response to treatment or overall prognosis (liver related death or liver transplantation).
Conclusion: Despite the high prevalence of NAFLD/NASH in one fifth of AIH patients, there is no evidence that NAFLD/NASH acts as an aggravating factor since response to treatment and the overall prognosis of AIH patients were not affected. However, the low number of patients with AIH and NASH could be responsible for these findings. Nevertheless, special attention might be needed for those with established AIH-related cirrhosis and concurrence NAFLD/NASH.

FRI-030
Treatment choice and long-term prognosis for elderly PBC
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Background and aims: Primary biliary cholangitis (PBC) is a chronic and progressive cholestatic liver disease of presumed autoimmune pathogenesis that usually affects middle-aged women. PBC onset is increasing in the ageing population of Japan.
Method: We compared differences in characteristics, clinical findings, treatment choice and prognosis with UK-PBC score between elderly and younger-onset PBC patients.359 patients were enrolled from 2005 to2018 and divided into > 65 and < 65 years groups. We retrospectively examined the treatment choice and long-term prognosis for elderly PBC. This multifacility observational study in the Niigata prefecture had an ethical screening committee in each facility.

Factors (Median) (range) (n)	< 65 y.o.	≥ 65 y.o.	p value
n	260	99	-
Gender (Male / Female)	26 / 234 (90%)	20 / 79 (79.8%)	0.013
Age (years)	52 (28-64)	69 (65-92)	-
Male (years)	55 (38-64)	69 (65-92)	-
Female (years)	52 (35-64)	70 (65-79)	-
Family history of PBC (+ / - / unknown)	7 (2.6%) / 235 / 18	4 (4.0%) / 87 / 8	0.678
mother, daughter / sister, brother / father	4 / 2 / 1	2 / 2 / 0	-
Symptoms (+ / -)	52 (20%) / 208	16 (16%) / 83	0.453
itching / jaundice / ascites / edema / EV	45 / 5 / 7 / 7 / 2	15 / 1 / 5 / 9 / 7	-
s1-PBC / s2-PBC	47 / 5 (1.9%)	15 / 1 (1.0%)	>0.999
Other autoimmune diseases (+ / -)	89 (34.2%) / 171	29 (29.2%) / 70	0.450
SjS / Thyroiditis / RA / SLE	40 (15.3%) / 20 / 12 / 3	15 (15.1%) / 3 / 3 / 0	-
AIH / CREST / PSS / Myositis / Others	8 (3%) / 5 / 7 / 3 / 11	3 (3%) / 4 / 0 / 1 / 3	-
Malignancies (+ / -)	24 (9.2%) / 236	14 (14.1%) / 85	0.187
HCC / Colon / Gastric / MMK / Lung / Others	2 / 6 / 3 / 6 / 2 / 5	1 / 5 / 3 / 3 / 0 / 3	-

Figure: Background (at the time of diagnosis)

Results: 99 cases, age > 65 years, were defined as elderly PBC and 260 cases, age < 65 years, were defined as younger-onset PBC. The symptomatic PBC ratios were 16% vs 20%. There was no significant difference in ALP and γ-GT levels. However, Alb and platelet levels were decreased in elderly PBC (p = < 0.001). There were AMA/M2 antibody negative cases (14.8% vs. 10.7%, p = 0.457) as well as Scheuer stage 4 cases (11.1% vs. 0%, p = 0.084) As for the treatment choice observation, there were 4 vs. 17 cases. For UDCA treatment only, there were 81 vs. 171 cases and did not exit significant difference. For UDCA and Bezafibrate (BF) combination treatment, there were 11 vs. 71 cases and there were significantly few cases in elderly patients. UDCA alone dosage example, the UDCA + BF combination treatment had good reactivity in both groups. Treatment reactivity did not exit the significant difference in UK-PBC risk score. However, the elderly group had lower weight than the younger group, so the UDCA dose per weight was higher in the elderly group. Regarding long-term prognosis between liver transplant and liver-related death, the significant difference did not exist. UK-PBC score and GLOBE score have high sensitivity and specificity in both groups (AUC 0.987 P < 0.001 vs. AUC 0.987 P < 0.001)
Conclusion: There was no significant difference in laboratory data at the time of diagnosis, treatment reactivity, and long-term prognosis. The prognosis of liver-related death as an end point was equal and the factors for prognosis were not identified. It is necessary to try the problem of treatment policy for the elderly person PBC case and the long-term convalescence should be re-examined.

FRI-031
Association between serum immunoglobulin G levels and intrahepatic plasmacytic gene signature in human autoimmune hepatitis
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Background and aims: Atypical autoimmune hepatitis (AIH) without a hallmark hypergammaglobulinemia are on the increase in number and their association with acute onset cases is an emerging topic. The aim of the study is to define specific gene signature in the human AIH liver that associates with serum immunoglobulin G (IgG).
Method: The patient cohort consisted of 17 cases of AIH, including ones with acute manifestation. According to the International Autoimmune Hepatitis Group simplified criteria, patients whose serum IgG exceeded over 1.1 × upper limit normal were classified into high IgG group (n = 8). Hepatic RNA were extracted from biopsy samples and microarray hybridization was performed on Human Oligo chip 25k array (TORAY, Japan). Commercially available hepatic RNA from 4 healthy volunteers were used as controls (CON). Normalization of raw intensity values, followed by analysis of data were performed using GeneSpring (Agilent Technologies, U.S.A.). We first extracted genes whose expression differed 1.5 folds < between AIH and CON (FDR corrected $p < 0.05$, Genes A: n = 2067). Next, gene signatures between high and non-high IgG group were compared (FDR corrected $p < 0.05$). For deconvolution of disease activity with regard to plasma cell gene signature, gene probes whose expression profile were correlated (Pearson, $r_s > 0.85$) with both with *TNFRSF17* and *POU2AF1* were extracted among Genes A (B, n = 48). For personalized analyses, each patient sample was compared to the average of CON for each gene probe in Genes B. The level of regulation of plasma cell gene signature was calculated as the percentage difference: % up-regulated minus % down-regulated gene probes. Canonical pathways analysis was performed using Ingenuity (version 01-10, Q3 2018, QIAGEN, GmbH)
Results: Significantly upregulated canonical pathways among Genes A (Z score > 2.0) were identified exclusively as those with immune-inflammatory function, that is, Neuroinflammation Signaling Pathway, Dendritic Cell Maturation, Th1 Pathway, Calcium-Induced T Lymphocyte Apoptosis, Th2 Pathway, ICOS-ICOSL Signaling of T Helper Cells, and Role of NFAT in Regulation of the Immune Response, in ascending order of p value. Serum IgG (mg/dl) values (median, range) among IgG high and non-high group were as follows: 2270, 1900-4310 vs 1590, 923-1860, $p < 0.01$. Although genes fulfilling FDR corrected $p < 0.05$ between high and non-high IgG group were not demonstrated, the activity of plasma cell gene signature was correlated with levels of serum IgG, but not with those of ALT (r_s = 0.554, $p < 0.05$, vs r_s = -0.271, *not significant*).

Conclusion: AIH transcriptome in the liver may not be distinguished by serum IgG levels. Nevertheless, serum IgG is likely a useful surrogate marker for the plasma cell activation and infiltration in the AIH liver in situ.

FRI-032

Liver transplantation ameliorates chronic fatigue and improves quality of life in patients with primary sclerosing cholangitis

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Background and aims: A significant proportion of patients with primary sclerosing cholangitis (PSC) requires liver transplantation (LTx). Although an improvement of pruritus has been found after LTx in patients with chronic cholestatic liver diseases, the effect of this procedure on chronic fatigue, which is supposed to be central in its origin, remains controversial. PBC-40 questionnaire, initially designed for the assessment of health related quality of life (HRQoL) in primary biliary cirrhosis (PBC), has also been found to be a reliable tool in patients with PSC (Liver Int 2015;35:1764-71). Here we aim to assess the effects of LTx on chronic fatigue and other measures of HRQoL in patients with PSC

Method: Seventy patients (47 males, mean age at LTx 35 ± 11) who underwent LTx for PSC in our centre between 02/2012 and 04/2018 were prospectively enrolled. SF-36 and PBC-40 were applied before LTx and at 2 time points after LTx, the first one (time point P1) at median 11 months after the procedure in all 70 patients and at median 28 months (time point P2) in 19 patients. Matched control group included of 72 adults without chronic or acute liver diseases (46 males, age 36 ± 10 years). Kolmogorov-Smirnov test was used to determine whether data were normally distributed. Quantitative traits were assessed using Mann-Whitney or Student's t-test, as appropriate.

Results: Liver transplantation caused a significant improvement of chronic fatigue assessed with fatigue domain of PBC-40 (30 ± 10 before OLTx vs 20 ± 8 at P1; $p < 0.0001$) with further improvement at P2 (18 ± 8). Significant improvement in all domains of PBC-40, in particular itch ($p < 0.0001$) cognitive ($p < 0.0006$) and social/emotional ($p < 0.0001$), was seen after LTx. In terms of general well-being, evaluated with SF-36, a significant improvement caused by LTx was also observed ($p < 0.001$ for all its domains). HRQoL assessed with SF-36 remained significantly worse in transplanted patients with PSC at both P1 and P2 when compared to healthy controls.

Conclusion: Liver transplantation in patients with PSC leads to significant decrease of chronic fatigue. It also improves other measures of health related quality of life which include itching, cognitive and emotional functions. Quality of life in these patients remains however worse as compared to matched healthy controls.

FRI-033

Long-term obeticholic acid treatment is associated with improvements in collagen morphometry in patients with primary biliary cholangitis

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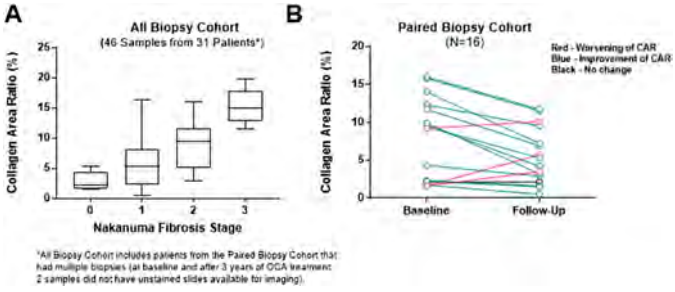
Background and aims: Obeticholic acid (OCA) is a potent, selective FXR agonist approved for the treatment of PBC based upon biochemical improvements predicted to improve transplant-free survival. An optional liver biopsy substudy was conducted in a subset of patients from the Phase 3 POISE trial to determine the impact of OCA treatment on progression of liver fibrosis. Results, using standard histologic grading, showed that the majority of patients treated with OCA either improved or had no worsening of fibrosis over 3 years. New technologies, such as second harmonic generation (SHG) microscopy, allow quantitative measurement of the molecular features of fibrosis using high-resolution stain-free imaging of collagen 1 and 3. This post-hoc analysis assessed the impact of OCA treatment on collagen morphometry using biopsy samples from the POISE substudy.

Method: Patients included in this analysis had an inadequate response or intolerance of UDCA, biopsies ≤ 1 year from double-blind baseline and after ~3 years of OCA treatment. Unstained slides were used to quantify collagen using SHG and 2-photon microscopy. Stained biopsy samples were masked, randomized and scored by consensus of 2 blinded pathologists utilizing Nakanuma Staging for histologic evaluation. Two cohorts were identified: an All Biopsy Cohort, defined as all adequate biopsy samples (determined by the pathologists) with collagen data, and a Paired Biopsy Cohort, defined as patients with both a baseline and follow-up biopsy and collagen data.

Results: The All Biopsy Cohort was composed of 31 patients (46 samples total, mean age 56 years, 90% female, 97% received UDCA), and the Paired Biopsy Cohort was composed of 16 patients (59 years, 94% female, 100% received UDCA). In the All Biopsy Cohort, trends were observed between increasing median Collagen Area Ratio (CAR) (Fig A), Collagen Fiber Density (CFD), and Collagen Reticulation Index (CRI) and increasing Nakanuma Fibrosis Stage. In the Paired Biopsy Cohort, the majority of patients (12/16) had a reduction in CAR after 3 years of OCA treatment (Fig B). The median (Q1, Q3) change and percent change from baseline was CAR −2.1 (−4.6, −0.3) and −31.1% (−46.1,−11.4), CFD −0.8 (−2.5, 0.0) and −35.3% (−57.0, −2.5), and CRI −0.1 (−0.3, 0.0) and −7.4% (−20.8, −1.1).



Conclusion: In this analysis, 3 years of OCA treatment resulted in a reduction in CAR, CFD and CRI, supporting the overall trend of improvement or no progression in the histologic components of PBC

FRI-034

Clinical phenotype of significantly elevated serum IgG4: Single center experience

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Background and aims: Elevated serum IgG4 has been associated with multiple diseases. For that, elevated serum IgG4 level is an insufficient single diagnostic tool. The appropriate cutoff for serum IgG4 not well establishes. Although elevated IgG4 level more than 2xULN has better specificity around 90%. Our aim of this study to determine the clinical, imaging, and serological features of patients with elevated IgG4 more than 2xULN.

Method: We conducted a retrospective study using computerized search to identify all patients with elevated serum IgG4 level at the Toronto Centre for Liver Disease during the 5-year period from January 1, 2013 to February 28, 2018. Subjects with elevated serum IgG4 equal or more than two times the upper limit of normal (≥ 2xULN) were included. Demographic data, clinical features, imaging study and laboratory test results at presentation were retrieved.

Results: A total of 89 patients with elevated serum IgG4 were reviewed. 38 cases (42.7%) had elevated serum IgG4 levels ≥ 2 × the upper limit of normal were included in this cohort. In all, 68% of patients were males with median age 56 at time of presentation. Fifty percent of patients were non-Caucasian and two-thirds of them were Asians. Prevalence of IBD was 24% (n = 9) with similar prevalence of other autoimmune disease, including RA, Sjogren's disease, vitiligo, hypothyroidism. Prior history of malignancy observed in 4 cases colon cancer, laryngeal cancer and MALT lymphoma.

Majority of cases were diagnosed with IgG4 related disease 42% (n = 16). PSC was accounted for 26% of cases (n = 10), followed by autoimmune pancreatitis 18.4% (n = 7). Other etiologies were also observed in this cohort, such as AIH, AIH overlap with PSC, PBC, PVT with liver cirrhosis and secondary sclerosing cholangitis.

Although PSC patients tend to be younger than the others, 9 out of 10 PSC cases developed advanced fibrosis or cirrhosis. Three cases required liver transplantation for PSC cirrhosis. Surprisingly, two out 3 them were found to have incidental HCC and cholangiocarcinoma on explanted liver. Further comparison between AIP, IgG4RD and PSC patients is in table 1.

Conclusion: Serum IgG4 measurement has insufficient accuracy and established cut-off values are lacking. PSC patients with elevated serum IgG4 could present with more aggressive disease. IgG4/IgG1 ratio tend to differentiate between PSC and IgG4 RD although cut off is not well defined.

FRI-035

Clinical outcomes associated with additional fibrate treatment in UDCA-refractory PBC patients: A multicenter study

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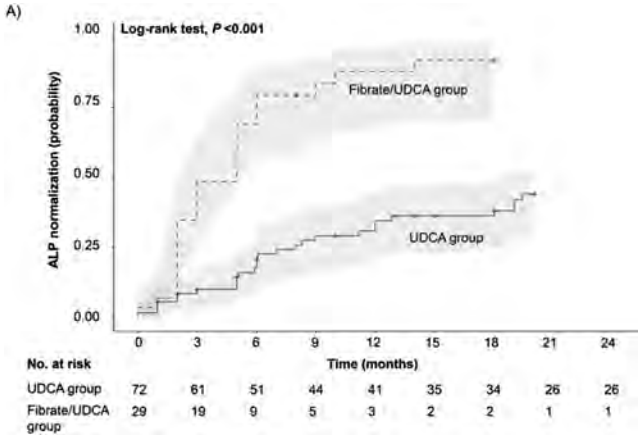
Background and aims: There is no proven treatment for ursodeoxycholic acid (UDCA)-refractory primary biliary cholangitis (PBC) except obeticholic acid. Although fibrates have been reported to improve biochemical parameters, the long-term effects remained unclear. This study evaluated the effect of fibrate on clinical outcomes of UDCA-refractory PBC.

Method: Patients whose alkaline phosphatase (ALP) was not normalized with at least 13 mg/kg of UDCA treatment for > 1 year were included from two tertiary referral centers. The primary outcome was ALP normalization. Secondary outcomes included the development of liver cirrhosis and hepatic deterioration. Immortal time bias was adjusted using the Mantel-Byar method.



Results: A total of 101 UDCA-refractory PBC patients were included: 72 patients received UDCA alone (the UDCA group) and 29 patients received UDCA plus additional fibrate treatment of 160 mg/day fenofibrate (n = 26) or 400 mg/day bezafibrate (n = 3) (the fibrate/UDCA group). The baseline differences between two groups were not significant except for UDCA dose [median 900 mg/day (interquartile range (IQR) 600-1400 mg) in the UDCA group and 1200 mg/day (IQR 800-1200 mg) in the fibrate/UDCA group, P < 0.001], serum aspartate transaminase levels [median 39 IU/L (IQR 31-62 IU/L) in the UDCA group and 32 IU/L (26-44 IU/L) in the fibrate/UDCA group, P = 0.02] and albumin levels [median 4.2 g/dL (IQR 3.8-4.3) in the UDCA group and median 4.3 g/dL (IQR 4.1-4.4) in the fibrate/UDCA group,

Figure: Table 1: (abstract: FRI-034)

		AIP (n=7)	IgG4RD (n=16)	PSC (n=10)	p-Values
Age, median (range)		71 (52-78)	64 (38-85)	40 (23-62)	**<0.001**
% male		4 (57.1%)	14 (87.5%)	7 (70.0%)	0.259
Ethnicity, n (%)	Caucasian	2 (28.6%)	10 (62.5%)	6 (60.0%)	0.609
	Non-Caucasian	5 (71.4%)	6 (37.5%)	4 (40.0%)	
IgG4 (mean+SD)		5.8+4.5	5.5+3.4	2.9+1.7	0.117
IgG4/IgG1 ratio (mean+SD)		0.73+0.60	0.89+0.26	0.26+0.12	**0.037**
ALT (mean+SD)		29+20	51+60	76+60	0.257
ALP (mean+SD)		92+65	154+143	326+192	**0.009**
Bilirubin (mean+SD)		9+3	44+79	12+6	0.292

P = 0.002]. During the follow-up period, the probability of ALP normalization was significantly higher in the fibrate/UDCA group [hazard ratio (HR) = 4.78, 95% confidence interval (CI) = 2.75-8.27, P < 0.001]. Among 59 non-cirrhotic patients (44 in the UDCA group and 15 in the fibrate/UDCA group), 19 patients (43.2%) in the UDCA group and none in the fibrate/UDCA group developed cirrhosis (HR = 0.12, 95% CI = 0.001-0.90, P = 0.04). Hepatic deterioration (Child-Pugh score increase of ≥ 2 points or signs of decompensated liver cirrhosis) occurred in 17 patients (23.6%) of the UDCA group and none in the fibrate/UDCA group which the difference was significant (HR = 0.12, 95% CI = 0.001-0.90, P = 0.04). Neither the risk of hepatocellular carcinoma development (p = 0.31) nor that of transplantation-free survival differ significantly (p = 0.26).

Conclusion: In patients with UDCA-refractory PBC, additional fibrate treatment is associated with a higher probability of ALP normalization and a lower risk of cirrhosis development and hepatic deterioration.

FRI-036

Perception by patients with autoimmune and chronic cholestatic disease of their own health condition: Results of a survey led by the French patient association (ALBI)

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Background and aims: Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), Autoimmune Hepatitis (AIH) and Low-Phospholipid Associated Cholelithiasis (LPAC) syndrome are rare chronic liver diseases affecting people of all ages with various outcomes. The purpose of this study was to assess the burden of symptoms for patients and the impact on their daily life.

Method: A survey, with 57 questions, was designed by the French Association for Patients with Inflammatory Biliary Diseases (ALBI) in collaboration with the Medical Reference Center in Saint-Antoine Hospital. Out-patients were invited to respond by Emails and advertising on ALBI website. Results are self-reports by patients.

Results: 585 patients completed the survey: 304 PBC, 149 PSC, 63 AIH, 51 LPAC syndrome and 18 without established diagnosis. Most patients were from France, 10% living in other countries (French-speaking countries such as Belgium, Switzerland or Canada). The global health condition was judged good, fair and bad in 64%, 28% and 8% by PBC patients, 57%, 31% and 12% by PSC patients, 60%, 31% and 10% by AIH patients and 39%, 47% and 14% by LPAC syndrome patients. When asked to compare their global heath condition to people their age, patients reported it was altered in 40%, 62%, 50% and 65% for PBC, PSC, AIH and LPAC syndrome, respectively. The proportion of patients feeling that their daily life activities were quite or very disrupted because of their liver disease was 51%, 63%, 70% and 72% in PBC, PSC, AIH and LPAC syndrome patients, respectively. The 3 most frequent reported symptoms were, in decreasing order of frequency: fatigue, joint pain, and disturbed intestinal transit by PBC patients; fatigue, disturbed intestinal transit and abdominal pain by PSC, AIH and LPAC syndrome patients. Pruritus was only 8th rank after insomnia and abdominal bloating.

Conclusion: The impact of autoimmune and chronic cholestatic liver diseases on the patient's life varies a lot depending on individuals. A majority perceive themselves in reasonably good conditions, noting however that their daily life has been altered. A minority consider that their health has deteriorated significantly. Global perception is more positive for PBC patients, whereas patients with LPAC syndrome have mostly negative perceptions. This study demonstrates that the perception of the liver disease varies significantly between patients and encourages a better listening of physicians to their patient feeling.

FRI-037

Change in lipids: Characteristics and response to obeticholic acid in TARGET-PBC, a diverse, large United States real-world cohort

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Background and aims: Hyperlipidemia is often associated with primary biliary cholangitis (PBC) but does not appear to increase cardiovascular risk. Use of obeticholic acid (OCA) in PBC has been associated with a reduction in total cholesterol (TC) primarily related to lowering high-density lipoproteins (HDL). A mild increase in low-density lipoproteins (LDL) is also observed. The aim of this study was to determine the impact of OCA on lipid profile when treating patients with PBC in a real-world setting.

Method: TARGET-PBC is a longitudinal observational study of PBC patients at 35 U.S. sites. Data is captured from redacted medical records within a database utilizing centralized data abstraction. All clinical diagnoses and treatment decisions are at the discretion of the treating provider.

Results: Out of 516 enrolled patients, 82 participants were treated with OCA for at least 3 months and constituted our study population. The median duration of OCA treatment was 15.5 months, median age at diagnosis 48; 91.5% were female, 85.4% White, 26.8% Hispanic, 84% AMA positive, 14.6% with autoimmune hepatitis overlap syndrome. Twenty-eight participants (34.1%) were taking statins. Seventeen patients (20.7%) discontinued use of OCA primarily due to pruritus (n = 8, 47.1%). Forty-two patients (51.2%) were cirrhotic, of whom 14 (33.3%) had evidence of prior decompensation. The following median percent changes were observed in all OCA patients: alkaline phosphatase −25.7% (n = 70, p < 0.0001), −8.59% TC (n = 33, p = 0.0098), −13.1% HDL (n = 32, p = 0.0057), −3.08% LDL (n = 31, p = ns) and −9.59% in triglycerides (n = 32, p = ns). The median percent changes for statin and non-statin users on OCA were as follows: TC (−4.93% (n = 14) vs. −10.0% (n = 19), CI −8 (−24.5, 8.29)), HDL (−8.89% (n = 15) vs. −15.0% (n = 17), CI.37 (−13.6, 14.34)), LDL (1.56% (n = 13) vs. −9.92% (n = 18), CI −19 (−46.5, 9.06)) and triglycerides (−9.81% (n = 15) vs. −9.38% (n = 17), CI.47 (−21.9, 22.80)). Median LDL change after OCA treatment was greater among cirrhotics (−12.4%) compared to non-cirrhotic patients (0%, p = 0.046).

Conclusion: In addition to a clear improvement in liver chemistries, use of OCA was associated with a significant reduction in HDL and TC. OCA was not associated with an increase in LDL among non-cirrhotic PBC patients, but rather a decrease in LDL among cirrhotics, possibly related to natural history of disease. Additional studies are required to understand the impact of OCA on the lipid profile of patients.

FRI-038

Good performance of the biochemical response criteria after three months of ursodeoxycholic acid treatment in patients with primary biliary cholangitis

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Background and aims: Response to ursodeoxycholic acid (UDCA) therapy in patients with primary biliary cholangitis (PBC) is assessed by different validated biochemical criteria, which identify those patients that could benefit from further therapies. Nevertheless, these criteria have been evaluated at 12 and 24 months of treatment and, therefore this may delay the start the use of new agents in patients with suboptimal response. The aim of the current study has been to evaluate the performance of the known criteria three months after starting UDCA therapy.
Method: The study was carried out in cohort of PBC patients from a single centre, who started UDCA therapy with 13-16 mg/kg/d. The clinical features and liver biochemistries were assessed before and after 3, 6, 12 and 24 months of UDCA therapy. Ludwig's histologic stage was documented in 87 patients. The biochemical criteria (Barcelona, Paris I, Toronto and Paris II) were calculated at 3, 6, 12 and 24 months. The performance of these criteria was evaluated at 3 months as compared with those validated at 12 months (Toronto at 24 months).
Results: 95 patients (age 53 (44-65 years, 90.4% female) were included with alkaline phosphatase (AP) of 1.45 (1.1-2.9) times upper normal levels (UNL). After a year of treatment, non-response to UDCA was: Paris I 25.5%, Barcelona and Paris II 42.1%, and Toronto 21.4%. Lack of response was also evaluated with the aforementioned criteria at 3 months: Barcelona 52%, Paris I 28.8%, Paris II 48.6% and Toronto 31.8%. The sensitivity (S), specificity (Sp) and area under de curve (AUC) at 3 months were: Barcelona 72.7% S, 82.5% Sp and AUC 0.76; Paris I 88.6%S, 83.3% Sp and AUC 0.86; Toronto 100% S, 64.7% Sp and AUC 0.84; Paris II 80% S, 87.5% Sp and AUC 0.84. When patients with Ap < 1.5 ULN were excluded, the specificity of all criteria at 3-months increased over 80%, with a decrease in sensitivity below 70%, except Paris I with S 77.5%. Patients with no response at 3 months that became responders at 12 months had early disease (histologic stage I 100% vs 50%, p = 0.01), lower median bilirubin (0.75 [0.6-0.9] vs 1.2 [0.8-1.3]mg/dL, p = 0.04), and bilirubin < 1mg/dL (87.5% vs 40%, p = 0.02). No other clinical, histological and biochemical differences were observed.
Conclusion: The good performance of the biochemical response criteria to UDCA after 3-months suggests that these criteria are able to identify early non-responders and therefore, patients requiring additional therapies.

FRI-039

Autoimmune hepatitis-related cirrhosis: The importance of treatment response and the utility of Baveno VI criteria

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Background and aims: The information regarding diagnosis and prognosis of autoimmune hepatitis-related cirrhosis (AIH-C) is scarce. We aimed: 1) to describe patients with AIH-C and their prognosis, 2) to determine the utility of elastography (FS) in the diagnosis of AIH-C, and 3) to evaluate the performance of Baveno VI and expanded Baveno VI criteria in predicting the absence of varices needing treatment.
Method: 112 patients with AIH-C (defined by radiological and histological criteria) were included in a retrospective, multicentre, cohort study. Clinical, histological and laboratory data were analysed. Liver stiffness was evaluated using FS. Baveno VI (platelets > 150, 000 and elastography < 20kPa) and expanded Baveno VI (platelets > 110, 000 and elastography < 25kPa) criteria were evaluated in 63 patients (95 endoscopies). Portal hypertension (PHT) was defined by radiological and laboratory data, and presence of varices.
Results: Median age was 56 years-old (42-65). Most of the patients had advanced fibrosis at diagnosis (F3-F4, n = 81, 73%). Fourteen patients (15%) were non-responders to standard treatment, and 7 required second line therapy. Median FS was 12, 2kPa (IQR 7.4-17.3), 59% and 51% of patients had a FS below the usual cut-offs for the diagnosis of cirrhosis (14kPa and 12.5kPa, respectively). After a median of 3.9 years, 52 (46%) patients presented PHT, more frequently in non-responders (71.4% vs 43%, p = 0.05). Sixteen patients (16%) had varices needing treatment. Negative predictive value of Baveno VI and expanded Baveno VI criteria was 100%, suggesting that 35% and 52% of the endoscopies could have been saved, respectively. Within a median time of 6.9 years (IQR 3.8-14.5) of follow-up, 24 patients (21%) presented decompensation (more frequently in non-responders; 42% vs 13%, p = 0.01), 1 (1%) had hepatocellular carcinoma, 3 (3%) underwent liver transplantation and 5 (5%) died. Cumulative 20-year survival was significantly higher in responders to treatment (86% vs 54% in non-responders, p = 0.04).
Conclusion: Patients with AIH-C are diagnosed in an advanced stage of the disease. Lack of response to standard therapy has a negative impact on disease course and patient survival. Elastography does not seem to correlate with severe fibrosis stage in AIH. Baveno VI criteria are useful and could save an important number of endoscopies.

FRI-040

Imaging and clinical correlations of macro regenerative nodules in primary sclerosing cholangitis

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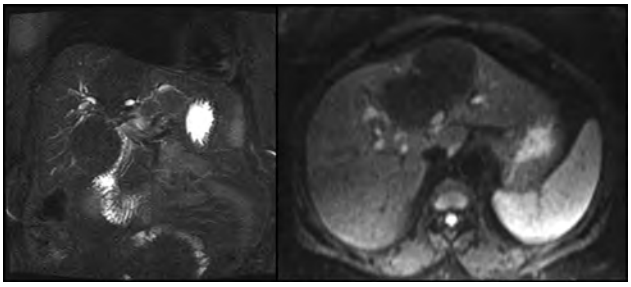
Background and aims: Primary Sclerosing Cholangitis (PSC) is a progressive cholestatic disorder of unclear pathogenesis. An association of macro regenerative nodules (MRN) and PSC has been vaguely described in the literature. In this study we further assess their frequency, characteristics on MRI and relationship with clinical features.
Method: This is a retrospective study including patients with PSC and at least one MRI done between 2000 and 2018. Two radiologists reviewed all MRI imaging. Patients status post partial hepatectomy or liver transplantation were excluded. We collected demographic, clinical and laboratory information within 3 months of the MRI and outcomes data. Chi-square and Wilcoxon sign rank tests were used to evaluate associations between these characteristics and MRNs.

Results: A total of 97 patients were included. Fifty-two (54%) were male, 45 (46%) female, 71 (74%) Caucasian, 78 (80%) with large duct PSC, and 47 (49%) with IBD. Median disease duration at the time of first MRI was 4.9 years (range 0.03-49.1). MRNs were present in 63 (70%).
MRNs were hypertrophic hepatic nodules with healthy bile ducts, associated with architectural distortion of surrounding areas and of the biliary system. They are distinguishable from other entities by lacking copper, zync, fat and iron within nodules. When available, gadoxetate disodium contrast-enhanced studies revealed functioning hepatocytes within MRN. Segments 4b and 3 were most frequently involved. For 61/97 patients a subsequent MRI was available; 38 (62.2%) had MRNs on both studies; 5 additional patients developed MRNs on follow-up study.
Presence of MRN was not associated with age at diagnosis, gender, race, cirrhosis, platelet count, bilirubin or INR. MRNs were associated with spleen size > 12 cm (81.2% vs. 58%, p = 0.024), use of UDCA (75% vs. 50%, p = 0.027) and with alkaline phosphatase above the upper limit of normal (65.7% vs 45%. P = 0.08). There was no association between MRNs and clinical outcomes including gastrointestinal bleeding, ascites, encephalopathy, malignancies, liver transplantation or death.



Conclusion: MRN's exhibit specific characteristics on MRI imaging of PSC patients and should not be confused with cirrhotic nodules or malignancy. In our 3 cases evaluated with hepatobiliary imaging, functioning hepatocytes were present in MRN's. Their etiology and significance remain unclear; further studies are required to elucidate their significance.

FRI-041

Pharmacokinetics, safety, and tolerability of seladelpar in subjects with hepatic impairment

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Background and aims: Primary Biliary Cholangitis (PBC) is a rare autoimmune disease manifested by chronic cholestasis. Patients can progress to cirrhosis, particularly if they do not respond adequately to UDCA treatment. Seladelpar, a potent and selective peroxisome proliferator-activated receptor-delta (PPARδ) agonist, has demonstrated potent anti-cholestatic and anti-inflammatory activity in patients with PBC. Seladelpar decreases the synthesis of bile acids in hepatocytes and also reaches cholangiocytes as it is cleared through the biliary system. We evaluated the pharmacokinetics (PK) and safety of a single 10 mg dose of seladelpar in subjects with varying degrees of hepatic impairment (HI).
Method: Subjects with mild, moderate, or severe HI (defined per Child-Pugh score) and healthy control subjects matched to the moderate HI subjects were enrolled in an open-label, non-randomized, parallel-group, single-dose PK study. Blood samples were collected to assess the PK of seladelpar. Safety and tolerability were assessed throughout the study.
Results: Thirty-two subjects completed the study and were analyzed for PK: 8 subjects with mild, moderate, and severe HI, and 8 healthy controls. Mild HI did not significantly impact seladelpar PK comparing to controls: seladelpar C_{max} increased by 20%, while seladelpar AUC increased by 10%, while $T_{1/2}$ did not change. However, moderate and severe HI impacted seladelpar PK comparing to controls: seladelpar C_{max} increased to 5-fold, AUC increased to 2-fold, while $T_{1/2}$ did not change. Single doses of 10 mg seladelpar were well-tolerated by subjects with varying degrees of hepatic impairment. All adverse events were mild in severity, except for 1 severe SAE of esophageal varices hemorrhage in a subject with a history of intermittent bleeding from esophageal varices. This SAE was considered unlikely related to study treatment. No clinically important changes in vital signs, physical examination findings, or laboratory values were observed.
Conclusion: Mild HI did not significantly change the PK of seladelpar and dose adjustments in this population do not appear necessary. However, given the magnitude of the increases in seladelpar exposure in the moderate and severe HI subjects, dose adjustments in these populations might be necessary. Single-dose administration of seladelpar appeared to be well tolerated and safe in subjects with varying degrees of hepatic impairment.

FRI-042

Prevalence and male/female ratio of autoimmune liver diseases are increasing over time in Japan: Hospital-based epidemiological study

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Background and aims: Prevalence of autoimmune liver diseases (AILD, including autoimmune hepatitis; AIH, primary biliary cholangitis; PBC, primary sclerosing cholangitis; PSC) is reported to be increasing worldwide. In addition, change of male-female ratio is another notable trend in AIH and PBC. We conducted epidemiological studies of AIH and PBC in 2004 and of PSC in 2007. In 2018, we again performed a nation-wide, hospital-based epidemiological study to clarify prevalence of AIH, PBC and PSC, to clarify time trend in epidemiology of AILD in Japan.
Method: The hospitals used in the study were selected randomly from a list of all hospitals in Japan. The selection rate was determined according to a stratification based on the number of beds in the hospital. Thus, hospitals with a high number of beds had a greater probability of being selected. The selection rate was 100% for hospitals with 500 beds or more or university hospitals, whereas only 5% of hospitals with fewer than 100 beds were selected at random. In addition, all specialized hospitals that had previously reported patients with AILD were selected for the study. After selection, we sent questionnaires describing the diagnostic criteria for AILD and asked to describe the number and gender of patients with AILD. The epidemiological study was performed in an identical method for AIH/PBC in 2004 and for PSC in 2007, and we compared the results.
Results: We selected 1, 793 hospitals or departments of paediatrics, internal medicine, gastroenterology, hepatology and surgery were selected from all over Japan. Of them, 1, 078 (60.1%) responded to the questionnaires. The number of reported patients with AIH, PBC and PSC were 7, 679, 10, 847, and 906, respectively, and the statistically-estimated number of patients were 30, 325 (95%CI, 29, 586-31, 063) for AIH, 37, 045 (36, 172-37, 917) for PBC, and 2, 306 (2, 247-2, 365) for PSC. The prevalence of AILD was calculated as 23.9 for AIH (8.7 in 2004), 33.8 for PBC (11.6 in 2004), and 1.80 for PSC (0.95 in 2007) per

100, 000 Japanese population. Furthermore, female/male ratio of AILD in the current study was 3.89 for AIH (6.94 in 2004), 4.26 for PBC (7.06 in 2004) and 0.88 for PSC (1.36 in 2007).
Conclusion: The current and previous epidemiological studies demonstrate that increasing trend of prevalence as well as male/female ratio of all AILD, AIH, PBC and PSC in Japan. These results suggest alteration of environmental triggering factors and provide definite needs for case-control studies.

FRI-043
Primary biliary cholangitis-Autoimmune hepatitis overlap syndrome: Characteristics and response to obeticholic acid in TARGET-PBC, a diverse, large United States real-world cohort
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Background and aims: A subset of PBC patients have an overlap syndrome with AIH. Patients with overlap may have poorer response to ursodeoxycholic acid (UDCA) and higher rates of progression to cirrhosis. The aim of this study was to compare clinical characteristics and outcomes in PBC patients with and without overlap.
Method: TARGET-PBC is an ongoing observational study of PBC patients at 35 U.S. sites. Data is captured from redacted medical records. All clinical diagnoses and treatment decisions are at the treating provider's discretion.
Results: Overlap was reported in 71/485 patients (14.6%). Median age at diagnosis was 52 years for both groups; gender (85.9% vs. 90.1% female), race (74.6% vs. 86.4% white), ethnicity (21.1% vs. 17.1% Hispanic) and frequency of ≥ 1 autoimmune conditions (55% vs. 59%) were similar between groups. The autoantibodies in overlap vs. PBC patients at study enrollment were: antimitochondrial (73.8% vs. 87.5%, p = 0.004), antinuclear (64.4% vs. 47%, p = 0.035), and smooth muscle (51.4% vs. 21%, p = 0.0002). Median IgG levels at study entry did not differ: overlap 1393 vs. PBC 1256, possibly because most overlap patients were on immunosuppressant treatment. Liver biopsy reports were available for 74.6% and 61.4% of overlap and PBC patients. Interface hepatitis was more common (81.8% vs. 43.8%, p < 0.0001) and median fibrosis score was greater (3 vs. 2, p = 0.002) in overlap patients. Cirrhosis was present in more overlap patients (47% vs. 36%, p = ns) and evidence of prior decompensation was present in more of the overlap cirrhotic patients (60.6% vs. 48%, p = ns). The frequency of pruritus and fatigue was similar between groups. Fifty-one patients (72%) with overlap were treated at last follow-up with UDCA and 11 (15.5%) with UDCA + OCA. The mean alkaline phosphatase reduction in OCA-treated overlap patients was 20.3% vs. 24.7% in OCA-treated PBC patients. The mean total bilirubin reduction in OCA-treated overlap patients was 14% compared to a 10.4% increase in OCA-treated PBC patients. The most common adverse event and reason for discontinuation with OCA was pruritus for both groups.
Conclusion: AIH overlap was diagnosed in 15% of this cohort. Overlap patients were more likely to have antinuclear and smooth muscle antibodies, interface hepatitis, and advanced fibrosis, but were otherwise similar to PBC patients. OCA was administered to 11 overlap patients with safety and efficacy comparable to PBC patients.

FRI-044
PNPLA3 polymorphism is associated with disease progression in patients with autoimmune hepatitis
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Background and aims: Autoimmune hepatitis (AIH) is an inflammatory liver disease leading to liver fibrosis and cirrhosis. Immunosuppressive treatment can attenuate disease progression. However, patients may develop significant liver fibrosis/cirrhosis over time, some despite biochemical response to immunosuppressive therapy. Single nucleotide polymorphisms (SNPs) such as PNPLA3 (rs738409), TM6SF2 (rs58542926), and MBOAT7 (rs641738) are associated with liver fibrosis progression. Recently, a splice-variant in HSD17B13 (rs72613567:TA) has been shown to be protective in liver disease patients. Aim of this study was to analyze, whether these SNPs play a role in the clinical course of patients with AIH.
Method: We included 242 patients into this study who were treated between 1982 and 2018 for AIH in our department. Genomic DNA was isolated from whole blood. SNPs were determined by PCR analysis using Primers/Probes (Thermofisher). Data at first visit and at the end-of follow-up were analyzed and non-invasive fibrosis scores were calculated. Statistical analysis was performed using SPSS, a p value < 0.05 was considered significant.
Results: Mean age at diagnosis was 39.2 ± 18.2 years with 25.6% being male. The median follow-up was 10 years (range 32 days-34 years), 12.4% of the patients died or required liver transplantation. The allelic frequencies of the four determined SNPs are presented in Table 1. Patients with the homozygous variant HSD17B13 had a later onset of disease (49 vs 36 years, p < 0.01). At the end of follow-up 35.2%, 20% and 53.3% of all patients presented with significant fibrosis as determined by an APRI-score > 0.7, a Fib-4 score > 3.25 and a DeRitis-score > 1, respectively. Homozygous presence of the PNPLA3 variant was associated with significant fibrosis as determined by APRI (80% vs. 32.6%, p < 0.01) and Fib-4 score (50% vs 18.6%, p < 0.05) as well as significantly diminished liver function as determined by CHE, albumin, prothrombin test and higher bilirubin levels (all p < 0.01) and increased liver related mortality or liver transplantation (p < 0.05). Neither TM6SF2, MBOAT7 nor HSD17B13 had an influence on the development of significant fibrosis/cirrhosis or parameters of liver inflammation/synthesis at the end-of follow-up.

	PNPLA3	TM6SF2	MBOAT7	HDS17B13
homozygous ancestral	141	206	87	136
heterozygous variant	89	32	110	79
homozygous variant	12	4	45	25

Conclusions: While AIH patients with detectable HSD17B13 splice variants were diagnosed at an older age, patients with the homozygous PNPLA3 variant had an increased risk of liver disease progression. Determination of PNPLA3 variants in patients with AIH may help to identify patients at risk for a more progressive natural course.

FRI-045
Treatment of patients with primary biliary cholangitis with seladelpar for 52 weeks improves predicted transplant-free survival
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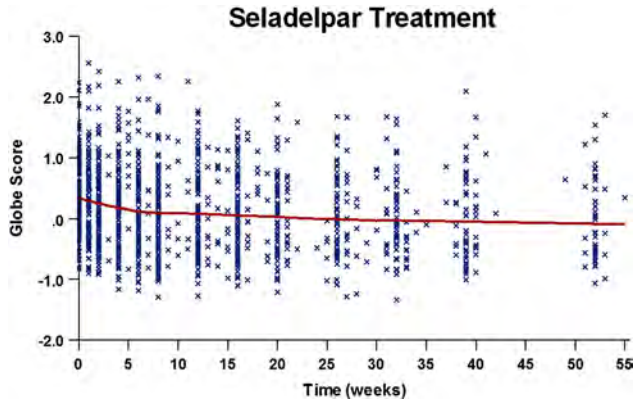
Background and aims: Treatment options for patients with primary biliary cholangitis (PBC) are still needed. The Globe score is a validated prognostic tool that can be implemented to estimate transplant-free survival. Seladelpar is a peroxisome proliferator-activated receptor δ agonist in development. Our aim was to evaluate the predicted changes in transplant-free survival associated with treatment with seladelpar based on the Globe score.
Methods: Patients with an incomplete response to ursodeoxycholic acid (UDCA) that were enrolled in an ongoing Phase 2 trial of seladelpar and who were treated with either 2mg (n = 11), 5mg (n = 53), or 10mg (n = 55) of seladelpar were included (n = 119). The Globe score was calculated at baseline, 26 weeks, and 52 weeks of treatment to estimate transplant-free survival at 3, 5, 10, and 15 years.
Results: The mean age of patients enrolled was 57.8 (SD 9.0), 94% (n = 112) were female, and the majority were treated with UDCA. Median baseline alkaline phosphatase and bilirubin were 261 u/L and 11.5 µmol/L, while mean baseline albumin and platelets were 40 g/L and 228 × 10^9/L. The Globe score decreased over time in patients treated with seladelpar (**Figure**). For those with an available Globe score, 76 patients received treatment for least 26 weeks, while 48 patients received treatment for 52 weeks. At baseline, 26 weeks, and 52 weeks, the mean Globe score was 0.419, 0.018, and −0.006, respectively. This represents a total decrease of 0.425 from baseline to 52 weeks (p < 0.001). The decline in Globe score at 52 weeks was more pronounced in the 5mg and 10mg treatment groups (−0.443 and −0.434) compared to the 2mg group (−0.271). There were improvements in the predicted transplant-free survival at 3 years (93.6 vs 95.6%), 5 years (89.0% vs 92.3%), 10 years (74.2% vs 81.4%), and 15 years (60.2% vs 70.4%).



Conclusion: Longer-term use of seladelpar improves the estimates of transplant-free survival assessed by the Globe score.

FRI-046

Raising awareness and messaging risk in patients with primary biliary cholangitis: The rapid Global PBC Screening Test

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Background and aims: Primary biliary cholangitis (PBC) is slowly progressive but impactful, and there is an increasing choice of effective therapies. Too many risk scores however exist, and such tools can appear complex. We sought to simplify risk evaluation with the goal of early triaging patients to specialist clinics.
Method: We utilized patient data from the Global PBC Study group. Ursodeoxycholic acid-treated patients with available bilirubin and alkaline phosphatase (ALP) at baseline (n = 2643) or 1 year (n = 2681) were included. Patients were categorized into colour risk groups (red, amber, and green) based on age at the start of treatment, bilirubin, and alkaline phosphatase. Those with abnormal bilirubin, ALP > 3 × ULN, and under 50 years old were categorized as red (high risk); those with normal bilirubin, ALP ≤ 3 × ULN, and above 50 years old were categorized as green (low risk). Meanwhile, other combinations were denoted as amber (intermediate risk). The transplant-free survival rates associated with each group were estimated with Kaplan-Meier curves and the Globe score.
Results: At baseline, there were 156 (6%) patients identified as red, 1451 (55%) as amber, and 1036 (39%) as green. The 10-year transplant-free survival rates associated with each colour was 60.7%, 77.2%, and 88.2%, respectively (p < 0.001). The corresponding median 10-year survival when estimated by the Globe score was 64.5%, 85.4%, and 84.4%. Similarly, at 1 year there were 72 (3%) red, 1199 (45%) amber, and 1410 (52%) green categorizations. While the 10-year transplant-free survival rates associated with each was 43.0%, 74.9%, and 83.8% (p < 0.001), median 10-year survival estimates by the Globe score were 68.3%, 90.7%, and 86.5%. Of those who were categorized at baseline and 1 year (n = 2122), 471 experienced a change in categorization from baseline to 1 year. The red group had the highest proportion of patients who changed (61% [86/140]) primarily to the amber group (n = 80). Furthermore, 32% (375/1171) of patients in the amber group changed, of which the majority were to a green categorization (n = 354). Lastly, only 3% (22/811) of patients in the green group changed, but none to the red highest-risk group.

Conclusion: Clinicians can easily, rapidly and effectively stratify risk of future events in PBC using a simple "traffic light" test. Applying this at baseline and at 1-year adequately identifies risk; we propose "Red" patients at baseline, and "Red and Amber" patients after 1 year of UDCA be offered referral to dedicated PBC clinics.

FRI-047

Metabolic syndrome delays biochemical remission in autoimmune hepatitis

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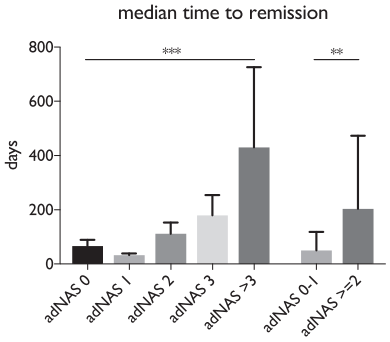
Background and aims: In this study, we examine the prevalence of metabolic syndrome in patients with autoimmune hepatitis (AIH), including the impact on histological findings and efficacy of treatment response.
Method: Patients with biopsy-proven AIH were identified from a departmental database at a single centre, using Systemetized Nomenclature of Medicine (SNOMED) codes. Medical records were reviewed for anthromorphic, biochemical and histological data. The presence of fatty liver disease was graded using an adjusted NAS (aNAS) score that included steatosis and ballooning but not lobular inflammation. Response to corticosteroid treatment was examined with regard to the time to normalization of transaminases.
Results: Between the years of 2010 and 2017, 70 patients with biopsy-proven AIH were identified. Median age at diagnosis was 55 years and 80% of patients were women. At presentation, the median ALT value was 268 U/L and median IgG was 22.5 g/L. Two patients were cirrhotic according to Ishak stage. Observing the cohort in entirety, the median BMI was 26 kg/m^2: 23 patients were overweight (BMI 25.0-29.9kg/m^2) and 9 were obese (BMI > 30kg.m^2). Six patients had diabetes mellitus. In addition to AIH, 42 patients had histological evidence of fatty liver on biopsy. Hepatic steatosis was seen in 28 biopsies and ballooning was seen in 26 biopsies. Patients with a greater aNAS score took longer to respond to corticosteroid therapy (log rank p = 0.066) (**figure 1**), with a median time to remission in of 50 (± 12) vs. 203 (± 65) days in patients with a NAS 0-1 vs. NAS ≥ 2, respectively (p = 0.003).



Conclusion: Obesity and diabetes are common amongst patients with AIH. Co-exisiting NAFLD is frequently seen on biopsy in addition to AIH, and may delay response to induction therapy.

FRI-048

Faecal calprotectin in PSC-IBD is a prognostic marker of cholangitis associated complications

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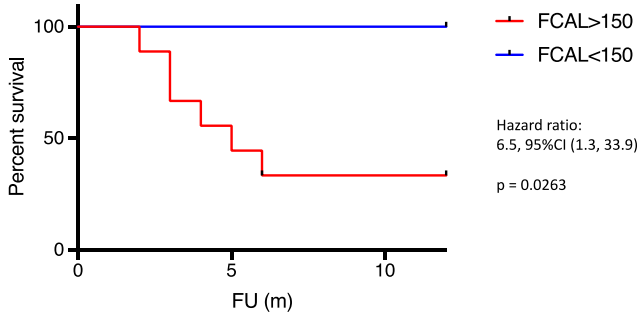
Background and aims: Primary sclerosing cholangitis (PSC) is a chronic inflammatory condition of the bile ducts leading to fibrosis and end stage liver disease. A lack of robust non-invasive biomarkers has been hindering disease monitoring and development of optimal therapies. We have previously noted that the high levels of faecal calprotectin (fcal) seen in PSC-IBD patients belie the mild or quiescent intestinal inflammation. An unsupervised proteomics study identified biliary calprotectin as a potential biomarker. Here, we test the hypothesis that fcal is a marker of biliary injury in PSC.
Method: We analysed paired endoscopic activity data (UCEIS) and fcal results of patients with PSC-IBD (n = 20) or UC (n = 20) who underwent colitis surveillance in the context of a colitis surveillance pilot study. Relevant clinical data was recorded prospectively. Recruiting consecutive patients attending for ERCP (n = 8) allowed for the concomitant testing of biliary and faecal calprotectin.
Results: As expected, fcal strongly correlated with severity of mucosal injury (UCEIS) in UC [r = 0.82, 95%CI (0.58, 0.92), p < 0.0001]. However, the correlation was weaker in PSC-IBD [r = 0.59, 95%CI (0.19, 0.82), p = 0.006]. Moreover, in patients with PSC-IBD and quiescent colitis (UCEIS: 0-1) fcal concentration was significantly higher in comparison to UC patients with comparable endoscopic activity [279ug/g (10, 1560) vs. 30 (10, 161), p = 0.015)]. A trend towards abnormal liver biochemistry was seen in those PSC-IBD with higher fcal [ALP: 250IU/L (113, 561) vs. 83 (59, 170), p = 0.06, GGT: 351U/L (117, 1014) vs. 51 (29, 153) p = 0.02, AST: 53U/L (26, 85) vs. 37 (22, 43), p = ns]. UC patients with quiescent colitis and fcal > 150 had a higher risk of colitis relapse in 12 months [HR = 7.6, 95%CI (1.8, 33.6)] in comparison to those with fcal < 150. However, in patients with PSC-IBD and quiescent colitis a fcal > 150 was associated instead with a higher risk of cholangitis associated complications (need for antibiotics or stent insertion), HR = 6.5, 95%CI (1.3, 33.9). Strikingly, biliary calprotectin concentration showed a strong correlation with fcal concentration (r = 0.90, p = 0.04).



Conclusion: In patients with PSC-IBD and quiescent colitis the identification of a raised fcal is likely to herald complications of inflammation in the bile ducts rather than the colon. In this setting, fcal may be a valuable prognostic biomarker of cholangitis.

FRI-049

Real world experience of obeticholic acid (Ocaliva) for the treatment of primary biliary cholangitis in the secondary care setting

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Background and aims: Primary biliary cholangitis (PBC) is a condition that involves the destruction of interlobular bile ducts, which can lead to end-stage chronic liver disease. PBC activity is monitored through serum alkaline phosphatase (ALP) and bilirubin levels. Increased ALP and bilirubin levels have been shown to correlate with disease progression and disease outcome, respectively. The POISE Study Group demonstrated that obeticholic acid (OCA) reduces these biochemical parameters but was also associated with

side effects (SE). We evaluated the use of OCA in the treatment of PBC patients at our Trust.

Method: PBC patients who had not responded to, or who were intolerant to ursodeoxycholic acid (UDCA) monotherapy at a dose of 13-15mg/kg/day were discussed at our Hepatology multi-disciplinary team meeting. Twenty nine patients were started on OCA between July 2017 and November 2018. Patient's bloods were sampled one, three and six months after starting OCA; a patient telephone helpline was also made available and SE were recorded.

Results: The mean patient age was 62 years (range, 31-79); 25/29 (86%) patients were female and 4/29 patients (14%) were male. 18/29 (62%) patients had not responded biochemically to UDCA and 11/29 (38%) patients had stopped UDCA due to SE; prior to OCA use.

15/29 (52%) patients have so far received at least six months of OCA; of these patients we identified an ALP reduction (mean, 80.5 u/L; p = 0.006; range, −307 to +71) and a trend in bilirubin reduction (mean, 1.6 µmol/L; p = 0.137; range, −11 to +5).

The most commonly reported SE was pruritus, reported in 19/29 (66%) patients; 12/29 (41%) patients described mild to moderate pruritus which was tolerable; 7/29 (24%) patients experienced severe pruritus; of these seven patients, only 3/7 (43%) restarted and tolerated OCA at a lower dose following a two week interruption. Furthermore three patients experienced liver decompensation leading to a dose reduction in two patients and discontinuation in one patient. In total SE leading to discontinuation occurred in 9/29 (31%) of patients.

Figure: Comparison of YTHT and Poise 5-10mg Titration Arm Results

	York Teaching Hospital Trust	Poise 5-10mg Titration Arm
Mean age	62 years	56 years
Mean Fibroscan	10.7 kPa	10.7 kPa
UDCA usage	18/29 (62%)	65/70 (93%)
Mean baseline ALP	291 IU/L	326 IU/L
Mean ALP reduction	80.5 IU/L	87.7 IU/L
Mean baseline bilirubin	14.3 µmol/L	10.3 µmol/L
Mean bilirubin reduction	1.6 µmol/L	0.34 µmol/L
Reports of pruritus	19/29 (66%)	39/67 (58%)
Discontinuations due to SE	9/29 (31%)	4/67 (6%)

Conclusion: Six months of OCA treatment was associated with a significant reduction in ALP but not bilirubin, similar to the POISE study group. We found the incidence of pruritus to be only slightly higher than the POISE study group but more of our patients withdrew from OCA due to the SE. We continue to monitor our OCA patient group and await our longer term clinical outcomes with interest.

FRI-050

Antibodies to human beta-tubulin isotype 5 in autoimmune liver disorders-re-evaluation of their specificity and clinical relevance

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Background and aims: From previous studies there was strong evidence that human beta-tubulin isotype 5 (TBB-5) is the corresponding antigen for pANCA (perinuclear antineutrophil cytoplasmic antibodies) in autoimmune liver diseases (AILD) (1, 2). Thus, anti-TBB-5 antibodies (abs) have been found in 88% of patients with pANCA-positive autoimmune hepatitis (AIH) and 72% of pANCA-positive patients with primary sclerosing cholangitis (PSC). Aim of the present study was to re-evaluate their diagnostic relevance.

Method: Sera from 350 patients with pANCA-positive or -negative AIH, 41 patients with pANCA-positive or -negative PSC, 250 patients with primary biliary cholangitis (PBC), 49 patients with viral hepatitis, 57 patients with alcoholic liver disease (ALD), 52 patients with non-alcoholic fatty liver disease or non-alcoholic steatosis hepatitis (NAFLD/NASH), 8 patients with storage diseases and 62 healthy individuals were analysed by ELISA for anti-TBB-5 abs of the IgG- and IgA-type. Recombinant human TBB-5 was expressed in E.coli as a histidine-tagged protein.

Results: The incidence of IgG anti-TBB-5 abs was significantly higher in patients with AIH (33%) and PSC (27%) than in the other groups of patients (up to 18%; $p < 0.05$) and healthy controls (3%; $p < 0.0001$). Also reactivity towards this antigen was significantly higher in patients with AIH as compared to patients with other liver disorders. However, there was no correlation with the presence or absence of pANCA. Interestingly, IgA anti-TBB-5 abs were predominantly found in patients with ALD (40%) but hardly in patients with AILD or NAFLD (up to 12%; $p < 0.005$), and also reactivity was significantly higher in the ALD-patients as compared to the other groups.

Conclusion: We could confirm the high association of IgG anti-TBB-5 abs with AIH and PSC. However, they were found also in pANCA negative patients; vice versa, strongly pANCA positive patients were anti-TBB-5 negative, indicating that TBB-5 is not the only target of pANCA. In contrast, IgA anti-TBB-5 antibodies were strongly associated with ALD. I.e. the determination of anti-TBB-5 abs of the IgG- and IgA-type may be helpful in the serological differential diagnosis of autoimmune and alcoholic liver disorders as well as NAFLD.

Terjung B, Spengler U, Clin Rev Allergy Immunol 2009; 36: 40-51.
2) Terjung B et al, Gut 2010; 59: 808-816.

FRI-051

Pregnancy outcomes in women with autoimmune hepatitis

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Background and aims: A significant proportion of female patients with autoimmune hepatitis (AIH) are of child-bearing age. With the advent of in vitro fertilization, improved drug safety profiles and publication of positive outcome data, pregnancy in AIH is increasingly common. Despite a few Scandinavian population-based studies, there is a paucity of conclusive data for certain pregnancy related outcomes in AIH. There is reproducible data on the increased risk of pre-term births, with miscarriage (MC) rates seemingly unaffected. Stillbirth rates and impact of immunosuppression (IS) are not fully defined. This study will aim to look at the incidence and severity of adverse pregnancy outcomes in our cohort of females with AIH.

Method: Pregnancies in patients with a diagnosis of "definite" AIH were identified through an earlier prospectively collated database and subsequent clinic consultations. Details on baseline pre-conception characteristics, diagnosis, histology, medications and fibrosis stage were obtained from medical records. Maternal complications and MCs were documented, along with gestation length and live birth rates. Statistical analysis was performed with Chi squared test. A p value of < 0.05 was statistically significant.

Results: Since 1983, 99 self-reported pregnancies were identified in 61 mothers with AIH at King's College Hospital. Median age of conception was 28 years (range 16-44). Cirrhosis or advanced fibrosis was present in 31/99 (31%) pregnancies. There were 77/99 (78%) pregnancies on IS at conception; 34 on monotherapy, 40 on dual therapy and 3 on triple therapy. In 99 pregnancies, 76 live births (77%) occurred, with 10 early MCs, 10 terminations and 2 intrauterine deaths. The miscarriage rate in cirrhotics was 10% versus 12% in non-cirrhotics (p = 0.82).

Of the live births, 51 (67%) were term (> 37 weeks), 7 (9%) were pre-term (32-37 weeks) and 3 (4%) were very pre-term (< 32 weeks). Of the cirrhotic pregnancies, 13/33 were pre-term. In the non-cirrhotic group, 7/31 were pre-term (p = 0.15). In our cohort, IS did not affect pre-term rates (36/55 vs 8/9, p = 0.16).
Liver related complications occurred in 12/99 (12%) pregnancies, including flares, decompensation and cholestasis. There was no difference in the rate of liver complications between cirrhotic and non-cirrhotic groups (12% vs 12%, p = 0.91). IS during pregnancy was not a risk for developing liver related complications (12/82 vs 0/17, p = 0.09). A flare during/after pregnancy occurred in 24/82 (29%) on IS, compared to 8/17 (47%) not on IS (p = 0.15).
Conclusion: Pregnancy in AIH, with or without cirrhosis, appears to have favorable outcomes in most patients. Larger corroborative studies could elucidate which pre-conception factors predict poor outcomes. High risk patients may warrant in depth pre-conception counselling and closer follow-up with the Hepatologists and Obstetricians, ideally in a combined clinic.

FRI-052

Long-term bezafibrate therapy does not prevent the progression of primary biliary cholangitis in patients with advanced disease

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Background and aims: Combined treatment with ursodeoxycholic acid (UDCA) and fibrates has the potential both to improve liver biochemistries and to reduce the symptoms of primary biliary cholangitis (PBC), but the long-term effects of this regimen has not been completely evaluated. The current study was addressed to explore the outcome of the combined treatment is terms of survival free of transplantation and development of events of PBC progression.
Method: 54 PBC patients (51 female, age 53 -IQR 36-58- years) treated with UDCA for at least a year and alkaline phosphatase (ALP) above 1.5 times upper normal levels (× UNL) were treated with bezafibrate (400 mg/day) plus UDCA (13-16 mg/kg/day). Changes in clinical features, liver biochemistries and outcome after therapy were assessed. In 48 patients, liver stiffness (LS) as an index of fibrosis was assessed before and at the end of observation. The globe score (GS) as a prognostic index was measured as well.
Results: After a median of 5.9 (4.4-5.8) years a significant improvement of biochemical cholestasis was observed, although without changes in LS (9.4 ± 1.1 vs 10.9 ± 1.7, kPa, p:n.s). ALP normalized in 28 patients (52%) after a median of 17 months. Sixteen patients (33%) have a baseline LS ≥ 9.6 kPa, and 17 patients (31%) a GS > 0.3. Eight patients (15%) progressed to more advanced disease and died (2), were transplanted (3), developed hepatocellular carcinoma (1) or had events of decompensation (2). All of these patients did not normalize ALP, six had a baseline LS ≥ 9.6 kPa and six (75%) had a baseline GS > 0.3. In the patients with poor outcome, improvement of liver biochemistries was observed as well (ALP: 3.9 ± 0.6 to 2.3 ± 0, 5, p = 0.04; ALT: 105 ± 13 to 69 ± 13 u/L, γGT: 480 ± 131 to 131 ± 39 u/L, p = 0.03), but a significant decrease in albumin (39.2 ± 1.3 to 32.9 ± 1.3 g/L, p = 0.008) and platelet count. Moreover, the probability of poor outcome according to the Kaplan-Meir analysis was significantly higher in the patients with lack of ALP normalization (p = 0.005), and baseline LS ≥ 9.6 kPa (p = 0.002) or GS > 0.3 (p = 0.004).
Conclusion: Long-term treatment with bezafibrate in addition to UDCA resulted in biochemical response with normalization of ALP in a short period of time in more than half of the patients. However, this treatment does not prevent the progression of primary biliary cholangitis in the patients with more advanced disease, despite of the improvement of biochemical cholestasis.

FRI-053

Overlap of primary biliary cholangitis and autoimmune hepatitis. Natural history and prognosis in a large cohort of patients from Spain

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Background and aims: Primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) occurring concurrently is called "overlap syndrome" (OS). It may be diagnosed in a previously healthy subject, or may arise in the course of PBC. The natural history and prognosis are not fully established, nor the characteristics of PBC patients who develop OS across the course of the cholestatic disease. Then, this study was aimed at assessing the course and prognosis of the OS in PBC.
Method: Data from 2120 patients with PBC included in the Col-Hai registry were analyzed. 1955 patients were diagnosed as PBC and 165 as OS (7.8%). Clinical and laboratory data at presentation, and features of cirrhosis or portal hypertension (PH), decompensation events and liver related death or transplantation were recorded. Moreover, patients with no overlap at diagnosis who develop this condition during the course of PBC were evaluated separately. There were 3 groups: no overlap (PBC), overlap at diagnosis (OS) and overlap diagnosed within the PBC follow-up (OS-PBC).
Results: At diagnosis OS patients were younger (49.8 ± 14 vs 54.8 ± 13 years, p < 0.001) with higher transaminases (2.7 ± 2.4 vs 1.6 ± 1.5 UNL, p < 0.001) and γGT (6.6 ± 7 vs 6.1 ± 6 UNL; p = 0.001) and lower bilirubin (0.9 ± 1.5 vs 1.5 ± 2 mg/dl, p = 0.03). Global and UK-PBC scores were similar, but in OS patient's prognosis stratified by age was poorest (67 vs 92%, p < 0.001), and with lower UDCA response to Paris I, Paris II and Rotterdam criteria than in PBC. Time to cirrhosis or PH was shorter (11.8 ± 1.5 vs 18.1 ± 0.7 years, p = 0.07), with no differences in time to death or transplantation. 25 PBC patients (1.3%) had OS-PBC, within a period of 7.9 ± 4 years. OS-PBC patients were younger at diagnosis of PBC (44.2 ± 12 vs 54.8 ± 13 years,

p < 0.01) with similar response to UDCA and Global and UK-PBC scores than in patients who did not developed OS. OS-PBC patients developed more features of cirrhosis or PH during follow-up (54% vs 21%, p < 0.001) in a shorter period (6.5 ± 1.2 vs 18.1 ± 0.6 years, p < 0.001) and lower time to liver-related death or transplantation (p = 0.05) than the PBC patients. No significant differences in survival free of transplantation were observed between PBC and OS groups.
Conclusion: Overlap PBC-AIH syndrome is observed in younger patients and associated with faster progression of the disease. Prognosis scores and response to treatment do not predict overlap development in during the course of PBC.

FRI-054
Immune-related hepatitis as an independent entity from autoimmune hepatitis: clinical, prognostic and therapeutic differences
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Background and aims: Immunotherapy has revolutionized Oncology. However, patients can develop adverse events that mimic autoimmune conditions. Real-world data concerning immune-related hepatitis (irH) is lacking. The aim of the study was to describe the characteristics, prognosis and treatment of a cohort of irH.
Method: Retrospective study including all cases of irH referred from 2013 and diagnosed according to the Oncology guidelines. Patients were compared with autoimmune hepatitis (AIH) diagnosed within the same period.
Results: 63 cases were recorded: 25 (40%) irH and 38 (60%) AIH. 59% women, 94% Caucasian, mean age 58 ± 15. At diagnosis, 86% presented acute hepatitis. irH were older (64 vs 54, p = 0.04) and less severe at presentation (9% acute liver injury or failure vs 32%, p = 0.046). Symptoms were less frequent in irH (32% vs 68%, p = 0, 005), including fatigue (p = 0.002) and jaundice (p = 0, 015). Bilirubin (p = 0, 001), proteins (p = 0, 02), γglobulins (p < 0, 001) and IgG (p < 0, 001) values were lower in irH, as well as the presence of ANAs ≥ 1:80 (p < 0, 001). The majority of irH had received antiPD1/L1 (72%) and/or antiCTLA (36%). Liver biopsy did not show signs of cirrhosis in any irH vs 16% of AIH (p = 0.04). The majority of AIH were classified at least as probable according to the AIH score, but it was not useful for irH (94% vs 11%, p < 0.01). Initial dose of corticoids in irH was higher (64 vs 40mg, p < 0.001) but duration was shorter (2.5 vs 10 months, p < 0.001). Weeks to decrease corticoids < 20mg/d was similar, as well as the proportion of flares. A lower percentage of irH received a second immunossupressant (41% vs 97%, p < 0, 001) and just 1 case required second line therapies vs 28% of AIH (p = 0.05). IrH achieved complete remission sooner (2.8 vs 6 months, p = 0.049). Rate of infections was 18% and similar between the two groups, although prophylaxis with cotrimoxazole was more common in irH (p < 0.02). Mortality was higher in irH (p = 0.04), although liver-related ones were similar (10% vs 9%, p = 0.67). Among AIH, 19% developed decompensation during follow-up, 2 (5%) hepatocarcinoma and 2 (5%) required transplantation.
Conclusion: AntiPD1/L1 and antiCTLA were the immunotherapies more commonly associated with irH, 9% presenting as severe acute hepatitis and mortality rate of 10%. Diagnostic scores for AIH are not useful in irH. Most cases resolved with corticoids and though the initial dose tends to be higher, duration of treatment is shorter than AIH.

FRI-055
Failure to normalize ALT and IgG in Autoimmune Hepatitis is associated with more advanced liver disease: Perspectives from a multi-ethnic Canadian AIH registry
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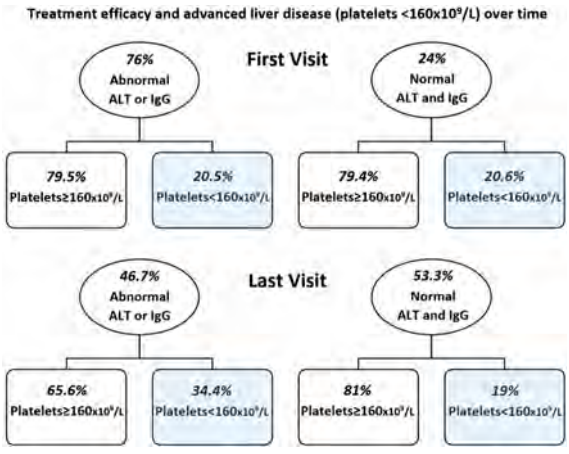
Background and aims: Autoimmune hepatitis (AIH) is infrequent but impactful, with management that remains heterogeneous. We sought to define diversity of disease in Canadian practice.
Method: Data on patients with a clinical diagnosis of AIH within the Canadian Network for Autoimmune Liver disease were abstracted for demographic, clinical, and biochemical data between November 1999 and October 2018. Paired T-tests/Wilcoxon tests were used for continuous data and chi-square/McNemar's tests for categorical data. Logistic regression and receiver operator characteristic were applied.
Results: The cohort included 412 patients with follow-up of at least 1 year. Median age was 54.6 years (39.4-69.6), 75.2% were female, and 18.0% had clinical features of overlap with either PBC (56.8%) or PSC (43.2%). Our multi-ethnic cohort was 63.6% Caucasian, 11.9% Asian, 8.9% Black, 4.4% Middle Eastern, 2.7% Latin American, 1.7% Indigenous Canadian, and 3.9% mixed ethnicity. 78.6% of patients had Type 1 AIH and 1.2% had Type 2 AIH. ANA, SMA, and LKM were negative in 20.1%. At first visit, median ALT was 59 U/L (31-156), IgG 16.9 g/L (12.6-23.8), AST 56 U/L (30-142), total bilirubin 12 µmol/L (8-24), and platelets 232x10^9/L (175-287). Median ALP was 101 U/L (66-160) and GGT 82 U/L (33-188). 76% of patients had abnormal ALT or IgG at first visit; at last visit 53% had normal ALT and normal IgG. Thrombocytopenia (platelets < 160x10^9/L), as a sensitive marker for cirrhosis, identified 20.5% of patients at first visit with advanced disease compared to 26.2% at last follow-up (p = 0.006). Of those at last visit with abnormal ALT or IgG, 34.4% had a surrogate of cirrhosis compared to 19.0% in patients with normal ALT and IgG (p < 0.01; Figure). Across follow-up, median ALP of patients with clinical overlap features was 178 U/L (95-222) compared to 79 U/L (61-108) in patients with AIH alone (p < 0.0001). Across follow-up, patients with overlap features had GGT of 130 U/L (47-218) compared to 44 U/L (24-97) in those without (p < 0.01). Univariate logistic regression demonstrated that higher GGT values were associated with increased odds of overlap features (p < 0.0001), but GGT demonstrated only moderate ability to discriminate overlap features (AUC = 0.677).



Conclusion: In a multi-ethnic Canadian registry of overwhelmingly Type 1 adult AIH, the majority of patients are over the age of 50. When stratified by achievement of established treatment goals, the burden of advanced liver disease is significantly increased in those without normal ALT or IgG.

FRI-056

Obeticholic acid as adjunctive therapy in Primary Biliary Cholangitis: A review of early real-world experience

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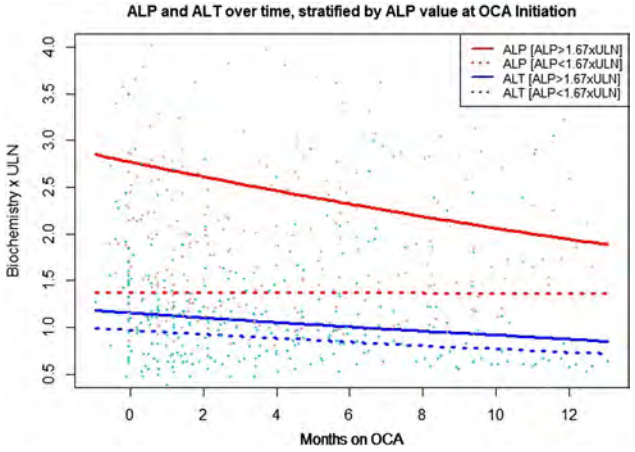
Background and aims: Patients with Primary Biliary Cholangitis (PBC) with incomplete response to UDCA are at risk of progressive liver injury and in need of alternative therapy. In May 2017, obeticholic acid (OCA) was approved in Canada as adjunctive therapy for PBC. We sought to describe our experience of the real world use of OCA use in high risk PBC.

Method: Available data on patients initiated on OCA within the Canadian Network for Autoimmune Liver disease were included. Medical records were abstracted for patient demographics. Clinical and biochemical data were collected at baseline and at defined intervals in follow-up. Repeated measures models (SAS 9.4) were used to assess changes in alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin over time.

Results: 40 patients were initiated on OCA between August 2017 and October 2018 based on treating hepatologists' clinical evaluation of individual risk of disease progression. Mean age was 54.7 (± 9.8) years, 92.5% (n = 37) were female, 90% (n = 36) were AMA positive, and median liver stiffness was 10.6 kPa (7.8-15.0). Median follow-up time of OCA-treated patients was 7.0 (3.6-10.6) months. At OCA initiation, median ALP was 264 U/L (IQR 190-379), ALT was 43 U/L (30-57), AST was 44 U/L (36-57), total bilirubin was 13 µmol/L (9-16), and platelets were $229x10^9$/L (174-268). After 12 months of OCA treatment, ALP had decreased by a mean of 64 U/L ($p < 0.01$) and ALT had decreased by 11 U/L ($p < 0.04$). AST showed a decreasing trend of 5.1 U/L (p = NS) while total bilirubin remained stable (decrease of 0.03 µmol/L; p = NS).

13 patients had ALP < 1.67xULN at OCA initiation, one of whom also had total bilirubin > 2xULN. In these patients with lower ALP at initiation, ALP remained stable ($p = 0.98$) while ALT showed a significant decline ($p < 0.05$) similar to that observed in patients with ALP ≥ 1.67xULN ($p = 0.25$; Figure). AST and total bilirubin showed the same non-significant trends in patients with lower ALP at OCA initiation.

Worsening of itch occurred in 52.5% (n = 21) patients. 7.5% (n = 3) of patients discontinued therapy, 2 due to worsening pruritus and 1 due to variceal bleed. Dose reduction to 5 mg weekly occurred in 7.5% (n = 3) of patients due to clinical suspicion of progressive disease.



Conclusion: In this real word cohort, use of OCA in addition to UDCA in patients with high risk PBC was associated with improvement in biochemical markers of cholestasis and inflammation.

FRI-057

A review of primary biliary cholangitis practice in Wales: Time for specialist care

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Background and aims: Therapeutic advances in primary biliary cirrhosis (PBC) make assessment of treatment response a critically important issue. We studied the clinical practice around PBC in Wales. Population of Wales is over 3 million people with rural/urban diversity. Clinical services reflect the diversity with small district hospitals and large liver units.

Method: We developed a clinical audit tool with UK-PBC and EASL guidelines. Data was retrospectively collected by specialist trainees in each health board, including demographic information, clinical management and differences in adherence to standards between clinicians. We interrogated ursodeoxycholic acid (UDCA) use, appropriate dosing, documentation of symptoms, prevalence of cirrhosis and referral for transplant.

Results: Total of 406 living patients with diagnosis of PBC were identified across five Welsh health boards.
Out of 406 patients, majority were females (n = 297, 73%), mean age at diagnosis of 59.7 years (± 13.5). Serological testing for PBC (AMA > 1/40) was present in 88.5% patients at time of diagnosis. Mean Alkaline Phosphatase (ALP) at diagnosis was 334U/L (56-2020). Liver biopsy was performed in 26.6% of patients and was more likely to be requested by a hepatologist than a general gastroenterologist, p = 0.039 (Chi Square).
Mean follow-up since diagnosis was 7.9 ± 6years.
Symptoms of pruritus and fatigue were documented in 29.2% and 32.9% of recent clinic records respectively.
Hepatologists followed PBC patients up more frequently with 70.7% of their patients seen at 6 monthly intervals whereas general gastroenterologists were more likely to follow-up patients annually, p < 0.001.
Of 214 patients with recent clinic letters, 179 (83.6%) were on UDCA. Patients managed by hepatologists were more likely on the appropriate dose of UDCA (92.9%) compared to gastroenterologists (39.3%), p = 0.018. Hepatologists were better in recording assessment of response at 1 year (86.8%) compared to gastroenterologists (62.5%), p = 0.024.
Of the total cohort, 47.8% patients had cirrhosis, with screening performed for hepatocellular cancer in 54.3% and varices in 38%. Out of 82 patients with documentation of conversation about transplant, 26 patients were considered with 12 undergoing liver transplant.
Conclusion: This study provides a unique insight into current services for PBC patients across Wales. Despite widely available guidelines, there were significant discrepancies in adherence to standards between hepatology and gastroenterology managed patients. In particular, patients managed by hepatology were likely to receive optimal UDCA dosing and have response documented at 1 year. This study has also uncovered areas requiring improvement like documentation of fatigue and pruritis. These findings will be used to review the PBC care pathway in Wales to improve adherence to standards and access to new therapies.

FRI-058

Randomized controlled trial to compare efficacy of albumin dialysis using MARS versus new adsorbent recirculation for pruritus treatment

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Background and aims: Albumin Dialysis is a therapy option for pruritus in cholestatic liver disease. The aim was to compare the efficacy between MARS with a new albumin dialysis device.
Method: A Prospective randomized crossover study was conducted in 4 sites. Randomly subjects received either MARS first and new HepalbinCluster[12] albumin dialysis (OPAL) second or vice versa. Clinical scores, Visual Analogue Score, standard laboratory tests as well as albumin binding function, free fatty and bile acids were measured before and after each treatment.
Results: 8 subjects suffering from cholestatic liver disease and pruritus were enrolled. Subjects in both arms were comparable and results are listed in Figure 1 (Table):

Baseline	Mars 1st n = 4		Opal 1st(Hepalbin Cluster12) n = 4	
Gender (f/m)	(0/4)		(3/1)	
Age	44.50 + 21		47.25 ± 18	
	All Mars Therapies (n = 8)		All Hepalbin Cluster12 (n = 8)	
	Pre	post	pre	post
Mean Art. Pressure	93 ± 11	102 ± 20	96 ± 8	96 ± 16
Hemoglobin (mmol/l)	7.3 ± 1.6	7.0 ± 1.5	7.1 ± 1.5	6.8 ± 1.5
Platelets	226 ± 115	189 ± 92	214 ± 122	196 ± 115
Quick (%)	66 ± 30	63 ± 31	72 ± 31	71 ± 34
Antithrombine III	90 ± 42	90 ± 41	90 ± 48	89 ± 45
Creatinine	74 ± 23	47 ± 18	77 ± 25	50 ± 19
Bilirubin (umol/l)	254 ± 184	207 ± 148	291 ± 173	207 ± 110
Bile Acids (umol/l)	122 ± 88	67 ± 52	125 ± 121	35 ± 25
Free Fatty Acids-FFA	697 ± 618	1196 ± 715	828 ± 596	813 ± 534
Alb-Binding Capacity	64 ± 10	65 ± 14	63 ± 9	70 ± 6
Alb-Uptake FFA	14 ± 11	14 ± 14	15 ± 13	27 ± 31
Pruritus-VAS	4.9 ± 3.7	3.9 ± 3	6.5 ± 3.5	3.4 ± 3.3
Hepatic Encephalop.	0.5 ± 0.8	0.33 ± 0.5	0.57 ± 0.5	0.57 ± 0.5
MELD	20 ± 7	20 ± 6	22 ± 7	20 ± 9

Conclusion: With a new adsorbent albumin dialysis could reduce albumin bound toxins (e.g. bilirubin and free fatty acids) more effectively, which resulted in a significant improvement of albumin binding and fatty acid uptake. Which one of the changes are responsible for the more profound improvement of pruritus remains unknown and requires more research.
The procedure was safe in all subjects.

FRI-059

Systematic review and meta-analysis of bezafibrate in combination with ursodeoxycholic acid in patients with treatment refractory primary biliary cirrhosis

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Background and aims: Primary biliary cirrhosis (PBC) is a cholestatic liver disease characterised by chronic inflammation and accumulation of bile acids resulting in bile duct and hepatocyte damage. If untreated, ongoing inflammation and tissue damage can lead to progressive fibrosis, cirrhosis and end stage liver disease. Ursodeoxycholic acid (UDCA) has been shown to prolong transplant free survival for patients with PBC and is widely accepted first line therapy. However, patients who have progressive disease refractory to UDCA treatment have limited treatment options. Bezafibrate (BEZA) is a peroxisome proliferator-activated receptor alpha agonist with anticholestatic properties that has been used in this setting. We performed a systematic review and meta-analysis to assess the efficacy of BEZA in combination with UDCA for patients with PBC refractory to first line treatment.
Method: We performed a systematic review of randomised trials, crossover trials and self-controlled clinical trials for this indication. A systematic review of MEDLINE and the Cochrane Library was performed and an expert in the field was consulted. A meta-analysis of the results was performed for the outcomes of alkaline phosphatase (ALP), mortality, pruritus and adverse events prompting treatment cessation. For continuous variables a mean difference was calculated with 95% confidence intervals. For dichotomous outcomes a risk ratio (RR) was calculated. A random effects model was chosen. Heterogeneity of outcomes was assessed using the Chi-squared and I^2 tests.
Results: 181 papers were identified, and 10 papers included in the final analysis including 307 patients. Mean age of subjects was 57 years and 97% were female. 9/10 studies were deemed at a high risk of bias, predominantly due to issues with lack of randomisation and assessor or participant blinding. In the meta-analysis, compared with

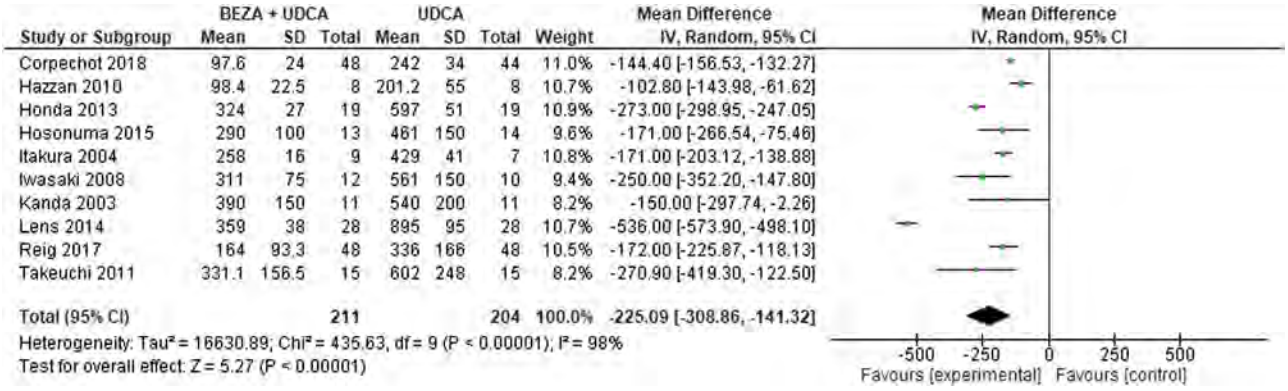

Figure 1: (abstract: FRI-059): Alkaline Phosphatase

UDCA alone, BENZA+UDCA demonstrated: a mean ALP reduction of 225 IU/L (95%CI 309 -141, p = < 0.001) (figure 1), an improvement in pruritus RR 0.41 (95% CI 0.24 to 0.70, p = 0.001), a significant number of adverse events prompting discontinuation of treatment 13 vs 1 (p = 0.01) and no significant difference in mortality (p = 0.11). There was evidence of heterogeneity for the outcome of ALP (I^2 = 98%, Chi-squared p = < 0.001), however all studies included demonstrated a significant reduction in ALP for BENZ + UDCA compared with UDCA alone.

Conclusion: We have demonstrated that based on the current literature, BEZA in combination with UDCA appears safe and efficacious treatment for PBC refractory to UDCA monotherapy to improve liver biochemistry and patient symptoms. Further studies are required to assess the long-term effectiveness of this therapy to demonstrate definitively that an improvement in liver biochemistry will result in improvement in progression of liver disease.

FRI-060

Effects of the ileal bile acid transport inhibitor A4250 on pruritus and serum bile acids in patients with biliary atresia: phase 2 study results

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Background and aims: Biliary atresia (BA) is an important cause of neonatal cholestasis, which may progress to biliary cirrhosis and end-stage liver disease. Management of cholestasis and pruritus is often limited to dietary support, supplementation of fat-soluble vitamins, treatment of cholangitis and symptomatic relief; new, non-invasive treatment options are needed. Ileal bile acid transporter (IBAT) inhibition is a novel therapeutic concept for the treatment of cholestatic pruritus and progression of cholestatic liver disease (CLD). The effects of A4250 (a potent, selective, reversible IBAT inhibitor that decreases enteric bile acid reuptake with minimal systemic exposure) are reported in BA patients.

Method: A phase 2, open-label, multi-centre study evaluating A4250 safety and tolerability in paediatric CLD with pruritus (including BA) was conducted. Efficacy end points were change in serum bile acid levels and pruritus. Patients received oral A4250 10-200 µg/kg/day for 4 weeks.

Results: Three female patients with BA were enrolled and received A4250 30 µg/kg/day; all 3 completed the study. No serious treatment-related adverse events (AEs) were reported. Most AEs, including some increased transaminases, were transient. Two BA patients had reductions in serum bile acids and pruritus captured by both visual analogue scale (VAS; 0-10) and Whitington scale (0-4; **Table**). These data, though limited, are consistent with results from the overall study population of paediatric patients with chronic CLD. A third patient who had relatively low baseline serum bile acids did not have reductions in serum bile acids or pruritus (**Table**).

Table:

Effects of A4250 on bile acids and pruritus in patients with biliary atresia

Patient	1	2	3
Age, years	14	4	2
Baseline parameters			
ALT, U/L	36*	151*	65*
Albumin, g/L	37*	36*	35*
Bilirubin, total, µmol/L	8.0	38.3*	19.3*
GGT, U/L	51*	326*	181*
Bile acids, µmol/L			
Baseline	42.8	136.2	131.5
End of treatment	42.6	57.8	64.7
VAS-Itch			
Baseline	6.59	5.07**	5.72
End of treatment	7.14	1.00	4.04
Whitington-Itch			
Baseline	2.57	2.57**	2.00
End of treatment	2.00	0.29	1.00

*Value outside normal limits.
**Patient had missing baseline diary entries; value is mean from days 1-7 after single dose.

Conclusion: Orally administered A4250 was well tolerated in these patients, and the reductions in serum bile acids and improved pruritus observed suggest that further investigation of A4250 in children with BA is warranted.

FRI-061

Colorectal cancer, colectomy rates and inflammatory bowel disease activity following liver transplantation in primary sclerosing cholangitis: A systematic review and meta-analysis

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Background and aims: Primary sclerosing cholangitis [PSC] is the classical hepatobiliary manifestation of inflammatory bowel disease [IBD] for which liver transplantation [LT] is the only curative therapy. We provide pooled incidence rates [IR] and time trends of (1) colorectal cancer [CRC], (2) flares in IBD activity and (3) colectomy rates post LT, through systematic review and meta-analysis.
Method: A systematic literature search of Medline and Embase was undertaken to identify studies that were pertinent to our research objectives from 1981 to 2014. Included studies were assigned to one or more of the three analytical streams (indicated above). The "meta" package (R Studio (V.1.1.463)) and Revman was used to pool IRs and HRs from individual studies using a random effects model.

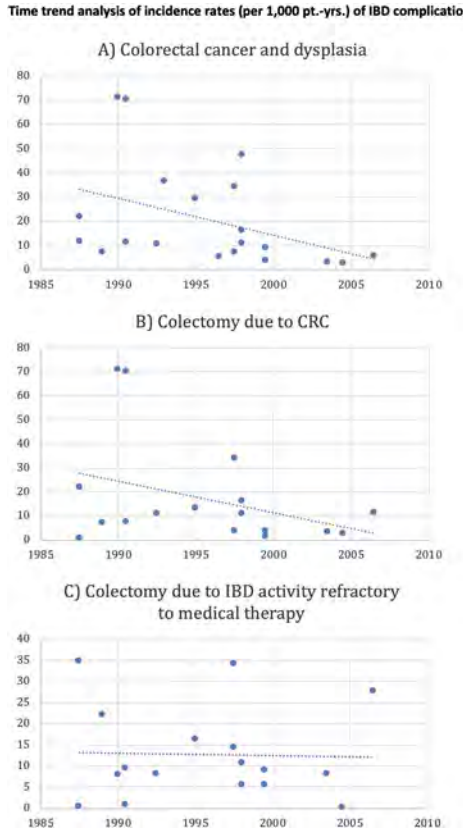

Figure 1:

Results: Forty-two studies qualified for inclusion in the systematic review. Twenty studies detailing the clinical course of 1994 patients (cumulative 9874 patient years) were pooled to assess the incidence of dysplasia or CRC (combined end point) and CRC only; IR 14.97 cases (95%CI 9.74-23.02) and 9.21 (95%CI 6.01-14.09) per 1000 person years, respectively. Heterogeneity was considerable (I^2 = 86%). The incidence of post LT CRC was seen to be decreasing over time **(Fig 1A)**. Colectomy rate following OLT was 23.18 per 1000 person years (95% CI 16.74-32.08) (I^2 = 84%). The IR for colectomy due to dysplasia/CRC was 11.25 cases per 1000 person years (95% CI 6.43-19.68) and seen to be decreasing over time (**1B**). By contrast, deterioration in IBD activity necessitated colectomy in 13.26 cases per 1000 person years (95% CI 9.95-17.66), with no change over time (**1C**). Nine studies reported clinical course of IBD post LT according to endoscopy findings/ escalation in IBD therapy. 27.6% of patients (n = 584) experienced deterioration in IBD activity post LT. The effect of 5-aminosalicylates [5ASA] on risk of CRC (2 studies), colectomy (1 study) and IBD activity (2 studies) was examined. Due to study heterogeneity, this data could not be analysed. The effect of ursodeoxycholic acid [UDCA] on the risk of CRC after LT was examined by 3 studies. Due to data availability, only 2 studies could be pooled. UDCA increased the risk of CRC post LT; HR 2.90 (95%CI 1.37-6.11). Studies examining the impact of UDCA on colectomy and IBD activity post LT were inconclusive. No study examined the role of anti-TNF therapy in context of study objectives.
Conclusion: This is the first comprehensive systematic review and meta-analysis of IBD related outcomes post LT in the PSC cohort (CRC, dysplasia, colectomy overall and by indication and IBD activity). The risk of CRC mandates ongoing colonoscopic surveillance in the PSC/ IBD LT population, although the incidence appears to be decreasing. Identification of risk predictors impacting IBD course is of critical importance, given that IBD deterioration appears to be the principal indication for colectomy post LT.

FRI-062

Identifying research priorities in primary sclerosing cholangitis: Driving clinically meaningful change from the patients' perspective

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Background and aims: Primary sclerosing cholangitis [PSC] is a disease with no curative medical treatment, a progressive yet often unpredictable clinical course, and complex symptom burden. Our aim was to prospectively inform basic and targeted outcomes' research in PSC, by examining the opinions, attitudes and experiences of those living with the disease.
Method: This was a cross-sectional study led by the UK charity "PSC Support" in partnership with "**albi**" France. Participants were invited to detail the most difficult aspects of living with PSC and develop a hierarchy of key research priorities based on present unmet need. Concurrently, we gauged patient willingness to undergo specific interventions as part of PSC research and attribute confidence levels to currently proposed therapeutic end points.
Results: Between 10/2014 and 03/2017 we captured the views of 636 respondents (450 patients, 186 caregivers) who collectively reported 1318 concerns relating to the most difficult part of living with PSC-the most prevalent theme related to the emotional impact of disease (**Fig. 1A**). 79% of emotional impact responses related to "uncertainty;" specifically the unpredictable nature of disease progression, and

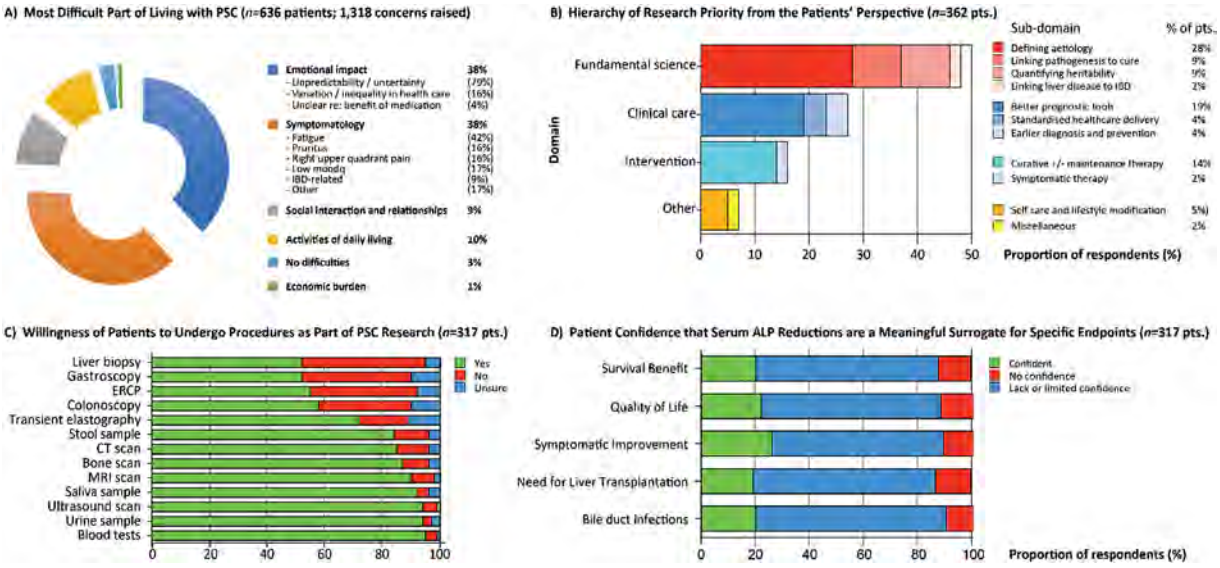

Figure: (abstract: FRI-062)

inability to be given a clear individual prognosis. A further 16% of emotional impact responses related to variation and inequality in healthcare delivery. When asked to identify future PSC research questions important to them, 362 participants responded. The most common questions were deemed "fundamental," specifically to identify cause of disease and magnitude of heritability, in addition to strengthening efforts toward more effective risk stratification/ prognostic models that operate at a high degree of confidence (**1B**). 317 patients detailed their readiness to undergo specific procedures as part of research (**1C**); 52% being willing to undergo liver biopsy. When asked specifically about serum alkaline phosphatase, fewer than 25% of participants were confident that a reduction would lead to less acute cholangitis episodes, confer symptomatic benefit, or improved transplant-free survival **(1D**).

Conclusion: For patients, the unpredictable nature of PSC results in far-reaching feelings of helplessness and uncertainty, including toward the inconsistencies and variation in healthcare delivery. The low confidence in currently proposed surrogate end points, suggest need to develop novel non-invasive end points for clinical trials.

FRI-063

Low-dose prednisone increases the risk of adverse events in autoimmune hepatitis patients

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Background and aims: Autoimmune hepatitis (AIH) requires long-term immunosuppressive therapy. Studies on dose-related side-effects of steroids are predominantly performed in rheumatic diseases whereas data in patients AIH is scarce. We aim to assess cataract, diabetes mellitus and osteoporotic fractures during the long-term treatment of patients with AIH.

Method: Medical charts of 480 patients (77% women) with an established diagnosis of AIH were reviewed for cataract, diabetes mellitus and fractures occurring after diagnosis. Prednisone was assessed per follow-up year per mg per day and correlated with adverse events in a multivariate longitudinal generalized estimated equations model, corrected for age, gender, cirrhosis and concomitant features of primary sclerosing cholangitis (AIH-PSC) or primary biliary cholangitis (AIH-PBC). Patients who were prescribed budesonide, were censored from the date of initiation of budesonide onwards.

Results: A total of 5813 years with a median of 13 years per patient (range 1-40) were recorded. The median age at diagnosis was 44 years (range 2-88). Prednisone use increased the odds ratio for new-onset cataract and diabetes mellitus (Table) in a dose related pattern, but not of fractures. Prednisone was used by 435 (91%) patients in a median dose of 7 mg/day (1.7-34.0) during 5 years (1-39). Cataract developed in 38 (8%) and diabetes mellitus in 46 (10%) patients. In 61 (13%) patients, 88 fractures occurred including fractures of; vertebral compression (n = 31), femur and hip (n = 9), tibia or fibula (n = 8), humerus or radius or ulna (n = 18), (meta)carpal (meta)tarsal or phalanx bones (n = 14), or other (n = 8). Patients with cirrhosis at diagnosis (n = 65; 18%) were not at greater risk of fractures (p = 0.4) compared with patients without cirrhosis (n = 302; 82%).

Table: Multivariate analysis of corticosteroid related adverse events

	Cataract		Diabetes mellitus		Fracture	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
No prednisone	1.0	0.03	1.0	< 0.001	1.0	0.08
Prednisone 0.1-5.0 mg/day	1.7 (0.7-3.7)		3.7 (1.3-11.0)		2.3 (1.2-4.2)	
Prednisone 5.1-10 mg/day	2.1 (0.9-5.1)		6.7 (2.4-18.6)		1.5 (0.7-3.0)	
Prednisone > 10 mg/day	4.9 (1.7-14.2)		26.0 (8.8-76.9)		2.0 (0.7-5.8)	

Corrected for age, gender, and AIH-PSC and AIH-PBC variant syndromes.

Conclusion: Patients with AIH who were treated with prednisone had an increased risk of cataract and diabetes mellitus, but not of fractures. A dose-relation with prednisone and adverse events was observed.

FRI-064

Systematic review and meta-analysis of risk factors for recurrent primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic inflammation of the bile ducts leading to fibrosis and eventually cirrhosis. Aetiology of PSC remains unknown and no specific treatment can delay or arrest the progressive course of the disease with orthotopic liver transplantation (OLT) remaining the only curative option. Nonetheless, recurrent primary sclerosing cholangitis (rPSC) can occur after liver transplantation (rPSC) with considerable morbidity often leading to retransplantation. In the past decade large cohorts of patients with PSC undergoing OLT were analysed to identify risk factors for rPSC. The current systematic review and meta-analysis was conducted to summarize all available data to define risk factors for rPSC.
Method: The search of the following databases was performed: Pubmed, Embase, Web of Science, Cochrane library for articles published until March 2018 using the medical subject headings sclerosing cholangitis, recurrence, liver transplantation, risk and risk factors. Studies addressing risk factors for developing rPSC after liver transplantation were eligible for inclusion in the review. Studies able to provide data to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) were included in the meta-analysis. Quality of included studies was independently evaluated by two authors with the Newcastle Ottawa Scale (NOS) for cohort studies. Statistical analysis was performed using Cochrane Review Manager.
Results: The electronic database search yielded 449 results. Sixteen retrospective cohort studies met the inclusion criteria for the review. Twelve studies were included for meta-analysis. Studies scored a median of 8 points (6-9) on the NOS. After excluding possibly overlapping cohorts we analysed recurrence a total cohort of 1899 patients, with median age ranging from 31 to 49 years, 1330 were male (70.0%) and 321 developed rPSC (16.9%). We found that colectomy before OLT, HR 0.63 (95% CI: 0.41-0.99), presence of cholangiocarcinoma (CCA) before OLT, HR 2.81 (95% CI: 1.34-5.87), presence of inflammatory bowel disease (IBD), HR 1.76 (95% CI: 1.19-2.61), donor age, HR 1.02 (95% CI 1.01-1.04), MELD score per point, HR 1.05 (95% CI: 1.02-1.08) and development of acute cellular rejection (ACR), HR 2.37 (95% CI: 1.30-4.32) were associated with the risk of rPSC.
Conclusion: IBD presence, CCA before transplantation, donor age, MELD score and development of ACR were risk factors for rPSC. Performing a colectomy before liver transplantation was protective for rPSC.

FRI-065

The Amsterdam cholestatic complaints score is a valid patient reported outcome measure for cholestatic symptoms in PSC patients

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Background and aims: The presence and intensity of symptoms such as pruritus, fatigue, abdominal pain and fever in primary sclerosing cholangitis is highly variable. In both patient care and clinical trials there is need for a validated questionnaire that accurately measures disease burden. Several studies have used the Amsterdam Cholestatic Complaints Score (ACCS), which evaluates pruritus, fatigue, abdominal pain and fever, as patient reported outcome measure. Still, the ACCS has not yet been validated. The aim of this study is to prospectively validate the ACCS in a Dutch PSC cohort.
Method: Two hundred and twelve patients from the EpiPSC 2 prospective registry were approached for a digital survey. The ACCS was compared to several validated questionnaires: The 5D-itch scale, Liver Disease Symptom Index (LDSI), a Visual Analog Scale (VAS) for itch, fatigue and pain and the EuroQol-5D-5L (EQ-5D) to measure general quality of life. Construct validity was determined using Spearman's rho correlation. To investigate if the sensitivity of the ACCS could be increased by introducing distinct questions for symptom severity and frequency, an adapted version of the ACCS was developed and tested in parallel.
Results: A total of 154 PSC patients (73%) completed the survey. The itch, fatigue and pain score and the ACCS sum score showed mostly high correlations with relevant domains of the different validated questionnaires (table 1). The item fever showed only low correlations. The adapted version of the ACCS was not superior to the original version.

Table 1: Correlations of the ACCS with other questionnaires.

		Spearman's rho (confidence limit closest to 0)			
ACCS item	Domain	ACCS		Adapted ACCS	
Itch	VAS Itch	0, 699	0, 592	0, 717	0, 622
	LDSI Itch	0, 860	0, 785	0, 831	0, 745
	5D Itch score	0, 841	0, 753	0, 860	0, 780
	EQ-5D Index	–0, 418	–0, 279	–0, 395	–0, 523
Fatigue	VAS Fatigue	0, 772	0, 685	0, 832	0, 771
	LDSI Sleepiness	0, 658	0, 543	0, 675	0, 570
	LDSI Sleepiness impact	0, 719	0, 615	0, 711	0, 609
	EQ-5D Index	–0, 641	–0, 530	–0, 628	–0, 509
Pain	VAS RUQ-A pain	0, 665	0, 548	0, 682	0, 566
	LDSI RUQ-A pain	0, 833	0, 737	0, 835	0, 739
	EQ-5D Pain	0, 540	0, 405	0, 534	0, 395
	EQ-5D Index	–0, 412	–0, 266	–0, 402	–0, 255
Fever	EQ-5D Pain	0, 255	0, 089		
	EQ-5D Index	–0, 142	–0, 284		
Sum score	EQ-5D Health status	–0, 605	–0, 486		
	EQ-5D Index	–0, 644	–0, 541		

VAS = visual analog scale, LDSI = liver disease symptom index, EQ-5D = EuroQol-5D-5L, RUQ-A = right upper quadrant abdominal

Conclusion: The ACCS is a simple and valid instrument to quantify cholestatic symptoms in PSC patients. The sum score mirrors impairment of quality of life.

FRI-066

Rituximab therapy is effective for inducing remission in IgG4-RD hepatobiliary disease: A retrospective case series

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Background and aims: IgG4-related disease (IgG4-RD) is a multi-organ inflammatory condition that affects the hepatobiliary system and leads to sclerosing cholangitis and autoimmune pancreatitis. First line therapy includes corticosteroids followed by immunomodulator use. However, case reports suggest that Rituximab (RTX) may be an option for corticosteroid-dependent cases following first line therapy failure. Given the paucity of data using RTX for IgG4-RD, we report our experience of RTX treatment efficacy to induce remission in our patient population.

Method: We performed a retrospective case series review of patients from our clinic with hepato-biliary IgG4-RD who had received RTX treatment. After excluding patients with overlapping PSC, we selected five cases of IgG4-RD sclerosing cholangitis who received RTX between 2014 and 2018. Patient charts were reviewed for serum IgG4 treatment response and overall outcomes. Statistical differences were compared using ratio paired t tests with significance set at $P < 0.05$.
Results: All patients were male with a mean age of 72.2 ± 1.9 years. Previous immunosuppressive exposure included prednisone dependence (5/5), azathioprine failure (5/5) and patients were maintained on either mycophenolate (4/5) or 6-Mercapto Purine (1/5) post-RTX treatment. All patients achieved clinical IgG4 remission following two 1000mg RTX infusions two weeks apart. There was a significant reduction in serum IgG4 levels ($p = 0.02$). None of the patients developed infection nor required hospitalization. There were no infusion reactions
Conclusion: Rituximab therapy is effective for inducing remission in IgG4-RD hepatobiliary disease. Patients tolerated the treatment well with no reported side effects. Larger cohort studies are required to confirm these initial findings.

FRI-067

Management of primary biliary cholangitis in the pre-obeticholic acid era, and the rate of non-response to ursodeoxycholic acid (UDCA), in a large real-world cohort of PBC patients in Italy: The CLEO-AIGO database

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Background and aims: Until the recent advent of obeticholic acid (OCA), UDCA has been the only drug approved for the treatment of PBC. Response to UDCA was proved crucial for the prediction of PBC prognosis, and different response criteria were proposed by some reference centres for PBC. However, rates of non-response to UDCA from real-world series are poor or absent. Here we aimed to evaluate PBC management in the pre-OCA era, and the rate of non-response to UDCA, in a large real-world cohort of PBC patients.
Methods: Hepatology/Gastroenterology centres belonging to "Club Epatologi Ospedalieri" (CLEO) and "Associazione Italiana Gastroenterologi Ospedalieri" (AIGO) were invited to participate to the study, and asked to: 1) extract all patients followed for PBC, without any selection or exclusion, and fill in the database provided; 2) for patients already on OCA, give data concerning the last control pre-OCA.
Results: Thirty-three centres were enrolled throughout Italy, with a total of 681 patients. After excluding 74 patients (11%) diagnosed as overlap PBC/autoimmune hepatitis, 607 patients were analysed, mean age: 64.5 ± 11.9 yrs; 91.4% females; F/M 10.7/1; mean age at PBC diagnosis: 55.6 ± 12.1 yrs, mean disease duration: 8.9 ± 7.6 yrs. Ninety-six% of patients were on treatment with UDCA at a mean dose of 14.8 ± 3.9 mg/kg/day. In patients with at least 1 year of UDCA treatment (561), rates of non-response to UDCA were evaluated according to the computable ncriteria (Table). Only 3.4% of patients received second-line off-label treatments (fibrates, budesonide etc.). Compared to patients in reference studies[1-4], mean alkaline phosphatase levels on UDCA treatment, and the age-adjusted prevalence of F3/F4 fibrosis, appeared lower.

Table.:

	CLEO-AIGO UDCA NON-RESPONDERS	UDCA NON-RESPONDERS IN ORIGINAL COHORTS	REFERENCE
PARIS-I	26.4%	39%[1]	[1]Corpechot C et al, Hepatology 2008
PARIS-II	39.1%	52%[2]	[2]Corpechot C et al, J Hepatol 2011
TORONTO	20.3%	43.5%[3]	[3]Kumagi T et al, Am J Gastroenterol 2010
GLOBE (Age-specific)	15%	30%[4]	[4]Lammers W et al, Gastroenterology 2015

Conclusion: A mildly better response to UDCA is observed in a real-world PBC population from Italian centres not specifically focused on PBC/autoimmune liver diseases, probably due to migration of some of most severe/advanced cases towards reference centres. UDCA dose and compliance were optimal and, in the pre-OCA era, increasing UDCA daily dose was most common than second-line off-label treatments for non-responsive patients.

FRI-068

Quantitative biliary tree imaging by MRI: Evaluating new technology across patient cohorts with autoimmune liver disease

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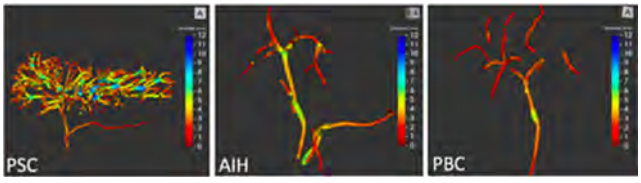
Background and aims: Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique for the evaluation of biliary disease. Despite widespread use there remain limitations such as variable quality bile duct depiction and subjective assessment. We sought to understand the potential utility of quantitative MRCP (MRCP+), particularly in Primary Sclerosing Cholangitis (PSC), evaluating a well characterised cohort of prospectively imaged patients.

Method: Patients with PSC, autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) were recruited for heavily T2-weighted MRCP imaging at base-line and 1-year follow-up. Scans were processed with MRCP+ to enhance and quantify the tubular structures. The underlying algorithms combine multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms.

Results: A total of 284 MRCP images were processed, consisting of PSC (44), AIH (35) and PBC (59) patients with both baseline and follow-up scans. PSC patients had higher biliary tree volumes (11.3ml; $p = 0.006$) and stricture scores (21; $p = 0.015$) than those with AIH (6.5ml and 10.9, respectively) and PBC (7.1ml and 10.2, respectively). Higher-risk PSC patients (ALP > 1.5xULN) had a significantly higher number of dilated ducts (14.8; $p = 0.04$) than the lower-risk PSC patients (6.9; ALP < 1.5xULN without cirrhosis). Increases in MRI-derived iron corrected T1 (cT1) whole liver inter-quartile range (a proposed measure of heterogeneous fibro-inflammation) was associated with increases in biliary tree volume (Pearson correlation $R = 0.78$-0.85, $p < 0.001$).



Conclusion: We demonstrate that quantitative MRCP (MRCP+) provides measures that have the potential to objectively differentiate patients with PSC. Quantitative biliary tree imaging, furthermore warrants investigation prospectively as a standardised application for disease and therapy monitoring in PSC.

FRI-069

Quantitative MRCP imaging: Preliminary observations in a cohort of paediatric patients with liver and biliary diseases

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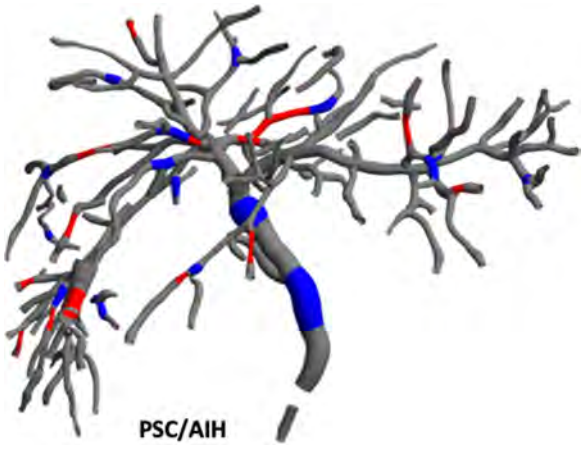
Background and aims: Magnetic resonance cholangiopancreatography (MRCP) is commonly used for the evaluation of biliary disease but has significant limitations, including variable quality bile duct depiction and subjective assessment. This is particularly true in paediatric assessment, where biliary changes may be less advanced. We sought to understand the potential utility of quantitative MRCP (MRCP+™)in paediatric patients, particularly those with overlapping autoimmune hepatitis (AIH) and Primary Sclerosing Cholangitis (PSC).

Method: Recruited patients (6-18 yrs; AIH (51), AIH/PSC (10), Wilson's disease (6), other (7)) and 21 healthy controls underwent multi-parametric MRI with LiverMultiScan™ and heavily T2-weighted three-dimensional MRCP imaging for MRCP+ processing to enhance and quantify the tubular biliary structures and assess liver parenchyma. The underlying algorithms combine multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms.

Results: PSC patients had an increased number of candidate strictures and dilatations (defined as a change in diameter > 30%) than healthy controls ($p = 0.007$) and AIH patients ($p = 0.019$). Furthermore, the percentage severity of strictures and total length of dilated and strictured regions were greater in PSC patients than healthy controls ($p = 0.019$; $p = 0.008$) and AIH patients ($p = 0.045$; $p = 0.035$). AUROCs of 0.80-0.95 were observed for a range of quantitative biliary metrics assessing AIH/PSC against Health or AIH patient groups. Increases in MRI-derived iron corrected T1 (cT1) whole liver inter-quartile range (which can reflect heterogeneity of fibro-inflammation) was associated with increases in the total length of dilated and strictured regions (Pearson's correlation $R = 0.88$; $p = 0.05$), suggesting parenchymal disease association with biliary metrics.



Conclusion: We report findings demonstrating that quantitative MRCP (MRCP+) provides measures that could objectively differentiate patients with PSC from healthy or other liver disease patients, with potential for monitoring and severity assessment applications.

FRI-070

Long-term clinical outcomes in patients with autoimmune hepatitis according to treatment response in Asian country

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Background and aims: As surrogate markers for autoimmune hepatitis (AIH), serum alanine aminotransferase (ALT) and immunoglobulin G (IgG) are convenient to measure and follow-up under immunosuppression by international guidelines. However, the long-term prognosis of patients who achieve complete biochemical

remission (CBR) in comparison with patients who achieve only biochemical remission (BR) is uncertain.
Method: A total of 291 patients (89.7% female) diagnosed with AIH were retrospectively evaluated by reviewing electronic medical records. Liver biopsy was done in 231 (79.4%) of patients. According to International Autoimmune Hepatitis Group revised criteria, 200 (68.7%) and 91 (31.3%) patients met criteria for definite and probable AIH, respectively. BR was defined as normal serum ALT levels after starting treatment, while CBR was defined as normal serum ALT and IgG levels. Liver-related outcomes included liver-related death, liver transplantation, and development of hepatocellular carcinoma.
Results: With immunosuppressive treatment, 168 (57.7%) patients achieved CBR, 87 (29.9%) patients achieved only BR, and 36 (12.4%) patients did not achieve remission within 1 year after starting treatment. With a median follow-up duration of 6.6 years (range: 0.6—21.2 years), the annual incidence of liver-related mortality was lower in patients with CBR (0.25/100 person-years [PY]) than in patients with BR (0.72/100 PY), although this difference was not statistically. Twenty-seven liver-related adverse outcomes occurred. The annual incidence of liver-related adverse outcomes was significantly higher in patients with BR than in patients with CBR (2.06/100 PY vs 0.58/100 PY, P = 0.003)
Conclusion: Patients who achieved CBR had a lower risk of liver-related adverse outcomes than patients who only achieved BR, suggesting that CBR is a more reliable surrogate marker to reflect long-term clinical outcomes in AIH patients.

FRI-071

AMA-positives without PBC and healthy subjects have similar bile acid profiles but are different from PBC patients

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Background and aims: Antimitochondrial antibody (AMA) positivity may precede the development of primary biliary cholangitis (PBC). It is unclear whether changes in serum bile acid (BA) composition already occur in subjects with AMA but without the clinical diagnosis of PBC. We therefore aimed to determine the serum BA profile across the clinical spectrum of AMA-positivity including subjects with known PBC (UDCA responders and non-responders), newly diagnosed PBC, AMA-positives without PBC, AMA-negatives (negative AMA at second testing) and healthy controls in order to identify potential changes in BA homeostasis that may be linked to early mechanisms of disease in AMA-positivity.
Method: We identified 446 subjects (85 males, 361 females) tested positive for AMA over a ten-year period. To assess the subsequent clinical and biochemical course, these subjects were invited for a follow-up visit. Clinical follow-up data were determined in 271 subjects after 6.8 ± 5.1 years. Serum BA profiles were available in 161 subjects. By the time of follow-up, 87 patients had died. Composition of the BA pool in those 161 patients was compared to 59 age-matched healthy controls (28 males, 31 females). Concentrations of 20 serum bile acids were measured using a commercially available mass spectrometry based kit (Biocrates Lifesciences®, Innsbruck, Austria).
Results: AMA-positives without PBC showed similar CDCA concentrations compared to healthy controls, but only controls were significantly lower than PBC patients ($p < 0.05$).
Conjugated primary BAs glycocholic acid (GCA), glycochenodeoxycholic acid (GCDCA), taurocholic acid (TCA) and taurochenodeoxycholic acid (TCDCA) were all higher in treated PBC patients compared to AMA-positive subjects without PBC and healthy controls ($p < 0.05$). Regarding conjugated secondary serum bile acids glycodeoxycholic acid (GDCA) and taurodeoxycholic acid (TDCA), AMA-positive subjects without PBC had similar concentrations compared to PBC groups and were higher compared to healthy subjects ($p < 0.05$). Glycoursodeoxycholic acid (GUDCA) was higher in UDCA treatment responders compared to AMA-positives without PBC and controls ($p < 0.001$), while tauroursodeoxycholic acid (TUDCA) was higher in both PBC groups compared to AMA-positives without PBC ($p < 0.001$) but not controls ($p = 0.30$).
Conclusion: AMA-positive subjects were characterized by a serum BA profile similar to that of healthy controls except increases of conjugated secondary bile acids GDCA and TDCA, which showed similar concentrations to those in PBC patients.
Patients with PBC (UDCA responders and non-responders) have significantly increased primary and secondary conjugated serum BA concentrations.
These findings suggest that rises in GDCA and TDCA may represent an early finding of altered BA homeostasis in AMA positives without clinically overt PBC.

FRI-072

Alteration of glucocorticoid metabolism in patients with cholestasis

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Background and aims: Cholestasis might lead to an impairment of adrenal function. Bile acid and adrenal steroid metabolism share the precursor cholesterol. In addition, the bile acid receptors farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5) are expressed in the adrenal glands. Previous findings from our group have shown that mice fed bile acids or subjected to common bile duct ligation develop hypercortisolemia. We thus aimed to assess adrenal gland function in patients with cholestasis.
Method: Adrenal gland function was assessed in 36 patients with cholestasis and in 33 hospitalized patients without cholestasis. Total serum cortisol, adrenocorticotropic hormone (ACTH), aldosterone and dehydroepiandosterone-sulfate (DHEAS) were measured. In addition, relative increase of cortisol (delta cortisol) was calculated in 39 patients 20 and 30 minutes after administration of 1 µg-ACTH as a marker of relative adrenal insufficiency. Bile acid levels and bile acid pool composition were determined by high-resolution mass spectrometry.
Results: Patients with cholestasis per definition had markedly elevated levels of alkaline phosphatase (AP) (median 403 U/L, interquartile range (IQR) 229-664), bilirubin (median 7.4 mg/dL, IQR 2.8-12.2) and serum bile acids (median 157 µmol/L, IQR 23-223). Baseline cortisol (223.2 ± 59.4 versus 186.1 ± 62.3 ng/ml, $p = 0.014$) and maximum cortisol after ACTH stimulation (331.2 ± 56.4 versus 285.9 ± 47.8 ng/ml, $p = 0.015$) was significantly higher in patients with cholestasis compared to controls. Levels of delta cortisol, ACTH, DHEAS and aldosterone were comparable between both groups. In the cholestasis group, baseline cortisol correlated with bilirubin (Spearman's rho = 0.503, $p = 0.002$), but not with AP, total serum bile acids and levels of conjugated and unconjugated bile acid species. Patients with duration of cholestasis < 6 months ($n = 30$) had significantly higher baseline cortisol levels than those with long standing cholestasis (> 6 months, $n = 6$; 232.3 ± 59.9 versus 178.1 ± 31.2 ng/ml, $p = 0.04$).
Conclusion: Glucocorticoid but not mineralocorticoid homeostasis is altered in patients with cholestasis. Elevated serum cortisol levels in patients with cholestasis correlate with bilirubin as a marker of disease severity. ACTH stimulation leads to an adequate rise in cortisol levels thus excluding relative adrenal insufficiency. Lack of

ACTH increase in cholestasis indicates a direct effect of cholestasis on adrenals and not on the pituitary gland. Further studies are needed to elucidate the mechanism of cortisol elevation in patients with cholestasis and its clinical significance.

Acute liver failure and drug induced liver injury

FRI-076

On the role of inflammation in acute paracetamol injury

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Background and aims: Paracetamol (acetaminophen; APAP) is one of the most commonly used medications and is generally considered a safe analgesic, although misuse and overdoses do occur with serious consequences. APAP is primarily metabolized in the liver, and overdose causes hepatic injury that is mediated by APAP-generated metabolites triggering oxidative stress and inflammation. We are interested in the role of the gut-liver axis in acute hepatic injury because it has been implicated as a possible contributory factor in the development of chronic liver diseases such as alcoholic liver disease. We investigated the effect of APAP injury in a rodent model with gut inflammation, the *Winnie* (*Win*) mouse model.
Method: 5 to 6-week-old C57Bl/6 (WT) and *Win* mice were challenged with i.p. injections of 500 mg/kg of vehicle control (saline only) or APAP. Mice were euthanized 9-hour post administration. Colon length and weight were measured. Liver weights were measured, and samples were collected for HandE staining. Visiopharm™ software used to quantify area of liver necrosis. Cytokine expression measured using qPCR from liver samples.
Results: Our data show that 9-hours after APAP administration there is significant liver necrosis in WT and *Win* mice compared to vehicle controls ($p = 0.0001$ and $p = 0.0004$, respectively). Interestingly, the amount of liver necrosis was significantly higher in *Win* mice compared to WT mice ($p = 0.008$). Liver weights were not affected by APAP challenge. Inflammatory cytokines expressions were upregulated in liver tissues following APAP challenge. In this experiment, colon sizes were significantly different following APAP administration. There was a statistically significant reduction in the colon lengths of animals challenged with APAP compared to saline control (WT, $p = 0.004$; *Win*, $p = 0.001$). The weights of shorter colons were comparable to the weights of saline mice.
Conclusion: In our study, we have demonstrated that APAP can induce significant liver injury as shown by the total area of necrosis as early as 9-hour post administration. Interestingly, the amount of liver injury due to APAP was significantly higher in *Win* compared to WT mice. It is important to note that *Win* mice develop spontaneous colitis leading to a point mutation in the Muc2 gene, and this leads to increased intestinal inflammation and gut permeability. These differences between WT and *Win* mice highlight the potential impact of the liver-gut axis on the severity of liver disease and injury. These findings raise the question of how altered gut permeability and inflammation leads to enhanced injury and whether it is due to an already primed immune system due to gut inflammation or due to enhanced bacterial translocation occurring. It also raises the question of whether patients with chronic gut inflammation may be at increased risk for paracetamol induced liver injury.

FRI-077

Influence of drug categorization according to labelling information in the phenotypic presentation of drug-induced liver injury (DILI): An analysis in the Spanish DILI registry

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Background and aims: The Liver Toxicity Knowledge Base (LKTB) has classified the hepatotoxic potential of drugs according to drug-labelling information into four categories (Chen M. et al 2011). We aimed to analyze the performance of this classification and its clinical correlation using the Spanish DILI Registry database.
Method: We classified demographics, clinical and laboratory data of 864 DILI cases from the Spanish DILI Registry induced by 188 causative drugs into the four LTKB groups: "adverse reactions," "warning and precautions," "box warning" and "withdrawn." Of the total number of drugs included in the Spanish DILI Registry, 7 were unclassified by LKTB and 49 were not included in LTKB.
Results: One hundred one cases (22%) had safety information included in the adverse reactions group; 269 (54%) in warnings and precautions; 72 (14%) in box warning; and 48 (10%) in the withdrawn group. Age and sex distribution were similar between groups with mean values of 53-57 years and 39-57% female, respectively. Diabetes mellitus ($p = 0.058$) and hypertension ($p = 0.010$) were more frequent in drugs with less stringent regulatory status. Except for median daily dose that was significantly lower in DILI cases related to drugs in the adverse reactions group ($p < 0.001$), this group and the warning and precautions group did not differ in any of the other variables analyzed. DILI cases related to drugs in the box warning and withdrawn groups presented with longer latency ($p < 0.001$), hepatocellular damage ($p = 0.004$) and higher TBL and ALT and lower ALP values ($p < 0.001$), more frequently fulfilling Hy's Law ($p = 0.016$) compared to the remaining groups. The fraction of cases with physicochemical properties linked to a higher risk of hepatotoxicity (lipophilicity + daily dose $\geq$ 100 mg [R02], R02 + reactive metabolite formation [R03]) was low across the 4 groups with percentages of 11-27 and 0-16, respectively.
Conclusion: Classification of drug hepatotoxic potential according to the LTKB system shows good correlation with standard clinical and laboratory parameters of severity in DILI. Overall, the drugs with physicochemical properties believed to be associated with DILI risk were scarcely represented and did not correlate with increasing hepatotoxic potential according to labelling information in the Spanish DILI Registry. Analysis of hepatotoxicity drug-labeling information in bona fide DILI cases may help to refine liver safety drug classification.
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FRI-078

Serious liver injury induced by nimesulide: An international collaboration reporting 57 cases

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Background and aims: Nimesulide (N) is a potent non-steroideal antiinflamatory drug with analgesic and antipyretic properties, that is still marketed in many countries around the world. **Aim:** To analyze the clinical phenotype, outcome, and histological features in the largest series of N-induced liver injury (N-DILI) reported so far.
Method: We analyzed 57 Argentinian and Spanish N-DILI cases, recruited from 1988 to 2009. Other causes of liver diseases (viral, autoimmune, metabolic, obstructive, alcohol and ischemic) were ruled out. Demographics, clinical presentation, laboratory findings, and outcome were analyzed. Causality was assessed by RUCAM scale.
Results: Forty six (81%) patients were women (59 ± 16 years). Mean N dose was 200 mg/day, mostly prescribed for pain (arthritis and traumatisms). Mean time to onset 68 ± 81 days (range: 3-466 days). Forty six patients (81%) presented jaundice, and 60% of them required hospitalization. Hepatocellular, mixed and cholestatic patterns were present in 37 (65%), 12 (21%)and 8 (14%) of patients, respectively. Liver test mean values (xULN) were: ALT 17 ± 19, AST 19 ± 26 andALP 2.0 ± 1.5, whereas total bilirubin was13 ± 11 mg/dL. Liver histology was obtained in 14/57 (25%) patients, with a wide spectrum of liver lesions observed including: hepatocellular (hepatitis, massive and submassive necrosis), mixed (cholestatic hepatitis with and without eosinophilia), and pure cholestasis patterns. Mean time to recovery in 49 (86%) patients was 79 ± 88days (range: 6-550 days). Severity index was severe in11 (18%) and fatal in 6 (10.5%)patients. Eleven (19%) patients developed acute liver failure (ALF) of whom 5 recovered spontaneously. RUCAM scale was "probable" in 18 (32%), "possible" in 12 (21%), and "highly probable" in 27 (48%) patients. Comparing the cases with latency < 15 days (n = 12) with those with > 15 days (n = 45) did not show significant differences in terms of age, gender, symptoms, liver tests, results, and presence of ALF. Immunoalergic features were not detected in any case at presentation.
Conclusion: Nimesulide-induced DILI presented mainly in women with hepatocellular damage and was associated with ALF and death in a high proportion of patients. Latency < 15 days did not lead to less severe forms of liver injury aspreviously reported.

FRI-079

HLA B*14:01 is associated with Trimethoprim-sulfamethoxazole induced liver injury

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Background and aims: Trimethoprim-sulfamethoxazole (TMP-SMZ) is a common cause of drug induced liver injury (DILI). Variations in the HLA locus are the most common genetic risk factor for idiosyncratic forms of DILI, but their role in the pathogenesis of TMP-SMZ DILI is unclear. We conducted a study to investigate the relationship between genetic variants in the HLA I and II loci and TMP-SMZ DILI.
Method: We studied Caucasian TMP-SMZ DILI cases with definite, highly likely, or probable causality scores enrolled into the DILIN and population controls from eMERGE-I (phs000360.v3.p1 in dbGaP). We performed HLA sequencing on all TMP-SMZ DILI cases by Illumina MiSeq platform, and imputed the HLA for eMERGE-1 controls using the variants in the MHC region by HLA genotype imputation with attribute bagging (HIBAG) program. Fisher exact tests were used to test the allele frequency (AF) difference between cases and controls. Considering the rare nature of TMP-SMZ DILI, we used Firth logistic regression to test HLA effect with sex adjusted. We selected top alleles based on false discovery rate (FDR) ≤ 0.2, and performed haplotype association tests by haplotype score tests (haplo.stats R package) for two and three loci windows within Class I and II, respectively.
Results: There were 51 TMP-SMZ DILI cases and 12, 402 eMERGE-I controls of European descent. Selected characteristics of DILI cases were: 55% female, mean age 48.6 years, median peak ALT 506 IU/L, and median peak bilirubin 7 mg/dL. Thirteen HLA alleles met the FDR ≤ 0.2 threshold, with *B*14:01*, *DQA1*05:01*, and *DQA1*05:05* exhibiting the most significant associations (FDR < 0.05). However, the imputed *DQA1* alleles in controls were unreliable due to the discrepancy of their AF to published population AF (eg, AF = 0.126 vs. 0.25 for *DQA1*05:01*). The *B*14:01* was significantly more frequent among cases than controls (4.9% vs 0.09%, p = 0.002), and differences remained significant in Firth models (OR = 8.69; 95% CI: (3.18, 19.45); $p = 2.3 \times 10^{-4}$). Interestingly, all five *B*14:01* carriers also possessed *C*08:02*. This pattern was further confirmed by the significant association between the *C*08:02-B*14:01* haplotype and TMP-SMZ DILI ($p = 1.33 \times 10^{-5}$). Latency, serum enzyme levels, severity scores, and outcomes of individuals carrying *HLA B*14:01* were not different from others without this variant.
Conclusion: *HLA B*14:01* is significantly associated with TMP-SMZ DILI in Caucasians. This relationship may be linked to *HLA B*14:01-C*08:02* haplotype.

FRI-080

Herbal medicines induces severe liver injury than western medications: A nationwide multicenter retrospective research

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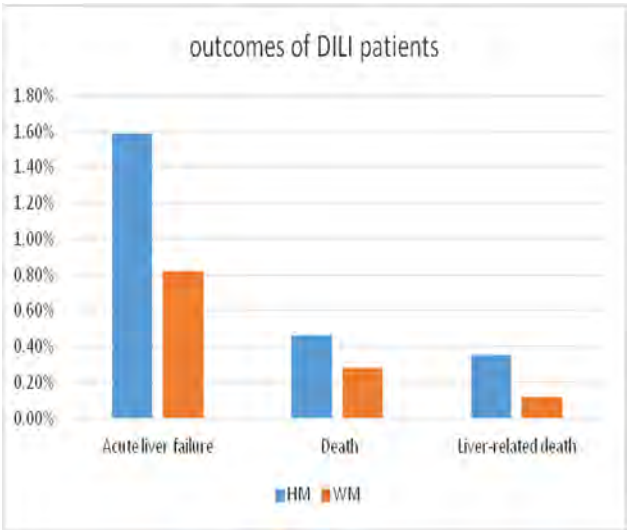
Background and aims: Herbal medicines (HM) are widely used, however, the clinical features of HM-induced liver injury are not yet clarified. This study aims to intensive investigate the differences between HM DILI and western medications (WM) DILI.
Method: A nationwide multicenter retrospective research among 308 medical centers in major cities of China.29, 478 DILI patients, who were hospitalized from January 1, 2012 to December 31, 2014. Patients whose RUCAM scores are more than 6 just took either only HM or only WM as causative agent of DILI were analyzed. The data on demographics, clinical characteristics, suspicious drugs, and outcome assessments of eligible cases were collected and systematically evaluated.
Results: A total of 3711 HM and 8859 WM cases were enrolled in the study. The mean age of the HM group was 48.24 ± 14.64 years, and that of the WM group was 44.70 ± 17.19 years (p < 0.0001). Females (59.3%)were predominant in the HM group. The average serum level of ALT, AST, ALP, TBIL and DBIL at baseline and peak value was significantly higher in the HM group (p < 0.0001). Although the general mortality of the two groups did not differ significantly (p = 0.1491), the liver-related death varied significantly between HM group and WM group (0.35%vs0.12%, p = 0.0369). The incidence of Hy's cases, acute liver failure, and chronic DILI was more frequent in

the HM than the WM group (45.03% vs.14.13%, 1.59% vs.0.82%, 14.4% vs.8.78%, respectively).



Conclusion: Depending on clinical characteristics and outcomes, HM might cause severe liver injury and liver-related mortality than WM.

FRI-081

Characterisation of severe liver injury induced by immune checkpoint inhibitors

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Background and aims: Immune checkpoint inhibitors (ICI) are established treatment for different oncologic disease. Immune-relate adverse events associated with ICI are rare complication. Immune mediated hepatitis (IMH) is detected in 3.5% of cases. The aim of our study was to detect an association between the clinical presentation, pattern of histological findings and treatment.
Method: A multicenter retrospective observational study of 10 patients treated with ICI that were referred to the liver units for grade ≥ 3 hepatitis. Of them, 4 received anti-programmed cell death protein 1 (PD-1) (nivolumab, pembrolisumab), 3 received anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) in combination with anti-PD-1 (nivolumab, ipilumumab), 2 received anti-PD-1 in combination with adenosine A2a receptor antagonists (pembrolisumab, preladenat) and 1 received anti PD ligand 1 in combination with paclitaxel. Liver investigations were undertaken in all patients, including viral assays, autoimmune tests and liver biopsy, histological review. Immunostaining of liver specimens was performed in few.
Results: Ten patients were included, median age was 58 years, 6 (60%) were male. Median time between immunotherapy initiation and the development of IMH was 4 (range, 1-7) weeks and median number of immunotherapy injections was 2 (range, 1-3). 7 patients (70%) developed grade 4 IMH (AST or ALT > 20 times ULN, bilirubin > 10 times ULN), all of them demonstrated similar histologic pattern: portal edema, cholangiolar proliferation accompanied by neutrophils and bile duct damage. 6 of the 7 patients had pericentral necrosis as well. 3 patients developed grade 3 IMH (AST or ALT > 5 and < 20 times of ULN, bilirubin > 3 times ULN). Liver biopsy performed in 2, disclosed a distinguished histologic pattern: lobular hepatitis with ill formed granuloma in one (combination of CTL-4 and PD-1) and minimal portal and lobular hepatitis in the second (combination of PD-L1 with paclitaxel). 5 patients (three grade 4 IMH and two grade 3) improved after oral corticosteroids. 5 patients (50%) (four grade 4 IMH patients and one grade 3) failed to improve after methylprednisolone pulse therapy 500 mg/day and required the addition immunosuppressive drug; 4 patients improved. 2 patients died; one due to liver failure associated with the IMH and the second due to the progression of the primary oncological disease after cessation of ICI treatment. In one patient, immunotherapy was reintroduced with IMH recurrence.
Conclusion: ICI for metastatic cancer can be associated with IMH. Liver biopsy is helpful for the evaluation of the severity of injury and diagnosis. IMH may have different clinical and histological pattern. The management is tailored according to the severity of the IMH. The severe liver injury and outcome detected in our study might reflect the late referral of severe cases. Larger studies are required to confirm our results.

FRI-082

Super stealth immunoliposomes as a strategy to overcome liposome-induced liver toxicity

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Background and aims: Immunoliposomes (ILs) are nano-delivery systems functionalized with monoclonal antibodies or antibody fragments, with the double aim of ameliorating the pharmacokinetics and tolerability of incapsulated drugs and permitting targeted therapy. Binding poly-ethylene-glycol (PEG) chains to their surface, thus obtaining stealth ILs, delays their elimination, which is mainly due to the clearance operated by the reticuloendothelial system (RES). Recently, to further improve their biopharmaceutical and pharmacokinetic features, the so called "super stealth liposomes" have been proposed, by adding mPEG-dendron-phospholipids. However, these nano-sized materials can accumulate in the liver and cause hepatic toxicity. On the basis of these considerations, the aim of this study was to evaluate, at the histological and molecular level, the *in vivo* liver toxicity of two formulations, one of stealth (SIL) and one of new super-stealth IL ($SSIL_2$), both loaded with doxorubicin, in Sprague-Dawley rats.
Method: A dose of 2.5 mg/kg of doxorubicin-loaded immunoliposomes (SIL and $SSIL_2$) was administered via caudal vein to Sprague-Dawley female rats (n = 3 per group) and vehicle-administered rats were used as controls. Rats were sacrificed 48 hours after the treatment. Hepatic toxicity of the formulations was assessed by: 1) standard histological analysis performed on 5-µm sections of liver tissues stained with HandE; 2) mRNA hepatic expression of IL-1β, IL-6 and TNF-α; 3) reactive oxygen species (ROS) concentration in liver tissues. The results were compared by one-way ANOVA followed by Dunnett's *post-hoc* test. $p < 0.05$ was considered statistically significant.
Results: Rats treated with SIL showed hepatic histological alterations, i.e. numerous granulomatous lesions, sometimes associated with apoptotic bodies, whereas in rats treated with $SSIL_2$ only few isolated granulomas could be observed in the otherwise healthy livers. The expression of both IL-1β and TNFα was significantly increased only in in SIL-treated rats ($p < 0.001$ vs controls) and did not change in $SSIL_2$-treated rats with respect to controls. Accordingly, the concentration of hepatic ROS increased significantly in SIL-treated rats ($p < 0.001$ vs controls) and was comparable to that of controls in $SSIL_2$-treated rats.
Conclusion: SILs are able to induce dramatic alterations of the hepatic parenchyma, probably due to their preferential deposition in hepatic tissue, which is particularly rich in RES cells. Conversely, $SSIL_2$

caused only limited histological liver alterations. Therefore, $SSIL_2$s, besides their pharmacokinetic advantages, permit to overcome the hepatic toxicity caused by SIL administration, thus representing a smart strategy to improve the tolerability of cancer therapy.

FRI-083

Impact of acetaminophen on acute liver failure of unknown cause

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Background and aims: Acute liver failure (ALF) is a rare but serious condition but no specific etiology is found in 20 to 30% of cases. These undetermined cases have a poor prognosis and higher death rate post transplantation. The aim of this study was to evaluate if in patients who develop ALF of unknown cause (ALF-UC) acetaminophen use below toxicity threshold impacts on the prognosis.
Method: This study is an ancillary program from HASIPRO: a multicenter prospective French cohort study aimed to investigate prognostic factors related to ALF-UC and looking for new etiologies. ALF-UC is defined by INR up to 1.5 without any identified cause at diagnosis. To be enrolled in the cohort, patients should have not taken more than 3 g/day of acetaminophen and acetaminophen would not be the cause of ALF according to physicians' discretion.
Results: From june 2013 to dec 2016, 70 patients with ALF-UC were included: 27 patients (median age: 42y[22-80]; women: 51, 85%) took acetaminophen and 43 (45y[18-82); 74, 42%] with no acetaminophen use. In the acetaminophen group, patients used a median dose of 3 [0, 85-8] g/day. At baseline there is no significant difference between both group except for median AST level (acetaminophen: 2442UI/L [21-18 330]; non-acetaminophen: 610UI/L [46-12 788]; P = 0.007), ALT level (acetaminophen: 2150UI/L [30-10 349]; non-acetaminophen: 732UI/L [71-8506]; P = 0.005) and phosphatemia level (acetaminophen: 0, 65 mmol/L [0, 35-1, 6]; non-acetaminophen: 0.9 [0.4-1.6]; P = 0.039). Median MELD score was 27 [11-40], no statistically different between both groups. Survival rate without transplantation at 3 month wasn't different between both groups (p = 0.15). In the acetaminophen group, 10 patients were transplantated and 20 in the other group (p = 0.43). Median time to transplantation was 4.5 [1-33] days versus 3 [1-48] days (p = 0.47). Death rate in the acetaminophen group was 11.1% and 16.3% in the other group (p = 0.73).
Conclusion: In patients with ALF-UC, use of acetaminophen does not impact the prognosis. Despite a clinical-biological profile compatible with an ALF induced by acetaminophen with higher AST level and lower phosphatemia, acetaminophen alone could not explain patient's phenotype.

GST and NRf2 gene mutations predisposing to acetaminophen toxicity are currently on going. Results will be presented during the meeting.

FRI-084

Targeting Toll-Like Receptor 4 signalling with TAK-242: A novel therapy for acute liver failure

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Background and aims: Acute liver failure (ALF) is associated with multi-organ injury and poor prognosis. Toll-like receptor 4 (TLR-4) ligands, lipopolysaccharides (LPS) and damage associated molecular patterns (DAMPs), are increased in ALF and knocking out TLR4 protects from ALF. This study aimed to evaluate whether the TLR4 signalling pathway was altered in a rodent ALF model and whether TLR4 inhibition would be a potential therapy.
Method: ALF was induced in Sprague Dawley rats (n = 10/group) by injecting Galactosamine (GalN) (400 mg/kg) and LPS (0.05 mg/kg i. p.). Animals were treated with TAK242 (TLR4 Inhibitor, 10 mg/kg) or saline i.p. 45 min after ALF induction. Biochemistry, ELISA, mRNA TLR-pathway expression, brain water content, TUNEL staining and immunohistochemistry were used to assess the effect of treatment on organ injury. Immortalised human monocytes (THP-1) and hepatocytes (HHL5) were incubated with LPS (100 and 2000ng/ml)±TAK242 (200nM) *in vitro* and their responses were measured with IL1b-ELISA or TUNEL staining, respectively.
Results: LPS incubation led to a dose-dependent increase in IL1b secretion and apoptosis in THP-1 and HHL5 cells, respectively. LPS response in both cell lines could be abrogated by co-incubation with TAK242 (THP-1 LPS100 ng/ml: IL1b 42.4pg/ml±8.3 vs. 24.7pg/ml±9.1; HHL5 LPS100 ng/ml: TUNEL positive cells 72%±21.6 vs. 20.7%±9.5). TAK242 reduced the severity of acute liver injury evidenced by lower ALT levels (355.1IU±155.7 vs. 275.6IU±176.9, p = 0.246) and declined apoptotic areas within the liver (p = 0.004). Circulating cytokines IL1b (p < 0.001), TNFa (p = 0.002) and IL10 (p = 0.306) were reduced by TAK242. Whilst the brain water content was lower (p = 0.004), creatinine levels remained unchanged but apoptotic areas within the kidney were reduced (p = 0.06) by treatment. mRNA expression of TLR4-related genes, Fos (p = 0.008), TRAF6 (p = 0.008) and MyD88 (p = 0.03), were significantly down-regulated after GalN/LPS injection but remained unchanged after TAK242. Hepatic TNFa and IL6 gene expression was up-regulated in ALF and significantly reduced by TAK242 (TNFa p = 0.004, IL6 p = 0.004). Liver TLR4 expression (mRNA and protein) remained unchanged in all groups.
Conclusion: The data highlights the importance of TLR4 signalling in the development and maintenance of ALF. TLR4 inhibition with TAK242 reduced the severity of hepatic injury and inflammation as well as systemic inflammation suggesting that TLR4 is a potential therapeutic target for ALF.

FRI-085

Development and validation of a novel non-invasive model to predict drug-induced liver injury recurrence

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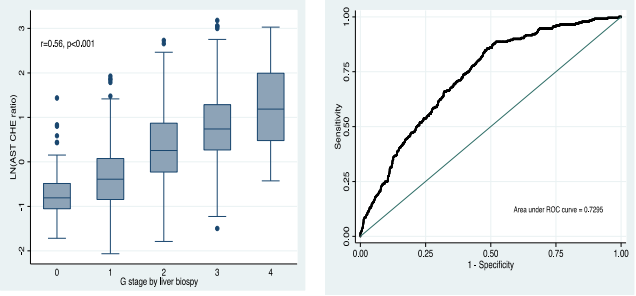
Background and aims: The incidence of drug-induced liver injury (DILI) is increasing, and it is hard to be cured due to high recurrence rate in many cases. In the present study, we aimed to develop a novel

non-invasive model to predict the recurrence of DILI, so as to increase its therapeutic effect.
Method: The retrospective cohort study enrolled DILI patients who underwent liver biopsy (LB) in our hospital from January 2008 to December 2017. All the patients were followed up at least 3 times with an interval of 3 to 6 months. The end point was the recurrence of DILI, defined as aminotransferase (ALT or AST) or bilirubin rising at least 2 times of its upper limit of normal value (ULN) within 6 months after the end of treatment. The prediction model was established based on Logistic regression, and its diagnostic performance was evaluated by ROC analysis.
Results: All of 2201 patients were randomly split into two sets (1467 in training set and 734 in validation set). The recurrent rate in training set was 15.6%, comparable to that in the validation set (12.8%, p = 0.08). Univariable analysis showed that recurrent patients had a higher proportion of female, older age, higher AST, lower cholinesterase (CHE) and PLT compared to those without recurrence. Moreover, G3 or above were 14 times more likely to relapse. Furthermore, a novel non-invasive model (AST/CHE ratio index, ACRI) was established based on the results of multivariable analysis, which was calculated by AST (/ULN)/CHE (/lower limit of normal value, LLN). ACRI was correlated significantly with G stage, with a higher correlation coefficient than CHE or AST level alone (r = 0.56, p < 0.001). The area under ROC for ACRI to predict the recurrence was 0.73 (95% CI: 0.70-0.76) in the training set, using ACRI of 1 as the cut-off point, the sensitivity and specificity were 85.6% and 51.3% (see Figure). The corresponding values in the validation set were 0.71 (95% CI: 0.66-0.76), 80.0%, and 49.1%, respectively.



Conclusion: Liver inflammation grade G3 or above is a robust predictor for recurrence of DILI, meanwhile ACRI provides an alternative non-invasive approach with a better diagnostic accuracy than currently available parameters. More than 80% recurrent DILI patients could use this algorithm without resorting to LB, which might help clinicians to initiate steroid treatment at an appropriate time or without delay, thus to decrease the recurrence rate of DILI.

FRI-086
Stem cell treatment on acute liver failure model using semipermeable Poly Lactic-co-Glycolic Acid membrane pouch

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Background and aims: It is very well known that stem cell treatment was effective in liver failure condition. Although most studies suggest stem cell injection via systemic vein was generally safe, there is still some concern with cell therapies of creating a cell embolus. We tried to check possibility and feasibility using semipermeable Poly Lactic-co-Glycolic Acid (PLGA) membrane pouch whether it can minimize cell embolus and maximize paracrine effects in acute liver failure model as well as it's possible mechanism.
Method: Animal model was induced by injecting thioacetamide (TAA) (100 mg/kg, i.p.) three times every other day. The mice were divided in 3 groups: 1) TAA; 2) mesenchymal stem cell (MSC) injected via tail vein; 3) PLGA-membrane including MSCs implanted on dorsum, to evaluate histological improvement and liver function. Moreover, quantitative RT-PCR was performed for evaluating gene expression level.
Results: Necrotic area, portal inflammation of liver was reduced in both MSC treatment groups (tail vein, and membrane pouch) compare to control group. But there was no difference between tail vein injection group and PLGA membrane pouch group. More giant cells which seem to be related with cell proliferation were observed in PLGA membrane group compare to the TAA group. Migration of stem cells to lung and liver was detected in tail vein injection group, but did not observe in membrane pouch group. Large portion of injected stem cell in membrane pouch changed cell morphology, and stained with PAS and CYP2E1. Stem cells survived in membrane pouch until 3 weeks in In vitro setting, and secretes more human growth factor, and fibroblast growth factor compared to monolayer cultured MSCs.
Conclusion: MSCs injected into membrane had beneficial effect via secreting growth factors on acute liver failure model.

FRI-087
The good use of paracetamol: prospective assessment of the knowledge of prescribers (practitioners, residents), pharmacists, care providers (nurses, others) and students in an university medical center

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Background and aims: Paracetamol is the most commonly used drug in Western countries. Its use is markedly commonplace since it may be obtained without any prescription. A recent nationwide study (SALT III) showed that paracetamol-induced acute liver failure is an increasing and main cause of acute liver failure leading to registration for liver transplantation (42.1% including 17.6% of paracetamol misuse) (EASL2018). The study is aimed to assess the knowledge of prescribers (practitioners, residents), care/drug providers (nurses, pharmacists, others) and students about paracetamol use in an university medical center.
Method: Prospective study performed using a questionnaire comprising 5 questions regarding paracetamol prescription in adult patients, focused on the place of paracetamol among causes of acute liver failure; the maximum unitary dose; the time intervalle between dosing; the maximum daily dose in chronic usage; the potential co-factors promoting paracetamol hepatotoxicity. The questionnaire has been validated by the Committee for the security of medication use (COSEMED) of the hospital and submitted since November 2017 during professional meetings or via hospital intranet website.
Results: To date, 1118 questionnaires have been completed by 130 medical practitioners from all specialities, 201 medicine residents, 30 pharmacists, 408 nurses, 248 others care providers, 101 medicine students. The global quantitative and quantitative results are shown in the table.

Table: Percentage of correct answers to global and specific questions according to professional category

	Medical practitioners n = 130	Residents n = 201	Pharmacists n = 30	Nurses n = 408	Other care providers n = 248	Students n = 101
Global correct responses to all questions	72.5	66.7	73.7	65.9	60.5	54.6
Paracetamol as cause of liver failure	82.6	78.1	77.3	74.1	60.4	66.1
Maximum unitary dose	98.3	99.4	100	99.1	95.9	84.5
Minimum intervalle between doses	93.0	97.7	95.5	98.2	97.2	83.5
Maximum dose in chronic use	47.8	14.4	50.1	36.9	32.3	10.1
Promoting factors of hepatotoxicity	40.9	43.9	45.5	21.3	16.9	28.9

Conclusion: The knowledge regarding the good use of paracetamol is insufficient for the maximum chronic dosage, the risk of paracetamol hepatotoxicity and its contributing factors. These results encourage to promote a more intensive and specific teaching of all care providers involved in the use of this drug.

FRI-088

The good use of non steroidal anti-inflammatory drugs (nsaids): prospective assessment of the knowledge of prescribers (practitioners, residents), care providers (nurses), pharmacists and students in an university medical center

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Background and aims: NSAIDs are among the most commonly used drugs in western countries. Their use is markedly commonplace since some of them may be obtained without any prescription such as ibuprofen and naproxen. NSAIDs are responsible of various adverse events and are frequently associated with paracetamol, the main drug causing acute liver failure. The study is aimed to assess the knowledge of prescribers (practitioners, residents), care/drug providers (nurses, pharmacists) and students about NSAID adverse effects and their risk factors in an university medical center.

Table: Percentage of correct answers to global and specific questions according to professional category.

	Medical Practioners n = 95	Residents n = 180	Pharmacists n = 25	Nurses n = 113	Students n = 101
Global % of correct responses	59.1	56.2	60.2	41.6	38.1
Overall adverse effects of NSAIDs	66.7	59.0	47.8	13.7	17.9
Hepatotoxicity effects of NSAIDs	75.9	45, 5	52.1	45.1	32.7
Relationship of adverse effects with the dose	43.7	45.5	39.1	29.4	23.2
NSAID hepatotoxicity when combined to paracetamol	55.1	44.5	78.2	54.9	47.4
No specific safety of NSAIDs not requiring prescription	99.1	98.1	95.7	96.1	97.9
Mechanisms of NSAID adverse effects	39.0	31.8	30.4	13.7	4, 2

Method: Prospective study performed using a questionnaire comprising 5 questions regarding NSAID prescription and their adverse effects in adult patients, focused on: the types of NSAID adverse effects; their dose relationship; the hepatotoxic risk when combined with paracetamol; the safety of NSAIDS not requiring a medical prescription; the mechanisms of adverse effects towards the stomach, skin and liver. The questionnaire has been validated by the Committee for the security of medication use (COSEMED) of the hospital and submitted since November 2017 during professional meetings or via the hospital intranet website.
Results: To date, 514 questionnaires have been filled by 95 practitioners from all specialities, 180 medicine residents, 113 nurses, 25 pharmacists, 101 medical students. The global and qualitative quantitative results are shown in the table. Overall, the knowledge for all questions is limited even in medical practitioners.
Conclusion: The knowledge regarding the adverse effects of NSAIDs and their promoting factors is insufficient in all professional category. These results encourage to promote a more intensive and specific teaching of all care providers involved in the use of these drugs.

FRI-089

Genetic deletion of Keap in hepatocytes improves liver damage, but triggers hepatitis in an Nrf2-dependent manner, in experimental toxic liver injury

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Background and aims: Drug-induced liver injury (DILI) is an increasing health problem in developed countries. Acetaminophen (APAP) toxic liver injury is characterized by extensive oxidative damage. The Kelch-like ECH-associated protein 1/Nuclear factor erythroid 2-related factor (Keap1/Nrf2) system is a master regulator of the defense against oxidative stress. In the current study, we examined the contribution of Nrf2 in hepatocytes to DILI.
Method: Animals with hepatocyte-specific deletion of Keap1 ($Keap1^{\Delta hepa}$) and floxed mice ($Keap1^{f/f}$) were challenged *i.p.* with carbon tetrachloride (CCl_4, 0.6 ml/kg) and acetaminophen (APAP, 500 mg/kg) and sacrificed at different time points ranging from 0 to 28 days. Liver samples were processed for histopathological examination, and protein (IF, IHC and WB) and mRNA expression were evaluated. In parallel, the Nrf2/Keap1 axis was thoroughly studied in human HepaRG cells.
Results: Toxic challenge caused reduction of markers of liver damage (eg: AST, ALT) and decreased levels of reactive oxygen species (ROS) as observed in DHE and 4-HNE in $Keap1^{\Delta hepa}$ and $Keap1^{f/f}$ mice. Furthermore, toxicity caused significantly increased body vs liver weight (LW/BW) ratio in $Keap1^{\Delta hepa}$ mice. In addition, toxic liver injury triggered necroinflammation in periportal areas in $Keap1^{f/f,}$

whilst it was dramatically enhanced in Keap1$^{\Delta hepa}$. Concomitantly, reduced necrosis in Keap1$^{\Delta hepa}$ was linked with decreased number of TUNEL-positive cells. Interestingly, collagen deposition evaluated as Sirius red (SR) staining was significantly elevated in mice with deletion of Keap1 (Keap1$^{\Delta hepa}$) in hepatocytes compared with Keap1$^{f/f}$ animals. These results were associated with elevated markers of fibrosis and hepatic stellate cell (HSC) activation including αSMA and Collagen IA1. Deletion of Keap1 in hepatocytes suggested an overexpression of Nrf2 which led to increased inflammatory milieu in these animals.

Conclusion: Deletion of Keap1 in hepatocytes triggered overexpression of Nrf2 leading to increased inflammation and fibrogenesis but reduced cell death and liver damage. These data highlight the important role of Nrf2 in hepatocytes in DILI.

FRI-090

Enhanced ASPP2 improves liver injury by way of an inflammatory immune regulatory mechanism in acute liver failure

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Background and aims: Acute liver failure (ALF), an inflammation-mediated hepatocellular injury process, is a clinical syndrome that results from hepatocellular apoptosis and hemorrhagic necrosis. The apoptosis stimulating protein of p53-2 (ASPP2), a haploinsufficient tumor suppressor, is a pro-apoptotic member of the p53 binding protein family. However, the role of ASPP2 in the pathogenesis of ALF and its regulatory mechanisms remain unclear.

Method: The expression of ASPP2 were analyzed using the liver biopsy samples from HBV-related hepatocarcinoma (HCC) patients and ALF patients. ASPP2$^{\pm}$ and ASPP2$^{+/+}$ Balb/c mice were used to examine the effects of ASPP2 on liver injury induced by D-galactosamine (D-GalN)/lipopolysaccharide (LPS) in vivo. The inflammatory immune mechanism of ASPP2 were also explored in bone marrow-derived macrophages (BMDM) in vitro.

Results: The expression of ASPP2 was significantly upregulated in liver tissue of ALF patients with HBV infection and ALF mice induced by D-GalN/LPS, and significantly down-regulated in HCC patients. Compared with wildtype mice, the ablation of ASPP2 (ASPP2$^{\pm}$) significantly ameliorated the hepatocellular damage, evidenced by reduced serum alanine aminotransferase (sALT and sAST) levels, well-preserved liver architecture compared with controls. The liver protective effect of ASPP2± was dependent on an inflammatory immune regulatory mechanism, because ASPP2 is required to regulate liver inflammation by selectively depressing tumor necrosis factor-α (TNF-α) and promoting interleukin-6 (IL-6) in vivo and in vitro, moreover, the luciferase assay results showed that overexpression of ASPP2 could bind to the promoter sequence of TNF-α and IL-6. The molecular mechanistic investigations elucidated that the enhanced ASPP2 promoted liver injury by regulating PPARα-autophagy pathway, because inhibition of PPARα by siRNA abrogated liver protection and decreased autophagy again induced by ASPP2±.

Conclusion: Our novel findings document the key inflammatory immune regulatory function of ASPP2 in the pathophysiology of ALF, and provide a rationale to target ASPP2 as a refined therapeutic strategy to ameliorate acute liver injury.

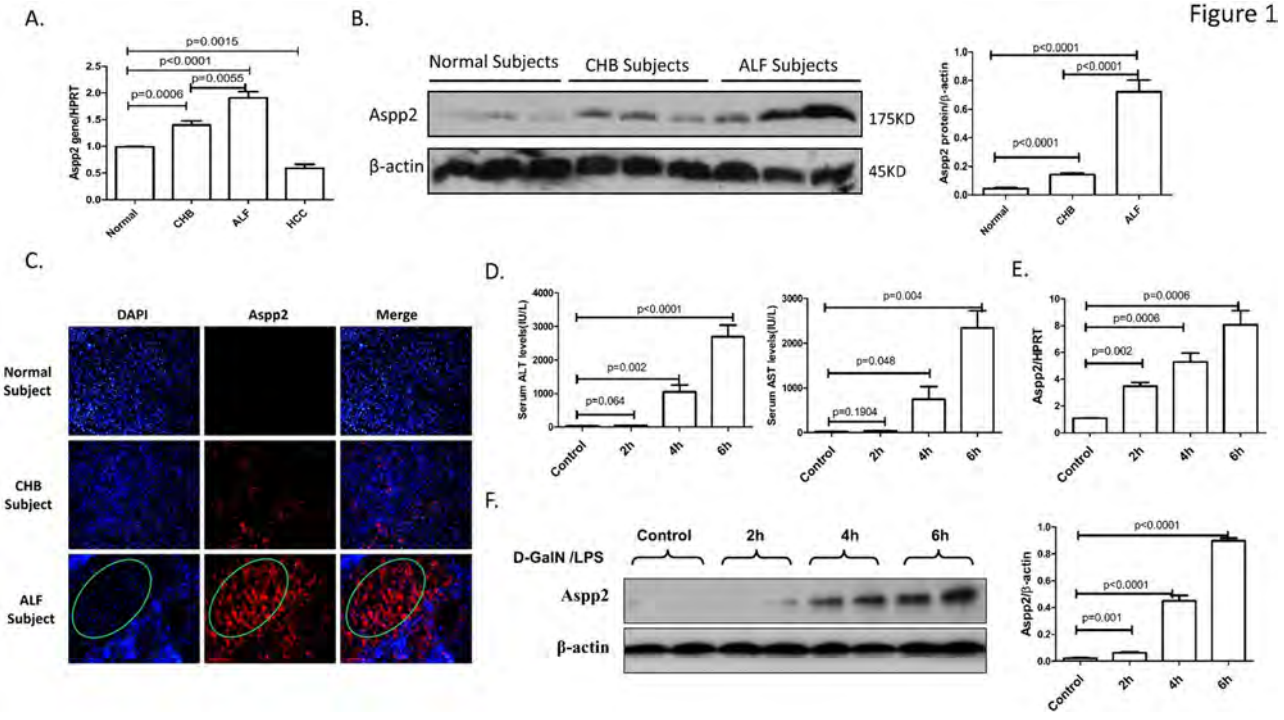

Figure 1: (abstract: FRI-090): Increased expression of Aspp2 in the liver of ALF

Figure 2

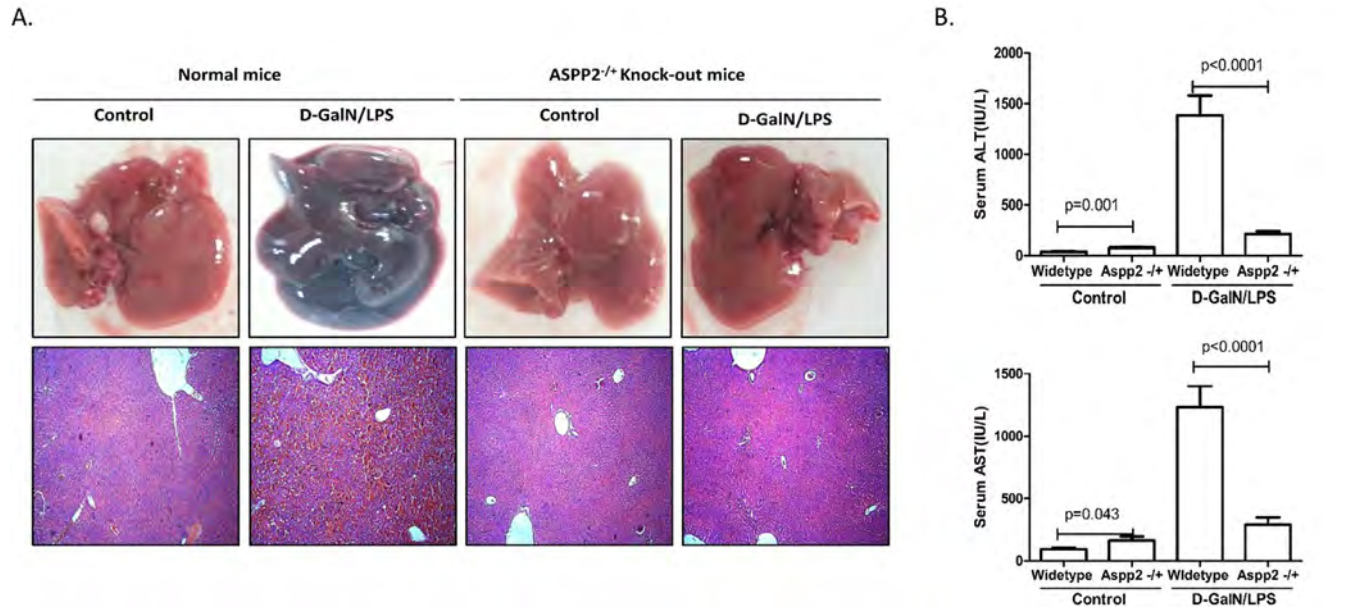

Figure 2: (abstract: FRI-090): Aspp2 knockdown protects mice from D-GalN/LPS -induced liver injury

Figure 3

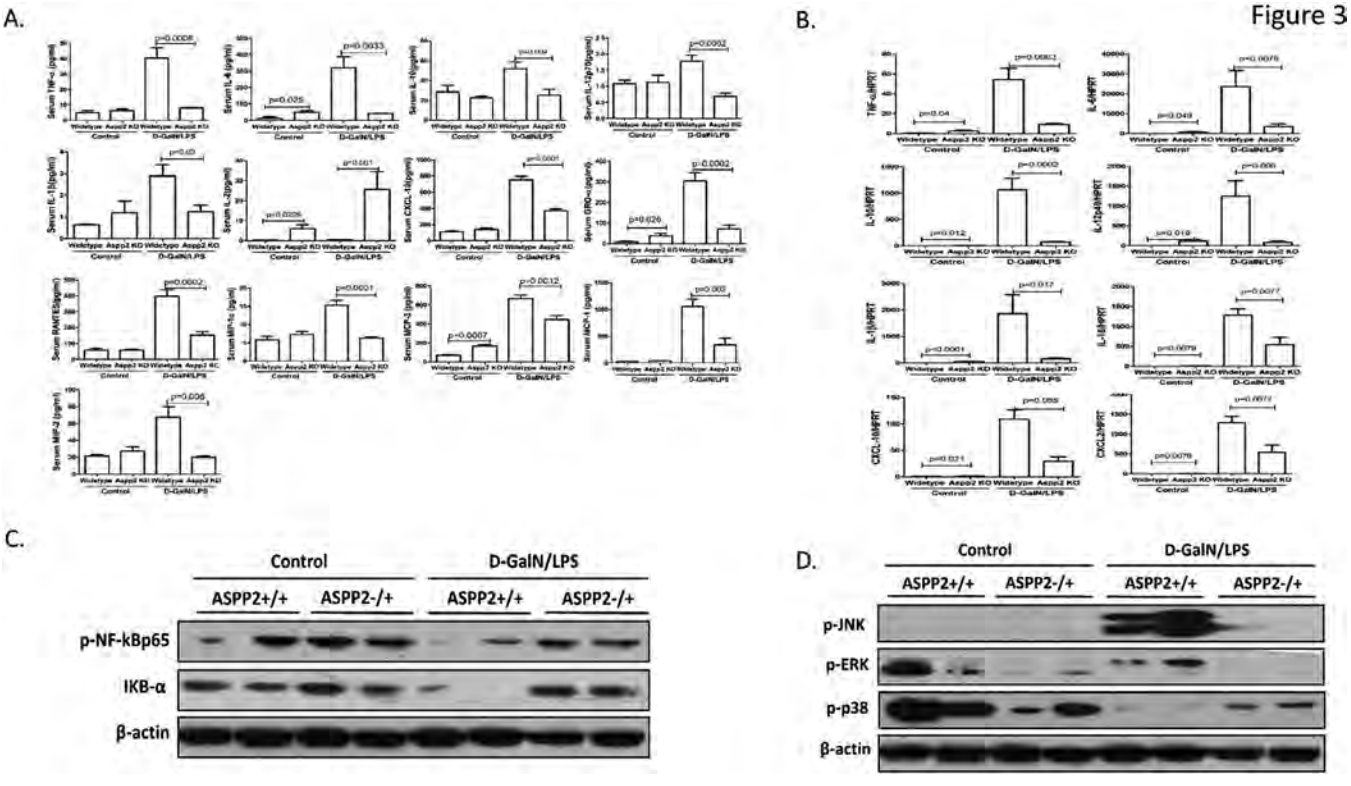

Figure 3: (abstract: FRI-090): Aspp2 knockdown protects mice from D-GalN/LPS -induced liver injury by suppressing liver inflammation

Figure 4

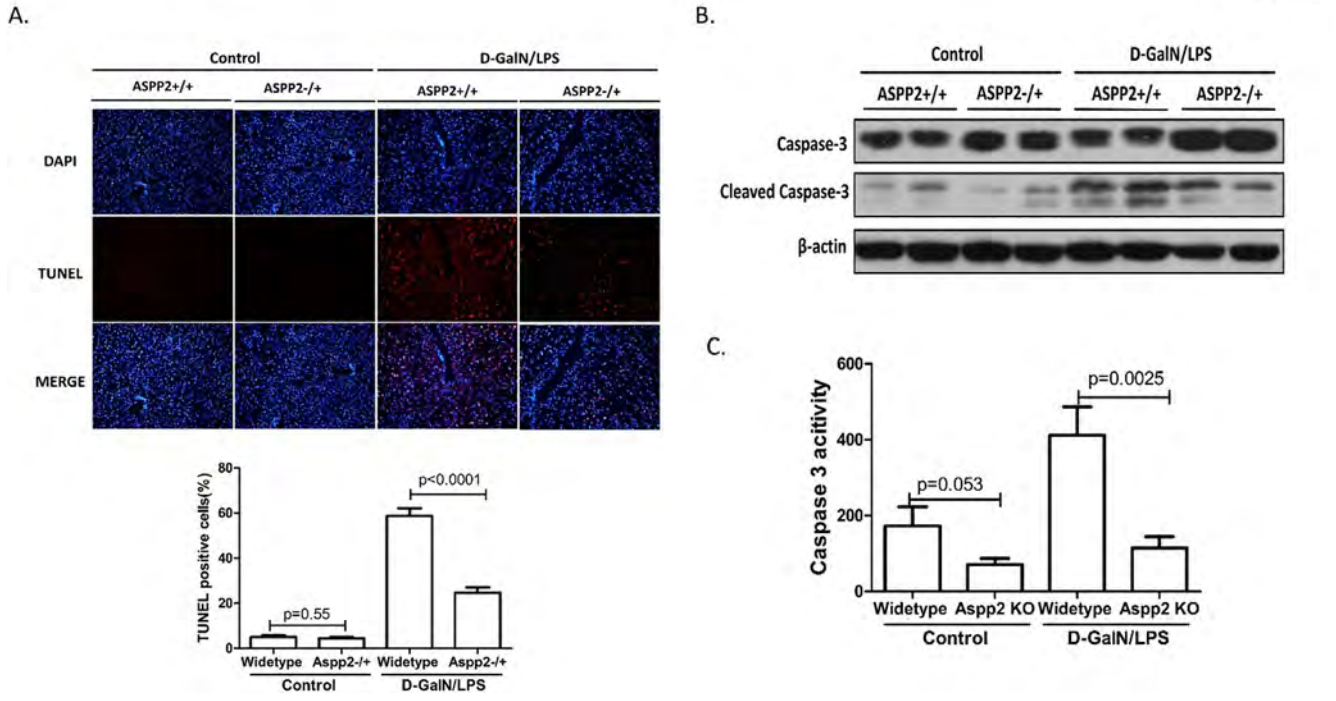

Figure 4: (abstract: FRI-090): Aspp2 knockdown inhibits hepatocyte apoptosis to protects mice from D-GalN/LPS -induced liver injury

Figure 5

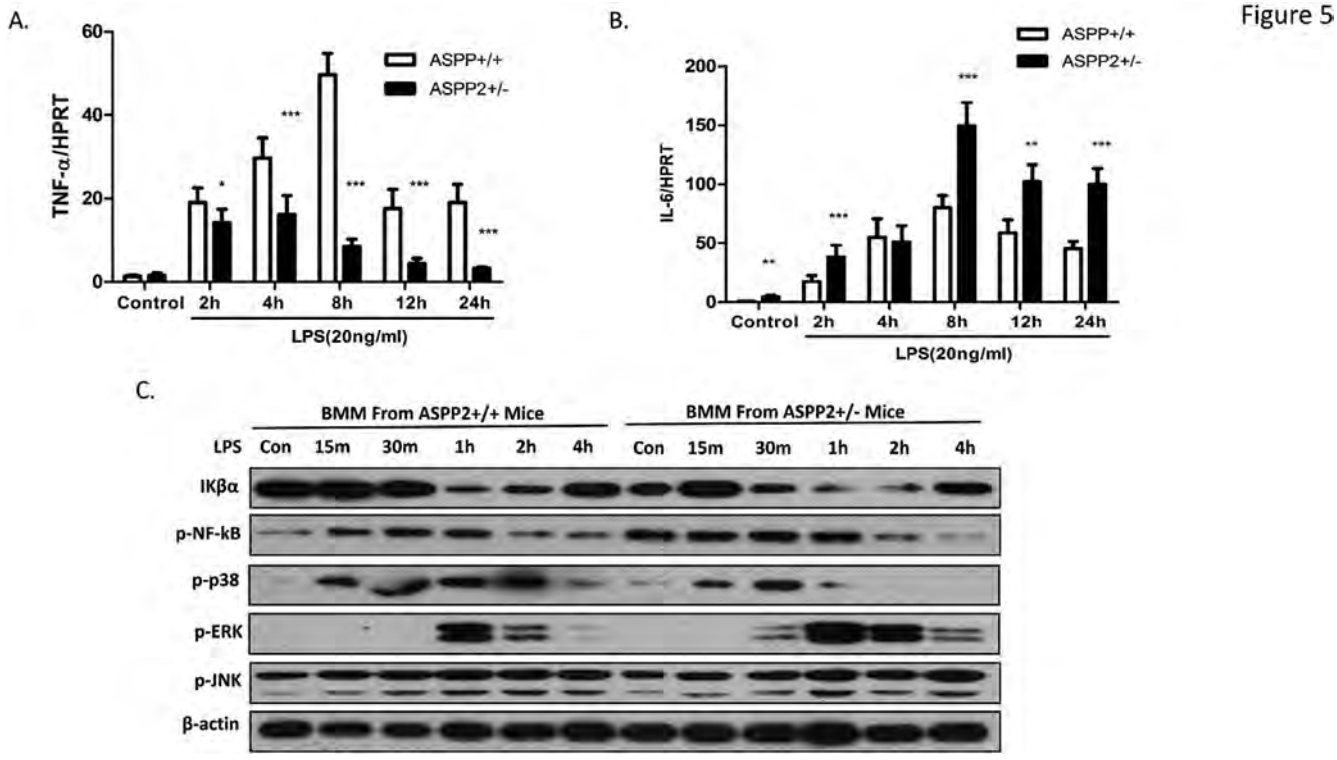

Figure 5: (abstract: FRI-090): Aspp2 selectively regulates TNF-α and IL-6 expression in macrophage induced by LPS

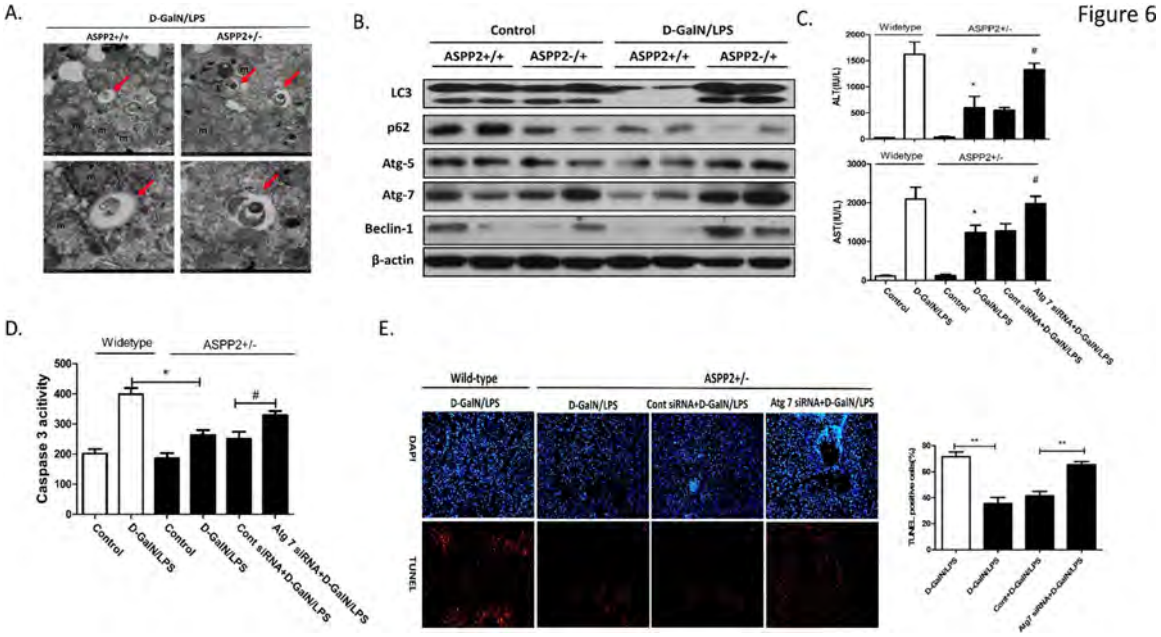

Figure 6: (abstract: FRI-090): Aspp2 knockdown protects mice from D-GalN/LPS -induced liver injury by promoting autophagy

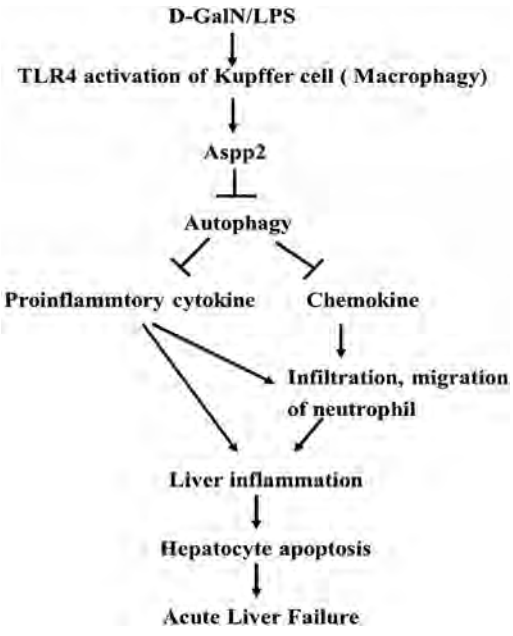

Figure 7: (abstract: FRI-090): A proposed model for the Aspp2-autophagy pathway in acute liver failure

FRI-091

HGF protector effect in intrahepatic cholestasis

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Background and aims: Cholestasis is a common syndrome in a large number of hepatic diseases such as drug-induced cholestasis, which is produced due to a primary lesion of the bile ducts, either functional or obstructive, generating oxidative stress in the liver. Hepatocyte growth factor (HGF) and its receptor c-Met represent the first defense line against hepatotoxic factors inducing Nrf2 activation which, in turn, activates its target genes leading to an antioxidant and repair response. The aim of this work was to characterize the anticholestatic molecular mechanisms deployed by HGF in a murine model of inflammatory cholestasis induced by the α-naphthil-isothiocyanate (ANIT).

Method: CD1 mice were, treated or not with ANIT (60 mg/kg, ig) for 48 h. After 24 h of ANIT treatment, HGF (10 μg/kg, iv) was administrated. Forty-eight hours after ANIT treated animals were euthanized. Blood, bile and liver tissue were obtained. Liver function test (AST, ALT, ALP, GGT, bile salts and bilirubin), histology studies (H-E staining), analysis of gene expression of ABC transporters by qRT-PCR, content of antioxidant proteins by Western blot, immunofluorescences and collection of bile (excretion of bile salts) were performed.

Results: ANIT treated animals, showed hepatomegaly, and cholecystitis, effects reverted by HGF administration. The increment in liver function test induced by ANIT, significantly diminished to control values under HGF treatment. Histology revealed extensive necrotic foci and inflammatory infiltration; HGF induced a significant decrement in necrotic areas, and less inflammation. HGF also restored the bile flux and bile salts excretion. These findings, could be related to the HGF-induced expression of key genes related to liver protection, in fact, HGF alone, induced the expression of *Abcc3,*

Gpx1/2, HO1, and catalase. Most of them directed by Nrf2 activation, which in addition was increased, judged by an EMSA assay. Furthermore, HGF preserved the canalicular structure ("double rail"), disturbed by ANIT treatment, remarkably HGF treatment alone, induced the canalicular width. To gain more confidence, we extended the ANIT treatment time up to 108 h and we noticed renal damage, judged by proteinuria and the content in urine of HSP72, HGF induced renal protection improving such kidney damage marker, in addition to a damage prevention in the liver, similar findings were observed in the pancreas.
Conclusion: Our results clearly show that HGF induces a wide anti-cholestatic response, protecting the liver and commonly compromised organs in this liver disease such as the kidneys and pancreas. HGF/c-Met could be of interest as a key target of therapeutically relevance.
Conacyt 252942, 280788, Antonio Ariza Cañadilla-FUNDHEPA grant and UAM.

FRI-092
Metamizole as a leading cause of drug-induced liver injury
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Background and aims: Drug-induced liver injury (DILI) is a heterogenous entity leading to acute liver damage. Large multicentre DILI registries have identified the most frequent agents causing DILI, among which antimicrobials are the leading causes. Metamizole or Dipyrone is banned from the market in some countries such as the United States but is approved and frequently applied in other countries including Germany. Elevation of liver enzymes is not listed as a potential side effect on the label of metamizole in Germany. Since metamizole can cause allergic reactions we hypothesized that it may also cause immune-mediated DILI. We here determined the frequency and pattern of metamizole-induced DILI at our tertiary care centre in Germany.
Method: Consecutive DILI cases who presented to the I. Department of Medicine at the University Medical Centre Hamburg-Eppendorf were analysed retrospectively. Cases of acute hepatitis other than DILI were excluded. Notably, autoimmune hepatitis was ruled out by clinical follow-up of DILI cases to assure that liver enzymes did not rise again after the drug had been stopped.
Results: 154 DILI cases with acute icteric hepatitis were admitted to our centre from 2008 to 2017. After phenprocoumon, metamizole was the second most frequent putative agent causing DILI (23 of all 154 DILI cases, 14, 9%). In 14 cases, metamizole was the sole drug causing DILI, in the other 9 cases concomitant drugs like statins or NSAIDs were also potential causative agents. In 4 of the 23 metamizole-induced DILI cases, patients were accidently re-exposed to metamizole resulting in another episode of acute icteric hepatitis, stressing the lack of awareness of metamizole being a DILI-causing drug. The biochemical pattern on admission of all metamizole cases was hepatocellular with median levels of ALT (823U/l) by far exceeding median ALP levels (131U/l). Median MELD score on admission was 12. 61% of metamizole-induced DILI cases showed the presence of autoantibodies such as ANA and/or anti-SMA. 15 of 23 patients with metamizole-induced DILI received a liver biopsy. The histological pattern of an acute hepatitis with infiltrating lymphocytes was present in all metamizole cases and 8 of 15 patients showed centrilobular necrosis. Interface hepatitis, the histological hallmark of autoimmune hepatitis, was not present in metamizole-induced DILI cases. 68% of metamizole DILI cases were treated with steroids. In 21 of the 23 metamizole-induced DILI cases liver damage resolved. 2 patients developed acute liver failure, received liver transplantation and are still alive.
Conclusion: Acute icteric hepatitis or acute liver failure are not mentioned in the German label of metamizole or dipyrone as side effects. Our study reveals that in Germany, metamizole is a frequent and underrated agent causing DILI, and can lead to acute liver failure.

FRI-093
Low volume plasma exchange in patients with acute liver failure: A real world study
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Background and aims: High volume plasma exchange (HVPLEX) (8-12 litres per procedure) can improve transplant free survival in acute liver failure (ALF). HVPLEX is expensive, blood bank resource intensive and can be associated with complications such as volume overload. It is not known whether using smaller volumes for PLEX is efficacious in ALF. The aim of this study was to determine the efficacy of low volume PLEX (LVPLEX).
Method: Consecutive patients with ALF admitted to a single intensive care unit (ICU) between 2013 and 2018 (n = 58) were studied. The decision to use LVPLEX was made by the duty hepatologist. Daily volume exchange was 5-7.5% of ideal body weight (average 3 litres) and replacement fluid was either Fresh Frozen Plasma (FFP) or a combination of FFP, albumin or a crystalloid solution. Outcome measures included resolution of ALF, bridge to liver transplantation (OLTx), death, and changes in the biochemical, physiological and organ function status. Outcomes were compared to ALF patients admitted to ICU (2008-2012) prior to the introduction of LVPLEX at our centre (PrePLEX) (n = 61).
Results: 59% (n = 34/58) of patients with ALF were treated with LVPLEX (age 40 [32-54], 68% female). 71% (n = 24/34) met Kings College poor prognostic criteria (KCppc). 24/58 patients did not receive PLEX (NoPLEX) (age 41 (35-49), 54% female). LVPLEX was commenced in the first 24 hours of ICU admission (n = 27), within 48 hours (n = 4) or after 48 hours (n = 3). Median length of treatment was 3 (IQR 2-3) days. The main clinical effect of LVPLEX was a significant reduction in average noradrenalin requirement from 0.25 (0.14-0.59) mcg/kg/min prior to starting to PLEX to 0.07 (0.02-0.27)mcg/kg/min after PLEX treatment (p = 0.004). 69% (n = 11/16) of those receiving LVPLEX were successfully bridged to transplantation compared to 76% (n = 10/13) in the NoPLEX group and 67% (n = 12/18) PrePLEX. There was no difference in overall transplant free survival with LVPLEX 38% (n = 5/13) vs. 35% (n = 8/23) PrePLEX, and (n = 0/3) in the NoPLEX group survived. However, in those that met KCppc and were not listed for OLTx, use of LVPLEX was associated with numerical improvement in survival; 63% (n = 5/8) vs. 47% (n = 8/17) PrePLEX.
Conclusion: LVPLEX did not impact the survival of patients listed for OLTx but numerically improved survival of ALF patients who met KCppc but were ineligible for OLTX listing. Further clinical trials are required to define patient selection and the ideal treatment dose for PLEX in ALF.

FRI-094

Targeting NEDDylation protects liver from acute drug-induced damage

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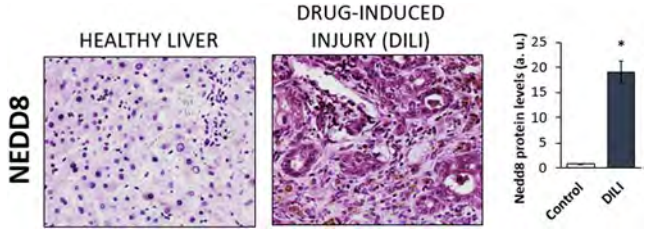
Background and aims: Drug induced liver disease (DILI) is the leading cause of liver transplantation in the USA and most of Europe. Only in the USA, each year, 30000 patients are admitted to the intensive care units because of an acetaminophen overdose (APAP) from which 10000 need of a transplant. Until date, the only effective therapy available is the treatment with N-acetylcysteine, with low chances of rescuing the liver, making new therapies a need. Our group has been focused on the NEDDylation process, a post-translational modification already reported to be altered in HCC and previous stages such as cirrhosis.

Method: NEDD8 has been determined in human sample sections by IHC and a pre-clinical assay has been developed with DILI animal models by APAP overdose (500 mg/kg) in wild-type (Wt) and NAE1 heterozygote (NAE1$^{\pm}$) mice. *In vitro* experiments with primary hepatocytes have also been developed.

Results: NEDDylation is induced in human patients, *in vivo* DILI models and *in vitro* primary hepatocytes and its inhibition prevents liver from APAP-induced damage both in *in vivo* and *in vitro* models. As a consequence of NEDDylation inhibition, IκBα is downregulated and p65 translocation into the nucleus, inhibited by APAP overdose, is allowed. Proteomics analysis suggest IκBα as a possible NEDDylation target.



Conclusion: NEDD8 inhibition prevents liver from being damaged by a drug overdose by promoting IκBα degradation, which allows p65 or NF-κB to be internalized into the nucleus in presence of APAP.

FRI-095

The overweight role in the occurrence of hepatotoxic reactions during chemotherapy of chronic lymphocytic leukaemia

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Background and aims: Chemotherapy (CT) in pts with chronic lymphocytic leukemia (CLL) is followed by risk of hepatotoxic reactions onset that limit further full-scale program treatment and can cause inefficiency of the therapy.

The aim-to determine the role of overweight and obesity in hepatotoxic reactions occurrence in pts with CLL dynamically during CT.

Method: 73 pts with CLL, who were given 6 courses of CT according to FCR (fludarabine, cyclophosphamide, rituximab) regimen were examined. The average age was 67.4 ± 11.7 years, 19 (26%) pts were women, 54 (74%)-men, ECOG I-II. The pts were classified by Rai System: II stage-22 (30.1%), III-18 (24.7%), IV-33 (45.2%) pts. The body mass index (BMI) was determined. The pts were followed-up during 6 courses of CT. The liver function was assessed by the activity of ALT, AST, ALP, GGT, bilirubin, protein in the blood serum, which were carried out twice during each CT course: at baseline and on the 5th day after starting CT. To assess the severity of hepatotoxic reactions the CTCAE scale was used.

Overweight was detected in 26 (35.6%) pts: BMI = 25-29.9-in 21 (28.8%), BMI > 30-in 5 (6.8%). Depending on the overweight presence the pts were divided into 2 groups: I (n = 47) -CLL with normal body weight, II (n = 26)-CLL and overweight.

Results: Before the CT all of the 47 pts with CLL and BMI within normal ranges of the Ist group had normal values of functional liver state. Among 4 (15.4%) pts with CLL of the IInd group having overweight, ALT activity was elevated up to the grade I according to CTCAE.

Dynamic follow-up of pts with CLL of the Ist group revealed hepatotoxic reactions in 11 (23.4%) pts after II CT course according to FCR regimen, 6 (12.7%) patients out of them had elevation of ALT activity, 3 (6.4%)-increase of GGT activity, 2 (4.2%) decrease of total protein level. Defined hepatotoxic reactions were characterized by grade I of the CTCAE and were isolated and reversible. Further abnormalities in biochemical blood tests during next CT courses were not determined.

Hepatotoxic reactions among the pts of the IInd group with overweight were defined during the dynamic follow-up in 12 (46.2%) pts, in 8 (30.7%) out of them-after the 2nd CT course and in 4 (15.4%)-after the 4th CT course according to the FCR regimen. Elevation of ALT activity took place in 12 (46.2%) pts: in 10 (38.5%)-up to the grade I, in 2 (7.7%)-up to the grade II according to the CTCAE, which in 4 (15.4%) pts was associated with AST increase up to the grade I, in 4 (15.4%)-GGT increase, in 3 (11.5%)-total bilirubin grade I increase, in 1 (3.8%)-total protein decrease. Hepatotoxic reactions in the pts of the IInd group were irreversible and had tendency to severity increase on the background of cytostatics' cumulative dosage rise.

Conclusion: Overweight is the leading risk factor of hepatotoxic reactions onset, which are characterized by increase of their severity associated with cumulative CT dosage rise.

FRI-096

Technetium-99m-GSA within the first 3d after admission as an early predictor of outcome in severe acute liver injury

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Background and aims: Patients with severe acute liver injury (SLI) without pre-existing chronic liver disease usually recover spontaneously. However, some SLI patients progress to acute liver failure (ALF), with varying degrees of hepatic encephalopathy. ALF is associated with high mortality, which can be substantially reduced by liver transplantation. Therefore, distinguishing SLI patients who might progress to ALF and are at risk of death is important when evaluating patients needing liver transplantation. Technetium-99m-diethylenetriaminepentaacetic acid galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy is a method used to evaluate liver function. The present study aimed to determine whether ^{99m}Tc-GSA scintigraphy could predict the prognosis of SLI patients.

Method: This prospective observational study included 54 SLI patients with a prothrombin time-international normalized ratio ≥ 1.5. ^{99m}Tc-GSA scintigraphy was performed within the first 3 d after admission. For the procedure, 185 MBq of ^{99m}Tc-GSA was injected into a cephalic vein, and images were then obtained using a dual-head gamma camera with a 20-min scan time (15 s/frame). Time-activity curves were generated from regions of interest for the entire liver and

heart. The hepatic accumulation index was calculated by dividing the radioactivity of the liver regions of interest by that of the liver-plus-heart regions of interest after 15 min (i.e. LHL15). The relationship between each variable and SLI prognosis was evaluated using a univariate analysis, followed by a multivariate statistical analysis.
Results: Twelve (22.2%) patients died or underwent liver transplantation (poor outcome), and the LHL15 value was significantly lower in these patients (0.678) versus those who survived (0.848; $p < 0.0001$). The optimal LHL15 cut-off for distinguishing a poor outcome and survival was 0.737, with a sensitivity of 91.7%, specificity of 92.9% and area under the curve of 0.976 (95% confidence interval, 0.917-1.007). At the cut-off, positive and negative predictive values were 78.6% and 97.5%, respectively. In the multivariate analysis, LHL15 was the only independent predictor of a poor outcome (95% confidence interval, −0.559 to −0.063, $p = 0.0141$).
Conclusion: ^{99m}Tc-GSA scintigraphy may help predict the prognosis of SLI patients. In clinical practice, ^{99m}Tc-GSA scintigraphy may be an adjunctive diagnostic tool for indicating those SLI patients at risk of progressing to ALF and requiring liver transplantation.

FRI-097
PBI-4050 treatment decreases sepsis-induced liver injury in mice
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Background and aims: Prometic's lead drug candidate, 2- (3-pentylphenyl)acetic acid (PBI-4050), is a dual G protein-coupled receptor GPR40 agonist/GPR84 antagonist that exerts antifibrotic, anti-inflammatory, and antiproliferative action. Previous studies found that PBI-4050 reduces carbon tetrachloride and bile-duct ligation induced fibrosis. Here, we tested whether PBI-4050 would offer hepatic protection in an acute model of liver injury induced by sepsis-related endotoxemia.
Method: Eight-week old male C57BL/6N mice were given either vehicle (H_2O) or PBI-4050 (200 mg/kg) daily by gavage for 2 weeks and challenged with a single intraperitoneal dose of bacterial lipopolysaccharides (LPS; 10 mg/kg) and sacrificed after 24 hours.
Results: LPS-induced sepsis was confirmed by significant elevations in several circulating pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, CXCL1, RANTES, MCP-1, INFγ), all of which were significantly decreased by PBI-4050 treatment. LPS was associated with hypoalbuminemia, which was significantly prevented in PBI-4050-treated mice. Histological assessment revealed mild microsteatosis in both groups, while hepatocyte morphology (size, cytoplasmic density) was increased in vehicle-treated LPS mice, but not in PBI-4050-treated mice. Interestingly, Kupffer cells were also increased in PBI-4050-treated mice compared to vehicle-treated LPS mice. Gene expression analysis revealed that PBI-4050 modulated several pro-inflammatory (NOS2, IL-6 and CXCL1) and ER-stress related genes (DDIT3, ATF4 and PDIA4). Finally, PBI-4050 reduced ER-stress proteins CHOP, phospho-eIF2α and GRP78 induced by LPS in the liver.
Conclusion: Taken together, PBI-4050 treatment in septic mice decreased systemic inflammation and liver injury, improved plasma albumin levels and dampened the ER-stress pathway. These data suggest PBI-4050 treatment may offer protection from sepsis-mediated acute liver injury.

FRI-098
Targeting cholesterol with atorvastatin protects against valproic acid-induced sensitization to acetaminophen hepatotoxicity
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Background and aims: Mitochondrial cholesterol (mChol) accumulation is associated with chronic liver diseases, including fatty liver disease and hepatocellular carcinoma. Increased cholesterol trafficking to mitochondria alters membrane physical properties, including the transport of cytosol GSH into mitochondrial matrix, which results in mitochondrial GSH (mGSH) depletion. As GSH is a critical player in drug-induced liver injury (DILI), we hypothesized that altered mChol homeostasis contributes to DILI. Valproic acid (VPA) is a widely prescribed epileptic and anticonvulsant drug, and patients under VPA therapy have been shown to develop acetaminophen (APAP) hepatotoxicity. Therefore, our aim was to examine the role of targeting cholesterol by statins and its trafficking to mitochondria mediated by StARD1 in VPA sensitization to APAP-mediated hepatotoxicity and acute liver failure.
Method: WT C57BL/6J male mice were fed with normal chow (Ctrl) or high-cholesterol diet (2% Cholesterol and 0, 5% Sodium Cholate, HC) followed by a single dose of APAP (300 mg/Kg, ip). Mice were dosed daily by oral gavage with atorvastatin (Pfizer, 10 mg/kg) or vehicle 7 days before being treated three times every 12 h with VPA (400 mg/Kg, sc) followed by a single dose of APAP (300 mg/Kg, ip). Moreover, mice with hepatocyte-specific StARD1 deletion (StARD1$^{\Delta Hep}$) were analysed for VPA sensitization to APAP mediated hepatotoxicity. Liver damage by ALT and HandE, cholesterol trafficking and GSH homeostasis were examined following VPA plus APAP cotreatment. Expression of StARD1, MLN64, ER stress markers and lipogenic transcription factors were examined by qPCR and WB.
Results: Mice fed a cholesterol-enriched (HC) diet, which exhibited enhanced hepatic cholesterol loading in mitochondria, were highly sensitive to APAP-induced liver injury, determined by serum ALT levels and HandE. Livers from HC+APAP displayed increased mChol transporters and ER stress markers expression and mChol accumulation, resulting in GSH depletion. Interestingly, atorvastatin therapy prevented the mChol loading and reduced the expression of StARD1, MLN64 and ER stress markers in mice treated with VPA+APAP. Atorvastatin therapy protected mice from VPA plus APAP liver injury, revealed by the HandE staining and the significant serum ALT decrease. Moreover, StARD1$^{\Delta Hep}$ mice were resistant to VPA+APAP mediated hepatotoxicity, exhibiting decreased mChol accumulation and mGSH repletion compared to StARD1 $^{f/f}$ mice.
Conclusion: Cholesterol exacerbates liver toxicity following APAP administration and its targeting by atorvastatin protects against the hepatotoxic effects of VPA-induced sensitization to APAP hepatotoxicity. Similar findings are observed in StARD1$^{\Delta Hep}$ mice indicating that the selective mChol pool plays an important role in DILI.

FRI-099
PD-1+ monocytes and macrophages contribute to impaired microbial clearance following acute liver failure
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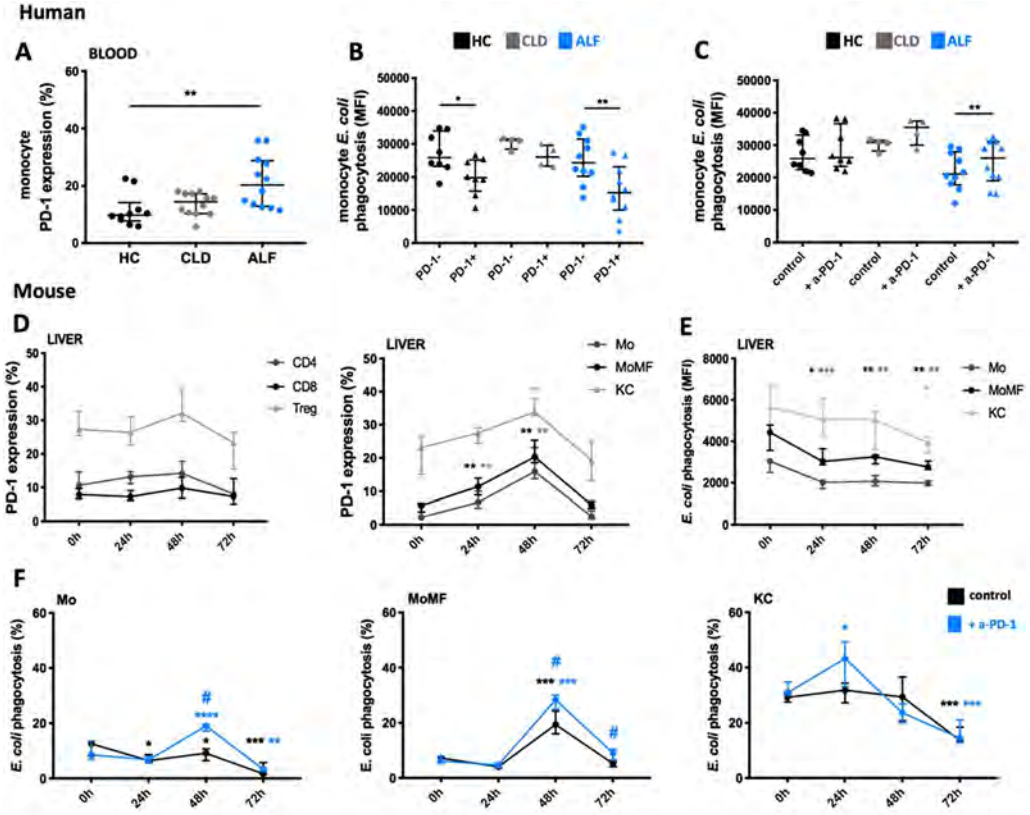

Figure. (**A**) PD-1 expression levels of blood monocytes in healthy controls (HC), chronic liver disease (CLD) and acute liver failure (ALF) patients. (**B**) Phagocytosis of *E. coli* (pHrodo) in PD-1- versus PD-1+ monocytes in HC, CLD and ALF. (**C**) Phagocytosis of *E. coli* (pHrodo) in HC, CLD and ALF monocytes with/without anti-PD-1 mAb pre-treatment. (**D**) PD-1 expression levels of mouse liver CD4+, CD8+ T cells, Tregs, monocytes (Mo), monocyte-derived macrophages (MoMF) and Kupffer cells (KC) after APAP overdose. (**E**) Phagocytosis of E. coli (pHrodo) by mouse liver Mo, MoMF and KC after APAP overdose. (**F**) Phagocytosis of E. coli (pHrodo) by mouse liver Mo, MoMF and KC after APAP overdose in mice treated with isotype control or anti-PD-1 mAb . Non-parametric (Mann-Whitney) statistical analysis was used. Data shown as median values with IQR. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. # p<0.05, comparison between groups. Programmed-cell-death-protein-1 (PD-1).

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Background and aims: Patients with paracetamol (APAP)-induced acute liver failure (ALF) show defective innate immune responses to microbial cues, promoting increased susceptibility to infections and mortality. Interestingly, recent studies in sepsis and cancer have associated the expression of programmed-cell-death-protein-1 (PD-1) by monocytes and macrophages with reduced phagocytosis. Therefore, we examined the expression of PD-1 and its role in regulating microbial clearance in human and murine ALF.
Methods: Using flow cytometry, we determined PD-1 expression in circulating T cells, Tregs and monocytes isolated from healthy controls (HC, n = 10), chronic liver disease (CLD, cirrhosis; n = 12) and ALF (n = 12) patients. Monocyte *E. coli* (pHrodo) phagocytosis was assessed *ex vivo* and *in vitro* after anti-PD-1 monoclonal antibody (mAb, 10μg/ml) treatment. WT mice dosed with APAP (250 mg/kg) were treated with isotype control or anti-PD-1 mAb (200μg) at 24 h before and after APAP (n = 5/group). Using liver intravital confocal imaging and flow cytometry, we measured and visualized: (a) PD-1 expression of Tcells, Tregs, monocytes and macrophages, (b) macrophage phagocytosis following *E. coli* (pHrodo) systemic administration.
Results: Patients with ALF showed a higher proportion of PD-1+ monocytes than HC and CLD (**A**) whereas PD-1+ Tcells and Tregs were similar between groups. PD-1+ monocytes have reduced *E. coli* uptake when compared to PD-1- cells (**B**). PD-1 expression correlated negatively with phagocytosis index (r = -0.70, p < 0.001) and anti-PD-1 treatment increased phagocytosis in ALF (**C**). In mice, Tcell and Treg PD-1 expression remained unaltered while PD-1 was up-regulated in liver monocytes (Mo), monocyte-derived macrophages (MoMF) and Kupffer cells (KC) at 24 h and 48 h (**D**). Following injury, there was impaired *E. coli* uptake in the liver by these subsets (**E**), with PD-1+ cells phagocytosing less. Anti-PD-1 treatment led to similar liver injury (ALT levels, necrosis) and increased Mo and MoMF phagocytosis, compared to control group (**F**).
Conclusions: We reveal the expansion of human and murine PD-1+ monocytes and liver macrophages following ALF. These PD-1+ cell subsets contribute to impaired microbial clearance, thus targeting PD-1 may provide novel therapeutic strategies in ALF. Future work will better characterize the importance of PD-1 on monocytes and macrophages and its mechanisms underlying innate immunosuppression in human and experimental liver injury.

FRI-100
Protective effects of glutathione and lipoic acid against cadmium-induced oxidative stress in rat's liver

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Background and aims: Cadmium is a widespread, toxic industrial pollutant, which is introduced into the organs through food, air and

tobacco smoke. Cd poisoning leads primarily to damage of the liver tissue and testes in laboratory animals. We analyzed the effects of cadmium exposure on the model system of experimental animals, the thiobarbituric acid (TBA)-reactive substance (TBARS) level, and the activity of xanthine oxidase (XO) and catalase in liver of rats, with and without glutathione and lipoic acid (LA).
Method: The experimental animals were divided into six groups, regarding cadmium, glutathione, and LA intake. The concentration of TBARS in the homogenate was determined by spectrophotometric method according to Andreeva et al. The specific activity of XO was determined spectrophotometrically by the method of Hashimoto et al. Catalase activity in tissues was determined by spectrophotometric method according to Goth.
Results: The increased level of TBARS and the increased activity of XO in rat liver in cadmium poisoning are statistically significant compared to control ($p < 0.001$). Glutathione and LA applied along with cadmium lowered TBARS level and reduced XO activity ($p < 0.001$). Catalase activity in the liver tissue was increased in the group, which was administered cadmium ($p < 0.001$).
Conclusion: Glutathione and LA, as physiological antioxidants have reduced the level of lipid peroxides and the activity of XO, in conditions of cadmium poisoning, and can be used as protectors.

FRI-101
FGL2 deficiency resists viral fulminant hepatitis through abrogating inflammatory macrophage activation
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Background and aims: Virus-induced acute liver failure (or viral fulminant hepatitis, VFH), is devastating liver disease without specific intervention agents. Understanding the molecular and immune mechanism underlying VFH progression will give implications on therapeutic targets. Fgl2 is a membrane protein expressed on macrophages and promotes fulminant hepatitis progression, however, the detailed mechanism underlying immune alterations and through which Fgl2 modulates immune response during VFH remains unclear.
Method: Hepatic macrophages were analyzed in *fgl2*$^{-/-}$ mice and wild type littermates infected with murine hepatitis virus strain 3 (MHV-3) which induced VFH in mice. Liver damage was assessed in mice with macrophage depletion after infection. Phagocytosis, polarization, and inflammatory signaling were evaluated in fgl2$^{-/-}$ macrophages in response to Lipopolysaccharide or viral stimulation.
Results: In patients of HBV-associated liver failure, inflammatory macrophages were accumulated in periportal region with high level of Fgl2 expression. In murine VFH model, macrophages predominated infiltrating leukocytes. Kupffer cells (KCs) were replaced of by infiltrating monocyte-derived macrophages (MoMFs) in which Ly6C^{high} MoMFs dominated macrophage population. Fgl2 was robustly induced on proinflammatory MoMFs and KCs following viral infection. Depletion of macrophages ameliorates liver damage in wild type mice and synergically in fgl2$^{-/-}$ mice after viral infection. In Fgl2-deficient mice, infiltrating macrophages were significantly reduced with lower portion of Ly6C^{high} MoMFs and more Ly6C^{low} MoMFs during VFH. Fgl2 depletion impaired macrophage activation by attenuating IRF3, NF-κB, and p38 activation in response to either lipopolysaccharide stimulation or viral infection.
Conclusion: Proinflammatory infiltrating macrophages were the major source of inflammation during VFH progression. Fgl2 induction on these cells orchestrates a positive feedback look for macrophages-derived inflammatory expansion leading to VFH progression by directly promoting classical inflammatory signaling.

FRI-102
Metabolomic and inflammatory mediator based biomarkers analysis for identification of severe drug induced liver injury
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Background and aims: To describe the differences of serum metabolomics and immune mediators between Severe and Non-severe idiosyncratic drug-induced liver injury (DILI) patients, and to select biomarkers for identifying the severity of DILI.
Method: A gas chromatography-mass spectrometry (GC-MS) and an ultra-performance liquid chromatography-mass spectrometry (UPLC-MS)-based metabolomics approach were used to explore metabolomics differences in serum samples from 29 DILI patients at disease severity grade 3 (Non-severe) and 27 patients at severity grade 4 (Severe), while 36 controls were also included. Full length and fragmented keratin-18 and 27 immune mediators were determined by ELISA.
Results: Between Severe and Non-severe groups, alkaline phosphatase ($p = 0.021$) and International Normalized Ratio (INR) ($p < 0.001$) were significantly different. Severe group showed a higher M30 serum level than Non-severe group. Multivariate analysis of GC-MS and UPLC-MS both showed a good separation between any two of health control, Non-severe and severe groups. According to the OPLS-DA model, 14 metabolite of GC-MS and 17 metabolites of LC-MS were selected. Among them, 16 metabolites upgraded and 15 downgraded in Severe group. Pathway analysis revealed major changes in primary bile acid biosynthesis, alpha-Linolenic acid metabolism, etc. PDGF-bb, IP-10, IL-1Ra, MIP-1b and TNF-a showed significant difference between severe and non-severe groups, and most of the metabolites had negatively correlation with these immune mediators. Then the representative metabolites and immune mediators were integrated in an OPLS-model and the model revealed clear separation of Severe and Non-severe groups ($R^2Y = 706$, $Q2 = 0.674$, $AUC = 0.983$).
Conclusion: We identified thirty-one differentially expressed metabolites and five immune mediators implicated in different severity of idiosyncratic drug-induced liver injury. Primary bile acid biosynthesis, alpha-Linolenic acid metabolism, etc. were involved in the severity progression. The model of metabolites and immune mediators showed clear separation of different severity of DILI, indicating that these biomarkers could be potential to identify the severity of DILI.

FRI-103
A sublethal dose of acetaminophen suffices to induce the unfolded protein response in hepatocytes through an IRE1alpha-JNK1-XBP1s-dependent mechanism
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Background and aims: Acetaminophen (APAP) overdose is the leading cause of acute liver failure (ALF) in developed countries.

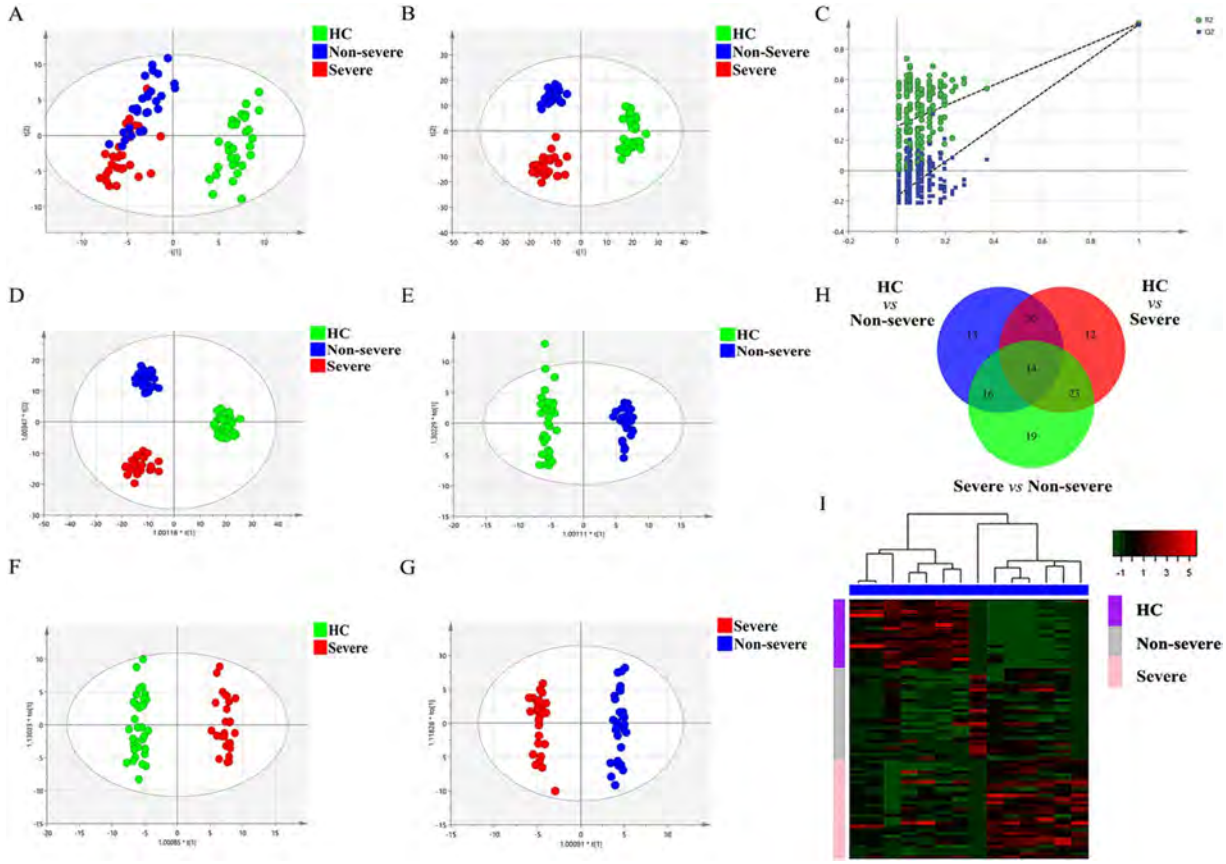

Figure: (abstract: FRI-102)

Activation of the unfolded protein response (UPR) as a consequence of endoplasmic reticulum (ER) stress has recently reported in APAP toxicity. However, the role of the UPR in APAP toxicity remains unclear. In this study, we investigated the role of the UPR during ALF.
Method: Overnight fasted C57/BL6 male mice aged 12-14 weeks, were challenged with a sublethal injection of APAP [0, 75, 150 and 300 (mg)/kg)]. Control mice received an equivalent volume of vehicle (PBS). In parallel, human liver HepaRG cells were challenged with APAP [10 mM]. Twenty-four hours later mice were sacrificed, and tissue collected. Histopathological examination of liver and HepaRGs, immunofluorescence and immunohistochemistry, Western Blot and Real time (RT)-qPCR studies and transmission electron microscopy (TEM) were performed.
Results: Mice: Serum ALT increased proportionally to the concentration of APAP reaching its peak at 300 mg/kg whilst APAP triggered strong hepatic damage further characterized by necrotic foci in the liver parenchyma and massive hepatocyte death (quantified by TUNEL-positive staining). Interestingly, markers of inflammasome formation such as NRLP3, IL-1β and TNF were significantly elevated, which was associated with strong infiltration of $CD11b^{+}$, F4/80+ and CD45+ macrophages. Importantly, increased mRNA and protein expression of pIREα, and XBP1 s, BIP and CHOP-markers of UPR, were observed in mice challenged with 300 mg/kg APAP together with elevated phosphorylation of JNK1. Interestingly, Oil-Red-O and triglyceride content revealed further cellular stress through ER-induced hepatic steatosis and lipogenesis. Moreover, specific inhibition of XBP1 in hepatocytes reversed APAP-induced injury. Animal studies were validated in human HepaRG cells.
Conclusion: Our study strongly suggests that high concentrations of APAP induce the UPR associated with ER stress-induced lipogenesis, ultimately leading to hepatocyte death and ALF. This mechanism is linked to the activation of IRE1α-JNK1-spliced X-box binding protein-1 (XBP1 s) in hepatocytes.

Cirrhosis and its complications: Experimental and pathophysiology

FRI-106
Combining endozepine-4 and blood ammonia: Does it improve the diagnosis of hepatic encephalopathy in patients with liver cirrhosis?

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Background and aims: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that covers a wide range of disturbances in which cerebral function deteriorates. Although the pathogenesis of HE is multifactorial, ammonia has a pivotal role in the genesis of the disease and has been demonstrated to exert a glutamate-related neurotoxicity which in turn may alter the γ-aminobutyric acid (GABA) receptor system. Endozepine-4, an endogenous ligand for the benzodiazepine recognition site of the GABA receptor, may play an important role in the pathogenesis of HE and can be useful in the monitoring of patients with hepatic coma.

The purpose of this work was to evaluate the serum levels of endozepine-4 in patients with hepatic encephalopathy. Moreover, its relation with grading of encephalopathy and ammonia level was studied

Method: This study was carried out on eighty individuals classified into three groups: Group I: Forty patients with hepatic encephalopathy. Group II: Twenty patients with liver cirrhosis without hepatic encephalopathy. Group III: Twenty apparently healthy volunteers as controls. Serum endozepine-4 was measured by ELISA.

Results: Serum endozepine-4 was significantly higher in hepatic encephalopathy patients than in those with liver cirrhosis and controls (Z = 4.69, 5.48) (p = 0.000). Moreover, it was significantly higher in liver cirrhosis patients than controls (Z = 3.03, P = 0.002). Grading of hepatic encephalopathy according to the West Haven Criteria revealed: Grade 1 in 2 patients, Grade 2 in 18 patients, Grade 3 in15 patients and Grade 4 in 5 patients. Significant positive correlation was observed between endozepine-4 and grading of HE (r = 0.52, P = 0.001). Also Significant positive correlation was observed between endozepine-4 and blood ammonia levels (r = 0.48, P = 0.001). Roc curve analysis revealed that endozepine-4 at a cut off > 51 pg/ml is diagnostic of hepatic encephalopathy (AUC 0.83) with a sensitivity of 82.5%, PPV of 89.1, NPV of 69.56% and accuracy of 81.66%. While blood ammonia level at a cut off > 133 mcg/dl is diagnostic of HE (AUC 0.83) with a sensitivity of 77.5%, PPV of 86.11%, NPV of 62.5% and an accuracy of 76.6%. Binary regression analysis model of combined endozepine-4 and ammonia is significant (X^2 32.15, P = 0.000) in predicting hepatic encephalopathy with sensitivity of 92.5%, PPV 86%, NPV 82% and accuracy of 85%.

Conclusion: Serum Endozepine level is a useful marker for diagnosis and grading of hepatic encephalopathy. Moreover, combined measurement of both blood ammonia and serum endozepine-4 have a good predictive value of occurrence of hepatic encephalopathy in patients with liver cirrhosis.

FRI-107

Emerging role of taurine conjugated bile acids in the gut liver axis and on hepatic bile acid receptors in chronic hepatitis C

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Background and aims: Bile acids (BA) are mediators in gut-liver cross talk and impact host metabolism through BA receptors (BARs). Many BARs have higher affinity for conjugated BA. The aim was to evaluate conjugated BA in the gut liver axis in chronic liver disease.

Method: HCV patients had liver biopsy with portal vein cannulation; portal and peripheral blood obtained before (P1) and 1 year after DAA therapy (P2). Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy and ELISA assessed 24 BA, taurine and glycine amino acids (AA); and FGF19, respectively. Fecal microbiome and liver transcriptome were evaluated by 16S-rRNA and RNA-Seq, respectively. BA were summed as free, taurine, glycine conjugated (Free-BA, Tau-BA, Gly-BA). All correlations after FDR correction (p < 0.1).

Results: In P1 (n = 29), 16 were Non-Cirrhotic (NC) and 13 Cirrhotic (Cir) by Ishak Fibrosis. Peripheral Tau-BA (not Gly-BA or Free-BA) were higher in Cir compared to NC (Mann-Whitney p < 0.05). Peripheral Tau-BA (not Gly-BA or Free-BA) were inversely linked to portal glycine AA. Of 177 microbial genera, portal glycine AA correlated inversely with Lachnospira, Lachnobacterium, Veillonella, and Hemophilus, and positively with Dorea and Ruminococcus. In portal serum, Tau-BA (not Gly-BA or Free-BA) were associated with higher FGF19. Among classic BARs i.e. FXR, TGR5, LXR, PXR, VDR, CAR, S1PR2, peripheral Tau-BA correlated with hepatic mRNA expression of FXR, LXR beta, and S1PR2; and portal Tau-BA with FXR, TGR5, LXR beta, and S1PR2. Peripheral and portal Gly-BA only correlated with S1PR2. Free-BA showed no link with BARs. In P2 (n = 23), all achieved SVR with no change in fibrosis. Tau-BA and Gly-BA decreased overall (Wilcoxon paired p < 0.05). Tau-BA was higher in Cir than NC, even after SVR.

Conclusion: Among all peripheral BA groups, only Tau-BA were elevated in cirrhosis. Our findings suggest a link between gut microbiome and portal glycine levels, and an influence of portal glycine levels on hepatic Tau-BA conjugation. Association of hepatic BA receptors and portal FGF19 predominantly with Tau-BA is an important finding as BARs and FGF19 mediate host responses of immunity and metabolism. Despite an overall reduction, elevated Tau-BA in cirrhotics even after SVR suggests a relationship between Tau-BA and cirrhosis, independent of HCV. Overall, these findings highlight pathological and possibly therapeutic implications of Tau-BA and BA receptors in chronic HCV and in cirrhosis.

FRI-108

Gut-derived GABA is strongly linked with cognitive impairment in cirrhosis

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Background and aims: Hepatic encephalopathy (HE) consists of a subclinical minimal (MHE) and clinically apparent overt (OHE) stage. Both stages demonstrate significant alterations in the gut-brain axis that can worsen outcomes and are hypothesized to be due to hyperammonemia and inflammation. However, the gut microbiota produce other neurotransmitters such as tryptophan metabolites and GABA (gamma aminobutyric acid), which need to be evaluated in HE.

Aim: Determine association of HE and cognitive performance with ammonia and gut-derived neurotransmitters in cirrhosis.

Method: Outpatients with cirrhosis underwent cognitive testing, ammonia, cirrhosis severity testing and stool collection. Cognitive testing was performed using the psychometric hepatic encephalopathy score (PHES < -4 = MHE, high score is good). Stool was analyzed for neurotransmitters GABA and tryptophan derivatives (tryptophan, serotonin, melatonin, 5-hydroxytryptophan, N-acetyl serotonin, 5-hydroxyindoleacetic acid (5-HIAAA) and kynurenine). In the entire group, we compared patients with/without MHE with respect to MELD score, ammonia, and neurotransmitters, which were also correlated with PHES scores. Similar analyses were performed in patients without prior OHE. Multi-variable analysis for PHES scores as dependent variables using demographics, cirrhosis details, OHE, ammonia and gut-derived neurotransmitters was performed for each group.

Results: *Entire group*: 63 pts (MELD 10.4, age 58.8, 20 alcoholic cirrhosis, 21 prior OHE who were on rifaximin) were enrolled. 34 pts (21 OHE) had MHE on PHES. Patients with MHE had higher fecal GABA concentrations but statistically similar levels of other neurotransmitters and ammonia (Table). PHES score was negatively correlated with GABA (–0.44, p < 0.001) but not with ammonia (–013, p = 0.37), MELD score (–0.23, p = 0.08) or other neurotransmitters. On multi-variable analysis, PHES was predicted by GABA (p = 0.001) and age (p = 0.022). *Patients without prior OHE*: In these patients, there was a greater increase in fecal GABA concentrations in MHE *vs*. no-MHE with similar levels of other neurotransmitters and ammonia (Table). A similar relationship continued in this subgroup, where the correlation of PHES with GABA was stronger

(–0.72, p < 0.001). No linkage with ammonia (0.06, p = 0.91), MELD score (0.07, p = 0.63) or other neurotransmitters was recorded. On multi-variable analysis, PHES score was predicted by GABA (p < 0.0001) and age (p = 0.039).

mean±SD unless specified	All patients (n=63)			Patients without prior HE (n=42)		
	No-MHE (n=22)	MHE (n=41)	P value	No-MHE (n=16)	MHE (n=26)	P value
Age	57.2±8.2	59.6±7.2	0.13	55.6±8.9	59.1±5.4	0.09
Gender(M/F)	19/3	34/7	0.72	13/3	20/6	0.74
Alcoholic etiology	8/14	12/29	0.33	5/11	6/20	0.56
MELD score	11.1±4.1	10.0±3.9	0.84	9.9±4.1	8.3±2.4	0.92
Venous Ammonia	43.5±23.8	44.1±25.1	0.47	40.9±22.5	37.1±19.3	0.69
HE Rx: no/lact+ rifax	16/6	26/15	0.45	16/0	26/0	1.0
PHES median(IQR)	**-0.5 (3.00)**	**-6.0 (6.5)**	**<0.001**	**0.0(3.75)**	**-6.0 (5.5)**	**<0.0001**
Fecal neuro-transmitters (ng/ml)						
GABA	**725±1497**	**2060±4645**	**0.05**	**214±237**	**1336±1697**	**0.001**
Tryptophan	1792±1989	1756±1364	0.53	1632±882	1763±1233	0.37
Serotonin	3.29±3.95	3.92±4.25	0.30	4.24±4.54	4.33±5.05	0.48
Melatonin	0.82±0.84	0.72±0.82	0.66	0.96±0.84	0.73±0.83	0.77
5-hydroxytryptophan	1.89±3.58	6.1±14.0	0.054	2.42±4.15	8.0±16.8	0.08
N-acetyl serotonin	0.67±0.78	0.91±0.96	0.17	0.64±0.81	1.06±1.0	0.10
5-HIAAA	0.70±1.54	0.46±1.67	0.70	0.90±1.81	0.18±0.49	0.90
Kyunerine	0.12±0.09	0.11±0.09	0.59	0.12±0.10	0.09±0.08	0.76

Conclusion: Gut-derived GABA was associated with impaired cognitive performance in cirrhosis independent of prior OHE, lactulose/rifaximin therapy, cirrhosis severity or hyperammonemia, while tryptophan-based neurotransmitters were not linked. Strategies focused on GABA reduction in the gut could form an additional strategy to improve HE severity and progression.

FRI-109

Increased plasma leukotriene B4 in decompensated cirrhosis associates with disease progression and leads to increased skin window neutrophil infiltration

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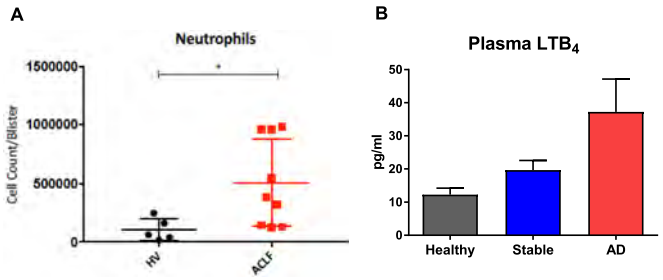
Background and aims: Patients with advanced liver disease are highly prone to bacterial infection secondary to immune dysfunction combined with increased systemic inflammation. Recent studies have shown several circulatory chemokines involved in leukocyte migration and chemotaxis to be increased in decompensated cirrhotic patients, which correlated with survival. Leukotriene B_4 (LTB_4) is a pro-inflammatory lipid mediator that displays strong chemoattractant properties, and we aimed to investigate if its circulating levels were altered in outpatients with ascites and acute decompensation/Acute-on-chronic liver failure (AD/ACLF) inpatients, and whether this correlated with disease progression.

Method: Plasma LTB4 levels from AD/ACLF, outpatients with ascites and healthy volunteers were quantified by High Performance Liquid Chromatography. Expression of enzymes and receptors involved in synthesis and signaling of LTB_4 was assessed by real-time qPCR in primary monocytes and neutrophils. ACLF patients underwent forearm cantharidin blister formation (Cantharone, Dormer Laboratories) with cells counted and stained for flow cytometry.

Results: Neutrophil numbers were significantly increased in our *in vivo* skin blister model of sterile inflammation in AD/ACLF patients compared to healthy volunteers (Figure A). This associated with elevated plasma LTB_4 in both outpatients with ascites and AD/ACLF patients, being highest in AD/ACLF (Figure B). In addition, increased expression of several genes involved in the LTB_4 synthetic pathway was observed in outpatients with ascites and AD/ACLF circulating neutrophils and monocytes, as well as significantly higher levels of the LTB_4 receptor (BLT1) in neutrophils with levels correlating with disease progression.



Conclusion: Contrary to previous studies, we have shown that AD/ACLF patients display significantly higher neutrophil recruitment to a site of inflammation than healthy volunteers. Moreover, plasma levels of the chemotactic LTB_4 increased according to disease progression. We also found that the LTB_4 synthetic machinery was increased in cirrhotic patients, again related to disease progression. This human *in vivo* study supports a novel role for increased LTB_4, causing exuberant leukocyte transmigration in AD/ACLF perhaps underlying the increased systemic inflammatory response that denotes a poor prognosis in these patients. Further studies are required to determine whether this lipid mediator represents a potential therapeutic target.

FRI-110

A nutraceutical supplement rich in docosahexaenoic acid improves portal hypertension in a pre-clinical model of chronic liver disease

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Background and aims: High levels of oxidative stress in the liver play a key role in the physiopathology of chronic liver disease and portal hypertension (PH). Previous studies demonstrated the effectivity of pharmacological and genetic antioxidant strategies improving PH. However, said strategies have not moved to the bedside. Considering the lack of effective and safe treatments for PH, in this study we evaluated the effects of an antioxidant nutraceutical supplement rich in docosahexaenoic acid triglycerides (DHA-TG) as a possible novel therapy to improve PH.

Method: *In vitro*. The phenotype of human hepatic stellate cells (LX-2) incubated 72h with DHA-TG (10-50 µM) was evaluated in terms of activation (α-SMA and TGFβR) and proliferation markers (PDGFRβ and proliferation assay).
In vivo. Male Wistar rats with chronic liver disease induced by chronic administration of thioacetamide (12 weeks) were treated for two weeks with DHA-TG (500mg/kg/day) or placebo (olive oil) (n = 12 per group). At the end of the treatment the following parameters were evaluated: hepatic and systemic DHA-TG bioavailability using GC-MS, hepatic and systemic hemodynamics (portal pressure, mean arterial pressure, portal blood flow), hepatic oxidative stress (dihydroethidium staining), hepatic fibrosis (sirius red staining), hepatic stellate cell phenotype (HSC: collagen I and α-SMA) and biochemical analysis of serum.

Results: *In vitro*. DHA-TG promoted HSC deactivation in a concentration-dependent manner (data for 50 µM: –93% in α-SMA, –92% in TGFβ, –98% in PDGFRβ, all p < 0.05) without altering their viability.
In vivo. Rats with chronic liver disease treated with DHA-TG showed significantly increased omega-3 index and decreased the omega-6: omega-3 fatty acid ratio in erythrocytes and liver, thus confirming the effectiveness of the treatment. Importantly, rats receiving DHA-TG

exhibited a significant improvement in PH (−14% in portal pressure; p = 0.03) without changes in portal blood flow, suggesting a reduction in intrahepatic vascular resistance (−25%; p = 0.15). The mechanisms underlying this hemodynamic improvement included a reduction in intrahepatic oxidative stress (−21%; p = 0.02), HSC deactivation (−46% in α-SMA protein expression; p = 0.05), together with a tendency to improve hepatic fibrosis (−17%; p = 0.1) with no changes in biochemical parameters.

Conclusion: The present pre-clinical study demonstrates that an antioxidant nutraceutical supplement rich in DHA-TG improves moderately, but significantly, PH and chronic liver disease. These results encourage the evaluation of this type of non-pharmacological therapeutic strategy as a new treatment for PH and cirrhosis.

FRI-111

Albumin modulates endosomal TLR9 signaling in human peripheral leukocytes: A mechanism for its anti-inflammatory role in ACLF

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Background and aims: Human serum albumin (HSA) is an effective therapy in patients with advanced liver disease at risk of developing acute-on-chronic liver failure (ACLF), a clinical condition characterized by recurrent infections and intense systemic inflammation that lead to organ failure (s) and high short-term mortality. Recent studies have demonstrated that HSA downplays systemic inflammation independently of its oncotic properties, although the mechanisms underlying these anti-inflammatory actions are unknown. In the current study, we investigated the molecular mechanisms of HSA in peripheral innate immune cells exposed to a bacterial pathogen-associated molecular pattern molecule (PAMP).

Method: Plasma levels of 42 cytokines-chemokines were measured by bead-based Luminex panels in a group of patients with acute decompensated (AD) cirrhosis under HSA therapy. Peripheral leukocytes (PBMC and PMN) from patients with AD cirrhosis and healthy donors were challenged with bacterial DNA rich in unmethylated CpGs (2 μM) in absence or presence of HSA at 15 mg/ml. Experiments were performed in both preventive and therapeutic modes. The expression of cytokine and interferon stimulated genes (ISGs) was determined by real-time PCR. Cytokine levels were measured by Luminex immunoassay. Phagocytosis was assessed by a fluorimetric assay and respiratory burst by flow cytometry. Leukocyte HSA uptake and intracellular trafficking were monitored by confocal microscopy.

Results: Patients with AD receiving albumin therapy showed significantly reduced circulating levels of tumor necrosis factor (TNF) alpha, interleukin (IL) 6, IL-10 and granulocyte colony-stimulation factor (G-CSF). Similar anti-inflammatory effects were observed *in vitro* in PBMC and PMN stimulated with CpGs and incubated with HSA. No changes in phagocytosis and respiratory burst were detected, indicating that HSA therapy did not compromise leukocyte defensive mechanisms against pathogens. Immunofluorescent confocal microscopy analysis revealed that FITC-labeled HSA was taken up by leukocytes and internalized in intracellular vesicles that were positively stained with EEA1, a marker of early endosomes. Moreover, FITC-labeled HSA colocalized with CpGs in the endosome, the intracellular compartment where CpGs bind to its receptor, TLR9. Consistent with this, HSA also blocked the expression of poly- (I:C)-induced ISG genes (i.e. OAS and CXCL10), which is exclusively mediated by endosomal TLR3. The immunomodulatory effects of HSA were partially mediated by FcRn and independent of its oncotic and/or scavenging properties.

Conclusion: These findings demonstrate that HSA interferes with the leukocyte endosomal TLR signaling pathway, thus providing a mechanism for the anti-inflammatory properties of HSA infusions in patients with AD cirrhosis.

FRI-112

Prediction of treatment failures in a multicentre feasibility trial using human albumin solution to prevent infection in acute decompensation of liver cirrhosis

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Background and aims: Infection is a major cause of death in advanced liver disease. We previously identified PGE_2 mediated immune suppression in acute decompensation patients and its effects were antagonised by albumin. In a single arm, 10-centre study to pilot daily HAS in order to prevent infection, 22/79 patients developed nosocomial infection in the 14 day treatment period. This study aims to link clinical characteristics with laboratory immune assays to predict treatment failure when using HAS as an immunorestorative agent.

Method: Inpatients (n = 79) with complications of cirrhosis and serum albumin < 30g/L were recruited. Daily 20% HAS was infused according to serum albumin level. We evaluated patients that developed a nosocomial infection (NI, n = 22) vs. those that did not (NO, n = 57). Ex vivo immune function was assessed by measuring TNFα production from LPS and *S.Aureus* stimulated monocyte derived macrophages (MDMs) in the presence of patient plasma taken on different treatment days. Albumin-PGE_2 binding function was assessed using ^{3}H-PGE_2 equilibrium dialysis with patient plasma.

Results: 59% of nosocomial infection (NI) patients had a baseline infection at hospital admission as opposed to 25% of patients without nosocomial infection (NO). Mean MELD score was high in both groups (20-22). A higher number of NI patients had ACLF at baseline (32%vs.23%). There were no significant differences in mean volume of HAS infused (≈115mls/day) or baseline serum albumin. In both groups there was a significant improvement in LPS-induced MDM TNFα production in the presence of post HAS treatment plasma (NI:+15.2% (4.6, 25.9, p = 0.008) NO:+8.7% (2.6, 14.8, p = 0.006) when serum albumin had reached > 30g/L. However following this improvement the NI patients had a mean 45.4% decrease in LPS-induced MDM TNFα production at the time of infection (−18.6 to −72.3, p = 0.002) which improved with MDM PGE_2 receptor antagonism. Gram-positive stimulated cells mirrored these results with an even larger impact of PGE_2 receptor blockade. Plasma albumin PGE_2 binding capacity initially improved after patient IV HAS treatment, but significantly dropped in the NI group the day prior to infection (−17.9% (−3.9, −31.9, p = 0.014)) despite serum albumin concentrations remaining > 30g/L.

Conclusion: HAS has been shown to have immunomodulatory potential ex-vivo, however in this study 28% developed NI despite initial improvements in ex vivo immune function and albumin binding. NI patients had a downwards reversal of this initial improvement in both assays, which was PGE_2 dependent. It may be that over time albumin-PGE_2 binding sites become saturated (e.g. with drugs, bilirubin or endotoxin) that renders HAS ineffective or infusions are unable to fully reverse the effects of PGE_2 in end stage liver disease. A future approach may be to use of PGE_2 receptor antagonists in combination with HAS therapy to restore immune function.

FRI-113

Matrix stiffness modulates the phenotype of hepatic cells in cirrhosis and modifies the sinusoidal effects of statins

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Background and aims: During chronic liver disease (CLD), continued injury induces activation/dedifferentiation of liver cells, leading to formation of scar tissue and stiffening of the liver. Measurement of liver stiffness is an accurate diagnostic tool for fibrosis assessment in CLD. Since stiffness predicts prognosis within each stage of CLD, and since cells may change their phenotype when cultured *in vitro* on matrices with different stiffness, it is **hypothesized** that increased liver stiffness may not only be a consequence of CLD but a primary factor driving its progression.
Method: Primary liver cells (hepatocytes: Hep; stellate cells: HSC; sinusoidal endothelial cells: LSEC) were isolated from healthy and cirrhotic (CCl_4 or thioacetamide) rats and cultured for 72h on polyacrylamide gels with increasing stiffness mirroring healthy and fibrotic/cirrhotic liver matrix (0.5kPa, 13.5kPa, 30kPa). Cells' phenotype was assessed by quantitative morphology, mRNA, protein and functional analyses. Validation experiments were performed in primary human liver cells. In addition, influence of matrix stiffness on the protective effects of simvastatin (SMV) was determined in rat cirrhotic cells.
Results: Phenotypical changes of healthy sinusoidal cells were proportional to stiffness. Indeed, healthy cells at 30kPa displayed larger area, altered morphology, significantly worsened mRNA expression of activation markers [Hep: hepatocyte nuclear factor 4α (HNF4α), albumin; HSC: collagen I, α-smooth muscle actin (α-SMA); LSEC: laminin b1, eNOS] and impaired functionality (Hep: −80% albumin and urea synthesis, HSC: +150% α-SMA fiber formation, LSEC: −40% nitric oxide (NO) synthesis and decreased fenestrae) compared to healthy cells on 0.5kPa gels. On the other hand, cirrhotic cells displayed a significant amelioration of the same markers of phenotype and functionality when cultured on soft surfaces compared to stiffer ones (Hep: +570% albumin, +94% urea synthesis; HSC: −70% α-SMA fiber; LSEC: +90% NO synthesis). Finally, SMV showed statistically significant greater effects deactivating cirrhotic HSC at lower stiffnesses [greater morphology change and higher reduction of α-SMA (−82% in 30kPa vs −94% in 0.5kPa) and collagen I (−19% in 30kPa vs −55% in 0.5kPa)], while its effects on Hep's phenotype were mostly evident on stiff matrices [greater morphology shift, increased HNF4α (+56% in 30kPa vs +13% in 0.5kPa)].
Conclusion: Stiffness determines the phenotype of liver cells; a stiffer environment (mirroring CLD progression) prompts deregulation of healthy cells, while a softer environment (mirroring CLD improvement) leads to improved phenotype of cirrhotic cells. Importantly, efficacy of statins is modulated by matrix stiffness. Thus, targeting liver stiffness may represent a novel therapeutic strategy for CLD management to be added to the existing armamentarium.

FRI-114

Progression of splenic fibrosis in cirrhotic patients with portal hypertension

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Background and aims: Among several non-invasive evaluation of portal hypertension (PH), measurement of spleen stiffness by ultrasound is becoming a reliable method to predict esophageal variceal bleeding, while underlying mechanisms for the increased spleen stiffness remain unclear. We aimed to elucidate the pathological changes of spleen and the underlying mechanisms in patients with PH accompanied by thrombocytopenia and splenomegaly.
Method: Histological examination was performed using splenic tissues from 42 HCV-positive patients with PH who underwent laparoscopic splenectomy (platelet counts; 59.5 (21-111) × $10^3/\mu l$), in comparison with those from patients without PH. All research protocols of this study were approved by the institutive Ethics Committee.
Results: In addition to splenic sinus congestion; dilatation of splenic sinus and narrowing of splenic cord, diffuse fibrosis was detected in the splenic cords in the red pulp of patients with PH. The degree of the fibrosis well correlated with severity in thrombocytopenia ($p = 0.011$) and splenomegaly ($p < 0.001$). Cells expressing α-smooth muscle actin (SMA) dramatically increased in the cord of patients with PH, and its expression was network-patterned. Morphological analysis showed that reticular cells in the splenic cord most likely expressed α-SMA, suggesting transformation of reticular cells to myofibroblastic cells. Expressions of nicotinamide adenine dinucleotide phosphate oxidases (NOXs) 2 and 4, oxidative stress markers such as nitrotyrosine, and transforming growth factor (TGF)-β were markedly upregulated in the red pulp of patients with PH, suggesting significant contribution of oxidative stress to the mechanism of the splenic fibrosis.
Conclusion: Splenic fibrosis progresses along with advancement of portal hypertension. This fibrosis progression possibly contributes to the increased spleen stiffness in patients with PH. Reticular cells in the splenic cord possibly participate in this process through the mechanism including oxidative stress.

FRI-115

Toll-like receptor 4: A novel therapeutic target for the treatment of hyperammonemia

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Background and aims: In cirrhosis, lipopolysaccharide (LPS) acts synergistically with ammonia in mediating the severity of hepatic encephalopathy (HE). Although LPS results in neuroinflammation, it is not clear whether it induces hyperammonemia (HA) contributing to HE. This study addressed the following: 1) Does LPS worsen HA in a rodent model of cirrhosis 2) Does treatment with an antagonist (TAK242) of the LPS receptor, toll-like receptor-4 (TLR4), prevent HA and 3) Is a TLR4 knock out ($TLR4^{-/-}$) animal protected from HA.
Method: *Study 1:* Sprague Dawley rats were treated with LPS (0.025 mg/kg, ip.) 4 weeks after bile duct ligation (BDL). 4 groups of rats were studied: sham (n = 4), BDL (n = 4), BDL+LPS (n = 6) and BDL+TAK242 (10 mg/kg ip.) 3 hours before LPS injection (n = 7). *Study 2:* 4 groups of mice were studied: wild type control (WTC, n = 5), WT with HA (WTH, n = 5), $TLR4^{-/-}$ control ($TLR4^{-/-}$C, n = 5) and $TLR4^{-/-}$ with HA ($TLR4^{-/-}$H, n = 5). HA was induced by addition of 0.28M ammonium chloride to drinking water for 3 days. For both studies, plasma ammonia levels and liver gene expression of the 5 urea cycle enzymes (UCEs; OTC, CPS1, ASS1, ASL, ARG1) were assessed. Gene expression was assessed using qPCR and shown as relative gene expression ($2^{-\Delta\Delta CT}$) compared to sham/WT.
Results: *Study 1:* There was a stepwise increase in plasma ammonia throughout the sham, BDL and BDL+LPS groups ($p < 0.001$). Rats pretreated with TAK242 had significantly lower plasma ammonia as compared to the BDL+LPS group ($p < 0.01$, **figure**) and a lower coma rate (85% vs. 0%). Gene expression of all UCEs showed a stepwise decrease in sham, BDL and BDL+LPS rats (all $p < 0.05$), which was prevented by TAK242 treatment (all $p < 0.05$). This was most pronounced for the key, rate-limiting enzyme carbamoyl phosphate

synthetase 1 (CPS1), for which expression levels in the TAK242 group were restored to that of the sham animals (**figure**). *Study 2:* In the TLR4$^{-/-}$ mice, the increase in plasma ammonia levels was lower compared to WT mice ($p < 0.001$). HA resulted in a significant increase in relative expression levels of CPS1 and Argininosuccinate Syntethase 1 (ASS1) in both WT and TLR4$^{-/-}$ animals (both $p < 0.05$).

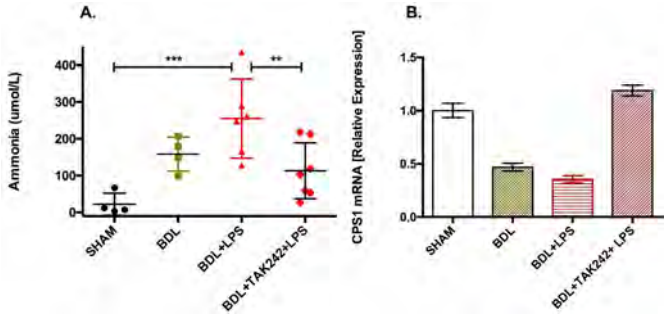

Figure: Plasma ammonia levels (A) and relative gene expression ($2^{-\Delta\Delta CT}$) of the rate-limiting UCE CPS1 (B).

Conclusion: This study shows for the first time that UCE gene expression and the consequent HA is modulated by the LPS-TLR4 pathway. Inhibition of TLR4 with TAK242 offers a novel therapy for HA in cirrhosis.

FRI-116

Capturing the complexities of the immune system in patients with advanced cirrhosis using a whole blood culture system reveals a robust inflammatory response to endotoxin stimulation

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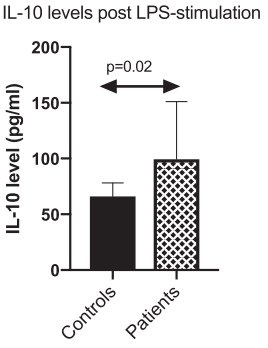
Background and aims: Systemic inflammation and cirrhosis-associated immune dysfunction (CAID) in cirrhosis contribute to the development of complications, infection and organ failure. CAID shifts from a pro-inflammatory phenotype in compensated cirrhosis to a state of immune paresis in decompensated cirrhosis and acute-on-chronic liver failure (ACLF).
To date, immune responses in cirrhotic patients have been studied *ex-vivo* using peripheral blood mononuclear cells or isolated immune cell subsets, poorly reflecting the complex interactions between circulating cells, cytokines and metabolites. The TruCulture® (Myriad RBM, Austin) system uses whole blood preserving physiological cellular interactions. It captures global immune cell activity at the time and place of sample collection, thus minimizing bias and variability introduced by cell subset isolation. This study aimed to assess the global immune response of patients with advanced cirrhosis, without evidence of sepsis or organ failure.
Method: 19 patients with cirrhosis (underlying aetiology of alcohol-related liver disease, non-alcoholic fatty liver disease or treated viral hepatitis) were recruited and compared to healthy controls (HC) (n = 7). Median Model for End-Stage Liver Disease (MELD) score was 14 (10-16). Exclusion criteria included other causes of liver disease, active infection, antibiotic or immunomodulator use, immunodeficiency, malignancy, organ failure and hepatorenal syndrome.
Whole blood was drawn directly into 3 TruCulture® tubes (unstimulated, pre-loaded with lipopolysaccharide (LPS) or heat-killed *E.Coli* 0111:B4 (HKEB)) and incubated in dry heat blocks at 37°C for 24 hours. A mechanical separator was used to stop the reaction. Analysis of the supernatant was performed in batch by multiplex assay.
Results: Patients with cirrhosis exhibited a robust pro-inflammatory response to HKEB and LPS with production of interferon (IFN) gamma 1, IFN alpha 2, IFN gamma 2/3 and IFN beta that was not seen in HCs. Patients had significantly higher IL-6 ($p = 0.005$) and IL-10 ($p = 0.02$) levels post LPS-stimulation compared to HCs. IL-10 production negatively correlated with MELD score ($r = -0.51$; $p = 0.02$).



Conclusion: In cirrhotic patients exposed to bacterial products, the response of the un-manipulated circulating compartment is characterised by an exaggerated inflammatory response orchestrated by IL-10, interferons, and IL-6. IL-10 is most significantly influenced by the degree of liver failure, suggesting it plays a key role in the inflammatory events associated with end-stage liver disease.

FRI-117

The gain of function mutation of SerpinB3 (SCCA-PD) is associated with the severity of portal hypertension and complications onset in patients with advanced liver disease

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Background and aims: Hepatic fibrosis and portal hypertension are determinants of clinical outcome in chronic liver disease and TGF-beta is the key fibrogenic cytokine involved in the activation of hepatic stellate cells. SerpinB3 (or SCCA1) can directly activate stellate cells and SerpinB3 transfected cells up-regulate TGF-beta, an effect that requires the integrity of the reactive site loop of this serpin. The polymorphic variant SCCA-PD presents a substitution in the reactive center loop (Gly351Ala), determining an improved anti-protease activity. Our aim was to assess the effect of SCCA-PD on TGF-beta expression *in vitro* and the clinical characteristics and outcome of a cohort of cirrhotic patients carrying or not this polymorphic variant.
Method: TGF-beta mRNA and protein levels were determined in Huh-7 and HepG2 cells transfected with either wild-type SerpinB3 (SCCA-WT) or SCCA-PD. TGF-beta expression was also evaluated in the human stellate cell line LX2 in response to recombinant SCCA-WT or SCCA-PD proteins. SCCA polymorphism was determined in 86 cirrhotic patients, prospectively followed up for a median period of 81 months. The results were analyzed in relation to clinical data at baseline and the onset of new complications during follow-up.
Results: Transfected cells showed increased TGF-beta, compared to controls and this finding was more prominent in cells transfected with SCCA-PD (SCCA-WT vs SCCA-PD, mRNA: $p = 0.027$, protein: $p = 0.009$). Accordingly, in LX2 cells recombinant SCCA-PD induced higher TGF-beta production, compared to SCCA-WT protein ($p = 0.01$). SCCA-PD was detected in 30% of the enrolled patients that at baseline presented more severe thrombocytopenia (60 vs. 109 x10^9/L, $p = 0.012$) and varices F2-F3 (36% vs. 15%, $p = 0.041$), despite having similar age to SCCA-WT patients (53 + 8 vs 55 + 9 years). Patients carrying SCCA-PD presented a higher MELD score (14 vs. 11 $p = 0.02$) and during follow-up they developed a higher number of cirrhosis complications (56% vs. 20.3%, $p = 0.016$). SCCA-PD (HR = 2.80, p =

0.021), MELD score (HR = 1.17; p = 0.002) and ascites (HR = 3.99; p = 0.003) were identified as independent predictors of cirrhosis complications by Cox regression analysis.
Conclusion: SCCA-PD is able to induce TGF-beta synthesis *in vitro* more efficiently than SCCA-WT. Patients with cirrhosis carrying the SCCA-PD polymorphism present signs of more severe portal hypertension and develop more frequently cirrhosis complications during follow-up, supporting a role of this polymorphic variant in liver disease progression.

FRI-118

Decreased cognitive performance is associated with reduced resting state connectivity and gray matter atrophy in patients with minimal hepatic encephalopathy

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Background and aims: Patients with minimal hepatic encephalopathy (MHE) show mild cognitive impairment associated with cognitive alterations and changes in connectivity. We assessed the relationship of abnormalities of resting-state functional connectivity (rs-FC) and gray matter (GM) volume with cognitive alterations and biochemical parameters associated to MHE. We also evaluated the relationship between memory in MHE and structural and functional connectivity (FC) changes in the hippocampal system.
Method: Twenty-six cirrhotic patients without MHE (NMHE), 13 with MHE, and 24 controls were cognitive assessed with a battery of psychometric tests. Atrophy was determined using Voxel-Based Morphometry and rs-FC was assessed by ICA analysis. Receiver operating characteristic (ROC) curves was performed to assess the diagnostic utility of rs-FC and GM reduction for the discrimination of patients with and without MHE. We also assessed the relationship between alterations in memory and the structural integrity and FC of the hippocampal system.
Results: MHE patients showed significant decrease of GM volume and lesser degree of rs-FC in different networks related to attention and executive functions as compared to controls and NMHE. There is a progressive reduction in rs-FC in the default mode network with the progression of cognitive impairment. MHE patients showed GM reduction in right frontal lobe, right insula and right cerebellum compared to NMHE patients. Alterations in GM volume and rs-FC correlated with cognitive tests.
MHE patients showed impairments in learning, memory, and recognition, compared to NMHE and controls. Cirrhotic patients showed reduced fimbria volume compared to controls. Larger volumes in hippocampus subfields were related to better memory performance in NMHE patients and controls. MHE patients presented lower FC between the L-presubiculum and L-precuneus than NMHE patients, and a reduced FC between L-presubiculum and subiculum seeds and bilateral precuneus, which correlated with cognitive impairment and memory performance.
Conclusion: Decreased cognitive performance is associated by reduced rs-FC and GM atrophy in MHE patients. These changes could have predictive value for detecting MHE.
Alterations in the FC of the hippocampal system could contribute to learning and long-term memory impairments in MHE patients. This study shows the association between alterations in learning and long-term memory and structural and FC disturbances in hippocampal structures in cirrhotic patients.
Supported by Ministerio Economía, Industria y Competitividad-Instituto Salud Carlos III (FIS PI15/00035; FIS PI18/00150) to CM; Ministerio Ciencia e Innovación (SAF2017-82917R) to VF; Consellería Educación Generalitat Valenciana (PROMETEOII/2014/033; PROMETEU/2018/051 to VF, CM), co-funded with European Regional Development Funds (ERDF).

FRI-119

Distinct salivary microbiome profile in patients with decompensated cirrhosis

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Background and aims: Patients (pts) with cirrhosis have altered salivary and enteric microbiome, characterized by the presence of dysbiosis. Invasion of the gut by oral bacterial species, may contribute to changes of gut microbiota and consequently to the development of decompensating events.
Method: We collected salivary samples from 28 pts with stable DeCi [20 males, MELD: 12 ± 4, Child-Pugh score: 7 ± 2, viral cause of cirrhosis: 11, hepatocellular carcinoma: 5 pts] along with 26 healthy controls. Exclusion criteria were active or recent infection, use of antibiotics or recent (last 6 months) decompensating event. DNA was extracted and next-generation sequencing of the samples was conducted on the Ion Torrent instrument.
Results: There was no difference between pts and controls in gender, age, or smoking. Overall, 14 phyla and 113 families were identified in the 54 study subjects; 13 phyla and 95 families in controls, 13 phyla and 103 families in pts. The most abundant phyla were Firmicutes (38.43%) and Bacteroidetes (29.88%); in controls Firmicutes accounted for 36.12% of total abundance and Bacteroidetes 31.96%, in patients Firmicutes accounted for 40.86% and Bacteroidetes 27.69%. In family level, Micrococcaceae detected to be more abundant in patients (p value = 0.024); Clostridiaceae (p = 0.004) and Clostridiales Family XIII Incertae Sedis (p = 0.0006), Sphingomonadaceae (p = 0.001), Enterobacteriaceae (p = 0.004), Spirochaetaceae (p = 0.025) were more abundant in controls. Beta diversity assessed by PERMANOVA test confirmed statistically significant differences in community composition between controls and pts (p = 0.008). PERMDISP2 procedure resulted to insignificant results (p = 0.32), which means that these differences are not due to dispersions of the samples within the groups. Sensitivity analysis on Boruta wrapper algorithm selected the most representative genera able to classify controls from patients; Rothia, Serratia, Atopobium, Butyrivibrio, Neisseria, Alloprevotella and Mogibacterium were indicative of DeCi (AUC = 0.815).
Conclusion: Abundances of bacterial taxa showed differences in DeCi pts compared to healthy controls. Salivary microbiome of pts was significantly different from controls. We first report a distinct salivary microbiome profile related to the presence of DeCi.

FRI-120

Structural liver disease rather than portal hypertension is the predominant factor for hepatic macrophage activation in patients with cirrhosis, portal vein thrombosis and idiopathic portal hypertension

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Background and aims: Macrophage activation is involved in the development and progression of chronic liver disease and may play a role in portal hypertension. We have demonstrated associations between portal hypertension and the macrophage activation markers soluble CD163 (sCD163) and soluble mannose receptor (sMR) in patients with liver cirrhosis. It is unknown whether this association is only seen in the presence of structural liver disease or also present in patients with non-cirrhotic portal hypertension e.g. idiopathic portal hypertension (IPH) or portal vein thrombosis (PVT). We aimed to investigate the association between macrophage activation markers and portal hypertension in IPH patients and PVT patients with and without cirrhosis.
Method: In a cross-sectional design, we studied plasma levels of sCD163 and sMR in 26 patients with IPH, 20 patients with non-cirrhotic PVT, 17 patients with cirrhosis without PVT, 31 patients with cirrhosis and PVT and 15 healthy controls. All patients and healthy controls had liver vein catheterisation for measurement of hepatic venous pressure gradient (HVPG) and additional clinical and biochemical data was obtained.
Results: Median sCD163 concentration was 1.51 mg/L (95%CI: 1.24; 1.83) in healthy controls, 2.16 mg/L (1.75; 2.66) in patients with IPH and 1.96 mg/L (1.49; 2.56) in patients with non-cirrhotic PVT. There was no difference between IPH and non-cirrhotic PVT patients; but IPH patients had higher levels than controls ($p < 0.05$). These groups had all significantly lower sCD163 levels compared to patients with cirrhosis without PVT (5.19 mg/L (4.18; 6.46)) and cirrhosis with PVT (6.31 mg/L (5.16; 7.73)) ($p < 0.01$, all). Similar significant differences were observed for the sMR. There was no correlation between HVPG and sCD163. Soluble MR was only correlated to HVPG in patients with cirrhosis with PVT (Rho = 0.455, P = 0.01).
Conclusion: Soluble CD163 and sMR levels were higher in patients with cirrhosis with or without PVT compared to patients with IPH and patients with non-cirrhotic PVT. This suggests that hepatic macrophage activation and elevated sCD163 and sMR levels are primarily driven by the structural liver disease per se and not portal hypertension.

FRI-121
Portal hypertension in nodular regenerative hyperplasia is caused by vascular remodeling with extensive regression of portal vein branches

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Background and aims: Non-cirrhotic portal hypertension (NCPH) is the main complication in nodular regenerative hyperplasia (NRH). The pathophysiology of NCPH remains unclear. Animal studies suggest that remodeling of the sinusoidal vasculature may induce NCPH. However, sinusoidal changes cannot fully explain NCPH since most NRH patient with NCPH have (false) normal hepatic venous pressure gradients (HVPG) suggesting an additional pre-sinusoidal component for the increased vascular resistance in the portal vein (PV). This concept is supported by biopsy findings in NCPH patients, which often show malformed portal vein branches in the portal tracts. We therefore hypothesize that vascular remodeling of the pre-sinusoidal PV vasculature is the driver in the development of NCPH and represents the site of hemodynamic resistance.
Method: Notch1−/− MxCre mice developing NRH with NCPH (histologic verification of NRH by reticulin/HE/CD34, intravascular PV pressure measurement) were used (Dill et al. Gastroenterology). Whole livers of mice (NRH vs. C57BL/6 controls, n = 4 each) were perfused using a novel polymerizing contrast agent (µAngiofil®) and scanned *ex vivo* by latest generation high-resolution microangio-computed tomography (HR microCT, voxel size 5 um; SkyScan, Bruker). MicroCT-based 3-dimensional (3D) reconstruction was then generated to analyze the complete PV vasculature. Next, filament tracer-based analysis (Imaris®) was used for quantitative and

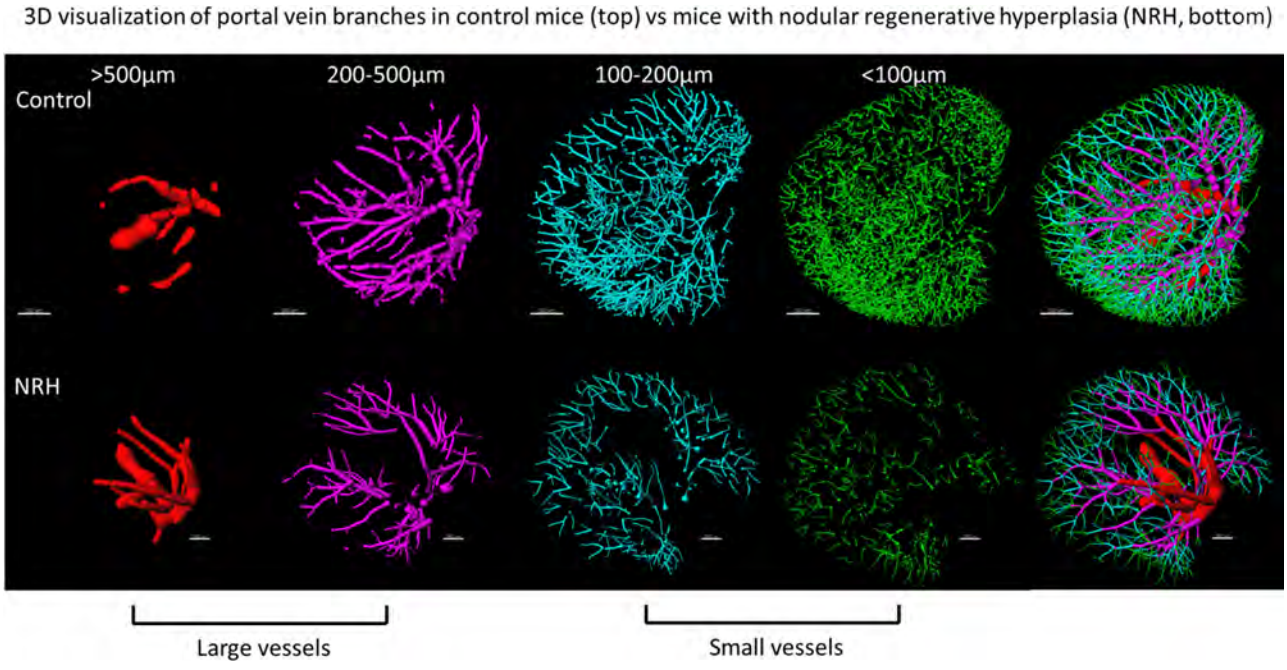

Figure: (abstract: FRI-121)

qualitative morphometry of the vasculature followed by hemodynamic analysis *in silico*.
Results: Whole liver microCT-based imaging allowed detailed imaging of the complete PV vasculature down to pre-sinusoidal PV branches. Subsequent 3D visualization revealed a highly aberrant vascular network in NRH mice. Filament tracer analysis showed extensive reduction (figure) in the number of PV branches by 30%, massive decrease by 80% of small vessels (< 200 um diameter) and terminal (pre-sinusoidal) PV branches as well as a significant reduction of the cumulative PV vascular diameter by 64% leading to increased vascular resistance by hemodynamic analysis located in the pre-sinusoidal PV branches.
Conclusion: Whole organ HR microCT allows unprecedented detailed analysis of the complete PV vasculature and insight into the pathogenesis of vascular liver diseases. NRH mice show substantial vascular remodeling with massive regression of portal vein branches leading to increased pre-sinusoidal vascular resistance and portal hypertension.

FRI-122

Sarcopenia improves after sustained virologic response to DAAs in chronic hepatitis C patients with cirrhosis, but not in those who develop HCC

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Background and aims: Sarcopenia is frequently observed in cirrhotic patients and is associated with increased morbidity and mortality. In NASH patients, sarcopenia is associated with insulin resistance, and parallels the progression of liver fibrosis and the risk of developing HCC. Data are scanty in HCV cirrhotic patients. We assessed the impact of HCV clearance on sarcopenia in DAA treated patients with cirrhosis.
Method: The loss of skeletal muscle mass was evaluated by measuring the L3 skeletal muscle index (L3SMI) in 23 consecutive patients (median age 68.9 years, range:42.5-80.8) with HCV (genotype 1a: 5; 1b: 11; 2: 1; 3: 5 and 4: 1) compensated cirrhosis (MELD:6-12) who had CT scans available within 6 months pre-therapy (PT) with DAAs and 6-18 months after completion. The cut-off value used to define sarcopenia was 50 cm^2/m^2 in males (16) and 39 cm^2/m^2 in females (7). Liver function test and metabolic parameters (Cholesterol, Glucose, Insulin, HOMA index, BMI, NAFLD score) were measured at PT, end of therapy (EOT) and at week 48 of post-treatment follow-up.
Results: All patients achieved SVR with 24 week SOF+LDV (17) or SOF+DCV (7) treatment. Twelve patients had previously treated HCC: in 8 of them HCC recurred during or after DAAs therapy. In other 4 patients HCC occurred de novo. In post-treatment follow-up a significant increase of serum cholesterol ($p = 0.038$), and a decrease of BMI ($p = 0.038$) and of NAFLD score ($p = 0.012$) were observed. Sarcopenia was present in 19 (82.6%) patients before and in 14 (60.9%) after DAAs ($p = 0.014$). Overall, median muscle density improved post-DAAs [36.5 (11.4-55.6) pre-DAAs vs 41.0 (20.6-65.9) post-DAAs, $p = 0.003$], increasing in 19 (82.6%) patients. Muscle density increased significantly ($p = 0.003$) in patients who did not develop HCC, remaining stable in those developing HCC (Figure). HCC developed in 0/4 patients without PT-sarcopenia, in 8/15 (53.3%;1 de novo, 7 recurrent) with PT-sarcopenia who increased muscle density and in 4/4 (100%; 3 de novo, 1 recurrent) with PT-sarcopenia who decreased muscle density ($p = 0.018$).

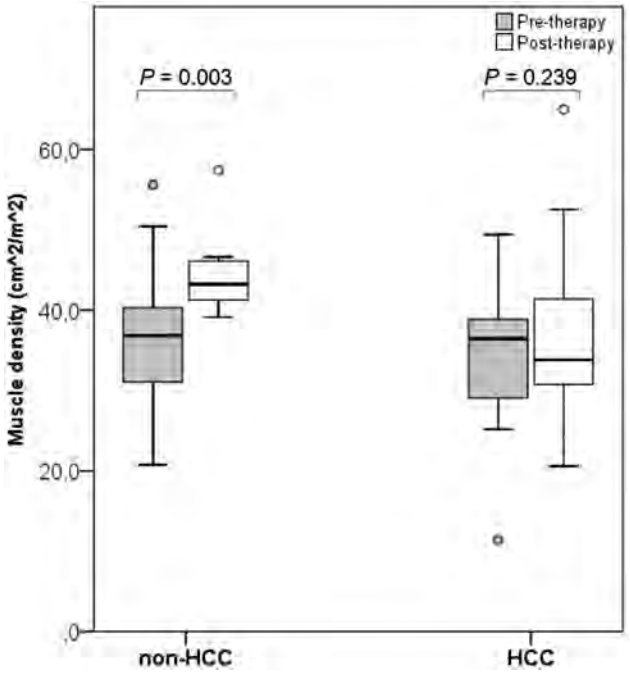

Figure: Muscular density by time-point (pre/post-DAAs) and HCC status

Conclusion: DAAs therapy in cirrhotic patients induces a significant increase of muscle density, even if reverses sarcopenia only in a minority (26.3%) of them within 6-18 months from EOT. The lack of muscle density increase is associated with a higher incidence of HCC. Further studies are required to confirm our observation and to understand the underlying physiopathology.

FRI-123

Transcriptomic and functional analysis of Kupffer cells in patients with cirrhosis reveals a tumour associated macrophages profile and an impaired immune response that are associated with increased risk of infections

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Background and aims: Patients with decompensated cirrhosis are at high risk of bacterial infections. During homeostasis, resident macrophages from the liver (Kupffer cells [KCs]) play a key role in the phagocytosis of circulating bacteria. The aim of this study was to characterize the transcriptomic and functional profile of KCs in liver cirrhosis and their relationship with the risk of infections.
Method: KCs were isolated from livers of patients with cirrhosis ($n = 4$) and controls ($n = 5$) and the profile was determined by RNAseq. Molecular pathways of KCs were analysed through GSEA and GO. Protein-protein interaction network (PPIN) was generated with the top 100 de-regulated genes from KCs of cirrhotic compared to KCs from control livers. Protein analysis was performed by FACS from KCs from patients with cirrhosis ($n = 8$) and controls ($n = 6$). Pro-inflammatory response was evaluated in vitro with LPS in KCs from patients with cirrhosis ($n = 5$) and controls ($n = 5$). In vivo phagocytic

capacity of KCs by SPECT with 99mTc-phytate in patients with cirrhosis (n = 21) and in a control group (n = 5).
Results: The expression profile of KCs is different depending on whether they reside in a cirrhotic or control liver. GO analysis revealed that pathways differentially expressed in KCs from cirrhotic livers are involved in immune response. GSEA showed that KCs from patients with cirrhosis have greater expression of M1 markers with respect to M2 (NES: 1.68, p < 0.01 vs. NES: 0.8, p < 0.01). PPIN revealed that most connected nodules corresponded to tumour associated macrophages (TAM) markers, associated with immunosuppression. Over-expression of TAM markers (PDL1, MARCO, CD80, CD163) in cirrhotic KCs was confirmed by FACS. KCs from cirrhotic livers showed a reduced expression of pro-inflammatory cytokines (IL6, CCL20, TNFα) in response to LPS. In vivo phagocytic capacity of KCs was reduced in patients with cirrhosis as shown by a decrease in hepatic uptake and blood clearance of 99mTc-phytate. Patients who presented infections within a 3-month follow-up had an impaired baseline phagocytic capacity (liver/spleen +bone marrow uptake ratio 0.29 vs 0.88, p = 0.02).
Conclusion: KCs from patients with cirrhosis have a TAM profile, with an altered functionality consistent of a reduced pro-inflammatory response and poor phagocytic capacity, which is associated with an increased risk of infections. Restoration of the immune profile and response of KCs may be a good strategy to prevent infections in patients with cirrhosis.

FRI-124
Increased prevalence of low-frequency and rare NOD2 variants in patients with liver cirrhosis
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Background and aims: In recent years, genome-wide association studies (GWAS) have robustly identified common genetic risk variants for cirrhosis of various etiology (Karlsen and Lammert J Hep 2015). However, heritability is not fully explained, since low-frequency and rare variants are typically missed by GWAS (Auer et al. Genome Med 2015). Hence, we explored the association of common low-frequency and rare variants in the Nucleotide-binding oligomerization domain containing 2 (*NOD2*) gene with cirrhosis, investigating the three known risk variants and two novel single nucleotide variants (SNV) recently identified by high-resolution mapping (Huang et al. Nature 2017) in patients being screening for the INCA trial (Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites, EudraCT 2013-001626-26).
Method: In 17 tertiary care hepatology referral centers throughout Germany, potential study participants were genotyped for the three *NOD2* (p.R702W, p.G908R and c.3020insC) and the two additional variants p.N289S and rs72796367 (intronic), using PCR-based allelic discrimination assays. Prevalence rates and allelic frequencies of the *NOD2* variants were correlated with clinical phenotypes in patients with compensated and decompensated cirrhosis.
Results: Overall, 2, 952 patients were identified and genotyped for the five *NOD2* variants. The most common risk variant was p.R702W (allele frequency 5.8%, 340 patients), followed by c.3020insC (3.6%, 211 patients), and p.G908R (1.8%, 108 patients). The allele frequencies of the rare variants were 2.8% (rs72796367, 167 patients) and 1.0% (p.N289S, 57 patients). Within a subgroup of patients recruited at the academic medical centers Homburg and Halle (n = 750), the prevalence of these variants did not differ when stratified for Child-Pugh classes A-C, compensated/decompensated cirrhosis, or liver stiffness measurements (transient elastography).
Conclusion: According to available data in healthy adults, the *NOD2* variant allele frequencies in the ExAC and dbSNP databases are 3.5% (p.R702W), 2.0% (c. 3020insC), 1.5% (p.G908R), 0.7% (rs72796367) and 0.6% (p.N289S). In our patients with liver cirrhosis treated in tertiary care hepatology centers, the prevalence of the three common *NOD2* risk variants as well as p.N289S is about twice as high as the frequency in the general population, and about four times higher for SNV rs72796367. Investigation of the molecular mechanisms of this association, in particular pathological bacterial translocation and alteration of gut microbiota, is warranted.

FRI-125
The phase angle determined by bioelectrical impedance is a predictive factor of hospitalization, falls and mortality in patients with cirrhosis
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Background and aims: Patients with cirrhosis often present alterations in body composition. The measurement of the phase angle (PA) is a quick method for the evaluation of the corporal composition calculated from the resistance (linked to the state of hydration of tissues) and the reactance (linked to the cellular mass). The PA can be a more precise tool than other nutritional, biochemical or anthropometric parameters to assess the frailty and prognosis in patients with chronic diseases. However, data in patients with cirrhosis are still very scarce. The aim of our study was to analyze the prognostic value of the PA to predict events related to frailty (hospitalization, falls and mortality) in patients with cirrhosis.
Method: Outpatients with cirrhosis were consecutively included, and the PA was determined by bioelectrical impedance with the BIA 101 system (Bodygram TM 1.31, Akern). The measurement was made after 10 minutes of rest in supine position with 4 conventional electrodes: 2 placed on the hand and 2 on the contralateral foot. Patients were prospectively followed to determine the incidence of hospitalizations, incidence of falls, and mortality.
Results: We included 100 patients (age 63.8 ± 9.3, men 68%, alcohol etiology 63%, frailty according to the Fried Index 25%, MELD 9.0 ± 2.5 and PA 5.4 ± 1.5°). During a mean follow-up of 21.1 ± 5.9 months, 30% of patients required hospitalization, 23% presented falls and 15% died. In the multivariate analysis, the PA ≤ 4.6° and the degree of comorbidity (Charlson) were independent predictive factors of hospitalization (HR 3.787, 95%CI 1.437-9.984, p = 0.007, and HR 1.713, 95%CI 1.038-2.828, p = 0.035, respectively). The PA ≤ 4.6° was the only predictive factor for falls (HR 4.755, 95%CI 1.831-12.343, p = 0.001), and serum sodium and PA ≤ 4.6° were predictive factors of mortality (HR 0.728, 95%CI 0.606-0.876, p = 0.001, and HR 9.165, 95% CI 1.894-44.349, p = 0.006, respectively). Patients with PA ≤ 4.6° (n = 31) showed a higher probability of hospitalization, falls and mortality at 2-years follow-up than patients with PA > 4.6° (n = 69) (36% vs 11%, p = 0.002, 44% vs 11%, p < 0.001, and 25% vs 3%, p = 0.001, respectively). The PA showed a positive correlation with muscle strength and

testosterone concentration; and a negative correlation with Fried Index, MELD, albumin, creatinine and cystatin C.
Conclusion: The phase angle is a predictive factor of hospitalization, falls and mortality in outpatients with cirrhosis.

FRI-126
Innovative potential biomarkers in spontaneous bacterial peritonitis from ascitic fluid
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Background and aims: Spontaneous bacterial peritonitis (SBP), a bacterial infection of ascitic fluid without intra-abdominal, surgically treatable focus, is a severe complicationindecompensatedliver cirrhosis with a 1-year-mortality of 70%. Translocation of intestinal bacteria from the gut to mesenteric lymph nodes into the ascitic fluid is regarded to be the underlying process. Diagnosis of SBP is assured with detection of > 250 polymorphonuclear (PMN)cells per µl. Since patients need an immediate antibiotic treatment, molecular markers indicating a beginning SBP need to be identified to improve early diagnosis of SBP.
Method: To identify novel potential biomarkers for SBP, ascitic fluid was collected from patients suffering liver cirrhosis. Protein levels of lactoferrin, C3a, IP-10, IL-6, IL-8 and IL-10 within ascitic fluids were determined by ELISA.
Results: In total, 69 ascitic fluid samples from 41 patients between 36 and 77 years of age (87% male, 22% female) were analyzed. Genesis of liver cirrhosis was alcohol-toxic (58.5%), cryptogenic (19.5%), nutritiv-toxic (7.3%), viral (4.9%), autoimmune (2.4%), PBC (2.4%), non-alcoholic steatohepatitis (2.4%) and Budd Chiari Syndrome (2.4%). In 11.6% of the samples diagnosis of SBP was confirmed. Lactoferrin levels in ascitic fluids of SBP samples (mean 1006 ng/ml) were higherthan in ascitic fluids without SBP (mean 75ng/ml). Follow-up samples indicated that lactoferrin concentrations were elevated in early stages of SBP and coincided with the course of the disease and therapeutic response.C3a levels also correlated with the course of disease, but were reduced in infected ascitic fluids (mean 511ng/ml) compared to non-SBP samples (mean 975 ng/ml). IP-10 was detected in all samples, but did not display any correlation with disease activity. Although relevant amounts of cytokines IL-6, IL-8 and IL-10 were detected in ascitic fluid of liver cirrhosis patients, an association of these parameters with early onset of SBP was not observed.
Conclusion: Lactoferrin and C3a levels in ascitic fluid of liver cirrhosis patients correlate with the onset and course of SBP. Notably, a lower PMN-cutoff resulted in an enhanced specificityfor SBP. High levels of inflammatory molecules and cytokines highlight the tremendous inflammatory activity in ascitic fluids of liver cirrhosis patients. These results put SBP in a novel perspective and provide options for earlier diagnosis and treatment.

FRI-127
Measuring dynamics of portal pressure and vital parameters in conscious rats using real-time telemetry
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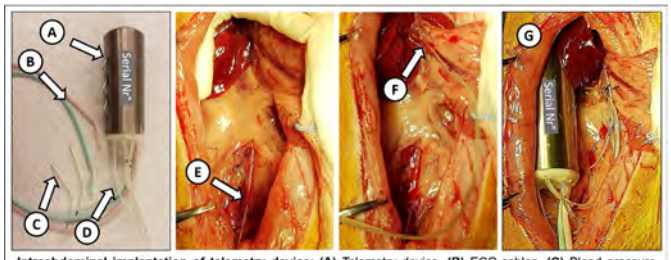
Background and aims: Portal pressure represents an excellent integrative readout for severity of liver disease. Thus, an improvement of portal hypertension is an accepted surrogate parameter in clinical trials. In cirrhotic rodent models, evaluation of the portal hypertensive syndrome is usually performed under anaesthesia at a terminal end point due to invasive measurements. Thus, we aimed to establish a system for telemetric pressure measurements in conscious cirrhotic rats.
Method: After median laparotomy, we implanted a telemetric device (PPBTA-L2, TSE Systems) into the abdomen of Sprague-Dawley rats of 350-400g bodyweight (see Figure). One solid state pressure tipped sensor was implanted into the abdominal aorta, while the second was placed in the portal vein. Intravascular pressure probes were secured with tissue glue and specifically aligned to compensate for tension forces due to body movements and intestinal peristalsis. Two ECG leads were subcutaneously sewed to the thoracic and abdominal wall to measure heart rate. Moreover, temperature and X/Y/Z-axis activity were recorded via integrated sensors. In a subgroup, the bile duct was ligated to induce cholestatic cirrhosis. Portal and arterial pressure, heart rate, temperature and activity level were longitudinally monitored every 6 hours.



Intraabdominal implantation of telemetry device: **(A)** Telemetry device, **(B)** ECG-cables, **(C)** Blood pressure probes, **(D)** Temperature probe **(E)** Blood pressure probe in the abdominal aorta, **(F)** Blood pressure probe in the portal vein **(G)** Implanted telemetry device.

Results: Surgical implantation required microsurgery skills and yielded in high success rates (85%). Healthy rats presented a long-term survival of > 8 weeks without complications. In healthy rats, mean arterial pressure (90 ± 9 mmHg), heart rate (311 ± 33 bpm) and portal pressure (9.7 ± 2.8 mmHg) were within physiological ranges and followed a circadian rhythm. In bile duct ligated rats, experiments are currently ongoing. First readouts showed a steady increase in portal pressure.
Conclusion: Telemetric hemodynamic measurements allow monitoring of dynamic and circadian changes of portal pressure, arterial pressure and heart rate in cirrhotic rats in real-time without anaesthesia. This new method requires precise surgical skills, yet facilitates a detailed long-term follow-up and provides a setting for studying pharmacodynamics of novel compounds for the treatment of portal hypertension. On top, it supports the 3Rs by methodological refinement and reduction of required animals if multiple timepoints need to be analysed.

FRI-128
Mesenchymal stem cells cultured in hypoxic conditions had multi-directional effects on mice with liver cirrhosis through prostaglandin E2 and miR210 production
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Background and aims: Mesenchymal stem cells (MSCs) are easily expanded; can be acquired from medical waste such as adipose and umbilical cord tissues; are influenced by culturing conditions; and have multiple functions, such as anti-inflammatory, anti-oxidative, and anti-fibrosis effects as well as angiogenesis. We analyzed the multi-directional effects of MSCs cultured in hypoxic conditions and their underlying mechanisms in treating liver cirrhosis model mice.
Method: Human bone marrow-derived MSCs cultured in hypoxic (5% O_2; hypo-MSCs) and normal oxygen conditions (21% of O_2; nor-MSCs) were compared by cap analysis of gene expression (CAGE), with or

without serum from liver cirrhosis patients. The therapeutic effects of MSCs such as serum liver enzymes, fibrosis regression and oxidative stress in the liver were evaluated by administering 1×10^6, 2×10^5, or 4×10^4 cells/mouse of hypo- and nor-MSCs from the tail vein into a CCl_4-induced liver cirrhosis model mouse. Intra-vital imaging was performed using a two-photon excitation microscope to confirm different migration paths of the MSCs to the liver.

Results: CAGE analysis revealed that mRNA expression levels of prostaglandin E synthase *Ptges* and miR210 in hypo-MSCs were significantly higher than those in nor-MSCs. *In vivo* analysis revealed that, while both hypo-MSCs and nor-MSCs reduced the serum levels of ALT, oxidative stress, and fibrosis compared to the control mice in a dose-dependent manner, hypo-MSCs had more therapeutic effects compared to nor-MSCs. We further confirmed this by an *in vitro* study wherein hypo-MSCs had effectively changed the polarity of macrophages to an anti-inflammatory phenotype via prostaglandin E2 (PGE2) and miR210 reduced the rate of apoptosis of hepatocytes. Intra-vital imaging after administration showed that both hypo- and nor-MSCs were trapped mainly in the lungs and minor population of both cells had migrated into the liver, with no difference between their distributions.

Conclusion: Hypo-MSCs had a greater therapeutic effect, mediated by PGE2 and miR210 production, compared to nor-MSCs. These results revealed that MSCs can be manipulated to induce better therapeutic effects in liver cirrhosis, which can be used for effective cell therapy in the future. MSCs produce multiple factors that can affect multi-directional effects; that Is MSCs are working as "conducting cells" in the liver cirrhosis.

FRI-129

A defect in the Nrf2/HO-1 pathway and Nox2 activation results in regulatory T cell mitochondrial dysfunction in alcohol related cirrhosis

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Background and aims: Alcoholic liver disease is a major cause of chronic liver disease in the western world with mortality continuing to rise. The molecular and cellular events underlying the progression of liver disease remain poorly understood, with immune-mediated injury and oxidative stress highlighted as factors driving disease progression.

The effects of oxidative stress are mediated, in part, by nuclear factor E2-related factor 2 (Nrf2), a transcription factor regulating an array of antioxidant genes in the liver. Here we report a previously unrecognized functional deficit in circulating regulatory T cells (Tregs) isolated from patients with alcohol-related cirrhosis (ARC), correlating with disease severity. We propose a mechanism to explain this defect, showing that a dysregulated Nrf2 pathway and subsequent NADPH oxidase 2 (Nox2) activation leads to Treg mitochondrial dysfunction and loss of suppressor function.

Method: Tregs were isolated from peripheral blood of patients with ARC (abstinent > 6 months) and healthy controls (HC). CFSE dilution assay was used to assess Treg suppressor function. Western blots/ELISA were used to quantify Nrf2 and Heme Oxygenase-1 (HO-1) expression. Imagestream® assessed Nrf2 translocation. Tregs isolated from spleens of Nrf2 KO/WT mice were assessed by flow cytometry and CFSE dilution assay. Intracellular reactive oxygen species (ROS) production, lipid peroxidation and apoptosis rate of ARC Tregs were determined by flow cytometry. The Seahorse Platform was used to measure glycolysis (extracellular acidification rate; ECAR) and oxidative phosphorylation (oxygen consumption rate; OCR) post 24hrs stimulation with anti-CD3/CD28. Nox2 activation was studied by confocal microscopy, assessing the co-localization of p47phox and gp91phox.

Results: ARC Tregs displayed reduced suppressor function with a lower expression of HO-1 and a defect in Nrf2 transnuclear migration as compared to HC Tregs. In agreement, Tregs isolated from $Nrf2^{-/-}$ mice displayed reduced expression of regulatory markers and suppressive function compared to WT mice. Additionally, culture of HC Tregs with a specific inhibitor of HO-1 reduced their suppressive function.

ARC Tregs also demonstrated higher baseline ROS production, lipid peroxidation and apoptosis rate as compared to HCs and exhibited a higher ECAR and OCR, after oligomycin injection, indicative of mitochondrial uncoupling. Furthermore, we demonstrate activation of Nox2, secondary to increased intracellular heme build up, as a mechanism for the intracellular ROS production and mitochondrial dysfunction [figure].

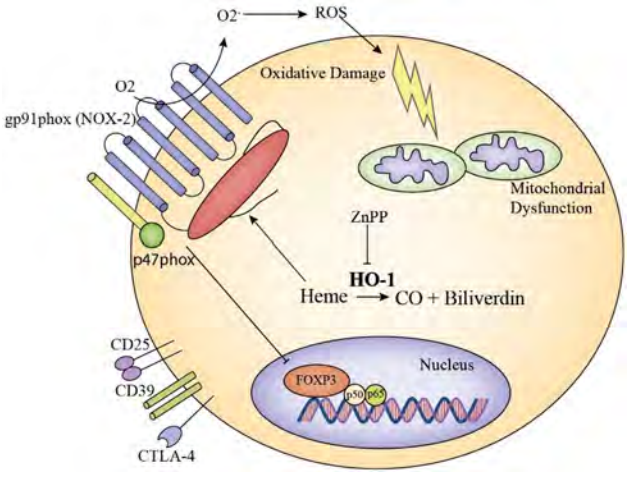

Figure: Dysregulated Nrf2/HO-1 pathway leads to build up of intracellular heme, activation of Nox2 and Treg mitochondrial dysfunction

Conclusion: Modulation of the Nrf2 pathway provides a therapeutic target to enhance Treg function in order to halt/prevent liver disease progression.

FRI-130

Changes in the extracellular matrix of the heart and the liver assessed by MRI with T1-mapping are closely linked in cirrhosis: Is inflammation the shared pathway?

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Background and aims: Changes in the composition of the hepatic extracellular matrix are well-established in cirrhosis. Novel MRI with T1-mapping and extracellular volume (ECV) quantification directly reflects intrinsic tissue changes. Recently, we reported an increased cardiac ECV in patients with cirrhosis reflecting alterations in the myocardial extracellular matrix. The relation between hepatic and cardiac ECV has never been addressed. Our aim was therefore simultaneously to investigate changes in liver ECV and myocardial ECV in patients with cirrhosis, and to study the role of inflammation.

Method: We performed a prospective study including 52 patients with cirrhosis (8 Child class A/37 Child B/7 Child C) and 14 healthy controls. Contrast-enhanced MRI with T1-mapping and ECV quantification was performed with a 3.0-Tesla scanner and myocardial ECV and liver ECV were calculated. Inflammatory markers (IL-6, IL-8, IL-

1b, IL-18, TNF-α and stromal-cell derived factor 1α (SDF1α) were measured from plasma samples. In the controls, contrast-enhanced MRI alone was performed.
Results: Liver ECV and myocardial ECV, both, were significantly increased in cirrhotic patients compared to controls (liver ECV: 44.4 ± 11% vs. 33.7 ± 7%, p = 0.001 and myocardial ECV: 31.2 ± 6 vs. 27.4 ± 3%, p = 0.04) and were individually correlated (r = 0.484, p = 0.001). Liver ECV was correlated with Child score (r = 0.421, p = 0.003), MELD (r = 0.410, p = 0.004), IL-6 (r = 0.37, p < 0.01), and SDF-1α (r = 0.56, p < 0.001). Similarly, myocardial ECV significantly correlated with Child score, MELD, IL-6 and IL-8.
Conclusion: Cardiac ECV as well as liver ECV in cirrhosis are increased and mutually related. This may reflect altered extracellular matrix composition of both the heart and the liver and low-grade inflammation most likely seems to be a common pathway for these changes.

Viral Hepatitis A, B, C, D, E: Immunology

FRI-131
Impact of HBsAg level on cellular immune responses in HBeAg negative patients with chronic hepatitis B virus infection

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Background and aims: Worldwide 250 million people are persistently infected with hepatitis B virus (HBV) leading to 686.000 deaths annually. The level of hepatitis B surface antigen (HBsAg) produced by HBV-infected hepatocytes could have an immunomodulatory role in HBV infected patients. However, the correlation between HBsAg level and HBV-specific T cell immune responses in patients with chronic HBV (CHB) and HBeAg negative has not been well defined. We investigated HBV-specific immune responses in HBeAg negative patients with different levels of HBsAg during the natural course of chronic hepatitis B.
Method: 44 HBeAg negative patients were categorized into 4 groups based on their HBsAg level (HBsAg < 100 IU/ml, HBsAg 100–999 IU/ml, HBsAg 1, 000-9, 999 IU/ml, HBsAg ≥ 10, 000 IU/ml). PBMCs were isolated from these patients and different subsets of immune cells were phenotypically characterized using 14 color flow cytometry. Furthermore, IFNγ+ HBV-specific T cell responses were measured after in vitro culture with overlapping peptides covering polymerase, surface and core of HBV genotype D in the presence or absence of anti-PD-L1 antibody.
Results: Patients with different levels of HBsAg showed similar frequencies of memory, naïve and effector T cells, γδ T cells, Treg cells, MAIT cells, B cells, NK cells, monocytes and DCs. Interestingly, the frequency of γδ T cells, Treg cells and CD1c- myeloid DCs was significantly increased in CHB patients compared to healthy individuals.
Stimulation of PBMCs with HBV overlapping peptides induced core- and polymerase-specific T cell responses. However, surface-specific T cell responses were hardly detectable. We observed a trend towards higher HBV-specific T cells in patients with HBsAg < 100 IU/ml. In patients with HBsAg ≥ 10, 000 IU/ml a high variability of T cell responses were detected. Interestingly, in these patients stronger T cell responses were associated with young age, female gender and low HBV DNA. In general, CD4+ T cell response to in vitro stimulation with HBV overlapping peptides was stronger than CD8+ T cell responses. Blocking the PD-1/PD-L1 pathway during in vitro culture significantly increased the core-specific T cell response in patients with HBsAg < 100 IU/ml.
Conclusion: Our data suggests that HBsAg level per se may have only a minor impact on the cellular immune responses. Patients with HBsAg < 100 IU/ml, showed slightly stronger T cell responses to in vitro HBV peptide stimulation especially after using checkpoint inhibitors. Therefore, patients with low HBsAg levels may demonstrate better responses to immune-modulatory treatment.

FRI-132
In vitro modulation by TLR8 agonist GS-9688 of multiple regulatory cell types in patients with chronic hepatitis B

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Background and aims: HBV-specific T cell responses are characterised by functional exhaustion and premature deletion. Immunosuppressive cell types targeting this antiviral T cell response include granulocytic myeloid-derived suppressor cells (gMDSC), CD4 + regulatory T cells (Tregs), and regulatory TRAIL + NK cells. Signalling through different toll-like receptors (TLR) induces selective cytokine profiles capable of differentially modulating immune cell subsets. Here we have tested the impact of a selective small molecule agonist of TLR8 (GS-9688), currently in Phase 2 trials for the treatment of chronic HBV infection (CHB), on these three different regulatory populations and on HBV-specific CD8 + T cells *in vitro*.
Method: PBMC obtained from a cohort of CHB patients were treated with 1-500 nM GS-9688 for 2-7 days. Cytokine responses were measured by luminex assay. Sixteen-colour flow cytometry was used to analyse changes in the frequency and phenotype of gMDSC (CD11bhighCD33+HLADR-CD14-CD15+, n = 14 CHB patients), Tregs (CD4+CD25hiCD127loFoxp3+, n = 8 CHB patients), NK cells (CD3-CD56+, n = 20 CHB patients) and HBV-specific CD8+ T cells (binding a panel of HLA-A2/peptide dextramers, n = 12 CHB patients).
Results: In line with previous studies, GS-9688 induced cytokines in PBMC cultures (e.g. TNF-α, IFN-γ, IL-12p70 and IL-18) with the potential to modify regulatory cell subsets. Consistent with this cytokine profile, GS-9688 treatment induced gMDSC to switch to a more mature and less suppressive phenotype, resulting in a > 50% reduction in the frequency of this regulatory cell type ($p < 0.001$). Similarly, GS-9688 treatment induced a dose-dependent reduction in the frequency of conventional Tregs ($p < 0.05$). In contrast, GS-9688 triggered dose-dependent activation of CD56bright and CD56dim NK cells, and a rapid upregulation of their expression of the death ligand TRAIL ($p < 0.05$). Despite this, HBV-specific CD8+ T cell frequencies remained stable, suggesting they were protected from NK cell TRAIL-mediated deletion in the presence of GS-9688.
Conclusion: Overall, these in vitro data suggest that GS-9688 has the potential to reduce the suppressive activity of regulatory populations in the liver that collectively limit the antiviral response of HBV-specific T cells. Further studies will explore how HBV-specific T cells are protected from deletion by the GS-9688-driven expansion of TRAIL+ NK cells and whether these changes are recapitulated using intrahepatic lymphocytes.

FRI-133

HCV neutralizing antibody responses in natural infections mapped by metric multi-dimensional scaling reveals new insights into HCV antigenicity and broadly neutralzing antibodies

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Background and aims: Characterization of HIV patients with elite neutralizing antibody responses led to discovery of broadly neutralizing antibodies and their epitopes, thus promoting vaccine design. Here we aimed to develop an HCVcc-based screening panel for identification of elite neutralizers.
Method: Polyclonal immunoglobulins from more than 100 patients infected with HCV genotype 1-6 were purified and HCVcc neutralization was quantified across 14 isolates representing 6 viral genotypes. Metric multidimensional scaling was used for HCV neutralization cartography to plot neutralization maps. Various normalization methods and weighted-stress schemes across different dimensions were explored and leave-one-out (LOO) errors were computed to select the best normalization/weighing method. K-means clustering combined with elbow method, silhouette error, and gap statistics were employed to guide virus clustering and selecting representative strains.
Results: Vast differences in neutralization sensitivity of HCV strains were detected, with Jc1 (GT2) being most resistant and SA13 (GT5a) being most sensitive. Viruses mapped to six neutralization clusters, in part composed of viruses from different subtypes and genotypes. There was no correlation with the genetic distance of strains, suggesting that neutralization clustering differs from sequence-based clustering. Antibodies from GT1 infected individuals formed a compact cluster whereas antibodies from other genotypes were intermixing and varied broadly in neutralization capability.
Conclusion: Representative isolates from six neutralization clusters reconstructed the neutralization space with even slightly lower LOO error than the full panel of isolates. Viruses representing these clusters are well suited for high resolution profiling of virus-antibody neutralization and they may reflect viral functional and antigenic properties important to consider in HCV vaccine design.

FRI-134

Comparative analysis of intrahepatic and peripheral chemokine responses in chronic hepatitis B, C and D in vivo

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Background and aims: While the important role of chemokines in disease progression has been analysed for several liver diseases, less is known about the differences in chemokine expressions between hepatitis B and D.
Method: Serum levels of various chemokines were analysed by Bead Conjugation Assay in the sera of 29 chronic hepatitis B (CHB) patients and compared to other hepatitis virus infections (21 HDV, 12 HCV) and 16 healthy controls. To analyse the intrahepatic chemokine expression in human hepatocytes, chemokine levels were analysed in the livers of chimeric uPA/SCID/beige (USB) mice measuring gene expression of human hepatocytes using species-specific RT-qPCR assays.
Results: Proinflammatory chemokines CXCL8, 9, 10 and 11 as well as CCL5 were highly induced in human hepatocytes of HDV (7.7-, 5.4-, 68.1-, 82.5- and 86.1- fold median induction) and HCV infected (62.1-, 10.2-, 696.7-, 525.6- and 154.9-fold) USB mice. In comparison, only mild (CXCL10: 8.7- and CXCL8: 3-fold) or no significant inductions (CXCL9, 11 and CCL5) could be observed in HBV infected hepatocytes. Despite the absence of adaptive immunity, high chemokine induction elicited by infected human hepatocytes was accompanied by significant induction of the human fibrotic marker hTIMP-1 in HBV, HDV and HCV infected mice. Notably, hTIMP-1 enhancement was highest in HBV/HDV infected chimeric mice ($p = 0.0034$). Compared to the RNA expression levels in hepatocytes of infected mice, we found significant up-regulation of CXCL8, 9, 10, 11 and CCL5 not only in serum of chronic hepatitis C and D but also in CHB patients compared to healthy controls, even if CXCL10 levels were higher in hepatitis C and D patients. Of note, chemokine increase did not correlate with viremia, but with fibrosis, since levels of CXCL8, 10 and 11 were higher in patients with F3-F4 compared to those with F0-F2 fibrosis.
Conclusion: HBV, HDV and HCV trigger a pattern of chemokine induction in patients, which can be observed also in human hepatocytes of chimeric mice lacking adaptive immunity. HDV induced expression of CXCL8-11 and CCL5 in human hepatocytes is substantially higher than in HBV monoinfection and resembled that determined in HCV infection. Correlation of CXCL8-11 with fibrosis in chronic viral hepatitis suggests their potential role as indicators for chronic hepatitis B and D disease progression.

FRI-135

Toll-like receptor signalling induces changes in the Hippo signalling pathway that counter regulates innate immune responses in hepatocytes

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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 immune genes as well as oncogenes are induced in primary murine hepatocytes (PMH) exposed to HBV particles. Another remarkable study showed that Hippo signalling is activated by Toll receptor in *Drosophila* and regulates innate immune response. We here investigated the relation between Hippo signalling and innate immune responses in liver cells.
Method: Reanalysis of GEO (GSE69590) data was performed to search for eligible pathways associated with HBV infection. PMH were isolated and treated with TLR ligands (LPS, PAM3CSK4) and HBV particles. Immunocytochemistry (ICC) was performed to intracellularly locate YAP and P65 proteins. Dual-luciferase reporter (DLR) assay, chromatin immunoprecipitation (ChIP) and electrophoretic mobility shift assay (EMSA) were combined to prove the direct regulation of the *Nfkbia* promoter by the YAP/TEAD4 transcription factor complex. Short hairpin RNA (shRNA)-induced gene knock down and over expression of selected factors were analyzed.
Results: Reanalysis of Chip data showed that Hippo signalling and NF-kB signalling were affected in primary human hepatocytes 40 hours after HBV infection. To verify these results, PMH were exposed to HBV particles for different time points. ICC and Western blot results showed that YAP and P65 time-dependently translocated into nucleus. Interestingly, IkBa was entirely disappeared 30 minutes after exposure to HBV, then its expression recovered constantly,

representing a rapid innate immune control mechanism. Bioinformatic analysis of *Nfkbia* promoter indicated the presence of several TEAD4 bind sites. ChIP assay, binding site mutated DLR assays and EMSA confirmed that Yap/Tead4 transcription factor complex bound and activated the *Nfkbia* promoter. Hepa1-6 cell line was transfected with an RFP-reporter plasmid containing the *Nfkbia* promoter region. The treatment with LPS, PAM3CSK4 or the MST1/2 inhibitor (XMU-MP1) led to increased RFP signals. Overexpression and knockdown of YAP in the transduced Hepa1-6 cell line directly affected RFP/IkBa expression, shown by ICC and flow cytometry.
Conclusion: The Hippo signalling pathway harbours regulatory tasks in the rapid innate immune response. These findings directly links inflammation and growth control, and might explain tumor progression in non-cirrhotic HBV-infected patients.

FRI-136
Hepatitis B core antibody (anti-HBc) mirrors activation of hepatitis B virus-specific immune responses and exhibits direct effect on hepatitis B virus control
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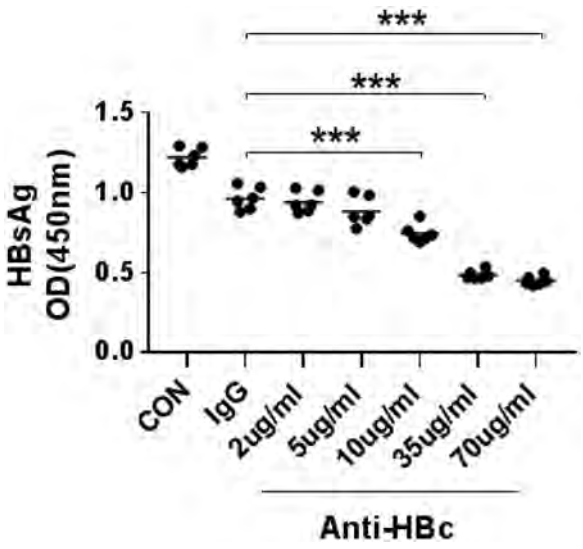
Background and aims: Our previous work has shown that quantitative levels of hepatitis B core antibody (qAnti-HBc) at baseline is a useful predictor of antiviral therapy efficacy in HBeAg-positive CHB patients (GUT, 2016). However there is little known whether Anti-HBc is only a biomarker or it also plays a role in controlling HBV, therefore, we aim to investigate the role of Anti-HBc in chronic HBV infection.
Methods: Mouse model with hepatitis B virus (HBV) was established by tail vein injection of pAAV8-HBV1.3 plasmid. After one month, the stable HBV carrier mice were intraperitoneally injected with acetaminophen (APAP). The serum levels of qAnti-HBc, ALT and hepatitis B core-related antigen (HBcrAg), and the frequency and function of intrahepatic CD8+ T cells from mice were detected. Moreover, serum qAnti-HBc, the phenotype and function of lymphocytes in peripheral blood and HBcAg expression in the liver tissue from patients with chronic HBV infection were analysed by ELISA, flow cytometry and Immunohistochemistry respectively. In addition, *in vitro* assays were performed to examine the ability of Anti-HBc in suppressing HBV replication.
Results: The levels of ALT and HBcrAg were significantly elevated at day 1 after APAP injection in the HBV mouse model, and the levels of qAnti-HBc were sequentially elevated. A significant correlation was found between the serum qAnti-HBc levels and the frequency of intrahepatic effector CD8+ T cells (CD44-CD62L-), and there was also a positive correlation between serum qAnti-HBc levels and the frequencies of intrahepatic IFN-gamma+CD8+ T cells and IL-21+CD8+ T cells in the mouse model. Moreover, in patients with chronic HBV infection, serum levels of qAnti-HBc were correlated with the intrahepatic levels of HBcAg, the frequencies of periphery effector CD8+T cells (CCR7-CD45RO-), and HBcAg-specific CD8+ T cells respectively. An *in vitro* assay revealed that high levels of Anti-HBc were able to directly suppress HBV replication in HepG2.2.15 cells. Furthermore, Anti-HBc mediated the activation of complement to lyse HepG2.2.15 cells and resulted in significantly reduced the levels of HBsAg and HBeAg in the culture supernatant.
Conclusion: The generation of Anti-HBc mainly results from the release of HBcAg from HBV-infected hepatocytes, and this marker mirrors the activation of CD8+ T cell responses against HBV. The notable demonstration of the direct antiviral effect of Anti-HBc suggests that this antibody may have a potential value in the treatment of chronic HBV infection.



FRI-137
l-carnitine impedes hepatitis B surface antigen loss through immunosuppressive effect in chronic hepatitis B virus infection
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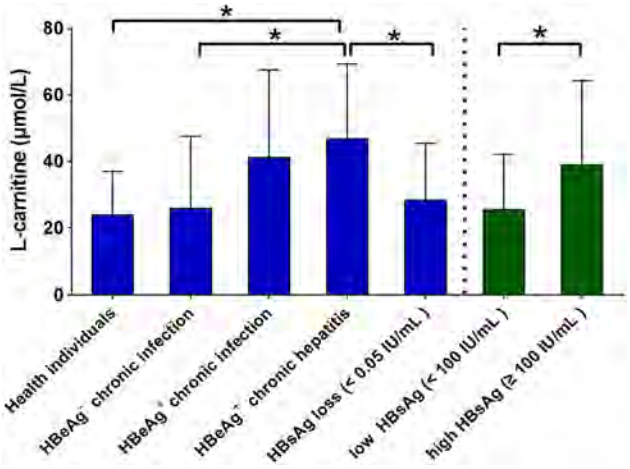
Background and aims: Achievement of hepatitis B surface antigen (HBsAg) loss represents the hallmark for functional cure of chronic hepatitis B (CHB). Previous study has documented an association between lower baseline levels of plasma L-carnitine (L-Cn) and treatment-induced HBsAg loss in CHB patients. Herein, we aimed to investigate the profile of plasma L-Cn in patients with chronic HBV infection and its effect on immunological function of lymphocytes.
Method: Seventy-four patients with chronic HBV infection were classified into 4 groups according to the EASL guidelines (2017): hepatitis B e antigen (HBeAg) negative chronic infection (n = 28), HBeAg positive chronic infection (n = 13), HBeAg positive chronic hepatitis (n = 17), and HBsAg loss (n = 16). According to the HBsAg levels, these patients were also classified into 2 groups: low HBsAg < 100 IU/ml (n = 28) and high HBsAg ≥ 100 IU/ml (n = 46). Another 22 healthy individuals were enrolled as controls. Plasma L-Cn levels were measured by enzyme-linked immunosorbent assay. *In vitro* assays were performed to assess the effect of L-Cn on distinct lymphocytes; the frequency and function of lymphocytes were analyzed by flow cytometry. In addition, HepG2.2.15 cells were lysed and mouse model with acute liver injury was established by intraperitoneal injection of acetaminophen (APAP) to investigate the origin of L-Cn, and the levels of L-Cn in supernatant or serum were detected.
Results: The plasma levels of L-Cn in the HBeAg-positive chronic hepatitis group were significantly higher than that in the groups of HBsAg loss, HBeAg-negative chronic infection and HCs. Intriguingly, compared with the low HBsAg group, high HBsAg group has significantly elevated plasma levels of L-Cn (figure). Moreover, a negatively correlation between plasma levels of L-Cn and HBV DNA load, while a positive correlation between plasma levels of L-Cn and liver pathological inflammatory grades were found. Of note, plasma L-Cn levels were significantly increased after the second administration of APAP injection in mouse model with acute liver injury, and HepG2.2.15 lysates exhibited an ascending level of L-Cn in a cell-density-dependent manner. *In vitro* assays revealed that L-Cn significantly suppressed the proliferation and IL-21production of

circulating chemokine (C-X-C motif) receptor 5+CD4+ T cells, and reduced the production of immunoglobulin G by B cells. In contrast, L-Cn upregulated the frequencies of arginase-expressing granulocytic myeloid-derived suppressor cells (gMDSC) and IL-10-secreting regulatory T cells, as well as the expression of eomesodermin (Eomes) in CD8+ T cells.



Conclusion: Excess L-Cn released from the injured hepatocytes displays immune suppressive properties, thus may impede the achievement of HBsAg loss in chronic HBV infection, implicating that L-Cn may serve as a potentially therapeutic target for HBV infection.

FRI-138

HBVcore- versus HBVpolymerase-specific CD8+ T cells differ in chronically HBV-infected patients

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Background and aims: Chronic Hepatitis B virus (HBV) infection is characterized by the presence of impaired HBV-specific CD8+ T-cell responses. T-cell exhaustion induced by persistent antigen stimulation is considered a major mechanism underlying HBV-specific CD8+ T-cell failure. However, due to low frequencies of detectable HBV-specific CD8+ T-cell populations in chronically HBV-infected patients, it is currently unknown whether HBV-specific CD8+ T cells targeting different epitopes are similarly impaired and share molecular profiles indicative of T-cell exhaustion.
Method: To enhance detection of HBV-specific CD8+ T-cell responses, we performed pMHCI tetramer-based enrichment of circulating CD8+ T cells specific for HBV core- and polymerase-derived epitopes in 88 cHBV patients with low viral loads. Subsequently, phenotypic and functional in-depth analyses were performed using multicolor flow cytometry. Patients were pre-selected for autologous viral sequences that matched the targeted epitopes by the analyzed HBV-specific CD8+ T cells.
Results: We were able to detect HBV-specific CD8+ T cells *ex vivo* in the majority (> 80%) of tested patients. Specifically, core- and polymerase-, but not envelope-specific CD8+ T cells were frequently found. Interestingly, these HBV-specific CD8+ T cells exhibited a predominantly less differentiated memory-like phenotype characterized by CD127+PD1+, showed low TOX expression and lacked signs of terminal exhaustion, possibly reflecting weak ongoing cognate antigen recognition. However, within the HBV-specific population, we found significant differences in phenotype and function between core- and polymerase-specific CD8+ T cells. Indeed, more core-specific CD8+ T cells displayed the CD127+PD1+ memory-like phenotype compared to polymerase-specific CD8+ T cells. This observation is in line with the advanced differentiation of polymerase-specific CD8+ T cells towards more severe T-cell exhaustion marked by higher CD38, KLRG1 and Eomes expression accompanied by low T-bet levels and down-regulation of CD127. Polymerase-specific CD8+ T cells also exhibited a reduced expansion capacity compared to core-specific CD8+ T cells that was linked to dysregulated TCF1/BCL2 and high Eomes expression in polymerase-specific CD8+ T cells. These differences were only detectable in HBV-specific CD8+ T cells obtained from chronically infected patients and not from patients who resolved HBV.
Conclusion: Overall, the results of our study show different molecular mechanisms underlying impaired T-cell responses with respect to the targeted HBV antigens core versus polymerase in cHBV infection. This may have potential implications for the design of immunotherapeutic approaches in HBV cure.

FRI-139

Intrahepatic transcriptional profiling of chronic hepatitis B patients during interferon-alpha treatment

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Background and aims: Interferon-alpha (IFN-alpha) treatment for chronic hepatitis B (CHB) is favored for inducing long-term immunological control with a finite duration treatment, but high variability of response has been observed. The interplay between viral replication and host immune responses during IFN-alpha treatment remains to be clarified. We aimed to comprehensively analyze the changes of intrahepatic host gene expression during pegylated IFN-alpha (PegIFN-alpha) treatment in CHB patients.
Method: Gene expression profile of seventeen CHB patients with paired liver biopsies at baseline and week 24 of PegIFN-alpha treatment were compared. Changes of immune cell composition during PegIFN-alpha treatment were estimated by cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT). Gene set enrichment analysis (GSEA) of innate and adaptive immunity were correlated to treatment response.
Results: Intrahepatic transcriptional profiling revealed a significant upregulation of antiviral effectors. Immune cell composition analysis showed that CD8 T cells significantly reduced, while B cells significantly increased after 24 weeks of PegIFN-alpha treatment. GSEA results suggested an enhanced regulation of both innate and adaptive immune responses, and comparison of several most significant differentially expressed genes (DEGs), including RSAD2, DDX60, CD8A, IL18A, between responders and non-responders suggested that PegIFN-alpha treatment had boosted innate immune response in both groups of patients, while some adaptive immune effectors almost remained at the same levels in responders but were significantly downregulated in non-responders after treatment.
Conclusion: These data show a remarkable alteration of intrahepatic gene expression profile in CHB patients during PegIFN-alpha treatment. Innate immune response is enhanced, while T cell response is estimated to be unchanged, or even attenuated, which might also correlate to poor treatment response. With further validation, this study would help achieve better understanding of the antiviral mechanisms of IFN-alpha treatment and facilitate patient selection.

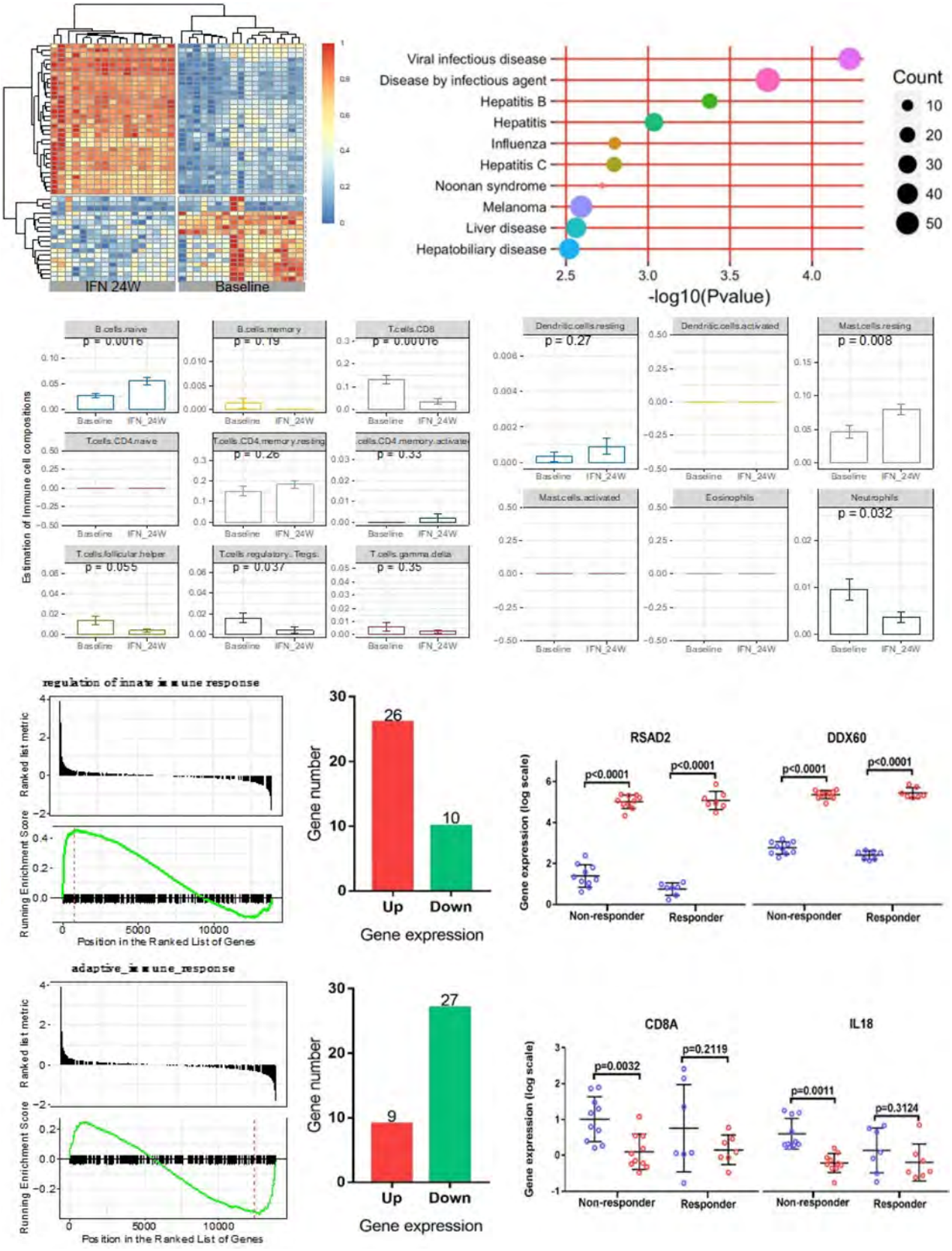

Figure: (abstract: FRI-139)

FRI-140

Chemokine (C-X-C motif) ligand 13-mediated recruitment of intrahepatic chemokine (C-X-C motif) receptor 5+CD8+ t cells contribute to viral control in chronic hepatitis B patients and hepatitis B virus mouse model

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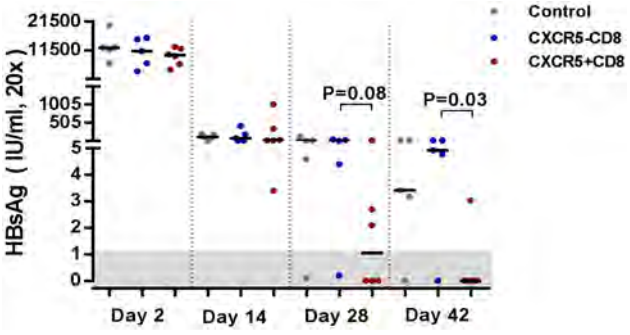
Background and aims: Exhausted CD8+ T cells are not a homogeneously dysfunctional population, while instead consist of phenotypically and functionally distinct subpopulations during chronic viral infection. Recent publications demonstrate that a special subset of CD8+ T cells expressing chemokine (C-X-C motif) receptor 5 (CXCR5) exhibits more potent antiviral efficacy. However, there are limited data regarding its impact in chronic hepatitis B virus (HBV) infection.

Methods: The frequency of circulation CXCR5+CD8+ T cells and the levels of chemokine (C-X-C motif) ligand 13 (CXCL13) were detected in a clinical trial cohort of chronic hepatitis B (CHB) patients with nucleotide drugs based therapy. A series of membrane markers on peripheral and intrahepatic CXCR5+ and CXCR5- CD8+T cells obtained from patients with chronic HBV infection were analyzed by flow cytometry, as well as the expression of HBV-specific interferon (IFN)-gamma. Additionally, purified CXCR5+ and CXCR5- CD8+T cells from mice with pAAV-HBV1.2 injection were adoptively transferred to the recipient HBV mice and then serum levels of HBsAg were sequentially monitored.

Results: An expansion of circulation CXCR5+CD8+ T cells were observed in patients with chronic HBV infection and this population maintained decent antiviral ability; moreover, high frequency of circulation CXCR5+CD8+ T cells was associated with virological response in CHB patients with antiviral therapy. Although the CXCR5+ subset have higher expression of PD-1 than the CXCR5- subset, they demonstrated a status of activation with memory potential by the evidence of enhanced expression of CD69 and CD38 as well as CD62L and CCR7. Additionally, high expression of intrahepatic CXCL13, which recruits CXCR5+CD8+ T cells, were presented in patients with chronic HBV infection and high levels of serum CXCL13 were also observed in CHB patients with a complete treatment response. Notably, intrahepatic CXCR5+CD8+ T cells obtained from patients with HBV infection displayed higher expression of IFN-gamma upon stimulation with HBV peptides. More strikingly, this CXCR5+ subset exhibited more potent ability in the control of HBV replication because recipient infected mice showed significantly decreased levels of serum HBsAg compared with CXCR5- subset (figure).



Conclusion: CXCL13 promotes the recruitment of CXCR5+CD8+ T cells to the live and this population contributes to viral control in chronic HBV infection. These data reveal a novel CD8+ T cell subset that may play an important role in future strategies for treatment of chronic HBV infection.

FRI-141

Rapid decrease in titer and breath of neutralizing anti-HCV antibodies in HIV/HCV-coinfected patients who achieved sustained virological response

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Background and aims: Hepatitis C virus (HCV) has an envelope crowned by the E1-E2 envelope proteins, which are the main target for neutralizing anti-HCV antibodies (HCV-nAbs). In this study, we have analyzed the titers, breadth, and dynamics of HCV-nAbs in HIV/HCV-coinfected individuals who achieved sustained virological response (SVR) with HCV therapy.

Methods: We carried out a retrospective study (before-and-after design) in 29 patients from GESIDA 3603b study. All patients were treated with peg-IFNα+ribavirin or peg-IFN-α/ribavirin/DAAs between February 2012 and February 2014. Neutralization assays were performed for five chimeric HCV expressing E1-E2 glycoproteins from 1a (H77), 1b (J4), 2a (JFH1), 3a (S52) and 4a (ED43) genotypes. The 50% inhibitory dose (ID50) and the area under the curve (AUC) were assessed at baseline (before anti-HCV treatment) and at 24 weeks after SVR.

Results: All patients were on combined antiretroviral therapy (cART), the median of CD4+ T-cells was 695 cells/mm^3, 14 patients were F4 ($\geq$ 12.5 Kpa), the median of $\log_{10}$ HCV-RNA was 6.62 IU/ml, and 13 patients were coinfected with HCV-GT1a, 3 GT1b, 8 with HCV-GT3 and 5 with HCV mixed infection. At baseline, most plasmas were able to neutralize 1a (H77), 1b (J4), 2a (JFH1), and 4a (ED43) genotypes, while 3a (S52) was barely neutralized. At week 24 after SVR, the majority of neutralizing titers decreased significantly ($p \leq 0.05$), becoming undetectable against 3a (S52) in all patients and 2a (JFH1) in several of them. Patients with high HCV-nAbs titers against a specific recombinant virus also had high titers against the other chimeric viruses ($r > 0.4$; $p \leq 0.05$). Patients with the highest titers a baseline also had the highest titer at the end of follow-up. A positive correlation between the values of $CD4^+/CD8^+$ ratio and the HCV-nAbs titers against H77 (1a) [AUC ($r = 0.454$; $p = 0.013$) and ID50 ($r = 0.450$; $p = 0.014$)] was found.

Conclusion: Although high titers of broad-spectrum HCV-nAbs were found in HIV/HCV-coinfected patients, a significant decrease in those titers took place shortly after SVR. Our findings should be considered in the design of future prophylactic measures against HCV infection, since the preservation of protective HCV antibody levels against HCV reinfections could be questioned in HIV/HCV-coinfected individuals who eliminated HCV after HCV therapy.

FRI-142

Interferon regulatory factor 5 and soluble fibrinogen-like protein 2 in hepatitis B virus related liver diseases

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Background and aims: The host immune responses are believed to regulate the hepatitis B virus (HBV) infection and subsequently liver disease progression. Interferon regulatory factor 5 (IRF5) is a transcriptional mediator, vital for virus-mediated activation of interferon and Fibrinogen-like protein 2 (FGL2), secreted by T cells is an important effector molecule in the regulation of T and B cells mediated immunity. The *IFR5* locus specific genetic variants and the sFGL2 plasma levels in acute and chronically infected patients with HBV were investigated. Also, *FGL2* mRNA was quantified among 32 dyads (tumor and non-tumor) of liver biopsy tissues.
Method: *IFR5* genetic variants (*rs13242262A/T, rs77416878C/T, rs10488630A/G, and rs2280714 T/C*) were genotyped by direct sequencing among 379 patients with HBV and 242 healthy individuals. The plasma levels of sFGL2 were quantified by ELISA among 296 patients with HBV and 258 healthy individuals. Quantification of FGL2 mRNA was performed using real-time PCR.
Results: *IRF5* alleles rs13242262 T and rs10488630G contributed to an increased risk of liver cirrhosis (LC vs. CHB: OR = 1.5, 95%CI = 1.1-2.3, adjusted P = 0.04; LC vs. CHB: OR = 1.7, 95%CI = 1.1-2.6, adjusted P = 0.019, respectively) and the reconstructed haplotype *IRF5*TCGT* had a significant association with liver cirrhosis occurrence. The sFGL2 levels were significantly elevated in HBV patients with acute hepatitis and liver cirrhosis, and clinical outcomes of HBV-related liver diseases. *FGL2* mRNA was up-regulated in tumor compared to adjacent non-tumor tissues (p = 0.043) (Figure).

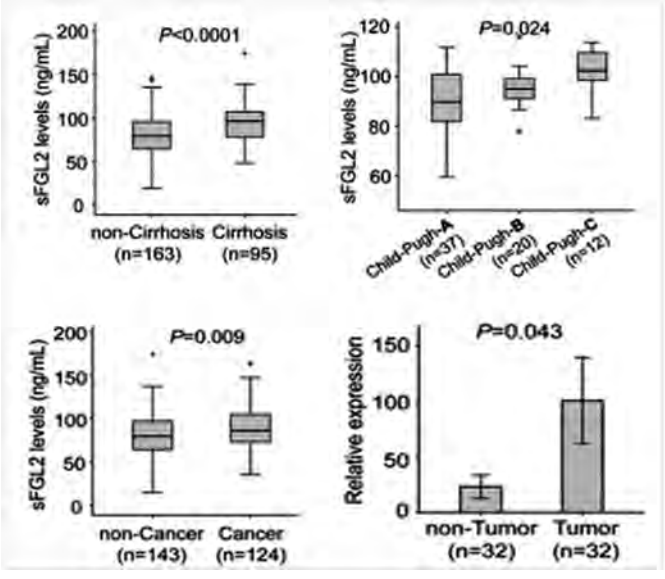

Figure: Association of FGL2 expression with clinical outcomes of HBV patients. FGL2 expression in serum and tumour among different classified groups. NS: Not significant; AST and ALT: Aspartate and alanine amino transferase. P values were calculated by Whitney-Wilcoxon test or Kruskal-Wallis test where appropriate while comparisons of *FGL2* mRNA relative expression were performed using Paired-samples t-test.

Conclusion: The *IRF5* variants may contribute as a host factor in determining the pathogenesis in chronic HBV infections and the sFGL2 levels are induced by HBV infection and correlated with the progression and clinical outcomes.

FRI-143

Liver-resident HBV-specific CD8+ T cells are long-lived and can be replenished by allogenic responses following transplantation

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Background and aims: We recently identified a population of tissue-resident memory CD8 T cells (TRM) expressing liver homing/retention markers (CXCR3+CXCR6+, CD69+CD103+), adapted to maintain efficient non-cytolytic antiviral function in the human liver. These CD8 TRM were absent from the circulation, preferentially expanded in patients with partial HBV immune control (HBeAg-chronic infection), remained in the liver after resolution of infection and contained HBV-specific CD8 T cells directed against epitopes from all major HBV proteins (Pallett LJ. et al J Exp. Med. 2017).
Method: To definitively investigate the lifespan and derivation of global and HBV-specific CD8 TRM, we took advantage of access to a liver allograft explanted after 11 years in an HLA-mismatched recipient, where monoclonal antibodies were available to distinguish donor-derived (HLA-A2+) and recipient-derived (HLA-A2- A3+) leukocytes. The donor had resolved HBV infection (anti-HBcAb+) that reactivated following liver transplantation.
Results: Remarkably, global and HBV-specific donor-derived CD8 TRM were still detectable within the explanted liver 11 years post-transplantation, confirming the long-lived nature of CD8 TRM within their local microenvironment. Furthermore, a significant proportion of recipient-derived CD8 T cells within the allograft had acquired a tissue-resident phenotype, revealing that repopulation from the peripheral compartment can contribute to the pool of intrahepatic CD8 TRM. We also identified recipient-derived, HLA-A3+ CD8 T cells able to bind HBV-specific HLA-A2-restricted multimers, implying that allogeneic CD8 T cell responses can be directed against HBV within an infected liver allograft. Further samples are being used to distinguish donor versus recipient derivation of different hepatic antigen presenting cells.
Conclusion: In summary, analysis of this case of HLA-mismatched liver allograft/recipient T cells in the setting of HBV infection suggests that hepatic CD8 TRM can be long-lived, replenished from the periphery and therefore contribute to antiviral immunity.

FRI-144

Performance study of new geenius HCV supplemental assay

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Background and aims: The new Bio-Rad Geenius™ HCV Supplemental Assay is a qualitative single-use immunochromatographic test for the confirmation of individual antibodies associated with infection caused by the Hepatitis C Virus (HCV) in human venous whole blood, serum or plasma samples.
Geenius™ HCV Supplemental Assay is intended for use as an additional screening and/or diagnostic test to confirm the presence of antibodies to HCV for specimens found to be reactive by screening procedures.
It is associated with Geenius™ system (reader and software) and results are automatically interpreted.
The aim of this study, performed by Bio-Rad RandD department was to evaluate the performance of this new assay and to compare with reference assays.

Method: A full validation of this new rapid test has been performed. Specificity has been evaluated on fresh negative blood bank samples (n = 500) as well as on samples from hospitalized patients (n = 200). Sensitivity has been tested on specimens from chronic HCV infected patients (n = 276) and on 20 commercial seroconversions panels. Performance of Geenius™ HCV Supplemental Assay has been compared with INNO-LIA® HCV Score.
All results were obtained using automatic reading with Geenius™ system.
Results: Regarding specificity, we obtained no false positive result and only 1, 60% (8/500) and 1, 50% (3/200) indeterminate results were found among blood bank samples and hospitalized patient samples respectively.
A comparative study has been realized between Geenius™ HCV Supplemental assay and INNO-LIA® HCV Score. On 250 blood donor specimens, 249 were found negative and 1 was found indeterminate with Geenius™ HCV Supplemental Assay. On the same population, 240 were found negative and 10 were found indeterminate with INNO-LIA® HCV Score. On 200 hospitalized patients, specimens, 197 were found negative and 3 were found indeterminate with Geenius™ HCV Supplemental Assay; 181 were found negative, 16 were found indeterminate and 3 were found positive with INNO-LIA® HCV Score. Overall, specificity for Geenius™ HCV Supplemental Assay is 99% and 92.75% for INNO-LIA® HCV Score respectively.
A sensitivity of 100% was obtained with Geenius™ HCV Supplemental Assay (276/276) on samples from chronic HCV infected patients.
Sensitivity obtained on the 20 seroconversion panels tested was equivalent to INNO-LIA® HCV Score Assay.
Conclusion: Performance obtained with the Geenius™ HCV Supplemental Assay during evaluations met the required specifications in terms of specificity and sensitivity. Results have shown a better specificity and an equal sensitivity than INNO-LIA® HCV Score. The new Geenius™ HCV Supplemental Assay is the first unitary and quickest one assay for the confirmation of the presence of antibodies to HCV with automatic reading and interpretation. The expert software allows a complete automation of the reading and a complete traceability.

FRI-145

Direct acting antiviral treatment decreases inhibitoryTIM-3 immune checkpoint receptor expression on NK cells in patients with chronic HCV

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Background and aims: In chronic HCV hepatitis immune cells have increased expression TIM-3 checkpoint inhibitor receptor that downregulates T cell activation, resulting T cell exhaustion. In contrast to immune dysfunction of adaptive immune response high levels of TIM-3 expression on NK cells was associated with an activated phenotype towards cytotoxicity. Elimination of hepatitis C virus with direct-acting antiviral (DAA) treatment may modify host immune response via changing TIM3 immune checkpoint molecule expression. In this prospective study we aimed to analyse changes in TIM3 receptor expression by peripheral blood mononuclear cells in chronic HCV hepatitis patients during DAA treatment.
Method: Methods: Phenotype distribution and expression of TIM-3 by peripheral blood CD3+, CD4+, CD8+ T cells, regulatory T cells, NK, NK dim, NK bright, NKT cells and monocytes were determined by multicolor flow cytometry in 14 patients with chronic hepatitis C pretreatment and after 12 weeks of dasabuvir, ombitasvir, paritaprevir/ritonavir combination treatment. Blood samples were collected baseline (BL), at the end of treatment (EOT) and at 12 weeks after EOT (SVR12) All patients achieved sustained virological response (SVR12).
Results: Results: While the percentage of NK bright cells significantly decreased during DAA therapy (BL: 3, 1%, SVR12: 1, 7%), the percentage of peripheral blood CD3+ T lymphocytes was significantly higher at SVR12 compared to baseline values (BL: 47% vs SVR12: 56, 3%). TIM-3 expression by NKT (BL: 4, 9% vs SVR12: 3, 5%) and by NK bright cells (BL: 64% vs SVR12: 50, 4%) decreased significantly after treatment. DAA treatment did not alter TIM-3 expression by CD3+, CD4+ and CD8+ T cells.
Conclusion: Sustained virological response was associated with increased percentage of peripheral CD3+ T cells and with decreased inhibitory TIM-3 checkpoint inhibitor expression by NKT and NK bright cells. Our data suggest that DAA therapy via decreasing the expression of TIM-3 inhibitory immune checkpoint molecules on specific NK cell subpopulations may modulate NK cell activity and via decreasing cytotoxicity agains T cells may contribute to the recovery of exhausted adaptive immune responses.

FRI-146

Long-term nucleos (t)ide-analogue treatment in chronic hepatitis B eAg (−) together with a low level of HBsAg leads to a non-exhausted HBV-specific T CD8+ response

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Background and aims: HBV-specific T CD8 cell response is exhausted in chronic viral Hepatitis B (HBV) eAg negative (CHBe (−)). Nucleos (t) ide-analogue (NA) treatment can control viral replication but it must be administered indefinitely. Nevertheless, a non-exhausted specific T CD8 HBV response could allow functional cure and consequently NA discontinuation. To this end, we have compared the specific T CD8 HBV response of CHBe (−) patients in treatment with NA depending on the duration of treatment and the HBsAg level.
Methods: 37 HLA-A2+ CHBe (−) patients were included: 25 patients in treatment for less than 6, 5 years (< 6, 5y) and 12 patients for more than 6, 5 years (> 6, 5y). Serum levels of HBs antigen (HBsAg) were determined. Peripheral HBV-Core epitope18-27 CD8 T cells were visualised by flow cytometry, using co-staining with pentameric complexes, anti-CD3 and anti-CD8 (CD8+/Pent+). In CD8 +/Pent+ cells, the following was analysed: the PD-1/CD127 phenotype; interferon-gamma production (IFNg); CD107a mobilization; specific antigen proliferation capacity.
Results: The level of HBsAg was negatively correlated with the duration of the treatment ($r = -0.333$; $p = 0.044$) and was higher in the group of < 6.5y (3.36log IU; Interquartile range (IQR) 1.2) than in the > 6.5y group (2.7log IU; IQR 2.9), ($p = 0.023$). The frequency of CD8+/Pent+ cells out of total CD8+ cells was higher in the > 6.5 y group (0.9%; IQR 0.08) than in the < 6.5y (0.006%; IQR 0.02) group ($p = 0.001$). CD8+/Pent+ cells were detected in 100% of cases in the > 6.5y group, whereas only in 20% of the < 6.5y group ($p = 0.001$). Moreover, in the > 6.5 y group, the HBsAg level was negatively correlated with the frequency of CD8+/Pent + cells ($r = -0.786$; $p = 0.036$). > 6.5y treatment and < 3.2log IU HBsAg level was positively correlated with proliferative capacity of the CD8 +/Pent+ cells ($r = 0.668$; $p < 0.001$). The degranulation capacity of CD8 +/Pent+ cells was positively correlated with > 6.5y treatment and < 3.2log IU HBsAg level ($r = 0.794$; $p = 0.006$). Globally, the > 6.5y group was able to express a higher CD107a (277 median fluorescence intensity (MFI); IQR 278) than the < 6.5y group (MFI 166, IQR 84), ($p < 0.05$). IFNg production was higher in the > 6.5y group with < 3.2log IU HBsAg (111MFI; IQR 174) than in the other groups (MFI 48; IQR 52), ($p < 0.05$). CD8+/ Pent + cells in both groups expressed a PD-1+/CD127+phenotype

Conclusion: Treatment with NA for more than 6, 5 years and HBsAg level lower than 3.2log IU is associated with the presence of an HBV-specific T CD8 cell population, with a PD-1+/CD127+phenotype and restored effector capacity that could impact the development of a functional cure.

FRI-147

Gradual restoration of HCV-specific CD8+ T cell frequency but persistence of altered phenotype in cirrhotic HCV-infected patients after successful direct-acting antiviral therapy

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Background and aims: Chronic hepatitis C virus (HCV) infection impairs the phenotype and function of CD8+ T cells specific for HCV or other unrelated pathogens such as Cytomegalovirus (CMV) or Epstein Barr Virus. Nonetheless, it has been shown that these alterations could be partially restored following interferon-free therapy. Here, we focused on the potential restoration of HCV-specific CD8+ T cells in patients with established cirrhosis after successful therapy.
Method: 29 HLA-A*02:01 positive patients with chronic HCV infection and liver cirrhosis were prospectively included in the study. Peripheral blood was collected at the beginning of treatment (BL), at week 4 during therapy and at weeks 12 and 48 after end-of-therapy (FU12 and FU48, respectively). HCV-specific CD8+ T cells were analysed by flow cytometry after *in vitro* expansion in the presence of HLA-A2-restricted HCV peptides. HCV epitope sequencing was performed by Sanger method. As controls, CMV and Influenza (Flu)-specific CD8+ T cells were analysed in HCV-infected patients and in 10 healthy individuals, matched by age and sex.
Results: The frequency of HCV-specific CD8+ T cells increased gradually from BL to FU48 (p = .0001) in the majority of patients (72%), as well as the number of patients with more than one positive response against the analysed HCV epitopes (41%, *P* <.0001). This restoration was observed in CD8+ T cells targeting either conserved or variable HCV epitopes. However, despite viral clearance during the first weeks of therapy, CD8+ T exhausted cells, defined by co-expression of co-inhibitory receptors PD-1 and TIM-3/CTLA-4, persisted until FU48.
Interestingly, the frequency of CMV-, but not Flu-specific CD8+ T cells, was greater in HCV-infected patients than in controls even at FU48 (p = .03). In addition, patient CMV- and Flu-specific CD8+ T cells expressed higher levels of PD-1, Tim-3 and CTLA-4 compared to controls (p < .05).
Conclusion: Despite the rapid on-therapy viral eradication, restoration of HCV-specific CD8+ T cell response was gradual and continued up to FU48, even though not in all patients. Expression of co-inhibitory receptors persisted altered not only in HCV- but also in CMV-/Flu-specific CD8+ T cells. These results suggest that, HCV may leave a sustained imprint in antiviral CD8+ T cell responses in cirrhotic patients, whose clinical relevance remains unknown and requires further investigation.

FRI-148

Downregulation of innate and adaptive gene expression alleviated by host protein osteopontin in an immunocompetent model of hepatitis B infection

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Background and aims: Host-virus interactions during early phase of Hepatitis B virus (HBV) infection are not well understood and studies are hampered by lack of good models. We have recently developed an immunocompetent model of HBV infection, human Precision-Cut Liver Slices (hPCLS), which we have shown to recapitulate alcohol mediated liver injury/inflammation and fibrosis. Using hPCLS, our aims were to investigate:1) host immunity during early phase of HBV infection. 2)role of host protein/profibrogenic factor Osteopontin (OPN) in virus-host interactions.
Method: hPCLS were produced from healthy portion of post-resection liver tissue and infected with HBV inoculum at 2×10^{10} genome equivalents/slice. Infected hPCLS were cultured for 7 days ± recombinant OPN (rOPN) at 1000 ng/ml. Media was replaced every day post infection. Intracellular and secreted HBVDNA were quantified by qPCR, cccDNA and HBsAg levels were measured by high-sensitivity Droplet Digital PCR and ELISA respectively. In addition, total RNA from the slices was extracted, reverse-transcribed and run on 96 human innate and adaptive immunity PCR array (Qiagen).
Results: HBV infection in hPCLS was successfully attained and viral replication maintained for 7 days. In each, 24hr period we observed secreted HBVDNA levels of 5-6 Log copies/ml; intracellular HBVDNA of 5-7 Log copies/ml and cccDNA levels at 2 Log copies/ml. The early phase of HBV infection (day2/3) resulted in the abolition of type I Interferon and RIG1/IRF3 signalling when compared to non-infected hPCLS. In addition, a marked impairment of the expression of chemokine involved in recruitment of innate and adaptive immune cells to the liver was observed including CCL2, CXCL10. We also observed significant reduction of pathogens recognition receptors (PPR) such as TLR2, TLR8, NOD2 and in pro- and anti-inflammatory cytokines IL-1, IL-2, IL-18 and IL-5, IL-4, IL-13. rOPN led to 4-fold increase in HBVDNA, HBsAg and cccDNA inducing 13-fold increase in expression of antiviral genes including potent anti-HBV genes such IFN-inducible protein MX1 and in chemokines genes favouring a pro-fibrogenic milieu including CCL2 and CCL5.
Conclusion: Here we describe a novel and robust immunocompetent model HBV infection and reveal that during the early phases of infection, HBV actively inhibits immunity. We confirm the immune and fibrogenic modulatory functions of OPN and show its active involvement in driving HBV replication. We identify OPN as a new antiviral and anti-fibrotic target for HBV infection.

FRI-149

Comprehensive transcriptome analysis of liver biopsies from chronically infected HBV patients

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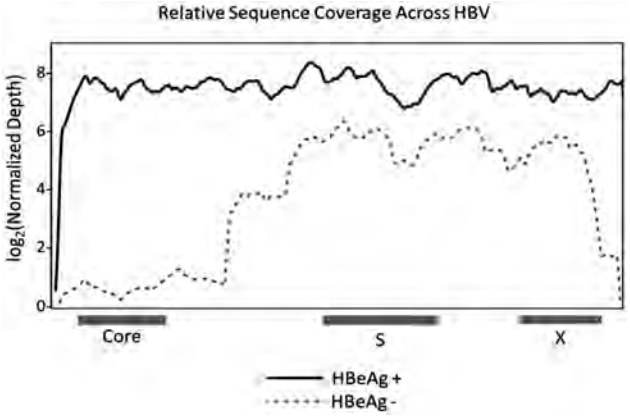
Background and aims: Our current knowledge of the interaction between chronic HBV infection and the immune microenvironment comes from animal models and patients with human hepatocellular carcinoma (HCC). Here, we describe the intrahepatic transcriptomes from chronically HBV (CHB)-infected, non-HCC patients to characterize the host immune cell phenotypes and viral transcripts.
Method: Liver biopsies were obtained from chronic hepatitis B patients enrolled in an open-label Phase 4 trial with TDF and/or

PEG-IFN-alpha (GS-US-174-0149).Next-generation sequencing was performed on 54 samples from 46 patients with high quality mRNA libraries, which included 8 pairs of longitudinal biopsies baseline and 96 weeks post-antiviral treatment. A multimodal bioinformatics pipeline was used to analyze both host and viral transcriptomes including viral transcript quantification, detection of HBV integration events, and cell-type enrichment analysis using the xCell algorithm.
Results: Using gene set enrichment analysis we found two unique immune signatures in baseline samples: 1) high CD4+ memory T cells, high CD8+ TCM, high Th2, high PD-L1, and 2) low CD4+ memory T cells, low CD8+ TCM, high Th1, low PD-L1. Preliminary correlations found a trend toward ALT levels ($p = 0.052$), however, a complete analysis of baseline and disease factors is ongoing. Additionally, a subset analysis of the paired liver biopsy samples revealed an enhancement of the latter immune signature. Our deep sequencing approach also enabled detection of viral transcripts. In HBeAg positive patients, we see coverage across the entire HBV genome, suggestive of transcription from cccDNA (Figure 1). However, in HBeAg negative patients, we observe loss of coverage in the core region and downstream of DR1, suggestive of transcription largely from HBV integration (Figure 1). This suggests that the contribution of viral transcripts from cccDNA is dramatically reduced in HBeAg negative patients, thereby revealing the contribution of viral transcripts from HBV DNA integration. We also observed this pattern of HBV transcription in patients following who lost HBeAg following antiviral treatment.



Conclusion: Here, we report the first transcriptome characterization of intrahepatic immune and viral signatures in CHB patients without HCC. RNA-seq analysis of longitudinal biopsies will allow for an understanding of how the immune microenvironment and viral transcripts are affected by treatment which will provide insight into necessary steps needed for a functional cure.

FRI-150

Association of the immunodominant HLA-B35:01 restricted CD8+ T cell epitope with clustered viral evolution in HBV polymerase

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Background and aims: CD8+ T-cell exhaustion and viral escape are considered as the main mechanisms in chronic HBV infection; however, the relative role of viral escape herein is not well defined. Until now, viral escape has been mainly described for the core protein. In this study, we aimed to address the role of viral escape from CD8+ T cell responses targeting HBV polymerase.
Method: 114 patients chronically infected with HBV genotype D were analyzed by HLA class I typing and HBV full-genome sequencing. HLA class I associated HBV polymorphisms were identified. Corresponding to a cluster of three HLA-B35:01 associated HBV polymerase sequence mutations, the optimal epitope peptide was determined. Tetramer-based enrichment of CD8+ T-cells specific for the novel HLA-B35:01 polymerase epitope as well as two previously described HLA-A01:01 and HLA-A11:01 restricted core- epitopes was performed. A cohort of 51 patients with chronic HBV genotype D infection was screened.
Results: Several HLA class I associated sequence polymorphisms were observed in the polymerase protein, including a striking cluster of three HLA-B35:01 associated polymorphisms (pol174, 180 and 181) located within a single predicted HLA-B35:01 restricted CD8+ T cell epitope. The epitope was confirmed after peptide-specific expansion followed by intracellular interferon-gamma staining in 3 HLA-B*35:01+ patients. By using a sensitive ex vivo tetramer-based enrichment protocol, we were able to detect polymerase-specific CD8+ T cells responses in 4/20 HLA-B35:01+ patients. The frequency was similar to the detection rate of CD8+ T cells targeting a previously described immunodominant HLA-A01:01 and a HLA-A11:01 epitope with 2/9 HLA-A01:01+ and 3/22 HLA-A11:01+ patients, respectively. Phenotypical analysis of the CD8+ T cells targeting the polymerase-specific HLA-B*35 restricted epitope differs from CD8+ T cells targeting the core- specific HLA-A11 restricted epitope. HLA B35:01 polymerase- specific CD8+ T cells expressed higher levels of KLRG1 and Eomes and lower levels of T-bet. Furthermore, less HLA B35:01 polymerase-specific CD8+ T cells revealed the CD127+PD1+ memory-like phenotype in comparison to HLA-A11:01 core-specific CD8+ T cells.
Conclusion: We identified a novel HLA-B35:01 restricted HBV-specific CD8+ T cell polymerase epitope. This epitope was associated with viral escape mutations at several positions, indicating that viral escape in polymerase may be more constrained compared to viral escape in the core protein. In conclusion, these results could provide the basis for the development of novel therapeutic vaccination strategies targeting non-escaping epitopes and immunomodulatory therapies restoring the function of HBV -specific CD8+ T cells with the aim of virus elimination.

FRI-151

Characterization of regulatory T cells and the role of PD-1 and TNF-alpha in spontaneous hepatitis B surface antigen seroclearance in chronic hepatitis B

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Background and aims: Spontaneous seroclearance of hepatitis B surface (HBsAg) is associated with enhanced HBV-specific T cell response. $CD4^{+}CD25^{high}$ $CD127^{low/-}$ regulatory T cells (Tregs) possess HBV-specific immunoregulatory effects. Whether Tregs are involved in HBsAg seroclearance remains to be determined. We aimed to investigate the changes of Tregs in chronic hepatitis B (CHB) patients achieving spontaneous HBsAg seroclearance.
Methods: We recruited CHB patients who achieved spontaneous HBsAg seroclearance for at least 6 months (experimental group), and treatment-naïve age- and sex-matched hepatitis B e antigen-negative controls. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Pague density gradient centrifugation method. The frequency, transcriptional factor (FoxP3), different inhibitory phenotypes (PD-1, CTLA-4, LAG-3 and GITR), and immunoregulatory cytokines (TNF-alpha, IFN-gamma, TGF-beta, IL-10 and IL-17A) of Tregs were detected by multicolor flow cytometry (BD LSR Fortessa Analyzer, San Jose, CA).
Results: Twenty-seven patients with HBsAg seroclearance were recruited (mean age 53.70 ± 7.93 years, 55.6% male). Median duration from achieving HBsAg seroclearance to PBMCs collection was 1.47

(interquartile range 0.72–2.73) years. Median HBsAg and HBV DNA levels in the control group (n = 27) were 2.74 (1.59-3.42) log IU/ml and 3.22 (1.96-3.81) log IU/ml, respectively. The mean frequency of Tregs and the expression of FoxP3 in the experimental group were comparable to the control group (3.39% vs. 3.35% and 65.95% vs. 65.37%, respectively; both p > 0.05). The mean expression of PD-1 on Tregs was significantly lower in the experimental group than that in the control group (9.65% ± 3.27 vs. 12.03% ± 4.49; p = 0.03). No significant differences were found for CTLA-4, LAG-3 and GITR phenotypes (all p > 0.05). In the experimental group, Tregs had a greater expression of TNF-alpha when compared to the control group (37.89% ± 9.50 vs. 28.87% ± 9.04; p = 0.001), with no significant differences noted in the production of IFN-gamma, TGF-beta, IL-10 and IL-17A (all p > 0.05). In the control group, a significant inverse correlation was observed between the proportion of TNF-alpha-expressing Tregs and serum level of HBsAg (r = -0.669, p < 0.001).
Conclusion: The reduced expression of PD-1 and/or increased production of TNF- alpha may attenuate the immunosuppressive capability of Tregs, and may contribute to the "functional cure" of CHB.

FRI-152

Immunoregulatory activity of preimplantation-factor on HCV stimulated primary human hepatocytes demonstrates preclinical activity for treating inflammatory liver diseases

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Background and aims: Liver disease can be driven by chronic inflammatory processes that damage the liver over many years. Currently, effective immunomodulatory agents, with minimal side effects, that can regulate inflammation in the liver to promote liver health in the setting of chronic liver disease have not been developed. PreImplantation-Factor (PIF) a non-viral therapeutic protein that is currently in phase II clinical trials, is an endogenous embryo-derived peptide that comprehensively (i.e. locally and systemically) imparts this determining immune regulatory activity safely. A better understanding of the effects of PIF on models of inflammatory liver disease will provide strong justification for later-phase therapeutics discovery and development efforts in appropriate patient populations with liver disease. The aims of this study are focused on understanding the potential benefits of PIF for patients with viral liver diseases by specifically focusing on inflammatory responses activated in primary human hepatocytes (PHHs).
Method: To determine the mechanisms through which PIF modulates the antiviral response in HCV infected PHHs, multiple techniques were employed. RNAseq and qPCR analyses were performed on HCV treated PHHs, with and without sPIF, to determine which inflammatory pathways are modulated. M.O.Is of 0.5, 1.0, 5.0 and 50 and multiple time points including 24 and 48-hour infections were utilized in the presence of multiple doses of PIF. Further analysis was performed on the genes and pathways identified by RNAseq that were affected by sPIF. Proteomics was performed to identify PIF binding partners in hepatocytes.
Results: HCV infected PHHs demonstrated a robust induction of inflammatory genes that was significantly impacted following treatment with sPIF. RNAseq analysis demonstrated a broad and reproducible modulation of HCV regulated genes. Specifically, downregulation of Interferon Regulatory Factor 3 (IRF3) and Peroxisome proliferator-activated receptor alpha (PPAR-alpha) dependent pathways (p < .001) was observed. qPCR analysis verified downregulation of inflammatory genes including CXCL10 and CCL5 (p < .001) in HCV infected PHHs following sPIF administration. Mass spectrometry was utilized to identify PIF binding partners, in uninfected primary hepatocytes, that may mediate these effects.
Conclusion: These studies provide strong data, using well-validated and predictive human cell-based models, that there is a high likelihood that PIF treatment will be beneficial for viral-induced liver disease. Collectively, we expect the outcomes of these experiments to greatly add to our understanding of PIF activity while providing a significant contribution to the data supporting the validity of PIF for the efficacious treatment of viral-induced liver disease through a non-viral biologic approach (PIF Proprietary).

FRI-153

Potent hepatitis B core-specific B cell responses associate with clinical parameters in untreated and virally suppressed chronic HBV patients

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Background and aims: Exhaustion of virus-specific T cells is a hallmark of chronic HBV (cHBV) infections, but the HBV-specific B cell response is less well studied. Previously, we identified B cell-related transcriptomic changes in blood and liver of cHBV patients in different clinical phases. We now examined, the number, phenotype and function of HBcAg-specific B cells during cHBV, in comparison to HBsAg-specific B cells.
Method: Serum and PBMC were obtained from 137 cHBV patients, both untreated (n = 114) belonging to different clinical phases as NUC treated (n = 23), and 22 healthy HBsAg-vaccinated controls. The phenotype of overall and HBV-specific B lymphocytes was studied by FACS using DyLight650 and DyLight550 dual fluorescently labelled HBsAg and HBcAg in combination with antibodies against CD3, CD10, CD19, CD27, CD21, CD38, and FcRL5. In vitro anti-HBs and anti-HBc antibody production was measured after polyclonal PBMC stimulation by ELISPOT assays. Anti-HBs and anti-HBc antibodies were measured in serum and in supernatant by ELISA.
Results: Serum levels of anti-HBc, but not anti-HBs antibodies associate with the clinical phases of cHBV, characterized by increasing titers in patients with ALT rise (p < 0.0001). In vitro, a similar profile is seen for the number of spot-forming anti-HBc-producing cells and their levels in the supernatant of these cultures (p < 0.0001). Also the number of HBcAg-specific B cells in blood followed this pattern (p = 0.0035). In contrast, HBsAg-specific B cells show no typical numeric or functional changes in cHBV and are vastly outnumbered by HBcAg-specific B cells in blood (92.8-fold, P < 0.0001). HBcAg-specific B-cells are enriched for a CD21- and CD21 + CD27 + memory B cell profile compared to total B cells (3.6-fold and 2.0-fold, P < 0.0001 respectively), but demonstrate a less activated phenotype (activation marker CD38: 0.8-fold, P = 0.0017; inhibitory IgG co-receptor FcRL5: 2.3-fold, P < 0.0001). Interestingly, complete viral suppression in the NUC cohort, led to reduced numbers of HBcAg-binding B cells and in vitro production of anti-HBc antibodies (all P < 0.05). For the total chronic HBV cohort, HBV DNA levels positively correlated with in vitro anti-HBc production levels (r = 0.388, P = 0.0008) and with the number of HBcAg-binding B cells (r = 0.323 P < 0.05).
Conclusion: HBcAg-specific B cells vastly outnumber HBsAg-specific B cells in blood of chronic HBV patients, are enriched for a classical memory B cell phenotype and show no impairment with increasing HBV DNA titers.

FRI-154

Augmentation of HBV-specific CD4 T cell responses via combined OX40 stimulation and PD-L1 blockade

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Background and aims: Chronic hepatitis B virus (cHBV) infection is a common cause of progressive liver disease that eventually may lead to hepatocellular carcinoma. Antiviral therapeutic options are still limited and aren't able to induce viral clearance. HBV-specific T cells are crucial for HBV control and have recently been shown to be protective in patients following discontinuation of antiviral therapy. Thus, T-cell based immunotherapy appears to be a promising therapeutic approach. In this project, we aimed to identify immunological pathways that are able to improve functionality of HBV-specific CD4 T cells.
Methods: The expression of relevant costimulatory and coinhibitory molecules (e.g. CD127, OX40 and PD-1) on HBV- and Influenza (Flu)-specific CD4 T cells were analyzed using MHC class II- tetramer technology in 11 cHBV patients and 11 healthy volunteers, respectively. Using overlapping peptides (OLPs) spanning the entire HBV-polyprotein, we screened 66 patients (cHBV, genotype D) for CD4 T cell responses. Control responses (Flu, Epstein-Barr virus [EBV] and tetanus toxoid [TT]) were analyzed in 59 healthy donors (HD). Stimulation with recombinant IL-7, an agonistic OX40-antibody or blockade of PD-L1 was performed in antigen-specific *in vitro* cultures. Cytokine secretion and expression of transcription factors were analyzed by flow cytometry.
Results: CD127, OX40 and PD-1 were more strongly expressed on HBV- compared to Flu-specific CD4 T cells. HBV-specific CD4 T cells were identified in 27% of chronically infected patients and predominantly targeted the HBV polymerase and core proteins whereas responses to the surface protein were not detectable in cHBV patients. Consistent with the elevated *ex vivo* surface expression combined OX40 stimulation and PD-L1 blockade resulted in an increased frequency of IL-21 and IFN-g secreting CD4 T cells after antigen-specific *in vitro* culture. In addition, Tfh- and Th1-associated transcription factors Bcl6 and T-bet were strongly expressed in cytokine producing cells. In line with a lower expression of OX40 and PD-1 on Flu-specific CD4 T cells *ex vivo*, the augmentation of cytokine production was observed to a lesser extent for viral control responses to Flu and also EBV epitopes in HD.
Conclusion: Collectively, our observations demonstrate that synergistic effects of combined OX40 stimulation and PD-L1 blockade augment the secretion of Th1 and Tfh signature cytokines IFN-g and IL-21, suggesting that these pathways are promising candidates for immunotherapeutic interventions during cHBV infection.

FRI-155

Characterization of a library of CD4+ T cells for T-cell therapy of HBV infection

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Background and aims: Hepatitis B virus (HBV) infection remains a severe health problem with chronically infected patients being at increased risk of developing liver cirrhosis and hepatocellular carcinoma. Current treatment options control viral replication. However, viral clearance is not achieved. Since virus eradication is known to be accompanied by a strong T-cell response in patients with resolved HBV infection, adoptive T-cell therapy represents a promising therapeutic approach. We have recently demonstrated that CD8+ T cells grafted with T-cell receptors (TCR) restricted by major histocompatibility complex (MHC)-I have the potential to cure HBV infection in vitro and in vivo. Nevertheless, also CD4+ T cells are known to play an important role in resolving HBV infection and may therefore potentially benefit adoptive cell therapy. We thus aimed at identifying, cloning and characterizing MHC-II restricted TCRs from HBV-specific CD4+ T cells.
Method: HBV peptides derived from surface, core or polymerase antigens were selected by in silico prediction and used to stimulate PBMC from donors who had cleared HBV infection. HBV-specific CD4+ T cells secreting TNF-α were sorted by flow cytometry and clonally expanded from a single-cell level. Subsequently, sequences of TCR α- and β-chains of MHC-II restricted TCRs were identified, codon-optimized and cloned into a retroviral vector combined with murine constant domains. After retroviral transduction, all TCRs were expressed on primary T cells and characterized in depth regarding their MHC-II restriction, specificity, binding affinity and functionality.
Results: A total of 23 TCRs specific for seven different epitopes from HBV surface, core or polymerase antigens were generated. Through co-culture with a panel of partially matched lymphoblastoid cell lines (LCL), six different MHC-II restrictions were identified. They included HLA-DRB1*01, *07, *04 and *13 or HLA-DPB1*02 and *04, with worldwide phenotype frequencies ranging from 5 to 35% each. Seventeen TCRs recognized at least three peptide variants of HBV genotypes A-D and twelve TCRs had a high binding affinity with EC50 values in a low nanomolar range. Similarly, a strong activation by intracellularly processed viral antigen was observed for twelve TCRs. Interestingly, most TCRs were equally able to activate both CD4+ and CD8+ TCR-transduced T cells. Upon antigen recognition, CD4+ T cells secreted predominantly TNF-α and IL-2, whereas CD8+ T cells produced almost exclusively IFN-γ.
Conclusion: Taken together, we generated and characterized a set of 23 MHC-II restricted TCRs recognizing epitopes derived from HBV core, surface and polymerase antigens. These TCRs enabled CD4+ as well as CD8+ T cells to recognize antigen on MHC-II in a nanomolar range, resulting in antigen-specific T-cell activation.

FRI-156

Hyperactivation and proliferation of B cells in hbeag positive hepatitis B patients revealed by high throughput RNA sequencing

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Background and aims: To determine expression profiling of circulating B cells from patients with HBeAg-positive chronic hepatitis B virus (HBV) infection and healthy volunteers with the history of HBV vaccine immunization.
Method: Peripheral blood CD19+ B cells isolated from 4 HBeAg-positive CHB patients and 4 HBV vaccinated healthy controls were analyzed by high-through RNA sequencing. GO analyses and signaling pathway enrichment analysis including KEGG pathway analysis and Reacome pathway analysis were used to identify differentially expressed genes (DEG) among different groups. Our interested gene expressions were further validated by both of qPCR and Flow cytometry.
Results: 1401 differentially expressed genes (DEG) were identified from B cells of HBsAg positive CHB patients versus HBV vaccinated

healthy controls. Interestingly, the DEGs were enriched in biological progress especially in immune system process. The ribosome pathway was down regulated in HBsAg positive chronic hepatitis B patients may result in p53 suppression leading to B cells activation and proliferation. Specifically, we identified that cell activation and proliferation related genes including BACH2, CTLA4, TLR4, NFAM1, ZAP70, NOD2, PELI1 and PRDM1 were upregulated in HBsAg positive CHB patients.

Conclusion: For the first time, we identified a panel of potential genes and signaling pathways associated with the hyperactivation and proliferation of B cells in CHB patients, which might serve as promising targets for novel therapies to treat chronic hepatitis B infection.

Viral hepatitis B/D: therapy

FRI-157

Novel HBV capsid assembly modulator inhibits pregenomic RNA encapsidation by accelerating capsid assembly kinetics and disrupting core protein dephosphorylation

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Background and aims: Currently approved anti-HBV agents do not eliminate cccDNA from infected cells, whereas, some experimental capsid assembly modulators (CAMs) have an important impact in several steps of HBV viral replication including capsid assembly, reverse transcription, and pregenomic RNA (pgRNA) and polymerase protein packaging. Importantly, the dynamic of HBV core protein phosphorylation/dephosphorylation also controls several steps of viral replication and can be altered by these modulators. To better understand how our novel CAM blocks pgRNA encapsidation or cccDNA amplification, we evaluated their impact on core phosphorylation dynamics and HBeAg secretion.

Method: HepAD38 cells were cultured with 5 µM CAMs, (GLP-26 or GLS4). After 7 days, HBV capsids were purified and resolved into fast [DNA-containing capsids = hyperphosphorylated (hyper-P)] and slower migration [(empty capsids or core protein free dimers = hypophosphorylated (hypo-P)] in native agarose gel electrophoresis. Particles were transferred to nitrocellulose membrane, and immunoprobed for capsid imaging. Additionally, HBeAg antigen production (EIA), and pgRNA (RT-PCR) were quantified. Combinations with GLP-26, ETV and TAF were performed in AD38 cells.

Results: GLP-26 enhanced kinetics of capsid assembly that were hyperphosphorylated (Hyper-p = empty capsids and/or core-protein-free dimers), inhibited pgRNA (EC_{50} = 0.11 µM) and HBeAg production (EC_{50} = 0.003 µM). In contrast, GLS4, misdirected capsid assembly to form noncapsid polymers, however with lower inhibition of pgRNA or HBeAg *vs* GLP-26 (28-fold or > 33-fold greater potencies of pgRNA and HBeAg *vs* GLS4. GLP-26-treated cells maintained 2-2.3 log reduction in HBV DNA for 9 days post GLP-26 washout, vs 0.9-1.2 log reduction for ETV or TAF, independent of presence of ETV, TAF or media alone.

Conclusion: These results demonstrate that 1) GLP-26 accelerates capsid assembly kinetics of empty capsids, preventing viral DNA replication via inhibition of pgRNA encapsidation, and 2) GLP-26 alters both capsid structures and core protein dephosphorylation dynamics, which can interfere with pgRNA encapsidation and cccDNA amplification. GLP-26 confers sustained viral suppression for 9 days after removal of drug, similar to reduction in HBV observed for cells maintained with ETV or TAF. These data support additional studies in animals and eventually in humans to evaluate the ability of these agents to control and/or eliminate HBV *in vivo*.

FRI-158

Bone and renal safety are improved in chronic HBV patients switched to tenofovir alafenamide (TAF) after either 2 or 3 years of prior tenofovir disoproxil fumarate (TDF) treatment

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Background and aims: TAF, a novel prodrug of tenofovir, has shown similar efficacy to TDF in Phase 3 studies with less bone and renal effects. As part of a protocol amendment to extend double blind (DB) treatment for 1 additional year (Week 96 to Week 144), only ~50% consented in time for this change; the remainder had already been receiving open-label (OL) TAF after Week 96. Here, we evaluate the 4 year (Week 192) safety and efficacy of switching to OL TAF in patients who had received DB TDF treatment for either 2 or 3 years.

Method: In 2 identically-designed studies, 1298 HBeAg-negative and HBeAg-positive CHB patients (873 TAF, 425 TDF) were randomized and treated with either TAF or TDF. In the TDF group, 180 patients were switched to OL TAF at Week 96 (OL TAF 96 Wk), while 202 patients switched from DB TDF to OL TAF at Week 144 (OL TAF 48 Wk). Safety assessments including changes in bone (hip and spine BMD) and renal (CrCl by Cockcroft-Gault [$eGFR_{CG}$]) parameters, viral suppression, and biochemical responses were assessed at Week 192 using the time of rollover to TAF as the respective OL baseline (BL). Within group changes in bone and renal parameters were assessed by paired t test or Wilcoxon signed rank test.

Renal and Bone Safety at Year 4 (Week 192)

	OL TAF 96 Wk. (N=180)	OL TAF 48 Wk. (N=202)
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	+3.0 (-2.4, +10.2) p<0.0001[a]	+1.5 (-4.8, +9.6) p=0.0212[a]
Hip BMD, mean (SD) % change	n=134 +1.25% (2.69%) p<0.0001[b]	n=190 +0.83% (2.39%) p<0.0001[b]
>3% increase / >3% decrease in hip BMD	18.7% / 5.2%	11.6% / 2.6%
Spine BMD, mean (SD) % change	n=133 +1.56% (3.39%) p<0.0001[b]	n=190 +1.62% (3.12%) p<0.0001[b]
>3% increase / >3% decrease in spine BMD, (%)	34.6% / 9.0%	27.9% / 5.8%

All results expressed as change from open-label (OL) baseline (defined as Week 96 for OL TAF 96 Wk and Week 144 for OL TAF 48 Wk patients). $eGFR_{CG}$ is creatinine clearance by Cockcroft-Gault method, BMD is bone mineral density by dual energy x-ray absorptiometry (DXA), Q is quartile. [a]Week 192 vs OL baseline by Wilcoxon signed rank test; [b]Week 192 vs OL baseline by paired t test.

Results: Patient characteristics were similar for those receiving OL TAF for 1 or 2 years following DB TDF treatment. Significant increases in $eGFR_{CG}$ from OL BL were observed within each group at Week 192 (Table). Significant increases in hip and spine BMD from OL BL occurred within each group, the magnitude was greater after 2 years of OL TAF only for hip BMD. Within each group, virologic suppression (HBV DNA < 29 IU/ml) was maintained from OL BL to Week 192 in patients who remained on TAF treatment (OL TAF 96 Wk group: 88% and 88%; OL TAF 48 Wk group: 94% and 93%, respectively), while at Week 192, within each group the rate of ALT normalization by 2018 AASLD criteria increased from OL BL after switching to TAF (55% OL TAF 96 Wk and 37% OL TAF 48 Wk).
Conclusion: In CHB patients treated with TDF for 2 or 3 years, recovery of renal and bone parameters occurred at Year 4 suggesting reversibility of these parameters. Virologic control was maintained and ALT normalization increased following the switch from TDF to TAF.

FRI-159

Can HBcrAg and pre-genomic HBV RNA predict the risk of ALT flares after nucleoside analogue therapy withdrawal: delineating the clinical utility of new biomarkers?

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Background and aims: We have previously demonstrated that significant ALT flares after nucleos (t)ide analogue (NA) withdrawal in HBeAg-negative non-cirrhotic chronic hepatitis B (CHB) patients who were suppressed on NA therapy for at least 3 years are associated with detectable HBcrAg (> 2 log_{10}U/ml) and detectable pregenomic (pg) HBV RNA (> 1.65 log_{10}U/ml). The proportion of patients with significant ALT flares after stopping NA was 20% in our pilot cohort (n = 15), but data from "real-life" cohorts are lacking. We have evaluated the proportion of non-cirrhotic HBeAg-negative treated patients (fully suppressed with undetectable HBV DNA for at least 5 years on NA) with detectable HBcrAg and pgHBV RNA after 3 and 5 years of therapy.
Method: We have studied 66 HBeAg-negative, tenofovir (TDF) treated non-cirrhotic CHB patients across HBV genotypes (A:18%, B:3%, C:15%, D:15% and E:49%), who had suppressed HBV DNA for at least 5 years (median duration 7.5 yrs, range 5.5 –11.5 yrs). 73% were male, and their median age was 45 years. Plasma samples at baseline, year 3 and year 5 on-treatment were tested for serological/virological markers: HBV DNA by TaqMan (Roche, log_{10}IU/ml); quantitative HBsAg by Abbott Architect [log_{10} IU/ml], HBcrAg levels by CLEIA Fujirebio [log_{10}U/ml] and concentrations of pgHBV RNA were measured using the Abbott Diagnostic real-time PCR assay (Butler E et al, Hepatology 2018) [LLQD = 1.65 log_{10}U/ml]. Baseline and on-treatment levels of serological/virological markers were compared between patients according to detectable HBcrAg/pgHBV RNA vs. undetectable HBcrAg/pgHBV RNA status at year 3 and year 5.
Results: All patients with HBcrAg < 2 log_{10}U/ml had simultaneously levels of pgHBV RNA < 1.65log_{10}U/ml. All patients achieved persistently HBV DNA < 20IU/ml after 6 months of therapy. While at baseline only 4 (6%) patients had undetectable HBcrAg and pgHBV RNA, by year 3, 46 (70%) patients and at year 5, 57 (86%) of treated patients had undetectable HBcrAg and pgHBV RNA. Patients with detectable HBcrAg at year 3 had significantly higher median baseline concentrations of HBV DNA (4.91 vs. 3.99 log_{10}IU/ml), HBsAg (4.01 vs. 3.67 log_{10}IU/ml), HBcrAg (4.45 vs. 3.15 log_{10}U/ml) and pgHBV RNA levels (2.1 vs. 1.79 log_{10}U/ml) (all p < 0.01). At year 3 and year 5 the patients with detected HBcrAg/pgHBV RNA had significantly higher HBsAg, HBcrAg and pgHBV RNA at these time-points than HBcrAg/pgHBV RNA negative patients.
Conclusions: After 3 years on treatment 30% patients have still detectable HBcrAg and pgHBV RNA, suggesting viable transcriptional activity despite nucleoside analogue inhibition of HBV DNA. These data suggest heterogeneity of this cohort and warranting individual approach if NA stopping therapy is considered. Including biomarkers of transcriptional activity, HBcrAg and pgHBV RNA, into the treatment/disease management algorithms should be considered.

FRI-160

The role of soluble propragmmed cell death protein 1 on HBV relapse after cessation of entecavir therapy in HBeAg-negative non-cirrhotic patients

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Background and aims: Recent study showed serum soluble programmed cell death protein 1 (sPD-1) is an important immune-related marker for assessment of HBV activity. However, it remains unclear whether serum sPD-1 levels could predict HBV relapse or HBsAg loss after cessation of nucleos (t)ide analogues (NAs) therapy. The aim of this study is to investigate the role of sPD-1 on HBV relapse and HBsAg loss after discontinuation of entecavir therapy.
Method: A total of 252 HBeAg-negative non-cirrhotic patients who had stopped entecavir treatment for at least 12 months were recruited. sPD-1 levels were check at baseline, end of treatment and post-treatment 6 months. All patients fulfilled the stopping criteria proposed by the Asian Pacific Association for the Study of the Liver (APASL) 2012 guideline.
Results: The mean of sPD-1 levels were 4.81 ± 0.81, 4.19 ± 0.80, 4.20 ± 0.81 log pg/ml, respectively, at baseline, end of treatment and post-treatment 6 months. During entecavir treatment (mean: 169.2 ± 40.1 weeks), sPD-1 decline from baseline to end of treatment was 0.62 ± 0.48 log pg/ml. HBsAg decline levels, HBV genotype C, and higher baseline HBV DNA levels were independent factors of sPD-1 decline. sPD-1 decline levels were correlated with HBsAg decline levels during entecavir therapy (R^2 = 0.55, P < 0.001).
The 6-year cumulative rates of virological relapse, clinical relapse, and HBsAg loss were 70.8%, 57.3%, and 31%, respectively, after cessation of entecavir therapy. Older age, HBV genotype B, higher baseline HBV DNA and end-of-treatment HBsAg levels, and higher sPD-1 levels at post-treatment 6 months were independent factors of virological relapse. Older age, HBV genotype B, and higher sPD-1 levels at post-treatment 6 months were independent factors of clinical relapse. End-of-treatment HBsAg levels was an independent factor of HBsAg loss.
We utilized a sPD-1 at post-treatment 6 months of 3500 pg/ml as the optimal values for predicting HBV relapse and HBsAg loss after cessation of entecavir therapy. Of the patients who achieved sPD-1 < 3500 and ≥ 3500 pg/ml, the 5-year cumulative rates of virological and clinical relapse, and HBsAg loss were 37.6% vs. 81.7%, 27.1% vs. 67.4%, and 49.7% vs. 12.3%, respectively (all p < 0.001).
Conclusion: sPD-1 decline was highly correlated with HBsAg decline during entecavir therapy. sPD-1 levels at post-treatment 6 months was a useful marker to predict HBV relapse and HBsAg loss after discontinuation of entecavir treatment.

FRI-161

Complication is a major risk factor for mortality of cirrhotic hepatitis B virus-related acuted-on-chronic liver failure patients: A multi-national study from Asian-pacific region

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Background and aims: Cirrhosis is a unique entity of chronic liver disease which is still a controversial determinant to mortality of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF).
Method: In this prospective-retrospective study, 709 patients with HBV-ACLF defined by the Asian Pacific Association for the Study of Liver ACLF Research Consortium (AARC) criteria were enrolled from 12 Asian-Pacific countries. Cirrhosis were evaluated as a risk factor intervening short-term (28 and 90 days) transplant-free mortality. Meanwhile, Current main prognostic models Tongji prognostic predictor model score (TPPMs), Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH-ACLFs), CLIF consortium organ failure score (CLIF-C OFs), CLIF-C acute-on-chronic liver failure score (CLIF-C ACLFs), Model for End-Stage Liver Disease score (MELDs) and MELD-sodium score (MELD-Nas) were measured for predicting ability of mortality with area under the receiver operating characteristic curves (AUROCs).
Results: Among 709 HBV-ACLF patients, cirrhotic group (62.91%) showed significantly higher mortality and complications (ascites, infection and gastrointestinal bleeding) than non-cirrhotic group. Only 36.1% and 40.1% of patients met CLIF-C criteria in non-cirrhotic and cirrhotic group respectively, who showed significantly higher mortality and complications than those who did not satisfy the CLIF-C criteria. Furthermore, in major patients who did not meet CLIF-C criteria, cirrhotic group exhibited higher mortality and complication occurrence than non-cirrhotic group, without significant difference of organ failures. TPPMs (0.870, 0.792), who set number of complications as determinants, showed prior ability than COSSH-ACLFs (0.843, 0.773), CLIF-Cs (0.819, 0.753), CLIF-OFs (0.735, 0.698), MELDs (0.784, 0.727) and MELD-Nas (0.773, 0.733), in cirrhotic patients. Number of complications more than 1 was an independent risk factor in cirrhotic HBV-ACLF patients.
Conclusion: Cirrhosis has its advantages in HBV-ACLF risk stratification. TPPMs possess high predicting ability in cirrhotic HBV-ACLF patients. Complication other than organ failure is the major risk factor for mortality of cirrhotic HBV-ACLF patients.

FRI-162

Prime-boost vaccination strategies using chimpanzee-adeno and MVA viral vectored vaccines encoding multiple HBV antigens (CPmutS) and class II invariant chain molecular adjuvants induces robust T-cell and anti-HBs antibody response in mice

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Background: Current therapies for HBV suppress viral load but rebound occurs on cessation of therapy; novel therapeutic strategies are urgently required.
Aim: To develop a potent therapeutic HBV vaccine that will induce B and T-cells to all major HBV antigens.
Method: First generation HBV immunogens (HBV-$CP_{mut}S$) with and without class II shark invariant chain (SIi), were designed to encode precore (PreC), core, non-functional polymerase (P_{mut}) and large surface antigen in chimpanzee adenoviral (ChAd) vectors [Figure 1a (i)]. These were then modified for incorporation into ChAds and Modified Vaccina Ankara (MVA): SIi, PreC, core, P_{mut}, NΔPreS1 and PreS2 were generated under a CMV (ChAd) or F11 (MVA) promoter to induce HBV specific T cells, whilst tissue plasminogen activator (TPA), CΔPreS1 and surface was generated separately using F2A (in ChAds) or mH5 promoter (in MVA) in order to generate envelope protein and anti-HBV B cell responses [Figure 1a (ii)]. The order of the HBV (core, pol and Pre-S1 and pre-S2) genes were rearranged within the ChAd and MVA to prevent the generation of immune responses to inter-gene regions when used in prime boost strategies. Vaccines were tested in CD1, Balb/c and C57BL6 mice. HBV-specific T-cell responses were assessed using IFN-ϒ ELISpot and intracellular cytokine (ICCS) assays. Anti-HBs antibodies were assessed using ELISA.
Results: The inclusion of SIi significantly enhanced T-cell magnitude of spleen lymphocytes (3821 vs. 386 mean total SFU/10^6 splenocyte, $p < 0.0001$, in CD1 mice). ChAd vaccine alone generated very high magnitude of CD8+ HBV specific T-cell responses to all HBV antigens, but CD4+ responses and HBsAb responses were not detected. MVA prime vaccination alone induced low level T-cell response at 878 SFU/10^6 splenocytes in Balb/c mice. However, ChAd prime/MVA boost showed induction of high magnitude of T cells (4022 and 6063 mean total SFU/10^6 splenocytes in Balb/c and C57BL6 respectively) (Figure 1b) and anti-HBs antibodies. ICCS showed that HBV specific CD8+ and CD4+ T cells were highly polyfunctional producing IFN-ϒ, TNF-α, and IL-2. Importantly, T cells to the non-HBV SIi, F2A and the inter-gene regions were not generated.
Conclusion: We have generated genetically adjuvanted ChAd and MVA vectored HBV vaccines that induce high-magnitude B and T cells, for use in prime/boost vaccination strategies. These pre-clinical studies pave the way for new studies of HBV immunotherapy in humans with chronic HBV infection.

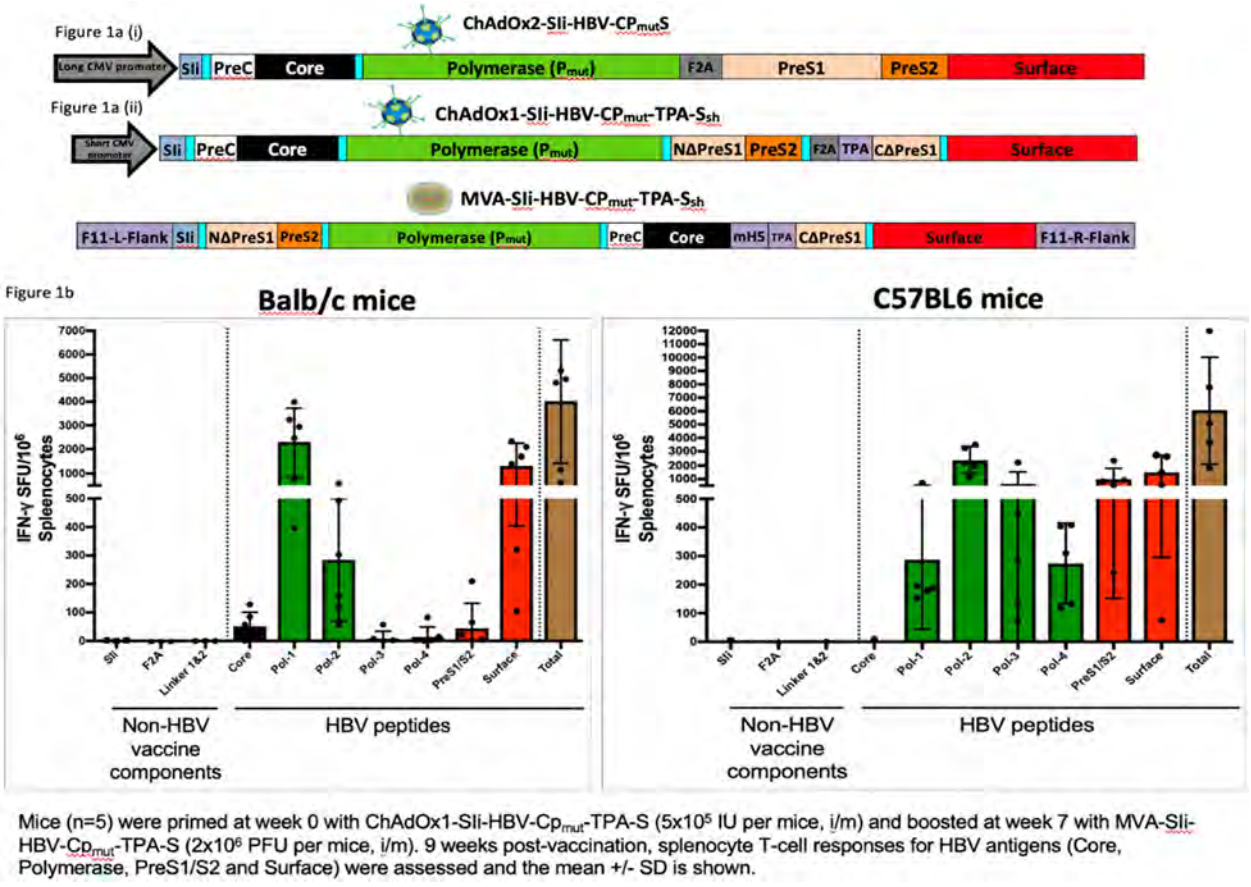

Figure 1: (abstract: FRI-162): (a) ChAd/MVA HBV vaccines. (b) IFN-ϒ ELISPOT response to ChAdOx1-SIi-HBV-CP_{mut}-TPA-S_{sh} prime and MVA-SIi-HBV-CP_{mut}-TPA-S_{sh} vaccination

FRI-163

Reduced liver-related complications after 13 years of follow-up of interferon-alpha treatment for HBeAg-positive chronic hepatitis B: The ELITE-B study

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Background and aims: Interferon-alpha (IFN-α) treatment of chronic hepatitis B (CHB) is finite and leads to relatively high loss of serum HBeAg and HBsAg compared to nucleo (s)tide analogue (NA) therapy. Response to IFN-α treatment and its long-term clinical outcomes are of great interest for current drug development.
Method: All consecutive HBeAg-positive patients treated with IFN-α or PEG-IFN-α at a European tertiary center between 1978 and 2014 were included. We reviewed medical charts and consulted the Municipal Person Records Database for patient information. Patients were invited for a single visit at the outpatient clinic in case of missing follow-up data. The end points included serologic (HBeAg/HBsAg loss), biochemical (ALT normalization), and virologic response (HBV DNA < 2000 IU/ml) at long-term follow-up (LTFU) and incidence of liver-related clinical events (decompensation/HCC), stratified by presence or absence of response. Person-years and 95% confidence intervals (CI) were used to analyze the incidence of liver-related events. Lookback period was used to prevent overestimation of incidence. Patients were excluded if events were reported < 6 months of the first IFN-α treatment start date (baseline).
Results: A total of 261 HBeAg-positive patients treated with (PEG) IFN-α were included in the analysis. The mean follow-up duration was 13 years. The cohort was mostly male (67%), with a median age of 31 years, and 57% Caucasian vs. 34% Asian. The median duration of the first (PEG)IFN-α treatment course was 27 weeks. At LTFU, HBeAg loss was found in 169 (65%) and HBsAg loss in 64 (25%) patients. The incidence of HBsAg loss was 2.3 per 100 person-years during a total follow-up of 2927 person-years. The incidence of liver-related events per 100 person-years was significantly lower in patients who achieved biochemical response (0.3 (0.1-0.6) vs.1.3 (0.7-2.3)), virologic response (0.2 (0.1-0.5) vs 1.8 (1.0-3.4)) and HBeAg loss (0.2 (0.1-0.5) vs 1.5 (1.0-2.5)). There was no reduction in the incidence of liver-related events with respect to HBsAg loss (0.5 (0.2-1.5) vs 0.6 (0.4-1.1)). Patients who achieved HBsAg loss were significantly older at baseline compared to those who did not have HBsAg loss, and the 3 patients who lost HBsAg but experienced a liver-related event during follow-up were all cirrhotic at baseline.
Conclusion: In our large single tertiary centre cohort with the longest follow-up duration to date, the risk of liver-related adverse outcomes was profoundly reduced, however not fully eliminated with HBeAg loss, and biochemical and virologic response to (PEG)IFN-α treatment. HBsAg loss did not lower the risk, presumably due to presence of cirrhosis and older age at the start of treatment.

FRI-164

Prognostic value of various liver scoring systems in cirrhotic chronic hepatitis B patients with and without tenofovir disoproxil fumarate treatment

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Background and aims: Various scoring systems predict risk of decompensating events and deaths (Child-Pugh, model for end-stage liver disease [MELD], albumin-bilirubin [ALBI]) and chronic hepatitis B (CHB)-related hepatocellular carcinoma (CU-HCC, REACH-B, PAGE-B). The performance of these scores in CHB patients with cirrhosis treated with tenofovir disoproxil fumarate (TDF) is unclear. We aimed to investigate the predictive value of these scores for hepatic decompensation, hepatocellular carcinoma (HCC) and death.

Method: Two CHB cirrhotic cohorts were retrospectively studied. Cirrhosis was defined by liver histology, thrombocytopenia (< 150×10^9/L) and/or features of portal hypertension on imaging. TDF cohort included consecutive patients from 3 tertiary centres (Hong Kong, South Korea, United States) who received TDF 300 mg/day for ≥ 12 months. Control cohort included historical untreated patients.

Results: 808 TDF-treated and 291 control patients were studied. There were 72 decompensating events, 113 HCC and 41 deaths at 5 years follow-up. Among untreated controls, baseline Child-Pugh, MELD and ALBI scores were predictive for decompensation and death at 5 years (**Table 1**). Child-Pugh, MELD, REACH-B and CU-HCC scores were predictive for HCC. The best areas under receiver operator characteristics curve for decompensation, HCC and death were Child-Pugh, CU-HCC and ALBI, respectively. Among TDF-treated patients, scores lost their predictive value for events except Child-Pugh, and CU-HCC was still predictive for HCC and PAGE-B became predictive for HCC. TDF treatment led to significant improvements after 1-year follow-up compared to baseline which were sustained at 5 years follow-up in all scores except PAGE-B and ALBI.

Table 1: Predictive value of each scoring system based on univariate Cox regression model for liver events and deaths at 5-years follow-up

SCORE	UNTREATED PATIENTS			TDF-TREATED PATIENTS		
Decompensation	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Child-Pugh	2.32	1.76–3.05	**< 0.001**	1.25	0.39–4.00	0.712
MELD	1.22	1.13–1.31	**< 0.001**	1.10	0.92–1.30	0.288
ALBI	6.18	4.14–9.22	**< 0.001**	1.66	0.62–4.47	0.318
HCC	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Child-Pugh	1.84	1.38–2.45	**< 0.001**	1.37	1.03–1.82	**0.032**
MELD	1.16	1.04–1.29	**0.008**	1.02	0.93–1.11	0.696
CU-HCC	1.09	1.03–1.15	**0.002**	1.05	1.02–1.08	< 0.001
REACH-B	1.31	1.04–1.64	**0.021**	1.04	0.96–1.12	0.393
PAGE-B	1.03	0.93–1.15	0.556	1.09	1.03–1.16	**0.007**
Death	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Child-Pugh	2.18	1.54–3.09	**< 0.001**	0.85	0.18–4.00	0.832
MELD	1.35	1.19–1.52	**< 0.001**	0.97	0.69–1.38	0.883
ALBI	4.89	2.84–8.74	**< 0.001**	1.22	0.23–6.41	0.816

Conclusion: Baseline liver prognostic scores have predictive value for decompensation, HCC and death in untreated CHB patients with cirrhosis which is diminished or lost in TDF-treated patients. TDF treatment led to sustained improvements in most prognostic scores.

FRI-165

No detectable resistance to tenofovir in patients with Adefovir- and Entecavir-resistant chronic hepatitis B after 240 weeks of treatment with tenofovir disoproxil fumarate monotherapy

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Background and aims: A major challenge in the treatment of chronic hepatitis B (CHB) patients is to maintain long-term viral suppression without emerging the drug-resistant mutations. Monotherapy with tenofovir disoproxil fumarate (TDF) is efficacious in patients with lamivudine-, entecavir- (ETV), or adefovir (ADV) resistant hepatitis B virus.

Method: We conducted two multicenter, randomized, open-label trials (IN-US-174-0202 and IN-US-174-0205) designed to compare the efficacy and safety of TDF monotherapy with that of TDF + ETV combination therapy in multiple-drug CHB patients with multiple drug failure and persistent viremia. Patients were randomized 1:1 to receive TDF monotherapy or TDF + ETV combination therapy for 48 weeks, and then to maintain TDF monotherapy or to switch to TDF monotherapy. One study enrolled patients with ETV-resistance without ADV-resistance (n = 90), and the other patients with ADV-resistance (n = 102). Resistance mutations were determined by restriction fragment mass polymorphism analyses and direct sequencing of the pol/RT. Resistance profile was surveilled for patients who experienced virologic breakthrough (VB: increases in HBV DNA levels ≥ 1 $\log_{10}$ IU/ml from nadir on two consecutive tests) or persistent viremia (HBV DNA > 60 IU/ml) at Week 240 or discontinuation.

Results: Over the 240-week treatment period, 94 patients with ADV-resistance and 82 patients with ETV-resistance completed up to 240 weeks of TDF monotherapy. Three (3.3%) patients in the ETV-resistance group and 4 (3.9%) patients in the ADV-resistance group experienced VB ($p > 0.99$). All of which were associated with decreased adherence to study medication (less than 80%) and were transient requiring no treatment modification. During VB, some of the baseline resistance mutations, but no additional substitutions, were detected in pol/RT region of HBV in the patients. Among the 12 patients who discontinued the study, none had VB at drop-out, but 2 had HBV DNA > 60 IU/ml at the last time point of treatment, where no additional substitutions were detected in pol/RT gene compared to baseline. At week 240, 1 and 8 patients in the ETV-resistance and ADV-resistance groups, respectively, had HBV DNA levels > 60 IU/ml ($p = 0.04$). Among them, 2 patients in the ADV-resistance group had at least one detectable HBV resistance mutation at week 240, all of which were present at baseline. No patients developed additional substitutions in pol/RT compared to baseline.

Conclusion: TDF monotherapy maintains effective suppression of HBV DNA through 240 weeks of treatment with no evidence of additional resistance mutations in patients with ADV- and ETV-resistant CHB.

FRI-166

Treatment recommendations for chronic hepatitis B and the risk of hepatocellular carcinoma

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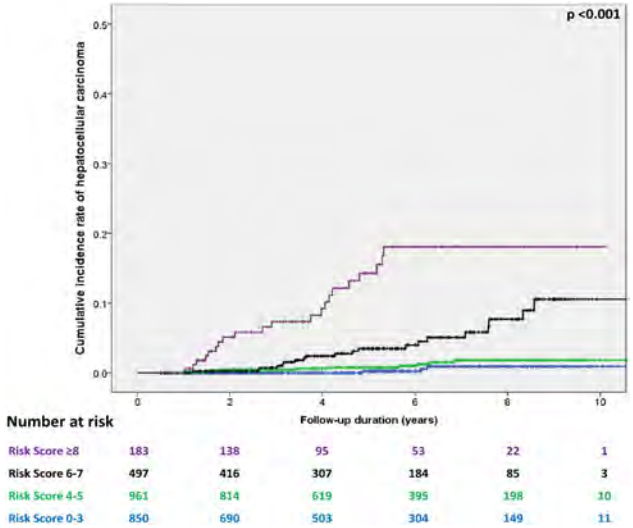
Background and aims: Ideally, those who are not indicated for antiviral therapy for chronic hepatitis B virus (HBV) infection should be at null risk of developing hepatic complication. We assessed the incidence of hepatocellular carcinoma (HCC) in those outside of current treatment recommendations and risk factors associated with HCC development.
Methods: A multi-center, retrospective cohort of 3, 624 patients who were monitored without antiviral treatment was analyzed. Incident HCC risk according to the Asian Pacific Association for the study of the Liver (APASL), the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) treatment recommendations was assessed. Risk score was developed using independent factors associated with HCC development among patients who were outside current treatment criteria.
Results: During a median follow-up of 4.6 years, incident HCC was diagnosed in 161 (4.4%) patients. Proportions of patients developed HCC outside treatment recommendation according to APASL, AASLD, and EASL criteria were 64.0%, 46.0%, and 33.5%, respectively. The 5-years cumulative HCC incidence rate was 13.9% for cirrhotic patients with low-level viremia and 6.1~7.3% for chronic hepatitis patients with elevated HBV DNA levels plus mildly elevated alanine aminotransferase levels. Among patients who were outside treatment recommendation, age, sex, hepatitis B e antigen, cirrhosis, alanine aminotransferase, and platelet levels were independent factors associated with HCC development. When these factors were used to calculate risk score for each patient, those with score ≥ 8 showed high HCC incidence rate (14.3% at 5-year), although they were currently outside treatment recommendation.



Conclusion: HCC was observed among patients who were outside current treatment criteria indicating careful attention for HCC and efforts to identify patient at risk are required.

FRI-167

Effectiveness and safety with tenofovir alafenamide (TAF) for hepatitis B in US clinical practice

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Background and aims: TAF provides similar efficacy to tenofovir disoproxil fumarate (TDF) but with an improved safety profile particularly for renal injury. Here, we assess clinical experience with TAF for patients with HBV in US Clinical Practice.
Method: The TRIO HBV Registry, consisting of 1078 enrolled patients from 6 academic and 4 community-based centers serving 17 US States, was created to understand real-world HBV treatment. Data presented here are limited to 250 registry patients who initiated TAF between Nov 2016 and Apr 2018, received ≥ 6 months of TAF therapy, and were followed up to 18 months. Baseline measures were closest to but between −30 to +60 days from regimen start. Measures in other time periods were those with the maximum date while on TAF. Comparisons to baseline were made using paired 2-tailed T-Tests. eGFR was calculated using the CKD-EPI equation.
Results: Characteristics of the study population: median age 52 years, BMI 24.3 kg/m2, male (147/250, 59%), Asian ethnicity (220/250, 88%), HBeAg positive (54/250, 22%), osteopenia/osteoporosis (47/250, 19%), and FIB-4 > 3.25 (17/250, 7%). Mean and median TAF duration was 13 months as of data collection. 233/250 (93%) of patients receiving TAF switched from TDF (214/233, 92%), entecavir (16/233, 7%), or other therapies (3/233, 1%). At TAF initiation, 17/250 (7%) patients had baseline HBV DNA ≥ 2000 IU/ml. Of the 17, 16 patients had controlled HBV (< 2000 IU/ml) after 6 or 12 months of TAF therapy. One patient had a 50% viral reduction to 30, 000 IU/ml after 6 months of therapy but did not achieve suppression. 233/250 (93%) patients had baseline HBV DNA < 2000 IU/ml; of these, 226 were assessed after 6 or 12 months of therapy and all had maintained HBV suppression (< 2000 IU/ml). 224/250 (90%) patients had baseline eGFR ≥ 60 ml/min and 26/250 (10%) < 60 ml/min with minimum 28 ml/min. In paired comparisons, mean eGFR increased 5% from baseline 85.7 to 90.1 ml/min ($p < 0.001$) after 6 months of TAF therapy ($n = 213$). Of 158 patients with eGFR measures after 12 months of TAF, the mean eGFR increase was 4% from baseline 86.9 to 90.5 ml/min ($p = 0.001$). For patients with baseline eGFR < 60 ml/min, mean eGFR increased 16% from 48.4 to 56.0 ml/min after 6 months ($n = 24$, $p < 0.001$). In the eGFR < 60 ml/min subset with 12+ months of TAF, the change in eGFR was 14% from baseline 54.0 to 61.4 ml/min though this change did not reach significance ($n = 11$, $p = 0.066$).
Conclusion: In US, clinical practice experience with TAF indicates effective HBV suppression after switching and improved renal function in real-world application. Continued long-term monitoring is critical to assess potential effects of prolonged treatment with lower dose tenofovir.

FRI-168

Understanding HDV and HBsAg kinetics during nucleic acid polymer REP 2139 mono-therapy in HBeAg-negative chronic HBV/HDV co-infected patients via mathematical modeling

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Background and aim: REP 2139-Ca and REP 2139-Mg were previously shown to clear hepatitis B surface antigen (HBsAg) and establish functional control/cure in chronic HBV infection. In a recent study (REP 301) REP 2139-Ca also eliminated detectable HDV viral load in chronic HBV/HDV co-infection and established functional control/cure of HDV. Here we sought to estimate HDV-HBsAg-host parameters and REP 2139-Ca efficacy against HDV and HBsAg using mathematical modeling.

Method: Twelve treatment naive HBeAg negative participants with high serum HDV RNA and serum HBsAg concentrations of more than 1000 IU/ml with documented chronic HDV infection for 10 months to 18 years were recruited as described (Lancet Gastroenterol Hepatol.2017;2 (12):877–889). Serum HDV and HBsAg levels were measured every two weeks. A dual mathematical model of HDV and HBsAg dynamics (Hepatol. 2014; 60 (6): 1902–1910) was modified to account for a direct effect of REP 2139-Ca in blocking HDV production consistent with the direct interactions of REP 2139 with HDAg reported in a recent in vitro study (Hepatol. 2017;66 (Suppl1): 504A). The model was simultaneously fit to measured data during REP 2139-Ca monotherapy. Two patients were excluded from modeling due to late response or early fluctuations in HDV during REP 2139-Ca monotherapy.

Results: Mean baseline values for HDV and HBsAg were 6.6 [IQR 6.08–7.1] Log U/ml and 4.2 [4.0–4.4] log IU/ml, respectively. The model was able to simulate/estimate the simultaneous decline of HDV and HBsAg at 25 days [16–35] in 8 of 10 participants as well as the earlier HDV decline at 25 [19–30] days compared to HBsAg decline at 32 [20–33] days observed in the remaining 2 participants. HBsAg and HDV clearance rates were estimated to be 0.42 [0.34–0.53] and 0.31 [0.27–0.38]/d corresponding to HBsAg half-life of $t_{1/2}$ = 1.65 d and HDV $t_{1/2}$ = 2.2 d, respectively. The HDV-infected cell death/loss was estimated to be 0.056 [0.024-0.078]/d corresponding to an infected cell $t_{1/2}$ = 12.4 d. The overall efficacies of blocking HDV and HBsAg production were 98.3 [97.0–99.9] % and 96.5 [94.1–99.6]%, respectively, with both efficacies over 99% in 50% of patients.

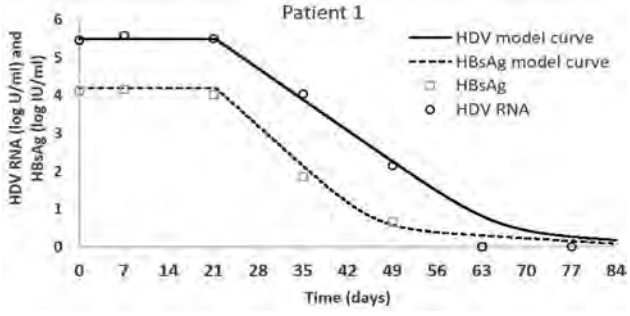

Figure: A representative model fit with measured HDV and HBsAg data during REP 2139-Ca monotherapy. ALT and anti-HBs remained unchanged (not shown)

Conclusion: During REP 2139-Ca monotherapy, inhibition of both HDV and HBsAg production was observed in 83% of REP 2139-Ca treated participants. The decrease in HDV RNA prior to the decline in HBsAg observed in 2 participants is consistent with a direct effect of NAPs on HDV independent of blocking HBsAg production, however the ability of the model to support this direct effect is limited by the sampling frequency available. Modeling provides important new insight into HDV and HBsAg kinetic parameters and REP 2139-Ca efficacy in blocking HDV and HBsAg. This modified dual model could be used to guide treatment duration.

FRI-169

Liver transplantation for hepatitis B induced end stage liver disease: Is it possible to do away with anti virals after liver transplantation?

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Background and aims: Hepatitis B induced end stage liver disease/ hepatocellular carcinoma is one of the leading causes of liver transplantation in Asian countries. Recurrence of Hepatitis B (HBV) has always been a concern in patients undergoing liver transplantation (LT) for HBV. Most strategies revolve around use of peri operative HBV immune globulin (HBIG) and long term use of antivirals (entecavir/tenofovir). Our group has previously shown that successful LT is possible without the use of HBIG[1], and such patients have remained recurrence free in the long term. This study aims to demonstrate that even withdrawal of antivirals is possible in patients undergoing LT for HBV.

Method: All patients undergoing LT for HBV induced end stage liver disease/HCC between January 2014 and June 2017 were included in the study. Pre operative anti viral treatment status, HBV DNaA levels were assessed as well as the MELD score where applicable. Demographic characteristics like sex, age distribution, country of residence was included. Post operative antiviral treatment and immunization status was recorded as well as anti HBs antibody titres to detect sero conversion. HBV DNA levels in the post operative period were assayed. Survival rate, HBV recurrence rate were assessed.

Results: 963 LT were performed in our center between Jan 2014 and June 2017, out of which 173 cases (17%) were due to HBV either alone or in combination with HDV/HCV or both. 155 (90%) were on antivirals prior LT. None of the recipients received HBIG perioperatively. All recipients received antivirals (entecavir-85%, tenofovir-15%) after LT. Post operative immunization was given to all recipients, first dose of the three dose regimen being given at least 3 months after transplant. Anti HBs antibody titres were measured 4 to 6 weeks after the last dose of vaccine. Patients who achieved an anti HBs antibody titres of more than 10 IU/ml underwent a HBV DNA quantitative analysis and 100% were found to have undetectable levels. Such patients accounted for upto 6% of the total LT recipients. No increase in HBV recurrence was seen in this subgroup of patients on follow-up.

Conclusion: Post LT anti virals can be discontinued in upto 6% of recipients in our series without any increase in recurrence in this subgroup of patients.

FRI-170

Real-world effectiveness and renal safety of tenofovir alafenamide fumarate among chronic hepatitis B patients in Canada

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Background and aims: Tenofovir alafenamide fumarate (TAF), a new prodrug of tenofovir, has recently been approved for chronic hepatitis B (CHB) treatment. In phase 3 studies with highly selected patients, TAF resulted in fewer renal adverse changes compared to tenofovir disoproxil fumarate (TDF). We aimed to study the effectiveness and renal safety of TAF therapy in a real world setting among CHB patients in Canada.
Method: CHB patients from 9 academic institutions across Canada who received TAF (either Nucleot (s)ide Analogue (NA) naïve or experienced) were studied as part of the Canadian Hepatitis B Network (CanHepB). Kidney function was measured by serum creatinine, estimated glomerular filtration rate (eGFR) as per Cockcroft-Gault and serum phosphate. Patients who received TDF with eGFR between 60 and 90 ml/min/1.73m^2 before switching to TAF were followed 72 weeks before and after switching.

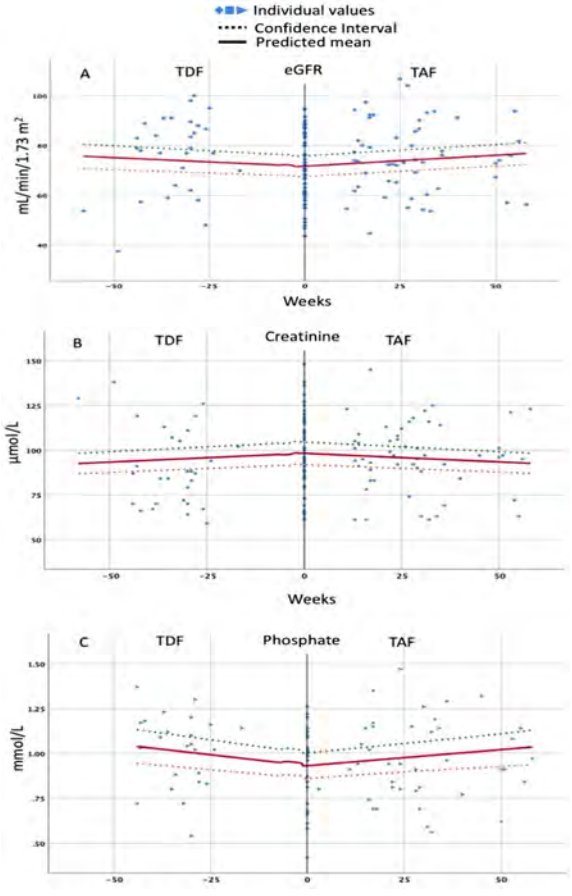

Figure: A. Changes in eGFR; B. Changes in Creatinine; C. Changes in Phosphate

Results: Of 170 patients receiving TAF, 107 (63%) switched from TDF, 43 (25%) switched from another NA and 20 (12%) were NA naïve. Overall, at start of TAF treatment (baseline), the mean (SD) age was 52 (12) years, 122 (74%) patients were male and 66/16/10% of patients were Asian/Caucasian/Black. Majority had HBV DNA < 20 IU/ml (82%), 51 (38%) were HBeAg positive and mean eGFR (SD) 82.7 (21.4).

Among the TDF switch group, eGFR declined within the mild renal impaired group (−0.01 [95 CI% −0.1-0.0] per week; P = 0.05) and creatinine increased during TDF therapy (+0.10 [0.04-0.16] µmol/L per week; P < 0.001). After TAF switching, creatinine decreased significantly (−0.10 [95 CI% 0.04–0.16] µmol/L per week; P = 0.04) and eGFR increased significantly (+0.09 [0.02- 0.15] per week; P = 0.01). Serum phosphate decreased during TDF therapy (−0.002 [−0.005–0.0001] mmol/L per week; P = 0.03) and increased following TAF switch (+0.001 [0.00-0.003] mmol/L per week; P = 0.03). Patients with eGFR > 90, showed no significant change after switching to TAF (+4.26 [10.70–2.43; P 0.73). ALT showed a declining trend after switching (−0.002 [−0.003–0.0002] $\log_{10}$ IU/ml per week; P = 0.08) and HBV DNA remained suppressed. Among the other NA switch group, ALT showed a declining trend from baseline to 24 weeks (−0.6 [−1.4–0.2] × upper limit normal (ULN), p = 0.1).
Among NA naïve group, serum HBV DNA and ALT levels declined significantly from baseline to 24 weeks (mean [95% CI]: −3.8 [−4.8–2.8] $\log_{10}$ IU/ml, P < 0.001; −1.8 [-2.6–1.0] (ULN), p < 0.001).
Conclusion: In CHB patients previously on TDF with mild renal impairment, switching to TAF led to a significantly improved kidney function. Viral load remained suppressed and ALT levels minimally declined. NA Naïve patients showed a significant decline in DNA and downward trend in ALT levels. Extended follow-up in a larger population will be presented at the meeting.

FRI-171

A phase 1 single ascending dose study of the safety, tolerability and pharmacokinetics of CRV431

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Background and aims: CRV431 is a non-immunosuppressive cyclosporine A (CsA) analog that displays a variety of therapeutic activities in experimental models as a result of its potent inhibition of cyclophilin isomerases. In a mouse model of non-alcoholic steatohepatitis CRV431 reduced liver fibrosis and tumor burden. In cellular and *in vivo* models of HBV infection CRV431 reduced HBV DNA, HBsAg, HBeAg, pregenomic RNA and cccDNA. Single dose rat and monkey studies demonstrated dose-dependent CRV431 exposures and half-lives ($t_{1/2}$) greater than 24 hours. These experiments along with other preclinical safety, ADME, and early toxicology results led to the development of a clinical program. The present, single human dose study was designed to investigate safety, tolerability, and pharmacokinetics of CRV431.
Method: In this phase 1 study, single ascending oral doses of 75, 225, 325, and 525 mg CRV431 were administered sequentially to cohorts of 8 healthy subjects randomized 6:2, active: placebo. CRV431 was administered orally in a self-microemulsifying drug delivery system (SMEDDS) formulation in an aqueous medium. Placebo consisted of the SMEDDS formulation, without CRV431. Serial evaluations of adverse events (AEs), physical examinations (PE), concomitant medications, vital signs, clinical safety laboratory tests, and ECGs were collected. Whole blood levels of CRV431 were quantitated using a validated LC-MS/MS methodology.
Results: Data from the 75 mg, 225 mg 325 mg and 525 mg healthy volunteer cohorts showed that CRV431 was rapidly absorbed with T_{max} values ranging from 1-4 hours. Whole blood exposure, $AUC_{inf\text{-}obs}$ and C_{max}, of CRV431 was dose-related up to the 325 mg and ranged from 20, 917-103, 833 hr.ng/ml and 334-1655 ng/ml, respectively, across the four cohorts. Terminal elimination t½ was approximately 100 hours.
Safety results demonstrated that CRV431 was well tolerated with no serious adverse events (SAE), no dose-limiting toxicities or dose-dependent adverse events. Overall, the incidence of adverse events

and laboratory abnormalities was low and similar among cohorts. All AEs were mild and not drug related.
Conclusion: CRV431 appeared to be safe and well tolerated. The favorable safety profile, pharmacokinetic profile and *in vitro* anti-viral results warrant further clinical development of CRV431 in HBV-infected patients.

FRI-172
Outcomes of response guided therapy with pegylated interferon alpha 2a in chronic hepatitis B and D
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Background and aims: Pegylated Interferon alpha is currently the only available drug for the treatment of chronic hepatitis D. The reported on-treatment virologic response varies between 17 and 47% with relapses in more than 50% of these patients. No stopping rules have been defined and the duration of the treatment is not clearly established, but should be within 48 and 96 weeks.
Method: 76 patients with compensated liver disease treated with peginterferon according Romanian National protocol for the treatment of hepatitis D were retrospectively analysed. According to our protocol, the duration of treatment is up to 96 weeks, with the following stopping rules: less than 2 log HDV RNA decrease by week 24 and less than 1 log decrease every 6 months afterwards. 6 months after stopping the treatment, it can be restarted for unlimited cycles. We monitored our patients for a total period of 4 years (including those that repeated the cycle).
Results: 45 men and 31 women, with a mean age of 44 years and a mean body mass index of 26.2 were included. 13 patients had HBV DNA values greater than 20000 IU/ml, in the others HBV was supressed. 4 patients were HBe Ag positive. 16 patients had cirrhosis, 18 F3, 7 F2 and 35 F0 or F1 according to non-invasive assessments prior treatment.
During the first course of therapy, 45 patients had at least one moderate adverse reaction to treatment, most frequently neutropenia. In one patient, the treatment was stopped due a serious adverse event (osteomyelitis). Treatment doses had to be reduced in 19 patients.
After the first 6 months of treatment, 27 patients (35.5%) had a greater than 2 log HDV RNA decrease, 19 of them achieving undetectable HDV RNA. 17 patients (22.3%) had undetectable HDV RNA 24 weeks after stopping 96 weeks of treatment and none relapsed in the following 2 years. Of these 17 patients, 6 were cirrhotic, 4 had F3. Lower fibrosis stage was not a predictor for a favourable virologic response. Undetectable HDV RNA at 24 weeks was the only parameter that predicted a long-term suppression of HDV RNA. In 49 patients, the treatment was stopped after 6 months according to our national guidelines, but it was restarted 6 months after. 5 of these patients finished a 48 weeks course of treatment, none achieved undetectable HDV RNA.
Conclusion: Using stopping rules like the one we used might select the patients in which long term suppression can be achieved. Undetectable HDV RNA at week 24 is an independent predictor for long term HDV suppression.

FRI-173
Modeling HBV kinetics in mice treated by a novel TLR7 agonist, alone or in combination with entecavir
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Background and aims: Current antiviral treatment do not eradicate virus and need to be taken lifelong to present virus resurgence. The main obstacle to cure is the fact that the virus is able to escape from the immune response, via the production of a large amount of subviral particles (SVPs) coated with HBs-antigen (HBsAg) that act as a decoy for the immune response. In order to stimulate the immune response, a promising strategy is to use a toll-like receptor 7 (TLR7) agonist, that induces the production of IFN-α and cytokines and stimulates antigen presentation. Here we aimed to use a viral dynamic model to characterize for the first time the antiviral response during treatment with a TLR7 agonist used alone or in combination with ETV
Method: We used data collected by Hoffmann-La Roche in a mouse model. A total of 118 animals were analyzed, treated with either a placebo (n = 24), ETV (n = 6), TLR7 agonist (n = 76), or the combination of both (n = 12) at various dosing regimen and for period of 6 to 9 weeks of treatment. We developed a viral dynamic model that describes the interplay between virions, SVPs and antibodies. We hypothesized that TLR7 agonist may induce the production of anti-HBs. However, a low amount of anti-HBs may be rapidly occupied by binding to virions and SVPs and forming immune complexes, and such immune complex-associated antibodies can be difficult to detect. The immune complexes may be eliminated and cause an extra decay of their kinetics.
Results: A model of chronic hepatitis B, integrating the role of anti-HBsAg in virus elimination, could successfully reproduce all the observed data in both monotherapy and combination groups. ETV efficiently blocked HBV DNA production (ε = 99.9999%) but had no effect on HBsAg or anti-HBs titers. In contrary, the TLR7 agonist had a triple mechanism of action, whereby production of both virions and SVPs were successfully blocked. Production of virions could be reduce 93.80% for and 99.70% at the dose of 100 mg/kg QW and QOD, respectively, whereas reduction of the production of SVPs could be reduced by 99.70% up to 99.97%. In addition, our model suggested that the treatment led to an increase in anti-HBs concentrations, thereby allowing for further reduction of viremia and HBsAg titers on the long run. Eventually, a model assuming a Loewe additivity of ETV and the TLR7 agonist in reducing virion production could well reproduce the data observed during combination therapy.
Conclusion: The model provides a novel framework to analyze the effect of immunomodulatory drugs that is consistent with destabilization of viral production and stimulation of antibody production, which may contribute as combination partner in the perspective of a cure. Future analyses including other drugs in combination with TLR7 agonist and clinical studies are needed to confirm the potential of this therapeutic class.

FRI-174
Discovery of novel therapeutic targets for decreasing HBsAg, focusing on host proteins binding to HBV RNAs
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Background and aims: Chronic hepatitis B virus (HBV) infection remains a major health concern, with an estimated 240 million chronically infected patients worldwide. The indications of chronic HBV infection are high levels of viral load (HBV DNA) and significantly larger numbers of noninfectious particles containing viral S antigen

(HBsAg). Currently approved drugs, nucleos (t)ide analogues, effectively reduce HBV DNA but only rarely result in a functional cure (defined as sustained HBsAg loss). Therefore, a critical need arises for novel therapies that reduce HBsAg levels and restore virus-specific immune responsiveness in patients. We have found that two subregions in 3' untranslated region of 2.1/2.4 kb HBV RNAs, here referred as "region X" and "region Y," regulate HBsAg production (unpublished data). Here, focusing on region X and Y, we aimed to screen host proteins to identify novel therapeutic targets reducing HBsAg.

Method: Host proteins binding to region X and Y were determined by following two methods. (1) The lysate of HepG2.2.15 hepatoblastoma cells was incubated with *in vitro*-transcribed RNA corresponding to above two regions, and binding proteins were pulled-down. The proteins pulled-down were identified by SDS-PAGE and LC-MS/MS. (2) Host proteins binding to region X and Y were presented by searching an RNA-binding protein database. siRNAs specific to the proteins determined by above two methods were transfected into HepG2.2.15 cells, and the effects on the HBsAg production were analyzed.

Results: Among those proteins either identified by pull-down assays or presented by database search, knockdown of 7 proteins showed potent anti-HBsAg effects, more than 90% reduction in HBsAg, without affecting cell viability. Interestingly, these were all nuclear-localizing proteins. Some of them were reported to regulate RNA splicing, stability or nuclear export of mRNA while the others were functionally unknown. Then, expression levels of 2.1/2.4 kb HBV RNAs were quantified, and silencing of these proteins showed less than 80% reduction in those RNAs, that was slightly milder reduction compared with that in HBsAg protein. These data suggested that the proteins identified here could regulate HBsAg production by affecting RNA processing or dynamics.

Conclusion: Host proteins binding to region X and Y in 2.1/2.4 kb HBV RNAs were shown to be attractive therapeutic targets to reduce HBsAg, suggesting novel insights for better understanding of HBV virology.

FRI-175

Frequency, severity and impact of Peg-IFNa-associated flares in HDV infection: Results from the HIDIT-II study

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Background and aims: Treatment with PEG-IFNa is currently the only treatment option of hepatitis D virus (HDV) infection. ALT flares may occur during and after interferon-based therapies of hepatitis B monoinfection and are considered as beneficial. However, hepatitis flares could represent a concern in hepatitis D which is frequently associated with more advanced disease stages. We analyzed the frequency, severity and impact of hepatitis flares in the HIDIT-2 study.

Method: HIDIT-2 has been a randomized multicenter study performed in 14 sites in Germany, Greece, Romania and Turkey. 120 patients were treated for 96 weeks with PEG-IFNa2 with tenofovir dipivoxil (TDF) or placebo (Wedemeyer et al., Lancet ID 2019). Hepatitis flares were defined as ALT increases above ten times the upper limit of normal or increases of more than 2.5 fold above baseline or nadir values.

Results: ALT flares occurred in 28 patients during treatment (< week 96) and in 17 patients post-treatment until follow-up week 24. While there was no differences between the two treatment arms in ALT flare patients during treatment (37.8% PEG-IFNa+Placebo vs. 31.1% PEG-IFNa+TDF), ALT flares tended to be more frequent after treatment in TDF-treated patients (17.9% PEG-IFNa+Placebo vs. 8.5% PEG-IFNa+TDF ($p = 0.1$). The majority of flares happened between treatment week 8 and 24 (20 patients; median flare week 12). Flare frequency was similar in patients with and without cirrhosis (31% and 32%, respectively), none of the cirrhotic patients experienced hepatic decompensation due to flares. ALT flares were associated with HDV RNA declines (> 1log10 cop/ml) within the next two visits in 53.5% (15/28) of patients and with HBsAg drops (0.5 > log10 IU/ml) in 8 patients (3 PEG-IFNa+Placebo and 5 PEG-IFNa+TDF). Post-treatment week 120 HDV RNA levels were similar in patients who had experienced flares and in patients w/o flares (2.25E+05 cop/ml vs. 2.29E+05 cop/ml). ALT flares during treatment were associated with undetectable HDV RNA at week 120 in 11 patients.

Conclusion: ALT flares occur frequently during and after PEG-IFNa therapy of hepatitis D. Flares are associated with virological responses in some patients. These findings are of relevance for combination therapies with antiviral agents and PEG-IFNa.

FRI-176

Orally administered TQ-A3334 to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics single and multiple ascending doses in healthy Chinese subjects

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Background and aims: TQ-A3334 activated toll-like receptor (TLR)-7 to induce specific cytokines and chemokines to inhibit HBV, such as IFN-α and IFN-inducible protein-10 (IP-10). The primary objectives are to evaluate the tolerability, pharmacokinetics, and pharmacodynamic (PD) biomarkers of orally TQ-A3334 administered to healthy chinese subjects.

Method: This is a randomized, double-blind, placebo-controlled SAD study in 32 healthy adult subjects. A total of four cohorts (0.2 mg, 0.5 mg, 1.0 mg, 1.8 mg). The first cohort, 2 subjects in 0.2 mg dose were randomly assigned to TQ-A3334 treatment. Other cohorts (0.5 mg, 1.0 mg, 1.8 mg), 8 subjects was randomly assigned to TQ-A3334 treatment, and 2 subjects to placebo treatment, and the ratio of male and female was 1:1. For single-dose administration, a sentinel group of 2 subjects, will be evaluated at least 3 days prior to any subsequent dosing. Safety, PK and PD data will be collected at each cohort. Pharmacodynamic biomarker include cytokines (IFN-α, TNF-α, IL-6, IL-1RA, MCP-1 and IP-10) and ISG expression (ISG-15, MX-1, and OAS-1).

Results: Pharmacokinetics

The plasma concentration of the TQ-A3334 increased rapidly and reached its peak at 0.5 h after drug administration on day 1. The Cmax and AUC of TQ-A3334 increased near proportional (the ration : 1.53-

2.9) to the dose TQ-A3334 from 0.2 mg to 0.5 mg. The linear PK properties was characterized by moderate to high clearance (CL), high volume of distribution (Vd), and moderate to slow elimination (half-life [t1/2] = 56-169 hours). No sex differences were apparent.

Pharmacodynamics

TQ-A3334 could induced the expression of ISG (MX1, ISG15, OAS1), IFN-α, IP-10, IL-1RA and MCP-1 between 12 and 72 hours postdose above 0.2 mg cohort, and it was dose-related, whereas no relevant changes of cytokines could be detected in 0.2 mg cohort.

Safety

Clinical safety assessment available for all 32 subjects, TQ-A3334 was well tolerated. Main drug-related adverse events (AEs) were grade 1 or 2. No drop-outs, no serious adverse event (SAE). Most AEs were lymphopenia, neutropenia, fever, rigors, headache, dizziness, and nausea after 7-12 hours post dose. 2 female subjects only experienced transient lymphopenia and neutropenia in grade 3, proximal to dosing suggestive of on-target effects of TQ-A3334.

Conclusion: TQ-A3334 was well tolerated from 0.2 mg to 1.8 mg, and induced changes of cytokines and chemokines that will be benefit for patients chronic infected with HBV. Meanwhile, TQ-A3334 response in females was more obvious than males based on above data. And more information needs to be explored in clinical studies in future.

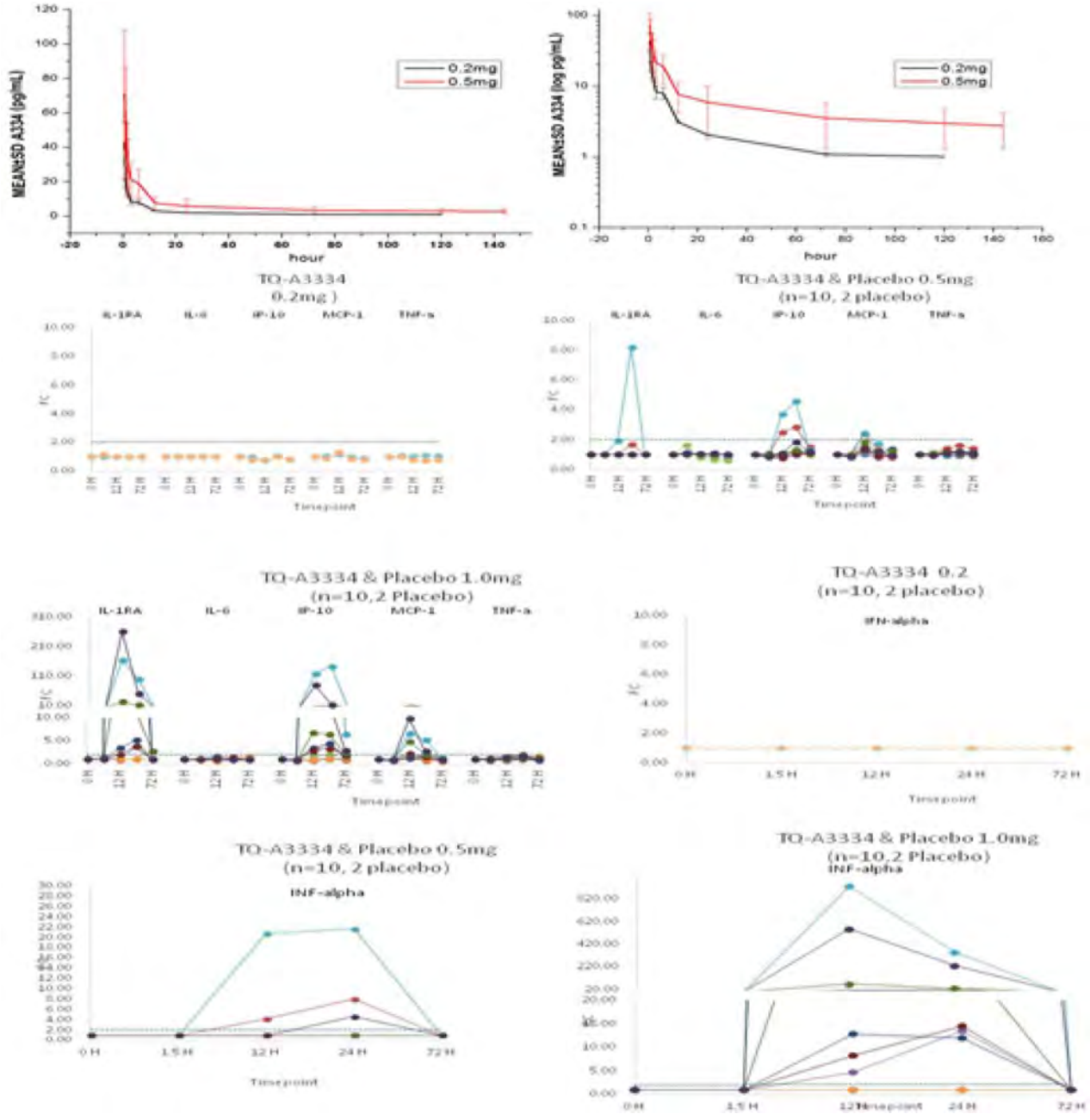

Figure: (abstract: FRI-176)

FRI-177

Association of prophylactic anti-HBV therapy with improved long-term survival in patients with hepatocellular carcionoma undergoing transarterial therapy

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Background and aims: The effect of prophylactic antiviral therapy (AVT) on survival of patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) remains unknown. The aim of this study was to determine whether prophylactic AVT could improve long-term survival in patients undergoing transarterial therapy (TAC).
Method: Between 2000 and 2016, 2, 890 newly diagnosed HBV-related HCC patients treated with TAC as the initial therapy were screened to analyze two groups based on prophylactic use of antivirals. Treatment effects were analyzed using propensity score (PS) matching (1:1) separately for the entire cohort and each subgroup. The primary end point was overall survival.
Results: A total of 1, 547 patients met the inclusion criteria and 1, 084 were PS-matched for the two groups. Mean follow-up duration was 16.55 months (IQR range: 4.97-46.67). In the entire unmatched cohort, patients receiving prophylactic AVT survived significantly longer than those not, with 10-year overall survival rates of 26.8% vs. 9.6%, respectively. Among AVT-untreated patients, baseline high-viremia and HBV reactivation during treatment were significantly associated with shorter survival. Regarding types of antivirals, survival was significantly longer for patients receiving high-potency antivirals than those receiving low-potency antivirals. In the PS-matched cohort, the prophylactic AVT group survived significantly longer than the non- prophylactic group, irrespective of viral status or tumor stage. Prophylactic AVT remained an independent factor for survival. The association of prophylactic AVT with decreased risk of mortality persisted in patient subgroups after adjusting for baseline risk factors. Sensitivity analyses also confirmed estimated treatment effects.
Conclusion: Prophylactic AVT is associated with significantly improved long-term survival among patients undergoing TAC. High-potency antivirals are indicated for this approach.

FRI-178

The clinical significance and predictors for precipitous HBsAg decline in off entecavir therapy HBeAg negative patients

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Background and aims: Increased HBsAg loss in off Nuc therapy HBeAg negative patients has been observed in several studies. A study further showed off therapy gradual decrease of HBsAg level with a "precipitous HBsAg decline" (> 0.5 $\log_{10}$IU/ml in 1 year) prior to HBsAg loss was noted. However, whether such HBsAg kinetics also present in off Nuc un-treated patients who remained HBsAg seropositive and the predictors for precipitous HBsAg decline were unknown. This comparative study aimed to address these issue.
Method: From CGMH off Nuc cohorts, patients stopping entecavir monotherapy with subsequent HBsAg loss ("study group") and an 1:1 "control group" with persistent HBsAg seropositivity matched in age, gender, end-of-treatment (EOT) qHBsAg and follow-up duration were recruited. Serial serum samples were assayed retrospectively for quantitative HBsAg (qHBsAg) and compared. Cox regression analysis was applied for predictor (s) of "precipitous HBsAg decline." All statistical analysis were performed by SAS 9.4.
Results: Study group and control group each included 36 patients with sustained response (SR) and 12 patients with un-retreated clinical relapse (CR). All study patients showed similar trend of gradual qHBsAg decrease with a "precipitous HBsAg decline" (> 0.5 log10IU/ml in 1 year) prior to HBsAg loss. Control group" patients also showed gradual qHBsAg decrease but "precipitous HBsAg decline" occurred less frequently (39.6% vs 100%; P < 0.001), with later onset (from EOT: 15.1 vs 5.7 months; P = 0.003) and less steep slop (−0.6 vs −1.65 log10IU/year; P < 0.001). The sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of "precipitous HBsAg decline" for HBsAg loss was 100%, 60.42%, 71.21% and 100%. Lower EOT HBsAg level [aHR: 0.999 (0.998-1.000), P = 0.015] and genotype C [aHR: 1.947 (1.098–3.453); P = 0.023] were two independent factors associated with the occurrence of "precipitous HBsAg decline." Among patients with "Precipitous HBsAg decline," a decline > 0.76 $\log_{10}$ IU/ml/year predicted HBsAg loss with AUROC: 0.882 (0.801–0.964; P < 0.0001) and a PPV of 92.9%, NPV of 66.7%.
Conclusion: Steep "precipitous HBsAg decline" is a pre-requested event for HBsAg loss.

FRI-179

Antiviral therapy might not be required for chronic hepatitis B patients in the immune-tolerant phase with a significantly low incidence rate of liver-related events

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Background and aims: Antiviral therapy (AVT) for chronic hepatitis B (CHB) patients in the immune-tolerant (IT) phase has been controversial. We assessed whether AVT for CHB patients in the IT-phase contributed to a better prognosis by comparing the risks of hepatocellular carcinoma (HCC) and liver transplantation (LT) among patients in the persistent IT-phase, those in the IT-phase, but who later received AVT due to a change in status, and those in the immune-active (IA) phase treated with AVT.
Method: A total of 3, 467 patients with CHB between 2007 and 2016 were enrolled. The IT-phase was defined as hepatitis B e antigen positivity, HBV-DNA level > 20, 000 IU/ml, and normal ALT. The incidence rates was estimated using the Kaplan-Meier method, and compared between groups using the log-rank test.
Results: The median age of the study population (2, 510 men and 957 women) was 49.8 years. Of the 129 patients in the IT phase at enrolment, 57 (44.2%) were in the persistent IT phase, whereas 72 (55.8%) subsequently received AVT due to a change in viral status. A total of 3, 338 patients in the IA phase were treated with AVT. During the follow-up period (median 56.3 months), there were 57 (44.2%) patients in the persistent IT phase, 72 (55.8%) in the IT phase who later were treated with AVT, and 282 (8.1%) who developed HCC. The 72 patients in the IT phase at enrolment who started AVT due to a change in viral status were later grouped with the 57 patients in the persistent IT phase group. The incidence rates of HCC and LT and the mortality rate were significantly higher in patients in the IA phase treated with AVT than in those in the IT phase (both P < 0.001, log-rank test). When the study population was stratified into three groups, (1) persistent IT phase, (2) IT phase at enrolment and later receiving AVT due to a change in viral status and (3) IA phase treated with AVT, the rates of HCC and LT incidence and mortality were highest in patients in group (3), followed by group (2), and lowest in group (3) (log-rank P = 0.027 for HCC; P = 0.044 for LT and mortality).
Conclusion: In our study, patients in the IT phase had an extremely low rates of HCC, LT and mortality compared with those in the IA phase treated with AVT (0.8% vs. 8.4% for HCC; 0.8% vs. 11.3% for LT and mortality; all P < 0.05). Thus, patients who require AVT should receive surveillance for HCC development, whereas patients in the IT phase receiving AVT may not be considered.

FRI-180

JNJ-64530440, a novel capsid assembly modulator: single- and multiple-ascending dose safety, tolerability and pharmacokinetics in healthy volunteers

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Background and aims: JNJ-64530440 (JNJ-0440) is a potent hepatitis B virus capsid assembly modulator with a dual mechanism of action. The safety, tolerability and PK of single and multiple doses of 1° and 2°-generation tablet formulations of JNJ-0440 were evaluated in healthy adults in a double-blind Phase 1 study (NCT03439488).
Method: Adults (n = 10 per cohort) were randomized 8:2 to receive a single dose of JNJ-0440 or placebo under fasted (50, 150, 300 and 900 mg) or fed (300, 750, 1000, 2000 and 4000 mg) states. Multiple once-daily doses of 750 and 2000mg JNJ-0440 with food were evaluated over 7 days. JNJ-0440 plasma concentrations were determined using liquid chromatography-tandem mass spectrometry and PK parameters estimated using non-compartmental analysis (WinNonlin, Certara, Princeton NJ). Safety and tolerability were assessed throughout.
Results: 100 adults have completed dosing. There were no withdrawals due to adverse events (AEs), serious AEs, or dose limiting toxicities. AEs and lab abnormalities were mostly Grade 1 or 2. Related AEs (n ≥ 2) included headache (n = 8), fatigue (n = 2) and contusion (n = 2). No clinically relevant changes in electrocardiograms were observed.
PK results are presented in the table.
Conclusion: Single-doses of JNJ-0440 up to 4000 mg, and multiple once-daily doses up to 2000mg for 7 days, were safe and well tolerated in healthy adults. PK was less than dose proportional and achieved concentrations expected to have antiviral activity. Evaluation in HBV-infected patients is ongoing.

FRI-181

Efficacy and safety of switching therapy from tenofovir disoproxil fumarate to tenofovir alafenamide for hepatitis B virus infection

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Background and aims: Hepatitis B virus (HBV) infection is a major public health threat that increases the risk of developing liver failure and hepatocellular carcinoma. Nucleos (t)ide analogs suppress HBV replication and reduce the risk of HCC and HBV-associated mortality. Tenofovir alafenamide (TAF) is a new prodrug of tenofovir that has been developed to treat patients with chronic hepatitis B at a lower dose than tenofovir disoproxil fumarate (TDF) via a more efficient delivery of tenofovir to the hepatocytes. We compared the efficacy and safety of TDF and TAF, investigated the switching therapy from TDF to TAF.
Method: Consent for TDF and TAF therapy was obtained from 117 and 67 patients, respectively, from August 2014 to January 2018. Total 45 and 14 patients were administrated TDF and TAF, respectively, as naïve therapy for > 48 weeks. 36 patients were switched from TDF to TAF. Antiviral effect and renal function safety were assessed.
Results: At week 48, the differences in the antiviral effect of patients receiving TDF and TAF as naïve therapy were similar in terms of reduction in the HBV deoxyribonucleic acid (DNA) (–5.6 ± 1.8 log IU/L vs. – 5.0 ± 1.7 log IU/L; p = 0.34) and Hepatitis B surface antigen (HBsAg) (– 0.29 ± 0.64 log IU/ml vs. – 0.15 ± 0.42 log IU/ml; p = 0.71). The proportion of patients who received TDF and TAF and had higher than normal levels of alanine aminotransferase (ALT) by AASLD criteria at baseline that normalized at week 48 were 45.2% and 57.1%, respectively. Decrease in the estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault method was significantly observed in 48w TDF treatment (– 5.34 ± 7.69 ml/min/1.73 m2 ; p < 0.001).
The switching therapy from TDF to TAF did not increase the HBV DNA and HBsAg at 24 weeks. Although the eGFR worsened after TDF (– 4.36 ± 6.22 ml/min/1.73 m2) irrespective of TDF administration period, it improved significantly at week 4 (+1.12 ± 5.41: p = 0.002) and week 24 (+1.06 ± 7.20; p = 0.006) after switching from TDF to TAF.
Conclusion: TDF and TAF showed adequate antiviral effect as naïve therapies. Furthermore, switching the therapy from TDF to TAF contributed to the maintenance of antiviral effect and the renal dysfunction recovery in real world.

FRI-182

Anti-viral treatment in patients with immune tolerant-phase chronic hepatitis B may be cost-effective

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Background and aims: Currently, antiviral therapy for chronic hepatitis B (CHB) patients in immune tolerant (IT, chronic HBV infection) phase is generally not recommended. There has been a need for studies assessing benefits of antiviral therapy in IT-phase. A recent study showed that untreated IT-phase patients had higher risk

Figure: (abstract: FRI-180)

	Single-dose (mg)									Multiple-dose (mg)			
										750 QD fed (2°) × 7 days		2000 QD fed (2°) × 7 days	
Mean (SD)	50 fasted (1°)	150 fasted (1°)	300 fasted (1°)	300 fed (1°)	900 fasted (1°)	1000 fed (1°)	750 fed (2°)	2000 fed (2°)	4000 fed (2°)	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/ml)	687 (254)	1591 (322)	2335 (1030)	4254 (1026)	6345 (2310)	12606 (2356)	6323 (2123)	12646 (4104)	19838 (5598)	8168 (1985)	7159 (1483)	11183 (4273)	16038 (2190)
AUC_{24h} (ng.h/ml)	7719 (2040)	17910 (4518)	24187 (8215)	41877 (7604)	65823 (24724)	118815 (21096)	67491 (16645)	132263 (46841)	222158 (61532)	88027 (19539)	86006 (18892)	128577 (53850)	174330 (28982)
C_{24h} (ng/ml)	146 (45)	342 (127)	471 (130)	608 (197)	1058 (658)	1678 (431)	1039 (244)	1790 (717)	2849 (363)	1280 (329)	1373 (433)	2005 (1063)	3639 (1076)

AUC_{24h}; area under the plasma curve over 24 h; C_{24h}; concentration at 24 h; C_{max}: maximum plasma concentration; 1°: first generation tablet formulation; 2°: second generation tablet formulation.

of hepatocellular carcinoma (HCC) than treated immune active (IA, chronic hepatitis B) phase patients. We aimed to evaluate the cost-effectiveness of starting antiviral treatment from IT-phase (IT-Tx) compared to delaying the treatment to immune active phase (IA-Tx).
Method: We designed a Markov model to compare expected costs and quality-adjusted life-years (QALYs) between IT-Tx group and IA-Tx group from healthcare system and societal perspectives. Transition probabilities and costs were obtained from a cohort of 4, 965 HBeAg-positive, treatment-naive CHB patients at Asan Medical Center. Literature review was conducted for other parameters. The starting age of the simulated cohort was 30 years old, and the cycle length was 1 year. Cost and effectiveness were discounted at a 5% annual rate, and incremental cost-effectiveness ratio (ICER) was calculated for 10-year horizon and evaluated with various HCC risks.
Results: The cost-effectiveness analysis showed that IT-Tx group had $6, 532 incremental costs and additional 0.288 QALY per patient compared to IA-Tx group with 10-year cumulative HCC risk of 10%. Through the base-case analysis ICER was $22, 642/QALY. The result indicated that IT-Tx was borderline high cost-effective based on the implicit ICER threshold of $20, 000/QALY in Korea. As HCC risk increased, IT-Tx became acceptable in cost-effectiveness. When the HCC risk increased over 11.3%, ICER went below the threshold. The analysis including the cost of lost productivity showed that IT-Tx was dominant, which had superior effectiveness and less costing, with HCC risk greater than 6.8% (ICER < 0).

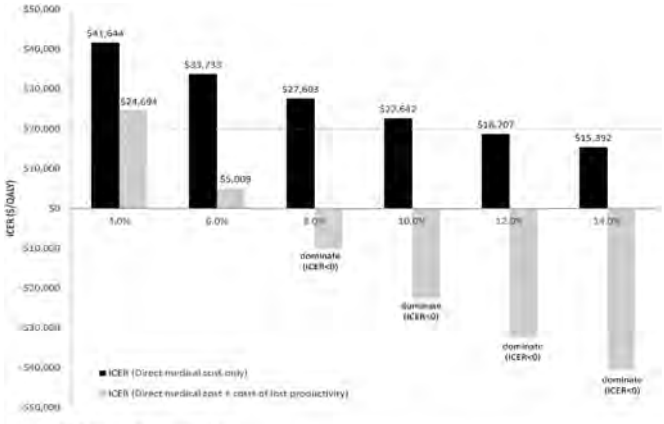

Figure 1. ICER change with various HCC risk.
When an intervention showed superior efficacy and less costing and consequently the ICER had a negative value, it is referred to as a 'dominant' strategy. In case of dominant strategy, usually ICER was not estimated. But in the current work, to compare the difference according to an addition of the costs of lost productivity ICERs were calculated even though below zero

Conclusion: To start antiviral therapy for CHB patients in IT-phase was borderline high cost-effective from healthcare system perspective dealing with the only medical costs, however, it was a dominant strategy in view of societal perspective covering also the costs for lost productivity.

FRI-183

A phase 3 study comparing switching from tenofovir disoproxil fumarate to tenofovir alafenamide with continued TDF treatment in virologically-suppressed patients with chronic hepatitis B (CHB): week 48 efficacy and safety results

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Background and aims: TAF, a novel prodrug of tenofovir (TFV), was recently approved for treatment of CHB. TAF has greater plasma stability, more targeted delivery of TFV to the liver, and reduced circulating levels of TFV compared to TDF at approved doses. TAF has shown efficacy non-inferior to TDF with improved renal and bone safety in viremic CHB patients at Weeks 48 and 96. We evaluated efficacy and safety in stable, virally-suppressed patients who were switched from TDF to TAF vs. continued TDF for an additional year.
Method: In this Phase 3 study (NCT02979613), CHB patients on TDF for ≥ 48 weeks with HBV DNA < LLOQ (local laboratory) 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. After this, all patients received open-label TAF for an additional 48 weeks. The primary efficacy analysis was the proportion of patients with HBV DNA ≥ 20 IU/ml at Week 48 based on the modified US FDA-defined Snapshot algorithm; the study was powered to show non-inferiority in efficacy of TAF compared to TDF, with a 4% margin. Key prespecified secondary safety end points were assessed sequentially: changes in hip and spine bone mineral density (BMD), and changes in estimated creatinine clearance by Cockcroft-Gault ($eGFR_{CG}$). Markers of bone turnover and renal tubular function were serially assessed. Viral resistance was evaluated by population sequencing those patients who experienced virologic breakthrough or viremia at the time of discontinuation.

Table. Efficacy and Safety at Week 48

n/N (%)	TAF (N=243)	TDF (N=245)	P value
Efficacy parameters			
HBV DNA ≥20 IU/mL[a]	1/243 (0.4)	1/245 (0.4)	0.95[b]
HBV DNA <20 IU/mL	234/243 (96.3)	236/245 (96.3)	0.98
No virologic data in Week 48 window	8/243 (3.3)	8/245 (3.3)	–
ALT normal (central laboratory)[c,d]	217/243 (89.3)	208/245 (84.9)	0.14
ALT normal (2018 AASLD criteria)[e]	192/243 (79)	184/245 (75.1)	0.31
HBeAg seroconversion[f]	2/78 (2.6)	0	0.13
HBsAg seroconversion	0	0	–
Safety parameters			
Hip BMD, mean (SD) % change (g/cm^2)	+0.66 (2.08)	-0.51 (1.91)	<0.001
Spine BMD, mean (SD) % change (g/cm^2)	+1.74 (3.46)	-0.11 (3.13)	<0.001
CTX, median (Q1, Q3) % change (ng/mL)[g]	-29.4 (-44.2, -14.3)	+7.1 (-14.8, 32)	<0.001
P1NP, median (Q1, Q3) % change (ng/mL)[h]	-19.4 (-32.2, -7.5)	+1.70 (-12.5, 17)	<0.001
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	+0.99 (-4.47, 6.31)	-2.74 (-7.87, 1.98)	<0.001
RBP/Cr, median (Q1, Q3) % change[i]	-17.7 (-41.3, 17.2)	+18.6 (-15.3, 67.3)	<0.001
β2MG/Cr, median (Q1, Q3) % change[i]	-36.0 (-61.9, -1.1)	+10.7 (-33.9, 90.6)	<0.001

[a]HBV DNA results are by modified US FDA-Snapshot algorithm; other efficacy results are missing=failure. [b]By stratified Cochran-Mantel-Haenszel tests. [c]ALT normal is the proportion with ALT ≤ULN at Week 48 regardless of baseline status (i.e. includes those ≤ and >ULN at baseline). [d]Central lab ULN 43 U/L males, 34 U/L females; [e]2018 AASLD ULN 35 U/L males, 25 U/L females. [f]Only includes patients HBeAg-positive at baseline. [g]C-type collagen sequence (bone resorption marker); [h]Procollagen type 1 N-terminal propeptide (bone formation marker); [i]Retinol binding protein/creatinine (tubular marker); [i]Beta-2 microglobulin/creatinine (tubular marker).

Results: 488 patients were randomized and treated at 42 sites in 8 countries. At baseline the groups were similar: median age 52 y

(22% ≥ 60 y), 71% male, 82% Asian, 68% HBeAg-negative, and median ALT 23 U/L. Median $eGFR_{CG}$ was 90.5 ml/min; 45% and 50% had low BMD by T scores at hip and spine, respectively. Median (Q1, Q3) duration of prior TDF was 222 (145, 305) weeks. Key efficacy/safety results are summarized in the Table. TAF demonstrated non-inferior efficacy to TDF with a similar rate (0.4%) having HBV DNA ≥ 20 IU/ml at Week 48, (difference in proportions: 0.0%, 95% CI, −1.9% to +2.0%). TAF treatment resulted in increases in hip/spine BMD with less impact on bone turnover makers; switching from TDF to TAF also resulted in increased $eGFR_{CG}$ and decreases in markers of tubular function. Rates of ≥ Grade 2 adverse events (AEs) and serious AEs were low and similar between groups. No viral resistance was observed in the 3/243 (1.2%) and 2/245 (0.8%) TAF and TDF patients, respectively, who qualified for testing.

Conclusion: Virologically-suppressed CHB patients who were switched to TAF demonstrated noninferior efficacy to continued TDF with improved bone and renal safety.

FRI-184

Function and drug combination studies in cell culture models for AB-729, a subcutaneously administered siRNA investigational agent for chronic hepatitis B infection

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Background and aims: Developing a cure for chronic hepatitis B must address viral persistence and likely requires combination of drugs with different modes of action. AB-729 is a siRNA agent that acts on all HBV RNA transcripts, enabling inhibition of HBV replication and suppression of all viral antigens including HBsAg; this may facilitate reinvigoration of host immune responses. A novel high avidity N-acetylgalactosamine (GalNAc) moiety mediates targeting of AB-729 to hepatocytes, the site of HBV infection. Here we describe HBV cell culture models capable of demonstrating both cellular entry and gene silencing functionalities of GalNAc-siRNA, and present in vitro characterization of AB-729 anti-HBV activities as monotherapy as well as in combination with approved and investigational drug modalities.

Method: AB-729 activity was studied in adeno-associated virus-transduced HBV-expressing primary mouse hepatocytes (PMH), HBV-infected primary human hepatocytes (PHH) and transiently- and stably-transfected HBV cell lines. Drug combination studies were conducted using three-dimensional modeling for drug-drug interactions and analyzed using MacSynergy II software.

Results: Asialoglycoprotein receptor (ASGPR) levels decreased rapidly during in vitro culture of primary hepatocytes, providing a narrow time window for GalNAc-mediated cellular entry of AB-729. Congruent with this, EC50 shifts of 24- and at least 478-fold were observed in PMH and PHH treated with GalNAc-siRNA at 4 h compared to 24 h or 4 days post-plating. AB-729 reduced HBV RNA, HBeAg and HBsAg expression, with 5.6-19.4 nM EC50 values in PMH. Commercial transfection agent had to be utilized to conduct a standard HBV genotype and resistance mutant susceptibility panel for the siRNA component of AB-729. Pairwise testing with tenofovir alafenamide, peg-interferon-alpha-2a and AB-506, a next-generation investigational capsid inhibitor, showed that AB-729 was able to combine productively with each of these drug modalities and without significant effects on cell viability.

Conclusion: Standard HBV cell lines can be used to characterize the activity of the AB-729 siRNA whereas two primary hepatocyte systems were able to model both the cell entry functionality and anti-HBV activities of AB-729. Preclinical investigations demonstrate that AB-729 and AB-506 when combined have distinct but mechanistically compatible antiviral activities and may feasibly be used in future combination therapeutic regimens.

FRI-185

Virological and immunological predictors of long-term ouctomes of peginterferon alfa-2a therapy for HBeAg-negative chronic hepatitis B

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Background and aims: Predictors of long-term outcomes of peginterferon (PegIFN) therapy for chronic hepatitis B (CHB) remain to be explored. The aim of this study was to evaluate the predictive value of virological and immunological biomarkers and long-term outcomes of PegIFN therapy for HBeAg-negative CHB.

Method: 57 HBeAg-negative CHB patients receiving 48 weeks PegIFN therapy were prospectively followed for a median period of 5.3 years after the end of treatment (EOT). Serum HBsAg, HBV DNA, CXCL9 and IP-10 levels were measured in all patients. Flow cytometry analysis for frequencies of regulatory T cells, $CD4^+CD69^+$, $CD8^+CD69^+$, $CD8^+PD\text{-}1^+$, $CD4^+CXCR3^+$ and $CD8^+CXCR3^+$ cells were performed in 23 patients with available peripheral blood mononuclear cells. The definition of viral relapse and clinical relapse after EOT followed APASL guidelines. Factors associated with long-term HBsAg loss, viral relapse and clinical relapse were analyzed.

Results: Baseline CXCL9 levels significantly correlated with frequencies of $CD4^+CXCR3^+$, $CD8^+CXCR3^+$ and $CD4^+CD69^+$ cells, while $CD8^+PD\text{-}1^+$ cells population significantly correlated with HBV DNA, ALT levels and frequencies of $CD8^+CD69^+$ and $CD8^+CXCR3^+$ cells. The cumulative incidences of HBsAg loss and clinical relapse at year 7 were 31.6%, and 0%, respectively, in patients with sustained off-treatment virological response (SVR), and 6.7% and 67.4%, respectively, in patients without SVR. In patients with SVR, the viral relapse rate was 18.1% at year 7. By multivariate analysis, CXCL9 > 200 pg/ml (HR = 8.154, p = 0.038) and HBsAg < 750 IU/ml (HR = 10.507, p = 0.036) were baseline predictors of HBsAg loss, while HBsAg decline at EOT > 1 log (HR = 23.296, p = 0.005) was the on-treatment predictor of HBsAg loss. Baseline CXCL9 > 80 pg/ml (HR = 0.092, p = 0.047), $CD8^+PD\text{-}1^+$ cells > 21% (HR = 25.618, p = 0.007), HBsAg decline > 10% at week 12 (HR = 0.026, p = 0.024) and HBsAg decline > 50% at EOT > 1 log (HR = 0.075, p = 0.033) were independent predictors of viral relapse. $CD4^+CD69^+$ cells > 2.5% (HR = 0.167, p = 0.020) and HBsAg decline > 10% at week 12 (HR = 0.180, p < 0.001) were independent predictors of clinical relapse.

Conclusion: Baseline serum CXCL9 levels could predict HBsAg loss and viral relapse after PegIFN therapy for HBeAg-negative CHB. Populations of T cell subsets, such as $CD8^+PD\text{-}1^+$ and $CD4^+CD69^+$ cells, might predict viral and clinical relapses. Combining virological and immunological biomarkers could predict long-term outcomes of PegIFN therapy for HBeAg-negative CHB.

FRI-186

Entecavir plus pegylated interferon alfa-2a and sequential HBV vaccination increases the chance of HBsAg-seroclearance: Results from a randomized controlled E+VIP trial

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Background and aims: HBsAg-seroclearance is considered as a functional cure in chronic hepatitis B patients, but is rarely achievable with oral nucleos (t)ide analogs (NAs) alone. We conducted a randomized controlled trial to evaluate the efficacy and safety of additional pegylated interferon alfa-2a (Peg-IFN) plus sequential hepatitis B virus (HBV) vaccination.
Method: A total of 111 patients who achieved serum HBV DNA < 20 IU/ml and quantitated HBsAg (qHBsAg) < 3, 000 IU/ml with entecavir were randomly assigned (1:1:1) to the treatment group (entecavir +Peg-IFN [180 μg every week over 48 weeks] +sequential HBV vaccination [20 μg of HBsAg; at weeks 52, 56, 60, and 76]), the control group (entecavir only), or the explorative group (entecavir +Peg-IFN +concurrent HBV vaccination [at weeks 4, 8, 12, and 28]). The primary end point was HBsAg-seroclearance at week 100 and secondary end points included change in qHBsAg titer and safety.
Results: There was no difference in baseline qHBsAg and HBV DNA among groups. In intention-to-treat analysis, the treatment group showed significantly higher chance of HBsAg-seroclearance at week 100 than control group (16.2% vs 0%, $P = 0.025$), but the explorative group (5.4%) failed to reach significant difference ($p = 0.54$). The changes in median qHBsAg titer from baseline to week 100 was −67.7% in the treatment group and −36.3% in the control group (Figure 1). Adverse events were significantly more frequent in the treatment group than the control group (81.1% vs 2.7%, $P < 0.0001$). However, the frequency of serious adverse events did not differ significantly between groups (2.7% vs 2.7%, $P = 1.00$).

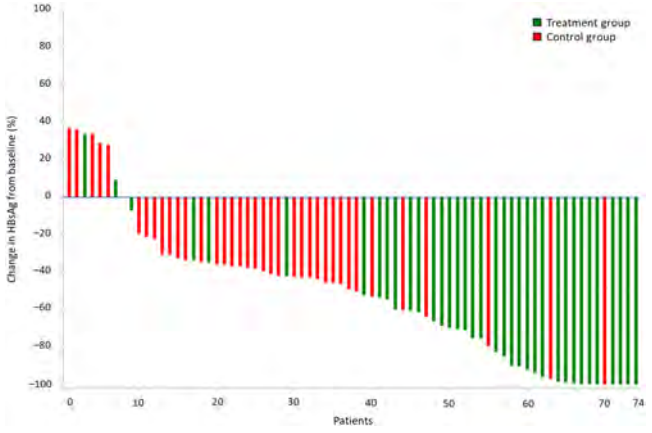

Figure 1: Maximal change of qHBsAg titer in each patient.

Conclusion: Entecavir plus an additional Peg-IFN treatment followed by sequential HBV vaccination with intensified schedule significantly increases the chance of HBsAg-seroclearance compared to entecavir alone. ClinicalTrials.gov number: NCT02097004.

FRI-187

Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and liver-related events in patients with chronic hepatitis B: A propensity score analysis

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Background and aims: The use of tenofovir (TDF) and entecavir (ETV) in chronic hepatitis B (CHB) patients has led to a decrease in the incidence of hepatocellular carcinoma (HCC) and liver-related events. However, whether there is a difference between the two agents in the extent of improving such clinical outcomes has not been clarified thus far. We aimed to compare the effects of TDF and ETV on HCC risk reduction and liver-related events.
Method: A total of 7, 015 CHB patients who were treated with TDF or ETV between February 2007 and January 2018 at the liver units of the Catholic University of Korea were screened for study eligibility. We have excluded the patients with HCV or HIV co-infection, antiviral therapy less than 6 months, HCC or liver transplantation (LT) prior to or within 6 months since the initiation of antiviral therapy, other malignancies at baseline, TDF and ETV combination therapy, and conversion from TDF to ETV or from ETV to TDF. The remaining 3, 282 treatment-naïve patients (1541 TDF, 1741 ETV) were finally analyzed using the inverse probability of treatment weighting (IPTW) method. Primary end points were HCC development and occurrence of liver-related events within 5 years since the initiation of antiviral therapy. Liver-related event was defined as the occurrence of either HCC, LT or liver-related death.
Results: The mean age was 47.4 years and 59% of the patients were male. 60.5% of the patients had chronic hepatitis, 31.6% compensated liver cirrhosis (LC) and 7.9% decompensated LC. Both in the unmatched and IPTW models, no difference was observed in HCC incidence rates (HR 0.962; 95% CI, 0.707-1.308, IPTW model). Also, although a marginally lower tendency in the occurrence of liver-related events was observed in the TDF group, no statistically significant difference was observed in both models (HR, 0.867; 95% CI, 0.651-1.154, IPTW model). In the multivariate analysis, male sex, old age, cirrhosis and platelet count less than 150, 000/mm^3 were identified to be the independent predictors of both HCC and liver-related events.
Conclusion: This large observational cohort study has demonstrated that intermediate-term clinical outcomes including HCC and liver-related events do not differ according to the use of either TDF or ETV. However, a further long term analysis should be carried out before we conclude whether TDF or ETV may result in different clinical outcomes in any aspect.

FRI-188

Sequence analysis of baseline and on-treatment samples from HBV-infected chronic hepatitis B patients treated for 28 days with JNJ-56136379 monotherapy

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Background and aims: JNJ-56136379 (JNJ-6379) is a potent capsid assembly modulator (CAM) currently in Phase 2a clinical development. In a Phase 1b study (NCT02662712), treatment-naïve chronic hepatitis B HBeAg-positive and -negative patients received oral JNJ-6379 (25, 75, 150, and 250 mg once-daily) for 4-weeks. Potent

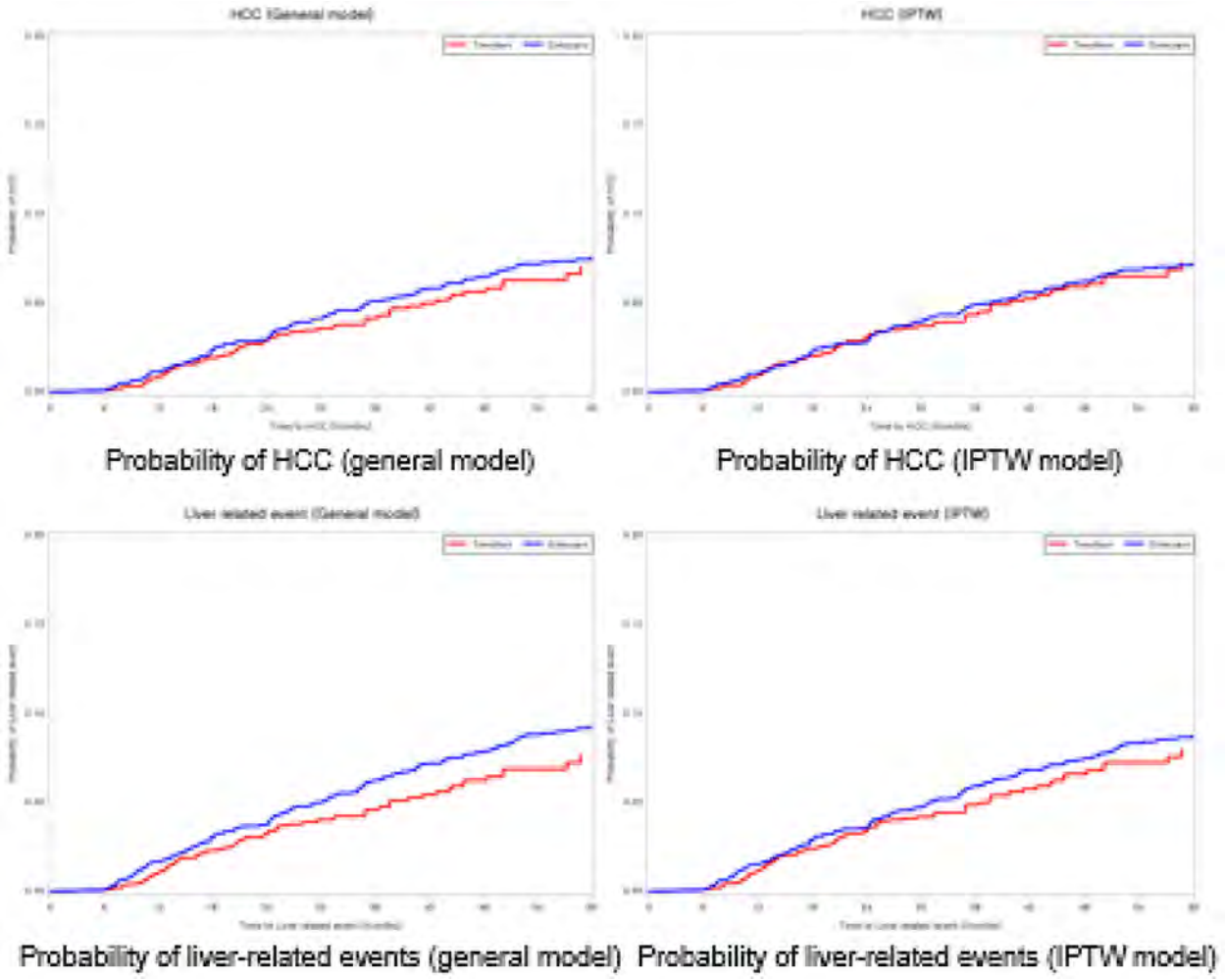

Figure: (abstract: FRI-187)

antiviral activity was observed. Here we present the resistance analysis of this study.

Method: HBV DNA was extracted from serum samples collected over the study period and the HBV full genome was sequenced using next generation sequencing (NGS). Baseline amino acid (aa) polymorphisms were defined as changes versus the universal HBV reference sequence (frequency > 15%). Emerging mutations were defined as aa changes from patient-specific baseline sequences (frequency < 1% at baseline and > 15% post-baseline). The analysis focused on 28 HBV core protein aa positions described as part of the CAM binding pocket. Impact of aa substitutions on JNJ-6379 *in vitro* activity was assessed in a transient replication assay using a genotype (GT) D backbone.

Results: Overall, 27 of 51 patients with baseline NGS data available had ≥ 1 polymorphisms at any of the 28 HBV core protein positions of interest. The highest prevalence of baseline polymorphisms was observed at Positions 38 (31.4%), 105 (21.6%), and 109 (15.7%). Polymorphisms at these positions tested as site-directed mutants did not reduce JNJ-6379 *in vitro* activity. One of 51 (2.0%) patients (GT-A, JNJ-6379 75 mg treated) carried a baseline polymorphism known to reduce JNJ-6379 *in vitro* activity (Y118F, 6.6-fold change in EC_{50} value). This patient had a pronounced decline in HBV DNA levels of 2.77 log_{10} IU/ml from baseline to levels below quantification by the end of 4 weeks' treatment. In 1 of 22 JNJ-6379 treated patients with post-baseline NGS data available, an emerging substitution at 1 of the 28 HBV core protein positions of interest was detected. This patient (GT-E, JNJ-6379 150 mg treated) had an emerging Y118F mutation at Day 8, which persisted until the end of follow-up. HBV DNA decline in this patient was slower but continued until the end of treatment with a maximum decline of 2.19 log_{10} IU/ml.

Conclusion: Baseline polymorphisms reducing JNJ-6379 *in vitro* activity were rare. One patient carried a baseline polymorphism which reduced JNJ-6379 activity *in vitro* and the same aa substitution was emerging in another patient without a clear impact on JNJ-6379 virological response.

FRI-189

HBcrAg decline in JNJ-56136379-treated chronic hepatitis B patients: Results of a phase 1 study

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Background and aims: JNJ-56136379 (JNJ-6379) is a potent capsid assembly modulator which binds to HBV core protein, interfering with capsid assembly and formation of cccDNA. In a Phase 1b study (NCT02662712), patients with HBeAg-positive or -negative chronic hepatitis B received once-daily oral JNJ-6379 or placebo for 28 days.

JNJ-6379 was well tolerated and resulted in potent HBV DNA and HBV RNA reductions. Here we present an exploratory analysis of hepatitis B core-related antigen (HBcrAg) changes during JNJ-6379 treatment.
Method: Treatment-naïve chronic hepatitis B patients with screening serum ALT levels < 2.5x ULN were included in this study. ALT, HBV DNA, HBeAg, and HBsAg levels were assessed using standard assays. Exploratory analysis included serum HBV RNA assessed with qRT-PCR assay, and HBcrAg assessed using the Lumipulse platform (Fujirebio). The HBcrAg assay detects HBeAg, HBcAg and p22cr protein with a LLOQ of 3.0 logU/ml and LOD of 2.0 logU/ml.
Results: Fifteen of 57 (26%) patients were HBeAg-positive and were enrolled in the 25 mg (N = 6), in the two 75 mg (N = 8) and the 250 mg (N = 1) sessions. Mean (SD) baseline HBcrAg levels were 7.8 (1.3) logU/ml and 3.3 (1.5) logU/ml in HBeAg-positive and -negative patients, respectively. 15/15 and 17/42 (40%) HBeAg-positive and -negative patients, respectively, had HBcrAg levels ≥ 3.5 logU/ml at baseline, sufficient to determine a ≥ 0.5 logU/ml reduction in HBcrAg. Treatment with JNJ-6379 for 28 days resulted in ≥ 0.5 logU/ml (range 0.7 to 1.7) declines in HBcrAg from baseline in 6/12 (50%) HBeAg-negative patients with baseline HBcrAg ≥ 3.5 logU/ml and Day 28 data available, compared to 0/4 receiving placebo (range 0.1 to -0.2). Among JNJ-6379-treated HBeAg-positive patients, 1/10 (10%) experienced on-treatment decline of ≥ 0.5 logU/ml in HBcrAg, compared to 0/5 placebo-treated subjects.
Interestingly, patients with HBcrAg decline had either ALT levels > 1xULN at baseline or transient on-treatment ALT elevations. No relevant changes in HBeAg (in HBeAg-positive patients) or HBsAg were noted following short-term JNJ-6379 treatment, suggesting that the HBcrAg reductions observed in some patients might be due to direct inhibition of release of the HBV core protein.
Conclusion: Following 28 days of treatment with JNJ-6379, a reduction in HBcrAg levels occurred in a subset of patients, while no changes in HBeAg or HBsAg were observed. This will be examined further in the ongoing Phase 2a JNJ-6379 (JADE) study.

FRI-190

Incidence and predictors of flares after discontinuing nucleos (t) ide analogue therapy in HBeAg negative patients with chronic hepatitis B: Results from the randomized controlled STOP study

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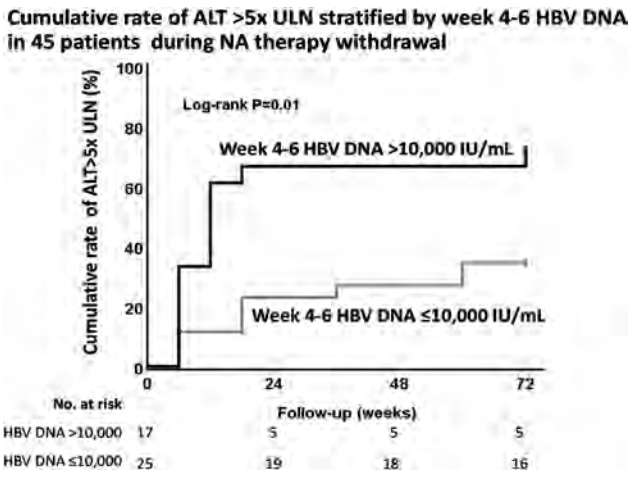
Background and aims: HBeAg negative patients with chronic hepatitis B (CHB) often develop flares after stopping nucleos (t)ide analogues (NA) therapy, but early prediction of off-therapy flares remains difficult. In this prospective randomized controlled trial, we determined the cumulative incidence of flares and evaluated response-guided prediction after stopping long-term NA therapy.
Method: Patients at a North-American hospital were eligible if they had received entecavir/tenofovir therapy for ≥ 1 year and achieved virologic suppression (HBeAg seroconversion combined with undetectable HBV DNA ≥ 12 months in HBeAg positive patients, or undetectable HBV DNA ≥ 36 months in start of therapy HBeAg negative patients). Patients were randomized 2:1 to stop or continue NA therapy for 72 weeks. Patients were retreated in case of HBeAg seroreversion, persistent HBV DNA > 20, 000IU/ml or HBV DNA > 2, 000 with ALT > 5xULN. Predictors of flares (ALT > 5x ULN) were studied by Cox proportional-hazards regression.
Results: Of 67 included patients (60% male, 97% Asian), 45 (67%) patients were assigned to stop and 22 (33%) to continue NA therapy. NA-induced HBeAg loss occurred in 37/67 (55%) patients. At randomization the mean duration of NA therapy was 8 (4) years and HBsAg level was 3.0 (0.7) log IU/ml. Within the stop group 24/45 (53%) patients continued to have a normal ALT and HBeAg negative status compared to 95% in the continue group. By week 72 off-therapy, 38 (84%) NA stop patients developed ALT > ULN, of whom twenty (49%) had ALT > 5xULN and fourteen (31%) had ALT > 10x ULN. Among patients with an ALT > 10x ULN, the median ALT was 16 (13-23)×ULN (peak: 40). Although one patient developed a bilirubin of 68 umol/L, none decompensated or died.
Independent predictors of ALT > 5xULN were male sex (OR: 6.5 (4.0-10.4); p < 0.005) and serum HBV DNA (1.3 (1.1–1.5); p < 0.005) at week 6 off-therapy. Specifically, a week 4-6 HBV DNA > 10, 000 IU/ml predicted a higher risk of ALT > 5xULN compared to ≤ 10, 000 IU/ml (3.0 (1.3-7.1); p = 0.01; see Figure). Quantitative HBsAg at the end of therapy was not predictive for ALT > 5xULN (p > 0.05).



Conclusion: In this prospective randomized controlled trial, the cumulative rate of off-therapy flares was 49% in HBeAg negative patients with CHB. Male sex and week 4-6 HBV DNA values independently predicted a flare. The proposed threshold of HBV DNA > 10, 000 IU/ml facilitates off-therapy identification of patients with a high risk of flares who may need more intensive follow-up and earlier retreatment.

FRI-191

EDP-514, a novel HBV core inhibitor with potent antiviral activity both in vitro and in vivo

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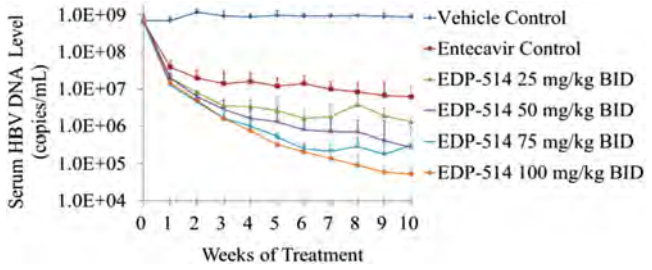
Background and aims: Current therapies for hepatitis B virus (HBV) can effectively suppress viral replication but rarely lead to a functional cure, which necessitates the development of new antiviral drugs. The HBV core protein plays an essential role in multiple steps of viral life cycle and has been proposed as a potential therapeutic target. EDP-514 is a novel HBV core inhibitor with favorable pharmacokinetic and safety profile. Here, we describe the anti-HBV activities of EDP-514 *in vitro* and in a chimeric mouse model with humanized liver.
Method: The effect of EDP-514 on viral capsid assembly was determined *in vitro*. Its anti-HBV activities at different stages of the viral lifecycle were characterized in stable cell lines (HepG2.2.15, HepAD38 and HepDE19) and primary human hepatocytes. Activities against different HBV genotypes and resistance mutants were assessed in transiently transfected HepG2 cells. The *in vivo* efficacy of EDP-514 was evaluated in HBV genotype C-infected PXB mice

which were generated by transplantation of urokinase-type plasminogen activator/severe combined immunodeficiency (uPA/SCID) mice with human hepatocytes.

Results: EDP-514 induced the assembly of empty capsids *in vitro* and in HBV infected cells but did not lead to core protein aggregation or degradation, confirming it is a class II core inhibitor. EDP-514 inhibited HBV DNA replication with an EC_{50} of 18, 27 and 17 nM in HepAD38, HepDE19 and HepG2.2.15 cells, respectively. In addition, EDP-514 prevented the *de novo* formation of cccDNA in primary human hepatocytes with an EC_{50} of 35 nM. The compound was active across HBV genotypes A-H with potencies ranging from 9-32 nM and its efficacy was not affected by known nucleos (t)ide resistant variants. Combination of EDP-514 with nucleos (t)ide or class I core inhibitors led to synergistic antiviral effect *in vitro*. Moreover, EDP-514, given orally at 25, 50, 75 and 100 mg/kg BID, reduced HBV DNA by 2.75, 3.42, 3.27 and 4.13 logs, respectively, in PXB mice after 10 weeks of treatment.



Conclusion: EDP-514 is a novel HBV core inhibitor with an attractive preclinical profile. It is a potent inhibitor of HBV replication and prevents *de novo* cccDNA formation. *In vivo*, EDP-514 treatment of HBV-infected PXB mice results in a rapid and sustained viral load reduction of > 4-log. Overall, these data support the further development of EDP-514 as a therapeutic candidate for the treatment of HBV.

FRI-192

Tenofovir disoproxil fumarate treatment in chronic hepatitis B patients with cirrhosis reduces hepatic decompensation, hepatocellular carcinoma and death

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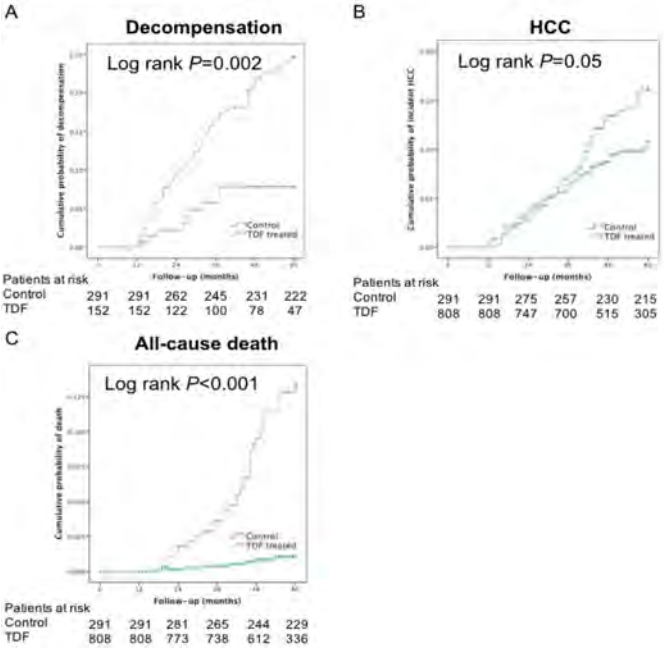
Background and aims: Lamivudine and entecavir have been shown to reduce decompensation, hepatocellular carcinoma (HCC) and death in chronic hepatitis B (CHB) patients with cirrhosis. Tenofovir disoproxil fumarate (TDF) is a potent antiviral agent with no documented resistance to date, but its impact on cirrhotic patients is unclear. We aimed to investigate the effectiveness of TDF therapy in CHB patients with cirrhosis.

Method: We studied 808 TDF-treated and 291 untreated CHB cirrhotic patients from 3 tertiary centres (Hong Kong, South Korea, United States). Cirrhosis was defined by liver histology, thrombocytopenia ($< 150 \times 10^9$/L) and/or features of portal hypertension on imaging. TDF cohort included consecutive patients from three tertiary centres who received TDF 300 mg/day for ≥ 12 months. Control cohort included historical untreated patients

Results: TDF-treated patients were 69% men, mean age 54 ± 10 years, and 47% hepatitis B e antigen (HBeAg) positive, 55% had prior (non-TDF) antiviral therapy. Untreated controls were 78% men, mean age 50 ± 9 years and 24% HBeAg positive. At 5-years follow-up, there were 72 decompensating events, 113 HCCs and 41 deaths (28 liver-related) from both groups combined. Undetectable Hepatitis B virus DNA was achieved in 90.8% of TDF-treated patients. 5-year cumulative probabilities in TDF-treated vs. control cohorts were (**Figure 1**): 8% vs. 22% for decompensation (p = 0.002), 10% vs. 15% for HCC (p = 0.05) and 1% vs. 12% for death (p < 0.001). On multivariate Cox regression, TDF treatment was independently associated with reduced risks of decompensating events (hazard ratio [HR] 0.41, *P* = 0.046), HCC (HR 0.42, *P* = 0.001), all-cause death (HR 0.05, *P* < 0.001) and liver-related death (HR 0.09, *P* < 0.001). Other independent predictors for events were: decompensating events (albumin [HR 0.92, *P* = 0.015], platelet count [HR 0.99, *P* < 0.017] and INR [HR 9.89, *P* = 0.002]), HCC (albumin [HR 0.94, *P* < 0.001]), all-cause death (INR [HR 21.24, *P* < 0.001]) and liver-related death (albumin [HR 0.89, *P* = 0.012]). A sensitivity analysis performed including only patients who received no prior antiviral therapy before TDF showed TDF was still independently protective for HCC (HR 0.49, *P* < 0.001), all-cause death (HR 0.05, *P* < 0.001), liver-related death (HR 0.06, *P* < 0.001), and almost for decompensating events (HR 0.49, *P* = 0.068).

Figure 1. Kaplan-Meier analysis of cumulative probability of (A) Decompensation, (B) HCC, and (C) death in TDF-treated vs. untreated CHB patients with cirrhosis



Conclusion: Among patients with cirrhosis, TDF treatment reduces risks of hepatic decompensation and HCC by more than 2-fold and death by 95% at 5 years

FRI-193

Long-term renal and bone safety of tenofovir disoproxil fumarate in chronic hepatitis B patients with cirrhosis

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Background and aims: Although real-life data suggest that TDF is generally safe, there are renal and bone safety concerns. Long-term data in patients with cirrhosis is limited. We aimed to investigate long-term renal and bone toxicity of TDF therapy in chronic hepatitis B (CHB) patients with cirrhosis.
Method: We studied two CHB cirrhotic cohorts: one treated with TDF and one untreated historical control group. Cirrhosis was defined by liver histology, thrombocytopenia ($< 150 \times 10^9$/L) and/or features of portal hypertension clinically or on imaging. TDF cohort included consecutive patients from 3 tertiary centres (Hong Kong, South Korea, Unites States) who received TDF 300 mg/day for ≥ 12 months. Estimated glomerular filtration rate (eGFR) as calculated by CKI-EPI and 5-year cumulative probabilities of chronic kidney disease (CKD) progression ≥ 1 stage and fracture were compared.
Results: For renal outcomes, we analysed 935 TDF-treated (baseline mean eGFR 92 ml/min/1.73m^2) and 69 untreated cirrhotics (baseline mean eGFR 85 ml/min/1.73m^2). At 5-years follow-up, there was less eGFR decline in TDF-treated patients vs. controls (−5 ml/min/1.73m^2 vs. −13 ml/min/1.73m^2, $P < 0.001$) (**Figure 1**). 5-year probability of CKD progression was lower in TDF-treated patients vs. controls (19% vs. 42%, $P < 0.001$). TDF treatment was associated with less CKD progression (hazard ratio 0.4, $P < 0.001$) even after adjusting for age, baseline eGFR and prior antiviral therapy. For bone outcomes, we analysed 443 TDF-treated and 291 untreated cirrhotic patients. During the study period there were 21 fractures in both groups combined. The 5-year probability of fracture was similar in TDF-treated patients vs. controls (5% vs. 3%, $P = 0.174$). There was no significant change in serum phosphate levels in TDF-treated patients during follow-up.
Conclusion: Among CHB patients with cirrhosis, TDF treatment appears safe with no significant increase in eGFR decline, CKD progression, or fracture risk compared to untreated patients.

FRI-194

The novel antiviral agent inarigivir inhibits both nucleos (t)ide analogue and capsid assembly inhibitor resistant HBV in vitro

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Background and aims: Inarigivir is a synthetic dinucleotide that activates the RIG-I antiviral pathway resulting in inhibition of HBV replication. Inarigivir has been demonstrated to also have direct antiviral activity against HBV *in vitro* by inhibiting reverse transcription following the packaging of its pgRNA into the nucleocapsid. The study aim was to test the *in vitro* antiviral potency of Inarigivir against a panel of nucleos (t)ide analogue resistant, capsid assembly inhibitor resistant and precore stop codon variants of HBV.
Method: Huh7 cells were transfected with replication competent clones of HBV known to be resistant to lamivudine (rtL180M + rtM204 V and rtM204I), adefovir (rtA181 V + rtN236 T) or entecavir (rtL180M + rtT184G + rtS202I + rtM204 V) as well as a panel of HBVs with substitutions in the core protein (cT33I or cY109A or cT118F or cV124A) and also the HBeAg-negative G1896A stop codon variant. The amount of HBsAg secreted into the cell culture supernatant was measured by quantitative EIA, whilst HBV DNA replication was evaluated by Southern blot. Following transfection, cells were incubated for 5 days with daily medium change of Inarigivir and scored as drug sensitive if a dose-response in antiviral effect at 2 or 25 or 50μM Inarigivir on HBsAg secretion/HBV DNA replication was seen and the inhibition exceeded 20% compared to the untreated control. Resistance was defined as < 20% reduction in HBsAg or HBV DNA levels compared to untreated controls with no dose response in antiviral effect observed at the drug concentrations tested.
Results: Inarigivir effectively inhibited replication of all HBV isolates associated with antiviral drug resistance and to a level comparable to the wild-type HBV whilst lamivudine had no effect. Inarigivir also inhibited all four of the capsid variants tested compared to wild-type HBV whilst the BAY 41-4109 anti-HBV compound had no antiviral effect on these isolates. Finally, Inarigivir retained its antiviral activity against HBV containing the G1896A stop codon mutation that is needed for HBeAg production.
Conclusion: Inarigivir was active, at the level of HBsAg production and secretion as well as active HBV DNA replication, against a panel of

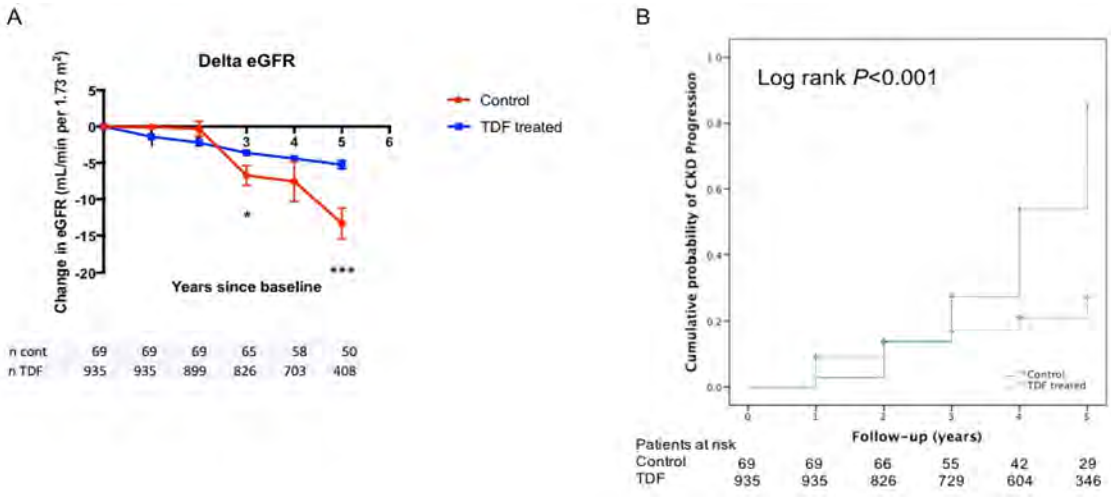

Figure: (abstract: FRI-193)

antiviral drug and capsid inhibitor resistant variants and also HBV with the G1896A substitution. This indicates that treatment with Inarigivir should result in retention of antiviral activity against isolates of HBV that are resistant to these two groups of antiviral agents.

FRI-195

Long-term effect of nucleos (t)ide analogs on hepatitis B surface antigen in chronic hepatitis B patients

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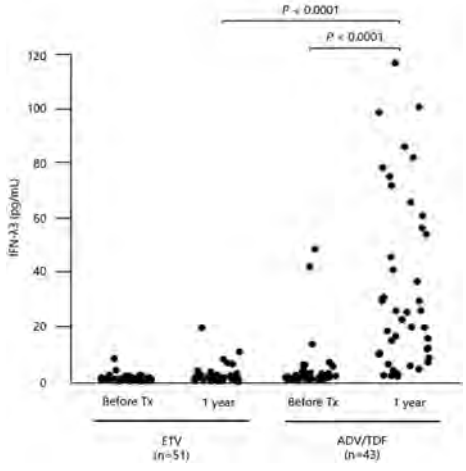
Background and aims: Nucleos (t)ide analogs (NAs) treatment against chronic hepatitis B (CHB) has ability to reduce liver disease progression, the risk of HCC development, and HBV-related mortality However, long-term benefits of NAs on hepatitis B surface antigen (HBsAg) reduction are still not known. This study aimed to investigate the long-term effect of NAs on HBsAg reduction and evaluate the effect of interferon-lambda3 (IFN-λ3) induction by NAs on HBs Ag reduction.
Method: A total of 176 patients [121 treated with nucleoside analog entecavir hydrate (ETV) and 55 treated with nucleotide analog adefovir dipivoxil (ADF) or tenofovir disoproxil fumarate (TDF) with clinically evident chronic hepatitis B (chronic hepatitis, 121; liver cirrhosis, 55) were enrolled in this study. Among them, a total of 94 patients (ETV, 51; ADV/TDF, 43) were measured IFN-λ3 before the initiation of therapy and 1 year post-therapy.
Results: The change (mean±SD) in serum HBsAg levels from baseline to year 9 was −0.47 ± 0.60 and −1.57 ± 1.17 $\log_{10}$ IU/ml in ETV and ADV/TDF groups, respectively ($p = 0.0064$). The proportions of patients with HBV DNA lower limit of quantification, alanine aminotransferase normalization, the rate of hepatitis e seroconversion were not significantly different between ETV and ADV/TDF groups during the study period. Serum IFN-λ3 levels were significantly higher in patients receiving nucleotide analogs (ADV/TDF: 25.5 pg/ml) than in the patients receiving nucleoside analog (ETV: 1.3 pg/ml) at 1 year post-therapy ($p < 0.0001$).



Conclusion: Long-term nucleotide analog (ADV/TDF) treatment rapidly reduced HBsAg levels compared with nucleoside analog (ETV). Serum IFN-λ3 levels is negatively correlated with HBsAg reduction in patients limited to initial HBsAg, HBV genotype, and therapeutic response.

FRI-196

The development of HCC in chronic hepatitis B patients with nucleos (t)ide analogs: Focus on hepatitis B surface antigen and core-related antigen

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Background and aims: Although overseas reports indicate that a high HBs antigen (sAg) level is a risk factor for HCC in chronic HBV patients (pts) treated with nucleoside analogs (NAs), HCC often occurs in pts with low sAg levels in Japan, where many elderly pts develop this condition. The HBV core-related antigen (crAg), a similar risk factor, is derived from covalently closed circular DNA, like sAg. However, sAg and crAg levels differ in some NA-treated pts. We aimed to examine the association between sAg and crAg levels after NA therapy and the development of HCC.
Method: We included 356 pts who had received entecavir (ETV) or tenofovir for ≥ 3 years and achieved sustained viral suppression of HBV DNA (mean age at 3 years of NA therapy, 54 years; men, 212; HBeAg positive, 77; and genotype C, 267). Exclusion criteria included an adefovir treatment history, resistant with lamivudine and/or ETV, HCC history, and HCC development within 3 years of NA therapy. Cumulative HCC incidence and contributing factors for HCC were assessed. According to sAg (IU/ml) and crAg (U/ml), levels at 3 years of NA therapy, the pts were stratified into 4 groups: group 1, sAg ≥ 1300 and crAg < 3.0; group 2, sAg < 1300 and crAg < 3.0; group 3, sAg ≥ 1300 and crAg ≥ 3.0; group 4, sAg < 1300 and crAg ≥ 3.0. Cumulative HCC incidence was analyzed in each group; log-rank test was performed to assess differences among the groups. We used sex, genotype, diabetes mellitus-treatment history, familial history, presence or absence of steatosis, alcohol consumption, and HBeAg, sAg, crAg, M2BPGi, FIB-4 and AFP levels at 3 years of treatment as factors in the Cox proportional hazards model. Cut-off values were calculated by receiver operating characteristic curve analysis. Numerical values were expressed as mean; p < 0.05 was considered to indicate significance.
Results: The Cumulative HCC incidence was 3.1% and 10.8% at 5 and 10 years, respectively. An sAg level < 1300 (hazard ratio [HR], 5.9; p = 0.005), a crAg level ≥ 3.0 (HR, 4.0; p = 0.004), age ≥ 55 years (HR, 11.3; p = 0.002), and presence of diabetes mellitus (HR, 3.4; p = 0.003) were identified as contributing factors for HCC. The cumulative HCC incidence in groups 1, 2, 3, and 4 were 0%, 0%, 1.9%, and 10.3% at 5 years and 0%, 5.8%, 4.4%, and 31.3% at 10 years, respectively. Group 4 showed a significantly higher incidence rate than groups 1, 2, and 3.
Conclusion: Analysis stratified by sAg and crAg levels showed that HCC did not occur in pts with an sAg level ≥ 1300 and a crAg level < 3.0 at 3 years after NA therapy initiation, whereas HCC incidence was the highest in those with an sAg level < 1300 and a crAg level ≥ 3.0. Pts at high risk of HCC after NA therapy can be mainly identified by sAg and crAg levels.

FRI-197

Prediction of elastographic reversion of cirrhosis after 5 years of entecavir or tenofovir disoproxil fumarate therapy in caucasian chronic hepatitis B patients

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Background and aims: Long-term follow-up of phase III clinical trials has shown that reversion of histological cirrhosis may be achieved in CHB patients after ≥ 5 years of ETV or TDF therapy. However, predictors of such reversion of cirrhosis have not been well defined, while a follow-up liver biopsy cannot be routinely performed in clinical practice. We assessed predictors of elastographic reversion of cirrhosis at 5 years of ETV/TDF in CHB patients.
Method: We included 348 adult Caucasian CHB patients of the PAGE-B cohort who had compensated cirrhosis before ETV/TDF and available reliable liver elastography at 5 years of therapy. Compensated cirrhosis before ETV/TDF was diagnosed mostly by histological findings or by well accepted ultrasonographic and/or endoscopic findings. Elastographic reversion of cirrhosis at 5 years of ETV/TDF therapy was diagnosed in cases with reliable liver stiffness measurements (LSM) < 12 kPa.
Results: At 5 years, LSM < 12 and ≥ 12 kPa was observed in 246 (71%) and 102 (29%) patients. In univariable analyses, elastographic reversion of cirrhosis was associated with lower BMI (p = 0.002) or BMI ≤ 30 vs > 30 kg/m^2 (77% vs 49%, p < 0.001), current alcohol use < 20 vs ≥ 20 g/day (80% vs 67%, p = 0.049), absence vs presence of diabetes (80% vs 58%, p = 0.006), higher platelets (p < 0.001) or platelets ≥ 150 vs < 150 x10^9/L at baseline (76% vs 64%, p = 0.014), higher platelets (p = 0.001) or platelets ≥ 150 vs < 150 x10^9/L at year 5 (75% vs 62%, p = 0.017), lower HBV DNA at baseline (p = 0.012), prior use of interferon (p = 0.001) or other nucleos (t)ide analogues (p < 0.001), normal (≤ 40 IU/L) vs elevated ALT at year 1 (74% vs 50%, p = 0.002), therapy with TDF vs ETV (74% vs 62%, p = 0.038), but not with age, gender, smoking, HBeAg status at baseline or year 5, normal ALT at baseline or year 5, baseline albumin levels, virological on-therapy remission. Logistic multivariable regression analysis showed that elastographic reversion of cirrhosis was independently associated with baseline BMI ≤ 30 kg/m^2 [OR: 2.92 (95% CI: 1.23-6.94), p = 0.015], absence of diabetes [OR: 3.16 (1.21-8.27), p = 0.019] and TDF therapy [OR: 3.21 (1.38-7.46), p = 0.007].
Conclusion: Elastographic reversion (LSM < 12 kPa) of compensated cirrhosis after long-term antiviral therapy can be achieved in > 70% of CHB patients and appears to be associated with absence of obesity and diabetes, as previously reported in clinical trials with histological follow-up, as well as with TDF compared to ETV therapy.

FRI-198

A Phase 1, double-blind, randomized, placebo-controlled, first-in-human study of the safety, tolerability, pharmacokinetics and pharmacodynamics of oral JNJ-64794964, a toll-like receptor-7 agonist, in healthy adults

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Background and aims: JNJ-64794964 (JNJ-4964) is an oral toll-like receptor-7 agonist in clinical development to treat chronic hepatitis B infection. This first-in-human study assessed the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single- (presented here) and multiple ascending doses of JNJ-4964 in healthy adults with/without food.
Method: In this ongoing study, subjects received a single oral dose of 0.2 (N = 6), 0.6 (N = 6), 1.25 (N = 8) or 1.8 mg (N = 6) JNJ-4964 or placebo (N = 2/dose group) in a fasted state and were followed up for 4 weeks. The 1.25-mg group were evaluated for food effect in a cross-over manner with ≥ 6 weeks' interval. PD analyses comprised an IFN-alpha ELISA, a Luminex panel of 13 other cytokines including IP-10, TNF-alpha and MCP-1, and an IFN-stimulated gene (ISG) expression analysis for ISG15, MX1 and OAS1 using qPCR.
Results: All single doses were safe and well tolerated. No serious adverse events (AEs) occurred. 10/34 adults reported mild (≤ Grade 2), transient and reversible AEs at least possibly related to study drug: 5 had fever and flu-like symptoms that resolved within 24-48 hours; 4 had transient, asymptomatic lymphopenia (< 0.9×10^9/L). In the 1.25 mg group, the incidence of AE reporting was lower for the fed compared to the fasted state.
JNJ-4964 exposure post-administration was dose proportional for 0.2-1.8 mg doses. Individual profiles showed rapid JNJ-4964 uptake with an early t_{max} (0.5-1 h), followed by a rapid distribution phase, but with a variable and long median terminal half-life of 190-540 h. $AUC_{0\text{-}24h}$ was ~20% lower in the 1.25-mg fed compared to the fasted state.
ISG and cytokine levels peaked within 12-24 h and returned to predose levels 48-96 h post-administration. Induction of all 3 ISGs was observed in every group, including all dosed subjects in the 1.25 and 1.8-mg groups. Increased cytokine expression was observed in 0/6, 1/6, 5/6 and 7/8 dosed subjects in the 0.2, 0.6, 1.25, and 1.8 mg fasted dose groups, respectively. IFN-alpha increased ≥ 2-fold in 4/8 and 2/6 dosed subjects in the 1.25 and 1.8-mg groups, but not in the 0.2 and 0.6-mg groups. Cytokine and ISG expression were reduced in the 1.25-mg fed compared to the fasted state.
Conclusion: Single oral doses of 0.2-1.8 mg JNJ-4964 in healthy adults were generally safe, well tolerated, exhibited dose proportional PK and induced cytokines/ISGs. AEs were mild and reversible. Preliminary data supports continued development of JNJ-4964.

FRI-199

First in Human, single ascending dose clinical trial of AIC649 in patients with chronic hepatitis

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Background and aims: AIC649 is an immunomodulator known to induce loss of woodchuck hepatitis surface antigen (WHsAg) and induce anti-WHsAg antibodies, suggesting that AIC649 may achieve functional cure in chronic hepatitis B (CHB) patients (pts). This randomized, multi-center, double-blind, placebo-controlled trial was conducted to assess the safety, tolerability and pharmacodynamics of single ascending intravenous doses of AIC649 in CHB pts.
Method: In total, 32 male and female, 18 to 65-year-old, treatment-naïve and -experienced, HBeAg-negative and -positive pts with CHB were included. At each of the 4 dose steps, 8 pts received a single dose of AIC649 (6 pts) or placebo (2 pts) and were followed for 3 months. Safety assessments included overall tolerability, clinical laboratory and adverse events. HBV parameters were assessed over the whole time course, immunological parameters between baseline and day 14. The high dose groups 3 and 4 were additionally assessed for HBV parameters at 6 and 12 months post-treatment.
Results: Treatment-emergent adverse events (TEAEs) were reported for fewer AIC649-treated pts (20/24, 83.7%) than for placebo (8/8, 100%). No pt receiving AIC649 had drug-related, severe, or serious TEAEs. There were no apparent effects of AIC649 upon vital signs, electrocardiography, hematology, clinical chemistry, or urinalysis. There were no hepatic flares.
Following a single dose of AIC649, there was evidence of innate activation with increases in IL-1β, IL-6, IL-8, IFN-γ and reduction in IL-10 plasma levels. IFN-γ showed a consistent response in the highest dose group. The CD4 T cell effector memory population appeared to consistently expand from dose group 2 upwards.
HBV DNA and HBsAg levels did not substantially change in most pts. However, 2 pts (1 placebo, 1 dose group 3) showed a clear reduction in HBV DNA at the end of follow-up. The AIC649-treated pt achieved HBeAg loss with anti-HBe seroconversion and despite unchanged HBsAg levels, became transiently anti-HBs Ab positive. In dose groups 3 and 4, a total of 3 pts had marked peaks in HBV DNA levels post-treatment: In 2 pts HBsAg levels did not change but in 1 pt (dose group 4) this was followed by a continuous reduction in HBsAg levels to 32% at 1 year post-treatment.
Conclusion: A single intravenous dose of AIC649 was safe and well tolerated in all dose groups. Despite the heterogeneity of the pts in the trial, there was evidence that a single dose of AIC649 stimulates immunity.

FRI-200

Spend less get more;cost effectiveness of various models of care in hepatitis C treatment

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Background: With its unrestricted access to directly acting antiviral drugs, Australia is committed to eradicating hepatitis C (HCV) infection.The strategies used to augment treatment uptake include innovations in models of care (MOC) and decentralization of care.
Aims: To study the short (24 weeks) and long-term (lifetime) cost-effectiveness of four different MOC in HCV treatment.
Method: A cohort Markov model-based probabilistic cost-effectiveness analysis (CEA) was undertaken extrapolating upto 30 years from cost and outcome data collected from a 24-week study in which patients, initiated on HCV therapy for a year from 1st March 2016 at four major public hospitals in South Australia after excluding those with cirrhosis and after liver transplantation, were studied. The MOC were classified depending on the person providing patient workup, treatment and monitoring into: MOC1 (specialist); MOC2 (mixed specialist and nurse); MOC3 (nurse); MOC4 (General Practitioner, GP).Incremental costs were estimated from a Medicare perspective. Incremental outcomes were estimated based on the sustained viral response (SVR) and quality adjusted life years (QALY) gained. A cost-effectiveness threshold of $50, 000 per QALY gained, the implicit criterion used for assessing the cost-effectiveness of new pharmaceuticals and medical services in Australia, was assumed for QALY outcomes. Net monetary benefit (NMB) estimates based on this threshold were also calculated.
Results: 1373 patients, 64% males, mean age 50 (SD 11) years were studied. At 24 weeks, the SVR of 97% was not different between MOCs ($p = 0.093$). In CEA, MOC4 and 2 clearly dominated MOC1 both at 24 weeks and over 30 years with higher QALYs and lower costs. Similarly, NMB were highest in MOC 4, followed by MOC2 as shown in the table below.

Table:

Time Horizon	Costs (AUD)/QALY	MOC 1	MOC 2	MOC 3	MOC 4
10 years	Mean total health care costs	$77, 479	$77, 217	$77, 395	$77, 003
	Mean QALYs gained	6.3801	6.3856	6.3788	6.3857
	Net Monetary Benefit	$241, 527	$242, 063	$241, 547	$242, 283
20 years	Mean total health care costs	$77, 812	$77, 341	$77, 779	$77, 121
	Mean QALYs gained	10.2725	10.2830	10.2701	10.2833
	Net Monetary Benefit	$435, 812	$436, 811	$435, 725	$437, 043
30 years	Mean total health care costs	$77, 953	$77, 393	$77, 942	$77, 170
	Mean QALYs gained	12.5134	12.5279	12.5100	12.5283
	Net Monetary Benefit	$547, 715	$549, 003	$547, 560	$549, 242

Conclusion: Decentralized models of care using GP (MOC4) and mixed consultant nurse model (MOC2) were cost effective ways of promoting HCV treatment uptake.

FRI-201

Hepatitis B virus vaccine immunogenicity in anti-HBC+ immunocompromised patients with low anti-HBS levels: Preliminary results of the Hepbare study

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Background and aims: Anti-HBc+ subjects are at risk of HBV reactivation when undergoing immunosuppression. Some studies have shown that anti-HBs titles < 100mUI/L are associated with a higher rate of reactivation. Our aim was to assess the immunogenicity of HBV vaccine in immunocompromised anti-HBc+ patients with anti-HBs < 100mUI/L.

Method: Hepbare is a post-authorization effectiveness study whose primary aim is to assess the immunogenicity of HBV vaccine (anti-HBs > 100mUI/L) in immunocompromised anti-HBc+ adults with low anti-HBs titers. Secondary aim: to assess the efficacy of HBV vaccine to prevent reactivation. Inclusion criteria: immunocompromised subjects HBsAg-/anti-HBc+ with anti-HBs < 100mUI/L and undetectable HBV DNA. Exclusion criteria: previous HBV vaccination or criteria for antiviral prophylaxis (anti-CD20 therapy, chemotherapy, stem cell transplant or anti-HBc+ liver graft). Patients were randomized to control or vaccination group (0-1-2 months, plus booster in case of response or revaccination at double dose if antiHBs < 100 mUI/ml).

Results: To date 65 subjects have been recruited: 65% male, median age 62 years (IQR 50-68), 90% Caucasians, median time of immunosuppression 3 years (IQR 2-7). Conditions: 52% solid organ transplantation, 19% rheumatological, 17% dermatological and 9% IBD. Immunosuppression: 26% monoclonal antibodies, 19% calcineurin inhibitors, 18% purine inhibitors, 16% methotrexate, 14% calcineurin + purines inhibitors. 39% also received corticoids. Randomization: 33 (51%) vaccine and 32 (49%) control group. Baseline, 44% presented anti-HBs < 10mUI/L. In the vaccine group, 58% developed anti-HBs > 100mUI/L after the first vaccination schedule and anti-HBs statistically increased (18 vs 205 mUI/ml, p = 0.05). Response was higher in subjects with basal anti-HBs 10-100 mIU/L than anti-HBs < 10mUI/L (75% vs 20%, p = 0.08). Among non-responders, only 25% developed anti-HBs > 100mUI/L after the second schedule (overall response 64%). Follow-up showed a progressive decrease on anti-HBs levels, with 50% of subjects persisting anti-HBs > 100mUI/L. No changes in anti-HBs were observed in the control group (p = 0.67). To date, no subjects have shown HBV reactivation.

Conclusion: Preliminary analysis of Hepbare showed that 64% of the subjects develop anti-HBs > 100mUI/L after HBV vaccination, although the titers tended to decrease during follow-up. Further data is needed to assess the clinical impact of vaccination on the risk of HBV reactivation.

FRI-202

Outcomes of hepatitis B patients transplanted without hepatitis B immunoglobulin

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Background and aims: Hepatitis B immunoglobulin (HBIG) is routinely used in conjunction with nucleoside analogues (NA) following liver-transplantation (LT) in patients with hepatitis B virus (HBV) to reduce the risk of donor graft infection from recipient HBV. This treatment regimen was established prior to the routine incorporation of NA into clinical care. Data are emerging which question the role of HBIG post LT when NA's with a high barrier to resistance are being co-administered.

Method: All patients undergoing LT for HBV related cirrhosis between November 2015-17 were maintained on their NA therapy (Entecavir or Tenofovir). Only those patients with a HBV DNA > 10, 000iu/ml received high dose intravenous HBIG for 8 days in the immediate post-operative period with hepatitis B surface antibody (HBsAb) monitoring. Post LT, HBV DNA and HBsAg status were recorded and compared to a historic cohort treated with both HBIG and NA therapy to assess safety and efficacy.

Results: Over the 2-year period 18 patients with HBV were treated post-LT with the new protocol. Median age was 56-years (31-68 years). All patients were receiving NA therapy at the time of LT and had a HBV DNA of < 10, 000 copies/ml. At the time of LT, 15 patients had an undetectable HBV DNA and the remaining 3 patients had VL of 23, 84, and 23 copies/ml. Patient and graft survival at 1-year was 88% (16/18) and 78% (14/18) respectively. All deaths and graft failure were surgical or sepsis related. Following LT, HBV DNA was undetectable in 94% (15/16) of patients. The patient with detectable HBV was on entecavir, having previously been exposed to lamivudine, on switching to tenofovir viral suppression was achieved. HBsAg status was available in 11/18 patients and negative in 9/11.

Comparison was made to a retrospective control group treated post-LT with both HBIG and NA. This group were matched to age (p = NS), HBV viral load (p = NS), disease severity (UKELD) (p = NS) and indication for LT. Patient and graft survival at 1-year was 100%. Following LT, HBV DNA was undetectable in all patients and HBsAg status was available in 14/18 patients and negative in 13/14.

Conclusion: Omitting HBIG peri- and post-LT in patients with a low viral load appears a safe and effective treatment strategy in this small cohort. The cost of HBIG is £15, 000 per patient which produced a cost saving of £270, 000 in this cohort. Larger and longer term studies are required to confirm this observation.

FRI-203

Inhibition of hepatitis B virus replication by FAM176A via activation of PI3K-AKT-mTOR signaling pathway

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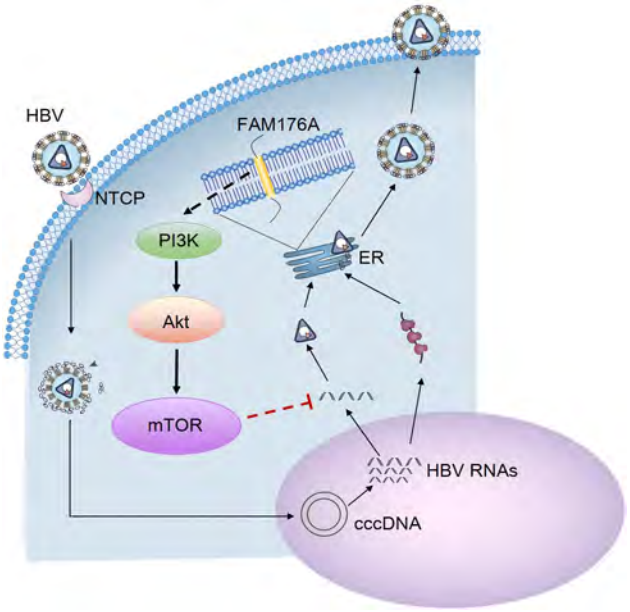
Background and aims: Hepatitis B virus (HBV) replication activity is much higher in immune tolerant phase than in inactive carrier phase, however, the immune responses are comparable between these two phases. We previously reported mRNA levels of several intrahepatic genes were higher in inactive carriers, including FAM176A, MANEAL, TOMM34, ZMYM3, and CSTF2. In these study, we focused on FAM176A and aimed to investigate whether FAM176A inhibits HBV gene expression and replication. If so, the mechanism by which FAM176A regulates HBV needs to be further explored. Current antiviral therapies for chronic hepatitis B (CHB) patients are limited.

We also evaluated whether FAM176A could be used as a candidate for treating CHB.
Method: Histochemistry analysis of FAM176A expression between above two CHB phases; Serial cell models and animal models were used to investigate whether FAM176A regulates HBV replication; RNA sequence analysis of signal pathway involved in FAM176A-mediated HBV regulation; FAM176A functional domain analysis through targeted mutagenesis; CHB mouse models were used for evaluation of FAM176A's antiviral activity based on gene therapy.
Results: FAM176A protein levels are higher in in inactive carrier patients than in immune tolerant patients. FAM176A inhibits HBV gene expression and replication in vitro and in vivo. FAM176A induces activation of PI3K-Akt-mTOR pathway to decay HBV RNA. Transmembrane domain of FAM176A in endoplasmic reticulum is indispensable for FAM176A-mediated antiviral activity. FAM176A is a promising candidate in treating CHB mice.



Conclusion: FAM176A activates PI3K-Akt-mTOR pathway to inhibit HBV replication, and harbors robust potential in treating CHB.

FRI-204
ASPP2: A potential strategy to inhibit HBV replication through reducing hepatocytes autophagy
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Background and aims: Hepatitis B virus is such a virus that can induce cell basal autophagy and use cell autophagy to facilitate its own replication. Alteration of hepatocytes autophagy was found to have impacts on cellular HBV replication.
Method: Liver cell models (HepG2, HepG2.2.15 and Hep3B cells) were used to investigate the function of ASPP2 on the autophagy of HBV infected hepatocytes, as well as its indirect effects on HBV replication. GFP-LC3 puncta, autophagy related gene mRNA and protein expressions were used to evaluate the level of cell autophagy.
Results: Overexpression of ASPP2 was found to inhibit HBV induced cell autophagy, thus reduce HBV replication and HBsAg and HBeAg release. This function of ASPP2 on autophagy was prominent in p53-null liver cells (Hep3B cells). Overexpression of ASPP2 reduced Atg7 transcription, whereas reduction of ASPP2 increased Atg7 transcription. Atg7 silence restricted the function of ASPP2 on autophagy reduction evidently.
Conclusion: ASPP2 reduced cell autophagy and inhibited HBV replication by reducing Atg7 transcription in a p53 independent manner. ASPP2 could be a novel strategy to inhibit HBV replication.

FRI-205
Entecavir improves liver function and fibrosis in hepatitis B virus-associated cirrhosis: A 6 years-multicenter study
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Background and aims: Previously we reported that entecavir (ETV) improves liver function and non-invasive fibrosis markers in patients with HBV-associated cirrhosis after 2 years of treatment. This study extended observational period and aimed to confirm that 6 years of ETV treatment continuously improve liver function and fibrosis in patients with hepatitis B virus (HBV)-associated cirrhosis.
Methods: Previously enrolled 283 naïve patients with HBV associated-cirrhosis who completely finished 2 years of ETV study, were treated further by ETV (more than 4 years) between March 2007 and December 2017 in 4 tertiary institutions. Among them, the patients with HCC development (n = 61) and frequently skipping medication (n = 17) were excluded. For the evaluation of liver function or fibrosis, laboratory findings, model for end stage liver disease (MELD) score, Child-Pugh (CP) class, AST platelet ratio index (APRI), FIB-4 index, and liver stiffness measurement (LSM) value on Fibroscan were compared among at baseline, at 2 years, and 6 years after ETV treatment.
Results: A total 205 patients (mean age of 50 ± 9 years; 64.2% of male; 50.2% of HBeAg-positive; mean ALT of 139 ± 205 U/L; mean HBV DNA of 6.9 ± 1.2 $\log_{10}$ copies/ml) were finally enrolled. The ALT normalization rates were 78% at 2 years and 87.3% at 6 years. The undetectable HBV DNA rates were 95.6% at 2 years and 99.0% at 6 years. The HBeAg loss rate was 39% at 2 years and 86% at 6 years. Total bilirubin levels (1.9 ± 2.7 at baseline; 1.2 ± 0.6 at 2 years; 1.1 ± 0.6 mg/dL at 6 years, $P < 0.005$), platelet counts (105 ± 44 at baseline; 109 ± 46 at 2 years; 124 ± 53 x10^3/mm^3 at 6 years, $P < 0.001$), and APRI (3.7 ± 5.4 at baseline; 1.2 ± 1.1 at 2 years; 0.8 ± 0.7 at 6 years, $P < 0.001$) were continuously improved. The distribution of CP class was also continuously improved (A:74.1%, B:21.0%, C:4.9% at baseline; A:92.7%, B:6.8%, C:0.5% at 2 years; A:96.1%, B:3.4%, C:0.5% at 6 years, $P < 0.05$). Albumin levels (3.7 ± 0.6 to 4.2 ± 0.4 g/dL, $P < 0.001$), INR (1.26 ± 0.29 to 1.09 ± 0.12, $P < 0.001$), MELD score (10.9 ± 4.3 to 8.9 ± 3.0, $P < 0.001$), FIB-4 index (6.5 ± 6.4 to 3.6 ± 2.4, $P < 0.001$), and LSM value (28.8 ± 19.8 to 14.5 ± 9.2, $P < 0.001$) were initially improved from baseline to 2 years-treatment. However, the improvement rates of those were very slow after 2 years of ETV treatment.
Conclusion: ETV rapidly improves liver function and fibrosis in patients with HBV-associated cirrhosis after 2 years-treatment. After that, liver function and fibrosis were slowly improved.

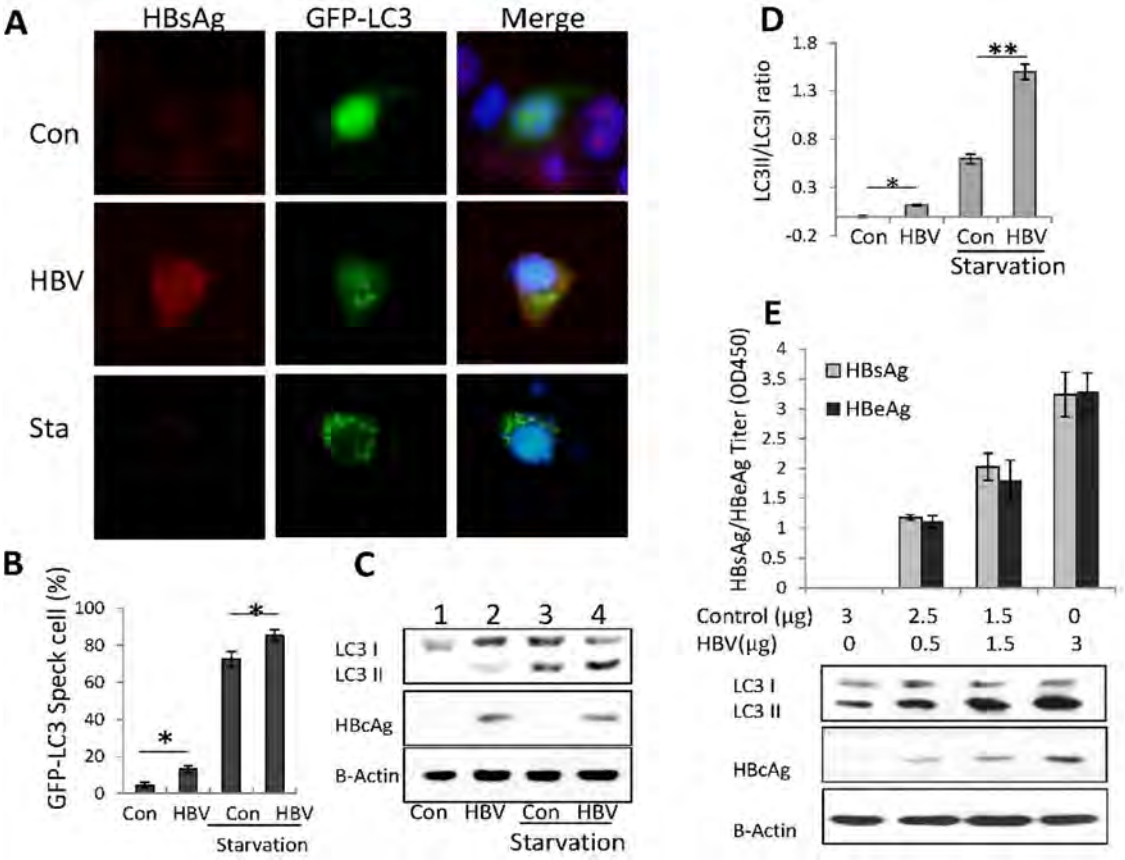

Figure 1: (abstract: FRI-205): HBV enhanced autophagy of it infected hepatocytes

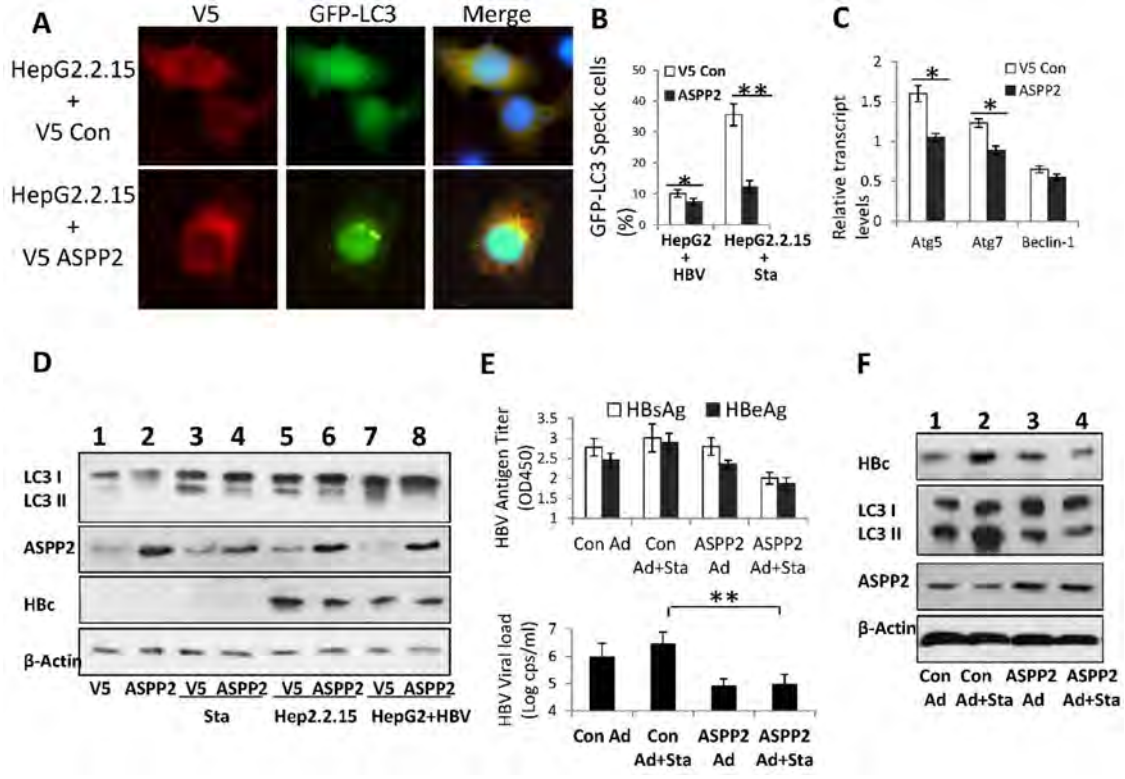

Figure 2: (abstract: FRI-205): ASPP2 inhibited HBV induced hepatocytes autophagy

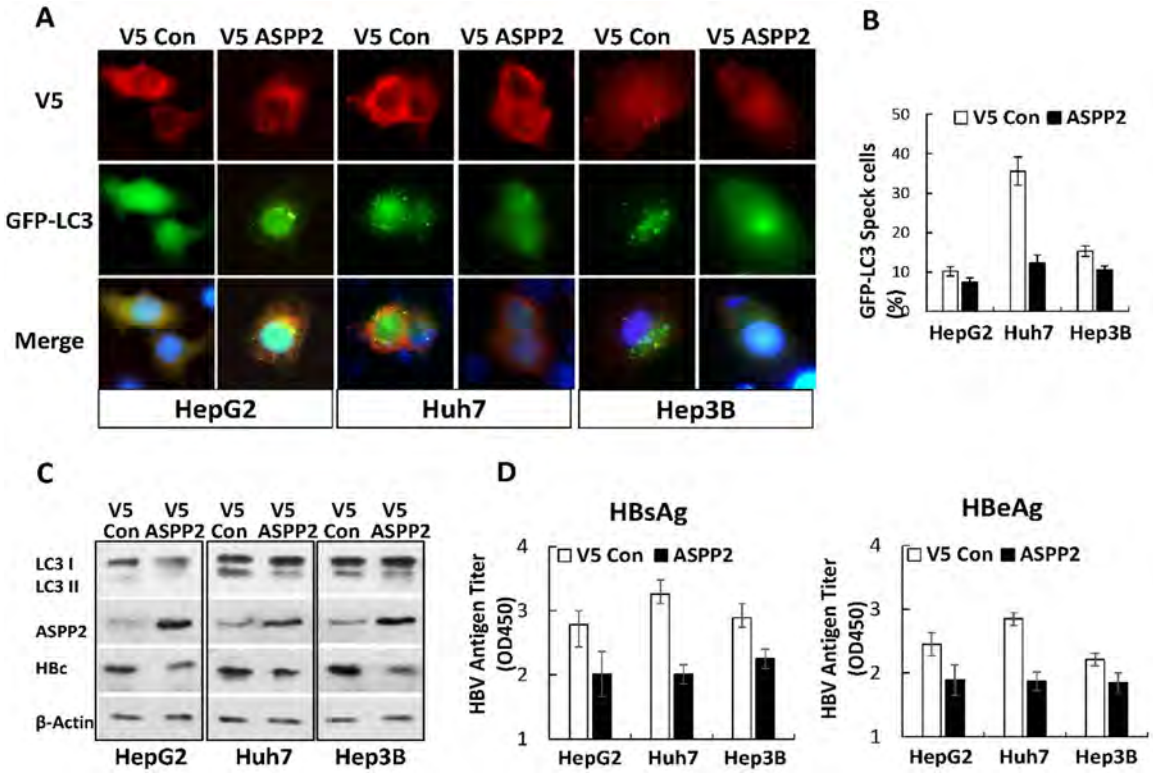

Figure 3: (abstract: FRI-205): ASPP2 inhibited HBV induced autophagy in a p53 independent manner

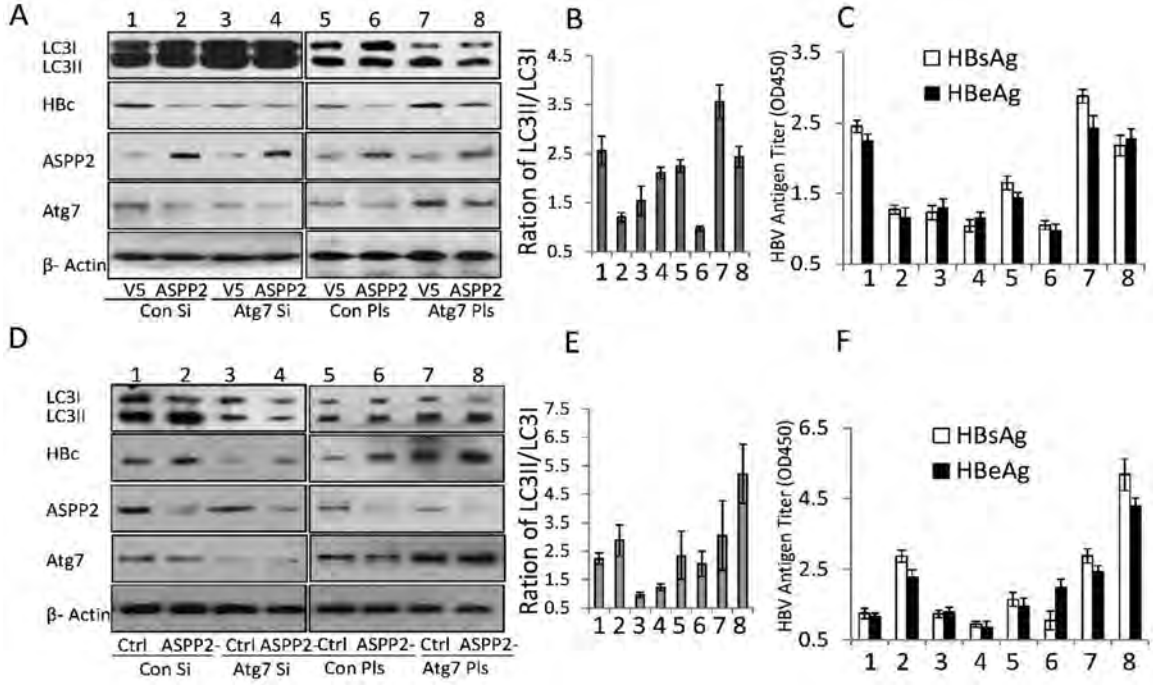

Figure 4: (abstract: FRI-205): ASPP2 inhibited HBV induced autophagy by reducing Atg7 transcription

FRI-206

Relationship between hepatitis B core related antigen levels and sustained HBeAg seroconversion in patients treated with nucleos (t)ide analogues

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Background and aims: HBeAg seroconversion experienced during nucleo (s)tide analogue (NUC) therapy is often not sustained. We aimed to study whether hepatitis B core related antigen (HBcrAg) levels predict sustained HBeAg seroconversion.
Method: We studied HBeAg-positive patients treated with NUCs for at least six months. We quantified HBcrAg at baseline and at the time of HBeAg seroconversion and studied the relationship with HBeAg seroconversion and subsequent relapse.
Results: HBcrAg was quantified at baseline in 196 patients (130 treated with entecavir or tenofovir). Baseline HBcrAg levels correlated with HBV DNA (r 0.658, p < 0.001), HBeAg (r 0.738, p < 0.001) and HBsAg (r 0.247, p = 0.001), and varied by HBV genotype (7.30/7.70/8.14/7.65 log U/ml for genotypes A/B/C/D; p = 0.001 by ANOVA). Baseline HBcrAg levels were lower in patients who achieved HBeAg seroconversion (n = 55) than in those who did not (7.42 versus 7.86 log U/ml, p = 0.017); the unadjusted hazard ratio (HR) was 0.802 (95% CI: 0.656-0.980, p = 0.031). The association was however not sustained in multivariate analysis (adjusted HR 0.972, p = 0.883). HBcrAg remained detectable in all patients at the time of HBeAg seroconversion. Higher HBcrAg at the time of HBeAg seroconversion was an independent predictor of subsequent HBeAg relapse (observed in 16 patients; adjusted HR 1.855 (95% CI: 1.099-3.133, p = 0.021). None of the patients with HBcrAg < 4.90 log U/ml (n = 13) experienced relapse. Fifteen patients discontinued treatment after at least 6 months consolidation therapy and 5 (33%) experienced HBeAg relapse subsequently. HBcrAg levels at the time of HBeAg seroconversion were higher in patients who experienced relapse than in those who did not (5.89 versus 5.42 log U/ml, p = 0.039)
Conclusion: Baseline HBcrAg level is not an independent predictor of HBeAg seroconversion during NUC therapy. HBcrAg remains detectable in patients after HBeAg seroconversion. Patients with high HBcrAg levels at the time of HBeAg seroconversion have a high risk of relapse.

FRI-207

Subgroup analysis of patients undergoing switch of nucleos (t)ide regimen for HBV treatment during the prospective BONIKA trial

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Background and aims: Infinite duration of nucleos (t)ide (NUC) treatment of chronic hepatitis B (cHBV) prones longterm toxicity. In the prospective BONIKA Study (NCT-Nr. 02267473) hepatitis **B** patients under **o**ral **N**UC treatment undergo **i**ntermittent **k**idney function **a**ssessment with a combination of serum and urine parameters to detect early renal tubular dysfunction (RTD).
Method: Between 10/2014 and 01/2017 in Frankfurt 179 mono-infected HBV patients under NUC treatment consented and were regularly screened for RTD by analyses of serum phosphate (**sPh** < 2, 6 mg/dl)), serum uric acid (**sUA** < 3, 4 mg/dl), urine alpha-1 microglobuline (**uMG** > 12 mg/l) and urine glucosis (uGlc positive). By definition a RTD is diagnosed when at least 2 of the above abnormalities are given. Here a subgroup of patients with NUC treatment changes till 05/2018 was monitored over 12 months after switching.
Results: In this subcohort of 179 patients under NUC-treatment (115 Tenofovir Disoproxil [TDF]/47 Entecavir [ETV]/12 Lamivudine [LAM]/5 other NUCs) a total of 20 patients had a treatment switch. 10 patients were switched due to deterioration of renal tubular function (2x Fanconi syndrome, 7x RTD per definition, 1x proteinuria + elevated creatinine). All these 10 patients were on treatment with TDF before switching. 9 patients were changed to ETV and one to Tenofovir Alafenamide (TAF). Renal parameters were further monitored (see table 1). Viral replication was persistently suppressed after switch to ETV/TAF. 10 patients were switched for other reasons (6x insufficient viral suppression, 1x family planning, 1x elevated liver enzymes, 1x patient wish, 1x gastrointestinal side effects) to either TDF or ETV.
Conclusion: Relevant RTD requiring a change in treatment was only observed under TDF treatment. Switching to ETV in case of RTD improves the renal condition and shows reliable viral suppression. Serum phosphate is normalizing, but tubular proteinuria often persists in case of progressed RTD, which emphasizes the relevance of early detection of RTD.

Median (*m*)	Prä-switch	3 months post-switch	6 months post-switch	1 year post-switch	p prä-switch vs 1 y post switch
Switch RTD (n = 10/8 without Fanconi)					
Serum phosphate (mg/dl)	1.98/2.1	2.4/2.4	2.62/2.54	2.64/2.64	**0.005/0.032**
Serum uric acid (mg/dl)	4.7/5.3	4.85/5.65	5.2/6.5	4, 85/5.7	0.757/0.678
Serum creatinine (mg/dl)	1.33/1.33	1.31/1.27	1.23/1.16	1.3/1.19	0.420/0.260
Urine alpha1 micro-globuline (mg/l)	35.6/27.5	5.0/4, 9	21.8/9.3	14.4/9.3	0.069/**0.046**
Switch other reasons (n = 10)					
Serum phosphate (mg/dl)	3.3	2.55	3.27	3.39	0.220
Serum uric acid (mg/dl)	4.6	4.1	4.1	3.8	0.944
Serum creatinine (mg/dl)	0.8	0.84	0.88	0.86	0.489
Urine alpha1 micro-globuline (mg/l)	4.9	4.9	19	4.9	0.655

Figure: (abstract: FRI-207)

FRI-208

Predictors of treatment response during addition of pegylated Interferon alfa-2a to an onging nucleos (t)id treatment in chronic hepatitis B: Results from the PADD-ON trial

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Background and aims: Addition of pegylated interferon alfa-2a (Peg-IFN) to an ongoing NUC therapy accelerates HBsAg decline and clearance in patients with chronic hepatitis B (cHB). However, decision for Peg-IFN should be well-balanced, as its drug-related side effects are more frequent compared to nucleos (t)ide treatment. Here we report about predictors of treatment response from the PADD-ON study to guide treatment decision

Method: HBeAg-negative cHB patients (HBsAg > 100 IU/ml) under effective NUC treatment for ≥ 1 year were randomized to receive additional Peg-IFN (180 µg/week) for 48 weeks (Peg-IFN group, n = 112) or continuing NUC monotherapy (control group, n = 58) in a prospective open-label phase IIb study (EudraCT-Nr: 2011-002812-10). The modified intention-to-treat (mITT) population (n = 165), covering ≥ 1 post-baseline HBsAg assessment is reported. Primary response after 48 weeks of treatment was defined by reduction of ≥ 1log10 in serum HBsAg concentration compared to baseline. Secondary end points were HBsAg seroconversion and overall HBsAg concentrations. Adverse events (AEs) were assessed. Predictors for treatment response were analysed by multivariate cox regression. Fisher's Exact test#, T test$, chi2-test§.

Results: Primary response (HBsAg log drop) was achieved in 24.5% (n = 26/110) of the Peg-IFN group compared to 1.9% (n = 1/55) in the control group (p < 0.0001#). Six patients (5.5%) in the Peg-IFN group developed an HBsAg-seroconversion, whereas none occurred in the control group (p > 0.05#). In the Peg-IFN group HBsAg loss was observed in 15.8% (n = 16/110), whereas the control group failed HBsAg clearance (p < 0.05§). Most patients (94.6% in the Peg-IFN- and 58.6% in the control- group) experienced at least one AE. No death was reported.

Multivariate analysis confirmed the treatment group (p = 0.0038§) and baseline HBsAg < 1000 U/ml (p = 0.0002§) as predictors for the primary response. HBsAg loss was associated with the treatment group (p = 0.0014), baseline HBsAg < 1000 U/ml (p = 0.042§) and overall NUC treatment duration (p = 0.048§). Anti-HBsAg seroconversion only correlated with baseline HBsAg < 1000 U/ml (p = 0.047§) and overall NUC treatment duration (p = 0.041§). In all explorative settings gender, age, serum transaminases, liver function as well as the NUC regimen (tenofovir versus entecavir) had no impact on treatment response.

Conclusion: The addition of Peg-IFN to an ongoing NUC regimen accelerates HBsAg reduction in comparison to standard NUC therapy of HBeAg negative cHB patients. Particularly patients with longer NUC pre-treatment duration and lower baseline HBsAg levels show better response rates.

FRI-209

Exploring TH1/TH2 adjuvants to improve the efficacy of the therapeutic vaccination against chronic hepatitis B

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Background and aims: With the limitation of current treatments to cure HBV infection, therapeutic vaccination becomes an interesting new strategy to treat chronic hepatitis B. To this end, we have developed a therapeutic hepatitis B vaccine, termed *TherVacB*, which is based on two protein immunizations using particulate, recombinant HBV S and core antigens (HBsAg, HBcAg) and a boost using a modified vaccinia virus Ankara (MVA) vector expressing HBV antigens. We found success of therapeutic vaccination largely depends on an appropriate adjuvant for the protein priming, which simultaneously generates neutralizing antibody responses and elicits potent CD4 and CD8 T-cell responses.

In order to improve the efficacy of our *TherVacB* regimen, we composed and investigated a series of novel HBsAg/HBcAg adjuvants formulations based on either liposomes, or squalene-in-water emulsion enriched by saponin QS21 and optionally by monophosphoryl lipid A (MPL).

Method: Firstly, HBsAg/HBcAg adjuvants formulations were tested for their stability and antigen integrity *in vitro*.Afterwards, the immunogenicity of selected adjuvants formulations was evaluated in the C57BL/6 wild type and AAV-HBV transduced mice, where persistent HBV replication was established. In addition, the secreted cytokine profiles by *in vitro* re-stimulated splenocytes were determined to assess the adjuvant effects on Th1/Th2 immune response pattern.

Results: Six selected vaccine formulations proved to be stable and antigens remained intact for at least 2 weeks. Immunogenicity study in naive mice showed the new formulations elicited not only very high anti-HBs levels, but also robust HBV-specific CD4 and CD8 T-cell responses outcompeting previously tested adjuvants. In AAV-HBV mice, immunization with four most promising liposomal as well as non-liposomal formulations resulted in a 3-log decrease in serum HBsAg levels, accompanied by very high anti-HBs titers. In addition, high percentages of IFNγ-secreting HBV-specific T cells were detected in the livers of mice after immunization with most of the novel HBsAg/HBcAg formulations. After immunizations, overall 40-70% decrease in serum HBeAg and numbers of HBV-positive hepatocytes was shown. The highest antiviral effect was observed for the optimized liposomal formulation containing QS21 and MPL. *Ex vivo* stimulation of isolated splenocytes with HBV antigens resulted in

detection of not only IFNγ, but also IL4 and IL5, suggesting that the new vaccine formulations induced a balanced Th1/Th2 response in mice. Similarly, immunizations elicited comparable HBsAg-specific IgG1 and IgG2a antibody levels. Last but not least, all vaccine formulations were safe and well tolerated.
Conclusion: The liposome based adjuvant formulations improved the efficacy of therapeutic vaccination in chronic hepatitis B mouse models, and thereby are promising candidates for the *TherVacB* regimen.

FRI-210

Establishment of high rates of functional cure of HBeAg negative chronic HBV infection with REP 2139-Mg based combination therapy: Ongoing follow-up results from the REP 401 study

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Background and aims: The REP 401 study (NCT02565719) is assessing the safety and efficacy of REP 2139-Mg (clinical lead) or REP 2165-Mg combined with tenofovir disoproxil fumarate (TDF) and pegylated interferon α-2a (pegIFN) in Caucasian patients with HBeAg negative chronic HBV infection.
Method: Lead-in TDF therapy in 40 patients was followed by randomization into an experimental group (48 weeks of TDF, pegIFN and REP 2139-Mg or REP 2165-Mg) or an adaptive control group (24 weeks of TDF + pegIFN followed by cross over to 48 weeks of experimental therapy). All patients were subsequently entered into a treatment-free follow-up scheduled for 48 weeks. Viremia is monitored on the Abbott Architect and Realtime platforms.
Results: Baseline HBsAg was > 1000 IU/ml in all patients and 14775.7 ± 9302 and 9018 ± 8743 IU/ml in adaptive control and experimental groups. Therapy was well tolerated except for one withdrawal due to pegIFN-related depression. Two additional participants withdrew where therapy was well tolerated. Antiviral responses between REP 2139-Mg and REP 2165-Mg were indistinguishable and not related to HBV genotype or HBsAg, ALT or fibrosis (Fibroscan) at baseline. Following the introduction of TDF, HBV DNA was well controlled in all patients during therapy. Following the introduction of NAPs, HBsAg reduction was > 1 log in 36/40 patients and became < 1 IU/ml in 28/40 and < 0.05 IU/ml in 24/40 participants. Transaminase flares occurred in 38/40 patients and were correlated with reductions in HBsAg, were self-resolving during therapy and not accompanied by any evidence of liver dysfunction. Transaminase flares were especially pronounced (400-1748 U/L) in patients where HBsAg became < 1 IU/ml and were accompanied by profound elevations in anti-HBs (up to 255, 055 mIU/ml).
As of the date of submission, treatment-free follow-up has been extended to 24 or 48 weeks in 34/40 patients completing treatment. Persistent and stable inactive chronic HBV (HBV DNA < 2000 IU/ml with normal ALT) is present in 15/34 (44%) of participants. An additional 14/34 (41%) participants have functional cure (HBsAg and HBV DNA target not detected). Liver function has normalized in 94% of patients (versus 47% at baseline) and median hepatic stiffness consistent with F0 (≤ 7kPa) is present in 81% of patients (versus 52% at baseline).
Conclusion: A finite REP 2139-Mg based combination therapy with TDF and pegIFN is well tolerated and results in a high proportion of patients achieving control of infection not requiring further therapy under current guidelines. Transaminase flares appear therapeutic in nature and may reflect an immune mediated clearance of infected hepatocytes essential in establishing persistent control of chronic HBV infection.

FRI-211

Evaluation of the safety and tolerability of transaminase flares during antiviral therapy in patients with HBeAg negative chronic HBV infection or HBV/HDV co-infection

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Background and aims: The onset of transaminase flares during antiviral therapy of chronic HBV infection or HBV/HDV co-infection is an important consideration in the pursuit of functional cure of HBV and HDV infection. The high proportion of transaminase flares observed during NAP-based therapy in HBV infection (REP 401 study NCT02565719) or HBV/HDV co-infection (REP 301 study NCT02233075) affords a unique opportunity to evaluate factors predicting transaminase flares during therapy, the tolerability of different flare geometries during therapy and how flares correlate with antiviral response during therapy and the establishment of functional cure.
Method: Data from all 52 participants from the REP 301 (12) and REP 401 (40) studies were included in the analysis. Baseline data used in the analysis was HBsAg, ALT, AST, GGT and median hepatic stiffness (MHS, as measured by Fibroscan). Serial on-therapy biochemistry data included ALT, AST, GGT, Alk. Phos, bilirubin, albumin, INR and MHS at the end of treatment and during follow-up. Serial virologic data included HBsAg, anti-HBs, HBV DNA and HDV RNA.
Results: Three different transaminase flare geometries were observed during therapy: a single flare self-resolving during therapy, a single flare with a persistently elevated transaminase tail during therapy and a "double" flare with two distinct peaks.
Flare geometries, transaminase maxima or transaminase AUC during therapy were not correlated with baseline HBsAg, ALT, AST, GGT or MHS (up to 30.7 kPa in this participant population). No alterations in bilirubin, albumin or INR were observed with any flares and patients were asymptomatic throughout these flares including the absence of jaundice. Increased MHS at end of therapy was asymptomatic and correlated with transaminase AUC but decreased or normalized during follow-up.
The occurrence of transaminase flares was correlated with the introduction of pegIFN in patients who experienced HBsAg reduction and was more pronounced in patients where HBsAg reduction became < 1 IU/ml. Flares were also accompanied by pronounced increases in circulating anti-HBs during therapy. The strength of transaminase flares was also correlated with the establishment of functional cure of HBV or HDV or the establishment of inactive chronic HBV.
Conclusion: Transaminase flares are very common during NAP-based therapy of HBV infection or HBV/HDV co-infection and appear well tolerated, suggesting that in the context of these infections, transaminase flares can occur without impacting liver function. Flares are also correlated with HBsAg reduction, increases in circulating anti-HBs and the establishment of functional control/cure of HBV and HDV infection, suggesting they are a component of a restored immunological control of these infections.

FRI-212

HBV RNA can be detected more frequently than HBcrAg but decreases during long term treatment with nucleos (t)ide analogues up to 14 years in patients with HBeAg negative chronic hepatitis B

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Background and aims: Hepatitis B virus (HBV) RNA is a new serological marker that correlates with intrahepatic cccDNA. HBV RNA levels were shown to remain detectable in HBeAg positive patients in spite of suppression of HBV DNA by treatment with nucleos (t)ide analogues (NAs). However, in HBeAg negative patients the kinetics of HBV RNA during long term NA treatment are yet unknown. The aim of our study was to examine whether HBV RNA may still be detectable after long term treatment with NA and how it correlates with other HBV replication markers.
Method: A total of 96 patients with HBeAg negative chronic HBV infection (mean age 65 ± 9 [range, 40-84] years, 74 (77%) male, 50 (52%) with liver cirrhosis, 96 (100%) HBV genotype D) who had achieved undetectable HBV DNA levels for > 8 years (mean 117 ± 32 [range, 71-172] months) during NA treatment were retrospectively analyzed. All had achieved normal ALT during NA treatment over at least 6 years. Thirty-four patients (35%) had achieved undetectable HBV DNA for longer than 10 years. The current treatment consisted either of tenofovir (TDF, n = 90) or entecavir (ETV, n = 6) and had been conducted for a mean duration of 89 ± 11 [range, 43-119] months. HBV biomarker levels were measured from 288 serum samples stored at –20°C at the time points year 4, 7 and 10-14 (mean 117, range 120-172 months) of undetectable HBV DNA during NA treatment. HBV RNA was quantified after reverse transcription using a specific real-time PCR (LOD 160 copies/ml), HBV DNA by real time PCR (Roche, LOD 9 IU/ml), HBcrAg and HBsAg by ELISA (Lumipulse G, Fujirebio, LOQ 3 log U/ml and Abbott Architect, LOD 0.05 IU/ml, respectively).
Results: HBV RNA levels were above the LOD at years 4, 7 and 10-14 in 32%, 18% and 5% of samples by a mean of 2.8 ± 0.8 (2.2-5), 2.6 ± 0.5 (2.2-4), and 2.3 (2.2-4) $\log_{10}$ copies/ml. Mean HBsAg levels 3.1 ± 0.5 (1.3-4.3), 2.7 ± 0.6 (0.9-4.2) and 2.5 ± 0.7 (0.6-4.1) while HBcrAg levels were below LOQ in all but 4 samples. Correlation of HBV RNA with HBsAg levels was weak at all time points (r = 0.1, 0.2 and 0.1, respectively). Detection of HBV RNA was not associated with HBsAg levels, patient age, presence of cirrhosis, development of hepatocellular carcinoma (p = n.s.).
Conclusion: In HBeAg negative patients achieving long term suppression of HBV DNA during NA treatment HBV RNA can frequently be detected even after long treatment periods, but its quantity seems to decline over time. More sensitive detection methods for HBV RNA should be validated for its characterization as HBV replication marker on long term NA treatment.

FRI-213

HBV RNA at 6 months predicts HBeAg loss in nucleos (t)ide analogue treated HBeAg positive patients: Demonstration of clinical utility?

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Background and aims: HBeAg loss in patients with HBeAg-positive chronic hepatitis B is an important treatment end point and a pre-requisite for functional cure. Only around half of patients achieve HBeAg loss after five years of treatment with nucleos (t)ide analogues (NUC), despite nearly all achieving profound HBV DNA suppression. It is still unclear, but critical to understand, whether newer biomarkers differentiate patients who will achieve serological end points such as HBeAg loss. In this single-centre retrospective longitudinal cohort study, we evaluated HBV RNA and hepatitis B core-related antigen (HBcrAg) concentrations in NUC treated HBeAg-positive patients, with the aim of characterising differences that predict HBeAg loss.
Methods: Consecutive HBeAg-positive patients started on NUC therapy in 2012 with adequate stored serum samples were analysed. Baseline characteristics included age, sex, HBV genotype, ALT and liver fibrosis assessment by transient elastography or histology. Serum from baseline, 3, 6 and 12 months into NUC therapy and last follow-up were tested for HBV DNA, quantitative hepatitis B surface antigen (HBsAg), HBcrAg and HBV RNA concentrations.
Results: 28 patients received treatment with tenofovir disoproxil fumarate. After median follow-up of 64 months, 17 patients (61%) achieved HBeAg loss and 26 patients (93%) were HBV DNA negative. There were no significant differences at baseline between patients who subsequently lost HBeAg and those who remained positive. There was a strong correlation at baseline between HBV DNA and HBcrAg (r = 0.862, p < 0.001), and HBV DNA and RNA (r = 0.704, p < 0.001). This correlation was subsequently lost with treatment.
During treatment, median HBV DNA and quantitative HBsAg were similar between the groups at all time points (Figure 1). In contrast, early differences in HBcrAg concentrations were seen at 3 months (p = 0.019) and HBV RNA at 6 months (p = 0.006); by last follow-up, patients who achieved HBeAg loss had significantly lower HBcrAg and HBV RNA levels (median HBcrAg 5.8 vs 3.8 logU/ml, p = 0.026; median HBV RNA 3.94 vs. 0.83 logU/ml, p < 0.001). HBV RNA decline from baseline at 6 months was greater in those who achieved HBeAg loss (p = 0.038). Furthermore, HBV RNA decline had good predictive value for HBeAg loss; a 1 logU/ml decline at 6 months had a positive predictive value of 71.4% and area under the receiver operating curve of 0.747.
Conclusion: In this study, HBV RNA decline after 6 months of NUC therapy predicted HBeAg loss with good performance. HBV RNA decline presents an important goal for novel therapies, with HBV RNA suppression potentially being associated with favourable treatment end points.

FRI-214

Novel hepatitis B virus X gene mutants emerge during antiviral therapy to increase covalently closed circular DNA accumulation conferring pseudo-drug-resistance and increaing hepatocellular carcinoma risk

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Background and aims: Hepatitis B virus (HBV) × (HBx) gene mutants have been found in late stage HBV infection and play a critical role in hepatocarcinogenesis. However, little is known about whether HBx mutants can emerge during long-term antiviral therapy to adapt for antiviral drug-induced stress. The aim of this study was to identify and characterize previously unrecognized HBx mutants developed in patients conferring lamivudine (LAM) resistance or suboptimal response to entecavir (ETV).
Method: From January 2006 to December 2012, 46 patients with phenotypic and genotypic LAM resistance and 6 with suboptimal response to ETV were enrolled. HBx gene was sequenced. The identified HBx mutants were characterized in hepatocytes. Patients were followed until development of hepatocellular carcinoma (HCC) or loss-to-follow-up.

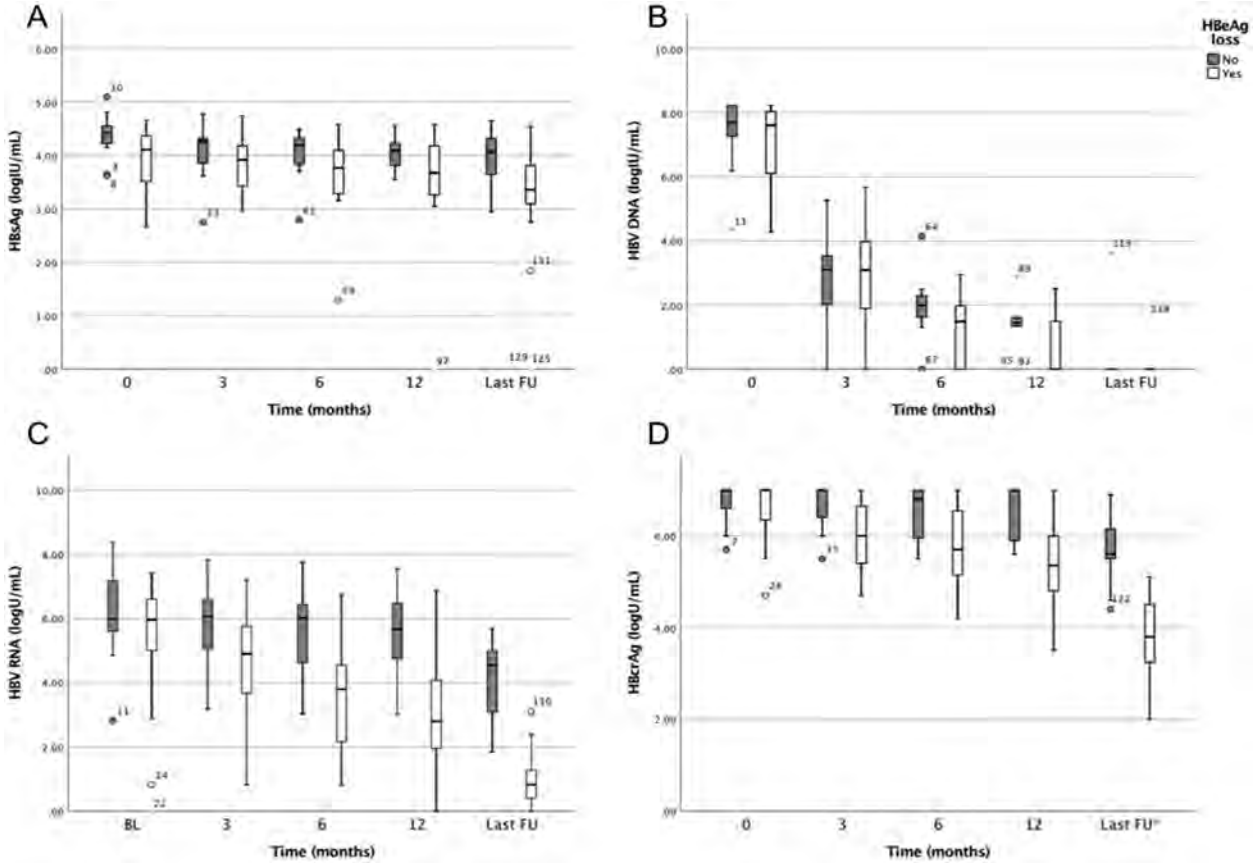

Figure 1: (abstract: FRI-213): Box plots of HBsAg (A), HBV DNA (B), HBV RNA (C) and HBcrAg (D) concentrations during treatment with nucleos (t)ide analogues in HBeAg-positive patients (*last FU; median duration 64 months).

Results: HBx sequence analysis identified novel HBx mutants, including 15 with asynonymous mutations, 11 with deletion mutations and 2 with insertion mutations. Transactivation assays showed that these HBx mutants manifested a significant decrease of transactivation ability on pre-S1 promoter with an increase of transactivation ability on HBx promoter. Transfection of plasmids expressing HBx mutants into HepG2 cells containing a replication-competent clone resulted in altered intracellular small to large and middle surface protein ratios, increased nuclear fractions of core protein, increased nuclear-to-cytoplamic HBV-DNA ratios, and increased covalently closed circular DNA (cccDNA). Consequently, antiviral drug sensitivity assays revealed a pseudo-drug-resistance phenotype. Longitudinal follow-up for these patients revealed that 5 patients developed HCC. Characteristics of HBx mutations shared by these HCC patients were analyzed.

Conclusion: In conclusion, novel HBx mutants emerged during LAM or ETV therapy. They manifested an altered transactivation activities on HBV pre-S1 and X promoters, leading to increased nuclear fractions of core protein, HBV-DNA, and cccDNA, which conferred a drug-resistance-like phenotype. Some of these mutants might be responsible for subsequent development of HCC.

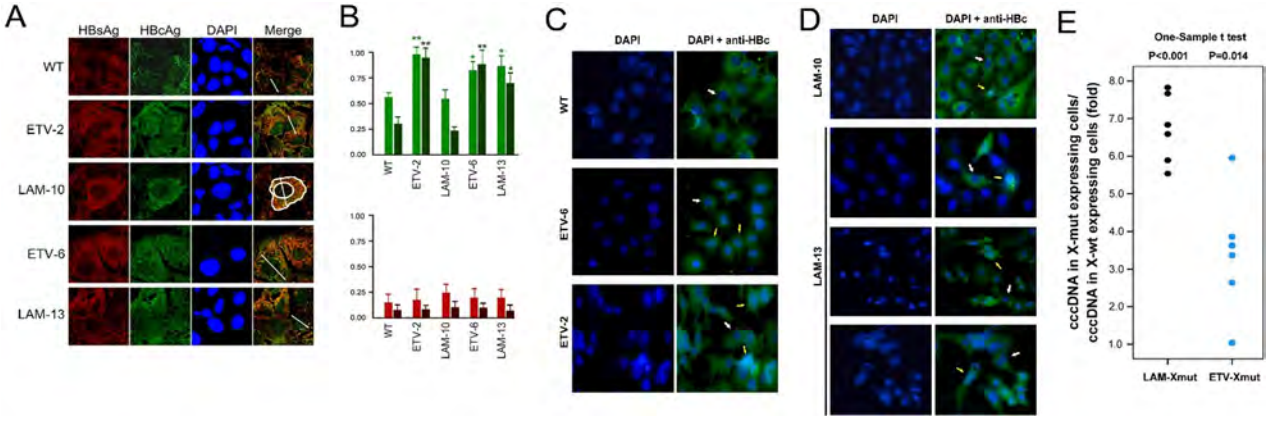

Figure: (abstract: FRI-214)

FRI-215

Continuing besifovir dipivoxil maleate versus switching from tenofovir disoproxil fumarate for treatment of chronic hepatitis B: 144 weeks results of phase 3 trial

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Background and aims: Besifovir dipivoxil maleate (BSV) is an acyclic nucleotide phosphonate with a potent antiviral activity against hepatitis B virus (HBV). An antiviral efficacy of BSV for forty-eight week was shown to be comparable to tenofovir disoproxil fumarate (TDF) with improved renal and bone safety. We evaluated the efficacy and safety of BSV in treatment-naïve chronic hepatitis B patients in 144 weeks follow-up study.
Method: After 48 weeks of double-blind comparison of BSV to TDF, patients continued to participate in the open-label BSV study. We evaluated antiviral efficacy and drug safety for both BSV group (BSV-BSV) and the group switched from TDF to BSV (TDF-BSV) up to 144 weeks. The primary end point was the proportion with HBV DNA < 400 copies/ml (virological response).
Results: Among 197 patients who received randomized treatments, 170 (87%) patients entered the open-label phase, and 153 (78%) completed 144 weeks of the study. The virological response rate of those who have taken BSV over 144 weeks is 87.65% while 92.11% of patients who switched the treatment from TDF were respondent (p = 0.36). HBeAg seroconversion and ALT normalization rates were similar between the groups. There were no drug resistant mutations to BSV and no adverse events related to bone mineral density or renal function.
Conclusion: BSV maintained efficacy in both suppression of HBV DNA and ALT normalization over 144 weeks without any evidence of resistance to BSV. Also, BSV is safe, well tolerated, and effective for those who have switched to BSV from TDF.

FRI-216

Tenofovir monotherapy versus tenofovir plus entecavir combination therapy for multi-drug resistant chronic hepatitis B: Five year follow-up data of multicenter prospective cohort study (Final results)

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Background and aims: For the management of multidrug resistant (MDR) chronic hepatitis B (CHB), tenofovir (TDF) monotherapy or tenofovir plus entecavir (ETV) or tenofovir monotherapy for MDR CHB has been suggested However, long term data comparing TDF monotherapy and TDF plus entecavir are limited. Herein, we report a multicenter cohort study for the evaluation of TDF-based therapy for MDR CHB.
Method: The inclusion criteria were CHB patients with resistance to more than 2 nucleos (t)ide analogues and hepatitis B virus (HBV) DNA level over 200 IU/ml. Patients with decompensated cirrhosis or hepatocellular carcinoma were excluded. Primary end point was cumulative virologic response defined by undetectable HBV DNA (< 20 IU/ml) until month 60.
Results: A total of 256 patients were enrolled and 230 patients were included for analysis. Mean age of patients were 49 years and 77.8% were male. Mean baseline HBV DNA level was 4.2 ± 1.4 log IU/ml. Genotypic resistance to L-nucleoside analogues (L-NA)+adefovir (ADV) (75 patients), L-NA+ETV (103 patients), L-NA+ADV+ETV (50 patients) were confirmed at enrollment.
Initial treatments for MDR CHB were TDF monotherapy (n = 52) or TDF+ETV combination therapy (n = 178). Virologic response rates of the whole cohort at year 1, year 2, year 3, year 4, and year 5 were 77.4%, 87.0%, 90.1%, 89.2%, and 92.2%, respectively. At year 5, virologic response rate was not significantly different between the TDF monotherapy group and TDF-based combination group (87.5% vs. 92.9%, respectively, p = 0.499 by Fisher's exact test). The cumulative virologic response rate of TDF monotherapy was not significantly different at year 5 (96.2% vs. 97.8%, respectively, p = 0.881), and was not inferior to combination therapies considering that 95% confidence interval (−3.3% ~ 6.5% at year 5) did not include the 10% of non-inferiority margin.
Conclusion: TDF based therapy was effective for the treatment of MDR CHB for during 5 years of follow-up. The efficacy of TDF monotherapy was not inferior to the TDF based combination therapy.

FRI-217

Safety, antiviral activity, and pharmacokinetics of a novel hepatitis B virus capsid assembly modulator, JNJ-56136379, in Asian and non-Asian patients with chronic hepatitis B

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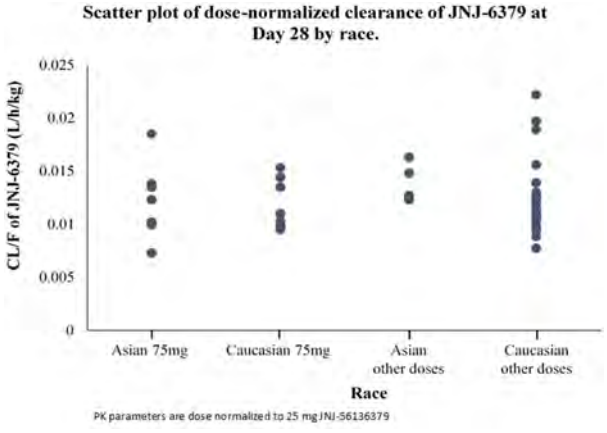
Background and aims: The capsid assembly modulator, JNJ-56136379 (JNJ-6379), was well tolerated in healthy volunteers and patients with chronic hepatitis B (CHB) in a first-in-human study. Significant antiviral activity was observed in patients with CHB at doses up to 250 mg QD (NCT02662712). Here we compare safety, antiviral activity, and pharmacokinetics of JNJ-6379 in Asian and non-Asian patients with CHB.
Method: Non-cirrhotic, treatment-naïve, HBeAg-positive or -negative patients with CHB were enrolled to receive single daily doses of JNJ-6379 of 25, 75, 150 or 250 mg, or placebo, for 4 weeks with 8 weeks' follow-up. 57 patients participated in European and Asian sites across doses. There were two 75 mg groups; 12 patients (8 JNJ-6379:4 placebo) in European sites, and 9 patients (7:2) in Asian sites.
Results: In the overall study population, 14 patients were Asian, and 38 were Caucasian. All patients were Caucasian in the 75 mg European group, and Asian in the 75 mg Asian group. There were 3 Asian patients in the 25 mg group, and 1 in each of the 150 mg and 250 mg groups.
Amongst patients treated with the 75 mg dose, 57% in the Asian group and 50% in the European group reported an AE. No serious AEs or deaths occurred.
After 4 weeks dosing at 75 mg, mean (SD) HBV DNA decreased by 2.89 (0.48) $\log_{10}$ IU/ml in the Asian group, and by 2.92 (0.58) $\log_{10}$ IU/ml in the European group; serum HBV DNA was below the lower limit of quantification for the assay for 2 and 3 patients, respectively.
Mean apparent clearance was lower in the 75 mg Asian group (0.754 L/h) compared to the 75 mg European group and other dose groups (mean apparent clearance ranged from 0.928 to 0.982 L/h). This resulted in higher dose normalized C_{max} and AUC values in the 75 mg Asian group than the 75 mg European group. However, after correction for body weight, CL/F was comparable between Caucasian and Asian patients (Figure). Dose-proportionality was observed over the entire dose range of 25 mg to 250 mg QD. Mean $t_{1/2}$ was long, and similar for all dose groups, ranging from 103.3 to 148.0 hours.



Conclusion: JNJ-6379 was well tolerated, and resulted in similar pharmacokinetics over the entire dose range. Antiviral effects were comparable in Asian and non-Asian CHB patients receiving daily 75 mg doses for 4 weeks. These data support further evaluation of the same dose of JNJ-6379±nucleos (t)ide analogs in a larger cohort of patients at European and Asian sites in a Phase 2a study (NCT03361956).

FRI-218

Dynamic changes of serum hbv pgrna levels in patients with chronic hepatitis B treated with entecavir or peg-interferon

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Background and aims: Serum hepatitis B virus (HBV) pregenome RNA (pgRNA) levels may independently predict virological and serological response during antiviral therapy. This study aimed to find the correlation between serum HBV pgRNA levels and other biomarkers, further investigate the dynamic changes of serum HBV pgRNA levels and its clinical significance during treatment.
Method: A real-time polymerase chain reaction (PCR) was developed for quantitative analysis. HBV pgRNA levels were retrospectively determined in serial serum samples from 136 patients with chronic HBV infection who have received entecavir or peg-interferon treatment. Receiver operating characteristics (ROC) analysis was performed to evaluate the prediction value in HBeAg seroconversion of individual biomarkers.
Results: The mean serum HBV pgRNA level was 6.41 [1.94] copies/ml at baseline, which was higher in HBeAg-positive patients of 7.20 [1.54] copies/ml than in HBeAg-negative patients of 4.60 [1.51] copies/ml ($p < 0.001$). Baseline HBV pgRNA levels correlate strongly with HBV DNA levels ($r = 0.82$, $p < 0.001$), moderately with HBsAg levels ($r = 0.69$, $p < 0.001$), and weakly with serum alanine aminotransferase ($r = 0.28$, $p < 0.05$). Peg-IFN treatment induced a stronger decline in HBV pgRNA level from baseline to week 4 of 1.36 [1.28] copies/ml, to week 24 of 2.20 [1.48] copies/ml, and to week 48 of 2.87 [1.53] copies/ml in comparison to entecavir (ETV) monotherapy ($p < 0.05$). ETV treated patients with HBeAg seroconversion showed a stronger decline in HBV pgRNA level at week 4, 12, 24 and 48. At baseline, the area under ROC (AUC) of HBV pgRNA was 0.68, comparable to those of HBV DNA (AUC = 0.66) and HBsAg (AUC = 0.64) in ETV treated patients; however, in peg-IFN treated parents, the AUC of HBV DNA was highest in predicting seroconversion, followed by HBV pgRNA and HBsAg (AUC = 0.63 and 0.60, respectively). No significant difference was noted for AUCs among these biomarkers ($p > 0.05$). During treatment, the best prediction of HBeAg seroconversion in ETV treated patients was HBV pgRNA at week 4 (AUC = 0.71, the corresponding cut-off value, sensitivity, specificity, PPV and NPV were 7.95 log10copies/ml, 83%, 56%, 40%, 91%), while in peg-IFN treated patients, HBV pgRNA level at week 24 allowed the best prediction (AUC = 0.70, the corresponding cut-off value, sensitivity, specificity, PPV and NPV were 3.55 log10copies/ml, 89%, 62%, 44%, 94%).
Conclusion: Serum HBV RNA levels may serve as a brand new biomarker in the evaluation of patients with chronic HBV infection during antiviral therapy.

FRI-219

RO7049389, a core protein allosteric modulator, demonstrates robust decline in HBV DNA and HBV RNA in chronic HBV infected patients

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Background and aims: RO7049389 is a small molecule, Class I HBV core protein allosteric modulator (CpAM) resulting in formation of aberrant core protein aggregates. RO7049389 is expected to interrupt viral assembly, inhibit HBV replication, and potentially restore host immune response to HBV. RO7049389 effectively suppresses HBV replication in in-vitro cell-based assays and in-vivo animal models.
Method: The ongoing Phase I study investigates the safety, tolerability, pharmacokinetics (PK) of RO7049389 and explores the anti-HBV effects in untreated chronic HBV infected patients.
Results: The safety, PK and tolerability data from SAD and MAD in healthy volunteers (HV) has been previously reported (EASL 2018). PK, safety and pharmacodynamic data are presented from 3 proof of mechanism cohorts in chronic HBV infected patients: 200 mg BID (n = 7) and 400 mg BID (n = 7) with standard meal and 600 mg QD fasted (n = 7) for 28 days.
Patients had a similar PK profile to that of HVs with no evidence of accumulation in C_{max} and AUC_{tau} of RO7049389.
Substantial decline in HBV DNA and RNA was shown in all POM cohorts (Table 1). HBV DNA was reduced to below the lower level of quantification (HBV DNA < 20IU/ml) in 8/18 patients who took active drug. No viral breakthrough during dosing was observed. There were no significant changes in the HBsAg or HBeAg antigen level during 28 days of dosing.
Overall, blinded data review showed similar safety profile in both HVs and patients. A total of 39 adverse events (AEs) were reported in 14 of 22 HBV patients, 3 patients had treatment emergent Grade 3 ALT/AST increase which resolved without treatment in follow-up. One pre-dose SAE was reported and the patient was replaced. No AEs leading to drug discontinuation were reported and no clinically significant changes in any safety parameters tested were observed.

Table:

Table1:Median decline (range) from baseline	200mg BID	400mg BID	600mg QD
HBV DNA log10 IU/ml	2.7 (0.6–3.4)	3.2 (2.2–5.3)	2.9 (2.0–3.7)
HBV RNA log10 copies/ml	1.6 (0-2.5)	2.3 (0-4.0)	Pending

Conclusion: RO7049389 demonstrated robust anti-HBV activity over 28 days of dosing in patients with chronic HBV infection and is well tolerated. This agent will be further evaluated in combination with other agents.

FRI-220

Antiviral effect and predictors of hepatitis B surface antigen seroconversion in children of 1-6 years old with chronic hepatitis B

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Background and aims: This study was aimed to observe the long-term antiviral therapeutic outcome in patients with chronic HBV infection and explore the factors related to HBsAg sero-conversion in children of 1-6 years old.

Method: Two hundred and thirty six children aged 1-6 years old with chronic hepatitis B were admitted to the Children's liver Disease Department from January 2012 to May 2018, and were enrolled into our study. After follow-up study, all the data were collected and a retrospective analysis was performed. Meanwhile, the clinical data of 148 patients aged 7-18 years old were also collected and analyzed as control.
Results: 1) A total of 384 patients with chronic HBV were enrolled. Among them, 236 patients were 1-6 years old, 148 patients were 7-18 years old. The positive rate of HBeAg in two groups was 90.8% and 85.5%, respectively. In 1-6 years old group, 44.5% achieved HBsAg seroconversion and the mean seroconversion time was 60.8 ± 42 weeks; in 7-18 years old group, 6.9% achieved HBsAg seroconversion and the mean seroconversion time was 114.8 ± 70.5 weeks. 2) In the baseline, the numbe of total lymphocytes、T cell、CD4+T cell、B cell in peripheral blood of HBsAg seroconversion patients at the age of 1-6 years old were higher than that of 7-18 years old patients ($p < 0.05$). 3) The number of CD4+T cell、B cell in peripheral blood of HBsAg seroconversion patients at the age of 1-6 years old were higher than that of HBsAg non-seroconversion patients ($p < 0.05$). 4) In group 1-6 years old, the age of treatment、sex、HBeAg、AST、the number of peripheral total lymphocytes、T cell、CD4+T cell、B cell were significantly associated with the achievement of HBsAg seroconversion by univariate analysis. 5) Among children aged 1-6 years, only the age of treatment was significantly associated with the achievement of HBsAg seroconversion by multivariate analysis.
Conclusion: The age of treatment was a predictor for HBsAg seroconversion, higher HBsAg seroconversion rate can be obtained before 6 years old. The detection of peripheral lymphocyte subsets has certain clinical predictive value for understanding the immune status and disease outcome of patients.

Viral hepatitis C: Clinical aspects except therapy

FRI-221

Management of drug-drug interactions in chronic hepatitis C patients treated with second generation direct acting antivirals in Belgium

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Background and aims: The new generation of oral direct-acting antivirals (DAAs) demonstrate both high efficacy and high

tolerability. However, none of the DAAs are completely free of drug-drug interactions (DDIs), which can significantly alter the drugs exposure, efficacy and toxicity. The aim of the study was to describe the use of comedications and the changes made before starting DAA treatment and assessing prevalence of patients at risk for potential DDIs.

Methods: 405 patients were included in an observational study at 11 centers in Belgium from Jan17 till Oct17. Data were collected on patients' characteristics, previous and most recent HCV treatment, comorbidities (MedDRA), comedications (ATC code) and changes made in comedications at start of DAA treatment. Patients received following DAAs: EBR/GZR; OBV/PTV/r±DSV; SOF/DCV; SOF/LDV; SOF/VEL. Potential clinically relevant DDIs were assessed based on information available at www.hep-druginteractions.org.

Results: Median age was 55 years, 60.5% were male, and 20.5% were cirrhotic. Patients were treated with SOF/VEL (31.1%), EBR/GZR (27.4%), SOF/DCV (26.4%), OBV/PTV/r±DSV (8.4%) or SOF/LDV (6.7%). Most common comorbidities were arterial hypertension (27.2%), HIV co-infection (22.5%) and type 2 diabetes mellitus (14.3%). Ninety percent of the patients took comedications, ranging from 1 to 16 per patient. The predominant therapeutic classes were psycholeptics (28.6%), antivirals for systemic use (24.2%) and drugs for acid related disorders (21%). Of the 365 patients on comedications, 20.3% required an adaptation of their comedication. Drugs used for acid related disorders (31%) and antiviral drugs (33%) were most frequently changed prior to DAA treatment. Lipid modifying agents (43%) and drugs for acid related disorders (21%) were most frequently stopped. Modifications to the comedications of patients at the start of their DAA treatment decreased the risk for potential clinically relevant DDIs from 34% (136/405) to 22% (91/405). Patients treated with EBR/GZR (11%); SOF/DAC (19%) and SOF/VEL (22%) were the least exposed to potential clinically relevant DDIs. Patients treated with SOF/VEL underwent the most adaptations (29%) to their medication scheme compared to patients treated with EBR/GZR (12%).

Conclusion: This study suggest that physicians are aware of potential DDIs between comedications and DAAs but that there is still a clear gap between the clinical practice and the theoretical recommendations.

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Redundancy of elastography in mono-infected HCV individuals less than 30 years old -Development of Dillon's Rule

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Background and aims: The Hepatitis C Virus (HCV) is a blood-borne, causing chronic infection, defined as the persistence of HCV RNA for at least 6 months after initial infection. Chronic HCV infection predisposes individual patients to liver fibrosis, cirrhosis and hepatocellular carcinoma. Of those with chronic HCV infection; it is estimated that 16–20% of individuals will go on to develop liver cirrhosis within 20 years.

There has been a revolution in the treatment of chronic HCV infection with almost universal cure. The issue is now to minimise the steps required to start treatment, especially as we seek to treat younger more difficult to engage groups. Currently fibrosis is assessed before starting treatment. We sought to validate the theory that those individuals who were mono-infected with HCV; young and with no additional hepatic insult were unlikely to have significant fibrosis.

Method: We performed a retrospective analysis of the Tayside Hepatitis C dataset; with collation of relevant basic demographics including age, sex and baseline Fibroscan© measurements pre-treatment. Previous validation of transient elastography (TE) in HCV has suggested that a cut off of less than 11kPa would significant fibrosis.

Results: Our complete cohort consisted of 719 individuals with HCV who had elastography performed before undergoing HCV therapy. We stratified for age across 5 year intervals. The results are summarized in the figure below.

Within this patient cohort we established that no patient under 30 had a TE score > 9 kPa without a co-existent history of hazardous alcohol consumption; and only a single individual within the 31–35 group had a fibroscan > 11kPa in absence of hazardous alcohol ingestion or co-infectivity with a hepatotropic virus.

Age Range	*Total (n =) (M/F)*	*Transient Elastography (Mean; Range)*	*Transient Elastography > 9kPa*	*Transient Elastography > 11kPa*
< 30 Years	99 (62/37)	5.71 (3.2–10.6)	1	0
30–35	111 (82/29)	8.9 (2.1–26.6)	6	4

Conclusion: Going forward we therefore propose that those patients < 30 years old do not necessitate elastography prior to treatment. The vast majority of patients between 30 and 35 years (> 95% in our dataset) are also likely to be suitable for treatment without elastography in the absence of other co-existent factors for fibrosis; most notably alcohol in this cohort.

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Contribution of HBV and HCV infection in mortality of B-NHL subjects

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Background and aims: Lymphoma, especially the Non-Hodgkin's B Lymphoma (B-NHL) is one of the globally prevalent type of cancer with rapidly increasing prevalence. Hepatitis B and C virus (HBV, HCV) is found to increase the risk of NHL development with some geographical differences. Mongolia is a country with very high prevalence of HBV, HCV and HBV/HDV infection. However, it is not known if the viral hepatitis infections are higher in the B-NHL subjects and if these chronic infections affect the survival of the B-NHL subjects. In this study we aim to determine the prevalence of HCV, HBV and HBV/HDV among the B-NHL subjects and its influence on the survival rate of these patients.

Method: We have done a retrospective analysis of patients diagnosed with B-NHL, at the Hematology Center of the First State Hospital of Mongolia between 2015 and 2017. Patients were divided into two groups with survival rate less and more than 12 months, after being diagnosed with B-NHL and comparatively analyzed by age group, Ann Arbor staging of lymphoma and HBV, HCV infection. HBV and HCV prevalence of B-NHL patients were compared with general population survey results.

Results: Overall, 178 B-NHL patients (77 males, 101 females) with average age 53.9 were enrolled in the study. In total, 24 (13.5%) patients had HBV infection and 13 (7.3%) had HBV/HDV double infection which was similar to the general population prevalence. However, HCV prevalence among B-NHL subjects was 5 times higher

than the general population prevalence (Table 1). As shown in Table 1, 46 (25.8%) subjects had survival rate less than 12 months after being diagnosed with B-NHL including 15 (19.5%) in B-NHL group without viral hepatitis infection, 5 (20.8%) in HBV positive B-NHL group, and 26 (33.8%) in HCV positive B-NHL group. Furthermore, HCV positive B-NHL group mortality rate was doubled in comparison to B-NHL group without viral hepatitis infection in Ann Arbor stages.

Table 1: B-NHL groups by Ann Arbor staging comparing with general population prevalence

	B-NHL group without HBV or HCV		HBsAg positive B-NHL group		Anti-HCV positive B-NHL group	
	Ann Arbor		Ann Arbor		Ann Arbor	
Survival rates	1 and 2	3 and 4	1 and 2	3 and 4	1 and 2	3 and 4
≤ 12 months	2 (6.4%)	13 (28.2%)	0	5 (33.3%)	3 (13%)	23 (42.5)
> 12 months	29 (93.6%)	33 (71.8%)	9 (100%)	10 (66.7%)	20 (87%)	31 (57.5%)
Total	31 (100%)	46 (100%)	9 (100%)	15 (100%)	23 (100%)	54 (100%)
Total n/ (%)	77/ (43.3%)		24 (13.4%)		77 (43.3%)	
Healthy people	930/1158 (80.3%)		128/1158 (11.1%) HDV pos 77/128 (60%)		100/1158 (8.6%)	

Conclusion: Our study demonstrated very high prevalence of HCV among B-NHL subjects, but the prevalence of HBV and HBV/HDV infection rate was similar to the general population. In addition, 12 months' survival rate of B-NHL patients is negatively affected by the hepatitis C but not by the HBV infections as shown in Table 1. These results indicate that clinicians need to pay extra attention to the B-NHL patients with chronic HCV infections.

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Reaching out to the undiagnosed people with hepatitis C infection in Belgium: A pilot study

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Background and aims: Whereas the prevalence of hepatitis C virus (HCV) infection in the general population is low (0.57%), data for HCV antibody (Ab) prevalence in Belgium show rates of 60-80% in people who inject drugs (PWID). Despite the severe health and economic burden, targeted screening is not yet broadly executed in Belgium, and if executed for PWID, it is mostly focussed on PWID receiving opiate substitution therapy. In this pilot study we want to reach subgroups who are often completely isolated from care such as young opiate injectors and amphetamine injectors. By contacting the community of drug injectors, we want to outreach to PWID who avoid drug treatment centers, using the screening for HCV as a bridge to re-integration in society.

Method: The participants were recruited by outreaching. For this pilot study we organised three screening events in Antwerp and Hasselt, Belgium. The location of these events were communicated in advance, using posters and flyers to inform possible candidates and planned in accordance with the local authorities, health care workers, pharmacists and general practitioners. Possible candidates were 18 years of age or older, were not in follow-up at Freeclinic Antwerp or CAD Limburg and had a history of drug use. The eligible candidates were tested by fingerprick for HCV Ab using the Oraquick® test. While waiting on the results (20 minutes), an encoded questionnaire was filled out and a Fibroscan® was performed to score the grade of fibrosis. Participants received a fee of 10 euros.

Results: During the first three screening days at Hasselt, 96 persons were included. Of those participants 24 (25.0%) tested HCV Ab positive using the fingerprick test. One result was false positive after blood analyses. Out of the 23 (24.0%) HCV Ab positives confirmed by blood sample, five (21.7%) persons were not aware of their HCV Ab status. In total, 15 out of 23 (65.2%) were HCV RNA positive. Whereas three are starting treatment, the remaining 12 (80.0%) could not be treated yet due to the strict reimbursement criteria in Belgium. In Antwerp 26 persons were screened of whom two (7.7%) tested positive for HCV Ab.

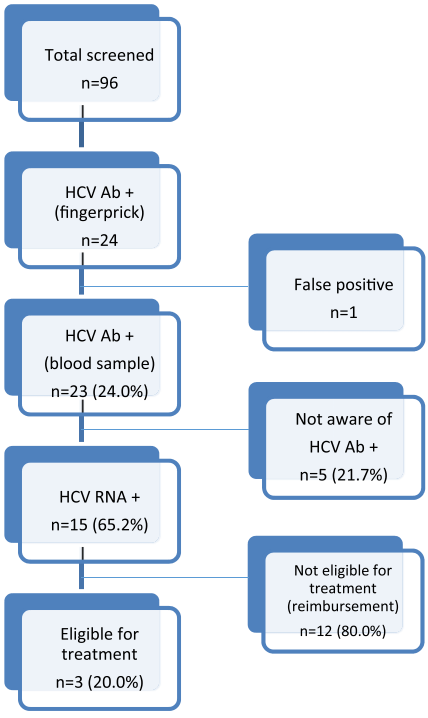

Figure: Results of three days screening in Hasselt, Belgium

Conclusion: The outreach method does work in Belgium and allows to reach isolated subgroups. However, the Belgian reimbursement criteria remain a burden in treating those screened and potentially new diagnosed people. This pilot project will be continued and validated by another team in Belgium during the next year.

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Universal access to direct-acting antivirals treatment is not not enough to prevent late stage presentation of hepatitis C infection

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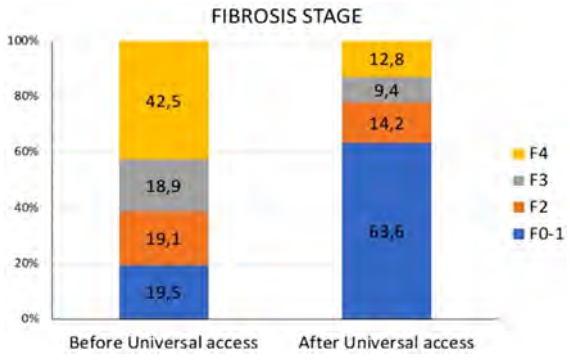
Background and aims: Hepatitis C virus (HCV) infection is asymptomatic for a long period of time. Previous antiviral treatments in the period prior to direct antiviral agents (DAA) had low efficacy and many side effects. Therefore, patients were typically referred and treated by the hepatologist in advanced stages. Nowadays, The National Strategic Plan for HCV in Spain, from July 1st 2017, allows universal access to treatment with DAAs with no restrictions.
To study the application of the national plan and its impact in the management of new HCV infected patients. To describe features of this group with no restrictions to be treated.
Method: Hepa-C database is the National registry of HCV patients, directed by the Spanish Association for the Study of the Liver. Naive patients from the Hepa-C cohort who were treated with DAA were included in the study. Only the first antiviral treatment was analyzed. Data collected from May 2011 to present time was analyzed.



Results: We included 6053 naïve HCV infected patients. Before the universal access to DAA, 61.8% of the whole cohort started treatment (Group A). This group included 61.4% patients with advanced fibrosis (F3 or greater). Patients treated during non-restriction period (Group B) showed lower proportion of advanced fibrosis, 22.2% ($p < 0.001$). Regarding this group with advanced fibrosis, we found a high proportion of patients with advanced liver diseases (clinical signs of cirrhosis or portal hypertension, and/or previous liver decompensation or hepatocellular carcinoma [HCC]), 55.6% [group A] vs 31.2% [group B] ($p < 0.001$). Including these patients with advance liver disease, there is a significant decline in the proportion of subjects presenting with esophageal varices (group A, 56.9% vs group B, 38.9%, $p < 0.001$), hepatic encephalopathy (A- 11.3% vs B- 5.3%, $p = 0.05$) and HCC (A- 9.6% vs B- 5.3%, $p = 0.002$).
Conclusion: There is a clear switch in fibrosis stage and liver disease features at the time of starting HCV treatment triggered by a wide access to DAA. Despite this policy allowing universal access to DAA antiviral treatment in Spain, there is still a significant number of patients who are diagnosed and treated with advanced fibrosis stages (F3-4). This issue may suggest the importance of establishing universal screening programs for the detection of cases in earlier stages of liver disease.

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Modeling early viral kinetics during observed HCV acute infection in post lung transplantation recipients

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Background and aims: Lung transplantation from HCV-infected donors to uninfected recipients allows a unique opportunity to evaluate very early HCV kinetics during acute infection. The aim of this study was to use agent-based modeling to characterize viral-host dynamics from infection to steady state in immunosuppressed transplant recipients.
Method: HCV^+ donor lungs were transported in cold static preservation, placed on normothermic ex-vivo lung perfusion for 6 h, and transplanted into HCV-uninfected recipients. HCV was tested daily for 1 week, then weekly for 12 weeks. Detailed viral kinetics are currently available for 16 of the 21 participants, of whom 7 (3M, 4F) reached HCV steady-state prior to antiviral treatment, which was initiated at 21 days (median) post-transplant. In the model, hepatocytes are represented as individual agents with the introduction of free virus into the blood. When uninfected agents are exposed to HCV, they become infected and enter an eclipse phase in which they do not secrete virus. Infected hepatocytes then proceed to a productive phase in which they release virions that go on to infect additional cells/agents. Viral and host parameters were defined based on trial design, measured kinetics and previous estimates.
Results: HCV had 3 kinetic phases: (i) lower plateau (i.e. viral eclipse), (ii) amplification and (iii) steady state. The viral eclipse phase (median 2 log IU/ml) lasted for about 2 days. Individual viral amplification kinetics (phase ii) could be stratified into rapid ($n = 2$) and slow ($n = 5$) viral spread groups with median slopes of 1.03 vs 0.46 log IU/ml/day, reaching viral plateau (median 6.22 vs 7.76 log IU/ml) at 7 vs 14 days post infection, respectively. Preliminary modeling simulations reproduce the HCV kinetics pattern well when: (1) the eclipse phase lasts between 10 and 48 hours, (2) a median initial transmitted HCV viral load of 4 log IU/ml is predicted, and (3) the following parameters were assumed to be different in the rapid vs. slow HCV spread patients: (i) ~4-fold higher HCV infection rate, (ii) ~1 day shorter production cycle with HCV reaching its max production, in a given infected cell, within ~3 vs ~4 days pi, and (iii) ~7/10-fold lower steady state production rate (~7 vs 10 virions/h) assuming the same number of infected cells at steady state.
Conclusion: HCV exhibits a simple infection pattern (i.e. viral eclipse, exponential amplification, culminating in viral steady state) that provides a framework to understand viral-host dynamics in acute HCV infection. We hypothesize that observed interpatient variability in kinetic parameters may be related to differences in innate antiviral responses among patients. Considering the relatively small amount of HCV expected to be introduced into the recipient from the perfused

lung, the surprising high initial transmitted virus load predicted by the model (4 log IU/ml) also needs further investigation.

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Interleukin-6 −174G/C genotype and interleukin-10 ATA haplotype are associated with clinical comorbidities in chronic hepatitis C patients

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Background and aims: Patients with chronic hepatitis C (CHC) have both higher prevalence of diabetes mellitus type 2 and increased cardiovascular risk compared to individuals without the infection. More recent studies have pointed that an imbalance between pro-inflammatory and anti-inflammatory cytokines might induce some extrahepatic manifestations. Taking into account the scarcity of data about the influence of cytokine gene polymorphisms on the clinical comorbidities such as diabetes and hypertension (high blood pressure), we determined the genotypic and allelic frequencies of the Interleukin (IL) *IL6* (−174G/C), *IL*-10 (−1082G/A), *IL*-10 (−592A/C) and *IL*-10 (−819C/T) single nucleotide polymorphisms (SNP), and their association with clinical characteristics in CHC patients.
Method: In this cross sectional study, we prospectively enrolled 255 consecutive CHC patients and 186 age- and sex-matched healthy blood donors who underwent a detailed clinical evaluation. *IL*6 and *IL*10 SNP polymorphisms were evaluated by Taqman SNP genotyping assay. The *IL*10 haplotypes GCC, ACC and ATA are associated with high, intermediate and low production of IL-10, respectively. The *IL*6-174GG and −174GC genotypes are associated with higher IL-6 plasma levels but, the genotype −174CC is linked to a low production of this cytokine. Plasma concentrations of IL-6 and IL-10 were determined using the Human Th1/Th2 Cytometric Bead Array kit. Multivariate analysis evaluated the associations. The study was approved by the Ethics Committee of UFMG.
Results: The frequencies of the *IL*6 and *IL*10 SNPs did not differ between the CHC patients and controls. Diabetes mellitus was independently associated with the IL6-174G/C (OR = 0.40; 95%CI = 0.21-0.77; $P = 0.006$) and hypertension (OR = 7.00; 95%CI = 3.38-14.49; $p < 0.001$). *IL*10 ATA haplotype was associated with liver cirrhosis (OR = 2.23; 95%CI = 1.03-4.86; $P = 0.04$). The median [interquartile range (IQR)] of IL-6 plasma levels [8.94 (6.34-11.97) vs. 6.44 (5.60-7.74) pg/ml; $p < 0.001$] was significantly higher in patients with cirrhosis than in those without cirrhosis.
Conclusion: The *IL*6-174G/C and *IL*10 ATA haplotype provoke an imbalance between pro-inflammatory and anti-inflammatory cytokines, which may influence the clinical course of hepatitis C and CHC-related extrahepatic comorbidities.

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Community-based hepatitis C treatment of people who inject drugs and their injecting network is feasible and effective: Results from the TAP (Treatment And Prevention) study

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Background and aims: People who inject drugs (PWID) are at risk of hepatitis C virus (HCV) infection and transmission of HCV within their injecting network. However, many barriers have limited engagement of PWID in specialist-led care. The HCV Treatment and Prevention (TAP) Study aimed to test the feasibility and effectiveness of treating PWID and their injecting partners concurrently in community settings using a nurse-led model of care.
Method: The TAP Study is a community-based trial using a networks-based approach to treatment (clinicaltrials.gov, NCT02363517). Eligible PWID were those with chronic HCV mono-infection, who injected drugs in the same time and place with ≥ 1 person in the previous six months. Participants were randomised to receive sofosbuvir/velpatasvir treatment individually, or concurrently with their HCV-infected injecting partners. Participants were recruited via mobile street-based vans or primary health clinics. Nurses performed study assessments including FibroScan and venepuncture, and delivered treatment from the mobile clinic after case discussion with clinical investigators. We report pooled SVR12+ (co-primary outcome) and treatment uptake. Follow-up to 72 weeks post-treatment for reinfection incidence by randomised group (co-primary outcome) is ongoing.
Results: The TAP Study screened 336 PWID and enrolled 241 participants; 114 primary participants with 127 injecting partners. Median age of participants was 39 years (range 20-59 years), most were male (167, 69%), unemployed (189, 78%), had previously been incarcerated (144, 60%), and 22% (52) reported unstable housing. Treatment was commenced in 93 (85%) primary participants and 37 (55%) viraemic injecting partners; prior incarceration was associated with failing to enroll or start treatment. There were no study or drug related serious adverse events. In per-protocol analysis, among 130 participants who started treatment, 114 had HCV RNA measured at or after SVR12, and 96 (84%) achieved SVR12+. There were six known relapses, two non-responders, three unspecified treatment failures and 10 confirmed reinfections. During 98 person years of follow-up to date, reinfection incidence is 10.2/100 person years. In modified intention to treat analysis, 74% achieved SVR12+, mostly due to failure to attend for assessment.
Conclusion: Nurse-led HCV treatment for active PWID is feasible and effective for community-based active PWID. Recruiting and treating injecting partners is challenging but is potentially an important model to interrupt HCV transmission-longer follow-up is needed before assessing the randomised impact of treatment on reinfection.

FRI-229

Reflex testing in patients with chronic hepatitis C in Spain improves healthcare outcomes and is cost effective

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Background and aims: To achieve the goal towards hepatitis C virus (HCV) elimination proposed by the World Health Organization

(WHO), interventions to improve testing, facilitate linkage and treatment are necessary. Our analysis estimated the impact on healthcare and economic outcomes of reflex testing in chronic HCV diagnosis (single blood sample, one-step diagnosis) in Andalucía, Spain (8.39 million people), from a National Health System perspective.

Method: A decision tree model was developed to estimate the impact on detection, referral to specialists, loss of follow-up and access to treatment comparing one-step diagnosis versus standard diagnosis, in which HCV viremia is not investigated in the first visit. A total of 269, 526 individuals were estimated to be screened for HCV (67% outpatient and 33% inpatient care). In both scenarios, diagnosis was based on HCV antibody testing, HCV-RNA (viral load) and genotyping. Patient follow-up included: initial visit, diagnosis testing, referral or not to specialists and, where appropriate, treatment. The unit costs (€, 2018) of the health resources were obtained from databases of the Andalusian Health Service. The pharmacological cost was not considered. All data for the model were obtained from literature or, if not available, from an Expert Panel.

Results: In the analysis, a total of 2, 830 individuals of the tested population would be detected as positive for HCV antibody, of whom 1, 876 would be HCV-RNA+ve. From this population, using one-step diagnosis, 1, 389 chronic HCV patients were referred to specialised care (1, 320 treated) and 1, 063 patients (1, 009 treated) with standard diagnosis. No HCV-RNA-ve patient were referred to specialist using one-step diagnosis versus 540 with standard diagnosis. Compared to one-step diagnosis, using standard diagnosis 63% more patients were not referred to specialists and 30% more patients were considered a lost to follow-up. When compared reflex testing to standard diagnosis, savings of €184, 928 linked to one-step testing are obtained, and savings of €3, 634 per patient with HCV-RNA+ referred to specialised care.

Conclusion: Reflex testing simplifies the HCV diagnosis procedure, enhancing linkage to care as more patients with chronic infection are identified and treated, making better use of healthcare outcomes, and contributing to achieve the WHO HCV elimination target. In addition, reflex testing would generate economic savings to the Health System.

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Rapid starts to stop hepatitis C: Same day hepatitis C treatment starts enhancing patient engagement and follow-up in a vulnerable, treatment naïve group living with hepatitis C

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Background and aims: Hepatitis C virus (HCV) elimination requires alternate care models for key populations. Beyond diagnosis, engaging people in HCV treatment that leads to treatment completion and cure is one of the greatest barriers to HCV elimination. Human immunodeficiency virus (HIV) research has demonstrated better HIV and non-HIV health care engagement with rapid, same day treatment start. Our aim is to determine if rapid access to HCV treatment improves engagement in HCV and non-HCV health care.

Method: Prince Edward Island, Canada is a Canadian province with a Phase 2 provincial, coordinated HCV elimination program. Patients are identified and referred to the program through the public health department, community providers, or "bring a friend" strategies. Program staff facilitate baseline blood work, do pre-visit drug-drug interaction checks, and book a first appointment within 1-2 weeks of bloodwork. Treatment naïve patients without contraindications are offered glecaprevir/pibrentasvir treatment at the first visit. Self-reported medication adherence, side effects, sustained virological response (SVR12), and attendance at scheduled opioid substitution therapy (OST) clinic visits are recorded.

Results: Patients assessed between February and October 2018 were included. 102 patients were referred and 73 (71.5%) were seen for initial visits. 71/73 (97.2%) treatment naïve individuals started treatment, 67/71 (94.3%) on the first visit. Of those who attended the first visit and did not start immediately, 5 had medication interactions requiring adjustment, and 1 person was pregnant. There were 3 discontinuations for non-HCV related medical reasons, and 1 person was lost to follow-up before SVR. To date, all 52 people past the treatment completion date finished treatment, and 23/32 have documented SVR12 (9 people did not have SVR12 bloodwork but completed full treatment course). Importantly, individuals with difficulty attending opioid substitution clinic (OST) appointments before HCV treatment had improved attendance at appointments after HCV treatment start. Attendance at other health care appointments was variably improved. No safety issues were noted.

Conclusion: Rapid treatment start is safe, and has a very high rate of successful HCV and non-HCV care engagement. Same day, first visit HCV treatment start should be explored as an HCV elimination tool.

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Hostel-based models can improve the engagement of homeless individuals with liver services: VALID (vulnerable adults liver disease) study

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Background and aims: Homeless adults, a disenfranchised cohort, are particularly at risk of chronic liver disease (CLD) though they not engage with hospital services. Our aim was to establish a liver clinic at homeless hostels and assess service uptake, prevalence of CLD including hepatitis C virus (HCV) and HCV treatment outcomes

Methods: The liver service was set up in October 2015, at two large homeless hostels in SE England. Consecutive individuals aged > 18 yrs were offered alcohol (AUDIT) questionnaire and substance misuse assessment, blood borne virus (BBV) testing, mobile Transient Elastography (TE) and focussed treatment. Clinically significant hepatic fibrosis (CSHF) was defined as liver stiffness measurement (LSM) ≥ 8 kPa.

Results: To date 127/131 (97%) individuals approached have been enrolled. Mean age of participants was 47.6 (SD = 9 yrs), 76% being male. At baseline 89 (70%) were homeless/living in hostels/supported accommodation. Positive hepatitis C virus (HCV) antibody was detected in 59 (46%) participants, 81% (48/59) being HCV PCR positive [genotype 1 (48%) and 3a (48%)]. The majority (65%) were drinking alcohol more than recommended, the AUDIT questionnaire revealing alcohol dependency (scores of ≥ 20/40) in 61 (48%). One hundred and three (81%) had history of current/past substance misuse [68/127 (54%) IDU] with 91/127 (72%) having a diagnosis of a mental health illness. Of the 127 participants, 33 (26%) had CSHF (LSM ≥ 8 kPa) with 21 (17%) having cirrhosis (LSM ≥ 13 kPa). The aetiological factor/s for Cirrhosis were alcohol (n = 12, 57%), HCV (n = 1, 5%) and HCV+ alcohol (n = 8, 38%). Independent predictors of CSHF were a positive HCV RNA (OR: 1.90, 95% CI: 1.20-3.00, p = 0.006) and Alcohol AUDIT score > 20 (OR: 5.53, 95% CI: 2.13-14.33, p < 0.001). Of the 48 individuals with positive HCV RNA, 28 (58%) have commenced HCV treatment with direct acting antiviral (DAA) (26 in the community and two clinical trials). Of those with SVR12 data available (n = 17), 82% (n = 14) have achieved sustained virological response (SVR12). Thirteen patients (including 3 being retreated) are still on treatment/awaiting SVR results and one discontinued DAA. Compliance with treatment has been 97%.

Conclusion: This study reflects the high CLD burden in homeless individuals. In contrast to a common perception that homeless individuals do not engage with health services, 97% accepted the community service with 97% being compliant with DAA therapy. In a cohort of vulnerable adults, high alcohol AUDIT score and HCV RNA positivity were clinical predictors of CSHF.

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An outpatient endoscopy-based patient navigator model improves hepatitis C virus screening among high risk patients: A 3-year prospective observational study among a safety-net health system

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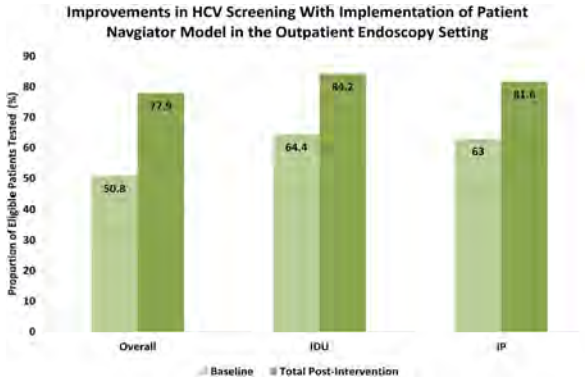
Background and aims: Despite guidelines recommending hepatitis C virus (HCV) screening among high-risk groups, overall HCV screening remains poor, and it is clear that novel models are needed to achieve WHO 2030 elimination targets. We aimed to evaluate the feasibility and real-world effectiveness of an outpatient endoscopy-based patient navigator model to improve screening among high risk populations.
Method: Consecutive adults undergoing outpatient endoscopy from July 2015-September 2018 at a safety-net hospital were prospectively assessed for HCV screening eligibility using U.S. Preventative Services Task Force guidelines. Eligible patients not previously tested were offered HCV antibody testing via a patient navigator intervention, and were followed to analyze test completion outcomes. The main outcomes evaluated were the proportion of patients screened, and HCV antibody positive (HCV Ab+). We further stratified patients by two high-risk groups: former/current injection drug users (IDU), and previously/currently incarcerated patients (IP). We compared outcomes among those previously tested at baseline (control), and the intervention group (tested). Between-group comparisons used chi-squared testing. Statistical significance was established by a p value < 0.05.
Results: Among 3, 264 patients evaluated, 69.2% (n = 2, 257) were eligible for HCV screening (mean age 57.2 ± 9.8, 48.7% male, 89.8% 1945-1965 birth cohort, 30.4% with ≥ 1 HCV risk factor (2.8% HIV positive, 3.5% chronic hepatitis B, 4.5% IDU, 18.8% IP, 6.4% pre-1992 blood transfusion). The overall proportion of eligible patients tested increased from 50.8% to 77.9%, from 64.4% to 84.2% among IDU, and from 63.0% to 81.6% among IP. Compared to the control group, the intervention group had lower proportions of IDU (5.8% control vs. 3.3% tested, p = 0.02), and IP (23.7% control vs. 12.9% tested, p < 0.001), as well as HCV Ab+ (13.8% control vs. 3.11% tested, p < 0.001). When stratified by risk factors, while the proportion of newly identified HCV Ab+ was still high, it did not vary significantly between the two groups among IDU (60% control vs. 40% tested, p = 0.17), or IP (19.5% control vs. 7.6% tested, p = 0.01). Among those not previously tested and thus in need of HCV screening, 41.2% and 45.5% of IDU and IP, respectively, did not complete HCV testing.



Conclusion: While a novel patient navigator-based model of HCV screening in the outpatient endoscopy setting is feasible and effective to improve HCV testing among the safety-net population, challenges remain in effectively engaging these high-risk and vulnerable patients into the HCV care cascade.

FRI-233

The impact of community-based rapid point-of-care testing on enhancing uptake of hepatitis C treatment for people who inject drugs in needle and syringe services

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Background and aims: Point-of-care (POC) diagnostics overcome barriers to conventional hepatitis C (HCV) testing in people who inject drugs by allowing testing outside of traditional health services, provision by non-clinical staff and same-day diagnosis. This study assessed the feasibility and impact on treatment uptake of POC HCV testing in needle and syringe exchange programs (NSPs).
Method: Rapid EC was a single arm interventional pilot study conducted in three inner-city community clinics with NSPs. Clinic staff offered clients not currently engaged in HCV care an OraQuick HCV antibody mouth swab test followed by a serum Gene Xpert HCV viral load. Same-day results were offered onsite, via phone, or at return visit. Participants received confirmatory standard-of-care blood tests and a follow-up appointment for liver fibrosis assessment, results provision and linkage to care. Six months after the intervention, a retrospective clinical audit was performed to determine the number of HCV RNA positive participants who initiated HCV treatment.
Results: 70/174 people (40%) who underwent POC testing for HCV were HCV RNA positive on laboratory testing. Of these, 44/70 participants (63%) were prescribed HCV therapy and 31 participants (44%) commenced therapy. 22 participants completed treatment at six months (31% of those who were HCV RNA positive), of whom 11 had documented SVR12; 5 people did not complete treatment. Treatment initiation varied by clinic service model, highest at clinics A (76%) and B (71%) where NSPs were embedded within community clinics compared with clinic C (27%) where the NSP was co-located but separate to the clinic (p < 0.001).
Conclusion: Provision of POC testing through NSPs was effective for linking people diagnosed with hepatitis C into care and treatment. Further studies are needed to define how best to incorporate POC testing into models of care for people who inject drugs to increase HCV treatment uptake and completion rates.

FRI-234

Viral interference between dengue virus and hepatitis C virus infections

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Background and aims: Dengue virus (DENV) and hepatitis C virus (HCV) infections are two members of Flaviviridae with global health concern. Both of them may lead to acute hepatitis episodes. Southern

Taiwan, is an HCV endemic region and has faced several dengue fever (DF) outbreaks in the past decades. We aimed to investigate the virological interaction between the two viral infections.
Method: We examined the disease courses of the DF patients during Jan 2014 through Dec 2015. The baseline and follow-up characteristics of virology and clinical profiles were retrospectively reviewed. For those with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, molecular diagnostic tests for HBV DNA and HCV RNA were conducted for further analysis. We also conducted a cell line study to survey viral interaction utilizing HCV Con1 cells infected with DENV1.
Results: A total of 1, 192 DF patients who were diagnosed by positive nonstructural protein 1 (NS1) tests were consecutively enrolled. Among them, 515 DF patients with HBV and/or HCV infections were recruited into the analysis. HCV prevalence was 6.21% (32/515) in these DF patients. HBV/HCV coinfection rate was 21.9% (7/32) in HCV patients. Positive HCV RNA was noted in 14 cases (43.8%, 14/32). HCV with viremia or not during DF did not determine dengue-related complications (dengue hemorrhagic fever or severe dengue). Of 14 positive HCV RNA patients, 11 were rechecked for viral loads (VL) at least one time after DF with the median follow-up interval of 23 months (range 12-35 months). The post-dengue VL was significantly higher than that during DF [5.43 (± 0.77) vs 3.09 (± 1.24) log IU/ml, p = 0.003]. The mean VL difference was 2.34 (± 1.15) log IU/ml. All had an elevation of VL by 0.5 logs. Moreover, we arranged an HCV gene sequencing examination for one subject using his serum samples during and after DF. The analysis reported a 99.8% identical genomic sequence between the two samples, so the possibility of HCV reinfection could be excluded. The experimental study showed DENV could infect con1 cells. HCV NS5A expression was significantly downregulated along with the increase in DENV NS1.
Conclusion: HCV is suppressed by DENV via viral interference.

FRI-235
Hepatitis C virus risk factors and test uptake in an English prison
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Background and aims: Prisons are a key demographic in the drive to eradicate hepatitis C virus (HCV) as a major public health threat. High rates of testing prisoners for HCV infection will therefore be a crucial determinant of the outcome of any elimination strategy, however rates of testing in the East Midlands region of England remain far below the targets set by NHS England of 50-75%. There is insufficient knowledge detailing the extent of risk factors for HCV amongst the prisoner population which may explain prisoners' choice in not accepting a test and to inform harm reduction activity. The aim of this study was to understand details of the risk factors present in an English prison and HCV test uptake.
Method: Men incarcerated in a category C prison in the East Midlands of England were surveyed. An anonymous questionnaire was distributed to the prisoners and returned to the healthcare department. The questions included length of time and number of prisons spent in current sentence, whether they had been tested in current sentence, reasons for not being tested, and risk factors for HCV.
Results: A survey response rate of 10.7% (n = 109/1018) was obtained from men aged 21 to 68 years. The time spent in their current prison ranged between less than 1 and 60 months and the number of different prisons stayed in during current sentence was between 2 and 9. 71% (78/109) had not been tested in their current prison and 45% (49/109) not tested at all in their current sentence. Only 35% (38/109) reported ever injecting drugs, of whom 21% (8/38) had not been tested during current sentence. Additional key risk factors for HCV reported were; 76% (83/109) sharing prison hair clippers), 69% (75/109) inhaled drug use and 44% (48/109) fighting in prison. Only 7% (8/109) reported no risk factors for HCV. Of those not tested who supplied a rationale (n = 70) 43% (30/70) reported a previous negative test result, 23% (16/70) were needle-phobic and 11% (8/70) were scared of being diagnosed with HCV.
Conclusion: Our study found evidence that prisoners with risk factors were not tested for HCV. Routine testing on admission to prison will ensure all those with risk factors for HCV are tested. Further, testing methods such as dried blood spots may overcome the resistance to testing due to venous blood sampling. The role of intra-prison risks such as fighting and sharing hair clippers warrants further exploration.

FRI-236
Hepatitis C virus related liver fibrosis in people who inject drugs at the Stockholm Needle Exchange evaluated with liver elasticy
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Background and aims: Sharing of unsterile injection equipment among people who inject drugs (PWID) is the major transmission route for hepatitis C (HCV). HCV is highly prevalent in PWID in the Stockholm needle exchange program (NEP). The frequency of advanced liver fibrosis among the participants is, however, unknown.
Method: From December 2016 to April 2018 all patients with chronic hepatitis C infection (CHC), defined as positive HCV RNA tests > 6 months, were offered liver fibrosis evaluation at the Stockholm NEP. This included liver stiffness measurement (LSM), and a medical history with expanded blood tests to evaluate the APRI and FIB-4 scores.
Results: A total of 2037 individuals were enrolled in the Stockholm NEP, during the study period, of which 1159 (57%) were HCV RNA positive. 964 (47%) participants had CHC. LSM was performed in 203 (21.1%) of eligible participants of whom 85% had mild fibrosis (Metavir F0-F2) and 15% advanced fibrosis (Metavir F3-F4). APRI score > 1 and FIB-4 > 3.25 only identified 30% of participants with advanced fibrosis. All 31 (100%) participants with advanced fibrosis on the other hand were detected when APRI score > 1 was combined with age of ≥ 40 years and an injection drug use (IDU) duration of ≥ 15 years.
Conclusion: All PWID with advanced fibroses in the Stockholm NEP were detected when age ≥ 40 years and IDU duration of ≥ 15 years were combined with an APRI score > 1. We found that the diagnostic work-up for advanced fibrosis can be simplified with this combination of easily available factors. This allows identification of PWID in need of immediate HCV treatment to prevent further disease progression. Furthermore, LSM can be avoided among PWID with mild fibrosis, identified by age < 40 years combined with IDU duration of < 15 years and APRI score < 1. This strategy enhances the HCV care cascade where LSM is not easy available, and will thus facilitate HCV treatment initiation.

FRI-237
Triple E (engagement, education and eradication) for patients chronically infected with hepatitis C: Results of a self-sustaining, comprehensive education, screening and treatment program for patients in substance abuse treatment facilities
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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 patients 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.
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 an integrated program to improve the care of patients with SUDs.
Method: This program provided 4 important fundamentals to substance abuse center sites: staff education, patient education and counselling, antibody (Ab) screening and secondary blood draw (if Ab positive) and linkage to care. Linkage to care links the patient directly to a hepatitis specialist (onsite or via telemedicine in areas where HCV providers are limited) and a CLDF healthcare provider for onsite counselling and management. Patient screening and outcomes data are measured and the results are reported here.
Results: This initiative encompassed 19 substance abuse center sites located in New Mexico (n = 13), Kentucky (n = 5) and Arizona (n = 1). Data were collected March, 2017 and the results as of November, 2018 are summarized in the Figure. Overall, 658 of the 1475 SUD patients (pts), who were unaware of their HCV status, tested positive for HCV Ab. Furthermore, 384 pts who had HCV RNA testing (n = 531) were linked to HCV care.

Figure: Patient Screening and Outcome Results

	Ab Screened	Ab Positive	Blood Draw Completed (on Ab Positive Patients)	Linked to Care (Patients who had Blood Drawn)	HCV RNA Detectable
Number of Pts	1475	658	531	384	369

Conclusion: Promising new direct-acting antiviral drug regimens offer the possibility of eradication of HCV. However, patient and provider HCV education, screening and effective linkage to care are necessary to effectively integrate these treatments into disease management. Based on these results, the CLDF anticipates that 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 an educational grant from AbbVie.

FRI-238
Shifty business: Task shifting is essential to sustained increases in hepatitis C care engagement
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Background and aims: Hepatitis C virus (HCV) elimination requires a marked, contemporaneous scale-up of both HCV diagnostics and therapeutics. To do this in publicly funded health systems, finding maximum efficiencies is paramount. In particular, revision of medically complex HCV care models is needed. One strategy is task shifting non-nursing roles to other skilled individuals, such as clerical staff who are supported and encouraged to work at full scope. Our objective is to determine the effect of skilled clerical staff on overall HCV wait times and treatment initiations.
Method: A publicly funded provincial HCV elimination strategy was developed in a medium sized Canadian province. Key elements include: centralized triage and referral, rapid treatment start, inclusion of incarcerated individuals, harm reduction strategies, and patient self-referral. Intrinsic to the low cost business plan is each individual working to full scope of practice. In particular, a medical clerk with advanced skills in database management and telephone based patient engagement was added to the HCV clinical team to complement an HCV experienced nurse and physician. The required amount of time to engage each patient, as well as the wait times before and after engagement were measured.
Results: We collected data from 3 time periods: pre-clerk (Jan-Dec 2017), clerk (Dec 2017- Aug 2018), and post-clerk (Oct 2018). Treatment initiations were an average of 2.25, 15.3, and 3 patients per month respectively during each of the periods. Median wait time, in days, for the pre-clerk and clerk period was 140 (IQR 84-235) and 35 (IQR 21-63.75), respectively. First appointment attendance was 54.5%, 82.2%, and 14.3% ($p < 0.05$, clerk vs post clerk period) respectively for the pre-clerk, clerk, and post-clerk time periods. The average per patient clerk time from consult received to patient booked was 165 minutes, with 55% of patients requiring greater than 2 phone calls to successfully engage in care.
Conclusion: Task shifting initial HCV patient engagement from a nurse to skilled clerical personnel is a successful tool to gain rapid scale-up of patient treatment initiation, despite being time intensive for the clerical person. Without this resource, wait times rapidly increase and do not promote HCV treatment, despite expert nurses and physicians. Models that encourage task shifting need to be supported longitudinally to maintain benefit in HCV elimination.

FRI-239
SAMBA II HCV: A new point of care molecular assay for HCV diagnostics and DAA monitoring
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Background and aims: SAMBA II is a point of care (POC) nucleic acid testing platform designed for developing countries and for use in low-level health care settings such as district hospitals and health centres. The SAMBA II instrument system is a fully automated system for sample extraction, nucleic acid amplification, detection and interpretation of the results. The lyophilized reagents are non-toxic and the kits are stable for up to one month at 55°C and at 7-9 months at 2-37°C, thus, no cold chain transport or storage of reagents is required. DRW have now developed a SAMBA II HCV test to identify and monitor chronic HCV infections using venous or finger-prick whole blood. The HCV test is intended for high-risk groups such as HIV-1 infected individuals, assessing DAA eligibility for anti-HCV seropositive blood donors worldwide and, in developed countries, for niche populations such as prisoners and IV drug abusers in prisons or rehabilitation facilities. The aim of this study was to assess the performance of the test.
Method: Based on NASBA technology with HCV core region primers, amplified nucleic acids are detected by specific anti-hapten conjugate labeled with colored particles wicked up on a test strip. Colored amplicon-conjugate are immobilized on a test line by hybridization to a specific capture probe; a control line indicates valid performance of the test. The test has been evaluated for sensitivity, specificity and subtype coverage using the WHO standard and genotyped samples prepared in whole blood.
Results: The limit of detection was assessed using the 5th WHO International Standard for HCV NAT diluted in K_2EDTA whole blood. Probit analysis determined that the concentration of HCV RNA in whole blood detected with 95% probability, was 751 IU/ml (95% confidence interval (CI): 592-1, 268 IU/ml). Three to seven samples of each of the six HCV genotypes were consistently detected by the test showing coverage of all genotypes.. In specificity studies no cross-reaction was observed with HIV-1, HIV-2, HTLV-1 HTLV-2, HBV or Epstein Barr virus and testing of 100 individual negative whole blood samples was 100%.

Conclusion: SAMBA II HCV whole blood preliminary data are consistent with a POC assay able to detect at least 1000 IU/ml of HCV of all genotypes in whole blood with excellent specificity. Field studies will be conducted in relevant geographic areas to demonstrate similar performance in patient/blood donor capillary whole blood prior to and post-DAA treatment.

FRI-240

Comparison of Abbott RealTime HCV genotype II, Abbott HCV genotype plus RUO with Roche Cobas HCV genotyping assays for hepatitis C virus genotyping

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Background and aims: Data comparing the diagnostic accuracy for Abbott RealTime Genotyping II with/without RUO testing and Roche Cobas HCV genotyping are limited.
Method: 342 HCV-viremic patients receiving Abbott RealTime HCV Genotype II and Roche Cobas HCV genotyping assays were consecutively enrolled. Patients with indeterminate and unsubtypable HCV genotype 1 (HCV-1) results by Abbott RealTime HCV Genotype II assay were tested by Abbott HCV genotype plus RUO assay to discriminate HCV-1a, 1b, or 6 infection. Direct sequencing at the core and NS5B regions was performed for patients with inconsistent and unsubtypable HCV-1 results by either Abbott RealTime HCV Genotype II or Roche Cobas HCV genotyping assay.
Results: 328 (95.9%) showed consistent results between Abbott RealTime HCV Genotype II and Roche Cobas HCV genotyping assays. Eleven patients with indeterminate results by Roche Cobas HCV genotyping assay had HCV-6e, 6 g, 6n and 6w infections. Abbott RealTime HCV Genotype II assay can correctly diagnose HCV-6w infection, but showed unsubtypable HCV-1 and indeterminate results HCV-6 g and HCV-6n infections, which were correctively diagnosed by Abbott HCV genotype plus RUO assay. In two HCV-1b patients, 1 and 2 of them showed indeterminate results by Abbott RealTime HCV Genotype II and Roche Cobas HCV genotyping assays, which were correctively diagnosed by Abbott HCV genotype plus RUO assay.
Conclusion: Abbott RealTime HCV Genotype II and Roche Cobas HCV genotyping assays show high consistent results. High indeterminate rates were found in HCV-6 infection by Roche Cobas HCV genotyping assay. Most patients with indeterminate and unsubtypable HCV-1 results by Abbott RealTime HCV Genotype II assay can be accurately diagnosed by plus RUO assay.

FRI-241

Barriers to HCV elimination among drug users: HepCare-Spain

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Background and aims: Active drug users, as people at risk of social exclusion with problems to access health care, may not be aware of their HCV status. To reach the objective of HCV elimination, it is necessary to detect nearly all individuals with HCV infection and give them access to treatment. The HepCare Europe (a collaboration between Bucharest, Dublin, London and Seville) project aims to assess in a new model of care for hepatitis C, which facilitates access to diagnosis and treatment of HCV infection in disadvantaged groups. We present data from HepCare-Spain with the aim of evaluating the prevalence of infection in these groups and the linkage to care of patients with active HCV infection.
Method: Within HepCare, the HepCheck subproject aims at improving HCV testing. As part of it, a health team travels to addiction treatment centers, therapeutic communities and non-governmental organizations to detect markers of HCV infection in blood or saliva. The HepLink subproject is designed to facilitate access to specialized care for patients with detectable HCV RNA. We describe the process of screening, the prevalence of positive anti-HCV and of detectable HCV-RNA among individuals invited to participate in HepCheck. We also describe the cascade of care of those with active HCV infection and engaged in HepLink.
Results: We invited 784 individuals to participate (January 2017-November 2018), 32 (4%) refused and 228 (29%) did not attend appointments. Of the 524 individuals screened, 415 (79%) of them were unaware of their HCV status. 452 (86%) participants were previous drug users, and 209 (40%) current drug users. Overall, 185 (35%) individuals showed positive anti-HCV, and 99 (19%) had detectable HCV RNA. 68 (69%) of those with active HCV infection attended the appointment to be fully evaluated for treatment, 15 (22%) of them failed their next appointment to start or plan DAAs. Treatment was initiated in 41/68 (60%) patients with these Results: SVR12, 36; relapsed, 2; dropped-out, 1; treatment ongoing, 10. Overall, HCV infection was eliminated in 36% (36/99) viremic patients.
Conclusion: In a population mainly constituted by drug users in Spain, a fifth of the subjects have active HCV infection. It is possible to link to specialized care and give access to DAA to HCV-infected patients who were not followed up or were unaware of their HCV status. However, the elimination of HCV infection in this group could not be possible, with the described strategy, due to losses to follow-up.

FRI-242

Absence of hepatitis C infection despite high-risk sexual behavior in a cohort of men who have sex with men screened in the community: preliminary results of SEXCHECK study

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Background and aims: Over the last decade, an outbreak of sexually transmitted acute HCV infection has been documented among HIV positive men who have sex with men (MSM). Specific sexual practices have been associated with the risk of HCV infection in this population. However, data about HCV in HIV-negative MSM population are scarce, and community screening programs may be helpful. Our purpose was to assess HCV prevalence in a cohort of HIV-negative MSM with high risk sexual behaviour.
Method: We recruited HIV-negative cis-men or trans-women who have sex with men and that presented one or more risk factors for sexual acquisition of HCV and/or HIV infection. Recruited individuals filled in a survey about sexual habits and underwent screening tests

for sexual transmitted infections (STIs), including HCV-RNA and anti-HCV. The study was conducted at the community-based, peer-lead "BLQ Checkpoint" managed by PLUS Onlus (Bologna, Italy), using rapid test (Oraquick HCV® on saliva for HCV-Ab and Xpert® HCV viral load on blood for HCV-RNA).
Results: 56 cis-men and 1 trans-woman were enrolled in this analysis. Median age was 40 (range 19-59). 46 individuals (80.7%), reported 10 or more partners in the last 6 months; 47 (82.5%) reported sporadic use of condom and in this subgroup 70% of insertive intercourses and 51.1% of receptive ones were with partner of unknown serological status. 27 individuals were on PrEP. 45 (78.9%) reported at least one high-risk sexual practice (sex toys sharing, group sex participation, fisting) in the last 3 months; group sex was the most common (70%). 17 (29.8%) reported chemsex use, 12 (21.1%) straws or needle sharing in the last 3 months. No active or previous HCV infections were found. 44 individuals (77.2%) reported a previous STI; 32.8% had positive syphilis test. At first evaluation, in 14 subjects PCR for *Chlamydia trachomatis* (6) *Neisseria gonorrhoeae* (5) or both (3) was positive.
Conclusion: Despite an high prevalence of risk factors in our cohort, no silent HCV infections were detected at baseline. Data about incidence of new infections will be obtained through prospective evaluation of the cohort and will help to understand the epidemiology of HCV in HIV-negative MSM population in Italy. Community-based screening with rapid tests was an effective and reliable way to reach this target population.

FRI-243
Utility of simple serum based tests to exclude cirrhosis prior to HCV treatment in non-hospital based settings
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Background and aims: Current guidelines suggest using transient elastography (TE) or APRI with a cut-off of < 1 to exclude cirrhosis prior to HCV therapy. An efficient serum based test could reduce the need for TE allowing more streamlined treatment in non-hospital settings. Recently FIB-4 (cut off 0.93) has been shown to have a high negative predictive value (NPV) for the presence of cirrhosis and to reduce the need for TE. We aimed to assess FIB-4 and APRI in our cohort of HCV patients and to validate FIB-4 < 0.93 in populations of HCV infected individuals with differing cirrhosis prevalence including those assessed and treated in primary care and prison.
Method: From our treatment database we identified patients with complete data. (n = 793) We calculated FIB-4 and APRI and correlated this with the presence of cirrhosis TE (> 12.5kPa). We analysed performance of FIB-4 and APRI using AUROC. We then calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and number of patients misclassified using published cut-offs in various populations with differing prevalence of cirrhosis.
Results: FIB-4 was superior to APRI for the diagnosis of cirrhosis (AUROC 0.868 vs 0.80). In secondary care (cirrhosis 32%) APRI < 1 had a NPV of 80% and misclassified 14% of patients with cirrhosis. FIB-4 < 0.93 had a NPV of 97% and misclassified 1%. In primary care patients and prisoners who had a lower prevalence of cirrhosis (15 and 8%) the NPV for APRI < 1 was 93% and 96% respectively but still 5% of patients with cirrhosis were misclassified. FIB-4 < 0.93 had excellent NPV in primary care (97%) and prisoners (100%).
Conclusion: The recently described FIB-4 cut off of 0.93 is highly efficient at ruling out cirrhosis in HCV patients. These patients can safely avoid TE thus streamlining treatment in primary care and other populations with a low prevalence of cirrhosis.

FRI-244
Platelet-derived growth factor alpha might mediate hepatic fibrosis by enhancing insulin resistance in patients with hepatitis C
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Background and aims: Insulin resistance (IR) represents one of the key regulatory mechanisms in the development of hepatic steatosis, the consequent hepatocyte injury and finally hepatic fibrosis. Both conditions represent a common feature in hepatitis C virus (HCV) infection and type 2 diabetes mellitus (T2DM). The platelet-derived growth factors (PDGFs) are key regulators of the connective tissue formation and potent mitogens for hepatic stellate cells. It was recently demonstrated that higher plasma PDGF-A concentration is associated with increased hepatic steatosis and fibrosis in T2DM. We aimed to investigate whether there is an association between PDGF-A serum concentration, IR and HCV mediated hepatic steatosis and fibrosis.
Method: This cross-sectional study comprised 107 non-diabetic participants aged 50.85 ± 1.57 years, 77 (71.96%) with HCV infection. The fasting PDGF-A concentration was determined by enzyme-linked immunoadsorbent assay. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score over 1.64 was categorised as IR. Fibrosis and steatosis were evaluated by ultrasound elastography (FibroScan®). The participants were divided into 4 groups: HCV negative group with IR (HCV^-/IR^-, N = 12), HCV positive group without IR (HCV^+/IR^-, N = 34), HCV positive group with IR (HCV^+/IR^+, N = 44) and 18 healthy controls. One-way ANOVA or Kruskall-Wallice test followed by Bonferroni's correction were used to test the differences on multiple levels by a single factor (independent) variable.
Results: There was a significant difference in liver stiffness indicating the degree of fibrosis with the highest mean value of 15.9 kPa in the HCV^+/IR^+ ($p < 0.001$ for all) and steatosis severity accessed by Controlled Attenuation Parameter ($p < 0.001$, for all) revealing the highest value in HCV^-/IR^+ (296.5 dB/m). The PDGF-A concentration correlated positively with steatosis ($r = 0.341$, $p = 0.007$) and fibrosis ($r = 0.264$, $p = 0.071$) severity. Both IR positive groups had higher PDGF-A compared to HCV^+/IR^- group ($p = 0.006$). In accordance with more pronounced steatosis, the HCV^-/IR^+ group revealed the highest PDGF-A concentration.
Conclusion: We demonstrated that PDGF-A concentration is associated with the severity of hepatic steatosis in HCV and non-HCV patients with IR; i.e. that PDGF-A could represent one of the key regulatory mechanisms in the pathway from hepatic steatosis towards fibrosis. These results provide better understanding of pathways that regulate fibrosis which might have a good potential in future therapeutic options development.

FRI-245
Improvement in cognitive impairment following 12 weeks of aerobic exercise in individuals with non-cirrhotic, chronic hepatitis C
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Background and aims: Cognitive impairment (CI) is reported to occur in 30-50% of individuals with non-cirrhotic, chronic hepatitis C (HCV). A virally induced, chronic inflammatory state is thought to be the main contributor to HCV related CI. In other chronic inflammatory diseases, aerobic exercise has been utilised to improve disease related CI. This study aimed to examine the effects of an aerobic exercise intervention (EI) on cognitive function in individuals with HCV.
Method: DAA-naïve HCVRNA positive individuals with proven CI were recruited to take part in a 12-week aerobic EI. A comprehensive assessment including measures of; cognitive function, cardiovascular fitness ($\dot{V}O_{2max}$), anthropometry and objective physical levels (PAL) was undertaken before the EI (T0), post completion of the EI (T1) and reassessed three months after T1 (T2). The EI consisted of two supervised and three unsupervised sessions per week with increasing intensity (45-75% heart rate reserve) and duration (24-45 minutes) for 12 weeks. Control participants did not participate in the EI. A two-way ANOVA with repeated measures was used to examine for significant differences compared to controls. Values are displayed as mean difference±standard deviation.
Results: 42 participants enrolled in the EI with 13 exercise and 20 control participants completing the EI with 76% mean adherence. In the exercise group, there was a significant improvement in the Trail Making Test A and B (TMT-A and B), the Montreal Cognitive Assessment (MOCA) and $\dot{V}O_{2max}$ at T1 (Figure 1) compared to T0 but these improvements were not maintained at T2 (p = NS).

Mean difference between T0 and T1	Group		*Time X Group Effect*
	Exercise Group	Control Group	
TMT-A (s)	-12.5 ± 5.85 *	-2.9 ± 13.58	p = 0.037
TMT-B (s)	-18.6 ± 24.4 *	8.1 ± 34.41	p = 0.035
MOCA	2.8 ± 2.04 ***	-0.4 ± 2.55	p = 0.001
Digit Symbol Test	6.7 ± 7.32	3.8 ± 4.61	p = 0.210
$\dot{V}O_{2max}$ (ml.min.kg)	6.3 ± 5.50 *	-0.4 ± 7.26	p = 0.013
PAL (min/week)	42.8 ± 241.00	-14.1 ± 257.90	p = 0.553

*, *** Indicates significantly different from T0 in the EG (p < 0.05, p < 0.001, respectively).

Conclusion: This is the first study to report the potential of aerobic exercise in ameliorating symptoms of HCV-related CI. Future studies investigating strategies to promote long term adherence to exercise to address extrahepatic manifestations of HCV infections are warranted.

FRI-246

Elimination of HCV in a Large Urban Health System in the United States: A Big-data Approach

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Background and aims: Chronic hepatitis C virus (HCV) infection leads to progressive liver disease that can result in liver failure and liver cancer. Innovative case-finding strategies are needed to make use of the highly effective direct acting antiviral drugs that are now available to cure HCV. The Aims of this study are to develop and apply methods for identifying HCV-infected patients across a large urban healthcare system and for linking them to HCV treatment.
Method: Electronic medical records (EMR) of the approximately 7.6 million patients in the Mount Sinai Health System (2000-2017) were queried and a list was generated of 27, 814 patients with International Classification of Diseases 9/10 diagnosis codes for HCV and/or records of HCV antibody or HCV RNA testing (see Fig. 1). A team of computer specialists, liver disease providers, care coordinators, and patient navigators is investigating the status of these patients and offering navigation/care coordination when appropriate.

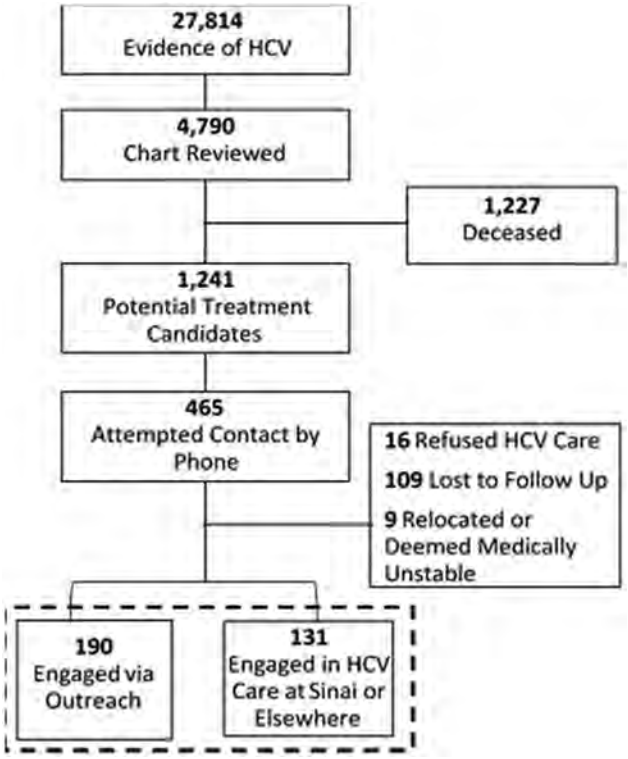

Figure: Patient Outreach Outcomes

Results: Of the 27, 814 patients, the records of 4, 790 (17%) have been reviewed thus far. Of those reviewed, 1, 227 (26%) were deceased and 1, 241 (26%) were HCV RNA positive treatment candidates. Thus far, we have attempted to contact 465/1, 241 (37%) patients by phone and succeeded in engaging 190/465 (41%) in the scheduling pipeline and/or in HCV treatment. Among the others, 131/465 (28%) were already actively engaged in HCV care at Mount Sinai or elsewhere; 16 (3%) said they did not want to pursue HCV treatment; nine (2%) had moved out of the geographic region and/or were too medically unstable for HCV treatment; and 109 (23%) could not be reached. Extrapolating from these results, as of 2017, there were approximately 3, 000 patients in the Mount Sinai System with positive HCV test results or an HCV-related diagnosis in need of outreach for engagement in HCV care.
Conclusion: Many patients in our urban healthcare system who had EMR data indicative of HCV infection had either died (26%) or failed to access HCV treatment by the end of 2017. Based on data collected using computer algorithms, manual chart review, and contact by telephone, we estimate that about 3, 000 patients with chronic HCV infection could be engaged in HCV care with adequate care coordination and patient navigation. Our findings of high mortality of HCV-positive patients who are left untreated highlight the urgent need for large-scale HCV case finding and care coordination.

FRI-247

Influence of HCV coinfection and HCV treatment on risk of diabetes mellitus in HIV infected persons

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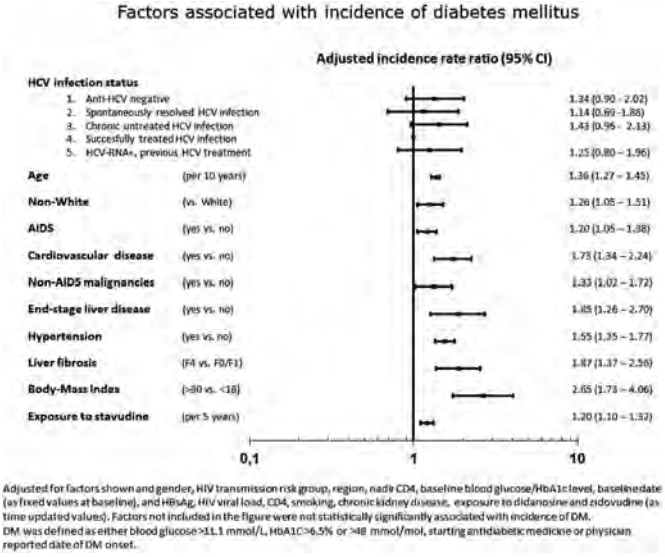
Background and aims: HCV infection has been associated with an increased risk of diabetes mellitus (DM). In how far this may change after successful HCV therapy as well as the contribution of fibrosis stage and HIV related risk factors in DM development remains unclear.

Method: All HIV positive individuals in the EuroSIDA cohort with known HCV status after January 2001 were included in one of five groups based on time-updated HCV-RNA and use of HCV treatment: 1) HCV-uninfected, 2) spontaneously resolved HCV infection, 3) chronic untreated HCV infection, 4) successfully treated HCV infection, 5) HCV-RNA positive despite previous HCV treatment. Individuals with DM at baseline were excluded. Poisson regression was used to investigate the association between HCV groups and DM.

Results: We included a total of 16, 034 HIV positive persons of which 6109 (38.1%) were anti-HCV positive and 460 (2.9%) had cirrhosis at baseline. The majority were male (74%), White (85%), and on ART (85%) with a median (IQR) age of 41 (35-49) years and CD4 cell count of 446 (290-639) cells/µl. During 123610 person-years of follow-up (PYFU); median 6 years (IQR 3-12) per person, 1019 (6.4%) developed DM. The crude incidence rate/1000 PYFU (95% CI) of DM was 8.7 (8.1-9.3), 6.3 (4.2-8.5), 7.4 (6.1-8.7), 6.7 (4.4-8.9), 7.4 (5.4-9.5) in group 1-5, respectively. In multivariable analysis (figure), there was a 43% increased incidence of DM in those with chronic untreated HCV compared to those successfully treated, although this was marginally significant ($p = 0.08$). Other HCV groups had similar incidence of DM compared to those successfully treated. The incidence of DM was significantly higher among persons with cirrhosis vs. F0/1 fibrosis and in those with end-stage liver disease (ESLD) vs. no ESLD. In addition, development of AIDS or serious non-AIDS events (cardiovascular events, malignancies) and hypertension, as well as older age, non-white ethnicity, higher body-mass index and increased exposure to stavudine were associated with increased incidence of DM.



Conclusion: In a large cohort of HIV/HCV coinfected persons, cirrhosis and ESLD were associated with increased risk of DM. There was some evidence that those successfully treated had a lower incidence of DM that those with chronic untreated HCV, but our results did not reach statistical significance, potentially due to limited power. Increased risk of DM was also associated with both HIV related and well-known general risk factors for DM.

FRI-248

Cost-effectiveness of elbasvir/grazoprevir (EBR/GZR) for treatment-naive (TN) patients with chronic hepatitis C virus (HCV) genotype 1b (GT1b) infection in Russia

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Background and aims: An estimated 4.1% of the population in Russia is infected with HCV, of which GT1b is the most common. EBR/GZR is a direct-acting antiviral (DAA) indicated for the treatment of GT1b in Russia. The objective of this study was to compare the cost-effectiveness of EBR/GZR to regimens currently used in Russia for the treatment of TN patients with GT1b HCV infection.

Method: A Markov model was constructed to evaluate the cost and effectiveness of EBR/GZR over a lifetime time horizon. The target population was TN patients infected with HCV GT1b, stratified by presence of cirrhosis. The model consists of 16 health states encompassing METAVIR fibrosis score (F0-F4), treatment success or failure, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplant, and liver-related death. The proportions of patients achieving sustained virologic response (SVR) were obtained from clinical trials. Other inputs were obtained from published sources. The primary outcome was incremental cost-utility ratio (ICUR) for EBR/GZR vs. each comparator.

Results: EBR/GZR is less costly and more effective (economically dominant) over all comparators in cirrhotic patients (Table). In non-cirrhotic patients, EBR/GZR was cost-saving vs. all comparators and economically dominant over all comparators except OMB/PAR/RIT +DAS and GLE/PIB, for which QALY differences were negligible.

Conclusion: EBR/GZR is economically dominant over other DAA regimens in cirrhotic patients, and is economically dominant or cost-saving vs. comparators in non-cirrhotic patients.

Table: Costs, QALYs, and the ICUR for EBR/GZR vs. Comparators

Treatment Regimen	Total Discounted Costs (RUB)	Total Discounted QALYs	Incremental Costs	Incremental QALYs	ICUR, EBR/GZR vs. Comparator (RUB/QALY)
Non-cirrhotic (F0-3)					
EBR/GZR	375, 971	11.9465	–	–	–
SIM+PegIFN+RBV	1, 078, 505	11.6691	−702, 534	0.2774	Dominant
DAC+ASN	619, 030	11.6732	−243, 059	0.2732	Dominant
OMB/PAR/RIT+DAS	465, 378	11.9545	−89, 407	−0.0080	Cost saving
GLE/PIB	693, 651	11.9653	−317, 680	−0.0188	Cost saving
NAR+RIT+ PegIFN+RBV	803, 808	11.7130	−427, 837	0.2334	Dominant
SOF+DAC	747, 917	11.9312	−371, 946	0.0152	Dominant
SOF+SIM	1, 266, 417	11.9006	−890, 446	0.0459	Dominant
Cirrhotic (F4)					
EBR/GZR	789, 288	11.0885	–	–	–
SIM+PegIFN+RBV	1, 595, 848	10.4310	−806, 560	0.6575	Dominant
DAC+ASN	853, 733	10.6546	−64, 445	0.4339	Dominant
OMB/PAR/RIT+DAS	895, 848	11.0885	−106, 560	0.0000	Dominant
GLE/PIB	1, 240, 233	11.0885	−450, 945	0.0000	Dominant
SOF+DAC	995, 087	11.0885	−205, 799	0.0000	Dominant
SOF+SIM	1, 518, 737	10.7847	−729, 449	0.3038	Dominant

FRI-249

HCV in french prisoner, the study 2017: Fewer patients but more treatment than in 2015

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Background and aims: Prevalence of HCV infection is high among prisoners. In France, medical units in prison (unite de soins en milieu pénitentiaire USMP) are under the responsibility of public hospital since 1994. In 2015, a French national 2015 survey describes the state of play of diagnosis and treatment of HCV prisoners. From 2016, all the prisoners can be treated whatever their liver fibrosis is. Objective: Describe national HCV diagnostic and therapeutic practices in french prisons in 2017 and to compare with the 2015 results according to an identical questionnaire.
Method: email survey about practices in 168 USMP.
Results: 71/168 (43%) of questionnaires were usable, covering 46% of prisoners in France. The number and prevalence (%) of HCV patients decreased from 1145 (4.3%) to 928 (2.8%); (average from 20 to 16 in each USMP) There was no significant differences in proposal and performing of HCV screening; systematic announce of HCV results increased from 72% to 79%. HCV DBS (n/n prisoners; 54%) was possible in 18% USMP. FIBROTEST (89%) was more frequently performed than FIBROSCAN (68%) in 2017. Number of on-site performed FIBROSCAN was similar. On-site hepatologist consultations decreased from 56% to 46% USMP with a frequency falling from 3.4 to 1.6 a month. Same proportion of USMP (67%) introduced at least one AAD treatment in 2017, number of treated prisoners increased from 145 to 260 (+79%) with a rate of treatment increasing from 12.7% to 28.1% (+126%); In 2017, 72% USMP compared to 59% in 2015 introduced DAA even if release was scheduled before the end of treatment. Weekly DAA dispensing was more frequent (27% versus 19% in 2015) however remained mostly daily (67% versus 79%). Treatment and post-release follow-up after were similar. Discussion: HCV care in prison was more efficient in 2017 than in 2015. Considering screening, systematic announce of the results remained low. Use of FIBROSCAN* to assess hepatic fibrosis was restricted. the number and percentage of treated patients increased. But, 1/3 of the USMP did not introduce any treatment during the incarceration of the prisoner. DAA dispensing surveillance remains low because of their high cost.
Conclusion: Prison environment constitutes a suitable environment for vulnerable population to access to HCV treatment. However DAA access remains limited.

FRI-250

Test to cure: Increase outreach linkage to care by use of real time HCV viral load

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Background and aims: HCV treatment for all was effective in France since 2017. HCV testing, diagnosis and treatment of drugs users and precarious people remain low. Lost follow-up was too important since several stages are necessary. Pangenotypic DAA were available and did not require no determination of viral genotype before treatment. Point-of-care HCV RNA testing offers advantage over antibody testing, enabling diagnosis of active infection with real time measure in a single visit. It is missing link between HCV DBS, liver fibrosis evaluation by FIBROSCAN and treatment. An Australian team concerning 210 drug users (30% positive HCV viral load) validated Xpert HCV Viral Load assay CEPHEID system with 100% feasibility, 95% sensibility, and 98% specificity. This technique of fast training can allow to develop projects of diagnosis to treatment session. Objective: estimate feasibility of test session to treat real time allowing the access in 5 hours to an antiviral treatment to vulnerable populations (drug users, migrants, psychiatric patients) to increase outreach screening and treatment.
Method: Eligible patients had to have known positive serology or risk behavior, an unknown or unchecked viral load after antiviral treatment; 5 to 7 patients were recruited by social or nursing interview. Between 9 am and 2 pm these patients had access to measure of the hepatic fibrosis by FIBROSCAN, HCV viral load in real time by Xpert HCV Viral load finger-stick samples, social interview, shared educational evaluation, collective workshops, specially harm reduction. Depiction of results by hepatologist and prescription of AAD allowed delivery of 1st month of treatment on-site or with support to pharmacy. A report was sent to GP.
Results: From March to October 2018, 73 patients were eligible; 11 sessions were realized on 8 sites: one drug unit, one prison, 6 social units; 4 patients did not come; 69 measures of viral load in real time were realized; 38 were positive (55%); 36 treatments were begun same day, only 2 were delayed due to default social rights; 19 patients had a negative viral load spontaneously and 12 following prior treatment. Social and nursing follow-up was made during and after the treatment according to procedures and biological tests standardized.
Conclusion: With these new mobile clinic model, by screening and real time measure in unity of place, adapted to precarious public, patients distant from system of care had access immediately to treatment.

FRI-251

Impact of hepatitis C treatment on patterns of drug use and subsequent treatment outcomes: High SVR rates despite increasing intravenous drug use in the post treatment period

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Background and aims: HCV treatment involves interaction with healthcare professionals with the potential to alter health behaviours. Little information exists on patterns of drug use post vs pre

treatment. We sought to identify changes in drug use and utilisation of Injecting Equipment Provision (IEP) amongst our patients.
Method: Non trial patients commencing Glecaprevir/Pibrentasvir in Glasgow prior to 01/05/2018 were identified from the Scottish HCV database. Data on baseline demographics, Opiate Replacement Therapy (ORT), and SVR12 were obtained. For patients on ORT, review of addictions notes identified (where available) self reported intravenous drug use (IVDU), non-IVDU, and toxicological evidence of drug use in the 3 months pre (PRE) and post (POST) treatment. Those attending specialist addictions clinics (not primary care ORT clinics) were linked with local IEP database by identifiers based on name/date of birth. Anonymous data was returned on; number of registered patients, and number/nature of IEP exchanges in the PRE and POST periods.
Results: 355 patients (251 (70.7%) male, mean age 45.2 (± 9.3), 33 (9.4%) with cirrhosis) met the inclusion criteria, of whom 222 (62.5%) were on ORT. Self reported drug use/positive toxicology was unchanged POST vs PRE period (table 1). POST there was a trend to increased self reported IVDU. 97/144 (67.4%) patients attending specialist addictions clinics linked to the IEP database. There was a numerical rise in patients accessing IEP. More patients accessed needles only, and fewer accessed foil (for heroin inhalation, an IVDU alternative) alone or in combination with needles. To date ITT SVR rates are high amongst those with and without drug use PRE: 114/121 (94.2) vs 62/64 (96.8), $p = 0.65$ or POST: 107/115 (93.0%) vs 57/58 (98.3%) $p = 0.14$. 3 patients died of probable drug related causes. There was one probable and one possible reinfection.

Drug Use	PRE (%)	POST (%)	*p*
Self reported drug use	114/197 (57.9)	117/193 (60.6)	0.58
Self reported IVDU	17/197 (8.6)	28/193 (14.5)	0.07
Any evidence of drug use (self reported or toxicology)	135/201 (67.2)	142/201 (70.6)	0.45
Patient with IEP Transactions	46/144 (31.9)	53/144 (38.8)	0.38
Patients with IEP needle only transactions	32/46 (69.5)	50/53 (94.3)	0.001
Patients with IEP foil transactions (± needles)	14/53 (26.4)	3/53 (5.7)	0.006

Conclusion: Overall drug use was stable between the PRE and POST periods, however there was a trend towards increased reported IVDU, numerically higher numbers attending for IEP, and a rise in patients accessing needle only IEP. Further qualitative work is required to explore these changing patterns, however these changes, together with the drug related deaths and reinfection observed, reinforce the need for promotion and linkage to harm reduction/IEP as a core part of HCV treatment. SVR rates remain high irrespective of drug use in the PRE or POST treatment period.

FRI-252
Comparing the efficacy of hepatitis C diagnostic pathways: Standard testing vs. targeted testing

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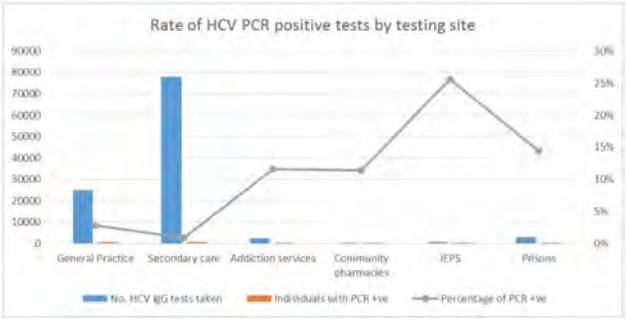
Background and aims: NHS Tayside is committed to eradicating the Hepatitis C virus (HCV) by 2030 in line with the World Health Organisation recommendations. This includes diagnosing at least 90% of those infected. With an estimated prevalence of 0.55% we anticipate that we should have 2700 people with chronic HCV. 2300 are known to the team and have either been treated and cured or are in line to be treated. A further 400 are not known to us. It is vital that we diagnose and treat these people in order to prevent further transmission of the virus and achieve elimination.

NHS Tayside have instituted a number of specialised pathways for testing and treatment of HCV amongst the most at-risk populations, including people who inject drugs (PWID), those on opiate substitution therapy and prison inmates. Widespread testing occurs in injecting equipment provision sites (IEPS), community pharmacies, substance misuse centres and the prison service. These models operate in addition to the standard viral hepatitis service.
Our aim was to analyse the efficacy of the new directed diagnosis pathways compared with standard testing.
Method: Data was collected for every Hepatitis C IgG and PCR test ever done in NHS Tayside. We attributed each test to a diagnosis pathway according to the testing source. Clinical records show the testing source for each individual in Tayside with positive antibody results. Pooling this data allowed us to assess pathway efficacy.
Results: Overall the diagnostic activity for HCV has increased over the last two decades. More markedly since 2012 when DAAs were becoming available. The standard diagnostic pathways (General practice and secondary care) show large volume testing with a low rate of PCR positivity. In contrast testing pathways aimed at high risk individuals show a higher PCR positive rate. See figure.



Conclusion: Utilisation of diagnostic pathways targeting populations most at risk of HCV are more effective at yielding new HCV diagnoses than standard pathways. These tailored diagnostic pathways will also resolve some of the health inequalities around drug use and provide methods of ensuring entry to treatment. We believe using targeted testing will find the majority of our undiagnosed population, as we are exhausting the standard pathways. This will help us to direct resources and achieve our aim of elimination by 2030.

FRI-253
Changing epidemiology of hepatitis C: A Hospital-level study

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Background and aims: After the mass treatment of the longstanding Hepatitis C virus (HCV) patients from the Hepatology clinics, there should be considerable variation in the prevalence and epidemiology of HCV infection. To update HCV epidemiology is critical, because different strategies are required to interrupt different patterns of HCV transmission. Our aim was to characterize the recently newly identified HCV patients for in-hospital treatment.
Method: Analysis of all the confirmed HCV infection cases (defined by positive HCV viral load) between September 2017 and September 2018, at a Tertiary hospital centre. Patient demographical and clinical characterization, including genotype, liver disease stage, transmission patterns and co-infection status, was performed.

Results: Initially retrieved 276 newly confirmed HCV infections. 48 cases were excluded due to previously confirmed infection (n = 16), ongoing follow-up at other hospitals (n = 4) or lack of information (n = 28). 228 patients (167 males [73.2%]; mean age 51.0 ± 11.2 years old) were identified for further analysis.
Patients were mainly referred to the hospital from primary care (n = 80, 35.1%), other in-hospital outpatient clinics (n = 77, 33.8%) and community support associations for drug users (n = 48, 21.1%). From antibody screening to hospital referral, there was an overall 5-year mean delay. Primary care accounted for the biggest referral delay (7.5 years) followed by community (4.8 years) and in-hospital outpatient clinics (1.2 years). Drug use was the predominant risk factor identified (n = 142, 62%). Liver fibrosis stage distribution was as follow: F0-1, n = 72 (31.6%); F2-3, n = 71 (31.1%); F4, n = 58 (25.4%). Genotype was also identified: G1a/b, n = 83/29 (49.1%); G2, n = 5 (2.2%); G3, n = 63 (27.6%); G4, n = 33 (14.5%); G5, n = 1 (0.4%). Human immunodeficiency virus co-infection was present in 10.9% of the sample.
Conclusion: Unexpectedly, there are only subtle temporal variations concerning HCV epidemiology. There is an even striking expression for drug use as an infection transmission route, and a weightier fraction of patients are being referred to the hospital by non-conventional health care institutions. However, the genotypes distribution did not change and there are still many cirrhotic patients being newly identified for treatment. Still, patients keep experiencing a long delay between screening to in-hospital treatment.

FRI-254
The impact of virally induced hepatic inflammation and low to moderate alcohol consumption on liver transient elastography (Fibroscan) in patients with chronic hepatitis C virus infection treated with direct-acting antivirals

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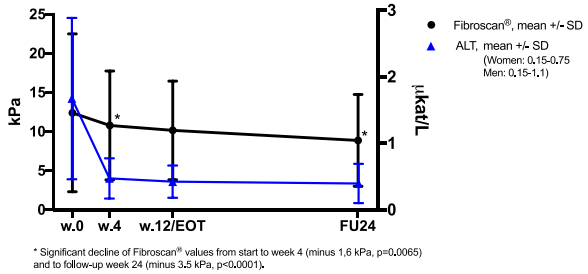
Background and aims: Fibrosis assessment using liver transient elastography (Fibroscan®) is important to discriminate patients with moderate or advanced fibrosis. Elastography might overestimate fibrosis for several reasons. This study evaluates the impact on Fibroscan® of DAA treatment and inflammation.
Method: 115 patients treated with DAA were included and repeatedly evaluated by Fibroscan®, HCV-RNA and ALT levels. Alcohol use was evaluated by a modified AUDIT-C questionnaire and phosphatidylethanol 16:0/18:1 (B-PEth), 2 times 3-4 weeks apart, before starting DAA.
Results: 22 patients were excluded mostly because of blood sampling difficulties, unwillingness to continue or breakthrough viremia (n = 3). 98 of the patients fulfilled the pretreatment part of the study concerning alcohol use and 85 patients, all with sustained virologic response (SVR), had complete data including Fibroscan® until follow-up 24 weeks after treatment (FU24).
ALT normalized at week 4 of treatment, together with HCV-RNA levels becoming undetectable or very low. In all 85 patients Fibroscan® mean values declined from baseline 12.4 kPa, week 4 10.8 kPa, EOT/week 12 10.1 kPa and FU24 8.85 kPa (Figure 1).

Figure 1: ALT and Transient Elastography (Fibroscan®) During and After DAA Treatment



* Significant decline of Fibroscan® values from start to week 4 (minus 1.6 kPa, p=0.0065) and to follow-up week 24 (minus 3.5 kPa, p<0.0001).

AUDIT-C evaluating the last 4 weeks of alcohol consumption at first visit correlated moderately with B-PEth levels (r: 0, 54), 56 had undetectable levels while 39 had light to moderate elevation (B-PEth 0.05-0.7 µmol/L). The mean alcohol consumption in the 98 evaluated patients did not change during the pretreatment period (p = 0.53, paired t-test), and mean Fibroscan® values also remained unchanged (p = 0.91, paired t-test). No significant change in liver stiffness was seen in 28 patients who reduced drinking, according to B-PEth, during the pretreatment period.
Conclusion: These new data with Fibroscan® evaluation early during DAA treatment, reveal a 2-phase decline with a first phase of almost 2 kPa, probably due to quickly resolving virally induced inflammation. After 4 weeks a second phase with slower decline is seen during continuing treatment up to 24 weeks after treatment (FU24), probably representing a true decline in fibrosis. Thus, DAA induced reduction of the Fibroscan® value 24 weeks after treatment, is a combined effect of reduced inflammation and fibrosis, representing approximately 50% each. Inflammation must be considered when using Fibroscan® for fibrosis assessment. AUDIT-C can be used to assess alcohol use in patients with chronic hepatitis C. However, a low to moderate alcohol consumption had no significant impact on Fibroscan® values in this study.

FRI-255
Dynamics of HCV epidemiology among HIV+ patients in Vienna

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Background and aims: HIV/HCV coinfection used to be mostly restricted to people who inject drugs (PWIDs), but recently, "high-risk" sex practices among HIV+ men who have sex with men (MSM) have been reported as routes of HCV transmission. At the same time, novel direct acting antivirals (DAAs) against HCV achieved sustained virologic response (SVR) rates > 95%. We retrospectively analyzed changes in HCV epidemiology in our cohort of n = 1874 HIV+ patients.
Method: HCV serology/PCR results were recorded at HIV diagnosis (baseline, BL) and at last visit (follow-up, FU) for all HIV+ patients with a clinical visit at our HIV-clinic between January 2014 and December 2016. The proportions of HIV+ patients with anti-HCV (+) and HCV viremia (HCV-RNA+) were assessed and stratified by the suspected route of transmission. Finally, rates of spontaneous or treatment-induced HCV clearance (anti-HCV (+) and HCV-RNA (–)) were calculated.
Results: N = 1806/1874 (96.4%) patients were tested for HCV. 359/1793 (20.0%) were anti-HCV (+) and 208/343 (60.6%) showed HCV viremia. The discrepancy between the total numbers of patients in the individual subgroups results from the retrospective study design, due to which HCV-testing did not follow a universal standardized protocol.
At BL, anti-HCV (+) was observed in 93.2% (276/296) of PWIDs and in 3.0% (25/823) of MSMs.
1644/1806 (91.0%) of the patients had an HCV test at FU. 50/1508 (16.6%) were anti-HCV (+) and 132/397 (33.2%) showed HCV viremia. 195/208 of the initially HCV-coinfected patients (93.8%) underwent FU HCV-testing: 30 (15.4%) had spontaneously cleared HCV, 76 (39.0%) had achieved SVR due to antiviral therapy and 89 (45.6%) were still HCV viremic. 168/187 (89.8%) of PWIDS and 43/715 (6.0%) of

MSM showed anti-HCV (+) at FU. Among the 1433 initially HCV-naive patients, 45/1294 (3.5%) acquired de-novo HCV infection.
Conclusion: HCV testing has been sufficiently implemented among HIV+ patients. Over a median FU period of 6.9 years, anti-HCV (+) prevalence remained stable (89.8 to 93.2%) in PWIDs and increased (3.0 to 6.0%) in MSM. Spontaneous and treatment-induced HCV clearance occurred in 15.4% and 39.0% of HCV/HIV+ patients, respectively. 89 (45.6%) patients remained untreated and 45 new cases of HCV (3.5% of the HIV+ population) were observed.

FRI-256
Procoagulant imbalance in chronic hepatitis C and its relationship with cardiovascular and liver damage
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Background and aims: Chronic C Hepatitis (CHC) is one of the most important causes of morbidity and mortality not only for liver but also for cardiovascular diseases, the last occurring mainly in the presence of metabolic syndrome and steatosis. A procoagulant imbalance, potentially responsible for cardiovascular disease has been reported in patients with NAFLD as well as in subjects with any causes of cirrhosis. Aim: to evaluate the complex interplay between the procoagulants and anticoagulants in naïve, non-cirrhotic CHC patients, the role of coexisting steatosis and the relationship among coagulation imbalance, liver and cardiovascular damage.
Method: From 2014 to 2018, 205 patients with CHC were enrolled. Clinical and biochemical parameters, cardiovascular assessment, (carotid and cardiac ultrasound), presence of steatosis (ultrasound), severity of liver damage [transient elastography and non-invasive fibrosis scores (FIB-4 and NAFLD fibrosis score)] and coagulation balance through the evaluation of procoagulants (FII and FVIII, anticoagulants [antithrombin and protein C (PC)], endogenous thrombin potential (ETP) and peak-thrombin ratio with/without thrombomodulin were determined at enrollment. Coagulation parameters of CHC patients were compared to those of 188 control subjects, enrolled among hospital employers and healthy patients" relatives.
Results: Ultrasound evidence of steatosis was detected in 87 patients (42%). No difference in carotid and cardiac parameters and in severity of liver fibrosis was observed in CHC patients with or without steatosis despite higher BMI, triglycerides, prevalence of hypertension, diabetes, use of statin and lower HDL values in patients with steatosis. Indexes of procoagulant imbalance defined as high FVIII, FVIII/PC ratio, ETP-ratio and peak-thrombin-ratio (with/without thrombomodulin) were significantly higher in CHC patients than in controls without differences between CHC with or without steatosis. Indexes of procoagulant imbalance were independently associated with liver fibrosis [FVIII and FVIII/PC ratio with FIB-4 (coefficient 7.6, SE 3.7, p = 0.04 and coefficient 0.1, SE 0.07, p = 0.03, respectively) and with carotid intima-media thickness (IMT) [FVIII/PC ratio with IMT (coefficient 0.8, SE 0.4, p = 0.05)].
Conclusion: Patients with non-cirrhotic CHC have a procoagulant-imbalance that may play a role both in their increased risk of cardiovascular disease and in severity of fibrosis.

FRI-257
Making OraQuick quicker: A hepatitis C point-of-care assay reduced to five minutes for viremic individuals
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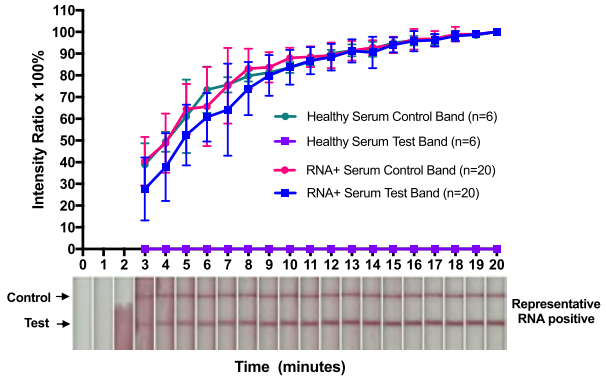
Background and aims: Point-of-care testing for hepatitis C virus (HCV) increases access to screening for hard-to-reach populations and in settings with high test volumes or limited laboratory facilities. OraQuick HCV Rapid Antibody Test (OQ) is an FDA-approved lateral flow-based enzyme linked immunosorbent assay (ELISA) that detects anti-HCV antibodies (Ab) in whole blood or serum. The approved assay requires results be determined 20-40 minutes after test initiation; however, field observations suggest it may be possible to decrease read-time (RT) for viremic individuals (VIs). Our aim is to determine whether a RT prior to 20 minutes can be established for VIs that is non-inferior to the required 20-40 minutes RT.
Method: Blood samples from 46 HCV VIs and 11 long term resolvers (defined as clearing HCV > 5 years prior) were tested with the OQ assay. Serial photos were taken for up to 20 minutes, and the time of first appearance of a positive band was recorded and confirmed by a second reader. Intensity ratio analysis was used to compare positive test bands at each time point to their final intensities. Negative controls included 6 uninfected subjects. Data collection is ongoing.
Results: By 5 minutes, 46/46 VIs had a positive result. The mean time to positivity was 2.6 minutes in VIs, compared to 7.4 minutes in the long-term resolvers ($p < 0.0001$). VIs were 65% male, median age of 59, median HCV RNA of 1.91×10^6 IU/ml, and 16 had cirrhosis. The long-term resolvers cleared the virus 5-14 years ago, following treatment, and all were cirrhotic. In contrast to the VIs, only 6 of 11 long-term resolvers were positive at 5 minutes. Based on these results, the probability of a VI testing positive by 5 minutes was 100% (95% CI, 92.3-100). Intensity analysis demonstrated that test bands from VI samples darken within 5 minutes to 52% (± 14%) of their final intensities, which is easily detectable (see figure). Kinetics of band intensity in viremic samples are shown in the figure, accompanied by a representative example.



Conclusion: Our results demonstrate that the OraQuick HCV Rapid Antibody test can reliably detect anti-HCV Abs by lateral flow in 5 minutes among viremic individuals. Although there may be value in documenting past HCV infection, the main goal of screening is to identify those infected. This shortened read time for testing may have important implications to improve engagement and linkage to care by facilitating follow-up HCV RNA in as little as 5 minutes.

FRI-258

Sustained virologic response among non-cirrhotic persons who inject drugs: Results from the CanHepC retrospective hepatitis C registry

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Background and aims: In Canada, most incident cases of hepatitis C virus (HCV) occur in those engaged in high risk activities including injection drug use (IDU). Limited data exists on characteristics and treatment outcomes in this population in Canada. The current study assessed baseline characteristics and treatment outcomes in those with a history of IDU in the Canadian Network on Hepatitis C (CanHepC) retrospective registry which includes patients from diverse clinical settings across Canada. Outcomes were compared to those without a history of IDU.
Method: The CanHepC retrospective registry has combined demographic and outcome data on patients with chronic HCV who were assessed at 13 academic and community sites across Canada. All non-cirrhotic individuals who had information available on current or past IDU as well as results for sustained virologic response (SVR) from the CanHepC retrospective registry were included in the current analysis.
Results: Between January 1, 2015 and December 27, 2017 a total of 1169 non-cirrhotic individuals were treated with direct-acting antiviral (DAA) regimens and had SVR results available at 13 sites across Canada. Of those, 610 (52.2%) had data available on IDU. Findings demonstrated that those with a history of IDU were younger (47.5 vs. 56.0 years, $p < 0.001$), more likely to be male (36.7% vs. 23.5%, $p = 0.001$) and were significantly less likely to be Caucasian (56.8% vs. 93.5%, $p < 0.001$). Genotype 1a was more common in those with a history of IDU (60.5% vs. 46.6%), as was the presence of mixed genotypes 1 and 3 (6.1% vs. 3.2%). SVR rate was found to be 94.4% (95% CI 92.2-96.6) in those with history of IDU which did not significantly differ from those without a history of IDU where SVR rates were found to be 97.0% (95% CI 94.6-99.4).
Conclusion: Individuals with a history of IDU in the CanHepC retrospective registry were more likely to be younger, male, and non-Caucasian. Despite IDU history, overall SVR12 rates in this Canadian cohort are excellent and do not differ significantly from those without any history of IDU.

FRI-259

Characteristics and sustained virologic response of persons reporting illicit substance use in the past 6 months: Results from the CANUHC prospective patient registry

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Background and aims: In Canada, most incident cases of hepatitis C virus (HCV) occur in those engaged in high risk activities including injection drug use (IDU). Limited data exists on disease characteristics and treatment outcomes in this population in Canada. The current study assessed baseline characteristics and treatment outcomes in those with a history of IDU in the CANUHC prospective registry.
Method: The Canadian Network on Hepatitis C (CanHepC) prospective registry is collecting demographic and outcome data on patients with chronic HCV who are assessed at academic and community sites across Canada. The prospective registry is enriched with populations of interest in Canada including persons who inject drugs (PWIDs). All individuals who reported illicit substance use within the 6 months prior to baseline were included in the current analysis.
Results: Between January 2016 and May 2018, 445 individuals who reported illicit substance use were enrolled in the registry. Of those, 97 (21.8%) reported use of one or more illicit substances in the prior 6 months. Those with recent substance use were significantly younger (47.6 vs. 51.6 years, $p = 0.005$), and less likely to be currently employed (10.8% vs. 38.0%, $p < 0.001$). This group also reported higher rates of past or current injection drug use (79.4% vs. 56.6%, $p < 0.001$) and were more likely to be Canadian-born (99.0% vs. 90.2%, $p = 0.005$). There were no significant differences in biological sex or proportion who identified as indigenous. Sustained virologic response (SVR) was available at the time of this abstract for 111 patients. Overall, SVR rate was 93.8% [95% CI 85.4-100.0], and did not significantly differ from those without reported recent substance use (96.2% [95% CI 92.0-100.0]).
Conclusion: Individuals with recent substance use in the CANUHC prospective registry were more likely to be younger, Canadian-born and unemployed. Despite current substance use, overall SVR12 rates in this Canadian cohort are excellent and do not differ significantly from those without recent reported substance use.

FRI-260

Improving hepatitis C care cascade through electronic health engagement

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Background and aims: There are multiple challenges in the hepatitis C [HCV] care cascade. Electronic health engagement could emerge as a tool in linking patients to the HCV care cascade. There is an emerging epidemic of people who inject drugs (PWID), contract HCV and then fail to seek treatment for this curable illness. One challenge in testing PWID, particularly in community settings, is linkage to care and treatment following a positive test. Our aim is to link individuals that are HCV RNA positive to care and utilize our online patient database management system (PDMS) with Substance Abuse Treatment Centers to fulfil the linkage portion.
Method: Longitudinal prospective cohort study with HCV screening at the above centers and utilization of a HIPPA compliant PDMS (www.linkagetocare.com). A centrally located Linkage to Care Specialist (LTCS) is notified immediately when an individual's information is entered in the system by the treatment center or self-referred. The LTCS educates the individual and proceeds to link them to care.
Results: January 2017-October 2018, 1838 patients were referred to LTC; 53% self-referred and 47% referred from 38 facilities in 27 states; 94% Texas; 69% were uninsured; 55% were between the ages of 21-40; 59% males. 855 HCV RNA positive patients; 680 (80%) patients were contacted by LTCS; 470 (69%) referred to a medical provider; 22% patients awaiting lab results; 9% lost contact. Patients were connected with an LTCS within 2 days after referral and were contacted twice

before scheduling their first appointment. 172 (37%) patients made it to their first appointment; 83 (48%) initiated therapy; 52% were completing evaluation; 62 (75%) finished therapy or achieved SVR12; 88% were seen in office vs. 12% through telemedicine. Additionally, 55% of patients were from sober living homes, 33% from treatment facilities and 12% from medical clinics.
Conclusion: Targeting PWID is an effective way of reducing the prevalence of HCV infection and ultimately eliminating HCV in our communities. Our study accentuates a promising role for patient engagement in electronic health portals as a tool in linking patients to the hepatitis C care cascade. With the LTC program, there is an increase in patient compliance with linkage to care as compared to current care models. Therefore, continued efforts are needed to increase and improve PWID HCV patient electronic health engagement.

FRI-261
Large-scale screening is not useful to identify individuals with hepatitis B or C virus infection: Final results of a Swiss prospective study

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Background: Current treatments are able to control HBV replication and to eradicate HCV in almost all cases. Further improvements in the management of HBV and HCV infections will be possible by focusing on treatment impact at a population level for which screening is an essential step. As many patients with HBV or HCV infection are still undiagnosed, large-scale screening could be useful.
Aim: To investigate whether large-scale screening for HBV or HCV infection (e.g. risk-based vs. age-based) could identify infected individuals.
Method: Individuals between 18 and 80 years attending the pre-operative consultation prior to minor surgery in a general surgical outpatient clinic were tested for HBsAg, anti-HBc and anti-HCV from November 2014 to November 2018. The presence of anti-HCV was confirmed by an Immunodot test. HBV DNA and HCV RNA were determined in HBsAg- and anti-HCV-positive individuals.
Results: Among 3000 individuals tested, 7 were positive for HBsAg (0.26%) and 4 had detectable HBV DNA. Twelve individuals were positive for anti-HCV antibodies (0.44%). Two of them had detectable HCV RNA (0.07%) and 10 had undetectable HCV RNA (5 spontaneously and 5 after a successful antiviral treatment). When compared to HCV negative people, HCV positive individuals had already been screened more frequently for HCV (83.3% vs. 12.8%, $p < 0.001$) as well as for HBV infections (66.7% vs. 21.5%, $p = 0.001$), had more frequently anti-HBc antibodies (33.3% vs. 4.2%, $p = 0.001$), had more frequently HCV household members (16.7% vs. 1.7%, $p = 0.02$), and had used more frequently intravenous drugs (66.7% vs. 0.1%, $p < 0.001$), nasal drugs (58.3 vs. 6.2%, $p < 0.001$) or cannabis (58.3% vs. 7.9%, $p < 0.001$). None of HCV positive individuals were immigrant from an endemic area. The median age of HCV positive individuals was not different from that of those who were HCV-negative (52 years [range: 39-59] vs. 44 years [95% CI: 43-45], $p = 0.1$). Most of the positive individuals were already aware that they were infected (86% of the HBV positive individuals and 100% of the HCV viremic individuals).
Conclusion: In this prospective study performed in a general surgical outpatient clinic, a large-scale screening was not useful to identify individuals with undiagnosed HBV or HCV infection. Screening for HBV and HCV infection should focus on individuals with well-known risk factors.

FRI-262
Genetic variants in the promotor region of the macrophage migration inhibitory factor are associated with severity of HCV-induced liver fibrosis

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Background and aims: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine, which is characterized as an important regulator of the innate immune system in different diseases. Two polymorphisms of the MIF promotor-the single nucleotide polymorphism (SNP) –173 G/C and the microsatellite polymorphism –794 $CATT_{5-8}$-show a prognostic relevance in different inflammatory diseases including chronic liver diseases. The aim of the underlying study is to investigate a correlation between these two MIF promotor polymorphisms and the severity of HCV-induced liver fibrosis.
Methods: First, the genotypes of the SNP –173 G/C (rs755622) are determined using taqman genotyping assay in DNA samples extracted from whole blood from 500 patients with HCV-induced liver fibrosis. Second, the repeat number of the microsatellite 794 $CATT_{5-8}$ (rs5844572) is analyzed by specific PCR-based DNA-amplification followed by high resolution gel electrophoresis and fragment length analysis. A correlation between the genotypes of both polymorphisms and the histological grading and staging of HCV-induced fibrosis is investigated.
Results: Concerning the genotypic distribution of the SNP polymorphism only 3% of all patients show the C/C genotype compared to a higher frequency of the G/G and G/C genotype (66%; 31%). Accordingly, a higher repeat number in the microsatellite (7/X) shows only a low prevalence (2%) in our cohort. Interestingly the C/X genotype in the –173 G/C-SNP is associated with a significant lower stage of fibrosis than the G/G genotype (mean fibrosis stage 1.87 vs. 2.06); this effect is even more pronounced regarding the C/C genotype vs. G/G genotype (1.54 vs. 2.06). Additionally, there is a positive correlation between a low repeat number in the microsatellite –794 $CATT_{5-8}$ (genotype CATT5/5; 5/6; 6/6) and the presence of stage 2 and higher levels of fibrosis.
Conclusion: The mentioned MIF promotor polymorphisms correlate with the severity of HCV-induced liver fibrosis. Here, the C/C genotype in the –173 G/C-SNP is associated with a significantly lower fibrosis stage. Our results therefore argue for a prognostic relevance of these two promotor polymorphisms that therefore could represent promising biomarkers in HCV-induced liver disease.

FRI-263
The VirA+EmiC project: Opt out hepatitis B and C testing of 38704 patients in an urban emergency department

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Background and aims: Previous studies of screening attendees to urban emergency departments (ED) have indicated high detection

rates of hepatitis B (HBV) and hepatitis C (HCV). The current study evaluated the feasibility and detection rates in a large urban emergency department in the United Kingdom.

Method: Over a 9 month period consecutive attendees to an urban ED, who had clinically indicated blood sampling, underwent opt out testing for HBV surface antigen (HBsAg) and HCV (Antibody [Ab]) using an electronic preselected blood order set. All HCV Ab reactive results were followed by reflex HCV antigen (Ag)testing (Abbott Architect). Attendees who were identified as either HBsAg, or HCV Ag were then linked to care by the study team. Seroprevalence estimates and risk factors (age, sex, ethnicity, homelessness, and HIV) associated with seropositivity were estimated using univariable and multivariable Poisson regression.

Results: 81, 088 patients attended the ED, of whom 38, 704 patients (49% male, median age 45yrs [31-62yrs]) had blood sampling. 29, 240 (75.5%) underwent testing for HBV and/or HCV. Of the 28, 941 patients tested for HBsAg, 244 (0.8%, 95% confidence interval [CI] 0.7%-0.9%) were positive. Of the 28, 939 patients tested for HCV, 539 (1.9%, 95%CI 1.7%-2.0%) were HCV Ab positive. Of these 462 patients had HCV Ag measured, of whom 264 (adjusted seroprevalence 1.1%) were HCV Ag positive.

A high HBsAg seroprevalence was observed among patients aged 50-59 years (1.6%), with Black or Asian ethnicity (1.9%, 95%CI 1.6-2.4%), and with HIV infection (4.3%, 95%CI 2.1-8.7%). In the adjusted model, risk factors for infection were being male (relative risk (RR): 1.6, 95%CI 1.2-2.1%), of non-White British ethnicity (RR > 4), being homeless (RR: 1.9, 95% CI 1.0-3.5) or being HIV positive (RR: 4.1, 95%CI 1.9-8.9%). A high HCV Ab seroprevalence was observed in patients aged 30-49 years (2.9%, 95% CI 2.6-3.3%), male (2.9%, 95% CI 2.6-3.2%), homeless (22.1%, 95%CI 19.2-25.3%) and HIV infection (12.3%, 95%CI 8.0-18.4%). In the adjusted model risk factors for HCV Ab positivity were being male (RR:2, 95% CI 1.6-2.5), age 30-49 years (RR:4.4, 95% CI 3.1-6.4), homeless (RR:10.1, 95% CI 8.7-13.0), and being HIV positive (RR:3.6, 95% CI 2.2-5.8)

To date 35 HCV Ag patients have been contacted, 24 were eligible for linkage, and of there 20 have attended clinic.

Conclusion: In this large study of opt out Hepatitis B and C testing good uptake rates are achievable, with a high detection rate of hepatitis B and C. For hepatitis B the greatest risk factor was being of non-white ethnicity, and for hepatitis C being homeless. Linkage to care remains a challenge.

FRI-264

Silencing clusterin supress the progression of hepatitis C virus-related HCC by regulating autophagy and attenuating HCC cell properties

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Background and aims: Hepatitis C virus (HCV) induced hepatocellular carcinoma (HCC) threatens human health worldwide. At present, effective therapeutic target for HCV-HCC is still absent.

Method: Twelve patients with HCV-related HCC and 3 age- and gender-matched liver transplant donors were included in the study. Differentially expressed mRNAs in plasma of the patients with HCV-HCC were detected by digital gene expression (DGE) profile analysis. Hepatic clusterin and autophagy-related genes were detected through qRT-PCR and Western blot. Meanwhile, we set up HCC cell lines stably expressed HCV core protein, and detected the expression of CLU and autophagy-related genes by qRT-PCR and Western blot, and also observed autophagy by transmission electron microscopy. Furthermore, we knocked down CLU by siRNA transfection and then detected cell autophagy by transmission electron microscopy, cell apoptosis and cell cycle by flow cytometry, cell proliferation by Cell Counting Kit-8 (CCK-8) kit, and cell invasion by Transwell assay, as well as the expression of related genes were detected by qRT-PCR and Western blot.

Results: We found that CLU was dramatically increased in tumor tissues of HCV-HCC and HCC cell lines stably expressed HCV core protein, which accompanied with the increased autophagy and pro-autophagy gene expression. When knockdown of CLU in HCC cell lines, we found that cell autophagy was dramatically decreased, autophagy marker LC3B II/I ratio was decreased, and the pro-autophagy genes like Beclin1, Atg7 and lamp2 was downregulated. On the other hand, the anti-autophagy genes or regulators including p62, p-mTOR were notably upregulated. Meanwhile, cell apoptosis was increased, pro-apoptosis gene BAX, PARP, AKT, Caspase3 and Caspase9 were dramatically increased, and anti-apoptosis gene Bcl2 was decreased. Also, knockdown of CLU could regulate cell cycle and inhibit proliferation, and inhibit cell invasion, which accompanied with downregulated matrix metalloproteinase (MMP) 2 and N-cadherin and upregulated tissue inhibitor of metalloproteinase (TIMP) 1, E-cadherin and Vimentin.

Conclusion: CLU could promote the progression of HCV-related HCC by regulating autophagy. Knockdown of CLU could attenuate tumor properties of HCC cell lines, which might be a potential therapeutic target of HCV-related HCC.

Gut microbiota and liver disease

FRI-265

Twelve weeks of effective resistance training did not change the gut microbiota in patients with cirrhosis

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Background and aims: Increasing evidence demonstrates that physical activity may modulate the gut microbiota composition and stimulate a health-promoting effect in healthy individuals and in patients with chronic diseases e.g. diabetes. In cirrhosis, the composition and changes of the gut microbiota affect disease severity and complications, including higher relative abundance of gram-negative proteobacteria. We examined if 12 weeks of resistance training could alter the microbiota in patients with cirrhosis.

Method: 39 patients with cirrhosis Child Pugh A/B were randomized 1:1 to either an exercising group performing 12 weeks of progressive resistance training three times per week or a non-exercising control group. Diet was protein-rich Northern European. Stool samples were collected at week 0 and 12 from 17 exercisers and 14 controls and analyzed using 16S rRNA sequencing. Microbial taxa at the family level were studied between and within groups at baseline and post-exercise.

Results: Diet, use of antibiotics and hepatic encephalopathy treatment (lactulose, BCAA, rifaximin) were equal among groups and the resistance training increased muscle mass and strength. There were no changes in Shannon diversity or UniFrac between groups at baseline and study-end. Two patients in the exercise group did not improve their muscle strength. These patients had a higher relative abundance of Proteobacteria (Piscirickettsiaeae, Hyphomonadaceae, Caulobacterales) compared to those who improved muscle strength (n = 15). Interestingly Proteobacteria were higher in these patients at baseline as well.

Additionally, patients with diabetes (n = 9), showed no difference in their microbiota versus patients without diabetes. Former versus current smokers showed an increase in Rikenellaceae and a decrease in Firmicutes and Clostridia.
Conclusion: Although based on a secondary outcome of a randomized clinical trial, our findings lend no support to the hypothesis that the beneficial effects of physical activity to involve gut microbiota.
Yet, the microbiota may affect the results of resistance training and exercise-improved muscle strength may be associated with lower Proteobacteria constituents at baseline and at study-end.

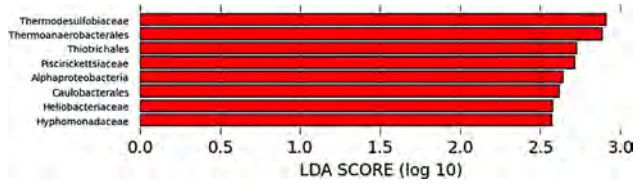

Figure 1: Taxa showing higher relative abundance at 12 weeks in those who ultimately did not improve after resistance training compared to those who improved

FRI-266
Saccharomyces boulardii modulates the colonic microbiota towards a more favourable composition in patients with non-alcoholic fatty liver disease (simple steatosis)
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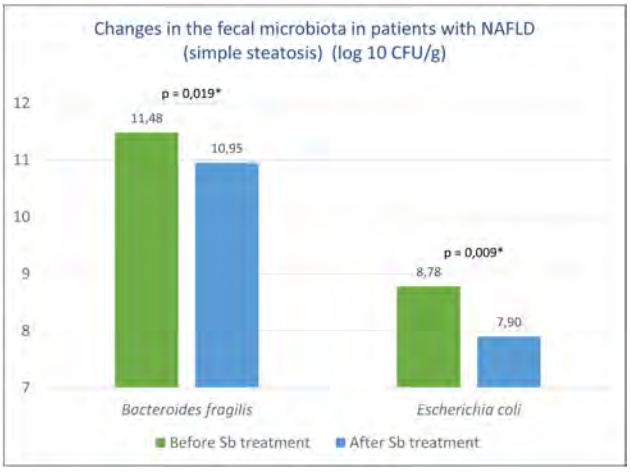
Background and aims: Recent experimental studies show that *Saccharomyces boulardii* maintains the integrity of the intestinal barrier and exerts some anti-inflammatory effects. The aim of this study is to investigate changes in the composition of fecal microbiota and some clinical parameters following treatment with lyophilized *Saccharomyces boulardii* in patients with NAFLD (steatosis only).
Method: 25 adult patients with NAFLD (steatosis only) were enrolled in the study. The quantitative real-time polymerase chain reaction (qRT-PCR) was used for fecal microbiota assessment. All patients were treated with oral lyophilized *Saccharomyces boulardii* CNCM I-745® for 90 days (3 capsules 250 mg per day).
Results: The count of *Escherichia coli* in patients with NAFLD steatosis was initially higher than the reference values obtained from healthy volunteers. Lyophilized *S. boulardii* (Sb) for 90 days significantly reduced *Bacteroides fragilis* group and *Escherichia coli* (Figure) There were no significant changes in other fecal microbiota (total bacterial count, *Lactobacillus* group, *Bifidobacterium* spp., *Faecalibacterium prausnitzii*, etc.). Treatment with *S. boulardii* improved symptoms and quality of life in patients with NAFLD steatosis and significantly reduced VLDL and atherogenic index. Patients with overweight or obesity showed a decrease in body weight. In all patients, steatosis showed no progression as assessed by FibroMax® test, liver ultrasonography and telomere test.



Conclusion: *Saccharomyces boulardii* CNCM I-745® significantly reduced initially elevated fecal *Escherichia coli* in patients with NAFLD steatosis to normal values, thus reducing the risk of additional liver damage by endogenous ethanol and inhibiting the choline deficiency. *S. boulardii* significantly lowered *Bacteroides fragilis* group, thus reducing the risk of endotoxemia. The lack of progression of steatosis after 90 days suggests the effectiveness of *S. boulardii* in patients with NAFLD. Lyophilized *Saccharomyces boulardii* modulates the composition of the gut microbiota in patients with NAFLD steatosis and restores intestinal barrier integrity, thus preventing the progression of the disease.

FRI-267
Serial measurement of serum dextran absorption by novel competition ELISA demonstrates larazotide acetate significantly improves "leaky gut" in a Western diet murine model of metabolic liver disease
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Background and aims: Integrity of the gut epithelial barrier is critical to preventing bacterial translocation; increased Gut Permeability (GP) ("leaky gut") contributes to inflammation and the development of numerous liver diseases. Larazotide Acetate is a gut-specific intestinal permeability re-normalizing agent that acts by regulating tight junctions. The purpose of the study was to test efficacy of larazotide at high and low doses via drinking water and oral gavage in the DIAMOND™ mouse model, which develops significantly leaky gut that worsens with advancing liver disease status.
Method: 60 DIAMOND™ mice were weight randomized to 8 groups, placed on either normal chow (NDNW) or Western Diet (42% fat, 4% sugar water, WDSW) and aged up to baseline 8 wks (NAFLD) then dosed with larazotide at 1 mg/ml or.1 mg/ml ("HD" and "LD," respectively) in sugar water, or gavaged twice daily with.3 mg or.03 mgs ("HD" and "LD," respectively) in aqueous vehicle. Pioglitazone, an insulin sensitizer lacking impact on gut permeability, was gavaged at 27 mg/kg. Mice were dosed from baseline 8 wks to study end at 16 wks. GP was assessed at baseline and end with modified competition ELISA for serum dextran; mice were gavaged with 4 kDa dextran @ 600 mg/kg and 20 µL of serum was taken by tail vein nick 4 hours later for dextran measurement. Serum and liver were collected at necropsy and LFTs and histology were assessed.
Results: Serum dextran levels at baseline were very low in all groups; as expected GP increased by 16 wks on WDSW and in pair-wise comparison, average serum dextran in the bottle VC, gavage VC, and

pioglitazone groups increased 16x (p = .005), 63x (p = .084) and 6x (p = .032) over their respective baselines. Larazotide treatment significantly attenuated GP deterioration; in paired T-tests HD bottle and LD gavage groups were not statistically different from their baselines. Comparison of serum dextran levels between groups at end of study showed that the biggest effects were in the HD bottle and LD gavage groups (both groups were significantly lower than either VC, pioglitazone, LD bottle and HD gavage; see P value matrix). The LD bottle group did not differ statistically from VC groups or pioglitazone.

Conclusion: This study demonstrated that leaky gut develops rapidly between 8–16 wks on WDSW in the DIAMOND™ mouse model, and that oral administration of larazotide effectively retards the deterioration in gut permeability; administration by high-dose bottle or low-dose gavage was the most effective. Since the time course did not allow development of histologic liver disease indicative of non-alcoholic steatohepatitis, it was not possible to evaluate the impact on liver function and longer duration on a high fat diet which are being investigated in ongoing studies.

FRI-268

Microbiota signature differs significantly between NAFLD and healthy controls but not between NAFL and NASH

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Background and aims: Previous studies have shown that gut dysbiosis is associated with non-alcoholic fatty liver disease (NAFLD). However, the data regarding differences in microbiota composition between the two NAFLD phenotypes, i.e. non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) are inconsistent. In this prospective cross-sectional study we aimed to evaluate the association between gut bacterial dysbiosis and the presence of NAFLD in general and NAFL and NASH in particular.

Method: Ninety patients with NAFLD (n = 21 NAFL, n = 47 NASH; n = 23 without liver biopsy) and 21 healthy controls (HC) were enrolled. Taxonomic composition of gut microbiota was determined using 16S rDNA gene sequencing of stool samples. Linear discriminant analysis (LDA) effect size (LEfSe) analysis, followed by multivariate logistic regression was performed to detect differences in the bacterial composition of gut microbiota between the groups.

Results: Mean age of all study subjects (n = 111) was 44.5 years (SD±14.3) and 54 (49%) were women. Comparing NAFLD to HC we observed three phyla and nine families to differ significantly (p < 0.05) between the two groups. After multivariate analysis only the differences in abundance of *Bacteroidetes* (phylum) and *Ruminococcaceae* (family) between NAFLD and HC remained significant. LEfSe found no phyla but twelve families to be significantly different between biopsy-proven NAFL and NASH (p < 0.05). However, after multivariate logistic regression (adjusted for the presence of metabolic syndrome) the difference in gut microbiota composition between NAFL and NASH was no longer statistically significant.

Conclusion: The gut microbiota composition seems to differ significantly between NAFLD and HC but not between NAFL and NASH. Thus, whereas bacterial gut microbiota signature could serve as a biomarker for the diagnosis of NAFLD, this might not be sufficient to accurately distinguish between NAFL and NASH.

FRI-269

Regulation of lymphangiogenesis by Paneth cells in normal physiology and experimental portal hypertension

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Background and aims: The mesenteric lymphatic network contributes to the transport of fluid and intestinal mucosal associated immune cells along the gut-liver axis. We hypothesized that Paneth cells, as part of the innate intestinal immune system, regulate the development of lymphatic vessels and affect portal pressure under the control of intestinal bacteria.

Method: We induced Paneth cell depletion in Math-1 Lox/LoxVillcre^{ERT2} mice by injecting three consecutive doses of tamoxifen and performed partial portal vein ligation (PPVL) to induce portal hypertension. After 14 days, intestinal and mesenteric lymphatic vessels were assessed by immunohistochemistry (IHC) using lymphatic vessel endothelial hyaluronic acid receptor 1 (Lyve-1) antibody. The lymphatic vessels were quantified using Metamorph to calculate pixel ratio. Expression of genes involved in the regulation of lymphatic vessels was evaluated by RT^2 profiler PCR array in intestinal tissue. Intestinal organoids from control and Paneth cell depleted mice were exposed to different bacterial derived products. Proteomic analysis of conditioned media was performed using MaxQuant to analyse differentially regulated proteins in lymphangiogenesis in the absence of Paneth cells and/or in portal hypertension.

Results: Portal pressure was significantly attenuated in Paneth cell depleted mice compared to control mice after PPVL (n = 11/group, 9.78 ± 1.23 cmH_2O vs 11.45 ± 1.41 cmH_2O, respectively, $p < 0.002$). Depletion of Paneth cells resulted in a significantly decreased density of lymphatic vessels compared to control as assessed by IHC (n = 5, pixel ratio), in the intestine (0.176%±0.12 vs 0.367%±0.15, p = 0.01) and in the mesentery (0.160%±0.06 vs 0.404%±0.20 p = 0.001). Quantitative PCR showed a decreased expression of genes involved in the regulation of lymphangiogenesis, including VEGF-C, VEGF-D, VEGF-A, Nrp2, Angpt-2, Tie-1, Tie-2, TGF-α, HGF and CXCL-1 in Paneth cell depleted mice. In the absence of Paneth cells, proteomic analyses showed a significant downregulation of several proteins involved in lymphatic vessel development and morphogenesis, as well as in processes of lipid metabolism and transport.

Conclusion: In the absence of Paneth cells, the intestinal and mesenteric lymphatic vessel networks were significantly underdeveloped. This resulted in an attenuated portal hypertension. These findings suggest that Paneth cells not only play an antimicrobial role in the intestine, but also contribute to the regulation of lymphatic vessels and portal pressure

FRI-270

Association between gut microbiota and hepatocellular carcinoma in patients with chronic liver disease

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Background and aims: It has been reported that insulin resistance and high fat diet and dysbiosis of gut microbiota are possible causes of carcinogenesis of NASH and NAFLD in animal models. Moreover, it has been reported that there are changes of gut microbiota in patients with hepatocellular carcinoma (HCC) compared with that in patients

without HCC. Therefore, in order to investigate whether gut microbiota is associated with HCC, we determined the differences of gut microbiota by using the next generation sequencer between patients with and without HCC in patients with chronic liver disease.
Method: One hundred and twenty-five out of 133 patients with chronic liver disease have participated in this study. We analyzed fecal samples from 82 patients with HCC and 43 patients with non-HCC in 125 patients suffering from chronic liver diseases and 16 healthy controls. After extracting DNA from feces, the V3-4 region of the 16S rRNA gene was amplified and measured by Illumina Miseq. QIIME and Lefse (Linear discriminant analysis effect size) were used for statistical analysis, and PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) was used to predict metagenome functional profile of microbial community based on marker genes. We determined the difference in relative abundance of each microbiota among the patients with HCC and non-HCC in patients with chronic liver diseases. Furthermore, we selected the key microbiota, it has gradually decreased relative abundance with significant difference in the following order; HCC > non-HCC > controls.
Results: Characteristics of the patients showed following results in chronic liver disease: male/female = 78/47, Child A/B/C = 98/23/3, among 82 patients with HCC, hepatitis C/hepatitis B/non B non C = 39/12/31, and there was no significant difference in alpha-diversity among patients with HCC and non-HCC. In patients with HCC, *Veillonella, Klebsiella, Pseudoramibacter Eubacterium, Enterococcus* were significantly increased and *Sutterella* was significantly decreased compared with patients with non-HCC ($p < 0.05$). *Veillonella* was selected as key microbiota at the genus level. Bacterial groups which have genes related to ketone body biosynthesis and degradation were increased in patients with HCC, and bacterial groups which have genes related to taurine degradation were decreased.
Conclusion: Increased oral indigenous bacteria such as *Veillonella* might be associated with the difference between patients with HCC and non-HCC.

FRI-271
Rifaximin alleviates endotoxemia with improved intestinal hyperpermeability with partially modified fecal microbiota in cirrhotic patients
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Background and aims: Rifaximin is a minimally absorbed antibiotic effective for hepatic encephalopathy (HE). However, the mechanism of how rifaximin affects HE remains unclear. In this study, we assessed the mechanistic effect of rifaximin on intestinal permeability and gut microbiota in patients with decompensated cirrhosis.
Methods: Thirty clinically stable patients with decompensated cirrhosis (Child-Pugh score > 7) were assessed by cognitive neuropsychological testing, endotoxin activity (EA), and serum proinflammatory cytokines at baseline and after 4 weeks of rifaximin treatment (400 mg thrice a day). Intestinal permeability was assessed by serum levels of soluble CD163 (sCD163), mannose receptor (sMR), and zonulin. Fecal microbiome was analyzed by 16S ribosomal RNA (rRNA) gene sequencing.
Results: Treatment with rifaximin improved hyperammonemia and cognitive impairment, and decreased EA. Rifaximin also lowered serum levels of sCD163 and sMR, but not zonulin. Decreases in sCD163 and sMR were positively correlated with EA decrease (ΔsCD163: $R = 0.680$, $p = 0.023$; ΔsMR: $R = 0.613$, $p = 0.014$, *vs* ΔEA). Rifaximin did not change the diversity or major components of the gut microbiome, although the relative abundance of *Veillonella* was reduced. Serum levels of proinflammatory cytokines were also unchanged.
Conclusions: Rifaximin alleviated HE and endotoxemia with improvement of intestinal hyperpermeability in patients with decompensated cirrhosis. This effect is partially associated with a minor change in bacterial composition, although further investigation is required to clarify other key mechanisms to preserve intestinal barrier function.

FRI-272
Identification of novel glycans that target gut microbiota-associated ammonia production
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Background and aims: The human gut microbiome impacts health and disease by affecting metabolism, nutrition, immune function, and other organ systems. The gut microbiome plays a significant role in the production and consumption of ammonia, which is central to the pathogenesis of hepatic encephalopathy (HE). Existing therapies, such as lactulose, reduce blood ammonia but are poorly tolerated. We sought to develop Microbiome Metabolic Therapies (MMTs) that include synthetic, novel oligosaccharide compositions (glycans) to reduce net ammonia production by the gut microbiome with good tolerability. Glycans are found in many food products, and many are Generally Recognized As Safe under US FDA regulation.
Method: Ex vivo screening of more than 200 glycans across healthy human microbiome samples identified glycans that reduced ammonia concentration to a variable degree. Ten glycans were further tested in an ex vivo assay with 19 fecal microbiome samples from hepatically impaired patients. One of the top-performing glycans was then evaluated in a placebo-controlled, randomized, double-blind clinical study in 47 healthy human subjects. Subjects were given a standard dose of lactose ^{15}N-ureide as a tracer for bacterial urease activity both at baseline and at the end of 21 days of oral administration of the test glycan or 1 of 3 comparator compounds. Total ^{15}N-nitrogen excretion in urine is indicative of hepatic exposure to ammonia produced by colonic gut bacteria. Assessment of GI tolerability included the Gastrointestinal Tolerability Questionnaire (GITQ), which assesses symptoms like flatulence and abdominal cramping, and the Bristol Stool Scale (BSS), which assesses stool consistency.
Results: One of the top-performing glycans in the ex vivo screen, KB195, reduced ammonia to levels equal to or less than lactulose in 74% (14/19) of the microbiome samples from hepatically impaired patients. In the clinical study, subjects showed a clinically relevant decrease in ^{15}N-nitrogen excretion after ingestion of KB195 vs the placebo control ($p = 0.002$). Tolerability of KB195 was comparable to that of placebo at all doses in both GITQ and BSS.
Conclusion: An ex vivo screening in human microbiome samples was effective in identifying an MMT that showed a clinically relevant reduction of gut-derived ammonia in a clinical study and was well tolerated. Future clinical studies aim to demonstrate improved management of patients with HE by reducing ammonia and targeting other unmet needs.

FRI-273
Intestinal microbiota signature related to hbeag seroconversion after oral antiviral therapy
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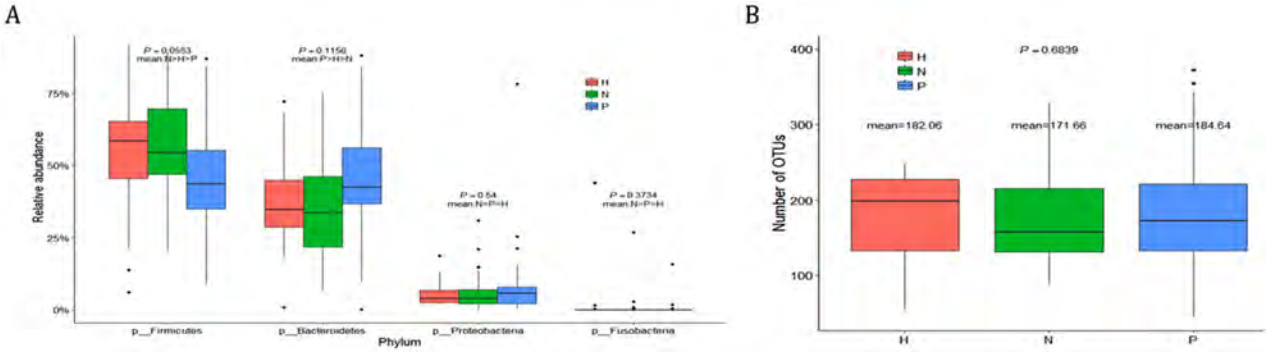

Fig. 1: (abstract: FRI-273): Taxonomic and diversity analysis of fecal microbiota in CHB patients with or without HBeAg seroconversion, and healthy subjects.

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Background and aims: The occurrence of hepatitis B e antigen (HBeAg) seroconversion is a landmark event indicating immune control on hepatitis B virus (HBV). Currently, there is limited knowledge regarding the association between the composition of intestinal microbiota and HBeAg seroconversion after oral antiviral therapy.
Method: In this cross-sectional study, we collected information on fecal microbiota from the patients with CHB who have oral antiviral therapy and evaluated whether these were associated with HBeAg seroconversion. Thirty-five of these subjects displayed HBeAg seroconversion in the first 3 years after the initiation of oral antiviral therapy, while the remaining 39 subjects remained HBeAg positive even after over 3 years of therapy. Samples were analyzed using 16S ribosomal DNA sequencing. The HBeAg and anti-HBeAg levels were measured for each subject, and the HBV DNA was measured by quantitative PCR.
Results: Using classical approaches, no differences were found between the microbiota from patients with and without HBeAg seroconversion. However, a computational statistical and machine learning approach allowed us to identify a microbial signature for HBeAg seroconversion, consisting of 47 bacterial operational taxonomic units. The microbial signature was able to discriminate patients who achieved HBeAg seroconversion from those who

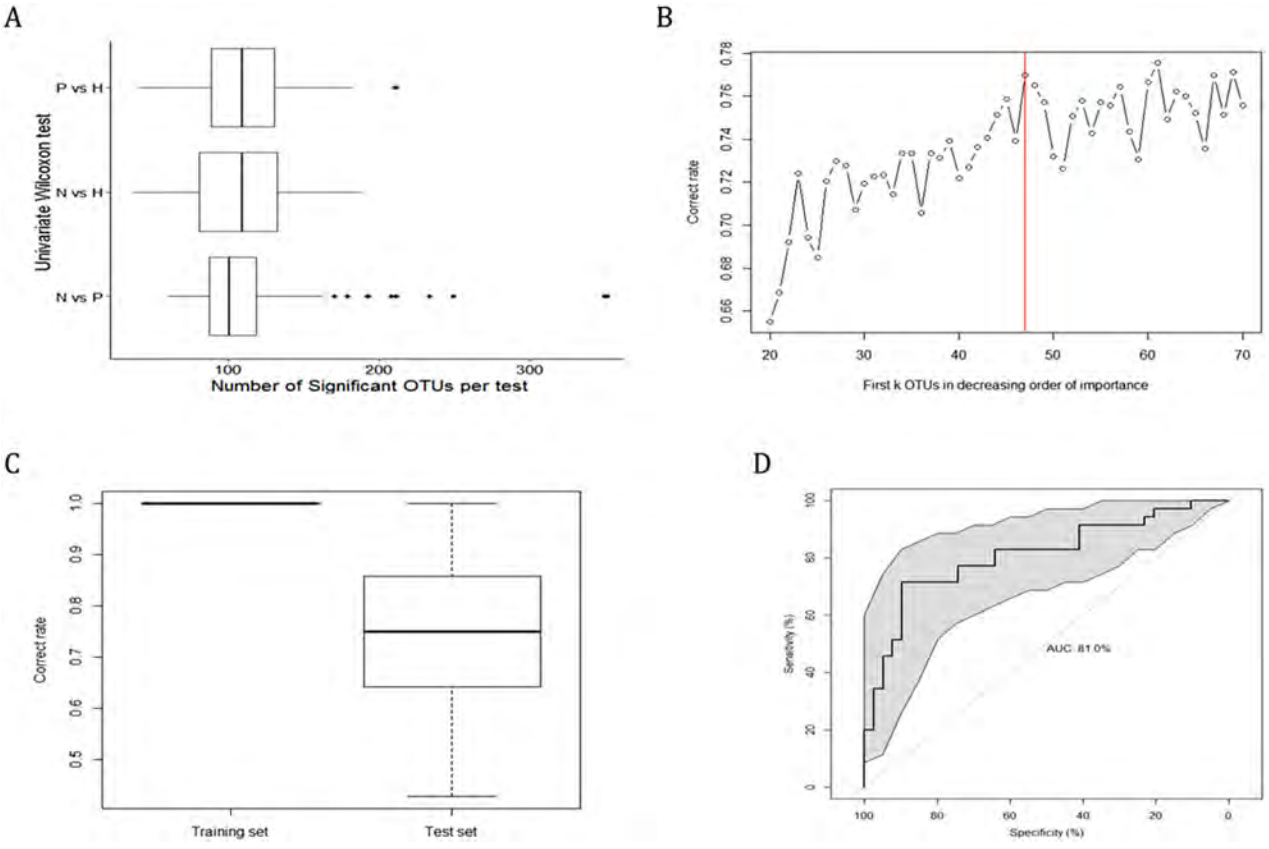

Fig. 2: (abstract: FRI-273): Univariate comparison and machine learning based on HBeAg seroconversion.

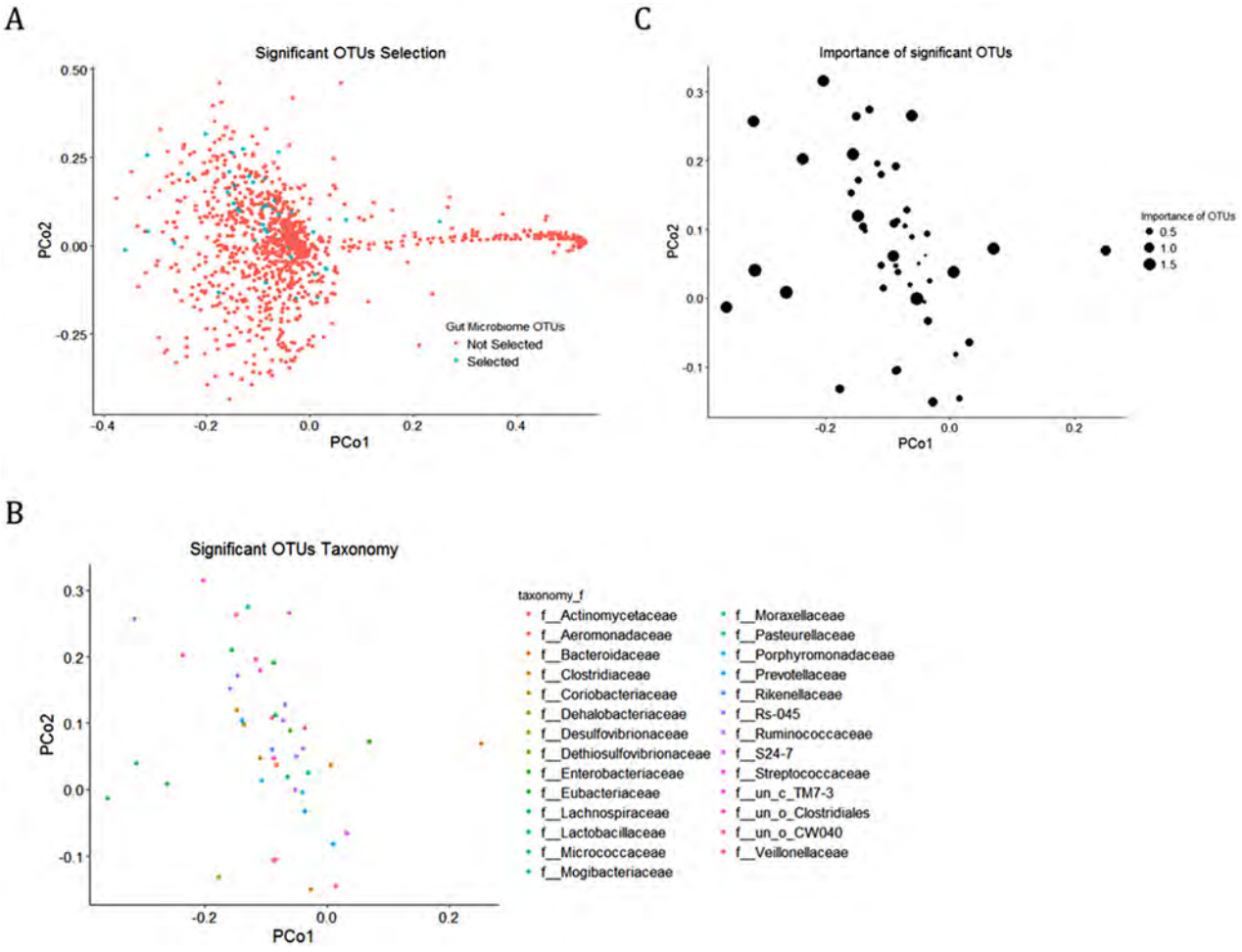

Fig. 3: (abstract: FRI-273): Taxonomic assessment of OTU microbiota signature for HBeAg seroconversion.

remained HBeAg-positive. Using random forest method, we further constructed a prediction model based on the gut microbial signature, with the area under curve being 0.81 for the test set. Based on our results, HBeAg seroconversion was found to be associated positively with AST, and several genera belonging to *TM7-3,* and *Actinomycetaceae* families.

Conclusion: By analyzing the fecal microbiota from the patients with and without HBeAg seroconversion, we identified intestinal microbiota signatures that is associated with HBeAg seroconversion after oral antiviral therapy.

FRI-274

Exercise modulates gut microbiota and intestinal barrier functionality counteracting early obesity and NAFLD in an in vivo model

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Background and aims: Childhood obesity has reached epidemic levels, representing one of the most serious public health concerns associated with metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and gut microbiota alterations. Physical exercise is known to counteract obesity and NAFLD progression and modulate gut microbial balance. We aim to evaluate the benefits of exercise on metabolic status, gut microbiota composition and intestinal barrier functionality in an *in vivo* model of early obesity and NAFLD.

Method: 21 days old male Wistar rats fed with control or high fat diet (HFD) were subjected to an interval aerobic training protocol. Fecal microbiota was sequenced by Illumina MiSeq system and parameters related to metabolic syndrome, fecal metabolome, including bile acids (BAs) profile, and gut-liver axis alteration were measured.

Results: Exercise decreased HFD-induced body weight gain, metabolic syndrome and hepatic steatosis, as a result of its lipid metabolism modulatory capacity. The microbiome and metabolome were substantially modified as a consequence of diet, age, and exercise intervention. Training protocol counterbalanced a subset of changes in microbial composition and functionality associated with early obesity and NAFLD, showing a modulatory effect on gut microbiota composition related to a specific metabolomic function that could counteracts dysbiosis caused by HFD. Thus, exercise triggered a microbiome and metabolome pattern similar to the control group, allowing to identify a bacterial genera profile associated with a specific metabolomic signature which correlated with clinical outcomes in our study. Moreover, exercise intervention also reduced TLR-4-dependent inflammatory response, downregulating NF-kappa B transcriptional activity induced by HFD. These effects of exercise appear to be mediated by its capacity to preserve

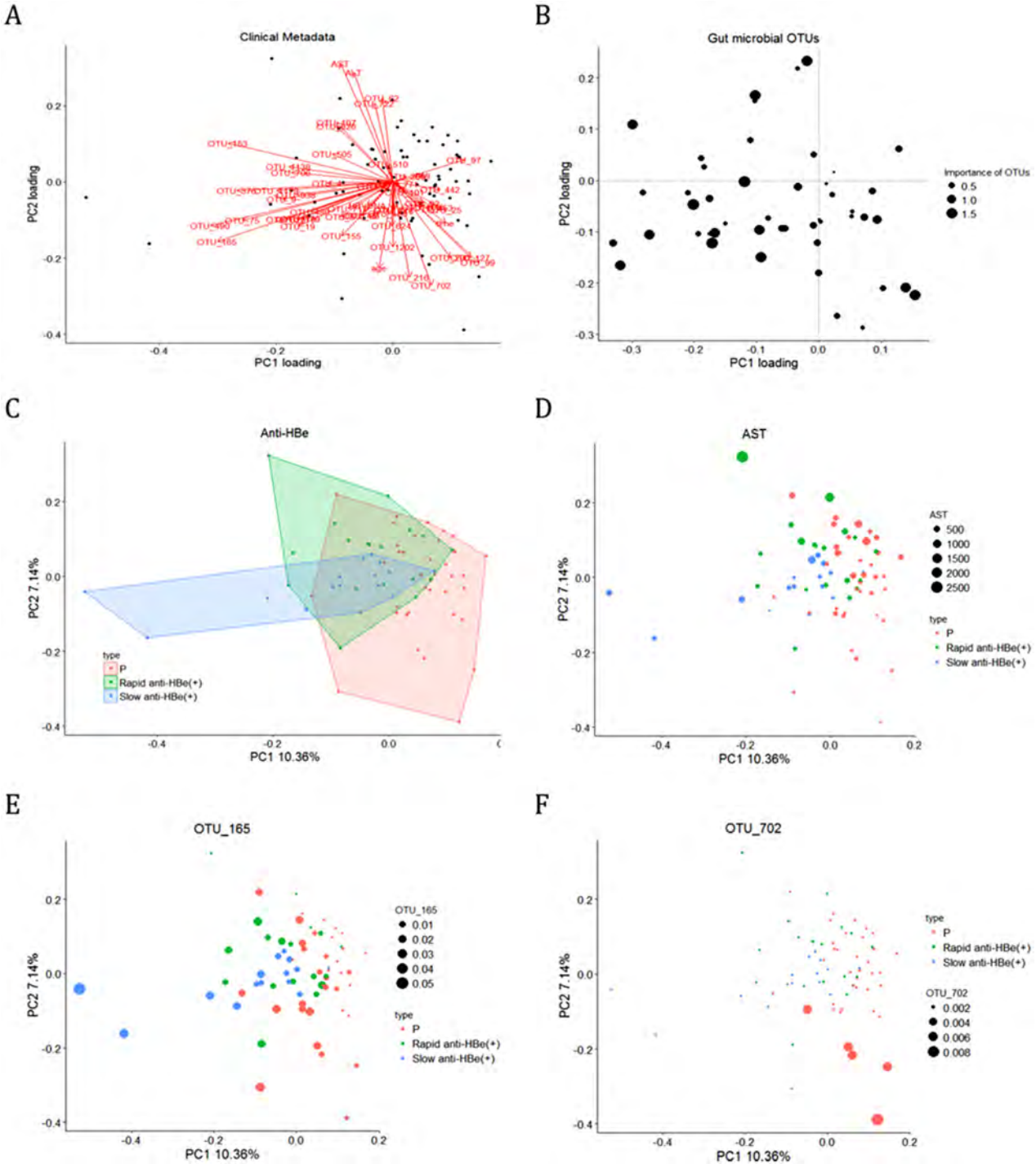

Fig. 4: (abstract: FRI-273): Interactions between clinical, microbial ecology parameter and microbial signatures for HBeAg seroconversion.

intestinal barrier functionality, which in turn prevented gut-liver axis deregulation and improved BAs homeostasis.

Conclusion: Our results suggest the existence of a HFD-determined deleterious microbiota profile that results positively modified by exercise intervention, leading to a functionally protective microbiome able to counterbalance altered gut-liver axis and BAs circulation.

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FRI-275

Fecal microbiota profiles as a diagnosis marker in PSC and PSC-IBD patients compare to healthy controls

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, strongly associated with inflammatory bowel disease (IBD). Neither the cause of PSC, nor the mechanisms by which PSC patients develop IBD are known. Previous studies found that the intestinal microbiota may play a role in disease pathogenesis. In this study, we explored the gut microbiome signature of PSC and PSC-IBD patients.
Method: In this study, patients with PSC (n = 17) or PSC-IBD (n = 18) and 30 healthy controls were recruited. Fecal samples were collected and analyzed using metagenomic methods based on 16 sRNA sequencing and bioinformatics analysis.
Results: Patients with PSC (with and without IBD) demonstrated a distinct microbiome signature as compared to healthy controls, including a significant decrease in bacterial quantity and diversity (Faith's PD p value = 1.211726e-08, unweighted Unifrac p value = 0.001). Significantly decreases in 261 species, alongside over-representation of 32 species was noted in patients with PSC as compared to controls. Patients with PSC demonstrated increased levels of Blautia (p value = 0.038) and Clostridium XlVa (p value = 0.0009). Patients with PSC-IBD showed a similar and significant decrease in bacterial quantity and diversity compared to controls (Observed OTU's p value = 3.9848E-07). Among patients with PSC, a significant decrease in bacterial quantity and diversity (Observed OTU's p value = 0.018) was documented in patients with FUT-2 secretor phenotype compared to non-secretor phenotype PSC. Moreover, patients treated with proton pump inhibitors, showed lower bacterial alpha diversity (p value = 0.038). Ursodeoxycholic acid had no significant effect on the microbiome of patients with PSC. In addition, a decrease in alpha diversity (p value = 0.0006) and an altered microbiome composition (p value = 0.004) were observed in smoking patients.
Conclusion: In this study, we observed significant alterations in the microbiome of patients with PSC and PSC-IBD compared to healthy controls. We observed a significant increase in Blautia and Clostridium XlVa, species that are correlated with significant decrease in bacterial amount and diversity. Moreover, PSC was characterized by dysbiosis (an increase in pathogenic bacteria and decreased levels of beneficial bacteria), with a stronger effect than the concomitant development of IBD. Many of the bacteria altered in PSC are pathogenic species, and associated with IBD. Our findings are expected to enhance our understanding of the specific microbial alterations in PSC, with and without IBD, and to advance the development of novel treatment strategies for PSC and PSC-IBD.

FRI-276

Effect of korean red ginseng on non-alcohlic steatohepatitis: Randomized controlled trial

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Background and aims: Korea Red Ginseng (KRG) has been known as a natural product with anti-inflammatory and hepatoprotective effect in liver disease. Gut microbiota plays an important roles in the pathophysiology of non-alcoholic statohepatitis (NASH). We evaluated the effect and mechanism of KRG on patients with NASH.
Method: Between January 2017 and April 2018, a total of 94 patients (KRG: 45 and placebo: 49) were prospectively randomized to receive the 30 days of KRG (2, 000 mg/day, ginsenoside Rg1+Rb1+Rg3 4.5 mg/g) or placebo. Liver function test, fatigue score, pro-inflammatory cytokines, lipopolysaccharide (LPS), and stool microbiome analysis by 16S rRNA-based sequencing were examined and compared after therapy.
Results: In KRG group, the mean levels of alanine aminotransferase (75.6 ± 40.7→65.3 ± 41.9 IU/L, P = 0.040), gamma glutamyl-transferase (95.1 ± 78.0→80.2 ± 69.9 IU/L, P = 0.004), and fatigue score (34.2 ± 14.2 → 26.0 ± 12.7, P < 0.001) were significantly improved after the administration of KRG. The decline of LPS was seen in both groups but it showed a big drop in red ginseng group (p < 0.05). Changes in microbiome in the stool were observed in the KRG group. KRG group showed a rise in *Firmicutes* and *Proteobacteria* in patients with increased alanine aminotrasferase level. Placebo group revealed contrary results. In patients with improved alanine aminotrasferase, *Firmicutes* and *Proteobacteria* in KRG group were decreased and *Actinobacteria* in placebo group was increased in the stool analysis
Conclusion: KRG might be effective in improving liver enzymes, endotoxin, and fatigue by modulating gut-microbiota in patients with NASH. KRG can be used as a next therapeutic option in patients with NASH.

FRI-277

Effect of probiotics in the treatment of NASH: A randomized clinical trial

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Background and aims: Same promising results in the improvement of NAFLD and NASH have been identified following the treatment with probiotics. The aim of this study was to evaluate the effect of probiotic supplementation on hepatic fibrosis, aminotransferases, systemic inflammatory markers, metabolic profile and microbiome composition in NASH patients.
Method: In a double-blind, placebo-controlled clinical trial, 43 NASH patients were randomized to receive probiotics (Lactobacillus acidophilus 1x109 CFU and Bifidobacterium lactis 1x109 CFU-Probiotic Group) or placebo (Placebo Group) for 6 months. Patients were evaluated at 0, 3 and 6 months, including BMI and laboratory tests (AST, ALT, HDL, LDL and total cholesterol, triglycerides, glucose, insulin, C-reactive protein, ferritin, interleukin-6, TNF-α, MCP-1 and leptin). Liver biopsy and/or Fibromax™ (non-invasive test to evaluate liver fibrosis), were performed at baseline and repeated after 6 months of treatment. Faecal DNA was extracted and 16S rRNA gene-based analysis was used to profile gut microbiota. Results are presented as medians.
Results: After 6 months of treatment, Probiotic Group presented a significant reduction in AST level (37.0 vs. 34.0 p = 0.012), APRI score (0.41 vs. 0.35 p = 0.042), C-reactive protein (6.6 vs. 4.5 p = 0.026) and ferritin (169.0 vs. 138.5 p = 0.008) compared to within group baseline values. Compared to within group baseline values, HDL (47.5 vs. 52.0 p = 0.020) and total cholesterol (186.0 vs. 205.0 p < 0.001) increased significantly in the Probiotic Group. There were no significant differences between groups after treatment.
Conclusion: This trial identified that NASH patients treated with probiotic supplementation presented reduced AST levels and APRI score and had some inflammatory and metabolic parameters improved. However, treated and untreated groups of NASH patients were not different at the end of the study in relation to main outcomes.

NAFLD: Experimental and pathophysiology

FRI-278

RIP3-dependent signalling exerts divergent effects on liver steatosis and carcinogenesis in experimental non-alcholic fatty liver disease

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Background and aims: Regulated necrosis or necroptosis was recently described as a novel cell death pathway activated downstream of death receptor stimulation and dependent on receptor-interacting protein 3 (RIP3) kinase activity. Although necroptosis has already been implicated in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), its specific contribution remains poorly explored. Here, we aimed to evaluate the impact of RIP3 signalling in steatosis, inflammation, fibrosis and carcinogenesis associated with experimental NAFLD.
Method: C57BL/6 wild-type (WT) or RIP3-deficient ($RIP3^{-/-}$) 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. Tissue samples were processed for histological and biochemical analysis of hepatic damage and carcinogenesis, insulin resistance and oxidative stress, and for lipidomic analysis.
Results: CDAA-fed WT mice exhibited all the typical histological features of liver injury associated with non-alcoholic steatohepatitis, including steatosis, hepatocellular ballooning, immune cell infiltration, and fibrosis, which became more prominent over time. RIP3 deficiency ameliorated CDAA-induced inflammation and fibrosis, and decreased the NAFLD activity score. In agreement, hepatic gene expression of pro-inflammatory mediators was also significantly decreased in CDAA-fed $RIP3^{-/-}$ mice, compared with WT, at both 32 and 66 weeks. Intriguingly, $RIP3^{-/-}$ mice displayed increased body weight gains, as well as increased liver fat accumulation at both time-points, compared with WT mice on the CSAA or CDAA diets. Lipidomic analysis showed that deletion of RIP3 shifted hepatic lipid species profiles, while increasing insulin resistance, as assessed by homeostasis model assessment-estimated insulin resistance, compared with WT mice on CSAA or CDAA diet. Concomitantly, insulin receptor phosphorylation in muscle tissue was decreased at 66 weeks. Finally, $RIP3^{-/-}$ mice on the CDAA diet for 66 weeks tended to display reduced incidence of macroscopic preneoplasic nodules, accompanied by significantly reduced Ki67 positive hepatocytes. Indeed, microarray analysis and subsequent validation studies showed that the absence of RIP3 hampered the expression of oncogenes and signalling pathways controlling tumour microenvironment.
Conclusion: Overall, hepatic RIP3 plays an opposing role in controlling steatosis versus inflammation and carcinogenesis in CDAA-fed mice, leading to dissociation between these phenomena that are usually considered linked in NAFLD.
Funding: PTDC/BIM-MEC/0895/2014; SAICTPAC/0019/2015 from FCT, Portugal.

FRI-279

Stat2 is a pathogenic factor in human non-alcoholic steatohepatitis and mouse models of liver injury and mediates fatty acid-induced Inflammasome activation in hepatocytes

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Background and aims: Inflammation and liver cell injury drive the progression of non-alcoholic steatohepatitis (NASH) and lead to liver fibrosis. We have previously reported that loss of Stat2 is protective from LPS-induced NF-kB-mediated inflammatory cytokine production in mice. We hypothesised that Stat2 is a pathogenic factor in the response to liver injury in NASH. We tested this hypothesis using liver tissue from NASH patients, mouse models of liver injury, RNA sequencing of primary hepatocytes and siRNA-mediated knockdown in human liver cells.
Method: Expression of Stat2 in NASH and normal liver was assessed by immunohistochemistry. In vivo effects of stat2 loss on liver injury and inflammation were assessed using carbon tetrachloride (CCl_4)-induced liver injury in wild type, $Stat2^{-/-}$ mice. RNA sequencing was used to assess the global transcriptomic effects of Stat2 on inflammation in primary hepatocytes isolated from wild-type (WT) or $Stat2^{-/-}$ mice. Silencer RNA was used to knockdown Stat2 in the HepG2 human liver cell line prior to treatment with a 2:1 oleate: palmitate fatty acid mixture.
Results: Hepatocyte nuclear expression of Stat2 was significantly greater in NASH (n = 39) compared to normal liver (98% vs 35%, p < 0.0001). Similarly, Stat2 expression increased in WT liver tissue following treatment with CCl_4 and $Stat2^{-/-}$ mice were protected from CCl_4-mediated liver injury with reduced histological inflammation and necrosis, serum ALT (2165 vs 1090 iU/ml, p = 0.03) and IL-6 levels (562 vs 38 pg/ml p = 0.02). To model the Stat2-mediated inflammatory response, primary WT and $Stat2^{-/-}$ hepatocytes were treated with LPS and global gene expression was assessed by RNAseq. We found significant differences in genes involved in intracellular signal transduction, inflammation and metabolism. We found significant reduction in the production of secreted cytokines and chemokines (IL-6, IL-10, CCL3, CCL5, CXCL2, CXCL10) from $Stat2^{-/-}$ hepatocytes. Knockdown of Stat2 in HepG2 cells by two different siRNAs prior to fatty acid-induced injury resulted in inhibition of inflammasome activation; caspase-1 (by western blot) and IL1beta mRNA levels (7.4-fold, p < 0.0001) and reduced IL8 production (2-fold, p = 0.0002).
Conclusion: Stat2 is a pivotal mediator of inflammation and hepatic damage. Stat2 loss leads to reduced hepatocyte injury, inflammatory signalling and inflammasome activation, suggesting that Stat2 or a downstream mediator may be a therapeutic target in human NASH.

FRI-280

Common dietary component, wheat amylase trypsin inhibitors, driver of chronic liver disease in pre-clinical models of NASH and liver fibrosis

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Background and aims: The gut-liver-axis has emerged an important driver of chronic liver disease. Accordingly, specific food derived immunogenic signals may be important contributors to non-alcoholic fatty liver disease (NAFLD) and liver fibrosis. A common immunogenic component in food are wheat amylase trypsin inhibitors (ATI) that resist intestinal degradation and activate intestinal macrophages and dendritic cells via toll like receptor 4. Once activated in the gut, these cells migrate to the peripheral organs such as liver to propagate the inflammatory stimulus. We therefore studied how far nutritional ATI would affect NAFLD and liver fibrosis in preclinical models.
Methods: Male C57Bl/6J mice received a carbohydrate and protein (zein from corn) defined low fat or high fat diet (HFD), with or without 30% of the protein being replaced by wheat gluten (G, naturally containing 0.15g ATI per 10g), or 0.7% of the replaced by purified ATI for 8 weeks. Male Mdr2−/− FVB mice were fed defined,

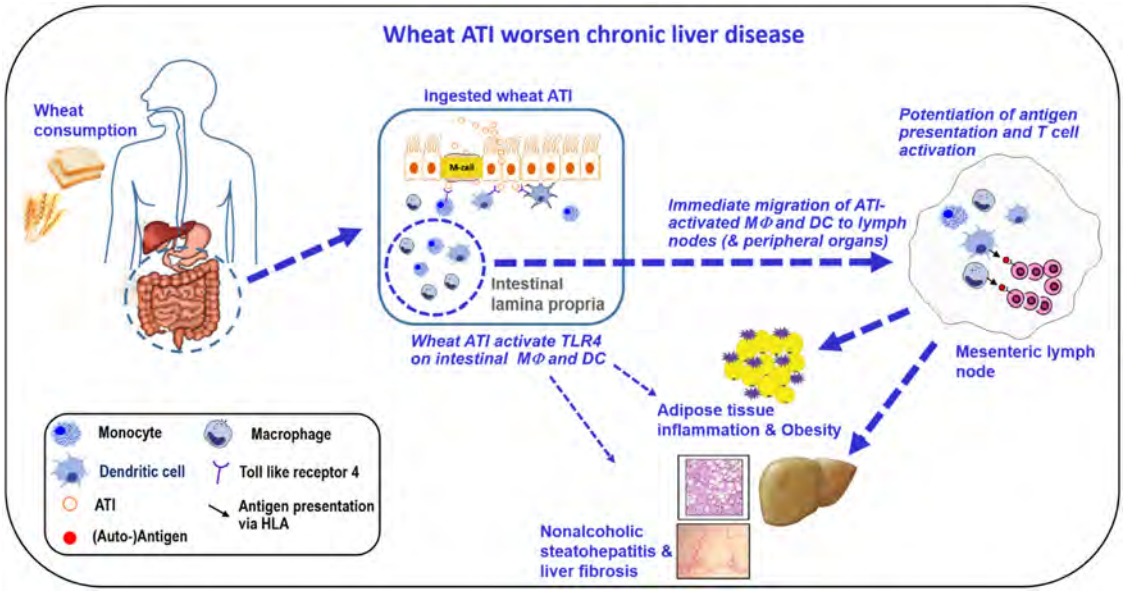

Figure: (abstract: FRI-280)

ATI containing and ATI free diets for 6 weeks. In the NASH model, insulin resistance (IR) was assessed test.

Results: Mice on the HFD gained weight and developed insulin resistance (IR) as determined by an intraperitoneal glucose tolerance test. Compared to the HFD alone, mice fed the HFD/G/ATI or the HFD/ATI diets gained significantly more weight and displayed significantly higher serum transaminases and triglycerides, increased liver, epididymal, mesenteric and inguinal fat, and a higher IR. ATI feeding promoted liver and adipose tissue inflammation, M1 macrophage polarization and infiltration, and enhanced the fibrogenic response in the liver. Moreover, there were significant increases in hepatic CD68+ macrophages, CD86+ dendritic cells and MHC-II+ cells in the distal part of the intestine of HFD/ATI compared to HFD diet fed mice. In biliary fibrotic Mdr2−/− mice, transaminases and liver weights in the ATI fed group were significantly increased compared to the ATI free group. Overall, liver transcripts for il1b, tnf-a, cd68, col1a1, a-sma and col3a1, mmp9, mmp13 and timp1 were significantly upregulated in the ATI fed vs ATI free groups. Moreover, in Mdr2−/− mice ATI feeding increased ductular reactions, hepatic CD68+ macrophage infiltration, and accelerated fibrosis progression as evidenced by a higher collagen deposition (Sirius red morphometry) and alpha-SMA+ myofibroblasts.

Conclusions: When ingested in quantities comparable to average human consumption, wheat ATI exacerbate the key features of rodent NAFLD and the metabolic syndrome despite their irrelevant caloric value. Moreover, dietary ATI promote liver fibrosis in the NASH and the Mdr2KO mouse model of PSC. The postulated mechanism is outlined in **Fig.1.**

FRI-281

IL-4 receptor alpha knock-out mice are protected against fibrotic NASH in a representative mouse model of non-alcoholic steatohepatitis

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Hepatic macrophages derive from resident phagocytes (Kupffer cells) or circulating monocytes (monocyte derived macrophages). They critically modulate fibrosis progression or regression depending on disease aetiology and stage, especially in NAFLD/NASH where massive proinflammatory macrophages recruitment to the liver can occur. It was reported that elevated serum levels of IL-4 and IL-13 correlate with the severity of liver fibrosis (F3-F4 > F0-F1) in NASH patients. IL-4 and IL-13 signal via two different but overlapping receptors having the IL-4 receptor alpha (IL-4Ra) as common subunit. We therefore studied mice with IL-4Ra deletion in a representative mouse model of NASH.

Methods: Male Balb/C wild type, IL-4Ra$^{-/-}$ and macrophage-specific deleted (LysM^{cre}IL-4Ra$^{-/lox}$) mice and their respective littermate controls (bearing either only the Cre or the floxed genes) were fed a choline-deficient, L-amino acid-defined (CDAA) vs a choline supplemented (CSAA) diet for 12 weeks.

Results: Both KO strains displayed a significant decrease in liver weights compare to their respective wild type controls upon CDAA diet feeding. This was accompanied by reduced NASH activity as evidenced by the NAS score (adapted for mice) in both IL-4R$^{-/-}$ and LysM^{cre}IL-4Rα$^{-/lox}$ mice vs their wildtype controls. CD68^{+} macrophages, MPO^{+} neutrophil inflammatory foci, infiltration by inflammatory monocytes (CD11b^{+}F4/80^{-}Ly6G^{-}Ly6c^{high}) were significantly decreased in the livers of the IL-4Ra KO mice. Based on Sirius Red morphometry, the fibrosis score was > 2 in the wildtype mice and reduced to < 1 in both KO strains. Accordingly, hydroxyproline content and the number of alpha-SMA+ myofibroblasts was significantly and comparably mitigated in both IL-4Ra deficient strains. This was paralleled by significantly suppressed hepatic transcript levels for col1a1, tgfb, mmp9 and tnfa.

Conclusion 1. General ablation of the IL-4Ra or its selective ablation in macrophages comparably suppressed steatosis, inflammation and fibrosis in the CDAA model of NASH; 2. IL-4Ra targeted therapies are a novel treatment option for fibrotic NASH and may be superior to therapies that block IL-4 and IL-13 cytokines.

FRI-282

Effect of the farnesoid X receptor agonist, obeticholic acid, in hepatocellular carcinoma: Is it NASH-dependent or -independent?

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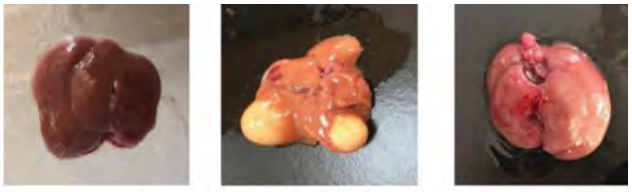
Background and aims: Non-alcoholic steatohepatitis (NASH) has now become the second leading cause of hepatocellular carcinoma (HCC) making liver transplantation a compelling demand. Unlike other liver disorders, NASH-associated HCC (NASH-HCC) was not recognized until recently. Besides the identified multifaceted effects of the nuclear farnesoid X receptor (FXR) on metabolic disorders, it was also identified as a tumour suppressor acting as an intriguing bridge between metabolic regulation and carcinogenesis. Herein, the present study aimed at investigating the potential effect of obeticholic acid (OCA), a potent FXR agonist FDA-approved drug for primary biliary cholangitis, in two different etiology-based HCC animal models among which is NASH-HCC.

Method: Two animal models were used: (1) NASH-HCC induced by diethyl nitrosamine (DEN) and a high-fat choline-deficient diet (HFCD) [DEN+HFCD] and (2) HCC induced by DEN and carbon tetrachloride (CCl_4) [DEN+CCl_4]. In [DEN+HFCD], three-week-old male mice received a one-time i.p. injection of 25 mg/kg DEN and was kept on a HFCD diet during the entire experimental period. However, in [DEN+CCl_4], mice received a one-time i.p. injection of 1 mg/kg DEN and starting 8 weeks of age, they received a twice per week i.p. injections of 0.2 ml/kg CCl_4 till the end of experiment. OCA (10 mg/kg/day, p.o.) was started after 20 weeks of induction for a duration of 8 weeks for [DEN+HFCD] model and 12 weeks for [DEN+CCl_4] model. Histopathological and immunohistochemical analyses of liver sections against alpha fetoprotein (AFP), caspase-3, and signal transducer and activator of transcription-3 (STAT3) were performed. Tissue adiponectin, transforming growth factor (TGF)-beta1, and interferon (IFN)-gamma were determined by ELISA. Tissue FXR, small heterodimer partner (SHP), p53, AFP, and TGF-beta1 gene expression was determined using qRT-PCR.

Results: Gross appearance of mice livers showed nodules in control and not in treated groups. OCA showed significant amelioration in dysplastic foci compared to control groups of both models. IFN-gamma, TGF-beta1, AFP, and STAT3 levels were lower in treated groups. Meanwhile, caspase-3 and adiponectin were higher in treated groups compared to their respective controls. Moreover, OCA treatment showed elevation in FXR, SHP, and p53 gene expression levels.



Conclusion: Activation of FXR by OCA attenuated the development and progression of both NASH-dependent and -independent HCC which may suggest its potential use to prevent NASH progression to HCC besides a potential towards treatment of HCC patients independent of NASH.

FRI-283

Impact on NAFLD of long-term weight loss after bariatric surgery

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a common characteristic of morbid obese patients, both diabetic (T2D) and non-diabetic (ND). Roux-en-Y Gastric Bypass (RYGB) leads to significant weight loss, improvement in metabolic profile and has been indicated as a possible treatment of NAFLD. Our aim was to evaluate presence of NAFLD 7 years after RYGB and significant weight loss.

Method: : The cohort comprised 21 subjects (11 T2D and 10 ND; BMI 50.2 ± 2.5 and 48.3 ± 2.3 kg/m^2) that were studied before RYGB and again after 7years with meal tolerance test (MTT) and the infusion of stable isotope tracers to measure glucose and lipid metabolism, hormone profile, endogenous glucose production (EGP), lipolysis (RaGlycerol) and insulin resistance (IR) in liver (Hep-IR = EGPxIns) and adipose tissue (Lipo-IR = RaGlycerolxIns). Magnetic resonance imaging (MRI) was performed to evaluate hepatic triglyceride accumulation (HTG), visceral (VF) and subcutaneous fat (SC). Imaging data were compared with Fatty Liver Index (FLI).

Results: At baseline the group included 11 T2D and 10 ND. Seven years after RYGB, all subjects were ND, and N = 7 were no NAFLD (HTG < 5.5%), N = 7 had moderate NAFLD (HTG 5.5–20%) and N = 7 severe NAFLD (HTG > 20%), despite similar distribution of T2D and BMI at baseline.

Subjects with no-NAFLD were the ones with higher weight loss (37% of original weight vs 35% in moderate and 26% severe NAFLD) reaching a BMI of 29.2 ± 0.9 vs 32.1 ± 2.0, 36.7 ± 2.0 in the other 2 groups. Moreover, across the 3 group there was a significant increase in VF (44.10 ± 15.4 76.7 ± 26.5; 106.1 ± 18.4 cm^2) and SC (184.2 ± 27.8; 339.2 ± 27.9; 354.9 ± 43.1 cm^2). VF and SC were correlated with HTG (r = 0.60 for VF and 0.68 for SC, p < 0.006) and BMI (r = 0.63 for VF and 0.62 for SC, p < 0.003). We observed a significant reduction in Hep-IR and Lipo-IR, ALT, AST and GGT and lipid profile with normalization of high values. No NAFLD showed lowest values of Hep-IR and Lipo-IR, due to a strong correlation between HTG with Hep-IR (r = 0.53; p = 0.002;) and Lipo-IR (r = 0.62; p = 0.008).

HTG at 7y was significantly associated with BMI (r = 0.63, p < 0.005), amount of weight loss (r = -0.48 p = 0.03). and FLI (r = 0.79; p = 0.0007).

Conclusion: Despite significant weight loss (> 25%) and resolution of T2D, 7y after RYGB only 30% of studied subjects had HTG within the normal ranges. Presence of NAFLD at 7y was associated with persistence, although decreased, insulin resistance both at the level of the liver and adipose tissue.

FRI-284

A combination of fenofibrate with a liver-targeted acetyl-CoA carboxylase inhibitor enhances efficacy while reversing plasma triglyceride increases in a murine model of NASH

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Background and aims: Acetyl-CoA Carboxylase (ACC) 1 and 2 catalyze the rate-limiting step in de novo lipogenesis (DNL) and

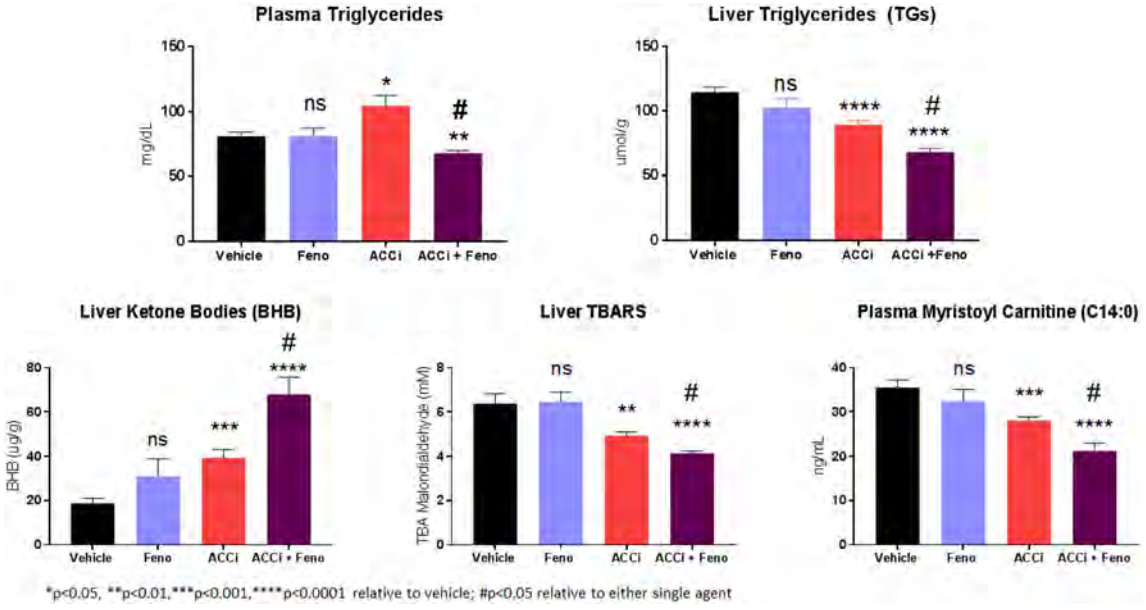

Figure: (abstract: FRI-284)

inhibit mitochondrial beta-oxidation, respectively. GS-0976, a liver-targeted ACC1/2 inhibitor, is in clinical development for NASH. In patients with NASH, GS-0976 reduces hepatic steatosis and liver biochemistry, but may increase plasma triglycerides (TGs), particularly in patients with pre-existing hypertriglyceridemia. We and others have shown repression of PPAR-alpha transcripts with ACC inhibition, which could contribute to the increased plasma TGs. A clinical study evaluating the safety of co-administration of fenofibrate, an approved PPAR-alpha agonist, with GS-0976 is ongoing. The aim of this study was to evaluate the preclinical efficacy of the combination in a murine model of NASH.

Method: Male C57BL/6 mice were administered a fast food diet (FFD) enriched in fat, cholesterol, and sugar for 9 months and were then treated with either vehicle, a liver-targeted ACCi inhibitor at 5 mg/kg PO QD (ACCi), fenofibrate at 50 mg/kg PO QD (Feno), or both, for 15 days (n = 11-14 per treatment). End points include hepatic TGs by a biochemical colorimetric assay, hepatic beta-hydoxybutyryl-CoA (BHB) and plasma acylcarnitines by quantitative LC/MS/MS, and lipid peroxidation by TBARS, and plasma TGs.

Results: Hepatic BHB, a measure of beta-oxidation, increased with fenofibrate (64%, ns) and was significantly increased with ACCi relative to vehicle (105%, $p < 0.001$). The combination significantly increased BHB relative to vehicle (260%, $p < 0.0001$) and relative to the levels of either single agent ($p < 0.01$). Conversely, hepatic TGs, plasma myristoyl carnitine levels (C14:0), and lipid peroxidation were non-significantly reduced with fenofibrate, significantly reduced with ACCi (22%, 21% and 23%, respectively, $p < 0.01$), and significantly reduced with the combination relative to vehicle (40%, 40% and 35%, respectively, $p < 0.0001$) and either single agent ($p < 0.05$). Plasma TGs were significantly increased with ACCi (30%, $p < 0.05$), not changed by fenofibrate, and decreased below baseline with the combination (16% inhibition, $p < 0.01$).

Conclusion: The addition of fenofibrate to an ACCi improved efficacy and reversed the increase in plasma TGs observed with ACC inhibition. These data support further investigation of fenofibrate in combination with GS-0976 in patients with NASH and hypertriglyceridemia.

FRI-285

The benchmarks obeticholic acid and elafibranor show variable effects on NASH and hepatic fibrosis in diet-induced or chemically-induced animal models

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Background and aims: To select relevant NASH and hepatic fibrosis models for drug efficacy studies, we here evaluated the curative effects of the benchmarks obeticholic acid (OCA, an FXR agonist) and elafibranor (GFT505, a PPARalpha/delta dual agonist) in various preclinical models.

Method: For each model, blood and liver were collected for biochemistry, liver histology and NAS scoring at the end of the treatment period to evaluate drug efficacy.

Results: Concomitant with a severe body weight loss, methionine choline deficient (MCD) diet for 4 weeks in mice resulted in liver steatosis, inflammation and perisinusoidal (stage 1) to periportal (stage 2) fibrosis. While OCA markedly increased plasma ALT/AST levels and only reduced steatosis, GFT505 strongly reduced ALT/AST and NAS score.

Diet-Induced NASH (DIN) using a 25-week high fat/cholesterol/fructose diet in mice, resulted in strong liver steatosis, limited inflammation and stage 1 to stage 2 fibrosis. In this obese and insulin resistant mouse model, both OCA and GFT505 significantly improved ALT/AST levels and NAS scoring. However, OCA better reduced fibrosis, but unlike humans, reduced LDL-cholesterol by 45% ($p < 0.001$ vs. vehicle)

DIN hamsters also developed obesity and insulin resistance, strong liver steatosis with evident inflammation and hepatocyte ballooning, and peri-portal to bridging fibrosis (stage 3). GFT505 reduced plasma ALT by 52% ($p < 0.01$ vs. vehicle) and significantly improved total NAS score, including fibrosis score (21% lower, $p < 0.01$ vs. vehicle). In this DIN hamster model, OCA showed limited benefits on NASH with concomitant dyslipidemic side effects, similar to humans (higher plasma LDL-cholesterol and lower HDL-cholesterol).

Thioacetamide intoxication for 13 weeks in rats induced stage 3 fibrosis, but both OCA and GFT505 failed to improve liver lesions.

Carbon tetrachloride intoxication for 4 weeks also resulted in stage 3 fibrosis in mice. Both OCA and GFT505 significantly reduced % Sirius

Red labelling in the liver, but GFT505 showed a more pronounced effect and was the only drug to reduce fibrosis score significantly (33% lower, $p < 0.001$ vs. vehicle).
Conclusion: OCA and GFT505 show variable effects in NASH and hepatic fibrosis animal models. Depending on the context and drugs mechanisms of action, the characteristics of each preclinical model have to be carefully considered, to better translate drug efficacy data to humans.

FRI-286
Integrated transcriptomic analysis of human NASH livers, rodent models and hepatic stellate cells reveals molecular mechanisms underlying ASK1-mediated hepatic fibrosis

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Background and aims: Apoptosis signal-regulating kinase 1 (ASK1) is a redox-sensitive protein kinase that promotes phosphorylation of JNK and p38 MAPK leading to hepatocyte apoptosis, inflammation, and fibrosis. Treatment with the ASK1 inhibitor selonsertib (SEL) was recently shown to reduce liver fibrosis in patients with NASH. Defining the mechanisms by which ASK1 promotes fibrogenesis is of clinical interest given that liver fibrosis is an important determinant of clinical outcome and mortality in NASH. We used a translational research approach to identify ASK1-dependent genes that are concordantly modulated in hepatic stellate cells (HSCs), in rodent models of NASH and in human NASH livers.
Method: HSCs (LX-2 cells) were transfected for 24 hours with an adenoviral construct containing human ASK1 in the absence or presence of SEL, then subjected to RNAseq to delineate differentially expressed genes (fold change > 2 compared to control, $p < 0.05$). These data were then integrated with liver RNASeq data from two rodent NASH models in which ASK1 inhibition was shown to reduce liver fibrosis (choline-deficient high-fat diet in rat and fast food diet in mice), and with liver RNAseq data from patients with NASH (comparison of F1 vs. F4 stages of fibrosis). The effects of ASK1 inhibition on HSC migration were evaluated by transwell chamber and gap-closure migration assays, and by confocal microscopy.
Results: Integrated analysis of RNASeq data sets revealed a 31-gene signature modulated by ASK1 activity in HSCs and in rodent NASH livers, which was concordantly dysregulated in human NASH livers at F4 stage. ASK1 activity significantly increased expression of multiple genes involved in cell migration, adhesion, and motility. For example, ASK1 activity concordantly upregulated the expression of CD44 and fibroblast growth factor-inducible 14 (Fn14), which are expressed on HSCs, promote cell migration, and have a causal role in liver fibrosis. SEL dose-dependently reduced HSC migration induced by either TGF-beta or PDGF-bb, and reduced the formation of lamellipodial protrusions, demonstrating a functional role for ASK1 in promoting cytokine-induced HSC migration.
Conclusion: Using a translational approach, we identified an ASK1-dependent hepatic gene signature in NASH and revealed cytokine-induced HSC migration as a novel fibrogenic mechanism mediated by ASK1. These data provide mechanistic insight into the anti-fibrotic effect of SEL in patients with NASH.

FRI-288
Physiological levels of cardiotrophin-1 (CT-1) contribute to fasting-induced free fatty acid mobilization

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Background and aims: It is becoming clear that several human liver-related pathologies are caused by altered adipose tissue expansion and altered lipid metabolism. Cardiotrophin-1 (CT-1) is a member of the interleukin-6 (IL-6) family of cytokines. CT-1 is a nutritionally regulated metabolic gene with a key role in glucose and lipid metabolism and is expressed in several metabolic tissues such as white adipose tissue (WAT), skeletal muscle and liver. We have previously reported that CT-1 is induced after 48 hours fasting. Here, we aimed at analysing the role of CT-1 in fasting, a physiological stress that elicits well-known metabolic adaptations.
Method: A differential study was carried out with wild-type (WT) and CT-1 deficient mice in fed and fast conditions (24 and 48 hours). White adipose tissue (WAT), liver and skeletal muscle were examined. Biochemical data (glucose, free fatty acid and ketone bodies) were determined. Analysis of proteins was studied by Western-blot, mRNA levels were quantified by real-time PCR and histological studies were performed with HandE and oil-red staining. Adipocyte size was quantified using the software adiposoft.
Results: We observed that CT-1 mRNA was upregulated in WAT, liver and skeletal muscle upon fasting. By nutrient deprivation (24 and 48 hours), CT-1 knock-out mice exhibited less weight loss than WT animals, higher WAT mass with bigger adipocytes than WT. Physiological levels of CT-1 controlled lipid catabolism in WAT via induction of hormone sensitive lipase (HSL) phosphorylation, induction of lysosomal acid lipase (Lipa), autophagy and fatty acid oxidation. Concomitantly, circulating free fatty acids and levels of ketone bodies were significantly decreased in CT-1 null mice. The defective adaptation to fasting of young CT-1 null mice was associated with decreased lipid droplet accumulation and enhanced autophagy in the fasted livers.
Conclusion: We conclude that CT-1 plays a relevant role in fasting adaptation through the regulation of lipid metabolism. Physiological levels of CT-1 contribute to fasting-induced free fatty acid mobilization.

FRI-289
Effect of MSDC-0602K treatment on the metabolome of a diet-induced murine model

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Background and aims: MSDC-0602K is a second-generation thiazolidinedione (TZD) designed to selectively modulate the mitochondrial pyruvate carrier (MPC), which conducts pyruvate across the mitochondrial inner membrane to the matrix. MSDC-0602K is currently being evaluated in a 52-week, phase 2b dose-ranging clinical trial in subjects with biopsy-proven NASH. (EMMINENCE trial, NCT02784444). This study sought to characterize the changes of MSDC-0602K in the hepatic metabolome of a dietary mice model of NASH, and to determine potential circulating biomarkers that reflected the therapeutic effect on the liver.
Method: Male DIAMOND™ mice received either high fat sugar water diet (WDSW) or chow diet normal water (CDNW) for 24 wks. Mice on WDSW were randomized to MSDC-0602K (30 mg/kg/day) or Vehicle (VC) and gavaged QD from 16-24 wks ($n = 10$/group), and results were compared to baseline WDSW positive controls (baseline PC, $n = 5$) and 24-wks CDNW negative natural history controls (NC, $n = 5$). Metabolites were extracted from snap-frozen liver and serum samples and analyzed via ultra-high performance liquid chromatography coupled to mass spectrometry (UHPLC-MS).
Results: Relative to VC, histological improvement in ballooning occurred in mice treated with MSDC-0602K without changes in steatosis. However, triglyceride profile in the hepatic tissue was significant altered by the treatment, being changes dependent on the esterified acyl chains. While saturated and monounsaturated species decreased in MSDC-0602K group (vs. VC), polyunsaturated species

increased. Similarly, there was a significant decrease in saturated diglycerides in the treated group compared to VC group. MSDC-0602K also significantly lowered the levels of ceramides and lysophosphatidylcholines, species previously associated with hepatic lipotoxicity and NASH progression. Several metabolites significantly altered by MSDC-0602K in the liver were also lowered in serum samples (vs. VC). This is relevant, since serum and not liver should be the base for the non-invasive identification of human NASH responders to this treatment. Among them, several polyunsaturated fatty acids, triglycerides and lysophosphatidylcholines.
Conclusion: Administration of MSDC-0602K regulated the levels of triglycerides in the liver, reducing saturated and increasing polyunsaturated species, and reduced the levels of lipotoxic species. The results also revealed metabolites that are specifically altered by MSDC-0602K and that may be used as non-invasive biomarkers reflecting its therapeutic effect on the liver.

FRI-290

The role of bile acids profile and insulin reistance for the prediction of gallstone disease in a prospective cohort of blood donors

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Background and aims: Bile acids (BAs) play an important role in lipid and glucose homeostasis. The aim of this study is to evaluate the association between the single and total BAs' profile and the presence of gallstone disease (GD) in a large blood donor population.
Method: This is a prospective study (SOLENNE), in which 280 blood donors were consecutively enrolled. Subjects with previous cholecystectomy, overt gastrointestinal disease or assuming drugs were excluded. Routine laboratory tests, BA fraction quantification by high-performance liquid chromatography-mass spectrometry (HPLC-MC), as well as abdominal ultrasound (US), were performed for each patient. The HOMA-Index was calculated for each patient in order to assess insulin sensitivity. A propensity score was calculated and used as a co-variate at uni- and multivariate analysis, in order to adjust per known confounding factors (age, sex, Body Mass Index [BMI]). The study was approved by local ethical committee.

Table Legend: Predictors of gallbladder disease presence at ultrasound in healthy blood donors.

	Univariate analysis		Multivariate analysis	
	OR (95% IC)	p value	OR (95% IC)	p value
G-DCA	4.330(1.636-11.465)	0.003	3.942(1.443-10.773)	0.007
T-DCA	60.477(2.756-1327.281)	0.004		
HOMA-Index > 2	3.047(1.175-7.902)	0.022	1.443(1.012-7.015)	0.047
HOMA-Index > 2.5	2.5800.9781-6.807)	0.056		

#Adjusted for propensity score including: age, sex, BMI.

Results: Out of the 280 subjects included in the final analysis, GD was found in 20 (7.1%) of them. Subjects with GD were older and presented higher BMI, glucose levels and IR prevalence, when confronted to subjects without GD disease. Levels of tauro (T)- and glyco (G)-deoxycholic acid (DCA) were also significantly higher in the GD group ($p = 0.0018$ and $p = 0.007$, respectively); their association with GD presence was found significant at univariate analysis. At the multivariate analysis adjusted for the propensity score, G-DCA (OR, 3.942, 95%IC, 1.443-10.773) and insulin-resistance (IR) (OR, 1.433, 95% IC 1.012-7.015) were independent predictors of GD presence ( ). When stratified by G-DCA level's terciles, GD and IR prevalence progressively increased, and IR was independently associated with GD only in patients with higher levels of G-DCA (3rd tercile).
Conclusion: G-DCA is independently associated with presence of GD, and therefore could play a crucial role in the pathogenesis of gallstone formation. IR could play a role in the development of GD, especially in patients with higher levels of G-DCA.

FRI-291

Glucokinase sensitizes hepatocarcinoma cells to the lipogenic activity of fructose and controls accumulation of lipid droplets and secretion of triglyceride-rich lipoproteins

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Background and aims: Human hepatocarcinoma cell lines are in vitro models for the study of lipid metabolism, hepatic steatosis and carcinogenesis. However, these cells have an unbalanced lipid metabolism that is strongly dependent on exogenous fatty acids to synthesize triglycerides and lipoproteins. This motivates the need for a physiologically relevant hepatocyte *in vitro* model allowing a deep analysis of the cellular mechanisms that regulate glycolysis, *de novo* lipogenesis and lipoprotein synthesis in normal and pathological situations.
Method: Like virtually all cancer cells, hepatocarcinoma cells express the "cancer-type" hexokinase isoenzyme HK2. Here, we restored the hepatic hexokinase isoenzyme (glucokinase, GCK) expression in the paragon hepatocarcinoma cell line Huh7 invalidated for HK2 by CRISPR-Cas9. Endo- and exo-metabolites have been analysed by a combined approach of biochemistry and high-field Nuclear Magnetic Resonance metabolomics.
Results: Metabolomic analysis highlighted that although glucose consumption was not affected, a profound metabolic remodelling occurred following hexokinase isoenzyme switch. GCK induced lipid droplets accumulation as well as secretion of triglyceride-rich $ApoB^+$ lipoproteins. Accompanying the lipogenic activity of GCK, the TCA cycle is rewired at the level of pyruvate entry and succinate dehydrogenase and pentose phosphate pathway is activated. With this metabolic profile, GCK-expressing cells become responsive to fructose by accumulating intracellular lipids as well as secreting large amount of $ApoB^+$ lipoproteins.
Conclusion: Restoring GCK expression in hepatoma cells has induced a large scale metabolic remodelling with a balanced lipid metabolism mimicking *in vivo* lipogenesis. This physiologically-relevant hepatocyte model will certainly provide improved clues to control liver inflammation, NAFLD and tumorigenesis.

FRI-292

Liver polyploidization during NAFLD: A gatekeeper against the replication stress

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Background and aims: Over the past decades, the rising incidence of HepatoCellular Carcinoma (HCC) has paralleled to the increase

prevalence of obesity. The liver is a central organ affected by high level of fat accumulation, defined as Non-Alcoholic Fatty Liver Diseases (NAFLD). Alarmingly, hepatic steatosis (NAFL) combined with chronic inflammation and liver injuries cause Non-Alcoholic Steatohepatitis (NASH), the more severe form of NAFLD and a precursor of HCC. Increasing evidence indicates that NAFLD strongly affects the intrinsic proliferative properties of hepatocytes. Several signs of impaired proliferation status were reported in fatty hepatocytes such as telomeres attrition and senescence's engagement. Recently, our team demonstrated that fatty hepatocytes divide preferentially by endoreplication (skip mitosis) due to the activation of the **D**NA **D**amage **R**esponse (DDR). Endoreplication is considered as an alternative division program in a context of genomic stress and leads to the genesis of polyploid contingents.

Methods and Results: We developed a powerful quantitative and qualitative technological approach to define ploidy profiles on tissue liver sections. We demonstrated a dramatic enrichment of highly polyploid hepatocytes (≥ 8n) in NASH murine models (**H**igh-**F**at **H**igh-**S**ucrose/**C**holine-**D**eficient **H**igh-**F**at **D**iets) but also in NASH human patients. Importantly, this population is barely seen in normal condition. Within fatty parenchyma, polyploid fraction co-localize with lipid droplets suggesting an adaptation process to store and/or metabolize lipids more efficiently. We go further to decipher why the DDR is activated in fatty parenchyma leading to the genesis of the polyploid fraction. Transcriptomic analysis reveals an enriched gene set involved in DNA repair in fatty hepatocytes. In this context, DNA synthesis parameters were measured in dividing primary hepatocytes cultures (HFHS/CTR). DNA combing assay reveals that NAFL hepatocytes exhibit a dramatic reduction of replication fork speed with the presence of stalled fork. Regarding the presence of DNA breaks by Comet assay, replicating NAFL hepatocytes display high level of breaks associated with a pan-nuclear of gamma-H2AX staining. Additional molecular analyses reveal a specific activation of ATR/pRPA^{S33} pathway, specifically activated by single-strand DNA Breaks. Interestingly, double-strand DNA Breaks are found in replicating NASH hepatocytes.

Conclusion: Collectively, our results showed that dividing fatty hepatocytes harbor Replication Stress; RS being recognized as a hallmark of cancer. We suggest that the genesis of polyploid hepatocytes could buffer these DNA lesions and thus represent a defense mechanism in NASH-HCC sequence.

FRI-293

Recipient PNPLA3 and TM6SF2 genotypes and risk of NAFLD folllowing liver transplantation

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Background and aims: Liver transplant recipients are more likely to develop de-novo or recurrent non-alcoholic fatty liver disease (NAFLD), most of them fulfilling the criteria for metabolic syndrome (MetSy). Our aim was to assess the impact of single nucleotide polymorphyisms of PNPLA3 rs738409 "M-variant" (43928847C > G) and TM6SF2 "K-variant" (19268740C > T) on the presence of metabolic syndrome and cardiovascular risk in these patients.

Method: We assessed 61 liver transplant recipients for clinical and biological features and genetic polymorphism. The cardiovascular risk was assessed using the Framingham risk score.

Results: HCV cirrhosis was the main indication for liver transplantation (69% of patients), 62.3% were males and the mean age at evaluation was 56 years. The rs738409 polymorphism of PNPLA3 I148M was encountered in 70.5% of the study population with 46% heterozygous I/M and 24.5% homozygous M/M mutation. The non-parametrical test (Mann-Whitney) identified a significant association between the PNPLA3 M-variant and higher BMI (> 25) ($p = 0.0063$) and higher Framingham cardiovascular risk score ($p < 0.001$). TM6SF2 rs58542926 K- variant (E167K) was present in a lower proportion of patients compared to PNPLA3 M-variant-24.5% (14.5% homozygous and 10% heterozygous). When tested with the same Mann-Whitney test for independent samples the TM6SF2 K-variant was significantly associated with higher Framingham risk score ($p < 0.0001$), BMI > 25 ($p = 0.0007$), and the presence of metabolic syndrome ($p = 0.0001$).

Conclusion: Recipient PNPLA3 and TM6SF2 genotypes confer a genetic predisposition to liver graft non-alcoholic fatty liver disease along with a higher post-LT cardiovascular risk, independent of the graft genotypes. Assessment of the PNPLA3 and TM6SF2 polymorphisms in LT recipients will possibly modify clinical practice in the future.

FRI-294

Mitochondrial GNMT-complex II is recovered by miR-873-5p targeting in NAFLD

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Background and aims: Non-alcoholic fatty liver disease is one of the major chronic liver diseases in developed countries, including alterations from steatosis and non-alcoholic steatohepatitis to advanced fibrosis in at risk patients. Non-alcoholic fatty liver disease patients with and without fibrosis may develop hepatocellular carcinoma. Non-alcoholic fatty liver disease -related mechanisms include impairments in lipid uptake, mitochondrial fatty acid beta-oxidation, de novo lipogenesis and/or inefficient very-low-density lipoprotein assembly and secretion.

Glycine-N-methyltransferase (GNMT) is the enzyme responsible for a large amount of transmethylation reactions, comprising 1% of the soluble protein in liver. The importance of GNMT is to maintain the SAMe/SAH ratio, which represents an indicator of the methylation

capacity of the cell. In this work we explore the involvement of GNMT in non-alcoholic fatty liver disease pathogenesis and the influence of the GNMT regulator miR-873-5p targeting in fatty liver progression.
Method: We evaluate the miR-873-5p as biomarker in serum samples and liver biopsies of non-alcoholic fatty liver disease patients. In addition, we employ *in vitro* and *in vivo* non-alcoholic fatty liver disease models to assess the role of GNMT in fatty liver progression, and the targeting of the miRNA miR-873-5p as non-alcoholic fatty liver disease therapy.
Results: In the present study, we describe for the first time the role of GNMT in the mitochondria, particularly interacting with the complex II in the electron transport chain, and increasing mitochondrial functionality and fatty acid beta-oxidation. There is also a decrease in hepatic oxidative stress, protecting it from fatty liver progression.
In particular, miR-873-5p was found to be upregulated in liver and serum from non-alcoholic fatty liver disease patients, correlating with GNMT depletion. Treatment of diet-induced non-alcoholic fatty liver disease in mice based on anti-miR-873-5p improved GNMT mitochondrial function.
Conclusion: In conclusion, we show the potential of miR-873-5p as novel non-alcoholic fatty liver disease biomarker and introduce a new therapy by targeting this microRNA, which results in the restoration of GNMT levels and the improvement of the newly identified GNMT function in mitochondria.

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Advanced glycation end products (AGEs) exacerbate NAFLD progression to liver fibrosis via receptor for AGEs (RAGE) in high fat fed mice

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, affecting up to 30% of the adult population. Advanced glycation end products (AGEs), formed as a result of non-enzymatic reaction between reducing-sugars and proteins, have been suggested as a second hit that drives NAFLD progression to liver fibrosis. We therefore investigated the role of the best characterized AGE receptor, RAGE, in mediating AGE effects in mice with NAFLD.
Method: Two groups of C57Bl/6 mice were fed a high fat (HF) diet for 40 weeks and one group was induced diabetes at 15 weeks of diet (HF+D) to increase endogenous AGE formation. Third group of mice was fed a baked HF diet to increase dietary AGE intake (HF+B, 1 hour at 160°C) and was made diabetic. Two groups of RAGE knockout mice were fed on either the HF or HF+B and were made diabetic. At 40 weeks, animals were sacrificed to collect liver tissues for gene expression analysis of RAGE, proinflammatory and profibrotic cytokines and collagen 1 by qPCR and quantification of fibrosis by picrosirius red staining. Plasma was harvested for liver function test. Dietary AGE content was determined by GC/MS. Gene expression of proinflammatory cytokines was determined after murine Kupffer cells (KUP5) were exposed to AGEs (200μg/ml) in the presence or absence of RAGE antagonists (RAP and FPS-ZM1).
Results: Baking increased AGE content in the diet. Long-term consumption of HF diet produced steatosis and mild fibrosis after 40 weeks. Both diabetes and high AGE diet caused upregulation ($p < 0.05$) of liver RAGE expression in wild type mice. The increased expression of tumour necrosis factor α (TNF-α) ($p < 0.01$), Toll like receptor-4 and CD14 ($p < 0.05$), transforming growth factor-β1 ($p < 0.0001$) and collagen I ($p < 0.05$) in HF+D or HF+B fed wild type mice was abrogated ($p < 0.01$) by RAGE deletion. Moreover, in wild type mice, diabetes and high dietary AGEs led to an increased ($p < 0.0001$) collagen expression, leading to severe liver fibrosis. Importantly, HF+D or HF+B-induced NAFLD progression to liver fibrosis was strongly inhibited by RAGE deletion. Increased ($p < 0.0001$) expression of RAGE, TNF-α, monocyte chemoattractant protein-1, interleukin-6 and −1β by KUP5 cells was completely ($p < 0.0001$) abrogated by incubation with RAGE antagonists.
Conclusion: Baking increases dietary AGE levels. Increased dietary AGEs, and diabetes which likely increases endogenous AGE production, trigger NAFLD progression to liver fibrosis by acting via RAGE. Blocking RAGE provides protection against AGE-induced NAFLD progression to liver fibrosis.

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Interaction between the soluble guanylate cyclase and the NLRP3 inflammasome in Kupffer cells: Implications for the anti-inflammatory actions of sGC stimulation in liver

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Background and aims: The inflammasome is a multiprotein complex that promotes the maturation of pro-interleukin (IL)-1 beta and pro-IL-18 to their active forms through the activity of caspase-1. The NLRP3 inflammasome, formed by NLRP3, ASC and caspase-1, is critical in initiating the "cytokine storm." Cyclic nucleotides, such as cyclic guanosine-3," 5'-monophosphate (cGMP), play a major role in cell signaling and tissue homeostasis. Soluble guanylate cyclase (sGC) is the enzyme that catalyzes the conversion of GTP into cGMP. We demonstrated that sGC expression and cGMP levels were significantly reduced in livers of mice with non-alcoholic steatohepatitis (NASH) and that could be corrected by the use of sGC stimulators, which produced a remarkable anti-inflammatory effect. Here, we explored whether the anti-inflammatory effects of sGC-cGMP stimulation are linked to the inactivation of the hepatic NLRP3 inflammasome.
Method: *In vitro* and *ex vivo* experiments were performed in primary Kupffer cells and precision-cut liver slices (PCLS), respectively, incubated with LPS+ATP. *In vivo* experiments were performed in mice with NASH induced by a choline-deficient L-amino acid-defined high-fat diet. Gene expression was analyzed by qPCR and protein expression by Western blot and ELISA. Ly6C+Cd11b+ monocytes were identified by flow cytometry.
Results: Kupffer cells showed constitutive expression of sGC and NLRP3 inflammasome components. Incubation of Kupffer cells with LPS+ATP significantly induced NLRP3 expression and triggered IL-1beta production, effects that were significantly attenuated by sGC stimulation. Interestingly, sGC stimulation reduced TIMP-1 and TGF-beta expression in Kupffer cells, indicating that sGC stimulation also has the ability to inhibit the production of pro-fibrogenic factors by liver macrophages. Similar effects were observed in PCLS. Anti-inflammatory actions were confirmed *in vivo*, in which sGC stimulation significantly abrogated protein expression of inflammasome components (i.e. NLPR3, ASC, caspase-1 and IL-1beta). Interestingly, flow cytometry analysis of peripheral blood revealed that sGC stimulation increased the number of patrolling and tissue repair $Ly6C^{Lo}$ monocytes, while reducing the population of pro-inflammatory $Ly6C^{Hi}$ monocytes.
Conclusion: These findings provide potential novel mechanisms of action for the anti-inflammatory properties of sGC stimulation in experimental NASH.

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Trans-signaling blockade induces mature-onset obesity and insulin resistance in mice via suppression of PPARalpha

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Background and aims: IL-6 has been shown to play crucial roles in metabolic homeostasis and weight gain in experimental models; but the controlling molecular mechanism (s) and their physiological and clinical relevance remain unclear. Interestingly, evidence from clinical studies has revealed statistically significant correlations of body mass index in diabetic patients with increased levels of soluble gp130 (sgp130)-a specific inhibitor of IL-6/IL-11 signaling mediated via their respective soluble receptors (sIL-6R/sIL-11R), or so called trans-signaling. Paradoxically, while total IL-6 ablation in IL-6 knockout mice reportedly induces mature-onset obesity, hepatosteatosis and insulin resistance (Matthews et al., 2010; Wallenius et al., 2002), inhibition of trans-signaling in mice carrying a recombinant sgp130 transgene (sgp130Fc) prevented HFD-induced recruitment of adipose tissue macrophages and did not exacerbate weight gain, liver steatosis, or insulin resistance in young HFD-fed mice (Kraakman et al., 2015). Here we have examined the hypothesis that IL6 trans-signaling plays a protective role against mature-onset obesity and fatty liver in aging mice.
Method: Sgp130Fc transgenic mice and wild type littermate control mice were maintained under normal dietary conditions and analyzed at 2, 5 and 14 months-of-age, for weight gain, glucose tolerance, liver steatosis, and for differential expression of liver proteins by proteomics and bioinformatics analysis.
Results: Blockade of trans-signaling in sgp130Fc mice resulted in mature-onset obesity becoming apparent at about 6 months of age with increased adipose tissue visualized by MRI, increased gonadal fat pad size, adipocyte hypertrophy, and hyperleptinemia appearing at 12 months. Sgp130Fc mice also displayed hepatosteatosis and peripheral insulin resistance, without gut microbiota dysbiosis or defective mitochondrial fat oxidation. Proteomics analysis revealed a strong correlation between the metabolic phenotype in sgp130Fc mice and a profound decrease in hepatic PPARα activity from 2 months of age, as confirmed by qPCR and Western blot analyses, which was associated with increased hepatic miR-21 expression. PPARα is a known target of miR-21. Importantly, treatment with the PPARα agonist, fenofibrate rescued the sgp130Fc mice from obesity, steatosis, and insulin resistance.
Conclusion: Our findings reveal a profound PPARα-mediated role for IL-6 trans-signaling in the prevention of age-dependent obesity, insulin resistance, and fatty liver in mice.

FRI-298

Hypoxia-inducible factor 2 alpha drives lipid accumulation in human hepatocytes through the fatty acid translocase CD36

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Background and aims: Molecular mechanisms by which hypoxia might contribute to hepatosteatosis, the earliest stage in non-alcoholic fatty liver disease (NAFLD) pathogenesis, remain still to be elucidated. We aimed to assess the impact of hypoxia-inducible factor 2α (HIF2α) on the fatty acid translocase CD36 expression and function *in vivo* and *in vitro*.
Method: NASH features, and HIF2α and CD36 expression were evaluated in livers from animals in which von Hippel-Lindau (*Vhl*) gene is inactivated ($Vhl^{f/f}$ deficient mice) or both *Vhl* and *Hif2α* are simultaneously inactivated ($Vhl^{f/f}Hif2\alpha^{f/f}$ deficient mice), and from 33 biopsy-proven NAFLD patients and 18 subjects with histologically normal liver. Additionally, modulation of CD36 expression as well as intracellular lipid content was determined by qPCR and flow cytometry, respectively, in hypoxic HIF2α-silenced human liver cells.
Results: Livers from $Vhl^{f/f}$ deficient mice showed histologic features of non-alcoholic steatohepatitis (NASH) and increased *Cd36* mRNA and protein amounts, whereas both significantly decreased and NASH features markedly ameliorated in $Vhl^{f/f}Hif2\alpha^{f/f}$ deficient mice. Moreover, in hypoxic human liver cells, CD36 expression and intracellular lipid content were significantly augmented. Noteworthy, in these hypoxic liver cells, CD36 knockdown significantly reduced lipid accumulation, and HIF2α silencing markedly decreased both lipid accumulation and *CD36* gene expression. In addition, both HIF2α and CD36 were significantly overexpressed within the liver of NAFLD patients and, interestingly, a significant positive correlation between hepatic transcript levels of *CD36* and erythropoietin (*EPO*), a HIF2α-dependent gene target, was observed in NAFLD patients.
Conclusion: This study provides evidence that HIF2α drives lipid accumulation in human hepatocytes by upregulating CD36 expression and function, thus contributing to hepatosteatosis setup.

FRI-299

Transcriptomic and epigenetic characterization of a NAFLD murine model

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Background and aims: Epigenetics play an important role in the progression of non-alcoholic fatty liver disease (NAFLD). The aim of our study was to unravel how the interaction between genes and miRNAs expression could affect the development of non-alcoholic steatohepatitis (NASH) in a murine model.
Method: Fifty-two male six-weeks mice C57BL/6J were fed a HFHCC diet (40% Kcal fat, 1% cholesterol and 42g/L glucose/fructose in drinking water) (n = 40) or standard diet (n = 12) being sacrificed at 13, 26, 39 and 52 weeks. Anatomorphological features, histological, biochemical and metabolic parameters were measured. Liver RNA was extracted and the transcriptomic and epigenetic profile were studied by ClarionS and miRNA4.0 arrays including > 22, 000 transcripts and > 3, 000 miRNAs (mature and pre-miRNA) (ThermoFisher, CA, USA). The interaction was evaluated by using TAC software (ThermoFisher, CA, USA).
Results: HFHCC diet induced NASH in mice, characterized by a gain in weight and BMI, macro-microvesicular steatosis (> 90%), inflammatory foci at lobular, portal and periductal levels, followed by presence of hepatocyte degeneration (ballooning) and moderate fibrosis. The model also showed a progressive increase in the hepatic, lipidic and glucidic parameters. Besides, we also detected several foci of

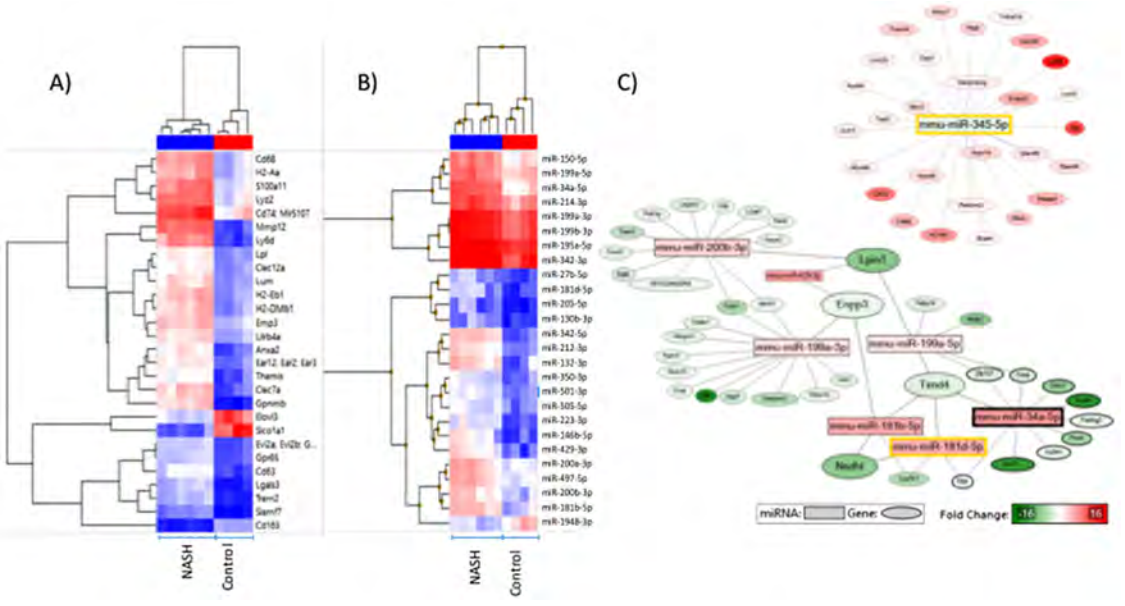

Figure: (abstract: FRI-299)

cellular alterations in > 40% animals and nodules in > 20%. The transcriptomic gene enrichment analysis allowed us to identify changes in pathways similar to human NASH. At early stages, changes in lipid metabolism, proliferation and inflammatory signaling were observed. Nevertheless, advanced stages showed an increase in oxidative stress, senescence and innate immune response pathways. Besides, we found upregulation of several pluripotency-related factors such as Sox2, Nanog and Klf4 at 52 weeks. In comparison to control, NASH animals showed up to 28 genes differentially expressed ($p < 1x10^{-8}$;fold±10;FDR < 0.05) Similarly, the epigenetic profile revealed 26 miRNAs with differences ($p < 0.001$;fold±2;FDR < 0.05). Finally, by analyzing the target gene prediction of miRNAs we could confirm the interactions miRNA-genes (miRNAome).

Conclusion: HFHCC model comprises the main clinical and histological characteristics of human NASH, including slow progression to fibrosis and hepatocellular carcinoma, covering the needs in the field for future preclinical studies. Besides, by deciphering the miRNAome of NAFLD new biomarkers and therapeutic targets could be developed and detected. In this sense, we found that overexpression of four miRNAs (miR-200b, miR-199a, mir181b and miR34a), through regulating several genes, could play a role in NAFLD pathogenesis.

FRI-301

The differential expression of the CIDE family is associated with NAFLD progression from steatosis to steatohepatitis

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Background and aims: Improved understanding of the molecular mechanisms responsible for the progression from a "non pathogenic" steatotic state to Non-Alcoholic Steatohepatitis (NASH) is an important clinical requirement. The CIDE family members (CIDEA, B and FSP27α and β) regulate lipid homeostasis in the liver by controlling lipid droplet growth and/or VLDL production. However, CIDE proteins, particularly FSP27, have a dual role in that they also regulate cell death. Here, we aim to evaluate the relative expression level of the three CIDE members over the transition from simple steatosis to NASH, and to assess the contribution of CIDEC to hepatocyte steatosis and death.

Method: The CIDE family was studied in the livers of mice challenged with a high fat diet (33 weeks; exhibiting obesity and hepatic steatosis) or a methionine choline deficient diet (from 2 to 7 weeks; exhibiting progression of the NASH features) and in liver biopsies from 38 obese patients. FSP27 was downregulated or overexpressed in human and mouse hepatocytes to study its role in lipid droplet synthesis and cell viability.

Results: We here report that hepatic expression of CIDEA and FSP27α and β was similarly upregulated in a dietary mouse model of obesity and hepatic steatosis. In contrast, CIDEA expression decreased, whereas only FSP27β expression was strongly increased in a dietary mouse model of steatohepatitis. The inverse expression pattern of CIDEA and FSP27β was amplified with the increasing severity of the liver inflammation and injury. In morbidly obese patients, the hepatic expression of CIDEC2 (human FSP27β homologue) strongly correlated with the NAFLD activity score, hepatic inflammation, liver injury and hepatocyte apoptosis. The hepatic expression of CIDEA tended to increase with obesity but decreased with NAFLD severity. The hepatic expression of CIDEB was not modified with obesity or NAFLD in mouse and human. In hepatic cell lines, the downregulation of FSP27beta resulted in the fractionation of lipid droplets but overexpression of FSP27 decreased the anti-apoptotic BCL2 expression. This, in turn, sensitized cells to apoptosis at baseline and in response to oleic acid.

Conclusion: Considered together, our animal, human and in vitro studies indicate that modification of the FSP27β/CIDEC2 to CIDEA ratio is related to NAFLD progression and liver injury.

FRI-302

Impact of exercise on advanced fibrotic stage of NASH and liver carcinogenesis

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Background and aims: In the absence of approved pharmacotherapy, lifestyle interventions incorporating exercise remain the cornerstone of treatment for NASH. However, benefits of exercise on fibrotic NASH are unexplored. We queried whether exercise arrests the histological and carcinogenic progression of NASH in an experimental model.
Method: Male C57Bl/6N mice aged 10 weeks were assigned randomly to either control diet (CD, n = 11) or choline-deficient high-fat diet (HFD, n = 33). At 12 weeks, CD mice were harvested and the HFD mice were randomized either for harvest (n = 11) or for 8 further weeks of sedentariness (SED, n = 11) or treadmill exercise (EXE, n = 11) (1 h, 5 days/week, speed 12.5m/min). Changes in plasma biochemistry, protein expression and triglycerides in liver, histology and scanning electron microscopy, and mitochondrial bioenergetics (Oxygraph-2k Oroboros) were assessed. Fibrosis was quantified (MetaMorph software) on Sirius Red stained sections.
Results: Compared to SED mice, EXE showed reduced plasma ALT (138 vs 259 U/l), bilirubin (16 vs 29 µmol/l), triglycerides (0.67 vs 0.82 mmol/l), cholesterol (1.84 vs 2.57 mmol/l) and bile acids (58.9 vs 78.7 µmol/l), as well as liver triglycerides (1512 vs 2613 nmol/mg) ($p < 0.05$, EXE vs SED). Histologically, EXE livers showed less ballooning degeneration (median score 0 vs 2; $p = 0.0006$) and a lower NAS score (median 6 vs 8; $p = 0.0009$). Importantly, exercise prevented the progression of fibrosis (4.74 vs 9.17 pixel percentage ratio; $p < 0.0001$) [Fig.1]. Additionally, exercise activated AMPK with consequent inhibition of mTORC1, reducing the development of hepatocellular adenoma (70% vs 100%, $p = 0.0075$). Defenestration of endothelial cells was present in all HFD groups, regardless of exercise. In mitochondrial bioenergetics studies, maximum and complex IV driven respiration was reduced in NASH but only at 12 weeks commensurate with a down-regulation of cytochrome oxidase 4 protein. Leak respiration increased in all NASH groups and was unaffected by exercise.
Conclusion: Exercise improves biochemical and histological parameters in an experimental model of established NASH and impedes the progression of fibrosis and liver carcinogenesis. Our work supports the benefits of exercise independently of other lifestyle changes.

FRI-303

How to develop a differentiated FXR agonist: GS-9674 shows a reduced side effect profile in mice, monkeys amd human phase I studies compared to its predecessor Px-102

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Background: FXR agonists such as Obeticholic Acid (OCA) have proven to be effective pharmacotherapies in liver diseases such as

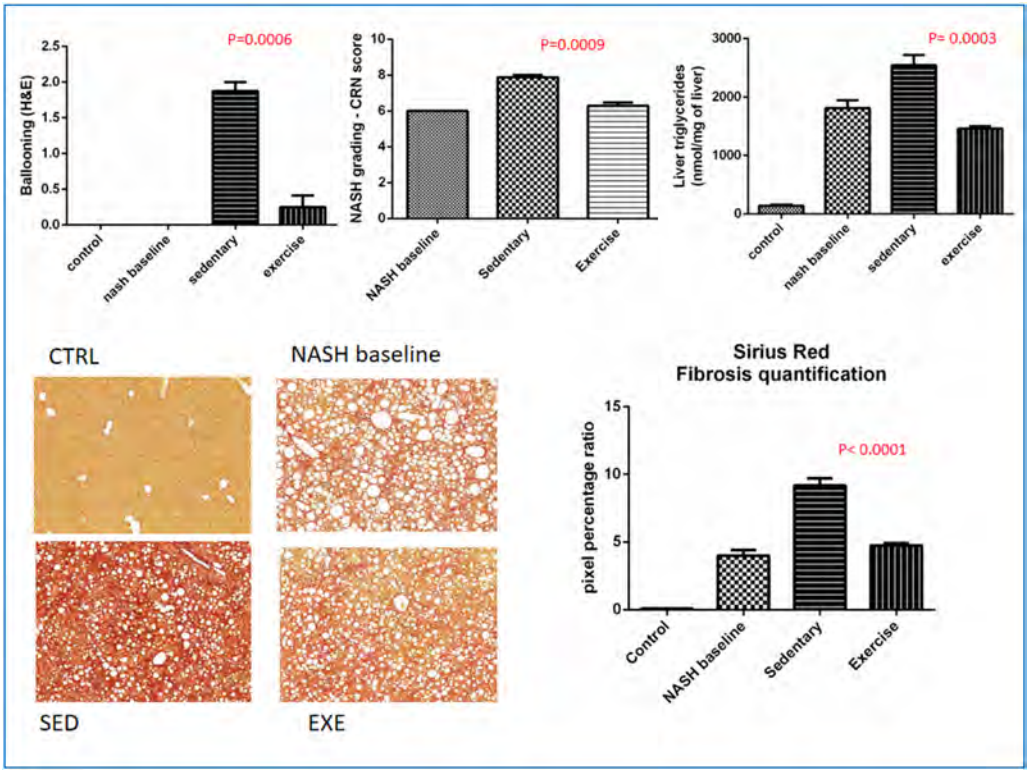

Figure: (abstract: FRI-302)

Primary Biliary Cirrhosis (PBC) or Non-alcoholic Steatohepatitis (NASH). With regards to NASH, FXR agonists have demonstrated anti-steatotic, anti-inflammatory and anti-fibrotic effects in preclinical studies and clinical trials. However, clinically, liabilities such as LDL-c increases, HDL-c lowering and pruritus have been reported with FXR agonists, with the first two suggestive of an increased atherogenic and thus cardiovascular risk.

Methods/Results: We initially developed a fully synthetic, non-steroidal FXR agonist, Px-102 and tested it in preclinical NASH animal models and in a single ascending (SAD) and seven-day multiple dose (MAD) phase I study. In the SAD study, Px-102 was given as oral suspension (0.05 to 4.5 mg/kg). FXR agonism was evident from dose-proportional increases in plasma FGF19. The MAD study revealed daily increases superimposed on the circadian rhythm. However, LDL-c and HDL-c also changed and time and dose-dependent increases of ALT and AST as well as individual cases of pruritus were noted. These unwanted side effects prompted a quest for a differentiated FXR drug candidate. To probe for less liabilities, we established an appropriate animal model recapitulating the pattern of FXR-induced changes to screen structurally related FXR agonists of similar potency. Here, C57BL/6J mice on a high fat diet (HFD) showed similar changes whereas $FXR^{-/-}$ mice of the same background showed no Px-102 induced effects.

The new candidate, GS-9674, showed no ALT increases and only very moderate cholesterol changes. Comparing the reduction in fibrosis of GS-9674 with Px-102 in a choline-deficient HFD rat model of fibrosis revealed similar efficacy at 30 mg/kg versus 10 mg/kg of Px-102. Moreover, GS-9674 had no effects on HDL-c whereas Px-102 lowered HDL-c in a HFD-monkey model despite similar FGF19 induction. Finally, GS-9674 was tested in a SAD and 21 days MAD human phase I study and displayed dose-dependent induction of FGF19 and repression of C4, whereas cholesterol parameters remained unchanged up to 300 mg/day.

Conclusion: In this translational effort the human side effects of Px-102 were recapitulated in an appropriate animal model. Using the model as a screen we identified GS-9674 as a differentiated FXR agonist with intestinally biased activity and clearly reduced side effects for further clinical development in NASH, PBC, and PSC.

FRI-304

Elafibranor and pioglitazone reduce NASH and fibrosis in a genetically-obese dietary-induced NASH mouse model

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Background and aims: Dietary-deficient mouse models of NASH present limitations due to their associated weight loss resulting in an altered metabolic profile to man. To resolve this issue we have developed a genetically-obese dietary-induced mouse model (*ob/ob* H-FFC) of NASH and fibrosis which is more congruent with man. We have evaluated this paradigm with the clinically effective compounds elafibranor and pioglitazone.

Method: Elafibranor (30 mg/kg po, once daily) and pioglitazone (15 mg/kg po, bi-daily) were evaluated in male *ob/ob* (B6/Cg-Lepob/J, n = 11-13) mice fed a high fat/fructose/cholesterol diet (H-FFC) for 85 days. Genetically obese (*ob/ob*) mice on a standard rodent diet were also included. Plasma liver enzymes, liver lipids, liver collagen and liver histology including NAFLD activity scoring (NAS) were assessed at the end of the study.

Results: The *ob/ob* H-FFC mice had significantly ($p < 0.05$ vs. control *ob/ob* mice) increased fibrosis, total NAS (a combination of steatosis, hepatocellular ballooning and lobular inflammation) and lobular inflammation. Plasma AST and ALT were also significantly ($p < 0.05$) increased alongside liver collagen and liver lipids (triglyceride, cholesterol and NEFA). We observed a small reduction in body weight from day 60 onwards, no change to plasma glucose but a significant ($p < 0.001$) reduction in plasma insulin in the *ob/ob* H-FFC mice versus the *ob/ob* standard diet controls. A summary of the effects of elafibranor and pioglitazone can be seen in Table 1.

	ob/ob H-FFC + elafibranor vs ob/ob	*ob/ob* H-FFC + pioglitazone vs ob/ob
Hepatic Pathology		
Steatosis	↓	-
Lobular Inflammation	↓	↓
Hepatocellular Ballooning	-	-
Fibrosis	↓	↓
NAS	↓	↓
Liver analysis		
Collagen	↓	↓
Triglycerides	↓	↓
NEFA	↓	↓
Cholesterol	↓	-
Plasma analysis		
ALT	↓	↓
AST	↓	-
Glucose	-	↓
Insulin	-	↓
Other parameters		
Bodyweight	↓	↑

Conclusion: Elafibranor and pioglitazone both improved NAS and fibrosis in the *ob/ob* H-FFC mouse model. While both compounds also reduce the liver enzyme ALT, liver lipids and collagen, the improvements observed with elafibranor were more marked. Due to the minimal effect on body weight and plasma glucose the *ob/ob* H-FFC diet mouse model is an improvement on dietary deficient models for the assessment of potential treatments of NASH and fibrosis with translatability to the clinic.

FRI-305

Long acting GLP-1/Glucagon co-agonist ameliorates steatosis, inflammation and fibrogenesis in a rodent model of NASH

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Background and aims: Glucagon-like peptide 1 (GLP-1) analogues are utilized in the treatment of type 2 diabetes and obesity, due to their well-characterized effects on body weight, glycemic control and cardiovascular benefits. Glucagon could provide additional efficacy through direct effects on hepatocyte metabolism, cholesterol synthesis, and anti-oxidative pathways. In preclinical models, GLP-1/Glucagon receptor (GG) co-agonists have shown greater body weight reduction and anti-steatotic properties than GLP-1 alone, and human studies has shown antisteatotic effect without deleterious effects on fasting or postprandial blood glucose. Here we aimed to evaluate the efficacy of a novel, long-acting GG co-agonist in a rodent diet-induced model of NASH.

Method: Male C57Bl/6 mice fed a diet high in trans-fat, fructose and cholesterol (FFC) for 36 weeks and randomized on fibrosis score at baseline, received once daily s.c. administration of vehicle or three different doses of the long-acting (LA) GG co-agonist for 8 weeks. In addition a reference group of animals was treated with semaglutide, a GLP-1 analogue. Hepatic steatosis, inflammation and fibrosis were assessed from liver biopsies using immunohistochemistry and morphometric analyses. Plasma levels of lipids and liver enzymes

were determined, and hepatic gene expression was analyzed by RNA sequencing.
Results: The LA GG co-agonist dose-dependently reduced body weight by 0-22% as compared to vehicle treatment, while semaglutide induced a body weight loss of 18%. Plasma levels of ALT, as a measure of liver injury, were reduced in all treatment groups with body weight loss. The co-agonist reduced hepatic steatosis to a greater extent compared with semaglutide at equal body weight loss, as demonstrated by three independent methods. The co-agonist, as well as semaglutide, significantly decreased histological markers of inflammation such as CD11b and Galectin-3, in addition to markers of hepatic stellate activation (SMA) and fibrosis (collagen I). Results from pathway analyses at the mRNA level suggest that the LA GG co-agonist plays an additional role in preventing oxidative stress, as the glucagon component normalised expression of a genetic pathway, encoding enzymes involved in methionine metabolism and generation of glutathione.
Conclusion: We have shown that a long acting GG co-agonist reduces hepatic steatosis, inflammation and fibrosis in a mouse model of NASH, supporting evaluation in clinical trials.

FRI-306
RIP3 deficiency restores mitochondrial bioenergetics and function in experimental NAFLD
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Background and aims: Mitochondrial dysfunction, liver cell damage and inflammation constitute key pathogenic mechanisms underlying non-alcoholic fatty liver disease (NAFLD) progression to non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. To curb hepatic fat accumulation, metabolic adaptation, such as increased mitochondrial fatty acid oxidation (mtFAO), may take place. Of note, increased mtFAO without collateral up-regulation of the mitochondrial respiratory chain (MRC) activity leads to reactive oxygen species (ROS) overabundance. In this regard, we have previously shown that receptor interacting protein 3 (RIP3) kinase deficiency attenuates diet-induced liver oxidative stress, injury, inflammation and fibrosis. Here, we aimed to evaluate the role of RIP3 depletion on restoration of the MRC activity in experimental NAFLD progressing from steatosis to the development of preneoplastic lesions.
Method: C57BL/6N wild-type (WT) and RIP3$^{-/-}$ mice were fed either a choline-sufficient, amino acid-defined control diet (CSAA; n = 38) or a choline-deficient, amino acid-defined diet (CDAA; n = 38) for 32 and 66 weeks. Liver samples were collected and processed for assessment of steatosis, inflammation, fibrosis and hepatocyte proliferation. Citrate synthase and MRC complex I, II, II+III and IV activities were investigated. Mitochondrial biogenesis markers (PGC1α, NRF1, TFAM), and ROS detoxification markers (SOD1, SOD2) and SIRT3 were also analyzed.
Results: RIP3 depletion ameliorated CDAA-induced inflammation, fibrosis and oxidative stress, while decreasing the NAFLD activity score and the incidence of preneoplastic lesions. Compared to CSAA-fed WT mice, citrate synthase activity was slightly diminished at both 32 and 66 weeks of CDAA feeding. In addition, at 32 weeks, the CDAA diet resulted in significantly decreased enzymatic activities of MRC complex I, II, II+III and IV in WT mice compared to CSAA-fed animals. Strikingly, RIP3$^{-/-}$ mice showed an overall protection against CDAA-induced impairment of MCR complex activity, notably at 32 weeks. mRNA expression of PGC1α, NRF1 and TFAM was downregulated in CDAA-fed WT mice at both 32 and 66 weeks, but significantly increased in RIP3$^{-/-}$ mice. Similarly, SOD1, SOD2 and SIRT3 mRNA levels were downregulated in CDAA-fed WT mice, while RIP3 depletion significantly abrogated this effect at 32 weeks.
Conclusion: In conclusion, impaired MRC complex activity correlates with inflammation, fibrosis and ROS overproduction in experimental NAFLD. RIP3 deficiency restores MRC complex activity, enhances mitochondrial biogenesis, increases ROS detoxification capacity and, collectively, halts NAFLD progression.
Funding: FCT PTDC/BIM-MEC/0895/2014 and SAICTPAC/0019/2015 grants; EU H2020 Marie Sklodowska-Curie 722619 grant.

FRI-307
Metadoxine prevents diet-induced non-alcoholic steatohepatitis in mice
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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver disorders worldwide. Metadoxine appears to be a effective strategy to manage alcoholic steatohepatitis. However, its role during non-alcoholic steatohepatitis (NASH) remains poorly defined. The study aimed to assess the therapeutic efficacy and mechanisms of metadoxine in NASH
Method: Male C57BL/6J mice were obtained at 8 weeks of age. Mice were randomly divided into three groups of six animals. The treatments were as follows: 1): Control group fed with standard diet. 2) NASH group received a 42% fat "high fat/western-style" diet (HF) ad libitum for 16 weeks. 3) Metadoxine group received HFD and a single oral dose of metadoxine (200 mg/kg) was administered. Mice body weight, liver weight, fat mass was measured. Sera were collected for the analysis of biochemical markers and livers were obtained for further histological staining and gene expression analysis. Each liver tissue specimen was scored based on the criteria proposed by Knodell, Lee for steatosis and inflammation. Transmission electron microscope (TEM) was used to investigate the effect of metadoxine on the cell ultrastructure. The expression of inflammation genes, lipogenesis genes, and oxidative stress genes were assessed by real-time PCR and western blot.
Results: After 16-week dietary intervention, metadoxine decreased the body weight and the liver weight compared to the HFD group. Liver sections showed that HFD mice developed marked macrovesicular and microvesicular steatosis, as well as multifocal necrosis compared to the control group. However, metadoxine treatment abolished steatosis in metadoxine treated mice. Consistent with the results on steatosis on HandE staining, less lipid droplets were observed in the metadoxine treated animals in Oil Red O-stained sections. As compared to the controls, HFD feeding increased serum concentrations of ALT, AST and marked accumulation of TC, LDL-C, and GLU. Metadoxine treated mice showed lower serum biochemical markers than HFD mice. Moreover, we found mRNA levels of TNF-α, IL-1β, NF-κB, IκBα were higher in HFD-fed mice than control group. However, metadoxine treatment could decrease these genes and protein expression. In addition, metadoxine significantly increase the expression of lipogenesis genes (PPAR-α/γ, SREBP1c, FASN and ACO). We also analyzed the effects of metadoxine on oxidative stress gens, such as NRF2, SOD1, HO-1, NQO1. Hepatic mRNA levels of these genes were increased in HFD group, and metadoxine treatment further enhanced the expression of oxidative stress factors.
Conclusion: Our data established a therapeutic role of metadoxine in NASH development. Metadoxine has a protective effect on NASH and its mechanims may be related to decrease the lipid accumulation, inhibit the oxidative stress and ultimately deduce inflammation.

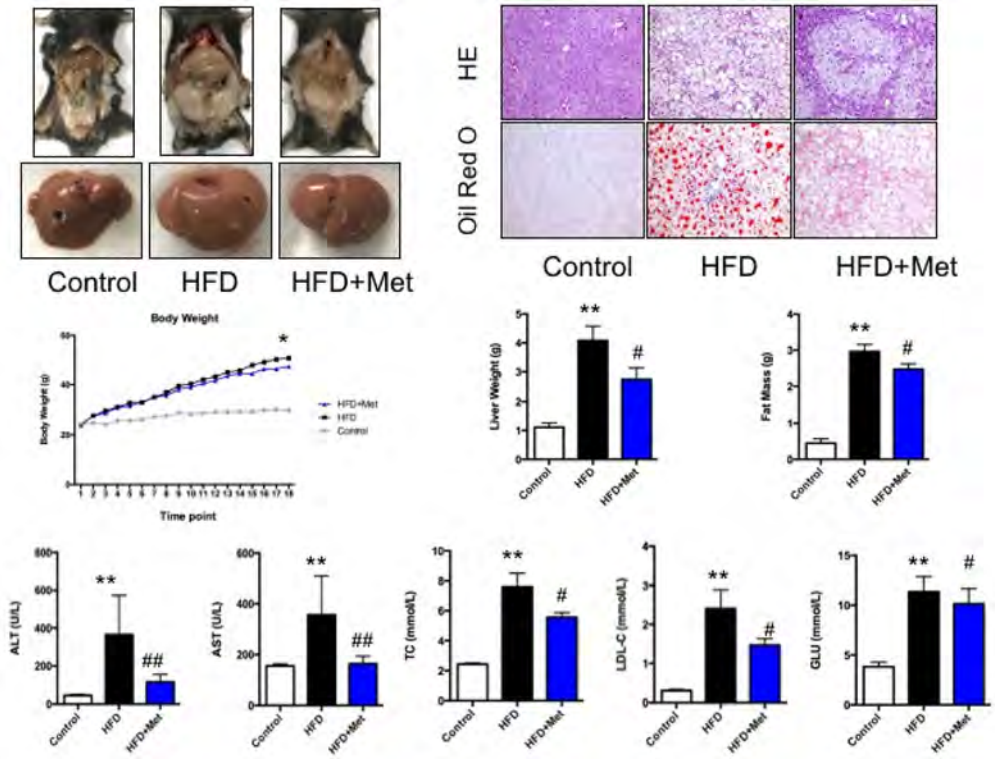

Figure 1: (abstract: FRI-307)

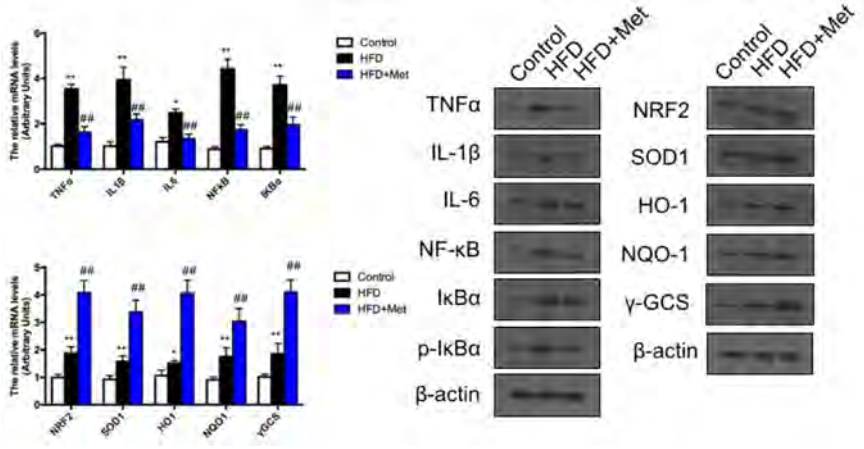

Figure 2: (abstract: FRI-307)

FRI-308

Inhibition of alpha 2A adrenergic receptors reduces liver inflammation in experimental NASH

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Background and aims: Fatty liver disease (NAFLD) is increasing worldwide. Patients with the inflammatory state of non-alcoholic steatohepatitis (NASH) have increased risk of developing cirrhosis and hepatocellular carcinoma. Noradrenaline (NE) may trigger development of NASH. NE increases the release of pro-inflammatory cytokines through alpha 2a subtype adrenergic receptors (Adra2a) on Kupffer cells (KCs) and Adra2a gene expression in KCs is upregulated in rats with systemic inflammation. We aimed to examine the role of the Adra2a in a rat model of NASH and investigate Adra2a antagonism as a possible treatment for progression of NAFLD.

Method: Male Sprague Dawley rats were fed either high fat high cholesterol (HFHC) to induce NASH or normal chow (NC) diet ad libitum for 16 weeks. Rats in the HFHC group were randomised to receive the Adra2a antagonist YoHCl (titrated to 0.4mg/kg daily) in drinking water for the final 8 weeks. Subsequently, formalin fixed

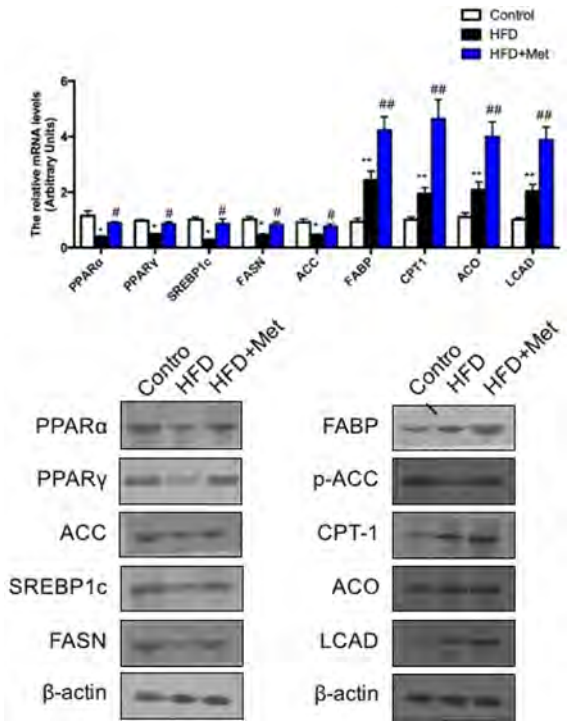

Figure 3

liver sections were stained with HandE for NAS scoring. Pro-inflammatory changes were investigated in liver tissue using qPCR, ELISA, and CD68 immunohistochemistry.

Results: HFHC diet increased liver/body weight ratio (6.51 (0.89) vs 2.76 (0.25); $p < 0.0001$), which was reduced by YoHCl (5.73 (0.44); $p = 0.034$). Histologically, HFHC-group livers showed severe steatosis and NASH with ballooning and increased NAS score (5.83 (0.41) vs 0.11 (0.33); $p < 0.0001$), that was reduced in YoHCl-treated HFHC animals (4.33 (1.12); $p = 0.001$).

HFHC diet increased CD68 stained area (3.92 (1.02) vs 0.70 (0.40) %; $p < 0.0001$) providing evidence of increased inflammatory cells of the monocyte/macrophage lineage. Also, qPCR analysis showed higher gene expression of chemokines involved in immune cell chemotaxis (Ccl3, Cx3Cl1, CxCl1, CxCl5; all $p < 0.001$) and ELISA analysis showed higher levels of CxCl5 (158.4 (34.7) vs 130.6 (11.4) pg/mg protein; $p = 0.014$) and Cx3Cl1 (1256 (225) vs 809 (114) pg/mg protein; $p < 0.0001$). Importantly, CD68 stained area (3.07 (0.56) %; $p = 0.034$), chemokine gene expression, and liver tissue levels of Cxcl5 (134.8 (10.8) pg/mg protein; $p = 0.014$) and Cx3cl1 (955 (112) pg/mg protein; $p = 0.0009$) were all reduced by YoHCL indicating a reduction in hepatic inflammation.

Conclusion: This study demonstrates that Adra2a antagonism reduces immune activation and inflammatory hepatic changes in NAFLD. This suggests Adra2a antagonism may slow progression of NAFLD. The potential for therapeutic translation in NAFLD patients warrants further investigation.

FRI-309

Hepatitis B virus B and T cell specific responses are reduced in adults with a body mass index > 35 and non-alcoholic fatty liver disease and in a mice model of NAFLD compared to adults with a BMI of < 35 patients and normal animals

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Background and aims: Due to the obesity epidemic, many individuals are at risk of the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). Obesity and cirrhosis are associated with poor HBV vaccine responses, but vaccine efficacy has not been assessed in NAFLD.

Method: In this ongoing multi-site prospective study, HBV naïve NAFLD adults were given 3-dose HBV or HBV/HAV vaccine (Engerix B® or Twinrix®) and stratified based on body mass index (BMI) < or > 35. Anti-HBs levels were measured at 1-3 mo post 3rd vaccine dose. In subjects enrolled at the coordinating site, peripheral blood mononuclear cells (PBMC) were isolated from whole blood at baseline and post vaccination. Flow cytometry based T- cell proliferation assays with 10^7 CFSE labelled PBMC/sample and analysis of memory B and T cell phenotypes was done. In complementary pre-clinical studies, C57BL/6 mice were fed either a normal chow vs. high fat diet (HFD) for 20 weeks (N = 40;10/group) and given 2 doses of Engerix-B® either at baseline or after inducing NAFLD phenotype, and anti-HBs levels were assessed at 2 weeks' post 2nd dose.

Results: To date, 61 (32F, median age 49 y [26-63]), HBV naïve NAFLD adults were enrolled, of whom 33 completed the 3-dose HBV or HBV/HAV vaccine series. In total, 21 had BMI > 35 (13 F, median age 49y, 3 diabetic, median ALT 32 U/L, median liver stiffness measurement (LSM) 5.7 kPa, median BMI 38.2) and 40 patients had BMI < 35 (19 F, median age 51y, 7 diabetic, median ALT 40 U/L, median LSM 4.9 kPa, median BMI 30). In 33 NAFLD patients who completed HBV vaccination series to date, mean anti-HBs levels were significantly lower in the group with BMI > 35 compared to those with BMI < 35 (203.7 IU/L±92.2, N = 11 vs. 707.2 IU/L±92.6, N = 22, $p = 0.004$). T-cell recall response was assessed in 23 to date, only 1/8 with BMI > 35 vs. 13/15 with BMI < 35 showed stimulation index values > 2 suggesting HBsAg specific CD3+CD4+ T_H cell proliferative response *ex vivo*. The results of experiments in mice, vaccinated either prior to or after inducing HFD NAFLD phenotype, also showed lower anti-HBs levels vs. controls, $p < 0.05$.

Conclusion: Significantly reduced HBV vaccine specific antibody and T- cell responses were found in NAFLD patients with BMI > 35. In addition, a similar blunted anti-HBsAg response was observed in mice with HFD induced NAFLD. This clinical and animal model data will inform optimal immunization protocols in high risk obesity class individuals with NAFLD.

FRI-310

Alcohol dehydrogenase activity in liver and blood is altered in non-alcoholic fatty liver disease

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Background and aims: Results of studies in humans and animal models suggest that the development of non-alcoholic fatty liver disease (NAFLD) is associated with increased ethanol levels, even in the absence of any alcohol consumption. It further has been proposed that these elevated ethanol levels may results from an increased ethanol synthesis of intestinal microorganism. However, studies also suggest that activity of alcohol dehydrogenase (ADH), the key enzyme involved in alcohol metabolism, may be impaired in NAFLD. The aim of the present study was to determine if ADH activity is altered in

blood of patients with various stages of NAFLD and if these alterations reflect ADH activity in liver tissue.
Method: Fasting blood samples were obtained from 64 patients with biopsy proven NAFLD (simple steatosis: n = 20, non-alcoholic steatohepatitis (NASH): n = 44), and 16 age-matched controls. Furthermore, liver tissue and fasting blood samples were obtained from 10 patients with NAFLD (simple steatosis/NASH with beginning fibrosis) and 8 disease free controls all undergoing liver resection for different medical reasons. In addition, C57Bl6 mice were either fed a fat-, fructose- or cholesterol-rich (FFC) diet to induce NASH, or a control diet (C) for 13 weeks. ADH activity in serum and plasma, respectively as well as in liver tissue was determined using an enzyme assay and ADH 1 and 4 protein levels were determined using Western blot.
Results: While ADH 1 protein levels were significantly higher in serum of patients with NAFLD than in controls, the relative ADH activity was significantly lower in patients with NAFLD, decreasing with increased disease stage (control > steatosis > NASH). Furthermore, relative ADH activity in liver tissue of patients with NAFLD was also significantly lower than in disease-free controls whereas protein levels were similar between groups. In line with these findings, in livers and plasma of FFC-fed mice showing macrovesicular fat accumulation and hepatic inflammation, as well as significantly higher plasma ALT activity than C-fed mice, relative ADH activity in plasma and liver tissue was significantly lower than in control animals. Furthermore, fasting insulin levels were inverse correlated with relative ADH activity in plasma.
Conclusion: Taken together, our data suggest that relative ADH activity in liver tissue is markedly lower in settings of NAFLD and that similar alterations are also found in blood.

FRI-311

Gut lymphatic vascular disorder associates with severity of cirrhosis in non-alcoholic fatty liver disease

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is an important cause of cirrhosis. Enhanced intestinal/gut permeability is observed in about 40% patients with NAFLD. As there is a close association between altered gut permeability and its lymphatic system, in the current study, we investigated the gut lymphatic vessels in NAFLD patients.
Methods: Duodenal (D2) biopsies were collected from NAFLD patients with: compensated cirrhosis (n = 7), decompensated cirrhosis (n = 8) and non-cirrhotic controls (n = 5). Real time-PCR analysis for intestinal permeability and lymphatic marker genes including ZO1, OCLN, LYVE1, VEGFR3 and CCL2 were studied. Lymphatic vessel morphology was assessed by VEGFR3 immunohistochemistry (IHC) in the biopsies and plasma TNF-α levels were analyzed by ELISA.
Results: The expression of intestinal permeability gene, ZO1 was significantly downregulated (suggestive of increased intestinal permeability) in decompensated as compared to compensated and control groups ($p < 0.05$ versus both). The gene expression of lymphatic endothelial cell marker, VEGFR3 was substantially higher in decompensated as compared to controls ($p < 0.05$). A negative correlation was seen between the expression of ZO1 and VEGFR3 genes in decompensated patients. Gene expression of chemokine CCL2, an important marker of activated lymphatic endothelial cells, was upregulated in both groups as compared to controls. Histologically, VEGFR3 protein expression was evident in the lymphatic vessels which demonstrated a substantial increase in

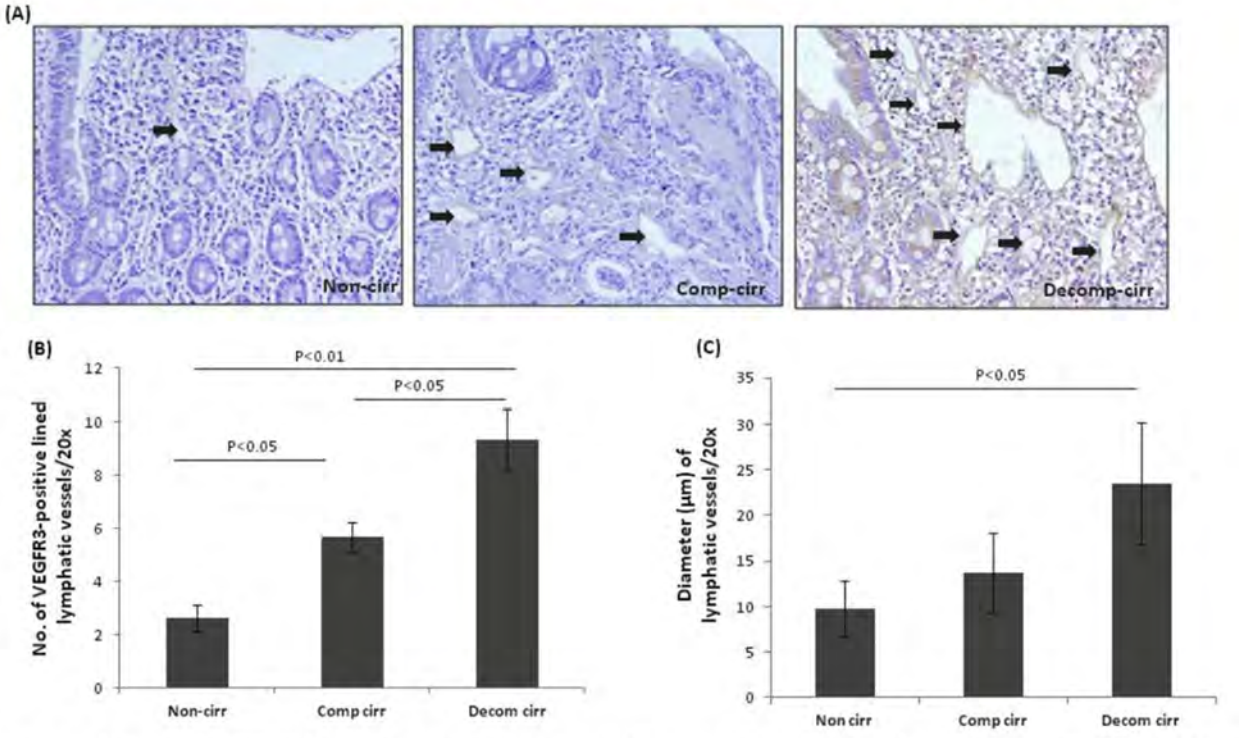

Figure: Lymphatic Vessels in NAFLD. (A) Representative images (20x) showing VEGFR3 immunohistochemical staining of duodenal biopsies in patients with NAFLD. (B) Histogram depicting quantification of VEGFR3-positive lymphatic vessels. (C) Histogram depicting diameter of lymphatic vessels. Data represents mean ± SD. n= 4 each.

decompensated as compared to compensated cirrhosis ($p < 0.05$). Morphologically, a marked dilation of VEGFR3-positive lymphatic vessels was observed in the mucosal and submucosal regions in biopsies of decompensated cirrhosis compared to controls (23.47 ± 6.6 versus 9.7 ± 3 μm, $P < 0.05$). Decompensated group also displayed higher plasma TNF-α levels as compared to other two groups ($p < 0.001$ versus both). Increased VEGFR3 protein expression correlated significantly with MELD scores ($r = 0.86$, $p = 0.01$).
Conclusion: Our results demonstrate that patients with decompensated NAFLD cirrhosis show increased intestinal permeability that correlates with deranged and altered VEGFR3-positive lymphatic vessel density. To summarize, gut lymphatic vascular disorder strongly associates with severity of cirrhosis in NAFLD.

FRI-312
Increased levels of bile acid in feces plays an important role in pathophysiology of non-alcoholic steatohepatitis
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Background and aims: Recently, several evidences suggest that the bile acid (BA) plays important roles in the pathogenesis of (NASH). Previous reports demonstrated the increased serum BA in NASH patients compared to non-NASH patients. It is reported that the increased level of BA improves the gut-permeability which plays an important role in NASH pathogenesis. The aim of this study is to assess the change of fecal BA level in NASH patients and mechanism that explains the relationship between BA and the NASH pathogenesis.
Method: In the human study, 15 healthy control subjects and 30 patients with biopsy-proven NASH (15 mild fibrosis [F0-2] and 15 severe fibrosis [F3-4]). A single stool sample was collected from each participant. Metabolomics analysis was used to analyze the BA level contained in patient's fecal sample. In the animal study, Eight-week-old male C57BL/6J mice were randomly distributed into 7 groups, each containing 10 mice: a chow diet fed mice (B), a high-fat high-fructose high-cholesterol diet fed mice (H) which is diet-induced (NASH) model with liver fibrosis of mice, B + 0.5% cholic acid (CA)-fed mice (BC), and H + 0.5% CA fed mice (HC) group, and H + 0.3% cholestimide-fed mice (HCL), Chow-fed germ-free mice (GFB), CA-fed germ-free mice (GFC). Gut-permeability were assessed by using fluorescein isothiocyanate (FITC).
Results: In the human study, fecal cholic acid was significantly increased in NASH patients with F3-4 to the healthy control. Similarly, the fecal total bile acid level and cholic acid level were significantly increased in the H group compared to the B group in mouse study. Gut permeability measured by the FITC absorbance, serum endotoxin levels, hepatic free cholesterol, and CYP7a1 mRNA level were all significantly increased in the H, HC, and BC group compared with B group. All of them were improved in the HCL group. Moreover, Gut permeability measured by FITC absorbance as well as serum endotoxin level were increased in the BC group compared to the B group. Surprisingly, neither intestinal permeability in GFB nor GFC were altered significantly, suggesting that the increase in gut-permeability by CA is mediated by gut-microbiota, rather than by the direct action of CA. The significant decrease in fecal BA levels and increase in ALT/AST levels were observed in hepatic CYP7a1 (enzyme for BA synthesis) knock down by CYP7a1 SiRNA to H mice, despite the increased gut permeability in the same mice, suggesting that the inhibition of BA synthesis lead liver injury but improve the gut permeability in diet induced NASH model mice.
Conclusion: Our results suggest that the increase in bile acid synthesis may be a part of protective effect for liver damage that was triggered in reaction to the pathogenesis of NASH, which however, lead to the increased gut permeability. Taking together, removing the excess bile acid may be the novel therapeutic approach for the treatment of NASH.

FRI-313
A novel farnesoid X receptor agonist, TERN-101, reduces liver steatosis, inflammation, ballooning and fibrosis in a murine model of non-alcoholic steatohepatitis
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Background and aims: The Farnesoid X Receptor (FXR) is a nuclear hormone receptor that controls the conversion of cholesterol into bile acids and maintains homeostasis of multiple metabolic pathways. Activation of the FXR pathway using synthetic FXR agonists may help control metabolic disorders such as non-alcoholic steatohepatitis (NASH). TERN-101, a novel non-steroidal agonist of FXR in early stage clinical trials, was tested in a mouse model of NASH.
Method: Male C57/Bl6J mice were fed a high fat diet (60% kcal) to induce obesity (> 36g mouse) prior to daily oral drug treatment and biweekly intraperitoneal carbon tetrachloride (CCL_4) treatment. Following 28 days of TERN-101 dosing, serum lipids, liver enzymes and liver tissue were analyzed for changes from baseline. Plasma 7-alpha-hydroxy-4-cholesten-3-one and RNA levels of genes known to be regulated by FXR in liver and intestinal tissue were measured as biomarkers of FXR activation.
Results: In diet-induced obese mice chronically treated with CCL_4 and TERN-101, TERN-101 caused a dose-dependent increase in FXR-mediated gene expression showing on-target activity inducing pathways that modulate lipid metabolism, inflammation and fibrosis. The NAFLD activity score was markedly reduced by all doses of TERN-101 tested with an 80%, 58% and 67% reduction from baseline at 100, 30 and 10mg/kg (mpk, $p < 0.0001$), respectively. Steatosis was reduced to healthy control (lean mice) levels at 30mpk and hepatocellular ballooning at 100mpk ($p < 0.001$). Hepatic inflammation was also reduced in TERN-101 treated mice ($p < 0.01$ at 10mpk). The reduction in liver steatosis seen by histopathology correlated with a reduction in liver triglycerides seen at all doses of TERN-101, with liver levels equivalent to healthy control mice at 30mpk ($p < 0.001$). Triglycerides and total cholesterol were also reduced in the serum of TERN-101 treated mice. In addition, TERN-101 reduced the liver fibrotic area, with a 32%, 26% and 26% reduction from baseline at 100, 30 and 10mpk ($p < 0.0001$), respectively. Finally, a dose-dependent reduction in the serum ALT and AST levels in TERN-101-treated mice was seen.
Conclusion: TERN-101 is a potent agonist of FXR that reduces liver steatosis, ballooning, inflammation and fibrosis in a mouse model of NASH while also lowering serum triglycerides, total cholesterol and alanine aminotransferase levels.

FRI-314
A novel semicarbazide-sensitive amine oxidase inhibitor, TERN-201, reduces NAS and fibrosis in rodent models of non-alcoholic steatohepatitis
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Background and aims: Semicarbazide-Sensitive Amine Oxidase (SSAO), also known as vascular adhesion protein (VAP-1), is a dual function cell adhesion molecule with a unique amine oxidase ecto-enzyme activity significantly increased in patients with Non-Alcoholic Steatohepatitis (NASH) and independently associated with liver fibrosis stage. SSAO catalyzes 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. SSAO inhibition is anticipated to reduce inflammation and fibrosis in NASH patients. TERN-201, a novel, selective SSAO inhibitor was tested in rodent models of NASH and fibrosis.
Method: Diet-induced obese (DIO) mice fed a high-fat diet or non-obese rats were orally dosed with TERN-201 daily and biweekly or triweekly intraperitoneal carbon tetrachloride (CCL_4) treatment, respectively. Following 28 days of dosing, liver tissue was analyzed by histology for changes from baseline in relevant parameters of the Non-Alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) using hematoxylin and eosin staining and fibrosis using Sirius Red staining. RNA analysis of genes known to be induced in fibrosis and inflammation was used to study the mechanism of action of TERN-201.
Results: DIO mice chronically treated with CCL_4 and TERN-201 had a dose-dependent increase in plasma methylamine, showing SSAO target engagement in dosed mice. The NAFLD activity score was reduced by TERN-201 treatment with a 42% reduction from baseline at 20 mg/kg (mpk, $p < 0.005$), primarily driven by a reduction in hepatocellular ballooning (80% reduction from baseline at 20mpk, $p < 0.05$). Liver inflammation was elevated in CCL_4-treated rats and was reduced ~80% from baseline at 20mpk TERN-201 ($p < 0.0001$). This correlated with a similar reduction in liver CD11b RNA suggesting inflammation may be reduced by reduction in inflammatory cells infiltrating the liver. Fibrosis was also reduced ~57% at this dose ($p < 0.05$) with a reduction in collagen1a1 RNA of ~80% at 20mpk TERN-201 ($p < 0.0001$).
Conclusion: TERN-201 is a potent SSAO inhibitor effective in rodent models of NASH and fibrosis. Daily dosing of TERN-201 reduced the NAFLD activity score in a diet-induced obese mouse model of NASH, primarily through a reduction in hepatocyte ballooning. TERN-201 reduced liver inflammation and fibrosis in a rat CCL_4 model of liver fibrosis.

FRI-315

Lipoprotein lipase deficiency in myeloid cells aggravates the progression of non-alcoholic steatohepatitis

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Background and aims: Lipoprotein Lipase (LPL), an enzyme that hydrolyses triglyceride-rich lipoprotein particles, is mainly expressed in macrophages, adipose and muscle tissue. Moreover, LPL may regulate macrophage polarization. While absent in healthy liver, hepatic LPL expression is upregulated in murine non-alcoholic fatty liver disease (NAFLD). Our aim was to evaluate the source of LPL in non-alcoholic steatohepatitis (NASH).
Method: LPL expression was assessed in samples from healthy liver tissue and human NASH by qPCR. Moreover, LPL expression was quantified in different liver cell populations isolated from mice. $LPL^{flox/flox}$ × Lysozyme2-Cre recombinase (LysM-Cre) mice were used to create a myeloid cell-specific LPL knockout. Crossing $LPL^{flox/flox}$ mice with Albumin-Cre recombinase (Alb-Cre) mice enabled a hepatocyte-specific LPL deletion. Mice were fed a high fat, high carbohydrate, high cholesterol diet for 24 weeks to induce NASH. The NASH phenotype was characterised by histology, qPCR and ALT levels.
Results: LPL expression in healthy liver was low but significantly increased in livers of patients with NASH. Liver macrophages were identified as the major source of the low basal LPL expression in healthy livers. Also in NASH, hepatocytes are not the source of the increased LPL expression as deletion of LPL in hepatocytes does not affect the hepatic LPL expression level in mice with NASH. Consistent with this, hepatocyte-specific LPL deletion did not affect NASH severity in mice compared to LPL-competent littermates. In contrast, LPL deletion in myeloid cells significantly blunted the NASH-induced increase of hepatic LPL expression. This lead to a more severe NASH phenotype in the LysM-Cre positive mice indicated by significantly higher expression levels of pro-inflammatory (like TNFalpha; 1.6 fold), pro-apoptotic (like Bim; 1.4 fold) and pro-fibrotic genes (like Col1alpha1; 1.9 fold). Sirius red staining of fibrillary collagen indicated enhanced NASH-induced liver fibrosis in mice with myeloid cell-specific LPL deficiency compared to wildtype littermates.
Conclusion: The enhanced hepatic LPL expression in NASH is caused by liver macrophages rather than hepatocytes. LPL in liver macrophages appears to attenuate NASH progression. According to the results, LPL alteration in liver macrophages could be a potential tool for NASH therapy.

FRI-316

Liver fetuin-A in activated macrophages is a key feature of non-alcoholic steatohepatitis in mice and humans

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Background and aims: Fetuin-A, a plasma multifunctional protein known to play a role in insulin resistance, is usually presented as a liver secreted protein. However, fetuin-A adipose tissue production has been also described. Here, we evaluated fetuin-A production by the liver and the adipose tissue during NAFLD-NASH development.
Method: Male foz −/− mice fed a normal diet (ND) or a HFD for 4 (short term HFD or SHFD), 12 (long term HFD or LHFD) or 30 weeks (very long term HFD or VLHFD) were used to induce early steatosis, marked steatosis or definite fibrosing NASH, respectively. Fetuin-A was evaluated by ELISA, PCR, Western-blot and immunofluorescence in those animals and in NAFLD-NASH patients undergoing bariatric surgery (n = 5) and from the hepatology clinic (n = 49). Fetuin-A was also quantified in hepatocyte and adipocyte cell culture experiments.
Results: Foz −/− mice fed a SHFD developed liver steatosis and increased circulating levels of fetuin-A compared to ND fed mice. On liver slides, fetuin-A and steatosis were mainly located in the centrilobular region. In LHFD mice, macrophage activation was observed within the liver together with elevated fasted plasma glucose, raised fetuin-A blood levels and localization of fetuin-A immunostaining in steatotic hepatocytes. VLHFD mice were characterized by the occurrence of NASH. Fetuin-A was located at this time-point not only in steatotic hepatocytes but also in some macrophages forming lipogranuloma. A high quantity of fetuin-A protein was present within the adipose tissue. However, compared to the adipose tissue, liver fetuin-A mRNA expression was significantly higher.
In humans, fetuin-A was located in steatotic hepatocytes in NAFLD-NASH patients and within some lipogranuloma and macrophage clusters in NASH patients. Circulating fetuin-A was significantly correlated with blood glucose levels rather than with NASH severity in terms of fibrosis. Liver m-RNA expression was 5000 times increased compared to adipose tissue mRNA expression.
In cell culture, fetuin-A was evidenced only in the supernatant of hepatocytes but not in the supernatant of adipocytes.
Conclusion: Fetuin-A is produced by steatotic hepatocytes at early time points in NAFLD and correlates with insulin resistance both in mice and humans. In NASH, fetuin-A also co-localizes with activated liver macrophages. Future experiments on foz −/− mice will help to progress in the role of fetuin-A on NASH pathogenesis and macrophage activation.

FRI-317

Progression of fatty liver disease to steatohepatitis and liver fibrosis is associated with altered Oncostatin M type I and type II receptor expression

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Background and aims: One of the cytokine families most prominently associated with liver inflammation, obesity and metabolic response, is the family of IL-6-type cytokines, in particular IL-6 itself, but also its less well investigated relative oncostatin M (OSM). IL-6 and OSM have been shown to be intimately connected with our body's reaction to physical, metabolic and pathogen-induced stress. Reports over the last two decades have clearly pointed out that these cytokines have anti-inflammatory as well as pro-inflammatory signaling activities which very much depend on the cellular and physiological context in which they are released or the receptors they utilize for signaling. Much attention has been given to IL-6 as well as its mode of action, however, recent studies implicate that OSM is much more strongly involved in disease pathogenesis than anticipated so far. Its physiology, however, is far less well understood. Here, we investigate its potential contribution to the progression of liver diseases.
Method: Since OSM can signal via two receptor complexes which might have more pro- or anti-inflammatory activities, respectively, we characterized their expression profile in vivo in liver samples from different rodent models of liver inflammation and fibrosis or in vitro in hepatoma cell lines stimulated with different inflammatory cytokines using quantitative real-time PCR, Western blot analysis and flow cytometry.
Results: We found a distinct decrease of components of the type I OSM receptor complex in livers from mice fed different high fat diets, after intraperitoneal injection of pro-inflammatory cytokines or in Abcb4−/− mice. At the same time the type II OSM receptor complex appeared to be strongly upregulated. Similar observations were made in HepG2 cells treated with IL-1β. In vitro experiments carried out with pharmacological inhibitors of various signaling pathways indicated an important role of the mitogen-activated protein kinases ERK1/2 in the downregulation process for the type I receptor complex.
Conclusion: Dysregulation of the expression levels of the type I and type II OSM receptor complexes appears to be a conserved feature in the progression of inflammatory liver diseases. Consequently, alterations in OSM receptor levels might be a possible diagnostic marker for the assessment of progressive liver inflammation.

FRI-318

Effects of fatty acids and polyphenols from extra virgin olive oil in a murine animal dietary model knockout for the LDL receptor

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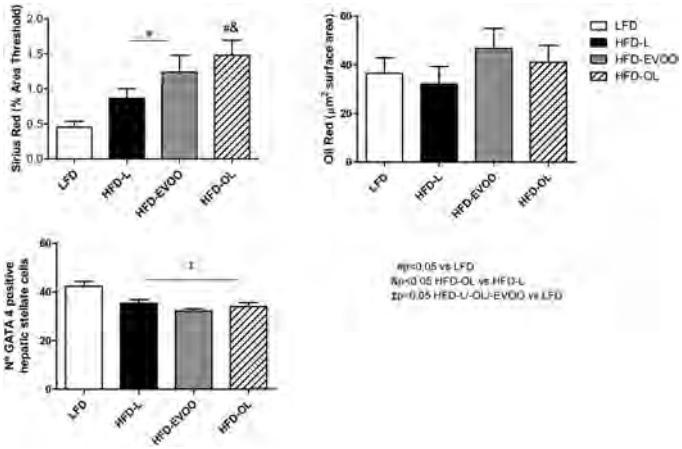
Background and aims: Metabolic syndrome (MS) is the combination of health risk factors which includes obesity, insulin resistance, dyslipidemia and non-alcoholic fatty liver disease. The consumption of olive oil can prevent its onset. Therefore, our aim was to evaluate the pathophysiological changes caused by MS in a murine animal model lacking from the LDL receptor that were fed with three different diets: high fat diet based on lard (HFD-L), high fat diet based on monounsaturated fats from extra virgin olive (HFD-MUFA-EVOO) and high fat diet based on monounsaturated fats from extra virgin olive oil rich in polyphenols (HFD-MUFA-OL).
Method: KO Leiden LDLR−/− female mice, 5 weeks of age (n = 120), were distributed in 4 groups of 30 animals and fed, during 8 months, with different diets: control, HFD-L (45% of caloric intake coming from lard), HFD-MUFA-EVOO (45% of caloric intake coming from olive oil) and HFD-MUFA-OL (45% of caloric intake coming from olive oil rich in polyphenols). We evaluated their body weight (BW), lipid profile (LDL, HDL, triglycerides and total cholesterol levels), glycemia, intraperitoneal glucose tolerance test (IPGTT), insulinemia, transaminases (AST and ALT) and liver histology (H-E, Oil red, GATA 4 and Sirius Red). Moreover, we studied the mechanisms involved in SM with a liver microarray analysis and we checked the expression of genes involved in these routes by RT-qPCR.
Results: KO Leiden LDLR−/− mice developed MS with severe hepatic damage. All mice fed with a HFD showed significant ($p < 0.001$) increased BW vs control fed mice. KO-HFD-MUFA-OL and KO-HFD-MUFA-EVOO mice showed significant increase in glycemia ($p < 0.05$), insulinemia ($p < 0.05$) and liver damage (transaminases, fatty liver and fibrosis) ($p < 0.05$) vs KO-HFD-SFA. KO-HFD-MUFA-OL mice showed significant increase in total-cholesterol ($p < 0.05$) vs KO-HFD-L. Ingenuity Pathway Analysis confirmed deregulation of metabolic routes such as non-alcoholic fatty liver disease and fatty acid degradation and metabolism in all high fat diets. Individual RT-qPCR confirmed the results of the Array.



Conclusion: Thus, the HFD-MUFAs did not improve the liver damage and not reduce metabolic abnormalities associated with HFD induced fatty liver disease in mice. Our data suggest that Leiden LDLR−/− strain are susceptible to suffer from to severe liver damage when fed with HFD, regardless of the lipid profile of the diets, including the HFD-MUFA-OL group.

FRI-320

TM6SF2 silencing impairs lipid metabolism and trafficking in HepG2 cells carrying the I148M PNPLA3 variant and MBOAT7 deletion

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Background and aims: The inter-individual variability in phenotype observed in patients affected by non-alcoholic fatty liver disease (NAFLD) may be attributable to genetics. The I148M PNPLA3 and E167K TM6SF2 variants alongside the rs641738 polymorphism in MBOAT7/TMC4 locus represent the main genetic risk factors for NAFLD development and progression. We previously generated an in vitro model of steatosis by inducing full knockout of MBOAT7 in HepG2 hepatoma cells. Aim of this study was to investigate whether TM6SF2 silencing impacts on lipid homeostasis in this model.
Method: We silenced TM6SF2 in HepG2 cells which are homozygous for the I148M PNPLA3 variant and full knockout for MBOAT7 by Crispr/Cas9 technology (PNPLA3 148M/M MBOAT7−/− TM6SF2−/−). We further analyzed gene expression in 125 severely obese patients (Bariatric Cohort), of whom RNA-seq data were available.
Results: As expected, TM6SF2 mRNA and protein levels were reduced in PNPLA3 148M/M MBOAT7−/− TM6SF2−/− cells compared to PNPLA3 148M/M MBOAT7−/− ($p < 0.01$), along with the expression of genes involved in lipoprotein assembly (MTTP) and Triglycerides (TG) synthesis (DGAT2), usually co-expressed with TM6SF2 ($p < 0.05$). Moreover, cells lacking TM6SF2 showed a complete suppression of TG-rich lipoproteins secretion and a slight reduction in TG release ($p < 0.05$). The mRNA levels of genes-related to de novo lipogenesis (DNL), cholesterol biosynthesis and β-oxidation were also decreased ($p < 0.01$). Conversely, lipid droplets content was similar to those of PNPLA3 148M/M MBOAT7−/− cells, probably due to lipid synthesis and removal balancing. At univariate analysis, the expression of DNL ($p < 0.0001$), cholesterol ($p < 0.01$) and TG synthesis genes ($p < 0.001$) as well as circulating TG ($p < 0.05$) positively correlated with TM6SF2 mRNA levels in the Bariatric cohort. Similar to PNPLA3 148M/M MBOAT7−/− TM6SF2−/− cell model, at linear regression analysis TG synthesis was progressively decreased in patients who carry an increasing number of risk variants ($p = 0.02$).
Conclusion: We firstly generated a model of hepatocytes carrying mutations in genes involved in NAFLD predisposition. TM6SF2 silencing impairs lipid metabolism and trafficking, without altering lipid droplets content. Moreover, in obese patients, TG synthesis correlated with increasing number of risk variants. Further studies are required to investigate the impact of PNPLA3 148M/M MBOAT7−/−TM6SF2−/− phenotype to hepatic injury and/or malignant transformation.

FRI-321

Hepatocyte expression of the protein kinase ERK5 regulates insulin sensitivity

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Background and aims: Insulin resistance is a key element in the development of non-alcoholic fatty liver disease (NAFLD). The extracellular signal-regulated kinase 5 (ERK5) is a member of the mitogen-activated protein kinase (MAPK) family, and is highly expressed in the liver. ERK5 regulates the biologic actions of hepatocellular carcinoma cells and is critical for the development and growth of HCC. We recently generated hepatocyte-specific ERK5 knock-out mice (ERK5ΔHep). The aim of this study was to investigate the potential role of ERK5 in the insulin resistance associated with NAFLD.
Method: ERK5ΔHep and control mice were fed with a high-fat diet (HFD) for 16 weeks. At the end of the experiment, glucose tolerance test (GTT) and insulin tolerance test (ITT) were performed. A murine hepatocyte cell line was silenced for ERK5 using lentiviral vectors. Mitochondrial depolarization was assayed using the TMRE staining protocol. Measurement of mitochondrial mass was performed by flow cytometry using mitotracker dye and OXPHOS metabolism was measured with Seahorse analyzer.
Results: ERK5ΔHep mice subjected to HFD showed reduced insulin sensitivity in comparison to control group, as indicated by both GTT and ITT, whereas body weight was similar. In cultured hepatocytes ERK5 silencing led to reduced phosphorylation levels of Akt following insulin stimulation. Mitochondrial dysfunction is considered a critical component in the development of insulin resistance. Measurement of mitochondrial membrane potential showed a strong depolarization ERK5-silenced cells in comparison to control cells. We next evaluated the metabolic status of MMH through seahorse assay, and observed a clear shift from mitochondrial OXPHOS to glycolysis in cells with ERK knockdown. Moreover, flow cytometric assay showed an increased mitochondrial mass in ERK5-deficient cells. The transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a pivotal regulator of mitochondrial biogenesis and function, was overexpressed in ERK5-deficient cells, representing a possible link between ERK5 deficiency and the occurrence of insulin resistance.
Conclusion: Our study provides the first evidence that ERK5 loss induces insulin resistance in vivo in a NAFLD model. Impairment of mitochondrial function appears a major mechanism in mediating this effect.

FRI-322

Metabolic inflammation: The role of chemokine C-C motif ligan 2 in the crosstalk between liver tissue and muscle

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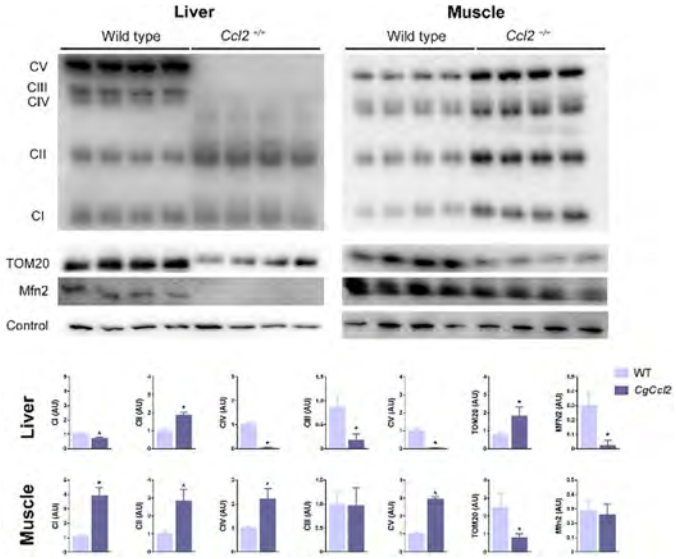
Background and aims: Chronic low-grade systemic inflammation is a compromised management of excessive energy intake and represents a significant factor that contributes to development of comorbidities, including non-alcoholic fatty liver disease (NAFLD). NAFLD is a metabolic abnormality with a strict inter-relationship derived to metabolically compromised tissues, such as liver and muscle. Chemokines play an important role in NAFLD initiation by multiple pathogenic drives; including mitochondrial dysfunction, autophagy and acute alterations into metabolism. The aim of this study was to determine the effect of Chemokine (C-C motif) Ligand 2 (CCL2) overexpression, a proinflammatory chemokine, can influence in the metabolic homeostasis in liver and muscle to understand the origin and progression of NAFLD.
Method: We carried this study using a cisgenic *Ccl2* overexpression mouse and wild-type C57BL/6J as a control for 22 weeks. After this period, we determined the liver and muscle status by biochemical and histological examinations. We evaluate the state of the AMPK/mTOR pathway and performed target metabolomics assays of energy and one carbon metabolism intermediaries (UHPLC-ESI-QqQ-MS and GC-EI-QTOF-MS) to understand the metabolic response.
Results: *Ccl2* overexpression was associated with hepatic metabolic alterations, including steatosis, dyslipidemia, hyperglycemia and high concentration of liver injury markers. These histological and biochemical alterations were associated with a liver disturbance in the mitochondrial oxidative phosphorylation (OXPHOS) complex, TCA cycle and transmethylation pathway. All of them, induce disturbing in the hepatic ATP synthesis. Contrary, muscle metabolic

analysis showed an important metabolic flexibility from liver alterations. We observed an increase in the catabolism mechanisms involved in energy synthesis. Specially, by an hyperactivation of OXPHOS activity, significantly increase of β-Hydroxybutyrate and lactate concentration as an ATP alternative source; together with an upregulation of pAMPK activity and autophagy.



Conclusion: We report that CCL2 is a potent targetable approach to NAFLD progression. In the same way, understanding the ability of the organism to adapt according to changes in metabolic and energetic demand it is essential to comprehend the progression and evolution of this pathology.

FRI-323

Pegbelfermin (BMS-986036) reduces serum levels of secondary bile acids in patients with non-alcoholic steatohepatitis

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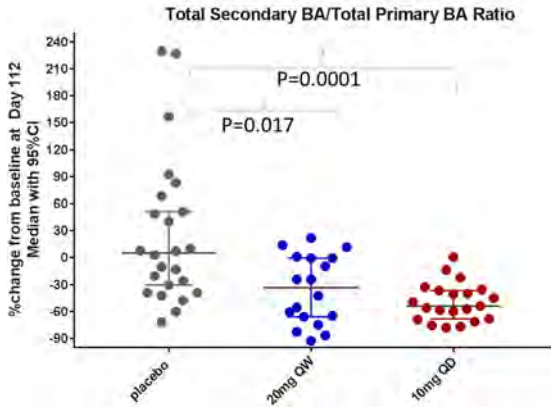
Background and aims: Bile acids (BAs) regulate cholesterol homeostasis and lipid digestion, and act as signalling molecules. Primary (1°) BAs (cholic acid [CA] and chenodeoxy-CA) are produced in the liver; the secondary (2°) BAs (deoxy-CA [DCA] and litho-DCA) are produced by the gut microbiome from 1° BAs. The 2° BA DCA and its conjugates glyco-DCA (GDCA) and tauro-DCA (TDCA) are elevated in patients (pts) with non-alcoholic steatohepatitis (NASH). Increases in DCA and related conjugates are linked to elevated hepatotoxicity, hepatocellular carcinoma (HCC), and colon cancer rates. Pegbelfermin (BMS-986036) is a PEGylated analogue of human fibroblast growth factor 21 (FGF21), a key regulator of energy metabolism. In the phase 2 trial MB130-045 (NCT02413372) in pts with NASH and fibrosis (stage 1-3), pegbelfermin significantly decreased hepatic steatosis and improved biomarkers of fibrosis, metabolic parameters, and markers of hepatic injury over 16 weeks. This exploratory, post hoc analysis of MB130-045 evaluated the effect of treatment (tx) with pegbelfermin on BAs.
Method: Serum samples were collected on Days 1, 57, and 112 during study MB130-045. Samples were analysed using ultra high-performance liquid chromatography and mass spectrometry to assess serum BA levels. Statistical analyses compared data from the pegbelfermin tx groups (once daily [QD] and once weekly [QW]) with the placebo (PBO) group using nonparametric comparisons with control using the Steel method; p values for each BA was adjusted for multiple comparisons using Bonferroni correction.
Results: Serum samples from 63 pts were available for analysis (PBO, n = 24; pegbelfermin QD, n = 21 and QW, n = 18). The median decrease from baseline in DCA, GDCA and TDCA ranged from 61%-84%. Significant reductions in serum concentrations of DCA, GDCA, and TDCA were observed in both pegbelfermin QD and QW groups vs PBO on Days 57 and 112 ($p < 0.005$). 1° BAs were not significantly changed following pegbelfermin tx. The ratio of total 2° BAs:total 1° BAs was significantly reduced with pegbelfermin QD and QW tx vs PBO ($p < 0.05$; figure). Additionally, decreases in 2° BAs resulted in a trend of lower total BAs ($p < 0.02$).



Conclusion: Pegbelfermin tx in pts with NASH and fibrosis resulted in the reduction of serum 2° BAs and the 2° BAs:1° BAs ratio. 2° BAs are associated with elevated risk of hepatotoxicity and HCC. Further investigation is needed to understand the mechanisms mediating the effects of pegbelfermin on BAs, such as BA synthesis and absorption, and microbiome activities.

FRI-324

Introducing a new pre-clinical model of advanced NASH that mimics the main pathophysiologic characteristics and transcriptomic signature of the human disease

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Background and aims: The lack of proper NASH animal models represents a limitation for studying the pathophysiology of this disease and for generating new therapeutic strategies. In a previous communication we described the development of a new pre-clinical rat model of mild NASH following an experimental protocol called "Barcelona Nash (BarNa) model," which combines CCl_4 inhalation with a high fat and high cholesterol diet for 10 weeks. The main aim of the present study was to reformulate this procedure to obtain a wider and more severe spectrum of the disease.
Method: Male Wistar rats were exposed to a 24-week BarNa model protocol consisting in 8 weeks of CCl_4 inhalation + phenobarbital, followed by 16 weeks of high fat and cholesterol diet + CCl_4. The BarNa model was compared to control rats matched to age (n = 6 per group). The following parameters were evaluated: steatosis and metabolic syndrome, lipotoxicity, cell death, inflammation, hepatic fibrosis and portal hypertension. Moreover, and to identify the gene sets commonly de-regulated between NASH patients and rats undergoing the BarNa model, whole hepatic transcriptome sequencing was performed in rat liver tissue and data compared to two independent cohorts of NASH patients using pathway enrichment analysis.

Results: When compared to control animals, the BarNa rats exhibited ($p < 0.05$ in all comparisons):
1-Steatosis and metabolic syndrome (+45% in body and fat weight); −19% in relative hepatic weight; 45% of hepatic tissue positive for Oil-Red staining; NAS Score of 9.3; glucose intolerance accompanied by 110% in plasmatic insulin).
2-Lipotoxicity (+75% in lipid peroxidation) and cell death (+6-fold TUNEL; +300% cleaved-caspase 3; +90% transaminases).
3-Hepatic inflammation (+65%, +133% and +200% in the infiltration of macrophages positive for CD68 and CD163, and neutrophils, respectively).
4-Hepatic fibrosis (+47% in Collagen I protein expression with 15% of the hepatic tissue positive for Sirius-Red staining) and hepatic stellate cells activation (+500% protein expression of α-SMA and +200% in desmin).
5-Portal hypertension (+50% in portal pressure [13.26 ± 0.8 vs. 8.77 ± 0.4 mmHg] as a consequence of hepatic vascular resistance increase [12.7 ± 2.3 vs. 5.1 ± 0.7 mmHg·min·ml^{-1}·g].

Analysis of the whole hepatic transcriptome evidenced that the BarNa model shares de-regulations in a significant part of pathways involved in the human disease pathophysiology including: insulin resistance, lipid metabolism, cell death, inflammation, fibrosis, endothelial dysfunction and mitochondrial dysfunction.
Conclusion: The present study defines a pre-clinical model of advanced NASH that mimics a broader spectrum of the human disease and shares a significant part of its gene signature. We herein propose the BarNa model as a reliable tool for studying the pathophysiology of NASH and for the development of new therapies.

FRI-325

rs641738 C > T variant near MBOAT7-TMC4 increases risk of fibrosis, NASH, and HCC: A meta-analysis

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Background and aims: Several genetic variants have been associated with clinical outcomes and progression of non-alcoholic fatty liver disease (NAFLD). rs641738 C > T variant near MBOAT7-TMC4 was initially identified as reaching genome-wide significance on association with alcoholic liver disease and subsequently several cohorts have reported links to NAFLD, though data is not uniformly consistent with recent reports of no effect. MBOAT7 is proposed as an acyltransferase with influence on lipotoxicity via modulation of very long-chain phosphatidylinositols but how this intergenic variant influence MBOAT7 is unclear.
Therefore we performed a meta-analysis to establish the effect of rs641738 C > T on clinical, histological, and biochemical features of NAFLD.
Method: MEDLINE, Embase, Google Scholar, and abstracts from EASL and AASLD meetings were searched for 'MBOAT7,' 'rs641738,' and 'TMC4.' Two authors independently reviewed abstracts and extracted data. Studies were included if they used a validated method of genotyping and reported on clinical, radiological, histological, or biochemical features of NAFLD. Primary outcome was the association between advanced fibrosis (F3-4) and rs641738 C > T. Meta-analysis was performed using both fixed and random effects models, reporting heterogeneity between studies. Recessive and dominant models were tested throughout. GWAS meta-analysis data was searched using Phenoscanner and LocusZoom for clinical and biochemical outcomes associated with rs641738 C > T.
Results: 16 studies (24, 260 participants) were included in the meta-analysis. rs641738 C > T was associated with advanced fibrosis (odds ratio (OR) 1.34 (95% CI 1.04-1.74)) and the presence of fibrosis (F0 vs. F1-4): OR 1.37 (95% CI 1.11-1.68). rs641738 C > T was associated with increased odds of hepatocellular carcinoma: OR 1.47 (1.01-2.13) and T-allele was also associated with the presence of NASH: OR 1.37 (95% CI 1.08-1.72). However rs641738 C > T did not increase the chance of a diagnosis of NAFLD (OR 1.09 (95% CI 0.99-1.19) or change in hepatic fat fraction (mean difference +1.6% (95% CI −0.9% to +4.1%). rs641738 C > T was not correlated with biochemical traits of insulin resistance or dyslipidaemia.
Conclusion: rs641738 C > T variant near MBOAT7-TMC4 is associated with fibrosis, non-alcoholic steatohepatitis, and hepatocellular carcinoma, but not total hepatic fat. These data suggest rs641738 C > T variant affects lipotoxicity without influencing triacylglycerol accumulation. Further mechanistic work is needed to understand the function of this variant.

FRI-326

Preclinical evaluation of endothelial dysfunction by peripheral artery tonometry and its correlations with untargeted metabolomic profiles

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has been associated with Metabolic Syndrome, insulin resistance and diabetes. It represents also a cardiovascular risk factor. Endothelial Dysfunction (ED), the pathophysiological basis of Cardiovascular Diseases (CVD), is present in NAFLD pts. However, not all NAFLD patients have a clinically demonstrable ED. Untargeted Metabolomics is a novel and powerful method to discover biomarkers then was used to evaluate ED in NAFLD patients by PAT and to correlate it with metabolomic studies.
Method: Metabolomic signatures were obtained from 49 patients with biopsy proven NAFLD (33 NAFL;16 NASH)by means of mass spectrometry and were correlated with PAT scores performed with an EndoPAT 2000 device.
Results: A statistical analysis with the "Partial Least Square Discriminant Analysis" (PLS-DA) was used to class separation in metabolomic profiles between NAFL and NASH patients with and without ED (cut-off value of EndoPAT score of 0.51), and to reveal the metabolites principally contributing to class differentiation. PLS-DA score plot showed a significant differentiation of metabolomic profiles in patients with or without ED, both in NAFL and NASH ($R^2 = 0.985$, $Q^2 = 0.842$, $p < 0.001$ and $R^2 = 0.996$, $Q^2 = 0.939$, $p < 0.001$, respectively). In particular: Propionate, Butyrate, Fumarate, Phenilacetate, Erythrose, Stearic and Aspartic Acid in NAFL and Homovanillic acid, Choline, Stearic Acid, Linoleic Acid, Butyrate, Valeric Acid in NASH, were significantly impaired in patients with ED.
Conclusion: Metabolomic profiles of NAFLD patients showed a statistically different pattern in patients with and without ED. They could be a useful tool to predict CVD risk in both simple steatosis and NASH.

FRI-327

Liver mitochondrial hydrogen sulfide oxidation: From nutritional physiology to non-alcoholic fatty liver pathology

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) encompasses all liver lesions from isolated steatosis to non-alcoholic steatohepatitis (NASH). However, the mechanisms behind the

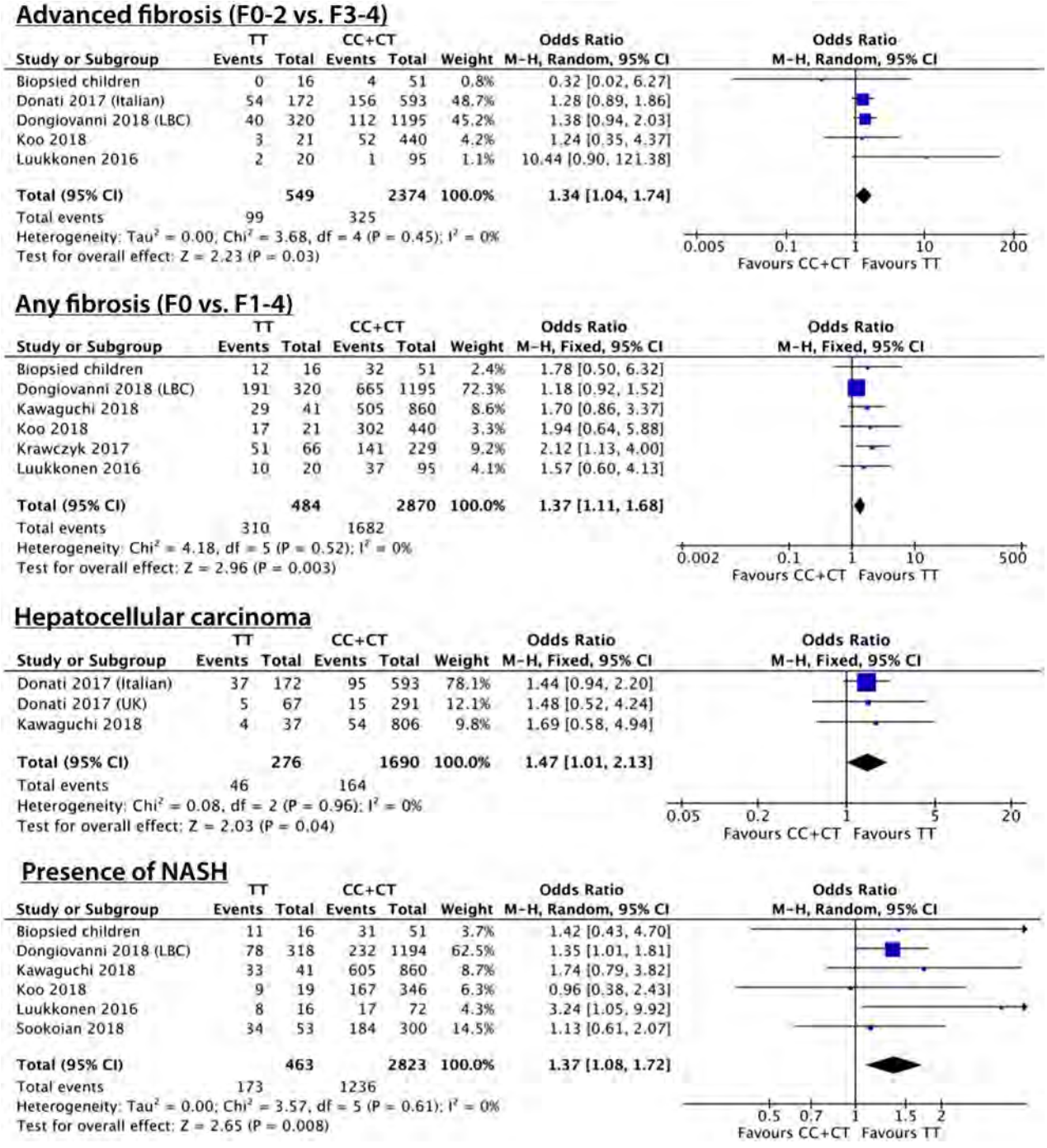

Figure: (abstract: FRI-325)

development of NAFLD are poorly grasped. Impaired liver biosynthesis of hydrogen sulfide (H_2S), the third gasotransmitter in mammals, has been reported in animal models of NAFLD, and H_2S supplementation was recently shown to prevent NASH development by decreasing hepatic steatosis, oxidative stress and inflammation. At high concentrations, H_2S blocks mitochondrial respiration through the inhibition of complex IV, whereas at low concentrations H_2S can be used as an inorganic energetic substrate for mammalian mitochondria. Our aim was to study if liver mitochondrial H_2S oxidation is regulated i) in different nutritional situations and ii) during NAFLD development, which currently remain totally unknown.

Method: Liver mitochondria were isolated from fed, 24h-fasted and re-fed C57Bl6/J mice as well as from mice fed a high fat-high sucrose (HFHS) diet to induce NALFD. Mitochondrial respiration and H_2S oxidation were measured using methods of oxygraphy (OROBOROS Instruments).

Results: Compared to fed mice, liver mitochondria from 24h-fasted animals presented a 2.4-fold decrease in the capacity to oxidize H_2S. Overnight refeeding after fasting restored mitochondria's ability of oxidizing H_2S, achieving values close to those observed in fed mice.

Regarding NAFLD development, mice fed a HFHS diet for 10 weeks, which led to increased body weight and adiposity, glucose intolerance but normal insulin sensitivity, exhibited unchanged liver mitochondrial H_2S oxidation capacity. However, after 20 weeks of HFHS diet that induced insulin resistance and NAFLD, liver mitochondrial H_2S oxidation was decreased by 1.3-fold. Importantly, the decrease in mitochondrial H_2S oxidation observed both in fasted and HFHS-fed mice occurred without any impairment of mitochondrial respiration.

Conclusion: In mouse liver, mitochondrial capacity to oxidize H_2S is under nutritional regulation and is impaired during NALFD development when insulin resistance is present.

FRI-329

Comparison of seladelpar and combinations with liraglutide or selonsertib for improvement of fibrosis and NASH in a diet-induced and biopsy-confirmed mouse model of NASH

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Background and aims: Complete resolution of non-alcoholic steatohepatitis (NASH) is challenging due to a multifactorial etiology of this complex disease. Combining therapies with complementary mechanisms of action may achieve better outcomes. Seladelpar, a potent PPAR delta agonist, attenuates multiple pathophysiologic pathways in NASH mouse models. Here we evaluate combinations of seladelpar with the GLP-1-R agonist liraglutide or the ASK1 inhibitor selonsertib in a diet-induced and biopsy-confirmed mouse model of NASH.

Method: Male C57BL/6J mice were fed a diet high in fat, fructose and cholesterol for 43 weeks. Mice with histologically confirmed steatosis (score ≥ 2) and fibrosis (stage ≥ 1) were randomized and treated daily for 12 weeks. Seladelpar, liraglutide, selonsertib, and obeticholic acid (OCA) were tested alone as were combinations of seladelpar with liraglutide (S+L) or selonsertib (S+Se) for their effects on fibrosis and NASH pathology. D_2O was administered to allow measurement of hepatic collagen fractional synthesis rate (FSR). Biochemical (hydroxyproline, ALT, AST, total triglycerides (TG) and total cholesterol (TC)), and liver histological (NAFLD Activity Score (NAS) and fibrosis) and RNAseq analyses were performed.

Results: Treatment with seladelpar alone or the S+L and S+Se combinations resulted in stark reductions in liver fibrosis as measured by hydroxyproline content compared to NASH vehicle and the other single agents ($p < 0.0001$). Morphometric analysis of picrosirius red staining gave similar results. Col 1α1 mRNA and other mRNA indices of fibrosis were significantly reduced with seladelpar, liraglutide and the S+L and S+Se combinations compared to NASH vehicle ($p < 0.0001$). A significant decrease in FSR of collagen I protein was observed with seladelpar, S+L, S+Se and liraglutide ($p < 0.05$). The proportion of mice with a 2-point or greater improvement in NAS was 82%, 100%, 67%, 36%, 17%, 8% and 0% for seladelpar, S+L, S+Se, liraglutide, selonsertib, OCA and NASH vehicle, respectively. Robust reductions in liver steatosis were observed: −56%, −76%, −43%, −43% and −36% for seladelpar, S+L, liraglutide, S+Se and OCA, respectively ($p < 0.0001$). Seladelpar reduced plasma ALT, AST, TG, TC and liver TG and TC, but these were further lowered in the S+L combination ($p < 0.05$).

Conclusion: Seladelpar had substantial anti-fibrotic and anti-NASH efficacy in a mouse model, but the anti-NASH activity is enhanced by combination with liraglutide.

FRI-331

Do N1-methylnicotinamide and nicotinamaide administration defferentially alleviated hepatic steatosis?

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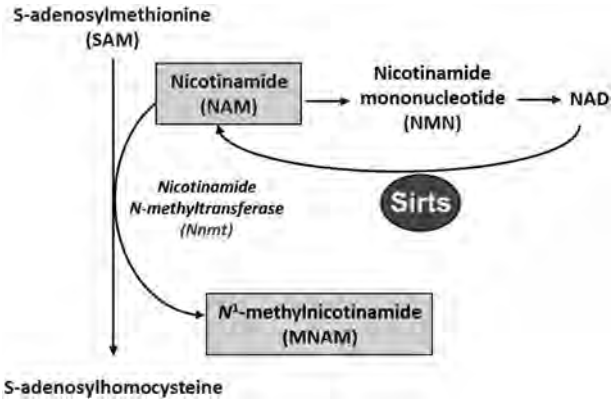
Background and aims: We previously reported that nicotinamide (NAM), a metabolite of NAD catalyzed by Sirtuins (Sirts), ameliorated hepatic steatosis (NAFLD) via Sirtuins (Sirts) activation by inhibition of fatty acid synthesis (EASL the international liver congress 2018 and NASH summit 2018). Interestingly, NAM is turned to nicotinamide mononucleotide (NMN) to replenish the attenuated NAD level in high fat diet (HFD); by contrast, NAM is turned to N^1-methylnicotinamide (NNMT) in normal diet (ND) designated as "NAM metabolic switch." MNAM also ameliorates NAFLD via Sirts activation (Hong S, et al. Nat Med. 2015;21:887-94). Therefore, we investigated MNAM as a therapeutic alternative for NAFLD.

Method: C57BL/6J mice (n = 40) were divided into 8 groups and fed with ND: ND+NAM (NAM mixed with ND to 0.1% wt/wt); ND+MNAM (MNAM mixed with ND to 0.1% wt/wt); ND+NAM+MNAM or HFD containing fat of 40%: HFD+NAM; HFD+MNAM and HFD+NAM+MNAM for 8 weeks. The contents of NAM-related materials in the liver, NAM, NMN, NAD, and MNAM were measured by LC/MS (Fig. 1). The expression of lipid metabolism-related genes was evaluated by real-time RT-PCR.

Results: MNAM administration was more effective in the reduction of body weight than NAM in HFD mice, leading to a similar body weight as ND mice. Combining NAM and MNAM on HFD had a stronger effect than administrating independently. HFD mice treated with NAM decreased the levels of NAD without effecting of MNAM, NAM, and MNM; however, HFD mice treated with MNAM significantly increased those of MNAM, NMN and NAD but not NAM. HFD mice treated with NAM+MNAM strongly increased all these four components. Interestingly, both SAM and MNAM similarly and completely suppressed the HFD-upregulated genes involved in fatty acid synthesis such as SREBP1c and fatty acid synthase. Lastly, the treatment with MNAM as well as NAM activated Sirtuins.



Conclusion: MNAM evidently attenuated NAFLD indicating that the hepatic steatosis preventive feature of *NAM* N-methyltransferase (Nnmt) knockout mice (Kraus D, et al. Nature. 2014;508:258-62) was

not due to reduction of MNAM, and that MNAM might directly activate Sirts. It is intriguing that MNAM also increased the contents of NMN and NAD, and that MNAM might attenuate the function of Nnmt to increase NMN and concomitant NAD^+ level to activate the Sirts. We believe MNAM as well as NAM have promising potentials in treating NAFLD. We are now checking metabolites of the microbiota and bile acid metabolism because we found both of them dramatically change in ND+NAM where NAM is mainly converted to MNAM (EASL NASH summit 2018).

FRI-332

Effect of combined farnesoid X receptor agonist and angiotensin 2 receptor blocker on established liver fibrosis in rats

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Background and aims: It is important to find agents with therapeutic effect on the established liver fibrosis for future clinical application. This study is designed to investigate the combination effect of INT747 with losartan on established liver fibrosis in rats fed a choline-deficient, L-amino acid-defined (CDAA) diet.
Methods: Fischer 344 rats given a choline-deficient L-amino-acid-defined (CDAA) diet for 12 weeks. After 4-week administration of CDAA diet, rats were administered either INT747, losartan or a combination of each at the dose of 30mg/kg/day for 8 weeks by oral gavage. The therapeutic effect of INT747 and losartan was evaluated along with liver fibrosis development, lipopolysaccharide (LPS)-toll like receptor 4 (TLR4) regulatory cascade, and intestinal barrier function. The direct inhibitory effect of both INT747 and losartan on activated hepatic stellate cells (Ac-HSCs) was assessed in vitro.
Results: The F344 rats fed with CDAA diet developed marked liver fibrosis with deposition of collagen fibers. Single treatment either with INT747 and losartan significantly attenuated development of liver fibrosis induced by a CDAA diet. The combination treatment with both agents exerted a more potent inhibitory effect as compared with either single agent along with the inhibition of hepatic mRNA expression of α-smooth muscle actin (α-SMA), Transforming Growth Factor-β1 (TGF-β1) and Toll-like receptor 4 (TLR4). LPS binding protein (LBP) mRNA expression and intestinal permeability were significantly attenuated by INT747 monotherapy and combination treatment, but were not significantly altered by losartan monotherapy. Semi-quantitative immunofluorescence microscopy revealed that INT747 and combination treatment reduced CDAA-induced inhibition of the expression of zonula occludens (ZO)-1 tight-junction-associated protein in intestinal epithelium, whereas Losartan had no significant effect on ZO-1 expression. In vitro, AT-II- and LPS-induced proliferation of Ac-HSC was significantly attenuated by losartan monotherapy and combination treatment. However, there was no significant effect of INT747 on Ac-HSC proliferation. Contrarily, ATII- and LPS-induced mRNA expression of TGF-β1, TLR4, and Myd88 were individually suppressed by INT747 or losartan. Combined therapy exerted more potent suppression than monotherapy with either agent.
Conclusion: INT747 and Losartan have a synergistic repressive effect on established liver fibrosis by reversing LPS-induced gut barrier dysfunction and suppressing HSC activation and proliferation. Combined treatment may represent a promising novel therapeutic approach for NASH and advanced fibrosis.

FRI-333

ATG7 genetic variant and defective autophagy: A novel risk factor for non-alcoholic fatty liver disease progression in patients with type 2 diabetes mellitus

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) represents an emerging cause of cirrhosis and hepatocellular carcinoma (HCC). Genetic factors play an important role in the pathogenesis of progressive NAFLD and HCC.
Method: We performed whole exome sequencing (WES) in 142 NAFLD-HCC cases from Italy and the UK, 59 Italian patients with NAFLD and advanced fibrosis, and 50 local healthy individuals. Clinical, biochemical data, personal and family history were also collected. Phenotypic characterization in carriers of the rs143545741 *ATG7* variant was performed.
Results: We have applied a novel bioinformatic pipeline for prioritization of rare variants predicted to severely impair protein function and increase the risk of progression to advanced NAFLD. Here we highlight a candidate loss-of-function variant in the ubiquitin-binding domain of *ATG7* as a novel risk factor for advanced fibrosis and NAFLD-HCC. ATG7 is involved in lipo-autophagy, a biological process of growing interest in liver biology and ATG7 deficient mice reportedly develop hepatomegaly and steatohepatitis. Moreover, autophagy may be involved in the pathophysiology of insulin resistance and type 2 diabetes mellitus (T2DM) through the regulation of pancreatic beta cells and insulin-target tissues (skeletal muscle, liver and adipose tissue). In our study, the rare rs143545741 variant (allelic frequency in the general population 0.001), encoding for the P426L protein variant, was associated with a 14-fold increased risk of advanced NAFLD ($p = 4.64*10^{-5}$, 95% CI = 4-33).
We identified 5 carriers of the *ATG7* variant. Four of them were male, 3 were overweight and two were obese; mean age was 66 ± 10 years. Two of these patients had NAFLD-HCC, while 3 had NAFLD and advanced fibrosis. There were no differences in the plasmatic concentrations of lipids, aminotransferases values, histological activity and BMI between carriers and non-carriers. Interestingly, a higher prevalence of T2DM in the group at risk was observed compared to patients negative for the genetic variant ($p = 0.04$) and all carriers had T2DM.
Conclusion: The rs143545741 C > T encoding for P426L variant in *ATG7* was associated with an increased risk of advanced NAFLD. The higher prevalence of T2DM in the mutated subjects supports a role of ATG7 in T2D development and/or a synergic effect with hyperglycemia in the progression of liver disease.

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Cerium oxide nanoparticles present antilipogenic and anti-inflammatory effects in rats with diet-induced non-alcoholic fatty liver disease

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. Oxidative stress and inflammation have been considered as key pathogenic mechanisms contributing to initiation and progression of injury. Cerium oxide nanoparticles (CeO_2NPs) have recently emerged as a powerful antioxidant, acting as ROS scavengers and anti-inflammatory agents. The current study was addressed to investigate the potential therapeutic effect of CeO_2NPs in an experimental model of NAFLD.

Method: Wistar rats were fed with a methionine and choline deficient diet (MCDD) for 6 weeks, receiving either 0.1 mg/kg of CeO_2NPs (n = 8) or vehicle (n = 7) twice a week during the 3rd and 4th week of MCDD intake. Biochemical parameters of liver function and hepatic fat content were assessed. Hepatic triglycerides (TG) and cholesterol esters (CE) were extracted and fatty acids (FAs) were quantified. Moreover, hepatic mRNA expression of genes involved in oxidative stress response and fatty liver metabolism was evaluated.

Results: As expected, in addition to having increased transaminases, hypercholesterolemia and hyperbilirubinemia, MCDD fed animals showed a dramatic increase in liver fat content as reflected by abundant intrahepatocellular lipid droplets (LD). CeO_2NPs administration to MCDD rats reduced the size and content of LD. This was associated with a decrease in the lipid components:TG and CE. TG monounsaturated fatty acids were significantly decreased after treatment, which was mainly due to a reduction in oleic acid. CeO_2NPs administration significantly decreased CE FAs, including saturated (myristic, pentadecylic and palmitic acids) and unsaturated FAs (palmitoleic, oleic, linolenic and gamma-linolenic acids). CeO_2NPs treatment also resulted in a significant increase in docosahexaenoic acid, a modulator of inflammatory response which has been considered as a potential treatment for NAFLD. Finally, CeO_2NPs administration reduced the expression of genes related to FA oxidation, adipokine signalling and antioxidant metabolism such as IL1b, Cpt1a and Ncf1.

Conclusion: CeO_2NPs attenuate inflammation, hepatic steatosis and partially revert the expression of genes involved in lipid metabolism and oxidative stress response in MCDD rats. These results demonstrate for the first time that CeO_2NPs have antilipogenic effect on rats with diet-induced NAFLD and suggest that they could be of therapeutic value in this condition.

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Lect2, a new hepatokine regulating cholesterol metabolism in liver during non-alcoholic fatty liver disease

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Background and aims: **N**on-**A**lcoholic **F**atty **L**iver **D**isease (NAFLD) is becoming the most common disease worldwide due to the growing epidemic of obesity and metabolic syndrome. NAFLD encompasses a broad spectrum of chronic liver diseases ranging from simple hepatic steatosis (NAFL) to its aggressive manifestation called **N**on-**A**lcoholic **S**teato**H**epatitis (NASH), which is characterized by the occurrence of chronic liver inflammation, hepatocyte cell death and ongoing tissue damage sensitizing dramatically to HCC emergence. NAFLD is characterized by the accumulation of lipid species within hepatocytes, including lipotoxic agents such as cholesterol. These lipotoxic agents could in turn triggered chronic inflammation, a significant risk factor to develop HCC. Recently, our team demonstrated that the protein Lect2 was a key player of the liver immune microenvironment regulating the aggressiveness of HCC. Interestingly, Lect2 was also recently described as a hepatokine that could be involved in NAFLD, but little is known about its functional role in liver cells and its contribution to the severity of NAFLD. Thus, the goal of this work is to decipher the mechanistic role of LECT2 in the liver during NAFL/NASH/HCC progression.

Method and Results: First, using both mouse model and a cohort of human patients, we showed that Lect2 mRNA levels were higher in NAFL and NASH livers compared to controls. To understand the role of Lect2 in NAFLD, we first assessed its implication in lipid metabolism under physiological context, comparing Lect2-deficient and WT livers. Our results showed an upregulation of key actors of lipogenesis (*Srebp-1c, Fas, Acc*) in Lect2-deficient mice compared to WT. Transcriptomic analysis reveals an enrichment of genes involved in cholesterol metabolism, in the catabolism of cholesterol in bile acids (*Cyp7a1, Abcg5/Abcg8*). Mechanistically, we evidenced that this molecular signature is associated with an upregulation of the nuclear receptor LXR activity, in Lect2-deficient mice. Under pathological context of NASH, using a High Fat High Cholesterol Diet, we evidenced that Lect2 deletion worsens inflammatory process and fibrosis development, comparing Lect2-deficient and WT livers. Finally, using a CD-HFD that recapitulates key features of human NAFL/NASH/HCC progression, we demonstrated that Lect2-deficient mice develop liver tumors significantly more and faster than control mice (100% of Lect2-deficient versus 20% of Controls at 13 months of CD-HFD diet).

Conclusion: We demonstrated that Lect2 regulates cholesterol metabolism through a LXR-dependant manner, suggesting its contribution in lipotoxicity mechanisms that occurs during NAFL/NASH/HCC progression. Altogether, these findings illustrate the critical importance of Lect2 in NAFLD.

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Lack of CCL2 limits the development of HCC in a model of obesity-associated carcinogenesis

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Background and aims: Overweight and obesity are associated with increased cancer risk. Obesity-promoted HCC development is dependent on enhanced production of tumor- promoting cytokines IL-6 and TNF which cause hepatic inflammation and activation of the oncogenic transcription factor STAT3. CCL2 is a multifunctional chemokine involved in various aspects of the pathogenesis of chronic liver disease, including non-alcoholic steatohepatitis. Recently, the protective effects of the deficiency of CCR2, the receptor for CCL2, have been reported. However, the phenotype of ligand deficiency may be considerably different from that of chemokine

receptors. In this study, we investigated the role of CCL2 deficiency in a model of HCC associated with fatty liver.
Method: 14 days old CCL2+/+ and CCL2−/− mice were injected with DEN 25mg/kg IP or saline. After 4 weeks from the injection mice were fed with control (CD) or high-fat diet (HFD) for 38 weeks. Number and size of tumors were evaluated, Gene expression was measured by quantitative PCR.
Results: No differences in food consumption were observed across experimental groups. In CCL2−/− mice body weight was 1.5 fold lower than in CCL2+/+ mice. ALT levels were increased in all mice receiving HFD, whereas no effects of DEN were observed. The elevation was significantly higher in CCL2+/+ mice. No tumors developed in animals not receiving DEN. In those exposed to the carcinogen, the number of tumors was significantly higher in mice on a HFD than in those on CD. The number and mean size of tumor was dramatically and significantly decreased in CCL2−/− mice compared to wild-type. Gene expression analysis in the non-tumoral liver indicated that absence of CCL2 reduced the expression of TGF-beta and TNF-alpha. In the tumoral tissue, significantly reduced exoression levels of TNF-alpha, IL-18 and IL-6 were observed in CCL2−/− mice.
Conclusion: Genetic knock out of CCL2 is involved in tumor growth and progression in an obesity induced HCC murine model, and is associated with modulation of cytokine expression both in tumoral and non tumoral tissue.

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Mitochondrial uncoupler HU6 reduces hepatic oxidative stress in the DIAMOND (TM) mouse model, thus abrogating NASH development
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Background and aims: The Gencia mitochondrial uncoupler HU6 was evaluated for utility in treating NASH in a diet-induced animal model of metabolic syndrome and NASH (DIAMOND™ mice); development of NASH in this model is driven by insulin resistance, oxidative stress, inflammation, and leaky gut induced by Western Diet (WDSW). The aim of this study was to investigate effects of HU6 on ROS formation and correlate these with disease progression.
Method: Mice were grouped into 5 groups: vehicle control (VC), high dose HU6 (HD), 5 mg/kg), low dose HU6 (LD, 1 mg/kg), WDSW positive (PC) and NCNW negative (NC) natural history controls. Mice were raised for 12 weeks on diet, corresponding to a baseline NASH F0 in the WDSW groups. Treatment groups were then gavaged once daily with aqueous vehicle or drug in vehicle for 8 weeks. Serum and liver tissue were harvested, snap frozen and fixed, and LFTs, blood lipids and histology on FFPE section stained with HandE and Sirius Red was performed. DNA/RNA oxidative damage was measured via ELISA from representative liver samples. Key chemokines were also assayed from mouse livers utilizing Luminex Bead-based multiplex assays.
Results: Serum ALT, AST and ALP levels in the HD group were significantly lower than in the VC ($p = 0.001$, 0.0004, and 0.0002, respectively) and PC ($p = 0.03$, 0.01, and 0.00008, respectively) groups. In the HD group the significant reduction in ballooning ($p = 0.0000001$), lobular inflammation and liver transaminotransferase levels is accompanied by a 72% reduction in MCP-1, 37% reduction in IP-10, 50% reduction in MCP-3 and a 43% reduction in MCP-2. Additionally, HU6-treated mice have a near 30% reduction in baseline oxidative damage to nucleic acids. Steatosis percentage and grade ($p = 0.001$ and 0.01, respectively) were reduced in the HD group, which correlated with significantly lower body weights and liver weights compared to the VC and PC groups. Composite histology scores (NAS and SAF activity scores) were also significantly improved in the HD group compared to VC and PC groups. While all VC and PC mice progressed to NASH, HU6 at 5 mg/kg prevented NASH development in all but one mouse.
Conclusion: HU6 significantly reduced measures of oxidative stress and chemokines, correlating with decreases in ballooning, inflammation, and progression from simple steatosis to NASH. HU6 also produced significant reductions in body and liver weight, correlating with decreased hepatic steatosis. HU6 impacted multiple drivers of NASH in this study, thus supporting the rationale for further study of HU6's therapeutic potential in NASH.

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Clinical translatability of a diet-induced obese mouse model of non-alcoholic steatohepatitis
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Background and aim: The Amylin (AMLN) diet-induced obese (DIO) mouse model has become one of the preferred preclinical animal models of non-alcoholic steatohepatitis (NASH). However, the translatable value of preclinical data in this model is still not properly validated. Our aim was to compare histology and liver transcriptome of AMLN DIO-NASH mouse liver samples with NASH patient biopsies.
Method: Liver samples were obtained from C57Bl/6J mice fed the AMLN diet (40% fat, 20% fructose, 2% cholesterol, AMLN DIO-NASH mice), a 60% high-fat diet (DIO mice) or chow (lean mice) for at least 30 weeks, and compared to human samples collected from lean (BMI < 25 kg/m^2), obese (BMI > 30 kg/m^2) and patients with histology-proven NASH (n = 12). Histopathological assessment of NAFLD activity score (NAS) and fibrosis stage was performed, and quantitative histology was used to analyze steatosis (HandE staining), inflammation (galectin-3 immunohistochemistry), and fibrosis (Pico-Sirius red staining). Global gene expression was finally characterized by next generation sequencing.
Results: Pathological evaluation showed no disease pathology in lean mice and human lean and obese subjects, while both normal DIO and AMLN DIO NASH mice, and human NASH patients, showed severe steatosis (score 3). Only AMLN DIO-NASH and NASH patients showed inflammation (score 1), ballooning (score 1 or 2) and fibrosis (score 1 or 2). The quantitative histology showed identical levels of liver lipid accumulation and similar levels of inflammation and fibrosis in AMLN DIO-NASH mice and human NASH patients, with slightly higher values in the mouse livers. RNAseq analyses from both mouse and human liver showed a pronounced shift in gene expression profile and perturbation of NASH-related pathways. In addition, prototypical NASH-related genes such as *Col1a1*, *Col3a1*, *Timp1* and *MCP-1* show analogous expression changes in mouse and human NASH samples.
Conclusions: A head-to-head comparison of the AMLN DIO-NASH mouse model and human NASH patients showed similar pathological scoring, quantitative histology, and gene expression validating the AMLN DIO-NASH mouse model as a clinically relevant model of human NASH.

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In vivo effects of a novel inhibitor of apoptosis signal-regulating kinase 1 in mouse models of liver injury and metabolic disease

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Background and aims: Apoptosis-Signal-Regulating-Kinase-1 (ASK1) is a redox-sensitive kinase. In the setting of oxidative stress, ASK1 activates mitogen-activated kinase (MAPK) signalling which, in turn, modulates the activity of apoptotic and inflammatory pathways. As a result, inhibition of ASK1 has been proposed as a therapeutic approach for the treatment of non-alcoholic steatohepatitis (NASH). EP-027315 is a novel, highly selective, and potent (IC_{50} < 1.25 nM) ASK1 inhibitor in cellular models of oxidative stress. Here, we evaluate the *in vivo* efficacy of EP-027315 in mouse models of liver injury (acetaminophen toxicity) and metabolic disease (diet-induced obesity).
Method: Inhibition of acute ASK1 activation was tested in C57BL/6 male mice (8 weeks of age) receiving a single dose of vehicle or EP-027315 (oral gavage) 1 hour prior to acetaminophen (APAP) administration (300mpk, i.p). Livers and plasma were harvested 6 hours after APAP treatment to evaluate the effects of EP-027315 on hepatic ASK1 signalling. To further characterize the pharmacologic effects of ASK1 inhibition on APAP-mediated hepatotoxicity, RNA-Seq analysis of livers was performed. In addition, inhibition of ASK1 was evaluated in diet-induced obese (DIO) mice fed a high-fat diet (D12492) for 24 weeks. MAPK signalling (ASK1, MKK4, JNK, p38) and apoptotic markers was evaluated using immunoblot or MSD assay in liver lysates. Hepatic injury and inflammation were assessed by plasma ALT, plasma IL-1beta, and histological evaluation of formalin-fixed tissues.
Results: In both the APAP liver injury and DIO mouse models, EP-027315 dose-dependently inhibited the activation of ASK1 and its downstream effector kinases. In addition, EP-027315, effectively suppressed multiple markers of apoptosis, including cytochrome-C release and cleaved PARP. Inhibition of ASK1 correlated with attenuation of liver damage by APAP (60% decrease ALT, $p < 0.05$) and reduced hepatocyte centrilobular degeneration. EP-027315 also exerted anti-inflammatory effects (75% decrease IL-1beta $p < 0.05$). RNA-Seq analysis confirmed the positive impact of EP-027315 on genes associated with apoptosis and inflammation.
Conclusion: EP-027315 effectively inhibited hepatic ASK1 activation induced by either acute liver injury or chronic metabolic stress. EP-027315 treatment suppressed liver injury, inflammation, and apoptotic pathways at both a transcriptional and protein level. These data support the further evaluation of EP-027315 for the treatment of NASH.

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Sexual aspects of liver metabolism: A computational approach

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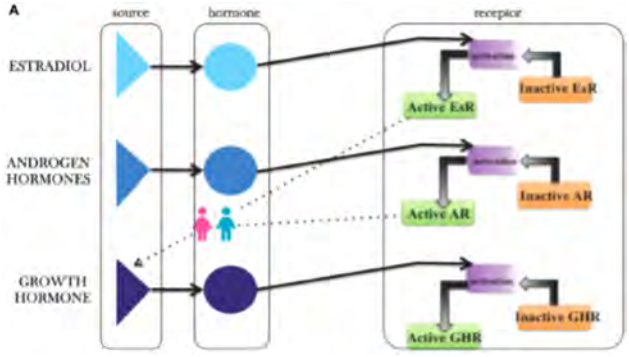
Background and aims: Liver is a known sexually dimorphic non-reproductive organ with over 1000 genes whose expression differs between females and males. This indicates that female and male livers are metabolically not identical organs. The liver pathologies usually prevail in one or the other sex, with different contributing genetic and environmental factors. Mathematical modelling can aid importantly in understanding the multifactorial liver disease etiology. The currently established computational models of hepatic metabolism that have proven to be essential for understanding of non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) are limited to the description of gender-independent response or reflect solely the response of the males. Herein we present *LiverSex*, the first sex-based multi-tissue and multi-level liver metabolic computational model.
Method: We used object oriented modelling to contruct the *LiverSex* mode based on *in silico* liver model *SteatoNet*. The crucial factor in adaptation of liver metabolism to the sex is the inclusion of estrogen and androgen receptor responses to respective hormones and the link to sex-differences in growth hormone release. For experimental validation of the mathematical model we applied gene expression data from livers of female and male mice on western diet.
Results: The model was extensively validated on literature data and experimental data obtained from wild type C57BL/6 mice fed with regular chow and western diet. These experimental results show extensive sex-dependent changes and could not be reproduced *in silico* with the uniform model *SteatoNet*. The *LiverSex* model identified the most important sex dependent metabolic pathways which are involved in accumulation of triglycerides representing initial steps of NAFLD. PGC1A, PPARα, FXR, and LXR were identified as regulatory factors that could become important in sex-dependent personalized treatment of NAFLD.



Conclusion: *LiverSex* represents the first large-scale liver metabolic model, which allows a detailed insight into the sex-dependent complex liver pathologies, and how the genetic and environmental factors interact with the sex in disease appearance and progression.

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Combining probiotics and an angiotensin-2 type 1 receptor blocker has beneficial effects on hepatic fibrogenesis in a rat model of non-alcoholic steatohepatitis

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Background and aims: Intestinal endotoxin is important for the progression of non-alcoholic steatohepatitis (NASH). By improving the gut microbiota environment and restoring gut-barrier functions, probiotics are effective for NASH treatment in animal models. It is also widely known that hepatic fibrosis and suppression of activated hepatic stellate cells (Ac-HSCs) can be attenuated by using an angiotensin-II (AT-II) type 1 receptor blocker (ARB). We thus evaluated the effect of combination probiotics and ARB treatment on liver fibrosis using a rat model of NASH.
Method: Fisher 344 rats were fed a choline-deficient/L-amino acid-defined (CDAA) diet for 8 weeks to generate the NASH model. MIYAIRI 588 were used for probiotics and 30 mg/kg/day of losartan

was used for ARB. Animals were divided into probiotics, ARB, and probiotics plus ARB groups. Therapeutic efficacy was assessed by evaluating liver fibrosis (Sirius Red and α-SMA staining), the lipopolysaccharide (LPS)-Toll-like receptor (TLR)4 regulatory cascade, and intestinal barrier function (zonula occludens-1 (ZO-1) staining). Microbiome of the rats were assessed by analyzing new-generation sequencing.

Results: CDAA group showed moderate liver fibrosis by assaying Sirius Red and α-SMA staining. Liver fibrosis was suppressed in both probiotics and ARB group, compared to that in the CDAA group. A more potent inhibitory effect on liver fibrosis was observed in the combination group of probiotics plus ARB, compared to that with either drug alone.

Hepatic TGF-β and TLR4 expression were increased in CDAA group. On the other hand, hepatic TGF-β and TLR4 expression were decreased in both the probiotic and ARB groups, compared to that in the CDAA group. Notably, the combination of probiotics and ARB resulted in a stronger inhibitory effect than either drug alone. Hepatic LBP mRNA was increased in CDAA group. In the probiotics group, LBP mRNA decreased compared to that in the CDAA group. In contrast, no significant effect was observed in the ARB group. Regarding the combination group of probiotics and ARB, LBP mRNA was decreased compared to that in the CDAA group, however, there was no additional benefit compared to probiotics alone. As well as hepatic LBP, probiotics, not ARB, reduced intestinal permeability by rescuing ZO-1 disruption induced by the CDAA diet. CDAA group showed different cluster compared with control group. In addition, probiotics administration improved the microbiome disrupted by the CDAA diet.

Conclusion: Combination of probiotics and ARB are effective in suppressing liver fibrosis via different mechanisms (thorough HSC, intestinal tight junction, gut microbiome). Currently both drugs are in clinical use; therefore, the combination of probiotics and ARB is a promising new therapy for NASH.

FRI-343
NEDDylation inhibition as a new potential therapy of non-alcoholic fatty liver disease

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Background and aims: NASH is a complex and chronic liver disease in which multiple mechanisms are implicated in its progression that limit novel therapeutic approaches. Thus, multi-target models might be a better physiological approach to understanding NASH and its treatment. One of the cutting-edge research topics is the study of post-translational modifications (PTMs) that have emerged as a faster and effective mechanism to regulate signaling pathways and metabolic reactions. NEDDylation is an ubiquitin-like reversible PTM characterized by the conjugation of Nedd8 (neural precursor cell expressed developmentally down-regulated 8) to target proteins that promote their stabilization. Our laboratory has described a marked increase of NEDDylatied proteome in liver as well as serum in patients and mice model with NAFLD.

Method: Animal procedure was make using male adult C57BL/6 mice (3-month old) fed with methionine (0.1%) and choline (0%) deficient diet (MCD diet) and control group fed with regular diet. After 2 week of feeding with 0.1%MCD diet a group of mice were treated with Pevonedistat or MLN4924 (60 mg/Kg) by gavage (Takeda Oncology, Cambridge, MA, USA) each 4 days as total of 2 weeks. Proteomic analysis. Liver samples were digested with trypsin and analyzed by LC-MS/MS using an LTQ Orbitrap XL (Thermo). The differential expression analysis was carried out using Progenesis software (Nonlinear Dynamics). Only proteins quantified with at least 2 different peptides identified with a FDR < 1% were considered for further analysis. Functional analysis of the differential proteins ($p < 0.05$, ratio > 1.5 in either direction) was carried out using the DAVID Functional enrichment tool (https://david.ncifcrf.gov/) and with Ingenuity Pathway Analysis (IPA, QIAGEN).

Results: In preclinical studies using Pevonedistat (MLN4924), an already approved FDA inhibitor of NEDDylation, we have been able to reverse steatosis, inflammation and fibrosis in a preclinical NASH mice model. In addition, we describe the reversion of NEDDylation levels in serum samples and tissues after the treatment. We found β-oxidation activity and ketone bodies levels were increased in the treatment group. Noteworthy, the levels of reactive oxygen species (ROS) and lipid peroxidation showed a significantly reduction after Pevonedistat treatment. Hepatic proteomic analysis after Pevonedistat treatment showed regulation of multiple pathways including fatty acid metabolism, peroxisomes, bile acid metabolism, ribosomes and endoplasmic reticulum stress.

Conclusion: NEDDylation plays an important role in the physio-pathology of NAFLD and NASH progression. Hence, understand the complexity of the relation between NEDDylation and NASH will pave the way to develop new therapeutic option.

FRI-344
Preclinical characterization of FM101, a first-in-class A3 adenosine receptor modulator for the treatment of non-alcoholic steatohepatitis

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Background and aims: Adenosine and its receptor are involved in energy metabolism and immune response regulation. Notably, the activation of A3 adenosine receptor (A3AR) inhibits cyclic AMP (cAMP)-protein kinase A (PKA) pathway, which subsequently regulates mitochondrial electron transport chain (ETC) and apoptosis. However, the mechanism how a biased agonist of A3AR, FM101 modulates liver mitochondria and the severity of non-alcoholic steatohepatitis (NASH) remains unclear.

Method: C57BL/6N mice were treated with fast food diet (FFD, 40% calories from fat, 0.2% cholesterol, RD Western Diet, plus fructose 23.1 g/l and glucose 18.9 g/l added to the drinking water) for 25 weeks, and orally administrated either or FM101 (30 or 60mg/KG) or vehicle for last 6 weeks. Liver tissues, primary hepatic stellate cells (HSCs) and Kupffer cells (KCs) were collected and analyzed by histology and qPCR. Oxidative phosphorylation (OXPHOS), mitophagy and mitochondrial turnover were measured by Seahorse machine, Mt-Keima and pMitoTimer system, respectively.

Results: In functional assay, FM101 act an agonistic role of A3AR as assessed by cAMP with the homogeneous time-resolved fluorescence (EC_{50} = 104 nM). However, FM101 inhibited the β-arrestin translocation in response to A3AR activation (IC_{50} = 44 nM). A3AR was predominantly expressed in KCs, and HSCs compared with hepatocytes. *In vitro* treatment with FM101 significantly inhibited activation of KCs and HSCs as demonstrated by downregulation of inflammatory cytokines (TNF-alpha, IL-6, IL-1beta), and pro-fibrogenic (COL1A1,

TIMP1 and ACTA2) gene expressions, respectively. *In vivo* treatment of FM101 decreased liver weight, and ratio of liver to body weight. Moreover, FM101 decreased serum level of ALT and cholesterol induced by FFD. Consistently, FM101 effectively ameliorated steatofibrosis as assessed by quantification of collagen deposition and profibrogenic mRNA expressions. Mechanistically, FM101 treatment strongly blocked mitochondrial ETC in KCs. Moreover, FM101 increased accumulation of damaged mitochondria and subsequent mitophagic degradation in response to CCCP treatment using pMitoTimer and Mt-Keima system, respectively. Consequently, CCCP-induced cell death in mouse macrophages was enhanced by FM101 treatment.

Conclusion: The biased agonist of A3 adenosine receptor, FM101, could have therapeutic potential for the treatment of NASH through induction of mitochondria-mediated KCs death.

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Whole transcriptome analysis uncovers NorUDCA as a ligand of the aryl hydrocarbon receptor

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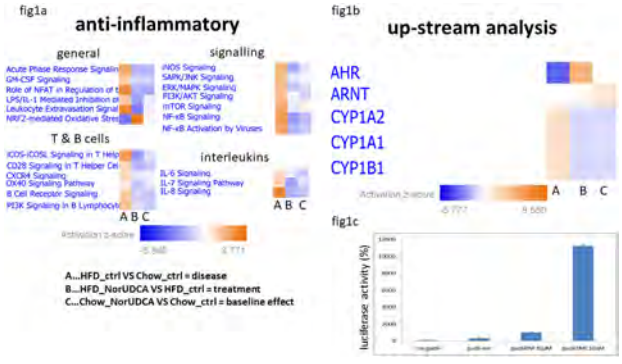
Background and aims: NorUrsodeoxycholicacid (NorUDCA) is a bile acid based drug currently in late clinical development for treatment of PSC and NASH. Despite its anti-inflammatory, anti-cholestatic/choleretic and anti-fibrotic effects, its molecular mechanism remains unknown. Therefore, we used unbiased whole transcriptome analysis to deepen our understanding of NorUDCA and explore its mechanism of action.

Method: Male C57BL/6J mice received either chow (A04, Safe Diets, France) or high-fat-diet (36% fat from butter, HF260, Safe Diets, France) ± 0.5% NorUDCA for 39 weeks. mRNA was extracted from livers (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) was used for further analysis. In vitro qPCR of AhR target genes hepa1c1c cells (mouse hepatocyte cell line) was done using NorUDCA±AhR ligands (ANF, BNF, 3MC, CH223191). In addition, we performed luciferase assays (gud6) and gel shifts in IHH (immortalized human hepatocytes) cells, either naive or co-transfected with mouse AhR±NorUDCA and compared it with BNF and 3MC.



Results: RNA-seq analysis revealed a striking differential regulation of canonical anti-inflammatory pathways (fig1a). Further, AhR was upregulated in HFD_NorUDCA vs HFD_ctrl (padj = 0.0058) and Chow_NorUDCA vs Chow_ctrl (padj = 0.0072), while its downstream targets cyp1a1 and cyp1a2 were downregulated (fig1b). A series of AhR-co-regulated pathways were clearly affected (e.g. fibrosis, inflammation, cell cycle). In hepa1c1c cells treated with both AhR ligands and NorUDCA, a mean suppression of cyp1a1 of at least 25% was observed. Luciferase assays in IHH cells demonstrated NorUDCA -binding to AhR, although weaker than BNF or 3MC (fig1c). Also, gel shifts confirmed the luciferase assays, as AhR was found less in the cytosol and more in the nucleus fraction of cells pre-treated with NorUDCA, BNF or 3MC.

Conclusion: Our data show that NorUDCA is a ligand of AhR in vitro and strongly affects it in vivo. This could explain several hepatoprotective effects seen in preclinical models and clinical studies. Moreover, RNA-seq data in mice hinted at more potential mechanisms and applications of NorUDCA like anti-proliferative and anti-inflammatory actions, which need to be evaluated in more detail in vivo and in clinical studies.

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The effect of exercise training and canagliflozin on hepatic lipid metabolism of non-alcoholic fatty liver disease

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Background and aims: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) is a possible pharmacological therapy for non-alcoholic fatty liver disease (NAFLD). Exercise is a robust treatment of obesity and NAFLD; however, effect of SGLT2i on exercise therapy is unclear. We investigated the effect of canagliflozin (CAN), exercise training and combination therapy on NAFLD and lipid metabolism in the liver.

Method: Male mice loaded with a high-fat diet for 4 weeks were housed in a normal cage (sedentary; Sed) or wheel cage (WCR). CAN was administrated for 4 weeks. Respiratory quotients (RQ) was analyzed in the metabolic cages. Pathological findings and mass spectrometry-based lipidomics were compared among 4 groups (Control/Sed, Control/WCR, CAN/Sed, and CAN/WCR).

Results: Body weight of Control/WCR and CAN/Sed was significantly lower than Control/Sed, and further weight loss was observed in CAN/WCR. RQ was significantly different among 4 groups (Control/Sed 0.80, Control/WCR 0.83, CAN/Sed 0.75, CAN/WCR 0.77, $p < 0.0001$). Hepatic steatosis and NAFLD activity score was ameliorated in Control/WCR, CAN/Sed and CAN/WCR comparing to Control/Sed (Control/Sed 2.25, Control/WCR 1.25, CAN/Sed 1.5 and CAN/WCR 0.25). In CAN/Sed and CAN/WCR, CPT1a and PGC1a expression was significantly increased and FAS and SCD1 were significantly decreased comparing to Control/Sed ($p < 0.05$), and these differences were more significant in CAN/WCR than CAN/Sed. Phosphorylated AMPK tended to increase in the order of Control/Sed, Control/WCR, CAN/Sed, and CAN/WCR. In lipidomics, CAN and/or WCR remarkably decreased triacylglycerols regardless chemical structure of triacylglycerols and average fold change in triacylglycerols of Control/Sed, Control/WCR, CAN/Sed, and CAN/WCR were 1.0 ± 0.08, 0.38 ± 0.21, 0.77 ± 0.11 and 0.46 ± 0.10. There was no significant difference in diacylglycerol, phosphatidylcholine and fatty acid including ω-3 and ω-6 polyunsaturated fatty acids. Erucic acid was significantly decreased only with CAN, and fold change of Control/Sed, Control/WCR, CAN/Sed, and CAN/WCR were 1.0 ± 0.23, 1.0 ± 0.15, 0.37 ± 0.08 and 0.47 ± 0.12.

Conclusion: Canagliflozin and exercise independently decreases hepatic triglyceride and ameliorates NAFLD. Canagliflozin activates AMPK additively to exercise effect, and suppress lipid synthesis and up-regulates β-oxidation. In order to decrease erucic acid, which is known cardiac disease risk, SGLT2i is a potential therapeutic choice.

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OPN inhibits autophagy and accelerates lipid accumulation in non-alcoholic fatty liver disease

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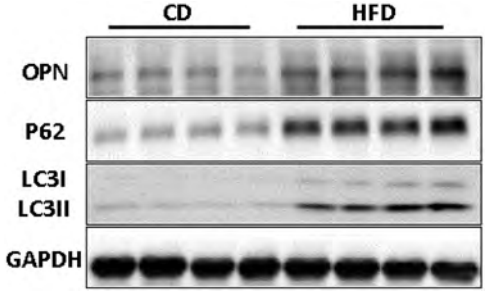
Background and aims: Non-alcoholic fatty liver disease (NAFLD) is associated with insulin resistance and obesity and prevalent throughout the world. NAFLD ranges from pure steatosis to a more severe stage termed non-alcoholic steatohepatitis (NASH) by fatty inflammation, which may in turn progress to hepatic fibrosis and cirrhosis. Recent studies have demonstrated that hepatic autophagy is impaired in NAFLD. In the present study, we investigated the impact of osteopontin (OPN), a secreted phosphoprotein 1, negative regulation of autophagy in the progression of NAFLD.
Method: ① In the construction of NAFLD mice experiment, C57BL/6 mice were randomly assigned to a high fat diet (HFD) group, which was further subdivided into 4 groups (0, 4, 8, 12 weeks) (n = 4) according to time points. Control mice were fed with chow diet (CD) (n = 4). ② Expression of OPN and LC3II/I, P62 in liver tissues were detected. ③ In vitro experiment, HepG2 cells were induced by free fatty acids (FFA) to simulate high-fat environment in vivo. Real-time PCR and Western blot were used to detect the expression levels of OPN, LC3II/I and P62. ④ SIRNA was used to down-regulate OPN expression and recombinant OPN protein was exogenously added. LC3II/I, P62 and lipid accumulation in HepG2 cells. ⑤ LC3-II expression levels were compared in the presence and absence of CQ (chloroquine) in order to detect that whether FFA treatment suppressed net degradation via autophagy. ⑥ Wild-type (WT) and OPN knockout (OPN−/−) mice were fed a high fat diet to study OPN effects in obesity-driven hepatic alterations.
Results: ① OPN was upregulated in association with autophagy impairment in the livers of mice fed with a high-fat diet ($p < 0.05$). The most obvious change was detected at week 12. ② In vitro experiment, as the concentration of FFA increased, the expression of OPN was also increased unlike within the control group, and the level of autophagy was gradually suppressed ($p < 0.05$). ③ The upregulation of OPN was associated with suppression of the late stage of autophagy as evidenced by accumulation of both LC3-II and p62 expression levels as well as decreased autophagy flux ($p < 0.05$). Its blockade by siRNA attenuated autophagy impairment and reduced FFA-induced lipid accumulation. ④ CQ obviously increased the levels of LC3-II expression in control HepG2 cells. However, further accumulation was not observed in FFA-supplemented cells, which suggested that FFA treatment inhibited autophagic flux, most likely through blockade at the autophagosome maturation step. ⑤ OPN deficiency ameliorated liver steatosis, at least in part, by the regulation of autophagy.



Conclusion: OPN is up-regulated and plays a pathogenic role in NASH by accelerating hepatocellular lipid accumulation and inhibiting autophagy. OPN may be a novel therapeutic target for regulating NASH development and progression.

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Monoacylglycerol lipase deletion protects against obesity-induced hepatic steatosis via PPARg regulation in adipose tissue and fatty acid malabsorption in the intestine

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Background and aims: Obesity is strongly associated with the development of non-alcoholic fatty liver disease (NAFLD). Accumulating evidence links metabolic lipases to the pathogenesis of NAFLD. Monoacylglycerol lipase (MGL) is the rate-limiting enzyme of the fatty acid (FA) degradation pathway hydrolyzing monoglycerides into glycerol and FAs but its role in NAFLD is still unclear. In the present study, we aimed to uncover the role of MGL in obesity-induced hepatic steatosis.
Method: Immunohistochemistry (IHC) for MGL was performed in lean and obese patients with NAFLD. Wild type (WT) and MGL knockout ($MGL^{-/-}$) mice were fed western diet for 12 weeks to study MGL effects in obesity driven hepatic alterations. Inflammation and fibrosis were assessed by serum biochemistry, liver histology and gene expression profile were analyzed in liver and adipose depots. Triglycerides (TG) were measured in liver tissue and FA in stools by colorimetric assays. Primary adipocyte progenitor cells (APC) and 3T3-L1 were processed for flow cytometry, rt-PCR and western blot analysis.
Results: We demonstrated that MGL abundance increased dramatically in livers of obese patients with NAFLD (IHC), whilst MGL deficiency in mice protects from obesity-induced hepatic steatosis (ALT −40%, AST −50%) by downregulating hepatic TG synthesis (TG content −40%, Pparg −60%, Srebp1c −70%, FAS −60%. Dgat1 −50% mRNA) and inflammation (F4/80 −50%, CCL2 −60%) without affecting fibrosis. Absence of MGL promoted fat storage in gonadal white adipose tissue (GWAT weight +70%, Pparg +70%, CD36 +40%, Dgat1 +50% mRNA), preventing ectopic accumulation in the liver, while favoring malabsorption of FAs in the intestine (+70% FA content in feces). Furthermore, in vitro experiments demonstrated increased APC size and lipid content (+70% BODIPY, Dgat1 +50%, Pparg +40%, adiponectin +40% mRNA), driven by PPARγ feedback regulation as further demonstrated in 3T3-L1 co-treated with GW-9662 and rosiglitazone (MGL mRNA −50%).
Conclusion: Our data emphasize that MGL deletion prevents NAFLD by lipid storage in GWAT and FFA malabsorption in the intestine, creating a futile cycle whereby the products of TG hydrolysis can be recycled into TG within the cell and/or sensed by PPARγ, finally resulting in a leaner phenotype.

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Development of humanized non-alcoholic steatohepatitis model using chimeric mice with highly repopulated humanized livers

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease. Although a significant number of new drugs for NASH are already in the development pipeline, there are no animal models of human (h-) NASH to estimate the efficacy and safety of potential new drugs. We have been producing humanized chimeric mice (PXB-mice) with livers highly repopulated with h-hepatocytes (h-heps). These mouse (m-) models are used to study drug metabolism, pharmacokinetics, toxicity of new

drugs, and efficacy of anti-hepatitis B and anti-hepatitis C therapeutic agents. In the present study, to develop the h-NASH model, we tried a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) (A06071302; Research Diets, Inc.) in PXB-mice.

Method: PXB-mice were fed with either the CDAHFD or a control diet for 12 weeks and body weight and h-albumin levels were determined. Mice were euthanized at 8 and 12 weeks. Alanine aminotransferase (ALT) activity and h-ALT1 levels were measured in m-plasma. Liver sections were histologically analyzed by HandE staining, silver staining and immunostaining. h- and m-mRNA expressions in the liver were determined by real-time quantitative PCR (qPCR) method.

Results: Mean body weight was lower in CDAHFD group than that in the control group, maintaining about 80% of the initial level. Increase in ALT activity and hALT1 level were observed in m-plasma at 2 and 4 weeks, which were recovered to normal in the CDAHFD group. Both liver weight to body weight and h-albumin levels in m-blood in the CDAHFD group were lower compared to those in the control group at 8 and 12 weeks. At 12 weeks, ballooning of h-heps and Mallory body-like structures in h-heps were observed only in the CDAHFD group. Increase in alpha-smooth muscle actin-positive stellate cell area, tunnel-positive h-heps, Ki-67 positive h-heps, Gr-1 positive neutrophils, and F4/80-positive macrophages was noted in the CDAHFD group compared with those in the control group at 8 and/or 12 weeks. Furthermore, perisinusoidal/pericellular fibrosis were observed with Sirius red staining and silver staining with increase in Sirius red-positive areas in the CDAHFD group compared with the control group at 12 weeks. qPCR revealed higher levels of h-TGFbeta1, h-CCL2, m-Tgfbeta1, m-Cxcl2, m-Col1a1, m-Col1a2, m-Col3a1, and m-Acta2 mRNA expressions in the CDAHFD group than the control group.

Conclusion: We successfully developed humanized NASH model using h-hep chimeric mice with CDAHFD diet.

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Dietary cholesterol mitigates bile acid toxicity in NASH and cholestatic mouse models

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Background and aims: It has been a long-standing observation from liver pathology that bile acids toxicity is associated with NASH and cholestasis disease progression. The effect of dietary cholesterol on phase 1 hepatocytes proliferation, degree of inflammation and fibrosis induced by bile acids is not clear. In our study we aimed to determine whether the dietary cholesterol can regulate bile acid toxicity in NASH and cholestasis models.

Method: The study was conducted using two models for bile toxicity, dietary induced NASH and MDR2ko mice model for cholestasis. Dietary induced NASH model used male wild type mice and was performed for 3 weeks. Mice were assigned to 4 groups (n = 32 mice) and were fed with one of the following diets: ND (standard AIN-93G diet, Control group), ND + cholesterol 1% (CHOL group), ND + Cholic Acid 0.5% (CA group), ND + Cholesterol 1% + Cholic Acid 0.5% (CHOL + CA group, atherogenic diet). In model of MDR2KO mice that prolonged for 6 weeks, mice were assigned to 2 groups, one that received standard AIN-93G diet and the second, was treated with ND + 1% cholesterol. After treatments, mice were euthanized, and blood serum and liver tissue were collected. Plasma serum was analysed for lipid profile, liver enzymes and blood glucose. Liver tissue damage was assessed by Masson Trichrome staining for fibrosis and histological analysis. Immune inflammatory response was determined by inflammatory parameters expression in hepatocytes and macrophages infiltration was represented by immunohistological analysis of the tissue with macrophage-specific antigen (F4/80). Furthermore, hepatocytes proliferation was analysed by determination proliferating cellular nuclear antigen (PCNA). Liver tissue hypoxia levels were assessed by immunohistological analysis of the tissue for hypoxia inducible factors expression (HIF-1α).

Results: It was observed that mice fed cholesterol enriched diets were significantly protected against cholic acid/bile acids-induced necrosis and liver damage. Bile acid treatments induced increased liver damage and increased peri-portal and intralobular fibrosis. Adding cholesterol dramatically attenuated liver damage and fibrosis. However, cholesterol induced liver inflammation and uncontrolled hepatocytes proliferation. HIF-1α and nuclear factor (erythroid derived 2) like 2 (Nrf2) defence genes were also activated by cholesterol. Interestingly, HIF-1α specific expression in Ito cells' nuclei was decreased by cholesterol treatment.

Conclusion: We are showing for the first time that dietary cholesterol may prevent the bile acid-induced damage by activating hepatocytes defence genes and proliferation. Moreover, cholesterol enriched diet attenuated liver fibrosis and cholestasis, through inhibition of HIF-1α in Ito cells.

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DNA methylation pattern of TM6SF2 influences NAFLD progression in genotype-dependent manner

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) arises due to complex interaction of genetic and environmental factors. Evidence suggests that transmembrane 6 superfamily member 2 (TM6SF2) E167K variant is associated with NAFLD susceptibility and progression. The loss of function mutation in TM6SF2 plays a pivotal role in hepatic lipid accumulation, however, it remains unknown if there is an interplay between genetic and epigenetic mechanisms modifying disease pathogenesis. In this study, we aimed to investigate whether epigenetic marks of TM6SF2 could affect development of hepatic steatosis and fibrosis.

Method: Histologically proven NAFLD patients and control subjects (hepatic resection due to benign liver lesions) were included into the study. Liver samples from 22 cirrhotic-NASH (F4), 24 mild-intermediate fibrosis stage (F1-3) NASH and 9 control patients (F0) were used to perform hepatic DNA methylation profiling in TM6SF2 gene using bisulphite modification and pyrosequencing. TM6SF2 gene expression and genotyping were determined using digital PCR and TaqMan RT-PCR assays, respectively.

Results: Pyrosequencing targeting several CpGs in TM6SF2 gene indicated significant methylation differences (> 7%) in promoter and first intronic regions between controls, mild-intermediate stage and cirrhotic patients. Interestingly, this difference was more prominent between TM6SF2 CC group versus CT/TT group (> 10%) suggesting genotype dependent epigenetic changes. In addition, TM6SF2 gene expression was also significantly altered associating with CpG methylation pattern and the genetic variation.

Conclusion: Here we report for the first time the association of DNA methylation profile of TM6SF2 gene in NAFLD progression. Differential methylation levels according to the E167K variant suggests the crosstalk between genetic and epigenetic pathways controlling the disease susceptibility and progression. Epigenetic editing could be employed to attenuate hepatic steatosis and fibrosis.

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Inflammation provokes hepatic but not adipose tissue diacylglycerol acyltransferase 2 expression and concomitant triglyceride synthesis in an experimental non-alcoholic fatty liver disease

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Background and aims: Triglycerides (TG) are the predominant energy storage molecules in eukaryotes, and the DGAT enzymes catalyse its synthesis. Two isoforms of DGAT (1 and 2) have been identified from a distinct gene family and are widely expressed in both human and rodent liver. Evidence suggesting that the two enzymes play different roles in TG metabolism in the milieu of fatty liver diseases indeed the molecular mechanism remains unclear. We aimed to investigate whether superimposed inflammation increases DGAT (1 and 2) overexpression and associated hepatic and adipose tissue TG synthesis in non-alcoholic fatty liver disease (NAFLD) and also to study the effect of FXR agonist INT-747 on the regulation of hepatic DGAT-TG pathway in NAFLD.
Method: 90 days after feeding HFD and chow, mice were orally administered INT-747 (Sigma, USA; 5mg/kg b.w. daily by gastric lavage) in the vehicle (corn oil) for 7 days or vehicle alone. In order to determine the effect of superimposed inflammation on the background of fatty liver, the treatment groups were given either lipopolysaccharide (LPS; 1 mg/kg in 0.8-1 ml of saline, IP) or vehicle (saline). The final study groups were as follows: (a) Chow fed control mice, (b) Chow + LPS, (c) HFD, (d) HFD + LPS, (e) HFD + INT-747, (f) HFD + INT-747+LPS. At the end of the study, at fourteen weeks, all mice were sacrificed. Blood, hepatic and adipose tissue were collected for various analysis.
Results: When compared to naïve mice, NAFLD mice showed markedly elevated hepatic ($p < 0.05$ and $p < 0.01$, respectively) and adipose tissue ($p < 0.05$) DGAT (1 and 2) protein expressions. LPS challenge to NAFLD mice showed further significant ($p < 0.05$) increase of hepatic DGAT 2, but not DGAT 1 whereas adipose tissue DGAT (1and2) were not altered significantly. INT-747 treatment to NAFLD mice and that received LPS showed significantly ($p < 0.05$) reduced DGAT 1 and 2 and hepatic TG synthesis. Moreover, cytokines (TNF α and IL-1 β), NFκB, iNOS, and 4-HNE protein expressions were significantly ($p < 0.05$) increased in NAFLD mice that received LPS. INT-747 treatment significantly ($p < 0.05$) lowered the above indices.
Conclusion: Our study is the first indication of evidence for an association between increased hepatic however not adipose tissue DGAT 2 and associated TG synthesis in NAFLD with superimposed inflammation. INT-747 treatment attenuated hepatic TG accumulation by downregulating DGAT 2 overexpression, thereby lowering the progression of NAFLD.

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Metabolic implications of methionine adenosyltransferase 1A depletion during fasting

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Background and aims: We recently demonstrated that half of NAFLD patients have a serum metabolic profile similar to the one observed in mice lacking MAT1A enzyme (MAT1A-KO mice). We proposed that this subtype of patients (M-subtype) could have lower MAT1A activity, and this is supported by studies showing decreased MAT1A expression in NASH patients. Since MAT1A expression increases with fasting, and considering that intermittent fasting has been shown to ameliorate liver steatosis, our aim in this study was to determine the effect of fasting on NAFLD progression in situations where MAT1A expression is compromised, similar to what would happen in NAFLD patients with an M-subtype.
Method: We collected liver and serum samples from fed and starved two-month old wild-type C57BL/6J and MAT1A-KO mice, and from C57BL/6J mice after *in vivo* silencing of MAT1A.
Results: We observed that starvation induces a more pronounced weight loss and adipose lipolysis when hepatic MAT1A was not expressed. Lipid hepatic content was not significantly different between wild-type and MAT1A-KO mice during the first 24h of starvation, but was drastically reduced in MAT1A-KO mice if starvation persisted during 36h. We observed that despite the huge increase in MAT1A protein expression in WT livers during starvation, SAMe levels decreased dramatically during prolonged fasting, and no differences was seen between wild-type and MAT1A-KO mice in total liver extracts. On the other hand, we found a pronounced decrease in SAMe levels in crude mitochondria isolated from MAT1A-KO mice than in control mice. This decrease in mitochondrial SAMe levels was associated with increased hepatic beta-oxidation, endoplasmic reticulum stress (ERS) and liver transaminases in MAT1A-KO-starved mice, suggesting a detrimental effect of fasting in livers from MAT1A-KO mice.
Conclusion: Altogether, our work suggests that despite the beneficial effect of fasting on body weight loss observed in MAT1A-KO mice, the increase in ERS, beta-oxidation and liver transaminases observed after starvation under MAT1A deficient conditions could promote the progression of NAFLD.

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Novel Gubra Amylin NASH diet-induced obese mouse model of biopsy-confirmed non-alcoholic steatohepatitis

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Background and aims: The Amylin Liver NASH (AMLN) diet-induced obese C57Bl/6J (DIO-NASH) and ob/ob (ob/ob-NASH) mouse models display clinical translatability with respect to key metabolic and liver pathological changes associated with non-alcoholic steatohepatitis (NASH). A recent FDA ban on trans-fats in foods has prompted the development of a new NASH diet capable of promoting a compatible level of disease, as AMLN diet contains trans-fat-containing Primex shortening. Here, we assessed the metabolic and liver pathological phenotype in C57Bl/6J and ob/ob mice fed a high-fat diet with a nutrient composition and caloric content comparable to the AMLN diet.
Method: Male ob/ob mice were fed AMLN diet (40% total fat kcal of which 18.5% were trans-fat kcal; 20% fructose; 2% cholesterol) for 16 weeks or a modified AMLN diet with Primex substituted by equivalent amounts of palm oil, termed Gubra Amylin NASH (GAN)

diet, for 8-12-16-24-30 weeks. C57 mice were fed GAN diet for 28 weeks.
Results: In ob/ob-NASH mice, the GAN diet was more obesogenic and adipogenic compared to the AMLN diet. GAN, but not AMLN, diet also impaired glucose tolerance in ob/ob-NASH mice compared to chow-fed C57Bl/6J mice. GAN and AMLN diets promoted comparable levels of steatosis, lobular inflammation and hepatocyte ballooning as well as similar fibrotic liver lesions and collagen-1a1 fractional area. Mild (stage F1) and moderate (stage F2) grade fibrosis was induced in DIO-NASH and ob/ob-NASH mice, respectively, when fed AMLN or GAN diet for 16 weeks. When fed GAN diet for ≥ 24 weeks, a significant proportion of ob/ob-NASH mice developed advanced fibrosis (stage F3). Also, the two diets promoted overlapping liver transcriptome changes.
Conclusion: Modification of the AMLN diet by substitution of Primex with palm oil results in a maintained NASH phenotype in C57 and ob/ob mice. Accordingly, the GAN diet induced clear metabolic and histopathological hallmarks of biopsy-confirmed NASH in both DIO-NASH and ob/ob-NASH mice, highlighting the suitability of these models for the characterization of novel drug therapies for NASH.

FRI-355
Elafibranor, a drug candidate for first line NASH monotherapy and a universal backbone for drug combination treatment

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Background and aims: Elafibranor (ELA), a PPARα/δ agonist, reverses NASH histology and decreases fibrosis in patients with advanced disease [1], and is currently being evaluated in the RESOLVE-IT phase 3 trial. Among other NASH treatment candidates, obeticholic acid (OCA), GS-0976 (GS), selonsertib (SEL) and cenicriviroc (CVC) have complementary actions with ELA.
Aim: to provide experimental evidence for ELA as a universal backbone for drug combination therapies in NASH.
Method: C57Bl/6J mice and Wistar rats were fed a fat and/or cholesterol supplemented choline deficient CDAA diet (modified CDAA) for 8-12 weeks to generate NASH with fibrosis. Histological evaluation was performed in a blinded fashion. NASH was assessed using the NASH Clinical Research Network Scoring System. Fibrosis area was determined by measuring the collagen positive area.
Results: The animals developed a severe NASH phenotype with abundant fibrosis.
Low doses of ELA (1 and 3 mg/kg) decreased NAFLD activity score (NAS) by 1 ($p < 0.0001$) and 2 points ($p < 0.0001$), respectively. Among the other compounds, only GS (10 mg/kg) reduced NAS by 1 point ($p = 0.04$) under conditions used in this study. Combination of ELA with GS (10 mg/kg) or CVC (10 mg/kg) but not with other compounds, improved NAS by 3 points ($p < 0.001$ for both compounds).
Monotherapy with ELA (1 mg/kg), ELA (3 mg/kg), OCA (10 mg/kg), SEL (30 mg/kg) and GS (10 mg/kg) reduced fibrosis area by 24% ($p = 0.0006$), 47% ($p < 0.0001$), 26% ($p = 0.15$), 32% ($p = 0.02$) and 38% ($p = 0.0001$), respectively. Further, OCA and SEL in combination with ELA decreased fibrosis area by 71% ($p < 0.0001$) and 49% ($p < 0.0001$), respectively. The effect of GS on fibrosis was not further potentiated by ELA.
PK studies in rodents did not show any relevant drug-drug interactions with respect to plasma exposure following ELA coadministration with OCA, SEL and CVC. The interaction with GS cannot be excluded and is currently under investigation.
Conclusion: Several NASH front-runner drug candidates can be safely coadministered with ELA in the advanced NASH model. ELA worked in synergy with most of the other candidates to efficiently attenuate fibrosis development despite a significant dose reduction for both drugs. We conclude that ELA is a universal backbone for combination drug therapies in NASH.

Reference

1. Ratziu *et al. Gastroenterology*. 2016 May;150 (5):1147-1159.

FRI-356
Single cell peripheral innate and adaptive immune signature of non-alcoholic steatohepatitis by cytometry time of flight

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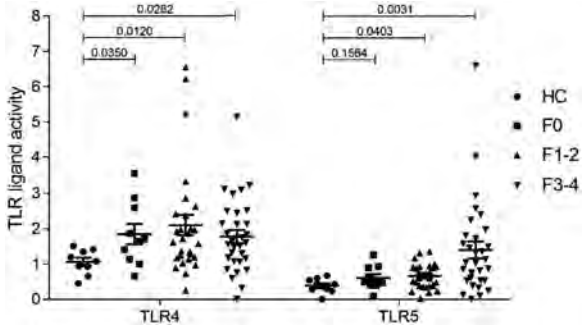
Background and aims: Inflammation is a hallmark of non-alcoholic steatohepatitis (NASH). Multiple 'hits' including lipotoxicity trigger inflammatory responses and contribute to disease progression and fibrosis. However, the peripheral immune response to these triggers, particularly in the early stages of disease, has received scant attention to date. We studied the peripheral immune phenotype in patients with NASH to gain novel insights into the pathogenesis of disease.
Method: We isolated peripheral blood mononuclear cells (PBMCs) from 16 patients with biopsy-proven NASH and advanced fibrosis ($n = 8$), mild fibrosis ($n = 8$) and 3 healthy controls. We designed a panel of 36 antibodies conjugated to heavy metals for cytometry by time of flight (CyTOF). To determine the potential of patient plasma to activate Toll-like receptors (TLRs), we used HEK cell lines co-transfected with human TLR4 and 5 genes in combination with an inducible reporter gene. Specific inhibitors of TLR4 (CLI-095) or TLR5 (TH1020) were used in assays of lipotoxicity with a mixture of free fatty acids (palmitic acid/oleic acid, 1mM/2mM).
Results: Principal component analysis of single cell CyTOF data revealed a distinct peripheral immune signature in patients compared to controls that suggested a type 1 immune skew with increased $CD4^+$ Th1 and $CD8^+$ T cell populations. Global expression of TLR5, but not TLR2 or TLR4, was increased in patients with advanced fibrosis compared to those with mild disease or controls ($p = 0.0027$), which we confirmed with conventional flow cytometry. In a separate cohort of 69 patients, plasma TLR4 activity was elevated in both mild and advanced disease compared to controls, but TLR5 activity was only evident in patients with advanced fibrosis. Both TLR4 and TLR5 activity was reduced but not abrogated by pre-treatment with protease K, but not DNase or RNase. To confirm the role of TLR activity in lipotoxicity we pre-treated HepG2 cells with specific inhibitors prior to injury with palmitate/oleate mixture. Fatty acid-induced IL-8 mRNA was reduced by inhibition of TLR5 (1.7-fold, $p = 0.0002$) but not TLR4, although fatty acids themselves did not activate TLR5 in the reporter assay.
Conclusion: Single cell CyTOF shows a distinct immune signature for NASH and a role for TLR5, but not TLR4, in lipotoxicity in NASH. TLR5 is not activated by fatty acids and only partially through protein mediators but other agonists that are likely to play a role are yet to be defined.



FRI-357

Fibrinogen-like protein 2 aggravates non-alcoholic steatohepatitis by enhancing inflammatory signaling in macrophages

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Background and aims: Fibrinogen-like protein 2 (fgl2), which is critical for immune regulation in inflammatory state, leads to production of proinflammatory cytokines and hepatic injury. This study aims to investigate the role of fgl2 in the pathogenesis of non-alcoholic steatohepatitis (NASH) and to explore the mechanisms.
Method: The wild type and fgl2 (−/-)C57BL/6 mice were subjected to methionine/choline-deficient (MCD) diet or high fat diet (HFD) for establishing NASH models. Fgl2 expression in liver was detected by immunofluorescent staining and western blotting. Hematoxylin-eosin staining and Oil-red staining were performed to detect liver injury and steatosis. ALT, AST, LDH, triglyceride and cholesterol in serum were observed. Bone marrow-derived macrophages were stimulated with LPS or free fatty acids (FFA). The NF-kappa B, p38-MAPK and NLRP3 inflamasome signaling pathways as well as lipid metabolism related molecules were tested both in vivo and in vitro using RT-PCR and western blotting. The levels of proinflammatory cytokines in cell supernatant and homogenate of liver tissues were tested by ELISA.
Results: The hepatic expression of fgl2 was markedly increased in murine models of NASH, this change was associated with enhanced infiltration of macrophages in liver. Compared with WT mice NASH models, inflammatory liver injury and steatosis were dramatically attenuated, in parallel with significant decreases of ALT, AST and LDH in fgl2-deficient test groups. In both liver tissues and bone marrow-derived macrophages from the NASH models, fgl2 deficiency resulted in reduced secretion of proinflammatory cytokines including TNF-alpha, IL-1beta, MCP-1 and IL-6. Meanwhile, activation of NF- kappa B and p38-MAPK signaling pathways as well as expression of NLRP3, pro-caspase-1, caspase-1 and pro-IL-1beta were significantly decreased. Genes involved in lipogenesis (SREBP-1c, HMGCR) were downregulated while those involved in lipometabolism (PPARalpha, PGC-1alpha) were upregulated in fgl2-deficient test groups.
Conclusion: Fgl2 promotes inflammation and steatosis in NASH by enhancing inflammatory activity of macrophages via multiple signaling pathways. Inhibition of fgl2 could effectively attenuate liver injury and steatosis and prevent disease progression of NASH.

FRI-358

Differentiation of glucagon and glucagon-like peptide-1 effects on hepatocytes

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Background and aims: Non-alcoholic steatohepatitis (NASH), is the aggressive subtype of fatty liver disease, that is currently palliatively managed by metabolic control. Oxyntomodulin, a natural dual agonist of GLP-1 receptor (GLP1R) and glucagon receptor (GCGR), is central to metabolic controls and prevents NASH in preclinical studies. It is unclear whether the impact on liver is through GLP1R or GCGR agonism. In this study, we intend to evaluate effects of glucagon and GLP-1 on primary hepatocytes procured from NASH and healthy subjects.
Method: Primary hepatocytes from NASH (N = 6) and healthy (N = 5) were treated for 4 hours with liraglutide (GLP1R agonist) and G1437 (GCGR agonist). Gene and metabolite profiling were conducted to identify pathogenesis in NASH, and to differentiate GLP1R and GCGR effects.
Results: Four main pathogeneses were identified in NASH hepatocytes by IPA analysis. Fibrosis (PDGFA, TIMP1, collagen IV) was increased, while the redox reaction (GSTA1, GSTA3) was inhibited in NASH, suggesting enhanced oxidative stress. Hepatocyte health was affected due to the inhibition of LXR/RXR and PXR/RXR in NASH and increased p53 signaling, resulting in cell apoptosis.
After the treatment of liraglutide, gene expression profiles were identical to the vehicle. In G1437 group, 344 genes were altered compared to controls ($\pm$ FC $\geq$ 1.6, p $\leq$ 0.1). Cellular cAMP was not changed by liraglutide, but increased by G1437, suggesting GCGR was activated, but not GLP1R. In IPA analysis, G1437 increased G6PC expression (FC > 5, p < 5e-04) in glycolysis, confirming GCGR activation. Surprisingly, GCGR activation significantly induced Wnt/β-catenin signaling, e.g. TCF7L2 (FC = +1.9, p_{adj} = 1e-7) and cyclin D1 (FC = +1.7, p_{adj} = 3e-5). TCF7L2 is an effector of Wnt signaling. In liver, TCF7L2 plays a central role in Wnt signaling, leading to cell growth and proliferation, and enhanced lipid and amino acid metabolism in hepatocytes. Consistent with proliferation, 6-glucophosphonate and ribose-1 phosphate in pentose phosphate pathway was increased by 2.76-fold and 1.8-fold respectively (p < 0.05), suggesting a shift to pentose-nucleotide biosynthesis in parallel to glycolysis. Metabolites in arginine-urea cycle were increased in hepatocytes (arginine by 1.87-fold, p < 0.05; citrulline by 1.94-fold, p < 0.05). Single nucleotide polymorphisms (SNPs) in TCF7L2 were associated with risk in diabetes (e.g., rs7901695; OR = 1.37, p = 1e-48). The increase in TCF7L2 by G1437 can lead to improved β-cell function, which are beneficial effects of GCGR activation in diabetes control.
Conclusion: Gene expression profiling clearly identified four pathogeneses pathways in NASH hepatocytes. GLP1R agonism does not have direct impact on hepatocytes, while activation of GCGR results in upregulated Wnt signaling and increased TCF7L2, a modulator of hepatocyte homeostasis in liver.

FRI-359

Ductular reaction predicts the progression of non-alcoholic fatty liver disease

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Background and aims: Ductular reaction (DR), which comprises an expansion of transit amplifying cells of the terminal branches of the

biliary tree, is often seen in advanced NAFLD and is believed to reflect hepatic progenitor cell (HPC) activation. This study aims to investigate the prognostic value of DR/HPCs in NAFLD for NASH development and fibrosis progression.

Method: We included 36 patients with biopsy-proven NAFLD at Freeman Hospital, Newcastle-Upon-Tyne Hospitals, UK, who underwent at least two liver biopsies more than a year apart. The histological semi-quantitative NAS CRN system was used to score steatosis (S0-3), ballooning (B0-2), lobular inflammation (I0-3) and to stage fibrosis (F0-4). HPCs were quantified in the portal/periportal area and parenchyma based on Keratin 19 immunostaining in the baseline biopsies and correlated with clinicopathological features. Parenchymal ductular cells were scored based on acinar zone topography (1-3) and pattern (single cells, ductular structures).

Results: In our cohort, the absolute number of periportal HPCs significantly correlated with elevated AST levels ($p < 0.01$). Moreover, the presence of HPCs into the parenchyma correlated with higher AST ($p < 0.01$), ALT ($p < 0.05$) and with the progressive increase of insulin levels ($p < 0.01$). The small sample size of the cohort did not allow us to highlight a significant association between the absolute number of either periportal or parenchymal HPCs and fibrosis progression or the occurrence of NASH, although a positive trend was reported. Comparing baseline and follow-up liver biopsies (mean time between biopsies 79 months, range 14-198), the presence of ductular structures in the parenchyma of the baseline biopsy was significantly associated with the progression of at least 1 stage of fibrosis (prevalence of 35% in progressors vs 6% in non-progressors, $p < 0.05$). In addition, a significant correlation with the increase of AST and ALT levels was noted (OR 1.028 and 1.026 respectively).

Conclusion: In a cohort of biopsy-proven NAFLD patients with follow-up biopsies, HPCs are associated with biochemical signs of inflammation and higher insulin levels. Moreover, the presence of parenchymal ductular structures predicts disease progression. Due to the lack of a prognostic biomarker for NAFLD, the development of this tool could acquire paramount importance for both stratifying patients at risk at baseline and the design of targeted therapies to patients with high likelihood of disease progression.

FRI-360

The role of Paneth cells in the pathogenesis of non-alcoholic fatty liver disease: A potential gut microbiota-associated mechanism

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is currently the most common liver disease worldwide. Paneth cells are granulated epithelial cells clustered in the bottom of small intestinal crypts, which secrete a variety of antimicrobial peptides and lysozyme to regulate the commensal gut microbiota. Paneth cell function has been associated with the pathogenesis of chronic liver disease in general, but its specific role in the pathogenesis of NAFLD remains poorly understood.

Method: Eight-week old C57Bl/6J male mice ($n = 20$) were given a high-fat diet (HFD) (60% kcal fat, Research Diets, New Brunswick, NJ) or low-fat diet (10% kcal fat) for 12 weeks. Paneth cell granules were pharmacologically depleted by intravenous dithizone (10mg/kg) treatment for every three weeks. Hematoxylin and eosin (HandE) and Oil Red O staining were used to visualize the lipid accumulation in the liver. The fecal samples were collected to extract metagenomic DNA (QIAGEN, Hilden, Germany). PCR-Based Denaturing Gradient Gel Electrophoresis (Bio-Rad, Hercules, California) and principal component analysis (PCA) were used to compare the differences in microbial structure.

Results: The relative lysozyme level in the small intestine was significantly decreased in dithizone treated HFD mice when compared to those without ($30.02\% \pm 4.01$ vs. no decrease, $p = 0.0075$). Dithizone treated HFD mice, when compared to non-dithizone treated HFD mice, had a borderline significant increased body weight loss ($42.21g \pm 2.90$ vs. $48.95g \pm 0.70$, $p = 0.0864$), a significant reduction both in liver mass gain ($1.2g \pm 0.14$ vs. $1.94g \pm 0.02$, $p = 0.0007$) and hepatic lipid accumulation (steatosis grade $20.73\% \pm 9.71$ vs. $70.52\% \pm 4.09$, $p = 0.0115$). In dithizone treated HFD mice, the relative mRNA level of tight junction gene zonula occludens-1 (ZO-1), a marker of gut permeability, was significantly higher than that in non-treated HFD mice ($36.10\% \pm 7.88$ vs. $1.75\% \pm 0.87$, $p = 0.0493$). A PCA plot based on DGGE profile confirmed a clear separation between dithizone and non-dithizone treated HFD groups, which two principal components (PC1) and PC2 contributed 57.889% and 34.939% to the total variability respectively. The abundance of *Bacteroides thetaiotaomicron* in dithizone treated HFD mice was doubled compared to non-dithizone treated HFD mice, with a trend towards significance ($150.30\% \pm 23.25$ vs.$75.93\% \pm 7.87$, $p = 0.0939$).

Conclusion: Depletion of Paneth cell granule ameliorates the severity of NAFLD, which may involve a gut microbiota-associated mechanism and alterations in intestinal permeability. Further metagenomic sequencing may identify specific microbiota profiles associated with the disease process of NAFLD.

Liver transplantation and hepatobiliary surgery: Clinical aspects

FRI-361

Impact of cardiovascular complications on patients' outcome after orthotopic liver transplantation

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Background and aims: Long-term complications after orthotopic liver transplantation (OLT) majorly impact on patients' outcome. However, data evaluating specifically the role of cardiovascular complications is sparse. Therefore, we conducted a retrospective single center study to investigate its frequency and its effect in liver transplant recipients.

Method: Out of 424 patients, who were transplanted between 2000 and 2009 at the University Hospital Leipzig, 343 patients with cirrhosis±hepatocellular carcinoma could be included. Epidemiological and clinical data were obtained retrospectively from patients' records. Cross-sectional and longitudinal analyses including multivariate Cox-regression analyses were applied.

Results: Out of 343 patients 204 (59.5%) were men and the main indication for OLT was alcoholic liver disease. In total 62 (18.1%) patients were transplanted with HCC. The median age was 52 (19-73). In total 106 patients (30.9%) had a cardiovascular disease (CVD) before OLT, most commonly arterial hypertension (AHT) ($n = 97$, 91.5%). Patients with CVD were older (54.6 vs. 50.0 years; $p < 0.001$) and had a higher BMI ($27.8\ kg/m^2$ vs. $26.1\ kg/m^2$; $p = 0.005$). Diabetes mellitus was more common amongst patients with previous CVD (47.4% vs. 18.1%, $p < 0.001$). After transplantation 40.5% (139) patients incurred new cardiovascular events (figure 1), again most frequently AHT ($n = 91$, 51.7%).

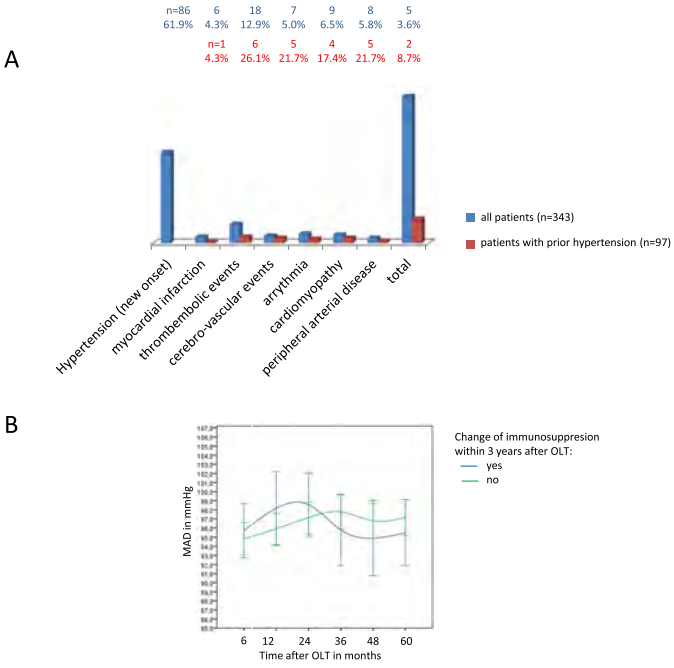

Figure: A: Cardiovascular complications after OLT listed for the overall cohort and patients with arterial hypertension before OLT. B: Absolute MAP in mmHg of patients with a change of immunosuppression (blue) and patients without change of immunosuppression (green) within 3 years after OLT.

28.6% of all patients died during the follow-up, of which 10.2% died of cardiovascular events. Patients' survival after transplantation with previous cardiovascular diseases, notably AHT, was significantly lower (112.2 vs. 148.4 months; p = 0.001). In long-term follow-up (>24 month) patient with new CVD had a trend towards a reduced survival time (171.3 vs. 184.2 month, p = 0.146).
The initial standard immunosuppression was based on calcineurin inhibitors (92.4%) ± mycophenolate (MMF; 67.3%). Patients, who were treated with MMF, had a trend towards lower prevalence of arterial hypertension (65% vs. 50%, p = 0.081). After switching the immunosuppression to an mTOR-inhibitor based regime (29.7% of all patients at year 5) there was a trend (delta MAP) in blood pressure compared to patients with standard CNI-based immunosuppression (p = 0.053).
Conclusion: Cardiovascular diseases have a significant impact on the outcome of patients after liver transplantation and are associated with metabolic complications. mTOR-inhibitors have the potential to be of benefit for patients with arterial. Whether this can be translated into an improved outcome should be the matter of future research.

FRI-362
Exercise training for liver transplant candidates

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Background and aims: Frailty is associated with increased morbidity and mortality, as these are tightly linked to decompensation and increased complication rates among liver transplant (LT) candidates. The aim of the study was to evaluate the efficacy of structured in- and outpatient exercise training program for cirrhotic patients who were referred for liver transplant evaluation.
Method: We retrospectively reviewed 472 consecutive LT patients between 2007 and 2016 at our centre. There were 208 patients who underwent LT prior to the implementation of the exercise training program (non-ETP) and 264 LT patients who underwent a comprehensive exercise training program (ETP) from 2012 and forward. Baseline characteristics, readmission rate, length of hospital stay (LOS), and post-operative LT complications were analyzed and compared between the two groups.
Results: The mean age for the ETP group was 56.3 compared to 53.2 in the non-ETP group (p = 0.0006). The mean indication for liver transplant in the ETP was liver tumor (34.1%) compared to viral hepatitis in the non-ETP group (p < 0.001). The ETG group had more comorbidities compared to the non-ETG group, (diabetes mellitus; 20.7% vs 35.4%, p < 0.0001, coronary artery disease; 20.7% vs 35.4%, p < 0.001). The remaining baseline characteristics were not significant different between the two groups. In addition, there was no significant difference in the post-operative complications between the two groups except for a higher rate of infection in the ETP group compared to the non-ETP group (18.3% vs 7.7%, p = 0.001). LOS and 90-day readmission rate were lower in the ETP compared to the non-ETP (LOS; 14 vs 17 days, readmission rate; 17.5 vs 19.7%). However, the results were not statistically significant.
Conclusion: In this study, there was a trend towards shorter length of hospital stay and reduced 90-day readmission rate in the exercise training program group compared to the non-exercise training program group. Further studies are required to validate the result.

FRI-363
Iron metabolism imbalance is associated with increased mortality following orthotopic liver transplantation

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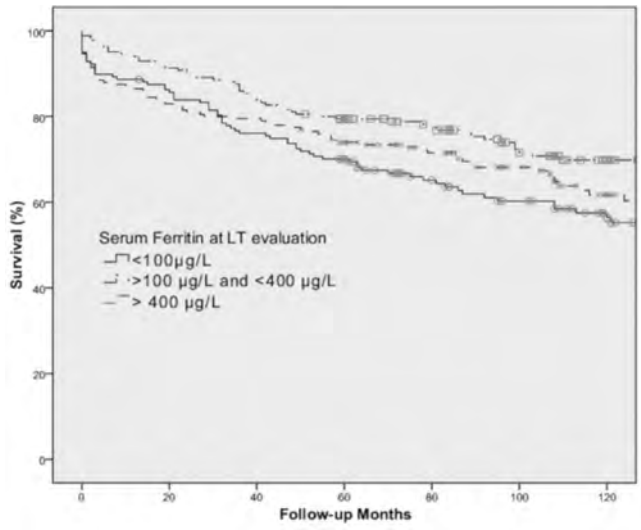
Background and aims: Liver transplantation (LT) is the best treatment for patients with end-stage liver disease. However there is a need for identification of factors associated with post-transplant mortality that could improve patient management. Results regarding the impact of iron metabolism in this setting are discrepant. The aim of our study was to evaluate in a large retrospective cohort the impact of pre-transplant iron metabolism markers on post-transplant survival.
Method: From 2001 to 2011, 553 patients who underwent LT between in our center with iron metabolism parameters available at LT evaluation were included. Data were prospectively recorded at the time of evaluation and at the time of LT. Follow- up data were obtained from local and national database.
Results: Median age at evaluation for LT was 55 [49-60.5] years. They were preferentially men (74.9%) with alcoholic related liver disease (61.5%). Hepatocellular carcinoma was present at evaluation in 214 patients. The median SF was 241[75.5-593.5] µg/L, 168 patients had SF < 100 µg/L and 200 had SF > 400 µg/L. The median TS was 43.6% [25.1-74.5] with 24.6% of patients having a TS higher than 75%. Median MELD was 15.1[10.6-20.7]. At the end of a 95 months follow-up 196 patients were dead, 38 because of infections. In multivariate analysis, overall survival was significantly associated with Transferrin Saturation (TS) > 75% (p = 0.007), Serum Ferritin (SF) (p = 0.005), hepatocellular carcinoma (p = 0.004), estimated glomerular filtration rate (CKD EPI Cystatin C equation) (p = 0.01), intensive care unit length of stay (p = 0.001) and number of packed red blood cell transfusion during surgery (p < 0.001). Kaplan Meier survival curves showed that patients with low SF (< 100 µg/L) and high SF (> 400 µg/L) have a lower survival than patients with normal SF, and show that TS > 75% was associated with an increased mortality at 6 months (p = 0.012) and at 12 months (p = 0.039). Increased TS (p = 0.042) and low SF (p = 0.015) were significantly associated with infection related

death. Neither TS nor SF were associated with higher risk of infection or pneumonia within 3 months after LT.



Conclusion: Our results show that imbalance in iron metabolism is significantly associated with post-transplant sepsis related mortality and overall mortality.

FRI-364

Frequency and impact of discordance between pre-transplant imaging and explant histology on post liver transplant outcomes for patients with hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality in patients with chronic liver diseases. Eligibility for transplant is usually determined using pre-transplant imaging, however this may not stage disease accurately. The aim of this study was to evaluate concordance between pre-transplant radiology and explant histology, seeking to identify any impact of lack of concordance on post transplant outcome.
Method: We conducted a single center retrospective cohort study of patients who were transplanted for HCC at the Royal Free Hospital, London, UK, between January 1st, 2016 and April 31st, 2018. We assessed factors associated with lack of concordance between Milan Criteria (MC) at last imaging and explant pathology, and its impact on post-transplant outcomes.
Results: During our study period, 63 patients were transplanted for HCC. The median age at diagnosis was 60.6 (interquartile range [IQR], 8.1) years, 84.1% of cases were male, and the most common cause of liver disease was Hepatitis C Virus (41.5%). Imaging alone was the method of HCC diagnosis in 82.5% of patients, using MRI in 61.9%. Overall, 82.5% of patients received pre-transplant bridging therapy, with transarterial chemoembolization being the most common modality in 75.5%. Furthermore, time to first bridging therapy was 2.4 (IQR 2.4) months, while time from HCC diagnosis to transplant was 10.4 (IQR 8.5) months. Based on explant pathology, 54.8% of patients were within MC, compared to 93.5% at diagnosis ($p < 0.001$), and 95.2% at last imaging pre-OLT ($p < 0.001$). There was no difference between MC at diagnosis and at last imaging ($p = 1.000$). Discordance between MC based on explant pathology and last imaging occurred in 25 (40.3%) patients. Factors predicting discordance included total number of nodules at last imaging ($p = 0.002$), the total number of diagnostic HCC nodules at last imaging ($p = 0.015$), and older age ($p = 0.029$). Type of imaging modality, use of bridging therapy, type of bridging therapy, and time interval between imaging and OLT were not associated with presence of discordance. The 12-month survival was 91%, and 2-year survival was 87%. There was one recurrence, with one recurrence-related death. Discordance between radiology and pathology MC had no definite impact on short-term post-OLT survival (log-rank, $p = 0.119$) or recurrence (log-rank, $p = 0.207$). On multivariate cox regression analysis, explant total number of HCC was predictive of worse survival (HR1.66, $p = 0.008$), as well as longer duration from diagnosis to OLT (HR1.12, $p = 0.057$)-but not last number of diagnostic HCC at last imaging.
Conclusion: Discordance between MC at last imaging and explant pathology was frequent. Although follow-up was short, this discordance does not predict worse survival, where as explant total number of HCC nodules did.

FRI-365

Efficacy of combined partial hepatectomy and cyst fenestration on health-related quality of life in polycystic liver disease

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Background and aims: Polycystic liver disease (PLD) is a progressive hereditary condition which can result in severe and symptomatic hepatomegaly in a proportion of patients. We investigated symptom relief and improvement of health-related quality of life after combined partial hepatectomy and cyst fenestration in a cohort of individuals with moderate to severe PLD.
Method: We performed a prospective study between November 2014 and May 2018 at a referral center in the United States (Mayo Clinic, Rochester MN). Patients received a questionnaire before surgery and six months after surgery. Total liver volume was measured where post-operative imaging was available. Primary end point was change in symptoms six months after surgery, measured with the PLD Questionnaire (PLD-Q). Change in symptoms was defined as clinically relevant when decrease in score was larger than the Minimal Clinically Important Difference (MCID), defined as half the standard deviation of the mean change in score. Secondary end point was change in quality of life, measured with the 12-Item Short Form Survey (SF-12), and the EuroQoL Visual Analogue Scale (EQ-VAS). All questionnaire scores range from 0 to 100. Complications were scored according to the Clavien-Dindo classification (grade 1 to 5).
Results: Of 17 eligible patients, 16 (94%) were included (mean age 52 years, 81% female). Surgery reduced median liver volume from 4917 ml (IQR: 3680-6400) to 2120 ml (IQR: 1755-2533), corresponding to a median reduction of 58% (IQR: 45-67%) for 12 patients. PLD-Q assessed symptoms decreased from 76.9 (IQR: 41.0-83.0) at baseline to 34.8 (IQR: 17.0-43.8) six months after surgery ($p = < 0.001$). The MCID was −16.5, resulting in a clinically relevant response in 9/13 (69%) patients. Physical Component Scale of SF-12 improved from 24.9 (IQR:17.4-26.5) to 45.7 (IQR: 34.6-55.3) ($p = 0.004$), while SF-12 Mental Component Scale increased from 40.5 (IQR: 25.9-59.0) to 55.4 (IQR: 50.8-58.9) ($p = 0.02$). EQ-VAS increased from 40.0 (IQR:36.8-48.8) to 72.5 (IQR: 63.3-92.3) ($p = 0.003$). Minor post-operative complications (grade 1 or 2) occurred in 8 patients (50%), major complications (grade 4) in 2 patients (13%). There was no procedure-related mortality.

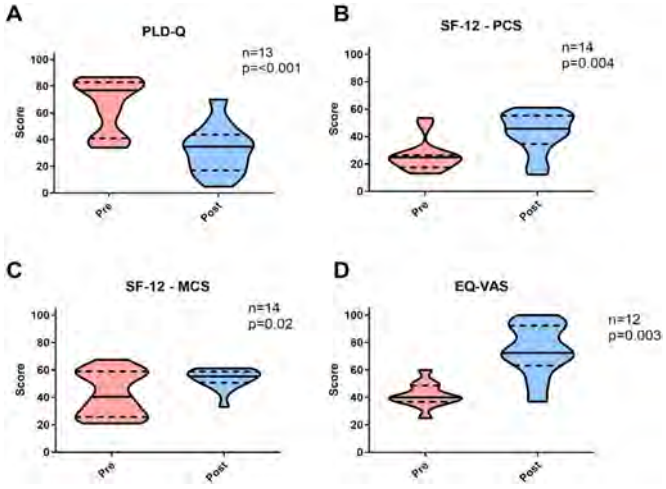

Figure: Patient-reported outcomes pre-surgery and six months post-surgery. Violin plots show the distribution of scores, median (solid line) and inter-quartile range (dashed lines) are superimposed. **Panel A** shows changes in polycystic liver disease questionnaire (PLD-Q) score. **Panel B and C** show changes in the physical component scale (PCS) and mental component scale (MCS) of the 12-Item Short Form Survey (SF-12) questionnaire. **Panel D** shows changes in EuroQol-Visual Analogue Scale (EQ-VAS) score.

Conclusion: Combined partial hepatectomy and cyst fenestration is effective in reducing symptom burden and substantially improved quality of life in selected patients with highly symptomatic PLD.

FRI-366

Portal vein thrombosis in patients on the waiting list for liver transplantation: A single center cohort study

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Background and aims: Portal vein thrombosis (PVT) is a well-recognized complication of end-stage liver disease. However, current literature is still inconclusive about its impact on the clinical course in liver transplant candidates.
The aim of this study was to identify the prevalence of and the risk factors for PVT, to assess the usefulness of anticoagulant therapy and to determine the impact of thrombosis as well as anticoagulation on postoperative outcomes, patient and graft survival.
Methods: We performed a single center retrospective cohort study in an expert liver transplant unit. Patient receiving liver transplantation between January 2006 and June 2016 were included. Relevant demographic, clinical and outcome data were retrieved from the medical records. For analysis, patients were stratified in two groups according to presence of PVT. Univariate and multivariate logistic regression analysis and survival analysis were performed.
Results: During the study period 390 adult patients underwent orthotopic liver transplantation. In 40 patients (10, 26%) PVT was diagnosed. In respectively 10 (2, 56%), 7 (1, 79%) and 23 (5, 9%) patients, the thrombus was identified at time of evaluation for transplantation, during waiting time and at time of transplantation. Among the 37 (9, 49%) cases who still had PVT at the time of transplantation, 20 (54, 05%) showed partial and 17 (45, 05%) showed complete thrombosis. In a multivariate analysis, body mass index (p = 0, 006; OR 1, 1; 95% CI: 1, 028-1, 177), previous treatment of portal hypertension (p = 0, 001; OR 3, 59; 95% CI: 1, 681-7, 671) and a history of encephalopathy (p = 0, 007; OR 2, 86; 95% CI = 1, 332-6, 142) were independently associated with the occurrence of PVT. A beneficial trend was present favouring the use of anticoagulation towards the accomplishment of recanalization (n = 3/7 versus 0/9; p = 0, 062). In the anticoagulated patients, only one mild bleeding episode (14, 3%) occurred. Operation time was increased (p = 0, 001) in patients where the thrombus was discovered incidentally during surgery. Length of stay was increased (p = 0, 012) in the presence of PVT. Patient and graft survival rates were similar between the groups with and without portal vein thrombosis after 5 year of follow-up. However, 1-year patient survival was significantly lower (p = 0, 031) in patients with PVT. Variables independently associated with the risk of 1-year and overall patient mortality included respectively the presence of portal vein thrombosis (p = 0, 032) and male gender (p = 0, 023).
Conclusion: PVT occurred in 10% of patients awaiting liver transplantation and had a deleterious effect on one year survival after liver transplantation. Anticoagulation is safe and showed a beneficial trend on recanalization of PVT and on the one year survival rate.

FRI-367

Pre-liver transplant profile of cardiovascular risk factors and its impact on early post-transplant outcome

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Background and aims: There are limited data about the optimal strategy of cardiovascular (CV) risk assessment during liver transplant (LT) candidate workup. We aimed to evaluate CV risk profile and its correlation with early post-LT cardiac events.
Method: We included 555 adult patients (pts) who consecutively underwent a first LT for cirrhosis at our Centre between January 2013 and December 2017, with a graft from brain-dead donor. CV risk factors (RF) were collected.
Pre-LT cardiac workup included electrocardiogram (ECG) and echocardiography (ECHO). Non-invasive stress testing was performed in pts with ≥ 1 CV RF. We recorded adverse cardiac events within 30 days post-LT.
Results: 78.2% were male; median LT age 56 years (y) [interquartile, IQR, 51-61]; median body mass index 25.3 kg/m^2 [23.2-27.8]. 47.4% affected by virus-related cirrhosis, 15.0% alcohol-induced, 11.5% alcohol+virus, 7.6% immune mediated, 4.1% NASH, 1.3% genetic haemochromatosis and 13.1% mixed etiology. Median time between listing and LT: 66 days [28-150]. Median MELD at LT: 14 [9-19], and 55.5% affected by hepatocellular carcinoma.
CV RF: 21.3% 60-64 y-old age, 11.7% ≥ 65 y; 8.8% body mass index > 30 Kg/m^2; 33.3% smoking abuse; 14.2% mellitus diabetes requiring insulin; 6.8% hyperlipidemia; 20.7% arterial hypertension; 0.7% ischemic heart disease (2 pts with coronary artery stent); 0.9% stroke/ischemic attack; 0.2% dialysis, 0.9% creatinine > 2 mg/dL.
26.3% of the pts had 0 CV RF; 42.7% 1 RF, 19.3% 2 RF, 8.8% 3 RF, 2.5% 4 RF and 0.4% 5 RF.
ECG showed ischemic changes in 1.1% and chronic atrial fibrillation in 0.4% of the pts.
ECHO showed: 96.6% with ejection fraction ≥ 55% and 96.4% with normal/stage 1 diastolic dysfunction.
44.7% of the pts underwent non-invasive stress testing (dobutamin/dipyridamole ECHO or myocardial scintigraphy), which was positive in 1.1% of the pts; all of them underwent coronary angiography which did not show coronary disease.
2 pts underwent pre-LT transcatheter aortic valve replacement for severe aortic stenosis.

4 pts were on successful vasodilator therapy for porto-pulmonary hypertension.
Within 30 days post-LT: 13 pts (2.3%) died, 1 of them for CV event (right heart failure in pt with pre-LT porto-pulmonary hypertension, on specific therapy); 12 pts (2.2%) underwent re-LT; *de novo* CV events (16 atrial fibrillation, 6 ventricular tachycardia/pulseless electrical activity, 1 ischemic heart disease, 2 cardiac failure, 1 Takotsubo syndrome, 1 pulmonary hypertension and 2 pulmonary edema) occurred in 27 pts (4.9%) who had a median number of CV RF of 1 *vs.* 1 in the 528 pts without post-LT CV events (p = 0.38, *t-test*).
None of the CV RF was significantly associated with early post-LT CV events.
Conclusions: Our 555 LT pts had a median number of 1 CV RF pre-LT. Within 30 days from LT, CV events occurred in only 4.9% of them and 1 pt died of heart failure. The number of pre-LT CV RF did not correlate with early post-LT CV outcome.

FRI-368
Clinical analysis of emergency liver transplantation in patients with high MELD score
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Background and aims: In general, patients with a high model for end-stage liver disease (MELD) score have a poor prognosis before and after liver transplantation. The current allocation system is based on the MELD score in emergency liver transplantation. Therefore, the mortality rate after liver transplantation in high MELD patients is an important consideration in future liver allocation system. This study was performed to identify poor prognostic factors and mortality rates in patients with high MELD score.
Method: From September 2001 to December 2017, living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) were performed in 851 and 157 patients in our center, respectively. The 81 patients with MELD score of 35 or more were analyzed. We divided 81 patients into postoperative survival group (POS) and postoperative mortality (POM) group. To assess the risks associated with high MELD score, we evaluated various preoperative and operative factors.
Results: Of the 81 patients, LDLT was performed in 49 (60.5%) patients and DDLT in 32 (39.5%) patients. Overall survival rates at 1, 3, and 5 years in 81 patients were 72.4%, 67.3%, and 67.3%, respectively. The POS group was 63 (77.8%) and the POM group was 18 (22.2%). In univariate analysis, the mean age of the POM group was higher (p = 0.028), the mean MELD score was higher (p = 0.045), the proportion of intubated patients was higher (p < 0.001) and the proportion of positive culture was higher (p = 0.042). There were more patients with mental status above stupor (p = 0.014). In multivariate analysis, age [p = 0.006, Exp (B) = 1.118], intubation status [p = 0.042, Exp (B) = 6.073], and culture positive [p = 0.036, Exp (B) = 5.218] were significant.
Conclusion: In patients with high MELD score, the 3-year and 5-year survival rates are not significantly deteriorated unless initial post-operative mortality is achieved. And the prognosis was poor in patients with old age, preoperative intubation or positive culture.

FRI-369
The role of adipose tissue in metabolic and cardiovascular complication after liver transplantation
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Background and aims: Metabolic and cardiovascular complications are an important burden in patients after liver transplantation (LT), for many reasons such as immunosuppressive therapy. Adipose mass is an independent predictor of morbidity in general populations; little is known in transplant setting. Therefore, the aim of this study is to evaluate the role of adipose mass at the time of LT, in the outcome for morbidity and mortality.
Method: We enrolled 173 patients (116 male and 56 female), liver transplanted for end-stage liver disease from 2000 to 2015. Nutritional assessment before LT was detected by the analysis of CT scan (L3-L4 slice), obtaining the area (cm2) of visceral, subcutaneous and intramuscular adipose tissue; we indexed them by height, getting SAT (for subcutaneous adipose tissue), VAT (for visceral adipose tissue) and IAT (for intramuscular adipose tissue).
Results: The most common cause of transplantation was viral hepatitis (43%), followed by alcohol disease (16%) and NASH (13%). At the time of LT, 42% of patients were obese or overweight according to BMI (corrected for ascites); 10% had cardiovascular diseases before LT (myocardial infarction, cerebral stroke, hemodynamically significant stenosis to major arterial vessels), 26% diabetes mellitus and 17% arterial hypertension.
After LT, there was a significant increase in cardiovascular complications (39%, vs. 10%; p = 0.03), diabetes mellitus (45%, vs. 26%; p = 0.02) and arterial hypertension (51% vs. 17%; p < 0.01).
Total fat area, IAT and SAT detected by CT scan before transplantation correlate significantly with the increase of cardiovascular complication after LT (p < 0.01), also in multivariate analysis (p < 0.01).
There were no correlations between fat and arterial hypertension or diabetes mellitus. Furthermore, adipose tissue did not play a role in mortality after LT.
BMI before transplantation, however, does not correlate with the increase in cardiovascular and metabolic complications after LT.
Conclusion: Patients after LT have increased metabolic and cardiovascular complications. Adipose tissue in CT before transplantation plays a fundamental role and correlates with the increase in cardiovascular complications, more than BMI, but not with mortality after LT. This could be useful in identifying patients at risk and in performing preventive treatments.

FRI-370
Application of an extended-release tacrolimus formulation allows dose reduction and stabilizes graft function after liver transplantation
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Background and aims: Immunosuppressive (IS) regimens after liver transplantation (LT) are in general based on the Calcineurin Inhibitor (CNI) Tacrolimus (Tac), however, its low bioavailability can be a problem. Bioavailability of the extended-release Tac formulation Envarsus® (ENV) is about 40% higher than that of the rapid-release Tacrolimus, Prograf®, allowing a dose reduction of up to 30%. Reduction in dose and, thus, in adverse events can be anticipated. This analysis examines the tolerability of Envarsus®, with the extended-release formulation of Tacrolimus, in a large real-world cohort post LT.
Method: Clinical and laboratory data from 170 patients who were switched to an ENV-based regimen at our center, was collected retrospectively and statistically analysed. Currently, all patients have reached an observation period of 6 months.
Results: The most frequent reason to administer ENV was the intention to reduce nephro- and neurotoxic CNI effects. Liver values (GOT 21 (8-534) U/L, GPT 22 (8-190) U/L, GGT 25 (7-660) U/L, bilirubin 0.2 (0.1-2.2) mg/dL) and renal function (S-creatinine 1 (0.55-1.57) mg/dL) of all patients remained stable 6 months after the start of application. Sleep, concentration and tremor disorders improved in

all patients after conversion. In 47% of patients who were determined as fast Tac metabolizers (n = 83), the ENV dose could be reduced up to 25% (P ≤ 0.003). IS with ENV had to be discontinued in only 7% (n = 12) of the patients.
Conclusion: ENV has no negative impact on liver and kidney function. In approximately 50% of the fast metabolizers the daily Tac dose could significantly be reduced upon switching to ENV, thus decreasing the risk of side effects and better tolerability in the long-term course.

FRI-371
Correlation between classification of circulating tumor cells in peripheral blood and early recurrence in patients with hepatocellular carcinoma after liver transplantation
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Background and aims: To investigate the detection and subtype identification of circulating tumor cells (CTC) in peripheral blood of patients with hepatocellular carcinoma, and to analyze the correlation with early recurrence after liver transplantation.
Method: A total of 25 recipients of liver transplantation for hepatocellular carcinoma were were enrolled in this study from January 2016 to January 2017. Extrahepatic tumor metastasis had not been found before 1iver transplantation by imaging examination, and the primary disease was diagnosed after liver transplantation by pathological examination. The CanPatrolTM CTC second generation capture technique combined with RNA in situ hybridization (RNA-ISH) was used to detect preoperative and postoperative peripheral blood CTC in patients undergoing liver transplantation. And the expression of related markers is classified and identified according to Epithelial-mesenchymal transition (EMT). Tumor recurrence and metastasis were recorded during follow-up.
Results: Of the 25 recipients, 3 patients (12%, 3/25) were negative for peripheral blood CTC before liver transplantation, and 22 (88%, 22/25) were positive. CTC has not been detected in peripheral blood of healthy volunteers. Univariate analysis showed that the total number of CTCs and the proportion of interstitial CTCs were closely related to the TNM stage of hepatocellular carcinoma and the degree of tumor differentiation. During follow-up, 8 of the 25 recipients relapsed (8 were positive for all CTCs, 7 of which were positive for interstitial CTC). The Cox risk ratio model showed that the number of interstitial CTCs could be used as an independent prognostic factor for predicting tumor recurrence after liver transplantation in patients with hepatocellular carcinoma. The recurrence time of interstitial CTC ≥ 1 was significantly earlier than that of interstitial CTCs ($p < 0.05$). The majority of CTC patients (19/25) had a decrease in the total number of CTCs after transplantation, but the proportion of peripheral blood CTC (6/8) in patients with postoperative tumor recurrence increased compared with the preoperative. Patients with an increased proportion of interstitial CTC after surgery had a shorter recurrence time than patients with a decreased (or constant) proportion of interstitial CTC.
Conclusion: The positive rate of CTC in peripheral blood of patients with hepatocellular carcinoma is high. The preoperative high CTC or high interstitial CTC ratio and the increase of postoperative interstitial CTC ratio are prone to tumor recurrence and interstitial type. CTC has stronger invasiveness and metastatic potential. Interstitial CTC can be used as an independent indicator to determine the time of tumor recurrence after liver transplantation in patients with hepatocellular carcinoma.

FRI-372
Next generation sequenzing outperforms standard microbiological cultivation for detection of bacteria in the biliary tract in patients with ischemic type biliary lesions and/or anastomotic stricture
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Background and aims: Recurrent bacterial cholangitis is a common complication in patients with ischemic type biliary lesions (ITBL) and/or anastomotic strictures (AS) after orthotopic liver transplantation. These patients frequently need antibiotic treatment and endoscopic retrograde cholangiography (ERC) to improve the bile flow. Antibiotic treatment is based on findings in standard microbiological cultivation (SMC) of bile samples. However, cultivations techniques are limited to a subset of bacteria easy to cultivate in human samples. Therefore, the aim of the present study was to evaluate the value of next generation sequencing (NGS) as additional diagnostic tool in patients with ITBL and/or AS compared to SMC.
Method: We sequenced the V1-2 region of the rRNA gene in stored bile samples of 242 patients with ITBL and/or AS on the Illumina MiSeq platform. Furthermore, in about one half of the patients SMC was performed (n = 135/56%).
Results: In patients with SMC performed, ERC revealed more often gallstones (27.1% vs. 39.3%; $p = 0.047$). Furthermore, stenosis were more often dilatated (69.2% vs. 82.2%; $p = 0.017$). These patients received more often antibiotic treatment before ERC (41.1% vs. 67.9%; $p < 0.001$) and had significantly higher cholestasis parameter (AP, $p = 0.007$ and GGT, $p = 0.001$). In patients with SMC results available, NGS, with a cut-off of at least 1% of relative abundance of detected genera, performed significantly better in detecting bacterial genera in bile samples than SMC (2.3 ± 1.2 vs. 6.9 ± 3.6; $p = 1.3^{*}10\text{-}32$). The discovery rate, defined as the total relative abundance in NGS of genera also detected in SMC, showed high variations with discovery rates ranging from 0.1% to 99.6%. Except of antibiotic treatment (62.6% vs. 91.7%; $p = 0.006$) only cholinesterase was associated with high discovery rates (> 80%) of SMC. Finally, NGS detected in almost all samples Fusobacterium spp. (99%), Bifidobacterium spp. (99%), Campylobacter spp. (89%) and Haemophilus spp. (87%) whereas these bacteria were not detected by SMC.
Conclusion: NGS is more sensitive in detecting bacterial genera in the biliary tract than SMC and no clinical parameters can be used to predict high discovery rates in SMC. NGS could be used for improved diagnostics for more specific and targeted antibiotic treatments in patients with ITBL and/or AS. However, more such studies are needed to deepen our understanding of microbes being involved in bacterial cholangitis.

FRI-373
Mismatch in C-locus Eplets between donor and recipient as independent factor of acute T-cell mediated rejection in liver transplantation
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Background and aims: HLA matching in solid organ transplantation is essential, especially in kidney, heart and lung transplantation, because of the proven benefits of increased graft survival and decreased incidence of acute rejection. Currently, the HLA match between donor and recipient is suffering a change in the way to interpretate the mismatches with the eplets definition. Eplets are highly polymorphic regions of the HLA molecule and constitute essential components oh HLA epitopes recognized by antibodies that explain the cross-reactivity with different HLA antigens. In renal transplantation, class II HLA eplet mismatch determination has been shown to be a superior method of risk stratification compared with traditional HLA antigen mismatch for predicting class II de novo DSA development, allograft rejection, transplant glomerulopathy, and allograft survival. However, the effect of eplet-mismatch in liver transplantation (LT) has not been studied in detail. The aim of this study is to investigate the relationship between the eplet-mismatch in LT and assess the impact with post-LT outcomes.
Method: HLA typing of 46 consecutive liver graft receptor-donor pairs was performed in our center from January 2016. Follow-up was censored at October 2018. The quantification of antibody verified eplet (VerEp) mismatch in locus-A, B, C, DQA and DQB was performed with HLAMatchmaker software, version 2.0.
Results: A total of 9 patients suffered an episode of acute T cell mediated rejection (TCMR). No significant differences were observed in the number of VerEp mismatches at the HLA-A, B, DRB, DQA and DQB loci. However, the number of VerEp mismatches at the C locus (VerEpC) was significantly increased in patients with acute TCMR: 2 (0-3.5) vs 0 (0-1), p = 0.016. After pooling the patients depending on their load of VerEpC, those with high VerEpC (≥ 2) had an increased risk of acute TCMR in comparison to patients with low VerEpC (< 2) [OR 4; IC95% (1.68-9.49), p = 0.006]. The time free of acute TCMR after LT between low and high VerEpC load was significant (log rank test p = 0.007). In multivariate analysis, high VerEpC load remained as an independent risk factor of acute TCMR (p = 0.032).
Conclusion: The measurement of VerEpC mismatch between donor-recipient prior liver transplantation could identify those at risk of developing acute TCMR.

FRI-374

Von Willebrand factor independently predicts mortality on the waitlist for liver transplantation and facilitates additional risk stratification in low MELD patients

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Background and aims: To this date, liver transplantation (LTx) poses the gold standard in treatment of patients suffering from end-stage liver disease. Well-known limitations of the current MELD based liver allocation comprise the lack of functional assessment of liver insufficiency and underestimation of complications resulting from portal hypertension and infection while on the waitlist. Accordingly, further optimization of the organ allocation process seems inevitable in order to reduce mortality prior to LTx. vWF-Ag was previously shown to play a major role in predicting long-term outcome of patients with chronic liver disease. Accordingly we aimed to evaluate if vWF-Ag could close the obvious functional disabilities of the MELD score in risk assessment of patients listed for transplantation.
Method: Retrospective analysis of 1237 patients listed for liver transplantation at our center between 2003 and 2016. To assure clinical relevance, vWF-Ag was prospectively collected and analyzed as part of the routine laboratory analysis. Receiver operating characteristic (ROC) analysis was applied to assess the discriminatory

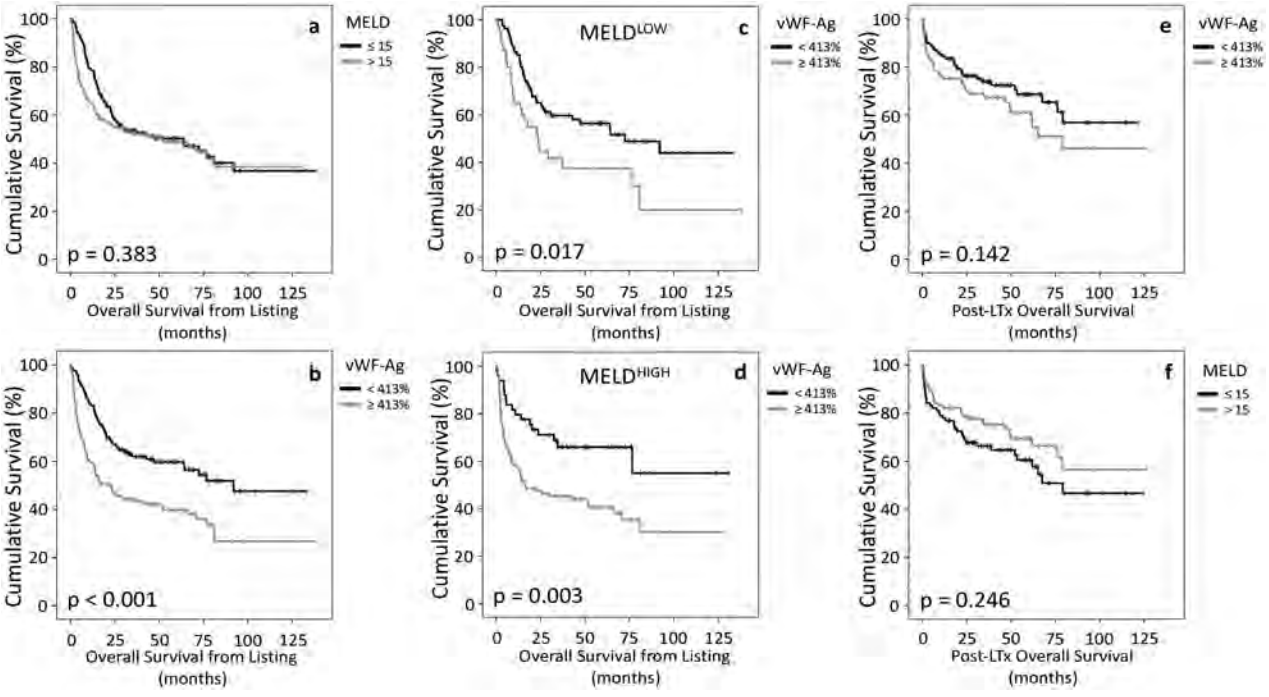

Figure: (abstract: FRI-374)

potential of vWF-Ag in patients listed for LTx. In addition, this statistical approach was used to identify the optimal cut-off level with the greatest accuracy of distinguishing high- and low-risk groups. Multivariable analysis (MVA) was used to investigate independency of predictive markers for waitlist mortality. Kaplan-Meier curves were plotted to visualize survival according to defined risk groups and log rank test was used to assess statistical differences.
Results: Detailed information on vWF-Ag at the time point of listing was available in 269 patients. Patients dying within 3 months on the waitlist displayed elevated levels of vWF-Ag (median vWF-Ag no mortality = 405%, median vWF-Ag mortality = 420%, $p < 0.001$). MELD and vWF-Ag seemed to be almost comparable in their predictive potential for 3-month DoL (AUC vWF-Ag = 0.739, AUC MELD = 0.770). we were able to define a cut-off using Youdens' J statistic at 413% of vWF at time of listing. The cut-off at 413% vWF-Ag was found to predict patients OS both when listed with low MELD score (median OS vWF-Ag^{LOW} = 72.4 months, median OS vWF-Ag^{HIGH} = 23.4 months, $p = 0.017$, Fig.3c) and high MELD score (median OS vWF-Ag^{LOW} = not reached, median OS vWF-Ag^{HIGH} = 16.2 months, $p = 0.003$, Fig. 3d)
Conclusion: vWF-Ag is able to independently predict on list mortality in patients listed for LTx. Importantly, vWF-Ag is able to further identify high risk patients despite a low MELD score and should therefore be incorporated in routine clinical decision making in patients on the waitlist. Ultimately, the data provided within this analysis suggests that the addition of vWF-Ag to the process of organ allocation could eventually result in a higher number of patients reaching the end point of transplantation and hence improve survival.

FRI-375

Direct oral anticoagulants are safe and effective in patients after liver/kidney transplantation

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Background and aims: The ideal anticoagulant therapy in patients after solid organ transplantation is still not clear due to lack of robust data for the use of direct oral anticoagulants (DOAC) in this population. The aim of our study was to describe the real-world effectiveness of DOAC after transplantation with a special emphasis on *in vivo* drug-drug interactions with the immunosuppressive therapy (IS).
Method: Patients after liver and kidney transplantation treated with DOACs between 2014 and 2018 in the out-patient clinic of the University Transplant Center Leipzig were included. Data regarding IS-dose adjustments and complications were collected from medical records and patient-questionnaire. In addition DOAC trough levels were measured.
Results: 42 Patients with liver (n = 21, 50%) kidney (n = 16, 38%) and combined (n = 5, 12%) transplantation were included. Mean age was 64.1 ± 9.6 years, 59.5% males. Mean glomerular filtration rate (GFR) at start of DOAC therapy was 46.6 ± 9.6 ml/min. Patients received either a CNI- (n = 32; 76%) or mTOR-inhibitor-based (n = 10, 24%) immunosuppressive therapy. 23 (55%) patients were treated with rivaroxaban, 19 (45%) with apixaban. The indication for anticoagulation was nonvalvular atrial fibrillation (n = 23), deep vein thrombosis (n = 9), pulmonary embolism (n = 5) and portal vein thrombosis (n = 5). DOACs were administered for a median of 16.0 (range 3.1-52.0) months (corresponding to 72.4 patient-years). No patient withdrew anticoagulation due to adverse events. The IS-dose after DOAC initiation was adjusted in 10 (26.2%) cases. In patients without IS-dose change (n = 27), mean IS plasma levels increased from baseline by 23.6 ± 35.4% (CNI: 25.7 ± 36.6%; mTORi 17.7 ± 33.7%). No rejection or ALT increase was observed in any patient. The mean change in GFR was +1.0 ± 7.1 ml/min in all patients.There were no documented major bleedings but one myocardial infarction in a patient with an underlying malignant disease. 18/30 (60%) patients who completed the questionnaire reported minor bleedings (gingival bleeding, hematoma) (12/15 with rivaroxaban and 6/15 with apixaban). Bleeding (epistaxis) was considered relevant in 3/30 (10%) cases. The trough DOAC levels were available in 22 patients and reached the therapeutic range in all patients.
Conclusion: Treatment with rivaroxaban and apixaban in our patients after liver and kidney transplantation was safe and effective. No major adjustments of immunosuppression were needed in our cohort. Although these data are encouraging, more data including also other DOACs are necessary to make a robust conclusion.

FRI-376

Early treatment with sorafenib and mTOR inhibitor in recurrent hepatocellular carcinoma after liver transplantation: Safety and survival

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Background and aims: Sorafenib (SOR) is currently used in hepatocellular carcinoma (HCC) recurring after liver transplantation (LT), generally in those patients unsuitable for surgical/locoregional treatments. The early introduction of SOR after HCC recurrence and its association with mTOR inhibitors (mTORi) are still debated. Therefore, we evaluated safety and effectiveness of SOR±mTORi in this setting.
Method: From January 2008 to June 2018 all the patients with HCC recurring after LT referring to two liver transplant centers were included if treated with SOR with or without mTORi. Surgical/locoregional treatments were performed before and during systemic treatment.
Results: Forty-eight non cirrhotic patients were enrolled (median age 58, 81% male, 77% on mTORi, 57% only extra-hepatic recurrence). Overall, SOR was started within 3 months after HCC recurrence and 2 months after surgery or locoregional treatments (65% of cases, 57% with curative intent). During 8 months (range 0.1-89) of administration, all patients had at least one SOR-associated adverse event (AE): 18 (38%) graded 1-2; 28 (58%) grade 3-4; 2 (4%) died, the first one due to massive gastrointestinal bleeding and the second one after the onset of severe diarrea. Dose was reduced in 32 (67%) patients, being AEs the main cause of reduction (median daily dose of sorafenib 494 mg). SOR was permanently discontinued in 42 (88%) for symptomatic progression (60%), AE (33%), liver graft dysfunction (5%), HCC complete response (2%). mTORi-associated AEs occurred in 45% (proteinuria 8%, oral ulcers 13%, hypertriglyceridemia 17%, ankle edema 13%), dose was reduced in 30% and withdrawn in 20%. Increase in liver functions tests was registered in 9 cases (19%), without evidence of drug-drug interaction. The best radiological response was objective response in 7 (15%) and stable disease in 23 (48%). The

median time to first radiological progression was 6 months (95%CI 5-7). Thirty-three patients (69%) died, all but two for HCC progression. The 1-, 3- and 5-year overall survival (OS) were 64% (95%CI 50-78%), 23% (95%CI 9-37%) and 18% (95%CI 4-32%). Median OS was 18 months (95%CI 8-27). Predictors of OS were SOR+mTORi (p = 0.03, HR 2.4, 95%CI 1.1-5.3) and HCC-curative treatment (p = 0.003, HR 3.0, 95%CI 1.4-6.2).
Conclusion: Early combination treatment with SOR and mTORi in HCC recurring after LT resulted in an acceptable safety profile and a role in increased patients' survival can be suggested.

FRI-377
Survival outcome after liver transplantation in US patients with hepatocellular carcinoma
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Background and aims: The incidence of hepatocellular carcinoma (HCC) has been dramatically increased in the United States over the last 3 decades. Liver transplantation (LT) is the only curative option for patients with early-stage HCC. Despite the high cost and risk of LT, limited reports addressed the impact of patients' clinico-pathological characteristics on post-transplant overall survival (OS). We aimed at investigating the independent impact of different clinico-pathological factors on OS of HCC patients after LT.
Method: Between 1997 and 2016, total of 6425 cirrhosis-induced HCC patients received LT and had been registered in the United Network for Organ Sharing (UNOS) database. SAS software was used for data extraction and statistical analysis. OS was defined as the time between HCC diagnosis and death (as result of all causes) or end of follow-up (censored observation). To identify independent prognostic factors on OS, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional models.
Results: The mean age (± SD) of all subjects was 60.5 (± 7.7) years. Majority of patients were men (77%). We observed 3% and 8% increase in the expected death hazard relative to each year increase in patients' age and each cm increase in tumor size. The HRs (95% CIs) were 1.03 (1.02-1.04) and 1.08 (1.05-1.11) respectively. Poor tumor differentiation and vascular invasion were significantly associated with poor survival. Multivariate HRs (95% CIs) were 1.38 (1. 25-1.52) and 1.42 (1.22-1.66) respectively; P < .01. No significant impact of other factors including, male gender, diabetes, BMI, portal thrombosis, lymph node involvement, number of tumors, year of listing, or days on waiting list. Stratifying the patients by cirrhosis etiology showed that patients with cryptogenic cirrhosis experienced the highest prevalence of HCC poor differentiation (9%).
Conclusion: Our analysis indicated that patients' age, poor tumor differentiation, and presence of vascular invasion are significant predictors of poor outcome in patients with cirrhosis-induced HCC who had LT. Giving the scarcity of organs, such model will pin point the high risk population for post-LT poor prognosis among HCC population. This may further assist in identifying and prioritization candidates for LT. Future validation of the results in prospective cohorts may be warranted.

FRI-378
Should we change the allocation policy for NASH patients?
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Background and aims: The need for liver transplants by far exceeds the current supply of cadaveric organs. The introduction of the MELD system reduced waiting list mortality. MELD does not account for liver disease etiology. Should certain diseases incur increased wait list mortality, their prioritization for transplant might need to be reconsidered.
The aim of this study is to assess the waiting time on our transplant list and survival rate from listing to transplantation and overall intention to treat survival.
Method: We analyzed data for all the patients listed in our center from 1/2013 till 09/2018 from our database. The death rate on the waiting list, wait time till transplant and death rate after transplant were calculated.
Results: During this period 406 pts were listed for liver transplantation, 20 patients were transplanted overseas and 55 patients were not include in the analysis (not eligible for liver transplantation due to HCC beyond Milan, significant comorbidity other than liver disease or improvement of the liver disease) so that 331 pts were available for analysis. 105 patients (31%) had NASH as primary liver disease. The mean waiting time was 26.2 months. Wait list mortality was 26% (86 pts) and the mean time from listing to death 11.5 m. The deceased patients suffered from NASH (41 pts, 48%) viral hepatitis (8), cholestatic diseases (4), alcohol related liver disease (3), HCC (2) and miscellaneous causes (7).
The survival at 1 and 3 years after transplantation was 78% and 77% respectively, however intention to treat survival from listing was only 63% and 55% respectively.
Conclusion: Almost half of the patients that died on the waiting list suffer from NASH. We suggest that this population might need other allocation policy or serious consideration of early LDLT.

FRI-379
Renal dysfunction between tenofovir and entecavir in patients with hepatitis B virus after liver transplantation
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Background and aims: Tenofovir, Nucleotide analogue polymerase inhibitor is already accepted as effective and tolerable drug for treatment of hepatitis B virus (HBV) as much as entecavir. There are some concerns about nephrotoxicity of tenofovir in patients with end-stage liver disease or liver recipients. We retrospectively investigated the renal function of tenofovir compare to entecavir in liver recipients with HBV.
Method: Among 468 patients with HBV who were underwent liver transplantation at Samsung Medical Center between 2008 January to 2015 December, tenofovir (n = 37) treated group was matched with entecavir (n = 132) group. (1:4, matching variables = age, pre-operative HBV DNA, eGFR, CTP score) Baseline characteristics and 1, 2, 3 year follow-up eGFR and creatinine levels after operation were compared between both group using GEE (Generalized estimating equation) analysis. Risk factors lowering eGFR value are also reviewed with univariate and multivariate analysis.

Results: Among baseline characteristics, age, pre-operative creatinine, eGFR and hepatic encephalopathy score showed statistical difference between tenofovir (n = 39) and entecavir (n = 429) group before propensity score matching. After matching, there was no statistical difference in pre-operative characteristics. Post-operative 1-year eGFR showed no statistical difference from pre-operative eGFR in both group. Post-operative 2-year eGFR (5.25 ml/min/1.73m^2 decrease, p = 0.04) and 3-year eGFR (7.43 ml/min/1.73m^2 decreased, p = 0.02) showed a little decreased from pre-operative eGFR, but there was no statistical difference and interaction between tenofovir and entecavir group (p = 0.42). Post-operative 1-year creatinine (0.28 mg/dl decreased, p = 0.02) and 2-year creatinine (0.24 mg/dl decreased, p = 0.049) showed improvement. 3-year creatinine showed decrease by 20 mg/dl without statistical difference (p = 0.10) from pre-operative creatinine. There was also no statistical difference and interaction between both group (p = 0.38) for creatinine change.
Conclusion: Tenofovir does not induce renal dysfunction in liver transplant patients with HBV compared to entecavir. The safety and renal dysfunction in tenofovir after liver transplantation will be investigated in the further studies.

FRI-380
Factors and models for predicting posthepatectomy liver failure in patients undergoing hepatic resection for hepatocellular carcinoma

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Background and aims: Hepatic resection has been a main treatment option for patients with hepatocellular carcinoma (HCC). The aim of this study was to seek predictive factors and to build predictive model for posthepatectomy liver failure (PHLF).
Method: A total of 1, 364 consecutive patients underwent hepatic resection between January 2016 and December 2017. Laboratory tests were assessed before, and 1, 2, 3, 5, 7, and 10 days after surgery. Posthepatectomy hepatic dysfunction was defined as an increase in the total bilirubin ≥ 2.9 mg/dL (50 μmol/L) or an increase INR on or after postoperative day 5, compared with the values of the previous day. PHLF includes posthepatectomy hepatic dysfunction, ICU stay, development of ascites requiring diuretics or drainage procedure, and mortality from any cause.
Results: Of 1, 256 patients with available data, mean age was 58.3 years and male comprised 80.6% of patients. 403 (32.1%) patients underwent major hepatic resection and 481 (38.3%) revealed cirrhosis at pathologic specimens. The mortality at 30 and 90 days were 0.3% and 0.9%, respectively. PHLF developed in 117 (9.3%) patients: posthepatectomy hepatic dysfunction in 62 (4.9%) patients, ICU stay in 18 (1.4%) patients, ascites in 42 (3.3%) patients, and death 11 (0.9%) patients. In multivariable logistic regression, age over 70 years (adjusted odds ratio [AOR]: 2.89, 95% confidence interval [95% CI]: 1.65-4.97), cirrhosis (AOR: 2.60, 95% CI: 1.67-4.08), albumin less than 3.5 (AOR: 2.17, 95% CI: 1.56-3.01), major hepatic resection compared with minor resection (AOR: 2.26, 95% CI: 1.41-3.62), and high indocyanine green (ICG) index at 15 minutes over 20% (AOR: 2.53, 95% CI: 1.21-5.46) were significantly associated with a high risk of PHLF. Interger values were assigned to each factor to develop a model that predicted PHLF, which presented an area under the curve of 0.780.
Conclusion: Cirrhosis, age over 70 years, major resection, lower albumin and high ICG level were associated independently with PHLF. A composite interger-based risk scoring model could accurately predict PHLF in patients undergoing hepatic resection for HCC.

FRI-381
Latent trajectory analysis of serum creatinine in patients with end stage liver disease: Predictors of pre- and post-transplant outcomes

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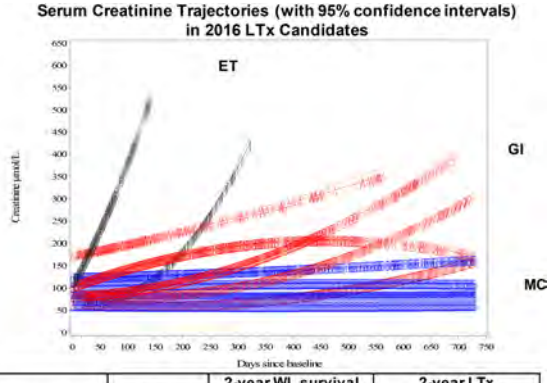
Background and aims: Renal impairment remains an important determinant of outcome in patients with end stage liver disease (ESLD). We identify clusters of serum creatinine (sCr) trajectory for liver transplantation (LTx) candidates with which to determine predictors of outcomes before and after LTx.
Method: In the US Organ Procurement and Transplantation Network registry, all adult primary LT candidates on the waiting list as of Jan 1, 2016 were identified. In eligible (baseline MELD > 15 and sCr < 1.5 mg/dL and ≥ 3 sCr data) patients, the nearest date on which a MELD score was available within the preceding 180 days of Jan 1, 2016 was taken as baseline. Subpopulations with heterogeneous disease trajectories were identified, using latent class growth mixture modelling to group individuals based on changes in sCr over two years of follow-up. Statistical fit was determined by Bayesian information criteria and trajectories with similar patterns were categorized into separate groups for analysis. Patient characteristics predictive of the sCr trajectory were identified with the multiple logistic regression analysis. The impact of the pre-LTx sCr on post-LTx renal function was assessed by the generalized linear model (GLM) procedure adjusting for the sCr at LTx.
Results: Three distinct trajectory groups were identified among 2, 044 patients (Figure), including (1) early deterioration (ED, shown in black in Figure), (2) gradual increase (GI, red), and (3) minimal change (MC, blue). These trajectories had a significant impact on two-year waitlist survival (0.15, 0.26 and 0.79 for ED, GI and MC, respectively) and LTx probabilities (1.00, 0.82 and 0.46 for ED, GI and MC, respectively). In the multivariable analysis, predictors of ED included bilirubin (odds ratio [OR] = 1.10, p < 0.01) and albumin (OR = 0.47, p < 0.01), as well as baseline sCr (OR = 5.92, p < 0.01). There were 555 patients who underwent deceased donor, single organ LTx for ESLD and had complete data. The median sCr at LTx was 2.65 mg/dL for ED, 1.83 mg/dL for GI, 0.93 mg/dL for MC. These differences diminished over time-the median follow-up sCr ≥ 180 days after LTx was 1.37 mg/dL, 1.30 mg/dL and 1.10 mg/dL for ED, GI and MC, respectively. These trends persisted in the multivariable GLM: ED was associated with larger improvement in sCr (–0.25, p = 0.04) compared to GI and MC, adjusting for sCr at LTx (0.22, p < 0.01), age (0.006, p < 0.01) and female sex (–0.19, p < 0.01).



Trajectory groups	N (%)	2-year WL survival probability	2-year LTx probability
Early Deterioration	50 (2.5)	0.15	1.00
Gradual Increase	192 (9.4)	0.26	0.82
Minimal change	1802 (88.2)	0.79	0.46

Conclusion: Using latent class trajectory modelling methods, we were able to define three distinct trajectory groups for sCr in LTx candidates with ESLD. Based on the sCr trend and pre- and post-LTx renal function, the ED trajectory likely corresponds to hepatorenal syndrome (HRS) type I or acute tubular necrosis, whereas GI reflects HRS-2. Significant recovery in sCr is seen after LTx, particularly in ED.

FRI-382

Biological assessment comprising alpha-fetoprotein, albumin-bilirubin score and C-reactive protein provides better prognostic competence than tumor size criteria in liver transplant patients with HCC

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Background and aims: Recently, the albumin-bilirubin (ALBI) score was shown to correlate with overall and cancer-specific outcome following liver resection for hepatocellular carcinoma (HCC). Respective data in the liver transplant (LT) setting is completely lacking. The aim of this retrospective study was to determine the power of pretransplant ALBI score for predicting oncological prognosis after LT for HCC.
Method: 123 HCC patients following LT were analyzed. The ALBI score at LT was determined by standard calculation formula. At final pretransplant radiographic imaging, tumors were staged as meeting or exceeding the Milan (MC) and the Up-to-seven (UTS) criteria. Recurrence-free survival (RFS) rates were determined by the Kaplan-Meier method. Uni- and multivariable Cox regression analysis was used for identifying pre-LT available prognostic factors. Concordance statistics was applied to compare the prognostic competence in predicting post-LT HCC relapse.
Results: Median post-LT follow-up was 80 months (range: 5-190). Cumulative risk of HCC relapse at 7 years post-LT was comparable between ALBI-grade 1 (10.5%) and ALBI-grade 2 patients (15.9%; p = 0.459), while being significantly higher in ALBI-grade 3 recipients (68.2%; $p < 0.001$). In multivariable analysis, AFP level $\leq$ 100 ng/ml (HR = 4.99; $p < 0.001$), ALBI-grade 1/2 (HR = 3.52; $p = 0.002$) and C-reactive protein level $\leq$ 1 mg/dl (CRP; HR = 2.61; $p = 0.026$) were identified as independent clinical promoters of disease-free outcome. RFS at 7 years post-LT was comparable between MC In patients (86.8%) and MC Out patients with ALBI-grade 1 (75.5%) or ALBI-grade 2 (75%; $p = 0.296$), and between UTS In patients (81.6%) and UTS Out recipients with ALBI-grade 1 (75%) or ALBI-grade 2 (67%; $p = 0.408$). In contrast, it was only 17.6% in MC Out and 30% in UTS Out patients with ALBI-grade 3 ($p < 0.001$), respectively. According multivariate significance, the following oncological risk scores were assigned: AFp > 100 ng/ml: 3; ALBI-grade 3: 2; CRp > 1 mg/dl: 1, finally leading to a summarized minimum of 0 (lowest oncological risk) and a maximum of 6 (highest oncological risk) risk points. Actuarial RFS rates at 7 years post-LT were 89% in the low risk group (score 0 to 3; n = 101), but only 27% in the high risk subset (score 4 to 6; n = 22; $p < 0.001$). C-indexes for predicting post-LT HCC recurrence were 0.79 for biological risk scoring, 0.67 for MC and 0.65 for UTS criteria, respectively.
Conclusion: The ALBI score is an important and easy available prognosticator of oncological outcome in liver transplant patients with HCC and should, therefore, be implemented in individual decision making process. Tumor biological risk assessment based on AFP value, ALBI-grade and CRP level identifies a subset of HCC patients that may benefit from LT independent from tumor size limitations.

FRI-383

Role of traditional cardiovascular risk factors in predicting long term survival after liver transplantation

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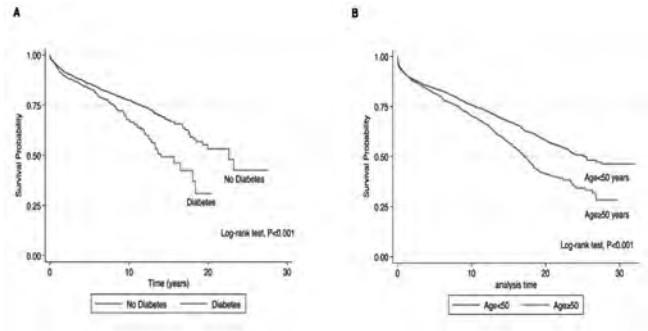
Background and aims: Cardiovascular (CV) death is a leading cause of long-term mortality following liver transplantation (LT). Identifying pertinent CV risk factors that impact on long-term survival may allow an opportunity for intervention.
Method: Outcome data was prospectively collected for all adult LT performed in Australia and New Zealand between 1985 and 2017, from the Australian and New Zealand Liver Transplant Registry. Risk factors including hypertension, diabetes, age, sex, obesity (body mass index $\geq$ 30 kg/m^2), pre-existing coronary artery disease (CAD) and non-alcoholic fatty liver disease aetiology were collected and entered in a multivariable Cox regression model.
Results: Among, 4, 538 adult LT performed, 1433 (31.6%) deaths including 240 CV deaths (17%) occurred during a median follow-up of 10.5 years (IQR: 4.9-17.9 years). On univariate analysis, age $\geq$ 50 years (log-rank test, p < 0.001), diabetes (p < 0.001) and obesity (p = 0.006) were associated with all-cause mortality (**Figure**). After Cox multivariable adjustment, diabetes (Hazard ratio [HR] 1.4, 95%CI 1.07-1.8, p = 0.01) and age $\geq$ 50 (HR 1.5 95%CI 1.2-1.9, p < 0.001) remained as independent predictors for all-cause mortality. Notably, pre-existing CAD did not predict long-term mortality (p = 0.24).



Conclusion: Presence of diabetes and age $\geq$ 50 independently increased the risk of long term mortality following LT. Whether intensive risk factor modification in high-risk populations improves long-term survival after LT remains to be tested.

FRI-384

Early cardiovascular mortality following liver transplantation: 30-year temporal trends from the Australian and New Zealand liver transplant registry

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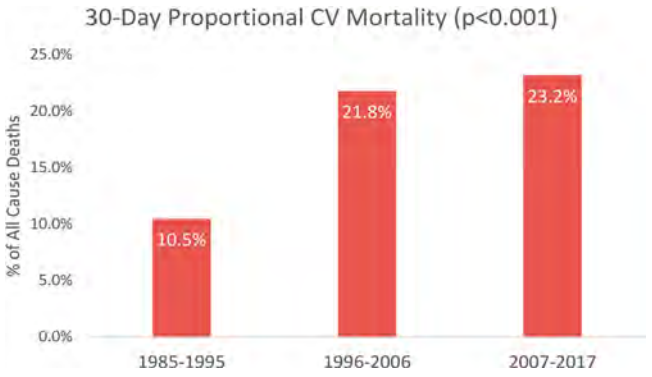
Background and aims: Liver transplantation (LT) poses significant cardiovascular (CV) risk for patients. Given the rising prevalence of non-alcoholic fatty liver disease and advancing age of LT candidates, delineating CV risk is increasingly important. We sought to characterize the incidence and modes of intraoperative and early ($\leq$ 30days) CV death post-LT.

Method: Prospectively recorded clinical and outcome data were collected for all adult LTs in Australia and New Zealand between 1985 and 2017. Data was collected from six participating centres and compared between Era 1 (1985-1995), Era 2 (1996-2006) and Era 3 (2007-2017).
Results: Among, 4, 538 adult LT performed, 201 (4.4%) deaths including 38 (19.0%) CV deaths occurred within 30-days. All-cause mortality fell across the 3 Eras. A significant reduction in all-cause mortality and overall early CV death was noted (1.1%-1.2%-0.6%, p < .001, Era 1-3). However, CV death as a proportion of all-cause 30-day mortality increased significantly (10.5%-21.8%-23.2%, *p < 0.001, Era 1-3, respectively- **Figure**). CV events were the leading cause of intra-operative mortality (40%) and second leading cause of overall early death (31.8%). Most common modes of CV death were cardiac arrest and congestive heart failure (44.7% and 23.7%, respectively, of CV deaths).



Conclusion: CV events are a leading cause of operative and early mortality following LT. Despite reductions in absolute all-cause mortality over 30 years, the proportion of deaths due to CV causes continues to rise. Improvements in preoperative risk stratification are needed.

FRI-385
Use of machine learning algorithms to predict HCC recurrence after liver transplantation: A proof of concept
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Background and aims: The liver transplant listing criteria for hepatocellular carcinoma (HCC) is controversial. Policies aim to prevent tumor recurrence but it has been difficult to encompass the numerous contributive factors. This study takes advantage of machine learning algorithms to incorporate all available features in a post-transplant recurrence prediction calculator.
Method: The calculator was developed using the University of Toronto HCC database, which is a comprehensive dataset including all patients with HCC listed for liver transplantation between 2000 and 2016. The dataset includes comprehensive features including serial imaging morphology, AFP, details of bridging therapy, treatment response, and post-transplant outcome.
A Cox proportional hazards model was used to model time to recurrence following transplant. The model was estimated through a least absolute shrinkage and selection operator (LASSO) penalized maximum likelihood procedure in order to encourage sparsity of the coefficients, thereby discouraging overfitting. The coefficients were learned on 90% of the data (the training set). The regularization hyperparameter was learned on the same set of training data. Performance was evaluated over 1000 iterations by assessing the area under the receiver operating curve (AUC) and concordance on the held-out data (the testing set). Variables selected by LASSO in over 50% of iterations were selected to run the analysis of the 5-year recurrence risk in the model. The same dataset was then used to train alternative recurrence risk algorithms (AFP score and MORAL) to compare its predictive power.
Results: The dataset included 694 patients who underwent liver transplant for HCC. The overall concordance of score with disease-free survival was satisfactory (concordance 0.706, sd: 0.075). The AUC for prediction of recurrence show the predictive power of the model (Figure 1). Including all variables meeting the selection criteria, the AUC at 5 years post transplantation was 0.756 (95% CI 0.708-0.804). By comparison, the AUC for AFP score at 5 years post transplantation was 0.616 (95% CI 0.558-0.675) and that of MORAL was 0.595 (95% CI 0.536-0.655).

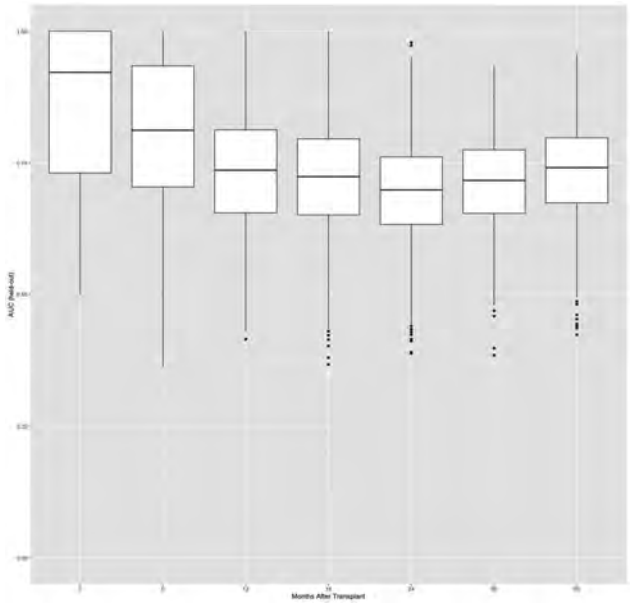

Figure 1: AUC of the Toronto HCC Recurrence Calculator at specific times.

Conclusion: A comprehensive HCC recurrence risk calculator using machine learning is possible with higher accuracy than other available scores.

FRI-386
Impact of acute-on-chronic liver failure on survival after liver transplantation
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Background and aims: The post-liver transplant (LT) survival of patients with an episode of Acute-on-Chronic Liver Failure (ACLF) has not been evaluated in depth. We aimed to estimate the effect of ACLF on survival at 365 days post-LT.
Method: Retrospective cohort of patients with cirrhosis aged > 17 years who underwent a liver transplant from Jan/2010 to May/2016. Follow-up started the date of LT until death, liver re-transplantation, loss to follow-up or for a total of 365 days. ACLF was defined according to CLIF-SOFA, evaluated on the day of transplantation. The risk of

post-transplant death is presented as a Hazard Ratio (HR) and was estimated using a Cox model weighted with inverse probability weighting (HR_{IPW}) taking into account the following receptor's potential confounders: MELD-Na, age, detectable HCV viremia and hospitalization in intensive care unit at the time of LT and Donor Risk Index (DRI).

Results: Of a total of 336 patients who underwent liver transplantation 185 met the selection criteria and were included: 125 (68%) underwent transplant without ACLF, and 60 (32%) with ACLF. ACLF grades: 1: 34 (57%); 2: 18 (30%); 3, 8 (13%). Main etiologies were HCV and alcohol-related cirrhosis. Survival at 365 days in patients who were transplanted without ACLF was 91% (95% CI: 84% –95%) vs 85% (95% CI: 73% –91%) in patients with ACLF, p = 0.2005. No effect of ACLF was observed on post-LT survival in the bivariate analysis [crude HR 1.76 (95% CI: 0.73-4.25, p = 0.207)], nor adjusted by confounders [HR_{IPW}1.38 (95% CI: 0.47-4.06, p = 0.548)].

Table: Characteristics according to the absence or presence of ACLF at LT

	Without ACLF N = 125	With ACLF N = 60	p
Donor			
Donor Risk Index	1.59 (1.28-1.94)	1.58 (1.28-1.94)	0.339
Recipient			
Male gender	77 (61.80)	36 (60)	0.834
Age-years	59.5 (54.2-64.9)	60 (50.4-64.6)	0.381
Intensive care unit at transplant	4 (3.2)	10 (16.67)	0.001
Child-Pugh score	10 (7-11)	11 (10.5-12.5)	< 0.0001
MELD Score	17 (12-23)	27 (23-30)	< 0.0001
Hepatocellular carcinoma	59 (47.20)	9 (15)	< 0.0001
HCV RNA positive at LT	51 (41.13)	15 (25)	0.032
HIV	4 (3.20)	4 (6.67)	0.277
Pre LT Hypertension	33 (26.40)	15 (25)	0.839
Pre LT Diabetes	36 (28.80)	14 (23.33)	0.433
Previous abdominal surgery	57 (46.34)	16 (27.12)	0.013
Leukocytes-x10^3/μL	5.0 (3.7-63)	4.4 (3.2-6.7)	0.899
Platelets count-x10^3/μL	74 (51-104)	63 (44-104)	0.572
Total Bilirubin-mg/dL	3 (1.4-5.8)	12.9 (4.5-21)	< 0.0001
Albumin-gr/dL	2.9 (2.6-3.5)	2.8 (2.4-3.27)	0.022
INR	1.6 (1.28-1.9)	2.46 (1.75-3.2)	< 0.0001
Creatinine-mg/dL	0.79 (0.68-0.96)	0.9 (0.75-1.14)	0.0137
Serum sodium-mEq/L	136 (132-138)	132 (128-136)	0.0472
Total psoas volume-cm^3	12.4 (6.9-27.3)	11.2 (5.95-17.67)	0.0125

Categorical variables are expressed in absolute numbers (percentages); continuous variables in median and IQR

Conclusion: No differences in post-LT survival was observed in patients with and without ACLF at the time of LT. Our study supports LT of these patients.

FRI-387

Risk factors associated with early post-operative acute kidney injury requiring renal replacement therapy following liver transplantation

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Background and aims: Liver transplant (LT) recipients are at high risk of developing post-operative acute kidney injury (AKI). Patient, graft and perioperative factors have been associated with this insult. Although the majority recover from this early post-operative AKI, the development of AKI is associated with increased incidence of chronic kidney disease, reduced graft and patient survival. We sought to evaluate risk factors associated with the severe phenotype of AKI requiring renal replacement therapy (RRT).

Method: All liver transplants performed at a high volume centre from 1/1/17 to 31/12/17 were reviewed. Patients who were aged under 18, received multi-organ transplants or had acute liver failure were excluded. Patient demographics, clinical and biochemical parameters pre-LT, organ characteristics and surgical technique utilised, post-LT biochemistry and use of RRT were collected from clinical notes. Univariate statistical analysis was performed between RRT and RRT free groups.

Results: A total of 164 patients were included with a median age at transplant 55.7 years. The incidence of AKI requiring RRT was 22.6%. The RRT group had: more severe liver disease at listing (UKELD ($p = 0.01$), MELD ($p = 0.004$)); a higher incidence of diabetes (*OR 3.03 CI 1.37-6.62 p = 0.006*), non-alcoholic fatty liver disease (NAFLD, *OR 3.3 CI 1.38-7.51 p = 0.007*), ascites (*OR 3.02 CI 1.36-7.18 p = 0.008*); lower eGFR at assessment ($p = 0.0009$) and immediately prior to LT ($p < 0.0001$); higher utilisation of DCD grafts (*OR 3.77 CI 1.74-8.34 p = 0.0008*); and higher opening AST ($p = 0.01$). Decrease in eGFR from assessment to LT was seen in 42 patients and associated with RRT ($p = 0.0002$). There was no significant difference in age, sex, re-do LT or use of a caval replacement.

Conclusion: A significant proportion of patients develop AKI requiring RRT following LT. A number of risk factors for this have been identified in this subgroup of patients, emphasising the multifactorial nature of the process. Few of these factors are modifiable in the setting of LT. Strategies to preserve renal function prior to LT in all recipients, with particular attention to those with more severe liver disease, NAFLD, diabetes and ascites, and minimising early allograft dysfunction may reduce post-LT AKI requiring RRT. Identifying patients at high risk of AKI informs post-LT immunosuppression strategy. The use of DCD grafts should also be carefully considered in this cohort to preserve renal outcomes.

FRI-388

Hepatitis C iInfected liver grafts transplanted into non-infected recipients are safe in the era of highly effective direct-acting antiviral therapy

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Background and aims: Availability of effective direct-acting antiviral therapy has raised the possibility of safely transplanting hepatitis C infected organs into hepatitis C naïve recipients. This study aimed to (1) determine the incidence of post-liver transplant hepatitis C infection in previously uninfected patients transplanted with hepatitis C infected liver grafts, and (2) assess response to therapy using direct-acting antiviral agents for hepatitis C naïve patients who develop hepatitis C post-transplant with hepatitis C infected liver grafts.

Method: Hepatitis C non-infected patients awaiting liver transplantation were given the option of consenting to accept a hepatitis C infected graft that was otherwise deemed programmatically to be an acceptable organ for transplantation. These patients followed the same post-transplant treatment algorithms using direct acting antiviral agents that were utilized in recipients who were hepatitis C infected prior to transplant.

Results: A retrospective chart review from March 2016 to July 2018 noted 15 patients that underwent liver transplantation with hepatitis C infected grafts defined as positive donor hepatitis C nucleic acid testing into HCV naïve recipients. All 15 recipients developed hepatitis C infection post-transplant documented by a quantifiable viral load post-transplant with genotypes 1a, 2, and 3. Direct-acting antiviral therapy was initiated between 19 and 138 days (median 51 days) after liver transplantation. All 15 recipients completed treatment for hepatitis C using one of the following regimens: ledipasvir/sofosbuvir, glecaprevir/pibrentasvir, or sofosbuvir/

velpatasvir. Nine recipients have achieved a sustained viral response 12 weeks post treatment, one recipient has achieved a sustained viral response 4 weeks post treatment, and post treatment data is pending on the remaining 5 recipients. All transplanted recipients in this cohort are recovering expectedly.

Conclusion: Hepatitis C uninfected patients on the liver waitlist transplanted with hepatitis C infected grafts universally develop infection with hepatitis C post-transplant. Fortunately, these patients can be successfully cleared of hepatitis C post-transplant. In short term follow-up, hepatitis C non-infected patients who receive hepatitis C infected grafts do not have a higher mortality than non-infected liver recipients transplanted with non-hepatitis C infected donor grafts.

FRI-389

Impact of coronary artery disease on long term mortality after liver transplantation

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Background and aims: Cardiovascular disease (CVD) is an important cause of post liver transplantation (LT) mortality and is higher than age-and gender matched cohorts. This happens despite careful pre-LT selection where patients deemed to be high risk for CVD are excluded from LT consideration. Thus, the key driver of this post-LT mortality is not known. We hypothesized that patients after LT have accelerated atherosclerosis and therefore, pre-LT coronary artery disease (CAD) would not be able to predict overall and CVD associated mortality post-LT.

Method: Protocol coronary angiography is performed in all patients aged > 50 years or risk factors (diabetes, hypertension, obesity, family history, smoking history) prior to LT. Those without risk factors and < 50 years old have non-invasive cardiac stress test and coronary angiography was limited to those with positive stress test. All adult patients receiving LT from 1/2007 to 1/2017 were included (N = 495). The primary and secondary outcomes were all cause mortality and CVD mortality, respectively. A Cox proportional hazards model was conducted on survival after LT adjusting for age, etiology of chronic liver disease, CAD, smoking, and diabetes.

Results: A total of 495 LTR were enrolled. The mean age of the LT recipients (LTR) was 55 ± 9 years and 358 (72%) were males. The prevalence of CAD as noted on angiography was 26% prior to LT. After median follow-up of 4.5 years (range:0-11 years), 120 (24.2%) deaths occurred, 29 (5.9%) of which were related to CVD. The 1-, 3- and 5-year survival rates were 91.5%, 84.4%, and 75.4%%, respectively. The overall mortality rates were similar between those with and without CAD at baseline (Figure 1). No association between presence, severity or history of CAD intervention with overall mortality was found. The etiology of liver disease was not related to overall mortality (Table 1). While NASH is closely associated with CAD (38.5% vs. 23.7% p = 0.009), in sub-group analysis CAD did not impact survival in patients transplanted for NASH cirrhosis [HR:1.47, 95%CI:0.47, 4.62].

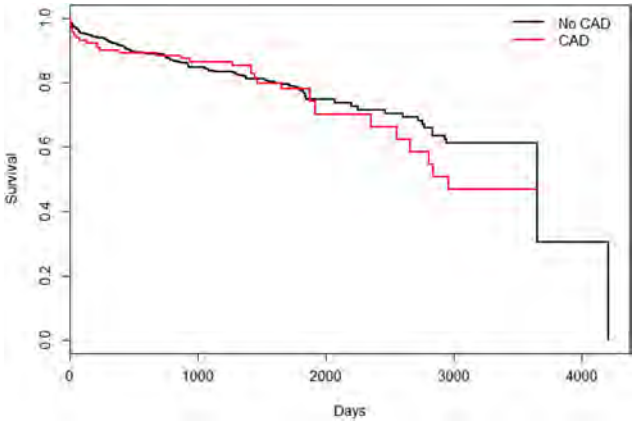

Figure 1: Survival curves of patients post-LT by presence of CAD.

Table 1: Cox proportional hazards model for overall survival post-LT

Characteristics	Hazard Ratio (95% CI)	p values
CAD present	1.00 (0.66, 1.53)	0.972
NASH	0.65 (0.37, 1.14)	0.131
Age	1.03 (1.00, 1.05)	0.034
Smoking	1.36 (0.94, 1.97)	0.106
Diabetes	1.37 (0.93, 2.02)	0.111

Conclusion: Despite aggressive attempts to risk stratify patients prior to LT, cardiovascular risk is not fully captured on pre-LT cardiac evaluation, lending further support to factors that are exacerbated post-LT. More importantly the prevalence of CVD mortality post-LT was much higher than the reported general population suggesting potential limitation in clinical management that need to be overcome if we are to improve long-term survival in LTR.

FRI-390

Management of dyslipidemia after liver transplantation

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Background and aims: Cardiovascular disease (CVD) remains a major cause of long-term mortality in liver transplant recipients (LTR). Adequate control of CVD risk factors like hypertension, diabetes, and dyslipidemia is therefore essential in this population. Although there is robust data supporting aggressive use of statin therapy in patients with documented CVD or dyslipidemia in general population, there is currently no data regarding post-liver transplantation (LT) CVD management or adherence to societal guidelines for management of dyslipidemia.

Method: Patients undergoing at liver transplantation at Virginia Commonwealth University from January 2007 to January 2017 were reviewed. All LTR had a thorough evaluation for coronary artery disease (CAD) prior to listing. Patients were considered eligible to be prescribed a statin if they had documented CAD on angiography or dyslipidemia. The primary end point consisted of percentage of eligible LTR receiving statins. Secondary end points were adverse events from statin use and patient survival. Associated factors to

statin use and mortality were assessed using a logistic regression and Cox proportional hazards models, respectively.
Results: The mean age of the 495 LTR patients in the sample was 55.3 ± 9.3 years. The median follow-up period was 4.5 years (range:0-11 years). In the post-LT period, 245 patients were eligible for statin therapy, and statin use was noted in 106 (43%) eligible patients. CAD was noted in 129 (26.1%) patients during the pre-LT evaluation, and 45% of these were on statin therapy post-LT. In the post-LT period 116 patients had dyslipidemia requiring statin therapy and 53% of them were on statin therapy. Factors associated with post-LT statin use included gender, CAD, diabetes (DM) and hypertension (HTN) (Table 1). Lower levels of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin were observed in patients using statins. Finally, no patients developed liver failure or acute liver injury from statin use. Statin was related to longer survival time [HR:0.20, 95%CI:0.11, 0.38]

Table 1: Adjusted effect for statin use and overall mortality

Characteristics	Statin Use		Overall Mortality	
	OR (95% CI)	p value	HR (95% CI)	p value
Age	1.00 (0.98, 1.02)	0.899	1.04 (0.99, 1.08)	0.066
Male	0.48 (0.31, 0.74)	< 0.001	0.74 (0.41, 1.33)	0.315
CAD present	1.57 (1.00, 2.45)	0.046	1.66 (0.99, 2.76)	0.053
NASH	1.65 (0.97, 2.81)	0.064	0.86 (0.43, 1.72)	0.662
Hypertension	1.62 (1.08, 2.43)	0.021	1.20 (0.72, 1.98)	0.490
Diabetes	1.96 (1.28, 3.02)	0.002	1.81 (1.07, 3.04)	0.026
Statin	-	-	0.20 (0.11, 0.38)	< 0.001

Conclusion: The statin therapy is underutilized in LTR. The use of statin therapy after LT did not cause significant elevations in liver enzymes. There was no increased in hepatic complications with statin use. There was survival benefit noted with statin use.

FRI-391

Biliary calprotectin, lactoferrin and dimeric pyruvate kinase after liver transplantation are markers for biliary damage and predict graft survival

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Background and aims: Biliary complications are an important cause of mortality and morbidity after liver transplantation. Endoscopic management is the mainstay for biliary strictures complicating LT. The prognosis of anastomotic strictures is largely beneficial and they resolve upon repeat endoscopic intervention. By contrast non-anastomotic strictures are often related to increased donor ischemia time and reperfusion injury while in many patients none of these risk factors can be identified. They carry a dismal prognosis with almost inevitable graft failure and need for re-transplantation. A reliable biliary marker for the assessment of irreversible versus reversible biliary damage would be of great value for patient triage and early consideration for re-transplantation.
Method: A cohort of 111 patients with liver graft complications after LT, who received ERC during 2006-2014 was analyzed. Bile fluid was collected during first ERC after LT. The cohort comprised 23 controls, 7 CMV infections, 8 biopsy proven acute rejections (ACR), 20 anastomotic strictures (AS), 15 non-anastomotic strictures (NAS) and 26 ischemic type biliary lesions (ITBL). Biliary calprotectin, lactoferrin and dimeric pyruvate kinase was measured by ELISA. Biliary markers were correlated with regard to the primary end point of re-transplantation free survival.
Results: Median calprotectin level in bile was 1426 pg/ml (range: 26-203100 pg/ml). Calprotectin was significantly higher in bile of ITBL and NAS compared to control, bile leakage, CMV infection, AS or ACR patients ($p < 0.001$) independent of serum liver values at ERC. Median biliary lactoferrin concentration was 153 pg/ml (range: 0-2714pg/ml). Lactoferrin was significantly higher in ITBL patients compared to the NAS ($p < 0.05$), AS or controls ($p < 0.001$). Median M2PK concentration was 296 pg/ml (range: 0-654pg/ml). Median M2PK values in ITBL were significantly higher compared to NAS ($p < 0.05$), AS ($p < 0.01$) and controls ($p < 0.001$). Calprotectin had the best predictive value for ERC diagnosed ITBL with an AUC of 0.838 at an optimal cutoff of > 3940 pg/ml for ITBL with a sensitivity of 81% and a specificity of 76%. Median re-LT-free-survival in the highest calprotectin and lactoferrin tertial was significantly reduced (24.5 months vs. not reached, $p < 0.01$ and 16.0 months versus not reached, $p < 0.01$). In multivariate analysis including age, gender, cold ischemia time, ERC radiographic classification of the biliary damage only biliary calprotectin ($p = 0.02$) and serum gGT ($p = 0.03$) were independent risk factors for reduced re-TL free survival.
Conclusion: Calprotectin and lactoferrin are bile markers for biliary damage and predict re-transplantation free survival. They can differentiate progressive biliary damage from reversible biliary damage or non-biliary liver value alterations after LT.

FRI-392

Sarcopenia associated with worse pre-transplant psychosocial status and predicted post-transplant diabetes

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Background and aims: suggested as an objective surrogate marker for frailty and functional performance. Debatable associations reported between Sarcopenia and Pre or post-transplant morbidity and mortality outcomes. CT scan is an acceptable modality to assess sarcopenia via Whole-body Lean Muscle Mass (WLMM); although lacks standardization. This study assessed the correlation between Sarcopenia and liver transplant outcome in the Israeli population.
Method: An observational retrospective study included 26 adult transplants (deceased donors) at the Hadassah Medical center 2008-2011; with feasible adequate quality Pre transplant abdominal CT. WLMM assessed, adjusted to stature and correlated to transplant outcomes.
Results: mean age at transplant 51 ± 12.3 years (81% males), mean Model for End-Stage Liver Disease 21.4 ± 4.96. The majority (77%) of patients had viral hepatitis. Patients grouped in relation to the WLMM threshold of 650. There were no significant differences in mean post-transplant survival (28.44 ± 16.9 vs. 23.43 ± 16.92), death (83.33% vs. 78.57%), graft rejections (33.33% vs. 64.29, $p = 14$), infections (50% vs. 53.8%), biliary complications (41.7% vs. 35.7%) or recurrence of liver disease (33.33% vs. 21.43%) between the high and low WLMM, respectively. However, the low Muscle Mass significantly correlated with worse Pre transplant psychosocial assessment including compliance ($p = 0.02$), insight ($p = 0.01$) and support ($p = 0.0001$). Moreover, the high Muscle Mass significantly correlated with increased post-transplant diabetes (41.67% vs. 0%, $p < 0.001$).
Conclusion: Sarcopenia (WLMM) prior to Liver transplantation correlated with Pre transplant psychosocial assessment. Whole high LMS predicted post-transplant diabetes. Larger transplant population and post transplant WLMM will be provided at presentation.

FRI-393

Arterial stiffness in the assessment of cardiovascular risk after liver transplantation

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Background and aims: Liver transplant (LT) recipients have a higher cardiovascular risk (CVR) than the general population. Assessment of CVR is based in clinical algorithms whose usefulness after LT is unclear. Before causing major cardiovascular events, atherosclerosis induces asymptomatic vascular lesion that can be quantified through the estimation of arterial stiffness, or by measuring the ankle-arm index (AAI), among others. We aimed to evaluate these markers of early atherosclerosis and their association with clinical cardiovascular risk factors after liver transplantation.
Method: Cross-sectional single-center study in which we included, during one year, all LT recipients with a follow-up of 12 (± 3), 60 (± 6) and 120 (±6) months after LT. The presence of CVR factors (diabetes, arterial hypertension, dyslipemia, smoking status, obesity) and their control was assessed, and the algorithms SCORE and REGICOR were calculated. Arterial stiffness was estimated by measuring wave pulse velocity with the Mobil-O-Graph® device, and AAI was calculated with a double digital oscilometer (WatchBP OfficeABI®).
Results: We included 122 liver transplant recipients with 12 (n = 39), 60 (n = 45) y 120 (n = 38) months of follow-up, at a median age of 58, 60 and 66 years, respectively (p = 0.02). The prevalence of arterial hypertension increased significantly with the time of follow-up after LT (51%, 67% and 82% at 12, 60 and 120 months, respectively, p = 0.01). On the contrary, we did not find significant differences in the prevalence of the remaining CVR factors. Similarly, there were no statistically significant differences either in clinical algorithms or in AAI according to the time of transplant follow-up. Wave pulse velocity significantly increased, being 8.2 m/s at 12 months, 8.9 m/s at 60 months and 9.4 m/s at 120 months (p = 0.014). Wave pulse velocity was significantly associated with age (p < 0.001), time of transplant follow-up (p = 0.007), the REGICOR algorithm (p = 0.05), and the grade of control of blood pressure (p = 0.02).
Conclusion: Quantitative estimation of arterial stiffness by measuring wave pulse velocity is associated with variables related to cardiovascular risk and its grade of control after liver transplantation and thus it may be a good marker of such risk in this population. Longitudinal studies are required in order to test its capacity to predict major cardiovascular events.

FRI-394

Impact of early kidney dysfunction in the incidence of major cardiovascular events after liver transplantation

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Background and aims: Major cardiovascular events (MACE) are increasingly frequent after liver transplantation (LT), and their risk factors are not well defined. Recent research has suggested an association between renal dysfunction and MACE, particularly in the short-term. We aimed to investigate the incidence of MACE after LT and evaluate their risk factors, both before and after LT, focusing on the relationship between renal dysfunction and the risk of MACE in the long-term.
Method: We designed a retrospective, single-centre study in which we included all recipients of a first, single-organ LT between January 1st 2007 and December 31st 2017. The incidence of MACE (arrythmia, coronary artery disease, cerebrovascular disease, peripheral artery disease) after LT was investigated, and risk factors before LT (cardiovascular risk factors, kidney function, characteristics of liver disease, age, gender), at discharge from transplant episode and 12 months after LT (cardiovascular risk factors, kidney function, immunosuppression) were evaluated.
Results: We included 627 patients, 117 (19%) of whom suffered at least one MACE at a median time of 18 (IQR 1-46) months after LT follow-up. Cumulative incidence of MACE was 8% and 20% at 12 and 60 months after LT, respectively. Most MACE episodes were arrhythmia (53%), coronary artery disease (27%) and cerebrovascular disease (19%). Age at LT, male gender and serum creatinine at LT were associated with the risk of presenting a MACE during the first month after LT at univariate analysis, with age (p < 0.001) and serum creatinine (p = 0.014) being independent risk factors at multivariate analysis. Male gender, age at LT, personal history of diabetes, arterial hypertension and MACE before LT, immunosuppression with cyclosporine A at transplant episode discharge, arterial hypertension 12 months after LT and serum creatinine at transplant discharge and 12 months after LT were associated with the incidence of MACE > 12 months after LT at univariate analysis. At multivariate analysis, age at LT (p = 0.019), male gender (p = 0.025), pre-LT personal history of MACE (p = 0.03) and serum creatinine 12 months after LT (p = 0.05) were independent predictors of the risk of MACE > 12 months after LT.
Conclusion: Our data suggest that renal dysfunction during the first months after LT is an early marker of cardiovascular risk in LT recipients. Whether renal-sparing immunosuppressive regimens also result in a decreased incidence of MACE should be evaluated in prospective, longitudinal studies.

FRI-395

Etiology of liver disease affects weight gain after liver transplantation

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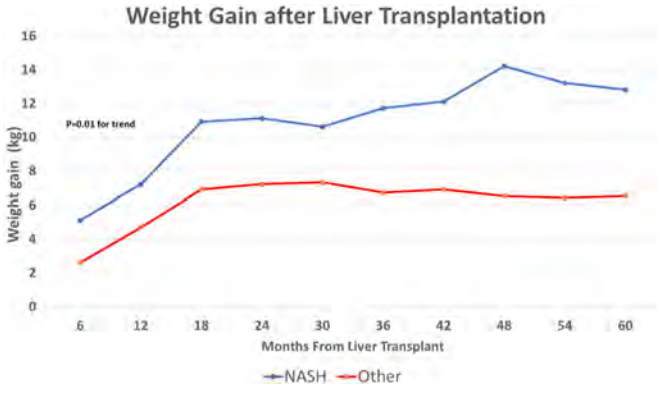
Background and aims: Weight gain after liver transplant (LT) is a key driver of cardiometabolic disease and associated mortality. There is little known about trends in post-LT weight gain including liver disease specific differences in weight gain after LT. The published data is limited by epidemiological studies linked to the SRTR database and with relatively short follow-up. Patient level data are needed to better understand weight gain after transplant to optimize management. Thus, the aim of the current study was to evaluate long-term weight trends after LT.
Method: All patients who had a LT between 2010 and 2016 were evaluated. To minimize the confounding effects of perioperative fluid weight, the baseline weight was the 1st weight after hospital discharge for LT. Body weights were collected at 6-month intervals from LT to end of follow-up to 1/2018. Patients with combined organ transplants and those who died within 1 year after LT were excluded. To keep the analysis focused, we evaluated patients transplanted for either NASH, alcohol or HCV related cirrhosis since these are the most common indications for LT.
Results: A total of 496 patients had a LT over the study period and met study criteria. The baseline distribution of etiology of liver disease was: HCV (N = 227), NASH (N = 78), and alcohol (N = 79). At the time of LT, the mean weight for patients transplanted for HCV, NASH, and alcoholic cirrhosis was 81 ± 18 kg, 84 ± 15 kg and 75 ± 17 kg, respectively (p = 0.004). The weight gain experienced by patients transplanted for NASH cirrhosis was higher than other etiologies of chronic liver disease (**Figure 1**). Patients with NASH started to gain weigh early after LT where they gained 7.3 ± 13 kg compared to 6.3 ±

9.8 kg for HCV and 3.5 ± 12.1 kg for alcohol (p = 0.05). This trend persisted for up to 60 months where patients gained the greatest degree of weight (p = 0.029). This trend persisted, and the difference was more pronounced at 60 months after LT (12.8 ± 13.1 kg for NASH vs. 6.5 ± 13.3 kg for other indications, p = 0.01). In patients with NASH, male gender was predictive of weight gain but this association was no longer significant after 24 months. In patients transplanted for NASH cirrhosis, age, diabetes, hypertension, and dyslipidemia at the time of LT were not predictive of future weight gain.



Conclusion: Weight gain after transplant is common in LT recipients regardless of etiology of liver disease. However, there is a liver disease specific impact on weight gain after LT in which patients transplanted for NASH cirrhosis are likely to gain the most weight after LT.

FRI-396

Hypoadiponectinemia as a predictor of cardiovascular events in liver transplant recipients

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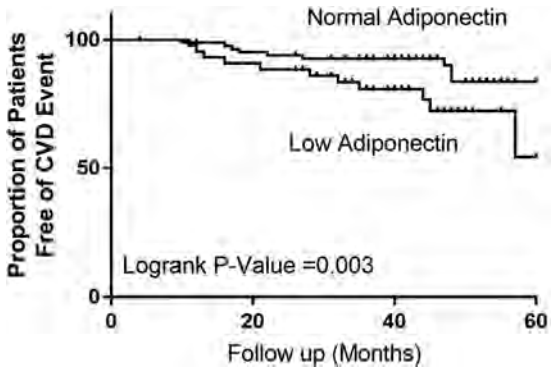
Background and aims: Cardiovascular disease (CVD) is an important cause of morbidity and mortality after liver transplantation (LT). Serum adiponectin levels inversely correlate with CVD related outcomes, but the relationship between hypadiponectinemia and CVD after LT is unknown. Thus, the aim of the present study was to prospectively evaluate this relationship in LT recipients (LTR).
Method: LTR were prospectively enrolled (N = 130) between 1/1/2012 and 1/1/2014. Baseline adiponectin levels were drawn at enrollment and patients were followed for CVD events. Hypoadiponectinemia was defined as serum adiponectin < 10 µg/ml. The primary end point was a composite CVD outcome consisting of myocardial infarction, angina, need for coronary revascularization, stroke or cardiac death.
Results: The mean age was 58 ± 11 years and prevalence of obesity, diabetes and dyslipidemia was 40%, 35% and 40%, respectively. A total of 20 CVD events were noted after median follow-up of 45 months. Hypoadiponectinemia was significantly associated with future risk of CVD event (HR 3.519, 95% confidence interval 1.180, 10.499, p = 0.024). This association was independent of traditional CVD risk factors including age, gender, obesity, hypertension, diabetes and choice of immunosuppression.
Conclusion: Hypoadiponectinemia is a strong independent predictor of future cardiovascular events in LTR can be incorporated in clinical practice to assess CVD risk assessment after LT.



FRI-397

Sepsis is a major risk factor for delirium post liver transplantation

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Background and aims: The aetiology of delirium post liver transplantation (LT) is typically multifactorial with pre-LT and post-LT risk factors. The presence of delirium in this cohort has been demonstrated to be associated with increased morbidity and mortality. This study aims to evaluate individual aetiologies of post-LT delirium and review the effect on intensive care unit (ICU) and hospital length of stay (LOS).
Method: We retrospectively analysed all adult LTs from 08/2016-08/2017 for chronic liver disease performed at King's College Hospital. We recorded patients' age, liver disease aetiology, previous neurological history, pre-LT; serum sodium, UKELD, encephalopathy and post-LT; evidence of sepsis, tacrolimus levels at day 5 and use of a renal sparing strategy. We analysed ICU LOS and ward LOS. Inclusion criteria were defined as a documentation of confusion or delirium post-LT in the absence of structural neurological abnormality. Data was collected and univariate and multivariate analysis were performed.
Results: 186 LTs were performed fulfilling inclusion criteria during this time. The incidence of post-LT delirium was 13.4%. ICU LOS was prolonged in patients with post-LT delirium (*Mdn = 5.0 v 3.0, U = 1442, n_1 = 25, n_2 = 160, P < 0.05 two tailed*) as was hospital LOS (*Mdn = 14.0 v 10.5, U = 1390, n_1 = 25, n_2 = 160, P < 0.05 two tailed*). Sepsis was diagnosed more frequently in patients with post-LT delirium than those without (*OR 4.6, CI 1.96-10.5, p < 0.005*). No significant associations were observed for patients with post-LT delirium and; serum sodium, UKELD, age or day 5 tacrolimus levels. Although not reaching clinical significance, post LT delirium may be associated between pre-LT encephalopathy (*OR 1.9, CI 0.82-4.32, p = 0.13*) and post LT acute kidney injury (*OR 2.2, CI 0.94-4.95, p = 0.08*). There were no significant differences seen in prevalence of underlying liver disease aetiology in patients with post-LT delirium although numbers were small for meaningful statistical analysis. Delirium was typically short-lived and did not affect survival.
Conclusion: Delirium post-LT is associated with increased ICU and hospital LOS. Sepsis post-LT was significantly associated with post-LT delirium. A high clinical suspicion for sepsis in patients with post-LT delirium should be advised.

FRI-398

Impact of sarcopenia and myosteatosis on post-transplant complications and survival

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Background and aims: Several studies have reported that sarcopenia is associated with a poor prognosis before transplantation. Recent data suggest that also myosteatosis is an important emerging prognostic factor in cirrhosis. However there is not definitive evidence about the role of sarcopenia and myosteatosis after liver transplantation. The aim is to investigate the correlation of sarcopenia and myosteatosis with complications and mortality after liver transplantation.
Method: 173 liver transplanted cirrhotic patients were enrolled between 2000 and 2015 at "Policlinico Umberto I" of Rome. Sarcopenia and myosteatosis were analyzed by CT scan (performed before transplantation) using the third lumbar vertebrae skeletal muscle and attenuation indexes, using previously validated gender- and body mass index-specific cutoffs.
Results: Patients were predominately men (n = 116, 67%). The most represented aetiologies were viral hepatitis (43%), alcohol (16%) and NASH (13%). The average age was 55.6 ± 9.1 years. The mean follow-up after liver transplantation was 55.6 ± 51.6 months. At the time of transplantation sarcopenia was present in 73 patients (42, 2%) and myosteatosis in 71 patients (41.2%). Days of hospitalization in intensive care, acute and chronic rejection, graft loss, neoplasia, cardiovascular events, dyslipidemia, arterial hypertension and diabetes were considered during the follow-up and there were no differences between patients with or without myosteatosis and sarcopenia. The presence of myosteatosis is not associated with mortality after transplantation (p = 0.9). The Kaplan-Meier curve showed a significantly higher mortality in the pre-liver transplant sarcopenic population vs non sarcopenic patients (p = 0.01).

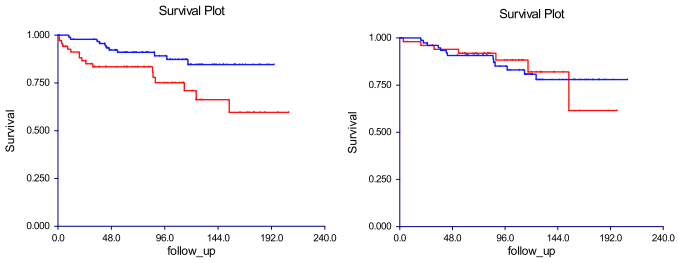

Figure: Survival after transplantation in sarcopenic patients Survival after transplantation in patients with myosteatosis p = 0.01 p = 0.9.

Conclusion: Neither myosteatosis nor sarcopenia are associated with a higher rate of post-transplant complications. Patients with myosteatosis do not have a worse prognosis after the liver transplant. Pre-transplant sarcopenia is a negative prognostic factor for post-transplant survival.

FRI-399

Impact of a temporary cardiac arrest in a brain dead liver donor on liver transplantation results

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Background and aims: The use of hepatic allografts from donors who have suffered a temporary cardiac arrest (TCA) is considered as a risk factor of liver failure following liver transplantation (LT) because he could lead to graft dysfunction. Conversely, some studies suggested a protective effect. The aim is to study the influence of TCA in brain dread donors (BDD) on LT outcome.
Method: Single institutional retrospective study on 429 consecutive LT (01/2008-06/2017). Exclusion criteria: retransplantation, multi-organ transplantation, splits and domino graft, controlled cardiac dead donors. A group of LT from TCA donor (n = 111) was compared to a group of no TCA (n = 318). Primary end point: arteriobiliary complications free survival (ABC free survival) during the first year post-LT.
Results: patients of the TCA group were younger than patients of the no-TCA group. Main cause of death was anoxia in the TCA group and vascular in the no-TCA group. The following characteristics donor were higher in the TCA group: AST and ALT levels (peak), γGT and ALP at day 1 after ICU admission, creatinine, PT and peak of lactate and bilirubin. Patient survival, graft survival and Early Graft Dysfonction were not different between the 2 groups. AST and ALT level at postoperative day 2 were lower in the TCA group. The ABC free survival was significantly higher in the TCA group compared to the no-TCA group (81% versus 70% at 1 year, p = 0, 044) at univariate analysis. However, this difference disappeared at multivariate analysis.
Conclusion: We failed to observe any deleterious effect of a TCA in BDD on LT outcome. On the contrary, some results were suggestive of a protective influence.

FRI-400

Poor long term outcome of patients undergoing liver transplantation with preterminal renal dysfunction

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Background and aims: With introduction of the Model of End Stage Liver Disease (MELD) based allocation system the number of patients undergoing orthotopic liver transplantation (OLT) with severely impaired renal function has significantly increased. Due to organ shortage nowadays, combined renal transplantation (KTx) and OLT are not routinely performed. Therefore, we here investigated long term outcome of patients undergoing OLT with advanced renal dysfunction.
Method: In this retrospective study all patients were included who underwent OLT at the University Hospital Hamburg-Eppendorf between 2011 and 2015 with chronic kidney disease (CKD) stage 4/5. Course of kidney function, need for dialysis, risk factors for poor renal outcome as well as patient survival were assessed.
Results: Altogether 60 patients (CKD 4: n = 22, 37%, CKD 5: n = 38, 63%) were included in the study. Median follow-up was 1099 days (IQR 66-1817). Directly postoperatively, 42 (70%) patients required dialysis for median 21 days (IQR 8-61). On long term follow-up 18/60 (30%) remained on dialysis, 5 of these patients (28%) subsequently underwent KTx after a median period of 274 days (IQR 201-1461). 29 patients (48%) had CKD 4/5 or had undergone KTx at end of follow-up. There was no difference in terms of age, CKD stage or time on dialysis prior to OLT or length of stay on ICU between patients with compensated renal function and those with poor renal outcome (CDK 4/5 or KTx) at last follow-up (p = n.s.). Furthermore, neither type of immunosuppression (CNI-free vs. CNI-based, mono, dual or triple immunosuppression), nor presence of diabetes, arterial hypertension or hyperlipidemia during follow-up were associated with poor renal outcome (p = n.s.). The only risk factor for poor renal outcome post OLT was post-operative need for dialysis.
Overall 3- and 5-year patient survival after OLT was 60% and 42% respectively. 1- and 5- year mortality was significantly higher in patients with poor compared to compensated renal outcome (59% vs.

13%, p < 0, 001 and 72% vs. 28%, p < 0.001 respectively), as illustrated in figure 1.

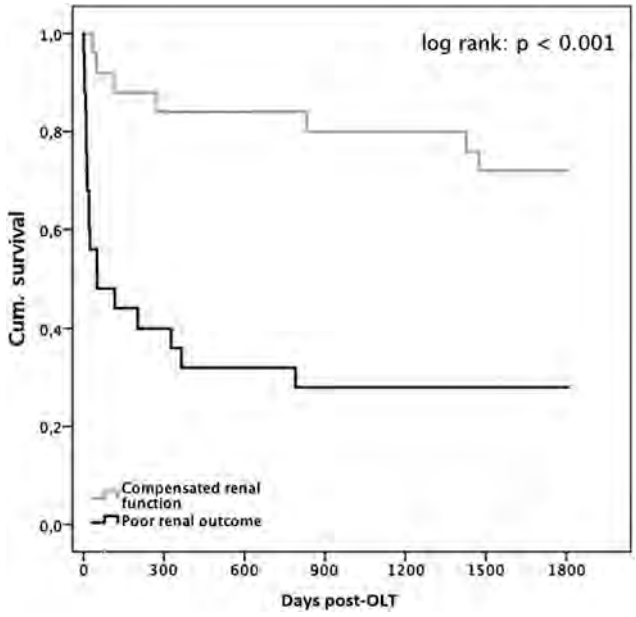

Figure 1: Kaplan-Maier plot of patient survival according to renal function after OLT (compensated: CKD 1/2/3; poor renal outcome: CKD 4/5 or KTx)

Conclusion: In this long-term follow-up study, about half of the patients with CKD 4 and 5 prior to OLT had poor long term renal outcome post transplantation, going along with a very low 5 year patient survival rate of only 28%. Only necessity of renal replacement therapy after OLT was associated with this poor outcome. Therefore, further studies should investigate if survival improves with combined OLT and KTx.

FRI-401

Direct-acting antiviral agents are not associated with an increased risk of hepatocellular carcinoma recurrence in liver transplant recipients with hepatitis C

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Background and aims: Prior data demonstrated a possible association between direct acting antiviral (DAA) and heightened risk of HCC recurrence after liver transplantation for individuals with hepatitis C virus related hepatocellular carcinoma (HCV-HCC). The aim of this study was to determine the relationship between direct-acting antiviral (DAA) treatment and post-transplant HCC recurrence.
Method: We conducted a retrospective cohort study of HCV-active patients (with detectable viral load subsequent to interferon-based therapy, or treatment naïve) who underwent liver transplantation for HCC at three centers between January 1, 2014 and June 30, 2017. The study group received DAA-containing therapy prior to liver transplantation while the control group did not. The primary outcome was the rate of recurrence of HCC post-transplant. Secondary outcomes were the rate of sustained virologic response (SVR12), HCV recurrence post-transplant, liver allograft failure, and death. Statistical analyses with t-test and chi-square were used to compare baseline variables. Kaplan Meier analysis and Cox proportional hazard models were used to investigate the risk of HCC recurrence.
Results: A total of 171 patients were included in the study (99 DAA; 72 controls). Post-transplant HCC recurrence rate was 9% (n = 15). The median follow-up time was 24 months (IQR 12, 26). DAA-treated patients and the control group were not statistically different for Model for End Stage Liver Disease (MELD) scores, wait time on the transplant list, and histologic assessment of the explanted liver.
Pre-transplant DAA was not associated with HCC recurrence (RR 0.40; 95% CI 0.12, 1.15; p = 0.09) while lymphovascular invasion (HR 4.36; 95% CI, 1.16, 28.3; p = 0.03) was associated with increased risk of HCC recurrence. SVR12 pre-transplant was 75% (39/52), which is significantly lower (p < 0.01) than the post-transplant SVR12 rate of 97% (59/61). Liver transplant graft failure (7% vs 3%; p = 0.21) and death (12% vs 14%; p = 0.19) were not statistically different among the DAA treatment group and the controls.

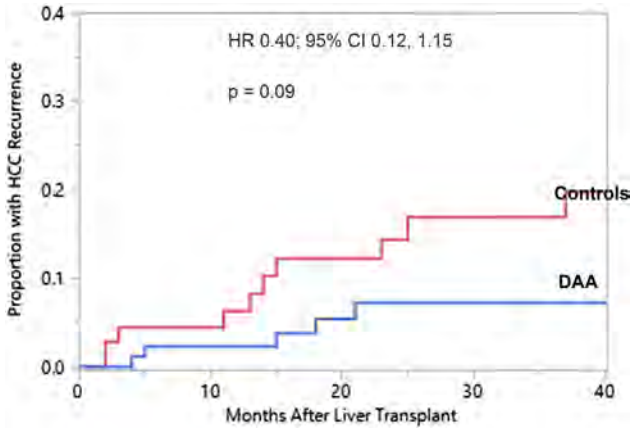

Figure: Inverse Kaplan Meier Curve for Hepatocellular Carcinoma Recurrence Post-Liver Transplant, by Pre-Transplant Direct-Acting Antiviral Therapy

Conclusion: DAA therapy for HCV is not associated with an increased risk of post-transplant HCC recurrence.

FRI-402

Outcomes after liver transplantation for argininosuccinate lyase deficiency: A longitudinal study

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Background and aims: Argininosuccinate lyase deficiency (ASLD) is a rare urea cycle defect, manifesting as recurrent hyperammonemia, neurocognitive decline, liver fibrosis and hypertension. Liver transplantation (LT) corrects the defect in liver and abolishes hyperammonemia, but its impact on extrahepatic manifestations is uncertain and poorly reported. We describe the outcomes of children undergoing LT for ASLD in our Centre.
Method: Retrospective analysis of the impact of LT on 7 patients with ASLD was done. Development and behavioral functioning were assessed by the Adaptive Behavior Assessment System-II (ABAS-II) and the Child Behavior Checklist (CBCL). Quality of life [QoL] assessments for the patients were done using the Pediatric Quality

of Life Inventory (PedsQL) and for the family using the Family Impact Module of the PedsQL.
Results: The primary indication for LT was poor metabolic control and developmental delay. Pre-transplant CBCL scores were impaired in internalizing, externalizing and/or total problems in 4/7 children. ABAS-II scores fell in the low average, below average, or borderline range of functioning in 6/7 children. PedsQL revealed impaired physical functioning in 5/6 subjects and impaired family functioning in 5/7 families. Median [range] age at LT was 4.2 years [2.4-6.6]. All 7 are alive and well with recent follow-up of 3.7 years [1-5.2]. No new seizures have occurred and currently all are receiving tacrolimus monotherapy. Current diet is unrestricted without any need of ammonia scavengers. Plasma amino acids and ammonia have normalized except for persistent hypercitrullinemia. One child has developed hypertension; well controlled with a single drug. All 7 demonstrated developmental progress and of those with school age participate in mainstream education. Three children had formal post-transplant assessment. ABAS-II global scores for 2/3 children improved to the Borderline range of functioning. CBCL scores improved to the normal range with 2/3 children signifying improvement in attention or somatic problems. PedsQL parent report revealed improved physical functioning, but mildly impaired school functioning in 3/3.
Conclusion: LT abolishes the hyperammonemia in ASLD and in the short term hypertension is unusual. The early impact of LT on developmental outcomes and QoL in ASLD suggests stabilization and diminished likelihood for continued decline. Longer follow-up is required to ascertain the ultimate impact of LT in ASLD.

FRI-403
Impact on post liver transplant outcomes of response to treatment with terlipressin and albumin in patients with hepatorenal syndrome
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Background and aims: Hepatorenal syndrome (HRS) is a relevant complication of cirrhosis and is associated with a poor prognosis. Terlipressin and albumin are effective in resolving HRS, but liver transplantation (LT) is still the best treatment of HRS. However, it is not clear of an effective treatment with terlipressin and albumin may improve outcomes after LT in patients with HRS. The aim of this study was to evaluate the impact of response to treatment with terlipressin and albumin on post-transplant outcomes in patients with HRS.
Method: We analyzed 2 cohorts of patients with liver cirrhosis listed for LT at our Centre between 2012 and 2016: a) patients who developed HRS before LT which were treated with terlipressin and albumin an b) patients without HRS transplanted during the study period (control group). Patients with HRS were classified as responders or non-responders to the treatment. We excluded patients with previous liver transplant or indication for combined liver and kidney transplantation.
Results: 82 patients with HRS before transplant were treated with terlipressin and albumin (first cohort) and the rate of response to therapy was 52%. Responders had a better transplant free survival (60% vs 33%, p = 0.006) 30 days after HRS, longer LT waiting list time (37 vs 17 days, p = 0.041) and lower MELD-score at the time of LT (23 vs 29, p = 0.007). Among patients with HRS who were transplanted (n = 63), non-responders showed a worse renal function in the first week after LT, higher need for RRT (0% vs 26%, p < 0.001) and higher rate of post-transplant infections (63% vs 87%, p = 0.037) than responders. There were no differences in length of stay, graft dysfunction, immunosuppressive protocols and trough levels of calcineurin inhibitors between responders and non-responders. Non-responder had a significantly higher incidence of CKD 1 year after liver transplantation than responders (60% vs 33%, p = 0.019). When also the control group was included in the analysis of predictors of CKD at 1 year, age (sHR = 1.04; p = 0.024), diabetes (sHR = 1.64; p = 0.048), AKI post-transplant (sHR = 1.81; p = 0.012), MELD at the time of transplantation (sHR = 1.03; p = 0.028), and no responder to terlipressin and albumin were found to be independent predictors for CKD, while responders had a similar risk of CKD than control group. There were no difference in term of survival between responder, no responder and control group.
Conclusion: Treatment with terlipressin and albumin improves renal function before LT, reduced need for RRT use and is associated with a lower prevalence of CKD at 1 year after LT. Non-response to terlipressin and albumin is an independent predictor of CKD at 1 year.

FRI-404
Multicenter experience evaluating outcomes of HCV-seropositive donors to HCV-seronegative recipients liver transplantation
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Background and aims: The introduction of direct-acting antiviral agents (DAA) in the context of organ shortage and high waitlist mortality among liver transplant (LT) candidates has resulted in increased interest in using grafts from hepatitis C virus (HCV)-seropositive donors. We report here our multicenter experience evaluating the outcome of HCV-seropositive donors to HCV-seronegative recipients LT.
Method: This is a retrospective analysis of prospectively collected database of ongoing multicenter IRB-approved research study expanded into clinical protocol to evaluate adult HCV-seronegative LT recipients who received grafts from HCV-seropositive donors.
Results: Since January 2018, 10 HCV-seronegative LT recipients received grafts from HCV-seropositive brain dead donors [3 with negative nucleic acid testing (NAT) and 7 with positive NAT] with the median allocated MELD-Na score of 20 (range 11-30). Three underwent simultaneous liver-kidney transplant (SLK) and 3 underwent repeat LT. The median waiting time prior to listing for HCV-seropositive donor was 266 days (range: 0-988). The median waiting time after listed for HCV-seropositive donor to LT was 57 days (range: 9-238). None of the patients who received HCV-NAT negative grafts developed HCV viremia at the median follow-up of 48 days (range 45-181) after LT. All 7 patients who received HCV-NAT positive grafts had HCV viremia confirmed within 5 days after LT with the median peak HCV RNA of 33.1 million IU/ml (range 1-97.5 millions). DAA treatment was started at the median time of 32 days (range 6-62) after LT: 5 patients received glecaprevir/pibrentasvir (G/P) for 12 weeks, 1 patient received 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) and ribavirin (RBV), and 1 patient is waiting for insurance approval. HCV RNA decreased after 1 week of treatment and all patients achieved negative HCV RNA by week 4 (range 1-4). Mild AST/ALT elevation was observed, but it was not associated with graft dysfunction. Two patients had mild biopsy-proven acute rejection. No graft loss or death was observed.
Conclusion: LT using HCV-seropositive grafts to HCV-seronegative recipients resulted in excellent short-term outcomes in our multicenter experience. The acceptance of HCV-seropositive grafts may

improve the chance of LT and reduce waitlist morbidity and mortality, especially in the certain population such as those awaiting SLK or repeat LT.

Table:

Patient	Age/ Sex	Allocated MELD-Na Score	Blood Type	Organ	Waiting Time before HCV+ Listing (days)	Waiting Time after HCV+ Listing (days)	HCV Genotype	DAA Regimen	Interval from LT to DAA Treatment (days)
1	33/F	22	A	LT	274	49	1a	LDV/SOF + RBV12 wk	45
2	63/F	15	O	LT	23	68	2	G/P12 wk	21
3	37/ M	23	A	SLK	988	32	3	G/P12 wk	67
4	58/ M	13	A	LT	7	23	2	G/P12 wk	6
5	69/ M	11	A	Re-LT	248	91	-	-	-
6	54/ M	19	O	LT	107	9	1b	G/P12 wk	27
7	66/F	19	A	Re-LT	275	238	-	-	-
8	63/F	30	O	SLK Re-LT	928	44	1a	G/P12 wk	25
9	60/ M	20	O	LT	0	73	-	-	-
10	66/F	29	A	SLK	305	65	2	Pending Insurance	N/A

FRI-405

Predictors of outcomes for patients with non-alcoholic steatohepatitis undergoing liver transplantation in the United States

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Background and aims: NASH is currently among the leading causes of liver transplantation (LT) in the U.S. **Aim:** To assess predictors of LT outcomes in NASH.
Method: We used the Scientific Registry of Transplant Recipients, and included all adult (18+) LT candidates waitlisted in 2001-2017 in the U.S. with the primary listing diagnosis of NASH with available clinical, demographic, and outcomes data. Independent predictors of receiving a LT were assessed using multiple logistic regression; independent predictors of post-transplant mortality were assessed using Cox proportional hazard model; patients were followed till March 2018.
Results: 27, 117 NASH patients were listed for LT (2001-2017) with complete data: 58.5 ± 9.2 years, 53% male, 77% white, 21% employed, 43% pre-LT type 2 diabetes (DM), 10% hepatocellular carcinoma (HCC), 58% were covered with private insurance, 29% with Medicare, and 10% with Medicaid. After listing, 54.8% of NASH patients were eventually transplanted (mean wait time 226 days), 24.4% dropped out of the list, and 3.3% improved. Factors independently associated with a lower chance of receiving a LT were older age (odds ratio (OR) (95% confidence interval) = 0.989 (0.985-0.993) per year), Hispanic ethnicity (0.78 (0.71-0.85)), being covered by Medicare (0.82 (0.75-0.88)) or Medicaid (0.74 (0.66-0.83)), being on life support (0.60 (0.47-0.76)), having hepatic encephalopathy (0.83 (0.75-0.91)), and prior history of non-liver transplants (0.59 (0.39-0.90)). Factors independently associated with a higher chance of receiving a LT were male gender (1.42 (1.33-1.52)), having listing status 1 (2.39 (1.34-4.25)) or HCC (2.15 (1.89-2.44)), ascites (1.68 (1.49-1.90)) or higher MELD score (1.005 (1.001-1.009) per 1 point) or being on dialysis (1.26 (1.15-1.37)) (all $p < 0.02$). Post-LT mortality was as follows: 11.9% at 1 year, 18.3% at 3 years, 23.8% at 5 years, 40.3% at 10 years. Independent predictors of higher post-LT mortality were an earlier year of LT (adjusted hazard ratio (aHR) = 0.94 (0.92-0.95) per year), older age (1.025 (1.019-1.031) per year), having Medicare (1.14 (1.03-1.26)) or Medicaid (1.23 (1.05-1.44)), being on life support, higher MELD score (1.006 (1.000-1.013) per point), pre-LT DM (1.14 (1.04-1.26)), re-transplant (1.90 (1.49-2.42)), and HCC (1.46 (1.23-1.73)) (all $p < 0.05$).
Conclusion: Comorbidities and socio-demographic factors are associated with waitlist and post-transplant outcomes in patients with NASH.

Nurses' research in Hepatology

FRI-407

Elevating liver disease management in Egypt: A Project Echo® experience

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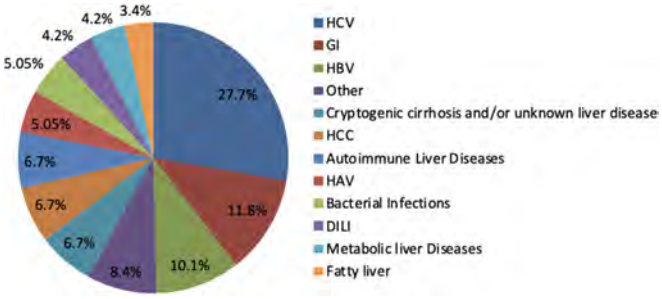
Background and aims: Chronic Hepatitis C infection (CHC) continues to be a major health burden in Egypt, with almost 10% of the general population affected. Despite efforts on eradicating CHC in Egypt, there are limited resources. Patients still suffer from complications of liver disease and a complex of health conditions, especially those living in underserved areas. *"Project ECHO®* [Extension for Community Healthcare Outcomes] *is a movement to demonopolize knowledge and amplify the capacity to provide best practice care for underserved people all over the world. The ECHO model™ is committed to addressing the needs of the most vulnerable populations by equipping communities with the right knowledge, at the right place, at the right time."* https://echo.unm.edu/wp-content/uploads/2018/07/ECHO_One-Pager_07.24.2018.pdf Using videoconferencing, International Liver Centers Foundation (ILCF) in Southern California replicated the ECHO Model™ with clinicians and researchers in Egypt. The goals of the ILCF-Egypt ECHO® are to guide Egyptian clinicians in the management of CHC and its complications, connect clinicians practicing in major cities in Egypt with those in rural areas and link senior practitioners with their junior peers.
Method: ILCF-Egypt ECHO® started in October 2017 with 3 clinicians (spokes) from Alexandria. The spokes are practicing at community hospitals in Alexandria and independent clinics in the surrounding communities. Sessions are held bi-monthly. A typical session lasts 2 hours and consists of 5 case presentations and a 20-minute didactic given by ILCF or an invited expert (Hub). Case presentations are sent in advance in a de-identified standard format with pertinent medical information. Each case presentation is followed by a discussion between the spokes and Hub. The Hub then forwards its final recommendations to the spoke.
Results: Initially, our focus was on Alexandria and its surroundings. The number of spokes steadily grew. Case presentations were focused on complicated cases of CHC. Currently, based on the spokes" requests, the majority of the cases and didactics are on other aetiologies of liver disease (see figure). The spokes and Hub also developed collaborative research projects including a 23-case report of leptospirosis.
Conclusion: ILCF-Egypt Project ECHO®: 1) is successful in connecting GI/Transplant Hepatology experts in the U.S. with clinicians in Egypt offering them world-class mentoring that would not otherwise be easily accessible; 2) addresses the void of guidance on unique, rare and complex cases; 3) provides linkages between senior and junior clinicians as well as those serving in cities and their counterparts in underserved communities in Egypt. This will ultimately provide

better access to much-needed specialized healthcare especially to those in underserved communities.



FRI-408

Self-stigma among patients with hepatitis B and C and its association with delayed diagnosis and treatment

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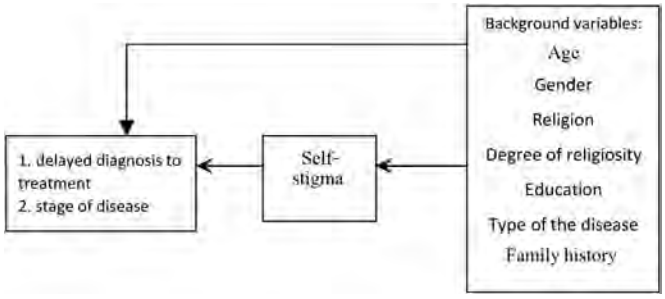
Background Stigma is one of the main issues that patients with hepatitis cope with (Paterson, Backmund, Hirsch and Yim, 2007). Hepatitis is linked to stigma because of disease transmission routes, namely, drug abuse or unsafe sex that are perceived to characterize groups of people who are not well accepted in society (Drazic and Caltabiano, 2013). Such stigma may cause serious psychological, social, economic and even health related repercussions (Cotler et al., 2012; Drazic and Caltabiano, 2013; Li et al., 2012). Timely diagnosis and referral to treatment is of utmost importance for hepatitis patients, in order to prevent disease progression and complications, improve quality of life, and prevent further transmission of the disease (Ben Ari, 2016; Modabbernia, 2013). Nevertheless, the effect of self-stigma on delayed diagnosis and treatment in patients with hepatitis B and C was scarcely studied (Li et al, 2012; Paterson et al, 2007; Poll, Allmark, Tod, 2017; Skeer et al, 2018; Subic, Zoulim, 2018; Sweeney et al, 2015; Veldhuijzen, 2010).

Aims of the study: To investigate the association between perceived self-stigma in patients with hepatitis B and C and the stage of disease at diagnosis and the time lag between diagnosis and first visit to the liver clinic.

Method: A cross-sectional study was conducted among patients and carriers of hepatitis B and C, who are followed and treated in the outpatient liver clinic of an academic hospital in Northern Israel.
Eligible patients fill a questionnaire that included items on socio-demographic information, and a rating of statements reflecting self-stigma (adapted from Li et al, 2012). Further clinical data were collected from patients' medical records.

Results: Enrolled in the study were 120 patients with hepatitis B or C. Patients with hepatitis C reported significantly higher levels of self-stigma (39.1 ± 11.9) than patients with hepatitis B (34.0 ± 10.4) {t (113) = -2.245, p < 0.05}.
A significant association was found between the level of self-stigma and the stage of the disease at diagnosis {t (98) = -2.590, p < 0.05}. Higher levels of self-stigma were reported by Hepatitis C patients with advanced disease (39.1 ± 11.4) compared to Hepatitis B patients with early disease (32.6 ± 11.5). No significant correlation was found between self-stigma and the lag-time from diagnosis to first visit to the liver clinic {t (113) = -0.584, p = 0.56}.

Conclusion: We found that patients with higher levels of self-stigma are diagnosed at more advanced stages of their disease. This highlights the importance of interventions to foster disease prevention and early diagnosis in populations at risk, in order to improve awareness, reduce self-stigma, encourage screening, and prevent morbidity from a curable disease.



FRI-409

Measuring the impact of a new liver specialist nursing service on patient care

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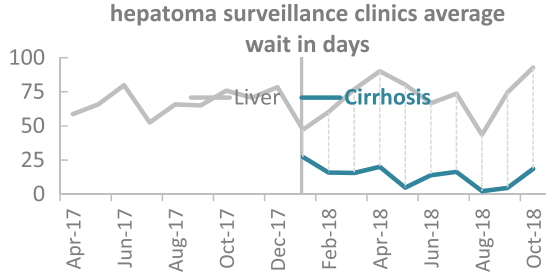
Background and aims: Mortality is high in patients admitted with decompensated chronic liver disease (DCLD). Management in the first 24 hours is critical to outcome. Historically, all hepatology reviews were by medical staff, and were frequently delayed due to competing service pressures. A pilot scheme for a specialist nurse-led in-reach and follow-up service was launched in April 2018, and the impact assessed.

Method: The nurse-led service provided daily input the acute medical unit, emergency department and non-specialist wards, and followed early management recommendations from the BSG/BASL DCLD care bundle, ensuring all appropriate investigations were completed. Appropriate patients were identified for specialist transfer, early discharge or day-case procedure. In addition, dedicated nurse-led hepatoma surveillance clinics for all cirrhotic patients were opened, as well as doubling capacity of the existing consultant-led early discharge clinic. The impact of the service on time from admission to specialist review, overall length of stay and out-patient surveillance waiting lists was audited at 6 months post-inception.

Results: The liver specialist nurse is now an integral part of hepatology reviews in the acute medical unit (AMU), with a major increase in use of the BSG/BASL DCLD care bundle by all clinical staff (82.5% of DCLD patients in the AMU between May to September 2018 had care bundle in place). Post-discharge clinic follow-up is now occurring within the required timeframe, along with more structured and timely cirrhosis surveillance clinics. The average waiting time for cirrhosis surveillance appointments is now 14 days compared to 71 days prior to the new service, an improvement of 80.3%. The introduction of the nurse-led paracentesis service significantly reduced length of stay for suitable patients by 90% (4.5 day, reduced to 12.5 hours, $P < 0.0001$). Importantly, the service has received excellent feedback from both patients and colleagues.



Conclusion: The introduction of a liver specialist nurse has had a positive impact on both inpatient and outpatient care. This is demonstrated by increased compliance to the BSG/BASL DCLD care

bundle, reduced length of stay-particularly in patients requiring large volume paracentesis, timely surveillance clinics, and increased availability of post discharge liver reviews.

FRI-410

Health literacy in outpatients with liver cirrhosis

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Background and aims: Health literacy (HL) is a concept covering a range of cognitive and social skills that comprises aspects necessary for patients to navigate in the healthcare system. Our study aimed to investigate HL in patients with liver cirrhosis and determine factors associated with low HL.
Method: Face validity of 3 HL questionnaires (paper versions): the Single Item Literacy Screener (SILS) [1question (Q)], the Brief Health Literacy Screening Tool (BRIEF) [4Q], 3 dimensions of the Health Literacy Questionnaire (HLQ) [15Q] were tested in a random order in 108 outpatients with liver cirrhosis. Patients were ask to complete the 3 questionnaires themselves, but could ask a nurse for help if needed
The 3 dimensions used from the HLQ were 'Social support for health' (S-scale), 'Ability to actively engage with healthcare providers' (E-scale), and 'Understand health information well enough to know what to do' (I-scale). Unpaired t-test was used to investigate differences on the HLQ scale scores. The effect sizes (ES) were calculated between groups using the Cohen's d.
Results: 105 patients (55% male; mean age 60 years; 65% alcohol-related liver disease) completed all 3 questionnaires. 39 patients (37%) needed help to complete even the 1Q SILS questionnaire. They were charaterised by: male gender, low level of education, no work, alcohol-related liver disease and severe cirrhosis. The HLQ revealed low level of HL in males (S-scale), and patients with low level of education (S-scale). The largest ES were found for employment (I-scale) (0.49), education (S-scale) (−0.43), comorbidity (I-scale) (0.42), and male (S-scale) (0.41).
Conclusion: One third of patients needed help to complete one single question about HL. Assistance is needed if asking about HL using questionnaires.
Subgroups of patients had both difficulties with the questionnaires and had low level of HL. The subgroups were mainly characterised by: male gender, low level of education, and alcohol-related liver disease.

FRI-411

Nurse-led out-patient-clinic for patients with cirrhosis

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Background and aims: The burden of liver disease continues to rise and the main driver for morbidity and mortality are the complications of decompensated cirrhosis. Increased patient participation and out-patient access, close monitoring for complications and early preventive interventions are presumed to improve survival.
In March 2017 we established a nurse-led out-patient-clinic for patients with cirrhosis with a patient-centered approach aiming at health promotion. The nurses working in the clinic were highly competent with several years of practice in clinical hepatology.
Local clinical guidelines were set up for treatment-related interventions i.e. medicine titration of diuretics and nonselective betablockers. Clinical and paraclinical limits requiring supervision were well defined. Furthermore, the nurses had access to supervision from specialized medical doctors also working in the clinic.
The aim is therefore to describe the patient population, type of visits, and the nurse interventions within 12 months after implementation of the clinic.
Method: All patient files with visits from August 1st 2017-July 31st 2018 were screened. Patients with first visit to the clinic from August 1st were included.
Data were processed using descriptive statistical methods, and results are presented using median (min-max) or percentages were relevant. All analyses were done using IBM SPSS statistics 22.
Results: 146 patients were screened, and 97 patients were included with a total of 296 visits in the period with a median visit of 2 (1-12). 29 patients (29.9%) of the patients were admitted during the period. The visits were distributed on 75% ascites control, 11% screening for minimal HE, HE controls 5, 5% diagnostic interview and 4% to adjustment of betablockers. Diuretics were adjusted in 86 visits (29%) of all the visits.
According to the defined limits for the need for supervision 30% of the visits were interdisciplinary discussed.

Table 1: Baseline data on included patients (results are median and min, max or percentages in parenthesis)

Age (years)	66 (45-92)
Gender (female/male)	46 (47.4%)/51 (52.6%)
Etiology	
Alcohol	74 (76.3%)
NASH	6 (6.2%)
Viral	7 (7.2%)
Cryptogenic cirrhosis	7 (7.2%)
Other reasons	3 (3.2%)
Child Pugh Score 1. visit	7 (5-12)

Conclusion: This study shows that the nurse-led out-patient-clinic is highly functional in monitoring for complications and medicine titration in an interdisciplinary setting. Further studies on outcomes are needed.

FRI-412

A collaborative approach to increase access to hepatitis C treatment for the homeless population in Cornwall

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Background and aims: There is a higher prevalence of Hepatitis C (HCV) amongst the homeless population (Beijer, 2012). Within Cornwall in 2017, our homeless population had a high number of known HCV positive people, but none entering treatment. There is a long standing community treatment program within Cornwall, offering testing, staging and treatment throughout the county by drug services supported by the hepatology department at the local hospital (Hampton, 2015). Competing priorities, including finding somewhere to stay each night has been recognised as a barrier to HCV treatment (Lambert et al, 2017). The aim of this project was to provide safe accommodation to enable access to HCV treatment and treat six homeless people over a 12 month period.
Method: A partnership was formed between local drug and alcohol services, Addaction, secondary care hepatology services and a housing provider who support homeless people in Cornwall. Cosgarne Hall would provide a room and support for people on HCV treatment and for two weeks after treatment to facilitate them moving to stable accommodation post treatment. Treatment would be delivered by community blood borne virus nurse in partnership with hepatology services in secondary care. All potential residents were assessed as suitable for the accommodation using their standard assessment. All people who were housed and underwent treatment were given a questionnaire post treatment to assess the psychosocial impact the project had. Data was also collected to see if the project had an impact on the housing situation of those treated. The final piece of data collected was the response to treatment using a

negative viral load at 12 weeks post treatment as a sustained virological response to treatment.
Results: The project has been running for six months and already there have been six homeless people who were offered and accepted accommodation through this project. They all commenced treatment and the table below shows the results.

Genotype	Fibrosis	Completed Treatment	SVR	Social situation pretreatment	Social situation post treatment
3a	Cirrhosis	Yes	Yes	Homeless	In Prison
3a	Non cirrhotic	Yes	Awaited	Recent move to supported housing	Remains in supported housing
3a	Cirrhosis	Yes	Awaited	Recent move to supported housing	Remains in supported housing
1a	Non cirrhotic	Yes	Awaited	Homeless	Remains in supported housing
1b	Non cirrhotic	On treatment	Awaited	Homeless	On treatment
1a	Cirrhosis	On treatment	Awaited	Recent move to supported housing	On treatment

Conclusion: Ensuring that homeless people have secure accommodation can help them to engage in HCV treatment. It is necessary to have a supportive housing provider who can both offer support to the people staying there and to have good community support to ensure that people do not need to travel to appointments and that the treatment easily accessible.

FRI-413
Integrating nurses in the management and care of patients with NAFLD: Better adherence and outcomes
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Background and aims: Non-alcoholic Fatty Liver Disease (NAFLD) has risen to epidemic proportions in the United States. It is estimated 30-40% of all Americans are obese, paralleling the rate of diagnosed NAFLD. The primary recommendation is lifestyle changes. There is no current medication approved regimen. It has been shown that asking a patient to change their lifestyle behaviours is difficult with inconsistent and poor results to making these changes. With the overwhelming burden of this disease, it is crucial for the Hepatologist (MD) to integrate their provider-extenders including nurses/nurse practitioners/allied health professionals (AHP) into the management and care of NAFLD patients. This is a single center experience in the role of AHP in a specialized community-based clinic in improving the health and outcome of patients with NAFLD.
Method: In a single community Hepatology center, we have set up a standardised protocol for patients referred for NAFLD. Patients with a confirmed NAFLD diagnosis are placed in "NASH-ville" clinics. These dedicated clinics encompass the concept of HALO (Health and Liver Optimization). At the first visit, the patient is asked to complete questionnaires identifying their lifestyle, diet, sleep patterns, fatigue levels, medications, and perception of BMI. Anthropometric measurements were also taken. Subsequent visits evaluated depression, nutrition, and changes in waist circumference, BMI, and physical well-being. Patients are seen every 1-3 months based on mutual goal setting between patient and AHP. Focus groups discussing diet, exercise can occur during scheduled clinic time, individual time is given for the nuances of each person, and the HALO approach was instituted for each patient and family member present.
Results: Patients with NAFLD needed more extended visits and time spent with them to allow for in breadth discussions of their lifestyle changes. Having the patient on board with their current disease state, setting goals and a tailored plan together with them was critical. This had a positive impact on their adherence to their management plan and ultimately their health outcomes. Implementing a dedicated "NASH-Ville" clinic has allowed our community-based clinic to see patients with a similar diagnosis together and individually.
Conclusion: Each NAFLD patient brings their family history, culture, habits, and co-morbidities to the situation requiring an individualized plan of care to assist in their improvement of health and lifestyle behaviours. MDs have extensive responsibilities and limited availability to spend adequate time with NAFLD patients. AHP have the ability to be more flexible/spend time in their schedules to accommodate the holistic needs of the patients. Both complement each other in the care of the patients and management of the disease. AHP's role had a positive impact on the continuity of care in NAFLD patients.

FRI-414
The impact of self and parental perception of body image on management in patients with NAFLD
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Background and aims: Treating patients with Non-Alcoholic Fatty Liver Disease (NAFLD) has been difficult as there is no standardized management plan except primarily improving healthy lifestyle measures. The environment in which one was raised in influences one's weight and perception. Understanding self-perception of body weight in this population provides an opportunity to understand the patient and their perception to help them improve healthy lifestyle changes. The aim of our analysis was to examine the role of perception of body image of patients with NAFLD of one-self to that of the patient's perception of their parents' body image.
Method: Between September 2017 and May 2018, 367 consecutive patients with a confirmed diagnosis of fatty liver were seen at a NASH-ville clinic in a hepatology practice in Southern California. Body size perception was assessed using the Stunkard Adult Image Figure scale. The Stunkard scale consists of 9 silhouette figures -two-specific gender scales that increase in size from very thin (figure 1) to very obese (figure 9). These figures were classified into underweight (figures 1 and 2), normal weight (figures 3 and 4), overweight (figures 5- 7) and obese (figure 8 and 9). The patient identified the silhouette figure most consistent with their perception of self and that of each of their parents. Other questionnaires and information about their medical records was collected.
Results: Based on BMI, 0.8% were classified as underweight, 10.5% normal, 27.4% overweight, 28.8% obese, and 32.5% morbidly obese. Table represents the correlation of self-perception of body image and grouped BMI. There was a statistical significant correlation between patient's BMI and their self-perception ($p < 0.05$). Same applies with patient's perception of their father's body image ($p < 0.05$). But that was not the case with the mothers.

		Self Perception					
		Underweight	Normal	Overweight	Obese	Morbidly Obese	**Total**
BMI	Underweight	0	0	0	0	2	**2**
	Normal	0	12	15	1	0	**28**
	Overweight	0	12	48	12	1	**73**
	Obese	0	6	33	27	11	**77**
	Morbidly Obese	0	3	18	29	37	**87**
Total		**0**	**33**	**114**	**69**	**51**	**267**

Conclusion: One's perception of self influences one's behaviour and motivation to change lifestyle. This analysis found that NAFLD patients had an accurate perception of their body weight and that of their parents unless one was morbidly obese or underweight. Looking at one's perception offers potential opportunities for clinicians to incorporate understanding of the unique challenge and potential obstacles in weight loss strategies. Identifying weight perception is a key tool in developing interventions to reduce obesity, ameliorate liver disease and improve overall health. Incorporating the family into the plan of care may influence all family members to improve healthy lifestyle behaviours.

FRI-415

"People are scared: what they don't know don't hurt them". A qualitative exploration of reasons for low uptake of hepatitis C virus testing in an English prison

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Background and aims: The prison population are central to the campaign to eliminate hepatitis C virus (HCV) as a public health threat. In the UK this has led to the introduction of a national 'opt-out' policy, requiring prisoners to be tested for HCV unless they decline, with a target to test 50-75% of those admitted. However, in a representative prison estate in the East Midlands of England (20, 000 prison entrants per annum) this policy has resulted in testing rates of only 13.4%. This qualitative exploration seeks to understand why the rates of test uptake are so far short of target.
Method: This qualitative study examines the experiences of 45 prisoners and 6 nurses of Hepatitis C testing in an English category C prison accommodating men nearing the end of their custodial sentence. The data collection method was face to face audio-recorded semi-structured interviews. The data were coded and analysed according to the research questions. This formed part of a larger study conducted in a realistic framework of evaluation. Interpretation of the data was aided by the use of NVivo and a thematic network approach.
Results: The key themes of *Fear*, *Insufficient Knowledge*, *Stigma*, *Privacy*, *Choice* and *Prison Life* have emerged as the principal barriers to test uptake. *Test Uptake Facilitators* were however identified by participants and a positive notion presented of prison healthcare being a *Health Farm*. It was highly evident that prisoners did not speak to each other about HCV and were fearful of catching this infection. Further, if identified as infected, social rejection by other prisoners was experienced, so fears of being found out were high. Privacy was highly valued and being seen attending the specialist hepatitis nurse clinic led to concerns by some prisoners. Levels of knowledge about all aspects of HCV by both prisoners and nurses were low and there were misunderstandings about the definition of an opt-out approach to testing, contributing to missed opportunities. Furthermore the prison regime, which necessarily prioritises security, can hamper opportunities for healthcare. Utilising time in prison positively to improve health was identified and most prisoners were accepting of the concept of routine testing on arrival.
Conclusion: In order to increase HCV test uptake a significant uplift in all factors affecting prison healthcare delivery, including nurse and prisoner education and support from the prison regime, are required. Providing information to prisoners aimed at allaying fears may encourage test uptake.

FRI-416

Assessment of written patient information pertaining to cirrhosis and its complications: A pilot study

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Background and aims: Written patient information may play an important role in the patient compliance of the cirrhosis disease but little is known on the quality and patients understanding of them. The aim of this pilot study was to assess the quality of written patient information pertaining to cirrhosis and its complications, and to explore patients' understanding of the written information.
Method: A web-based search was performed to retrieve written patient information from different Danish Gastroenterology and Hepatology departments. Baker Able Leaflet Design (BALD) criteria's and Ensuring Quality Information for Patients (EPIQ) questionnaire was applied to assess design, layout characteristics, and information quality of the written information. Readability was calculated using the Læsbarhedsindex (LIX) and the Simple Measure of Gobbledygook (SMOG). In addition, a cross-sectional study with a mixed-method design was carried out among eleven outpatients with cirrhosis at the Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark, using a questionnaire consisting of 28 closed and open questions regarding written patient information. Descriptive statistics were used for assessing the quality of the written information and for the closed-ended responses. Data from the open-ended responses were analysed in accordance with Kvale and Brinkmanns meaning condensation.
Results: The mean BALD score was 24 and the mean EQIP score was 70%. The mean LIX score was 46 and the mean SMOG score 15.8. Fifty percent of the patients stated that they had received written patient information, but only one patient was able to recall advices and/or instructions from the written information. Sixteen identical phrases from the written information were selected to explore patients' understanding. Four phrases were understood by 100% of the patients, six phrases by more than 50% of the patients, and six phrases were understood by less than 50% of the patients. The meaning condensation showed that knowledge and understanding of cirrhosis and its complications were not enhanced by the availability of the written information.
Conclusion: The written patient information had good design, layout, and information quality but was difficult to read. Patients appeared to relate poorly to the written information and demonstrated limited health literacy. These results suggest awareness among healthcare professionals in the importance of matching written patient information and patients' level of health literacy in order to ensure effective patient understanding and thereby disease compliance. Further studies on intervention to improve patients' health literacy are recommended.

FRI-417

Impact of a nurse educational program and accessibility in the management of patients with hepatocellular carcinoma under systemic treatment

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Background and aims: Management of sorafenib therapy in hepatocellular carcinoma patients (HCC) requires dose modifications due to adverse events (AE) and multiple visits until reaching the tolerated dose for each patient. Thus, a multidisciplinary approach

including expert nurses for patient education and counseling is key to improving treatment compliance.
Our study evaluates the impact of expert nurses in handling unscheduled phone-call visits regarding doubts and symptom management at the start of treatment. (≤ 60 days).
Method: A descriptive retrospective study based on prospective data of the nurse educational program and its impact during systemic therapy. The program includes an on-site educational appointment before starting sorafenib, on-site visits every month and unscheduled phone-call visits. We collected the number, causes, type of issues raised by patients and the resolution of the unscheduled phone-call visits.
Results: From Jan/2015 to Sept/2018 101 patients started sorafenib at BCLC. 93 of them made 357 unscheduled phone-call visits. 163 calls were excluded because of their administrative nature or lack of information. The remaining 194 unscheduled phone-call visits from 76 (75.25%) of the 101 patients were analyzed.
The median number of issues for each unscheduled phone-call visit was 1 (range; 1-4) and 424 types of issues were the cause of consultation. 52.5% (n = 137) of the issues were solved only by nurses and 47.5% (n = 124) needed physician intervention. The issues solved by nurses were classified as sorafenib-related AEs (43%), non-sorafenib related AEs (53%) and cirrhotic decompensations (4%). The most frequent treatment-related AEs solved by nurses were hypertension 13.9% (n = 19) and deposition alterations 12.4% (n = 17). Nurse interventions were care counseling (50%), educational intervention (28%) and resource management (22%).
5% of the patients were referred to the emergency department due to fever, hemorrhage, ascites and pain and 60% of them were admitted to the hospital.
Conclusion: The nurse educational program and the follow-up monitoring registered the use of unscheduled phone-call visits by 92% of sorafenib-treated patients. More than 50% of the issues were solved only by the expert nurse. Thus, this program reduces on-site visits, optimizes health resources and secures patient compliance to treatment. Therefore, our results demonstrate the key role of the expert nurse in the optimal management of patients under systemic treatment.

FRI-418
Evaluating patient's experience in liver transplantation: Role of the focus group technique

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Background and aims: Liver transplantation (LT) is the treatment of choice for patients with acute or chronic liver disease without other therapeutic alternatives. This is a common procedure in our environment and it is evaluated periodically using objective data. More recently, patients' feedback is also assessed to know the patients' subjective aspects (feelings, impressions, perceptions) of LT, and it is known as "the patient's experience". The aim of this study was to know the experiences in patients undergoing liver transplantation, and to identify improvement opportunities in this procedure.
Method: In order to know the experiences of the patients/relatives during the LT process, the technique of the focus group (FG) was applied. To prepare this group, the professionals involved in LT carried out the following activities: 1) a brainstorming session, applying the metaplan© technique, to gather the most relevant ideas and opinions about the process, 2) preparation of a document, based on the metaplan information, so that outside psychologist could moderate the FG; and 3) the selection of the participants in the FG: 4 caregivers and 8 transplanted patients. This group was held on 11/29/2016. Subsequently, the psychologist, who prepared a document with the information gathered from the FG, met with the transplant team to analyze the data and to identify possible improvement opportunities, which could be implemented in the daily work of the team.
Results: Transplant patients and their relatives considered the LT process well structured. They pointed out that the information about the process provided by the different professionals of the transplant team is unified, and refer a high degree of satisfaction with the staff. On the other hand, they emphasize the feeling of isolation in the Intensive Care Unit (ICU) and the lack of psychological support throughout all the process. Accordingly an intercom was used to enhance patient communication and visiting hours were more flexible. In addition, efforts are being made to incorporate a psychologist into the team, to help patients and relatives.
Conclusion: The FG has been an effective technique to identify important patient's subjective aspects in LT. That has allowed us to implement measures aimed at improving the patients' experience.

FRI-419
Is a lack of patient awareness holding back self-management of NAFLD?

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) affects 25% of the UK population and is a frequent manifestation of the metabolic syndrome (MetS). Lifestyle change can ameliorate the negative impact of NAFLD/MetS on long-term health, but requires patient engagement. Lack of NAFLD/MetS awareness in patients may act as a barrier to making healthy lifestyle choices. A questionnaire was developed to explore knowledge of NAFLD in our local population.
Method: Questionnaires were distributed at random to 100 patients attending various medical specialty outpatient clinics over a 12 week period. Questions explored understanding of causes and management of NAFLD.
Results: Respondents were 47% (n = 47) female; 52% (n = 52) male; 1% (n = 1) other; Age ranged from < 21 years (11%; n = 11); 21- 40 years (24%; n = 24); 41-60 years (39%; n = 39); > 60 years (26%; n = 26). Ethnic origin and educational achievement were representative of the local population: Most respondents had at least one self-reported risk factor for NAFLD/MetS: obesity (30%;n = 30); fatigue (30%; n = 30); hypertension (19%; n = 19); dyslipidaemia (15%; n = 15); depression (14%; n = 14); Type 2 diabetes (13%; n = 13); low exercise levels (12%; n = 12); high fat/processed diet (11%; n = 11).
39% (n = 39) of patients had heard of NAFLD. 7% (n = 7) self-reported having NAFLD and 6% (n = 6) knew someone with NAFLD lower than expected prevalence suggesting a lack of awareness. Overall awareness of NAFLD was poor; only 80% (n = 80) thought NAFLD could be harmful and 43% (n = 43) did not know that it could cause cirrhosis. Only 39% (n = 39) knew NAFLD is preventable, with no significant difference in knowledge between those with and without NAFLD (p = 0.49). Once established, 21%; (n = 21) thought NAFLD was irreversible.
Understanding the impact of lifestyle on NAFLD was limited. Only 25% (n = 25) correctly identified a target of 5-10% total body weight loss. Just over half (n = 54) recognised the Mediterranean diet as a

suitable dietary strategy. 21% (n = 21) incorrectly stated that rapid weight loss would be appropriate.
Conclusion: Despite high self-reported incidence of MetS risk factors, surprisingly few respondents had, or were aware of someone with NAFLD. Awareness of the impact and management of NAFLD was poor in people with and without NAFLD. Greater public education on NAFLD prevention and management by healthy lifestyle change is critical to long term reduction of prevalence and progression of NAFLD.

FRI-420
A nurse-led advice and lifestyle intervention shows high levels of patient-reported satisfaction and motivation in community-based management of NAFLD

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) affects 25% of the UK population but only a fraction develop advanced liver disease. For most, management focuses on cardiovascular risk reduction with responsibility increasingly devolved to primary care (PC). However PC is poorly resourced to discuss the diagnosis and importance of lifestyle change. We explored acceptability of nurse-led clinics to support PC management of NAFLD.
Method: As part of a randomised trial of a NAFLD Integrated Care Pathway participants in control and intervention arms were given information about diagnosis and healthy lifestyle change by a NAFLD specialist nurse. Interview and questionnaires at 1-year follow-up explored understanding of NAFLD, disease management and patient reported outcomes.
Results: 52 patients were recruited, (29% [n = 15] female; 71% [n = 37] male) with median age 48 (26-62) and 52 years (24-76), respectively. 19% (n = 10) withdrew before 1 year: 90% (n = 9) could not be contacted or declined; 10% (n = 1) moved away. 2 patients had pending visits at the time of data collection. 40 patients completed 1 year of follow-up, and were included in the analysis. Baseline patient awareness and knowledge of NAFLD was poor, but 100% (n = 40) said the nurse-led clinic had improved their understanding: 65% (n = 27) rated the information very helpful, with nobody rating it unhelpful (p = 0). 93% (n = 27) said discussing their Enhanced Liver Fibrosis test result aided understanding of their stage on the NAFLD spectrum, and encouraged self-management. All participants found the nurse helpful in discussing plans for sustainable lifestyle change. At 1-year, 22% (n = 9) reported psychosocial improvement, 54% (n = 21) better diet and 40% (n = 16) increased exercise. Objectively, 67% (n = 18) had reduced BMI by median 0.9 (–6.37-2.45), with 20% (n = 8) and 8% (n = 3) achieving > 5% or > 10% weight loss respectively. Worryingly, a questionnaire for healthcare professionals (HCP) conducted in parallel also revealed poor knowledge, with 27% (n = 40) unaware NAFLD is preventable, and 28% (n = 41) not realising NAFLD can cause cirrhosis.
Conclusion: Poor HCP and patient knowledge of disease impedes effective clinical management. Time spent discussing NAFLD and necessary lifestyle change with a trained nurse led to patient reported improvements in knowledge, and was considered helpful by all participants. Sustainability of change will be monitored at future follow-up. Nurse-led clinics could become a valuable part of community-based NAFLD services.

Rare liver diseases (including pediatric and genetic)

FRI-422
Genetic and pathophysiological factors leading to deficient acyl-CoA oxidase 2 (ACOX2) activity in hepatocytes, an alteration which causes oxidative and endoplasmic reticulum stress in liver cells

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Background and aims: Acyl-CoA oxidase 2 (ACOX2) is a key enzyme in cholic acid biosynthesis. Its partial deficiency (APD) results in accumulation of trihydroxycholestanoic acid (THCA) and has been recently described as a cause of asymptomatic hypertransaminasemia. Here we have explored the mechanisms controlling ACOX2 expression and the pathogenic consequences of the absence of its enzymatic activity.
Methods: Human hepatocytes, either immortalized or freshly isolated, and human hepatoma cells (HepG2 and Huh7) were cultured in the presence of bile acids (BA), FXR or PPAR agonists, recombinant FGF19, oncostatin M (OSM), IL-6, IL-1beta and TNF-alpha. ACOX2 expression was determined by quantitative real-time PCR and immunoblot. Specific inhibitors were used to investigate the signalling pathways involved in gene regulation. Predicted genetic variants in *ACOX2* ORF were generated by site-directed mutagenesis and overexpressed in Huh7 cells using lentiviral vectors. Their ability to metabolize THCA was measured by HPLC-MS/MS. Oxidative stress was determined by flow cytometry using specific probes. Endoplasmic reticulum (ER) stress was studied by measuring CHOP and GRP78 up-regulation plus spliced XBP1 generation by immunoblot and PCR, respectively.
Results: Several genetic variants of ACOX2 were able to retain its enzymatic activity, although others partially or completely blocked THCA biotransformation resulting in oxidative and ER stress. In human hepatocytes, ACOX2 expression was downregulated by BA, FGF19 and OSM. Similar but weaker effect was exerted by IL-6, IL-1beta and TNF-alpha, whereas PPAR agonists had no effect. After washing-out OSM from de culture, ACOX2 down-regulation persisted for more than 24 h, which was associated to strong OSM adhesion to extracellular collagen. Abrogation of the Janus kinase activity completely blocked the suppressive effect of OSM, while inhibition of the MAPKs p38 and JNK had no effect. Inhibition of ERK1/2 pathway partially overcame OSM-induced ACOX2 down-regulation, whereas it was able to completely block FGF19-mediated effect.
Conclusion: Inflammatory processes and cholestasis may affect ACOX2 expression. Moreover, the presence of inactivating mutations in *ACOX2* gene leads to altered BA metabolism and enhanced oxidative and ER stress.

FRI-423

Role of antithrombin deficiency in splanchnic vein thrombosis

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Background: The most frequent causes of splanchnic thrombosis (ST) are thrombophilia disorders and local inflammation-induced thrombosis, but in 30% of patients it is not possible to identify its aetiology. The most severe thrombophilia disorder is antithrombin deficiency (AT) caused by mutations in SERPINC1 gene. Recently, transitory AT deficiency triggered by the combination of molecular defects and inflammatory events have been described. Alterations in the N-glicosilation pathways have also been reported to cause AT deficiency. However, clinical screening of AT deficiency only includes anti-factor Xa activity. Patients requiring anticoagulation could remain untreated if a thrombophilia disorder was misdiagnosed. In addition, the incidence of ST among patients with AT deficiency has not been established.
Aim: Assess the role of molecular AT analysis in ST and evaluate the incidence of ST in patients with ATdeficiency.
Methods: 89 patients with ST in whom AT deficiency was ruled out by conventional methods underwent molecular and gene sequencing analysis of AT. Additionally, the incidence of ST was evaluated in 715 patients with known congenital deficiency of AT.
Results: AT variations were identified in 4 out of the 89 patients with ST: one patient with locally induced thrombosis had glicosilation alterations (he did not receive anticoagulation and presented with pulmonary thromboembolism 2 years later) while the remaining 3 presented heterozygote mutations in SERPINC1 gene: one with a previously unreported genetic variation (*p.Gly199Arg; c.595G > A*) with pathogenic potential. This patient did not receive anticoagulation and did not develop new thrombotic events. The other 2 patients presented ST in the setting of myeloproliferative neoplasms. One of them had the variation c.438C > T (p.Ala156Ala), scarcely reported in general population, and the thrombosis progressed despite anticoagulation. The last patient had the c.89 T > A (p.Val30Glu) variation enabling transitory loss of anticoagulant activity in stress conditions. This patient began anticoagulation and did not present new thrombotic events.
14 of the 715 patients (2%) with AT deficiency developed ST.
Conclusion: The molecular analysis of SERPINC1 in patients with ST could enhance the detection of AT deficiency. Detecting these variations could modify the therapeutic approach and prevent future thrombotic events. In addition, our results show that the incidence of ST in patients with AT deficiency is relevant (2%)

FRI-424

Estrogen-containing oral contraceptives are associated with polycystic liver disease severity in pre-menopausal patients

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Background and aims: Polycystic liver disease (PLD) is a progressive disease that occurs predominantly in females. It is hypothesized that exposure to estrogen results in higher liver volume but supporting evidence for this concept is contradictory. We aimed to assess the association between oral estrogen-containing contraceptives and history of pregnancies with disease severity in females with PLD.
Method: We performed a cross-sectional cohort study. Female PLD patients were identified from the International PLD Registry and included when imaging was available prior to any liver volume reducing therapy. Patients received a questionnaire to collect detailed information on estrogen use and pregnancies. We used multiple

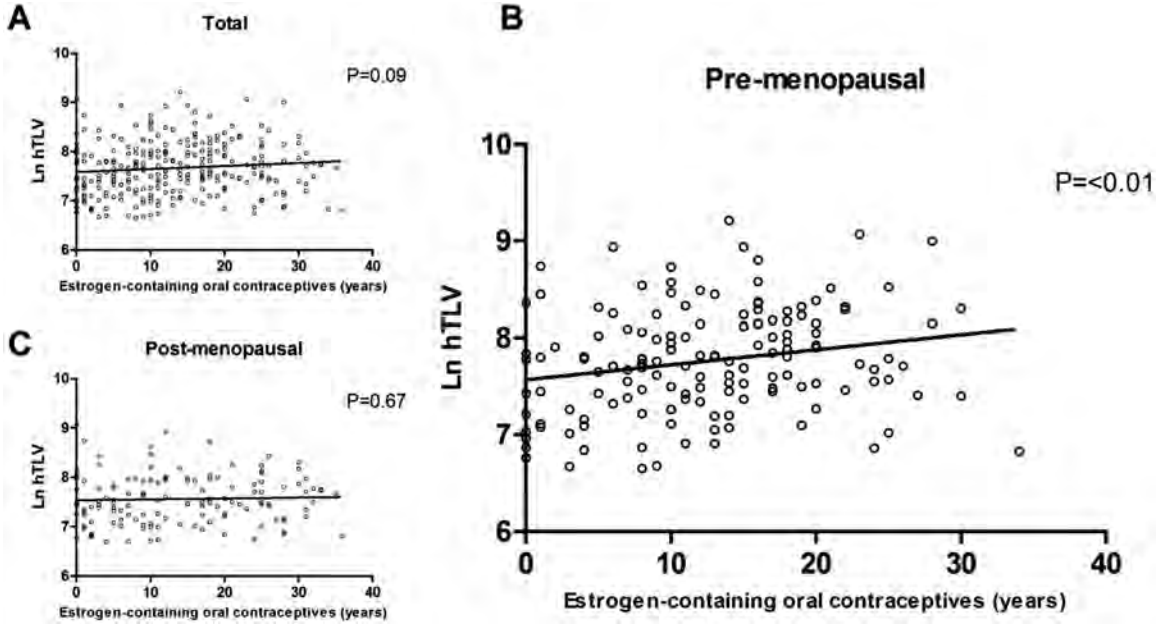

Figure: (abstract: FRI-423): Scatter plots and univariable regression lines, without correction for confounders, for estrogen-containing oral contraceptives in the total group (A) and pre-menopausal (B) and post-menopausal (C) subgroups. Natural logarithmic transformed height-adjusted total liver volume (Ln hTLV) is presented on the Y-axis.

regression analyses to assess associations of exposure to estrogen-containing contraceptives (years) and duration of pregnancies (months) with height-adjusted liver volume (hTLV) and adjust for confounders. Preplanned subgroup analyses were performed on pre-menopausal and post-menopausal patients.
Results: The questionnaire was returned by 287 out of 360 selected patients (80%). There was no significant association between estrogen-containing oral contraceptives and hTLV in the total group (B = 0.0068, P = 0.06) and post-menopausal subgroup (B = 0.00173, P = 0.70). By contrast, in pre-menopausal females use of estrogen-containing oral contraceptives led to higher polycystic liver volumes (B = 0.0144, P = 0.02). Each year of exposure corresponds with a 1.45% higher hTLV, equivalent to 15.5% higher hTLV for every 10 years of use. hTLV was independent of duration (B = -0.00113, P = 0.69) and number of pregnancies (B = 0.0485, P = 0.56).
Conclusion: Exposure to estrogen-containing oral contraceptives is associated with a higher hTLV in pre-menopausal females. Pre-menopausal PLD patients should avoid exogenous estrogens.

FRI-425

Maintenance therapy for Wilson disease with zinc: A comparison between zinc acetate and alternative zinc salts

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Background and aims: Our study evaluates treatment of Wilson Disease (WD) with zinc (Zn) acetate (FDA approved) and alternative Zn salts. Studies examining the effectiveness of Zn in WD are few and data on alternative Zn salts is limited. We describe one of the largest recent cohort studies of WD patients on Zn therapy and aim to improve our understanding of Zn as a treatment option.
Method: Single center retrospective review of 59 WD patients (age 6-88y, 32 females) treated with Zn (50-150 mg) from 0.8 to 52 years (median 26y). Most patients (n = 39) were on prior chelation therapy. An online survey was used to explore patients' experience using different Zn salts. We contacted 56 subjects; 31 completed the survey.
Results: Treatment response was evaluated using ALT and 24 h urine Cu. Urine Cu excretion (µg/24 h) was categorized as low < 25, target 25-100, or elevated > 100. Levels > 100 suggest medication or diet non-compliance, or treatment failure. Levels < 25 may indicate overtreatment. Target range was reached in 60% on Zn acetate, 65% on Zn gluconate and 50% on alternative Zn. Low urine Cu was not associated with a high ALT. Serum ALT was expressed as normal or a multiple (1-2, 2-3 or > 3 x) of the upper limit of normal (ULN). ALT was normal in 75% with target urine Cu but only in 16% with urine Cu > 100 µg. ALT elevations were not significantly different between Zn Salts (34% Zn acetate, 21% Zn gluconate and 28% alternative Zn, Kruskal-Wallis, p = 0.26).
Our online survey showed the mean age at diagnosis to be 18 years (2-43y). The average age of starting Zn was 26.8 years (3.5-65y). Most were on Zn acetate (45%) followed by Zn gluconate (42%). The majority were taking non-prescription Zn. Prior to Zn treatment 45% were symptomatic (45% neuro, 25% liver and 20% psychiatric). The majority (80%) had no WD symptoms on Zn. Only one person took Zn incorrectly. Most (80%) had previously been on alternative WD treatment. Patients switched from a different Zn salt (38%) mainly due to GI side effects (Zn acetate n = 11, Zn gluconate n = 5, Zn sulfate n = 1). Most reported no side effects on current Zn therapy (67%). Gastric side effects were experienced in 32%.

		Zn Acetate (n = 26)			Zn Gluconate (n = 19)			Alternative Zn (n = 7)		
Urine Cu (mcg/24 h)		< 25	25-100	>100	< 25	25-100	>100	< 25	25-100	>100
ALT	Normal	2	15	0	2	12	1	2	3	0
	1-2xULN	0	5	0	0	2	0	0	1	1
	2-3xULN	0	1	1	0	0	0	0	0	0
	3-4x ULN	0	0	2	0	1	1	0	0	0

Conclusion: Effective treatment with Zn preparations is possible in many WD patients. The potential for treatment failure in some suggests close monitoring is paramount for individuals on zinc therapy without both a normal ALT and an appropriate urine Cu excretion. More clearly defined parameters determining treatment success or failure will inform our clinical decision making for continuation of Zn treatment or a timely change to alternative therapy.

FRI-426

Overexpression of c-Jun N-terminal Kinase-1 coincides with the acquisition of cholangiocytic markers in experimental cholangiocarcinoma

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Background and aims: Cholangiocarcinoma (CCA) is an aggressive malignant adenocarcinoma characterized by biliary tract differentiation and the second most common primary liver tumour in Europe, with around 13, 000 new CCA cases diagnosed each year. However, the pathogenesis of CCA remains elusive and lack of a diagnostic tools impede a better outcome for patients. In the present study, we aimed to understand the molecular events that drive CCA initiation and development.
Method: HepG2 cells, and undifferentiated and differentiated HepaRG cells were cultured in presence of thioacetamide (TAA, 0-40 mM) and harvested for 0-24 h. D-JNK1-I [2 µM], an inhibitor of JNK, was used. In parallel, wildtype mice bred in a C57BL/6 background were injected *i.p.* with diethylnitrosamine (DEN, 25 mg/kg b/w) at day 14 postnatally. At 8 weeks of age, TAA (300 mg/l) was added into the drinking water. A second experimental group was treated only with TAA. All mice were sacrificed 28-35 weeks after the start of the treatment. Histopathological examination of cells and livers, immunofluorescence and immunohistochemistry, protein expression and real time (RT)-PCR studies were performed.
Results: The median lethal dose (LD50) of TAA was 34.53 mM and 36.11 mM for HepG2 and HepaRG cells, respectively (calculated using CCK8 and TUNEL staining). Since HepaRG progenitor cells (HPC) are able to differentiate into hepatocytes or cholangiocytes, we next studied phenotypic markers. Interestingly, high concentrations of TAA induced overexpression of JNK1 but blocked JNK2 activation in both HepG2 and HepaRG cells, and this effect was blocked by adding D-JNK1-I. This was coincident with the acquisition of cholangiocytic markers (A6, CK19) and loss of the hepatocytic phenotype (HFN-4α, ALB). This was further reversed by the addition of D-JNK1-I. Furthermore, these results were validated in both experimental models of CCA. Mice treated with DEN/TAA, acquired phenotypic markers of cholangiocyte differentiation which were concomitant with overexpression of JNK1 but loss of JNK2 phosphorylation.
Conclusion: Dysregulation of the JNK signaling pathway coincides with the acquisition of phenotypic markers of cholangiocytes. Addition of an inhibitor of JNK, reversed HPC differentiation. These findings may open up new therapeutic avenues for the treatment of CCA.

FRI-427

Liver humanized mouse as models for human metabolic liver diseases

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Background and aims: The objectives of these studies were to create liver-humanized mice where the liver is highly repopulated with hepatocytes from patients with severe urea cycle defects (UCD).
Patients with genetic defects in any of the urea cycle enzymes or two inner mitochondrial transport proteins can result in urea cycle defects. Two of the most common urea cycle defects are, carbamoyl phosphate synthetase I (CPS-I), ornithine transcarbamylase (OTC). Many animal models do not faithfully reproduce rare human disease. We propose the best model for diseases that affect metabolic activities in hepatocytes should utilize disease-affected human hepatocytes. If those studies can be conducted *in vivo*, the value of the model is enhanced.
Method: Mice that are immune and *Fumarylacetoacetate hydrolase*-deficient (FRGN) produce tyrosine metabolites that are toxic to mouse liver cells, and transplantation of human hepatocytes at that time, leads to the replacement of the mouse cells and high-level repopulation of the liver with human hepatocytes. Hepatocytes were isolated from two normal donors and from patients who received liver transplants for severe urea cycle defects, carbamoyl phosphate synthatase-1 (CPS-1) or ornithine transcarbamylase (OTC)-deficiency. Isolated mutant or normal human hepatocytes were transplanted into the liver of FRGN mice.
Results: When compared to mice highly repopulated with, normal, CPS1-proficient human hepatocytes, mice repopulated with CPS1-deficient human hepatocytes exhibited characteristic symptoms of human CPS1 deficiency including an 80% reduction in CPS1 metabolic activity, delayed clearance of an ammonium chloride infusion, elevated glutamine and glutamate levels and impaired metabolism of ^{15}N-ammonium chloride into urea. Mice repopulated with OTC-deficient human hepatocytes displayed an increase in blood ammonia levels on a regular protein diet and a delayed clearance of an ammonia challenge. Amino acid levels and ureagenesis studies with OTC-deficient, liver-humanized mice are ongoing.

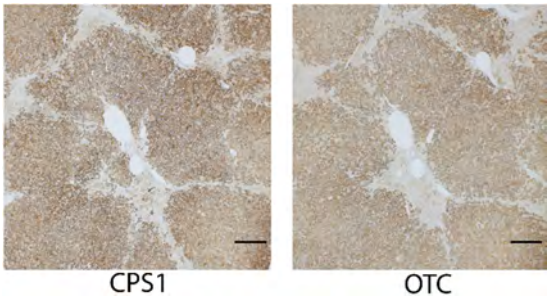

Figure: Humanized mice liver tissue after 80% humanization

Conclusion: We conclude that CPS1- or OTC-deficient, liver-humanized mice provide a faithful model for the human urea cycle deficiencies. The model reported here is expected to be useful for investigations of modified RNA, gene, cellular and small molecule therapies for CPS1-deficiency. Liver-humanized models for this and other monogenetic liver diseases affords the ability to assess the therapy on actual disease-affected human hepatocytes, *in vivo,* for long periods of time and will likely provide data that is highly relevant for investigations of the safety and efficacy of gene editing technologies and their translation to the clinic.

FRI-428

Prevalence and impact of sarcopenia in non-cirrhotic portal hypertension

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Background and aims: little is known on nutritional parameters in patients with chronic portal vein thrombosis (PVT) and idiopathic non-cirrhotic portal hypertension (INCPH).
The aim of this study is to assess the prevalence of sarcopenia, measured by the skeletal muscle index (SMI) at CT-scan, in patients with non-cirrhotic portal hypertension (NCPH). A control group of cirrhotic patients was also studied. Both groups were followed up to establish the relationship between sarcopenia and clinical outcomes.
Method: sixty-seven patients with NCPH (51 PVT and 16 INCPH) were included in the study group and 104 patients with liver cirrhosis in the control group. The axial plane passing through the intersomatic disk between L3 and L4 was evaluated for the quantitative analysis of muscle mass and the skeletal muscle index was calculated (SMI).
Results: sarcopenia was present in the 37.5% of patients with INCPH, 41.2% of patients with chronic PVT. In the control group it was registered a 40% of prevalence in patients with compensated cirrhosis and 61% in patients with decompensated cirrhosis.
During a mean follow-up of 51 ± 62 months, there was no difference in sarcopenic and non-sarcopenic patients with NCPH for episodes of ascites, hepatic encephalopathy, oesophageal varices and death. However, the incidence of refractory variceal bleeding requiring TIPS placement was significantly higher in comparison with non-sarcopenic ones (26% vs 8% p = 0.01). After TIPS placement (5 out of 10 patients who undergone TIPS had a CT-scan control after the placement), SMI significantly improved from 42.7 ± 8.9 to 47.5 ± 8.3 (p = 0.05) with an average increase of 4.7 ± 3.9 cm2/m.
Conclusion: in patients with NCPH sarcopenia is similar to that observed in compensated cirrhotic patients. Instead cirrhotic patients with MELD ≥ 15 present a higher prevalence of sarcopenia, suggesting that portal hypertension per se might play a role in the development of sarcopenia. This is supported by the significant amelioration of SMI value observed after TIPS placement. Moreover, sarcopenic patients seem may be more prompt to develop complication related to portal hypertension particularly a higher rate of refractory bleeding causing TIPS placement in the follow-up.
Our results suggest the importance of nutritional assessment in patients with NCPH and, in case of detection of sarcopenia, measures finalized to the amelioration in nutritional status should be taken into consideration.

FRI-429

Impact of allelic variants of platelet receptors and coagulation system genes in the development of clinical manifestations of Wilson's desease

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Background and aims: A variety of phenotypic Wilson's disease (WD) manifestations with the same mutations in ATP7B gene implies that there are some modifier genes that might influence the pathogenic mechanism and the WD clinical symptoms. We assess the effect of various genes polymorphisms combinations, including FII 20210G/A, FV 1691G/A, FVII 10976G/A, FXIII 103G/T, ITGA2 807C/T, ITGB3 1565 T/C, FBG −455G/A, PAI −6755G/4G, MTHFR 677C/T, on the clinical course of WD.
Method: The research includes 85 patients with Wilson's disease: 51 patients with predominant liver disease without neurological symptoms (abdominal form) and 34 patients with concomitant neurological symptoms (mixed form). Assessment of gene polymorphisms was carried out by PCR.
Results: Genotypes GA FII 20210 G/A and GA FV 1691G/A were more frequently observed in patients with neurological manifestations. The frequency of these genotypes nearly approached statistical significance (p = 0, 157 and p = 0, 061). The 4G allele of PAI −675 5G/4G gene was more common in the group with neurological symptoms than in the group without signs of CNS damage (OR 1.374; 95% CI 0.739-2.553). In the group with neurological manifestations, genotype 4G4G was observed more frequently (47.06%) than in patients with liver disease only (23.53%) (OR 2.889; 95% CI 1.135-7.350). The minor T allele of the ITGA2 807 C/T gene was observed more often in the group with mixed form of WD than in the group with abdominal form of WD (p = 0.018; OR 2.172, 95% CI 1.163-4.058). The combined genotype CT+TT was significantly more frequent in the group with neurological manifestations (82.35%) compared with the group without such symptoms (54, 90%) (p = 0.010; OR 3.833; 95% CI 1.355-10.846).
Conclusion: In Wilson's disease patients, genotypes FII 20210 G/A, FV 1691G/A, PAI-675 5G/4G, ITGA2 807 C/T are associated with development of neurological symptoms.

FRI-430
Preclinical validation of copper 64 as a translational tool for evaluating the pharmacodynamics of VTX-801 genen therapy in Wilson's disease
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Background and aims: Wilson's disease is an autosomal recessive metabolic defect of hepatocyte copper excretion into the bile, caused by absent or reduced ATP7B copper transporter function. The ATP7B transporter has dual role: it transports copper into the trans-Golgi compartment for incorporation into the plasma protein ceruloplasmin, and into the bile for excretion of excess copper stores. Recently, we have demonstrated that the administration of an adeno associated vector (AAV) encoding a mini version of the human *ATP7B* cDNA (AAV-miniATP7B) provides long-term correction of copper metabolism in Wilson's disease (WD) mice. In anticipation of a future gene therapy clinical trial, we considered the value of using biliary copper excretion as a pharmacodynamic biomarker. For that purpose, we have evaluated the excretion of radiocopper (^{64}Cu) into the faeces as an alternative biomarker in AAV-miniATP7B-treated WD mice.
Method: Male and female WD mice were injected with AAV-miniATP7B at 6 weeks of age. Three months later, radiocopper was injected intravenously in treated mice as well as in control mice of the same age (WT and Atp7B ±). Abdominal PET analyses were performed 24 and 48 h later. 24 h faeces, 24 h urine and serial blood samples were collected over a period of 72 h post radiocopper injection, at which time animals were sacrificed and organs collected (liver, kidney, lung, brain and spleen); the radioactive signal was then measured for each biological sample in a gamma counter.
Results: Faecal radiocopper excretion was significantly higher in control mice in comparison to WD mice, in which a signal was barely detectable; while in AAV-miniATP7B treated WD animals, radiocopper faecal elimination was restored. The overall kinetics of radiocopper in blood was also very different in controls and WD mice, and it was restored in treated WD mice. Finally, the radioactive signal in the liver was much higher in untreated WD mice compared to controls, and was reduced in treated WD mice.
Conclusion: In conclusion, faecal excretion of radiocopper represents a very promising biomarker to evaluate the therapeutic efficacy of *ATP7B* gene supplementation in WD patients.

FRI-431
Clinical spectrum of congenital hepatic fibrosis in children: 15 year experience from a tertiary care centre in north India
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Background and aims: Congenital hepatic fibrosis (CHF) is a fibrocystic liver disease associated with ductal plate malformation (DPM) of the intrahepatic bile ducts. Normal liver parenchyma is separated by broad bands of bland fibrosis and DPM consisting of irregular shaped bile ducts along with abortive portal venules. Literature pertaining to various presentations of CHF in children is limited; this study aims at providing insights into the same.
Method: A retrospective case review of 125 children with CHF diagnosed at a tertiary care center in Northern India from 2003-2018, on the basis of clinical, radiological, endoscopic evidence of portal hypertension, and histopathological findings on liver biopsy, was performed. Percutaneous liver biopsy was done in all cases and the biopsies were reviewed by a single observer.
Results: At presentation, 60% had cholangitic variant with infantile cholestasis and predominantly intermittent pale coloured stools. 72.8% were boys. Median age at presentation was 5 months, 48 months and 8 years for cholangitic, mixed and portal hypertensive variants respectively. Presentation was with jaundice in 56%, abdominal distension in 22.4% and upper GI bleed in 17.6%. Majority of them had striking left liverlobe enlargement and moderate splenomegaly confirmed on ultrasound.1.6% (2), developed hepato-pulmonary syndrome. 5.6% had positive family history. In contrast to the published literature, our cohort had low frequency of associated syndromes. 15.2% had kidney disease of which 11.2% had Autosomal Recessive Polycystic Kidney Disease (ARPKD), 3.2% had Medullary Sponge Kidney; 5.6% had Caroli syndrome.
Conclusion: Sporadic isolated CHF without associated renal manifestations is a common presentation. Cholangitic CHF is an underrecognized entity and should be considered in the differential diagnosis of infantile cholestasis.

FRI-432
Current long-term outcome of 302 patients with noncirrhotic nontumoral extrahepatic portal vein thrombosis
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Background and aims: What is known about the outcome of extrahepatic portal vein obstruction (EHPVO) is mostly based on relatively small studies enrolled from 1980s. The aim of the study was to assess the current long-term outcome of EHPVO, with close

Table 1: (abstract: FRI-431): Profile of children among different CHF variants

Characteristics	Cholangitic	Portal Hypertensive	Mixed
% (n)	60% (75)	24.8% (31)	15.2% (19)
Age in months, Median (IQR)	5 (4, 8)	96 (66, 144)	48 (9, 72)
Stools % (n)			
Persistent pale	17.3% (13)	-	5.3% (1)
Intermittent pale	58.7% (44)	-	21.1% (4)
Pigmented	24% (18)	100% (31)	73.7% (14)
Left lobe of liver (%)	93.3% (70)	100% (33)	94.7% (18)
Splenomegaly % (n)	94.7% (71)	87.1% (27)	89.5% (17)
Associated Disorder % (n)			
ARPKD	8% (6)	16.1% (5)	15.8% (3)
Medullary Sponge Kidney	2.7% (2)	6.5% (2)	-
Caroli syndrome	5.3% (4)	3.2% (1)	10.5% (2)
Investigations:Median, (IQR)			
Total Bilirubin (mg/dl)	9.2 (4.4, 14)	0.9 (0.7, 1.2)	1.4 (1.1, 8.1)
Conjugated Bilirubin (mg/dl)	6.4 (2.5, 9.5)	0.3 (0.2, 0.5)	0.7 (0.4, 5.6)
AST (U/L)	240 (123, 357)	65 (46, 89)	87 (69, 199)
ALT (U/L)	134 (76, 203)	62 (43, 82)	74 (58, 167)
ALP (U/L)	579 (313, 762)	270 (173, 456)	350 (232, 447)
Albumin (g/dl)	3.0 (2.6, 3.3)	3.3 (2.8, 3.9)	2.8 (2.2, 3.6)
INR	1.2 (1.1, 1.3)	1.1 (1.1, 1.2)	1.2 (1.1, 1.4)

attention to identify potential candidates for transjugular intrahepatic portosystemic shunt (TIPS).

Method: Between March 2002 and June 2016, all consecutive adults with EHPVO were screened from our prospectively acquired database. The strategy for cirrhotic portal hypertension was applied for all the patients. For those with recurrent variceal bleeding and without fibrotic main portal vein and complete superior mesenteric vein and splenic vein thrombosis (EHPVO-TIPS criteria), TIPS was attempted.

Results: 302 patients were included into the study and the median follow-up was 58.8 months. With similar treatment strategy to cirrhosis, the 5-year cumulative incidences of development of large varices, first variceal bleeding, and rebleeding was 25.1%, 34.9%, and 33.6%, respectively. TIPS was attempted in 41 patients with recurrent bleeding meeting EHPVO-TIPS criteria and 37 (90.2%) were successful with a reduced risk of recurrent variceal rebleeding (HR = 0.36, 95% CI: 0.16-0.83, p = 0.017). Shunt dysfunction and HE were observed in ten (27.0%) and seven (18.9%) patients, respectively. 41 (13.6%) patients died and only nine (22%) were related with variceal bleeding. The 5-year cumulative survival rate were 91.9% with age the only predictor.

Conclusion: The current outcome of EHPVO is good. In addition, EHPVO-TIPS criteria can improve the technical success rate of TIPS and reduce rebleeding rate in patients with recurrent bleeding.

FRI-433

Bevacizumab for the treatment of liver involvement in patients with hereditary hemorrhagic telangiectasia

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Background and aims: Liver involvement of HTT is related to the type of vascular shunting present and can be manifest clinically as high-output cardiac failure, portal hypertension or biliary disease There is increasing evidence that treatment with Bevacizumab can be efficient for high cardiac output (CO) heart failure secondary hepatic involvement of HHT but there isn't data about this treatment in other manifestations of liver involvement in HHT.

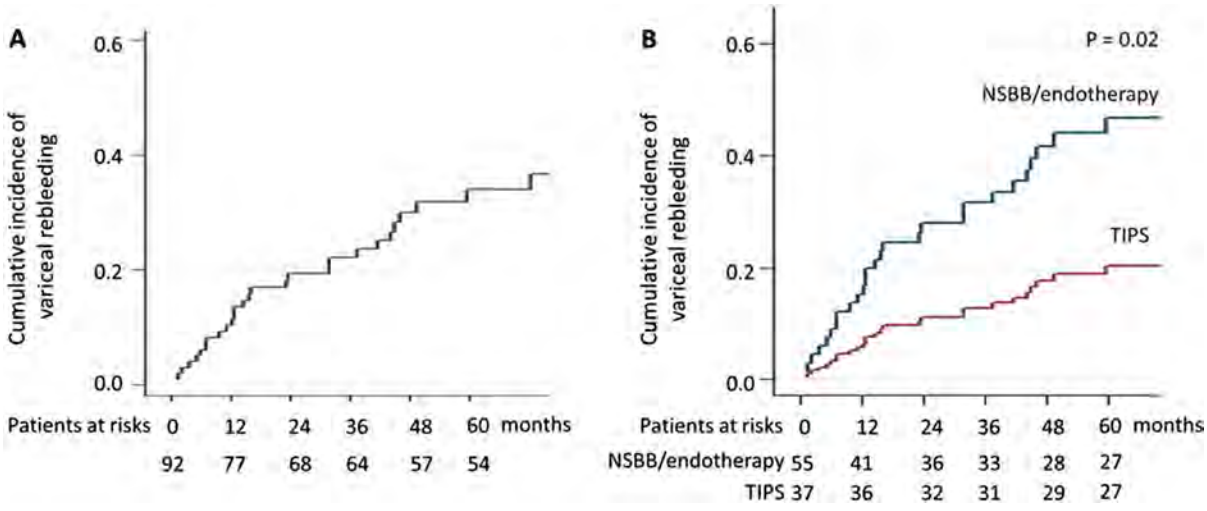

Figure 1: (abstract: FRI-432): Cumulative incidence of variceal bleeding under primary prophylaxis (A) and variceal rebleeding under secondary prophylaxis (B).

The aim of this study is to describe the successful outcome of patients with hepatic manifestations Of HHT treated with Bevacizumab.
Method: Retrospective case series using the patient's electronic data.
Results: Eleven patients were treated with Bevacizumab for clinical significant liver involvement of HHT. Ten of them were patients with high CO failure and one with liver decompensation only (portal HTN-ascites and encephalopathy). From the patients with high CO failure one had severe hepatic encephalopathy, one had severe ischemic cholangiopathy and one had refractory ascites with features compatible with portal HTN. All patients were treated with Bevacizumab 5 mg/kg every 2 weeks for 6 courses and then every 4-8 weeks for up to 3 years (3m-3years). All patients had significant clinical improvement of the heart failure and the other hepatic manifestations (ascites and encephalopathy).
Conclusion: Bevacizumab may be beneficial for the treatment of hepatic manifestation of HHT other than high cardiac output.

FRI-434

Role of next generation sequencing in the etiological diagnosis of splanchnic venous thrombosis

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Background and aims: Myeloproliferative neoplasms (MPN) are the most frequent cause of PVT. The mainstay of MPN diagnosis is based on the detection of mutations at JAK2V617F, JAK2 exon12, Calreticulin (CALR) or MPL. However, in some instances traditional techniques (Sanger sequencing) had low sensitivity, as they require at least 20% mutated leucocytes. Moreover, in up to 30-40% patients with PVT the etiological workup remains negative or only a local factor is identified (idiop/local-PVT). NGS allows the simultaneous evaluation of multiple genes associated with myeloid neoplasms even at low mutational levels, leading to a higher sensitivity than Sanger sequencing. Our aim was to explore the potential role of NGS identifying mutations/new etiological factors in a group of 44 patients with PVT that were negative for molecular markers using conventional techniques.
Method: We analyzed 44 DNA samples (4 MPN-PVT patients without mutations in JAK2/CALR/MPL genes by conventional techniques and 40 idiop/local-PVT patients). A panel of genes associated with myeloid pathology including TET2, ASXL1, CSF3R, RUNX1 and TP53 among others (Myeloid SolutionTMSOPHiAGENETICS®) was used. The analysis of the detected variants was carried out using SOPHiA DDM® software considering those non-synonymous variants with variant allele frequency (VAF) > 2%.
Results: In 2/4 (50%) with triple negative MPN-PVT, a mutation was identified in the "hotspot" region of exon 12 of JAK2. In addition, JAK2-exon12 was identified in 2/40 (5%) of idiop/local-PVT. No MPL mutations were detected. Of the remaining idiop/local-PVT, in 13/38 patients (34.2%) significant mutated genes were identified: 4 ASXL1 (2 associated with TET2), 4 CSFR3 (1 associated with TET2) and 5 isolated TET2. Interestingly, 3/13 (23%) patients with idiop/local-PVT with significant mutations had rethrombosis during follow-up while this only happened in 1/25 without significant mutations (4%) (p = 0.1).
Conclusion: NGS identified JAK2-exon12 mutations not previously detected by Sanger sequencing in 4 patients with PVT. In addition, NGS detected significant clonal mutations in approximately a third of patients with idiop/local-PVT. These patients seem to be exposed to a higher risk of rethrombosis. This preliminary result suggests NGS could be an useful diagnostic tool in patients with idiop/local-PVT and may lead to consider the use of long-term anticoagulation in those patients with significant mutations to prevent rethrombosis.

FRI-435

Progression to cirrhosis is not infrequent in patients with Wilson's disease despite treatment

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Background and aims: Wilson's disease (WD) has a very low prevalence. Thus, data on phenotipe/genotype at diagnosis and particularly on clinical outcomes in patients on therapy are scarce. We evaluated the clinical characteristics of patients with WD in a multicentric cohort comprising 4 centers in Spain.
Method: Clinical and laboratory variables, treatment and outcomes during follow-up were recorded. Categorical and quantitative variables were expressed in n (%) and median/IQR (25-75), respectively. Analysis extended from WD diagnosis until September 2018 or the development of events (transplantation/death). Molecular analysis was performed by Sanger and MLPA sequencing.
Results: 89 WD patients were included: 52.7% men, age at diagnosis 19 (12-31.5) years. The main phenotypic presentation was chronic liver disease (Leipzig H2) (69.2%); 79% of patients presented with ≥ 4 points in the Leipzig diagnostic score. WD was suspected mainly due to abnormal ALT levels (54.9%; ALT 87.5 UI/L [42-175]), whereas diagnosis due to neurological symtomps was infrequent (15.4%). Six patients (6.7%) presented as fulminant liver failure requiring liver transplantation. Up to 9.9% of cases were detected in a presymtomatic phase during family screening. Genetic analysis detected 1 (n = 30) or 2 (n = 29) mutations responsible for the disease in 95% of cases with available data (n = 62). The most prevalent mutations were p. Met645Arg (25.8%), p.His1069Gln (16.1%) and c.1708-1G > A (21%). First treatment was mainly penicilamine (68.5%), although 35 patients (57.4%) were discontinued, mainly due to adverse events. During clinical follow-up (70.3% adherence) the most frequent therapy was zinc (n = 44, 49.4%). In the last control, up to 60.4% of patients had normal ALT levels[median 30 (21-51)IU/L]. Nevertheless, after a median follow-up of 14.7 (9.6-25.5)years, 26 (28.6%) patients had developed liver cirrhosis, 13 (14.3%) patients presented gastro-esophageal varices and 2 (2.2%) cases were complicated with liver cancer; 12 patients received a liver transplantation (13.2%) and 3 (3.3%) died due to liver disease decompensation.
Conclusion: Hepatic phenotype was the most prevalent at diagnosis in this multicentric cohort of WD patients, and three recurrent mutations in the *ATP7B* accounted for 63% of patients. Despite medical therapy, cirrhosis development was remarkable, suggesting the need for a stricter monitoring of treatment adherence.

FRI-436

Congenital porto-systemic shunts in children: Preliminary results from the IRCPSS

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Background and aims: Our aim was to use data patients from centers participating in the first International Registry for Congenital Porto-Systemic Shunts (IRCPSS) to identify trends that might inform therapeutic strategies according to the anatomy of the shunt.
Method: Data were collected retrospectively (descriptive patient data, mode of presentation, complications, management). Intrahepatic (IH) was defined as porto-hepatic and extrahepatic (EH) as a porto-systemic communication occurring either upstream of the portal vein or originating at the portal vein. Persistent ductus venosus were considered EH.
Results: 246 children were identified and are summarized in Figure 1. IH and EH shunts were equally frequent. 24% of all CPSS were identified pre-natally and 76% post-natally. Among patients diagnosed pre-nataly, a majority had with IH shunts (75%). Among those diagnosed post-natally, EH CPSS were diagnosed later than IH CPSS. IH shunts were more often identified incidentally than EH shunts.
Symptoms: were equally frequent among patients with IH (57%) or EH (61%) CPSS. Hypoglycemia or cholestasis was more frequent in patients with IH CPSS. Patients with EH CPSS were more likely to have several symptoms than patients with IH CPSS. They were also more likely to have liver nodules on imaging.
Closure: 54% of IH CPSS and 5% of EH CPSS closed spontaneously. 35% of IH CPSS required medical or surgical closure of which nearly 40% for a preventive indication. 70% of patients with EH CPSS were closed through a procedure, of which 41% were preventive.
Conclusion: IH and EH shunts were equally frequent in this multicenter retrospective cohort of CPSS in children. CPSS are a cause of severe symptoms in children and should be sought in infants with hypoglycemia or cholestasis. In older children, they should be considered in the differential diagnosis of liver nodules, cardiopulmonary symptoms or neurocognitive deficits. Given the potential severity of complications, preventative closure was often performed, although timing and approach need further study, something which the IRCPSS aims to address.

n total=246	Intrahepatic n (%)	Extrahepatic n (%)	Total n (%)
Prenatal diagnosis (n=57)	43/57 (75.4 %)	14/57 (24.6%)	57/246 (23.2%)
Postnatal diagnosis (n=189)	82/188 (43.6 %)	109/188 (58 %)	188/246 (76.4 %)
Age at PN diagnosis (mean)	39.1 mo (0-200)	61.9 mo (0-192)	52.8 mo (0-200)
• incidental	41/68 (60.3 %)	32/89 (36%)	71/154 (46.1 %)
• symptomatic	47/81 (58 %)	67/109 (61.5%)	113/189 (59.8%)
Symptoms/signs	n=81	n=109	n=189
• hypoglycemia	12/81 (14.8 %)	6/109 (5.5 %)	18/189 (9.5 %)
• cholestasis	28/81 (34.6 %)	18/109 (16.5 %)	45/189 (23.8 %)
• cardiopulmonary	13/81 (16.1 %)	40/109 (36.7 %)	54/189 (28.6 %)
• neurocognitive	11/81 (13.6 %)	38/109 (34.9 %)	48/189 (25.4 %)
• asymptomatic	34/81 (42 %)	42/109 (38.5 %)	76/189 (40.2 %)
• liver nodules	22/125 (17.6%)	47/123 (38.2%)	68/245 (27.8%)
All (n=246)			
Age at closure	50.2 mo (1-230)	89.8 mo (.07-249)	72.8mo (.07-249)
-spontaneous	54/100 (54%)	5/98 (5.1%)	58/195 (29.7%)
-surgery	15/100 (15%)	45/98 (45.9%)	60/195 (30.8%)
-interventional radiology	29/100 (29%)	37/98 (37.8%)	65/195 (33.3%)
-liver transplant	2/100 (2%)	11/98 (11.2%)	12/195 (6.2%)
-not closed	24/119 (20.2%)	32/123 (26%)	56/240 (23.3%)

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Diagnosis of sickle cell liver disease may be aided by non-invasive tests

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Background and aims: Sickle cell liver disease (SCLD) continues to be poorly defined with most patients not being diagnosed whilst alive with reports of between 7 and 10% prevalence of cirrhosis in autopsy studies. The role of haemosiderosis, and historically, hepatitis C further clouded our diagnostic ability. With life expectancy increasing for patients suffering with sickle cell disease the burden of SCLD is expected to rise. The use of non-invasive tests may lead to a jump in our understanding thereby allowing earlier and more effective diagnosis and treatment. We hypothesise, non-invasive tests will aid the diagnosis of SCLD.
Method: All patients treated within a large tertiary center were screened for SCLD. Inclusion criteria consisted of all patients > 16 years old with genotype HbSS or HbSβ-thalassaemia with at least 1 episode of either a raised bilirubin (> 100μmol/L), ALT, ALP or clinical suspicion between Jan 15-Jun 16 regardless of treatment. We excluded patients who were pregnant. Blood tests were extracted with the mean calculated, excluding hospitalised episodes and post-transfusion tests. Patients were offered a Fibroscan® performed by experienced operators. Those within 1 week of an acute sickle crisis were not tested. Ferriscan® was performed at the clinicians discretion to measure liver iron concentration (LIC). All correlations were assessed using the non-parametric Spearman's rho in SPSS. The confidence intervals were calculated using the arctanh Fisher transformation in Python using the Python math module.
Results: 76 patients were examined with a mean age of 31.8yo and 74 with HbSS. 18 received no treatment, 10 hydroxyurea and 48 transfusions. Mean Hb was 87 (min. 66-max. 107)g/dl and Ferritin was 1976 (10-11626)μg/L. Liver function tests were grossly normal, Bilirubin-66 (10-219)μmol/L, ALT-29 (10-77) units/L, ALP-118 (28-473)IU/L and albumin 45 (34-78)g/L. Mean stiffness was 7.5 (3.4-36.2)kPa and LIC 13.2 (0.6-43)mg/g. Any fibrosis (> 6kPa) was found in 40 patients with 7 cirrhotics (> 12.3kPa). We correlated these with Fibroscan® to find a weak/moderate signal with ALP (r = 0.275, 95%CI: 0.05 to 0.47, p = 0.017), a weak signal for albumin (r = 0.238, 95%CI:

−0.44 to −0.01, p = 0.039) and no correlation with LIC (r = 0.149, 95% CI: −0.18 to 0.44, p = 0.37).
Conclusion: We can infer that Fibroscan® can aid the diagnosis of SCLD whilst not being affected by LIC and we are currently collecting biopsies to verify these correlations.

FRI-438
Histone deacetylase 5 methylation changes in mice and patients with Wilson disease

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Background and aims: Wilson disease (WD) is a genetic disease due to copper accumulation in the liver and brain. The clinical presentation is variable and suggests that environmental factors through epigenetic mechanisms may contribute to the disease phenotype. Histone deacetylases (HDACs) remove acetyl moieties from lysine residues of histone tails, resulting in transcriptional repression. Class II HDAC5 levels are believed to be greatly influenced by dietary factors, therefore lying at the interface between nutrition and epigenetic regulation of gene expression. The aim of the present study was to explore the methylation levels of HDAC5 in patients with WD and in an animal model of hepatic copper accumulation.
Method: Whole-genome bisulfite sequencing was performed on DNA from liver and whole blood of patients with WD compared to healthy subjects, primary sclerosing cholangitis, and non-alcoholic fatty liver disease patients (liver n = 21, blood n = 72). HDAC5 protein levels were confirmed in tx-j mice as model of spontaneous hepatic copper accumulation and compared to C3H control mice. Both tx-j and C3H female mice were started on choline-supplemented (choline 36 mmol/Kg of diet) and control diets (choline 8 mmol/Kg of diet) 2 weeks before mating and through pregnancy. The progeny was continued on the same diets until week 24 of age when mice were euthanized and livers were obtained.
Results: About one third of the genes near blood differentially methylated regions significantly overlapped with those identified in liver. Among overlapping genes, *HDAC5* gene was significantly hypermethylated both in the liver and blood from patients with WD with similar direction and gene body locations (FDR < 0.05). *HDAC5* hypermethylation was observed in patients with WD compared to healthy subjects and to subjects with other liver diseases. HDAC5 protein levels were more than twice reduced in livers of tx-j mice compared to wild-type mice but increased to control levels after penicillamine or choline supplementation. Concomitantly, the relative expression of acetylated histone 3 was increased in tx-j mice livers.
Conclusion: Our results suggest that *HDAC5* is a regulator of the interaction between nutrition factors and epigenetic mechanisms in WD and its levels appear to be affected by methyl groups availability.

FRI-439
Factor V and VIII may predict the risk of recurrent splanchnic thrombosis in patients with non-cirrhotic chronic portal vein thrombosis of local and idiopathic etiology not receiving anticoagulation

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Background and aims: Clinical guidelines do not recommend long-term anticoagulation in patients with non-cirrhotic splanchnic thrombosis of local or idiopathic etiology (NC-PVT) unless there is evidence of intestinal ischemia or recurrence. The aim of our study is to describe the risk of splanchnic and extra-splanchnic rethrombosis in these patients and the identification of predictors of recurrence.
Method: We prospectively included 64 patients with NC-PVT from the REHEVASC registry that, after discarding an underlying pro-thrombotic disorder, were classified as of local/idiopathic etiology. All these patients were not receiving long-term anticoagulation and had scheduled follow-up angioTAC/angioRMN studies during follow-up. Patients were censored at the time of rethrombosis or when the last imaging study was performed. Additionally, a detailed coagulation study was performed in 48 patients.
Results: During a median follow-up of 97 (10-206) months, 14/64 (22%) patients developed rethrombosis (50% asymptomatic) with an incidence of 1.6%, 8.4%, 17.4% and 27.3% at 1, 2, 5 and 10 years respectively. No clinical, biochemical or imaging parameters could predict development of rethrombosis. In the subgroup of 48 patients with a coagulation study, 10 (21%) had rethrombosis. Levels of factor V (being the best cut-off point by Youden 91%) and factor VIII ≥ 150% (value associated with recurrence of thrombosis in other territories) were significantly higher in patients who had rethrombosis. The incidence of splanchnic rethrombosis was 4.8% in patients with factor V < 91% and factor VIII < 150% at 10 years and 44.5% in patients with factor V ≥ 91% or factor VIII ≥ 150% (p < 0.01). Seven patients also had extrasplanchnic thrombosis (5 had also had splanchnic rethrombosis), then a total of 12 patients had the end point composed of rethrombosis and/or extrasplanchnic thrombosis. A factor VIII ≥ 150% and/or a factor V ≥ 91% confirmed its predictive capacity of new thrombotic events.
Conclusion: Risk of recurrent thrombosis in patients with idiopathic/local NC-PVT not receiving long-term anticoagulation treatment is not an exceptional event. Levels of factor V ≥ 91% and factor VIII ≥ 150% can help to select patients at high risk of rethrombosis who could benefit from long-term anticoagulacion.

FRI-440

Management of acute hepatic porphyria attacks in europe and united states: EXPLORE international, prospective, natural history study

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Background and aims: Acute hepatic porphyrias (AHPs) are rare, often misdiagnosed genetic diseases due to enzyme deficiencies involved in heme biosynthesis, leading to accumulation of neurotoxic heme intermediates. Clinical manifestations comprise potentially life-threatening neurovisceral attacks and chronic symptoms. At times, attack symptoms are managed through hemin, or prophylactically, with off-label hemin, GnRH, or carbohydrates. Given that differences exist among healthcare systems in Europe (EU) and United States (US), this study aimed to characterize AHP management in EU and US.

Method: EXPLORE (NCT02240784) is an international, prospective, natural history study of AHP patients. Eligible patients were those with ≥ 3 attacks/year or those on prophylaxis to prevent attacks. On separate questionnaires, investigators and patients reported attack history, including hemin use for attacks and off-label prophylaxis. Patients also reported perception of treatment effectiveness and ability to predict attack onset. Descriptive statistics were used to analyze outcomes, treatment location, and dosing frequency/duration by region.

Results: A total of 112 patients (EU: n = 63; US: n = 49) from 21 centers (EU: 14; US: 7) were enrolled (mean age 39 years; 89% female). In the year preceding the study, patients' mean (SD) attack rate was 9.2 (10.1) and 6.2 (7.8) for attacks requiring hemin or hospitalization. Attacks were managed at healthcare facilities (69%) and at home (31%). During attacks, hemin (69%), opioids (54%), and other medications (45%) were administered. Sixty-two patients (total: 55%; EU: 43%; US: 71%) reported use of any prophylaxis, and 52 patients (total: 46%; EU: 41%; US: 53%) reported prophylactic hemin use, mostly weekly (51%). Attack rate for patients on hemin prophylaxis was 10.0 (11.1), and for those who were not, 8.7 (8.9). Among EU patients who ever used hemin for attacks (78%), attack treatment spanned: 1 day (18%), 2-4 days (76%), and > 4 days (6%). Among US patients who ever used hemin for attacks (92%), treatment spanned: 1 day (13%), 2-4 days (51%), and > 4 days (36%).

Conclusion: Hemin prophylaxis was less frequent and hemin treatment duration for attacks was shorter in the EU than in US. Patient selection bias and variable access to treatments may account for this difference. Overall, attack rates and burden of illness remain high, regardless of prophylaxis treatment, underscoring the need for therapies to address AHP patients' unmet medical needs.

FRI-441

A novel heterozygous ABCB4, RUNDC3B and ABCB1 deletion associated with severe cholestatic liver disease in adults

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Background and aims: We report a large family with an autosomal dominant progressive cholestatic liver disease due to a heterozygous deletion involving *ABCB4*, *ABCB1* and *RUNDC3B*.

Method: DNA sequencing by next generation and Sanger sequencing of patient I.6 did not reveal known or potentially pathogenic nucleotide variants in *ABCB4, ABCB11, ATP8B1, JAG1* and *NOTCH2*; expanded copy number variation analysis of next generation sequencing data revealed a heterozygous deletion removing the 5' region of *ABCB4* and the entire coding sequences of *ABCB1* and *RUNDC3B* on chromosome 7. The same deletion was identified in 11 family members by quantitative polymerase chain reaction of *ABCB4* exon 1 and of the adjacent *ABCB1* exon 32, and by multiplex ligation-dependent probe amplification.

Results: Family tree and clinical characteristics of affected patients are presented in Figure. Two patients (I.4A and I.6) underwent liver transplantation.

All three symptomatic patients treated with UDCA normalized liver biochemistry and did not progress to cirrhosis over a follow-up period of 34, 15 and 15 years.

Age of clinical disease onset was highly variable. Child III.8 had neonatal cholestasis, with normalization on ursodeoxycholic acid (UDCA) and no progression of liver disease. The remaining affected children had no evidence of liver disease, but were not tested at birth. Of note, in symptomatic patients the liver histology at early disease stages was normal, even in the presence of elevated liver enzymes.

Hepatobiliary malignancies were remarkably frequent, affecting 3/5 cirrhotic patients, suggesting that this large deletion is a significant cancer risk factor in addition to cirrhosis, age and sex. While *ABCB4* defects are known to be associated with hepatic cancers even in the absence of cirrhosis, the consequences of *RUNDC3B* and *ABCB1* defects on the liver are unknown.

Conclusion: Our findings indicate that heterozygous deletions involving the *ABCB4, RUNDC3B* and *ABCB1* genes should be included in the genetic analysis of high GGT cholestasis, as patients have an elevated risk of developing chronic liver disease and hepatic malignancies, warranting cancer surveillance; UDCA treatment normalizes liver biochemistry, possibly preventing disease progression.

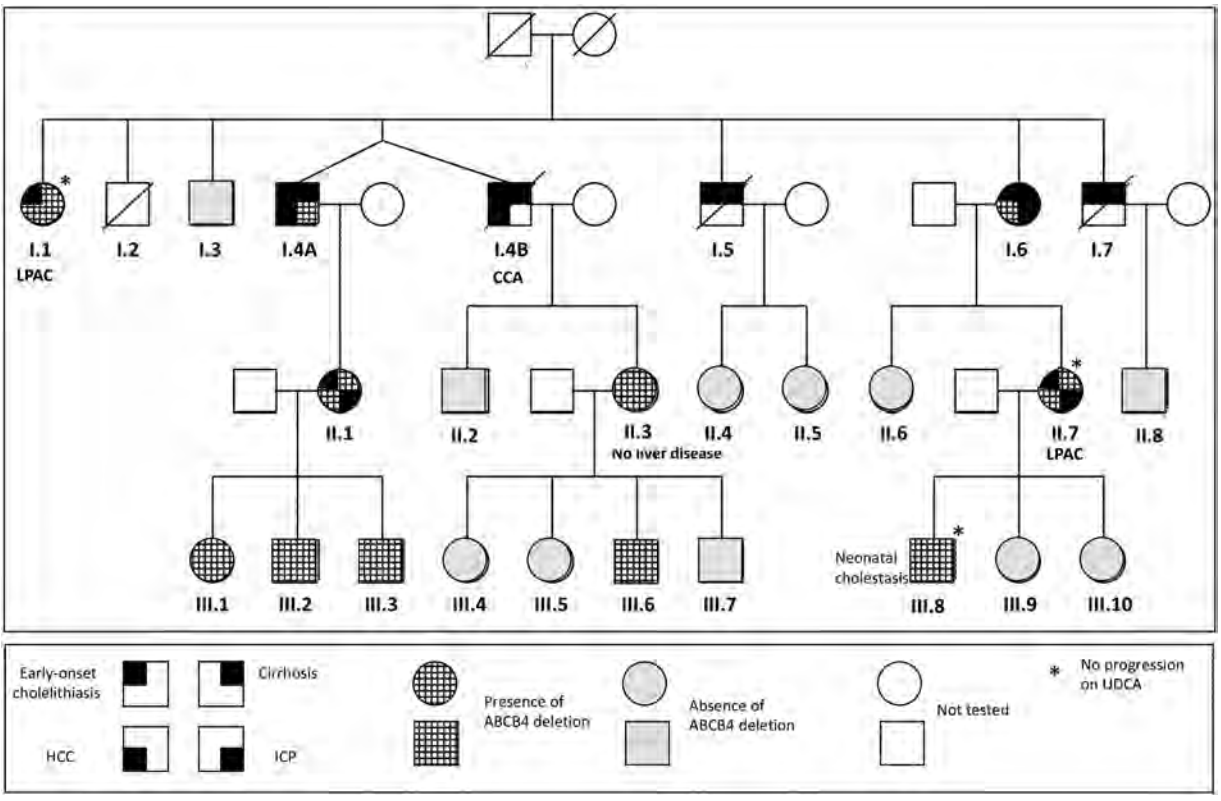

Figure: (abstract: FRI-441): Pedigree of the family. HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; LPAC, low phospholipid-associated cholelithiasis; ICP, intrahepatic cholestasis of pregnancy; UDCA, ursodeoxycholic acid. Subjects without black squares do not have liver disease. Subject I.2 died at age two days for unknown reasons.

FRI-442

Acute hepatic porphyria disease manifestations and daily life impacts in EXPLORE international, prospective, natural history study

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Background and aims: Acute hepatic porphyrias (AHPs) are rare, often misdiagnosed genetic diseases due to enzyme deficiencies involved in heme biosynthesis. AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP). Clinical manifestations comprise potentially life-threatening, neurovisceral attacks and chronic symptoms. This study aimed to characterize the disease manifestations and daily life impacts of AHPs in Europe (EU) and United States (US).

Method: EXPLORE (NCT02240784) is a prospective, international, observational study of the natural history and clinical management of AHP patients with recurrent attacks (≥ 3/year) or on prophylactic treatment to prevent attacks. At baseline, patients reported number of attacks, attack symptoms, chronic symptoms between attacks, and completed quality of life and health utilization questionnaires. During the 12-month study, patients also completed a porphyria attack symptom inventory questionnaire when they experienced attacks.

Results: A total of 112 patients (EU: 56%; US: 44%) from 21 centers (EU: 14; US: 7) were enrolled (mean age 39 years; 89% female; 93% AIP, 4% VP, 3% HCP). At baseline, the mean (SD) of all attacks reported in the last 12 months was 9.0 (10.6) for EU patients and 9.7 (9.2) for US patients. Most patients reported chronic symptoms between attacks (EU: 60.3%; US: 71.4%), often manifesting daily (EU: 63.2%; US: 80%). Pain and central nervous system involvement were the most common: abdominal (20.5%) or other origin (15.1%), anxiety (19.2%), tiredness (19.2%) and nausea (19.2%). At study entry, 47.3% of patients reported limited social interactions (EU: 37%; US: 61%) and 29% reported being unable to leave home due to their disease (EU and US: 29%). During attacks, most patients (98%) reported pain symptoms in abdomen (EU:77.5%; US:91.7%), back (EU: 65%; US: 83.3%), and arm/leg (EU:65%; US:70.8%). Pain associated with nausea was also common (EU: 65%; US: 87.5%). Patients also reported disorders of

mood or sleep during attacks, including tiredness (EU:75%; US:87.5%) and trouble sleeping (EU:80%;75%).
Conclusion: Overall, AHP patients in the EU and US showed similar symptoms during attacks and experienced comparable chronic symptoms. Some AHP patients also experienced negative impacts on daily life. Importantly, this study demonstrates that most AHP patients have chronic symptoms in addition to the significant burden associated with acute attacks.

FRI-443
Non-invasive fibrosis assessment in hyperferritinemia and hemochromatosis
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Background and aims: Ferritin is a surrogate of hepatic iron overload but also an indicator of inflammation and liver fibrosis, which are all common in hemochromatosis and other chronic liver diseases. Non-invasive assessment of fibrosis is important for the prognosis of chronic liver disorders and different ferritin thresholds have been proposed for hemochromatosis, NAFLD and chronic hepatitis C. The aim of the present study was to determine the prevalence of high ferritin and hepatic fibrosis as well as the association of these parameters in a large unselected cohort of patients with liver diseases of various etiologies.
Method: Between 200 and 2016 a total of 3362 patients were genotyped for the common hemochromatosis-associated gene polymorphisms (p.Cys282Tyr and p.His63Asp in *HFE*). Clinical and biochemical parameters and if available transient elastography were assessed at the time of genotyping and the non-invasive fibrosis score FIB-4 was calculated.
Results: Hyperferritinemia (> 300 µg/L for males and > 200 µg/L for females) was present in 2061 (61.3%) of patients. Fibroscan and FIB-4 showed a significant overall correlation ($r = 0.37$, $p < 0.001$). The prevalence of advanced fibrosis as indicated by elastography > 13kPa was 3% in hemochromatosis patients (p.Cys282Tyr homozygous), 4% in compound heterozygotes and 22% in patients homozygous of p.His63Asp. Single heterozygous patients and patients without *HFE* associated gene mutations had the highest prevalence of advanced fibrosis with 27.7%. These findings were confirmed when advanced fibrosis was defined as FIB-4 > 3.25. Patients homozygous for p.Cys282Tyr had a prevalence of advanced fibrosis (FIB-4 > 3.25) of 8.6%, followed by compound heterozygous patients (11.9%) and patients homozygous for p.His63Asp (15.4%). In the remaining genotypes 20.3-27% of patients presented with advanced fibrosis. Significant fibrosis (FIB-4 1.45-3.25) was present in 885 (26.4%) patients. When patients were stratified by HFE genotype again, homozygosity for the p.Cys282Tyr mutation in *HFE* was associated with the lowest fibrosis risk (FIB-4 < 1.35). Binary logistic regression analysis showed that age, ferritin, transferrin saturation and *HFE* genotype were independent predictors of significant and advanced fibrosis.
Conclusion: In conclusion, in hemochromatosis the serum-based fibrosis marker FIB-4 is a surrogate marker of significant and advanced fibrosis as determined by transient elastography. High ferritin is associated with significant and advanced fibrosis. Among patients with high ferritin, carriers of hemochromatosis-associated *HFE* mutations on both alleles are less likely to present with advanced fibrosis when compared with patients with high ferritin secondary to chronic viral hepatitis, alcoholic or non-alcoholic fatty liver disease.

FRI-444
VTX-803 AAV-mediated correction of progressive familiar intrahepatic cholestasis type 3 in a clinically relevant mouse model
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Background and aims: Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a rare monogenetic disease caused by mutations in the *ABCB4* gene encoding the multidrug resistance protein 3 (MDR3), which result in a reduction in biliary phospholipid (PL) content. This reduced biliary PL is not able to counteract the detergent effects of bile salts, leading to cholangitis, cholestasis, cirrhosis and ultimately liver failure. We attempted to treat *Abcb4* (−/−) mice with an hepatotropic AAV vector carrying a codon-optimized version of human *ABCB4* in order to achieve transgene expression and reversion of PFIC3 disease markers via restoration of PL in the bile.
Method: Huh7 cells were transfected with one of six AAV plasmids encoding three different MDR3 isoforms (A, B and C), of either a codon-optimized (co) or wildtype (WT) version of each gene and analyzed by immunofluorescence microscopy. Next, *in vivo* expression was confirmed by IHC following hydrodynamic injection (HDI) of *Abcb4* (−/−) mice with plasmids expressing isoform A (co and WT). Finally, two-week-old *Abcb4* (−/−) mice were treated intravenously with hepatotropic AAV viral particles expressing the selected transgene sequence coMDR3-A. Blood samples were harvested during the subsequent 12 weeks and levels of liver transaminases, alkaline phosphatase and bile salts were measured. At sacrifice, liver tissue was analyzed for AAV transduction and transgene mRNA by qPCR and RT-qPCR, respectively. Liver sections were stained for histological analysis and MDR3 quantification via IHC. Bile was harvested from gall bladders for phosphatidylcholine (PC) concentration measurement.
Results: From *in vitro* expression tests, only MDR3 isoform A was observed to localize to the membranes of hepatic cells. In addition, HDI studies showed that only coMDR3-A was expressed efficiently *in vivo*, localizing to biliary canaliculi. When AAV-coMDR3A was administered to *Abcb4* (−/−) mice, a sustained therapeutic effect was observed as serum biomarkers of liver disease decreased significantly compared to saline-treated control animals and animals treated at a lower AAV dose. Interestingly, male mice achieved a sustained therapeutic effect up through 12 weeks. However, the effect in females lasted through 12 weeks in half of the animals, while in the other half, the effect began to wane after 8 weeks. Upon sacrifice, markers of PFIC3 disease such as liver and spleen size, PC concentration in bile and liver histology were all significantly improved. Sustained MDR3 expression was detected in AAV-treated mice via RT-qPCR and IHC, showing specific localization of the transgene product to biliary canaliculi.
Conclusion: VTX-803 AAV-directed gene therapy successfully reverted the symptoms of PFIC3 disease in a clinically relevant mouse model with a sustained therapeutic effect up through 12 weeks post-treatment.

FRI-445

Safety and efficacy of trientine treatment in Wilson disease in patients withdrawn from d-Penicillamine: Final results from a prospective study

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Background and aims: Trientine dihydrochloride (Trientine; UNIVAR B.V.) is an established treatment for Wilson Disease. This study aimed to assess the efficacy, safety, and quality of life outcomes of trientine chelator-based treatment after withdrawal of d-Penicillamine and to follow the clinical course of neurological disease and hepatic disease over time. ClinicalTrials.gov Identifier: NCT02426905.
Method: This study was set up as a prospective, single-center investigation. A total of 52 patients were enrolled and assessments were performed at 6 and 12 months. Primary end point was investigator rated outcome of hepatic and neurologic symptoms. Additional efficacy assessments included parameters of copper metabolism, quality of life assessments and safety reporting (TEAE listing and discontinuation rate).
Results: The full analysis set (FAS) included data from 51 (98.1%) patients. The mean (SD) age was 42.3 (14.52) years and the patient population was predominately female (35 [67.3%]). The mean (SD) total trientine dihydrochloride dose during treatment was 1377.6 (368.78) mg per day. Fifty/51 patients (98.0%) treated with Trientine were responders, while only one patient (2.0%) showed a mild worsening of disease at Month 12.
The overall mean (SD) values for UWDRS-neurologic subscale assessment-was 11.3 (24.31) at Baseline, 9.7 (23.85) at Month 6 and 8.8 (22.86) at Month 12. The mean 24-hour basal urine copper excretion was similar at Month 6 and Month 12 (4.011 µmol/24 h versus 4.452 µmol/24 h, respectively) and the mean (SD) values for serum copper at Baseline was 4.505 (3.4036) µmol/L, 4.648 (2.9990) µmol/L at Month 6 and at 4.753 (3.6092) µmol/L at Month 12. The mean (SD) values for non ceruloplasmin bound copper at Month 6 was 1.1542 (0.92618) µmol/L and 0.9051 (0.88075) µmol/L at Month 12. Quality of life indicators (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) were stable and generally similar at Month 6 and Month 12.
During the study, 42 (80.8%) patients reported treatment-emergent adverse events (TEAEs) and 8 (15.4%) patients reported serious TEAEs. None of the serious TEAEs were considered treatment-related and no patients withdrew from treatment with trientine due to serious TEAEs.
Conclusion: Treatment with trientine was effective in maintaining stable hepatic and neurologic disease condition in patients with Wilson Disease. Trientine was generally safe and well tolerated.

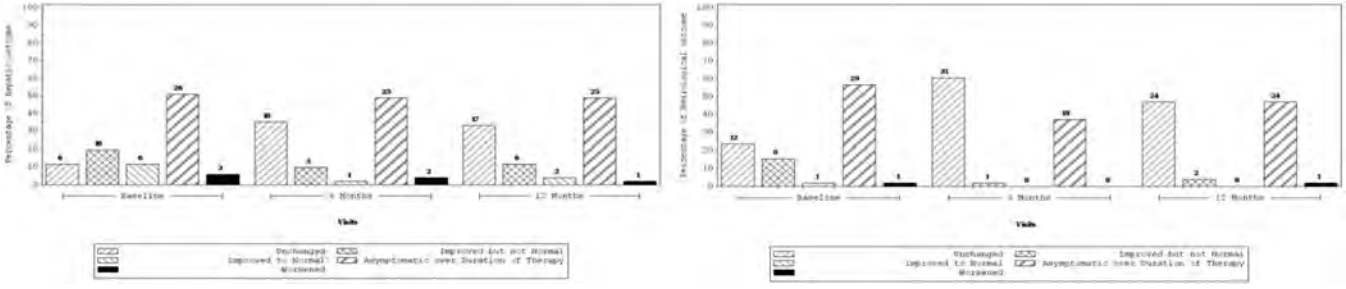

Figure 1a: Bar Chart Presenting Hepatic Outcome Over Time; Figure 1b: Bar Chart Presenting Neurological Outcome Over

Visit	Statistic	Trientine (N=51) Index Value (VAS based)	Index Value (TTO based)	Current Health Status
Baseline	n	51	51	51
	Mean (SD)	0.8143 (0.24785)	0.8566 (0.23788)	74.4314 (17.60343)
	Median	0.9029	0.8870	75.0000
	Min, Max	0.077, 1.000	0.175, 1.000	20.000, 100.000
Month 6	n	51	51	51
	Mean (SD)	0.8415 (0.23669)	0.8703 (0.20616)	76.4902 (16.80238)
	Median	1.0000	1.0000	80.0000
	Min, Max	0.077, 1.000	0.175, 1.000	25.000, 100.000
Change from Baseline to Month 6	n	51	51	51
	Mean (SD)	0.0272 (0.15465)	0.0217 (0.17932)	2.0588 (15.67981)
	Median	0.0000	0.0000	0.0000
	Min, Max	-0.339, 0.457	-0.526, 0.526	-35.000, 53.000
Month 12	n	51	51	50
	Mean (SD)	0.8350 (0.23330)	0.8601 (0.24054)	76.8000 (19.06333)
	Median	0.9029	0.8870	80.0000
	Min, Max	0.021, 1.000	-0.205, 1.000	20.000, 100.000
Change from Baseline to Month 12	n	51	51	50
	Mean (SD)	0.0207 (0.19623)	0.0085 (0.21154)	2.2800 (17.45085)
	Median	0.0000	0.0000	3.5000
	Min, Max	-0.619, 0.609	-0.639, 0.625	-35.000, 57.000

Note: Months are 6 and 12 post baseline (prospective part).
The Index values combine the five dimensions of the EQ-5D-3L to a single value using (1) a VAS based value set (2) a Time trade-off (TTO) based value set, both derived for the German population.
Current health status: Visual Analogue Scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state).

Figure 1c: Quality of Life (EQ-5D-3L) Index Values and VAS for Current Health

		6 Months			12 Months		
Dimension	Baseline	N [a]	1 n (%)	2 n (%)	3 n (%)	N [a]	1 n (%)	2 n (%)	3 n (%)
Mobility		51				51			
	1		41 (80.4)	5 (9.8)	0		40 (78.4)	6 (11.8)	0
	2		0	4 (7.8)	0		2 (3.9)	2 (3.9)	0
	3		0	0	1 (2.0)		0	0	1 (2.0)
Self-Care		51				51			
	1		48 (94.1)	0	0		45 (88.2)	3 (5.9)	0
	2		0	2 (3.9)	0		0	2 (3.9)	0
	3		0	0	1 (2.0)		0	0	1 (2.0)
Usual Activities		51				51			
	1		39 (76.5)	3 (5.9)	0		36 (70.6)	6 (11.8)	0
	2		0	6 (11.8)	1 (2.0)		3 (5.9)	3 (5.9)	1 (2.0)
	3		0	1 (2.0)	1 (2.0)		0	1 (2.0)	1 (2.0)
Pain/Discomfort		51				51			
	1		22 (43.1)	5 (9.8)	0		19 (37.3)	6 (11.8)	2 (3.9)
	2		7 (13.7)	12 (23.5)	1 (2.0)		5 (9.8)	15 (29.4)	0
	3		0	3 (5.9)	1 (2.0)		0	3 (5.9)	1 (2.0)
Anxiety/Depression		51				51			
	1		32 (62.7)	2 (3.9)	0		31 (60.8)	3 (5.9)	0
	2		5 (9.8)	9 (17.6)	1 (2.0)		9 (17.6)	5 (9.8)	1 (2.0)
	3		1 (2.0)	0	1 (2.0)		0	1 (2.0)	1 (2.0)

Note: Months are 6 and 12 post baseline (prospective part).
[a] Percentages are based on the number N of Patients with assessment of EQ-5D-3L at baseline and the respective visit.
Mobility: 1 = No problems in walking, 2 = Some problems in walking, 3 = Confined to bed.
Self-care: 1 = No problems with self-care, 2 = Some problems washing or dressing myself, 3 = Unable to wash or dress myself.
Usual activities: 1 = No problems with performing my usual activities, 2 = Some problems with performing my usual activities, 3 = Unable to perform my usual activities.
Pain/discomfort: 1 = No pain or discomfort, 2 = Moderate pain or discomfort, 3 = Extreme pain or discomfort.
Anxiety/depression: 1 = Not anxious or depressed, 2 = Moderately anxious or depressed, 3 = Extremely anxious or depressed.

Figure 1d: Shift Summary of Quality of Life (EQ-5D-3L)

FRI-446

Reduction of hepatic Z-alpha1 antitrypsin by RNA interference prevents and reverses liver disease including hepatic mitochondrial injury in the PiZ mouse model

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Background and aims: Autosomal co-dominant genetic disorder alpha-1 antitrypsin (AAT) deficiency causes pulmonary and liver disease. Individuals homozygous for the mutant Z allele accumulate polymers of Z-AAT protein in hepatocytes, where AAT is primarily produced, resulting in hepatocyte injury and fibrosis that may over time lead to cirrhosis and hepatocellular carcinoma. Injury to mitochondria, dilated endoplasmic reticulum (ER), microvesicular fat and other ultrastructural changes can be visualized by electron microscopy (EM). These livers also exhibit increased autophagic activity as a response to Z polymer accumulation. In this work, adult PiZ mice were treated with RNAi-based therapeutic ARC-AAT to reverse the AATD-associated liver disease phenotype.
Method: Efficacy of ARC-AAT, consisting of RNAi trigger plus an endosome-release agent, was evaluated in the PiZ mouse model that harbors the human Z-AAT gene and recapitulates AATD liver disease. Liver inflammation and Z-AAT polymer aggregates were assessed by histological evaluation. Soluble (monomeric) and insoluble (polymeric) Z-AAT in the liver were measured by semi-quantitative Western blotting. Expression of genes previously implicated in liver injury and development of fibrosis was measured by RT-qPCR. The intracellular state of hepatocytes, including dilated ER and mitochondrial injury, was assessed by EM.
Results: Male PiZ mice 11-17 weeks old at baseline had high levels of Z-AAT polymer aggregates in their hepatocytes. Mice treated biweekly with ARC-AAT for 32 weeks had sustained reduction of serum Z-AAT (> 90%) and similarly reduced soluble Z-AAT in the liver. They had 2.2-fold less Z-AAT polymer in liver lysate than saline controls and 1.6-fold less than baseline mice, indicating partial clearing. Reduction of disease phenotype was demonstrated by a 23-fold decrease in liver area of inflammatory foci and reduced expression of disease-related genes that contribute to inflammation and fibrosis. EM showed fewer autophagic vacuoles, normalization of ultrastructural cellular features and reduced mitochondrial injury in ARC-AAT treated mice compared to the saline control group.
Conclusion: Sustained RNAi treatment not only prevented accumulation of disease-causing Z-AAT polymer but also reduced pre-existing polymer, inflammation, expression of fibrosis-associated genes and damage to hepatic mitochondria. RNAi holds great promise for the treatment of patients with AATD-associated liver disease.

FRI-447

Clinical characteristics of liver cirrhosis and hepatocellular carcinoma occuring after Fontan operation

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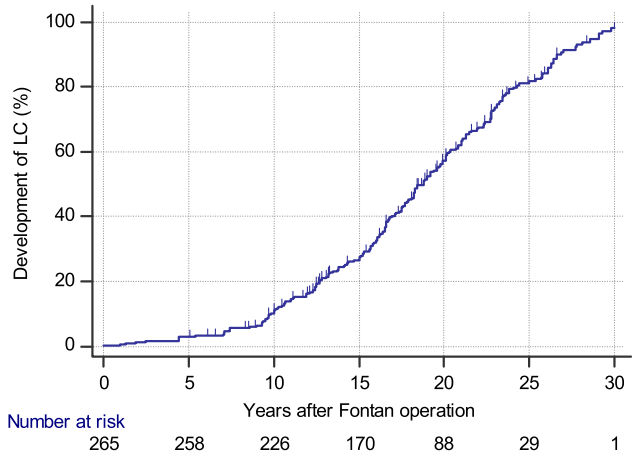
Background and aims: Hepatocellular carcinoma (HCC), which can be arising from cardiac cirrhosis, is one of the most serious late complications in patients after Fontan operation. In post-Fontan patients, benign arterial phase hyper-enhancing (APHE) nodules are frequently observed at multiphasic abdominal CT scan and are difficult to differentiate from HCCs. The aim of our study was to investigate the cumulative incidence of liver cirrhosis (LC), and to identify specific features which can distinguish HCC from benign APHE in patients after Fontan operation.
Method: We performed a retrospective cohort study of patients who had undergone Fontan operation and were followed at our hospital for more than 5 years, and who had undergone ultrasound or CT scan of the liver between January 2000 and December 2015. Cirrhosis was diagnosed using abdominal imaging tests such as ultrasound and CT. The clinical and radiographic features of HCC nodules were compared to those of APHE nodules who had undergone multiphasic abdominal CT scan.
Results: A total of 265 patients with a mean duration after Fontan operation of 19.3 ± 6.6 years were included in the study. The cumulative incidence of cirrhosis at 5, 10, 20, 30 years of duration after Fontan operation were 2.7% (7/265), 13.8% (28/254), 60.5% (135/223), 99.5% (203/204), respectively. The multiphasic abdominal CT

scan was performed in 82 patients and APHE nodules were observed in 42 patients. Of the 42 patients, 17 patients had APHE nodules more than 1 cm in size with washout on portal venous and/or delayed phase in cirrhotic liver. In these patients who met current non-invasive imaging diagnosis criteria for HCC, only 6 patients were diagnosed with HCC either by histology (n = 2) or clinical features (n = 4), and therefore, positive predictive value of current non-invasive imaging diagnosis criteria for HCC was only 35.3% (6/17). The presence of washout on portal venous phase ($p = 0.012$) and the serum AFP level ($p < 0.001$) were significantly associated with HCC nodules.



Conclusion: Cirrhosis is a frequently developed late complication in patients after Fontan operation, and its incidence has increased rapidly after 10 years from Fontan operation. Diagnosis of HCC in post-Fontan patients should not be made solely depending on the current imaging criteria, and presence of washout on portal venous phase and measurement of serum AFP might be helpful to differentiate HCC nodules from benign APHE nodules.

FRI-448

Correction of a metabolic liver disease after ex vivo gene editing of defective human primary hepatocytes

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Background and aims: Urea cycle disorders are inborn errors of ammonia detoxification. The most common urea cycle defect is ornithine transcarbamylase deficiency (OTCD). The only definitive treatment for the urea cycle defects is orthotopic liver transplantation. Partial and temporary corrections of OTC deficiency has been reported with hepatocyte transplantation. An attractive approach for treating inborn errors of metabolism is the genetic correction of patient's own cells and autologous transplantation. However, the efficiency and safety of *ex vivo* gene editing and correction of human primary hepatocytes have not yet been established.
Method: Human hepatocytes were isolated from normal patients, that is, those proficient in urea cycle activity and from an 8 month old patient who received a liver transplant for severe OTC deficiency. Human primary hepatocytes were genetically corrected, ex vivo, though CRISPR/Cas9 technology. Special mutant mice (FRGN) where the Fumarylacetoacetate hydrolase (*Fah*), *Rag2* and *Il2rg* genes are knocked out are profoundly immunodeficient and produce tyrosine metabolites that are toxic to mouse liver cells. When the protective drug, NTBC drug is removed, the animals progress to liver failure, and transplantation of human hepatocytes at that time, leads to the high-level repopulation of the liver with human hepatocytes.
Results: Molecular analysis revealed a one-point mutation in an intronic region of OTC which creates a new acceptor splice site and includes an intronic region in the OTC mRNA between exons 5 and 6 and a premature stop codon shortly after exon 5. OTCD primary hepatocytes were corrected *ex vivo* achieving editing efficiencies > 50%, after verification of DNA and mRNA and the metabolism of ^{15}N-ammonium chloride into urea was significantly enhanced in the gene-edited hepatocytes. Mice that were highly repopulated with uncorrected, mutant OTC human hepatocytes displayed elevated levels ammonia on a regular protein diet and a significant delay in the metabolism of an ammonia challenge.
Conclusion: In summary, mice created with mutant OTC human hepatocytes display characteristic symptoms of the human disease which can be corrected by *ex vivo* gene editing of human hepatocytes preocedures. This study provides evidence of the efficiency of correcting a liver metabolic disease *ex vivo*. Additional safety and specificity analysis are currently being investigated.

FRI-449

Complex ATP7B mutation patterns in Wilson disease and a evaluation of a yeast model for functional analysis of the individual variant

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Background and aims: Wilson disease (WD) is a rare autosomal recessive genetic disorder that is associated with various mutations in the *ATP7B* gene. Although *ATP7B* variants have been frequently identified, the exact mutation patterns remain unknown due to the absence of pedigree study, and the functional consequence of the individual *ATP7B* variant remain to be clarified.
Method: We recruited 65 clinically diagnosed WD patients from 60 unrelated families for the analysis of *ATP7B* variants and corresponding allele genotypes. The biological functions of the novel and representative *ATP7B* variants were evaluated by a yeast complementation assay.
Results: Pedigree analysis showed that besides *ATP7B* homozygous variants (8/65, 12.3%), compound heterozygous variants (43/65, 66.2%) were identified in the majority of the WD patients. More than 20% of the patients had one (13/65, 20.0%) or multiple (1/65, 1.5%) variants in only single allele, featured by a high ratio of splicing or frameshift variants. Six *ATP7B* variants were constructed into a pAG426GPD yeast expression vector to evaluate the functional consequence, and the results suggested different degrees of the disrupted function as severe, uncertain or mild, which were consistent with the corresponding phenotypes.
Conclusion: Our study revealed the complex *ATP7B* mutation patterns in WD patients and the applicability of the yeast model

system for the evaluation of functional consequence of *ATP7B* variants, which are essential for those WD cases difficult to interpret.

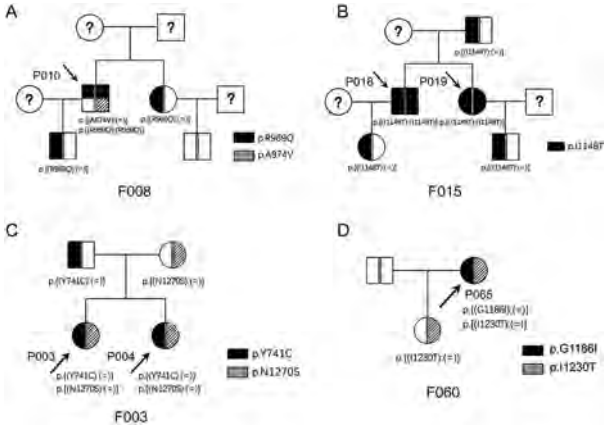

Figure 1: **Representative pedigree analysis of four families.** (A) Pedigree chart of family 8 (F008). The patient (P010) harboured homozygous mutation of p.R969Q, as well as heterozygous mutation of p.A874 V. (B) Pedigree chart of family 15 (F015). The patients (P018 and P019) harboured homozygous mutation of p.I1148 T. (C) Pedigree chart of family 3 (F003). The two patients (P003 and P004) both had compound heterozygous mutations of p.Y741C and p.N1270S in different alleles, which were inherited from their father and mother, respectively. (D) Pedigree chart of family 60 (F060). The patients (P065) had compound heterozygous mutations of p.G1186I and p.I1230 T in different alleles. The arrow indicates the propositus.

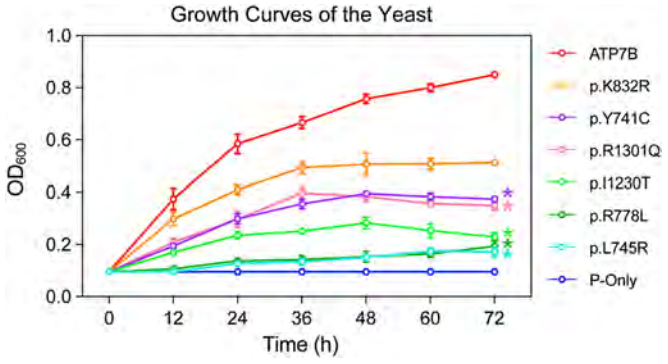

Figure 2. **Consequences of the predicted deleterious *ATP7B* variants on biological functions analysed by a yeast model**. The growth curve of the yeast. The growth of the strains transfected with $ATP7B^{Y741C}$, $ATP7B^{L745R}$, $ATP7B^{I1230T}$ and $ATP7B^{R1301Q}$ was significantly inhibited compared with that of those transfected with $ATP7B^{WT}$. *, p < 0.05, compared with the ATP7BWT and ATP7BK832R groups. Each line represents three biological replicates.

Liver tumours: Therapy

FRI-451

Transarterial chemoembolization versus best supportive care for patients with hepatocellular carcinoma with portal vein tumour thrombus

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Background and aims: Portal vein tumor thrombus (PVTT) can be divided into four types. This study aims to compare the efficacy and safety of treatment after transarterial chemoembolization (TACE) with best supportive care (BSC) in patients with hepatocellular carcinoma (HCC) with PVTT.
Method: This retrospective study was conducted on 1, 038 patients with HCC with PVTT who were treated either with TACE (n = 675) or BSC (n = 363). BSC did not include sorafenib. The two groups of patients were compared with or without propensity score matching to study the impact of possible bias in case selection. A subgroup analysis was subsequently performed by stratifying patients according to the stages of PVTT in the Cheng's PVTT classification.
Results: In PVTT types I-III, TACE was associated with significantly better overall survival (OS) than BSC ($p < 0.05$). No significant difference was observed in type IV PVTT ($p = 0.638$). Within each type of PVTT for patients who received TACE or BSC, OS was significantly worse in patients with type IV PVTT than in any of the other three types of PVTT (all $p < 0.05$). TACE was associated with better long-term OS than BSC after propensity score matching or on stratification by the PVTT types.

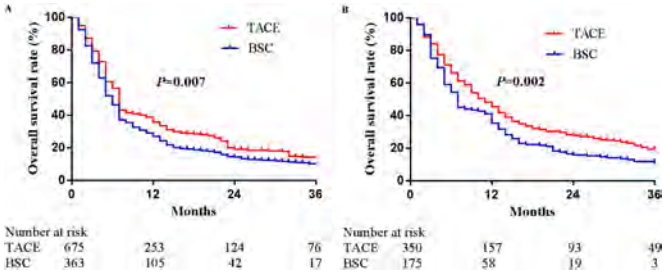

Figure 1: Overall survival rates for all the patients with HCC with any type of PVTT ('Total') or trios of propensity score-matched patients ('Matched') treated with TACE or best supportive care (matched in 2:1 ratio).

Conclusion: TACE was associated with better OS than BSC in HCC patients with PVTT types I-III but not type IV. Patients with type IV PVTT showed the worst prognosis, regardless of whether TACE or BSC was used.

FRI-452

Synergistic reduction of cancer proliferation and tumour growth in advanced murine hepatocellular carcinoma vis skewing and activation of innate and adoptive immunity

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Background and Aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the leading cause of death worldwide. HCC presents with a complex mutational landscape and thus treatment options remain limited. Drugable targets that induce a tumoricidal immune microenvironment may open novel therapeutic opportunities to control tumour progression and block metastatic spread. We assessed single and combined treatments of experimental syngeneic HCC with Zoledronic Acid (ZA, a bisphosphate) and Rapamycin (RA, an mTOR inhibitor), two drugs that display myeloid cell regulating potential.
Methods: Mdr2 (Abcb4)−/− mice and FVB wildtype were injected intraperitoneally with diethyl-nitrosamine DEN (10μg/g of bw) at the age of 5 days, followed by 0.05% phenobarbital in drinking water starting at the age of 3 weeks. Mice were treated with vehicle, (ZA

three times/week as ip injection, 100 µg/kg), RA (three times/week as oral gavage, 5 mg/body weight), or a combination of ZA and RA from age 5-6 months. After 6 months, tumour volume and number of nodules were counted. DEN injected Mdr2 (Abcb4)−/− and FVB mice served as additional controls. qPCR and IHC were performed, and FACS analysis was done using antibodies to CD11b, CD11c, Ly6C, Ly6G, CD86, CD4, CD8, CD25, CD3, CD90.2, CD206, F4/80, MHC-II, NK1.1, Foxp3 and CD19.

Results: Treatment with RA > ZA significantly reduced tumour growth in both Mdr2 (Abcb4)−/− and wildtype FVB DEN injected mice vs untreated controls. Moreover, the combination of ZA and RA synergistically reduced the volume and number of HCC foci highly significantly by 90 and 85%, respectively ($p < 0.0001$) compared to the single treatment and the untreated groups. FACS analysis revealed that the combination significantly reduced the population of tumor associated macrophages (TAM) and of myeloid derived suppresser cells, representing central tumour promoting myeloid cell populations. In contrast, myeloid derived dendritic cells that promote anti-cancer immunity were significantly upregulated. In parallel, total CD4 + T cells and especially CD4+CD25 regulatory T cells were significantly suppressed, while CD8+ cytotoxic T cells were significantly upregulated in the combination treatment vs the single treatment and especially the untreated groups. This was accompanied by reduced transcript levels of extracellular matrix remodeling (MMP2, MMP9, MPP12) and angiogenesis related genes (Cox2, HIF1α, VEGF CCL17). IHC staining revealed that Ki-67+ HCC cells were nearly undetectable, and IHC for CD68 and YM-1and CD31 confirmed a dramatic shift from tumour associated M2 to M1 tumoricidal macrophages and reduced angiogenesis in the combination treatment group.

Conclusions 1. Combination therapy of RA and ZA synergistically repolarized the immunosuppressive myeloid cells towards M1, and promoted CD8+ T cells, resulting in a robust anti-HCC response.

FRI-453

Rapamycin promotes tumoricidal immunity in murine HCC by inducing M1-type macrophages and dentritic cells polarization and enhancement of cytotoxic T-cells

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Background and Aims: Primary hepatocellular carcinoma (HCC) arises mostly in the background of hepatic injury and chronic inflammation. Chronic inflammation in HCC is associated with the infiltration of bone marrow derived cells, mainly tumour associated macrophages (TAM, M2) and myeloid-cell derived suppressor cells (MDSC). These cell types markedly suppress anti-HCC immune responses and are present in all stages of HCC. Rapamycin (RAPA) deregulates mTOR signalling in cancer cells and modulates the tumor microenvironment, thereby possibly promoting anti-tumour immunity. We hypothesized that RA may repolarize tumour promoting TAM and MDSC towards M1 macrophages, and augment dendritic cell (DC) tumor antigen presentation finally enhancing the priming of tumour specific cytotoxic T lymphocytes (CTL) with anti-tumour activity.

Methods Mouse bone marrow derived in vitro M1 or M2 polarized macrophages, and mature and immature DC were exposed to increasing concentrations of RAPA. Transcript and protein levels of M1/M2 markers (VEGF, Arg1, TGFβ1, IL-10, IL-12p70) and DC activation markers (CD86, CD40, MHC-II) were determined by qPCR and ELISA. Mice bearing a syngenic HCC (DEN/Mdr2KOand DEN/FVB wild type mice) received 3 doses of 5 mg RA/kg BW or vehicle (control) orally per week for a period of one month from age month 5-6. After treatment, mice were sacrificed to measure hepatic tumor number and volume and livers were assessed by HandE histology, IHC, qPCR and FACS. Cytokine level of IL-10 and IL-12p70 were quantified through ELISA in all sera samples.

Results: RA dose-dependently decreased M2 and immature DC markers (Arg1, TGFβ1, VEGF, IL-10) and increased M1 macrophage and mature DC transcripts (CD86, IL-12p35, MHC-II, CD40). This was paralleled by a significant upregulation of IL-12p70 and down-regulation of IL-10 protein secretion into the cell supernatant. In DEN/Mdr2KO mice RAPA reduced tumor cell proliferation as evaluated via Ki-67+ staining, and tumor number and volume by 70% and 68%, respectively vs the control group. Transcript and protein level also showed remarkable switching of macrophages from M2 to M1. Staining of YM-1+ and glypican+ M2 and CD68+ total macrophages in livers of RA treated HCC showed a significant upregulation of M1 > M2-type macrophages.CD3/CD8 ratio was also high in rapamycin treated group as compared to control group as depicted by immunohistochemistry. FACS analysis revealed a significant increase of mature DC (CD45+CD11c+MHC-II+CD86+) and CTL (CD45+CD3 +CD8+) in the RAPA treated mice vs vehicle.

Conclusions: RAPA 1. enhances the maturation of DC, improving tumor antigen presentation for CTL activation; 2. exhibits potent macrophage repolarizing activity (M2 to M1-type) in vitro and in vivo, thereby increasing anti-HCC immune responses and limiting angiogenesis.

FRI-454

Reappraisal of portal vein tumor thrombosis as a prognostic factor for patients with hepatocellular carcinoma

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Background and aims: The presence of portal vein tumor thrombosis (PVTT) is a poor prognostic factor for patients with hepatocellular carcinomas (HCC). HCC patients with PVTT are considered advanced stage regardless of the tumor factor and only sorafenib is recommended for those patients by current guidelines. This study was aimed to assess whether HCC patients with PVTT could have better prognosis with proper treatment in selective conditions.

Method: This single-center retrospective study involved 1, 171 patients diagnosed HCC from January 2005 to December 2006, before sorafenib era. Overall survival (OS) was estimated by the Kaplan-Meier method and Cox proportional hazards model. To control the different distributions of the covariates, inverse probability weighting using propensity score was conducted.

Results: The prognosis was dismal regardless of PVTT in patients with diffuse infiltrative type HCC, however, in nodular HCC, there was significant difference in the OS according to the presence of PVTT ($p < 0.001$). The level of PVTT, not only the presence of PVTT, was a major independent factor of the OS. Although there was no significant difference in OS between patients with PVTT at segmental branch and left or right portal vein (LPV/RPV) (log-rank P = 0.122), segmental PVTT was associated with significantly longer OS than PVTT at main trunk (log-rank P = 0.002). The level of PVTT was consistently associated with the OS in nodular HCC patients treated by TACE. In multivariate analysis, patients without PVTT showed significantly longer OS than those with main trunk PVTT ($p = 0.002$), while there were no significant differences between no PVTT and segmental ($p = 0.074$) or LPV/RPV ($p = 0.069$) PVTT. When we compared the OS of the patients without PVTT to those with PVTT below main trunk, there was no significant difference in OS according to the presence of PVTT ($p = 0.159$).

Conclusion: Active treatment such as TACE could be considered in selected patients even with PVTT. The level of PVTT as well as the type of HCC matters.

FRI-455

Effect of huaier granule on recurrence after curative resection of HCC: A multicenter, randomized clinical trial

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Background and aims: There is little evidence that adjuvant therapy after radical surgical resection of hepatocellular carcinoma (HCC) improves recurrence-free survival (RFS) or overall survival (OS). We conducted a multicenter, randomized, controlled, phase IV trial evaluating the benefit of an aqueous extract of trametes robinophila murr (Huaier granule) to address this unmet need.
Method: A total of 1, 044 patients were randomized in 2:1 ratio to receive either Huaier or no further treatment (controls) for a maximum of 96 weeks. The primary end point was RFS. Secondary end points included OS and tumor extrahepatic recurrence rate (ERR).

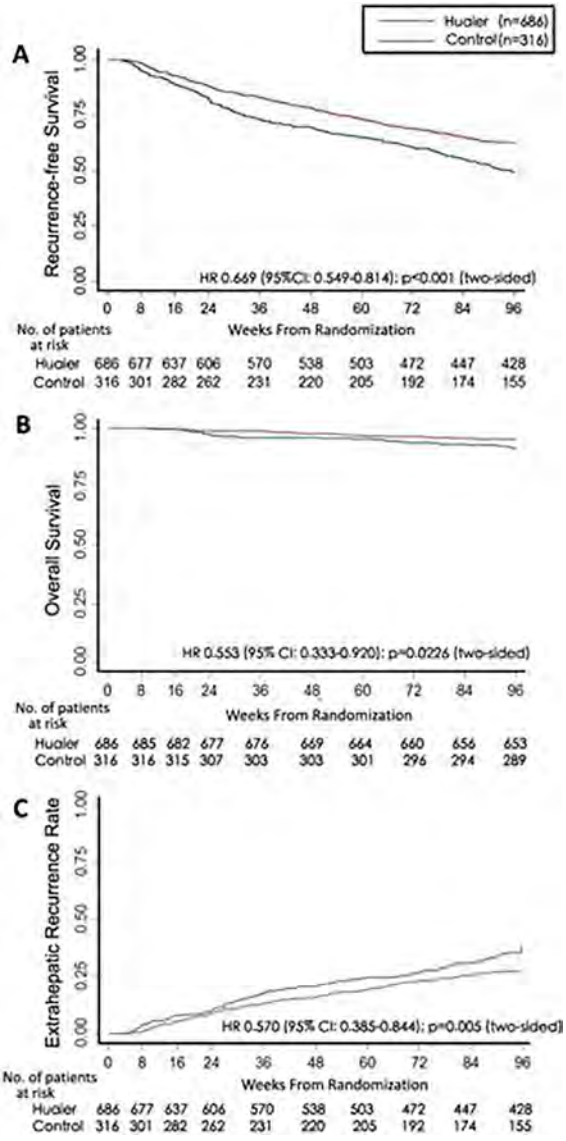

Figure: Kaplan-Meier analysis showing A, RFS, B, OS and C, ERR between Huaier and control groups

Results: The Huaier (n = 686) and control groups (n = 316) had a mean RFS of 75.5 weeks and 68.5 weeks, respectively (HR, 0.67; 95%CI, 0.55-0.81). The difference in the RFS rate between Huaier and control groups was 62.39% and 49.05% (95%CI, 6.74-19.94; p = 0.0001), this led to an OS in the Huaier and control groups of 95.19% and 91.46% respectively (95%CI, 0.26-7.21; p = 0.0207). The tumor extrahepatic recurrence rate between Huaier and control groups was 8.60% and 13.61% (95%CI, −12.59–2.50; p = 0.0018), respectively.
Conclusion: This is the first nationwide multicenter study, involving 39 centers and 1, 044 patients, to prove the effectiveness of Huaier granule as adjuvant therapy for HCC after curative liver resection. It demonstrated a significant prolongation of recurrence free survival and reduced extrahepatic recurrence in Huaier group.

FRI-456

MELD score is the only predictor for 30-day mortality in patients with ruptured hepatocellular carcinoma treated by emergent transarterial embolization

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Background and aims: Spontaneous hepatocellular carcinoma (HCC) rupture with intraperitoneal hemorrhage is a life-threatening complication. Trans-arterial embolization (TAE) or trans-arterial chemo-embolization (TACE) is effective for achieving initial hemostasis in acute stage. This study aims to investigate the predictors for 30-days mortality in patients with HCC rupture and treated with TAE/TACE.
Method: Patients with ruptured HCC with emergent TAE/TACE treatment during February 2005 and December 2015 in Chang Gung Memorial Hospital, Linkou branch were recruited. The pre-TAE/TACE features including age, gender, etiology, liver biochemistry, prothrombin time, Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, the presence of systemic inflammatory response syndrome (SIRS) and Barcelona-Clinic Liver Cancer (BCLC) tumor staging and liver function after TAE/TACE were collected. Mann-Whitney U test and independent student t test were applied for non-normal and normal distribution variables respectively while Chi-square test for categorical variables comparison.
Results: A total of 95 patients with 102 events were enrolled. Most of the patients (90.2%) were treated with TAE. 42.2% of these patients were Child-Pugh class A, 45.1% were class B and 12.7% were class C. The median MELD scores was 12.5 (range, 6-26) and median Na-MELD scores was 14 (range, 6-30). The successful rate of dynamic stabilization was 92.16%. The overall median survival time was 253.5 days. The 30-days mortality is 18.6%. Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease Score (MELD score), advanced Barcelona-Clinic Liver Cancer (BCLC) Stage, vessel thrombosis, metastasis, treatment naïve, systemic inflammatory response syndrome (SIRS), higher total bilirubin level after TAE were poor prognostic factors associated with 30-days mortality. By multivariate logistic regression analysis, MELD score (OR: 1.44 (1.12-1.84, P = 0.004) is the only independent predictor for 30-days mortality. The cut-off point of MELD score 13 is a good predictor of 30-day mortality (AUROC: 0.882; sensitivity: 100%; specificity: 62%; positive predictive value: 39%; negative predictive value: 100%).
Conclusion: Transaretrial embolization is effective in hemostasis in patients with HCC rupture. The cut-off value of 13 in MELD score might predict the 30 days mortality in patients with ruptured hepatocellular carcinoma treated by transarterial embolization.

FRI-457

Comparative long-term outcomes of laparoscopic liver resection and radio frequency ablation for hepatocellular carcinoma: Location of tumor matters

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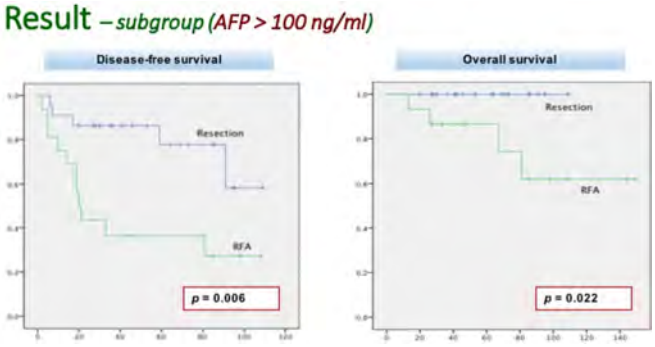
Background and aims: Laparoscopic liver resection (LLR) has been considered as standard surgery for small hepatocellular carcinoma (HCC) located in the anterolateral segments of the liver. However, there have been few reports comparing LLR and radiofrequency ablation (RFA) for HCC.
Method: We retrospectively compared short- and long-term outcomes of 105 patients with LLR and 272 patients with RFA for newly diagnosed single, < 4 cm size of HCC located on the anterolateral segments of the liver. We performed 1:1 propensity score matching (PSM) between two groups and matched 61 patients for both groups.
Results: After PSM, all variables including demographic, tumor factors and liver function were similar between two groups. There was no mortality in the two groups. The hospital stay was shorter in RFA group than LLR group (5.1 vs. 8.9 days; $P = 0.001$), however, there was no significant difference in complication rate between two groups (4.9 vs. 13.1%; $P = 0.114$). The 5-year overall survival rates were similar between two groups (83.6 vs. 84.5%; $P = 0.913$), but the 5-year disease-free survival rate was higher in LLR group (56.4%) than RFA group (41.8%; $P = 0.009$). In patients with alpha-fetoprotein > 100 ng/ml, LLR group showed better 5-year overall (100 vs. 80.0%; $P = 0.022$) and disease-free survival rates (76.6 vs. 45.5%; $P = 0.006$) than those in RFA group.



Conclusion: For single small HCC located in the anterolateral segments of the liver, LLR group showed similar complications and overall survival rate, but better disease-free survival rate compared to RFA group. LLR is recommended in patients with higher alpha-fetoprotein level.

FRI-458

Response evaluation using modified RECIST criteria predict outcomes better than RECIST 1.1 criteria in patients with HCC treated with Yttrium-90 radioembolization

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Background and aims: The response evaluation criteria in solid tumours (RECIST 1.1) have been commonly used for response evaluation of solid tumours including hepatocellular carcinoma (HCC). Because of the importance of the remaining 'viable cancer tissue' of HCC, the modified RECIST (mRECIST) have been adopted for HCC response evaluation. However, few studies have investigated which response evaluation method is better for predicting the treatment outcomes of HCC. Thus, we compared the performance of the RECIST 1.1 and mRECIST for predicting survival rates in patients with HCC treated with transarterial radioemoblisation (TARE) using Yttrium-90.
Method: Between 2012 and 2017, 102 patients with unresectable intrahepatic HCC treated with TARE were reviewed retrospectively. The RECIST 1.1 and mRECIST were used to evaluate the treatment responsiveness of HCC to TARE at 1, 3 and 6 months after TARE. A responder was defined as the sum of either a complete or partial response by each method and non-responder was defined as the sum of either a stable or progress response.
Results: The median age of the study patients (92 males and 19 females) was 64.1 years. The median alpha-fetoprotein and des-gamma-carboxyprothrombin levels were 42.0 ng/ml and 1693.5 mAU/ml, respectively. The median maximal tumor size was 8.3 cm, and multiple tumours were observed in 41 (36.3%) patients. During the follow-up period (median 20.7 months), 21 patients (20.6%) died, with a median survival of 32.5 months. Using the mRECIST, the treatment responders at 1, 3 and 6 months following TARE showed significantly better survival rates compared with the non-responders (hazard ratio [HR] = 5.736, log-rank P = 0.008 at 1 month; HR = 3.145, P = 0.022 at 3 months, and HR = 2.887, P = 0.061 at 6 months). In contrast, using the RECIST, the treatment responders at 1, 3 and 6 months In contrast, using the RECIST, the treatment responders at 1, 3, and 6 months showed no difference in survival from the non-responders. (all P > 0.05, log-rank test). According to multivariate analysis, non-responsiveness using mRECIST (HR = 0.217, P = 0.043 at 1 month; HR = 2.874, P = 0.05 at 3 months), as well as the serum albumin level, main portal vein thrombosis, and hepatic vein invasion, were independent predictors of mortality (all P < 0.05).
Conclusion: Risk stratification should be assessed by response evaluation using mRECIST in patients with HCC treated with TARE. Further validation in a large cohort is required.

FRI-459

Prognostic performance of ten non-invasive liver function tests in patients with hepatocellular carcinoma submitted to transarterial chemoembolization

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Background and aims: Various non-invasive liver function tests have been proposed to assess hepatic reserve (Child-Turcotte-Pugh (CTP); albumin-bilirubin [ALBI] grade, platelet-albumin-bilirubin [PALBI] grade, model for end-stage liver disease (MELD), fibrosis index based on 4 factors (FIB-4), aspartate aminotransferase-to-platelet ratio [APRI], Lok index, cirrhosis discriminant index (CDS), King's score, and Göteborg University Cihhosis Index [GUCI]) in chronic liver disease. However, their performance to predict the prognosis of patients with hepatocellular carcinoma (HCC) is unknown. We aimed to elucidate the prognostic role of ten currently used hepatic function models in patients with intermediate stage HCC undergoing transarterial chemoembolization (TACE).
Method: Between 2007 and 2018, TACE procedures in a tertiary center were prospectively identified and retrospectively analyzed.

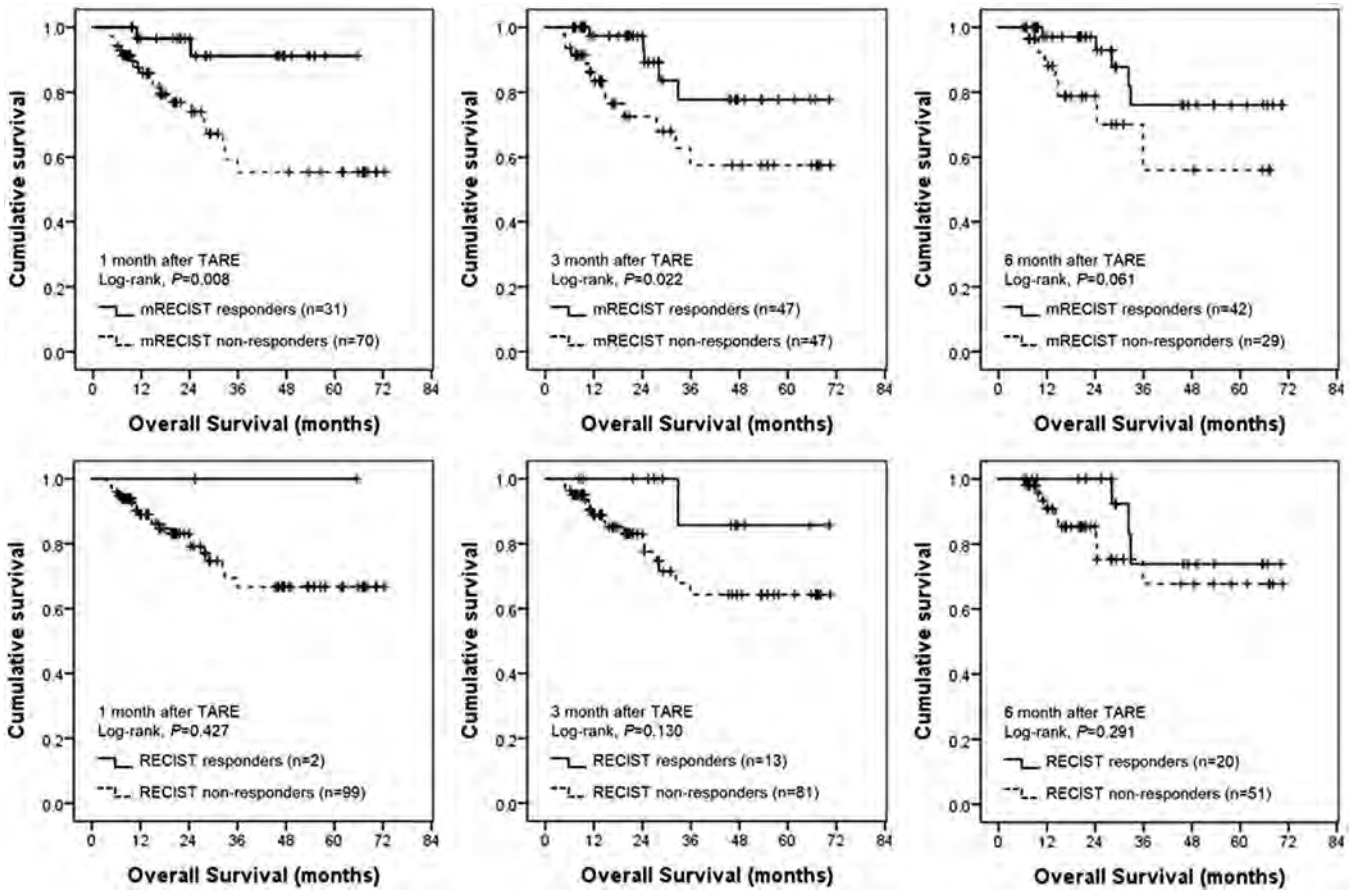


Figure: (abstract: FRI-458): Kaplan-Meier analyses for overall survival of the patients with HCC treated with TARE

For each TACE, baseline patient characteristics, tumor status and non-invasive hepatic function models at the time of procedure were collected. Each model was categorized into three classes (stage 1/2/3). Cox proportional hazards model was used to identify independent survival predictors.

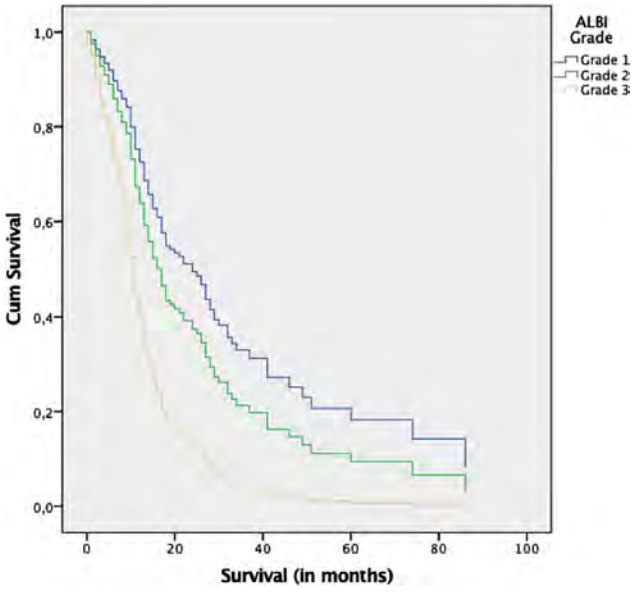
Results: A total of 206 TACE were performed in patients with a mean age of 68.9 ± 10.8 years, 77.2% were male. The main causes of liver disease were alcohol (39.8%) and HCV infection (32.5%). There was a single nodule in 59.2% of the cases, with a mean diameter of 41.6 ± 26.0 mm. TACE was performed with drug-eluting beads (DEB) in 87.9% of cases, with a mean doxorubicin dose of 41.4 ± 33.2 mg.

Median survival after TACE was 13 (IQR 7-24) months. One year after TACE, mortality was 35.9%. The value of albumin (OR 0.90, CI95% 0.87-0.93, p < 0.01) and sodium (OR 0.86, CI95% 0.77-0.95, p < 0.01) was related to 1-year mortality.

In the survival analysis of the ten calculated scores, we found significant differences for ALBI grade (median survival, stage 1/2/3-13/13/6 months; p = 0.01) and for CTP (median survival, stage A/B-13/8, p < 0.01).

In covariate adjusted multivariate Cox regression model, we found that ALBI grade 3 (HR 2.88; CI95% 1.32-6.25, p = 0.01, compared to ALBI 1-Figure) and the diameter of HCC treated nodule (HR 1.01, CI95% 1.01-1.02; p < 0.01) were significantly associated with survival.

Conclusion: Among ten non-invasive tests of hepatocellular function, only ALBI score independently predicted survival for HCC patients submitted to TACE.



FRI-460

What are the predictive factors for long-term survivors with advanced hepatocellular carcinoma treated with sorafenib?

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Background and aims: Sorafenib is the standard therapy for advanced-stage hepatocellular carcinoma (HCC) and progressive disease after locoregional therapy. Most of these patients have an overall survival (OS) of about 10 months. However, some patients seem to have a better response to sorafenib and consequently a significantly prolonged survival time. Few data are available about this specific group. Our aim was to assess characteristics and predictive factors of long-term survivors (OS > 24 months).
Method: We retrospectively reviewed 77 consecutive patients who started treatment with sorafenib for advanced-stage HCC (Barcelona Clinic Liver Cancer-C) or progressive HCC after locoregional therapy between Oct/2007 and Oct/2016.
Results: At time of initial sorafenib prescription, median age was 63.9 ± 10.4 years, mainly males (90.9%). All patients had cirrhosis and the most prevalent etiology was HCV infection in 41.6%, followed by alcohol-related disease (40.3%) and HBV infection (16.9%). The majority was Child-Pugh A (66.2%), had multinodular disease (74%) and had alpha-fetoprotein (AFP) level < 400 ng/ml (63.6%). Portal vein thrombosis (PVT) was present in 50.6%. BCLC distribution: 96.1% in stage-C and 3.9% in D. Time between HCC diagnosis and start of sorafenib was 7.9 ± 9.8 months. In most cases, sorafenib was the first-line treatment (62.3%). For those with previous treatment, transarterial chemoembolization was the most performed technique (58.6%).
Mean OS was 32.6 months (95% CI: 23.4-41.8) with 2-year survival rate of 38.9%. Fifty-four patients died (70.1%). Twenty-five patients had a survival time superior to 24 months (32.5%) after initiating sorafenib. In this subgroup, mean age was 60 ± 7.7 years. Most patients were male (80%) and had a HCV infection-related disease (52%). Ninety-two percent were Child-Pugh A (mean value: 5.6 ± 0.8 points), AFP level was < 400 ng/ml in 84% and mean MELD-Na^+ score was 10.1 ± 2.7 points. The majority presented with multinodular disease (64%) with absence of PVT (80%).
In multivariate analysis, predictive factors significantly related to long-term survival were: absence of portal vein thrombosis (p = 0.004, OR 0.123, 95% CI: 0.031-0.491) and MELD-Na^+ score (p = 0.037, OR 0.870, 95% CI: 0.764-0.992).
Conclusion: Although mean OS in this group of patients is low, it is of note that a sub-group can really benefit from this treatment and it is worth identifying those long-term survivors, in our study those without PVT and a lower MELD-Na^+.

FRI-461

Thermal ablation is a safe and effective treatment for intrahepatic cholangiocarcinoma in patients with cirrhosis

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Background and aims: Incidence of intrahepatic colangiocarcinoma (ICC) is increasing worldwide and liver cirrhosis is a well-established risk factor for its development. Surgery is the mainstay treatment, but its applicability is limited in cirrhotic patients. Thermal ablation, including radiofrequency ablation and microwave, is suggested as an alternative treatment, but there are scarce data regarding its efficacy and safety in this population. We aimed to assess the effectiveness, safety and overall survival of thermal ablation as first-line treatment of ICC in patients with cirrhosis.
Method: This is a retrospective analysis of all biopsy-confirmed ICC in cirrhotic patients treated in our unit from 2001 to 2017. Baseline characteristics, ablation procedures and complications were recorded. Time to recurrence (TTR) and overall survival (OS) were calculated using Kaplan Meier method.
Results: Twenty-seven patients were treated in this time period in our unit. 51.7% of patients were men with a median age of 63.7 years. The most frequent cause for cirrhosis was hepatitis C Virus (63%), 70.4% were Child-Pugh A and the majority had clinically significant portal hypertension. None of them had cancer-related symptoms (ECOG-PS 0) and tumor markers (CEA, AFP and CA 19.9) were not elevated. Median tumor size was 21 mm [IQR 20-28 mm], 21 cases were uninodular (stage Ia AJCC 8th edition) and 6 were at stage II. Finally, among those patients with single ICC, 10 of them had a single ≤ 2 cm ICC.
Complete response was achieved in 25 cases (92.6%). Median OS of the whole cohort was 30.6 months (CI 95%; 22.6-46.5), and recurrence was detected in 21 cases (77.8%) with a TTR of 10.1 months (CI 95%; 7.7-20.9 months). In those patients with single ≤ 2 cm ICC, the OS was 94.5 months (CI 95%; 11.7-not reached) and this OS is statistically superior to those patients with single ICC larger than 2 cm (24.3 months (CI 95%; 10.4-44.25 months), p = 0.04) and to those with multinodular disease (26.5 months (CI 95%; 20.23-41.4); p = 0.02). Regarding safety in the whole cohort, only two patients presented a treatment related complication.
Conclusion: Thermal ablation is a safe and effective alternative to surgery for ICC in patients with cirrhosis. The global OS is similar to the reported in surgical series, but the initial treatment success is hampered by a high rate tumor recurrence. Long-term survival after thermal ablation is achieved in patients with single ≤ 2 cm ICC and is statistically superior compared to single ICC > 2 cm or intrahepatic multinodular ICC.

FRI-462

A multicenter international study of sorafenib treatment in patients with hepatocellular carcinoma and chronic kidney disease undergoing hemodialysis

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Background and aims: As patients with hepatocellular carcinoma (HCC) under dialysis are excluded from clinical trials, there are no data about safety and efficacy of sorafenib in this specific population, which has no formal contraindication for this treatment. The aim of this study is to evaluate the rate, prevalence, tolerability and effectiveness of HCC patients undergoing dialysis and being simultaneously treated with sorafenib (dialysis-sor) in clinical practice.
Method: Retrospective, international, multicenter study, including centers from Latin-America and Europe to evaluate the aim of the study. For dialysis-sor patients, baseline characteristics as well as dose modifications, adverse events, treatment duration, and overall survival were recorded.
Results: Of 6156 HCC patients treated with sorafenib between June/2006 and March/2018 in 44 centers, 22 were dialysis-sor patients. Median age of the 22 dyalisis-sor was 65.5 years, 83.4% were male, 40.9% had hepatitis C, 75% had Child-Pugh A, 85% were BCLC C, and 54.6% had ECOG-PS 1. 17/22 patients presented history of arterial hypertension (AHT), 14/22 had diabetes mellitus (DM) and 3/22 had heart disease. 12/22 patients presented with both AHT and DM, which also were the leading causes for chronic kidney disease. 15/22 patients started sorafenib at full dose, while 7/22 at half dose. 17/22 of patients required at least one dose modification. Median time to first dose modification was 2.4 months (IQR 0.8-3.8). 5 patients never required any dose modification. Maximum and medium number of dose modifications were 4 and 2, respectively. The most frequent causes of first dose modification were asthenia 3/22, worsening of ECOG-PS 3/22 and diarrhea 3/22.
Median treatment duration was 10.8 months (IQR 4.5-16.9) and median overall survival was 17.5 months (CI 95%; 7.2-24.5). 18/22 patients permanently discontinued sorafenib and the remaining are still on treatment. The causes of sorafenib discontinuation were tumor progression 14/18, sorafenib-related 2/18 (diarrhea and peripheral arterial thrombosis) and non-sorafenib related AE 2/18 (liver decompensation and pulmonary edema).
Conclusion: This is the largest cohort describing patients with HCC under hemodialysis who received sorafenib treatment. Our data show that median time to the first dose modification, treatment duration, and overall survival were comparable to the results of the non-dialysis population, obtained from large clinical trials and real-world cohorts. However, in these patients, asthenia appears to be the main treatment related adverse event.

FRI-463

Long-term outcomes of irreversible electroporation for hepatocellular carcinoma

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Background and aims: Irreversible electroporation (IRE) is a relatively novel non-thermal ablation technique which has been shown to be both safe and efficacious for soft tissue tumours including hepatocellular carcinoma (HCC), not amenable to standard thermal ablative therapy. Our group has previously reported on our initial experiences with IRE in HCC patients, and the aim of this study was to report longer-term outcome data with this treatment modality.
Method: We identified all patients at our hospital who underwent IRE for HCC between 2008 and 2017 and analysed their clinical and demographic data until December 31, 2017. All patients had undergone multi-disciplinary team review with IRE determined as the most suitable treatment based on tumour size and location near solid organ or vascular structures. Our primary outcomes were complete ablation rates and local recurrence-free survival (RFS) based on follow-up imaging in patients who had a complete response.
Results: Overall, 22 patients (77% males, mean age 66.6 years) received IRE therapy to 30 HCC lesions with a mean size of 2.4 ± 1.0 cm during the study period. Twenty (66.7%) lesions were adjacent to important structures or organs. Twenty-five (83.3%) lesions were successfully ablated after one (n = 23) or two (n = 2) procedures. Lesion size of ≤ 2 cm was a significant predictor of successful ablation (p = 0.014). The mean follow-up time was 22.2 months from the first computed tomography scan confirming complete response using mRECIST. The mean local RFS was 64.9 months (95% CI 43.9-85.8) with a 12-month local RFS of 89%. No serious procedure related complications were observed.

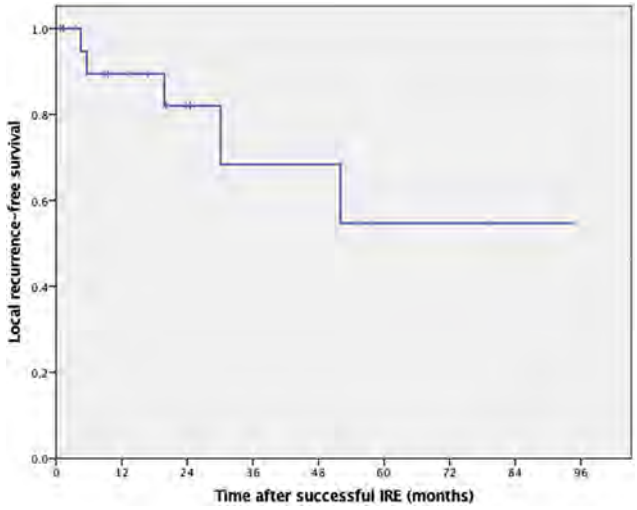

Figure: Kaplan-Meier estimated local RFS curve of 25 HCC lesions with successful IRE

Conclusion: IRE appears to be a safe and efficacious local ablative method for HCC, with high rates of complete response and good long-term local RFS. Further studies comparing this technique to microwave ablation and radiofrequency ablation are warranted.

FRI-464

Percutaneous microwave is better than radiofrequency ablation to obtain complete response in cirrhotic patients with very early and early hepatocellular carcinoma

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Background and aims: Percutaneous thermal ablations are widely employed treatments for hepatocellular carcinoma (HCC). It has been proved that complete necrosis in early HCC and cirrhosis is related to a better survival. We compared the efficacy of RFA and MW to obtain complete response (CR) in patients with HCC.
Method: This retrospective observational study was carried out on a cohort of 227 adult cirrhotic patients with a first diagnosis of early HCC (single node ≤ 50 mm or ≤ 3 nodules ≤ 35 mm), consecutively treated with RFA or MW between January 2013 and July 2018 at our Gastro-hepatology Unit. Diagnosis and treatment allocation followed EASL guidelines. The choice of RFA or MW was reliant on operators and local availability. Other treatments and combined therapies were excluded. Complete response (CR) was evaluated with multiphasic contrast-enhanced computed tomography (CT) or Magnetic Resonance Imaging (MRI) at 5-7 weeks after treatment and in the follow-up, relying on mRECIST criteria.
Results: 227 subjects (M/F 163/64, viral/non viral etiology 181/46, median age 63 years [IQR 56-73]) were included. A total of 295 nodules treated with RFA (212, 72%) or MW (83, 28%) was evaluated. However, a homogeneous subgroup of 184 patients with 220 comparable nodules in terms of diameter (15-35 mm) was considered. The two groups were also homogeneous for age, BMI, Child Pugh score, smoke and alcohol habits, complex position, ultrasound visibility and number of nodules per each patient. Overall, a complete response was achieved in 54/58 (93%) HCC after MW and in 126/158 (80%) HCC after RFA (OR 3.43; IC95% 1.14-10.3, p = 0.028). In 15-20 mm nodules, the two procedures were not significantly different (OR 3.41; IC95% 0.40-29.2, p = 0.264), however in 21-35 mm nodules MW was significantly superior in obtaining CR compared to RFA (OR 3.70; IC95% 1.00-13.7, p = 0.05). The rate of CR was inversely proportional to the number of nodules, but without statistical significance. Multivariate Cox-proportional hazard regression showed that MW was an independent predictor of CR in HCC nodules (OR 3.92, IC95% 1.26-12.2, p = 0.018).
Conclusion: In this study MW appeared to be superior to RFA to induce complete response in patients with very early and early HCC with major evidence in bigger nodules (21-35 mm). Further studies are ongoing to confirm these findings and to evaluate the effect on survival.

FRI-465

The INCRNA H19 is an oncogenic driver of HCC in chronic inflammation-mediated mouse model

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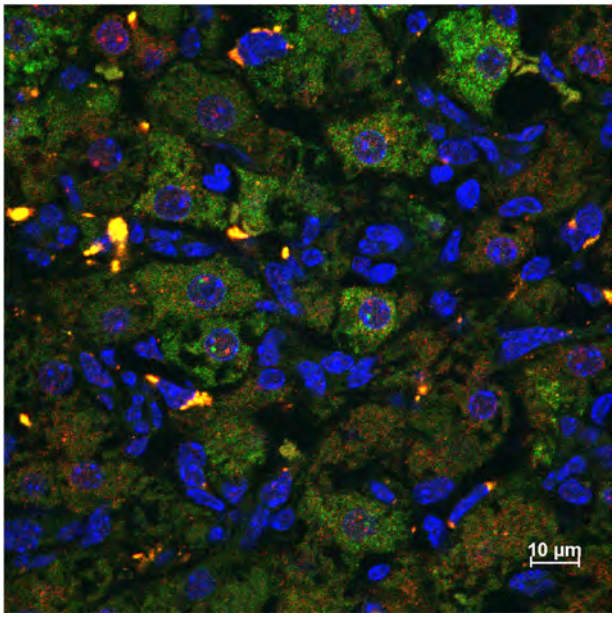
Background and aims. H19 is paternally imprinted and maternally expressed long non-coding RNA (lncRNA). H19 is an oncofetal RNA that is widely expressed in the embryo, is repressed at birth in most tissues, and is re-expressed in many cancer types, including HCC. The role of H19 in tumor initiation and progression has long been a

subject of controversy. The object of our study was to examine the role of H19 in chronic inflammation-mediated hepatocarcinogenesis using double knock out (dKO) Mdr2-KO/H19-KO mouse model and to elucidate the associated molecular mechanisms. The Mdr2 knock out (Mdr2-KO) mouse is a well-established model of chronic cholangitis and hepatitis, which results in HCC development. Previously, we have detected H19 is expressed in the liver of adult Mdr2-KO females.

Methods. We have transferred the H19 delta3 mutation (a 3-kb deletion of the H19 encoding region) from the 129Sv to C57BL/6 (B6) strain and generated the B6 Mdr2-KO/H19-KO (dKO) mice. Following spontaneous tumor development at the age of 16 months, female Mdr2-KO and dKO mice were sacrificed, tumors were counted and non-tumor (NT) and tumor (T) liver tissues were collected for analysis. Expression levels of the H19 and Igf2 genes were determined by real-time qRT-PCR. Cellular localization of H19 lncRNA was determined by single-molecule RNA-FISH (smRNA-FISH).

Results. Tumor incidence and tumor load were both significantly decreased in the liver of dKO vs. Mdr2-KO females. The expression levels of H19 and Igf2 were variable in non-tumor liver tissues of Mdr2-KO females and were significantly down-regulated in most matched tumors. Immunohistochemical staining revealed about two-fold reduction of Ki67-positive hepatocytes in non-tumor liver tissue of dKO vs. Mdr2-KO females. SmRNA-FISH demonstrated that H19 was expressed in a small fraction of hepatocytes (co-localized with Pck1 mRNA) which appeared sporadically, mainly in the zone 2. At early age, dKO mice had lower activity of liver enzymes in the blood compared to Mdr2-KO mice, pointing to a reduced injury of hepatocytes and cholangiocytes in the absence of H19. In human HCC samples (Nault et al., Gastroenterology 2015), H19 expression negatively correlated with activating mutations in the CTNNB1 gene (encoding β-catenin).



Picture: **H19 RNA in a non-tumorous liver of a 15-month-old B6 Mdr2-KO female mice**. H19 is marked with a "green" RNA probe and Pck1 is marked with a "red" RNA probe. There are at least three hepatocytes in this picture that have both one green dot and two red dots in their nuclei. Cytoplasmic H19 staining is also prominent. Every dot in the cytoplasm is one RNA molecule. This teaches to the prominence of H19 in chronic inflamed liver in the "pre-tumorous" liver.

Conclusions. Our results suggest that the global effect of lncRNA H19 in development of chronic inflammation-mediated HCC in the Mdr2-KO mouse model is not tumor suppressive, but rather pro-oncogenic.

FRI-466

A single centre experience of transarterial radioembolisation using Rhenium 188 for treatment of liver space occupying lesions

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Background and aims: Transarterial radioembolisation (TARE) is a treatment modality for Hepatocellular cancer as a bridging treatment before transplant or as a mainstay treatment in hepatocellular cancer with diffuse intrahepatic spread. It can be a salvage therapy in unresectable hepatocellular cancer due to poor liver reserves, performance status and when comorbid conditions prevent surgery in portal vein thrombosis. Re 188 is a high energy beta emitter isotope from Tungsten 188/Rhenium generator. Re-188 HDD (Lipiodol) (4-hexadecyl-1, 2, 9, 9-tetramethyl-4, 7-diaza-1, 10-decanethiol) is used for hepatocellular cancer treatment.

Method: Inclusion criteria-hepatocellular cancer Barcelona Clinic Liver Cancer (BCLC) B and C**,** portal vein thrombosis, failure of transarterial chemoembolization, large tumor unilobar or bilobar with adequate liver reserves, cholangiocarcinoma and diffuse disease with oligometastasis. Total of 35 patients were included, 27 were BCLC C with portal vein thrombosis, 4 patients did not have portal vein thrombosis. Non cirrhotic hepatocellular cancer with portal vein thrombosis in 2 patients and inoperable large cholangiocarcinoma in 2 patients. Tumor size < 5 cm in 6 patients, tumor > 5 cm in 20 and diffuse disease in 9 patients. Procedure was done by superselective cannulation, angiogram revealed tumor blush, adequate dose of Rhenuim was injected and feeding vessel embolised with gel foam. Response to therapy was observed after 6 weeks by Triple phase CT/MRI scan.

Results: As per m RECIST criteria, good response was noted in 14.3% (n = 5), partial response 11.4% (n = 4), stable disease in 28.57% (n = 10), progressive disease 22.8% (n = 8), lost to follow-up in 14.2% (n = 5) and response early to comment in 8.6% (n = 3). Time to progression was 4 months in patients (n = 3) who initially has a partial response/stable disease. Tumor rupture was noted in 2 patients. Doses of Rhenium up to 3 mci/ml were tolerated without much side effects. Response was largely determined by CHILD stage, volume of lesion and amount of activity administered. All patients with good and partial response were followed up for 10 months. Treatment side effects included mild fever (n = 11), transaminits (n = 21), mild abdominal pain (n = 3), rise in serum bilirubin (n = 17) and decompensation (n = 3).

Conclusion: Rhenium Transarterial radioembolisation is an effective approach in centres where Yttrium TARE is not feasible due to its attractive physical properties, simpler procedure and at one third of the cost.

FRI-467

Optimal time-point of response assessment was associated with tumour burden in patients with unresectable hepatocellular carcinoma undergoing repeated transarterial chemoembolization

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Background and aims: The optimal time-point of radiological response assessment remained controversial in predicting outcomes of patients with unresectable hepatocellular carcinoma (HCC) undergoing repeated transarterial chemoembolization (TACE), which may be affected by tumor burden. We aim to evaluate the prognostic values of not only the initial and best response, defined as complete and partial response (CR and PR), especially in different tumor characteristics, but also the time-point of achieving response.
Method: Between January 2010 and May 2016, 1549 treatment-naïve patients with unresectable HCC, well-preserved liver function and performance status 0-1 score undergoing TACE were recruited from 17 Chinese academic hospitals. Overall survival (OS) was analyzed and correlated with response, determined with modified Response Evaluation Criteria in Solid Tumors (mRCIST) criteria, and time-dependent Cox regression analysis was performed for multivariate analysis.
Results: Time-dependent multivariable analysis exhibited that both initial and best response had independent prognostic values (both $P < 0.001$) in patients with low and intermediate tumor burden (sum of tumor size and number ≤ 6, > 6 but ≤ 12). Whereas the best response, rather than initial response could predict OS in high tumor burden patients (tumor size + number > 12) ($p = 0.537$, $P < 0.001$, respectively). All these findings were consistent in different subsets. Patients who achieved initial CR or subsequent CR after repeated TACE (41.8 and 48.2 months, respectively) showed a significant higher OS than those with subsequent PR or persistent non-response (30.4 or 14.1 months, respectively, $P < 0.001$).
Conclusion: Particularly, the current study indicated that initial response was not always a predictor for OS. Seeking complete response regardless of time-points was determinative for favorable prognostication. Further validations still remain warranted.

FRI-468

Identifying optimal candidates for combining transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma: A multicenter observational study

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Background and aims: The benefits of combining transarterial chemoembolization (TACE) and sorafenib (TACE-S) over TACE alone in unresectable hepatocellular carcinoma (HCC) remains controversial; yet it should be noted that "unresectable HCC" are highly heterogeneous regarding to the baseline characteristics. Here, we aimed to investigate the predictors of survival benefits from added sorafenib and identify the optimal candidates for TACE-S.
Method: The multicenter observational study was conducted in seventeen Chinese tertiary hospitals for patients with unresectable, liver-confined HCC. Eligible patients with Eastern Cooperative Oncology Group performance status of 1 or less and Child-Pugh score of 7 or less were treated with TACE or TACE-S. Interactions between treatments and baseline variables were evaluated to find the predictors for survival benefits, based on which the patients were stratified. Multivariate models adjusted for baseline factors or propensity score were used to compare the overall survival (OS) and time-to-tumor progression (TTP).
Results: From January 2009 to December 2015, 1719 consecutive patients receiving TACE (n = 1406) or TACE-S (n = 313) were enrolled. Overall, though TACE-S improved TTP compared with TACE (adjusted hazard ratio [HR] 0.77, P = 0.013; Figure 1A), no difference of OS was observed (adjusted HR 0.92, P = 0.283; Figure 1B). Nevertheless, the tumor burden (sum of the maximum diameter of largest tumor [cm] and tumor number) and ALBI (Albumin-Bilirubin) score independently predicted the survival benefits from added sorafenib (interaction $P < 0.001$; Figure 1C and 1D). For patients with either moderate tumor burden (between 7 and 13) or low ALBI score (no more than −2.8), TACE-S significantly prolonged OS (adjusted HR 0.74, P = 0.005; Figure 1E) compared to TACE alone, whereas its superiority disappeared in the others (adjusted HR 1.15, P = 0.290; Figure 1F).
Conclusion: Not all the unresectable-HCC patients but those with moderate tumor burden or low ALBI score would get survival benefits

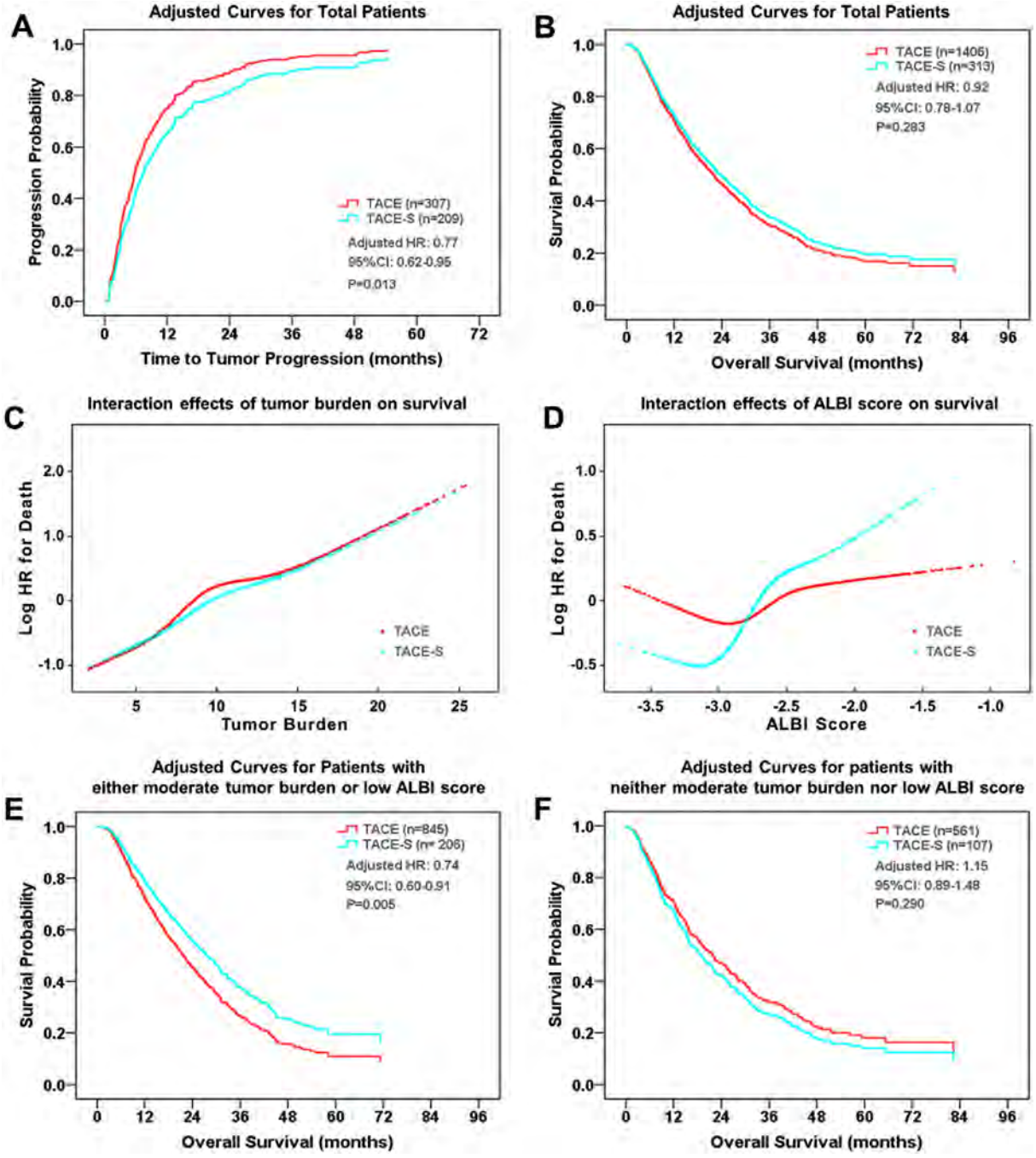

Figure: (abstract FRI-468)

from TACE-S compared to TACE alone. Future randomized-controlled trials focused on the subset are needed.

FRI-469

Vitamin K dosing could improve anti-cancer outcome of transarterial chemoembolization for patients with hepatocellular carcinoma-an open label, randomized, phase II study

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Background and aims: The ischemic surroundings make hepatocellular carcinoma (HCC) cells increase production and release of des-γ-carboxy prothrombin (DCP). There are many reports that the DCP is a paracrine angiogenetic factor as well as an autocrine tumor growth factor and that it enhances HCC growth. It was shown that excess dosing of vitamin K drastically declines the DCP production in tumor cells. We previously reported that vitamin K dosing enhanced anti-tumor action of sorafenib by diminishing DCP production of HCC. In this study, we aimed to clarify whether the vitamin K dosing could augment ischemic cell damage caused by TACE.

Method: Forty-five patients with BCLC stage B of HCC were enrolled. Patients were randomly assigned (1:1) to receive TACE + vitamin K dosing (vitamin K2: Glakay, Eizai Co., Ltd., Tokyo, Japan) or receive

TACE alone. In 22 patients, the vitamin K was dosed orally, 45 mg daily, from the day of TACE until 28 days after. Randomization was stratified by TACE-naïve or not, and by tumor size/number (or 5 cm/ one tumor vs others). Tumor necrosis by TACE was evaluated by dynamic CT or EOB-MRI 4weeks after TACE according to RECICL as well as modified RECIST. The treatment effect was classified into four categories: TE4 (100% necrosis), TE3 (50%-99% necrosis), T2 (the rest of T4, T3 and T1) and T1 (greater than 25% tumor growth) by the RECICL.

Results: TACE + vitamin K dosing showed the following outcome: 9 patients of TE4, 12 of TE3, 1 of TE2 and none of TE1, although the outcome of TACE alone was unfavorable; 5 of TE4, 9 of TE3, 6 of TE2 and 3 of TE1 (p = 0.015). The evaluation by modified RECIST also demonstrated better outcome of TACE + vitamin K group than TACE alone group; CR: PR: SD: PD was 8: 12: 2: 0 vs 5: 9: 6: 3 (p = 0.018). Therefore, effective rates were significantly higher in TACE + vitamin K group than in TACE alone group (91.0% vs 65.2%, respectively, P = 0.019). Four weeks after TACE, in TACE + vitamin K group, 21 of 22 patients (95.5%) showed the DCP level decline into normal range, whereas only 7 of 23 (30.4%) had decline to the normal range (p = 0.001). Arterial embolization causes massive necrosis of tumors. However, in surrounding portions of the necrotic areas or in tumors with insufficient embolization, viable HCC cells under ischemic situation seem to produce excess DCP and survive with enhanced angiogenesis induced by the DCP. Vitamin K dosing could jeopardize the survival of the viable tumor cells by suppressing the DCP production.

Conclusion: Vitamin K, a nontoxic agent, could improve the outcome of TACE by suppressing DCP production.

FRI-470

External beam radiotherapy as an effective and safe treatment in all stages of hepatocellular carcinoma with cirrhotic liver disease : A single institution experience

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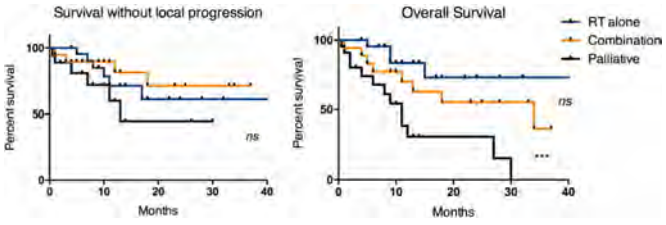
Background and aims: Recent data suggest that EBRT could be an efficient and safe local treatment of HCC. Yet, RT alone or in a combined strategy is rarely used for HCC patients.

Methods: We retrospectively analysed all patients with any stage of HCC who received RT as a sole therapy or combined with other treatments. We reviewed charts of 66 patients treated between 01/11 and 09/18. Indications of RT were contraindication or technical issues for others local therapies, remaining active lesions after first local therapy or heavy comorbidities not allowing systemic treatments. We aimed to evaluate outcome and safety.

Results: Mean age was 70 ± 1 years, women 13 (20%), men 53 (80%). 61pts (92%) were cirrhotic among which 56% were Child A, B in 42% and C in 2%. The BCLC stage was A in 41%, B in 15%, C in 41% and D in 3% of pts. Median tumor size was 41 mm. 19 (29%) patients were naïve of treatment, 30 (64%) previously received one another HCC treatment and 17 (36%) received > 1 previous treatment. RT was indicated as unique treatment, complementary treatment and as palliative therapy in 38%, 30%, and 32%, respectively. The median dose delivered was 42 Gray (Gy) with median of dose per fraction of 5 Gy, using 3D-conformal RT planning in 30% and stereotactic-body RT in 70% of pts. The median follow-up was 10.5 mths. 3 months after the end of RT, there were 17% complete responses (CR), 44% partial responses (PR), 35% tumor stability (TS) and 4% tumoral progression (TP). During overall follow-up, we observed 35% CR, 40% PR, 21% TS and only 4% TP. There was no statistical difference in terms of response between RT as unique treatment (21/23 patients) or combination treatment (13/20 patients) (p = 0.06). Among the 43 responders, response criteria were based on RECIST, mRECIST or both in 19%, 46% and 35% of cases, respectively. In the follow-up, 16 (24%) patients had no relapse, and among them, five patients underwent LT. 21% of patients had a local relapse after a median of 8.5 months, 53% had an intra-hepatic relapse at a median of 5.5 months and 19% had a metastatic relapse at a median of 4 months. 25 patients had subsequent treatment for a relapse. Tumor size was not statistically different in patients with or without local relapse (Mann-Whitney test, p = 0.07). RT was well tolerated; principal adverse events were asthenia (44% of patients), gastro-intestinal symptoms (14%), mild and transitory elevation of transaminases (9%) and signs of cirrhosis decompensating (9% of patients, requiring interruption of treatment). At the end of the study, 59% of patients were alive. Median overall survival was 34 months in the curative group and 11 months in the palliative group (Log-rank test, p = 0.0003).



Conclusion: RT should be considered as an effective and safe therapy alone or in combination in all stages of HCC and could be proposed for cirrhotic patients that present contraindication or failure for all others therapies.

FRI-471

Regorafenib may enhance efficacy of anti-program cell death-1 therapy in hepatocellular carcinoma through modulation of macrophage polarization

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Background and aims: Many multi-kinase inhibitors are being tested for potential synergistic antitumor efficacy with anti-PD1 therapy in HCC. In addition to their anti-angiogenic property, direct immune modulatory effects of these kinase inhibitors were not clearly defined.

Method: An orthotopic HCC model, generated by implanting BNL/MEA liver cancer cells into the subcapsular space of BALB/c mice, was used to evaluate in vivo treatment efficacy and safety of regorafenib and anti-PD1 therapy, alone or in combination. Expression patterns of immune-related genes in tumor samples after drug treatment were analyzed by RNA-Seq. Extent of macrophage polarization after regorafenib treatment was measured by expression of M1-related (TNFa, IL6) or M2-related genes (Arg1, CD206) in bone marrow-derived macrophages (BMDMs) using quantitative PCR, ELISA, or flow cytometry. The changes in T cell function after co-culture with

regorafenib-treated BMDMs were examined by cytokine assay, expression of T-cell related genes, and flow cytometry.
Results: Regorafenib 5 mg/kg/day, which corresponded to about half of the human dosage for clinical use, may produce synergistic antitumor efficacy with antiPD1 in terms of tumor regression and animal survival. Immune-related genes induced by regorafenib, independent of its anti-angiogenic effects, included genes related to T cell activation (IL2ra, CD69, Tespa1) and myeloid differentiation (Ccr7, Ly6c2, Tnf, Slfn4). This was consistent with increasing tumor-infiltrating interferon+/CD8+ T cells and M1 macrophages in regorafenib-treated tumors. Regorafenib at sub-micromolar range may induce M1 polarization in vitro. Co-culture of regorafenib-treated BMDMs increased proliferation and activation of CD8+ T cells, whereas direct exposure to regorafenib at same concentrations had negligible effects on T cell proliferation or function.
Conclusion: Low-dose regorafenib may modulate macrophage polarization, increase T cell activation, and thereby enhance efficacy of anti-PD1 therapy for HCC. Optimization of regorafenib dosage for rational design of combination therapy regimen may improve the therapeutic index in the clinic.

FRI-472
ALBI grade determines survival of nivolumab-treated patients with advanced hepatocellular carcinoma: a real-world observational study

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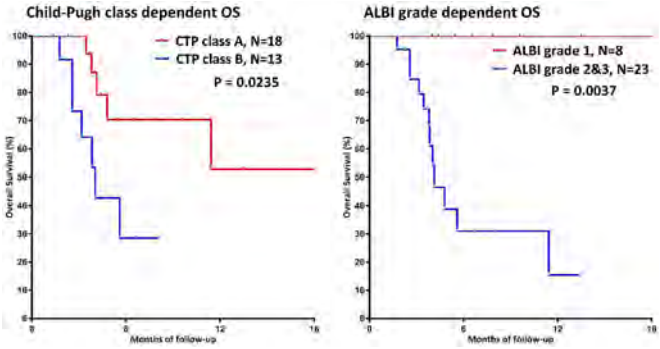
Background and aims: Immunotherapy with checkpoint inhibitor is a promising and FDA-approved treatment for advanced hepatocellular carcinoma (HCC), mainly after sorafenib failure. The treatment response of Nivolumab (anti-programmed cell death-1, PD-1) in real-world setting as the first line or second line treatment for advanced HCC was rarely reported. In addition, factors associated with treatment outcomes were unclear.
Method: From May 2017, 37 patients had received nivolumab treatment for advanced HCC in Taipei Veterans General Hospital. Among them, 31 patients with evaluable radiographic images following treatment before the date of data cut were enrolled for clinical assessment. Factors associated with survival were analyzed.
Results: Majority (80.6%) of the patients were in BCLC stage C, followed by 16.1% BCLC B. Twenty (64.5%) patients were sorafenib failure and 11 (35.5%) were sorafenib naïve. At the date of data cut, the disease control rate was 41.9% including 1 (3.2%) complete response, 5 (16.1%) partial responses, and 7 (22.6%) stable diseases. Median time to response was 61 days (IQR 40-64 days), and the median duration of response was 9.6 months (IQR 1.4-11.0) for responders. The median overall survival (OS) was 11.4 months (95% C.I. 1.9-21.0). Patients within Child-Pugh A (n = 18) had better OS than those at Child-Pugh B (n = 13) (median OS: not yet reached vs. 4.0 months, p = 0.023). The median OS was 11.4 months in sorafenib-failure cases; whereas, the median OS in sorafenib-naïve patient was not yet reached (p = 0.990). All patients at ALBI grade 1 status were still alive at the date of data cut and had significantly longer OS than those at ALBI grade 2 or 3 (median OS: not yet reached vs 4.1 months, p = 0.004). No factor was identified associated with treatment response. Till the date of data cut, 9 patients still kept ongoing nivolumab treatment. Grade 3/4 treatment-related adverse events were observed in 7 patients (3 ALT elevation, 6 AST elevation, and 2 hyperbilirubinemia). Besides, only one patient developed grade 2 immunotherapy-related pneumonitis.



Conclusion: ALBI grade 1 confers excellent survival under immunotherapy for advanced HCC. The treatment response of nivolumab was equivalent between sorafenib-naïve and sorafenib-experienced patients.

FRI-473
Safety and effectiveness of regorafenib in recurrent HCC after liver transplantation and progression on sorafenib: A real-life multicentre study

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Background and aims: Regorafenib improves the overall survival (OS) of sorafenib-tolerant patients who develop progression and it is the first second-line systemic treatment approved by EMA and FDA for hepatocellular carcinoma (HCC). However, there is no data of regorafenib in patients with HCC recurrence after liver transplantation (LT). Thus, the aim of this study is to evaluate the safety and outcomes of regorafenib in this population.

Method: This is a retrospective, multicentre and international study, including regorafenib-treated LT patients. The baseline characteristics and evolutionary events during sorafenib/regorafenib treatment were collected. Patients' management and radiological evaluations were performed according to centres' policy.
Results: From 2015 to 2018, 28 LT patients (57 years, 68% males, 54% performance status 1) from Europe and Latin-America were included. Median time from LT to regorafenib initiation was 3.9 (1.1-18.5) years, median time on sorafenib was 11.3 (0.7-76.4) months and from sorafenib discontinuation to regorafenib initiation was 14 (1-591) days. During regorafenib treatment (6.3 months), all patients had at least 1 adverse event (AE) of any grade, the most common grade 3/4 AEs were fatigue (25%) and dermatological reaction (18%). While no liver rejection episodes were observed, plasma levels of immunosuppressive drugs increased in 5 patients. Twenty-four patients developed radiological tumor progression: the most frequent patterns of progression were extra-hepatic growth (38%) and new extra-hepatic lesions/new vascular invasion (33%). Median OS from regorafenib initiation and sorafenib-regorafenib sequence were 12.9 (CI 95%; 6.7-19.1) and 38.4 (CI 95%; 18.5-58.4) months, respectively.
Conclusion: This is the first evidence that regorafenib is safe in patients after LT. The impact of sequential sorafenib-regorafenib treatment on OS in this population seems similar to the reported in no-LT patients.

FRI-474
AGT gene polymorphisms predict early dose modification of sorafenib for dermatological adverse events: towards tailored medicine for patients with hepatocellular carcinoma
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Background and aims: Sorafenib (SOR) is the standard of care of patients with advanced hepatocellular carcinoma (HCC). However, no biomarker exists able to predict treatment duration (TD) and overall survival (OS). It has been recently shown that the AGT gene polymorphisms (SNPs) can predict the early (< 2 months) occurrence of dermatological adverse events (eDAEs) requiring dose-reduction, which is associated with OS. We aimed to evaluate the ability of eDAE and genetic profile to predict the benefit of SOR in a large population of patients with HCC.
Method: We retrospectively evaluated 221 prospectively enrolled HCC patients treated with SOR (starting dose 800 mg) in five centers in Italy. Clinical and laboratory assessments were done monthly, radiologic tumour re-evaluation every 2-3 months. Treatment was maintained until progression, significant toxicity or patient's decision. Two SNPs (*rs699* and *rs4762*) of the AGT gene were assessed by using the TaqMan end point-genotyping assay. The end points of the study were: identification of baseline and time-dependant predictors of TD and OS and correlation with ATG gene SNPs.
Results: Baseline characteristics of patients included in the analysis were: age 69 years, 83% males, 46% HCV-pos, 86% Child-Pugh (CPT) A, 61% ECOG PS 0, 66% BCLC-C. Genetic distribution of AGT SNPs among the population were: 33% AA, 46% AG and 21% GG for *rs699*; 78% GG, 20% GA and 2% AA for *rs4762*. The median follow-up was 12 months (mos), the median TD 4 months and the OS at 24 months was 32% (CI 95% 26-39). At least one AE developed in 94% of patients; 46% patients required ≥ 1 dose reductions, which was due to AE in 88% and early in 62% of cases. eDAE developed in 26 patients (47% of those with an early reduction due to AE). Predictors of TD by time dependent covariate analysis were CPT (HR 2.11, 95%CI 1.06-4.16, p = 0.033), ECOG PS (HR 1.57, 95%CI 1.07-2.32, p = 0.022), and eDAE (HR 0.61, 95% CI 0.37-1.01, p = 0.05); while for OS were presence of varices (HR 1.40, 95%CI 1.01-1.95, p = 0.045), CPT (HR 2.24, 95%CI 1.13-4.41, p = 0.020), ECOG PS (HR 2.51, 95%CI 1.66-3.79, p < 0.001) and eDAE (HR 0.62, 95% CI 0.35-1.09, p = 0.097). The *rs4762* SNP was an independent predictor of eDAE (HR 3.01, 95% CI 1.14-7.99, p = 0.009), while the risk of eDAE was two-fold higher in carriers of at least one minor allele of both SNPs (p = 0.031).
Conclusion: eDAE during SOR therapy predicted TD and OS and AGT *rs4762* SNP was associated with eDAE occurrence. The AGT *rs4762* SNP could help to tailor treatment strategies in patients with HCC whenever different therapies will be available.

FRI-475
Experience impacts on reasons leading to sorafenib discontinuation and chance of long-term response
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Background and aims: Sorafenib is associated with various adverse events (AEs) potentially leading to permanent drug discontinuation. Common sense suggests that cumulative experience over a long timeframe might improve the management of drug-related AEs, with a potential benefit to the patients. However, the actual existence and the full extent of this phenomenon have never been investigated.
Method: We analyzed a large retrospective-prospective database gathering the clinical data of 201 patients from our Centre, who were consecutively prescribed with sorafenib between 2008 and 2017. We divided these patients in two groups according to the start date of sorafenib (2008-2012 vs 2013-2017), comparing clinical, laboratory and tumor characteristics. In particular, we verified: treatment duration, medium daily dose, reason of sorafenib discontinuation (as defined by Iavarone et al, Hepatology 2015), and overall survival (OS).
Results: One-hundred-three and 98 patients started sorafenib in 2008-2012 and 2013-2018, respectively. These groups did not differ in age, sex, performance status, liver function, and tumor staging. Due to more frequent dose reductions, the median average daily dose of sorafenib was lower in the 2013-2018 group (413 vs 518 mg/day, p < 0.001). In parallel, the median treatment duration increased in the same group (145 vs 112 day, p = 0.027), with no remarkable difference in the cumulative drug dose between the two groups (61.6 vs 58.1 g, p = 0.440). The rate of patients permanently stopping sorafenib for intolerance dropped from 23.3% in 2008-2012 to 7.1% in 2013-2017 (p = 0.002). The median OS was similar in the two groups (11.1 vs 11.6 months), but the rate of long-survivors (OS > 3 year) was higher in the 2013-2017 group (23.4 vs 9.7%, p = 0.001). To reduce the influence of deaths due to early progression, we performed a subgroup analysis of patients who achieved disease control as their best radiologic response. In this case, the OS in the 54 patients treated in 2013-2017 was significantly higher compared to that of the 51 patients treated in 2008-2012 (24.4 vs 20.6 months, HR 0.63, 95%CI 0.42-0.96, p = 0.031).
Conclusion: Increased experience in the management of sorafenib-related AEs may lead to increased treatment duration and better outcomes in sorafenib-responsive patients. This factor may be of paramount relevance in the era of sequential treatments based on

tyrosine-kinase inhibitors, as these molecules share a common toxicity-profile.

FRI-476

Repeated surgical resection versus radiofrequency ablation for recurrent hepatocellular carcinoma after surgical resection : A propensity score matching analysis

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Background and aims: Tumor recurrence rate remains high after curative surgical resection for early stage hepatocellular carcinoma (HCC). Repeated surgical resection and radiofrequency ablation (RFA) are treatment options for recurrent HCC within early stage, but which treatment modality provides better outcomes remains unclear. The aim of this study was to compare the recurrence rate and survival between the two treatment modalities for recurrent HCC.
Method: From August 2007 to September 2017, 158 patients undergoing repeated surgical resection (n = 45) or RFA (n = 113) for recurrent HCC after surgical resection were retrospectively enrolled. Factors associated with recurrence-free survival (RFS) and overall survival (OS) were analyzed.
Results: Patients in the RFA group had significantly smaller tumor size ($p < 0.001$) and lower AFP levels ($p < 0.001$). During a median follow-up period of 44.8 months, 109 (68.9%) cases developed tumor recurrence and 117 (74%) patients died. The complication rate was higher (17.8% vs 3.5%, $p = 0.005$) and the mean hospital stay was longer (13.3 vs 3.6 days, $p = 0.001$) in the repeated surgical resection group versus the RFA group. The median RFS was significantly longer in the surgical resection group than the RFA group (29.2 vs 11.5 months, $p = 0.030$), whereas the median OS was comparable between the surgical resection group and the RFA group (49.9 vs 41.1 months, $p = 0.164$). By multivariate analysis, age > 65 years (Hazard ratio (HR) = 1.55, $p = 0.025$), AFP ≥ 20 ng/ml (HR = 2.28, $P < 0.001$), RFA (vs surgical resection, HR = 2.26, $p = 0.001$) were independent predictors of poorer RFS, while tumor size ≥ 3 cm (HR = 0.54, $p = 0.041$) was the only independent predictor of OS. After propensity score matching, the median RFS remained significantly longer in the surgical resection group than the RFA group (29.2 vs 8.7 months, $p = 0.001$), while the median OS remained comparable between the surgical resection group and the RFA group (49.9 vs 42.9 months, $p = 0.393$). For recurrent tumor within BCLC stage 0, i.e. single tumor < 2 cm, the median RFS and OS were comparable between the surgical resection group and the RFA group (19.2 vs 13.0 months, $p = 0.325$), and (49.9 vs 44.8 months, $p = 0.930$) respectively.
Conclusion: Although surgical resection provides longer RFS than RFA for recurrent HCC after surgical resection, the OS were comparable between repeated surgical resection and RFA.

FRI-477

Factors associated with good postprogression survival in post-sorafenib progressed advanced hepatocellular carcinoma pateitns not eligible for regorafenib

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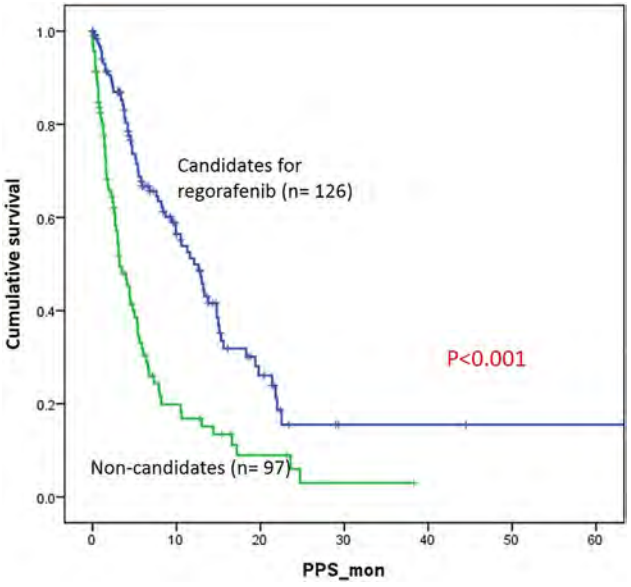
Background and aims: This study aimed to assess the prognostic factors associated with postprogression survival (PPS) in advanced hepatocellular carcinoma (HCC) patients who showed radiological progressive disease (PD) with sorafenib monotherapy, and were not eligible for 2nd-line regorafenib treatment.
Method: A total of 223 patients who were confirmed with radiological PD after sorafenib monotherapy from September 2008 to December 2017 were enrolled. We define those with Child-Pugh class A, ECOG PS 0 or 1 at progression, and who had tolerated sorafenib as candidates eligible for 2nd line regorafenib therapy.
Results: Among 223 patients with PD after sorafenib treatment, 126 (56.5%) patients met eligibility criteria for regorafenib treatment at first radiological confirmation of PD. The median PPS of the candidates for regorafenib treatment (12.1 months) was statistically longer ($p < 0.001$) than that of the non-candidates (3.2 months). Prognostic factor associated with good PPS in non-candidates for regorafenib therapy was absence of macrovascular invasion [hazard ratio = 0.5 (95% confidence interval 0.33-0.76)] at initial radiological PD.



Conclusion: Absence of macrovascular invasion at initial radiological PD may predict good PPS in advanced HCC patients who had progressed after sorafenib monoterapy and were not eligible for regorafenib treatment.

FRI-478

Survival outcomes of TACE in treatment-naive and recurrent HCC after curative resection: A propensity score-matched analysis

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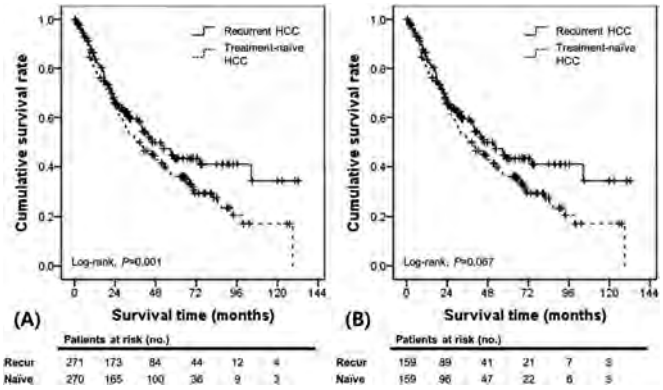
Background and aims: Transarterial chemoembolization (TACE) improves the survival of patients with hepatocellular carcinoma (HCC); however, TACE treatment outcomes of patients with treatment-naïve HCC (TN-HCC) and those with recurrent HCC after curative resection (R-HCC) have not yet been compared.
Method: We recruited 448 patients with TN-HCC and 275 patients with R-HCC treated with TACE as first-line anti-cancer treatment.
Results: At first TACE, patients with TN-HCC showed a significantly lower proportion of male gender (74.9% vs. 84.3%), higher proportion

of liver cirrhosis (61.9% vs. 49.3%), higher aspartate aminotransferase (median 48 vs. 31 IU/L) alanine aminotransferase (median 38 vs. 26 IU/L), alpha-fetoprotein (AFP) (median 96.6 vs. 7.7 ng/ml), and total bilirubin (mean 1.0 vs. 0.8 mg/dL) levels, longer prothrombin time (median 1.05 vs. 1.01 international normalized ratio), higher tumor number (mean 2.1 vs. 1.7), larger tumor size (median 3.1 vs. 1.6 cm), and lower proportion of Barcelona Clinic Liver Cancer stage 0-A (55.6% vs. 71.9%) than patients with R-HCC (all $p < 0.05$). Multivariate analysis showed that TACE for TN-HCC (vs. R-HCC) was an independent predictor of mortality (hazard ratio, 1.328; $p = 0.024$) with AFP level and tumor number (all $p < 0.05$). However, treatment outcomes between TN-HCC and R-HCC became statistically similar after propensity score-matched (PSM) analysis using liver cirrhosis, tumor size, and multiple tumors ($p < 0.05$).



Conclusion: Based on the similar TACE treatment outcomes observed with the PSM analysis, the current TACE treatment guideline for patients with TN-HCC might similarly be applied for patients with R-HCC.

FRI-479

Hepatocellular carcinoma with extrahepatic metastasis: Are there still candidates for transarterial chemoembolization as an initial treatment?

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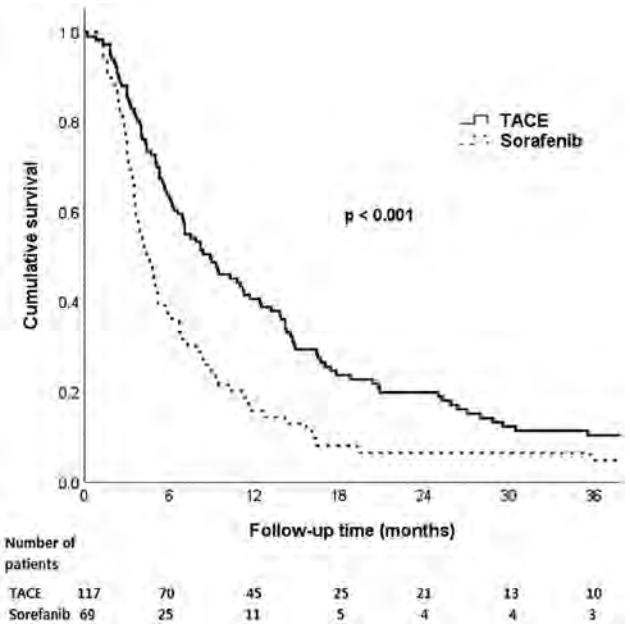
Background and aims: Currently, sorafenib is indicated for hepatocellular carcinoma (HCC) with extrahepatic metastasis (EHM), and many other systemic agents are becoming available. However, a few HCC patients with EHM still undergo transarterial chemoembolization (TACE) for intrahepatic tumor control. We aimed to investigate whether TACE is appropriate for patients with EHM, and if so, which subgroup may benefit from TACE.
Method: A total of 186 consecutive HCC patients (median: 55 years, male: 86.0%, hepatitis B virus: 81.7%, Child-Pugh Class A: 83.3%) with EHM (nodal metastasis: 60.8%, distant metastasis: 39.2%) between 2010 and 2014 were analyzed. Initial treatment included sorafenib in 69 patients, and TACE in 117 patients.
Results: During a median follow-up of 6.6 months (range: 0.2-94.6 months), mortality was observed in 90.3% (168/186). The median survival was better for patients who received TACE than those treated with sorafenib (8.2 months vs. 4.6 months, $p < 0.001$). However, baseline characteristics varied between patients initially treated with TACE and sorafenib, and the treatment modality was not an independent factor associated with overall survival (hazard ratio: 1.19, 95% confidence interval: 0.81-1.75, $p = 0.36$). In sub-group analysis, TACE was associated with better survival only among younger patients and those with segmental/lobar portal vein invasion.



Conclusion: In HCC patients with EHM, TACE was not an independent favorable prognostic factor compared to sorafenib. The concept of intrahepatic control in HCC patients with EHM may need to be reevaluated in the era of promising systemic therapies, although there can be specific subgroups who still benefit from TACE.

FRI-480

Laparoscopic right hepatectomy is feasible and safe in solitary hepatocellular carcinoma

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Background and aims: Laparoscopic liver resection has been reported as a safe and effective approach for the management of hepatocellular carcinoma (HCC). However, its perioperative and oncological outcomes have not been evaluated in right hepatectomy (RH) patients. Aim of present study is to compare the outcomes between laparoscopic RH (LRH) and open RH (ORH) in HCC patients.
Method: From January 2013 to August 2017, 345 patients with HCC underwent RH. Patients with portal vein tumor thrombosis, history of preoperative locoregional therapies, multiple tumors, bile duct tumor thrombosis, the history of abdominal operation, and serosal involvement were excluded. 189 patients were selected because of Child-Pugh class A and solitary HCC.
Results: The numbers of ORH and LRH groups were 134 and 55 patients. Among LRH group, four patients (7.3%) converted open conversion due to bleeding (n = 3) and close to the tumor (n = 1). Median tumor size of ORH and LRH was 4.0 cm and 3.5 cm, respectively ($p = 0.086$). Preoperative factors, preoperative AFP levels, and pathologic factors were not different between the two groups. Operation time in ORH group was shorter than in the LRH group (243 min vs. 271 min; $P = 0.032$), but amounts of blood loss in the ORH group was more than in the LRH (300 ml vs. 200 ml; $P < 0.001$). Two patients in the ORH group received red blood cells transfusion, but none in the LRH group were not transfused. Ten patients in the ORH group developed postoperative complications

(Clavien grade I and II), but three patients in the LRH group had postoperative complications (Clavien grade 1 and II). Median hospitalization in the ORH group was longer than in the LRH group (10 days vs. 7 days; P < 0.001). Disease-free survival (DFS) rates and patient survival (PS) rates at 1-, 2-, and 3-year were 92.1%, 89.2%, 87.4% and 95.3%, 92.4%, 90.2% in the ORH group and 100%, 94.1%, 94.1% and 100%, 100%, 100% in the LRH group, respectively. The DFS and PS in the LRH group were better than in the ORH group, but the difference did not reach significant levels.
Conclusion: LRH is feasible and safe for solitary HCC patients in experienced center. However, the oncologic outcome of LRH should be needed in further investigations.

FRI-481
Predicting hepatocellular carcinoma recurrence beyond Milan criteria after liver resection for solitary hepatocellular carcinoma
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Background and aims: Several hepatectomy patients with HCC who are initially transplantable (within MC) developed untransplantable HCC recurrence (beyond MC) after primary curative liver resection. The purpose of our study is to identify the risk factors of untransplantable hepatocellular carcinoma (HCC) recurrence after primary curative resection of solitary HCC and solitary HCC within Milan criteria (MC).
Method: We retrospectively reviewed 592 patients with recurrent HCC who underwent liver resection due to solitary HCC between 2005 and 2011.
Results: All patients were Child-Pugh class A. At primary curative hepatectomy, 411 patients (69.4%) were diagnosed with HCC within MC and 181 patients (30.6%) had HCC beyond MC. The mean time from primary hepatectomy to recurrence was 14 months (range, 1-116 months). At HCC recurrence, 93 patients (15.7%) were diagnosed beyond MC. Multivariate analysis showed that microvascular invasion and a tumor grade of 3 or 4 were closely associated with a high risk of HCC recurrence beyond MC in patients who had hepatectomy for solitary HCC. Of the 411 patients within MC at primary curative hepatectomy, 54 patients (13.9%) developed HCC recurrence beyond MC. Multivariate analysis also showed that microvascular invasion and a tumor grade of 3 or 4 were closely associated with HCC recurrence beyond MC in these patients.
Conclusion: The present study suggests that the presence of certain unfavorable histological factors in patients who underwent initial liver resection of transplantable HCC within MC with good liver function predicted the development of recurrent HCC beyond MC.

FRI-482
Ideal number of lymph nodes to harvest for intrahepatic cholangiocarcionoma
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Background and aims: Although lymph node dissection is recommended during hepatectomy for intrahepatic cholangiocarcinoma (ICC) by the American Joint Committee on Cancer (AJCC) 8th edition, the role of routine lymphadenectomy for ICC is still controversial. Moreover, AJCC recommends that at least 6 lymph nodes should be harvested during the lymphadenectomy. However, there is no clear evidence about this issue. In this study, we evaluated the minimum number of lymph nodes to harvest for ICC.
Method: Records from 180 patients who underwent radical hepatectomy for intrahepatic cholangiocarcinoma from January 2000 to December 2014 were retrospectively reviewed. The minimum number of lymph nodes to harvest was calculated via comparison of overall survival between N0 and N1 patients based on the Cox proportional hazard model.
Results: Median harvested lymph nodes were 5 [1-12]. About 20 percent (N = 37) of patients didn't undergo lymphadenectomy (Nx group). (**Table**) The Cox proportional hazard model showed that when the minimum number of lymph nodes examined was 6 or more, the hazard ratio between N1 versus N0 patients was statistically significant. (HR 2.18, 95% CI 1.11-4.26) The hazard ratio for N1 patients increased from 2.18 with 6 minimum number of lymph nodes examined to 2.62 with 10 minimum number of lymph nodes examined. (**Figure**)

Table: Basal characteristics of the patients

	N = 180
Age	62.9±9.9
Gender (M:F)	108 : 72 (1.5 : 1)
Hepatitis (B or C viral carrier)	28 (15.6%)
IHD stone	14 (7.8%)
CA 19-9	64.0 [12.2-410.5]
Neoadjuvant therapy	17 (9.4%)
Tumor size (cm)	4.7±2.5
Gross type	
IG	25 (13.9%)
PI	11 (6.1%)
MF	119 (66.1%)
Mixed	25 (23.9%)
Differentiation (N = 174)	
Well	32 (17.8%)
Moderately	82 (45.6%)
Poorly	55 (30.6%)
Undifferentiated	5 (2.8%)
LVI	111 (61.7%)
PNI	61 (33.9%)
Harvested LN	5 [1-12]
T stage	
T1	28 (15.6%)
T2	93 (51.7%)
T3	56 (31.1%)
T4	3 (1.7%)
N stage	
N0	92 (51.1%)
N1	51 (28.3%)
Nx	37 (20.6%)
TNM stage	
I	26 (14.4%)
II	63 (35.0%)
III	38 (21.1%)
IV	53 (29.4%)
Adjuvant therapy	71 (39.4%)
Median follow-up (months)	64.0 [54.3-73.7]

Conclusion: Intrahepatic cholangiocarcinoma patients undergoing radical resection should ideally have at least 6 lymph nodes harvested to be accurately staged.

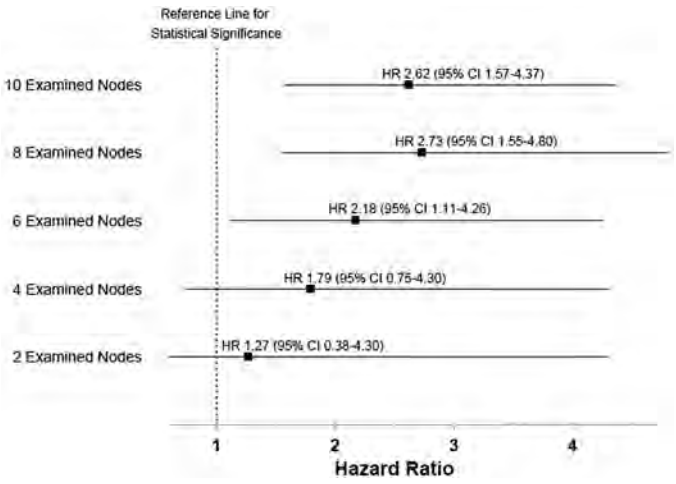

Figure: Results from the Cox proportional hazard model: hazard ratios between N1 and N0 patients stratified by the total number of lymph nodes examined

FRI-483

Endoscopic biliary drainage in patients with cholangiocarcinoma: Polyethylene versus self-expanding metal stents

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Background and aims: Endoscopic biliary drainage is the standard of care for patients with cholangiocarcinoma (CCA)-induced, obstructive jaundice. Self-expanding metal stents are supposed to be superior to polyethylene stents in terms of reduction of interventions and costs. So far, there are only few real-life data with respect to survival in this patient cohort.
Method: In this study, we retrospectively analyzed 422 patients with CCA treated with endoscopic biliary drainage from 2000 to 2015 at Hannover Medical School, Germany. The aim of this study was to assess whether metal stenting reduces the frequency of interventions and influences survival in a large, real-life cohort compared to polyethylene stenting.
Results: Overall, 422 patients with CCA treated with endoscopic biliary drainage were included in this study. Indication for endoscopic biliary drainage was most often obstructive jaundice (n = 397; 94.1%). Among these patients, 20 patients (5%) were initially treated with a metal stent, and 38 (9.6%) received a metal stent in the subsequent course. Median number of interventions per month was 2.4-fold reduced following metal stenting in patients, which have initially received polyethylene stents. Patients first treated with a metal stent had a more advanced tumor stage and a significantly shorter median overall survival (mOS) compared to patients who received a metal stent subsequently (7.5 vs. 15.2 months; p = 0.019). There was no difference in mOS for metal vs. polyethylene stenting following a propensity score match for the confounders curative resection and chemotherapy (13.2 vs. 13.7 months, p = 0.555).
Conclusion: Our data confirm that metal stenting reduces the frequency of interventions, but does not influence OS. Metal stenting should be considered particularly in patients with a good prognosis and a prolonged life expectancy.

FRI-484

The early clinical response at 2 weeks of lenvatinib therapy for patients with advanced HCC

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Background and aims: We previously reported that the disappearance of arterial tumor enhancement on CE-CT and the decrease in AFP levels after 2 weeks of sorafenib therapy were significant predictors of better survival for patients with advanced HCC. Lenvatinib has recently become available as a first line tyrosine-kinase inhibitor for unresectable HCC. The aim of this study was to investigate the early clinical response at 2 weeks of lenvatinib therapy for patients with advanced HCC.
Method: Between March and October 2018, a total of 23 patients who received lenvatinib as a first-line therapy were retrospectively enrolled to evaluate the early clinical response. Subjects were as followed; male/female, 15/8 cases; BCLC Stage (B/C), 10/13 cases; portal vein tumor thrombosis (Vp 0/2/3/4), 14/1/5/3 cases; tumor liver occupancy rate (50% > / > 50%), 15/8 cases; Child-Pugh score (CPS 5/6/7), 12/9/2 cases; ECOG-PS (0/1), 15/8 cases. The median AFP level was 44 ng/ml (2-54276). CE-CT images were taken at baseline, after 2 weeks and after 6 weeks of lenvatinib treatment. The antitumor responses were evaluated according to the modified RECIST. An AFP response was defined as a decline > 20% from baseline after 2 to 6 weeks of treatment in patients with > 20 ng/ml of AFP levels at baseline.
Results: At 2 weeks of lenvatinib therapy, the antitumor responses according to modified RECIST (CR/PR/SD/PD) were 0/12/11/0 cases (response rate, 52.2%; disease control rate, 100%). The response rates were as followed: 50% in 8 patients with Vp3 or 4 and 62.5% in 8 patients with > 50% of tumor liver occupancy rate, respectively. At 2 weeks, 16 patients were included for AFP response evaluation, and 13 of those patients (81.3%) were classified as AFP responders. At 6 weeks of lenvatinib therapy, the antitumor responses (CR/PR/SD/PD) were 0/8/9/0 cases (response rate, 47.0%; disease control rate, 100%; 6 cases were not taken). The response rates were as followed: 57.1% in 7 patients with Vp3 or 4; 60.0% in 5 patients with > 50% of tumor liver occupancy rate, respectively. At 6 weeks, 11 patients were included for AFP response evaluation, and 8 of those patients (72.7%) were classified as AFP responders. In 15 patients (88.2%), antitumor responses at 2 weeks by modified RECIST were consistent with those at 6 weeks. Regarding the deterioration of liver function, cases with the 2 points increase of CPS were as followed: 2 patients (8.7%) at 2 weeks; 1 (5.9%) patient at 6 weeks, respectively. Only one patient discontinued lenvatinib therapy within 6 weeks due to adverse events. Median duration of lenvatinib administration was 200 days.
Conclusion: In our initial experience, treatment response of lenvatinib therapy for patients with advanced HCC was favorable efficacy and acceptable tolerability. The early clinical response at 2 weeks may be a useful to evaluate the antitumor response of lenvatinib therapy.

FRI-485

Laparoscopic liver resection vs. Percutaneous radiofrequency ablation for small single nodular HCC: Comparison of treatment outcome

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Background and aims: The treatment outcome of percutaneous radiofrequency ablation (p-RFA) or laparoscopic liver resection (LLR)

have not been fully compared. The aim of this study was to compare LLR with p-RFA as first-line treatment in patients with small single nodular HCC ≤ 3 cm.

Method: From January 2014 to December 2016, a total of 566 patients with single nodular HCC ≤ 3 cm treated by either LLR (n = 251) or p-RFA (n = 315) were included. The recurrence-free survival (RFS) and

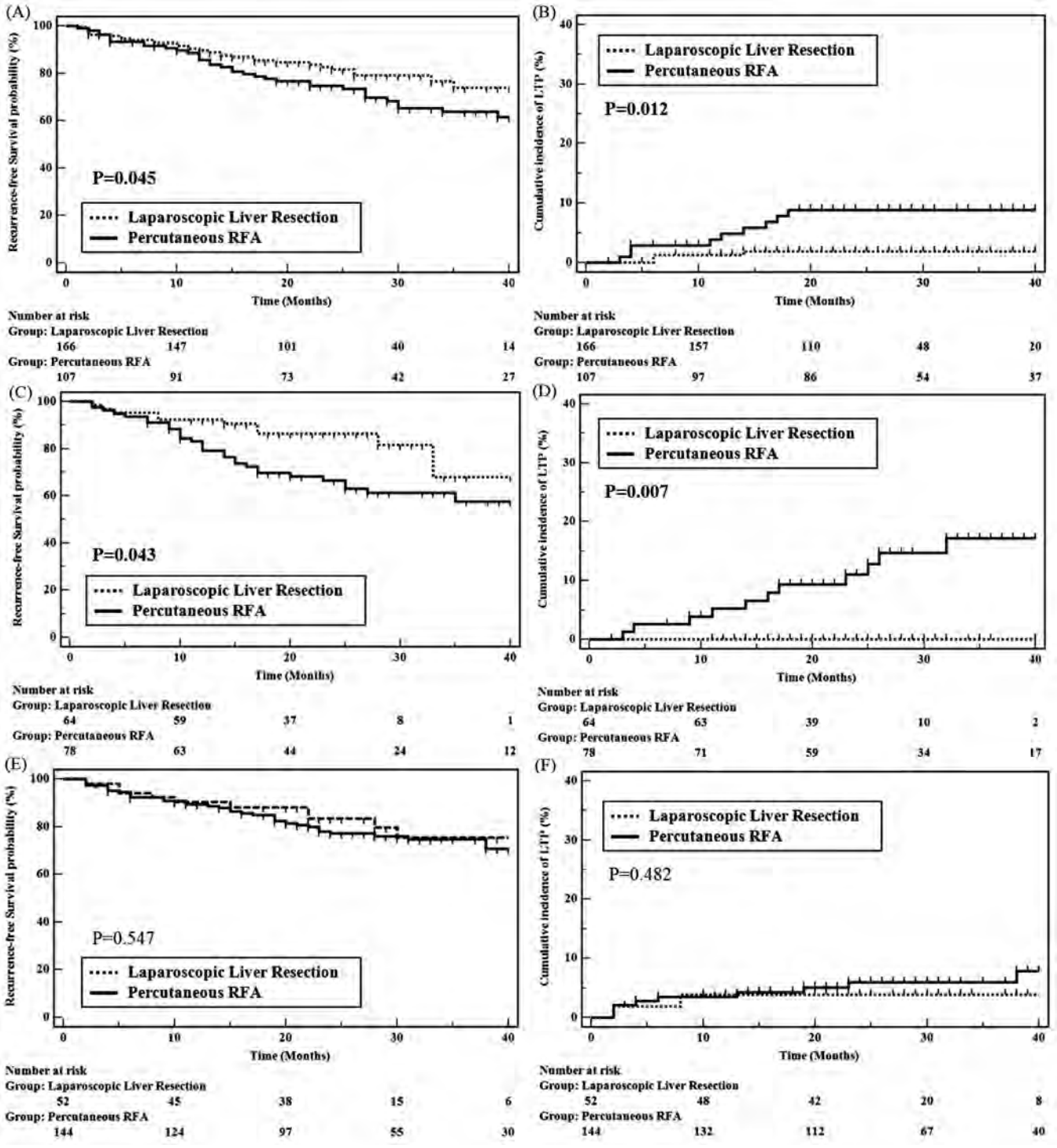

Figure: Estimation of recurrence-free survival and cumulative incidence of local tumor progression according to the tumor location. (A) Kaplan-Meier estimation of recurrence-free survival after laparoscopic liver resection for subcapsular tumor were compared with percutaneous RFA. (B) Cumulative incidence of local tumor progression after laparoscopic liver resection for subcapsular tumor was compared with percutaneous RFA. (C) Kaplan-Meier estimation of recurrence-free survival after laparoscopic liver resection for perivascular tumor were compared with percutaneous RFA. (D) Cumulative incidence of local tumor progression after laparoscopic liver resection for perivascular tumor was compared with percutaneous RFA. (E) Kaplan-Meier estimation of recurrence-free survival after laparoscopic liver resection for non-subcapsular and non-perivascular tumor were compared with percutaneous RFA. (F) Cumulative incidence of local tumor progression after laparoscopic liver resection for non-subcapsular and non-perivascular tumor was compared with percutaneous RFA.

cumulative incidence of local tumor progression (LTP) were estimated using Kaplan-Meier methods, and compared using log-rank test. Treatment outcome of two treatment modalities were compared in subgroup of patient according to the tumor location.

Results: The 3-year RFS after LLR was 74.4%, and significantly higher than p-RFA of 66.0% (p = 0.013), due to significantly lower cumulative incidence of LTP (2.1% at 3-year after LLR vs. 10.0% after p-RFA, P < 0.001). LLR provided significantly better local tumor control than p-RFA for subscapular tumor (3-year LTP rate of 1.9% vs. 8.8%, P = 0.012), as well as perivascular tumor (3-year LTP rate of 0.0% vs. 17.2%, P = 0.007). Regarding tumor located in liver antero-lateral portion, the cumulative incidence of LTP after LLR was significantly higher than p-RFA (3-year LTP rate of 0.0% vs. 10.7%, P < 0.001). However, there was no significant difference in LTP rates between LLR and p-RFA for non-subcapsular and non-perivascular tumor (p = 0.482) and for tumor in postero-superior liver portion (p = 0.380).

Conclusion: LLR could provide significantly better local tumor control and would be better for subcapsular or perivascular tumor as well as tumor located in antero-lateral portion of the liver than p-RFA.

FRI-486

Serum cytokines and chemokines correlated with tumor recurrrence and survival after surgical resection for overt and occult HBV-related hepatocellular carcinoma

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Background and aims: Serum cytokines and chemokines might reflect host anti-viral and anti-tumor immunity and could be potential biomarkers to predict outcomes of HBV-related hepatocellular carcinoma (HCC). The aim of this study was to evaluate the predictive value of serum cytokines and chemokines and outcomes of overt and occult HBV-related HCC after surgical resection.

Method: Serum samples of 80 HBsAg-positive HCC patients (overt HBV group) and 80 HBsAg-negative, HBV DNA-negative, intrahepatic HBcAg-positive HCC patients (occult HBV infection (OBI) group) were obtained from the Taiwan Liver Cancer Network. Serum levels of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), IL-10, IL-22, CXCL9, IP-10 and CCL5 were measured by Multiplex ELISA Cytokine Arrays. Factors associated with recurrence-free survival (RFS), early recurrence within 2 years of surgery, late recurrence after 2 years and overall survival (OS) were analyzed.

Results: The OBI group had significantly older age, larger tumor size, lower serum IL-6, IL-10, IL-22, CXCL9, CCL5 levels and higher TGF-β levels. Serum HBV DNA levels significantly correlated with serum levels of ALT, AST, IL-10, IL-6, CXCL9, CCL5, IL-22 and TGF-β, while tumor size significantly correlated with serum levels of AST, AFP, CXCL9, CCL5, IL-22 and TGF-β. During a median follow-up period of 71.9 months, 102 (63.7%) cases developed tumor recurrence and 70 (43.8%) patients died. By multivariate analysis, IL-6 > 14 pg/ml (hazard ratio (HR) = 1.898, p = 0.008) and tumor stage I-II (HR = 0.228, p < 0.001) were independent predictors of RFS. Tumor size > 5 cm (HR = 2.270, p = 0.003), presence of multiple tumors (HR = 2.602, p = 0.002) and presence of microvascular invasion (HR = 3.243, p = 0.007) were independent predictors of early recurrence. IL-22 > 25 pg/ml (HR = 3.608, p = 0.038), HBV DNA > 10^6 IU/ml (HR = 20.237, p = 0.001) and presence of cirrhosis (HR = 3.239, p = 0.043) were independent predictors of late recurrence. IL-6 > 14 pg/ml (HR = 3.382, p = 0.003), presence of microvascular invasion (HR = 3.206, p = 0.017) and tumor stage I-II (HR = 0.070, p < 0.001) were independent predictors of OS.

Conclusion: Serum cytokine and chemokine levels correlated with HBV viral load and tumor size, suggesting their role of host anti-viral and anti-tumor immunity. IL-6 significantly correlated with RFS and OS and could be a useful biomarker to predict outcomes of HBV-related HCC after surgical resection.

FRI-487

A new prognosis prediction model in patients with hepatocellular carcinoma after Yttrium-90 radioembolization

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Background and aims: Few studies have reported the treatment outcomes of trans-arterial radioemoblization (TARE) using Yttrium-90 (90Y) for hepatocellular carcinoma (HCC). We established and validated a new prognosis prediction model for patients with HCC treated with TARE.

Method: Between 2010 and 2017, 113 and 35 patients with intrahepatic HCC treated with TARE were selected for training and validation cohorts, respectively. The modified RECIST (mRECIST) criteria were used for response evaluation at 1, 3 and 6 months after TARE.

Results: In the training cohort, the median age was 64.1 years (92 male and 19 female) and the median survival after TARE was 50.3 months. A new prediction model for TARE (Y-scoring system) was established from the training cohort using five variables including low serum albumin (< 3.5 g/dL; hazard ratio [HR] = 5.446), high alpha-fetoprotein (AFP, >200 ng/ml; HR = 5.071), and tumor number ≥3 (HR = 2.933), portal vein thrombosis (HR = 4.915), and hepatic vein invasion (HR = 8.500), and two on-treatment variables including no des-gamma-carboxy prothrombin response (HR = 15.346) and progressive disease at 3 months after TARE (HR = 4.154), which were independently associated with mortality (all P < 0.05). The predictive accuracy of the Y-scoring system to predict 6 (area under curve [AUC] = 0.845), 9 (AUC = 0.868), and 12 months mortality (AUC = 0.886) after TARE was acceptable (all P < 0.05). In the validation cohort, the predictive accuracy of the Y-scoring system was similarly maintained (AUC 0.737-0.901 at 6 to 12 months).

Figure: Hazard ratios of independent risk factors, corresponding rounded risk score and predictive accuracy of candidate Y-scoring system to predict 6-12 months mortality. CI, confidence interval; AUC, area under the ROC curve.

Risk factors	Univariate	Multivariate analysis		Scoring
	P value	*P* value	Hazard ratio (95% CI)	
Serum albumin < 3.5 g/dL	< 0.001	0.001	5.446 (2.004-14.798)	2
Alpha-fetoprotein, baseline > 200 ng/ml	0.026	0.001	5.071 (1.949-13.196)	2
Three or more tumors	0.012	0.029	2.933 (1.116-7.706)	1
First order branch portal vein thrombosis	0.008	0.032	4.915 (1.147-21.066)	2
Hepatic vein invasion	0.014	0.003	8.500 (2.051-35.226)	3
No DCP response at 3 months	< 0.001	< 0.001	15.346 (4.424-53.235)	5
Progression by mRECIST criteria at 3 months	0.004	0.008	4.154 (1.453-11.872)	1

Cohorts	Time points after TARE	Total patients	Mortality	AUC (95% CI)	P value
Training	at 6 months	113	9 (8.0)	0.845 (0.684-1.000)	0.002
	at 9 months	102	12 (11.8)	0.868 (0.728-1.000)	0.001
	at 12 months	92	17 (18.5)	0.886 (0.797-0.975)	< 0.001
Validation	at 6 months	35	11 (31.4)	0.901 (0.767-1.000)	0.005
	at 9 months	32	15 (46.9)	0.818 (0.609-1.000)	0.017
	at 12 months	32	18 (56.2)	0.737 (0.516-0.958)	0.074

Conclusion: Our new predictive model can be used to stratify different prognoses for patients with HCC treated with TARE. Further validation from a large cohort is required.

FRI-488

Prognostic value of tumor markers after a complete response to transarterial chemoembolization in patients with recurrent hepatocellular carcinoma following curative resection

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Background and aims: The Prognostic values of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) are well-known. We investigated the prognostic contribution of tumor markers in patients who achieved a complete response (CR) to trans-arterial chemoembolization (TACE) for recurrent hepatocellular carcinoma (HCC) following complete resection.
Method: Between 2004 and 2017, 316 patients achieved a CR, based on the modified RECIST criteria, after repeated TACE for recurrent HCC following curative resection. Cox's regression analysis was performed to identify prognostic factors for overall survival (OS).
Results: The median age of the study population (269 males and 47 females) was 59.6 years. During the follow-up period, from the time of achieving a CR after TACE, the mean OS was 84.6 months, with 131 (41.5%) deaths occurring, and the mean PFS was 30.1 months, with 255 (80.7%) cases of recurrence. Of the total cohort, 265 (83.9%) and 42 (13.3%) patients obtained a CR at the first and the second TACE treatments, respectively. The AFP and DCP levels at the time of CR (median 4.8 ng/ml and 23.0 mAU/ml, respectively) both exhibited a linear relationship with OS in univariate Cox analysis (p = 0.040 and 0.009, respectively). Patients with elevated AFP (> 20 ng/ml, 58 [19.7%]) or DCP (> 40 mAU/ml, 47 [22.9%]) exhibited significantly low OS than those with normal values (86.5 vs. 71.3 months, P = 0.045 for AFP; 91.8 vs. 45.6, P < 0.001 for DCP, respectively). In a multivariate analysis, DCP at the time of CR was significantly predictive of mortality (hazard ratio [HR] = 2.646, P < 0.001), whereas AFP at the time of CR was not significantly predictive (p = 0.488). Two other variables exhibited only a tendency to be predictive; the time interval between the liver resection and the first following TACE (HR = 0.986, P = 0.053) and achieving CR after more than three TACE treatments (HR = 2.902, P = 0.050).

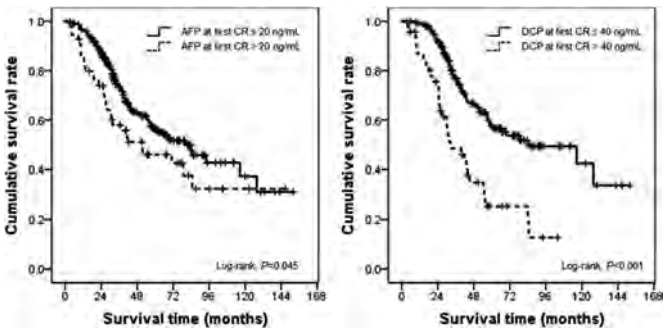

Figure: Kaplan-Meier analyses for overall survival of the patients with elevated tumor markers at the time of achieving CR.

Conclusion: The DCP level at the time of achieving a CR to TACE for recurrent HCC following curative resection was independently predictive of mortality. Thus, for a more refined risk stratification, not only radiological evaluation based on mRECIST criteria, but also the DCP response must be considered.

FRI-489

Downstaging by 90-yttrium radioembolization of unresectable locally advanced hepatocellular carcinoma: A single center experience

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Background and aims: Only one third of patients may benefit of potentially curative treatments at the time of their first diagnosis due to advanced disease. Tumor downstaging by loco-regional treatments may change unresectable HCC into a resectable tumor, providing the best chance of survivals. Increasing literature evidences suggest a role for radioembolization in downstaging locally advanced hepatocellular carcinoma.
Method: From june 2011, we treated all the patients with first diagnosis of unresectable hepatocellular carcinoma and portal vein thrombosis with 90-yttrium resin microspheres (Sir-Spheres®-Sirtex Europe) intrahepatic iniection with the aim to rescue them to a curative surgical treatment. A 3-years enrollment period and a 5-years follow-up were planned in order to adequately investigate survivals.
Results: Among the 24 enrolled patients (87% males, mean age 70 years) following radioembolization, 5 patients (group1) became eligible to surgical treatment, 8 patients (group 2) obtained partial response or stable disease without achieving eligibility for surgical treatment, while 11 patients (group 3) showed progression of HCC despite radioembolization. High tumor absorbed radiation doses (454 ± 157 Gy vs 248 ± 144 and 138 ± 63 respectively, p = 0.005) and low serum AFP levels (53 ± 86 ng/ml vs 1447 ± 2337 and 4603 ± 8619 p = 0.05) were the only variables significantly associated to successful downstaging of tumor. Median survivals were 70 ± 30, 24 ± 14 and 11 ± 4 months in the three groups respectively. No significant side effects were registered.
Conclusion: In our institution, after radioembolization about 20% of unresectable locally advanced hepatocellular carcinoma have been rescued to surgery This sequential strategy has provided long survivals otherwise impossible with an excellent safety profile.

FRI-490

The real world practice of systemic therapies in patients with advanced hepatocellular carcinoma in Japan: what has changed since lenvatinib approval?

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Background and aims: Lenvatinib, the third tyrosine kinase inhibitor (TKI) after sorafenib and regorafenib, has been used in the treatment of advanced hepatocellular carcinoma (HCC) in Japan since March 2018. We attempted to investigate the latest treatment of TKIs in

patients with advanced HCC from Japanese field practice and clarify the clinical issues of the era of "multi TKIs."
Method: Between March 26, 2018 (the date of lenvatinib approval) and the end of August 2018, we retrospectively collected data on advanced HCC patients who were administrated TKI (sorafenib, lenvatinib, or regorafenib) as the first-line systemic therapy and were then converted to TKI after the other (i.e., second or later lines) from 7 Japanese institutions. Radiological assessments were evaluated according to both the Response Evaluation Criteria in Solid Tumors (RECIST) and the modified Response Evaluation Criteria in Solid Tumors (mRECIST).
Results: A total of 104 patients received TKI therapy, of which 86 were men (83%), and the median age of the patients was 72 years. The most frequent etiology was hepatitis C virus (44%), followed by hepatitis B virus (14%), and alcohol abuse (27%). Of the 66 patients administrated with TKI as the first-line treatment of systemic chemotherapy, 47 (71%) were treated with lenvatinib. Among the patients who started TKIs as the first-line, the overall response rate (ORR) according to mRECIST was 43% for lenvatinib and 5% for sorafenib and that according to RECIST was 19% and 5%, respectively. The decreasing rate of α-fetoprotein value of ≥ 20% in these patients was 44% in lenvatinib and 23% in sorafenib. Of the 38 patients who received TKI as the second-line or later treatment, 17 patients (45%) were administered lenvatinib and 18 (48%) sorafenib. The ORR according to mRECIST in the second-line or later cohort was 45%. Regorafenib was administrated in 17 patients in this study (1 patient after lenvatinib and sorafenib, and 16 patients after sorafenib). Of 104 patients, 49 patients (47%) used ≥ 2 TKIs and 22 patients (21%) used 3 TKIs by the end of the observation period.
Conclusion: Lenvatinib has become the first alternative drug in the front line for advanced HCC patients in Japan. Since the ORR of lenvatinib in the first-line and second- or later lines patients were almost equal, lenvatinib may have a potential for use as not only the first-line drug but also as the second- or later-lines drug. "Using up all TKIs in patients' clinical courses" may be the treatment strategy during the era of "muti-TKIs" in patients with advanced HCC, although 21% of patients received all 3 TKIs by the end of the observation period.

FRI-492
Long-term outcome according to initial treatment modality in multiple hepatocellular carcinoma within the Milan criteria
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Background and aims: Although surgical resection is usually considered for a single tumor, several reports suggested that resection can be considered for multiple tumors and may provide a better outcome. We analyzed whether resection can provide a better long-term outcome for patients with multiple hepatocellular carcinomas (HCCs) within the Milan criteria.
Method: A total of 276 consecutive patients with multiple HCCs within Milan criteria and had preserved liver function, defined by Child-Pugh class A, who underwent resection (n = 48), radiofrequency ablation (RFA) (n = 87) or transarterial chemoembolization (TACE) (n = 141), as an initial treatment, between January 2009 and December 2013 were analyzed. Propensity score matching was conducted based on tumor size, tumor number, and ALBI grade (n = 138).
Results: The 5-year overall survival (OS) (93.7%, 68.1%, 59.4%, p < 0.001) and recurrence-free survival (RFS) (58.5%, 19.6%, 7.5%, p < 0.001) was better in resection group than RFA or TACE group. In multivariable analysis, initial treatment modality was independent factor associated with OS and RFS. However, patients who underwent resection had more preserved liver function and had different tumor characteristics compared to those received RFA or TACE. With similar baseline characteristics generated in the propensity score model, there was no significant difference in 5-year OS in patients who received resection and RFA (93.4% vs. 84.5%, p = 0.30), but better OS than TACE (61.6%, p = 0.001). The 5-year RFS was better for patients who received resection than RFA or TACE (59.3%, 24.5%, and 7.2%, respectively, p < 0.001).
Conclusion: Our findings suggest that resection can provide better long-term outcome than RFA or TACE in multiple HCC patients within the Milan criteria, indicating that resection can be considered as a first-line option if selected appropriately.

FRI-493
Efficacy of combination therapy with transcatheter arterial chemoembolization and radiofrequency ablation for intermediate-stage hepatocelluar carcinoma
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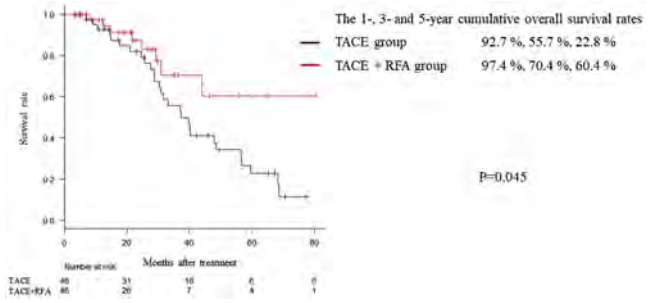
Background and aims: Transcatheter arterial chemoembolization (TACE) is the standard therapy for patients with intermediate-stage hepatocellular carcinoma (HCC). With development of systemic chemotherapy, TACE might be limited to cases that require radical treatment. However, TACE is not regarded as a curative treatment; therefore, addition of radiofrequency ablation (RFA) to TACE (TACE +RFA) might gain importance in clinic. However, the efficacy of TACE +RFA for intermediate-stage HCC remains unclear, due to highly diverse patient characteristics. This retrospective cohort study aimed to determine whether combination therapy with RFA and TACE was superior to TACE monotherapy for intermediate-stage HCC and identify cases in which this technique was the most effective.
Method: We selected patients with Barcelona Clinic Liver Cancer classification (BCLC) intermediate (BCLC-B) stage HCC who met the following eligibility criteria: (1) ≥ 20 years of age, (2) receiving initial therapy, (3) ≤ 7 tumors, and (4) maximum tumor diameter < 5 cm. In order to avoid selection bias, we excluded patients with HCC having more than 8 tumors or maximum diameter exceeding 5 cm. We performed propensity score matching (PSM) using potential confounding factors (e.g. age, sex, Child-Pugh score, maximal tumor size, tumor number, AFP, PIVKA-II, and etiology of chronic liver) All subsequent analysis was performed post propensity score matching. We retrospectively compared the cumulative overall survival rate and recurrence-free survival rate between the TACE+RFA and TACE groups. The study complied with the provisions of the Declaration of Helsinki and was approved by the Ethics Committee of our institution.
Results: Among the 103 patients, 92 were selected using PSM. The cumulative overall survival rates at 1, 3 and 5 years for the TACE+RFA group were 97.4%, 70.4% and 60.4%, respectively, which were significantly higher than those for the TACE group (92.7%, 55.7% and 22.8%, respectively, p = 0.045). The recurrence-free survival rates at 0.5, 1 and 2 years for the TACE+RFA group were 80.0%, 58.6% and 33.3%, respectively, which were significantly higher than those for the TACE group (34.5%, 8.8% and 2.9%, respectively, p < 0.01). The multivariate analysis identified AFP ≧100 (hazard ratio, 2.40; 95% CI, 1.28-5.90; p = 0.009) and TACE group classification (hazard ratio, 2.47; 95% CI, 1.11-5.49; p = 0.03) as independent risk factors predicting mortality. For the sub-group with α-fetoprotein (AFP) < 100 ng/ml, the TACE+RFA group demonstrated a significantly improved prognosis than the TACE group (p = 0.036).



Conclusion: Addition of RFA to TACE demonstrated a significantly improved prognosis and recurrence-free survival compared to TACE monotherapy in patients with intermediate HCC, and is recommended in cases with maximum tumor diameter < 5 cm, tumor number < 8, and AFp < 100.

FRI-494

Practice patterns and outcomes of transarterial chemoembolization in patients with hepatocellular carcinoma who were ineligible and eligible for transarterial chemoembolization at inclusion: Global OPTIMIS exploratory analysis

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Background and aims: Transarterial chemoembolization (TACE) is used to treat unresectable hepatocellular carcinoma (HCC) and is often administered outside of the recommended guidelines. It is critical to assess patient (pt) eligibility prior to TACE and to assess pts after TACE failure to ensure eligibility for subsequent effective therapies. Here we report results from an exploratory analysis of practice patterns and outcomes in TACE-ineligible and TACE-eligible pts.

Method: OPTIMIS was an international, prospective, non-interventional study evaluating pts with unresectable HCC for whom a decision to treat with TACE was made at study entry. In this analysis, TACE ineligibility was defined according to our study protocol-specified criteria based on international guidelines and consensus. Radiological tumour response was determined by investigator assessment. Liver function deterioration was determined in pts with available laboratory values.

Results: Globally, 1650 pts received TACE, including 636 pts (39%) who were TACE ineligible at inclusion. Of those, both extrahepatic spread and portal vein thrombosis were present in 19% of pts. In TACE-ineligible pts, the median time from first TACE to discontinuation was 1.2 months and 47% of pts only received 1 TACE, while 4% received ≥ 6. Complete response (CR), partial response (PR) and progressive disease (PD) rates to first TACE were 8%, 25% and 23%, respectively. After first TACE, chronic deterioration of bilirubin and albumin (CTCAE grade worsening 31-90 days post TACE) was noted in 15% and 38% of pts, respectively. Overall survival (OS) from the time of first TACE was 16.3 months in TACE-ineligible pts. At inclusion, 1014 pts (61%) were TACE eligible. In TACE eligible pts, the median time from first TACE to discontinuation was 4.2 months and 34% of pts only received 1 TACE, while 10% received ≥ 6. CR, PR and PD rates to first TACE were 17%, 27% and 16%, respectively. Chronic bilirubin and albumin deterioration after first TACE was noted in 9% and 25% of pts, respectively. OS from first TACE was 40.1 months in TACE-eligible pts.

Conclusion: These results indicate that a considerable number of pts with HCC in real-world practice are treated with TACE despite not being adequately indicated. Median OS was 16.3 and 40.1 months in TACE-ineligible and TACE-eligible pts, respectively. These data also highlight the importance of careful pt selection for TACE.

FRI-495

Post transarterial chemoembolization fever can predict poor survival in patients with TNM stage I hepatocellular carcinoma

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Background and aims: Transarterial chemoembolization (TACE) is the standard of care for intermediate stage hepatocellular carcinoma (HCC) patients. The post-embolization fever (PEF), occurred within 3 days after TACE, is observed in 20-73% patients. However, whether PEF is a predictor of poor survival after TACE is still controversial. Thus, we aimed to investigate the clinical significance of PEF on survival in different TNM stages HCC patients.

Method: From January 2010 to January 2016, a total of 820 patients were enrolled into analysis after exclusion of patients with Barcelona Clinic Liver Cancer (BCLC) stage D, TNM stage IV, double cancers, tumor rupture, adjuvant therapy with operation or ablation, combined other cancer treatments, and lost follow-up after first or second TACE. Survival analysis was performed with Kaplan-Meier curve and log rank test. Cox regression analysis was applied for predictors of survival after first TACE and logistic regression analysis for risk factors of PEF. Statistical analysis was done by the SAS software, version 9.4 (SAS institute, Inc., Cary, NC, USA).

Results: Patients in TNM stage I, II and III were 225, 335 and 260 respectively. The two-year overall survivals between PEF and non-PEF patients were 67.87% vs. 84.11% (p = 0.006), 72.62% vs. 76.76% (p = 0.144), 43.81% vs. 48.96% (p = 0.301), 73.32% vs. 58.11% (p < 0.001) in groups of TNM stage I, II, III and all patients. TNM stage III (adjusted HR: 2.360, P < 0.001), infiltrative type HCC (adjusted HR: 2.446, P < 0.001), higher N/L ratio (adjusted HR: 1.115, P < 0.001), ALBI grade≧2 (adjusted HR: 1.384, P = 0.037) and AFP level≧20 ng/ml (adjusted HR: 1.748, P < 0.001) were independent predictors for overall survival in all patients by the Cox regression analysis. In patients of TNM stage I, PEF (adjusted HR: 2.663, P = 0.016), WBC < 4000/uL (adjusted HR: 0.285, P = 0.014), and higher N/L ratio (adjusted HR: 1.295, P = 0.004) ratio were independent predictors for survival. Only tumor size≧5 cm (adjusted OR: 3.691, P = 0.001) was independent predictor for PEF in TNM stage I HCC patients.

Conclusion: HCC Patients have poor two-year overall survival if PEF presence after 1st TACE treatment. A significant impact of PEF on survival was only observed in TNM stage I HCC patients but not in stage II nor III. PEF, WBC count and high N/L ratio are independent predictor for survival in TNM stage I HCC patients receiving TACE. Larger tumor size can predict occurrence of PEF in TNM stage I HCC patients.

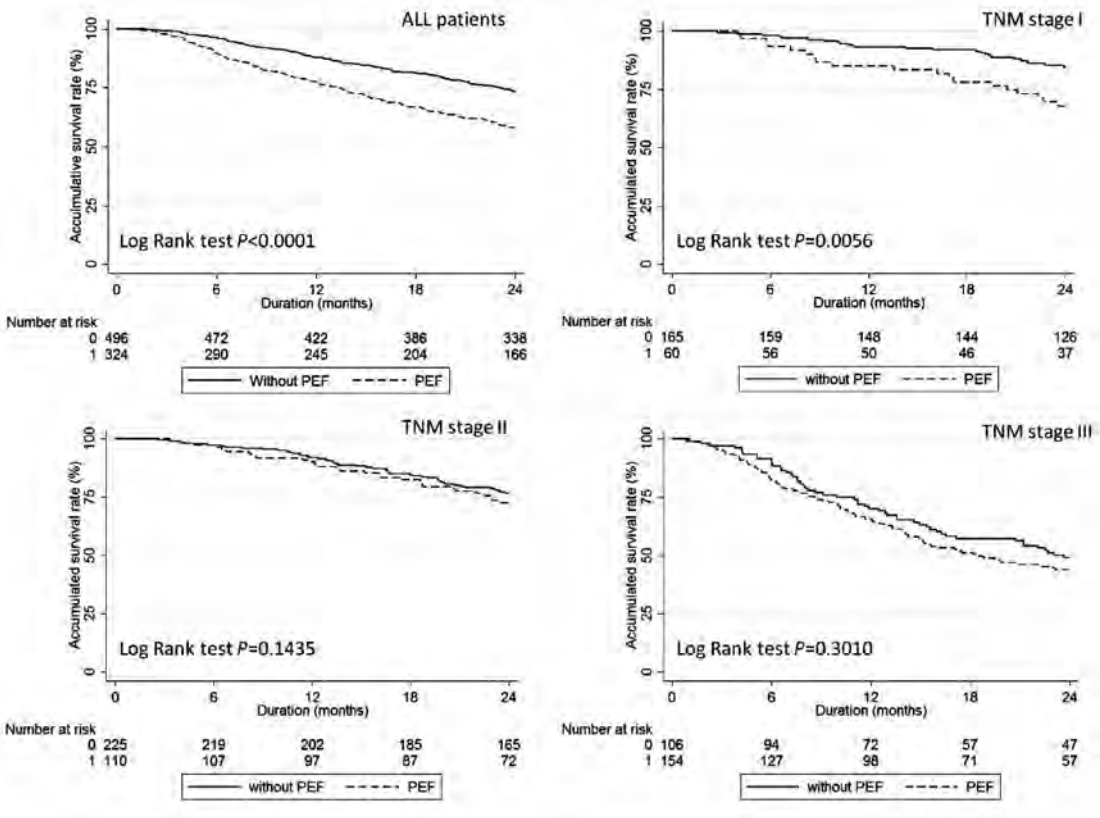

Figure: (abstract FRI-495)

FRI-496

Recurrence of hepatocellular carcinoma in patients with complete response treated with direct acting antivirals in clinical practice

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Background and aims: There is still controversy about the effect of Direct Acting Antivirals (DAA) on the early recurrence of Hepatocellular Carcinoma (HCC) in patients with complete response. The objective was to analyze the recurrence rate in patients with HCC who have received DAA and compare it with a control group who did not received antiviral treatment.

Method: Retrospective, observational and multicentric study in 5 tertiary hospitals in Madrid. Patients were selected from the Registry of Use of Antiviral Agents for HCV of Sermas (RUA-HCV) from November 2015-April 2016, all patients with HCC treated with surgery or ablation in complete response with at least 1-year of follow-up from the beginning of the DAA (Cohort A) and was compared with a consecutive historical group in the same centers that did not receive antiviral treatment (Cohort B). Clinical, oncological and radiological baseline and follow-up data were collected during DAA until the last visit in their clinical history.

Results: We analyzed 665 patients treated with DAA registered in RUA-HCV. Finally, Cohort A, included 76 patients, mean age 66 years (SD9.2), males 57.9%, HIV co-infection 5.8%, diabetes mellitus 27.6%. BCLC 0: 28.9%, A: 65.8%, B: 5.3%. In control group, 57 patients with no antiviral treatment were included, mean age 65.3 (SD12.8), males 73.7%, HIV co-infection 16%, diabetes mellitus 31.6%. BCLC 0: 12.3%, A: 82.5%, B: 5.3%. The median follow-up from the beginning of DAA was 15 months and 25 months in control group. There were no statistically significant differences between recurrence at 3, 6, 12 and 18 months in Cohort A/B: 9.2%/3.5%, 15.8%/19.2%, 30.2%/29, 8%, 38.1%/38.5%, despite the fact that all patients in cohort A obtained a sustained viral response. In Cohort A, a higher recurrence rate was observed in patients treated in the first 12 months after treatment of HCC compared to those who were treated later (85.2% vs. 24.5%) p = < 0.001. In fact, the cumulative probability of recurrence at 12, 18 and 24 months in patients who started DAA at a time ≤ 12 months compared with those who started > 12 months was 25, 5% vs 0%, 42, 9% vs 3, 1% and 56, 3 vs 34% p = 0.001. A propensity score matching was made, not observing changes in the previously obtained results.

Conclusion: There was no significant differences in terms of recurrence between patients treated with DAA and untreated. However, those patients treated at a time £ 12 months after complete response of HCC treatment showed a significantly higher recurrence than those treated at least 1 year after obtaining the complete response to the HCC.

FRI-497

Shifting to sorafenib is beneficial for hepatocellular carcinoma patients with transarterial chemoembolization refractoriness: A real world experience

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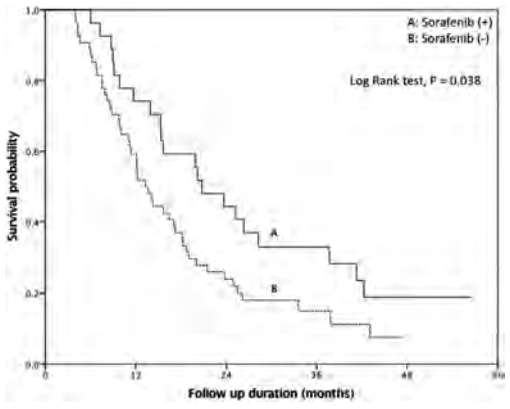
Background and aims: Transarterial chemoembolization (TACE) is the standard of care for intermediate stage hepatocellular carcinoma (HCC) patients. However, about more than one-third of the patients experience disease in progression post TACE treatment. Sorafenib is the first systemic therapy that shows significant survival benefit in advanced HCC. This study was aimed to investigate whether shifting to sorafenib be beneficial for those experienced TACE refractoriness.
Method: From 2005 to 2016, a total of 656 treatment-naive HCC patients receiving TACE treatment in Chang Gung Memorial Hospital, Linkou medical center were recruited. Based on Japan Society of Hepatology guidelines, we defined TACE refractoriness as progressive disease after two consecutive of TACE treatment within six months. Pre-TACE status including baseline characteristics, tumor staging, tumor burden, and parameters for liver function evaluation were analyzed. All the variables were compared between patients with and without TACE refractoriness.
Results: Among the 656 patients, the median age was 62.5 (27.3-91.5) years old, and 74.5% were male. TACE refractoriness events were documented in 202 patients (30.8%). Patients with advanced tumor stage, tumor number, tumor size, higher alpha-fetoprotein (AFP) level, fever episode after 1st TACE, and elevation of alpha-fetoprotein as well as Child-Turcotte-Pugh score were prone to encounter TACE failure. Multinomial logistic regression analysis revealed that tumor size more than 5 cm, baseline alpha-fetoprotein level more than 200 mg/dl, increase of AFP level more than 20%, and elevation of Child-Turcotte-Pugh score by 2 points between 1st and 2nd TACE were the independent predictive factors for TACE refractoriness. Patients with TACE refractoriness were prone to experience tumor metastasis (42.6% vs. 22.5%, $p < 0.001$) and to have higher mortality rate (5-years: 87% vs. 69%, $p < 0.001$). After documenting TACE refractoriness, patients were either shifting to sorafenib treatment (13.4%) or continuing TACE treatment/best supportive care (78.2%). After one-to-two propensity score matching for these two groups, patients shifting to sorafenib therapy had significantly longer median survival than continuing TACE treatment/best supportive care (20.8 [14.4-27.2] months vs. 13.3 [10.8-15.8] months, $p = 0.038$), though the progression-free survival was similar (9.0 [5.2-10.8] months vs. 6.2 [8.2-17.2], $p = 0.121$).



Conclusion: The incidence of TACE refractoriness was 30.8%. Tumor size, baseline AFP level and Child-Turcotte-Pugh score were good predictors for TACE refractoriness. For patients with TACE refractoriness, shifting to sorafenib gave better survival benefit than continuing TACE treatment/best supportive care.

FRI-498

A current status of therapeutic choice and feasibility for hepato cellular carcinoma patients over 70 years old

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Background and aims: Benefit of treatment in hepatocellular carcinoma over 70 years old should be greater than the reduction of survival period or maladjustment due to treatment. Based on these perspectives, we investigated how the detailed treatment of hepatocellular carcinoma in elderly patients and overall survival of each treatment modalities.
Method: From January 2003 to December 2005 and January 2008 to December 2014, the National Cancer Center (NCC) and Korean Liver Cancer Study group (KLCSG) collected 3, 006 clinical datas from HCC patients over 70 years old investigating Korea Central Cancer Registry (KCCR) receords at 54 medical centers in south Korea. Using this data we analyzed current treatment modality and overall survival of each modalities in treating HCC patients over 70 years old.
Results: In Period 2003-2005, there were 578 patients and in period 2008-2014, 2428 patients were analyzed. Transarterial therapy (period 2003-2005 : 49.1%, period 2008-2014 : 44.4%) was the most commonly used treatment modality. Among them, Transarterial chemoembolization (TACE) with gelatin sponge occupied largest proportion (96.1%, 65.6%). In overall survival analysis, surgical resection showed statically significant superiority than other treatment modalities ($p < 0.001$), followed by local ablation therapy and transarterial therapy in both periods. Other modalities showed no statistical differences including no treatment. Among transarterial and chemotherapy, there are no statistically significant differences between transarterial therapy modalities except sorafenib. However, there were no statistically significant differences in propensity score matching for surgical resection, local ablation therapy, and transarterial therapy for relatively early stage lesions.

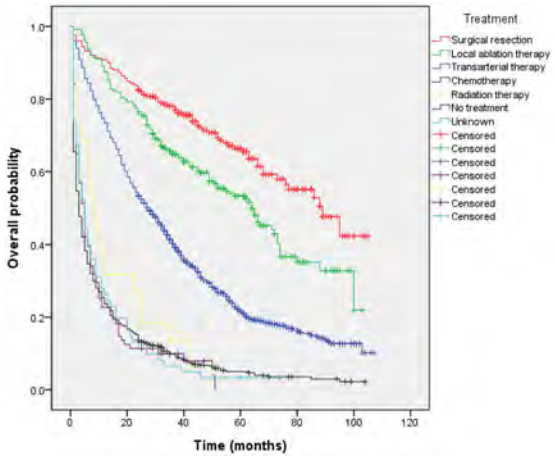

Figure: Overall survival analysis according to treatment modality in Period 2008-2014

In subgroup analysis, there was statistically significant difference between the surgical resection, local ablation therapy, transarterial therapy and the rest of other treatment modalities in the 70-75 year period. However, there was no significant difference between surgical

resection, local ablation therapy, transarterial therapy in the ages of 75-80 years and over 80 years period.
Conclusion: Transarterial therapy was the most commonly used treatment modality in Hepatocellular carcinoma patients over 70 years old. However, surgical resection showed statistically significant superior overall survival rate than other modalities.

FRI-499

Efficacy and hepatic safety of nivolumab treatment in patients with Child-Pugh B disease and advanced hepatocellular carcinoma in CheckMate 040

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Background and aims: Most patients (pts) with hepatocellular carcinoma (HCC) are diagnosed at an advanced stage. Pts with Child-Pugh (CP)-B liver function have a poorer prognosis and a historical overall survival (OS) with sorafenib (SOR) of ≈3-5 mo; hence, these pts have a high unmet need for effective and tolerable treatments. Nivolumab (NIVO), a PD-1 inhibitor, is approved in SOR-treated pts with advanced HCC (aHCC) based on data from CheckMate 040 (El-Khoueiry *Lancet* 2017). We present efficacy and hepatic safety data from the CP-B cohort of CheckMate 040, the first prospective immunotherapy study in pts with CP-B aHCC.
Methods: SOR-naïve (n = 25) or -experienced (n = 24) pts with CP-B7-B8 aHCC, with no hepatic encephalopathy or paracentesis within 6 mo or 3 mo of screening, respectively, received NIVO 240 mg IV for 30 min Q2W (flat dose) until unacceptable toxicity/disease progression. The primary end point was objective response rate (ORR) (investigator assessed [INV], using RECIST v1.1). Safety was assessed in all treated pts using NCI CTCAE v4.0.
Results: Median (range) follow-up was 11.8 (6.4-18.0) mo. Of 49 pts analyzed, 28 (57%) had vascular invasion or extrahepatic spread. Baseline CP scores of B7, B8, and A6 were reported in 37 (76%), 11 (22%), and 1 (2%) pt, respectively; 21 (43%) and 8 (16%) pts had HCV or HBV infection, respectively, and 19 (39%) pts had alpha-fetoprotein (AFP) levels ≥ 400 μg/L. INV ORR was 10%, disease control rate (DCR) was 55%, and median duration of response was 9.9 mo; 4 of 5 responders improved from CP-B at baseline to CP-A5 or -A6 status and sustained the improvement for at least 6 mo. Median OS was not reached for pts with a complete/partial response, and was 9.8 mo for pts with stable disease (SD) and 6.8 mo for pts with progressive disease, as best overall response. Serious treatment-related adverse events (TRAEs) occurred in 2 (4%) pts. TRAEs led to discontinuation in 2 (4%) pts. More pts with baseline AFp < 400 μg/L had SD (57%) and a higher DCR (68%) vs those with AFP ≥ 400 μg/L. Comparison data for pts with CP-A aHCC, and additional data by etiology, HBV/HCV viral kinetics, and extended follow-up for pts with CP-B aHCC will be presented.
Conclusion: In pts with CP-B aHCC, NIVO demonstrated promising efficacy and manageable safety, with no new safety signals. Hepatic AEs were manageable and did not lead to high discontinuation rates. Results support further investigation of NIVO as an option for pts with CP-B aHCC.

FRI-500

Sorafenib for recurrent hepatocellular carcinoma after liver transplantation: Intrinsic resistance or not?

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Background and aims: the use of sorafenib in patients with hepatocellular carcinoma (HCC) recurring after orthotopic liver transplantation (OLT) may be challenging. Increased toxicity from interaction with immunosuppressants are a common issue. Also, poor outcomes have been reported. However, it has not been investigated whether these outcomes derive from a dire clinical presentation or from a resistance to sorafenib. We aimed to compare the overall survival (OS) of sorafenib-treated post-OLT HCC with that other sorafenib-treated HCCs.
Method: We analyzed a large retrospective-prospective database gathering the clinical data of 487 patients from 6 Italian centres, who were prescribed with sorafenib between 2008 and 2017. Eighteen patients with HCC recurring after OLT were identified. A propensity score analysis comparing their clinical and tumor characteristics with those of 90 matched controls (sorafenib in patients without OLT) was performed. Propensity score included performance status, alfa-fetoprotein > 400 ng/ml, macrovascular invasion, extrahepatic spread.
Results: Characteristics of the OLT patients and matched controls are reported in the Table. Immunosuppressant in OLT patients included: everolimus (n = 10), tacrolimus (n = 4), sirolimus (n = 2), cyclosporine (n = 2). Toxicities were similar in the two groups. The median treatment duration [4.5 months (95%CI 3.0-6.1) vs 5.9 months (95% CI 4.0-7.9), p = 0.344] was comparable as well as the rate of radiologic disease control (44.4 vs 52.5%, p = 0.323). Finally, the OS was also similar [11.5 months (95%CI 9.2-13.8) vs 13.5 months (95%CI 9.7-17.3), p = 0.725] in OLT and non-OLT groups, respectively.

	OLT patients (n = 18)	Sorafenib controls (n = 90)	P
Males	16 (88.9%)	80 (88.9%)	1.000
Age	59 (56–67)	65 (62–74)	0.101
Performance status			
-ECOG-PS 0	14 (77.8%)	71 (78.9%)	1.000
-ECOG-PS 1	4 (22.2%)	19 (21.1%)	
BCLC stage			
-Intermediate	4 (22.2%)	21 (22.2%)	1.000
-Advanced	14 (77.8%)	69 (73.8%)	
Macrovascular invasion	2 (11.1%)	16 (17.8%)	1.000
Extrahepatic spread	13 (72.2%)	65 (72.2%)	1.000
Alfa-fetoprotein > 400 ng/ml	4 (22.2%)	19 (21.1%)	1.000

Conclusion: Extrahepatic spread was common in patients with HCC recurring after OLT, possibly reflecting the negative effects of immunomodulation. However, once sorafenib was started, treatment duration, radiological response and OS were comparable with those of controls. The prognosis of these patients seems to be more influenced by their clinical presentation rather than by a reduced efficacy of sorafenib.

FRI-501

Survival among patients with advanced hepatocellular carcinoma in the pre-TKI versus TKI eras

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Background and aims: The first multityrosine kinase inhibitor (TKI)—sorafenib—was approved as the standard of care to prolong overall survival (OS) in patients with advanced hepatocellular carcinoma (HCC) in 2009. Until date, several TKIs have been used in field practices. However, it remains unclear how these pharmaceutical innovations affect survival in the real-world setting. Here, we examined the changes in survival between the pre-TKI therapy and TKI therapy periods in advanced HCC patients.
Method: We identified advanced-stage HCC patients from the database of our institution between 2003 and 2016 and divided them into 3 groups: pre-TKI group (2003-2008), first-term TKI group (2009-2012), and second-term TKI group (2013-2016). OS was defined as the time from being diagnosed with advanced-stage HCC to either death from any cause or the date of last follow-up.
Results: A total of 547 patients who were initially diagnosed with advanced HCC were included in this study (pre-TKI group: 121 patients, first-term TKI group: 185 patients, second-term TKI group: 241 patients). Their median age was 69 years (range: 34-87 years), 50% had HCV infection, 19% had HBV infection, and 30% had non-viral infection. The rates of HCV infection decreased and those of non-viral infection increased over time (HCV infection rates: 64.5% [pre-TKI group], 54.1% [first-term TKI group], and 41.5% [second-term TKI group], non-viral infection rates: 16.5% [pre-TKI group], 25.9% [first-term TKI group], and 39.8% [second-term TKI group].
The receiving rates of TKI with pre-, first-, and second-term groups were 3.3, 52.4, and 50.6%, respectively. The OS of the second-term group was significantly longer than that of the other two groups (pre-TKI group: 9.1 months [95%CI 7.2-11.0], first-term TKI group: 8.7 months [95%CI 7.3-10.1], second-term TKI group: 13.3 months [95% CI 9.7-16.9]; p = 0.017). Of the 451 Child-Pugh ≤ 7 patients, who had indication of TKI in field practice generally, the OS of the second-term group was significantly longer than that of the other two groups (pre-TKI group: 9.6 months [95%CI 7.1-12.1], first-term TKI group: 9.8 months [95%CI 7.8-11.8], and second-term TKI group: 14.9 months [95%CI 10.9-18.9]).
Conclusion: Patients diagnosed with advanced HCC during the second-term TKI showed better survival outcomes than those diagnosed during the pre-TKI and first-term TKI. As sorafenib may not be manageable, the first-term TKI group did not show improved OS when compared with the pre-TKI group. Therefore, skillful use of TKI may improve the prognosis of advanced HCC patients.

FRI-502

Factors impacting survival in a large cohort of patients with unresectable hepatocellular carcinoma treated with Y-90 resin microspheres at a single centre

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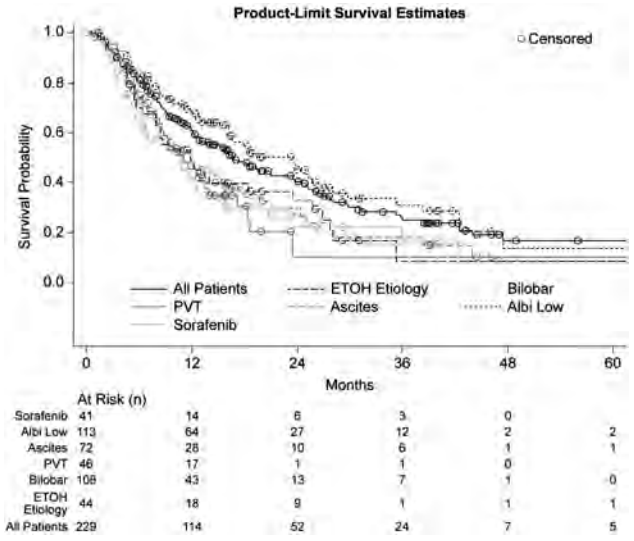
Background and aims: Locoregional treatment of unresectable hepatocellular carcinoma (HCC) with selective internal radiation therapy with Y-90 resin microspheres (Y-90 SIRT) has yielded median overall survivals (OS) of 8.0 to 14.4 months in prospective and retrospective studies of > 100 patients. In a previous study of patients treated at our centre from 2004 to 2013 (n = 111), OS was 13.1 months (Mantry et al. 2017), and we identified several factors associated with longer OS. We have extended this retrospective study to include patients treated through March 2017 in order to examine survival and predictive factors in a larger cohort.
Method: Demographics, disease aetiology and presentation, Y-90 treatment parameters, previous treatments, and OS were abstracted from the charts of patients with unresectable HCC treated with Y-90 SIRT at our facility from April 2004 through March 2017. Patients with incomplete data (< 20% of parameters available) were excluded. OS (from the first Y-90 SIRT treatment to death or last follow-up) was assessed with the Kaplan-Meier method and univariate Cox proportional hazards models.
Results: We analysed data from 229 patients with HCC who underwent 313 SIRT procedures. Most were male (76%) and white (59%); hepatitis C (61%) and alcohol (19%) were the most common aetiologies. Most patients (71%) had a single SIRT procedure, 24% had 2 procedures, and 5% had > 2 procedures; bilobar SIRT was sequential and considered 2 treatments.
Median OS was 16.6 months (95% CI 13.1, –). In a univariate analysis, alcohol aetiology (hazard ratio [HR] 1.5, 95% CI 1.0-2.3); the presence at baseline of bilobar disease (HR 1.9, 95% CI 1.3-2.6), portal vein thrombosis (HR 1.8, 95% CI 1.2-2.8), ascites (HR 1.6, 95% CI 1.1-2.3), and ALBI score (HR 1.5, 95% CI 1.1-2.0); and prior treatment with sorafenib (HR 1.8, 95% CI 1.2-2.7) were among the factors significantly associated with shorter OS (all $p < .04$).
Age, aetiology other than alcohol, and prior treatment other than sorafenib did not significantly affect OS.



Conclusion: In this large, single-centre study, OS after Y-90 SIRT was longer than that reported in many previous studies. Our long duration of experience and high volume of procedures support Y-

90 SIRT as an option for early therapy. Several factors, such as the presence of ascites or bilobar disease at baseline and alcohol as an aetiology, may predict shorter survival. Future analyses will include multi-variable models of predictive factors.

FRI-503

Sorafenib starting dose impacts on survival in the elderly population with hepatocellular cancer

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Background and aims: There is no consensus on the effect of sorafenib dosing on efficacy and toxicity among elderly patients (> 75years) with Hepatocellular Cancer (HCC). Advancing age is a significant risk factor for HCC, and the effect of sorafenib dosing on the elderly population has not been investigated in large, international studies. We aimed to compare a starting dose of 400 mg/day or less (low dose) with 800 mg/day (full dose) on toxicity and overall survival (OS) in an international multi-center study.
Method: 430 consecutive patients from 5 different international institutions who were treated with sorafenib were included in the study. Baseline demographic data, sorafenib dosing data including toxicities and response to treatment was collected.
Results: Median overall survival (OS) of the entire study population was 7.6months (95% CI: 6.71-8.56). When considering the elderly (n = 145), median OS was significantly lower (7.5 months vs 8.7, log rank p = 0.03). Starting dose had a significant impact on OS such that in patients over 75years receiving 800 mg (n = 103) had a median OS of 7.9months compared to 10.8months in those receiving low dose (n = 42), log rank p = 0.02 (Figure 1). Toxicity was similar between both groups.

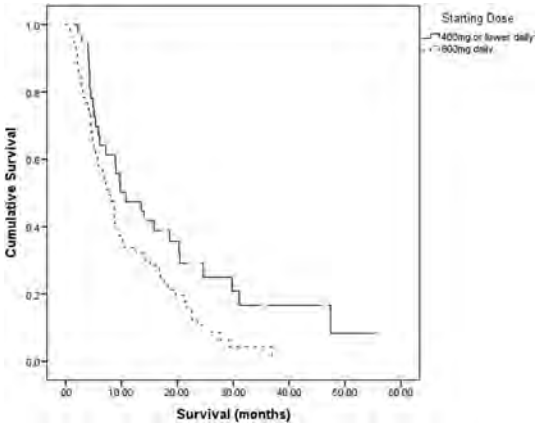

Figure 1: Overall survival in patients over the age of 75 receiving a starting dose of sorafenib of either high dose (800 mg daily) or low dose (400 mg or less), log rank test p = 0.02

Conclusion: Starting dose of sorafenib has a significant impact on OS in patients over the age of 75. Full dose should be used with caution.

FRI-504

Sorafenib use in patients with HCC on a background of non-alcoholic fatty liver disease

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Background and aims: Fuelled by a rise in obesity and related risk factors, the incidence of non-alcoholic steatohepatitis-related hepatocellular carcinoma (NASH-HCC) is rising. Data pertaining to the utility of sorafenib in this setting is needed, but lacking. We examined the efficacy of sorafenib in a multicentre cohort of patients with NASH-HCC and compared this with currently available data of sorafenib efficacy in other settings.
Method: An international data-set from centres in Europe and USA was prospectively collected on patients with NASH-HCC who had been treated with sorafenib. Kaplan Meier method was used to estimate progression-free and overall survival. Univariate and multivariate analyses by Cox regression were used to identify prognostic factors.
Results: 136 patients were identified across the three centres. The median progression-free survival was 5.03 months (95% CI: 3.78-6.21) and median overall survival (OS) was 7.99 months (95% CI: 6.08-9.91). In a subset with Child-Turcot-Pugh A and Barcelona Clinic Liver Disease B/C disease, the median OS was 8.00 months (95% CI: 5.15-10.84). Univariate analysis identified several significant factors however only CTP and BCLC scores remained significant in multivariate Cox regression.
Conclusion: The median OS of comparable patients with NASH-HCC treated with sorafenib in our study appears lower than historical data from both clinical trial and real-world data sets. In addition, these results suggest that patients with CTP-B/C and BCLC C disease likely derive little benefit from treatment. Prospective data is needed confirm this. As the burden of NASH-HCC continues to increase rapidly, these results will be important for treatment stratification and patient prognostication.

FRI-505

Early response and safety of lenvatinib for patients with advanced hepatocellular carcinoma in a real-world setting

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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 excluded patients with a history of systemic chemotherapy, bile duct invasion, and low platelet counts. This study aimed to investigate the efficacy and safety of lenvatinib for these patients and in the real-world setting.
Method: Patients who were administered lenvatinib for advanced HCC between April and October 2018 were enrolled. They were followed for more than 2 months, and the treatment response and safety were evaluated via dynamic computed tomography at baseline and 2 months after treatment initiation. Further analysis by stratifying patients according to compliance and non-compliance with the REFLECT inclusion criteria was conducted.
Results: A total of 41 patients were included. More than 50% (23/41) did not meet the REFLECT inclusion criteria. In total, 5 (12.2%), 20 (48.8%), 12 (29.3%), and 4 (9.3%) showed complete response, partial response, stable disease, and progressive disease, respectively. The objective response rate was 61.2%. The objective response rate (p = 0.8293) and disease control rate (p = 0.7965) was similar between patients who did and did not meet the REFLECT inclusion criteria. Moreover, the safety profile was also similar between the patients.
Conclusion: Lenvatinib showed high early 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.

FRI-506

A nationwide multicenter study in Japanese patients treated with lenvatinib in real world practice

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Background and aims: Lenvatinib (LEN) has been approved as a single agent for patients with unresectable hepatocellular carcinoma (u-HCC) since Mar 2018 in Japan. We performed a retrospective nationwide multicenter study in Japan, especially focused on the antitumor effect and adverse events in real world practice.
Method: A total of 131 u-HCC patients received LEN from March 2018 at 15 sites in Japan were registered. Tumour assessments in accordance with RECICT ver1.1 and modified RECIST were 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 was 73 (46-91)years, 102 (77.9%) patients were male, and median body weight (BW) was 60 (30-94) kg. The baseline liver function was Child-Pugh class A in 109 (83.2%) patients. Eighty-two (62.6%) patients were BCLC stage C. As the 2nd-line therapy (after sorafenib), 33 (25.2%) patients received LEN and 19 (14.5%) patients did as the 3rd-line (after regorafenib). Median observation time was 3.0 months and 8 patients died from HCC progression. The imaging findings of 66 (50.3%) patients were evaluated at 4-8weeks. Based on mRECIST, CR was shown in 5 (7.6%), PR in 22 (33.3%), SD in 28 (42.4%), and PD in 11 (16.7%). Overall response rate (ORR)ORR and disease control rate (DCR)DCR of tyrosine kinase inhibitor (TKI) naïve patients (n = 37) were 40.4% and 83.7%, while those of TKI experienced (n = 29) were 41.3% and 82.7%. Fifty-two patients started at 12 mg/day and dose reduction was necessary in 87.0% of the patients. The common any-grade AEs were hypertension (52.2%), diarrhoea (30.9%), decreased appetite (57.4.%), fatigue (51.6%) and proteinuria (41.0%). Hand-food skin reaction (HFSR) was observed in 28.9% of patients. The incidence of decreased appetite and fatigue were higher in the patients with lower BW (< 60 kg), even though the initial dose was based on actual BW.
Conclusion: The efficacy of LEN therapy in real world practice in Japan was equivalent to the phase 3 clinical trial. The response rate in TKI experienced patients was similar to TKI naïve patients. The incidence of HFSR during LEN in real world practice was lower than that of the sorafenib group in the phase 3 trial of LEN. AE profile was different from sorafenib and decreased appetite must be carefully monitored and managed.

FRI-507

Hepatocyte-specific role of c-Jun N-terminal kinase 2 for disease progression and therapy in chronic liver disease

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Background and aims: The c-Jun N-terminal kinases (JNKs) play a crucial role in liver physiology and disease pathogenesis by modulating cell death and inflammation. Here, we tested the hypothesis that *Jnk2* specifically in hepatocytes prevents chronic liver disease (CLD) progression and define the potential use of MAPK9 as a new therapeutic target. Therefore, we compared conventional hepatocyte-specific *JNK2* knockdown with disease stage-specific *JNK2* deletion using RNAi in an experimental model of CLD, the $NEMO^{\Delta hepa}$ mice.
Method: Double knock-out mice with hepatocyte-specific deletion of JNK2 and NEMO/IKKγ ($NEMO^{\Delta hepa}JNK2^{\Delta hepa}$, DKO) were generated and CLD progression was examined. *Jnk2* inhibition specifically in hepatocytes using siRNA (*siJnk2*) was first validated *in vitro* and then *in vivo* in wild-type (WT) and in $NEMO^{\Delta hepa}$ mice. *siJnk2* was administered at different CLD stages. Disease activity was analyzed using imaging analysis of fluorescence molecular and microcomputed tomography (FMT, μCT), protein expression, IHC, IF and histopathology.
Results: Twelve-week-old DKO animals showed significantly elevated serum transaminases and deteriorated liver parenchyma, together with immune cell infiltration compared to $NEMO^{\Delta hepa}$ mice and controls. Further, DKO mice display significant increased hepatic stellate cell (HSC) activation markers including αSMA and Col1A1 mRNA expression levels, which was confirmed by Sirius red staining. In contrast, *Jnk2* deletion in aged $NEMO^{\Delta hepa}$ mice caused a significant improvement of HCC development, as observed by reduction of total numbers of tumors. Concomitantly, analysis of specific HCC markers such as TNF-α, AFP, VEGF-B and c-MYC demonstrated significantly improved mRNA expression levels. RNAi for JNK2 specifically in hepatocytes impaired liver function at an early phase of CLD in $NEMO^{\Delta hepa}$ mice. *siJnk2* caused increased liver transaminases, hepatocellular apoptosis and compensatory proliferation. In addition, elevated HSC activation deteriorated hepatic fibrogenesis progression. In contrast, *siJnk2* in aged $NEMO^{\Delta hepa}$ mice (44-52 weeks) resulted in improved liver parenchyma and diminished serum values. In addition, FMT/μCT analysis revealed reduced hepatocellular apoptosis. Moreover, chronic *siJnk2* treatment dramatically reduced HCC formation in 52 weeks old $NEMO^{\Delta hepa}$ mice. This correlated with a reduced presence of premalignant and malignant liver tumors corresponding to dysplastic nodules and differentiated adenomas, respectively.
Conclusion: Progression of liver diseases is associated with different stages of phase transition. Our findings demonstrate a dependent role of JNK2 during CLD progression in $NEMO^{\Delta hepa}$ mice. Notably, formulated *siJnk2* delivery to hepatocytes in the late phase of CLD ameliorated NASH and HCC progression and thus might be an attractive therapeutic option for precision medicine in CLD.

FRI-508

How reliable is initial liver resection before salvage liver transplantation and what are the predictors of dropout?

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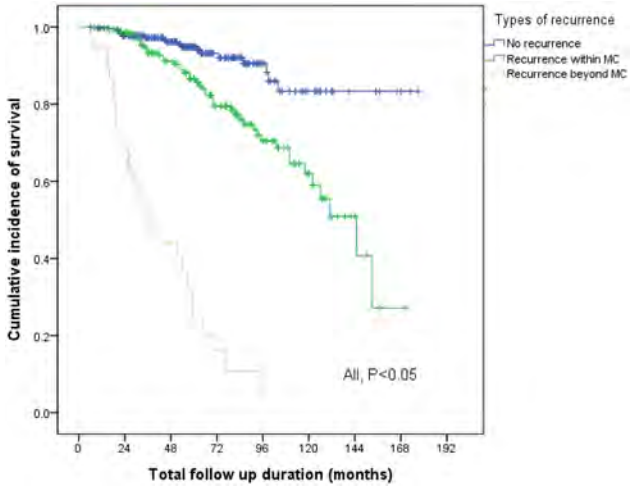
Background and aims: In the era of liver donor shortage, there is a controversy whether to undergo liver resection or liver transplantation (LT) at early stage HCC. Thus, we aimed to find the rate of HCC recurrence beyond Milan criteria (MC) after liver resection and factors that reliably predict recurrence beyond MC which lead to dropout of salvage LT.

Method: This study included patients diagnosed with HCC within MC at baseline and had liver resection as initial treatment from year 2002 to 2016. In total, 480 patients were enrolled.



Results: Among 480 HCC resected patients, 32.7% patients were in BCLC stage 0, 42.3% of resected HCC showed high Edmonson's grade (III-IV), 22.9% with lymphovascular invasion and 76.9% had liver cirrhosis. All patients were followed up for a median duration of 59 months (range, 6-177). During follow-up, a total of 214 recurrence occurred with 176 (37%) patients recurring within MC and 38 (8%) patients recurring beyond MC. Baseline PIVKA-II level were significantly higher for those who showed recurrence beyond MC 113 mAU/ml (range, 17-13, 622) than those who recur within MC 34 mAU/ml (range, 5-1, 562) ($p < 0.001$). Majority of HCC recurrence beyond MC developed within 2 years with cumulative incidence of 29%, 79% and 95% compared to 21%, 56%, and 88% for those who recur within MC at year 1, 2 and 5 (log rank, $P < 0.01$). Predictors for those who will recur beyond MC that hamper salvage LT were analyzed. In univariate analysis, multiple tumor number (2, 3 vs 1), BCLC stage (A vs 0), high Edmonson grade, lymphovascular invasion, gross finding (multinodular confluent, infiltrative vs. expanding nodular, expending nodular with perinodular expanding type) and high PIVKA level (> 100 mAU/ml) were associated with recurrence beyond MC. In multivariate analysis, high Edmonson grade, lymphovasular invasion, tumor gross findings and high PIVKA level were independent predictive factors of recurrence beyond MC. When scoring was made using the independent factors (score 0: none of the factors, score 1: at least 1 factor and score 2: at least 3 factors), patients with the highest score showed highest cumulative incidence of recurrence beyond MC followed by score 2 and 3 (log rank $P < 0.05$). Survival rate was significantly the lowest in patients that recurred beyond MC followed by within MC and no recurrence group (figure).

Conclusion: Our study involving large number of HCC resected patients showed that early HCC within MC that had low rate of lymphovascular invasion and high Edmonson grade at baseline showed relatively low rate of HCC recurrence beyond MC (8%) which imply that liver resection as first treatment before salvage LT could be more realistic than performing LT as first line in the era of organ shortage. However, those with high risk of recurring beyond MC as mentioned above should undergo salvage LT after liver resection before the development of recurrence.

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Cirrhosis and its complications: Clinical

SAT-001

Validity of urinary bio markers and cardiac echo in diagnosis of acute kidney injury in patients with liver cirrhosis

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Background and aims: Acute kidney injury in liver cirrhosis patients in specific acute tubular necrosis and hepatorenal syndrome carry bad prognosis and hence early recognition of the two entities is crucial. This study was done to test urinary Neutrophil Gelatinase Associated Lipocalin and Trefoil Factor 3 as well as cardiac echo as markers differentiating acute kidney injury aetiologies in patients with liver cirrhosis.

Method: It was conducted in Alexandria University Hospital from September 2017 till June 2018 enrolling 80 patients with liver cirrhosis diagnosed based on clinical, laboratory and ultrasonography divided into four groups. Group I, 20 patients with hepatorenal syndrome, group II, 20 patients with prerenal azotaemia and group III, 20 patients with acute tubular necrosis diagnosed based on the revised consensus recommendations of the International Club of Ascites 2015. Group IV, 20 patients with liver cirrhosis without renal impairment and an additional group V with 20 healthy individuals as controls. Urinary Neutrophil Gelatinase associated Lipocalin and Trefoil Factor 3 were measured by Quantikine® Enzyme Linked Immunosorbent Assay from RandD Systems Minneapolis, MN, USA.

Results: Urinary Neutrophil Gelatinase Associated Lipocalin was significantly higher in patients with acute tubular necrosis, followed by patients with hepatorenal syndrome and prerenal azotaemia followed by patients without renal impairment while urinary Trefoil Factor 3 was significantly highest in patients with acute tubular necrosis without significant difference between the other groups ($p < 0.001$). Cut off values of $\geq$ 14.40 ng/dl and > 28.76 ng/dl were found to differentiate acute tubular necrosis from hepatorenal syndrome with 85% and 90% sensitivity and 70% and 95% specificity for each marker respectively. Moreover, number of patients with diastolic dysfunction was significantly higher in patients with hepatorenal syndrome than acute tubular necrosis ($p < 0.001$). Also, uTFF3 was significantly lower in patients with diastolic dysfunction than those without ($p < 0.001$).

Conclusion: Urinary Neutrophil Gelatinase Associated Lipocalin and Trefoil Factor 3 are potential markers for diagnosing acute tubular necrosis from hepatorenal syndrome. Diastolic dysfunction in patients with liver cirrhosis and acute kidney injury favours diagnosis of hepatorenal syndrome. Lower uTFF3 values could predict development of diastolic dysfunction in patients with liver cirrhosis.

SAT-002

Lusutrombopag is a safe treatment option for thrombocytopenia in patients with chronic liver disease undergoing an invasive procedure: Pooled safety analysis from 3 studies

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Background and aims: Lusutrombopag (LUSU) is a thrombopoietin receptor agonist (TPO-RA) approved in Japan (2015) and the US (2018) for the treatment of thrombocytopenia (TCP) in patients (pts) with chronic liver disease (CLD) who are scheduled to undergo an invasive procedure. In a pooled analysis of 2 Phase 3 studies, LUSU reduced the need for platelet transfusions (PT) compared to placebo. Treatment with TPO-RAs has been associated with an increased risk of thrombotic events in pts with CLD. Thus, a thorough safety assessment of new agents is critical. A pooled retrospective analysis of 3 clinical studies was performed to assess safety of LUSU.

Method: Safety data from 3 double-blind, randomized, placebo-controlled studies in pts with CLD and TCP undergoing an elective invasive procedure (Phase 2b: M0626, Phase 3: L-PLUS 1 and L-PLUS 2) were pooled. Adult subjects with platelet counts (PC; $x10^9$/L) < 50 at baseline received LUSU 3 mg or placebo (PBO) for up to 7 days before a procedure scheduled 9-14 days after randomization. PT was mandated if the PC remained < 50 immediately prior to procedure. Adverse event (AE) data were collected from signing of informed consent through completion of posttreatment period or early termination.

Category, n (%)	Lusutrombopag 3 mg	Placebo
≥1 AE	112 (65.5)	115 (67.6)
≥1 AE leading to death	3 (1.8)	0
≥1 Serious AE	9 (5.3)	12 (7.1)
≥1 AE leading to withdrawal of study drug	0	1 (0.6)
≥1 treatment-related AE	13 (7.6)	14 (8.2)
≥1 treatment-related serious AE	2 (1.2)	1 (0.6)

AE, adverse event

Results: The pooled safety population included 341 pts (n = 171, LUSU; n = 170 PBO). Approximately 65% of pts in the LUSU and PBO groups experienced an AE (Table). Thrombotic and thromboembolic AEs occurred in 1.8% (3/171) of LUSU pts (cardiac ventricular thrombosis, n = 1 [pt had prior history of cardiac ventricular thrombosis]; portal vein thrombosis, n = 2) and 2.4% (4/170) of PBO pts (mesenteric vein thrombosis, n = 2; portal vein thrombosis, n = 2). Overall, bleeding-related AEs occurred in significantly less LUSU vs

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PBO pts (15 [8.8%] vs 27 [15.9%]), respectively. The 3 AEs leading to death were not considered treatment-related but due to the progression of underlying or concomitant disease.
Conclusion: In this pooled safety analysis, LUSU was safe and well-tolerated in pts with TCP and CLD undergoing invasive procedures. Approximately 50% fewer bleeding-related AEs were observed in pts treated with LUSU vs PBO.

SAT-003
Real-world data demonstrate safety and effectiveness of lusutrombopag in chronic liver disease patients with thrombocytopenia undergoing planned invasive procedures: Interim analysis

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Background and aims: Lusutrombopag (LUSU) is a thrombopoietin receptor agonist, developed by Shionogi and Co., Ltd. and approved in Japan (2015) and US (2018) for treatment (tx) of thrombocytopenia (TCP) in adult patients (pts) with chronic liver disease (CLD) scheduled to undergo planned invasive procedure. Ongoing post-marketing surveillance (PMS; Oct 2016-May 2021) collects safety and effectiveness data in Japanese clinics. As of Sept 2018, data from 338 pts, including 21 re–tx pts, were analysed for this interim report.
Method: PMS plans to enrol 1, 000 pts and follow them for 2 months (mo) after initial LUSU dose. Pts receiving ≥ 1 re-tx within 6 mo of initial tx are observed for 2 mo from start of each re-tx. This study captures data on adverse events (AEs) occurring during and after tx. Primary efficacy outcome is proportion of pts who do not require pre-operative platelet transfusion (PT).
Results: 334 pts were evaluable for safety (4 excluded: registration violations [n = 2]; overlapping pts [n = 2]) and 318 for efficacy (16 excluded: off-label use [n = 1]; off-indicated dosage/administration [n = 1]; use in unapproved population [Child-Pugh C; n = 14]). Most pts had liver cirrhosis (n = 315, 94%). Mean baseline platelet count (PC)±SD was 46 ± 14×10^9/L (range: 15-110; n = 315). There were 380 procedures in 334 pts, including 110 (28.9%) radiofrequency ablation, 59 (15.5%) transarterial chemoembolisation, and 49 (12.9%) endoscopic injection sclerotherapy. 14 adverse drug reactions (ADRs), including portal vein thrombosis (PVT; n = 4), increased ALT (n = 2), and increased AST (n = 2), were reported in 11 pts (3.3%). 41 serious AEs occurred in 29 pts (8.7%), including hepatic failure (n = 3; 0.9%), hepatic encephalopathy (n = 2; 0.6%), ascites (n = 2; 0.6%), and thrombosis (n = 1 splenic vein, 0.3%; n = 6 PVT, 1.8%); 7 were considered tx-related. Mean time to procedure after starting LUSU was 12.4 days. 282 (93%) of 303 pts without PT refractoriness underwent procedure without PT. After LUSU, mean maximum PC was 89 ± 35×10^9/L (range: 25-352; n = 288); mean maximum change from baseline PC was 42 ± 31×10^9/L (range: –6 to 276; n = 288). In 21 re-tx pts, no ADRs were reported during the observational period; PT avoidance rate was 100%.
Conclusion: Use of LUSU in real-world clinical practice demonstrates the product is safe and effective for CLD TCP pts undergoing planned invasive procedures (consistent with previously reported clinical trial data).

SAT-004
Bacterial translocation in patients with liver cirrhosis and variceal bleeding

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Background and aims: Bacterial translocation has been associated with increased bacterial infection risk in patients with liver cirrhosis. Endotoxaemia has been considered a critical trigger for variceal bleeding. The aim of the study was to investigate the presence of bacterial translocation in cirrhotic patients with variceal bleeding at admission.
Method: Blood samples were collected before any diagnostic/therapeutic intervention. Lipopolysaccharide (LPS), IgM and IgG antibodies against endotoxin, soluble CD14 and lipopolysaccharide binding protein (LBP) were measured by ELISA for the assessment of bacterial translocation and the Fatty acid-binding protein (I-FABP) for the evaluation of intestinal permeability. Bacterial DNA determination was performed by PCR, using universal 16SrRNA primers.
Results: Forty-one cirrhotics with variceal bleeding [median age: 58 years (range 47.5-66.5), M/F: 33/8, cirrhosis etiology: alcohol/HBV ±HDV/HCV/NASH/other: 24 (58.5%)/4 (9.8%)/7 (17.1%)/4 (9.8%)/2 (4.8%), CP stage A/B/C: 8/26/7)] and 43 stable cirrhotics [median age: 61 (54-65) years, M/F: 30/13, cirrhosis etiology: alcohol/HBV ±HDV/HCV/AH/other: 19 (44.2%)/15 (34.8%)/3 (7%)/3 (7%)/1 (2.2%)/3 (7%), CP stage A/B/C: 22/12/9)] were included. Three patients had overt infection (1 had detectable bacterial DNA) at admission. No statistical difference was observed in the bacterial translocation or intestinal permeability markers between the examined groups of any stage (table 1).

Table 1:

	Variceal bleeders	Stable cirrhotics
CP_A	**Median (IQR)**	
CD14 (pg/ml)	1946.1 (1531-4451)	2255.5 (1443-3120)
LPS (EU/ml)	1.9 (1-3)	2.4 (1-4)
IgM (MU)	33.6 (26-93)	48.2 (28-53)
IgG (MU)	185.1 (161-347)	200.5 (136-287)
LBP (μg/ml)	8.3 (0-13)	4.3 (3-5)
I-FABP (pg/ml)	2795.2 (1364-5250)	1379.5 (1060-1699)
CP_B		
CD14 (pg/ml)	3198.9 (1766-3412)	3121.6 (2008-3892)
LPS (EU/ml)	3.7 (2-19)	2.8 (2-4)
IgM (MU)	38.6 (21-54)	34.9 (31-83)
IgG (MU)	232.4 (175-350)	244.8 (115-563)
LBP (μg/ml)	5.4 (4-9)	4.5 (4-18)
I-FABP (pg/ml)	2247.2 (1771-5128)	1665.1 (665-3996)
CP_C		
CD14 (pg/ml)	3312.3 (2236-3674)	2725.8 (1980-3872)
LPS (EU/ml)	17.6 (2-33)	14.6 (3-35)
IgM (MU)	38.3 (20, 53)	116.2 (96, 129)
IgG (MU)	237.8 (194-603)	318.6 (284-375)
LBP (μg/ml)	1.8 (0-7)	7.8 (5-28)
I-FABP (pg/ml)	2484.8 (1229-4299)	3808.6 (1145-6199)

Conclusion: This study does not support a greater degree of intestinal barrier disintegration, endotoxemia or bacterial translocation in cirrhotics with variceal bleeding compared to stable cirrhotics.

SAT-005

Prognostic factors associated with mortality of acute variceal hemorrhage in cirrhotic patients : Multi-center results

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Background and aims: Acute variceal hemorrhage is a serious complication in liver cirrhosis associated with high mortality. Thus it is important to determine the risk factors associated with this high mortality.To investigate the risk factors for 5-day and 6-week mortality and rebleeding in acute variceal hemorrhage in cirrhotic patients treated by early vasoactive drugs with endoscopic management

Method: Retrospective study of acute variceal hemorrhage patients who underwent early vasoactive drugs with endoscopic treatment was collected since 1 October 2012 to 30 September 2018 in Phramongkutklao hospital and Maharat Nakhon Sri Thummarat hospital. Demographic information, medical histories, physical examination findings, and laboratory test results were collected. Survival analysis was estimated using the Kaplan-Meier method and compared using the log-rank test. The multivariate analysis was performed using the Cox proportional hazard model to identify independent risk factors for mortality and rebleeding at 5-day and 6-week

Results: Since 1 October 2012 to 30 September 2018 Phramongkutklao hospital 2654 cases of UGIB was EV bleeding 385 cases (14.5%) and Maharat Nakhon Sri Thummarat hospital 3753 cases of UGIB was EV bleeding 760 cases (20.25%) 5-day mortality was 110 (9.6%) and 6-week mortality was 141 (12.33%) out of total 1144 cases which associated risk factors through multivariate analysis composed of MAP < 50 (HR = 2.01, 95%CI:1.18-3.44, *P = 0.011*), and high risk stigmata EV on endoscopic finding (HR = 4.01, 95%CI:2.50-6.44, *P < 0.001*). And one additional risk factor that found only in 6-week mortality was Glasgow Blatchford score ≥ 6 (HR = 34.66, 95%CI:13.88-86.52, *P < 0.001*). Whereas GU and/or DU on endoscopic finding appeared to be protective factors of mortality. 5-day rebleeding was 155 cases (13.6%) and 6-week rebleeding was 244 cases (21.3%) which associated with risk factors through multivariate analysis composed of MELD score ≥ 18 (HR = 2.46, 95% CI:1.76-3.45, *P < 0.001*), Glasgow Blatchford Score ≥ 6 (HR = 2.20, 95% CI:1.19-4.05, *P = 0.012*), high risk stigmata EV on endoscopic finding (HR = 2.02, 95%CI:1.39-2.93, *P < 0.001*), weekend visit (H = 1.33, 95% CI:1.00-1.75, *P = 0.048*), duration of cirrhosis ≥ 2 years (HR1.59, 95% CI:1.06-2.39, *P = 0.025*), antiplatelet (HR = 1.83, 95%CI:1.06-3.17, *P = 0.031*) and NSAIDS use. (HR = 3.39, 95%CI:2.06-5.60, *P < 0.001*).

Conclusion: In this study, strong risk factors associated with 5-day and 6-week mortality in acute variceal hemorrhage were high risk stigmata on endoscopic finding, MAP < 50, and high MELD score accordingly. Additional risk factor in 6-week mortality was Glasgow Blatchford Score ≥ 6. 5-day and 6-week rebleeding risk factors also similar with mortality risk factors which included Glasgow Blatchford Score ≥ 6, antiplatelet and NSAIDS use, duration of cirrhosis and weekend visit.

SAT-006

Efficacy of oral thrombopoietin receptor agonist lusutrombopag in chronic liver disease by underlying disease aetiology

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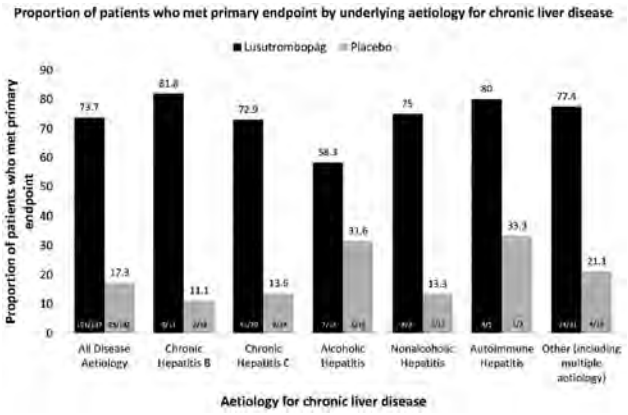
Background and aims: Lusutrombopag (LUSU) is an oral thrombopoietin (TPO) receptor agonist that has been approved in Japan (2015) and the US (2018) for treatment of thrombocytopenia (TCP) in patients (pts) with chronic liver disease (CLD) prior to invasive procedures. Certain aetiologies for CLD, such as alcohol abuse, may cause bone marrow suppression and low TPO production. The aim of this pooled analysis was to evaluate the efficacy of LUSU in pts with CLD by underlying disease aetiology.

Method: L-PLUS 1 (Japan) and L-PLUS 2 (global) were similarly designed, Phase 3, multicentre, randomized, double-blind, placebo-controlled studies. Pts with CLD and platelet count (PC) < 50×10^9/L scheduled for an invasive procedure were randomized 1:1 to LUSU 3 mg or placebo (PBO) and dosed orally once daily for up to 7 days. For this analysis, the per-protocol (PP) pt population (defined as all randomized pts with no major protocol violations) was pooled by underlying CLD disease aetiology. The primary efficacy end point was the proportion of pts who required no platelet transfusion (PT) prior to the invasive procedure and no rescue therapy for bleeding from randomization through 7 days post-invasive procedure.

Results: Of the 312 pts randomized, 270 pts were in the PP population (LUSU group: n = 137; PBO group: n = 133). Underlying aetiology for CLD in the PP population was: chronic hepatitis B, 10.7% (29/270); chronic hepatitis C, 47.8% (129/270); alcoholic hepatitis, 11.5% (31/270); non-alcoholic hepatitis, 8.5% (23/270); autoimmune hepatitis, 3.0% (8/270); and other hepatitis or mixed disease aetiology, 18.5% (50/270). The underlying aetiologies for CLD were generally similar between the 2 treatment arms. Overall, 73.7% (101/137) of pts in the LUSU group met the primary end point vs 17.3% (23/133) in the PBO group (difference of proportion, 55.8 [95% CI: 46.6, 65.0]; p < 0.0001). A greater proportion of pts met the primary end point in the LUSU arm vs PBO arm in each disease aetiology group (Figure). The proportion of pts experiencing ≥ 1 adverse event was 61.9% in the LUSU group and 64.5% in PBO group; 6.5% and 9.0% events, respectively, were deemed treatment-related.



Conclusion: Compared to PBO, LUSU was efficacious in avoiding the need for PT in pts with CLD-TCP scheduled to undergo invasive procedures, regardless of underlying disease aetiology.

SAT-007

Survival and risk factors of mortality after emergency transjugular intrahepatic portosystemic shunt for uncontrolled acute variceal bleeding caused by cirrhosis-related portal hypertension

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Background and aims: Few data are available regarding the prognosis of covered emergency transjugular intrahepatic portosystemic shunt (TIPS) for refractory variceal bleeding caused by portal hypertension in the era of Baveno V/VI consensus. The aims of this study were to assess survival and identify risk factors of death in these patients.
Method: All patients treated with emergency TIPS for refractory variceal bleeding due to cirrhosis related portal hypertension in two French tertiary centers between 2007 and 2017 were included. 45-days mortality was correlated with clinico-biological data at admission and with dispensed treatments using Kaplan-meier curves with the log-rank test as well uni and multivariate analysis using a Cox Model.
Results: 73 patients were included (80% of men, median age of 56 years old, 94.5% of alcoholic cirrhosis, median MELD at 22 and 43% of ACLF grade 3). All patients were managed according to the Baveno consensus, 73% of patients required vasopressors, 62% oral tracheal intubation and 23% renal replacement therapies. TIPS could not be performed in 1 patient and 8% of patients experienced acute pulmonary edema after TIPS. Rate of TIPS failure (including death or non-control of hemorrhage) at 5 days was 26%. The 45-day mortality was 49% (76% for ACLF grade 3, 91% for lactates > 5mmol/L and 93% for MELD > 30). No patient with an MELD > 30 was alive at 2 months. The causes of death at 45 days were multi-visceral failure (67%), refractory bleeding (22%) and sepsis (8%). In multivariate analysis, the MELD score (OR = 1.09, 95% CI [1.05-1.13], p < 0.001) and renal replacement therapies (OR = 4.5, 95% CI [2.00-10.11], p < 0.001) were independently associated with 45-day mortality. Despite initial antibiotic prophylaxis, 42% of patients developed an in-hospital infection, including 23% of multi-drug resistant bacteria and 18% of yeast. Overall survival was 40% at 2 years. 19% of patients had bleeding recurrence due to portal hypertension and 54% hepatic encephalopathy Type 2 diabetes was associated with the occurrence of hepatic encephalopathy.
Conclusion: After emergency TIPS for refractory acute variceal bleeding, 45-days mortality was 49% and could be predicted by the MELD-score. Early diagnosis and treatment of acute kidney injury and of infections will be useful to improve the prognosis of these patients. Due to the occurrence of rebleeding, implementation of standardized endoscopic and ultrasonographic surveillance should be discussed.

SAT-008

Quality of medical care measurement in hepatic cirrhosis outpatients: Is there room for improvement?

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Background and aims: Sets of indicators have been reported to measure cirrhosis related quality-of-care, and fulfilment of those are important in clinical practice. Adherence to those quality indicators in the few reported studies differs between 40 and 80%. The aims of our study were to assess adherence to cirrhosis-related quality-of-care measurements in outpatients' follow-up and to compare it depending on attendant physician's experience (junior vs senior doctor).
Method: Observational unicentric study. Clinical records of all cirrhotic patients visited during the second semester of 2017 as outpatients have been reviewed. General data, attendant physician's experience and 13 indicators of 5 great domains (cirrhosis aetiology, severity of the disease, hepatocellular carcinoma screening, variceal haemorrhage prophylaxis and vaccinations) have been collected.
Results: Of 591 patients' clinical records reviewed, 324 were included (123 excluded due to absence of cirrhosis, 39 due to liver transplantation, 47 treated from a hepatocellular carcinoma, and 58 not visited at the hospital). Cirrhosis aetiology was reported in 92% of cases, and severity and liver transplant indication in 75% and 78% respectively. Current alcohol consumption was reported in 79%. Updated ultrasonography was performed in 90% of the patients (9% requested but not scheduled, 1% not requested), but only 67% had all biannual ultrasonographies done. Initial upper endoscopy for variceal screening was performed in 97% of the cases, and follow-up endoscopies in 84%. Variceal bleeding prophylaxis was begun in 98% of patients in which was indicated. Beta-blockers dose was reported in 53% of cases, and it was not possible to assess its adequacy in 56%. Regarding vaccination policy, 71%, 49% and 42.9% received HAV, HBV and pneumococcus, respectively. There were significant differences between junior and senior doctors: in patients visited by junior doctors, aetiology, disease severity and beta-blockers dose were reports more frequently. Nevertheless, senior doctors had a better rate of current ultrasonography performed.
Conclusion: Our results could be considered excellent in variceal bleeding prophylaxis, good in hepatocellular carcinoma screening and worse in vaccinations. There were differences according medical experience, with a good quality of care in clinical records done by junior doctors. It is important to know the adherence to quality indicators in order to implement an improvement plan.

SAT-009

Pharmacokinetics of ertapenem in plasma and ascitic fluid in cirrhotic patients with spontaneous bacterial peritonitis

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Background and aims: Spontaneous bacterial peritonitis caused by multidrugs resistant bacteria is a therapeutic challenge and can decrease survival in cirrhotic patients. The exposure of ertapenem in plasma or ascitic fluid in cirrhotic patients is unknown. The aim of our study was to investigate if ertapenem concentrations in plasma or ascitic fluid were above the minimum inhibitory concentrations (MIC) of the main bacteria involved.
Method: Prospective unicentric study of patients with hepatic cirrhosis and nosocomial or health-care related spontaneous bacterial peritonitis. Demographic data and the episode features were recorded. Ascitic fluid and plasma concentrations of ertapenem were

analysed in day 1, 2 and 5 of treatment. Dose of ertapenem used was 1 gr daily. C50 was defined as the concentration above the MIC reached during at least 50% of time of the administration interval (a therapeutic goal in carbapenemics treatment), considering a maximum MIC of 1 mg/L (EUCAST).

Results: Between April 2017 and October 2018, 74 episodes of spontaneous bacterial peritonitis were admitted, and finally 20 episodes met the inclusion criteria. Most of the patients had moderate liver dysfunction measured by MELD and Child Pugh score. In 81% of the episodes infection were resolved at the fifth day of treatment, without therapeutics failures. In-hospital mortality was 11%. In 55% of the episodes ascitic fluid culture were positive, with a mean MIC of 0.1 mg/L [0.01-0.25] to ertapenem. Finally, 70 determinations (45 in plasma and 25 in ascitic fluid) were analysed. Ertapenem concentrations in ascitic fluid reached C50 in 48% of the samples, although this goal was reached in plasma in 86% of the samples. Diffusion ratio of ertapenem (concentration in ascitic fluid/ concentration in plasma) was 76.9% [21.1-161.5%]. In 63.6% of patients, concentration of ertapenem in ascitic fluid was below 1 mg/L during the first 36 hours of treatment.

Conclusion: Plasma concentrations of ertapenem were good, although the diffusion rate was low compared to the diffusion rate observed in studies in non-cirrhotic patients. In more than 50% of times and up to 63.6% of times in the first 36 hours of treatment, ertapenem concentrations in ascitic fluid did not achieve values above the maximum MIC during at least 50% of time of the administration interval, but was above of MIC of isolated bacteria in all cases. Our data suggest that concentrations of ertapenem used at a 1 gr dose may not be enough for carbapenem-sensitive bacteria with high MIC.

SAT-010

Predictors of mortality in Child B cirrhotic patients with acute variceal bleeding

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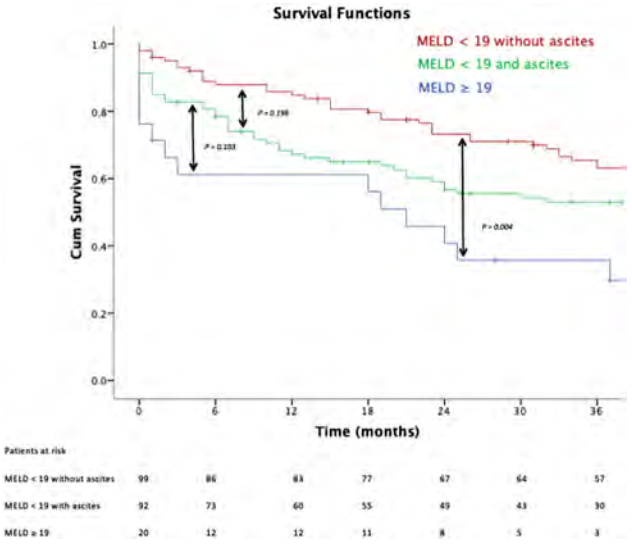
Background and aims: The prognostic factors of mortality in the subgroup of cirrhotic patients Child B with variceal bleeding are not well understood and differs between the previous published studies. These factors are important to consider the placement of preemptive TIPS. The aim of our study is to identify the predictors of mortality at 6 weeks and 12 months in patients with hepatic cirrhosis and moderate hepatic dysfunction (Child B) with variceal bleeding.

Method: observational study including patients with liver cirrhosis and moderate dysfunction (Child B) with variceal bleeding and without exclusion criteria for preemptive TIPS consecutively admitted at university hospital between January 2006 and December 2017. Patients were treated according to current clinical guidelines. A univariate and multivariate analysis of the predictors of mortality at 6 weeks and an actuarial survival analysis were performed.

Results: In 11 years, 283 Child B patients with variceal bleeding were admitted, and 69 patients were excluded for met exclusion criteria for preemptive TIPS. Of the 214 patients included, 106 (49.5%) had ascites at admission, in 63 (29.4%) active bleeding was observed in the initial endoscopy and 21 patients (10%) had MELD ≥ 19. Active bleeding was not a prognostic factor of mortality neither in 6 weeks (14.3% vs 9%, $p = 0.334$) nor 12 months (34% vs 22%, $p = 0.310$). The 6-week mortality of the entire cohort was 10.7%. 11 patients needed a rescue TIPS due to treatment failure. The univariate analysis showed that the presence of hepatic encephalopathy, ascites on admission, MELD ≥ 19 and treatment failure were predictors of mortality at 6 weeks. In the multivariate analysis, had MELD score ≥ 19 (OR 4.74 [1.59-14.1]), the presence of ascites (OR 3.18 [1.28-8.78]) and treatment failure (OR 3.15 [1.1-9.8]) were independent predictors of mortality. We have defined three groups with significant differences in mortality at 6 weeks: 21 patients (10% of all cohort) with MELD ≥ 19 with a mortality of 33.3%, 93 patients (43.5%) with a MELD score below 19 points and with ascites that presented a mortality of 14%, and a low risk group of 100 patients (46.7%) with MELD below 19 points and without ascites with a mortality of 3% at 6 weeks. Actuarial survival at 12 months, calculated using Kaplan-Meier method, was 58% of patients with MELD ≥ 19, 67.3% of patients with MELD below 19 points and ascites, and 84.8% of the low-risk group (MELD below 19 and without ascites).



Conclusion: The presence of MELD equal or above 19 points defines a group with high mortality at 6 weeks. Patients with MELD below 19 points and without ascites have an excellent prognosis at 6 weeks and at 12 months. Active bleeding at the index endoscopy should not be considered as a poor prognostic factor.

SAT-011

Cirrhotic patients:Is there any role to malnutrition in predicting mortality?

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Background and aims: Protein-caloric malnutrition and sarcopenia are common conditions in liver cirrhosis and are associated with poor prognosis and decreased survival. However, it remains to be enlightened whether deficient nutritional status predicts mortality in liver cirrhosis.

The aim of the study was to assess if the incorporation of sarcopenia into the Meld score (Meld-Psoas) may improve the prediction of mortality in liver cirrhosis when compared to Meld and Meld-Na scores

Method: retrospective study, included cirrhotic patients with computed abdominal tomography study between 2007 and 2017. Analytical parameters (creatinine, total bilirubin, INR and sodium) were analyzed and the transverse diameter of the right psoas muscle (TPMT) was determined at the cross-sectional level of L3-L4. The analytical parameters were collected within±7 days of the abdominal tomography.

The Meld-Psoas score: ([0.2xMELD]-[0.08xTPMT/height] +2), MELD and MELD-Na were calculated. A descriptive analysis and a ROC curve was performed to compare the predictive capability of each score to predict mortality at 6 weeks, 3, 6 and 12 months.

Results: 78 patients were included, 76.2% male gender with mean age of 56.5 ± 11.6 years. 89.7% of the patients presented alcoholic cirrhosis. 46 patients (59%) presented ascites and 10 (12.8%) hepatic encephalopathy. Patients presented a median creatinine of 0.89 (0.4-3.89)mg/dl, a bilirubin of 1.6 (0.25-18.61) mg/dl, INR of 1.4 (0.9-3.3) and sodium of 138.0 (123-145) meq/l. Regarding the scores, they presented a median Meld of 13.0 (6-43), a Meld-Na of 14.0 (6-42) and Meld-Psoas of 3.1 (1.32-9.4).

Meld-Psoas presented an AUROC of 0.90 (0.81-0.95, CI95%), 0.87 (0.77 -0.93) and 0.86 (0.77- 0.93) and 0.87 (0.78-0.94) predicting mortality at 6 weeks, 3, 6 and 12 months respectively.

Meld presented an AUROC of 0.88 (0.79-0.94), 0.83 (0.73-0.91), 0.83 (0.73- 0.91) and 0.84 (0.74-0.91) predicting mortality at 6 weeks, 3, 6 and 12 months respectively.

Meld-Na presented an AUROC of 0.87 (0.78-0.94), 0.82 (0.72-0.90), 0.82 (0.72-0.90), 0.84 (0.74-0.91) predicting mortality at 6 weeks, 3, 6 and 12 months respectively.

Meld-Psoas of 0.71 predicts 6 week mortality with a sensitivity of 100% and a specificity of 71%.

Conclusion: The incorporation of sarcopenia in Meld score (Meld-Psoas) presented an excellent accuracy in predicting mortality of cirrhotic patients, in particular 6 week mortality, superior than the observed in previous scores (Meld, Meld-Na).

SAT-012

Alterations in skin microbiota, serum bile acids and autotaxin modulate itching intensity in patients with cirrhosis

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Background and aims: Cirrhotics often complain of itching and have gut dysbiosis. Itching in non-cirrhotic cholestasis has been linked to autotaxin. Altered skin microbiota are associated with pruritic skin diseases but their impact on cirrhosis is unclear. Aim: To determine the effect of serum bile acids (BA), autotaxin, and skin microbiota on itching in cirrhosis.

Method: Cirrhotic outpts without PBC/PSC [with/without decompensation (decomp)] and controls underwent skin swabs for microbiota (16srRNA, 7 sites), serum BA analysis (LC/MS total, conjugated, primary BAs) and autotaxin, and 5D-itch scale (0-10, 10 = max intensity). Systemic inflammation (IL-6) and gut barrier (LPS binding protein LBP) were also tested. Skin sites tested were sebaceous (neck, forehead), dry (shin, forearm) and moist (umbilicus, lower abdomen, armpit). Data were compared between groups (cirrhosis/controls, decomp/not and 5D-scale ≥ 5/not). Linear discriminant analysis was used to compare microbiota. Correlation networks between serum BAs, skin microbiota were compared between cirrhotics with/without 5D ≥ 5.

Results: 70 subjects (20 controls, 59 years and 50 cirrhotics, 61 years, MELD 12, 20 decomp) were included. MELD score was higher in decomp (16 vs 9, $p < 0.001$) Itching: was worse in cirrhosis with greater proportion 5D score ≥ 5 compared to controls (Table). However, 5D scores between compensated and decomp pts were similar. Serum BA and autotaxin: All BA moieties and autotaxin were higher in cirrhosis (Table). Serum BAs were highest in those with 5D score ≥ 5 ($p < 0.05$-$p < 0.001$). Il-6 and LBP were also higher in cirrhotics and decomp pts. Skin microbiota: Composition was altered at all skin sites between controls and cirrhotics, compensated/decomp cirrhotics and those with/without significant itching. Gammaproteobacteria, Streptococcaceae and Staphylococcaceae were higher in cirrhosis, especially in 5D score ≥ 5 and were positively linked with serum autotaxin ($p < 0.03$-$p < 0.001$). IL-6, LBP or MELD score were not associated with itching intensity. On correlation networks, there was a significantly more complex interaction at every skin site between microbiota and serum BAs in pts with itching compared to those without itching.

*p<0.05 between groups	Controls vs Cirrhosis		Compensated vs Decompensated	
	Control (n=20)	Cirrhosis (n=50)	Comp (n=30)	Decomp (n=20)
Age	59.6±9.1	52.5±7.8	52.9±8.0	53.2±6.6
Gender (men)	16 (80%)	43 (86%)	26 (87%)	17 (85%)
Serum LBP (ng/ml)	2413±909	3120±1654*	2474±1338	3593±1725*
IL-6 (pg/ml)	1.9±1.4	14.2±8.5*	6.9±7.2	15.9±16.9*
Serum autotaxin(ng/ml)	189.3±58.4	440.0±221.0*	341±154	574±231*
Itching intensity (0-10)	0 (1)	3.0 (5.0)*	2 (5)	4.5 (4.75)
Itching intensity 5D≥5%	1 (5%)	18 (36%)*	8 (27%)	10 (50%)
Total serum BA	3.3 (4.1)	14.8 (48.5)*	9.8 (21.4)	60.5 (90.2)
Total Primary BA	1.5 (2.2)	8.0 (47.3)*	5.9 (15.3)	59.1 (86.4)*
Total Conjugated BA	1.5 (3.0)	10.0 (46.9)*	5.3 (11.8)	57.8 (90.5)*
Linear Discriminant Microbiota Changes	*Higher in controls*	*Higher in Cirrhosis*	*Higher in compensated*	*Higher in decompensated*
Neck	Chloroplast	Staphylococcaceae Clostridiales	—	Gammaproteobacteria, Fusobacteria, Streptococcaceae,
Forehead	Synergestetes, Deinococcus	—	—	Gammaproteobacteria, Alphaproteobacteria,
Shin	Actinobacteria	Gammaproteobacteria	—	Gammaproteobacteria, Alphaproteobacteria, Streptococcaceae
Forearm	Clostridiaceae, Fusobacteria	Staphylococcaceae Flavobacteriaceae	—	Gammaproteobacteria, Streptococcaceae
Umbilicus	Verrucomicrobiaceae Nitrosomonadaceae	Porphyromondaceae Leptotrichaceae	Actinobacteria	Gammaproteobacteria, Alphaproteobacteria, Streptococcaceae,
Lower Abdomen	Tenericutes, Rhizobiales	Gammaproteobacteria	Lactobacillaceae, Cyanobacteria	Gammaproteobacteria, Betaproteobacteria, Streptococcaceae,
Armpit	Clostridiaceae, Acidaminococcaceae	Staphylococcaceae	Peptostrepto coccaceae	Gammaproteobacteria, Alphaproteobacteria

Conclusion: Cirrhotics have higher serum BAs, itching intensity, serum autotaxin and altered skin microbiota compared to controls. The skin microbiota of patients with significant itching demonstrates higher potentially pathogenic Gammaproteobacteria and Streptococcaceae, which have strong correlations with serum BAs and autotaxin but not with cirrhosis severity, systemic inflammation or LBP. Skin microbiota could be a novel target for addressing pruritus in cirrhosis.

SAT-013

Potentially Preventable readmissions and complications in hospitalized patients with hepatic encephalopathy in a large multi-center cohort

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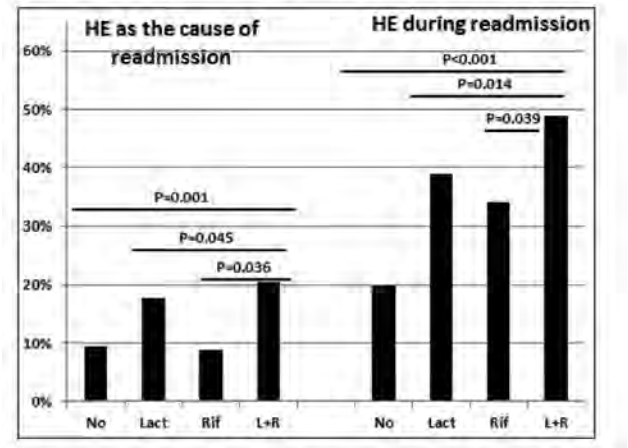
Background and aims: Hepatic encephalopathy (HE) is the major cause of readmissions and expenditure in cirrhotic pts in North America and quality improvement (QI) is needed.

Aim: Determine the rates/causes of potentially preventable readmissions and complications in hospitalized pts with HE using the North American Consortium for the Study of End-stage Liver Disease (NACSELD) cohort.

Methods: NACSELD prospectively enrolled admitted cirrhotics in 14 hepatology centers and followed them for 90 days post-discharge. QI analysis of HE was performed focusing (a) medication-related HE precipitants (b) aspiration in HE pts (c) initiation of HE Rx on discharge and (d) HE readmissions vis-a-vis lactulose/rifaximin use.
Results: Index HE episode: 2810 pts were studied, of whom 1677 (59%) were on HE Rx at admission (665 lactulose only, 153 rifaximin only, 859 both) and 930 patients were admitted for HE. The major precipitants were medication-related (32%) followed by acute kidney injury (18%), infections (17%), hyponatremia (16%) and others (17%). Medication-related precipitants were lactulose non-adherence 20%, lactulose overuse 1%, rifaximin underuse in 3%, opioids 4%, sleep aids 1% and psychoactive drugs 5%.
Index Hospital Course: *Grade3/4 HE*: 217 pts were admitted in grade 3/4 HE, of which 34 (16%) developed HE-related aspiration without ICU monitoring. *Rx change*: In all HE pts, rifaximin was initiated in 28%, with lactulose oral/enema in the rest. *On discharge*: The percent on HE Rx increased from 59% on admission to 66% at discharge (n = 1847 of 2810, n = 710 lactulose only, 151 rifaximin only and 918 both). 90-day outcomes: 421 pts died/were transplanted and were excluded. Remaining were 2447 (136 on rifaximin only, 639 on lactulose only, 855 on both and 790 without HE) pts, of whom 41% (n = 991) were readmitted. Readmission rate and discharge MELD was lowest in pts without HE compared to the rest (34%, 16 ± 6, p = 0.001) but were similar across all HE Rx pts[lactulose only (43%, 17.7 ± 7), rifaximin only (42%, 18.6 ± 6) and both (44%, 19.4 ± 6, p = 0.4). Major reasons for readmission were HE (16%), infection (10%) and GI bleeding (8%). Also, 36% of readmitted pts developed HE during the readmission. Within readmitted pts, HE-related readmission was lowest in those without prior HE. Of those on HE Rx, rate of HE readmissions or HE development during readmissions was significantly lower in pts only on rifaximin compared to the rest (Figure). A binary logistic ANCOVA model studying HE Rx and discharge MELD showed that the HE Rx was still significant (p = 0.009).

Figure: Percentage of Patients Discharged on HE-medications and 90-day readmissions



No: no prior HE, Lact: on lactulose alone, Rif: on rifaximin alone, L+R: on lactulose and rifaximin

Conclusions: HE is a common reason for readmission and several remediable steps in HE management that could adversely affect prognosis were identified in a large, multi-center inpatient cohort. These were related to medication-precipitated HE, need for monitoring to prevent aspiration and optimization of HE Rx at discharge, which should serve to reinforce better outpatient and inpatient management.

SAT-014

Efficacy of rifaximin soluble solid dispersion in patients with early decompensated cirrhosis and a Conn score of 0: A post hoc analysis of a randomized, double-blind, placebo-controlled trial

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Background and aims: Treatments to prevent early decompensation of cirrhosis are needed. Rifaximin soluble solid dispersion (SSD) increases gastrointestinal luminal water solubility of rifaximin molecule, while minimizing systemic exposure. Rifaximin SSD is being studied as immediate-release (IR) or sustained extended-release (SER) tablet. This post hoc analysis evaluated rifaximin SSD in preventing all-cause hospitalization or mortality in adults with less advanced cirrhosis and without covert/overt hepatic encephalopathy (HE; Conn/West Haven score of 0).
Method: In a phase 2, randomized, double-blind study, adults with cirrhosis and well-controlled ascites (grade 1), with no history of esophageal variceal bleeding or spontaneous bacterial peritonitis and Conn score of < 2, were randomized to 1 of 5 rifaximin SSD groups (IR 40 mg, IR 80 mg, SER 40 mg, SER 80 mg, IR 80 mg + SER 80 mg) or placebo (PBO) once nightly (qhs) for 24 wks. Patients with baseline Conn score of 0 who received ≥ 1 dose of treatment were included.
Results: Of 516 patients in the original study, 317 had Conn score of 0 (rifaximin SSD, n = 260; PBO, n = 57) and were included in post hoc analysis. In Conn score 0 group, a significantly lower rate of all-cause hospitalizations or mortality was observed with rifaximin SSD (5 groups pooled) vs PBO (26.9% vs 38.6%; p = 0.04) and the individual treatment group rifaximin SSD IR 40 mg vs PBO (18.8% vs 38.6%; p = 0.02; Table). Also, rifaximin SSD IR 40 mg significantly reduced all-cause hospitalization or mortality for subgroups of female sex, age < 65 y, white race, and MELDNa score of 11-18 (Table). Significant differences vs PBO not observed for the other 4 rifaximin groups (except rifaximin SSD IR 80 mg qhs for MELDNa ≤ 10 subgroup [p = 0.03] and SER 40 mg qhs for female sex subgroup [p = 0.04]). Rifaximin SSD was well tolerated.

Table: All-cause hospitalization or mortality

Subgroup	Rifaximin SSD IR 40 mg qhs (n = 48), n/n (%)	PBO (n = 57), n/n	p value vs PBO*	5 Rifaximin groups pooled (n = 260), n/n (%)	p value vs PBO*
Overall	9/48 (18.8)	22/57 (38.6)	**0.02**	70/260 (26.9)	0.04
Sex					
Male	8/33 (24.2)	14/41 (34.1)	0.26	46/164 (28.0)	0.29
Female	1/15 (6.7)	8/16 (50.0)	**0.009**	24/96 (25.0)	**0.03**
Age, y					
<65	8/39 (20.5)	19/46 (41.3)	**0.03**	59/212 (27.8)	**0.03**
≥65	1/9 (11.1)	3/11 (27.3)	0.34	11/48 (22.9)	0.76
Race					
White	8/41 (19.5)	19/49 (38.8)	**0.04**	59/225 (26.2)	0.05
Other	1/7 (14.3)	3/8 (37.5)	0.25	11/35 (31.4)	0.49
MELDNa score					
≤10	1/8 (12.5)	4/10 (40.0)	0.23	6/50 (12.0)	**0.02**
11-18	7/36 (19.4)	17/44 (38.6)	**0.047**	51/186 (27.4)	0.09
19-24	1/4 (25.0)	1/3 (33.3)	0.81	11/21 (52.4)	0.79
Child-Pugh class					
A	0/8 (0.0)	3/9 (33.3)	0.06	6/44 (13.6)	0.10
B	8/39 (20.5)	17/45 (37.8)	0.08	54/200 (27.0)	0.11
C	1/1 (100.0)	2/3 (66.7)	0.26	10/16 (62.5)	0.16

*Log-rank test stratified by country.

Conclusion: Once-daily rifaximin SSD IR 40 mg reduced all-cause hospitalization/mortality due to cirrhosis complications in patients with ascites, without HE.

SAT-015

Sarcopenia is associated with a worst prognosis in cirrhotic patients in the context of liver transplantation

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Background and aims: Muscle wasting (sarcopenia) affects 30 to 70% of cirrhotic patients. The presence of sarcopenia may be associated with a worst prognosis in cirrhotic patients awaiting and after liver transplantation (LT). To this day, few studies have evaluated and followed muscle mass (in terms of quantity and quality) after LT. The goal of this study was to assess the association between the evolution of sarcopenia and the prognosis of cirrhotic patients before and after LT.
Method: In total, 94 cirrhotic patients who underwent LT at the Montreal University Hospital Center-Liver Unit were included. Sarcopenia was assessed at the third lumbar level vertebrae using a computed tomography scan (CT-scan). The diagnostic of sarcopenia was based on previously established sex-specific cut-off values of skeletal muscle index. Patients were classified into two groups: (1) persistent or newly developed sarcopenia after LT (Sarc+); (2) resolved sarcopenia or absence of sarcopenia before and after LT (Sarc-). Muscle quality (myosteatosis) was assessed by calculating intramuscular adipose tissue content. The prognostic factors were collected 6 months before and during 1 year after LT through medical records and included the number of complications, the episodes of infections, the length of stay, and the frequency of readmissions.
Results: Sarcopenia persisted or was newly developed (Sarc+) in 62% of the patients (n = 58). It remained absence or was resolved after LT in 38% of the patients (n = 35). Muscle quality was significantly decreased post-LT ($p = 0.034$). The group Sarc+ experienced more complications pre-LT ($p = 0.012$) and post-LT ($p < 0.001$), infections post-LT ($p = 0.006$) and readmissions ($p = 0.048$) compared to the group Sarc-. The length of stay was longer for the group Sarc+ as opposed to the group Sarc- ($p < 0.001$).
Conclusion: Persistent and newly developed sarcopenia after LT appear to have negative outcomes on the prognosis of patients. Interventional strategies to optimize, increase or preserve muscle mass could help to improve post-operative recovery as well as the quality of life in patients who have undergone LT.

SAT-016

Impact of sarcopenia in patients undergoing transjugular intrahepatic portosystemic shunt insertion for refractory ascites

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Background and aims: Sarcopenia is associated with worse outcome in patients with cirrhosis, however its impact in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) insertion for refractory ascites is unknown. We therefore assessed the association of pre-TIPS sarcopenia on post-TIPS clinical outcomes and the impact of TIPS insertion on sarcopenia.
Method: We retrospectively evaluated all adult patients who underwent TIPS insertion for diuretic refractory ascites at the Royal Free Hospital, London, UK between January 2010 and April 2018. Sarcopenia was assessed using the total psoas muscle area index at the third lumbar vertebrae (L3-PMI, mm^2/m^2) based on cross-sectional imaging. Sarcopenia was defined as the lowest quartile of L3-PMI separately for male and female patients.
Results: 117 patients were included: median age was 55.7years, and 60% were male. The most common cause of liver disease was alcohol in 66% of patients. 31 patients were considered sarcopenic, (L3-PMI 244 vs 435, $p < 0.001$). On univariate analysis, body mass index (BMI), platelets, and MELD score were associated with the presence of sarcopenia. On multivariate (MV) analysis, only a high BMI was inversely associated with sarcopenia (aOR = 0.82, $p = 0.006$). During follow-up, 37 patients died, and 18 received a liver transplant. Median survival of the entire cohort was 48.9months. On MV cox regression, mortality was independently associated with increasing age (aHR = 1.04, $p = 0.03$), lower platelets (aHR = 0.99, $p = 0.03$) and higher MELD score (aHR = 1.10, $p = 0.03$). Hepatic encephalopathy (HE) occurred in 27 (25%) patients. On MV cox regression analysis, MELD was the only predictor of HE (aHR = 1.13, $p = 0.01$). Ascites control improved in 73 (66%) patients. On MV cox regression analysis, high bilirubin ($p = 0.003$) and absence of TIPS revision ($p = 0.001$) predicted improved ascites control. Sarcopenia or L3-PMI as a quantitative value did not have an impact on mortality, HE, or ascites control.
In patients with follow-up CT (n = 51), L3-PMI improved compared to baseline (L3 PMI 427 vs 489, $p < 0.001$), and the presence of sarcopenia decreased from 23.5% to 17.6% ($p = 0.37$). On MV cox regression, high bilirubin (aHR = 1.03, $p = 0.02$) and low albumin (aHR = 0.92, $p = 0.01$) were associated with improved L3-PMI. Baseline sarcopenia did not predict lack of improvement in L3-PMI.
Conclusion: Our results suggest that sarcopenia should not be considered as a contra-indication to TIPS insertion. TIPS might improve patients' nutritional status and sarcopenia and therefore long-term outcomes.

SAT-017

Anticoagulant effect of edoxaban in patients with cirrhosis: The POET study

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Background and aims: Cirrhosis is a prothrombotic condition characterized by complications such as portal vein thrombosis and venous thromboembolism. Anticoagulant treatment for prevention or treatment of these thrombotic complications is indicated. However, the optimal anticoagulant approach is uncertain. Direct oral anticoagulant drugs (DOACs) have potential advantages over traditional anticoagulant drugs. However, in vitro experiments have suggested altered anticoagulant potency of DOACs in patients with cirrhosis due to their altered hemostatic profile. In addition, as DOACs are metabolized by the liver and kidney, a concern for accumulation exists.
Method: 14 patients with Child-Pugh A and 1 patient with Child-Pugh B cirrhosis and 15 healthy controls received 60 mg edoxaban once daily orally for 7 days. Blood samples were taken at baseline and 2 hours after drug ingestion at day 1, 3, and 7. Thrombin generation (TG) tests were performed to assess the anticoagulant effect, and edoxaban plasma levels were calculated by edoxaban-calibrated anti-Xa assays.
Results: At baseline, TG was substantially elevated in cirrhotic patients compared to controls (endogenous thrombin potential 733 nM*min vs 417 nM*min, $p = 0.053$). Administration of edoxaban reduced TG in patients to 143, 162, 180, at day 1, 3, and 7, respectively. In controls, TG was reduced to 69, 80, 69, at day 1, 3, and 7, which was significantly lower than TG in patients ($p < 0.01, < 0.01, < 0.01$). The

relative reduction in TG compared to baseline was 75%, 72%, 72% in patients and 83%, 81%, 82% in controls at day 1, 3, and 7, respectively, which was significantly different between the groups. Edoxaban plasma levels were similar in patients and controls throughout the study with 196, 182 and 229 ng/ml in patients 182, 211 and 220 ng/ml in controls on day 1, 3 and 7, respectively.

Conclusion: We have shown that one week of edoxaban at a therapeutic dose of 60 mg results in comparable plasma levels in patients with cirrhosis compared to healthy controls. However, TG remained higher in edoxaban-treated patients, combined with a reduced relative reduction in TG. These results support the safety profile of DOAC treatment in this difficult-to-treat population, but question the optimal dosing of a DOAC in cirrhotic patients to adequately treat thrombosis.

SAT-018

Relation of CT determined sarcopenia and anthropometry to serum C-reactive protein levels in patients with chronic liver disease

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Background and aims: Sarcopenia, the progressive and generalised loss of skeletal muscle mass and strength, is recognised as common and prognostically important in patients with chronic liver disease (CLD), and associated with impaired survival. Its pathophysiology in CLD is not well understood. In other chronic illness sarcopenia is linked with chronic systemic inflammation and elevated serum pro-inflammatory markers, including C-reactive protein (CRP). We assessed patients with CLD undergoing liver transplant (LT) assessment for the presence of sarcopenia and its association with CRP levels.

Method: 88 patients with cirrhotic CLD, with no evidence of active infection or concurrent antibiotic usage, undergoing LT assessment were studied. Abdominal CT imaging was analysed using Sliceomatic software to determine L3 muscle area. L3 skeletal muscle index (L3SMI) was calculated with predefined cut-offs for CT-defined sarcopenia. Assessment of muscle strength was determined by hand grip strength (HGS) using dynamometry, performed by trained dietetic staff. Serum CRP was measured using an immunoturbidimetric method with the Siemans Advia 2400 analyser.

Results: Median age of patients was 53 (IQR 45-61) years, and MELD 13 (10-18), 36% were female and 29% had alcoholic liver disease. Median CRP levels were 7.6 (2.2-20.9) mg/L and 59% of patients had CRP elevated above the normal range. L3SMI was 38.5 (31.3-46.3) cm/M^2 with 74% of patients fulfilling CT criteria for sarcopenia. Median HGS was 32.7 (26.1-37.1) Kg and 44% of cases had < 85% predicted values.

There was no significant difference in CRP levels between patients with CT-defined sarcopenia and those without (7.7 (2.0-18.6) mg/L vs. 7.5 (3.2-28.5) mg/L (p = 0.43)), but CRP levels were elevated in patients with reduced HGS compared to those with normal HGS (11.1 (4.4-31.48) mg/L vs. 4.2 (1.9-15.2) mg/L (p = 0.009)). There was positive correlation with MELD and UKELD score (r = 0.258, p = 0.015 and r = 0.262, p = 0.014 respectively). CRP levels inversely correlated with HGS (r = -0.358, p = 0.002) but not with L3SMI (r = -0.100, p = 0.352).

Conclusion: We report for the first time the association between CRP and muscle strength in patients with CLD, suggesting systemic inflammation may have a role in its pathogenesis. The lack of association between CT-determined sarcopenia and CRP levels may reflect a greater role for chronic inflammation in loss of muscle strength than reduced muscle mass.

SAT-019

Minimal hepatic encephalopathy: Which test should we use in clinical practice?

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Background and aims: Minimal hepatic encephalopathy (MHE) in cirrhosis is a latent and asymptomatic neurological disorder. MHE has a prognostic value, especially before liver transplant or transjugular intrahepatic portosystemic stent shunt. Its presence greatly affects quality of life. A large choice of diagnostic tests is available. The best test seems to be the Psychometric Hepatic Encephalopathy Score (PHES) but is difficult to use in every day practice.

Method: Four non-invasive tests to diagnose MHE were performed in two centers in patients with cirrhosis without clinical evidence of hepatic encephalopathy (< grade I according to West-Haven criteria): PHES, *Critical Flicker Frequency* (CFF) with two pathological cutoffs set at 38 and 39Hz, *Simplified Animal Naming Test* (S-ANT) with cut-off set at 15 and venous ammonia. PHES was chosen as gold standard. Due to lack of normative data in France, were used normal values from Spain and Italy. Cohen's kappa coefficients were calculated. Area under curve was used to determine the value with the best sensitivity and specificity. We also performed an analysis to evaluate the risk of OHE at 6 months. Exclusion criteria were HE ≥ grade I, neuropsychiatric disorders, ophthalmological diseases, active bleeding or infection and treatments to reduce hyperammonia.

Results: 48 patients were included. 25 patients (50%) were Child-Pugh A, 19 (40%) Child B and 5 (10%) Child C. Median MELD was 12. MHE was diagnosed with PHES in 42% and 44%. Agreement between PHES and other tests was poor (k < 0.4), except between PHES and S-ANT (k = 0.41 and k = 0.4). Agreement between Spanish and Italian PHES was excellent (k = 0.87). Predictive values of these tests were moderate with positive likelihood-ratio between 2 and 5, and negative likelihood-ratio between 0.2 and 0.5. According to Younden index, best cutoff for CFF was 37Hz, close to values we use in practice. For S-ANT, best cutoff was 15, which is the value highlighted in a previous study. Benzodiazepines were associated with abnormal PHES (OR = 4; p = 0.04). Severity of liver disease, estimated by Child-Pugh and MELD, increases the risk of MHE but not significantly, mainly because of lack of power. On a univariate analysis, abnormal PHES using Spanish (p = 0.017) and Italian normative data (p = 0.023), S-ANT < 15 (p = 0, 049) were significantly associated with occurrence of OHE at 6 months during follow-up.

	CFF 38Hz	CFF 39Hz	S-ANT	NH3
PHES (SPA)	0, 33	0, 27	0, 45	−0, 44
PHES (ITA)	0, 3	0, 23	0, 41	−0, 29

Conclusion: Lack of agreement between PHES and CFF or S-ANT is not surprising as they evaluate different neurological functions. Venous ammonia appears to be of little interest in detecting MHE. Despite excellent agreement between Spanish and Italian data, it is essential to find normative data for PHES in France to generalize its use in practice. Abnormal PHES or S-ANT was significantly associated with occurrence of OHE at 6 months.

SAT-020

Transjugular intrahepatic portosystemic shunt implantation improves renal function in patients with ascites

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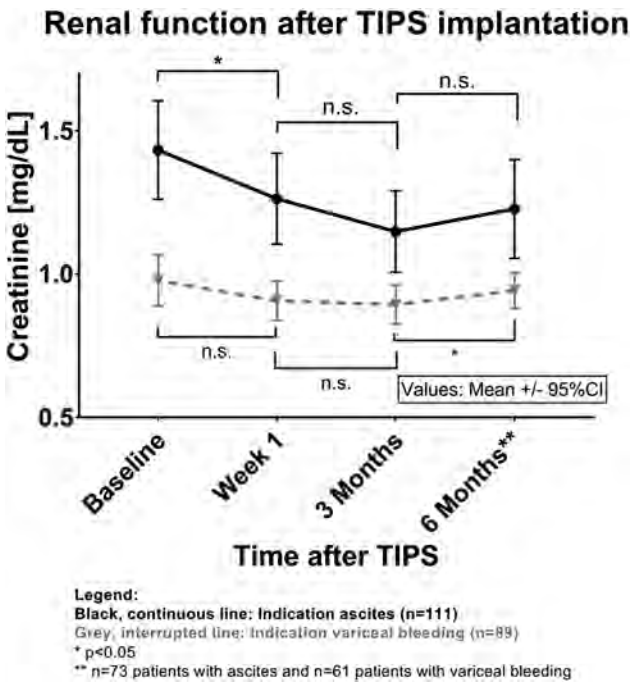
Background and aims: The implantation of a transjugular intrahepatic portosystemic shunt (TIPS) is used to treat complications of portal hypertension. Limited data is available on the course of renal function after TIPS.
Methods: In this single-center registry study, we retrospectively assessed serum creatinine (sCr) as a marker for renal function at baseline (prior to TIPS), and at 1 week (W1), 3 months (M3), and 6 months (M6) after TIPS implantation in patients with cirrhosis.
Results: 200 patients were included: etiology: 71.5% alcoholic liver disease; 76.0% male; mean age: 55.6 (SD±10) years; MELD: 12.9 ± 3.8; indication: 40% variceal bleeding (VB), 55.5% ascites, 4.5% bleeding +ascites. Patients with refractory ascites were older than those with VB (57.4 ± 8.8 vs 53.4 ± 10.8years; p = 0.002), but hepatic function was comparable (MELD 12.8 ± 3.7 vs 13.3 ± 3.9; p = 0.506). Median baseline sCr was 1.06 (range:0.38-5.88)mg/dL. sCr values were higher in patients with ascites than in those with VB [baseline: 1.29 (0.38-5.88)mg/dL vs 0.90 (0.39-2.65)mg/dL; p < 0.001]. sCr significantly decreased in patients with ascites already at W1 after TIPS implantation (median −13.4% (range:-64%-+212.9%), p < 0.0001). Afterwards, sCr mostly remained stable [rel. changes W1-M3: ascites: −1.44% (−73.5%-+335.3%), p = 0.4979; bleeding: +1.23% (−83.9%-+142.4%), p = 0.653], but slightly increased again between M3 and M6 in patients with VB [median:+7.3% (−28.4%-+169.8%), p = 0.013], but not in patients with ascites [median:+0.9% (−32.2%-+350%), p = 0.465].



Conclusions: TIPS appears to permanently improve renal function as early as W1 after implantation in patients with ascites. Although the retrospective design limits the significance of our findings, patients with VB didn't show improvements in sCr. Further prospective studies are warranted to confirm the impact of TIPS on renal function.

SAT-021

How to use platelets and liver stiffness to rule out esophageal varices needing treatment?

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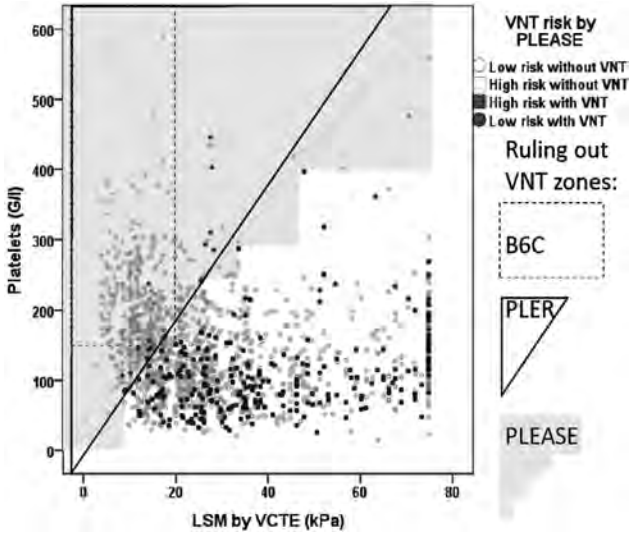
Background and aims: Original Baveno VI criteria (B6C), expanded B6C (EB6C) and ANTICIPATE score, based on platelets (PLT) and liver stiffness measurement (LSM by Fibroscan), allow to rule out varices needing treatment (VNT). Our objective was to evaluate and improve these tests.
Method: 1866 patients (1563 in derivation population and 303 in validation population) with chronic liver disease of various etiologies were included in a multicentric retro-prospective study (15 centers in 5 European countries). Three published tests (B6C, EB6C, ANTICIPATE score) were compared to three new tests: PLER (PLT/LSM ratio), PLES (logit score including PLT and LSM) and PLEASE (where the spared endoscopy rate was optimized via multiple cut-off pairs for PLT and LSM: figure).



Results: Patient characteristics (derivation population): male: 63.7%, age: 58.6 ± 11.1 years, VNT: 17.3%, BMI: 26.6 ± 4.6 kg/m², etiologies: virus: 62.1%, alcohol: 28.6%, others: 9.3%, LSM ≥ 10kPa: 93.5%. The tests are listed according to increasing spared endoscopy rate (%) with missed VNT rate (%, denominator: VNT) in brackets in the derivation population: B6C: 20.3% (p < 0.001 vs other tests) (missed VNT: 1.1%),

PLER: 27.6% (4.8%), ANTICIPATE: 29.2 (4.8%), PLES: 29.4 (4.4%), PLEASE: 33.3% ($p < 0.001$ vs previous tests) (4.8%) and EB6C: 37.1% ($p < 0.001$ vs others) (8.1%). In the validation population, results were: B6C: 23.4% ($p < 0.001$ vs others) (0%), PLER: 34.0% (5.4%), ANTICIPATE: 36.3 (2.7%), PLES: 37.3 (2.7%), PLEASE: 42.6% ($p < 0.001$ vs previous tests) (5.4%) and EB6C: 44.2% ($p < 0.001$ vs other tests except for PLEASE: $p = 0.522$) (8.1%). Results were evaluated according to etiology and MELD score due to their significant interaction in the prediction of spared endoscopy rate. Most tests were robust for sparing effect and missed VNT as a function of etiology and/or MELD score but the sparing effect was modest in MELD scores > 10. The cut-off of PLER for missed VNT rate at 5% was PLT/LSM ratio close to 10 whatever etiology.
Conclusion: B6C are very robust and EB6C are disqualified due to a high missed VNT rate. PLT and LSM can be used in two ways to screen VNT: the simple PLER usable everywhere in which VNT are ruled out when PLT (G/l) are ≥ 10 folds LSM (kPa); the PLEASE algorithm, usable via a free e-calculator, is the most performant test. Thus, the spared endoscopy rate can be safely (i.e. with acceptable missed VNT rate ≤ 5%) increased from 20-23% (in B6C) to 28-34% (PLER) and even doubled to 33-43% (PLEASE).

SAT-022

Transjugular intrahepatic portosystemic shunts is still an effective treatment for refractory variceal haemorrhage in patients with high MELD/Child Pugh scores

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Background and aims: The Baveno VI recommends that TIPS must be considered in patients who have failed endoscopic therapy or are at high risk of treatment failure (Child Pugh Class (CP) C < 14 or B with active bleeding) after endoscopic therapy. The benefit of TIPS to patients with advanced liver disease remains controversial with some studies suggesting poor outcome.
Method: We undertook a retrospective review of all TIPS (24 hour service) for acute severe VH since Baveno V in 2010 at our centre.
Results: 121 patients (31% Female) with median age 52-years were included. Aetiology of cirrhosis was alcohol in 71%. Median time to TIPSS was 1-day (IQR 2) with 95% done within 5-days; 89% of patients were transferred into our tertiary centre for their VH. Median ITU/hospital stay was 2/9 days (IQR 7/8). Median MELD was 15 (IQR 8) with 30-patients having a MELD ≥ 19 at presentation. Overall survival at 1, 3 and 12 months was 88%, 84% and 80%, respectively. Reduced survival at 3 months was associated with a higher pre-TIPS MELD score ($p < 0.001$) and CP score ($p < 0.001$); consolidation on CXR ($p < 0.01$) and Sengstaken tube placement ($p < 0.01$) but not peripheral blood WCC ($p = 0.1$), age ($p = 0.6$), post tips pressure gradient ($p = 0.1$) or days to index bleed ($p = 0.9$). In patients with a MELD ≥ 19 survival was 70%, 63% and 60% at 1, 3 and 12-months respectively and significantly worse than those with MELD < 19 ($p < 0.01$, all groups). In MELD ≥ 22 (n = 20) 1, 3 and 12-month survival was 64%, 59% and 53% respectively. Patients with a CPS ≥ 12, 1 and 3-month survival was 44% and 33% respectively, and significantly lower than those with a CPS < 12 ($p = 0.001$). Only 1 patient with a CPS ≥ 14 underwent a TIPS and survived. The only predictor of poor outcome in those with MELD ≥ 19 or CPS ≥ 12 was sengstaken tube placement ($p = 0.01$). Overall pre-procedure MELD/CPS score did not influence diameter of TIPS choice, nor concurrent variceal embolization. The requirement for a TIPSS reduction/occlusion for HE (4%) was not more common in MELD ≥ 19; nor was a return to radiology for uncontrolled bleeding (TIPSS dilatation±embolization (10%)).
Conclusion: In patients with refractory VH and high MELD/CP score, TIPS placement is not futile and potentially allows a 'window' for hepatic recompensation or liver transplantation. Moreover in contrast to recent published data we show timely and tertiary access to TIPS is possible and not restricted to those with less severe cirrhosis.

SAT-023

The lack of benefit of prophylactic transfusions of patients with cirrhosis and esophageal varices undergoing endoscopic variceal ligation

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Background: Endoscopic variceal ligation (EVL) of esophageal varices is commonly performed in patients with cirrhosis. Prophylactic administration of platelets and fresh frozen plasma (FFP) is recommended in subjects with low platelets/prolonged INR. In this analysis we evaluated post-EBL bleeding event in patients undergoing outpatient EBL and the use of prophylactic administration of blood products in this setting.
Methods: Retrospective analysis of consecutive EBL procedures in patients with cirrhosis from 01/2010-12/2016. Fresh frozen plasma (FFP) and platelet transfusion were administered at the discretion of the clinician if INR was > 1.5 and/or platelet count < 50×10^9/L. Patient demographics, endoscopic findings, bleeding events after EBL and the use of prophylactic FFP or platelets were recorded.
Results: 467 patients underwent 1174 EBL procedures: (70% male), etiology: HCV and alcohol (77%), median MELD 11, Child A/B/C (62/31/7%). EBL procedures were performed for primary (51%) and secondary (49%) prophylaxis. Median procedure per patient was 2 (1-4). The prophylactic transfusion protocol was only followed in 15% and 21% of patients that met criteria for an elevated INR and/or low platelets respectively. FFP and/or platelets were administered in 26 patients (5.6%) and in 63 procedures (5.4%). Bleeding occurred in 13 patients (2.8%) and in 21 procedures (1.8%). Bleeding was due to post-EBL ulcer in 11 patients and due to varices in 2. In 2 patients, bleeding occurred within 24 hrs and in the remaining it occurred within 2 weeks after EBL. In those that bled, 3 met criteria for transfusion; 1 received FFP and 2 with low platelets did not receive transfusion; the remaining 10 patients did not meet criteria for transfusion. Patients that bled had higher MELD scores and most underwent secondary EBL compared to those that did not bleed ($p = 0.01$).
Conclusion: The incidence of post EBL bleeding is low and correlates with advanced liver disease. There is no clear relationship between post-EBL bleeding, INR/platelet count, and prophylactic transfusion. Established cutoffs do not seem to predict bleeding in these patients. Prophylactic transfusion in the setting of outpatient EBL needs to be further evaluated.

SAT-024

Effect of acute kidney injury on long-term outcomes of spontaneous bacterial peritonitis in cirrhotics using ICA-AKI criteria

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Background and aims: Spontaneous bacterial peritonitis (SBP), a crucial complication of liver cirrhosis, is associated with high

mortality. Acute kidney injury (AKI) is an important risk factor for the prognosis in cirrhosis. Recently, a new AKI criteria (International Club of Ascites, ICA-AKI) has been introduced in patients with cirrhosis. This study aimed to investigate the effect of AKI on long-term mortality of SBP in cirrhosis using ICA-AKI criteria.

Method: A total of 157 cirrhotic patients with a first episode of SBP between January 2007 and December 2016 from three medical centers in Korea were analyzed. We investigated the long-term mortality with related risk factors of SBP in cirrhosis including the ICA-AKI criteria. The ICA-AKI stage at SBP diagnosis is as follows: stage 0, no increase of serum creatinine (SCr) or increase of SCr < 0.3 mg/dl; stage 1, increase of SCr ≥ 0.3 mg/dl or SCr ≥ 1.5-2 times from baseline; stage 2, increase of SCr ≥ 2-3 times from baseline; stage 3, increase of SCr ≥ 3 times from baseline, or SCr ≥ 4.0 mg/dl with an acute increase of ≥ 0.3 mg/dl, or initiation of renal replacement therapy. Stage progression was defined as a progression of AKI to a higher stage.

Results: The mean age was 58.6 years. The etiology of liver cirrhosis was alcohol (n = 73), hepatitis B virus (n = 70), hepatitis C virus (n = 9), and others (n = 5). At the diagnosis of SBP, 106 patients were Child-Pugh class C (67%), the mean level of MELD score was 20.6, and the mean SCr level was 1.7 mg/dl. The ICA-AKI stage was stage 0 in 91 (58%), stage 1 in 33 (21%), stage 2 in 19 (12%), and stage 3 in 14 patients (9%). Stage progression within 48 hours after SBP diagnosis was noted in 18 patients (12%). Of 157 patients, a total of 71 patients died (45.2%). The median time of overall survival was 6.7 months. Overall survival rates at 6, 12, 36, and 60 months were 50.2%, 45.2%, 43.7%, and 39.8%, respectively. Multivariable analysis showed that the risk factors for overall survival were Age ≥ 60 years (hazard ratio (HR) 1.74, $p = 0.029$), serum sodium level ≤ 130 mmol/L (HR 1.3, $p = 0.017$), ICA-AKI stage 1 (HR 2.51, $p = 0.003$), ICA-AKI stage 2 or 3 (HR 3.36, $p < 0.001$), and stage progression at 48 hours after SBP diagnosis (HR 2.57, $p = 0.004$).

Conclusion: AKI and its progression are significant risk factors for mortality in cirrhotic patients with SBP. The new ICA-AKI criteria may be a useful tool to evaluate the prognosis of cirrhotic patients with SBP.

SAT-026

Mid-arm circumference and triceps skinfold thickness independently predicts mortality in hospitalized patients with decompensated cirrhosis

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Background and aims: Malnutrition is common in patients with advanced liver disease. However, even with a high prevalence, malnutrition is often not diagnosed at admission to hospital. Hydric changes by the presence of edema and ascites are factors that lead to misdiagnosis, reinforcing the importance of using appropriate assessment tools. The aim of the study was to evaluate the nutritional status of hospitalized patients with decompensated cirrhosis by different tools and the predictive capacity of the nutritional assessment tools in predicting survival.

Method: this was a prospective cohort study performed with patients > 19 years of age with decompensated cirrhosis (ascites and/or hepatic encephalopathy, variceal bleed, spontaneous bacterial peritonitis, hepatorenal syndrome or Child-Pugh B or C) who were hospitalized by the Gastroenterology and Hepatology Division at Hospital de Clínicas de Porto Alegre, Brazil. Data were collected within 72 hours of admission, from April 2017 to April 2018. The severity of liver impairment was assessed by Child-Pugh criteria. Nutritional assessment comprised: mid-arm circumference (MAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), phase angle (PhA) and Subjective Global Assessment (SGA). Multivariate analysis according to Cox's model assessed the predictive power of nutritional parameters on survival.

Results: One hundred patients were assessed and the median time of follow-up of 6.9 (range, 1-10.9) months. By multivariate Cox analysis, in a model adjusted for Child-Pugh, malnutrition according to MAC (HR = 2.63, 1.4-4.9) and TSF (HR = 2.04, 1.1-3.9) is associated with an increased in-hospital mortality. The increment in 1 degree in PA was associated with protection against mortality (HR = 0.65, 0.47-0.89).

Table 1: Clinical and nutritional status according to the occurrence of death.

Mortality	Yes (n = 41)	No (n = 59)	p value
Age	61, 8 ± 10, 4	59 ± 10, 3	0, 196
Male	25%	38%	0, 889
Female	16%	21%	
Child-Pugh			
A	2%	7%	**0, 012**
B	20%	41%	
C	19%	11%	
MAC	26, 5 ± 3, 7	28, 9 ± 4, 3	**0, 003**
TST	15 (9-20, 1)	20 (11, 6-25)	0, 085
MAMC	21, 9 ± 2, 4	23, 3 ± 2, 6	0, 013
PhA	4, 8 ± 1, 1	5, 5 ± 0, 9	**0, 001**
SGA			
A	7%	24%	**0, 028**
B	24%	21%	
C	10%	14%	

Conclusion: Malnutrition, evaluated by classic anthropometric measures, is an independent predictor of mortality. Phase angle seems to be a good indicator for mortality. Our results suggest that these tools are not affected by hydric changes and may be useful and reliable bedside tool to evaluate nutritional status.

SAT-027

Effects of propranolol on liver- and spleen-stiffness measured by MR-Elastography in patients with cirrhosis

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Background and aims: MR-elastography (MRE) is a non-invasive diagnostic method and analyses shear wave movement through tissue to determine stiffness. The technique is often uses for detection and characterization of liver fibrosis and cirrhosis.

It is well-known that liver-stiffness increases postprandial due to increased portal blood inflow. To avoid false elevated values of the liver stiffness, fasting 4 hours prior to MRE or ultrasound elastography is recommended. However, evidence regarding non-selective beta-blockers (NSBBs) effect on the liver- and spleen stiffness is lacking. NSBB reduces portal pressure in responders owing partly to a reduced portal inflow, but unfortunately only 50% of the patients respond to the treatment. We therefore hypothesized that NSBBs reduces the liver- and spleen-stiffness due to a decrease in blood flow into the portal system.

The purposes of this study were to evaluate whether NSBB influences the liver- and spleen-stiffness in patients with cirrhosis and if MRE can predict the individual NSBB response.
Method: Twenty-one patients (7 women and 14 men) with cirrhosis and clinical indication for NSBB treatment underwent MRE, liver vein catheterisation (LVC), and registration of clinical and biochemical characteristics. The responders to NSBB were defined as a reduction in the hepatic venous pressure gradient (HVPG) ≥ 10%, or to HVPG < 12mmHg after intravenous propranolol administration (0.15 mg/kg bodyweight) during a LVC.
Results: Among the patients 52% were responders to the NSBB treatment. In these patients NSBB treatment reduced the mean liver-stiffness by 43.5 Pa (4.3%) and the mean spleen-stiffness by 95.7 Pa (7.5%). In patients with non-response to NSBB the mean reductions were 9.7 Pa (0.08%) in liver-stiffness and 39.2 Pa (3.3%) in spleen-stiffness after NSBB administration.
The reduction in HVPG after NSBB administration was not significantly associated with a reduction in spleen-stiffness or liver-stiffness after NSBB (NS).
Conclusion: Treatment with NSBB reduces liver and spleen-stiffness in NSBB-responders. However, the reduction in stiffness is unrelated to the reduction in HVPG.
Our results emphasize the importance of considering betablocker treatment when interpreting MRE results but MRE cannot be used to predict responsiveness to NSBB-treatment.

SAT-028

Diabetes is associated with TIPS failure in cirrhotic patients with refractory ascites

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Background and aims: Ascites is the most frequent clinical sign associated to portal hypertension in cirrhosis. When ascites becomes refractory (10% of patients with ascites), TIPS placement is a good therapeutic option which (effective in approximately 2/3of the cases). The aim of our study was to explore for possible predictors of TIPS failure in refractory ascites.
Method: 105 consecutive patients underwent TIPS placement from Feb 2014 to Dec 2017 at Niguarda Hospital, Milan; 38 patients received TIPS for refractory ascites. A covered stent with a nominal diameter of 10 mm was used in all cases. Response to TIPS was defined as complete (off diuretics) or partial (low dose diuretics required).
Results: Overall, median age was 58, the majority were male (71%), median time from the diagnosis of refractory ascites to TIPS placement was 24 weeks (range 12-44). Median MELD score was 11 (range 7-26). Child-Pugh score was B in 36 and C in 2. Three patients died from liver related events during the first six weeks (8%) and 6 within the first 6 months (16%). One patient underwent LT. The rate of hepatic encephalopathy after intervention was of 29% (11/38). Sixteen patients (16/25, 64%) had a complete response, 9 (9/25, 36%) a partial response and 7 (7/38, 18%) TIPS failure. No statistically significant differences were observed in responders *vs* non-responders in terms of median age at baseline, MELD score, Child Pugh classes, time-interval from diagnosis to TIPS insertion, diastolic disfunction (expressed as E/A), porto-systemic gradient pre and post TIPS and median dilatation of covered stent at insertion (see table). The only baseline feature associated with failure was the presence of diabetes at baseline: 71% (5/7) vs 24% (6/25), p = 0, 0318.

Table:

Variables	Responders (25)	Non-responders (7)
Age, years, median (range)	57, 5 (42-77)	58 (54-71)
MELD score, median (range)	9 (6-17)	10 (8-15)
Child-Pugh class B, % (n)	96% (24/25)	86% (6/7)
Time from diagnosis, median (range)	24 (12-44)	28 (12-48)
E/A, median (range)	0, 86 (0, 48-1, 36)	0, 95 (0, 64-1, 4)
Stent dilatation mm, median (range)	6 (5-8)	6 (6-10)
Portal pressure Gradient, mmHg, median (range)		
-Pre TIPS	21 (10-27)	18 (11-25)
-Post TIPS	11.9 (5-21)	11.8 (9-15)
Diabetes mellitus, % (number)	24% (6)	71% (5)

Conclusions: In our cohort the presence of diabetes is statistically associated with inefficacy. Larger studies are needed to confirm this preliminary results and to understand the underlying mechanisms of failure.

SAT-029

Prediction of hepatic hydrothorax in cirrhosis patients with ascites

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Background and aims: Hydrothorax is a common complication of ascites. It requires hospitalization and may cause respiratory failure, but its risk factors are unknown.
Method: To develop a model that predicts the cumulative risk of hepatic hydrothorax, we used data from three randomized trials on satavaptan treatment of ascites in 1, 198 patients with cirrhosis followed for 1 year. We excluded trial participants with heart failure, renal failure, cancer, or myxedema. The candidate predictors were clinical observations: age, gender, diuretic refractory ascites (yes/no), mean arterial blood pressure; serum biochemistry: creatinine, bilirubin, International Normalized Ratio, albumin, sodium and, platelet count; pharmacological treatments: non-selective beta-blockers, antidiabetics (insulin, metformin, or other oral antidiabetics), proton pump inhibitors, furosemide, and spironolactone; and presence of diabetes (yes/no) recorded at randomization. Predictors were included in a Fine and Gray regression model that considers death as a competing risk. We chose our predictors with backward selection and the Akaike Information Criterion as stopping rule, and reported sub-distribution hazard ratios (sHR). We evaluated discrimination with Wolbers C-index, and adjusted this measure for optimism bias with 1, 000 bootstrap simulations.
Results: We developed our prediction model on 942 patients, of whom 41 developed hydrothorax and 65 died. Serum bilirubin (sHR: 1.02, 95% CI: 1.01-1.03), treatment with non-selective beta-blockers (sHR: 0.43, 95% CI: 0.21-0.85), and antidiabetic treatment (sHR: 3.88, 95% CI: 2.02-7.46) predicted the cumulative risk of hydrothorax (Figure). We found a Wolbers C-index 1 year post randomization of 0.74 (95% CI: 0.65-0.84) after adjustment for optimism bias.
Conclusion: The cumulative risk for hydrothorax increased with serum bilirubin and antidiabetic treatment, whereas treatment with non-selective beta-blockers decreased it.

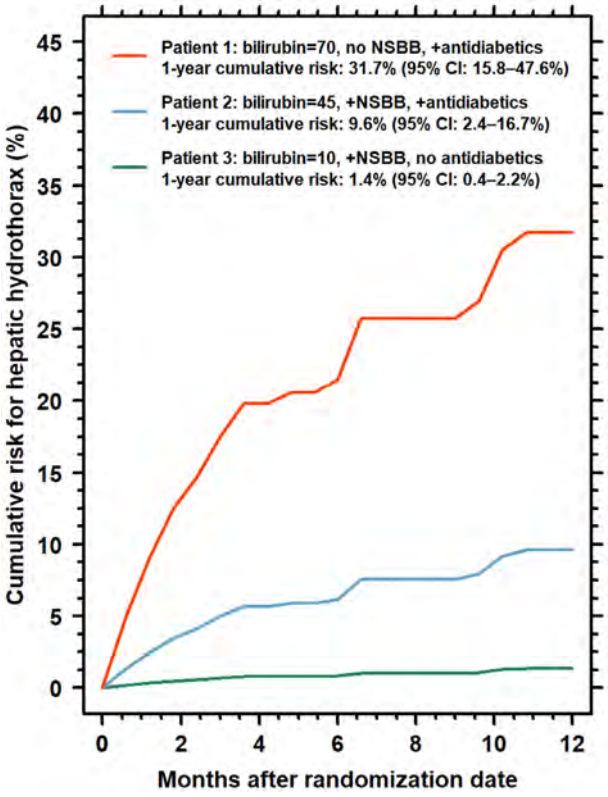

Figure: Illustration of the estimated cumulative risk for hepatic hydrothorax based on our prediction model for patients with 'high' (Patient 1), 'intermediate' (Patient 2), and 'low' (Patient 3) risk for hepatic hydrothorax. The values of each predictor are shown. NSBB = non-selective beta-blockers.

SAT-030

Annual contrast-enhanced MRI is highly effective in the surveillance of hepatocellular carcinoma in cirrhotic patients

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Background and aims: Current guidelines recommend patients with cirrhosis to undergo surveillance for hepatocellular carcinoma (HCC) with biannual ultrasonography (USG). However, the sensivity of USG to detect early stage HCC is suboptimal. We aimed to investigate the effectiveness of surveillance with annual contrast-enhanced magnetic resonance imaging (MRI) to detect HCC in earlier stages.

Method: We reviewed the prospectively collected data of 1261 cirrhosis patients, who were followed in our hospital between 2008 and 2018, to determine the patients with appropriate annual MRI surveillance. Patients were determined as low, intermediate and high risk HCC patients according to Toronto Risk Score. We recorded surveillance-related benefits, defined as early tumor detection and curative treatment, and surveillance-related physical harms, defined as computed tomography or magnetic resonance imaging scans, biopsies, or other procedures performed for false-positive or indeterminate surveillance results.

Results: A total of 294 (23.3%) patients underwent 989 MRI screenings in 10 years period. Thirty-five (11.9%) patients developed HCC, of whom 25 (72.7%) were detected at earlier stages (BCLC A or B) and 29 (84.8%) fulfilled Milan criteria. Twenty-nine (82.9%) were high risk HCC patients at the entry, while 4 (11.4%) were intermediate risk and 2 (5.7%) were low risk at the entry. Surveillance with annual MRI had a sensivity rate of 97.1% and specifity rate of 95.3% with an area under the receiver operating characteristic curve (AUC) of 0.96 (%95 confidence interval; 0.92-0.99) for the detection of HCC. Combination of annual MRI and AFP didn't add any value to MRI alone in detecting HCC (sensivity : 97.1%, specifity : 93.4%, AUC : 0.95). Surveillance-related benefits were observed in 28 (9.5%) patients, while only 16 (5.4%) experienced surveillance-related physical harms.

Table 1: General characteristics of patients who underwent surveillance with annual MRI for the detection of HCC

Age	60.24 (29-86)
Gender (M/F)	148 (50.3%)/146 (49.7)
Etiology of cirrhosis	
HBV	122 (41.5%)
HCV	58 (19.7%)
NASH	25 (8.5%)
ASH	21 (7.1%)
Others	68 (23.1%)
BMI	29.09 (17.72-47.75) kg/m^2
Child-Pugh Score	
A	229 (77.9%)
B	58 (19.7%)
C	7 (2.4%)
MELD	9 (6-16)
Toronto risk score	
< 120 (low risk)	27 (9.2%)
120-240 (intermediate risk)	139 (47.3%)
> 240 (high risk)	128 (43.5%)
AFP	4.57 (0.1-18) ng/ml
Tumor size	24.55 (8-70) mm
Number of tumors	
1	28 (72.5%)
2	5 (15%)
3	2 (7.5%)
HCC stage	
A (very early)	14 (42.4%)
B (early)	11 (30.3%)
C (intermediate)	10 (27.3%)
D (advanced)	0
Initial treatment	
Transplantation	6 (18.2%)
Rf ablation	19 (18%)
TACE	9 (24.2%)
BSC	1 (3%)

Conclusion: HCC surveillance with annual contrast-enhanced MRI alone has a high sensivity and specifity to detect HCCs in earlier stages in patients with cirrhosis with negligible surveillance-related physical harms in clinical practice.

SAT-031

Bleeding risk-scores for prediction of acute variceal bleeding outcome

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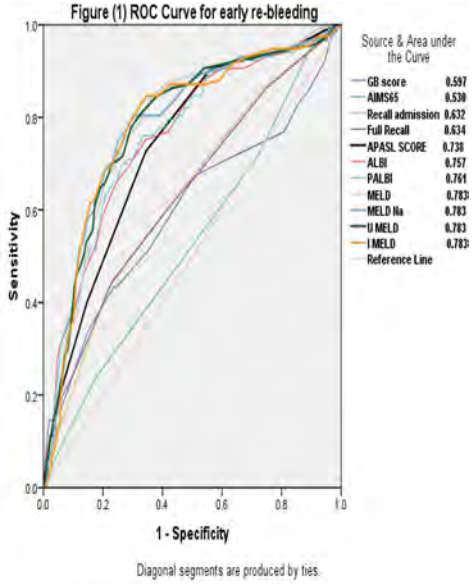
Background and aims: Variceal bleeding is a devastating complication of portal hypertension. The six-week mortality in patients with liver cirrhosis is 17%-28% and the risk of re-bleeding after acute variceal hemorrhage (AVH) is highest within the first six weeks with a peak in the first 5 days. This study is to evaluate bleeding risk-scores for predicting bleeding control, re-bleeding and six-week mortality in patients with acute variceal bleeding.

Method: Patients presenting with acute variceal bleeding were prospectively evaluated. Patients were resuscitated, were given intravenous antibiotics, and received blood and vaso-active drugs as needed. Endoscopy was performed as early as feasible within the first six hours of admission.

The following scores were calculated on admission and/or after urgent endoscopy: AIMS65, Glasgow Blatchford, Rockall and full Rockall score, the platelet-albumin-bilirubin (P-ALBI), ALBI, MELD, IMELD, MELD-Na, UMELD and the APASL severity score. Scores were correlated to control of acute bleeding, re-bleeding, in-hospital mortality, and 6 weeks mortality.

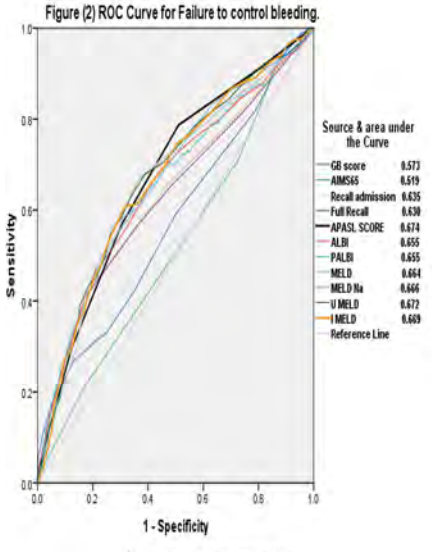
Results: Esophageal and/or gastric varices was the cause of acute bleeding in 703 cirrhotic patients (71.4% males, mean age 58.1 ± 10.3 years, 43.1% presenting with first attack of hematemesis, 38.3% had HCC, 21.5% had portal vein thrombosis, 18.2% with blood spurting from esophageal and/or gastric varices on endoscopy, 14.1% Child-Turcotte-Pugh (CTP) A, 47.2% CTP B, 38.7% CTP C). Bleeding was controlled in 422 patients (59.9%) and 210 patients died (29.8%), 122 patients (20.5%) during hospitalization, 69 patients died from cause not related to the acute hemorrhage (9.8%), 281 patients (39.9%) had re-bleeding after the first week. The area under the ROC curve (AUROC) for failure to control bleeding, mortality in hospitalization and at 6 weeks for each score are shown in the figures, with the IMELD score of > 31.5 offering the best prediction of bleeding control and mortality during hospitalization and at 6 weeks.

Figure (1) ROC Curve for early re-bleeding



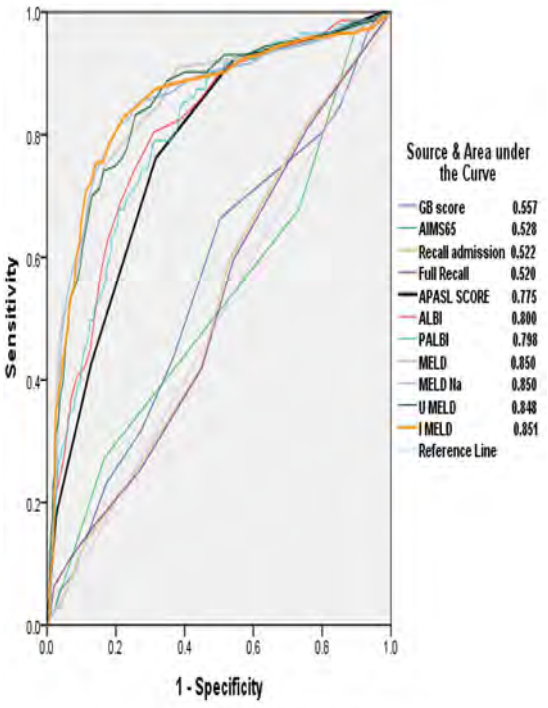
Diagonal segments are produced by ties.

Figure (2) ROC Curve for Failure to control bleeding.



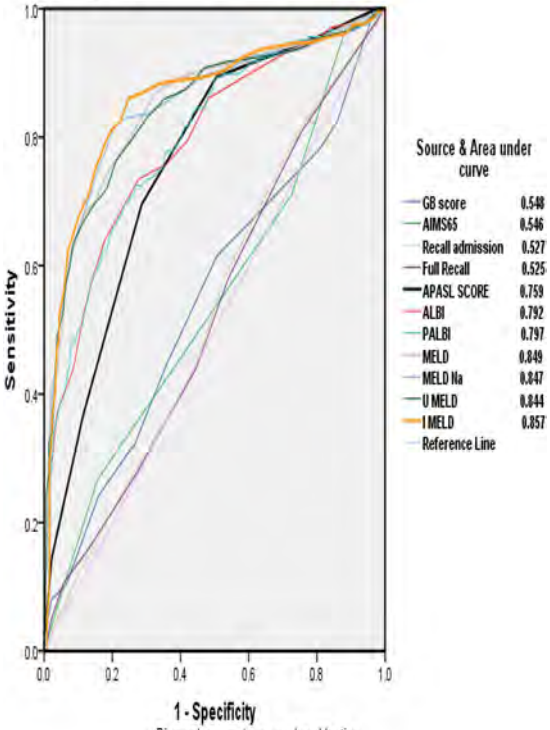
Diagonal segments are produced by ties.

Figure (3) Roc Curve for in hospital mortality



Diagonal segments are produced by ties.

Figure (4) ROC Curve for 6 weeks mortality.



Diagonal segments are produced by ties.

Conclusion: IMELD predicts re-bleeding, mortality during hospitalization and at 6 weeks following acute variceal bleeding better than other bleeding severity scores.

SAT-032

Spleen to liver stiffness ratio significantly differs between ALD and HCV and predicts disease specific complications

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Background and aims: Both liver stiffness (LS) and spleen stiffness (SS) are widely used to non-invasively assess liver fibrosis and portal hypertension, respectively. However, the impact of portal and lobular inflammation (HCV vs ALD) on SS/LS remains unclear so far.

Methods: LS and SS were prospectively assessed in 411 patients with ALD and HCV using Fibroscan (Echosens, Paris) including the effects of treatment interventions (alcohol withdrawal, HCV therapy). LS and spleen size were further analysed in a retrospective cohort of 449 patients with data on to in related to with liver-related decompensation and death.

Results: Both, SS and spleen size were significantly higher in HCV as compared to ALD (42.0 vs 32.6 kPa, $P < 0.0001$, 15.6 vs 11.9 cm, $P < 0.0001$) despite a lower mean LS in HCV (14.9 vs 28.5 kPa). Consequently, the SS/LS and spleen size/LS ratio were significantly higher in HCV (3.8 vs 1.72, $P < 0.0001$ and 1.46 vs 0.86, $P < 0.0001$) and it remained higher in HCV through all fibrosis stages. After treatment, LS significantly decreased in both diseases while SS only significantly declined in HCV. No significant changes of SS/LS were observed during treatment. In the prognostic cohort, ALD patients had higher LS values (30.5 vs 21.3 kPa), predominantly presented for jaundice (65.2%) which was also the major cause of death ($p < 0.01$). In contrast, in HCV, spleens were larger (17.6 vs 12.1 cm), the primary sign of decompensation (73.2%) and major cause of death ($p < 0.001$) was variceal bleeding.

Table showing a comparison between matched cohorts for LS

Parameter	ALD	HCV	P
Age	52.6 ± 10.8	54.8 ± 10.5	0.163
BMI	26.2 ± 4.0	25.5 ± 4.5	0.288
Sex	69%	67%	0.747
LS (kPa)	19.0 ± 11.7	19.8 ± 9.3	0.629
SS (kPa)	27.8 ± 17.6	47.7 ± 13.0	<0.001
Spleen size (cm)	11.8 ± 2.1	15.3 ± 2.8	<0.001
AST	73 ± 88	58 ± 44	0.0569
Albumin	4.0 ± 0.5	4.1 ± 0.5	0.040
Bili	1.6 ± 1.5	0.9 ± 0.5	<0.001
Platelets	174 ± 93	117 ± 51	<0.001
INR	1.4 ± 0.5	1.0 ± 0.2	<0.001

Conclusion: Both the SS/LS and the spleen size/LS ratio are significantly higher in patients with portal disease such as HCV as compared to lobular disease (ALD) and it predicts disease-specific complications and survival such as liver failure in ALD and variceal bleeding in HCV. In conclusion, combined LS and SS measurements provide additional information about disease aetiology and potential risk of decompensation.

SAT-033

Body fat composition determines outcomes before and after liver transplantation in cirrhosis

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Background and aims: A low body fat content in cirrhosis has been recently shown to be associated with poor outcome before liver transplantation. We conducted a study comparing different CT derived fat parameters regarding its prognostic impact on the development of complications and death on the waiting list and after liver transplantation.

Method: 612 patients with liver cirrhosis and no HCC listed for transplantation between 2001 and 2014 met the inclusion and exclusion criteria; including an abdominal CT scan (± 200 days to listing). 109 non-cirrhotic patients CT scan after polytrauma acted as controls. The paraspinal muscle fat index (PSFI), the subcutaneous fat index (SCFI) and the visceral fat index (VFI) were assessed at L3/L4 level, normalized to the height (cm^2/m^2). Parameters' cut offs were calculated according to the upper or lower tertile, as appropriate.

Results: Of 612 patients with liver cirrhosis, 63.6% had alcoholic liver disease, and 66.7% were male. The PSFI ($p = 0.002$), the SCFI ($p = 0.002$) and the VFI ($p < 0.001$) were lower in cirrhosis compared to controls. At baseline a low SCFI was associated with a higher rate of ascites ($p < 0.001$) and higher CRP levels ($p < 0.001$). Patients with high PSFI and VFI had higher creatinine values ($p < 0.001$), WBC levels ($p = 0.023$; $p = 0.007$) and more often metabolic complications such as diabetes ($p < 0.001$), arterial hypertension ($p < 0.001$) and increased BMI ($p < 0.001$) whereas the liver function (MELD score, Child-Pugh score) was not different between groups. After multivariate Cox regression analysis adjusting for age, BMI and MELD an increasing SCFI was associated with reduced risk of cirrhosis related complications (any complication HR 0.984 ($p = 0.001$), bacterial infection HR 0.984 ($p = 0.001$), SBP HR 0.97 ($p < 0.001$) and death (HR 0.985 ($p = 0.023$) on the transplant waiting list in both genders whereas a increased PSFI (HR 1.343 (1.133-1.592), $p = 0.001$) and VFI (HR 1.021 (1.006-1.036) were predictive for death within 1-year after transplantation only in men (fig 1).

Conclusion: The distribution of body fat is a major determinant for complications in cirrhosis before and after liver transplantation and results highlight the gender as a confounding factor. Further research on whether CT derived fat parameter should be implemented in patient prioritisation on the waiting list and surveillance strategies before and after liver transplantation is necessary.

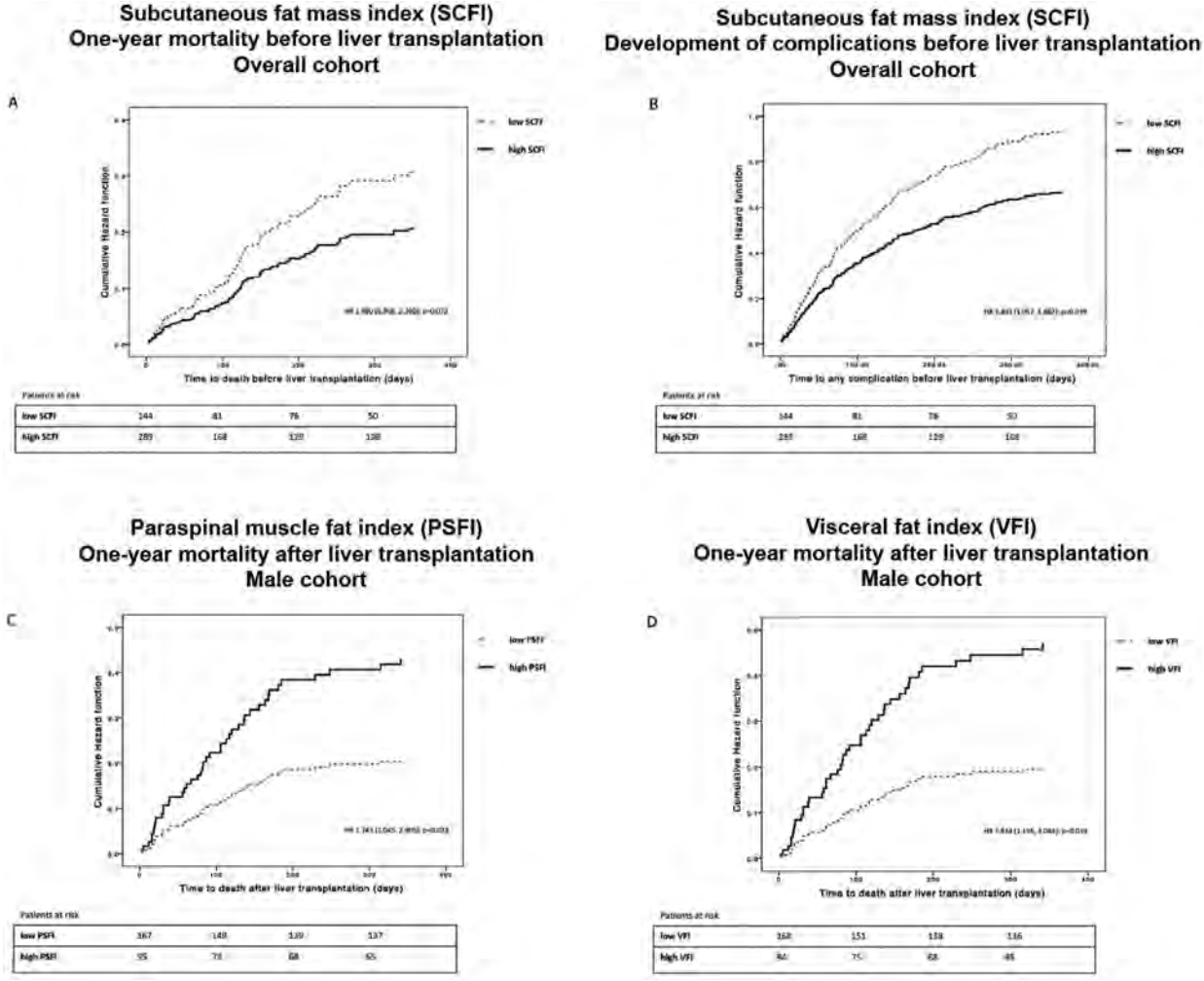

Figure: (abstract: SAT-033): Risk of death and complications in patients with low SCFI (A, B) or high PSFI (C) and VFI (D)

SAT-034

The psychomotor vigilance task: Role in the diagnosis of hepatic encephalopathy and relationship with driving ability

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Background and aims: Hepatic Encephalopathy (HE) can be interpreted as a syndrome of decreased vigilance, and has been associated with impaired driving ability. The aim of the present study was to evaluate the Psychomotor Vigilance Task (PVT), which is used to assess both vigilance and driving ability, in a group of patients with cirrhosis and varying degree of neuropsychiatric impairment.
Method: 145 patients (120 males, 59 ± 10 years, MELD 13 ± 5) underwent the PVT; a subgroup of 117 also completed a driving questionnaire; a subgroup of 106 also underwent the Psychometric Hepatic Encephalopathy Score (PHES) and the electroencephalogram (EEG), based on which, plus a clinical evaluation, they were classed as unimpaired (n = 51), as having minimal (n = 35) or overt HE (n = 20). All were followed up for an average of 13 ± 5 months in relation to the occurrence of accidents/traffic offences, HE-related hospitalizations and death. Sixty-six healthy volunteers evenly distributed by sex, age and education served as reference for the PVT.
Results: Patients as a group showed worse PVT performance compared to healthy volunteers, and PVT indices significantly correlated with MELD, ammonia levels, PHES and the EEG. Significant associations were observed between neuropsychiatric performance (unimpaired/minimal/overt) and license/driving status; PVT indices were also significantly different between classes of license/driving status. PVT, PHES and the EEG all predicted HE-related hospitalizations and death over the follow-up period; none predicted accidents/traffic offences. However, individuals with the slowest reaction times/most lapses on PVT were often not driving albeit in possession of a license. When patients whose own insecurity/doctor/family had stopped them driving because of HE-related reasons (n = 6 out of the 14 not driving despite having a license) were modeled as having an accident/fine over the subsequent 6 or 12 months (assumed accident/fine dates: 3 and 6 months, respectively), the PVT parameter lapses was a predictor of accidents/traffic offences, also after correction for MELD and age.
Conclusion: the PVT is worthy of further study in patients with cirrhosis, for purposes of both HE quantification and the assessment of driving ability.

SAT-035

The negative impact of skeletal muscle volume loss during transarterial chemoembolization for hepatocellular carcinoma

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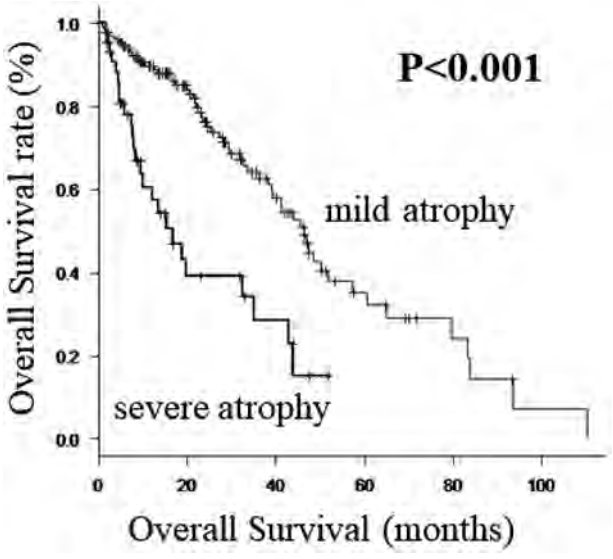
Background and aims: Sarcopenia has a negative impact on the prognosis of patients with hepatocellular carcinoma (HCC). We investigated the significance of skeletal muscle volume and its changes in HCC patients receiving transarterial chemoembolization (TACE).
Method: We retrospectively analyzed 179 HCC patients receiving TACE from 2006 to 2017. Skeletal mass index was calculated as the left-right sum of the major × minor axis of the psoas muscle at the third lumbar vertebra, divided by height squared (psoas muscle index [PMI]). Patients were classified into two groups (low and normal PMI) depending on an index < 6.0 and < 3.4 cm2/m2 for men and women, respectively. We assessed overall survival (OS) and TACE period (between the first TACE (pre) and the time of TACE refractoriness (post)). Changes in PMI per month during TACE period (CPMI; (PMI [pre]-PMI [post])/TACE periods) were calculated as an index of progressive muscle atrophy. Patients were classified into two groups (severe and mild muscle atrophy) depending on CPMI above the upper quartile.
Results: There were no significant differences in OS between groups with low and normal PMI at pre. Multivariate analysis showed that CPMI was significantly associated with poor OS (hazard ratio, 1.884; p = 0.001). Patients with severe muscle atrophy had a significantly lower OS than those with mild muscle atrophy (p < 0.001). Compared with patients with mild muscle atrophy, patients with severe muscle atrophy had a significant loss of liver function reserves at post.



Conclusion: Progressive loss of skeletal muscle volume is an important predictor of poor prognosis in patients with HCC treated by TACE. Preventing skeletal muscle volume loss is essential for good prognosis in patients with HCC.

SAT-036

Prognostic implications of encephalopathy to adequately define differentiated stages of decompensated cirrhosis

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Background and aims: In decompensated cirrhosis, ascites and variceal bleeding are the main decompensating events, and are well characterized. Hepatic encephalopathy (HE) usually occurs in top of these complications and worsens prognosis. This study aimed to clarify whether the development of encephalopathy has particular prognostic implications and hemodynamic features, which may define a differentiated stage in decompensated cirrhosis.
Method: We consecutively included patients admitted due to variceal bleeding (VB), differentiating those with bleeding-alone from those who also had ascites, and patients with ascites and varices without previous bleeding referred for primary prophylaxis. Patients with present (or previous) encephalopathy were identified to investigate the role in the prognosis of each stage of decompensated cirrhosis. Portal pressure was measured in all patients before starting therapy with β-blockers. Risk of outcomes was estimated in a competing risks framework considering death and liver transplant as competing events.
Results: 267 patients with VB (177 of them with ascites) and 131 with ascites without VB were included. Of these, 55 patients (33%) with VB-plus-ascites and 20 (15%) with ascites-alone had present HE. Patients with HE had significantly worse liver function than those without encephalopathy in each subgroup. The HVPG progressively worsen from patients with VB-alone to those with ascites-alone (17.9 ± 4 vs 19.4 ± 5 mmHg, P = 0.02) and to those with VB-plus-ascites (21.1 ± 4mmHg, P = 0.01). Among patients with ascites-alone, those with-HE had similar HVPG than those without-HE, while among patients with VB-plus-ascites those with-HE had higher HVPG than those without-HE (22.2 ± 5 vs 20.3 ± 5 mmHg, P = 0.05). The probability of survival without liver transplant (OLT) was better in patients with VB-alone than in those with ascites-alone (83%vs69% at 3 y, P = 0.01) and was better in these than in those with VB-plus-ascites (69%vs 49% at3y, P < 0.001). Among patients with ascites-alone, the probability of survival without OLT was worse in patients with-HE than in those without-HE (35%vs72% at 3 y, P = 0.03). Among patients with VB-plus-ascites, the probability of survival without OLT was worse in patients with-HE than in those without-HE (36% vs 55% at 3 y, P = 0.005). Overall, encephalopathy was an independent predictor of death or OLT (HR = 1.57, 95%CI = 1.04-2.38) after adjusting for relevant baseline factors including MELD, etiology of cirrhosis, HCC and age.
Conclusion: In each stage of decompensated cirrhosis, either ascites alone or VB plus ascites, HE is associated with worse liver function and a trend toward higher HVPG, and is also independently associated with greater risk of death or OLT. This suggests that in all stages of decompensated cirrhosis encephalopathy identify a sub-stage with worse prognosis.

SAT-037

Applying the new nutritional screening and assessment algorithm to estimate malnutrition prevalence in Greek cirrhotic patients as suggested by the 2018 EASL nutritional guidelines for chronic liver disease

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Background and aims: Malnutrition is common among cirrhotic patients and affects their quality of life and survival. An algorithm for nutritional screening and assessment in cirrhotic patients has been included in 2018 EASL guidelines on nutrition in chronic liver disease. The aim of our study was to apply this algorithm in a sample of cirrhotic patients and examine the association of malnutrition diagnosis with 1-year survival.
Method: 171 cirrhotic patients (57.3% male, mean age 59.5 ± 10.6 years) of any etiology and stage (50.9% compensated) were enrolled. Child-Pugh score (CP), dry weight in case of fluid retention and body mass index (BMI) were estimated. Nutritional screening was performed using the Royal Free Hospital Nutritional Prioritizing Tool and nutritional assessment using Subjective Global Assessment. Dietary intake (DI) was estimated utilizing three 24h recalls and considered adequate if it exceeded 75% of estimated needs. Appendicular Skeletal Muscle Index (ASMI) resulting from DEXA was used as an indicator of sarcopenia. Physical performance was assessed with Short Physical Performance Battery (SPPB). Data on one-year survival was available in a subgroup of 74 patients.
Results: According to CP, 119 (69.6%) patients were categorized as class A, 41 (24%) as B and 11 (6.4%) as C. Based on BMI, 2 (1.2%) patients were underweight, 51 (29.8%) had normal weight, 50 (29.2%) were overweight and 68 (39.8%) were obese. In the total sample, 11.7% of patients were at moderate and 31.6% at high risk for malnutrition. According to the proposed EASL algorithm 28.7% were malnourished, 7% sarcopenic and 0.6% sarcopenic obese. Malnutrition and sarcopenia were more prevalent in underweight/normal weight compared to overweight/obese (both $p < 0.001$), in alcoholic etiology disease ($p = 0.006$ and $p = 0.014$) and in CP classes B-C (both $p < 0.001$). Sarcopenia prevalence was also higher in men (12.2% vs 1.4% in women, $p = 0.008$). Malnutrition was inversely associated with 1-year survival (OR = 0.13, 95%CI 0.03-0.63, $p = 0.01$) after adjustment for age, decompensation and ASMI and so was sarcopenia (OR = 0.11, 95%CI 0.02-0.81, $p = 0.03$) after adjustment for age, decompensation and low DI.
Conclusion: According to EASL algorithm, the total prevalence of malnutrition was 28.7%, while 7.6% were classified as having sarcopenia. Furthermore, malnutrition and sarcopenia were inversely associated with 1-y mortality in cirrhotic patients.

SAT-038

Lusutrombopag for treatment of thrombocytopenia in patients with chronic liver disease who are undergoing planned invasive procedures: pooled safety analysis of bleeding-related adverse events

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Background and aims: Thrombocytopenia (TCP) is a common complication in patients (pts) with chronic liver disease (CLD). Lusutrombopag (LUSU) is a thrombopoietin receptor agonist approved in Japan (2015) and US (2018) for pts with TCP-CLD undergoing an invasive procedure. A pooled safety analysis was performed to assess differences in bleeding events (BE) following LUSU treatment, with or without platelet transfusion (PT).
Method: Safety data were pooled from 3 double-blind, placebo-controlled studies, in pts with TCP-CLD undergoing planned invasive procedure (Phase 2b: M0626; Phase 3: L-PLUS 1, L-PLUS 2). Pts enrolled in these studies were randomised to LUSU 3 mg or placebo (PBO) for up to 7 days prior to procedure. PT was administered if platelet count was $< 50\times10^9$/L prior to procedure. Pts were classified into 1 of 4 subgroups: LUSU with or without PT or PBO with or without PT. BE were summarized pre-, during, and post-procedure.
Results: Lower BE rates, regardless of severity and timing of onset, were observed for LUSU alone vs PBO+PT (Table). Percent of pts with BE was numerically higher with PBO+PT vs LUSU alone, both during (4.8% vs 3.2%) and post-procedure (7.1% vs 4.0%). Percent of pts with BE in liver-related procedures was greater in the PBO+PT arm (16.1%) vs LUSU alone (11.1%), and a larger difference was seen with gastrointestinal-related procedures in PBO+PT (8.9%) vs LUSU alone (2.0%).

Table: Bleeding Events by Severity and Timing of Onset (Pooled Safety Data)

Patients (%) [BE]	Pre-Procedure[a]	Procedure[b]	Post-Procedure[c]
Placebo with PT (n = 126)			
Severe	0	0	1 (0.8) [1]
Moderate	0	2 (1.6) [2]	0
Mild	12 (9.5) [14]	4 (3.2) [4]	8 (6.3) [13]
Total	12 (9.5) [14]	6 (4.8) [6]	9 (7.1) [14]
LUSU 3 mg without PT (n = 124)			
Severe	0	0	0
Moderate	0	0	1 (0.8) [1]
Mild	4 (3.2) [5]	4 (3.2) [4]	4 (3.2) [4]
Total	4 (3.2) [5]	4 (3.2) [4]	5 (4.0) [5]

Represented as: # of pts (% pts with BE) [# of events]
Pts could be counted >1x in same time period if they experienced 2 BE with different severities, but only 1x if severity was the same
The same patient could be counted > 1x if they experienced BE in different time periods
[a]Pre-procedure: BE prior to procedure. Includes BE in pts who did not undergo invasive procedure
[b]Procedure: BE on day of procedure (day 1)
[c]Post-procedure: BE after day of procedure (after day 1) regardless of procedural haemorrhage

Conclusion: In this post-hoc analysis, a trend toward lower BE rates was observed with LUSU alone vs PBO+PT, regardless of type of invasive procedure.

SAT-039

The assessment of sarcopenia by quadriceps muscle ultrasound in patients with liver cirrhosis

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Background and aims: Sarcopenia is a frequent complication in cirrhotic patients associated with worse prognosis. To date, Computed Tomography (CT) is considered the gold standard to quantify muscle mass in cirrhotic patients but it is not usable only for muscle assessment due to the cost, radiation exposure and logistics difficulties. Quadriceps muscle thickness detection by ultrasound has been recently proposed as an easier bedside tool to assess sarcopenia. The aim of our study was to evaluate the role of quadriceps thickness pressure index (TPI) in the detection of sarcopenia in comparison to CT assessed skeletal muscle index (SMI) in cirrhotic patients.

Method: Consecutive cirrhotic patients, who performed a CT scan between +8/-8 weeks from outpatient visit were included. Sarcopenia was evaluated by L3 SMI using the following cut-offs: < 39 cm^2/m^2 for females and < 50 cm^2/m^2 for males. The TPI was performed in the middle point on the line connecting the patella with the upper anterior iliac spine. Three measurements with pressure to collapse the muscle as much as possible were taken. TPI was obtained by the average of these measures normalized for the height².
Results: Eighty-three patients were enrolled in the study and the 58% of them were sarcopenic, according to CT scan. Sarcopenic patients were older (64 ± 10 vs 58 ± 8 p = 0.009), had a lower BMI (23 ± 3 vs 28 ± 4 p < 0.001) and lower TPI (4.6 ± 1.1 vs 7.1 ± 2.2 p < 0.001). We found a positive correlation between SMI and TPI (r^2 = 0.43; p < 0.001). The AUC for TPI considering sarcopenia by SMI was 0.79.

VARIABLES	SARCOPENIC PATIENTS n = 48 (58%)	NON-SARCOPENIC PATIENTS n = 35 (42%)	P value
Age (years)	64 ± 10	58 ± 8	0.009
Male gender n (%)	42 (%)	25 (87%)	0.06
Etiology of liver disease n (%) Viral Hepatitis NAFLD Alcohol Other	 (48%) (27%) (22%) (3%)	 (50%) (25%) (25%) 0	0.8
BMI (Kg/h²)	23 ± 3	28 ± 4	< 0.0001
Presence of HCC n (%)	25 (%)	15 (%)	0.7
SMI (cm^2/m^2)	42.8 ± 5.1	54.5 ± 8.1	< 0.0001
TPI (mm/m²)	4.6 ± 1.1	7.1 ± 2.2	< 0.0001

Values are expressed as mean ± standard deviation.
Abbreviations: NAFLD = non-alcoholic fatty liver disease; BMI = body mass index; HCC = hepatocellular carcinoma; TPI = quadriceps thickness pressure index.

Table: Characteristics of the patients based on the presence of sarcopenia.

Conclusion: The results of our study show that TPI is an effective index for the assessment of muscle depletion in cirrhotic patients. Ultrasound assessment of sarcopenia may allow monitoring the patients' nutritional status over time.

SAT-040

Is spleen stiffness the new frontier for non-invasive assessment of portal hypertension?

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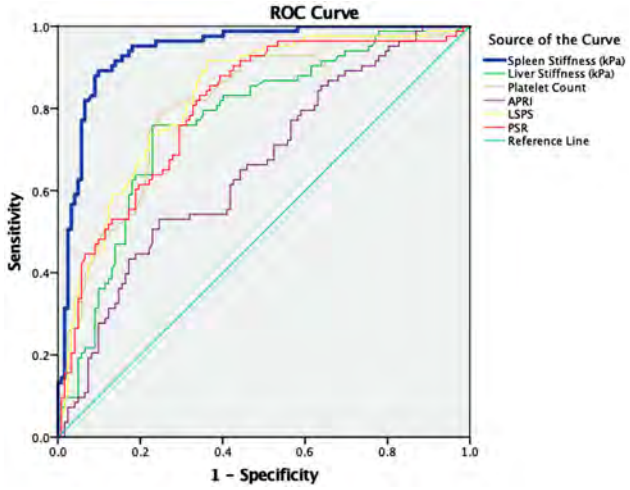
Background and aims: Elastography is a cutting-edge methodology, which has brought great enthusiasm to the study of tissue elasticity. Guidelines have been issued on liver stiffness (LS) in the clinical setting of liver cirrhosis and esophagogastroduodenoscopy (EGD) screening for esophageal varices (EVs). Our study aims to analyze spleen stiffness (SS) as a non-invasive method for the diagnosis of clinically significant portal hypertension (CSPH) in order to avoid EGD in low-risk patients for EVs.
Method: we measured the SS and LS in 205 patients with liver cirrhosis who had undergone endoscopic screening for esophageal varices. Besides, we enrolled 100 healthy controls (with previous EGD) who were negative for hepatic and lymphoproliferative disease. We used a 1-5 MHz convex probe for the ultrasound and elastographic (point Shear Wave Elastography, pSWE) examination. We compared SS discriminatory capacity for the presence of EVs to that deriving from other non-invasive procedures (LS, splenic dimensions, platelet count, APRI, PSR and LSPS). Optimal SS cut-offs were sought to exclude the presence of varices. We searched for correlations between SS and indirect signs of portal hypertension such as spleen dimension, platelet count and presence of portal hypertensive gastropathy (PHG).
Results: Cirrhotic patients have significantly higher SS and LS values than controls. SS was higher in cirrhotic patients with EVs (n = 83) v.s. patients without EVs (n = 122) and healthy controls (p < 0.001). SS showed an AUROC of 0.94 (95% C.I., 0.91-0.97), statistically different from the other predictors (p < 0.001). The cut-off, chosen according to Youden's Index of 38.69 kPa, showed sensitivity of 89.2%, specificity of 90.2%, NPV of 92.4%, and PPV of 86%. The cut-off of 30.23 kPa had 100% sensitivity and 100% NPV. The cut-off of 69.73 kPa demonstrated specificity and PPV of 100%. Correlation between SS and LS with PHG was equal to r_{pb} = 0.358 and r_{pb} = 0.286 respectively. The SS demonstrated higher correlation with splenic bipolar diameter (r = 0.363) and area (r = 0.420) if compared to LS (r = 0.263 and r = 0.328). Moreover, SS showed an association with platelet count greater than LS (r = 0.55 v.s. r = 0.38).



Conclusion: SS can play an essential role in the daily clinical management of cirrhotic patients with CSPH. LS has proven to be less performant as a predictor of EVs (AUROC 0.77), whereas both PSR and LSPS showed a slightly better performance (AUROC 0.81 and 0.83 respectively). SS showed significantly higher performance than other parameters, proving to be the best non-invasive test in the screening of EVs. We demonstrated that there is a certain degree of correlation between SS and splenic dimensions, platelet count and PHG; and that the actual correlation is superior to the one present between LS and those parameters. Overall, SS performed as a better surrogate in the study of portal hypertension and its consequences.

SAT-041

The adjunct of sarcopenia with MHE increases the 1 year risk of developing OHE

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Background and aims: Minimal hepatic encephalopathy (MHE) and sarcopenia are both underecognised complications of cirrhosis. Liver cirrhosis leads to sarcopenia by a decrease in muscle substrate production and an increase in muscle breakdown. This occurs by a reduction in the glycogen production by the liver leading to muscle proteolysis for energy, systemic inflammation and the reduction of clearance of metabolites including ammonia. This is particularly important in hepatic encephalopathy as the skeletal muscle is the second largest site for ammonia clearance leading to a cascading cycle. The aim of this study was to assess the incidence of MHE and sarcopenia to the risk of developing overt hepatic encephalopathy (OHE) over a 12 month period.
Method: In this prospective trial, patients were enrolled with liver cirrhosis at The Prince Charles Hospital over a 2 year period and followed for 12 months to assess for the development of OHE. An extensive exclusion criteria was used to reduce confounding factors; this included: active psychiatric condition, IVDU/drug use, neurological conditions, current significant alcohol intake, stroke, dementia, current infection, language barrier, active malignancy, vision impairment, uncontrolled sleep apnoea, electrolyte disturbance and grade 1-4 encephalopathy. Participants were tested for MHE using the Encephalapp Stroop test (Stroop), Psychometric hepatic encephalopathy score (PHES), Critical Flicker Frequency (CFF). Participants were also screened for sarcopenia by measuring handgrip strength using a jammer dynamometer.
Results: A total of 187 patients with cirrhosis were approached for recruitment of the trial. 17 patients declined to be part of the study and a further 98 patients were required to be excluded by the exclusion criteria. This allowed 72 patients to be enrolled in the study and to be assessed for MHE. By using a diagnostic regime of MHE by either an abnormal Stroop, PHES or CFF a total 37 patients were diagnosed with MHE, whilst 35 were classified as no MHE. The rate of OHE was dependent on the presence of sarcopenia and MHE as highlighted in Figure 1 (p value 0.0003). Moreover, th rate of OHE increased when both MHE and sarcopenia were present together.

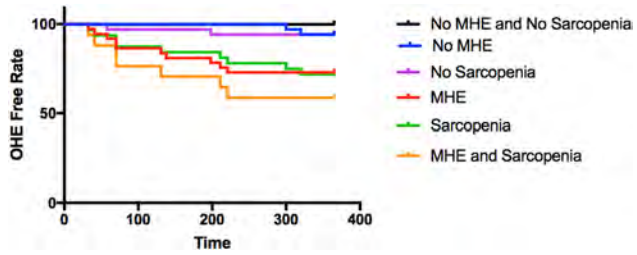

Figure: 12 month OHE Free Rate.

Conclusion: MHE and sarcopenia are important risk factors for the development of OHE. By assessing for MHE and sarcopenia in the outpatient setting, patients at risk of developing OHE can be easily identified allowing for early intervention, monitoring or treatment.

SAT-042

The stroop test is better at predicting the 6-month risk of developing overt hepatic encephalopathy compared to the PHES and CFF tests

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Background and aims: Minimal hepatic encephalopathy (MHE) is an underdiagnosed complication of cirrhosis. Whilst there are a number of testing modalities available, there is a paucity of data describing which test is the best at predicting overt hepatic encephalopathy. The current guidelines on hepatic encephalopathy recommend utilising two tests every six months to screen and diagnose MHE. MHE has been shown to be a predictor of progression of liver disease, driving accidents, falls and quality of life. However, the primary reason to test for MHE is to identify those patients at risk of developing overt hepatic encephalopathy (OHE). The aim of this study was to investigate the different outpatient testing modalities for MHE to identify the test with the highest sensitivity of predicting overt hepatic encephalopathy in the subsequent six months.
Method: In this prospective trial, patients with liver cirrhosis at The Prince Charles Hospital were enrolled over a 2 year period. An extensive exclusion criteria was used to reduce confounding factors; this included: active psychiatric condition, IVDU/drug use, neurological conditions, current significant alcohol intake, stroke, dementia, current infection, language barrier, active malignancy, vision impairment, uncontrolled sleep apnoea, electrolyte disturbance and grade 1-4 encephalopathy. Participants were diagnosed with MHE using the Encephalapp Stroop test (Stroop) > 190, Psychometric hepatic encephalopathy score (PHES) < -4 and Critical Flicker Frequency (CFF) < 39.The participants were followed for the subsequent 6 months to assess if they developed OHE.
Results: A total of 187 patients with cirrhosis were approached for recruitment in the trial. 17 patients declined to be part of the study and a further 98 patients were eliminated by the exclusion criteria. This allowed 72 participants to be enrolled in the study and to be assessed for MHE. A total of 7 participants developed OHE in the subsequent 6 months; 6 of these participants had an abnormal Stroop test, 5 had an abnormal CFF test and 4 had an abnormal PHES test. The Stroop test had the highest sensitivity with 85.71% [CI 48.69-99.27%,] compared the CFF sensitivity of 71.43% [CI 35.89-94.92%] and PHES sensitivity of 57.14% [25.02-84.18%], p value < 0.05. The specificity of the Stroop test was 64.62% [CI 52.48-75.12%], PPV was 20.67% [CI 9.84-38.39%] and the NPV was 97.67% [CI 87.94-99.88%] p value < 0.05.
Conclusion: MHE is a predictor of developing OHE independent to the clinical stage. This study highlighted the variation in predicting OHE by using different testing modalities. The Stroop test had the highest sensitivity of predicting OHE in the following six months. Aside from being a simple validated tool to diagnose MHE, it is also can be easily be incorporated into clinical practice allowing for prediction of patients at risk of developing OHE.

SAT-043

Is carvedilol better than propranolol in preventing variceal bleeding

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Background and aims: Cirrhotic patients reporting with hematemesis due to portal hypertension have a 15-50% consequential high death rate with approximately 7% per year development of new varices among this population subgroup
This study compared the effectiveness of carvedilol and propranolol for primary prevention of variceal bleed in cirrhotic patients. Along with that, patient compliance to drugs and side effects of the drugs were also checked.
Methods: CLD patients having varices (small and large without red signs) with no previous history of GI bleed, were randomized to group A (Carvedilol) and group B (Propranolol). The absence of variceal bleeding at the end of one year treatment for each patient was considered as effective treatment response.
Results: Total number of patients included in the study were 80. Overall bleeding occurred in 32.5% and 60% of the patients in group A and B respectively ($p = 0.026$). Bleeding was more common among patient with large as compared to small varices 76.92% versus 31.48% respectively in both groups. Among patients with large varices bleeding occurred in 63.6% and 86.66% of patients in group A and B respectively on follow-up ($p = 0.017$). On the other hand, in patients with small varices, bleeding occurred in 22.22% and 50% in group A and B respectively ($p = 0.03$). Regarding the response of beta blockers on pulse rate, the mean pulse rate dropped from 85.15 ± 5.49 to 69.5 ± 3.35 per minute in Group A while in Group B the initial pulse rate of 83.8 ± 5.33 decreased to 68.5 ± 7.09 per minute on 12 months follow-up ($p = 0.6$). Fatigue was the common side effect in both groups with no significant difference in the side effect profile. Patients were compliant to the treatment in both groups.

Table:

		Study Groups A	B	p value	Total
Controlled Bleeding	Yes	25 (62.5%)	13 (32.5%)	0.026	38 (47.5%)
	No	13 (32.5%)	24 (60%)		37 (46.25%)
	Lost follow-up	02	03		05 (6.25%)
Completed Large varices		04 (36.36%)	02 (13.33%)	0.002	06 (23.07%)
Large varices bleeders		07 (63.63%)	13 (86.66%)	0.017	20 (76.92%)
Completed Small varices		21 (77.77%)	11 (50%)	0.011	32 (59.25%)
Small varices bleeders		06 (22.22%)	11 (50%)	0.034	17 (31.48%)

Conclusion: In our cohort of cirrhotic patients, carvedilol group showed better response compared to propranolol group in the primary prevention of variceal hemorrhage. It was also concluded that in patients with large varices without red sign, combined EVBL and β-blockers should be employed for primary prophylaxis rather than beta blockers alone.

SAT-044

Serum Myostatin in liver cirrhosis: A marker beyond malnutrition

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Background and aims: Malnutrition is one of the most common complications of liver cirrhosis and mainly assessed by anthropometric measures (BMI, MAMC, Triceps fold), radiologically (DEXA scan and MRI), subjective measures as Subjective Global assessment (SGA) and Mini Nutritional test and biochemical markers (Myostatin and IGF-1). Myostatin, member of TGF β family, is a critical autocrine/paracrine inhibitor of skeletal muscle growth and mass. Myostatin inhibits skeletal muscle protein synthesis as well as increased proteolysis. The aim of the present work was to elucidate the relationship between Myostatin and the degree of malnutrition and to investigate its importance as a prognostic key in cirrhotics same as MELD score.
Method: A total 80 subjects were included in the study, seventy patients with liver cirrhosis and ten apparently healthy. Serum Myostatin was measured by ELISA.
Results: Serum myostatin was significantly higher in patients than controls ($U = 97$, $P = 0.001$). Among 70 patients with liver cirrhosis (51 were malnourished and 19 well nourished) serum levels of myostatin was significantly higher in malnourished cases ($U = 41.5$, $P = 0.001$). According to SGA (mild in 14 cases, moderate in 17 and high SGA in 20 cases), Serum myostatin was significantly higher in high SGA than moderate and mild SGA ($p = 0.001$). Moreover it was significantly higher in moderate SGA than mild SGA ($p = 0.002$). As regards child score, serum myostatin was significantly higher in Child C than Child B and Child A ($p < 0.05$). Regarding MELD score, a statistical significant positive correlation was found between Myostatin and MELD in malnourished patients groups ($p < 0.05$). Furthermore, serum myostatin was significantly higher in those cases with hepatic encephalopathy than patients without it ($U = 234$, $P < 0.001$). Roc curve analysis revealed that serum myostatin at cut off > 6.1 could discriminate malnourished from well-nourished cases with sensitivity 98.04%, specificity 84.2%, PPV 94.3%., NPV 94.1% and accuracy of 94.3%.
Conclusion: High serum Myostain is associated with profound malnutrition and might be used as a valuable marker as MELD determining poor outcome in patients with liver cirrhosis.

SAT-045

Prevalence, type and risk factors of colonization by multidrug-resistant bacteria in a large series of patients with decompensated cirrhosis

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Background and aims: Rate, type and risk factors of colonization by MDR strains in decompensated cirrhosis are poorly known.
Method: Single center prospective study including 316 consecutive patients (70% were admitted to the regular ward and 30% in the ICU). Rectal and nasal swabs were obtained at admission (48h) and weekly thereafter until discharge and cultured for ESBL-producing *Enterobacteriaceae*, carbapenem-resistant bacteria, MRSA and VRE.
Results: At inclusion, 23% of patients were colonized by MDR strains in rectal swabs and only 2.5% were MRSA nasal carriers. Prevalence of rectal (24% vs. 20%) and nasal (2% vs. 3%) colonization by MDROs was similar between patients admitted to the regular ward and those requiring ICU. Median follow-up was 181 days (70 to 333). Thirty-one percent of non-colonized patients became colonized by MDROs during follow-up in rectal swabs. In contrast, nasal colonization by MDROs was exceptional during follow-up (2%). Remarkably, 35% of MDROs rectal carriers at inclusion developed an over-colonization by a new MDR bacteria during follow-up. ESBL-producing *Enterobacteriaceae* were the most frequent MDROs isolated

in rectal swabs at inclusion (*Escherichia Coli and Klebsiella pneumoniae;* n = 40 and n = 18, respectively) and during follow-up (*Klebsiella pneumoniae and Escherichia Coli;* n = 29 and n = 25, respectively). Carbapenem-resistant-*Enterobacteriaceae* were isolated in 10% of patients colonized by MDROs at baseline, in 18% of those colonized during follow-up and in up to 40% of those overcolonized within the study period (p = 0.003). Multivariate analysis identified norfloxacin prophylaxis (HR: 10.2, p = 0.001), MDROs isolation in the previous 6 months (HR: 7.9, p = 0.005), hospital admission within the last 3 months (HR 5.7, p = 0.02) and long-term care facility (HR 4.2, p = 0.04) as independent risk factors for MDR rectal colonization at admission. The presence of ascites was identified as an independent predictor of MDROs rectal colonization during follow-up (HR: 1.7, p = 0.04).

Conclusion: Rectal colonization by MDR bacteria, mainly ESBL producing *Enterobacteriaceae,* is extremely frequent in patients with decompensated cirrhosis requiring hospitalization and often occurs after hospital admission. Previous contact with the healthcare system, norfloxacin prophylaxis and the presence of ascites are risk factors of MDRO colonization. Studies evaluating preventive strategies of rectal colonization in decompensated cirrhosis are urgently needed.

SAT-046

Clinical impact of rectal colonization by multidrug-resistant bacteria in patients with decompensated cirrhosis

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Background and aims: The clinical relevance and prognostic impact of colonization by MDR strains in decompensated cirrhosis is unknown.

Method: Single center prospective study including 316 consecutive patients (70% were admitted to the regular ward and 30% in the ICU). Rectal swabs were obtained at admission (48h) and weekly thereafter during hospitalization (s) and cultured for ESBL-producing *Enterobacteriaceae*, carbapenem-resistant bacteria, MRSA and VRE. Patients were followed up up to 1 year for the development of bacterial infections and mortality. MDR microbiological isolations were considered to guide antibiotic therapy and isolation strategies.

Results: Current median follow-up is 180 days (69 to 330). 156 patients were colonized by MDR strains at admission (23%) or became colonized during hospitalization (27%) with no differences between patients admitted to the regular ward and those requiring critical care. Overcolonization by a new MDR strain was observed in 26 patients (8%). ESBL-producing *Enterobacteriaceae* were the most frequent MDROs isolated followed by carbapenem-resistant-*Enterobacteriaceae*. MDR rectal carriers showed a higher incidence of infections caused by MDROs during follow-up: 37% vs. 6% (p < 0.0001). Median time from colonization to infection by MDROs was 30 days (15-90). The type of resistant bacteria responsible for infection was that colonizing the patient in 81% of the cases. Multivariate analysis identified rectal colonization by MDROs (HR: 9.99; 95%CI: 4.54-22.00; P < 0.0001) and MELD score (HR: 1.05; 95% CI: 1.009-1.09; P = 0.02) as the only independent risk factors for MDR bacterial infections during follow-up. Mortality rate was similar between patients with and without MDR colonization (34% vs. 28%) and with and without infections caused by MDROs (37% vs. 29%), suggesting that empirical antibiotic strategies guided by epidemiological surveillance can attenuate the poor prognosis associated to antibiotic resistance in cirrhosis.

Conclusion: Rectal colonization by MDR bacteria significantly increases the risk of infections caused by resistant strains at short-term. Empirical antibiotic strategies based on rectal colonization data seem to improve the prognosis of patients with decompensated cirrhosis infected by MDROs.

SAT-047

Easy surveillance method without need of special equipment for muscle volume loss in patients with chronic liver disease

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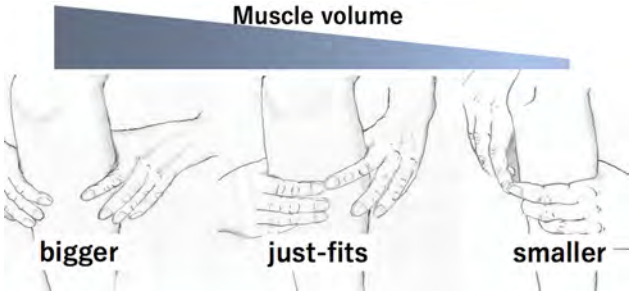
Background and aims: Muscle volume loss (MVL), a not rare complication in patients with chronic liver disease (CLD), has been reported to play a significant role in the prognosis of CLD patients. However, evaluation of MVL requires special equipment, thus development of an easy surveillance method without such specialized equipment is anticipated. Here, we evaluated the usefulness of the previously reported finger-circle test as screening for MVL in patients with CLD.

Method: We enrolled 358 outpatients with CLD [70.8 ± 10.2 years old; males 234, females 124; chronic hepatitis (CH) 136, liver cirrhosis (LC) 170, Child-Pugh (CP)-A 52; HCV:HBV:HBVandHCV:alcohol: others = 192:49:1:54:62] who underwent CT as screening for hepatocellular carcinoma (HCC) from December 2017 to March 2018. Muscle volume was manually calculated with CT findings using personal computer software and evaluated with previously reported cut-off value for psoas index (PI) that utilized values for psoas muscle area and height of young normal controls (NCs) [psoas index (PI): psoas muscle area (cm^2)/height $(m)^2$] to predict MVL (males: 6.50 ± 1.13 cm^2/m^2, females: 4.30 ± 0.90 cm^2/m^2). MVL was defined as mean-2 standard deviation (SD) of the PI of the NCs, while pre-MVL was defined as mean-1SD.

Each patient was administered the finger-circle test, developed to determine whether the maximum non-dominant calf circumference is larger than the individual subject's finger-circle circumference, formed with the index finger and thumb of both hand. Finger circle testing was carried out with the patient in a seated position, with turning up a hem. Based on those results, they were divided into the bigger, just-fits, and smaller groups.



Results: The bigger, just-fits, and smaller groups were composed of 192, 104, and 62 patients, respectively. The frequency of both pre-MVL and MVL increased with worse finger-circle test results [pre-MVL/MVL: bigger 63/16 (41.1%), just-fits 33/25 (55.8%), smaller 25/17 (67.7%) (p < 0.001)]. The PI values for bigger, just-fits, and smaller in males were 5.64 ± 1.34, 5.00 ± 1.25, 4.83 ± 1.46 cm^2/m^2, respectively (p < 0.001), while those in females were 4.31 ± 1.06, 3.93 ± 0.97, 3.42 ± 0.94 cm^2/m^2, respectively (p = 0.001). In males, the predicted PI value for just-fits was 5.25 cm^2/m^2 (sensitivity 0.619, specificity 0.667, AUC 0.654, 95% CI 0.583-0.724), which was an

approximation for pre-MVL as mean-1SD (5.37 cm^2/m^2) of the PI of the NCs. In females, the predicted PI value for smaller was 3.33 cm^2/m^2 (sensitivity 0.740, specificity 0.583, AUC 0.698, 95% CI 0.583-0.813), which was an approximation for pre-MVL as mean-1SD (3.40 cm^2/m^2).

Conclusion: The finger-circle test is easy to perform and does not require special equipment. Assessment of muscle volume should be considered in males when the finger-circle test result is just-fits or smaller, and in females when the result is smaller.

SAT-048

Changes in the intestinal microbiome during probiotic intervention in cirrhosis

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Background and aims: Liver cirrhosis is accompanied by significant changes of the intestinal microbiome including the regression of beneficial and autochthonous taxa. The aim of the study was to test the effects of a multispecies probiotic on gut microbiome composition.

Method: Gut microbiome composition of 58 patients with Child's A cirrhosis who received a daily dose (1.5*10^10 CFU) of a multispecies probiotic or placebo for six months was analysed by 16S rRNA gene sequencing.

Results: Microbiome composition of patients was enriched with probiotic strains Lactobacillus salivarius, Lactobacillus brevis and Lactococcus lactis. Furthermore, the abundance of short-chain fatty acid producing bacteria Faecalibacterium prausnitzii, Syntrophococcus sucromutans and Alistipes shahii was increased in the probiotic group compared to the placebo group. Changes in starch-utilizing bacteria of the species Bacteriodes vulgatus could be observed in both groups.

Conclusion: A six months intervention with a multispecies probiotic enriched the microbiome of cirrhotic patients with probiotic bacteria. The abundance of anaerobic and short-chain fatty acid producing bacteria was increased in patients in the probiotic group and changes in starch-utilizing bacteria were observed in both groups.

SAT-049

Lactate but not hemoglobin is a predictor for mortality in patients with liver cirrhosis and upper GI bleeding

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Background and aims: Acute upper gastrointestinal (GI) bleeding in patients with liver cirrhosis is associated with high mortality. Although lactate as predictor of survival in patients with liver cirrhosis has gained increasing attention, it's prognostic properties on acute upper GI bleeding have not been assessed so far. We therefore aimed to assess the impact of peak serum lactate levels in comparison to established parameters such as lowest hemoglobin or model for endstage liver disease (MELD) in cirrhotic patients with upper GI bleeding.

Method: We analyzed data from 159 consecutive patients with liver cirrhosis and first episode of acute upper GI bleeding who underwent endoscopy at a tertiary care hospital from 2009-2018. Source of bleeding, initial hemodynamics, laboratory values as well as 30-day and 90-day mortality have been assessed. We tested the prognostic performance of peak serum lactate, nadir hemoglobin and MELD score and compared it to $MELD^{Lactate}$, a score incorporating lactate and MELD.

Results: 131 patients (82%) had acute variceal bleeding, 25 (16%) had ligation-induced ulcer bleeding and 3 patients (2%) had peptic ulcers or unclear source of bleeding. Median MELD was 18 (IQR 12-25). Among the studied individuals 30-day mortality was 29% and 90-mortality 37%, respectively.

While peak lactate levels at time of bleeding were significantly higher in 30-day non-survivors (median lactate 6.2 mmol/l (2.0-13.6) versus 2.1 mmol/l (1.5-3.5); $p < 0.001$), nadir hemoglobin levels were not associated with patient's outcome (median hemoglobin 7.3 g/dl (6.6-8.3) vs. 7.1 g/dl (6.3-8.4); p = n.s.). Receiver operating curve analysis revealed highest predictive properties for $MELD^{Lactate}$ (AUROC 0.86), followed by MELD (0.8), peak lactate (0.73) and nadir hemoglobin (0.51), as shown in figure 1.

$MELD^{Lactate}$ predicted short-term mortality independently of age, hemoglobin, mean arterial blood pressure, severity of liver disease (MELD) and the Charlson comorbidity index (cox regression: HR 1.2 per 1-point increase of $MELD^{Lactate}$ score; 95%CI 1.11-1.29; $p < 0.001$).

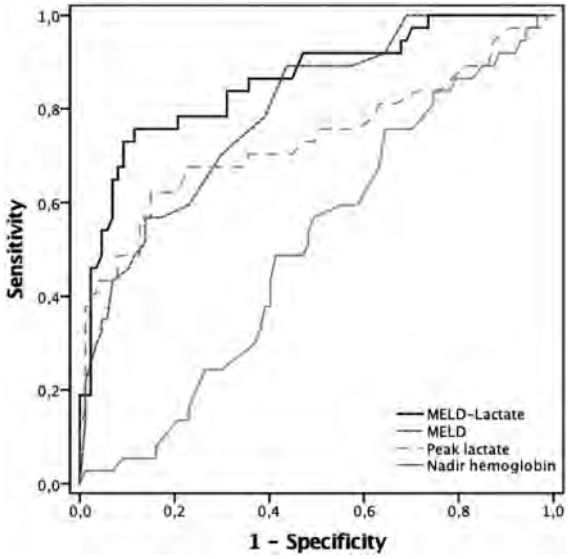

Figure: Receiver operating curve analysis in prediction of 30-day mortality (MELD, model for endstage liver disease)

Conclusion: In contrast to lowest hemoglobin levels at the time of bleeding, peak serum lactate was significantly associated with short-term mortality. Best prognostic properties were observed in combining MELD and lactate, a simple independent marker for mortality in patients with liver cirrhosis and acute upper GI bleeding.

SAT-050

Silymarins significantly improve long term survival in patients with liver cirrhosis regardless of MELD score

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Background and aims: Silymarin, the active ingredient in milk thistle, functions as an antioxidant and may decrease hepatic injury and inhibition of Kupffer cell function. However, despite its theoretical benefit in cultured cells, a systematic review that included 14 studies found no clear evidence showing a reduction in mortality in patients with chronic liver disease [1]. However it is still widely used as a nonprescription agent in patients with chronic liver disease. It is hence intriguing to study whether silymarin has beneficial effect in end stage liver disease.

Method: By analysing big data from the center for big data analytics and statistics of CGMH Hospital, 49380 patients who met the diagnostic criteria of liver cirrhosis (LC) between 2006~2017 were screened. Exclusion criteria included previously diagnosed HCC before enroll, age < 12 years old and no available staging information during follow-up. With silymarin group was defined as consecutive use of 3 tablets of silymarin a day for at least 3 months and came back to hospital for the prescription every month. Others were defined as control group. The primary outcome was 5-year (60 months) mortality analyzed by Cox-regression model after adjusting for time-dependent covariate MELD scores. Age, sex, cirrhotic etiologies, number of admissions and Charlson Comorbidity Index (CCI) were also adjusted in the multivariate analysis.

Results: Totally 12, 616 patients were enrolled after exclusion criteria **(Figure 1).** The mean age was 54.26 ± 15.13 year-old. 8, 462 (67.07%) were male. For the etiology of cirrhosis, 12.46% were HBV, 13.36% were HCV, 4.34% were HBV+HCV co-infection and 12.22% were alcoholic, while 57.62% were other aetiologies including NASH. Mean follow-up time was 62.32 ± 44.22 months. 2, 903 patients died during follow-up (23.01%).

There were 1, 175 patients in the silymarin group and 11, 441 patients in the control group. Age, etiologies of cirrhosis, CCI, number of admissions and MELD score, silymarin use correlated with primary outcome after long-term follow-up by Cox univariable analysis **(Figure 2).** After adjusting the above covariate and time-dependent MELD scores, consecutive silymarin use for at least 3 months were associated with lower hazard ratio (0.879), p = 0.0187 **(Figure 3).** As shown in **Figure 4** by Kaplan-Meier plot, use of silymarin group has better outcome curve than control irrespective of MELD score.

Conclusion: By Cox-regression model after adjustment for time-dependent MELD and other covariates including age, etiologies of cirrhosis, CCI and number of admissions, the hazard ratio for death was lower in the silymarin group. In this big data study, consecutive use of 3 tablets of silymarin a day for at least 3 months in patients with liver cirrhosis correlated with better survival outcome irrespective of MELD score

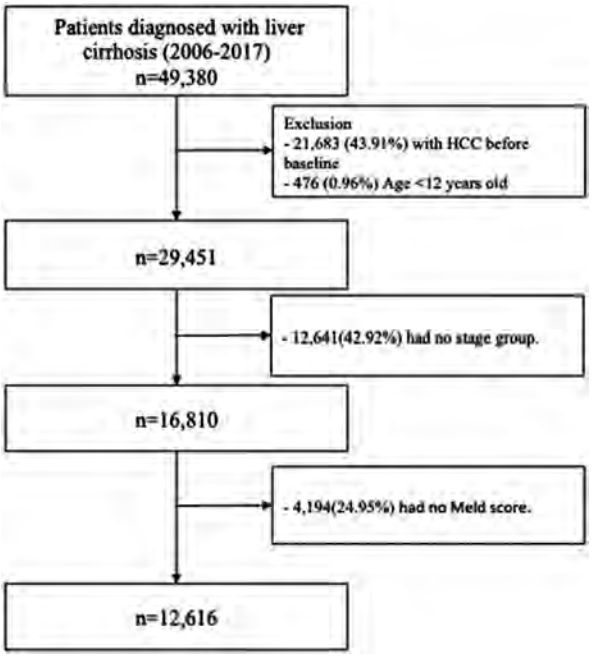

Figure 1:

Covariate				
Variable	Cox (Univariable) HR	LB of 95% CI for HR	UB of 95% CI for HR	p-valu
Age	1.018	1.016	1.021	<.0001
Sex				
Male	1.039	0.962	1.124	0.3272
Female	1			
Hepatitis B	1.585	1.452	1.728	<.0001
Hepatitis C	1.764	1.621	1.917	<.0001
Hepatitis B and	2.091	1.807	2.403	<.0001
Alcoholic liver	1.112	0.998	1.235	0.0446
CCI	1.132	1.122	1.142	<.0001
Number of adm	3.069	2.609	3.581	<.0001

Figure 2:

Variable	Cox (Univariable) HR	LB of 95% CI for HR	UB of 95% CI for HR	p-valu	Cox (Multivariable) HR	LB of 95% CI for HR	95% CI for HR	p-valu
Meldscore								
≤ 13	1				1			
> 13	3.137	2.910	3.383	<.0001	2.585	2.395	2.792	<.0001
Silymarin								
Without(0)	1				1			
With(1)	1.279	1.142	1.427	<.0001	0.879	0.784	0.982	0.0187

Adjust: age, Meldscore, Hepatitis B, Hepatitis C, Hepatitis B and Hepatitis C, Alcoholic liver, CCI, Number of admissions

Figure 3:

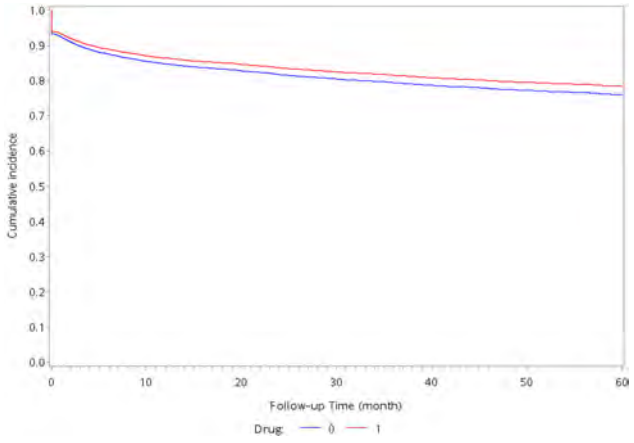

Figure 4:

Reference

1 Jacobs BP *et al. Am J Med.* 2002;113 (6):506–15

SAT-051

The effects of portal vein thrombosis to patients with cirrhotic variceal bleeding underwent endoscopic treatment

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Background and aims: Portal vein thrombosis (PVT) is frequent in patients with cirrhotic variceal bleeding, which could be a cause or a consequence of the progression of portal hypertension. So we aimed to evaluate the effect of portal vein thrombosis to the prognosis of patients with cirrhotic portal hypertension and underwent endoscopic treatment for the prophylaxis of bleeding.

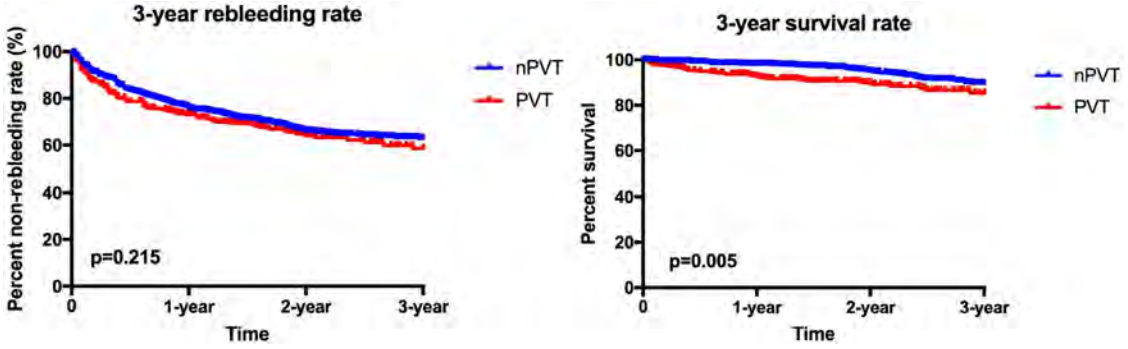

Figure: (abstract: SAT-051)

Method: We enrolled 1198 consecutive non-tumoral cirrhotic patients with cirrhotic gastroesophageal varices and received first endoscopic treatment between Jan 1st, 2008 and Dec 31st 2017. Patients were divided into PVT group (n = 294) and non-PVT (n = 846) group according to computer tomography angiography and follow-up.
Results: The mean age of included patients with cirrhotic gastroesophageal varices was 54.74 ± 36 with the ratio of portal vein thrombosis about 24.54%. There is 141 patients underwent splenectomy previous. At baseline, MELD score was similar between groups (9.25 ± 0.15 vs 9.12 ± 0.08, p = 0.437). And patients with PVT had a higher level of NLR (Neutrophil-lymphocyte ratio) 2.95 ± 0.20 vs 2.55 ± 0.07, p = 0.016). During a median follow-up of 25 months, no significant difference was observed between two groups in regard to variceal bleeding (32.42% vs 30.17%, p = 0.215). While Kaplan-Meier analysis revealed that 3-year mortality for patients with PVT was 10.03%, which was poorer than those without PVT 6.11% (p = 0.005). (Figure). Subgroup analysis showed patients with PVT without splenectomy had a higher rebleeding rate and mortality in 3-year (p < 0.05).
Conclusion: The development of portal vein thrombosis in cirrhotic portal hypertension in patients without splenectomy might influence the prognosis.

SAT-052

Right psoas muscle area: Prognostic factor in patients with cirrhosis Child Pugh class C included on the waiting list for liver transplantation

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Background and aims: Malnutrition and sarcopenia are frequent complications in cirrhosis and contribute to increased risk of sepsis-related mortality, poor quality of life, post-LT adverse outcomes. Sarcopenia is defined by cross-sectional imaging-based muscular assessment, however computed tomography (CT) scan determinations vary as well as cut-off values. The aim of our study was to identify risk factors for occurrence of infections and death before LT.
Method: All cirrhotic patients admitted on the waiting list for liver transplantation in our Hepatology Unit between years 2016–2017 underwent anthropometric assessments and abdominal CT scan including L3 and umbilical levels for measuring transverse psoas muscle thickness. Multiple regression was used to determine independent risk factors for occurrence of infections and death before LT.
Results: One hundred thirty two patients with liver cirrhosis were included. The average age was 53.9 ± 10.7 years, and 66% of patients were men. Child C class was encountered in 29.3% of patients and associated hepatocellular carcinoma was present in 17.8%. Large ascites (8-10 litres) was present in 27.7%. There is a moderate correlation between right psoas muscle area and adjusted BMI without ascites (r = 0.26, p = 0.007), arm circumference (r = 0.39, p = 0.0001), right hand grip (r = 0.45, p < 0.0001) and a very good correlation with the left psoas muscle (r = 0.85, p < 0.0001). There was no correlation between right psoas muscle area and skin fold. Patients with sarcopenia (defined as arm circumference < 22 mm and hand-grip < 45dyne) and Child Pugh Class C cirrhosis had a significantly lower right psoas muscle area compared to patients with Child Pugh class A/B cirrhosis (624cm3 vs 931.3cm3, p = 0.04). Right psoas muscle area was identified by multiple regression as independent risk factor for both infections and death while on the waiting list for LT (p = 0.03 for each). The value of the AUROC right psoas muscle area for predicting 1-yr mortality was 0.73 for a cut-off value of 608cm3.
Conclusion: Transverse right psoas muscle area was an independent predictor of mortality in cirrhotic patients. Psoas muscle area can be used as another negative prognostic factor in Child Pugh C cirrhosis.

SAT-053

Liver stiffness-spleen size-to-platelet ratio risk score detects esophageal varices and HCC risk in HCV- and HBV-related cirrhosis responsive to DAA

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Background and aims: Liver stiffness has been correlated to hepatic venous pressure gradient (HVPG). While the accurancy of LS in predicting clinically significant portal hypertension seems good, its discriminative ability in the prediction of esophageal varices (EV) appears inadequate. Thus, combination of different non-invasive methods could ameliorate the diagnostic accuracy. LSPS has been correlated with portal hypertension (mPH), EV and risk of hepatocellular carcinoma (HCC) in cirrhotic patients. The response to antiviral therapy with DAA reduces but does not eliminate the risk of HCC in HBV and HCV-related cirrhosis. The impact of SVR on mPH, clinical outcome and endoscopic monitoring of EVs, could be evaluated with LSPS.
Method: Data are presented from an ongoing longitudinal study, currently performed in 236 cirrhotic patients (115 HCV positive and 121 HBV positive) responsive to antiviral therapy with DAA. They underwent LSPS measurement before therapy and LSPS + HVPG measurement + gastroscopy after SVR 6 off-therapy in HCV and complete virological response (VR) from at least 12 months on therapy in HBV.
Results: LSPS < 0.6 and < 1.2 identified patients without CSPH (HVPG < 10mmHg; PPV 50%, NPV 100%) and without EVs (PPV 71%, NPV 96%), respectively. Patients who did not reach LSPS < 0.93 post SVR or VR were more likely to have appearance, persistence or progression of EVs (PPV 36%, NPV 97%). HCC developed in 29/236 (12%) of the patients, 3 with HCV infection and 26 with HBV infection and a longer

follow-up. LSPS ≤ 0.6 baseline or inducted by antiviral therapy was associated with a lower risk of HCC (NPV 98%).
Conclusion: LSPS is a useful non-invasive tool to exclude the presence of CSPH and Evs. Moreover, it could predict clinical outcomes, such as presence of EV avoiding unnecessary endoscopy and too frequent ultrasound. The impact of DAA therapy on HCC in HBV and HCV cirrhotic patient remains debated and requires a longer follow-up. However, LSPS ≤ 0.6 could identify a lower risk group in cirrhotic patients responsive to antiviral therapy.

SAT-054

A higher prevalence of colorectal adenomatous polyps in patients with liver cirrhosis compared with non-cirrhotics

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Background and aims: Recent studies suggested that non-alcoholic fatty liver diseases was associated with an increased risk for colorectal adenomas. However, there is paucity of data in literature on the true prevalence of colorectal polyps (CRP) in cirrhotics. We aimed to determine the impact of cirrhosis on the risk of CRP and whether risk may be influenced by sex and grade of cirrhosis.
Method: Over 6 months, colonoscopy (CS) was performed in 212 patients by experienced gastroenterologist at Baylor College of Medicine. Total of 111 men and 101 women were included. The mean age (± SD) was 59.4 ± 11.2 years. Under IRB approval and based on the results of the CS, patients were classified into 2 groups (gp): polyps-free gp (N = 97) and polyps gp (N = 115). Patients with polyps were further classified into adenomatous (N = 63), hyperplastic (N = 49), and others (N = 2). Evidence of cirrhosis was documented in 128 patients (60.4%). STATA was sued for statistical analyses. The associations between cirrhosis and CRP were assessed by multivariate logistic regression analyses. Odds ratio (OR) and 95% confidence interval (95% CI) was estimated after adjustment for confounding effects of epidemiological and clinical factors.
Results: Prevalence of CRP was higher in patients with cirrhosis (62.5%) than in patients without cirrhosis (41.7%), p = .003, indicating that patients with cirrhosis had approximately 3 fold increased risk of CRP as compared to patients without cirrhosis; the estimated OR (95% CI) is 2.6 (1.4-4.7) after controlling for confounding effect of age, sex, race, smoking, alcohol use, diabetes, history of cancers, hypertension, hyperlipidemia and renal diseases. The significant association was observed in women not in men, ORs (95% CI) were 3.3 (1.3-8.1) and 1.7 (.7-4.1) respectively and for adenomatous polyps: 7.4 (2.1-26.7) and not for hyperplastic polyps: 1.4 (.5-3.6), the association was independent of Child-Pugh score of cirrhosis. In the cirrhotic group, forceps and snare polypectomies were done in patients with and without cirrhosis with no significant difference in post-CS complications.
Conclusion: The current study demonstrated that cirrhosis is associated with risk of CRP and that sex may influence the association. Further studies may be warranted to explore the underlying mechanism behind CRP development in patients with cirrhosis. CS in cirrhotic patients is safe and not associated with significant post-colonoscopy complications as compared to non-cirrhotics.

SAT-055

Dobutamine counteracts the decrease in cardiac output after terlipressin in patients with cirrhosis and impaired kidney function but does not improve GFR: A randomised exploratory trial

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Background and aims: Acute kidney injury and hepatorenal syndrome (HRS) are frequent complications in patients with cirrhosis and ascites. First line treatment is the V1-receptor agonist terlipressin, that reverses HRS in approximately 40% of patients and reduces mortality, but also lowers cardiac output (CO). We hypothesised that counteracting terlipressins negative effects on CO with β-adrenoceptor agonist dobutamine infusion would potentiate the beneficial effects on the kidneys.
Method: Twenty-five patients with cirrhosis, ascites and impaired renal function (mean GFR = 47 ml/min/m^2; 95%CI 36 to 58) but without HRS, were randomized (2:2:1) into three groups: Group A received terlipressin followed by dobutamine, Group B received dobutamine followed by terlipressin, Group C received placebo. All investigations were performed after seven days on salt restricted diet (80 mEq NaCl) and discontinuation of diuretics and vasoactive drugs. Renal and cardiac function were assessed during 8 clearance periods of 30 minutes. Here we report dynamics of glomerular filtration rate (GFR) assessed by Cr-EDTA clearance, CO by the inert gas rebreathing method and plasma renin concentration (PRC) by radioimmuneassay.
Results: Dobutamine as monotherapy significantly increased CO (0.87 L/min, p = .025) and PRC (74.0 mIU/L, p = .022), but had no significant effects on GFR (−10.35 ml/min/m^2, p = .181) and MAP (−5.03 mmHg, p = .26). Terlipressin as monotherapy significantly improved GFR (18.9 ml/min/m^2, p = .005), MAP (13.8 mmHg, p = .001) and reduced CO (−1.08 L/min, p < .001). In the combined analysis, terlipressin alone had no significant effect on PRC (−25.4 mIU/L, p = .381). Addition of dobutamine on terlipressin significantly improved CO (1.36 L/min, p = .022) and PRC (78.6 mIU/L, p = .050), but the combination of dobutamine and terlipressin had no significant effects on MAP (3.67 mmHg, p = .499) or GFR (9.04 ml/min/m^2, p = .378).
Conclusion: Dobutamine increases CO and reverses the negative inotropic effect of terlipressin. However, combined treatment does not seem to translate into further increase in GFR. This may relate to the fact that combined therapy did not increase arterial pressure and thereby renal perfusion pressure beyond the effect of terlipressin alone. Moreover, dobutamine induce increasement in PRC, which may counteract the beneficial renal effects of terlipressin.
Figure shows the relative effects of dobutamine and terlipressin by group. Terli = terlipressin; Dobu = dobutamine; GFR = glomerular filtration rate; PRC = plasma renin concentration; CO = cardiac output; MAp = mean arterial pressure; SD = standard deviation

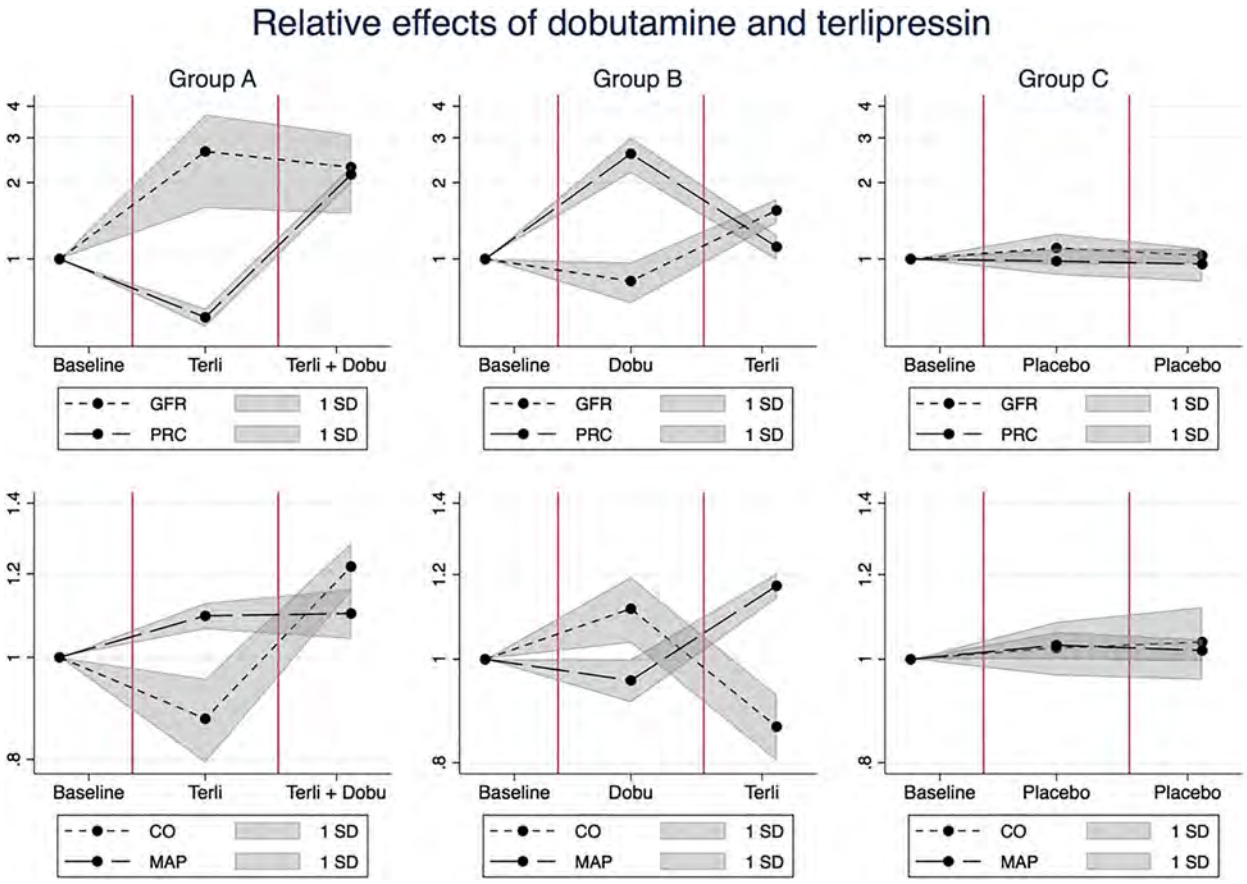

Figure: (abstract: SAT-055)

SAT-056

Development of a novel prognostic model for cirrhotic patients with difficult-to-treat ascites and low MELD scores

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Background and aims: Cirrhosis patients with difficult-to-treat ascites may have a very poor quality of life and high mortality despite a relatively low MELD score. We aimed to develop a model that is better than the MELD score at predicting survival through 1 year among patients with cirrhosis, MELD score ≤ 18, and difficult-to-treat ascites.

Method: We included stable outpatients included in the multinational SPARe-1 trial, a randomized comparison between satavaptan and placebo on top of diuretic treatment for the treatment of recurrent ascites in patients with cirrhosis. We used Cox regression with stepwise backward selection and fractional polynomial transformation of continuous variables to include the strongest predictors in the prediction model, which we called the SAM (Severe Ascites Mortality) score. Our main outcome was the difference in C index for 1-year mortality between the SAM score and the MELD score (with Na, per current UNOS guidelines). We used the bootstrap to correct for optimism bias in the development cohort, and we validated performance in an external cohort: the SPARe-2 trial participants.

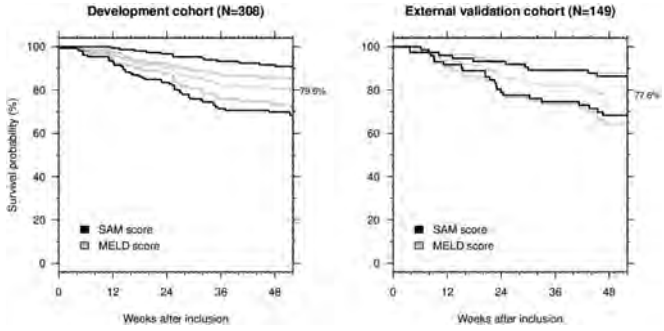

Figure: Observed survival probabilities for patients in the development cohort (left) and external validation cohort (right) divided by median SAM score (black) or by median MELD score (gray). In the development cohort, patients were clearly better separated by the SAM score than by the MELD score. In the external validation cohort, by contrast, the separation was similar for the two scores.

Results: The development cohort included 308 outpatients with difficult-to-treat ascites and MELD ≤ 18. Their overall 1-year survival probability was 79.6% (Figure). The final SAM score was computed as 0.1674 * (bilirubin/10)-0.6792 * (sodium/5); add 1.2866 if the patient has a history of SBP, and add 1.0676 if the patient has diabetes. The physical component score of the SF-36 did not make it into the final prediction model. The SAM score yielded a C index of 0.722, and the MELD score yielded a C index of 0.626. Consequently, the difference was 0.722-0.626 = 0.096. The estimated optimism bias was 0.087, meaning that the bias-corrected estimate of the C index in the development cohort was 0.096-0.087 = 0.009 (95% CI −0.008 to 0.101). The external cohort included 149 patients with refractory ascites and a slightly worse prognosis (Figure). In this cohort, the C

index was 0.690 for the SAM score and 0.664 for the MELD score. Thus, the difference was 0.690-0.664 = 0.026 (95% CI –0.066 to 0.119).
Conclusion: The SAM score includes 4 variables, but it performed better than MELD in these patients with difficult-to-treat ascites and a relatively low MELD score. The difference in C index was not statistically significant, yet the SAM score may be proven to be superior in patients with a low MELD score.

SAT-057

Proton pump inhibitors as a risk factor for hepatic encephalopathy and infections in cirrhotic patients: A clinical evidence

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Background and aims: Few non-conclusive studies suggest that long-term use of proton pump inhibitors (PPI) in cirrhotic patients is associated with bacterial translocation, hepatic encephalopathy (HE) and infections. The aim of our study was to evaluate the impact of PPI in the development of infections and HE in these patients.
Method: A cohort of cirrhotic patients admitted between January 2015 and June 2018 in a tertiary centre was retrospectively studied. Demographic, clinical and analytic data were collected, and patients with (group 1) and without PPI use (group 2) were compared regarding the incidence of HE and infections. Statistical analysis was performed by IBM SPSS version 25.
Results: A total of 396 patients were included (group 1: n = 183; group 2: n = 213). In 68.3% of group 1 patients there was no clinical indication for PPI use. Median age (69 ± 19 *vs.* 66 ± 21 years, p = 0.16), gender (male: 69.4% *vs.* 75.6%, p = 0.17), MELD-Na^+ score (18 ± 11 *vs.* 17 ± 11, p = 0.54), Child-Pugh score (B: 54.6% *vs.* 45.5% p = 0.19), aetiology of cirrhosis (ethylic: 73.8% *vs.* 69.5%, p = 0.44), incidence of hepatocellular carcinoma (8.3% *vs.* 17%, p = 0.14) and mortality (14.8% vs. 13.1%, p = 0.64) were not statistically different between groups 1 and 2, respectively. The incidence of HE was significantly higher in group 1 than in group 2 patients (39.3% *vs.* 24.9%, p < 0.01), no differences in its degree were noted (p = 0.67); the most frequent triggering factor in both groups was infection (84.3% vs. 41.5%, p = 0.63). Higher incidence of respiratory tract infections (23.5% *vs.* 15.5%, p = 0.04) and spontaneous bacterial peritonitis (SBP) (10.9% *vs.* 5.2%, p = 0.03) were found in group 1 vs. group 2; significant differences for skin and soft tissue infections (3.8% *vs.* 1.9%, p = 0.24) or urinary tract infections (10.9% *vs.* 12.2%, p = 0.69) were not found. In a multivariate analysis, PPI use was significantly associated with HE (OR: 1.96; 95%CI: 1.27-3.01), SBP (OR: 2.25; 95%CI: 1.05-4.84) and respiratory tract infection (OR: 1.68; 95%CI: 1.01-2.78).
Conclusion: The use of long-term PPI was associated with a greater incidence of respiratory tract infections, SBP and HE, favouring the hypothesis of increased bacterial translocation. Long-term PPI use should be restricted to cirrhotic patients with formal indication.

SAT-058

In hepatic cirrhosis, the systemic levels of short chain fatty acids inversely correlate with the level of endotoxemia, and are negatively associated with an increased inflammatory response, impaired liver function and a higher HVPG

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Background and aims: Short chain fatty acids (SCFA) are microbial products with homeostatic functions at intestinal and systemic levels. The intestinal dysbiosis present in cirrhosis can reduce the production of SCFA favoring inflammation and an increased gut permeability. These events may contribute to the translocation of bacterial products and the worsening of patients' hemodynamic state.
To determine in cirrhotic patients the levels of SCFA in peripheral (PER) and suprahepatic (SH) blood and their relationship with the inflammatory profile, the endotoxin levels and the hepatic venous pressure gradient (HVPG).
Method: We obtained PER and SH samples and, in an additional subgroup, portal vein (PV) blood from patients with cirrhosis to whom HVPG was determined. SCFA levels (acetic, propionic, butyric and isobutyric acids) were measured by mass spectroscopy and serum cytokines, nitric oxide and endotoxin (ETX) levels by ELISAs.
Results: 62 patients were included (71% men), 59 ± 11 years-old. The etiology was alcoholic in 27, HCV in 18, HCV+alcohol in 12, NASH in 3, and others in 2. MELD, CHILD, and HVPG median were 11 (7-29), 6 (5-11), and 16 (6-31) mmHg respectively. 29 patients had previous ascites, 45 esophageal varices (EV), 13 previous upper intestinal bleeding, 14 hepatic encephalopathy (HE) and 5 previous episodes of SBP. Mean values of SCFA (μM) were higher in SH compared to PER in all cases, with statistical significance in the case of acetic acid (32.9 ± 12.8 vs 23.1 ± 5.1, p = 0.001). In the subgroup of patients with PV, the concentrations of all SCFA were higher than SH and PER, confirming the intestinal origin of the SCFA. In this subgroup, the decrease in the concentration of butyric acid between VP and SH was correlated with the HVPG (r = 0.807, p = 0.0001). SCFAs were globally lower in PER and SH of patients with MELD > 11, reaching statistical significance for the butyric acid in PER (14.7 ± 4.0 vs 18.1 ± 4.2, p = 0.002) and SH (16.4 ± 4.6 vs 19.3 ± 5.3, p = 0.02). PER butyric acid levels negatively correlated with TNF-alpha (r = -0.438, p = 0.002), IL-6 (r = -0.477, p = 0.001), nitric oxide (r = -0.408, p = 0.004) and the HVPG (r = -0.409, p = 0.002). 37 patients showed detectable levels of ETX in PER and SH. The levels of all SCFA were lower in these patients compared to patients without ETX, with statistical significance for butyric acid in PER (15.4 ± 4.2 vs 18.1 ± 4.3, p = 0.02) and SH (16.6 ± 4.6 vs. 19.6 ± 5.4, p = 0.03). The concentrations of ETX and butyric acid were inversely correlated in PER (r = -0.609, p = 0.001) and SH (r = -0.761, p = 0.001).
Conclusion: In patients with cirrhosis, the decrease in SCFA concentrations, especially butyric acid, is associated with an increased inflammatory response and higher levels of ETX, as well as with an impaired liver function and increased HVPG, suggesting a possible pathophysiological role of SCFA in these alterations.

SAT-059

Prevalence and clinical characteristics of malnutrition in cirrhosis according to new EASL practice guidelines

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Background and aims: Prevalence of malnutrition is common in cirrhosis. EASL clinical practice guidelines on nutrition in chronic liver disease released very recently. We tried to investigate prevalence and clinical characteristics of malnutrition in cirrhosis according to new EASL practice guidelines as well as European Society for Clinical Nutrition and Metabolism (ESPEN) guideline.
Method: One hundred seventy three outpatients (Child A:140, B:24, C:9 subjects) with liver cirrhosis were recruited from the liver clinic between April 2018 and September 2018. Food frequency questionnaire, tetrapolar bioelectrical impedance analysis, hand grip test, subjective global assessment, and anthropometric measurement were performed. We applied the guideline published by ESPEN in 2015 and EASL in 2018 for defining malnutrition.
Results: Prevalence of malnutrition was 31.8% by definition of ESPEN guideline and 11.6% by definition of EASL guideline and two methods showed fair agreement. Prevalence of malnutrition increased according to degree of Child score and showed inverse relation with body mass index (BMI). Prevalence of malnutrition was 55.6% in Child C, and 62.5% in patient with < BMI 18.5 kg/m2. But etiology of cirrhosis did not associated with malnutrition. BMI, protein intake and sarcopenia were independent risk factor for malnutrition according to EASL guideline. Amount of protein intake showed highest AUROC value to predict malnutrition in EASL guideline
Conclusion: Prevalence of malnutrition was 27.9% in Child A, and 55.6% in Child C patients. Protein intake was independent risk factor of malnutrition in patients with cirrhosis.

SAT-060

Prognostic effect of subcutaneous adipose tissue on survival outcome in patients with liver cirrhosis

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Background and aims: Increasing evidence suggests that decreased skeletal muscle mass (sarcopenia) or adipose tissue assessed predicts negative outcomes in patients with cancer. In liver cirrhosis, while there is consensus that sarcopenia has been associated with higher mortality, the prognostic value of adipose tissue is not clear. We investigated the independent prognostic significance of visceral and subcutaneous adiposity in predicting mortality in liver cirrhosis.
Method: The cross-sectional areas (cm^2) of skeletal muscles and subcutaneous and visceral adipose tissues were measured on CT imaging at the level of the third lumbar (L3) vertebra. Adipose tissue markers, including the visceral adipose tissue index (VATI, cm^2/m^2) and subcutaneous adipose tissue index (SATI, cm^2/m^2), were estimated for 486 patients diagnosed with cirrhosis.
Results: Among the patients, most were male (82.9%) with a mean age of 51.9 ± 9 years and model for end-stage liver disease (MELD) score of 10.2 ± 3. The 5-year overall survival in patients with SATI < median ($42.7cm^2/m^2$) was 56.5%, while it was 78.6% in those with SATI ≥ median (p = 0.008). In multivariate analyses, a low SATI was significantly associated with poor overall survival (adjusted HR [aHR] = 1.709, p = 0.031) after adjusting for MELD score and aetiology of cirrhosis. The 5-year overall survival in patients with VATI < median ($38.3cm^2/m^2$) was 67.6%, while it was 60.5% in those with VATI ≥ median (p = 0.657). A low VATI was not associated with overall survival. The 5-year overall survival in patients with sarcopenia (≤ $52.4cm^2/m^2$ in males and ≤ $38.5cm^2/m^2$ in females) was 44.5%, while it was 74.5% in those without sarcopenia (p < 0.001). Sarcopenia was also associated with mortality (aHR = 2.114, P = 0.001). In the low SATI group, the patients with sarcopenia had lower survival rates than those without sarcopenia (p = 0.001).
Conclusion: Subcutaneous adipose tissues, but not visceral adipose tissues, appear to be associated with a reduction in mortality risk, demonstrating the prognostic importance of fat distribution in patients with cirrhosis. Moreover, the effect of subcutaneous adipose tissues on survival was more pronounced in patients with low muscle mass.

SAT-061

Performance of Baveno criteria with shear-wave elastography in patients with compensated advanced chronic liver disease

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Background and aims: Baveno VI and extended Baveno VI criteria have been proposed to avoid screening endoscopies. However, this approach has not been validated in the performance of shear wave elastography (SWE). Also, previous studies have validated the Baveno VI, mostly with hepatitis B or C virus. Therefore, further study has been needed to validate in other aetiology, especially alcoholic liver disease. We aimed to validate these criteria by 2D-SWE in compensated advanced chronic liver disease (cACLD) patients with alcohol as main aetiology.
Method: Clinical data from 305 patients with cACLD who underwent a liver stiffness measurement (LSM) with 2D-SWE and endoscopy were collected consecutively. Baveno VI (LSM < 20kPa and PLT > 150, 000 cells/μL) and extended Baveno VI (LSM < 25kPa and PLT > 110, 000 cells/μL) criteria were tested. High-risk varix (HRV) were defined as F2/3 varices or an F1 varix with red signs.
Results: Among the 305 patients, HRV was identified in 21.0% (n = 64). The main aetiology was alcoholic liver disease (61.1%), followed by HBV (29.8%) and HCV (9.1%). The Baveno VI criteria spared endoscopy in 118 of the 305 (21.6%) patients, and 7 (5.9%) presented with HRV and were therefore missed. The expanded Baveno VI criteria spared more endoscopies (60.0%) but missed more HRV (9.8%) compared with the Baveno VI criteria. Overall, the risk of missing HRV was high. The other classification rules described as the modified Baveno VI criteria were LSM < 25kPa and PLT ≥ 150, 000 cells/μL. A total of 131 of the 305 (43.0%) patients were within the modified Baveno VI criteria, of whom seven (5.3%) had missed HRV. And, after adding spleen diameter < 12 cm to the modified Baveno VI criteria, the number of spared endoscopies increased by 106/305 (34.8%), with three (2.8%) presenting with HRV, indicating that the risk of missing HRV was very low.
Conclusion: The Baveno VI and extended Baveno VI criteria with 2D-SWE were insufficient, with an HRV missing rate of over 5%. However, with the modified Baveno VI criteria together with spleen diameter < 12 cm on 2D-SWE, more endoscopies were spared, with a minimal risk of missing HRV in patients with cACLD and alcohol as the main aetiology.

SAT-062

Edema index measured by bioelectrical impedance analysis predicts ascites or acute kidney injury after liver resection for hepatocellular carcinoma

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Background and aims: Edema index (extracellular water/total body water, ECW/TBW) measured by bioelectrical impedance (BIA) has been reported to increase with decreased liver function in patients with liver cirrhosis. We investigated whether preoperative ECW/TBW values can predict the incidence of ascites or acute kidney injury (AKI) after surgery in patients with hepatocellular carcinoma
Methods: A total of 83 patients who underwent liver resection for hepatocellular carcinoma were prospectively enrolled from July 2016 to June 2018. BIA assessment of edema index was performed on the day of admission using the InBody 770 scale. Definition of postoperative ascites was defined as ascites drainage of more than 500 cc per day, or diuretics needed to control ascites.
Results: Among 83 patients, 39 patients (47%) had ascites or acute kidney injury after liver resection. In multivariate analysis, ECW/TBW > 0.384 was only significant risk factor for development of post-operative ascites or AKI (odds ratio [OR] = 8.11, 95% confidence interval [CI] = 1.56-42.03; p = 0.013). The subgroup analyses showed that pre-operative ECW/TBW > 0.384 is a significant risk factor for development for post-operative ascites or AKI in patients with liver cirrhosis (OR = 9.38, 95% CI = 1.62-54.24, p = 0.012) but not in those without liver cirrhosis (OR = 6.73, 95C CI = 0.79-57.60, p = 0.082).
Conclusion: The preoperative edema index (ECW/TBW) can be used as a predictor for the incidence of ascites or acute kidney injuries after liver resection, particularly in hepatocellular carcinoma patients with liver cirrhosis.

SAT-063

Third-generation cephalosporins are still useful as the empirical antibiotics for spontaneous bacterial peritonitis in Korea

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Background and aims: The third-generation cephalosporins (TGC) are currently recommended as the first-line empirical antibiotics for spontaneous bacterial peritonitis (SBP) in cirrhotic patients. However, recent studies reported that antibiotics with broader spectrum may be necessary, especially for nosocomial SBP. In this study, we aimed to evaluate whether current treatment strategy for SBP is still valid in Korea, where the resistance to antibiotics prevails
Method: This study retrospectively involved consecutive SBP patients at a tertiary center. The prevalence of TGC-resistant organism and treatment outcome among SBP patients was evaluated.
Results: A total of 287 patients with SBP were included: 110 patients (38.3%) were culture-positive. Thirty-eight (34.5%) of culture-positive patients revealed TGC-resistant organisms. As initial empirical antibiotics, 207 patients (71.9%) received the TGCs. Within 4 days of starting empirical antibiotics, 48 patients (23.1%) changed their antibiotics regimen: 22 non-response (< 25% decrease of ascites neutrophil within 48 hours), 9 culture results, and 16 clinical deterioration. Overall survival did not significantly differ between TGC-resistant SBP and TGC-susceptible SBP (hazard ratio [HR] = 0.890%, confidence interval [CI] = 0.580-1.570; P = 0.595) owing to appropriated antibiotics adjustment according to culture study results and/or treatment response at 48 hours. TGC-resistant bacteria was not an independent risk factor for earlier death (adjusted HR = 0.770; 95% CI = 0.494-1200; P = 0.247) after adjustment for CLIF-SOFA score.

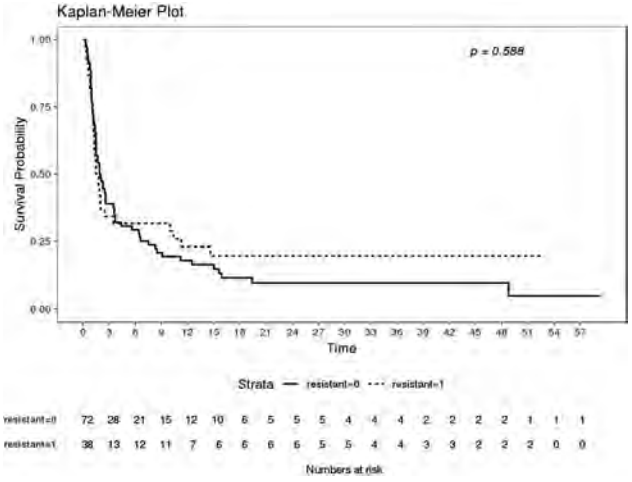

Figure: Overall survival (TGC-resistant SBP vs TGC-susceptible SBP)

Conclusion: Approximately a one-third of patients showed TGC-resistant bacteria in Korean culture-positive SBP patients. However, initial empirical antibiotic treatment with TGC is still effective if the antibiotic regimen is changed following non-response at 48 hours of treatment or culture study results or clinical deterioration.

SAT-064

The prognosis following bacterascites is as poor as spontaneous bacterial peritonitis

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Background and aims: Spontaneous bacterial peritonitis (SBP) is a clinically significant event with associated morbidity and mortality. The clinical and prognostic significance of bacterascites (BA) (the presence of organism on culture but ascitic WCC < 250 cells/mm³) is unknown. The aims of this study were to compare clinical demographics, pathogens and prognostic impact in patients with BA vs SBP.
Methods: Ascitic fluid cultures from consecutive cirrhotic patients over a 10-year period were reviewed to identify patients with SBP/BA. Baseline data obtained, and outcomes collated. Patients with previous SBP/BA were excluded, and only the index case was recorded. If patients progressed from BA-SBP within 72 hours they were classified as SBP. Patients were censored as dead at the time LT or actual death.
Results: 8890 ascitic fluid samples were reviewed identifying 119 cases of SBP and 141 cases of BA. Median age at presentation with SBP or BA was similar (55 vs. 56, p = 0.34) and aetiology was alcohol in 37% of SBP and 39% of BA (NS). Presenting laboratory parameters for SBP vs. BA differed in WCC (11.8 vs. 8.1, p < 0.001) and INR (2.1 vs 1.7, p = 0.01), but not platelets (130 vs 117, p = 0.21), bilirubin (131 vs 128, p = 0.81), creatinine (122 vs 118, p = 0.7), sodium (133 vs 135, p = 0.1) or albumin (29 vs 30, p = 0.16). MELD score was higher in patients with SBP compared to BA (22 vs 20, p = 0.03) as was UKELD score (56 vs 54, p = 0.02). Five patients were lost to follow-up. LT was undertaken in 18/119 (15%) in SBP group compared to 26/141 (18%) in BA group (p = NS). Patient survival was 52/117 (45%) at 1 year and 45/117 (38%) at 3 years in the SBP group compared to 62/138 (45%) and 48/138 (35%) respectively in the BA group (p = NS). Median time

to death in the SBP group was 316 days vs 325 days in the SBP group (NS). In BA 66/141 (44%) of cultures were pathogens, conversely in SBP, 62/119 cases were culture positive, of which 52/62 (84%) were pathogens ($p < 0.001$). The prevalence of bowel flora pathogens were the same in SBP/BA (86vs90%), but were more homogenous in SBP with enetrobacteriacae 78% vs 43% ($p < 0.001$). The overall ESBL rates were similar at 24% (SBP) and 26% (BA). A sub analysis comparing those with pathogens in BA vs SBP, showed no difference in MELD (22vs22) nor 1-year survival (40% vs 44%).
Conclusion: Prognosis following BA is as poor as SBP despite patients with SBP having significantly higher baseline liver severity scores and pathogens isolated. The role of secondary antimicrobial prophylaxis in BA needs to be defined.

SAT-065
Shear wave elastography for skeletal muscle: A novel approach to insulin resistance in cirrhosis
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Background and aims: Changes in muscle composition with loss of muscle mass have been proposed as additional potential mediators of the association between diabetes and disability. Several factors including decreased muscle mass, changes in muscle architecture and fiber type may account for the reduction of muscle strength in cirrhosis, featuring the development of sarcopenia. Stiffness measurement has attracted attention in clinical practice, and the recent Guidelines suggested that 2 dimensional shear wave elastography (2D-SWE) is a promising technique for the grading of hepatic fibrosis. Against the background, we hypothesized that the alternation of muscle function regarding the glucose metabolism may be reflected in the muscle elasticity. The aim was to examine the effect of muscle elasticity on the insulin resistance (IR) in cirrhosis.
Method: This is an IRB-approved cross-sectional study (October 2016 to October 2018) including cirrhosis patients who underwent both computed tomography (CT) and transcutaneous ultrasound (US); the former for skeletal muscle index at the L3 level (L3-SMI) and the latter for the 2D-SWE on the cross-section image of the right iliopsoas muscle to obtain the elasticity of right iliopsoas muscle (IP-E). IR was defined by homeostasis model assessment of insulin resistance (HOMA-IR) > 3.0.
Results: The study consisted of 99 cirrhosis patients (70.7 ± 9.4 years; 33 females), whose Child-Pugh Score ranging from 5 to 12 (6.2 ± 1.7). Forty patients were defined as having IR. IP-E ranged from 4.1 to 51.7 KPa (10.4 ± 6.0), and showed significant correlation with body mass index (BMI), L3-SMI, and HOMA-IR. There were differences between patients with and without IR, in BMI (25.6 ± 2.6 vs 22.6 ± 3.3, $p < 0.0001$), L3-SMI (44.1 ± 6.5 vs 40.0 ± 7.3, $p = 0.005$), and IP-E (13.3 ± 8.1 vs 8.4 ± 2.5, $p = 0.0005$). Multivariate analysis showed that IP-E and BMI were independent factors for IR. The sensitivity, specificity and area under the receiver operating characteristic curve for the diagnosis of IR were 70%, 76.3%, and 0.779, under the best cut-off value of 9.95.
Conclusion: Muscle elasticity is a target in the evaluation of IR, suggesting the novel aspect of the clinical application of 2D-SWE in cirrhosis.

SAT-066
Modified SAE technique provides a long last sustained hemodynamic response on splenic artery blood velocity in patients with cirrhosis and clinically significant portal hypertension
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Background and aims: Splenic artery embolization (SAE) is one of the perspective option for variceal bleeding (VB) prophylaxis. We started widely using SAE in cirrhotic patients since the 2003 year and observed, like many others investigators, restoration of VB risks in terms 3-6 months after the procedure. Modified SAE technique, as well as improved quality check protocol, were introduced into practice in our tertiary GI bleeding center since 2009.
Method: We used innovative multi-shaped "soft" coils for reduction of splenic arterial blood flow in 112 cirrhotic patients with clinically significant portal hypertension (CSPH) for VB prophylaxis. In group 1 were 77 patients who had experienced 1 or more (totally 232, or 3.02 per patient) VB episodes. Group 2 included 35 patients with non-bleeding varices, but with present ascites and splenomegaly. According to our prospective study design Doppler examinations (with splenic artery (SA) peak systolic (PSV) and diastolic velocity (DV) measurements) were conducted on the baseline and after SAE in 30 days, 3, 6 and 12 months. Additionally, we evaluated the resistive index (RI), spleen volume (SV), recidive rate (RecR) and recidive free period (RFP).
Results: In group 1 PSV SA mean according to end points (baseline/ 1 m/3 m/6 m/12 m; M cm/s ±SD) in our study were: 151.38 ± 51.037; 86.40 ± 32.889; 86.31 ± 33.321; 90.80 ± 39.380; 96.34 ± 40.420) and showed significant decreasing (–55 cm/s, $p < 0.001$) at final EP "12m". In group 2 we observed the same significant ($p < 0.001$) decreasing of PSV SA mean from 146.40 cm/s (baseline) to 96.17 cm/s (12 m). Decreasing of PSV and DV means started at EP "1m" and lasted till EP "12m". The same tendency was observed in 1 and 2 groups for DV SA (baseline/12 m; M±SD): 55.69 ± 20.645; 36.85 ± 14.042 and 57.09 ± 18.252; 41.61 ± 19.214; respectively, ($p < 0.001$ in both cases). Thus no significant changes were detected in RI calculation on baseline and EP "12 m": it decreased from 0.62 to 0.60 (gr.1) and from 0.61 to 0.57 (gr.2). Introduction of modified SAE technique resulted first of all in clinical benefit-in group 1 RecR of bleeding episodes dramatically decreased from 3.02 per patient/year to 0.4. In group 2 (no previous episodes) occurred single VB episode. The average RFP (in days) was 568 in gr.1 and 759 in gr.2 respectively. Spleen volume downed from 784 to 519 cm^3 in gr.1 and from 1000 to 673 cm^3 in gr 2 ($p < 0.01$).
Conclusion: Modified SAE could be regarded as reliable secondary and primary prophylaxis option in cirrhotic patients with CSPH due to sustained long lasted (1 year and more) decreasing effect on splenic blood flow. Also, it could be considered as "bridge therapy" in cirrhotic and CLD patients in the waiting list for OTP or undergoing another treatment strategy. At the same time, in our study RI doesn`t depict the tendency of hemodynamic changes.

SAT-067
Prospective assessment of sarcopenia as a prognostic factor for survival in patients with liver cirrhosis
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Background and aims: The Child Turcotte Pugh- and the Model for End Stage Liver Disease- (MELD) Scores are a well-known tool to

evaluate the risk of mortality in patient with cirrhosis. Both do not pay attention to the nutritional status of the patient. Several studies recently showed the correlation between sarcopenia and survival in patients with cirrhosis. However, there is still no consensus on measurement and cut-off values for determining sarcopenia. The aim of this study was to define cut-off values for the PMTH- (psoas muscle thickness height) and the TPMA- (transverse psoas muscle area) index normalized to the height for patients with a minor probability of survival. Moreover, we wanted to find out the correlation between sarcopenia and survival.

Method: Between 2010 and 2013, we included 162 patients with liver cirrhosis presenting at the university hospital of Mainz, Germany. Sectional radiological diagnostics were obtained from 90 patients to measure the PMTH- and TPMA-index. Outcome and survival data were prospectively collected during a 4-year follow-up. Continuous variables (mean±standard deviation) and categorial variables (numbers and percentages) were reported. The t-test for independent variables was calculated. For the multivariate analysis we applied the Kaplan Meier curve and the cox regression to survival rates.

Results: The average age was 57, 1 ± 13, 8 years and 65, 4% were men. Alcoholism (42%) and chronic viral hepatitis (35, 1%) were the most frequent liver diseases. Patients were classified as CTP Group A (45, 7%), B (29, 0%) and C (25, 3%), the average MELD score was 12, 4 points. The optimal TPMA-index cut-off (male 542, 88 mm^2/m, female 360, 45 mm^2/m) and PMTH (male 11, 42 mm/m, female 9, 50 mm/m) were determined by ROC-AUC analysis and Youden-index calculation. Following Kaplan Meier analysis TPMA and PMTH were significantly associated with overall survival ($p < 0.05$). However mutivariable cox regression only showed an influence of sarcopenia on survival for women (HR PMTH 0, 251 (0, 83-0, 0, 763), p = 0, 015).

Conclusion: Sarcopenia plays an important role in the outcome of patients with liver cirrhosis. With our results we can underline the effect of sarcopenia in women. With the help of our cut-off values we might differentiate patients with cirrhosis between a major risk and minor risk group.

SAT-068

Presence of liver cirrhosis is the strongest negative predictor of survival for patients admitted to intensive care unit

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Background and aims: Liver cirrhosis is a systemic disease with strong impact on whole body physiology especially in advanced stages. Accordingly, the outcome of patients with cirrhosis depending on intensive care treatment is poor. Aim of this study was to analyze the impact of cirrhosis on mortality of ICU patients in comparison to other frequent chronic diseases and conditions.

Method: Patients admitted to intensive care unit of the department of medicine of the university hospital Frankfurt in a three year period were included retrospectively into the study. Patients were followed until hospital discharge or death and clinical and laboratory parameters acquired from the electronic patient files. A binary logistic regression model was used to identify parameters associated with survival.

Results: A total of 567 consecutive patients admitted to intensive care unit were included into the study of which 99 (17.5%) had liver cirrhosis. The major reasons for ICU admittance were acute cardiac event (31.7%), infection/sepsis (29.1%) and respiratory failure (14.1%) in the non-cirrhotic group and deterioration of liver function (34.4%), infection (22.2%) and hemorrhage (15.2%) in the cirrhotic group. Median MELD score of patients with cirrhosis was 23 (7-40). In hospital mortality was 22.2% in the non-cirrhotics compared to 47.5% in cirrhotic patients (OR 3.163 95% CI 2.016-4.965), $p < 0.001$). In the multivariate logistic regression model adjusted for age, preexistent cardiac, pulmonary or kidney disease, SAPSII score, MELD score, actual malignancy, diabetes mellitus and immunosuppressive therapy liver cirrhosis remained the strongest independent predictor of in-hospital mortality (OR 5.456 95%CI 2.590-11.494, $p < 0.001$). In the cirrhotic group the need for kidney replacement therapy (48.5% vs. 21.2%, $p < 0.001$) and blood transfusion (47.8% vs. 45.1%, $p < 0.001$) was significantly higher than in non-cirrhotics. In the group of cirrhotic patients mortality increased with MELD score (< 16: 33.3%; 16-25: 46.3%; > 26: 55.0%).

Conclusion: In the presented study liver cirrhosis was the strongest predictor of in hospital mortality in patients needing intensive care treatment even when adjusted for MELD score and other chronic diseases and conditions associated with ICU mortality. Concerted efforts are needed to improve the outcome of cirrhotic patients and prevent disease progression and complications with the need for ICU treatment already in early stages of the disease.

SAT-069

Interleukin 6: A marker for hepatic encephalopathy

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Background and aims: The pathophysiology of hepatic encephalopathy (HE) is not completely understood. Key roles are attributed to increased serum ammonium and systemic inflammation. Recent studies could demonstrate that Interleukin 6 (IL6) is associated with the presence of minimal hepatic encephalopathy and mortality in cirrhotic patients. The predictive value of IL6 for risk stratification of patients with liver cirrhosis regarding first time overt HE (OHE) development has not been investigated yet.

Method: In- and outpatients with an established diagnosis of liver cirrhosis treated between March 2017 and August 2018 at the University Medical Centre Mainz were included into this prospective cohort study. 108 without a history of OHE patients were followed prospectively for 6 months. The primary end point was OHE development. Exclusion criteria were an OHE episode during the previous three months, current alcohol abuse, intake of psychotropic drugs, TIPSS, HCC or an active infection. A diagnosis of CHE was established by means of PHES and/or CFF and the West-Haven Criteria. IL6 was measured at the day of study inclusion.

Results: 297 patients were screened and 210 finally included into the study. Median age was 60 years (IQR 52; 66). 56.2% were male and most patients had compensated stage of liver cirrhosis (Child-Pugh A, B, C; 61%, 31%, 8%; Median MELD: 10). CHE was detected in 81 patients (38.6%). On multivariate logistic regression analysis, IL6 (OR = 1.025, 95% CI 1.010-1.535, p = 0.001) and a previous episode of OHE (OR = 3.653, 95% CI 1.535-8.695, p = 0.003) were independent predictors of CHE. In total, 108 patients without previous OHE were followed for 6 months regarding first time OHE. IL6 values in the highest quartile ($\geq$ 19pg/ml) were predictive for first time OHE after adjusting for MELD-Score, CHE status at study inclusion and CRP (sHR = 27.4, 95% CI 3.4-219.4, p = 0.002). The predictive value of IL6 measured by AUROC was higher (AUROC 0.936) as compared to MELD (0.755) and CRP (0.865) with respect to first time OHE.

Conclusion: IL6 constitutes an important marker to identify uninfected patients at high risk for OHE within the next 6 months.

SAT-070

A clinical pathway to manage patients with decompensated cirrhosis: Assessing the level of compliance with evidence based guidelines

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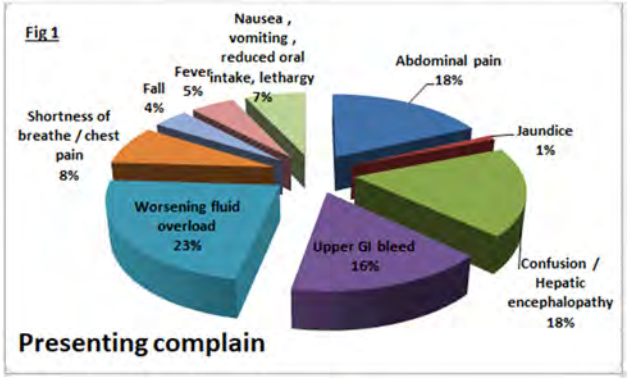
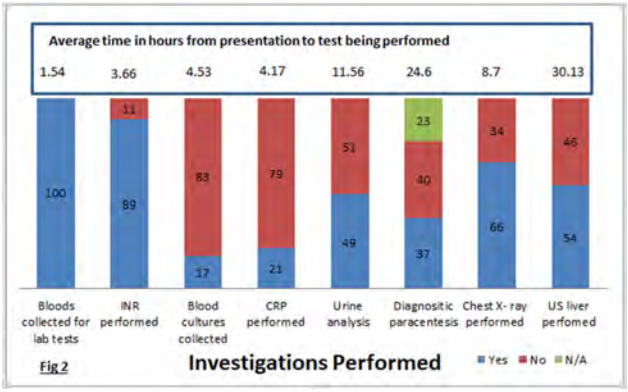
Background and aims: Acute admission to hospital with decompensated cirrhosis is increasing in Australia. Variable provision of clinical services in Queensland contributes to a 'post code lottery'and may lead to inequitable inferior outcomes with 28-day mortalities recorded at > 30%. To improve outcomes to multidisciplinary admitting teams an adapted 'BASL' tool kit was recommended to ensure evidence-based treatments were consistently delivered. The tool kit guides non- specialists through the acute investigations and management within 24 hours of admission. Implementation delays correlate with an increase in mortality. This study assesses the level of compliance with the recommended evidence-based guidelines in a major teaching hospital in Brisbane

Method: Retrospective observational study. Inclusion Criteria: Patients ≥ 16 years old presenting to the Emergency Department with decompensated cirrhosis between January 2016-January 2017. Data was manually collected from the patient notes.

Results: A total of 100 presentations to the ED by 53 patients with decompensated cirrhosis were included. Figure 1. demonstrates the distribution of presenting complaints. Aetiologies included, alcohol (n = 31, 58%), NASH (n = 9, 17%) and HCV (n = 5, 9%). Males accounted for 71% with a median age of 61 years (range 30-86).





Ascites-Diagnostic paracentesis not performed because: No clinical signs of SBP (n = 8, 20%): No reason given (n = 30, 75%): Risk of bleeding (n = 2, 5%). SBP was found in 5 patients, mean time to diagnostic tap and antibiotics was 27.6 hrs and 31.8 hrs respectively.

AKI: Accounted for 25% of admissions: Diuretics were witheld and fluid challenge administered in 52% (n = 13) and 40% (n = 10) respectively.

GIB: 94% of patients (n = 16), received IV proton pump inhibitors (mean time = 2.2 hrs) and octreotide (mean time = 4.1 hrs). Antibiotic prophylaxis was adminstered in 82% (n = 13) -mean time of 4.54 hrs.

HE: 33 patients presenting with HE underwent adequate investigations to identify common precipitants (n = 31, 94%), with the exception of SBP. 88% received lactulose as initial management (n = 29, 88%) at a mean of 9.3 hrs from presentation. Despite the absence of any contraindications for the administration of venous thromboembolic prophylaxis, it was administered in only 26% (n = 20) of the patients.

Conclusion: The uptake of recommended inital investigations amongst this cohort of patients was suboptimal. Presentations that incited a sense of urgency amongst non-specialist staff, such as GIB and HE faired better. Most presenting complaints warranted the exclusion of SBP, however, 52% (n = 40) of the patients with ascites (n = 77) did not undergo a diagnostic tap. The mean time to diagnostic paracentesis in this cohort was 24.6 hrs. We believe that implementing a care pathway will improve early compliance with investigations and interventions and improve outcomes. This is now being tested.

SAT-071

Insulin resistance in cirrhotic patients: results from a large prospective study

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Background and aims: Cirrhosis is a frequent disease inducing high morbidity and mortality. Available data suggest that cirrhosis could be associated with insulin resistance (IR) and diabetes mellitus (DM). We performed a prospective study to answer the following questions: is cirrhosis associated with IR and DM; is IR, independently from diabetes, associated with cirrhosis severity; are the different etiologies of cirrhosis associated with different levels of IR and finally does glucose homeostasis alterations correlate with higher morbidity and mortality?

Method: From February 2016 to September 2017, patients seen at the hepatology clinic were prospectively enrolled in this study. At inclusion, a complete assessment of glucose homeostasis was performed on fasted venous blood to calculate the homeostasis model assessment of insulin resistance (HOMA). Patients were separated in several cohorts, based on the presence or absence of cirrhosis (cirrhosis versus controls), absence or presence of treated DM and IR (HOMA > 2.5). We recorded the cause of the underlying liver disease and the number of hospitalizations due to cirrhosis complication and death during the study period.

Results: 107 patients with cirrhosis and 20 controls accepted to participate in this study. Both groups were comparable in terms of age, body mass index, creatinine and triglyceride levels but cirrhotic patients had significant lower levels of albumin, platelets and cholesterol and significant higher levels of AST and INR. There were 43% of patients with DM within the cirrhotic group compared with 25% of patients within the control group. In cirrhotic patients without DM, IR was more pronounced than in control patients (mean HOMA-IR: 5.9 ± 4.7 vs 2.8 ± 2.2, $p = 0.004$). We also found that IR was correlated with the severity of cirrhosis based on the MELD score ($r = 0.54$, $p < 0.001$). Different etiologies of cirrhosis were shown to exhibit different levels of IR ($p = 0.001$). DM was most prevalent in the NAFLD cirrhotic group with 75.6% of the patients treated for diabetes within this group. IR and DM were also associated with an elevated morbidity and mortality ($p = 0.005$).

Conclusion: Insulin resistance is more frequent in cirrhotic patients. The level of insulin resistance is correlated with cirrhosis severity and is associated with a higher rate of complications and a lower survival within the cirrhotic group. Whether an early diagnosis of insulin sensitivity in this population and an appropriate treatment will reduce such complications remains to be defined.

SAT-072

Predict improvement of liver cirrhosis after antiviral treatment in patients with chronic hepatitis B

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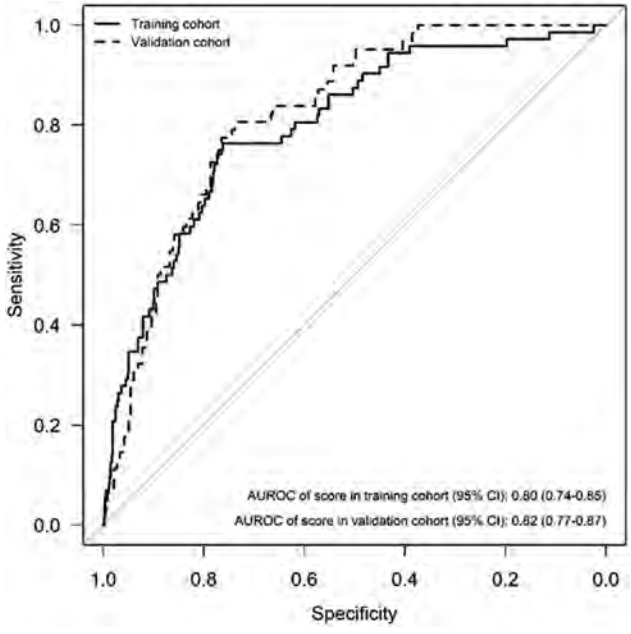
Background and aims: Improvement in Model for End-Stage Liver Disease (MELD) score over time under antiviral treatment is associated with reduced hepatic decompensation and death in patients with chronic hepatitis B (CHB)-related cirrhosis. We developed a prediction score for MELD score improvement.
Method: We identified patients with CHB-related cirrhosis and MELD score ≥ 15 at the start of entecavir and/or tenofovir disoproxil fumarate treatment from 2005 to 2016 in Hong Kong and from 2006 to 2017 in Severance Hospital, South Korea. The primary and secondary end points were transplant-free survival with > 5 point improvement in MELD score and with MELD score < 10 after 6 months of treatment, respectively. Patients with cancers up to 6 months of follow-up were excluded. Patients were randomly divided into training (60%) and validation (40%) cohorts. Prediction score was calculated as the weighted sum of selected clinical parameters.



Results: 999 cirrhotic CHB patients were included. During the first 6 months of treatment, 102 (10.2%) patients received liver transplantation and 294 (29.4%) patients died. At month 6, the mean MELD score of 605 patients with transplant-free survival improved from 19.8 ± 4.3 to 14.7 ± 6.0 (paired t test, P < 0.001); 276 (45.6%) patients achieved > 5 point improvement in MELD score. Five predictors including age, creatinine, platelet counts, international normalized ratio, and presence of hepatic encephalopathy were independently associated with improvement in MELD score. The prediction score achieved area under the receiver-operating characteristic curve of 0.80 (95% confidence interval [CI] 0.74-0.85) and 0.82 (0.77-0.87) in the training (N = 605) and validation cohorts (N = 394), respectively, on predicting transplant-free survival with MELD score < 10 at month 6 (Figure). The proportion of patients who achieved the primary and secondary end points at month 6 increased from poor, intermediate to good treatment responders defined by cut-offs of the score (chi-square test for linear trend, P < 0.001). The 1-year transplant-free survival (95% CI) in good, intermediate, and poor responders were 72% (62%-81%), 59% (53%-66%), and 43% (37%-50%) in training cohort, and 76% (64%-86%), 63% (55%-70%), and 43% (36%-51%) in validation cohort.
Conclusion: This simple score predicts on-treatment MELD score improvement and correlates with treatment response and clinical outcomes in patients with CHB-related cirrhosis.

SAT-073

Micronutrient deficiencies in patients with decompensated cirrhosis

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Background and aims: Patients with cirrhosis usually present malnutrition and micronutrient deficits, which leads to a worse prognosis of their disease and increased mortality.
Our main goal is to assess the deficit of micronutrients (vitamins and oligoelements) in cirrhotic patients admitted due to decompensation.
Method: Prospective unicentric study in patients with liver cirrhosis (LC) of any etiology admitted due to decompensation from October 2017 to October 2018. Demographic data, etiology of LC, presence of diabetes, Child-Pugh and MELD score were analyzed, reason of admission (ascitic decompensation (AD), infection, hepatic encephalopathy (HE), alcoholic hepatitis, acute kidney injury (AKI) and portal hypertensive bleeding (PHB). A blood test including determination of oligoelements (calcium, phosphorus, magnesium, zinc and copper) and vitamins (A, B1, B6, B12, C, D, E, K and folic acid) was performed.
Results: 87 patients were included. Mean age 63 ± 10.8 years, 80% men. The etiology of the cirrhosis was alcohol in 87.4%, 60% of whom had active consumption. Child-Pugh Score was A/B/C in 10.3%/50.6%/39.1%, respectively. Mean MELD of 16.7 ± 6.74. 39.1% were diabetics. The reason for admission was: AD/Infection/HE/alcoholic hepatitis/AKI/PHB in 85.1%/41.4%/21.8%/17.2%/21.8%/13.8%, respectively. The deficits of micronutrients detected were: vitamin A (93.17%), vitamin B6 (57.6%), vitamin C (52.3%), vitamin D (90.7%), zinc (92.9%), phosphorus (39%), magnesium (25%) and iron (40%). The deficits of vitamin B1, E, K and folic acid were 2.5%/14.9%/2.9%/6.3% respectively. Child C patients had lower values of vitamin A (p < 0.001) and zinc (p < 0.001) and higher values of iron (p = 0.015), ferritin (p = 0.05) and vitamin B12 (p < 0.001) in relation to Child A and B. Patients with a higher MELD score had lower values of vitamin

A (p < 0.001), vitamin E (p < 0.001), magnesium (p = 0.021) and zinc (p = 0.001) and higher iron values (p = 0.013), ferritin (p = 0.004) and vitamin B12 (p < 0.014).
Conclusion: Micronutrient deficiencies are common in patients with decompensated cirrhosis. The most frequently deficient vitamins are A, B6, C and D. Zinc deficiency is universal in this population. Severe hepatic insufficiency correlates with lower levels of zinc and vitamin A and higher levels of vitamin B12, iron and ferritin. The impact of systematic supplementation of these deficits should be explored in subsequent studies.

SAT-074

Prevalence and risk factors of colonization by multidrug resistant bacteria in cirrhotic patients admitted to the intensive care unit in a Spanish tertiary hospital

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Background and aims: Recent studies suggest that the prevalence of infections caused by multidrug-resistant (MDR) bacteria is increasing in cirrhosis, as in the general population. However, there are limited data about prevalence, risk factors and clinical impact of colonization by MDR bacteria in the cirrhotic population. In addition, resistance patterns can differ between different areas and hospitals. The objective of our study was to investigate the prevalence of colonization by MDR bacteria in critical patients with cirrhosis who require admission to the Intensive Care Unit (ICU) in our area and to evaluate the risk factors involved in colonization by MDR bacteria.
Method: We conducted a retrospective study including all adult patients with cirrhosis admitted to the ICU between March 2015 and July 2018 and who underwent triple (nasal/pharyngeal/rectal) swabs in order to investigate colonization by MDR bacteria, as part of the "*Zero Resistance*" (ZR) project at our hospital (Garnacho Montero J et al. Critical Care 2015; 19:114).
Results: 165 cirrhotic patients were admitted to the ICU during the study period and sixty five of them underwent triple swabs to investigate colonization by MDR bacteria according to ZR program recommendations at our centre. 15 patients (23%) were colonized by any MDR bacteria. The most frequent MDR isolated bacteria were spectrum β-lactamase- producing *Enterobacteriaceae* (66.7%), followed by methicillin-resistant *Staphylococcus aureus* (MRSA, 20%) and *S. maltophilia*. (13.3%). The presence of more than 3 risk factors from ZR checklist at the admission to the ICU (86.7% vs 48%; p = 0.008, OR 7.04 CI95% [1.44-34.48]), and antibiotic prophylaxis (60% vs 28%; p = 0.023, OR 3.85 CI95% [1.16-128]) were significantly related with MDR bacteria colonization. Although incidence of infection by MDR bacteria intra-ICU was higher in colonized patients, this difference was not statistatically significant (33%vs20% p > 0.05). In colonized patients who developed infection there was a 100% concordance between the colonizing and infectious agents.
Conclusion: MDR bacteria colonization is frequent in patients whit cirrhosis admitted to the ICU in our area. Antibiotic prophylaxis and/or the presence of at least 3 items from the *Zero Resistance* checklist are risk factors for MDR bacteria colonization in this population. There is a clear correlation between the colonizing and infecting bacteria in these patients.

SAT-075

Clinical efficacy of transjugular intrahepatic portosystemic shunt created with expanded polytetrafluoroethylene-covered stent-grafts: 8-mm versus 10-mm

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Background and aims: Conflicting data exist regarding the appropriate shunt diameter for transjugular intrahepatic portosystemic shunt (TIPS) creation in cirrhotic patients. This study was designed to compare the clinical efficacy of TIPS using stent-grafts with 8- and 10-mm diameters.
Method: In this retrospective study, cirrhotic patients who underwent TIPS technical successfully for the prevention of variceal rebleeding from December 2011 to June 2015 were included. Propensity score matching was performed to minimize baseline confounders.
Results: Baseline characteristics between two groups were comparable. There was no significant difference in variceal rebleeding between the two groups. 8-mm TIPS conferred a significant decrease in hepatic encephalopathy (HE) rate compared with the 10-mm TIPS (16.1% versus 32.6% at 1 year, 27.8% versus 53.2% at 3 years, $p = 0.034$). The cumulative survival rates were similar between the two groups: 93.3% and 79.6% at 1 and 3 years, respectively, in the 8-mm TIPS group vs. 87.3% and 72.1% at 1 and 3 years, respectively, in the 10-mm TIPS group (p = 0.451).

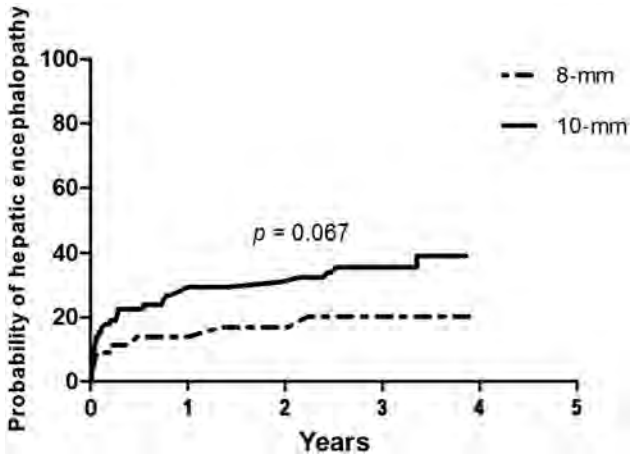

Figure: The probability of free of hepatic encephalopathy in the two groups.

Conclusion: The placement of 8-mm TIPS was sufficient to decompress the portal hypertension and prevent variceal rebleeding. The application of the 8-mm stent-graft can decrease HE rates compared with 10-mm stent-graft, although no survival benefit was observed.

SAT-076

Long term palliative abdominal drains versus large volume paracentesis in refractory ascites due to cirrhosis: a multi-centre feasibility randomised controlled trial (the REDUCe Study)

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Background and aims: Ascites develops in about 90% with advanced cirrhosis; when refractory to medical therapy, standard of care is repeated large volume paracentesis (LVP) with albumin support. Refractory ascites (RA) confers a median life expectancy of six months without liver transplantation (LT). LVP is not an optimal palliative strategy. One alternative is long-term abdominal drains (LTAD), used in advanced malignant ascites, also enabling community management. Our ultimate aim is to improve end of life care (EoLC) in advanced cirrhosis and RA. This feasibility randomised controlled trial (RCT) aimed to resolve uncertainties in designing a definitive RCT.
Method: Multicentre feasibility RCT with 1:1 randomisation between standard of care (LVP) vs. LTAD (Rocket Medical) in adults with RA, ineligible for LT. Both arms received prophylactic antibiotics. LTAD were inserted under ultrasound guidance. Community nurses undertook home visits to drain ascites dependent on symptoms; (maximum 6L/week), without albumin support. Follow-up was 12 weeks with home visits every two weeks for the following assessments: clinical, questionnaire based to include quality of life, palliative care needs, carer burden and health economics (HE). Here we report clinical and HE outcomes.
Results: Thirty six patients were randomised; 19 LVP (two withdrew, wanting LTAD) and 17 LTAD (one withdrew-insufficient ascites). Mean age (years) LTAD vs. LVP 66 + 10.4 vs. 68 ± 12; predominately male (76% vs. 74%). Participants were well matched at baseline in liver tests and prognostic scores: LTAD vs. LVP (serum bilirubin (μmol/L) 26 ± 15.8 vs. 16 ±10, serum albumin (g/L) 33 ± 4.2 vs. 31 ± 3.3, serum creatinine (mmol/L) 113 ± 46.7 vs.118 ± 53.1; MELD 14 ± 4.6 vs. 16 ± 7.2). One LTAD participant required hospitalisation for repeated LVP. Serum albumin (g/L) in the LTAD arm declined to 29 ± 3.3 at week two, subsequently remaining stable LTAD vs. LVP (29 ± 5.6 vs. 31 ± 5.5). Serum creatinine remained stable in both arms. There were no LTAD related serious adverse reactions. LTAD related adverse reactions included mild cellulitis (n = 4) and small volume leakage around LTAD insertion site (n = 3), all resolving rapidly. Peritonitis was rare, LTAD (possible) n = 1 and LVP n = 2. Overall mortality was 36% (12/33). Mortality and median survival (days in those who died) were 7/16 (44%) vs. 5/17 (29%), 53 days (IQR 43) vs. 61 days (IQR 35) in LTAD vs. LVP respectively. All but one death was liver related. Those in LTAD arm spent ≈20% less time in hospital. All nine alive in the LTAD arm at end of study elected to keep LTAD in. Detailed clinical and HE analysis is underway.
Conclusion: Preliminary data from the REDUCe study supports the safety and efficacy of palliative LTAD in RA due to advanced cirrhosis. LTAD allows successful management in the community with reduction in health resource utilisation. Proceeding to a definitive RCT is justified.
ISRCTN30697116

SAT-077

Intraperitoneal activation of blood coagulation via tissue factor-exposing extracellular vesicles in patients with advanced chronic liver disease

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Background and aims: In patients who underwent peritoneovenous (e.g., LeVeen) shunting for refractory ascites, overt disseminated intravascular coagulation occurred due to infusion of ascites into the blood circulation. More recently, procoagulant extracellular vesicles (EVs) exposing tissue factor (TF), the main initiator of blood coagulation, were identified in different body fluids.
We hypothesized that TF-exposing EVs may also be present in ascites, and that such EVs may activate coagulation in patients with advanced chronic liver disease (ACLD) and ascites.
Method: We determined routine and experimental coagulation parameters and performed clotting experiments to investigate bi-directional interactions between ascitic fluid and blood in patients with ACLD with (n = 25) or without (n = 25) ascites, who were matched for the severity of portal hypertension as assessed by hepatic venous pressure gradient (HVPG)-measurement.
Results: We found that ascitic fluid contains TF-exposing EVs that shorten the clotting time of plasma (panel A). EV-associated TF activity was high in ascitic fluid while activities of other measured coagulation factors were low (panel B). The opposite was observed in plasma of the same patients (panel C). Parameters of coagulation activation and fibrinolysis, however, were higher in ascitic fluid as compared to plasma (panels D/E). A constant dissemination of coagulation factors from plasma into ascitic fluid was indicated by strong correlations between albumin levels and coagulation factor activities in ascitic fluid (panels F/G). The procoagulant potential of ascitic fluid was completely abolished by filtration through a 0.1 μm membrane (panel H). Taken together with the finding of low EV-associated TF activity in plasma (panel C), our findings indicate that TF-exposing EVs did not pass the peritoneum and therefore did not enter the blood circulation. Yet, the thrombin generation potential in plasma was significantly increased in patients with ascites compared to HVPG-matched patients without ascites (panels I/J).
Conclusion: In patients with ACLD and ascites, the coagulation system gets activated intraperitoneally via TF-exposing EVs. TF-exposing EVs seem to be too large to pass the peritoneum, however, smaller intraperitoneally activated coagulation enzymes are likely to re-enter blood circulation. This may be the cause for the increased thrombin generation potential found in plasma of patients with ascites, indicating a procoagulant state.

SAT-078

Characterizing compensated cirrhosis patients with potential etiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Findings from large Italian administrative databases

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Background and aims: Cirrhosis due to NAFLD/NASH often is recognized only following a decompensation event. Patients with cirrhosis will benefit from timely identification of the underlying cause of cirrhosis. This study described the characteristics of patients with CC who have an underlying diagnosis of NAFLD/NASH vs those without.
Method: Hospitalized adult patients with first CC diagnosis via ICD-9-CM (index date) from 2011-2017 with and without NAFLD/NASH diagnosis were identified from 8 administrative databases of Italian local health units. Patients in both groups were excluded if they ever

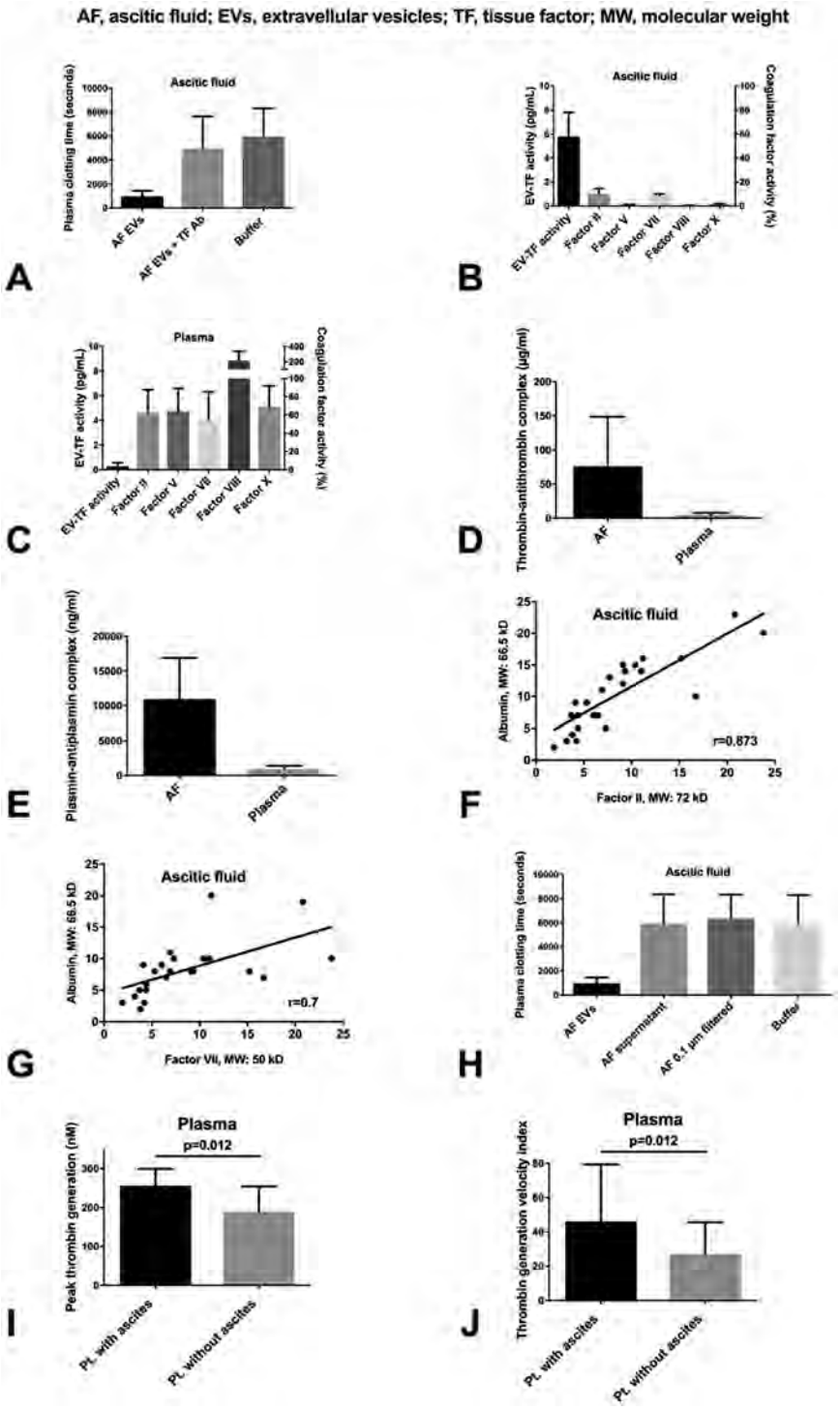

Figure: (abstract: SAT-077)

had viral or autoimmune hepatitis, HIV, alcoholism or alcoholic liver disease, toxic liver disease, Wilson's disease, Gaucher's disease, LAL-D, primary biliary or sclerosing cholangitis, or hemochromatosis. Remaining patients were followed from index date until the earliest of disease progression, end of coverage, death, or end of study period. Demographics, comorbidities, healthcare resource use and costs were compared between the two patient groups.

Results: A total of 3, 804 CC without a diagnosis of NAFLD/NASH (mean age 70.7 years, 49% female) and 131 CC-NAFLD/NASH (mean age 71.3 years, 50% female) patients were identified. Liver biopsy prevalence in the year before or 6 months after index date was 8% in CC without NAFLD/NASH and 11% in CC-NAFLD/NASH. The comorbidity burden appeared lower among CC without NAFLD/NASH — type 2 diabetes (CC without NAFLD/NASH: 37%, CC-NAFLD/NASH: 40%), cardiovascular disease (88%, 92%), both $p > 0.05$, renal impairment (12%, 23%), and hypertension (28%, 47%), both $p \leq 0.05$ [Figure]. Mean annual number of hospitalizations was lower in CC without NAFLD/NASH vs. CC-NAFLD/NASH (3.6 vs 4.2, $p \leq 0.05$). Similar trends were

observed in outpatient visits and pharmacy fills. Mean total annual costs was €17, 803 in CC without NAFLD/NASH, and €19, 681 in CC-NAFLD/NASH (p = 0.4).

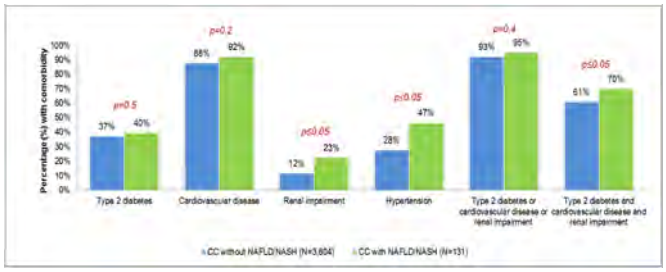

Figure: Comorbidity burden among hospitalized CC patients without and with NAFLD/NASH diagnosis in Italy

Conclusion: Upon exclusion of common liver disease etiologies such as viral or autoimmune hepatitis, or alcoholic liver disease, many CC cases in Italy may be due to unrecognized NAFLD/NASH. A higher comorbidity burden could potentially be driving identification of CC due to NAFLD/NASH. In anticipation of future treatments for NAFLD/NASH, patients would benefit from better identification of CC when due to NAFLD/NASH.

SAT-079

Respiratory infection in patients with cirrhosis and acute variceal bleeding on antibiotic prophylaxis: A multicenter observational study of 2138 patients

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Background and aims: Antibiotic prophylaxis is recommended to reduce the high risk of bacterial infection in patients with acute variceal bleeding (AVB). The aim of this study was to evaluate the incidence and risk factors of bacterial infection in patients with AVB receiving antibiotic prophylaxis.

Method: Sub-analysis of a multicenter, international, observational study of 2138 patients with cirrhosis admitted for AVB from October 2011 toMay 2015 to address the efficacy of pre-emptive TIPS. We excluded patients with infection at admission (368)and those who did not received antibiotic prophylaxis (114, 5%). Finally, 1656 patients were included in the analyses.

Results: Third generation cephalosporins (1263 patients, 76.3%) and quinolones (308 patients, 18.6%) were the main antibiotics used for prophylaxis. Bacterial infection developed in 336 out of the 1656 patients (20%): respiratory (156 patients, 46%), urinary (52, 3%),

bacteriemia (34, 10%), SBP (29, 9%), cellulitis (12, 3%), others (53, 16%) and unknown (30, 9%). We specifically analyzed the risk factors of respiratory infection, the most frequent infection observed. Patients that developed respiratory infection (n = 156; 9, 4%) were similar to non-infected patients (n = 1320) regarding etiology of cirrhosis (alcohol, 52 vs. 45%), Child (B/C, 51/30 vs. 52/24%), previous antibiotic use (12 vs. 11%). Respiratory infection rates were independent of the type of antibiotic prophylaxis. Differences between groups were associated with active alcohol abuse (44 vs. 34%; p = 0.01), oro-tracheal intubation (41 vs. 17%; p = 0.001), nasogastric tube (44 vs. 30%; p = 0.001), and balloon tamponade (8 vs. 2%; p = 0, 02). In multivariate analysis, active alcohol abuse (OR 1.7; 95%CI 1.4-2), nasogastric tube (OR 1.7; 95%CI 1.2-2.4), oro-tracheal intubation (OR 3.1; 95%CI 2.1-4.3) and balloon tamponade (OR 2.6; 95%CI 1.8-5.1) were independently associated with respiratory infection. Further, in multivariate analysis, oro-tracheal intubation (OR 1.5; 95%CI 1.1-2.1) and nasogastric tube (OR 1.3; 95%CI 1.0-1.7) were also independently associated with the development of any type of bacterial infection.
Conclusion: Five percent of patients with AVB do not receive antibiotic prophylaxis. Respiratory infection is the most common bacterial infection in patients on antibiotic prophylaxis, and its risk factors are airway manipulation and active alcohol use. Current recommendations of antibiotic prophylaxis show rather low efficacy to prevent respiratory infection in patients with AVB at high-risk.

SAT-082
Cholemic nephropathy is a cause of acute kidney injury in patients with liver disease and accompanied by loss of epithelial barrier in distal tubuli

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Background and aims: Impairment of renal function often occurs in patients with liver disease. The most common cause of acute kidney injury (AKI) in patients with liver disease is hepatorenal syndrome (HRS). Causes of non-HRS AKI include cholemic nephropathy (CN), a disease entity that is characterized by intratubular cast and tubular injury. Data from animal studies suggest bile acids as a trigger of CN. As data on patients with CN is mostly obtained from case reports or autopsy studies, we aimed to investigate the frequency, clinical course and histological characteristics of CN.
Method: We identified 149 patients who underwent kidney biopsy from 2000 to 2016 at the Department of Gastroenterology, Hepatology and Endocrinology. Of these 79 had a history of liver disease and deterioration of renal function, 45 of them fulfilled the criteria for AKI according to recent EASL guidelines and were included into this study. Laboratory values and clinical course of the patients were obtained by chart analysis. To characterize the tubular injury observed in the patients with CN, we evaluated kidney biopsies in a subset of patients (AKI with normal bilirubin (AKI-NB), AKI with elevated bilirubin (AKI-EB), and patients with CN) for inflammatory markers (CD4, CD8, CD15, CD68, CD163) and markers of tubular integrity (Aquaporin 2 (AQP2), alpha/beta-tubulin). Statistical analysis was performed using SPSS.
Results: The mean age of the 45 patients with AKI was 51.9 ± 10.7 years and 78% were male (35/45). Renal biopsy revealed the diagnosis of CN in 17.8% of the patients (8/45). Despite significantly higher MELD score at baseline (31 vs 22, p < 0.01), mortality in patients with CN was not increased. Univariate logistic regression analysis identified bilirubin higher than 5x the upper limit of normal (ULN), alkaline phosphatase higher than 3x the ULN as well as detectable bilirubin and urobilinogen in the urine as independent risk factors for the development of CN. The subset of patients with AKI included in the histological study (AKI-NB (n = 5), AKI-EB (n = 6), CN (n = 6)) did not differ in creatinine level, but was characterized by different bilirubin levels (11 vs 134 vs 525 µmol/l, p < 0.001). There was no difference in the inflammatory infiltrate or alpha/beta tubulin expression between the three different groups, but CN patients had lower numbers of M2 macrophages/monocytes (CD163) compared to patients with AKI-NB (p < 0.05). AQP2 expression was significantly reduced in patients with AKI-EB and patients with CN compared to patients with AKI-NB (p < 0.01).
Conclusion: CN is a significant cause of AKI in patients with liver disease. Loss of AQP2 was observed in patients with AKI and hyperbilirubinemia and might be a pathophysiological link between biliary cast and tubular injury. The observed lower numbers of M2 macrophages identified by CD163 in CN patients might explain an impaired renal repair capacity in patients with CN.

SAT-083
Simple non-invasive surrogates of portal hypertension predict clinical decompensation in overweight/obses patientes with cACLD

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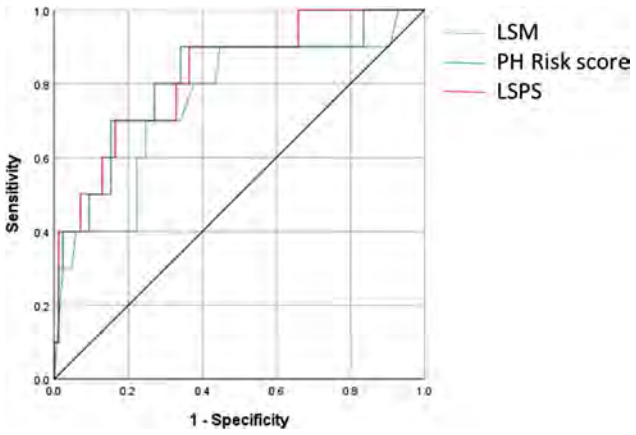
Background and aims: In patients with compensated advanced chronic liver disease (cACLD) and overweight/obesity, the prognostic value of simple non-invasive surrogates of portal hypertension (PH) for predicting first clinical decompensation has not been assessed in detail.
Method: Consecutive patients with cACLD (liver stiffness measurement (LSM) ≥ 10 kPa by XL probe) and overweight/obesity observed between 11/2015 and 01/2018 in two University hospitals (Berne, Switzerland; Montreal, Canada) were retrospectively studied. Clinical decompensation (ascites, PH bleeding, jaundice, hepatic encephalopathy) and severe bacterial infections were considered clinically relevant events and were recorded on follow-up. The association among clinical factors, LSM x spleen size/platelet count (LSPS), Portal Hypertension risk score (PH risk score), LSM and clinically relevant events was assessed. Areas under the receiver operating characteristic curves (AUROCs) were used to compare the discriminative ability of non-invasive tests for clinical decompensation.
Results: 202 patients (NASH = 52.2%; BMI 34.2 ± 7.0 Kg/m2, median Child score 5 [range 5-8]; median LSM = 16.8 kPa [IQR 12.2-24.3]) were followed up for a median (IQR) of 17 months (11-75). 15 of them developed clinically relevant events (10 decompensation, 5 severe bacterial infections). These patients had higher LSM (median: 27.4 vs.15.7 kPa, *P* < 0.001), lower platelet count (median: 113 ± 46 vs.179 ± 71G/L, *P* = 0.001), higher LSPS (median: 4.33 vs.1.21, *P* < 0.001), higher PH risk score (median: 4.17 vs. 0.26, *P* < 0.001) and worse liver function as compared to patients remaining compensated. LSM, LSPS and PH risk score showed a high discriminative ability (AUROC curve) to differentiate between patients developing or not clinical events in the follow-up: LSM 0.780 (95%CI 0.665-0.894; *P* <.0001), PH risk score 0.796 (95%CI, 0.688-0.904 *P* <.0001), and LSPS 0.828 (95%CI 0.734-0.921; *P* <.0001). Similar results were obtained in the subgroup of patients with NASH etiology (n = 105): LSM 0.754 (95%CI 0.583-0.924; *P*.008), PH risk score 0.811 (95%CI 0.654-0.97; *P*.001), and LSPS 0.825 (95%CI 0.690-0.959; *P*.001) (Figure).



Conclusion: Simple and readily available non-invasive surrogates of portal hypertension help identify patients with cACLD and obesity/overweight who are at increased risk of developing first clinical decompensation. The LSPS, (LSM by XL probe, platelet count and spleen size), is a useful simple predictor of clinical events in patients with cACLD due to NASH.

SAT-084

Validation of hand grip strength as a nutritional assessment tool for patients with advanced liver fibrosis

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Background and aims: Hand grip strength (HGS) is a non-invasive, simple and quick method to assess nutritional status on patients. Malnutrition frequently co-exist in patients with advanced liver disease and is associated with a significant increase in morbidity and mortality so it is important to find the right methods to diagnose and treat it. The purpose of this study was to explore the efficacy of hand grip strength measured by hand grip dynamometer as a nutritional assessment tool in patients with liver cirrhosis.
Method: Data were collected from 86 patients with advanced liver disease of different etiologies admitted in our Department. 34 (39.5%) were decompensated liver cirrhosis and 52 (60.5%) were compensated. We also had a control group which included 40 healthy volunteers with almost similar ages. We assessed the nutritional status of these groups according to the subjective Global Assesment (SGA) and the score PG-SGA and anthropometric measurements (skinfold-thickness, Body Mass Index, mid arm circumference and hand grip strength).
Results: The prevalence of malnutrition was 84% in patients with decompensated liver cirrhosis and only 10% in those with compensated disease. The ability of hand grip strength to predict malnutrition was highly significant (p = 0, 003), with a specificity of 85% and sensitivity of 65%. Multiple regression analysis showed that, together, the Scored Patients-Generated Subjective Global Assessment (PG-SGA), mid arm muscle area and HGS are significantly better than hand grip strength alone, specificity of 90% and 78% sensitivity.
Conclusion: The prevalence of malnutrition in cirrhotic patients is high in our area (84% in patients with decompensated liver cirrhosis). Hand grip strength is an accurate and simple nutritional assessment tool that is suitable for clinical practice, but for better assessment of the patients it should be used together with other complementary methods.

SAT-085

Selective improvement by rifaximin of changes in the inmunophenotype in patients who improve minimal hepatic encephalopathy

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Background and aims: Minimal hepatic encephalopathy (MHE) in cirrhotic patients is associated with specific changes in parameters of the immune system reflecting a more pro-inflammatory environment than in patients without MHE. The aims of this work were to assess the effects of rifaximin treatment of cirrhotic patients with MHE on: 1) MHE; 2) intermediate ($CD14^{++}CD16^{+}$) pro-inflammatory monocytes; 3) expression of early activation marker CD69 in T lymphocytes; 4) autoreactive $CD4^{+}CD28^{-}$ T lymphocytes; 5) differentiation of $CD4^{+}$ T lymphocytes to Th follicular and Th22; 6) serum IgG levels; and 7) levels of some pro-inflammatory cytokines.
Method: These parameters were measured by immunophenotyping and cytokine profile analysis in 30 controls without liver disease, 30 cirrhotic patients without MHE and 22 patients with MHE. Patients with MHE were treated with rifaximin and the same parameters were measured at 3 and 6 months of treatment. We assessed if changes in these parameters are different in patients who improve MHE (responders) and those who remain in MHE (non-responders).
Results: Rifaximin improved MHE in 59% of patients with MHE. In these responder patients rifaximin normalized all alterations in the immune system measured while in non-responders it normalizes only IL-6, CCL20, and differentiation of T lymphocytes to Th22. Non-responder patients do not show increased expression of CD69 before treatment.
Conclusion: Rifaximin normalizes changes in the immune system in patients who improve MHE but not in non-responders. Some alterations before treatment are different in responders and non-responders. Understanding these differences may identify predictors of the response of MHE to rifaximin.
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SAT-086

Opioid use is common among non-surgical inpatients with cirrhosis and is associated with increased length of stay and persistent use post-discharge

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Background and aims: Little is known about the prevalence and safety of opioid use among hospitalized patients with cirrhosis. We aimed to describe the patterns and complications of opioid use in this population.
Method: This retrospective cohort study included adult patients with cirrhosis admitted to a single hospital system from 4/2014 to 9/2015. We excluded hospitalizations with a surgery, invasive procedure or palliative care/hospice consult. We determined opioid use before hospitalization, during hospitalization, at discharge and 90 days post-discharge. We performed univariate analyses of opioid use and created logistic regression models for inpatient opioid use, intensive care unit transfer and in-hospital mortality. We used Poisson regression models to assess factors associated with length of stay.
Results: Of 217 inpatients with cirrhosis, 118 (54.4%) received opioids during hospitalization (median morphine milligram equivalent 9.8 mg/day), including 41.7% of patients without pre-existing outpatient opioid prescriptions. Younger age, depression and outpatient opioid prescription were independently associated with receipt of inpatient opioids. Hospitalization was longer among opioid recipients (mean 5.4 vs 3.7 days, p = 0.001) and this difference remained after adjusting for age, cirrhosis severity and medical comorbidities. There was no difference in intensive care unit transfers between opioid recipients and non-recipients. No deaths occurred. At discharge, 22 patients were newly started on opioids of whom 10 (45.5%) had opioid prescriptions at 90 days post-discharge.

Table: Multivariable Model of Inpatient Opioid Use

Characteristic	OR (95% CI)
Age	**0.96 (0.94, 0.99)**
Gender (Female = referent)	
Male	0.67 (0.35, 1.26)
Race (Black = referent)	
White	0.78 (0.31, 1.94)
Other	0.26 (0.06, 1.02)
Outpatient opioid prescription	**3.89 (2.09, 7.44)**
MELD	0.97 (0.91, 1.02)
Depression	**1.90 (1.01, 3.63)**
Charlson Comorbidity Index	0.97 (0.89, 1.07)

Conclusion: In non-surgical patients with cirrhosis, inpatient opioid use was common and associated with prolonged length of stay. A high proportion of patients newly discharged on opioids remained on opioids at 90 days post-discharge.

SAT-087

Screening endoscopy in patients with advanced chronic liver disease beyond portal hypertension: Higher prevalence of upper gastrointestinal neoplasia in comparison to a healthy screening population

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Background and aims: The Baveno VI criteria were proposed to help identify patients with compensated advanced chronic liver disease (cACLD) who could safely avoid screening esophagogastroduodenoscopy (EGD) for clinically significant varices. Although several studies have validated those criteria, all failed to acknowledge the possible role of the avoided EGD for the same time screening of upper GI neoplasia. We aimed to evaluate the presence, type and pathological characteristics of upper GI neoplasia in patients with cACLD who underwent screening EGD in a country with intermediate gastric cancer risk.
Method: This retrospective case-control study enrolled all asymptomatic cACLD patients who underwent EGD for varices screening from January 2008 to June 2018. Cases were matched with asymptomatic healthy individuals who underwent EGD for gastric cancer screening at the same time as colonoscopy performed for colorectal cancer screening.
Results: We included 1974 subjects (610 patients, 1364 controls), 46.3% male, with a median age of 58 (50-66) years. Besides a male predominance in cases (69.0% vs. 45.6%, p < 0.001), no other demographic characteristic differed between groups. The leading aetiology of ACLD was alcoholic liver disease (53.3%), followed by chronic hepatitis C (16.2%), and non-alcoholic fatty liver disease (7.9%). Of the 610 patients with cACLD, 1 (0.2%) had squamous-cell esophageal carcinoma, 13 (2.1%) gastric neoplasia [gastric cancer, n = 10; high-grade dysplasia (HGD), n = 2; low-grade dysplasia (LGD), n = 1], 1 (0.2%) duodenal neoplasia (LGD) and 3 (0.5%) ampullary lesions (LGD). Compared to controls, cACLD patients had a higher prevalence of gastric neoplasia [2.1% vs. 1%, p = 0.044; gastric cancer 1.6% vs. 0.8%, p = 0.08) and ampullary lesions (0.5% vs. 0%, p = 0.01). The prevalence of Helicobacter pylori infection was lower in patients compared to controls (36.2% vs. 47.2%, p = 0.004). In the 18 cACLD patients in whom were detected neoplastic lesions, 9 (50%) were diagnosed on the initial screening endoscopy. Five of these patients had transient elastography < 20 kPA and platelet count > 150000 before EGD.
Conclusion: The prevalence of esophagogastroduodenal neoplastic lesions, particularly gastric neoplasia, in cACLD patients who underwent screening EGD is significant, being higher compared to controls. EGD should therefore still be considered in patients with ACLD from countries with intermediate gastric cancer risk, independent of the Baveno criteria.

SAT-088

Sarcopenia and Myosteatosis are associated with minimal and overt hepatic encephalopathy in patients with liver cirrhosis

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Background and aims: Myosteatosis and sarcopenia are frequent in cirrhosis and related to some complications included overt hepatic encephalopathy. The aim of our study was to investigate the relationship between muscle alterations and minimal hepatic encephalopathy (MHE) and their respective role on the risk of overt HE.
Method: 64 cirrhotic patients (48M/16F) were included and submitted to Psychometric Hepatic Encephalopathy Score (PHES) and to Animal Naming Test (ANT) to detect MHE. Computed tomography was used to analyse the skeletal muscle index (SMI) and muscle attenuation. The incidence of the first episode of HE, taking into account the competing risk nature of the data (death or liver transplantation), was estimated.
Results: Myosteatosis was observed in 24 patients (37.5%), sarcopenia in 37 patients (58%) and MHE in 32 patients (50%). Both myosteatosis and sarcopenia were more frequent in patients with MHE (Table). At multivariate analysis, the variables independently associated to the presence of MHE were: sarcopenia (p = 0.05), previous overt HE (p = 0.04) and myosteatosis (p = 0.04). Thirty-one (48%) patients developed overt HE during 14.9 ± 12.5 months; myosteatosis was detected in 68% and sarcopenia in 84% of them. Variables independently associated to the development of overt HE were: sarcopenia (p = 0.001), previous HE (p = 0.03), MHE (p = 0.04) and myosteatosis (p = 0.03). Venous ammonia was significantly higher in sarcopenic patients (62.6 ± 17.7 vs 41.4 ± 16.1 μg/dl; p < 0.001) and in myosteatosic patients (65.2 ± 19.2 vs 46.7 ± 17.1 μg/dl; p < 0.001). The

incidence of HE was significantly higher in patients with sarcopenia or myosteatosis than in those without (p < 0.001).

Table: Comparison of demographic and clinical characteristics between patients with and without MHE.

	MHE- (n = 32)	MHE + (n = 32)	P value
Age (y)	56.2 ± 9.7	57.2 ± 10.5	0.69
Aetiology (virus/alchol/ other)	21/6/5	24/7/1	0.22
MELD	13.3 ± 5.2	14.2 ± 5.7	0.48
Previous HE (no/yes)	28/4	16/16	0.001
NH3	43.5 ± 16.3	63.8 ± 18.1	< 0.001
Animal Naming Test (n° of animals)	15.3 ± 5.2	11.4 ± 2.5	< 0.001
SMI (cm^2/m^2)	50.7 ± 10.9	41.8 ± 7.7	< 0.001
Sarcopenia (no/yes)	22/10 (31)	5/27 (84)	< 0.001
Muscle attenuation (HU)	37.2 ± 8.1	29.1 ± 7.4	< 0.001
Myosteatosis (no/yes) (%)	28/4 (12.5)	12/20 (62.5)	< 0.001

Conclusion: Myosteatosis and sarcopenia, probably by reducing the handling of ammonia, are independently associated to MHE and to the risk of overt HE in cirrhotics. In malnourished patients, the amelioration of nutritional status may be a possible goal to decrease these complications.

SAT-089

Evaluating the impact of non-selective beta-blocker use in decompensated cirrhosis based on setting of patient care

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Background and aims: Non-selective beta-blockers (NSBBs) are well established in the prevention of variceal haemorrhage in cirrhosis. Amelioration of bacterial translocation, implicated in sepsis, has also been described. NSBB use in decompensated cirrhosis however remains controversial. This study aimed to identify effects of NSBB use on mortality and infection rates in decompensated cirrhotics based on the setting of their care.
Method: A single-centre, UK based, retrospective analysis from November 2015-2017, identified two cohorts of decompensated cirrhotics; (a) patients attending a specialist cirrhosis clinic (b) cirrhotic patients acutely presenting to hospital, without specialist outpatient care prior to or after hospitalisation. Cohorts were stratified by Child-Pugh (CP) grading and disease severity matched.
Results: 213 patients (138 outpatients and 75 inpatients) with decompensated cirrhosis were identified (see Table 1). 112/138 outpatients (81%), and 46/75 (61%) inpatients survived at 1 year. In CP-B+C outpatients, NSBB use (versus non-use) favoured survival (p = 0.012), reduced 1-year incidence of primary infections requiring hospitalisation (p = 0.03), and reduced the need for all cause admission (p = 0.02). On binary logistic regression, factors independently associated with 1-year survival in CP-B+C outpatients were NSBB use [p = 0.004, OR 5.18 (CI 1.67-16.01)], lower baseline MELD score [p = 0.0001, OR 1.25 (CI 1.11-1.41)] and lower infection rates [p = 0.007 OR 1.72 (CI 1.17-2.58)].
In CP-B+C inpatients, NSBB use was not associated with reduced survival (p = 0.554) and no influence on infection was observed in these patients (p = 0.26). However, a lower proportion of NSBB users were readmitted to hospital at 6 months post discharge compared to non-users (10.5% vs 42.1%, p = 0.024).

Table 1: Patient demographics

	Outpatient Cohort (n = 138)	Inpatient Cohort (n = 75)
Sex		
Male	95/138 (69%)	48/75 (64%)
Female	43/138 (31%)	27/75 (36%)
Age (median, IQR)	58 (50-66)	56 (48-67)
Main aetiology		
Alcohol	91/138 (66%)	49/83 (59%)
Hepatitis C	19/138 (14%)	11/83 (13%)
NSBBs Use		
CP-B	61/89 (69%)	7/21 (33%)
CP-C	28/89 (31%)	14/21 (67%)

Conclusion: In patients with decompensated cirrhosis, NSBB use reduced mortality, need for admission and infection rates in the outpatient setting, and reduced readmission rates in inpatients. This supports a rationalised approach to the use of NSBBs based on disease severity and setting of care. The mechanism of this observed effect also warrants further investigation including the impact of NSBBs on immunological responses and bacterial translocation in cirrhosis.

SAT-090

Location of onset of acute kidney injury in cirrhosis affects survival

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Background and aims: The importance of acute kidney injury (AKI) as an independent predictor of outcomes in patients with cirrhosis is becoming increasingly clear with subtle changes in serum creatinine associated with adverse outcomes. The point at which AKI develops appears to influence outcomes in general hospital admissions, with hospital acquired AKI (HA-AKI) having worse outcomes than community acquired AKI (CA-AKI). With more refined diagnostic criteria for AKI in cirrhotics now being utilised, this study aims to describe the outcome for cirrhotic patients diagnosed with CA-AKI vs HA AKI.
Method: Patients hospitalised in a district general hospital in South-Wales (UK) with a confirmed diagnosis of liver cirrhosis of any aetiology over a 30 month period were analysed in this retrospective observational study. AKI was diagnosed and staged in accordance with KDIGO AKI criteria 2012 and the International Club of Ascites 2015 then divided into CA-AKI (criteria met < 48 hours of admission) and HA-AKI (criteria met ≥ 48 hours following admission).
Results: 542 admission episodes occurred during the study period with 171 episodes of AKI. CA-AKI contributed to 72.5% (n = 124) and HA-AKI 27.5% (n = 47). Inpatient mortality in the AKI group was 40.4% (n = 69), non-AKI group mortality 3.8% (n = 14). Inpatient mortality increased with each stage (Stage 1-3) of AKI in both the CA-AKI and HA-AKI group in a linear-by-linear association. Overall inpatient mortality in the CA-AKI group was 35.5% compared to the HA-AKI group of 53.2% (p = 0.04). 1 year mortality following incident admission was; non-AKI 36.8% (43/117), CA-AKI 54.4% (31/57), HA-AKI 71.4% (15/21) (p = < 0.01). AKI event (OR 7.29), rising bilirubin (OR 3.76) and advancing age (1.07) associated with increased mortality. Reduced mortality was seen in those with higher sodium (OR 0.94), higher albumin (OR 0.92) and the presence of alcohol related liver disease (OR 0.38).
Conclusion: Increasing AKI severity in the cirrhotic population is an independent predictor of adverse outcomes. In particular, patients

developing HA-AKI appear to be at a particular high risk of mortality. Efforts should be made to identify and mitigate risks of developing AKI amongst hospitalised cirrhotics and appropriate prompt escalation of treatment for those experiencing AKI in the context of cirrhosis.

SAT-091

The collagen hormone Endotrophin, a biomarker of type VI collagen formation-is associated with severe decompensation and predicts transplant-free survival in patients with trans-jugular intrahepatic portosystemic shunt

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Background and aims: In cirrhosis, the structural fibrillar type I, III and V collagens are known to be the predominant consequence of disease. However, a new understanding of the extracellular matrix (ECM) is emerging, in which fragments have been shown to hold important signaling functions, such as the collagen hormone Endotrophin, the pro-peptide of type VI collagen. Endotrophin has been shown to be associated with insulin resistance and induce fibrosis directly in other pathological settings. Here we investigated the association of Endotrophin and severe decompensation and predictor of mortality in patients with trans-jugular intrahepatic portosystemic shunt (TIPS).
Method: In 110 patients with decompensated liver cirrhosis, plasma samples were taken from portal and hepatic veins at time of TIPS insertion and two weeks later at an invasive TIPS control. Circulating levels of Endotrophin (PRO-C6) was assessed in plasma using specific monoclonal ELISA. PRO-C6 was stratified according to presence of ascites, hepatorenal syndrome (HRS), Child-Pugh category and MELD score. Kaplan-Meier and Cox regression analyses were used to investigate the association of PRO-C6 with 5-year transplant-free survival.
Results: Before TIPS insertion, similar levels of PRO-C6 were found in portal and hepatic vein ($p = 0.376$). However, two weeks after TIPS, PRO-C6 level was significantly higher in hepatic vein compared to portal vein ($p < 0.001$). Before TIPS, portal venous PRO-C6 levels were significantly higher in patients with HRS ($p < 0.001$), increasing degree of ascites ($p < 0.001$), MELD score > 11 ($p < 0.001$) and Child-Pugh class C ($p < 0.05$). Interestingly, no difference between the groups were observed when assessed in hepatic vein at TIPS insertion. Patients with PRO-C6 level above the median in portal vein before TIPS had significantly shorter transplant-free survival compared to patients with low PRO-C6 levels ($p < 0.05$) and was independently associated with survival in multivariate Cox adjusted for age, gender and MELD score. PRO-C6 was not associated with survival in hepatic vein.
Conclusion: The study shows for the first time that a non-structural collagen is associated with severe decompensation and is an independent predictor of mortality in liver cirrhotic patients with TIPS. PRO-C6 could be a potential prognostic marker to identify patients likely to deteriorate after TIPS. The signaling of collagens and in particularly Endotrophin warrants further investigation in the fibrosis field.

SAT-092

The efficacy and safety of rifaximin-a: a 2-year observational study of overt hepatic encephalopathy

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Background and aims: Five years after rifaximin-α registration as secondary prophylaxis for overt hepatic encephalopathy (HE) in the Netherlands, we aimed to evaluate the efficacy and safety of rifaximin treatment in a real-world pattern.
Method: After prospective identification of all patients using rifaximin-α for overt HE, the hospital resource use and adverse events were retrospectively registered in the first 6 months after initiation and compared to the prior 6 months.
Results: This study included 127 patients (71.7% male; median age 60.8 years (IQR 56.2-66.1); median MELD score 15.0 (IQR 12.1-20.4); 97.6% concomitant lactulose use). When comparing the first 6 months after rifaximin-α initiation to the prior 6 months, HE-related hospital admissions reduced (0.86 to 0.41 admissions/patient; $p < 0.001$), as well as the mean length of stay (8.85 to 3.79 bed days/admission; $p < 0.001$). No significant differences were found in the mean number of HE-related intensive care unit admissions (0.09 to 0.06 admission/patient; $p = 0.253$), the mean length of stay on the intensive care unit (0.43 to 0.57 bed days/admission; $p = 0.661$), emergency department visits (0.66 to 0.51 visit/patient; $p = 0.220$), and outpatient clinic visits (2.49 to 3.30 bed visit/patient; $p = 0.240$). Non-serious adverse events were recorded in 2.4% of patients.

	6 months prior to rifaximin-α initiation	6 months after rifaximin-α initiation	*p value*
HE-related admissions on the general ward per patient in 6 months, *mean (SD)*	0.86 (0.81)	0.41 (0.80)	< 0.001
HE-related hospital bed days on the general ward per admission in 6 months, *mean (SD)*	8.85 (11.20)	3.79 (9.37)	< 0.001
HE-related admissions on the intensive care unit per patient in 6 months, *mean (SD)*	0.09 (0.29)	0.06 (0.23)	0.253
HE-related hospital bed days on the intensive care unit per admission in 6 months, *mean (SD)*	0.43 (1.64)	0.57 (3.17)	0.661
AandE department visits per patient in 6 months, *mean (SD)*	0.66 (1.06)	0.51 (1.11)	0.220
Outpatient clinic visits per patient in 6 months, *mean (SD)*	2.94 (2.64)	3.30 (3.21)	0.240

Conclusion: The addition of rifaximin-α to lactulose treatment significantly reduces the number and length of HE-related hospitalizations for overt HE. Rifaximin-α treatment was safe and well tolerated.

SAT-093

Underutilization of hospice in inpatients with cirrhosis: The NACSELD experience

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Background and aims: The number of patients with cirrhosis continues to grow, resulting in an increasing rate of hospital admissions and liver related deaths. Little is known about patients discharged to hospice following hospitalization for complications of cirrhosis. Our aim was to understand the current pattern of hospice utilization in patients with cirrhosis by evaluating the North American Consortium for the Study of End-stage Liver Disease (NACSELD) cohort.

Method: Patients from 14 tertiary-care hepatology centers across North America prospectively consented non-electively hospitalized patients with cirrhosis. Patients were excluded if they had HIV, a transplant or non-hepatic malignancy. 2718 patients were consented, 5% (132) of whom were discharged to hospice. Random computer based propensity score matching was undertaken in a 1:2 ratio based on admission MELD score ± 3 points.

Variable	OR (95% CI)	P value
HE Grade III or IV HE	2.98 (1.36, 6.52)	0.006
Discharge Creatinine	1.49 (1.18, 1.88)	0.0008
Child Score	1.40 (1.15, 1.70)	0.0007
Discharge Bilirubin	1.05 (1.01, 1.09)	0.007
Na	0.94 (0.90, 0.99)	0.03
Maximum MELD Score during admission	0.91 (0.86, 0.99)	0.001
History of SBP	0.35 (0.14, 0.85)	0.02
On Transplant List	0.25 (0.10, 0.60)	0.002

Results: Patients discharged to hospice were older (60 vs. 56 years, p = 0.004), more likely to have NASH cirrhosis (27% vs. 16%, p = 0.02), more likely to have had ascites (80% vs. 71%, p = 0.05), but less likely to have had SBP (13% vs. 25%, p = 0.008) and be listed for liver transplantation (10% vs. 31%, p < 0.0001). Gender, percent with diabetes, body mass index, liver-related medications (with the exception of SBP prophylaxis) were similar among the groups. Because of propensity score matching, admission MELD was equivalent, but Child score was higher (10.9 vs. 10.1, p = 0.0007), and serum sodium was lower (132 vs. 134, p = 0.009) between the groups. Although the percentage of patients with a prior large volume paracentesis and prior hospitalization were similar between groups, patients discharged to hospice were more likely to have had a prior infection (41% vs. 29%, p = 0.03). Patients discharged to hospice had a longer length of index hospitalization (15.9 vs 12.7 days, p = 0.006), a higher discharge creatinine (2.62 vs. 1.60, p < 0.0001) and were more commonly diagnosed with hepatorenal syndrome (HRS; 40% vs. 18%, p < 0.0001). Table 1 shows multivariable modelling that found variables associated with discharge to hospice in our prospective multicenter cohort.

Conclusion: Patients with more advanced liver disease, hepatic encephalopathy, renal dysfunction, and those not candidates for liver transplantation were more likely to be discharged to hospice. However, in this sick multinational cohort of cirrhotic patients, it seems that hospice is underutilized (5%).

SAT-094

Effects of branched-chain amino acids on the progression of advanced liver disease: A Korean nationwide, multicenter, prospective, observational, cohort study

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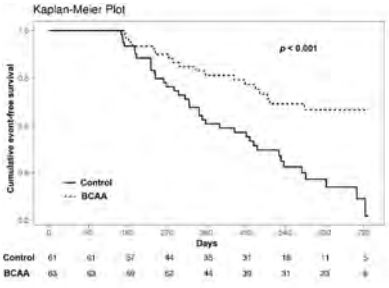
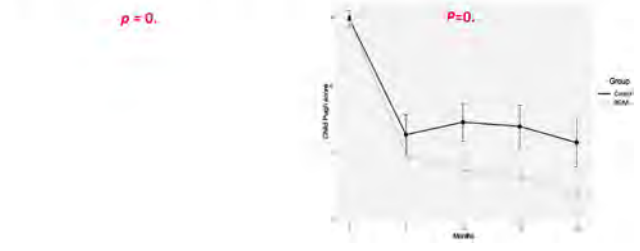
Background and aims: Malnutrition is a potential risk factor for progression of advanced liver disease. This study is to evaluate potential benefits of long-term oral branched amino acids (BCAAs) supplements in advanced liver disease





Method: Liver cirrhosis patients with Child-Pugh (CP) score from 8 to 10 were prospectively recruited from 13 medical centers. The patients supplemented with 12.45 g of daily BCAAs over 6 months or regular diet were assigned to either BCAA group or control group, respectively. We evaluated the effect of BCAAs therapy on the model

for end-stage liver disease (MELD) score, CP score, serum albumin, serum bilirubin, incidence of cirrhosis-related events, and event-free survival over 96 months.

Results: A total of 124 patients was enrolled (n = 63 in the BCAA group and n = 61 in the control group). Baseline characteristics of the patients including age, sex, CP score, and MELD score were not significant different between two groups. The MELD score (p = 0.009) and CP score (p = 0.011) were significantly improved in the BCAA group compared to the control group over time. However, serum albumin and bilirubin levels in the BCAA group failed to be improve over study period. Cumulative event-free survival in the BCAA group was significantly better than that in the control group (HR = 0.389, 95% CI 0.221-0.684, P < 0.001).

Conclusion: Long-term supplements of oral BCAAs could improve hepatic reservoir and delay the liver cirrhosis related complications in patients with advanced liver disease.

SAT-096

Large spontaneous portosystemic shunt (SPSS) area is associated with hepatic encephalopathy and predicts mortality in liver cirrhosis

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Background and aims: Spontaneous portosystemic shunts (SPSS) frequently develop during the progressive course of liver cirrhosis. Recent data suggested that the presence of a single large SPSS is associated with complications, especially with hepatic encephalopathy (HE). However, in cirrhotic patients the presence of more than one SPSS is common. This study aimed to evaluate the impact of total cross-sectional SPSS area (TSA) on the outcome of patients with liver cirrhosis.

Method: This is a retrospective international multicentric study, in which computed tomography (CT) scans of 724 patients with liver cirrhosis were evaluated for TSA. Clinical and laboratory data were recorded. The radius of each detected SPSS was measured and TSA was calculated. The clinical events during follow-up after the index CT-scan were recorded. Primary end point was 1-year survival. Secondary end points were acute decompensations (HE, variceal bleeding, ascites).

Results: A total of 301 patients (169 male) were included in the training cohort. 30% of all patients presented with more than one SPSS. Using a TSA cut-off at 83 mm^2 patients were classified as small TSA (S-TSA) or large TSA (L-TSA). L-TSA patients had significantly higher MELD (11 vs. 14) and MELD-Na (14 vs. 16) as well as higher prevalence of HE (12% vs. 21%) at baseline. During follow-up L-TSA patients showed significantly more episodes of overt HE (47% vs. 33%, p < 0.05). L-TSA patients had significantly higher 1-year mortality as compared to S-TSA patients (28% vs. 14%, p < 0.01). Multivariate analysis identified L-TSA (HR 1.737, 1.036-2.742) next to MELD (HR 1.181, 1, 142-1.220) and CLIF-C AD (HR 1.192, 1.100-1.292) score as independent predictors of mortality. These results were confirmed in an external multicentric validation cohort of 423 patients.

Conclusion: This study, for the first time, highlights the prognostic importance of TSA for mortality in patients with liver cirrhosis. Our results may have impact on the clinical decision to consider embolization of SPSS.

SAT-097

Non-invasive estimation of intravascular volume status in cirrhosis by dynamic size and collapsibility Indices of the inferior vena cava using bedside echocardiography

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Background and aims: Echocardiographic assessment of the inferior vena cava (IVC) diameter and collapsibility index (IVCCI) is a non-invasive point-of-care tool for the individual's intravascular volume status (IVS) but needs validation in cirrhosis. We evaluated IVC dynamics in cirrhosis and correlated it with conventional tools like central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP). The IVC collapsibility index (IVCCI) was the difference between the maximum ($IVCD_{max}$) and

minimum IVC diameters ($IVCD_{min}$) divided by the maximum IVC diameter, expressed as a percentage ([$IVCD_{max}$-$IVCD_{min}$]/$IVCD_{max}$ × 100%).

Method: A total of 673 consecutive cirrhotics were screened by 2D echocardiography with M mode and the IVC measurements including IVCD and IVCCI were performed. Of these, 125 patients underwent right heart catheterisation with recording of hepatic venous pressure gradient (HVPG), RAP, pulmonary artery (PA) pressure and PCWP. The CVP data was available in 80 (64%) patients, and finally 76 patients (84% male, 50% ethanol related, mean age 52.1 years, 57.8% with ascites, 39.4% with prior variceal bleed) with complete data were enrolled.

Results: The mean CVP measured was 12.8 ± 4.8 mmHg and the IVCCI was 29.5 ± 10.9%. The IVCD ranged from 0.97 to 2.26 cm during expiration and from 0.76 to 1.84 cm during inspiration with a mean of 1.8 ± 0.9 cm. The mean IVCD correlated with RAP (r = 0.633, p = 0.043), but not with HVPG (r = 0.344, p = 0.755), PCWP (r = 0.562, p = 0.072) or PA pressure (r = 0.563, p = 0.588). A strong negative linear correlation was observed between the CVP (mean 10.3 ± 4.4mmHg) and the IVCCI (r = -0.827, p = 0.023) in all patients and sub-stratified for those with (r = -0.748, p = 0.039) and without ascites (r = -0.761, p = 0.047). A strong positive correlation was revealed between the CVP and the $IVCD_{max}$ (r = 0.671, p = 0.037) and $IVCD_{min}$ (r = 0.612, p = 0.040), which remained significant even in presence of ascites. The $IVCD_{min}$ < 1.5 cm predicted CVp < 10 mmHg and indicated the need for further volume resuscitation with sensitivity of 91%, specificity of 79% and 96% negative predictive value.

Conclusion: IVCD and collapsibility index provides non-invasive volume status assessment in cirrhosis, independent of HVPG or ascites. Future prospective studies could be focused to bring about a steadfast formula for calculating fluid requirements in cirrhosis using dynamic IVC criteria.

SAT-098

Transjugular intrahepatic portosystematic shunt with 7 mm covered stent reduces hepatic encephalopathy without losing shunt function for prevention of portal hypertensive rebleeding

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Background and aims: Transjugular intrahepatic portosystemic shunt has been recommended by the Baveno consensus and the American Association for the Study of Liver Diseases guidance for portal hypertensive bleeding in cirrhosis. However, there is no international consensus yet regarding the priority diameter selection of the covered stents. The study aims to explore whether the 7 mm covered stents would equip with more advantages than 8 mm covered stents for the prevention of portal hypertensive bleeding in cirrhosis.

Method: In this retrospective study, cirrhotic patients receiving transjugular intrahepatic portosystemic shunt procedure with a 7 mm or 8 mm covered stent for the treatment of variceal rebleeding between January 2011 and September 2015 in a high volume center in China were analyzed. During a 24-month follow-up, the incidence and grade of hepatic encephalopathy were recorded. Covert hepatic encephalopathy (minimal or grade I) and overt hepatic encephalopathy (≥ grade II) were respectively defined. Propensity score matching was used to control for preoperative baseline characteristic imbalances. In addition, shunt dysfunction, variceal rebleeding, survival and a composite end point of all-cause rebleeding and death were assessed as outcome measures.

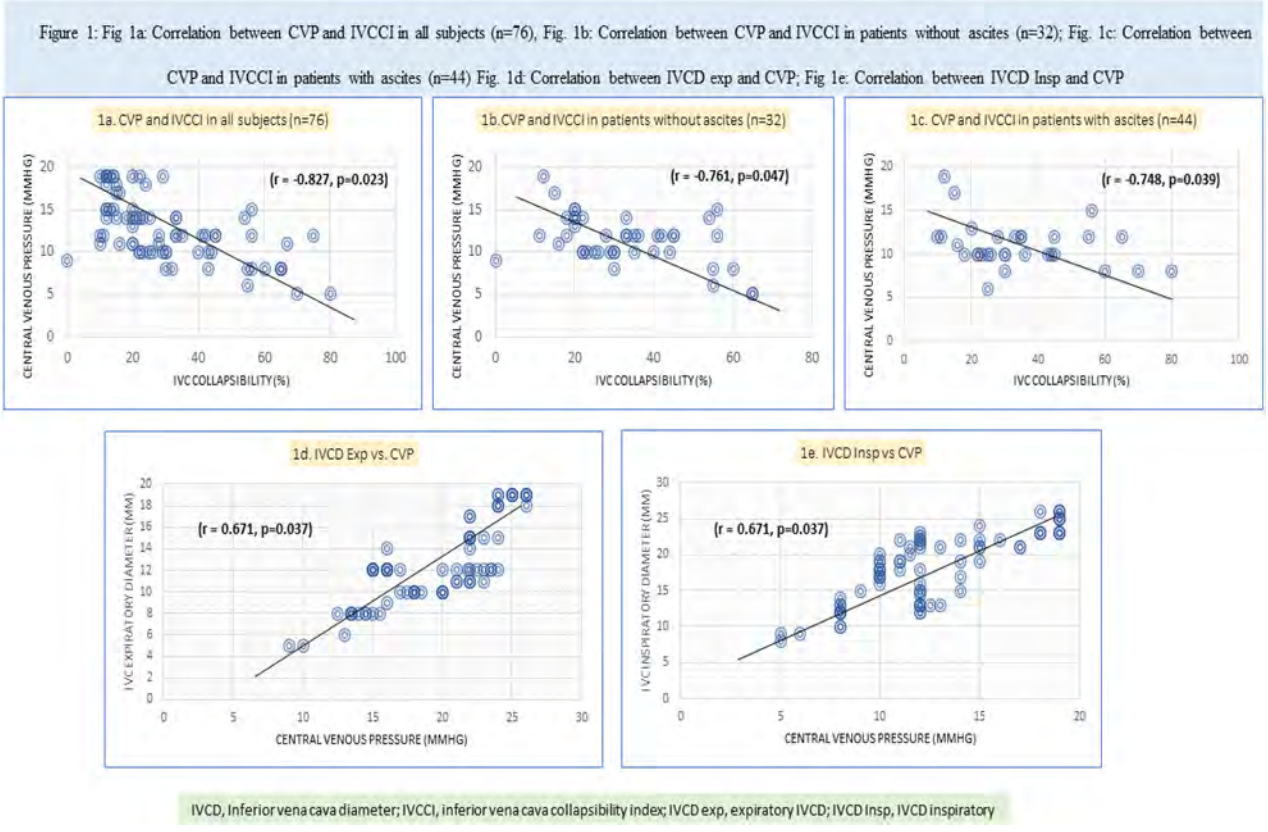

Figure: (abstract: SAT-097): Correlation between different IVC parameters and CVP

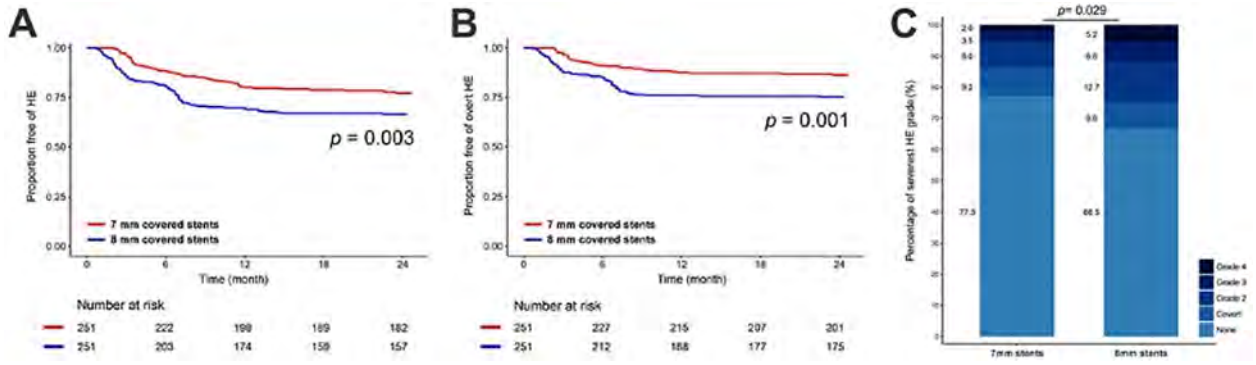

Figure: (abstract: SAT-098)

Results: A total of 502 eligible patients were enrolled. Accordingly, 251 patients with 7 mm covered stent were recruited, and patients with 8 mm covered stent were matched in a 1:1 ratio. During a 24-month follow-up, there was no significant difference between the 7 mm and 8 mm stents groups considering the free of shunt dysfunction rates, free of rebleeding rates, survival rates, free of all-cause rebleeding and death rates with p value equals to 0.915, 0.840, 0.735, 0.237 respectively. Notably, the group with patients receiving 7 mm covered stent had a higher free of hepatic encephalopathy rate (77.1% vs 66.4%, p = 0.003, Figure 1A) and overt hepatic encephalopathy rate (86.3% vs 75.2%, p = 0.001, Figure 1B) over the group with patients receiving 8 mm covered stent. Moreover, the percentages of severest grade hepatic encephalopathy episodes were significantly different between the groups (p = 0.029, Figure 1C).
Conclusion: Our study suggested a favorable overall outcome with 7 mm covered stents compared with 8 mm covered stents in transjugular intrahepatic portosystemic shunt procedure for portal hypertension rebleeding prevention in patients with cirrhosis.

SAT-099

Portal pressure gradient measured immediately after transjugular intrahepatic portosystematic shunt placement: Poor in predicting rebleeding in patients with portal hypertension

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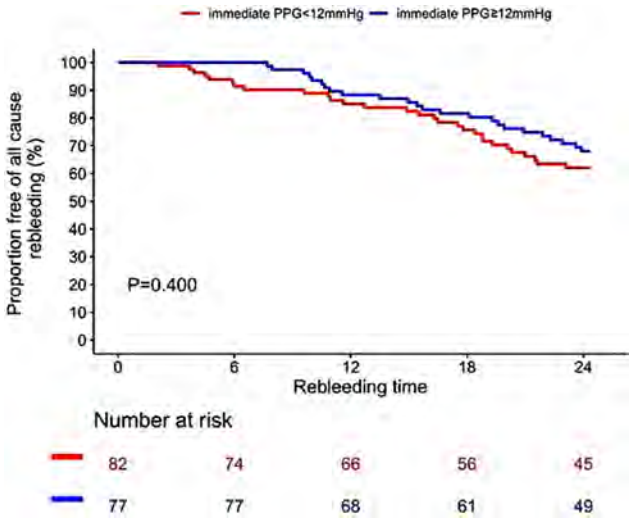
Background and aims: A portal pressure gradient above 12 mmHg after transjugular intrahepatic portosystemic shunt placement can indicate a postoperative rebleeding in patients with variceal bleeding caused by portal hypertension. A recent study has verified that measure timing influenced the accuracy of portal pressure gradient, which also found that portal pressure gradient measured immediately after transjugular intrahepatic portosystemic shunt placement (immediate portal pressure gradient) under general anesthesia and deep sedation could not be an indicator for rebleeding during follow-up. This study aimed to analyze the direct relationship between immediate portal pressure gradient measured under local anesthesia and postoperative rebleeding to investigate whether immediate portal pressure gradient could predict a rebleeding after transjugular intrahepatic portosystemic shunt in portal hypertension.
Method: This retrospective study included eligible patients receiving transjugular intrahepatic portosystemic shunt between January 2011 and September 2015 in China. Immediate portal pressure gradient was measured after transjugular intrahepatic portosystemic shunt placement under local anesthesia. A propensity score matching analysis was performed in 159 cases to match bleeding patients with non-bleeding patients at a ratio of 1:2 to reduce the confounding factors. Relationship between immediate portal pressure gradient with a threshold of 12 mmHg and a postoperative rebleeding was analyzed both in pre- and post-match samples.
Results: A total of 502 consecutive patients were enrolled. No significant difference was observed in occurrence of rebleeding between patients with immediate portal pressure gradient ≥ 12 mmHg and < 12 mmHg neither before nor after (8.7% vs. 12.8%, p = 0.09; 31.2% vs. 35.3%, p = 0.4) matching by a propensity score (Figure 1). Predictive performance of immediate portal pressure gradient for rebleeding was poor with the area under survival receiver operating characteristic curve of 0.415 (95% CI: 0.332-0.514).



Conclusion: Our study analyzed the direct association between immediate portal pressure gradient and a postoperative rebleeding. And we found that a threshold of 12 mmHg for portal pressure gradient measured immediately after transjugular intrahepatic portosystemic shunt placement under local anesthesia could not predict rebleeding after transjugular intrahepatic portosystemic shunt in portal hypertension.

SAT-100

Expanding the Baveno VI criteria for the screening of varices in advanced liver disease patients

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Background and aims: The updated Baveno VI guidelines recommend that screening for EGD can be avoided in patients with compensated advanced chronic liver disease (cACLD), who have liver stiffness < 20 kPa and a platelet count > 150, 000/μL.
The aim of this study was to validate the Baveno VI criteria in patients with chronic liver disease in order to determine their ability to rule out the presence of esophageal varices (EV) and avoid unnecessary endoscopies. We also searched for the best cut-off values in our center, to rule out the patients with significant portal hypertension category.
Method: This was a retrospective study of patients with liver cirrhosis admitted in our Department between January 2009 and September 2018. Patients were included in the study if Transient Elastography (TE), laboratory tests and upper endoscopy were performed in the same year. The study group (829 patients) was used to validate the Baveno IV criteria to predict significant esophageal varices. In the group of patients situated in the "gray zone" (between the cut-offs rule in and rule out significant esophageal varices) we searched for additional predictive factors. A cohort of 124 cirrhotic patients was used as a control group, to validate the cut-off values calculated for our center.
Results: The best thresholds to rule in significant esophageal varices in our study group (829 patients) were identified at PLT < 150, 000/mm3 and LSM > 29.5 kPa, and the best thresholds to rule out significant esophageal varices were identified at PTL > 150.000/mm3 and LSM < 19.4 kPa. In the validation cohort of 124 patients if we used the cut-off for ruling out, 25/124 met the criteria, and none of them had EV, Se = 100%. If we used the rule in cut-off, 36/124 met the criteria, but 1 of them didn't have EV, leading to Se = 97.2%. Diagnosis accuracies were 100% and 97.2%. Regarding the "grey zone" between 19.4 kPa and 29.5 kPa, 330/829 (39.8%) patients from the study group were in this zone. Albumin was associated with the presence of EV in the "grey zone". The best cut-off value for predicting significant EV was 3.4 g%. Adding the serum albumin to the Baveno VI criteria we increased the NPV from 98.4% to 99.3%.
Conclusion: Baveno VI criteria in our large cohort of cirrhotic patients had 98.4% accuracy. Adding serum albumin levels (< 3.4 g%) we increase the performance of Baveno VI criteria. We propose a new cut-off value of TE < 19.4 kPa in patients with platelets > 150.000 mg/dl, with an 100% accuracy in our center to rule out significant varices.

SAT-101

Detrimental effect of proton pump inhibitors in cirrhosis depends on common genetic variation

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Background and aims: Proton pump inhibitors (PPI) increase adverse events and potentially mortality in patients with cirrhosis. Common risk variants in the Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) and Membrane-bound O-acyltransferase domain-containing protein 7 (*MBOAT7*) genes contribute to progressive chronic liver disease. We aimed to investigate the impact of PPI intake on survival and the development of hepatic complications in patients with cirrhosis stratified for the risk variants.
Method: Overall, 998 patients with cirrhosis in two German academic medical centers in Homburg and Halle were included between 2014 and 2017. We defined PPI use as a daily dose ≥ 20 mg pantoprazole (or an equivalent dose of other PPI) taken continuously. Patients were genotyped for the risk variants rs738409 (*PNPLA3*) and rs641738 (*MBOAT7*) by allelic discrimination assays. Prospective follow-up was conducted, and transplant-free survival and complications were recorded, stratified by the presence of risk genotypes.
Results: In total, 700 PPI users (70%) were identified. Median age was 61 (53–68) years, and median MELD score was 11 (8–15). Cirrhosis was alcoholic in 537 (54%), viral etiology was present in 166 (17%) and other etiologies in 295 (29%) patients. Among the patients on PPI, 94% received pantoprazole (63% 40 mg, 30% 80 mg and 7% 20 mg daily, data available in 54%). In univariate Cox regression analyses were female sex, bilirubin, creatinine, albumin, INR, PPI, and alcoholic liver disease were associated with transplant-free survival. In multivariate Cox regression models, independent predictors in carriers of the wild-type variant were PPI (adjusted hazard ratio [aHR] 0.48, 95%

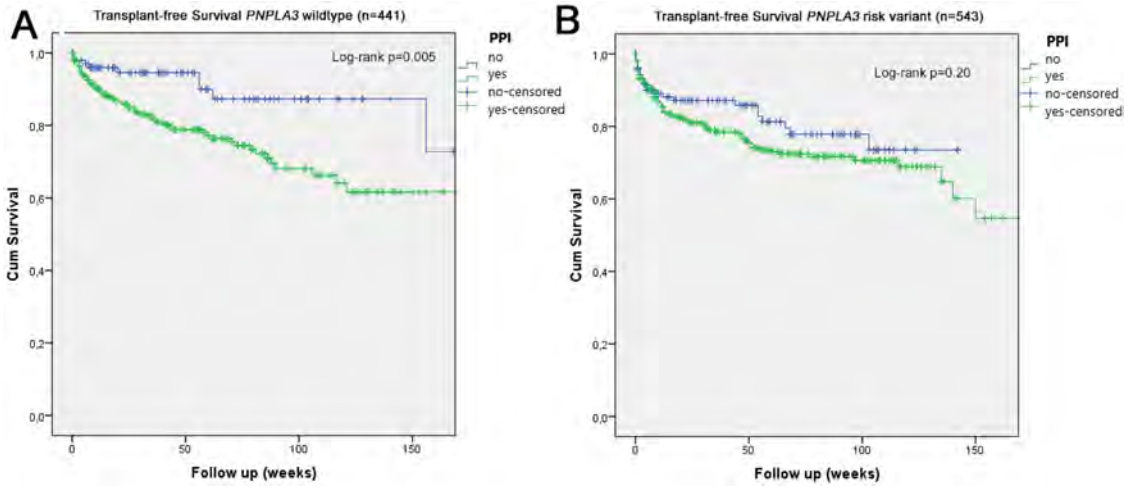

Figure: (abstract: SAT-101)

confidence interval [CI] 0.23-0.96; p = 0.039) and MELD (aHR 1.17, 95% CI 1.13-1.22; p < 0.001), whereas in carriers of the *PNPLA3* risk variant only MELD (aHR 1.16, 95% CI: 1.13-1.19; p < 0.001) was associated. The Presence of an *MBOAT7* variant, as well as the dose and type of PPI did not yield differences in the outcome. For hepatic complications in association with PPI intake, only bacterial infections were associated with a similar increased risk in patients with (Odds ratio [OR] 2.20, 95% CI 1.23-3.93; p = 0.007) and without (OR 2.23, 95% CI 1.23-4.05; p = 0.007) *PNPLA3* risk alleles.
Conclusion: In this large prospective cohort, reduced transplant-free survival in patients with cirrhosis taking PPI was present only in carriers of wild-type alleles of the *PNPLA3* risk variant. Mechanistic studies of this gene-environment interaction are warranted.

SAT-102
Cirrhotic patients with vitamin d deficiency fail to respond to oral replacement therapy
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Background and aims: Vitamin D deficiency and bone disease are highly prevalent in patients with advanced chronic liver disease. For bisphosphonate treatment for osteoporosis to be effective vitamin D levels must be replete. Moreover, vitamin D deficiency has been associated with an increased risk of infections and increased rejection rates following liver transplantation. The optimal dose and route of vitamin D replacement in cirrhosis is unknown. BSG guidance currently recommends 800 IU/day orally for all patients with cirrhosis/cholestatic liver disease.
Method: Retrospective review of 299 patients with chronic liver disease undergoing evaluation for liver transplant between 2015 and 2017. Vitamin D 'severe deficiency' was defined as < 25 ng/ml, 'deficiency' 25-50 ng/ml and normal > 50 ng/ml. Response to oral vitamin D therapy was recorded.
Results: 273 patients had vitamin D levels recorded. The prevalence of vitamin D deficiency in these patients was 57% (156/273) with 65/273 (24%) 'severely deficient' and 91/273 (33.3%) 'deficient'. Vitamin D therapy was being prescribed in 69 patients with levels < 50 ng/ml (44%), and 77 patients (66%) with levels > 50 ng/ml. Daily doses of prescribed vitamin D therapy did not significantly differ depending on the degree of deficiency, with median doses of 1, 000iu, 800iu and 800iu in those patients with vitamin D levels > 50 ng/dl, 25-50 ng/dl and < 25 ng/dl respectively (p = 0.53).
Data on vitamin D levels pre and post 3 months of treatment with Vitamin D therapy were available in 111 patients. Vitamin D therapy did not positively impact on Vitamin D levels at three months (Δ vitamin D) when comparing those on therapy (n = 64) to those not on therapy (n = 47) (1 vs −3, p = 0.13). Patients with vitamin D levels < 50 (n = 30) had a significantly greater increment in vitamin D at three months if they were taking > 1500 iu/day compared to those taking < 1500 iu/day (17 vs 2, p = < 0.05), however only 23% augmented their vitamin D levels to within the normal range of > 50 ng/dl with therapy. Advanced liver disease (MELD > 15) did not impact on response to vitamin D therapy (p = 0.74).
Conclusion: Vitamin D deficiency is prevalent, affecting over 50% of patients with advanced cirrhosis. Oral vitamin D replacement therapy is ineffective in cirrhotics at repleting stores over a 3 month period irrespective of dose given or MELD score. Evaluation of response to IM vitamin D therapy in cirrhotic patients is urgently required to guide guidelines to ensure effective therapy.

SAT-103
Bone disease does not correlate with severity of liver disease in cirrhosis
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Background and aims: Patients with chronic liver disease have increased risk of bone disease with reported prevalence of osteoporosis between 20–56% and a high prevalence of Vitamin D deficiency. The aetiology is poorly understood with a complex interplay between endocrine, metabolic, nutritional and physical abnormalities. We aim to evaluate the influence of epidemiological parameters on bone mineral density and vitamin D levels in chronic liver disease.
Method: Retrospective review of consecutive patients with chronic liver disease undergoing assessment for liver transplantation between 2015–2017. Data were collected on aetiology, liver severity, body mass index, functional assessment alongside vitamin D level and bone mineral density. Bone disease (Osteoporosis/osteopenia) was defined as per WHO classification and Vitamin D deficiency as a Vitamin D level < 50 nmol/L with severe deficiency < 25 nmol/L.
Results: 299 patients (72% male) with a median age 57-years (IQR 49-63) were included. Aetiology was alcohol (n = 96), viral hepatitis (n = 66), PBC/PSC (n = 62), NAFLD (n = 34), AIH (n = 22), and 'other' (n = 19). Median UKELD and MELD scores were 53 (IQR 50-57) and 14 (IQR 10-18.5) respectively.
At the time of evaluation for liver transplant, 199 (66.6%) patients had bone disease with 64/299 (21%) osteoporotic and 135/299 (45%) osteopenic. The prevalence of bone disease varied across aetiologies (ANOVA p = < 0.005), with PBC/PSC (69%) and AIH (82%) having the highest prevalence and NAFLD the lowest (37%). The overall prevalence of Vitamin D deficiency was 62%. Viral hepatitis (72%) had the highest rates and PBC/PBC (41.5%) the lowest (ANOVA p = < 0.005). Overall the MELD/UKELD score did not correlate with bone disease or Vitamin D deficiency, nor did it correlate in subgroup analysis of alcohol, viral, autoimmune or cholestatic disease aetiology. Predictors of bone disease included a low BMI (p < 0.01), reduced hand grip strength (p < 0.01), older age (p = 0.01) and autoimmune aetiology. Vitamin D deficiency conversely was associated with female sex (p = 0.02) but not BMI, hand grip strength or older age.
Conclusion: Bone disease and vitamin D deficiency are prevalent in chronic liver disease. Disease severity does not correlate with bone disease or vitamin D whereas more functional markers of frailty such as hand grip strength do. Further prospective research is needed to look at the role of vitamin D in cirrhosis.

SAT-104
Factors associated with renal replacement therapy and mortality following first episode of acute kidney injury in inpatients with cirrhosis
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Background and aims: Renal injury is associated with poor outcomes in cirrhosis. Prediction of renal replacement therapy (RRT) and mortality remains difficult in patients presenting the first episode of acute kidney injury (AKI). We aimed to compare the existing formulas to estimate glomerular filtration rate (eGFR), (MDRD-6, CKD-EPI, Royal Free Hospital-RFH) and assessed which predict outcomes.
Method: We retrospectively studied hospitalized patients with cirrhosis presenting a first AKI episode at our centre in 2012-2018. Patients on RRT, with HCC outside Milan criteria at baseline and who previously received OLT were excluded. Laboratory values used to estimate GFR were collected at diagnosis of AKI (D0) and D2 and in-hospital RRT, and death or OLT at 30 and 90-d were assessed.

Results: 143 patients were included (Age 59 ± 11 years, 62% male, BMI: 27.3 ± 5.8 kg/m^2, MELD score: 14.7 ± 5.7 and Child score 9 ± 2; aetiology: alcohol 29%, alcohol + metabolic component 25%, viral 21%, NASH 13%) and were followed-up for a median of 10 months (IQR 1-25). Males had higher creatinine at AKI presentation (p = 0.04 vs. females), but eGFRs were not significantly different (RFH-GFR 24.8 vs. 24.1 ml/min/1.73 m2 , p = 0.67). At AKI diagnosis, the grade of renal failure was 1 in 57%, 2 in 22% and 3 in 21%. Infection at admission (56%) was the strongest predictor of AKI grade (OR for grade ≥ 2: 2.9 95%CI 1.4-6.0, p = 0.004). RRT was performed in 15.4% and was associated with 55% 90-d mortality rate. Predictors of RRT were baseline creatinine (OR 1.009; 95%CI 1.005-1.014, p < 0.001), D0 urinary-Na (OR 0.998; 95%CI 0.997-0.999, p = 0.02), D0 presence of urinary casts (OR 3.7; 95%CI 1.3-10.4, p = 0.013) and alcohol +metabolic aetiology (p = 0.049 vs. other aetiologies). Death or OLT rate at 30-d and 90-d was 23% and 37% respectively. RRT and kidney function by creatinine and by all the proposed eGFR formulas predicted mortality; the strongest association was obtained on day 2 from the diagnosis of AKI. Among creatinine, MDRD-6, RFH-GFR and CKD-EPI, RFH-GFR showed the highest predictive value for RRT, 30-d and 90-d mortality.
Conclusion: Patients with alcohol aetiology and added metabolic component of cirrhosis have more severe AKI, requiring RRT more frequently and resulting in a higher mortality. RFH-GFR calculated on the second day after AKI diagnosis is a strong predictor of need for RRT and 30-d and 90-d mortality.

SAT-105
Rising economic burden following the diagnosis of compensated cirrhosis among hospitalized patients with Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis 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 examined the demographics, comorbidities and healthcare costs among NALFD/NASH patients once they develop CC in Spain.
Method: Adult patients with NAFLD/NASH diagnosis (ICD-9/10-CM) between 2006 and 2017 were identified retrospectively from the Spain hospitalization database that covers 192 private hospitals and 313 public hospitals, with more than 38 million patients. Following the initial NAFLD/NASH diagnosis, development of CC was identified using the first diagnosis date (CC index date). Patients were excluded if they had evidence of viral hepatitis, Wilson's disease, Gaucher disease, LAL-D, alcoholism including alcoholic liver disease, HIV, hemochromatosis or primary biliary or sclerosing cholangitis. Baseline measures were reported during 6 month pre-index duration, and healthcare costs were reported during 6 months pre-index and 6 months post-index duration. Mean per patient per month healthcare costs were obtained. Patients were followed from index date to earliest of 6 months, progression to different cohort, end of coverage, or end of study period.
Results: The study population included 8, 205 NAFLD/NASH patients (mean age 58.4 years; 54% males) and 139 CC patients (1.7% of NAFLD/NASH patients) (mean age 65.2 years; 59% males). The most common comorbidities were hypertension, diabetes, and hyperlipidemia with prevalence rates of 28%, 21%, 15%, respectively among NAFLD/NASH patients, and 32%, 27%, 12% respectively among CC patients. 45% of NAFLD/NASH patients and 24% of CC patients have ≥ 1 condition out of hypertension, hyperlipidemia, diabetes, renal impairment or cardiovascular diseases. The mean (± SD) per patient per month all-cause healthcare costs for CC patients averaged €3, 738 (± €1, 835) in the pre-index period and €5, 414 (± €2, 658) in the post-index period (+45%) (p < 0.001). The cost driver were inpatient costs, representing 41% of the total cost (€1, 529±€750) in the pre-index and 55% of the total cost (€2, 972±€1, 457) in the post-index period.

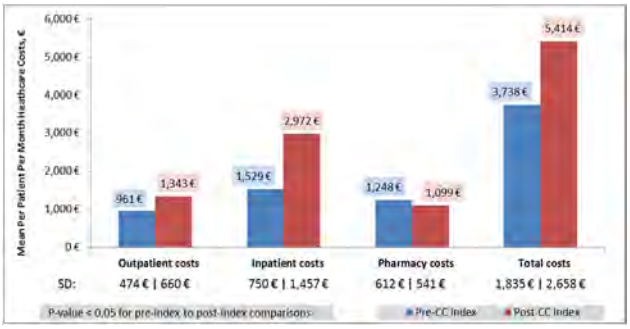

Figure: Mean Per Patient Per Month All-cause Healthcare Costs for NAFLD/NASH-CC patients

Conclusion: Hospitalized Spain NAFLD/NASH patients with CC have a high comorbidity burden. Per patient per month healthcare costs are high, following the CC diagnosis (+45%), with inpatient costs as the primary driver. Novel treatment options are needed to improve patient outcomes and limit the increasing costs in Spain due to NAFLD/NASH.

SAT-106
Prevalence and survival of fungal peritonitis in decompensated cirrhosis
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Background and aims: Fungal peritonitis in decompensated cirrhosis is exceedingly rare and little is known regarding true prevalence, presentation, clinical markers, pathogens and prognosis. The aim of this study was to evaluate all cases of fungal peritonitis in decompensated cirrhosis over a 10-year period at our institution.
Method: Retrospective review of ascitic fluid cultures from consecutive cirrhotic patients over a 10-year period were reviewed to identify patients with fungal peritonitis. Baseline demographic and clinical data at presentation alongside pathogens and outcomes were collated and compared to a matched control group of spontaneous bacterial peritonitis (SBP).
Results: 8890 ascitic fluid samples were reviewed; 213 had positive fungal cultures of which 8 occurred in the context of cirrhotic ascites. Underlying aetiology of cirrhosis was alcohol in 6 cases, median age 50, MELD 24 and 7/8 were CPS C. Indication for the ascitic tap was either pyrexia, abdominal pain or distension and 6/8 cases had had an invasive intervention in the 48 hours prior to the ascitic tap (paracentesis/gastroscopy) and 2 cases subsequently evolved with bowel pathology (obstruction/perforation). Ascitic WCC was predominantly neutrophils (> 90%) with total ascitic WCC counts > 1000cells/mm^3 in the majority of cases. All fungal cultures were Candida species (Candida albicans n = 8, glabrata n = 1), median culture time for positive result 48 hours (24-168 hours) and all albicans were sensitive to fluconazole; the glabrata was resistant. Two patients had a concurrent candidaemia. Seven out of the eight cases required escalation to ITU; 2/8 were alive at 90 days. In comparison to a control group of 119 SBP cases collated over the same time period patients with fungal peritonitis had non statistical differences in MELD (24 vs 22; p = 0.1) and peripheral WCC (13.5vs 11.7; p = 0.7), however there was trend towards significance in UKELD (62 vs 56; p = 0.07) and INR (2.3 vs 2.0; p = 0.07) and ascitic WCC (4870 vs 2765; p =

0.06). Death or LT at 1-year was 52/117 (44%) and 2/8 (25%) for SBP and fungal peritonitis respectively (p = 0.4).
Conclusion: Fungal peritonitis in the context of cirrhosis is an exceedingly rare but has a significantly poor prognosis perhaps related to delay in recognition of fungal pathogen. Validation of fungal biomarkers and incorporation into clinical practice may allow earlier recognition and treatment.

SAT-107

Effect of a multifactorial intervention (non-alcoholic beer, diet and exercise) on endothelial function, nutritional status and quality of life in patients with cirrhosis

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Background and aims: The implementation of nutritional strategies targeting several variables at once could benefit patients with cirrhosis. Non-alcoholic beer has different compounds derived from hops that exert antioxidant, anti-inflammatory and nutritional properties. The aim of this study was to evaluate the effect of diet + exercise and non-alcoholic beer on nutritional status, endothelial function and quality of life in patients with cirrhosis.
Method: Randomized open clinical trial conducted from 2015 to 2018. Patients with cirrhosis were randomized into two groups: A) Intervention (non-alcoholic beer +diet +exercise) B) Control (water +diet +exercise). Treatment consisted of 330 ml non-alcoholic beer per day or the same amount of water, plus an individualized dietary program and an exercise program with a pedometer-based bracelet to reach at least 5000 steps/day during 8 weeks. Endothelial function (flow-mediated dilation), biochemical and nutritional variables and quality of life (CLDQ) were evaluated.
Results: 40 patients were included in the study. The mean age was 53 ± 7 years, 65% were women, the main etiologies were HCV 32.6%, AIH 23.3% and NASH 20.9%. Mean MELD was 9 ± 2.2 and most patients were CTP A (86%). The adherence to the interventions was > 90% in both groups. Liver function tests, serum electrolytes, platelets and renal function remained stable throughout the study. No adverse events were observed in either group. PhA remained stable in the control group and showed a trend towards improvement in the intervention group; a higher proportion of improvement on nutritional status was observed in the intervention group. Quality of life improved in both groups, but predominantly in the intervention group and endothelial function improved in both groups. (Table 1)

Table 1: Changes on the study variables after intervention

	Control (n = 20)		Intervention (n = 20)	
	Baseline	Final	Baseline	Final
Child-Pugh	5.5 ± 0.9	5.4 ± 0.7	5.7 ± 0.9	5.3 ± 0.5*
MELD score	8 ± 2.3	8 ± 1.9	9 ± 2.2	8.1 ± 1.7
Phase angle	6 ± 0.7	6 ± 0.6	5.6 ± 0.5	5.7 ± 0.7
Improvement of nutritional status		28.6%		57.9%*
Number of steps	8593 ± 3020	11326 ± 4399	8522 ± 4068	11025 ± 3781
CLDQ (Global)	5.20 ± 0.9	5.5 ± 0.9	4.6 ± 0.9	5.3 ± 0.9*
Endothelial dysfunction	52%	16%*	32%	0%*

* p = < 0.05

Conclusion: Our intervention is safe and well tolerated in patients with cirrhosis, and shows improvement in nutritional status, endothelial function, severity of the disease and quality of life. The long-term benefits of this intervention should be further assessed.

SAT-108

Sarcopenia and nutritional status predict mortality in patients with cirrhosis undergoing liver transplant assessment

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Background and aims: The presence of sarcopenia has been shown to predict adverse outcomes in advanced liver disease. Here we examined the association of a validated nutritional assessment tool, and sarcopenia diagnosed by imaging, with short-term mortality in patients undergoing assessment for liver transplantation.
Method: 882 patients undergoing assessment for elective, first-time, liver transplantation at the Royal Free Hospital, London, were included in this study. Nutritional status and sarcopenia were assessed using the Royal Free Hospital-Global Assessment (RFH-GA) tool, which incorporates body anthropometrics and dietary intake, and the L3-psoas muscle index (L3-PMI) on CT, respectively. Individuals in the lowest quartile of L3-MPI were deemed sarcopenic.
Results: Of the study cohort, 32% were female, with a mean age of 53 (±11) years. 88% were listed for transplantation, while 56% received a liver graft. 20% of the study population died during the study period, which involved a mean follow-up of 183 (± 349) days. 94% of deaths were liver-related. The main liver disease aetiologies were alcohol (29.6%), viral hepatitis (29.6%), PSC (12.3%), NAFLD (7.9%), while hepatocellular carcinoma (HCC) was present in 28% cases. The Child-Pugh score A/B/C breakdown was 8%/46%/46% respectively, and the mean MELD score was 14 (±8). The RFH-GA indicated well-nourished in 35%, and mild/moderate or severe malnourishment in 40% and 25%, respectively. L3-PMI correlated significantly with body anthropometrics (eg. lean mass and dry weight), liver synthetic function (eg. Child Pugh), and RFH-GA (all p < 0.001). Both sarcopenia and RFH-GA were significant, independent predictors of mortality based on multivariate cox regression analysis of the overall cohort [hazard ratios of 1.96 (95% CI, 1.4-2.8, p < 0.001), and 1.6 (95% CI, 1.07-2.4, p = 0.02), respectively]. The combination with sarcopenia did not increase the predictive power of the MELD score for 3-month mortality.
Conclusion: This study demonstrates that poor nutritional status as indicated either by sarcopenia on imaging or by detailed nutritional assessment is a useful adjunct when evaluating patients with advanced liver disease. As this is a theoretically correctable condition, the optimisation of nutrition remains a key area for future study and novel therapeutic approaches for individuals with liver disease.

SAT-109

Spontaneous bacterial peritonitis: Will the diagnostic follow-up paracentesis be essential in approaching these patients?

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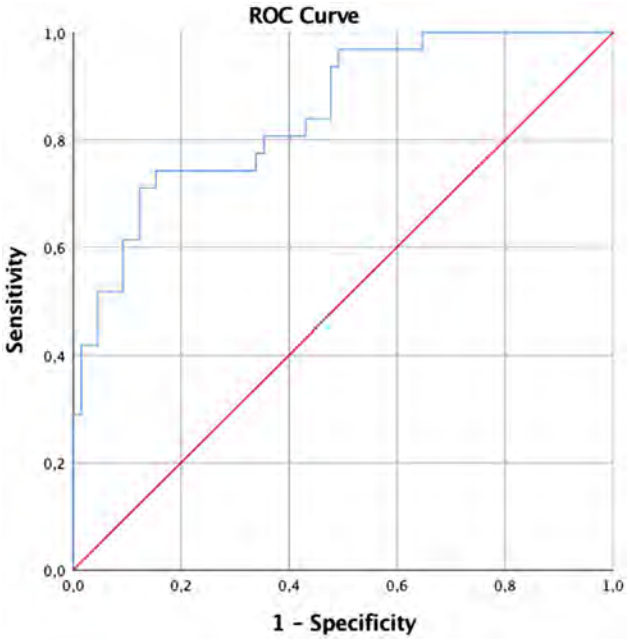
Background and aims: The European Guidelines advocate that, in cases of spontaneous bacterial peritonitis (SBP), another paracentesis should be performed to confirm the response to antibiotic therapy. Recent studies suggest that follow-up paracentesis, should only be performed if there is a clinical and/or analytic worsening. Our aims were to evaluate which patients with SBP benefit from the diagnostic follow-up paracentesis, according to clinical and analytical predictive factors of an inadequate response at the third day of treatment.

Method: Retrospective study conducted in a tertiary center, included the patients with SBP between January 2011 and June 2018. Clinical and analytical data was obtained at baseline and at the third day of antibiotic therapy. An adequate response to therapy, at the third day, was defined by a decrease of ≥ 25% in neutrophil count of the ascitic fluid.

Results: We included 103 cases of SBP (mean age of 61 ± 11 years; 78.6% men). Most patients (81.6%) had known ascites and 27.2% had a history of previous SBP. In 30.1% of cases the patients were under antibiotic prophylaxis for SBP. At the third day, 30.1% had an inadequate response to antibiotic therapy. At admission, the presence of diabetes mellitus (p = 0.034), a higher serum neutrophils count (p = 0.043), a lesser level of serum total proteins (p = 0.040) and a positive culture in ascitic fluid (p < 0.001) were related to inadequate response. At day 3, a higher level of serum urea (p = 0.018), creatinine (p = 0.030), CRP (p = 0.001), a higher count of serum leucocytes (p = 0.001) and neutrophyles (p = 0.001), the presence of fever (p = 0.047) and abdominal pain (p < 0.001) were associated to absence of response, too.

In the multivariate analysis, diabetes mellitus (OR = 5.33; 95% CI:1.24-22.96), positive ascitic fluid culture at admission (OR = 15.66; 95% CI:2.41-101.94), abdominal pain at day 3 (OR = 3.94; 95% CI:0.94-16.45; p < 0.06) and CRP at day 3 (OR = 1.02; 95% CI:1.00-1.03) were independently and significantly associated to inadequate response at the third day of empiric therapy. The predictive model presented good accuracy [AUROC of 0.85 (p < 0.001) (Fig. 1)]-a cutoff of 0.055 had a sensitivity, specificity, positive predictive value, and negative predictive value for absence of response to antibiotic of 100%, 35%, 42%, and 100%, respectively. With this model cutoff, 24% of repeated paracentesis could be precluded in our population sample.



Conclusion: These results evidence that, in approach of SBP, the performance of follow-up paracentesis, three days after the beginning of empiric therapy, should be individualized, according the conjugation of clinical and analytic variables. With our model a considerable number of unnecessary procedures may be avoided.

SAT-110

Impact of rifaximin monotherapy or rifamixin plus lactulose on markers of inflammation in patients with cirrhosis and a history of hepatic encephalopathy

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Background and aims: Systemic inflammation plays an important role in hepatic encephalopathy (HE) pathogenesis. Rifaximin, a nonsystemic antibiotic, may be used alone or in combination with lactulose for reducing the risk of overt HE recurrence in adults. This analysis evaluated impact of rifaximin alone or rifaximin plus lactulose (combo) on inflammatory markers in patients with history of overt HE.

Table: Median Inflammatory Marker Levels[a]

	Rifaximin Alone (n = 113)	Rifaximin + Lactulose (n = 108)
CRP		
Bsl, mg/L	2.6	3.7
EOT, mg/L	3.1	4.5
% change	20.4	38.5
IL-1beta		
Bsl, ng/L	17.2	26.6
EOT, ng/L	36.6	55.2
% change	20.4	21.3
IL-2		
Bsl, ng/L	57.0	65.5
EOT, ng/L	87.8	89.0
% change	48.7	118.4
IL-6		
Bsl, ng/L	13.7	12.8
EOT, ng/L	18.0	17.1
% change	24.2	24.4
IL-12		
Bsl, ng/L	9.1	9.0
EOT, ng/L	13.7	10.7
% change	-31.0	15.4
IL-13		
Bsl, ng/L	54.5	50.8
EOT, ng/L	56.4	54.0
% change	-12.8	-17.2
TNF-alpha		
Bsl, ng/L	35.5	33.0
EOT, ng/L	37.2	37.9
% change	38.5	28.1
Endotoxin		
Bsl, EU/ml	1.8	1.4
EOT, EU/ml	2.2	1.8
% change	7.7	14.8

[a]Statistical comparisons for differences between baseline to EOT not available for within treatment groups. Between-group differences from baseline to EOT levels for the inflammatory markers were not statistically significant (mean data [not shown]; p > 0.05).

Method: In a randomized, open-label trial, adults with cirrhosis with history of ≥ 1 overt HE episode during previous 6 months, currently in HE remission (Conn score ≤ 1), received rifaximin 550 mg twice daily (BID) or rifaximin 550 mg BID plus lactulose (titrated to 2-3 soft stools/d) for 24 wks. Blood samples were collected at baseline (bsl) and wks 4, 8, 12, 16, 20, and 24/end of treatment (EOT). Serum inflammatory markers (C-reactive protein [CRP], interleukins [IL-1beta, IL-2, IL-6, IL-12, and IL-13], tumor necrosis factor (TNF)-alpha, and endotoxin) were analyzed using a particle-based cytometric bead array immunoassay.

Results: 221 patients received rifaximin alone (n = 113) or rifaximin plus lactulose (n = 108); mean age was 58.1 vs 58.8 years and mean bsl Model End Stage Liver Disease score was 11.9 vs 11.8. Median bsl inflammation marker levels were comparable for rifaximin alone vs combo groups (**Table**). When assessed q 4 wks, change from bsl in each marker level was minimal for 2 groups, and between group-differences were not significant with the exception of IL-2 levels at wk 12 (rifaximin alone vs combo mean change: –76.7 vs 596.7 ng/L; p = 0.04). Bsl to EOT in inflammatory marker levels for rifaximin alone vs combo were not significantly different between 2 treatment groups (**Table**).
Conclusion: Low levels of inflammatory markers and no significant differences between the rifaximin alone and rifaximin plus lactulose groups suggest that rifaximin with or without lactulose has no deleterious impact on systemic inflammatory markers; the benefits of rifaximin may be independent of the status of systemic inflammation in this population cohort.

SAT-111

Procalcitonin level is a prognostic marker in patients with liver cirrhosis

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Background and aims: Bacterial infection is one of the critical complications of liver cirrhosis as well as gastrointestinal (GI) bleeding and refractory ascites. It leads not only to decompensation of liver cirrhosis and acute on chronic liver failure but also to multiple organ failure. Procalcitonin (PCT), a protein secreted in response to bacterial infection, has been widely used as a diagnostic marker of bacterial infection. The aim of this study was to investigate the association between serum PCT level and the prognosis of patients with liver cirrhosis.
Method: A total of 236 hospitalized patients with liver cirrhosis were retrospectively enrolled. Serum PCT levels were measured on admission using the Elecsys BRAHMS ® PCT automated immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).
Results: Elevation of serum PCT level to ≥ 0.05 ng/ml was observed in 151 patients (64%) regardless of the focal bacterial infection. Serum PCT level showed significant differences according to the Child-Turcotte-Pugh (CTP) classification, cause of hospitalization, and etiology. Serum PCT level was significantly higher in the patient with CTP-C, admitted for refractory ascites, GI bleeding or infection, and with alcoholic liver cirrhosis. Next, we investigated prognostic factors by using the Cox proportional hazard model. During the median follow-up time of 2.1 years, the 3-year cumulative survival rate was 62.4%. In the multivariate analysis, serum PCT level (≥ 0.05 ng/ml) was an independent prognostic factor of liver cirrhosis (hazard ratio, 1.78; 95% confidence interval, 1.16-2.74; p = 0.009). The 3-year cumulative survival rates of the patients with normal and elevated serum PCT levels were 72.9% and 56.0%, respectively (p < 0.001). In the subgroup analyses, serum PCT level was significantly associated with the prognosis of the patients with liver cirrhosis who were stratified by age, CTP classification, and presence of liver cancer.
Conclusion: Elevation of serum PCT level was observed in patients with liver cirrhosis regardless of the presence of bacterial infections and was significantly associated with poor prognosis.

SAT-112

Each additional infection significantly increases mortality in patients with decompensated liver cirrhosis

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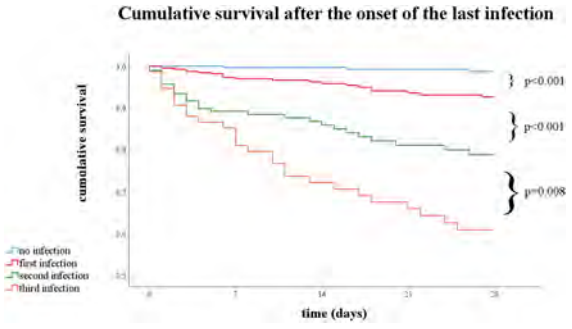
Background and aims: Bacterial infections are a hazardous complication in patients with liver cirrhosis. Mortality is four times increased. Moreover, patients with advanced liver cirrhosis suffer from an immune dysfunction that predisposes them for infectious complications. It is not uncommon that an individual patient develops several different infections during a single hospital stay. Here we aimed to investigate the impact of recurrent infectious episodes on mortality in patients with decompensated liver cirrhosis.
Method: Patients were recruited from the well-defined Hannover Ascites cohort. Overall, 669 consecutive patients with decompensated liver cirrhosis and ascites were eligible for the current analysis. Patients were followed up for the onset of bacterial or fungal infections from the time of hospital admission. Up to three infections were considered in each patient. 28-day mortality was calculated from the time of diagnosis of the last infectious episode. Multivariate Cox regression was performed including age, sex, MELD, platelets and the presence of esophageal varices to adjust for potential confounding factors.
Results: A number of 240 women (36%) and 429 men (64%) with a mean age of 56 years and median MELD of 17.5 were included. Only 224 (33%) individuals had no infection during the first 28 days of hospitalization. A single infection was diagnosed in 249 (37%) patients, 121 (18%) subjects developed a second infection and in 75 (11%) individuals at least a third infection was documented during follow-up. The most frequent infections were a spontaneous bacterial peritonitis and urinary tract infections. More than half of the patients (73%) developed the first infection within the first week after hospital admission. Following infections usually occurred shortly after the previous one (median 6-6.5 days). Each additional infection had a dramatic impact on mortality (Figure). The probability of a fatal outcome within the following 28 days increased significantly after each infection (first infection, Hazard Ratio; HR: 5.11; p = 0.009, second infection, HR: 20.90; p < 0.001; third infection, HR: 40.60; p < 0.001). In the multivariate analysis only MELD and the number of infections were associated with mortality.



Conclusion: In patients with decompensated liver cirrhosis mortality significantly increases after each additional infection. An adequate monitoring and preventive strategies are urgently required in this highly vulnerable group of patients.

SAT-113

Non-invasive assessment of HVPG with quantitative MRI measures of liver T1 and superior mesenteric artery velocity at 3T

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Background and aims: The majority of complications in liver cirrhosis arise from portal hypertension. Hepatic Venous Pressure Gradient (HVPG) is the gold standard measure, but is invasive and restricted to a small number of expert centres. We have previously validated MRI as a surrogate measure of HVPG at 1.5T using longitudinal relaxation (T_1) relaxation time and haemodynamic flow. Here, we evaluate quantitative MRI measures at 3T against HVPG in a new cohort.

Method: 43 patients were prospectively recruited (22NAFLD/11ALD/10other, aged 59 (27-83) years, 27 male) after undergoing a HVPG measurement for clinical indications. MRI was performed after a mean of 41 (SD 17) days on a 3 T Philips Ingenia DDAS scanner.

MRI Protocol: T_1 of the liver and spleen was measured with a respiratory triggered inversion recovery fat-suppressed spin-echo EPI scheme (9 axial slices, 10 inversion times 100-1500 ms, 58 ms temporal slice spacing, acquired in ascending/descending, acquisition time ~3 minutes). Phase-contrast (PC)-MRI was used to assess velocity, area and bulk flow in the superior mesenteric artery (SMA).

Data Analysis: T_1 data at each inversion time was motion corrected, and then fit on a voxel-by-voxel basis to generate M_0 and T_1 maps (MATLAB, Mathworks). Histogram analysis assessed the distribution of T_1 within the liver, with the mode of the distribution used to represent tissue T_1 and FWHM to assess heterogeneity. Q-flow software (Philips Medical Systems) was used to analyse the PC-MRI data to compute mean vessel cross sectional area, velocity, and flux over the cardiac cycle.

Statistical Analysis: All data was tested for normality using Shapiro-Wilk's, a Pearson correlation was used for normally distributed data and a Spearman correlation test used for non-parametric data.

Results: 28/43 patients had cirrhosis on biopsy. HVPGs ranged from 2-23 mmHg. 29 patients had HVPG ≥ 6 mmHg, 16 ≥ 10 mmHg and 10 had oesophageal varices. HVPG significantly correlated with SE-EPI T_1 ($R = 0.75$, $p < 0.0001$) and SMA velocity ($R = 0.70$, $p = 0.02$), Figure 1A/B. Splenic T_1 correlated with HVPG ≤ 10mmHg ($R = 0.63$, $p = 0.029$), >10mmHg no significance was observed ($R = 0.07$, $p = 0.868$), Figure 1C.

Conclusion: We have shown that 3T liver tissue T_1 and SMA mean velocity show good correlation with degree of portal hypertension and may be used as a surrogate for HVPG. Splenic Tissue T_1 has strong correlation for portal pressure ≤ 10mmHg but is not accurate in clinically significant portal hypertension.

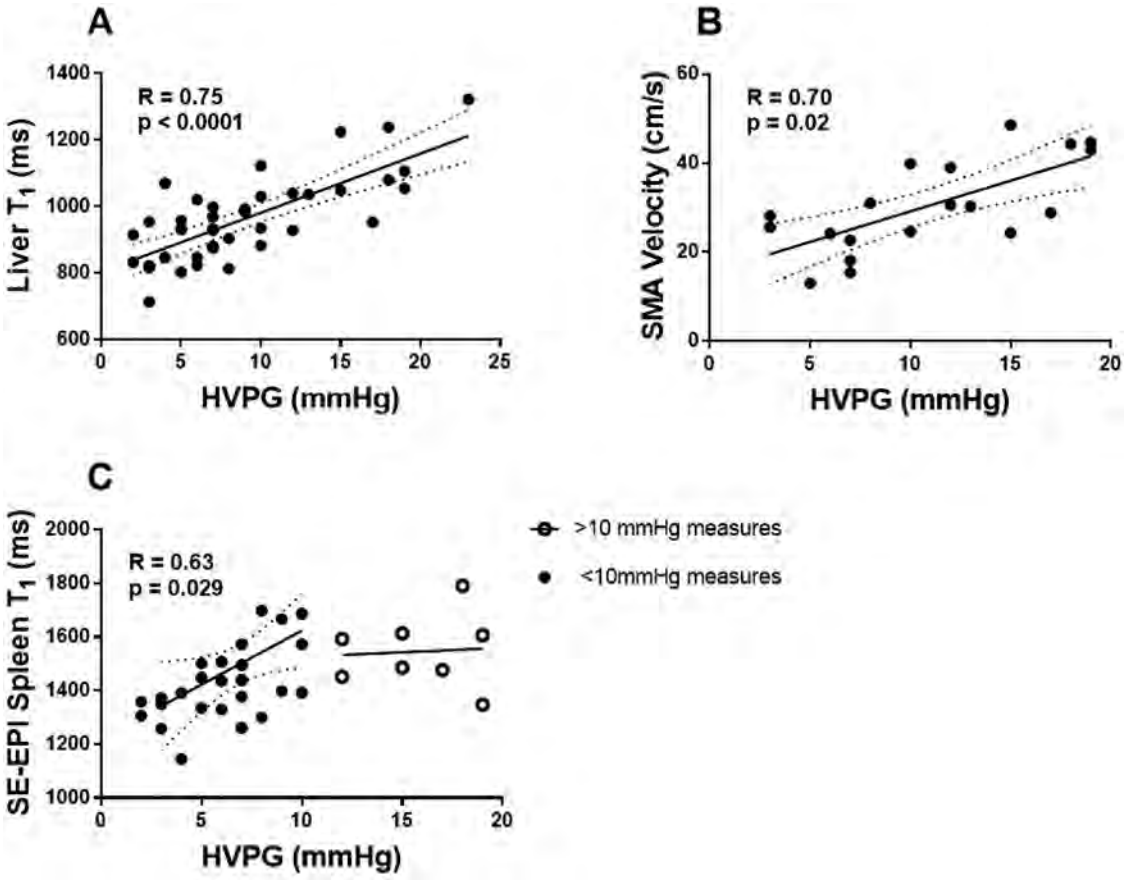

Figure: (abstract: SAT-113)

SAT-114

Impact of farnesoid X receptor polymorphisms on hepatic decompensation and mortality in cirrhotic patients with portal hypertension

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Background and aims: The nuclear farnesoid X receptor (FXR) regulates as key bile acid receptor critical pathways of metabolic and biliary homeostasis. FXR is involved in abnormal gut-liver axis signaling in advanced chronic liver disease (ACLD). However, the impact of FXR single nucleotide polymorphisms (SNPs) on portal hypertension-induced complications remains unknown. Thus, we investigated the association of FXR-SNPs with hepatic decompensation and transplant-free mortality in patients with portal hypertension.

Method: Two FXR-SNPs (*rs56163822* G > T, *rs35724* G > C) were genotyped in a cohort of 402 prospectively characterized patients with hepatic venous pressure gradient (HVPG) ≥ 6mmHg.

Results: While only 19 patients (4.7%) harbored a *rs56163822* T-allele, n = 267 (66.4%) patients had at least one minor *rs35724* allele (G/C or C/C). At the time of HVPG-measurement, *rs56163822* T-allele carriers had more pronounced liver disease (Child-Pugh-stage, CPS: 7 ± 2 vs. 6 ± 1 points; p = 0.034) and lower albumin levels (35.9 ± 5.9 vs. 38.9 ± 4.9 g/L; p = 0.026). In contrast, patients harboring at least one *rs35724* C-allele had less pronounced liver disease, as indicated by lower MELD (10 ± 3 vs. 11 ± 4 points, p = 0.016). Other baseline characteristics including the etiology of liver disease and HVPG were similar among FXR-SNP genotypes.

In CPS-A patients, the FXR *rs35724* minor allele was independently protective for the development of ascites (adjusted hazard ratio [aHR]: 0.411, 95% confidence interval (95%CI): 0.191-0.885, p = 0.023) and tended to reduce the risk of any hepatic decompensation (aHR: 0.625, 95%CI:0.374-1.044; p = 0.072) in multivariate analyses. Moreover, carrying the FXR *rs35724* minor allele was associated with reduced transplant-free mortality in CPS-A patients (aHR: 0.488, 95%CI: 0.252-0.946, p = 0.034) as well as in the overall cohort (aHR: 0.658, 95%CI: 0.434-0.998; p = 0.049).

In CPS-A patients, harboring the FXR *rs35724* minor allele tended to decrease transplant-free mortality in CPS-A patients (hazard ratio [HR]: 0.599, 95%CI: 0.319-1.127; p = 0.112; at 5 years: 82% vs. 69%). In female patients, this effect attained statistical significance (HR: 0.376, 95%CI: 0.148-0.959, p = 0.041; at 5 years: 83% vs. 56%).

Conclusion: The FXR *rs35724* C-allele seems to be protective for liver-related mortality in patients with ACLD. Prospective studies are needed to confirm the potential mechanism and independent prognostic value of the FXR *rs35724* genotype for hepatic decompensation and liver-related mortality.

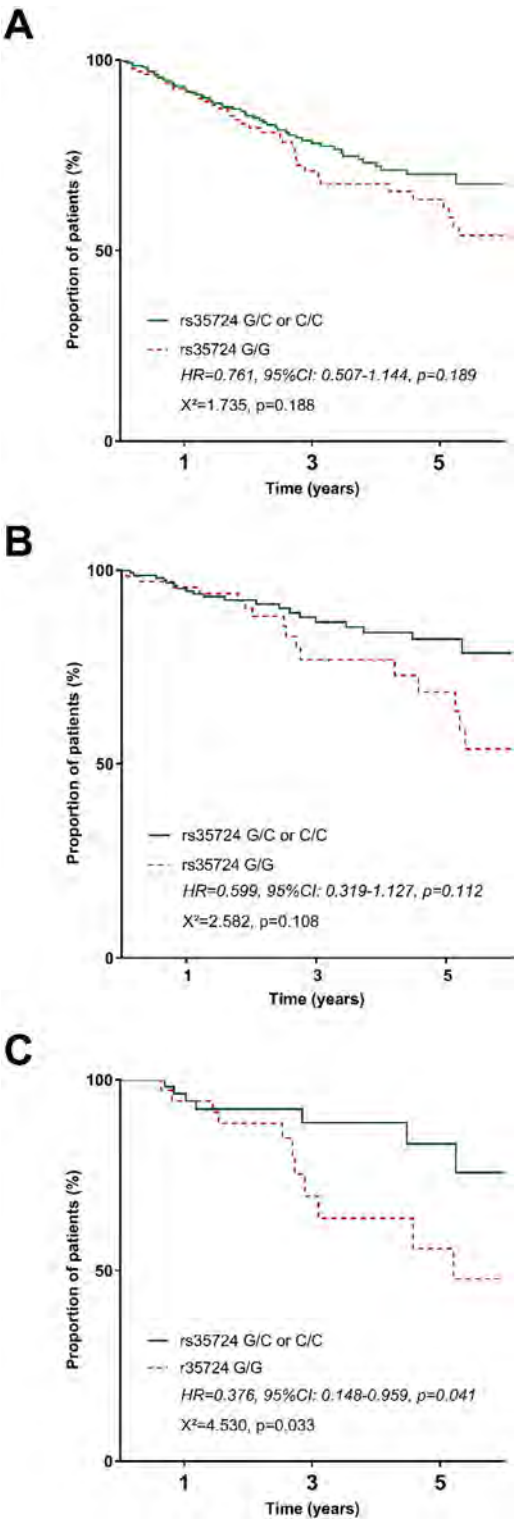

Figure: Kaplan-Meier analyses of transplant-free mortality in patients carrying FXR-SNP *rs35724* wildtype (G/G) or any minor alleles (G/C or C/C) in (**A**) the overall cohort, (**B**) compensated CPS-A patients and (**C**) female patients.

SAT-115

Fondaparinux vs low molecular weight heparin in the treatment of non malignant portal vein thrombosis in patients with cirrhosis

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Background and aims: Nonmalignant portal vein thrombosis (PVT) is a common complication of Cirrhosis. Treatment is advised in particular in liver transplant candidates with anticoagulation as first line option but the optimal anticoagulation's regimen and dose are still to be determined. Until now low molecular weight heparin (LMWH) or warfarin have been reported as treatments describing an efficacy of about 50%. Fondaparinux (FPX) is a factor Xa inhibitor which has been recommended for the treatment of deep vein thrombosis. In spite of its potential advantage due to the absence of induced thrombocytopenia, there are no data regarding the use of FPX in the treatment of nonmalignant PVT in patients with cirrhosis. The aim of our study was to compare FPX versus LMWH in terms of safety and efficacy in the treatment of PVT.
Method: Consecutive patients with non-malignant PVT treated with FPX or LMWH in university Hospital of Padua were retrospectively evaluated. The extension of PVT at baseline as well as its evolution on treatment were evaluated by both Doppler ultrasound and CT scan.
Results: 123 patients (69% male, mean age 59 ± 11 years) with cirrhosis and PVT were included. Main portal vein branch, splenic vein and mesenteric vein were involved in 84%, 13% and 36%, respectively. Forty patients (33%) were treated with FPX and eighty-two (67%) with LMWH. There was no difference between the 2 groups in terms of age, gender, CTP class, platelet count, extension of thrombosis and time occurred from diagnosis of PVT and the start of treatment. Patients treated with FPX had a significantly higher MELD-Na score than patients treated with LMWH (13 ± 4 vs 11 ± 3; p = 0.014). The probability of resolution of PVT at 36 months was significantly higher in patients treated with FPX than patients treated with LMWH (77% vs 51%; P = 0.002). When we adjusted the analysis for age, gender, severity, duration of PVT, and anticoagulant treatment dose (full dose vs prophylactic dose), the treatment with FPX was found to be an independent predictor of PVT resolution (HR = 0.45; P = 0.005) as well as a full anticoagulant dose (HR = 0.53; p = 0.026). There was no difference between the 2 groups in terms of incidence and severity of side effects and/or bleeding episodes. One patient treated with FPX and 3 patients in LMWH had a major bleeding episodes.
Conclusion: FPX seems to be more effective than LMWH in the treatment of PVT with a similar safety profile. Further studies should be performed to confirm these findings, in the meanwhile FPX can be considered among possible treatments of PVT.

SAT-116

Development and validation of a novel model for outcome in patients with cirrhosis and acute variceal bleeding

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Background and aims: Acute variceal bleeding (AVB) in patients with cirrhosis is associated with high mortality, ranging from 17% to 24% at 6 weeks. The existing prognostic models for AVB lack precision and require further validation. In this prospective study, we developed and validated a new prognostic model for AVB, and compared it with the existing models.
Method: We included 285 patients from March 2017-November 2017 in the derivation cohort and 238 patients from December 2017-June 2018 in the validation cohort. Two prognostic models were developed from derivation cohort by logistic regression analysis. Discrimination was assessed using area under receiver operator characteristic curve (AUROC).
Results: The six week mortality was 22.1% in derivation cohort and 22.3% in validation cohort, P = 0.866. Model for end stage liver disease (MELD) (odds ratio [OR], 1.106) and encephalopathy (E) (OR, 4.658) in one analysis and Child-Pugh score (OR, 1.379) and serum creatinine (OR, 1.474) in another analysis were significantly associated with 6-week mortality. MELD-E model (AUROC 0.792) was superior to Child-creatinine model (AUROC) in terms of discrimination. The MELD-E model had highest AUROC; as compared to other models- MELD score (AUROC 0.751, P = 0.036), Child-Pugh score (AUROC 0.737, P = 0.037), D'Amico model (AUROC 0.716, P = 0.014) and Augustin model (AUROC 0.739, P = 0.018) in derivation cohort. In validation cohort, the discriminatory performance of MELD-E model (AUROC 0.805) was higher as compared to other models including MELD score (AUROC 0.771, P = 0.048), Child-Pugh score (AUROC 0.746, P = 0.011), Augustin model (AUROC 0.753, P = 0.039) and D'Amico model (AUROC 0.736, P = 0.021).
Conclusion: In cirrhotic patients with AVB, the novel MELD-Encephalopathy model predicts 6 weeks mortality with higher accuracy than the existing prognostic models.

SAT-117

Enhanced liver fibrosis score is an accurate non-invasive predictor of clinically significant and high-risk portal hypertension

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Background and aims: Diagnosis of clinically significant portal hypertension (CSPH) depends on invasive measurement of hepatic venous pressure gradient (HVPG). Enhanced liver fibrosis (ELF) score was developed as a non-invasive test for liver fibrosis. Limited data on the correlation of ELF with portal pressure is available. Thus, we investigated (i) the correlation of ELF with HVPG, and the diagnostic accuracy of ELF for (ii) CSPH (i.e. HVPG ≥ 10mmHg) and (iii) high-risk portal hypertension (HRPH, i.e. HVPG ≥ 20mmHg).
Methods: ELF and HVPG were assessed within the prospective VICIS study. Patients with pre- or posthepatic portal hypertension, liver malignancy, previous transplantation, and non-cirrhotic portal hypertension were excluded.
Results: Among 187 patients (mean age 56.3 ± 0.9 years, 66.8% male), alcoholic liver disease (ALD, n = 63, 33.7%)) and viral hepatitis (n = 55, 29.4%) were the main etiologies. Child-Pugh stage (CPS) was CPS-A in 112 (59.9%), CPS-B in 52 (27.8%), and CPS-C in 23 (12.3%) cases.
Mean HVPG was 15.6 ± 0.5 mmHg, CSPH and HRPH were diagnosed in 146 (78.1%) and 57 (30.5%) patients. Median ELF was 11.2 (IQR 10.2-12.4) and 161 (86.1%) patients had ELF ≥ 9.8 indicating advanced fibrosis.
ELF significantly correlated with HVPG in the overall cohort (r = 0.485; p < 0.001). Area Under the Receiver Operating Characteristic Curve (AUROC) of ELF to detect CSPH was 0.76 in the overall cohort, while ELF-AUROC to diagnose CSPH was better in ALD (0.97) than in

patients with viral hepatitis (0.67). Importantly, CSPH could be ruled-out in ALD by ELF < 10.1 (sensitivity 96.6%) and in viral hepatitis by ELF < 9.0 (sensitivity 91.9%).
Among HCV patients who achieved SVR (n = 35), ELF was not able to identify patients with persistence of CSPH after SVR (AUROC: 0.69; p = 0.079).
ELF-AUROC for non-invasive diagnosis of HRPH was 0.73, while ELF-AUROC to diagnose HRPH was better in viral hepatitis (0.77) than in patients with ALD (0.66). HRPH could be ruled-in in ALD by ELF > 14.7 (specificity 97.0%) and in viral hepatitis by ELF > 12.7 (specificity 95.8%).
Conclusions: ELF correlates with HVPG and is an accurate non-invasive screening tool for CSPH in patients with advanced chronic liver disease of different etiologies. CSPH may be ruled-out in ALD patients by ELF < 10.1 and in viral hepatitis by ELF < 9.0. Importantly, ELF > 14.7 in ALD and ELF > 12.7 in viral hepatitis is highly suggestive of HRPH and may be used to triage patients to transjugular intrahepatic portosystemic shunt (TIPS).

SAT-118

Estimating proportion of cirrhosis and hepatocellular carcinoma attributable to hepatitis B and C in clinical centres in Sofia (Bulgaria) and Lisbon (Portugal): Results from a European pilot

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Background and aims: WHO set target to reduce mortality attributable to hepatitis B (HBV) and hepatitis C (HCV) by 65% by 2030. While national mortality data from cirrhosis (CIR) and hepatocellular carcinoma (HCC) exist, proportion of cases due to HBV and/or HCV are unknown. A study protocol was developed to calculate the attributable fraction of HBV, HCV and other risk factors for CIR and HCC in a standardised way and piloted in Sofia (Bulgaria) and Lisbon (Portugal).
Method: All patients presenting with CIR and/or HCC at the national reference centre in Sofia during 2016-2017 and the first 100 sequential patients with CIR and 100 with HCC presenting at national reference centre in Lisbon during 2015-2016 were included. Cases with CIR and HCC were identified based on ICD-10 codes in Sofia and on clinical criteria in Lisbon. Patients diagnosed with both CIR and HCC were classified as HCC. HBsAg and anti-HCV positivity were considered markers for chronic HBV and HCV, respectively. When markers for both HBV and HCV were present, HCV-RNA existence defined the case as being attributable to HCV. When viral markers were absent, excessive alcohol consumption (> 30 grs/day) or non-alcoholic-fatty liver disease (NAFLD) were considered main risk factors for CIR or HCC.
Results: Data for 518 CIR, 84 HCC cases were collected in Sofia and 100 CIR and 100 HCC in Lisbon. 70% of CIR and 80% of HCC cases in Sofia and 78% of CIR and 82% of HCC in Lisbon were males. 38% of CIR, 68% of HCC in Sofia and 53% of CIR and 71% of CIR in Lisbon were ≥ 60 years. In both sites, distribution of CIR and HCC cases did not differ by gender ($p_{Sofia} = 0.07$, $p_{Lisbon} = 0.48$) but patients with HCC were significantly older ($p_{Sofia} = 0.00$, $p_{Lisbon} = 0.03$). In Sofia the main risk factors for CIR were: alcohol 46%, HBV 18%, HCV 16% and NAFLD 4% and for HCC: HBV 37%, HCV 25%, alcohol 8%, NAFLD 8%. In Lisbon main risk factors for CIR were: alcohol 56%, HCV 25%, HBV 6%, NAFLD 6% and for HCC: alcohol 46%, HCV 37%, HBV 9%, NAFLD 3%. Considerable overlap between risk factors was observed (Fig1).
Conclusion: Viral hepatitis B and C were important risk factors for liver morbidity in both centres. The pilot demonstrated the feasibility of collecting data on viral hepatitis prevalence that can be used to estimate mortality attributable to HBV and HCV for monitoring elimination. Further consideration should be given to representativeness of samples collected from reference centres, assessment of cases with overlapping risk factors, data collection simplification.

Figure 1. Overlap of positivity for HBsAg,antiHCV and excessive alcohol consumption among cirrhosis and hepatocellular carcinoma cases included in the pilot

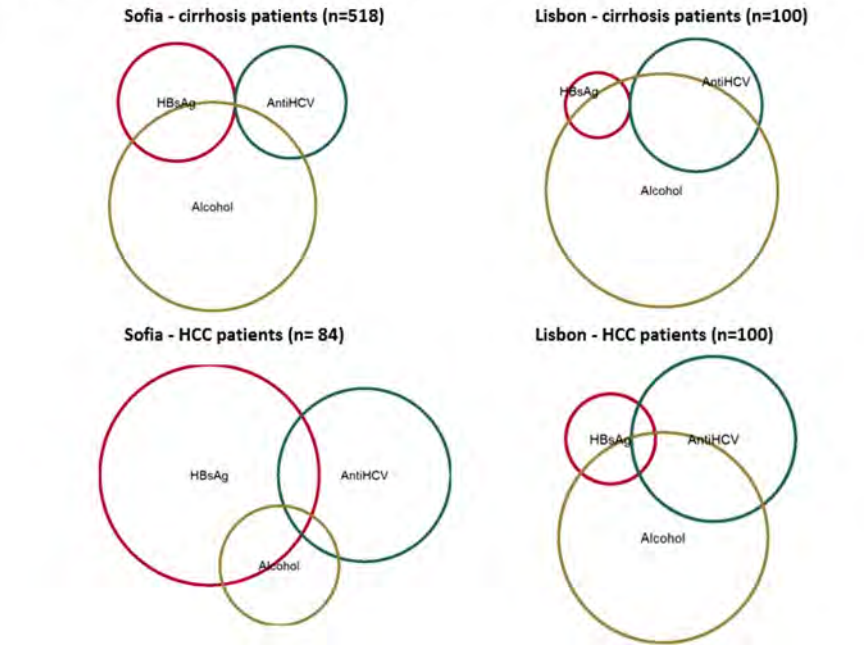

Figure 1: (abstract: SAT-118)

SAT-119

Comparison of liver frailty index at admission and 30 days after discharge from hospital in patients with advanced chronic liver disease

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Background and aims: Liver frailty index (LFI)-objective, reproducible and easy-to-use diagnostic tool for frailty, has been shown to predict (independently of MELD) outcome in outpts awaiting liver transplantation (LTx), and admitted to hospital with ACLD. To date, evolution of LFI after discharge from hospital has not been studied.
Aim: To determine LFI 1 month (M) after discharge in pts admitted to hospital with ACLD.
Method: Frailty-HEGITO-7 is a prospective observational study at the Liver Unit with small-volume LTx program. *Inclusion interval:* June 2017-February 2018. *Inclusion criteria:* admission with ACLD; age > 18y. *Exclusion criteria:* Extrahepatic malignancy, HCC > Milan, LTx or death or lost to follow-up (LFU) < 1M after discharge. Apart from standard evaluations for ACLD, all pts underwent testing for frailty by measuring LFI using internet calculator[3] at admission (LFI-A) and M1 after discharge (LFI-M1); their difference (ΔLFI-M1). At discharge, all pts received structured verbal and written (graphical) nutritional and exercise counselling by dedicated nurse.
Results: Enrolled and measured for baseline LFI were 200 pts, excluded 111 (due to: in-hospital and 1M mortality 14 and 24, LTx < M1 3, and LFU 70, respectively). Of 99 analyzed pts **at baseline**, median age was 58.9 years, females 33%, alcoholic liver disease 77%, MELD 14.5, **LFI 4.25, 34.7% were frail**. **At M1,** MELD was 14.7 (ns), **LFI 4.3 (ns), 24.5% were frail** (p = 0.06). Median **ΔLFI-M1** was –0.7% (p = 0.1). At M1, of 32 frail pts at baseline 15 (48.5%) improved to pre-frail, 17 stayed frail; of 63 prefrail pts at baseline 6 (9.7%) worsened to frail and 57 stayed prefrail; of 4 robust, 1 stayed, 2 became prefrail and 1 frail. Overall, of patients surviving 30 days 16% improved, 13% worsened, and 76% did not change their frailty status, respectively.
Conclusion: One month after discharge from hospital with lifestyle counselling, one in four pts changed frailty status-62.5% (15/24) for the better; LFI improved (albeit not significantly). This pilot study shows that frailty can be improved. Predictive factors, measures needed and prognostic impact of change in frailty status deserve further study.

SAT-120

Influence of previous acute decompensation and organ failure on the long-term prognosis in cirrhotic patients with decompensation

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Background and aims: To investigate long-term mortality according to the experience and time of previous acute decompensation (AD) and severity of organ failure in cirrhotic patients with AD
Method: A total of 1252 cirrhotic patients (male 943, alcohol 808, mean age 56.2 years) with AD were prospectively followed up. AD was defined as: acute development of overt ascites, hepatic encephalopathy, gastrointestinal bleeding, and infection. Organ failure was defined according to the chronic liver failure-sequential organ failure assessment (CLIF-SOFA). We determined subgroups using CLIF-SOFA scores as follows: high CLIF-SOFA (≧7) and low CLIF-SOFA (< 7).
Results: During follow-up duration (14.9 ± 10.6 months), long-term survival rate in the high CLIF-SOFA were significantly lower than those in the low CLIF-SOFA (149/319 vs 725/933, P < 0.001). Also, in 1009 patients who survived from for more than 3 months following AD (long-term survivors), the difference in long-term survival rates between groups was significant (p < 0.001). The presence of previous AD negatively affected long-term survival in two groups (low CLIF-SOFA, 82.6% vs 73.0%, P < 0.001; high CLIF-SOFA, 54.6% vs 40.4%, P = 0.041), and these findings also showed significant difference in long-term survivors (low CLIF-SOFA, 85.1% vs 75.1%, P < 0.001; high CLIF-SOFA, 80.5% vs 64.0%, P = 0.004). In total patients, patients with AD within 1 year showed a significantly lower survival rates than those without AD and with AD more than 1 year prior, although no significant difference was seen between patients with AD more than 1 year prior and without AD in two groups (low CLIF-SOFA, 82.6%, 79.0%, 65.9%, P < 0.001; high CLIF-SOFA, 54.6%, 50.7%, 33.0%, P = 0.003). However, in long-term survivors with high CLIF-SOFA, patients with AD within 1 year and with AD more than 1 year prior showed a significantly lower survival rates than those without AD (60.0% and 67.3% vs 80.5%, P = 0.004 vs P = 0.021, respectively)
Conclusion: Long-term prognosis was related to the degree of organ failure and previous AD. Especially, in long-term survivors with AD, previous AD was associated with high mortality regardless of the time of previous AD. It is necessary to decide the proper treatment policy.

SAT-121

Predicting sarcopenia in patients with cirrhosis based on clinical and laboratory parameters using machine learning

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Background and aims: In patients with cirrhosis, sarcopenia is associated with further complications and a reduced probability of survival. Gold standard for the diagnosis of sarcopenia is cross-sectional muscularity analysis. However, this requires access to CT or MR imaging technology, a specialized image analysis software and trained staff. The aim of this study was to develop a machine learning (ML) tool to identify patients with cirrhosis who are at risk for sarcopenia prior to radiological work-up.
Method: For the development of the ML tool, we used data of patients with cirrhosis who were assessed for liver transplantation between 2000 and 2014 in a tertiary care University Centre. As part of the transplant assessment, each patient had a routine CT analysis to assess muscularity at the level L3 with SliceOmatic V4.3 (Tomovision, Canada). Within the database, patients are described using the following features: age, aetiology of liver cirrhosis, hepatic encephalopathy (HE), BMI, albumin, bilirubin, INR, WBC, platelets, neutrophils, lymphocytes, platelets-lymphocytes-ratio (PLR), neutrophils-lymphocytes-ratio (NLR), C-reactive protein (CRP), ferritin, testosterone, triglycerides, homocysteine and vitamin D. Features were tested for log-normality and transformed if suitable. We considered various different ML algorithms and evaluated each using 5-fold cross-validation.
Results: Overall, 603 patients were included in this analysis (68% male; mean age 57 ± 8 [SD] years). Our cross-sectional image analysis

found 201 patients were sarcopenic (76% male), and 402 (63% male) were not. Aetiology of liver disease was hepatitis C (40%), followed by NASH (23%), alcohol (22%), autoimmune liver disease (8%) and hepatitis B (6%). Mean MELD score was 14.3 ± 7.7 (SD). The ML model was developed using the following features: BMI, gender, HE, alcoholic liver disease, PLR, NLR and CRP. A logistic regression model with cost-sensitive training (weight 1 for non-sarcopenic patients, weight 2.5 for sarcopenic patients) was identified as the best tool to predict sarcopenia in this patient population. The AUC of the model was 0.772 (95% CI 0.760-0.784), resulting in a sensitivity of 79.6% (95% CI 77.0-82.2) and a specificity of 66.2% (95% CI 61.9-70.5) for sarcopenia detection.
Conclusion: A ML classifier can accurately identify whether patients with cirrhosis have sarcopenia, based only on standard and easily accessible clinical and laboratory features.

SAT-122
Cirrhotic cardiomyopathy: An observational study pre-liver transplant
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Background and aims: Cirrhotic cardiomyopathy (CCM) is a form of cardiac dysfunction observed in patients with liver cirrhosis and can arise at any cirrhosis stage. However we still lack data on the prevalence of the problem and its implications pre and post-liver transplant. We conducted a retrospective analytical observational study at a regional pre-transplant assessment centre to explore the burden of disease in our population.
Methods: We reviewed patient records, transthoracic echocardiography results (ECHO), and cardiopulmonary exercise test (CPET) results of all patients who underwent liver transplant for chronic liver disease between 2014–2017. Cirrhotic cardiomyopathy was defined as systolic dysfunction or impaired diastolic relaxation using both Montreal criteria (2005) and British Society of Echocardiography (Echo) guidelines and correlated to CPET findings. Data was collected and analysed by using a tabulated database (Microsoft Excel 14.7.7) and SPSS.
Results: A total of 81 patients were identified (51 male). Mean age was 56 years (median 58, range 23-70). The commonest aetiologies were alcoholic liver disease (27%), HCV with or without HCC (20%) and NASH with or without HCC (15%). On Echo criteria evidence of cirrhotic cardiomyopathy was identified in 34 (42%) patients, including diastolic dysfunction (DDF) in 32 and reduced resting ejection fraction in 2. Other findings included isolated dilated left atrium in 9 (11%), isolated dilated left ventricle in 7 (8%) and intra pulmonary shunting in 4 (5%) patients. All patients underwent CPET with median V02 max of 17.8 (range 8.6-32) and anaerobic threshold (AT) median of 11.3 (range 6.4-21.1). In those with cirrhotic cardiomyopathy the VO2 max and AT were lower than in those without, (median 16 vs 18.5 ($p < 0.01$) and median 11 vs 12 ($p < 0.01$) respectively). We found no significant correlation between severity of liver disease (Child Pugh, MELD) and presence of cirrhotic cardiomyopathy.
Conclusions: Our study demonstrated that a significant proportion of transplanted patients have evidence of cirrhotic cardiomyopathy as assessed by echo. Cirrhotic cardiomyopathy was associated with impaired performance on CPET. This lends further support to the need for detailed study of the impact of cirrhotic cardiomyopathy on patient outcomes, both pre- and post- liver transplant. We also plan to undertake careful repeat analysis (ECHO) of patients post-liver transplant to assess for improvement in this common problem.

SAT-123
Serum Mac-2 binding protein glycosylation isomer and handgrip strength correlate with serum myostatin level in chronic liver disease
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Background and aims: Myostatin belongs to transforming growth factor β (TGF-β) family which has been reported as a key mediator of fibrosis in several organs, and negatively works for differentiation of skeletal muscle cells. In vivo, TGF-β/Myostatin pathway activity associated with muscle fibrosis and atrophy. Furthermore, recent study showed higher myostatin level in liver cirrhosis associated with unfavorable outcome, however, the precise mechanism between high myostatin level and poor prognosis in chronic liver disease is still unknown. The aim of our study is to elucidate the correlation between serum myostatin level and clinical parameters, especially Serum Mac-2 binding protein glycosylation isomer (M2BPGi) which we reported as predictor of liver fibrosis and hepatocellular carcinoma in previous study.
Method: This study was approved by Clinical Research committee in our hospital. 162 patients with chronic liver disease and 20 healthy control were enrolled, and serum myostatin level was calculated by ELISA method (GDF-8/Myostatin Quintikine® ELISA kit). We measured handgrip strength which has been reported to correlate with skeletal muscle function.
Results: 91 female patients and 71 male patients were included with a median age of 66 years. 53 patients were diagnosed liver cirrhosis. Serum myostatin level was 4780 pg/ml (1306-24815) in patient group, 4329 pg/ml (2438-16952) in healthy control group, respectively ($p = 0.2987$). For the female patients serum myostatin level was 4663 pg/ml (1306-22330), on the other hand, 4943 pg/ml (2188-24815) for male patients ($p = 0.9129$).The median myostatin level for Child grade B or C patients ($n = 17$) was 17213 pg/ml (3504-24815), for Child grade A patients ($n = 145$) was 4628 pg/ml (1306-18939) ($p = 0.0041$). Serum myostatin level significantly correlated with body mass index ($r = 0.1845$, $P = 0.0188$), albumin ($r = -0.432$, $P < 0.0001$), prothrombin time ($r = -0.4533$, $P < 0.0001$), total bilirubin ($r = 0.4243$, $P < 0.0001$), platelets ($r = -0.3461$, $P < 0.0001$), Child Pugh score ($r = 0.5464$, $P < 0.0001$), and M2BPGi ($r = 0.615$, $P < 0.0001$). In addition, handgrip strength significantly negatively correlated with myostatin level in female patients ($r = -0.218$, $P = 0.036$). Multiple regression analysis in patients revealed handgrip strength ($p = 0.0187$), body mass index ($p = 0.0265$), Child Pugh score ($p = 0.0281$), and M2BPGi ($p = 0.0019$) were independent factors associated with serum myostatin level.
Conclusion: Increased serum myostatin level reflected deteriorated liver function in previous report, and our study revealed similar results in the relationship between myostatin level and liver function. In addition, we presented M2BPGi and handgrip strength significantly correlated with myostatin level. These interesting results imply high myostatin level in liver disease mirror sarcopenia, severe liver fibrosis and potential of hepatocarcinogenesis.

SAT-124
Microbiological culture yield from ascitic fluid and changing antimicrobial sensitivities over time
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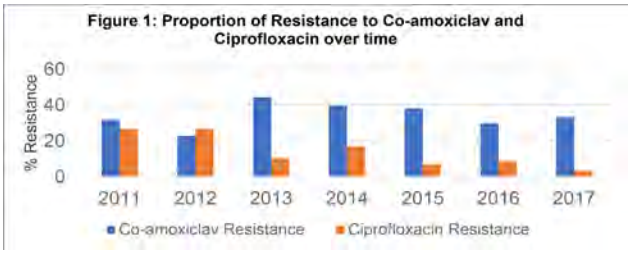
Background and aims: Diagnostic paracentesis is recommended for all ascitic patients to diagnose spontaneous bacterial peritonitis

(SBP). The majority of ascitic fluid cultures do not grow an organism although yield may be improved by inoculating blood culture bottles. Therefore empirical treatment based on fluid white cell count (WCC) is recommended but bacterial resistance to first line antibiotics is a concern. Our aim was to investigate the causative organisms in patients with SBP and antibiotic resistance in our region over a period of seven years.

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. These data were combined with an existing database on samples from North Glasgow from January 2011 to December 2013. Data on organisms cultured and proportions of antibiotic resistance when tested were collated and analysed.

Results: In total 9790 ascitic fluid samples were identified. Organisms were cultured in 1249 samples, 302 were identified as commensals leaving 947 of all samples (9.6%) with potentially pathogenic organisms. In those samples where WCC was available, WCC > 250/mm^3 had a sensitivity of 0.5 and specificity of 0.91 for culture positive ascites, whereas WCC > 500/mm^3 gave a sensitivity of 0.41 and specificity of 0.95. The most common pathogens cultured were Gram Negative Bacilli (52.4%; mainly Escherichia coli) followed by Entercoccus sp (12.3%), Streptococcus sp (10.7%) and Staphylococcus sp (8.3%). Resistance to co-amoxiclav was 34.5% (26% for gram negatives), ciprofloxacin 12.4% (12%), Tazocin 8, 2 (8.4%) Amoxicillin and Temocillin 6.4% (3.6%). Co-amoxiclav resistant organisms were also resistant to Tazocin in 24.4%, Ciprofloxacin in 18.9% and Temocillin in 7.8% of cases. Bacterial sensitivities over time are shown (Figure 1).



Conclusion: Only a minority of ascitic fluid samples will culture pathogens. Fluid WCC has high specificity but low sensitivity for pathogenic bacterial culture. Gram Negative Bacilli remain the most common organisms cultured. These show substantial rates of Co-Amoxiclav resistance, consistent over the 7 year period. However, a combination of Amoxicillin and Temocillin has relatively little resistance. Increasing sensitivity to quinolone antibiotics suggest antibiotic stewardship policies may be effective in reducing prevalence of resistant bacteria.

SAT-125

Animal naming test is simple and reliable for diagnosis of minimal hepatic encephalopathy and prediction of development of overt hepatic encephalopathy in patients with cirrhosis

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Background and aims: Minimal hepatic encephalopathy (MHE) is the mildest form in the spectrum of hepatic encephalopathy that impairs health-related quality of life. PHES remains the gold standard for the diagnosis of this condition. Animal naming test (ANT) is reliable and sensitive tool for diagnosis of MHE and can also predict overt episodes of HE. We compared usefulness of PHES and ANT for the diagnosis of MHE and for the prediction of the development of overt episodes of HE.

Method: Between July 2017 to June 2018, one hundred and three consecutive patients with liver cirrhosis without overt HE were subjected to PHES and ANT evaluation. MHE was diagnosed when the PHES was ≤ -5. Receiver-operating characteristic (ROC) curve was used to determine the optimum cut-off of ANT value for the diagnosis of MHE. The best sensitivity and specificity was found at < 14. Patients were followed-up every 3-6 months till October 2018.

Results: Thirty-seven (35.9%) patients had MHE as assessed by altered PHES. ANT (< 14) was present in 36 (34.95%) patients with MHE with sensitivity of 89.19% and specificity of 95.7%, PPV of 91.67%, NPV of 94.03% and diagnostic accuracy of 93.20%. The area under the curve for diagnosis of MHE was 0.978 (95% CI 0.954-1.0). MHE patients had significantly lower ANT as compared to non MHE patients and controls (10.81 ± 0.324 vs 15.27 ± 0.147 vs 15.78 ± 0.192, respectively, $P = 0.01$). MHE patients had lower hand grip strength compared to non-MHE patients and the control group (Males: 26 vs 30 vs 38, Females 25 vs 28 vs 28, p > 0.05). PHES significantly correlated with Child-Pugh (r = -0.421, $P = 0.001$) and model for end-stage liver disease (MELD) (r = -0.345, P = 0.001) scores. ANT correlated with PHES (r = 0.752, P = 0.001) and also with Child-Pugh (r = -0.408, P = 0.001) and MELD (r = -0.318, P = 0.001) scores. During follow-up, 14 patients in MHE group and 4 in non-MHE group developed overt episodes of HE (p = 0.001). Out of 37 patients with abnormal PHES 14 patients developed overt HE on follow-up and out of 36 patients with abnormal ANT 14 patients developed overt HE on follow-up. 33 patients had both PHES and ANT abnormal. 4 patients had PHES abnormal and ANT normal. 3 patients had PHES normal and ANT abnormal.

Conclusion: ANT is a simple and reliable test for the diagnosis of MHE and prediction of overt episodes of HE in patients of cirrhosis as compared to PHES and correlates well with the Child-Pugh and MELD scores.

SAT-126

Minimal hepatic encephalopathy: Proper diagnosis for a better quality of life

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Background and aims: Minimal hepatic encephalopathy (MHE), may affect up to 80% of cirrhotic patients. Despite the limitations in relation with age and education, currently, MHE is diagnosed using psychometric tests. Other diagnostic tools, as Critical Flicker Frequency (CFF) and STROOP test are promising alternatives to the psychometric tests but lack extensive validation. The aim of this study was to compare CFF with STROOP test in diagnosing MHE and to assess the impact of MHE on the quality of life of patients with liver cirrhosis.

Method: 85 consecutive cirrhotic patients admitted to our centre were included. None of the patients showed clinical signs of overt hepatic encephalopathy at examination. All subjects underwent a battery of five psychometric tests, CFF, STROOP and the chronic liver disease questionnaire (CLDQ). Performances of the diagnostic tests were measured calculating the ROC curves. The diagnosis of MHE was established with PHES score using the Spanish norms (http://www.redeh.org/phesapp/datosE.html). The CLDQ assessed 6 domains and

the overall QoL of the patients with a score ranging from 1 (very poor) to 7 (very good).
Results: Out of the 85 cirrhotic patients, 52 (61.2%) were compensated without any previous decompensation (subgroup 1) and 33 (38.8%) with previous or present decompensation, evaluated for TIPS insertion (subgroup 2). Twenty-nine (34.1%) patients presented MHE, of whom 15 (28.8%) in subgroup 1 and 14 (48.3%) in subgroup 2. Overall Stroop test has AUROC of 0.76 (95%CI: 0.65-0.86) ($p < 0.001$) and for CFF of 0.59 (95%CI: 0.45-0.72), $p = 0.2$. Stroop test has the best performance in subgroup 1 achieving 0.87 (95%CI: 0.77-0.96), $p < 0.001$ and the best cut-off value of 240 seconds (Se = 92.3%; Sp = 77.8%). Patients with MHE in comparison with those without MHE had significantly lower CLDQ in the overall score [4.55 (3.55-5.34) vs. 5.24 (4.79-5.93), respectively, $p < 0.01$] and in the following domains: abdominal symptoms [4.33 (2.67-6.67) vs. 6.00 (4.33-6.67), respectively p < 0, 05], systemic symptoms [4.20 (3.80-5.80) vs. 5.40 (4.40-6.00), respectively $p < 0.05$] and activity [4.00 (3.00-6.00) vs 5.67 (4.67-6.67), respectively $p < 0.01$].
Conclusion: Stroop test is superior to CFF in diagnosing MHE in compensated patients with liver cirrhosis. Patients with MHE experience a decrease in the quality of life, signalling the need of proper diagnosis and treatment of this condition.

SAT-127

The clinical course of recurrent versus refractory ascites in outpatients with cirrhosis

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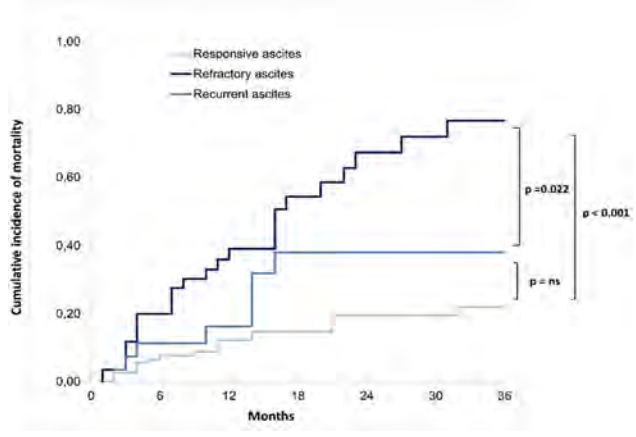
Background and aims: Refractory ascites has been defined by the International Club of Ascites (ICA) as an ascites that recurs early (within 4 weeks) after large volume paracentesis (LVP) and that cannot be prevented by medical therapy. Refractory ascites has a well known negative impact on mid-term survival. Recurrent ascites was defined by the ICA as an ascites that recurs at least 3 times within 12-month. However, its impact on survival is still unknown. The aim of the study was to assess the mid term-survival in outpatients with refractory, recurrent or responsive ascites.



Method: 199 consecutive patients with ascites attending our outpatient clinic from March 2008 were included in the study. Refractory ascites was defined according to the ICA criteria. For the purpose of the study, recurrent ascites was defined as above plus the need of at least 3 LVPs within 12 months with a time interval between LVPs > 4 weeks. Patients without refractory or recurrent ascites where defined as patients with responsive ascites. Clinical and laboratory data were collected at inclusion in the study. Patients were followed up until death, liver transplant (LT) or 36 months. LT was considered a competing event for mortality.
Results: Refractory ascites, recurrent ascites and responsive ascites were found in 56 (28%), 28 (14%) and 115 (58%) patients, respectively. No difference was found in MELD score among the 3 groups. During the 36-month follow-up, 52 patients died and 28 were transplanted. The 36-month cumulative incidence of mortality was significantly higher in patients with refractory ascites than in those with recurrent or responsive ascites (76.7%, 38.1% and 22%, respectively; $p < 0.001$ for the comparison between refractory and responsive ascites and $p = 0.02$ for the comparison between refractory and recurrent ascites), while no significant difference was found between those with recurrent ascites and those with responsive ascites. In multivariate analysis, age (sHR = 1.07; $p < 0.001$), MELD score (sHR = 1.17; $p < 0.001$) and refractory ascites (sHR = 3.88; $p < 0.001$) were found to be independent predictors of 36-month mortality.
Conclusion: Patients with refractory ascites have a significant worse prognosis than those with recurrent ascites, which in turns had similar outcomes than those with responsive ascites. These findings have relevant implications in clinical practice, when patients with ascites are considered for invasive procedures for the management of ascites, such as TIPS, or evaluated for priority in the LT waiting list.

SAT-128

The natural history of acute kidney disease in patients with cirrhosis

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Background and aims: The International Club of Ascites (ICA) in its consensus document has adapted the KDIGO criteria for the diagnosis of Acute kidney Injury (AKI) in patients with cirrhosis. AKI was defined as an absolute increase in serum creatinine (sCr) $\geq$ 0.3 mg/dl in 48 hours or an increase of sCr $\geq$ 50% during the last 3 months. As a consequence, the KDIGO criteria for the diagnosis of AKD should be also adapted in these patients by considering only: a) a Glomerular Filtration Rate (GFR) < 60 ml/min or b) a decrease of GFR $\geq$ 35% for less than 3 months. While it is well proven that AKD has an impact on mortality in the general population, there are no data in cirrhotic patients. The aim of the study was to assess the prevalence, the clinical course of AKD and its impact on mortality in patients with cirrhosis.
Method: 324 consecutive patients were included in the study. AKI and AKD were diagnosed according to ICA guidelines while Chronic Kidney disease (CKD) was defined according to KDIGO definition (a GFR < 60 ml/min for $\geq$ 3 months). Clinical and laboratory data were collected at inclusion in the study. Patients were followed up until death, liver transplant or for a maximum period of 5 years.
Results: At inclusion, 53 patients (16.2%) had already developed CKD. During the follow-up, 113 patients (34.9%) developed AKD, 15 among those with previous CKD and 98 among those with normal GFR. AKI preceded AKD in 21.2% of the cases. Twenty-eight patients with AKD (24.8%) developed AKI during or after the resolution of AKD, and 15 of them (53.6%) died. In 13 patients AKD (11.5%) then evolved to CKD (11.5%). In 53% of patients AKD was transient. The 5-year incidence of mortality was significantly higher in patients who developed AKD than in those who did not (61.7% and 15.4%, respectively) (Fig.1A) while no difference was found comparing patients who developed only AKD with those who developed AKD and AKI, CKD or AKD and CKD (Fig. 1B). In multivariate analysis, age (HR = 1.03; $p = 0.002$), GFR at inclusion (HR = 0.98; $p = 0.001$) and sCr $\geq$ 1.5 mg/dl (HR = 5.41; $p = 0.03$) were found to be independent predictors of AKD, while age (HR = 1.05; $p < 0.001$), CTP score (HR = 1.30; $p < 0.001$), and

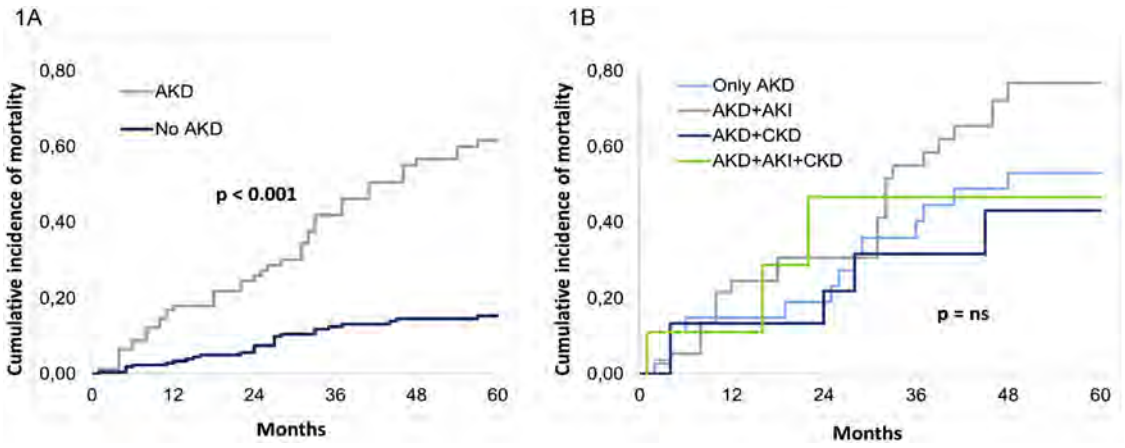

Figure: (abstract: SAT-128)

the development of AKD (HR = 3.27; p < 0.001) were found to be independent predictors of 5-years mortality.
Conclusion: AKD is a common type of renal impairment in patients with cirrhosis. The development of AKD increases the mortality in patients with cirrhosis independently from its clinical evolution.

SAT-129

Type 2 diabetes in patients with liver cirrhosis: prevalence, associated factors and influence on survival

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Background and aims: The presence of type 2 diabetes (DM) in patients with cirrhosis is frequent and the relationship between both is complex. Objective: to know the prevalence of DM and the factors associated with its presence in a series of patients with cirrhosis and analyze its influence on survival.
Method: 1456 patients with cirrhosis included in a HCC surveillance program were analysed and followed prospectively. Patients with cirrhosis due to NASH and those with ascites in the initial evaluation were not included. The majority were males (76%), with a median age of 54 years, Child-A (84%), 67% had esophageal varices and 42% had presented a previous episode of decompensation. Etiology: alcohol (49%), HCV (41%), HBV (7%) and autoimmune/cholestasis (3%). The diagnosis of the DM at the inclusion was established based on the presence of two glycemia values ≥ 126 mg/dl or anti-diabetic treatment.
Results: The prevalence of DM was 21.4%. In the univariate analysis, the presence of DM was associated with advanced age (p < 0.001), alcoholic aetiology (p < 0.001), BMI ≥ 30 (p = 0.004), GGT > LSN (p = 0.031), presence of varices (p = 0.027) and previous decompensation (p = 0.003). In the multivariate study, the only variables associated with DM were the age > 60 years (HR, 95% CI: 2.27, 1.57-3.29); BMI ≥ 30 (HR, 95% CI: 1.58, 1.09-2.30) and GGT > LSN (HR, 95% CI: 1.43, 1.02-2.00). During a median follow-up of 48 months (24-96), 546 patients died (406 without DM and 140 with DM). Survival at 5, 10 and 20 years was 78.9%, 43.9% and 31.7% in patients without DM and 74.5%, 36.8% and 20.5% in those with DM (p = 0.11). In the multivariate analysis, the variables that were associated with worse survival were: age > 60 years (HR, 95% CI: 1.83, 1.40-2.38), BMI < 25 (HR, 95% CI: 1.48, 1.14-1.92), AST > LSN (HR, IC95%: 1.54, 1.20-1.98), albumin ≤ 35 g/L (HR, IC95%: 1.46, 1.12-1.91), platelets < 125 × 10^3/mm3 (HR, IC95%: 1.55, 1.24-1.94) and previous decompensation (HR, IC95%: 1.76, 1.35-2.30). In contrast, cirrhosis due to HBV was associated with lower mortality (HR, 95% CI 0.53, 0.33-0.86). After adjustment with other variables, the presence of DM was not associated with higher mortality (HR, 95% CI: 1.11, 0.88-1.39).
Conclusion: 20% of patients with liver cirrhosis have DM in the initial evaluation and their presence is not related to the etiology of the disease. Although in the univariate analysis the presence of DM was associated with more advanced liver disease, the association disappeared after adjustment with other variables. The only variables independently associated with the presence of DM were age, BMI and high GGT. It is possible that the association with elevated GGT is a consequence of the coexistence of a component of NASH in the etiology of cirrhosis. Finally, the presence of DM does not decrease survival in patients with cirrhosis.

SAT-130

Incidence and outcome of portal vein thrombosis in 817 HBV and HCV compensated cirrhotic patients under antiviral treatment: a single center longitudinal study

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Background and aims: Long-term NUCs-treatment in HBV and direct-acting antivirals (DAAs) treatment in HCV improve cirrhosis outcomes, however portal vein thrombosis (PVT) risk is still undefined. We evaluated incidence and predictors of PVT in a large cohort of viral cirrhotics treated with antivirals.
Method: 817 cirrhotic patients without PVT were consecutively enrolled in a cohort longitudinal study: 260 caucasian HBV-monoinfected compensated cirrhotics starting TDF or ETV and 557 HCV CPT A-B cirrhotics consecutively receiving DAAs at a single center. Patients underwent regular blood tests, 6-month abdominal imaging and esophageal varices (EV) screening. PVT was graded according to Yerdel classification.
Results: 260 HBV-monoinfected cirrhotics were consecutively enrolled: median age 61 (21-83) years, 81% males, 88% HBeAg negative, PLT 153 (32-304) x10^9/L, spleen diameter 11 (7-20) cm, liver stiffness 8.8 (3-75) kPa, 13% with esophageal varices (EV) and 4 previously decompensated (1.5%), 59% NUCs-experienced. During 103 (16-138) months of study period 9 (3.5%) patients developed non-neoplastic PVT after 58 (23-92) months, with an 8-year cumulative probability of 3%. At multivariable analysis, only previous

decompensation (HR 16, 95%CI 2-113, p = 0.005) and EV at baseline (HR 27, 95%CI 5-136, p < 0.001) predicted PVT. PVT was associated with "de novo" ascites in only one patient and with HCC development in 5 patients (56%), but it did not never display any radiological features of neoplastic thrombosis throughout the entire follow-up.
557 HCV DAA treated cirrhotics were studied: median age 64 (28-87) years, 60% males, 83% CPT A, platelet count (PLT) was 118 (26-753) × 10^3/ml, spleen size 13 (7-24) cm, liver stiffness 17.0 (12.1-75.0) kPa, 32% had baseline EV. During 33 (1-47) months of follow-up, 10 (1.8%) patients developed PVT, with a 3-year cumulative probability of 2%. PVT patients were CPT B (50%), all had EV at baseline (small varices in 2, primary prophylaxis in 5, secondary in 3). PVT were Yerdel grade 1 in 5 patients, grade 2 in 3, grade 3 and 4 in 1 patient each. PVT was associated with HCC development in 2 patients, but none was due to tumor vascular invasion. PVT resulted in de novo or worsening of ascites in 4 (40%) patients, while it was asymptomatic in 6 (60%). At PVT diagnosis, EV worsened compared to baseline in 3 (30%) patients but no GI bleeding occurred. Baseline predictors of PVT reflected disease severity (CPT, MELD, bilirubin, albumin) and portal hypertension (EV, PLT). The 3-year cumulative probability of PVT was 5.2% vs 0% in patients with or without baseline EV, respectively (p = 0.002).
Conclusion: Among HBV NUC-suppressed and HCV treated with DAAs cirrhotics, non-neoplastic PVT is a rare complication, partial in most cases, but strongly associated with severity of liver disease at baseline. In HCV patients, PVT occurrence may cause clinical decompensation.

SAT-131

The impact of sustained virological response on the criteria used to rule out high risk esophageal varices in HCV-related compensated advanced chronic liver disease

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Background and aims: The Baveno VI criteria [platelet count (plt) > 150 × 10^9/l and liver stiffness measurement (LSM) < 20KPa] to rule out high risk esophageal varices (HRV) in chronic advanced viral-related liver disease (cACLD) perform efficiently in viremic patients. Further refinements of the Baveno VI criteria [Expanded Baveno VI criteria (Plt110/LSM25), or Plt125/LSM25 criteria] maintain high accuracy and spare more endoscopies. The Plt150/MELD6 criteria are less accurate in viremic cACLD patients. How sustained virological response (SVR) achieved by DAAs impacts on such criteria is unknown. We assessed the performance of Expanded Baveno VI, Plt125/LSM25 and PLT150/MELD6 criteria, as compared to the original Baveno VI criteria, to rule out HRV in 192 HCV-related cACLD patients with an SVR to DAAs.
Method: 192 consecutive cACLD patients undergoing regular endoscopic follow-up according to international guidelines (Baveno VI) were retrospectively evaluated. LSM, assessed by transient elastography, and plt closest to the follow-up endoscopy were considered.
Results: Out of 192 cACLD patients with an SVR, 8 (4%) had HRV after a median follow-up of 18 (0-36) from SVR achievement. All of them were identified by the original Baveno VI criteria, with 43 (22%) sparing endoscopies. The Plt125/LSM25 criteria maintained the same accuracy, sparing a significant amount of endoscopies (n = 73, 38%; p < 0.001 compared to Baveno VI). By converse, the Expanded Baveno VI criteria, while sparing 86 (45%) endoscopies, missed one (12.5%) out of 8 HRV patients. The Plt150/MELD6 score correctly identified all 8 SVR patients with HRV, sparing 76 (40%) endoscopies (p < 0.001 compared to Baveno VI criteria).
Conclusion: The Plt125/LSM25 and the Platelet150/MELD 6 score are useful tools to rule out HRV in HCV-related cACLD with an SVR to DAAs, sparing significantly more endoscopies than the original Baveno VI criteria, without losing accuracy. Conversely, the expanded Baveno VI criteria (Plt110/LSM25), although most effective in viremic cACLD patients, are less effective in SVR cACLD patients.

SAT-132

Incidence and prognostic factors of de novo development/worsening of esophageal varices in HCV-related compensated advanced chronic liver disease after sustained virological response achieved by direct antiviral agents

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Background and aims: The development/worsening of esophageal varices (EV) is reduced but not abolished by sustained virological response (SVR) in HCV-compensated advanced chronic liver disease (cALD). Baveno VI suggest performing endoscopy two- or three-years after SVR in patients with small EV or without EV at baseline but the level of evidence is low. Aim: We retrospectively evaluated incidence and predictive factors of "de novo" development/worsening of EV in 163 consecutive HCV-cACLD patients undergoing EV-surveillance according to Baveno VI.
Method: 258 HCV-related cACLD patients achieving SVR (January 2015- March 2017). Ninety-five were excluded (53 large EV at baseline, 29 incomplete data, 9 non-SVR, 4 lost to follow-up). Overall, 163 patients were evaluated: median age 63 years (39-86), males 57%, median BMI 26 (16-40), obese 15%, previous HCC 10%. Median time between SVR and follow-up endoscopy: 18 months (range:0-36).
Results: Thirty-eight of 163 patients (23%) had small, low-risk at baseline, which progressed to large EV in 6 patients. Among 125 patients without EV at baseline, 17 developed small EV and 108 remained without EV. Overall, 23 patients (14%) had EV appearance/progression and 130 patients (80%) did not change (108 patients without baseline EV and 22 with small EV). Baseline variables associated with EV appearance/progression were obesity, spleen-diameter, platelet, LSPS, albumin and diabetes. Variables at SVR12 associated with EV appearance/progression were ALT, GGT and platelet. Multivariable analysis, performed separately for baseline and SVR12 variables, identified LSPS at baseline (OR 1.207, 95% CI 1.032-1.412, p = 0.019), and GGT (OR 1.026, 95% CI 1.009-1.043, p = 0.003) and platelet-count at SVR12 (OR 1.013, 95% IC 1.002-1.026, p = 0.026) as the variables associated with EV appearance/progression. Finally, we tested an algorithm to rule-out endoscopic surveillance by combining LSPS < 1.326 and GGT < 25 (i.e. the cut-offs with sensitivity > 0.9 at the AUROC). "Low risk" patients for the algorithm were 83 (51%), thus entitling them for avoiding endoscopy. However, 3 patients (1 with small-EV and 2 with large-EV) would have been misclassified (2% of the series) with a 87% sensitivity.
Conclusion: De novo development/worsening of EV occurs in 14% of cACLD patients after SVR. An algorithm including LSPS at baseline and GGT at SVR 12 could halve the number of endoscopies with a misclassification rate for large-EV < 5%.

SAT-133

2D-Shear-Wave elastography predicts survival in advanced chronic liver disease

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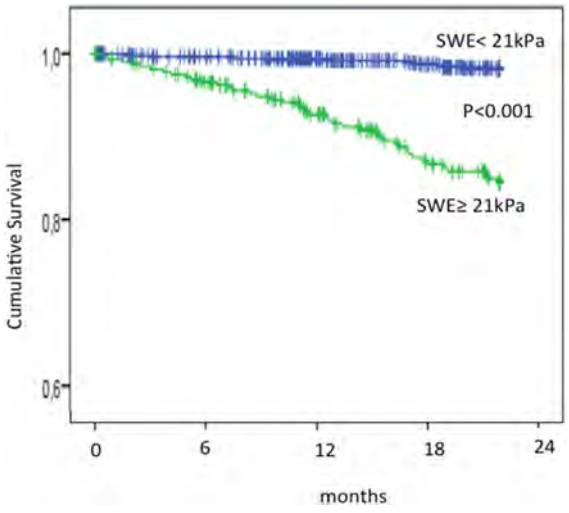
Background and aims: Measurement of liver stiffness is an established technique to assess significant fibrosis in patients with chronic liver disease. Moreover, it might be a useful surrogate marker to diagnose or rule out clinically significant portal hypertension. However, the value of 2-dimensional shear wave elastography (2D-SWE) to predict mortality in cirrhotic patients is unknown. The aim of this multicentre retrospective study was to assess the value of 2D-SWE using Aixplorer to predict mortality in chronic liver disease patients.
Method: Inclusion criteria were presence of chronic liver disease, valid 2D-SWE at baseline, no previous events of decompensation at baseline and at least one year of clinical follow-up after the index 2D-SWE measurement. Clinical and laboratory parameters were assessed at baseline. The primary outcome was overall mortality. For the selection of cutoff values, receiver operating characteristics (ROC) analysis with survival as end point was calculated. Kaplan-Meier curves were used to compare the survival rates of patients using the log-rank test. Univariate time-to-event analysis and multivariate Cox regression analysis was performed to identify independent predictors of survival.



Results: 2062 patients from 16 centres were screened and 1170 patients fulfilled the inclusion criteria and were included in the analysis with a median follow-up of 31.5 months. The median age of the population was 54 (range: 18-83) years, with 63% male patients. The main aetiology was viral hepatitis (38%), while 23% suffered from chronic alcoholic liver disease. The median liver 2D-SWE was 11kPa (range: 1-155). The AUC of SWE for mortality within 24 months was 0.81 (CI: 0.76-0.85) with the best Cut-off of 21 kPa (sensitivity 70%, specificity 80%). In univariate analysis age, MELD, creatinine, bilirubin, albumin, platelets, AST and SWE > 21kPa were significantly associated with overall mortality. In the cox-regression multivariate analysis SWE > 21kPa was independently associated with over all mortality (HR: 3.75 (2.13-6.61)), besides albumin (HR: 0.90 (0.87-0.93)) and age (HR: 1.06 (1.04-1.09).
Conclusion: This study shows for the first time that liver stiffness measured by 2D-SWE predicts mortality in patients with chronic liver disease. 2D-SWE of more than 21kPa might be helpful to stratify risk and guide patient management. NCT03389152

SAT-134

Hypercoagulopathy risk factors in liver cirrhosis due to non-alcoholic steatohepatitis and clinical manifestations of hypercoagulation during 5 years

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Background and aims: Characteristics and predictive effects of coagulation profile in liver cirrhosis (LC) with non-alcoholic steato-hepatitis (NASH) are now debated. The purpose of the work was to determine the risk factors of hypercoagulation in NASH LC patients and clinical manifestations of hypercoagulation during 5 years of observation.
Method: We analyzed 66 patients (ps) with NASH LC (11 females/55 males; age, 45.8 ± 5.7 yr; body mass index (BMI), 33.5 ± 2.8 kg/m^2): 24 ps with Child-Pugh class A (group I), 22 ps with Child-Pugh class B (group II), 20 ps with Child-Pugh class C (group III). The results were compared with those of 20 healthy volunteers. Biochemical, ultrasound, endoscopic, histological examination and elastography has been carried out. Circulating insulin, tumor necrosis factor alpha (TNFα), 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) were measured by the immuno-assay method.
Results: Hypercoagulopathy was detected in 41.7% of ps in group I, 72.7%-of ps in II group and 80.0%-of ps in group III; hypocoagulopathy-in 4.54% of ps with II group and 20.0% of ps with III group. In ps with NASH LC a statistically significant increase of FVIII (p = 0.009) and vWF (p = 0.003), PECAM-1 (p = 0.002), P-selectin (p = 0.003), PAI-1 (p = 0.001) and TAFI (p = 0.006) and decrease of AT III (p = 0.006), protein C (p = 0.001) vs. group IV were found. The direct correlations between vWF and Child-Pugh score, low density lipoprotein cholesterol (LDLC), TNFα, HOMA-IR, PAI-1, PECAM-1, P-selectin (r = 0, 5643; r = 0, 6438; r = 0, 7251; r = 0, 5924; r = 0, 7903; r = 0, 6257; r = 0, 6588; accordantly; p < 0, 001) and indirect correlations between FVIII and AT III, protein C (r = -0, 7015; r = 0, 8226; accordantly; p < 0, 001) were installed.
During 5 years of follow-up, in group I were clinical manifestations of hypercoagulation: 1 (4.2%) myocardial infarction (MI), 2 (8.3%)-acute coronary syndrome (ACS), 1 (4.2%)-ischemic stroke (IS), 3 (12.5%)-common carotid artery (CCA) stenosis > 50%, 1 (4.2%)- > 70%; group II-1 (4.5%), 3 (13.6%), 3 (13.6%), 5 (22.7%), 2 (9.1%) accordantly, 2 (9.1%)-

died by cardiovascular diseases; group III-2 (8.3%)-ACS, 1 (4.2%)-IS, 7 (35.0%)-died by cardiovascular diseases, 9 (45.0%)-died by decompensation of LC.
Conclusion: In NASH LC ps are mostly hypercoagulopathic; risk factors are an increase of Child-Pugh score, dyslipidemia, inflammation, insulin resistance, an increase in procoagulant and endothelial factors, antifibrinolytic activity and a decrease in AT III, protein C. In NASH LC clinical manifestations of hypercoagulation were MI, ACS, IS and death by cardiovascular diseases.

SAT-135

Splenomegaly status does not impact the efficacy of avatrombopag in increasing platelet counts and reducing platelet transfusions or rescue procedures for bleeding in chronic liver disease patients with thrombocytopenia

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Background and aims: Thrombocytopenia (TCP) is common in patients with CLD, increasing in severity with worsening liver disease. The clinical care of these patients requires multiple invasive procedures each of which carries a bleeding risk. Avatrombopag (**AVA**) is a thrombopoietin receptor agonist FDA-approved as an alternative to platelet transfusions (PT) for patients with TCP and CLD undergoing a procedure. The aim of this study was to assess whether splenomegaly (SM) affected efficacy.
Method: Two randomized, double-blind, placebo (**PBO**)-controlled Phase 3 trials (**ADAPT-1** and **ADAPT-2**) enrolled 435 adults with CLD and platelet counts (PC) < 50 × 10^9/L undergoing a procedure. Patients were divided by Baseline PC into **Cohort 1**- PC < 40 × 10^9/L and **Cohort 2**- PC 40 to < 50 × 10^9/L, and randomized 2:1 to once-daily oral **AVA** (60 mg or 40 mg, respectively) or **PBO** for 5 days, with the procedure done 5 to 8 days after the last dose. The primary efficacy end point in both studies was the proportion of patients not requiring a PT or rescue procedure, and the first secondary end point was the proportion of patients achieving a PC ≥ 50 × 10^9/L on Procedure Day. Patients with SM were identified at Baseline by investigators and designated with a status of 'yes' or 'no'.

	COHORT 1 (< 40 × 10^9/L) N = 251		**COHORT 2** (< 50 × 10^9/L) N = 184	
	AVA 60 mg (N = 160)	PBO (N = 91)	AVA 40 mg (N = 117)	PBO (N = 67)
Proportion of Patients Not Requiring a Platelet Transfusion or Rescue Procedure for Bleeding, %				
Overall	**66.9**	**28.6**	**88.0**	**35.8**
Splenomegaly Status: *No*	67.5 (n = 117)	27.5 (n = 69)	90.0 (n = 90)	42.9 (n = 49)
Splenomegaly Status: *Yes*	65.1 (n = 43)	31.8 (n = 22)	81.5 (n = 27)	16.7 (n = 18)
Proportion of Patients with Platelet Counts ≥ 50 × 10^9/L on Procedure Day, %				
Overall	**68.1**	**5.5**	**90.6**	**29.9**
Splenomegaly Status: *No*	69.2 (n = 117)	4.4 (n = 69)	92.2 (n = 90)	32 (n = 49)
Splenomegaly Status: *Yes*	65.1 (n = 43)	9.1 (n = 22)	85.2 (n = 27)	22.2 (n = 18)

Results: Overall, **AVA** was superior to **PBO** in both cohorts in the proportion of patients not requiring a PT or rescue procedure for bleeding (**Cohort 1**: p < 0.0001; **Cohort 2**: p < 0.0001). Efficacy in meeting the primary end point by SM status was generally similar, with a trend of less placebo-treated patients with SM meeting the primary end point. (**Cohort 1**: *No SM*: **AVA** 67.5%, **PBO** 27.5%; *With SM*: **AVA** 65.1%, **PBO** 31.8%; **Cohort 2**: *No SM*: **AVA** 90.0%, **PBO** 42.9%; With SM: **AVA** 81.5%, **PBO** 16.7%).
Conclusion: **AVA** was superior to **PBO** in increasing PC and reducing both the proportion of patients requiring a PT or rescue procedure for bleeding, and the proportion achieving a PC ≥ 50 × 10^9/L by Procedure Day. Efficacy was similar for both end points regardless of splenomegaly status, supporting the consistent efficacy of **AVA**. For patients with a PC < 40 × 10^9/L, < 1/10 **PBO**-treated patient achieved a PC ≥ 50 × 10^9/L regardless of splenomegaly status compared to ~7/10 **AVA**-treated patients.

SAT-136

Hepatocellular carcinoma does not impact the efficacy of avatrombopag in increasing platelet counts and reducing platelet transfusions or rescue procedures for bleeding in chronic liver disease patients with thrombocytopenia

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Background and aims: Patients with CLD and hepatocellular carcinoma (HCC) may require invasive procedures such as ablation and embolization. Thrombocytopenia (TCP) is common in patients with CLD and may increase the risk of bleeding with invasive procedures. Avatrombopag (**AVA**) is a thrombopoietin receptor agonist FDA-approved as an alternative to platelet transfusions (PT) for patients with TCP and CLD undergoing a procedure. This analysis assessed whether HCC status affected the efficacy of AVA.
Method: Two randomized, double-blind, placebo (**PBO**)-controlled Phase 3 trials (**ADAPT-1** and **ADAPT-2**) enrolled 435 adults with CLD and platelet counts (PC) < 50 × 10^9/L undergoing a procedure. Patients were divided by Baseline PC into **Cohort 1**- PC < 40 × 10^9/L and **Cohort 2**- PC 40 to < 50 × 10^9/L, and then randomized 2:1 to once-daily oral **AVA** (60 mg or 40 mg, respectively) or **PBO** for 5 days; the procedure was done 5 to 8 days after the last dose. The primary efficacy end point in both studies was the proportion of patients not requiring a PT or rescue procedure, and the first secondary end point was the proportion of patients achieving a PC ≥ 50 × 10^9/L on Procedure Day. Subgroup analyses of efficacy were also conducted based on HCC status.

	COHORT 1 (< 40 × 10^9/L) N = 251		COHORT 2 (40 to < 50 × 10^9/L) N = 184	
	AVA 60 mg (N = 160)	PBO (N = 91)	AVA 40 mg (N = 117)	PBO (N = 67)
Proportion of Patients Not Requiring a Platelet Transfusion or Rescue Procedure for Bleeding, %				
Overall	**66.9**	**28.6**	**88.0**	**35.8**
No HCC	68.4 (n = 117)	34.9 (n = 66)	91.7 (n = 84)	36.7 (n = 49)
HCC	64.3 (n = 42)	12.0 (n = 25)	81.3 (n = 32)	33.3 (n = 18)
Proportion of Patients with Platelet Counts ≥ 50 × 10^9/L on Procedure Day, %				
Overall	**68.1**	**5.5**	**90.6**	**29.9**
No HCC	68.4 (n = 117)	6.1 (n = 66)	91.7 (n = 84)	28.6 (n = 49)
HCC	69.1 (n = 42)	4.0 (n = 25)	90.6 (n = 32)	33.3 (n = 18)

Results: Overall, **AVA** was superior to **PBO** in both cohorts in the proportion of patients not requiring a PT or rescue procedure for bleeding (**Cohort 1**: p < 0.0001; **Cohort 2**: p < 0.0001). Efficacy by HCC status was generally similar between the different treatment groups for the primary end point. **Cohort 1**: *No HCC*: **AVA** 68.4%, **PBO** 34.9%; *HCC:* **AVA** 64.3%, **PBO** 12.0%; **Cohort 2**: *No HCC*: **AVA** 91.7%, **PBO** 36.7%; *HCC*: **AVA** 81.3%, **PBO** 33.3%. Similarly, efficacy results for the secondary end point were also generally comparable regardless of HCC status. **Cohort 1**: *No HCC*: **AVA** 68.4%, **PBO** 6.1%; *HCC*: **AVA** 69.1%, **PBO** 4.0%; **Cohort 2**: *No HCC*: **AVA** 91.7%, **PBO** 28.6%; *HCC*: **AVA** 90.6%, **PBO** 33.3%. Fewer HCC patients in the **Cohort 2** PBO arm reached the

primary end point compared to non-HCC patients though their baseline PC was similar.
Conclusion: **AVA** was superior to **PBO** in increasing PC and reducing both the proportion of patients with CLD who required a PT or rescue procedure for bleeding, and the proportion of patients who achieved a PC $\geq 50 \times 10^9$/L by Procedure Day. Efficacy was similar for both end points regardless of HCC status, supporting the consist efficacy of **AVA**.

SAT-137

Adverse drug reactions in patients with cirrhosis: analysis of spontaneous reports from the Dutch Pharmacovigilance Centre Lareb

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Background and aims: Patients with cirrhosis are susceptible for certain adverse drug reactions (ADRs), such as renal impairment and hepatic encephalopathy. However, not much is known. To obtain more ADR information, data from pharmacovigilance centers could be useful. We aim to describe the content of ADR reports from a pharmacovigilance center on patients with cirrhosis.
Method: We extracted all reports that mentioned "cirrhosis" from the database of the Dutch Pharmacovigilance Center Lareb. We excluded double reports, reports with cirrhosis as ADR and reports with an uncertain diagnosis of cirrhosis. The content of the included reports was quantitatively described.
Results: We retrieved 50 reports from the Lareb database. Twelve reports were excluded: two were double, in two others cirrhosis was the ADR and eight reports had an uncertain diagnosis of cirrhosis. Of the 38 included reports, 12 (32%) described the severity of cirrhosis of the patient. The reporter expressed this severity in a Child-Pugh class in seven and the other five reports mentioned severity in terms of decompensated or severe cirrhosis. The 38 reports concerned 49 suspected ADRs (median 1; range 1-3). These ADRs most often involved the following organ classes: "skin and subcutaneous tissue disorders" (n = 8; 21%), "nervous system disorders" (n = 6; 16%) and "gastrointestinal disorders" (n = 5; 13%). The most reported individual ADRs were: thrombocytopenia, a rash and an insult (all reported thrice). Two reports involved hepatotoxic events (one cholestatic hepatitis and one acute hepatitis). The pharmacovigilance assessor considered more than half (61%) of ADRs serious. In three, a death was reported. The medicines most frequently suspected for causing the ADR were: pegylated interferon-alpha-2a (n = 3), meropenem and norfloxacin (both n = 2). In one-fifth (21%) of reports the causality was evaluated as "probable" and in the remaining the causality was "possible".
Conclusion: The frequency of ADR reports on patients with cirrhosis is low in the Dutch Pharmacovigilance database. This suggests underreporting or inadequate documentation of cirrhosis as (co) morbidity. To indicate ADR risks in patients with cirrhosis, we advise to use a worldwide pharmacovigilance database.

SAT-138

Cirrhotic cardiomyopathy: A 2-year longitudinal follow-up study using advanced cardiac imaging

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Background and aims: Cardiac dysfunction is an established complication in cirrhosis, but the temporal relationship between progression of liver dysfunction, cardiac impairment and survival is unknown. The study aim was to investigate the development of structural and functional cardiac changes over time with the progression of cirrhosis and outcome
Method: In a prospective 2-year longitudinal follow-up study, we included 63 cirrhotic outpatients (Child class: A = 9, B = 46, C = 8) and 14 healthy controls. We assessed advanced cardiac characteristics such as cardiac MRI with extracellular volume (ECV) quantification, speckle tracking echocardiography, ECG and biomarkers at 0/6/12/18/24 months. Patients were followed-up for a median of 30 months with registration of acute decompensations (AD), liver transplantation (LT), and death.
Results: In the 34 patients who remained stable or improved in cirrhosis during the 2-year study period limited cardiac deterioration was seen. Conversely, patients who progressed, underwent LT, or died had more pronounced cardiac dysfunction with structural myocardial changes, and left atrial enlargement. During follow-up 25 patients developed AD, 4 underwent LT, and 20 died. Mean arterial pressure was the only cardiovascular parameter associated with death in a univariate analysis ($p = 0.037$), and the main predictors were MELD and age. However, last visit myocardial ECV was independently associated with the combined end point of LT/death ($p = 0.001$), and in AD patients a low cardiac index was independently associated with death ($p = 0.01$).
Conclusion: Patients with stable cirrhosis have limited progression in cardiac dysfunction over a 2-year period with modest impact on survival. However, cardiac function seems to deteriorate in relation to progression in cirrhosis and may influence survival in AD patients. Our results encourage careful cardiac monitoring in patients with advanced cirrhosis.

SAT-139

Predictive factors for the development of acute-on-chronic liver failure in a North American cohort of hospitalized patients with cirrhosis and decompensation

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Background and aims: Acute-on-chronic liver failure (ACLF), irrespective of definition, is often precipitated by an event that disturbs systemic or regional homeostasis, leading to failure of one of more extra-hepatic organs, associated with high morbidity and short-term mortality. The aim of the study was to characterize cirrhotic inpatients with ACLF and to identify admission predictors of development of ACLF, as defined by the North American Consortium for the Study of End-stage Liver Disease (NACSELD) in hospitalized patients with cirrhosis.
Method: NACSELD, a consortium of 14 hepatology centers, prospectively enrolled non-electively admitted cirrhotic inpatients. We compared those who developed ACLF (≥ 2 organ failures) ≥ 48 hours after admission (ACLF+, n = 125) to those who did not (ACLF-, n = 2516). We excluded 416 patients with ACLF within the 1st 48 hrs of

admission. Extra-hepatic organ failures (OFs) were defined as: circulatory = need for vasopressor support; renal = initiation of dialysis; cerebral = Grade III or IV hepatic encephalopathy; respiratory = need for ventilation.

Results: Compared to ACLF- patients, ACLF+ patients were younger (55.5 ± 8.3 vs. 57.4 ± 10.9 years) ($p = 0.045$), but were similar in gender (male: 58 vs. 62%), alcoholic etiology (28 vs. 31%) and diabetes (37 vs. 34%). ACLF+ patients had more cirrhotic complications, more recent hospitalizations [within 6 months (M)], and more were admitted with infection, hence a higher proportion of patients had systemic inflammatory response syndrome (SIRS) compared to the ACLF- group. Regarding OFs, 82, 36 and 7 patients had 2, 3 and 4 OFs respectively in the ACLF+ group, with no significant differences between subgroups, except more OFs increased the rate of dialysis. Mortality in hospital (42% vs. 3%) and at 30 days (50% vs. 7%) was significantly higher in the ACLF+ vs. ACLF- patients ($p < 0.0001$). Independent predictors of ACLF development ≥ 48 hours after admission included admission MELD (OR: 1.14; confidence interval 1.11-1.16), presence of SIRS (OR: 1.96; CI: 1.96-3.01), and hospitalization in ≤ 6 Ms (OR: 2.80; CI: 1.59-4.96).

Conclusion: Cirrhotic patients admitted with higher a MELD score, infection, signs of inflammation and a recent hospitalization are more likely to develop ACLF. This patient subgroup requires intensive monitoring for prompt recognition and management of ACLF.

Table:

Admission parameters	ACLF- (N = 2516)	ACLF + (N = 125)	P value
	% (n) or mean (SD)	% (n) or mean (SD)	
Admitted with infection	25% (625)	38% (48)	0.0008
Ascites	68% (1720)	85% (106)	0.0001
Refractory ascites	32% (800)	49% (61)	< 0.0001
Admission in ≤ 6 Ms	66% (1518)	8% (93)	0.0001
Rifaximin use	35% (853)	50% (61)	0.0006
SIRS	24% (606)	37% (45)	0.0025
Serum creatinine (mg/dL)	1.46 (1.39)	2.33 (1.71)	< 0.0001
MELD	18.76 (7.32)	26.91 (7.77)	< 0.0001

SAT-140

The natural history of stages 2 and 3 acute kidney injury in hospitalized patients with decompensated cirrhosis and ascites

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Background and aims: AKI occurs in ≈50% of hospitalized cirrhotic patients, with stage 1 AKI with a peak serum creatinine (SCr) < 1.5 mg/dl having a relatively benign course. Higher stages of AKI have been reported to have significantly worse prognosis in a European cohort. However, the natural history of stages 2 and 3 AKI in cirrhosis in North American patients has not been described. The aim of the study was to assess the prognosis and predictive factors for the development of stages 2 and 3 AKI in the North American Consortium for the Study of Liver Disease (NACSELD) cohort.

Method: Decompensated admitted cirrhotic patients with ascites who developed AKI per the International Ascites Club (IAC) 2015 definition from the NACSELD database were included, comparing patients with stage 1 versus stages 2 and 3 AKI with respect to demographics, laboratory values, AKI treatment response and survival.

Results: 760 of 989 AKI (43% of 2297 total eligible) patients with ascites formed the study cohort. There was no difference between the stage 1 (n = 419) and stages 2 and 3 (n = 341) patients with respect to demographics (males: 63%; mean age: 58 years; cirrhosis etiology (alcohol: 30%). When compared to stage 1 AKI patients, stages 2 and 3 patients were sicker (MELD: 25.9 ± 7.3 vs. 21.9 ± 7.5, $p < 0.0001$), were more likely to be on SBP prophylaxis, had higher white cell counts, were more likely to have SIRS on admission, and more developed a second infection during admission ($p < 0.05$ for all). Significantly more stages 2 and 3 patients were treated for their AKI (albumin: 74% vs. 67%, $p = 0.03$; midodrine/octreotide: 43% vs. 23%, $p < 0.0001$). Despite this, more of them had a progressive course (31% vs. 12%, $p < 0.0001$). AKI progression occurred more frequently in older patients who had hospital contacts in past 6 months. The in-hospital mortality was 20% for stages 2 and 3, vs. 6% for stage 1 ($p < 0.0001$), and was associated with lower 30-day transplant-free survival (56% vs. 81%, $p < 0.001$). Predictors of stages 2 and 3 AKI development were a higher admission MELD ($p < 0.0001$), presence of SIRS on admission ($p = 0.023$), and the development of 2nd infections ($p < 0.0001$).

Table: Outcomes of Stages 2 and 3 AKI

	Transient (*n* = 99)	Persistent (*n* = 130)	Progressive (*n* = 101)	*p value*
Baseline serum creatinine	0.94 (0.34)	1.14 (0.48)	1.25 (0.58)	< 0.0001
Peak Serum creatinine	2.71 (1.18)	3.56 (1.57)	4.73 (1.95)	< 0.0001
Δ Serum creatinine	1.78 (1.03)	2.42 (1.42)	3.49 (1.74)	< 0.0001
Started on dialysis (%, n)	4% (4)	16% (21)	41% (41)	< 0.0001
Admitted to ICU (%, n)	39% (39)	39% (50)	70% (71)	< 0.0001
Length of hospital stay (days)	19.3 (19.7)	21.8 (21.6)	23.2 (15.4)	0.0113

Conclusion: Sicker cirrhotic patients are more likely to develop stages 2 and 3 AKI, especially if there is a 2nd infection while admitted. They tend to have a progressive AKI course, with decreased transplant-free survival. Therefore such patients need careful monitoring and aggressive AKI treatment to improve outcomes.

SAT-141

The diagnosis of hepatorenal syndrome: How much does use of the 2015 revised consensus recommendations affect earlier treatment and serum creatinine at treatment start?

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Background and aims: In 2015, the International Club of Ascites (ICA) published revised consensus recommendations for the diagnosis of acute kidney injury (AKI) and HRS based on a dynamic

change in serum creatinine (SCr) rather than a static level of SCr of 2.5 mg/dL in patients with cirrhosis, in an effort to facilitate earlier treatment of HRS Type 1 (HRS1). The aim of this study was to estimate the effect of using the new ICA-AKI diagnostic criteria on timing of HRS treatment, applying these criteria to subjects ultimately enrolled in a large, prospective, randomized trial of patients with HRS1 treated with terlipressin (REVERSE trial) (Gastroenterology 2016; 150: 1579-1589).

Method: 2015 HRS-AKI criteria were retrospectively applied to individual patient's pre-enrollment serial SCr data from the REVERSE trial. The number of days between meeting current ICA HRS-AKI criteria and old HRS1 criteria were determined to estimate the impact of the new criteria on earlier treatment. SCr at HRS-AKI diagnosis using the new ICA 2015 criteria was compared to SCr at diagnosis of HRS1 using the 2007 diagnostic criteria to estimate the effect of the new criteria on SCr at the potential start of vasoconstrictor therapy

Results: Of 196 patients included in REVERSE, 141 subjects had data available for this analysis. 24/141 subjects (17%) had a decrease or no change in SCr (average –0.5 mg/dL) during interval (average 2.3 days) between meeting HRS-AKI versus HRS1 criteria. 117/141 subjects (83%) had an increase in SCr (average 1.7 mg/dL) during interval (average 4.0 days) between meeting HRS-AKI versus HRS1 criteria Additional results are shown in the Table.

Interval between HRS-AKI and HRS1 N = 141	**3.8** (3.3) days*
SCr at HRS-AKI diagnosis N = 141	**2.7** (1.1) mg/dL*
SCr at HRS1 diagnosis N = 141	**3.7** (1.1) mg/dL*
Fold increase SCr, AKI-HRS to HRS1 criteria	% of subjects (N = 117)
> 1 to < 1.5 fold	**53%**
1.5 to 2.0 fold	**22%**
> 2.0 fold	**25%**

*mean (SD)

Conclusions: Applying the new 2015 ICA AKI-based criteria for HRS is estimated to result in earlier treatment of patients by approximately 4 days, with treatment at a SCr approximately 1 mg/dL lower than when using prior HRS1 diagnostic criteria. A significant number of patients (47%) would receive treatment prior to a further ≥ 1.5 fold increase in SCr. Using the new ICA HRS-AKI diagnostic criteria will provide earlier treatment with potentially better outcomes.

SAT-142

Incidence of hepatocellular carcinoma and cirrhotic complications in patients with psychiatric illness: A territory-wide cohort study

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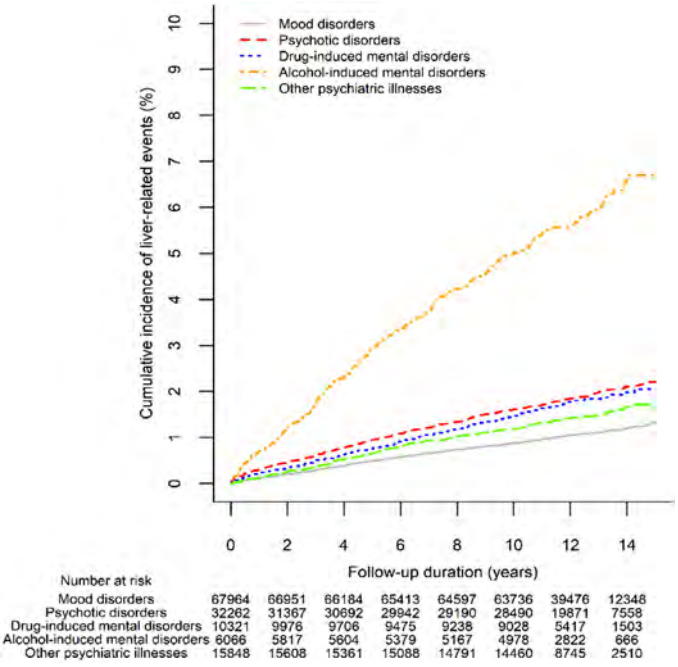
Background and aims: Because of high-risk behaviours, psychiatric patients are at risk of viral hepatitis and alcohol-related liver disease. Their sedentary lifestyle and side effects of psychiatric medicine are also conducive to obesity and non-alcoholic fatty liver disease. We aim to study the incidence of hepatocellular carcinoma (HCC) and cirrhotic complications in a territory-wide cohort of psychiatric patients in Hong Kong.

Method: We identified patients with psychiatric diagnoses from 2003 to 2007 using the Clinical Data Analysis and Reporting System. This system captures in-patient and out-patient data of all public hospitals and clinics in Hong Kong. The patients were followed for liver-related events (HCC and cirrhotic complications) and deaths until December 2017.

Results: Of 178, 225 psychiatric patients, we included 105, 763 adult patients without prior HCC and cirrhotic complications in the final analysis. During a median follow-up of 12.4 (interquartile range 11.0-13.7) years, 1, 520 (1.4%) patients developed HCC and/or cirrhotic complications (Figure). Compared with the general population, psychiatric patients had increased incidence of HCC (standardized incidence ratio [SIR] 1.70, 95% CI 1.54-1.87). The SIR was highest in patients with alcohol-related (SIR 3.48) and drug-induced mental disorders (SIR 3.34), but was also increased in patients with psychotic disorders (SIR 1.58) and mood disorders (SIR 1.48). Liver disease was the fifth most common cause of death in this population, accounting for 603 of 10, 614 (5.7%) deaths. Chronic hepatitis B (n = 375, 24.7%), chronic hepatitis C (n = 175, 11.5%), alcohol-related liver disease (n = 190, 12.5%) and non-alcoholic fatty liver disease (n = 78, 5.1%) were the leading aetiologies in patients with liver-related events. Importantly, 799 (52.6%) patients were not known to have liver diseases at the time of liver-related events.



Conclusion: HCC, cirrhotic complications and liver-related deaths are common in psychiatric patients, but liver diseases are often undiagnosed. More efforts are needed to identify liver diseases in the psychiatric population so that treatments and screening for HCC and varices can be provided to patients in need.

SAT-143

Albumin-bilirubin as a simple prognostic score for chronic hepatitis B-related liver cirrhosis

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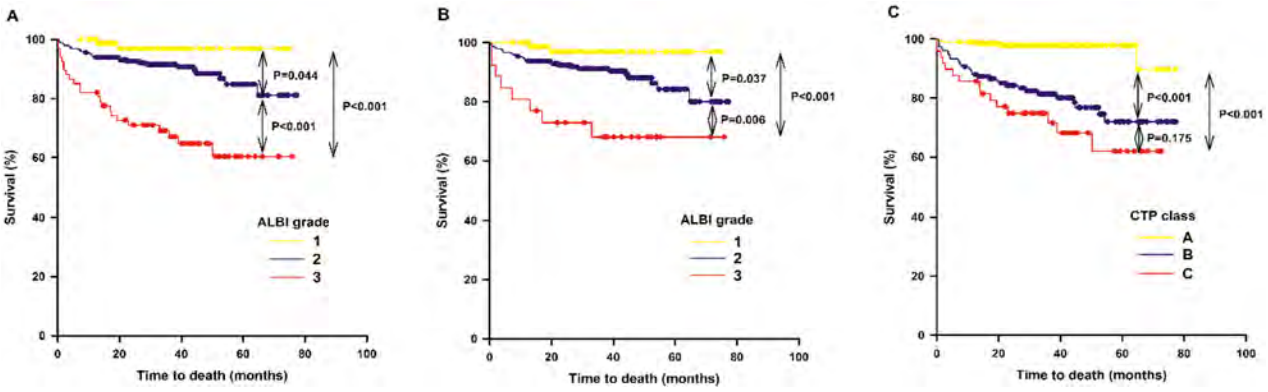

Figure: (abstract: SAT-143)

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Background and aims: The Albumin-Bilirubin (ALBI) score was developed recently to predict the long-term prognosis in patients with hepatocellular carcinoma. We aimed to investigate the performance of ALBI for predicting the severity and long-term prognosis of chronic hepatitis B-related cirrhosis (CHB-LC).
Method: Patients diagnosed with CHB-LC were enrolled from two medical centers between 2011 and 2017. The prognostic performance of ALBI was evaluated and compared with Child-Turcotte-Pugh (CTP) score and model of end-stage liver disease (MELD) score.
Results: This study enrolled 398 CHB-LC patients. The ALBI score increased with the severity of CHB-LC. ALBI was an independent predictor of liver-related mortality by multivariable Cox analysis. The receiver operating characteristic curves (ROCs) analysis revealed that ALBI score (0.756, 0.745, 0.739, 0.767 and 0.765) was superior to MELD score (0.655, 0.629, 0.641, 0.636 and 0.677, $P < 0.05$) and comparable with CTP score (0.785, 0.766, 0.768, 0.772 and 0.793, $P > 0.05$) for predicting 2-year, 3-year, 4-year, 5-year and global mortality. However, no significant differences were observed among three models in predicting 1-year mortality. Over a median follow-up of 33.9 months, patients with lower ALBI grade had a significantly lower mortality than patients with higher ALBI grade ($p < 0.05$). Similar results were observed in the CTP classes A and B subgroup.
Conclusion: ALBI score accurately predicts the severity and long-term prognosis in patients with CHB-LC in China. The prognostic performance of ALBI score was superior to MELD score.

SAT-144

Red blood cell distribution width to albumin ratio as a novel prognostic indicator for patients with chronic hepatitis B-related liver cirrhosis

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Background and aims: Simple, reliable non-invasive indexes to predict prognosis of chronic hepatitis B (CHB)-related liver cirrhosis (LC) are currently lacking. We aimed develop and test a novel index using routine laboratory results to predict the liver-related mortality of CHB-LC.
Method: Patients were enrolled from three medical centers. The derivation cohort contained 398 CHB-LC patients from two medical centers in China. A validation cohort of 198 CHB-LC patients was enrolled from Stanford University Medical Center. Multiple regression was used to identified the predictors. The prognostic value was assessed using Kaplan-Meier analysis.
Results: Red cell distribution width (RDW) and albumin ($p < 0.001$) were independent predictors for CHB-related decompensated cirrhosis (CHB-DCC) in derivation cohort. Thus, RDW to albumin ratio (RAR) was proposed. The receiver operating characteristic curves (ROCs) analysis revealed that RAR (0.771, 0.737 and 0.727) was comparable with CTP score (0.800, 0.743 and 0.746, $P > 0.05$) for

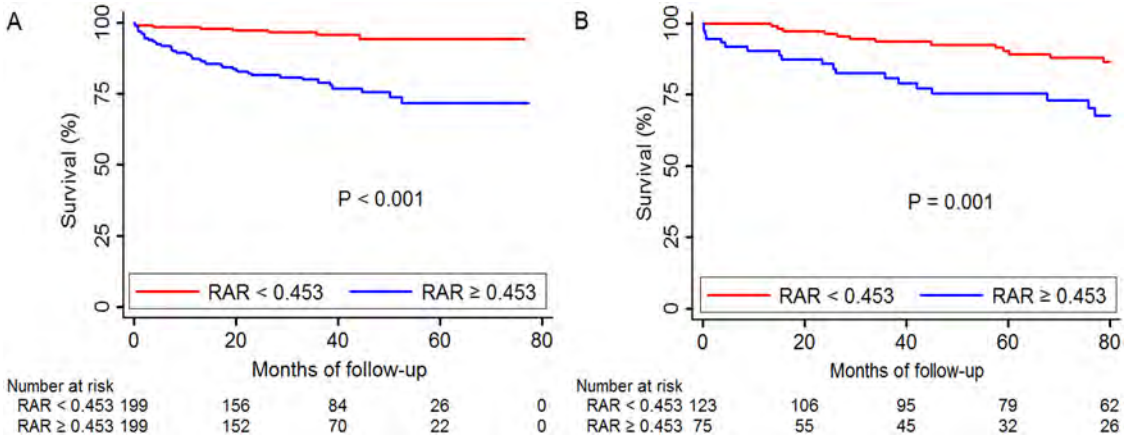

Figure: (abstract: SAT-144)

predicting 1-year, 3-year and 5-year liver-related mortality, and was superior to MELD score (0.624, P = 0.028) for predicting 3-year liver-related mortality, but was comparable with MELD score (0.694 and 0.639, P > 0.05) for predicting 1-year and 5-year liver-related mortality in the derivation cohort. Validation cohort had similar results. Over a median follow-up of 39.8 (IQR 22.8-62.1) months, CHB-LC patients with RAR ≥ 0.453 in both derivation cohort (22.1% vs. 4.0%, P < 0.001) and validation cohort (25.3% vs. 10.6%, P = 0.001) had significantly higher liver-related mortality.
Conclusion: The RAR, a novel easy-to-use index, accurately predicts CHB-LC related mortality in clinical practice.

SAT-145
The prognostic significance of hbeag status on the long-term outcome for chronic hepatitis b-related liver cirrhosis: A propensity score matching analysis
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Background and aims: Serum hepatitis B e antigen (HBeAg) status is a critical predictor of the progression in patients with chronic hepatitis B (CHB). However, there are still lack of evidences whether HBeAg status is related to the long-term outcome of patients with CHB related liver cirrhosis (CHB-LC). We aimed to investigate the prognostic significance of HBeAg status on the long-term outcome for CHB-LC using propensity score matching.
Method: 398 patients with CHB-LC were enrolled from two medical centers (2011-2017). To adjust for the selection bias of patients between HBeAg positive and HBeAg negative, we performed 1:1 match using propensity score matching. The Kaplan-Meier curve and Cox regression analysis was performed for the risk of LC-related death.
Results: After propensity score matching, 77 patients were final included in each group. There were no significant differences of liver related mortality between HBeAg positive CHB-LC patients and HBeAg negative CHB-LC patients before propensity score matching (8.2% vs. 14.9%, P = 0.094). However, after propensity score matching, CHB-LC patients with HBeAg negative (26.0%) exhibited a significantly higher mortality than CHB-LC patients with HBeAg positive (9.1%, p = 0.019) over a median follow-up of 32.1 (IQR, 17.7-50.1) months. Furthermore, after propensity score matching, HBeAg negative status (HR, 2.859; 95% CI 1.207-6.770; P = 0.017) was significantly associated with increased risks of liver related mortality in CHB-LC patients. After adjustment for other prognostic variables in the propensity score matched cohort, HBeAg negative status was still found to be associated with higher mortality (HR, 3.032; 95% CI 1.232-7.460; P = 0.016) in patients with CHB-LC.

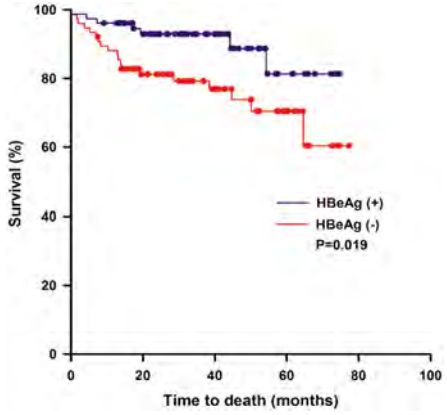

Figure: Survival curves of CHB-LC patients with HBeAg (+) or HBeAg (+) after propensity score matching.

Conclusion: HBeAg negative status appears to be an independently risk predictor of long-term mortality for patients with CHB-LC based on propensity score matching analysis.

SAT-146
Assessing liver function in patients who underwent balloon occluded retrograde transvenous obliteration
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Background and aims: Portal hypertension is one of the most fundamental sequelae of liver failure with clinical signs and symptoms representing the major source of morbidity and mortality. One of the effects is the development of portosystemic shunts to help alleviate the pressure from portal hypertension. Treatments have been developed to obliterate portosystemic shunts in order to reverse hepatic encephalopathy. One of these treatment options is balloon occluded retrograde transvenous obliteration (BRTO). There have been minimal studies assessing liver function and how it changes after undergoing BRTO. We aim to assess liver function over time in this cohort of patients.
Method: A retrospective chart review was conducted utilizing the Rush University Medical Center electronic medical record to evaluate patients age eighteen and older who underwent BRTO between 2013 and 2017, yielding data on 21 patients. Cochran's Q, McNemar, and Friedman tests were conducted to assess the changes in paracentesis frequency and amount over time. To examine whether there was a relationship between the change in frequency of paracentesis per patient across time and MELD score, Spearman correlation coefficients were calculated and compared to zero. To look at whether there was a relationship between the change in the number of patients who had paracenteses across time and MELD score, Wilcoxon-Mann-Whitney tests were conducted.
Results: The number, frequency, and amount of fluid removed per paracentesis increased after patients underwent BRTO (Figure 1). When MELD scores were examined as potentially related to a change in paracentesis over time, it was found to be correlated with the change in frequency of paracenteses conducted between pre-BRTO procedure and 90 days post-BRTO procedure with a trend towards significance (r = 0.48; p = 0.06). On average, patients had a higher MELD score 30 days post-BRTO versus at the time of the procedure with a median MELD of 15 at the time of the procedure and a median MELD of 18 thirty days post procedure (p = 0.03). Thirty and ninety day mortality were 9.5% and 14.3%, respectively.

Figure 1: Paracentesis frequency and amount in patients who underwent BRTO

	Pre-BRTO	30 days Post-BRTO	90 days Post-BRTO	p value
Number (%) of patients with paracenteses (38.1%)	2	(9.5%)	6 (28.6%)	8 0.009
Mean (SD) fluid removed from paracentesis (11.0)	0.44	(2.0)	1.7 (5.0)	5.3 0.001
Mean (SD) frequency of paracenteses per patient (3.0)	0.24	(0.9)	0.76 (1.6)	1.6 0.002

Conclusion: In this study, increasing MELD score was found to be associated with increasing frequency of paracenteses after a BRTO procedure. In addition, patients who underwent BRTO had a statistically significant increase in their MELD score. Further research is needed to evaluate the underlying reason for worsening MELD scores in these patients.

SAT-147

Interaction between renal and liver impairment on the risk of lactic acidosis in diabetic patients with chronic hepatitis B-related cirrhosis

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Background and aims: The risk of lactic acidosis across renal and liver function in cirrhotic patients with diabetes mellitus (DM) has not been well-documented. We examined the interaction between severity of renal and liver impairment on the risk of lactic acidosis in DM patients with chronic hepatitis B (CHB)-related cirrhosis.
Method: A territory-wide cohort of DM patients with CHB-related cirrhosis from January 2000 to December 2017 was identified using the Clinical Data Analysis and Reporting System that captures in-patient and out-patient data of all public hospitals and clinics in Hong Kong. Lactic acidosis was defined by diagnosis codes, and/or blood pH ≤ 7.35 with lactate > 5 mmol/L or arterial bicarbonate ≤ 18 mmol/L or venous bicarbonate ≤ 21 mmol/L. Renal and liver function were modelled by time-dependent estimated glomerular filtration rate (eGFR) category and Child-Pugh class. Time-dependent use of medications and comorbidities were included in Fine-Gray model adjusted for competing risk of death. We excluded patients with eGFR < 30 ml/min/1.73 m^2 or renal replacement therapy at baseline.
Results: 4, 627 DM patients with CHB-related cirrhosis were identified. Their mean age was 60.8 ± 10.8 years, 3, 360 (72.6%) were male; 1, 652 (35.7%), 2, 119 (45.8%), 574 (12.4%) and 282 (6.1%) had baseline eGFR ≥ 90, 60-89, 45-59 and 30-44 ml/min/1.73 m^2. 3, 440 (72.2%), 1, 088 (23.5%) and 199 (4.3%) were in Child-Pugh class A, B and C at baseline. At a median (interquartile range) follow-up of 5.3 (2.0-9.6) years, 1, 119 (24.2%) patients developed lactic acidosis. In Child-Pugh class A, the risk of lactic acidosis elevated in eGFR < 45 ml/min/1.73 m^2. The risk of lactic acidosis increased in Child-Pugh class B and C at any eGFR levels. The risk of lactic acidosis increased dramatically in Child-Pugh class C with eGFR < 30 ml/min/1.73 m^2 (Table).
Conclusion: The risk of lactic acidosis increases with renal and liver impairment in DM patients with CHB-related cirrhosis. Child-Pugh class C with eGFR < 30 ml/min/1.73 m^2 is associated with a 102-fold increase in risk of lactic acidosis.

SAT-148

The role of kidney biomarkers in cirrhotic patients with acute kidney injury: interim analysis of multicenter, prospective cohort study

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Background and aims: Current AKI criteria using serum creatinine (Cr) has some limitations to predict reversibility of renal function and discriminate renal parenchymal injury in cirrhotic patients. The aim of this study is to evaluate whether urine biomarkers [cystatin C, N-acetyl-β-D-Glucosaminidase (NAG)] can predict survival and response to terlipressin in cirrhotic patients with AKI.
Method: One hundred eleven cirrhotic patients who developed AKI were prospectively enrolled from 11 tertiary medical centers in Korea during 2016 to 2018. AKI was defined as increase in serum Cr (SCr) of 0.3 mg/dL or 50% increase of baseline in SCr with a final value above 1.5 mg/dL. Among them, the patients with SCr ≥ 2.5 mg/dL were diagnosed as hepatorenal syndrome (HRS) and treated with terlipressin. Urine samples were collected for the measurement of urine cystatin C and urine NAG at the diagnosis of AKI and/or HRS.
Results: Of 111 patients, 29 patients had HRS. The mean MELD score was 23.92 ± 8.90, and mean SCr was 2.20 ± 0.79 mg/dL. The baseline urine NAG (AKI stage I, 16.37 ± 16.48 mg/dL; stage II, 27.84 ± 36.70 mg/dL; stage III, 55.69 ± 62.93 mg/dL, P = 0.007) and urine cystatin C (AKI stage I, 0.50 ± 0.78 mg/dL; stage II, 0.67 ± 2.29 mg/dL; stage III, 1.07 ± 2.16, P = 0.558) increased as the baseline AKI stage increased. During median 2.6 months observational period, all-cause mortality was 39.4%. In patients with liver transplantation or death, urine NAG level tended to be higher than in survival group, but not statistically significant (30.56 ± 40.81 mg/dL vs. 20.80 ± 29.22 mg/dL, P = 0.101). However, this urine biomarkers were not yet different depending on the improvement of renal function and survival.
Conclusion: In the interim-analysis of our study, urine NAG and urine cystatin C are strongly associated with severity of AKI in patients with liver cirrhosis and may be helpful to predict transplant-free survival in these patients.

SAT-149

Optimal selection of sedative drug during endoscopy in cirrhotic patients to avoid minimal encephalopathy

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Background and aims: The indiscriminate use of sedative drug during endoscopy can pose a risk of minimal hepatic encephalopathy (MHE) in patient with liver cirrhosis,. However, it has not been studied yet which drugs are safest and most inviting on these

Table: (abstract: SAT-147)

Time-dependent eGFR category*	Child-Pugh class A N = 9, 484^		Child-Pugh class B N = 11, 269^		Child-Pugh class C N = 3, 662^	
	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
eGFR ≥ 90 N = 10, 468	Reference		4.06 (2.72-6.07)	< 0.001	25.04 (16.06-39.05)	< 0.001
eGFR 60-89 N = 18, 864	1.15 (0.74-1.78)	0.530	4.32 (2.84-6.56)	< 0.001	17.66 (10.68-29.20)	< 0.001
eGFR 45-59 N = 13, 107	1.59 (0.97-2.61)	0.067	10.98 (7.17-16.82)	< 0.001	19.33 (10.80-34.60)	< 0.001
eGFR 30-44 N = 8, 194	3.85 (2.32-6.36)	< 0.001	17.80 (11.65-27.21)	< 0.001	44.02 (26.80-72.32)	< 0.001
eGFR < 30 N = 3, 381	21.70 (14.33-32.86)	< 0.001	65.57 (44.15-97.39)	< 0.001	102.27 (68.17-153.41)	< 0.001

* 54, 014 records of eGFR category change were collected in follow-up.
^ 24, 415 records of Child-Pugh class change were collected in follow-up. aHR = adjusted hazard ratio, CI = confidence interval.

patients. The aim of this study is to evaluate which one among midazolam, propofol, or combination therapy, was the least likely to cause complications including MHE by using Stroop application in cirrhotic patients.

Method: This randomized prospective study included consecutive 60 patients who underwent upper GI endoscopy at tertiary hospitals in Korea. Patients were randomly assigned to one of three groups, midazolam, propofol, or combination group, and underwent Stroop test before endoscopy, and 2 hours after the completion of endoscopy. The vital signs was checked before and after the drug administration and the patient/physician/nurse satisfaction was scored after endoscopy.

Results: Mean age of the patients was 54.0 ± 9.30 years and 81.3% were male. Fifteen patients (46.9%) were child-pugh class A, and 17 (53.1%) were child-pugh class B or C. Alcohol was the most common etiology (21, 65.6%). Patients did not show significant changes in Ontime, Offtime on Stroop test before and after drug administration, and there was no significant difference between the three treatment groups. Also, there was no significant vital sign changes after drug use in all groups. However, with respect to subjective indicators, the satisfaction scores of patient and nursing staff was higher in the combined group than in the other two groups, and time to recovery was shorter in propofol than other groups.

Conclusion: In patients with cirrhosis, sedative endoscopy using midazolam, propofol, or combination therapy is relatively safe, and was not associated with increased risk of MHE. However, since there is subjective satisfaction or recovery time difference among sedative agents, it should be considered according to each individual patient.

SAT-150

Validation of Korean stroop test in the screening of minimal hepatic encephalopathy

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Background and aims: Minimal hepatic encephalopathy (mHE) has poor prognosis but hardly drawn attention when patients have no symptoms. We aimed to validate Korean stroop test in the screening of mHE.

Method: Chronic hepatitis B related liver cirrhosis (LC) patients without history of overt hepatic encephalopathy were recruited prospectively from 15 centers for two years. All participants completed Portosystemic encephalopathy syndrome test (PHES) and Korean stroop test. Korean stroop test is consisted of 2 On-states (color, word) and 2 Off-states (inhibition, switching). Correct response rates and response times were measured. Four types of "OnTime+OffTime" have been analyzed (color+inhibition, color +switching, word+inhibition, and word+switching). mHE was diagnosed when PHES scores less than −4. Healthy controls (HC) were also recruited (n = 376).

Results: Among 223 LC patients, 67.3% was male. Mean age was 53 years. Prevalence of mHE was 20.6%. Response times for each states showed negative correlation with PHES scores ($p < 0.001$). Also color +inhibition, color+switching, word+inhibition, and word+switching showed negative correlation with PHES scores, −0.361, −0.310, −0.442, and −0.336, respectively (all $p < 0.001$). The highest AUC in the discrimination of mHE among various "OnTime+OffTime" was word+inhibition (AUC 0.75, 95% C.I 0.67-0.84, $p < 0.001$). Mean values of word+inhibition were significantly different among the three groups, which were 54.6 ± 13.2sec, 63.4 ± 18.2sec, and 83.4 ± 27.8sec in HC, LC without mHE, and LC with mHE, respectively (all $p < 0.001$). Among various factors, time for word+inhibition was the only significant factor (OR 1.04, 95% C.I 1.02-1.06, $p < 0.001$) in multivariate analysis for diagnosis of mHE.

Conclusion: Korean stroop test is simple and valid method for screening of mHE.

SAT-151

What are the predictors of impairment of patient-reported outcome in non-alcoholic steatohepatitis?

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Background and aims: Patient-reported outcomes (PROs) assess patients' experience with their disease and its treatment. There is a paucity of data related to predictors of PROs in patients with NASH. Aim: To identify demographic and clinical factors associated with PROs in patients with NASH and advanced fibrosis.

Method: NASH patients with bridging fibrosis or compensated cirrhosis were enrolled in two phase 3 STELLAR trials of selonsertib (#NCT03053050, #NCT03053063). The PROs [Short Form-36 (SF-36), Chronic Liver Disease Questionnaire (CLDQ-NASH), EQ-5D, and Work Productivity and Activity Index (WPAI:SHP)] were collected prior to treatment initiation. Independent predictors of PROs were assessed using generalized linear regression models (betas (β; were expressed in % of a PRO range size; $p < 0.01$ was considered significant).

Results: 1, 667 NASH patients with PRO data were enrolled (58 ± 9 years, 40% male, 73% white, 56% from the U.S., 52% had cirrhosis, 69% diabetes). Prior to treatment, physical health-related PRO scores of NASH patients were significantly lower than general population norms ($p < 0.01$). In a series of multivariate analyses, independent predictors of various PRO domain scores included age (β = +0.15% to +0.47% per year), gender (β = -3.0% to -9.1% in female patients), race (β = -16.0% to -8.5% in black and β = +2.3% to +9.9% in Asian patients with reference to whites), the country of enrollment (β = +1.9% to +10.2% for NASH patients enrolled in the U.S.), smoking status (β = -7.5% to -3.1% in current smokers), body mass index (β = -0.99% to -0.18% per kg/m2) and cirrhosis (β = -3.4 to -1.8). In addition, the presence of other comorbidities was found to be independently associated with

lower PROs ($p < 0.01$) (Table). Of those predictors, both musculoskeletal disorders and higher BMI were primarily associated with worse physical health, increased fatigue, and decreased vitality, while having a psychiatric disorder (anxiety, depression, bipolar, sleep disorder) was the only predictor of decreased work productivity ($p < 0.01$).

Predictor of PROs in NASH	Beta (β), % of PRO range size
Diabetes mellitus	−6.1 to − 1.9
Gastrointestinal disorders	−7.3 to − 2.4
Musculoskeletal and connective tissue disorders	−11.8 to − 2.1
Nervous system disorders	−5.5 to − 2.5
Psychiatric disorders	−12.7 to − 2.5

Conclusion: The presence of cirrhosis and comorbidities contributes to impairment of PROs in patients with NASH.

SAT-152

Prediction of nosocomial acute-on-chronic liver failure in patients with cirrhosis admitted to hospital with acute decompensation

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Background and aims: Acute-on-Chronic Liver Failure (ACLF) develops during hospitalization in at least 10% of patients with cirrhosis admitted for an acute decompensation (AD) and greatly worsens their prognosis. Aim of the present prospective observational study was the early recognition and stratification of patients at risk for nosocomial ACLF (nACLF) through the identification of rapidly available predictors at hospital admission.
Method: 516 patients with cirrhosis consecutively hospitalized for AD between January 2014 and March 2016 were screened: 106 patients (21%) presented ACLF at admission and were excluded from the analysis; the remaining 410 were enrolled and surveilled during hospitalization for the development of nACLF.
Results: 59 (14%) patients developed nALCF after a median of 7 (IQR 4-18; min 2, max 45) days. At admission, they presented a more severe disease, a higher degree of systemic inflammation, and a higher degree of anemia than those (351; 86%) who remained free from nACLF. Competing risk multivariable regression analysis (considering death, liver transplantation, and discharge as competing events) showed that baseline MELD score (HR = 1.15 [95% CI: 1.10-1.21]; $p < 0.001$), hemoglobin (Hb) level (HR = 0.81 [95% CI: 0.68-0.96]; $p = 0.018$), and leucocyte count (HR = 1.11 [95% CI: 1.06-1.16]; $p < 0.001$) were independent predictors of nACLF. These factors were then categorized according to their optimal cut-off point associated to the highest Youden index (J) at receiver operating characteristic (ROC) curve: 13 points for MELD score, 9.8 g/dl for Hb, and 5.6×10^9/l for leucocyte count. By using these thresholds, the cumulative incidence of nACLF increased with the number of risk factors at admission, being 0, 6, 21 and 59% in patients with 0, 1, 2 or 3 risk factors, respectively ($p < 0.001$). Finally, the development of nosocomial bacterial infection, a well-known precipitating factor of ACLF, significantly increased the risk of nACLF, resulting in a cumulative incidence of 31, 59, and 83% in patients with 1, 2 or 3 risk factors respectively ($p = 0.025$). Interestingly, patients who did not present any of the 3 risk factors at admission did not develop nACLF despite nosocomial infection.
Conclusions: Easily available laboratory parameters, which are related to disease severity, systemic inflammation, and moderate anemia, can be used to identify and stratify at admission patients with AD at increasing risk of developing ACLF during hospitalization.

SAT-153

A systematic review and meta-analysis of the efficacy of magnetic resonance spectroscopy in the diagnosis of hepatic encephalopathy

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Background and aims: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome occurring in patients with significant liver dysfunction and/or portal-systemic shunting. The pathogenesis of HE is centred around the inter-organ trafficking of ammonia, a neurotoxin of intestinal origin, and exacerbated by infection and inflammatory states. Various imaging modalities have been used to explore pathogenic mechanisms and stratify the severity of HE. The aim of this metanalysis was to assess the value of magnetic resonance spectroscopy (MRS) in assessing patients with HE.
Method: Studies with more than ten cases and reliable HE diagnosis via neuropsychometric testing were identified from the electronic databases PubMed, EMBASE, CINAHL, LILACS and CENTRAL through to 25 July 2018 with no date restriction. Patients were stratified into: healthy controls, NHE (cirrhotic patients without hepatic encephalopathy), MHE (minimal hepatic encephalopathy) and OHE (overt hepatic encephalopathy). Analyses were organized by metabolite studied and brain region examined. Statistical meta-analysis was performed using the metafor package in R (v3.4.1). Pooled standardized mean differences between patient groups were calculated using a random effects model.

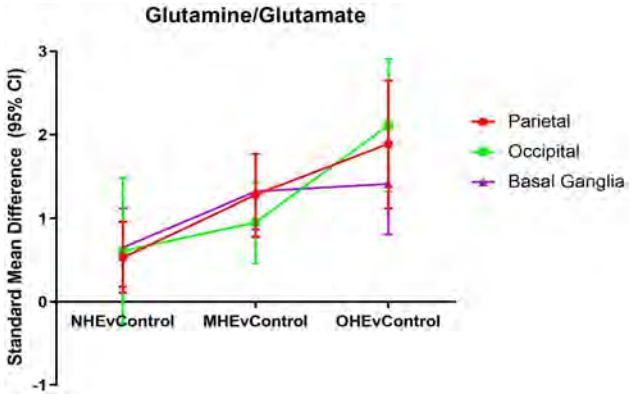

Figure: Glutamate/glutamine results in parietal, occipital and basal ganglia by HE grade. CI: Confidence interval, MHE: minimal hepatic encephalopathy, NHE: cirrhosis without hepatic encephalopathy, OHE: overt hepatic encephalopathy.

Results: From a search of 2198 citations, we identified 298 potentially relevant citations of which 37 studies of MRS imaging in HE met the inclusion criteria. Thirty-one studies (n cases = 1481) included data for Type C (cirrhosis-related) HE. We found the parietal region to be the most reliable in differentiating between patients with and without MHE, with standard mean differences of (+0.82, 95% CI +0.49 to +1.15, $p < 0.0001$, $I^2 = 37.45\%$) for glutamine, (−0.36, 95% CI −0.61 to −0.10, $p = 0.007$, $I^2 = 20.00\%$) for choline, and (−0.77, 95% CI −1.19 to −0.34, $p = 0.0004$, $I^2 = 67.48\%$) for myo-inositol respectively. We also found that glutamine was the metabolite that reliably correlated with HE grade in all brain regions (Figure).
Conclusion: The meta-analysis reveals that MRS changes in glutamine, choline, myo-inositol, particularly in the parietal lobe, correlate with the severity of HE. The vulnerability of the parietal lobe requires further study. MRS may be of value in the diagnosis of HE.

SAT-154

Acute hemodynamic response to I.V propranolol during hepatic hemodynamic study in 26 cirrhotic patients with portal hypertention and nonbleeding esophageal varices. Correlation with esophageal bleeding and survival

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Background and aims: Bleeding from esophageal varices (EVB) in cirrhosis carries 15-20% mortality. Primary prophylaxis with non-selective beta blockers (NSBB) or esophageal variceal banding reduces bleeding rate from 25% to 15% in 2 years follow-up (2yFU). Hemodynamic response to propranolol is a powerful predictor for EVB. Bleeding rate in responders is lower (5%) during 2 years of follow-up (FU) compared with non-responders (20-25%- almost as "natural history"). Studies indicated that "HVPG (hepatic vein pressure gradient)-guided therapy" may assist in "tailoring" prophylactic treatment for EVB and lower bleeding rates. AIM: To assess HVPG-guided therapy as a tool for to reduce EVB by "tailoring" prophylactic therapy.
Method: 150 hepatic hemodynamic studies (HVPG) were performed in Carmel Medical Center during the last 5 years. Of these, in 26 cirrhotic patients with esophageal nonbleeding varices a hemodynamic response to propranolol was assessed. Responders were treated with propranolol while NR with carvedilol 12.5 mg daily. Baseline clinical, laboratory and hemodynamic data were analyzed. Finally, the rate of bleeding during 2yFU was assessed in the R and NR.
Results: The majority had NASH cirrhosis. 17 of 26 patients (66%) were responders and 9 (33%) were NR. Bleeding rates during 2yFU was lower in the responders compared with the NR (5% vs. 12.5%, respectively, $p = 0.2$). The rate of EVB in all patients during FU was only 8%, supporting the importance of HVPG-guided therapy in avoiding bleeding in NR. However, mortality was similar between the two groups (NR 17% vs. R 22%, p = NS).
Conclusion: HVPG-guided therapy for primary prevention of EVB may be a powerful tool to reduce the risk of EVB in cirrhotic patients. The rate of EVB using HVPG-guided therapy is lower than empiric therapy with NSBB.

Viral Hepatitis A, B, C, D, E: Virology

SAT-159

Genetic determinants in critical domains of NS5A are associated with genotype 1b HCV-induced hepatocellular carcinoma

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Background and aims: A critical role of NS5A in promoting Hepatocellular Carcinoma (HCC) has been recently proposed. Here, we investigated genetic determinants in NS5A associated with HCC.
Methods: This study includes 273 patients (pts) chronically infected with HCV genotype 1b, all DAA-naïve: 50 pts diagnosed with HCC and 223 controls without HCC (154 cirrhotic and 69 No-cirrhotic). NS5A domain-I (aa:1-183) sequences were obtained for all pts, while NS5A domains-II (aa:250-342) and III (aa:356-447) sequences for 27/50 HCC and 65/223 No-HCC pts, by Sanger method from plasma samples. Association of mutations with HCC was assessed by Fisher Exact test. Shannon Entropy (SE) was used to define NS5A residues with significantly higher variability ($SE > 0$) in HCC ($p < 0.05$) compared to No-HCC pts.
Results: HCC and No-HCC pts had comparable median (IQR) log serum HCV-RNA [5.4 (5.2-6.0) vs 5.8 (5.2-6.1) IU/ml] and ALT [64 (37.5-85) vs 62 (41-96) U/L].
Six specific NS5A-I polymorphisms significantly correlated with HCC: H85Y (8.0 vs 1.8%, $p = 0.04$), T122M (8.0% vs 0.9%, $p = 0.01$), M133I (18.0% vs 3.6%, $p < 0.001$), T135I (6.0% vs 0.9%, $p = 0.04$), Q176T (6.0% vs 0%, $p = 0.006$) and Q181E (8.0% vs 0.5%, $p = 0.004$). By SE, three residues were more variable in HCC pts: C13R/S ($SE = 0.272$; $p = 0.01$), N137D/K ($SE = 0.210$; $p = 0.02$) and Q181E/G/H/P ($SE = 0.3$; $p < 0.001$). Mutations at these residues may affect NS5A capability to promote maturation of viral particles, favoring an intracellular accumulation of HCV proteins, a process known to induce cellular stress.
The analysis of NS5A-III domain revealed three specific polymorphisms, with a significantly higher prevalence in HCC: R357K (33.3 vs 10.8%, $p = 0.01$), G381S (22.2% vs 3.1%, $p = 0.003$), P397L (18.5% vs 4.6%, $p = 0.04$). By SE, the residue 390 was characterized by an increased variability in HCC vs no-HCC (S390D/V, $SE = 0.315$; $p = 0.01$). These mutations localize in the NS5A C-terminus, a region known to interact and downregulate p53 activity.
Finally, by SE, three NS5A-II residues appeared more variable in HCC pts: E275A/G ($SE = 0.315$; $p = 0.03$), S328I/P/T ($SE = 0.367$; $p = 0.05$)

and R330D (SE = 0.315; p = 0.04). These mutations reside adjacent to or within NS5A proline-rich domain, known to interact with YB-1 protein, playing a role in neoplastic transformation of hepatocytes.
Conclusions: The association of specific NS5A polymorphisms with HCC provide a focus for further investigations aimed at elucidating the molecular basis of HCV-mediated oncogenesis. These viral signatures, if confirmed in a larger population, could play a crucial role as prognostic markers of HCC, helping to identify patients at higher HCC-risk deserving more intense liver evaluation and/or early treatment.

SAT-160

Timing of exposure to dimethyloxalylglycine-mediated hypoxia determines opposite effects in an experimental model of hepatitis C virus infection

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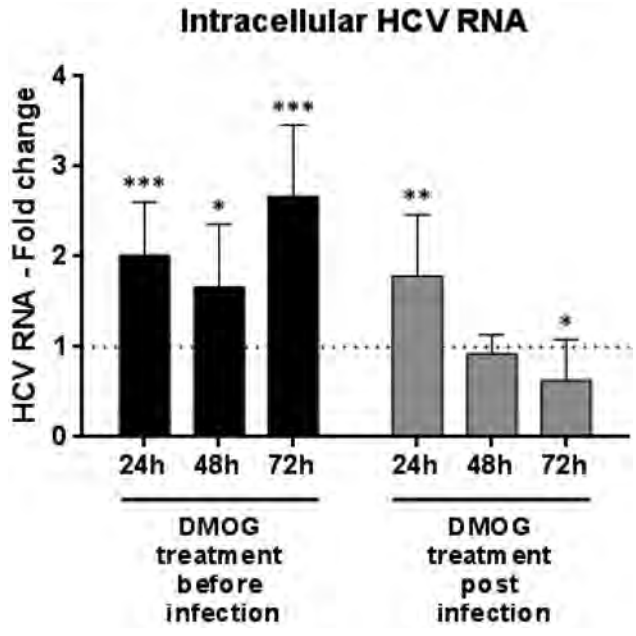
Background and aims: A cellular hypoxic state appears to influence hepatitis C virus (HCV) infection and may play a significant role in viral hepatocarcinogenesis. In fact, HCV induces a pseudo-hypoxic state in hepatocytes by stabilizing Hypoxia Inducible Factor-1alpha (HIF-1alpha), thus stimulating the transcription of different hypoxia-related genes (very-low-density lipoprotein receptor, VLDR; vascular endothelium grow factor, VEGF and others). Dimethyloxalylglycine (DMOG), a synthetic analogue of alpha-ketoglutarate, is commonly used to induce HIF signaling and has been shown to directly inhibit mitochondrial function. The aim of our study was to investigate the hypoxia effects mediated by DMOG on HCV infection *in vitro*.
Method: HuH7 cells were treated with DMOG, adding it to culture media either 16 hours before JFH-1 infection (MOI 0.1) or post JFH-1 infection and until the end of experiments. The effects of different DMOG concentrations (64, 320 nM 1.6, 8 and 40 μM) on viral infection were evaluated at 72 hours using the Focus Forming Units (FFU) assay. To verify the influence on intracellular HCV RNA expression, cells were exposed to DMOG (80 μM) at the same time points described above, and viral RNA was quantified at 24, 48 and 72 hours. Data in DMOG treated cells were normalized to those obtained in control infected cells.



Results: In FFU assay, the two higher DMOG concentrations tested showed significant differences (p = 0.013 and p = 0.028, respectively) based on timing in which the treatment is performed (before infection vs post infection). During the time course experiment (Figure), we observed two different kinetics in viral RNA levels. Cells treated before the infection showed a significant up-regulation in intracellular HCV RNA at all time points (2.01 fold at 24h, p = 0.0003; 1.67 fold at 48h, p = 0.017; 2.66 fold at 72h, p < 0.0001). In cells treated post infection, we observed an initial up-regulation at 24 hours (1.78 fold, p = 0.002) and a decrease in HCV RNA at 72 hours compared to control infected cells (0.93 fold at 48h, p = n.s.; 0.63 fold at 72h p = 0.019).
Conclusion: Depending on the timing of exposure, DMOG-mediated hypoxia exerts opposite effects on viral infection. The induction of a hypoxic state shortly before infection significantly favors HCV entry and/or its replication; on the other hand, prolonged hypoxic conditions after the cells have been exposed to the virus impair HCV replication in vitro.

SAT-161

Prevalence of HBV and syphilis co-infection in Ulaanbaatar population, Mongolia

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Background and aims: Mongolia has the highest rate of chronic hepatitis B and D infection in the world. Since currently there are no effective treatment for HBV/HDV infection, it is imperative to prevent further infection. Despite the birth dose HBV vaccination schedule, there are still significant number of acute infections are occurring. Thus, it is important to determine the transmission route of HBV/HDV. Previously it is thought that HBV/HDV is transmitted sexually. In this study, we aim to evaluate prevalence of HBV and syphilis infection pattern in adult population of Ulaanbaatar, Mongolia.
Method: Using the WHO STEP-wise approach, 4515 participants were randomly selected from 8 districts as representative of Ulaanbaatar city population in Mongolia between December 2017 to February 2018. Age and gender matched 552 or 1/8 samples from this random selection were used in the study. All 552 samples were tested for HBsAg by rapid test (CTK Biotech, US) and for syphilis by TPHA (Lorne Laboratories, UK). HBsAg positive samples were tested for anti-HDV by ELISA (Wantai Bio-Pharm, China).
Results: A total of 552 adults, 296 (53.6%) men and 256 (46.4%) women were included in the study. The overall HBsAg prevalence was found to be 51 (9.4%) and the prevalence does not vary significantly among age groups. 68.6% of all HBV infected people tested positive for anti-HDV, which confirm the result (61.0%) of Mongolian general population screening study performed in 2013 (Chen, Oidovsambuu, Hep. 2016). Furthermore, the prevalence of syphilis was determined to be 4.3% in urban adult population. Among syphilis positive subjects, HBsAg and anti-HDV seropositivity were 16.6% (4) and 12.5% (3), while it was 8.9% (47) and 6.1% (32) in syphilis negative group, respectively.

Table 1: HBV, HDV and syphilis prevalence by age groups

Age groups	*20-29*	*30-39*	*40-49*	*50+*	*Percent of sub-group*
Total number of samples (n = 552)	136	144	122	150	
HBsAg (+) (n = 51)	8	11	13	19	
Prevalence (%)	5.9	7.6	10.7	12.7	**9.4**
Anti-HDV (+) (n = 35)	3	5	11	16	
Prevalence (%)	8.5	14.2	31.4	45.7	**68.6**
TPHA (+) (n = 24)	9	6	2	7	
Prevalence (%)	6.6	4.2	1.6	4.7	**4.3**

Conclusion: Prevalence of HBV and syphilis coinfection as well as HDV and syphilis coinfection are high in Mongolian urban population. This result indicates sexual transmission would be one of the main routes of transmission for hepatitis B and B/D in sexual active contingents in Mongolia.

SAT-162

Serum HBV RNA as a predictor of incomplete HBV DNA suppression following initiation of nucleoside therapy in HBV/HIV co-infected individuals

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Background and aims: Hepatitis B core-related antigen (HBcrAg) and pre-genomic (pg) HBV RNA are markers of transcriptional cccDNA activity and emerging new biomarkers in the management of chronic HBV. Data on their clinical utility in HBV/HIV co-infection are lacking. A proportion of HBV/HIV co-infected patients, adhering to dual active antiretroviral therapy (ART) with suppressed HIV, have persistent HBV replication. In this pilot study we aimed to measure HBcrAg and HBV RNA concentrations, in chronic HBV/HIV patients at initiation of tenofovir (TDF) based ART, focusing on prediction of incomplete HBV suppression as an end point.
Method: 30 chronic HBV/HIV patients, on TDF based ART, were identified retrospectively and classified into 2 groups: those with fully suppressed HIV (< 50 copies/ml) and HBV (< 20IU/ml) at week 48 of ART (group A, n = 15) and those with persistent HBV replication despite undetectable HIV at week 48 (group B, n = 15). HBcrAg and pgHBV RNA were tested at baseline (initiation of TDF based ART). PgHBV RNA was measured by real-time PCR research assay Abbott Diagnostic (Butler E et al. Hepatology 2018) HBcrAg was measured by CLEIA assay (Fujirebio).
Results: There were no significant differences between groups A and B in sex, age, HBV genotypes, and baseline CD4 and baseline HBV DNA. There was a higher proportion of HBeAg+ patients in group B (87 v 47%, P < 0.05) but more patients in group A (43 v 0%, p < 0.05) achieved HBeAg loss by week 48. At baseline group B patients had higher HBsAg levels (4.53 v 3.99 $\log_{10}$ IU/ml, p < 0.01), HBcrAg levels (7.00 v 5.10 $\log_{10}$ U/ml, p < 0.001) and pgHBV RNA levels (6.23 v 3.82 $\log_{10}$ U/ml, p < 0.05) compared to group A. A baseline HBcrAg cut-off value of 6.85 $\log_{10}$ U/ml had good predictive value for incomplete HBV suppression at 48 weeks (sensitivity 93%, specificity 80%, PPV 82% and NPV 92%) and the area under the ROC curve (AUROC) was good at 0.891 (0.764, 1.000; 95% CI). A baseline pgHBV RNA cut off value of 5.42 $\log_{10}$ U/ml had good predictive value for incomplete HBV suppression at 48 weeks (sensitivity 80%, specificity 80%. PPV 80% and NPV 80%) and the AUROC was good at 0.830 (0.639, 1.000; 95% CI).
Conclusions: In this small HBV/HIV cohort baseline HBcrAg and pgHBV RNA levels were higher in those who failed to suppress HBV DNA despite good adherence to HBV active ART. There may be a role for these biomarkers in risk stratification of co-infected patients warranting closer surveillance and management. A larger cohort is planned to enable evaluation of their combined predictive with the aim to fully establish the clinical utility of HBcrAg and HBV RNA in this group.

SAT-163

HBeAg-negative chronic infection: more complex and conserved quasispecies in Hepatitis B X gene

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Background and aims: Patients with HBeAg-ve chronic infection (CI) usually have a favourable prognosis, however a small but relevant percentage are at risk for Hepatocellular Carcinoma (HCC). HBV X protein (encoded by *HBX* gene) plays a key role in viral replication and HCC development. The aim of this study is to analyse the complexity and conservation of the CIs viral quasispecies (QS) at the 5 'end of *HBX* and compare them with other clinical stages.
Method: Samples from 54 HBeAg-ve patients were included: 16 CI, 15 chronic hepatitis B (CHB), 6 liver cirrhosis (LC) and 17 HCC. All were treatment-naïve, with HBV-DNA > 1000 IU/ml, and infected with A-H viral genotypes. A region between nucleotides (nt) 1255 and 1611 was analyzed by Next Generation Sequencing (NGS). QS complexity was defined by Shannon entropy and Gini-Simpson indices, frequency of mutations (Mf) and nucleotide diversity (Pi). Conservation was studied by calculating the information content (IC) of each nt or aminoacid (aa) position. Intergroup variability was studied by calculating the groups' IC deviation from the general mean. The presence of aa mutations between groups was identified by aligning the haplotypes to the genotype consensus.
Results: CI patients showed higher Mf (median [IQR] = 17.5 [9.5-35.6]) and Pi (median [IQR] = 0.03 [0.02-0.04]) than CHB and HCC (Mf median [IQR] = 3.1[2.7-11.6] and 3.6[1.6-8.0]; Pi median [IQR] = 0.005 [0.004-0.02] and 0.005 [0.003-0.013] for respectively CHB and HCC). Four hyper-conserved regions were highlighted at nt level (1255-1286, 1411-1435, 1519-1543, 1575-1605), and one at aa level (63-72). A similar trend of conservation was observed between the groups, although the CIs were more conserved, mainly related to the CHBs (nt 1300-1375 and aa 20-50, p value < 0.05). A genotype D-specific pattern of mutations (A12S/P33S/T36D-G/P46S) was found in CI (median frequency of 81.7%).
Conclusion: HBeAg-ve CI patients presented more complex and conserved QS than the other groups, thus suggesting the presence in viral population of more haplotypes at low frequency with a higher mutational rate. The identified pattern of mutations in genotype D could indicate a genotype-specific evolution and may explain the low HBV replication rate in CIs. The observed hyper-conserved regions could be efficient targets for directed gene-therapy.
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SAT-164

Characterization of HBV kinetics during infection and treatment in primary human hepatocytes

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Background and aims: Detailed characterization of HBV kinetics during infection and treatment in primary human hepatocytes (PHH) is lacking. Thus, we characterized HBV kinetics in cultured PHH.
Method: Fresh PHH isolated from chimeric mice with humanized livers (PXB-cells, PhoenixBio, Co., Ltd), were inoculated with HBV in the presence of PEG8000 for 1 day (AB246341; genotype C) as described (Am J Pathol 2015;185:1275-85). Extra- and intracellular HBV DNA, extracellular HBsAg and cccDNA were measured at days 1, 2, 3, 5, 7, 10 and 12 post-inoculation (pi). Entecavir, ETV (10μM) and HBV entry inhibitor Myr-preS1 (6.25μg/ml) were initiated at inoculation and 24 h pi, respectively.
Results: Extra- and intracellular HBV DNA at day 1 pi were 6.78 and 4.39 $\log_{10}$ cp/well, respectively. Four kinetic phases of HBV infection initiation were identified for both extra- and intracellular HBV DNA. An expected 1st phase decline from day 1-3 of ~1.62 logs (half-life, $t_{1/2}$ = 9 h) and from day 1-2 of ~0.3 logs ($t_{1/2}$ = 24 h), respectively, followed by a 2 and 3 day plateau/eclipse phase, respectively. Thereafter, extra- and intracellular HBV DNA increased (doubling time, t_2 = 17h and t_2 = 24 h) (phase 3), followed by a slower increase (t_2 = 56 h and 77 h) from day 7 (phase 4). In contrast, HBsAg exhibited 2 kinetic phases: 1st phase decline of ~2.19 logs ($t_{1/2}$ = 7h) from an initial 1.65 cp/well, followed by a 2nd phase increase (t_2 = 47 h) from day 3 pi. A biphasic cccDNA amplification was observed with 1st phase rapid increase (t_2 = 7 h) between day 1 and 2, followed by a slower 2nd phase increase (t_2 = 137 h). Myr-preS1 had no effect on extra/intracellular HBV DNA or HBsAg. A similar 1st phase decline in extra/intracellular HBV DNA and HBsAg was seen ± ETV, but no subsequent increase was observed under ETV in contrast to untreated PHH. Interestingly, under ETV, cccDNA 1st phase increase was slower (t_2 = 31 h) and longer followed by a plateau.
Conclusion: A multiphasic HBV infection kinetics was observed in PHH. As anticipated, when initiated at the time of inoculation, ETV does not prevent infection, but does prevent intra/extracellular HBV DNA increase as well as 2nd phase accumulation of cccDNA. As expected, Myr-preS1 treatment 24 h pi did not prevent infection, but the lack of effect on subsequent intra/extracellular HBV DNA and HBsAg kinetics indicates nonsignificant HBV spread during this 12 day infection.

SAT-165

Identification of chromatin-accessible domains on the host genome and hepatitis B virus mini-chromosome in infected primary human hepatocytes

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Background and aims: HBV remains a major health problem worldwide with 250 million people chronically infected and at risk to develop liver cirrhosis and hepatocellular carcinoma (HCC). A complex host-virus interaction is responsible for both the dysfunction of HBV-specific B/T cells and the persistence of the viral cccDNA mini-chromosome, the two key challenges for HBV cure. The extent of HBV impact on the cellular transcriptome remains controversial. Transcriptional activation in eukaryotic cells has been tightly linked with disruption of nucleosome organization at open or accessible genomic sites of remodeled chromatin. We used ATAC-seq (assay for transposase-accessible chromatin followed by high throughput sequencing) to probe open chromatin and detect early changes in chromatin accessibility in HBV-infected PHHs.
Methods: ATAC-seq is based on the ability of hyperactive Tn5 transposase to fragment DNA and integrate into active regulatory regions in vivo. Nuclei from HBV infected (2h/24h/72h) PHHs were used for the Tn5 tagmentation and the subsequent library preparation. mRNA libraries were prepared in parallel using the TruSeq® Stranded RNA HT (w/Ribo-Zero™). Both ATAC-Seq and RNA-Seq libraries were sequenced (75×2 cycles) on a NextSeq 500 Illumina.
Results: After HBV infection an increasing number of genomic sites (including proximal extended promoter regions, distal intragenic and intergenic regions) change their chromatin accessibility over time (278 at 2h, 350 at 24h and 1095 at 72h), with a prevalence of more open, potentially transcriptionally active regions. About 30% of the impacted genes were non-coding RNAs (ncRNAs). RNA-seq analysis performed at the same times post infection showed an increasing number of differentially expressed genes (DEGs). Accessible chromatin regions are enriched for the binding motifs of the transcription factors SMADs, STAT3, TP53 and Suz12, a partner of Ezh2 in the PRC2 complex, and an enrichment in genes/ncRNAs involved in viral replication and the establishment of a pre-neoplastic state. The alignment of ATAC-seq and RNA-seq reads to the HBV genome allowed us to correlate the evolution of cccDNA chromatin accessibility with cccDNA transcription at the different times post-infection.
Conclusion: Altogether these results challenge the commonly accepted concept of HBV being a "stealth" virus and show that HBV infection impacts on host cell chromatin landscape and transcription.

SAT-166

Hepatitis C virus-based experimental models in the study of liver-driven altered glucose homeostasis

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Background and aims: Infection with hepatitis C virus (HCV) has been associated with insulin resistance. Although hepatitis C is now an easy-to-treat disease, the study of HCV physiopathology can still be useful as a model of altered glucose homeostasis. We have recently shown a significant improvement of peripheral insulin sensitivity upon viral replication suppression, in a cohort of 12 non-diabetic, lean patients infected with HCV genotype 3a treated with an interferon-free regimen. Concomitantly, the levels of some of circulating factors relevant in glucose homeostasis were significantly modified by treatment, suggesting the presence of liver-to-peripheral organ crosstalk (Gomes et al, AASLD 2018). We now aim to further investigate the role of the liver in the control of glucose homeostasis, by using HCV-based experimental models.
Method: Insulin-stimulated glucose uptake was assessed in human primary adipocytes treated either with sera from HCV-infected or non-infected subjects. C57BL/6J mice overexpressing the HCV-3a core protein in hepatocytes were subjected to glucose and insulin tolerance tests (ITT). Hepatic lipid accumulation was evaluated by oil-red-O staining. Phosphorylation level of Akt and AS160 was assessed by immunoblotting. Hepatokine expression levels were evaluated in the liver of HCV-3a core mouse model, and further

assessed in human and mice models of non-alcoholic fatty liver diseases (NAFLD).
Results: Insulin-stimulated glucose uptake was reduced in adipocytes treated with sera from HCV-infected patients as compared to non-infected controls. Overexpression of the HCV-3a core protein in the mouse liver led to the development of steatosis. Insulin sensitivity of mice was reduced, as shown by ITT and by decreased insulin-induced Akt-S473 phosphorylation in both liver and skeletal muscle. In mice livers, the expression of some hepatokines, previously found to be altered in treated patients of our cohort (i.e. Fetuin-A, Igfbp7, Angptl6 and Rbp4), positively correlated with the level of HCV core expression. Moreover, Igfbp7 mRNA expression was increased also in livers of high-sucrose, high-fat diet mice. In a human transcriptome meta-analysis of NAFLD patients, *IGFBP7* upregulation was associated with an advanced severity of the disease.
Conclusion: Taken together, these data indicate that HCV infection affects the hepatokine secretion profile to induce peripheral insulin resistance, providing a model of hepatogenous diabetes.

SAT-167

Hepatitis-E-genome sequencing via capture-probe targeting and NGS allows characterisation of viral variability

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Background and aims: Characterization of viral RNA-genomes seems to be still challenging. The lack of proof-reading-function of the RNA-dependent RNA-polymerase causes high variability-and in case of Hepatitis E it encourages development of quasispecies. High variability is linked to high pathogenicity, virulence and therapeutic resistance. Some mutations of Hepatitis E are associated with therapeutic failure of Ribavirin. Our aim was to establish a cost-efficient method for routine-diagnostic approaches to determine specific mutations and monitor quasispecies evolution to adapt individual therapy.
Method: We designed 203 of biotinylated 120mer-RNA-probes to prove all genotype 1 and 3 Hepatitis E viruses via BaitFisher method. Since 2016 blood-donors are tested to Hepatitis E-infections at Universitätsklinikum Hamburg-Eppendorf. Positive donors participated at this study. Additionally, we collected samples from a chronically infected patient-cohort. Plasma-samples of both cohorts were used for our investigations. Concentrated RNA-extracts were transcribed to cDNA, which was fragmentated via sonification (Diagenode Bioruptor®) to 200-500 bp fragments, adapter-sequences ligated and amplified. Biotinylated probes were hybridized to viral sequences and isolated via streptavidin-beads. Remaining content of viral origin was amplificated, following by a paired-end 2×250 bp-sequencing in Illumina MiSeq®.
Results: HEV-genomes could be enriched 10^4 fold. We obtained wide genome sequences from patients with viral loads > 10^3 copies/ml and found quasispecies in samples with viral loads > 10^4 copies/ml.
Conclusion: Using Capture Probe Targeting we succeed sequencing HEV-genomes from blood-samples via NGS. Reducing the number of probes lowered costs to 300-400 € per sample depending to depth of sequencing to determinate variants. This method allows to determinate quasispecies and viral evolution.

SAT-168

HBV splice DNA forms detected in serum in majority of patients with chronic HBV infection

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Background and aims: Splicing of the HBV genome has been extensively described in the literature. However, to-date HBV spliced forms have not been comprehensively characterized in large cohorts of patients with chronic hepatitis B (CHB). Here, the presence of HBV DNA spliced forms were investigated in > 1600 serum samples from CHB patients.
Method: Full HBV DNA genome deep sequencing data of 1622 CHB serum samples from clinical trials was analyzed using custom software. The presence of 23 previously described HBV spliced forms was investigated. In addition, qPCR analysis was used for quantification and validation of two major slice junctions. Associations of spliced forms with disease characteristics were also performed.
Results: Overall, HBV DNA spliced forms using a 1% cutoff were detected in 67% (74/112), 94% (308/328), 77% (605/783) and 66% (262/399) patients serum samples with genotypes A, B, C and D HBV infection, respectively. The most commonly observed splice junction, observed in 1070 patients, had donor and acceptor site at nucleotide position 2447 and 489 with intra-patient frequency of 1% to < 5%, 5% to < 10%, 10% to < 20% and ≥ 20% in 37%, 26%, 23% and 17% of patients, respectively. Detection of spliced forms were confirmed by quantitative PCR analysis of the two most common splice junctions in GTD with donor and acceptor site at nucleotide position 2447-489 and 2067-489. By qPCR the frequency of DNA spliced form was slightly lower compared to deep sequencing, in line with known amplification bias towards short amplicons. The presence of spliced forms > 1% was associated with HBeAg positive status across genotype A to D and independent of viral load (p value < 0.001). In addition, for GTC patients with HBsAg-loss or seroconversion all patients (6/6) had spliced forms > 1% with donor and acceptor site at nucleotide position 458 and 1385 respectively, whereas the overall prevalence of this splice junction in GTC was 8.9% (70/783). Nucleotide sequence of splice donor and acceptor sites and the subsequently generated open reading frames were highly conserved across genotypes (> 95%). The number of different putative proteins from splice variants is 34 with 11 of them containing a novel amino acid sequence.
Conclusion: There is a high prevalence of HBV spliced DNA forms observed by deep sequencing across GTA-D patient serum samples with potential relevance to disease characteristics and treatment outcomes.

SAT-169

Prevalence of resistance associated substitutions and phylogeographic analysis of HCV infection in Russia

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Background and aims: The prevalence of HCV infections in Russia is estimated to be 3-5% of the population with 1b and 3a subtypes being predominant. However due to limited HCV sequence availability the prevalence of resistance associated substitutions (RASs) in Russia is largely unknown. Here the prevalence of RASs as well as genetic similarity of Russian HCV strains to other countries was investigated.
Method: Resistance and phylogeographic analysis were performed on deep sequencing data of NS3, NS5A and NS5B from baseline patient samples with genotype (GT)1a, 1b and 3a HCV infection from Russia (n = 375), Asia (n = 1222), Europe (n = 2014) and North America (n = 4756).
Results: Differences in prevalence of RASs in Russia was observed compared to other regions (Table). For example, the prevalence of Y93H in 1b was slightly lower in Russia (6%) compared to 20% in Asia. Moreover, the prevalence of L159F in NS5B was comparable to specific countries in Europe, i.e. Estonia, Austria, Italy and Spain (26%-39%) but lower in Asia and North America. Of note, in Estonia 25% of population is ethnically Russian, who migrated to the country after WWII. In agreement, phylogeographic analysis revealed that L159F in GT 1b was originating 80-90 years ago in France with multiple subsequent introductions into Spain, Italy and Russia. In addition, GT 1b had four major introductions from USA and Western Europe into Russia whereas the origin of GT 3a in Russian linages was not as apparent.

		RAS	Russia	Asia	Europe	North America
GT1b	NS3	Any	113/245 (46%)	107/438 (24%)	95/255 (37%)	95/376 (25%)
		Y56F	103/245 (42%)	64/438 (15%)	82/255 (32%)	62/376 (17%)
	NS5A	Any	47/247 (19%)	376/1091 (35%)	138/593 (23%)	215/892 24%)
		L31M	7/247 (3%)	53/1091 (5%)	34/593 (6%)	51/892 (6%)
		Y93H	14/247 (6%)	219/1091 (20%)	63/593 (11%)	73/892 (8%)
	NS5B	Any	91/248 (37%)	29/1103 (3%)	121/552 (22%)	51/877 (6%)
		L159F	88/248 (36%)	13/1103 (1%)	113/552 (20%)	43/877 (5%)
GT3a	NS3	Any	1/82 (1%)	NA	2/434 (0.5%)	5/496 (1%)
	NS5A	Any	20/101 (20%)	4/70 (6%)	128/741 (17%)	126/902 (14%)
		L30S	10/101 (10%)	0/70 (0%)	24/741 (3%)	14/902 (2%)
		Y93H	2/101 (2%)	2/70 (3%)	35/741 (5%)	55/902 (6%)
	NS5B	Any	1/107 (0.9%)	0/70 (0%)	16/835 (2%)	25/937 (3%)

Conclusion: Prevalence of RASs as well as migration patterns showed that HCV in Russia were more similar to strains from Western Europe and North America than Asia. Information on migration patterns and prevalence RASs in Russia may provide information for treatment management as well as for planning HCV elimination.

SAT-170

A phenotypic resistance assay for clinical HCV isolates could help rationalise DAA therapy in individuals experiencing recurrent virologic failure

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Background and aims: Resistance-associated substitutions (RAS), particularly those that confer resistance to non-structural protein 5A (NS5A) inhibitors, can complicate the treatment of hepatitis C virus (HCV) infection. Current resistance assays use either JFH1-based HCV containing the RAS of interest or subgenomic replicons with an individual's subcloned NS5A region. However, a more life-like model would allow variants to be interpreted in the context of the individual's quasispecies pool. It was recently identified that over-expression of SEC14L2 in Huh7.5 cells allowed infection with clinical HCV isolates. Herein we present this system as a phenotypic resistance assay.
Method: SEC14L2 is a cytosolic lipid-binding protein that supports replication of clinical HCV isolates in Huh7.5 cells. We performed infection assays using this cell culture system and confirmed susceptibility to infection with clinical isolates. Next, we optimised cell culture conditions in order to enhance levels of infection. Finally, we performed phenotypic resistance assays using 100-fold dilutions of Ledipasvir. HCV-infected plasma was acquired from a local tissue bank or leftover plasma from the clinical viral sequencing service. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.
Results: Over-expression of SEC14L2 in Huh7.5 cells enables pangenotypic replication of clinical HCV isolates. The serum-free William's E medium supplemented with hepatocyte maintenance supplements and dexamethasone enhances levels of infection relative to standard cell culture media. This may be explained by an alpha-tocopherol dose-dependent enhancement of infection. Testing of genotype 1a clinical isolates found EC50 values comparable to that reported in replicon assays (range < 1pM-15.4pM). Testing of a genotype 1a clinical isolate containing the Y93H RAS (> 20% cut off) found an EC50 value 3-4x higher than wild-type (relative to G1a replicon assay); this is markedly lower than the > 1000x fold reported in the literature.
Conclusion: The SEC14L2 cell culture systems allows phenotypic resistance susceptibility testing in a manner that accounts for the quasispecies pool. Individuals with multiple failures to DAA combination therapy may benefit from a personalised approach to re-treatment and data from this assay can support the rationalisation of therapy.

SAT-171

HEV seroprevalence in blood donors in Turkey: Comparison of two commercial anti-HEV total Ab ELISA kit

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Background and aims: Previous Hepatitis E virus (HEV) seroprevalance studies have shown high variabilities in Turkey, leading to conflicting results. We aimed to re-evaluate HEV seroprevalance in blood donors by the sensitive Wantai and the widely used Dia.pro HEV total antibody (Ab) ELISA assays in Turkey and compare their performances.
Method: A total of 2011 blood samples, (807 from Ankara, 243 from Kayseri, 284 from İzmir, 200 from Malatya, 200 from Kahramanmaraş, and 277 from Van) were collected from volunteer blood donors. Each serum sample was tested for serum immunoglobulin G and M anti-HEV (total Ab) both by Wantai (Beijing, China) and Dia.pro (Milan, Italy) EIA kits. Serum samples with an absorbance greater than the cutoff value were considered as positive. Serial dilutions of the WHO anti-HEV reference serum were used to determine the concentration of anti-HEV antibody at the cut-off for each ELISA kits. For statistical analysis, $\chi 2$ test was performed and $p < 0.05$ was considered significant.
Results: The country-wide HEV seroprevalence was calculated as 11.3% (Dia.Pro) and 12.1% (Wantai) with seropositivity rates as 12.0%-12.5% in Ankara, 7.0%-7.8% in Kayseri, 14.5%-15.6% in Malatya, 8.1%-9.7% in İzmir, 14.5%-15.5% in Kahramanmaraş and 11.9%-13% in Van by Dia.Pro and Wantai kits, respectively. Among 2011 samples, 22 samples, which were negative with Wantai assay, were detected as anti-HEV positive by Dia.Pro assay, while 37 samples were anti-HEV positive with Wantai assay which were negative with Dia.pro indicating variability between the assays. Anti-HEV total Ab positivity was consistently detected with both assays in 206 (10.6%) samples. The lowest detectable antibody concentrations were 0.16 and 0.14 WHO units/ml, for Dia.Pro and Wantai assays, respectively.
Conclusion: Compared to the previous studies, HEV was shown to have a higher overall seroprevalance in Turkey as reflected by the results from the cities included in the study. Although not significant, the calculated seroprevalances demonstrated that Wantai kit has found higher rates of HEV positivity for all cities compared to Dia.pro kit. Despite the fact that similar results from both kits indicated a reliable accuracy for the calculated HEV prevalence, the observed variability in assay performances might be explained by the differences in HEV antigens used in each assay suggesting that the interpretation of the HEV serology results should be done with caution.

SAT-172

Novel mathematical modeling of HBsAg kinetics during long-term antiviral treatment: A pilot study

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Background and aims: The kinetics of serum hepatitis B surface antigen (HBsAg) levels during nucleos (t)ide analog (NA) treatment needs to be elucidated for the prediction of off-treatment durability of response in patients with chronic hepatitis B (CHB). The aim was to develop a novel method of mathematical modeling for HBsAg kinetics under long-term NA treatment.
Method: In this pilot study, we reviewed viral decay patterns and HBsAg kinetics in 184 CHB patients from a tertiary hospital in Korea who were treated with entecavir or tenofovir as their initial NAs, without evidence of antiviral resistance. HBsAg and immune effectors were added as new compartments in the model equations for hepatitis B viral dynamics. Parameter estimation was performed using the non-linear least square minimization method and non-linear Kalman filter algorithm.
Results: Mean age was 52.1 ± 10.9 years, and 112 patients (60.9%) were male. Patients received either entecavir (93, 50.5%) or tenofovir (91, 49.5%). Median follow-up duration was 72.5 months. At baseline, 70 patients (38.0%) were HBeAg-positive. Baseline liver stiffness by transient elastography was 6.9 kPa (median; interquartile range [IQR], 4.6-11.1), and alanine aminotransferase (ALT) was 81.0 IU/L (IQR, 39.3-161.8). Baseline HBV DNA and HBsAg titers were 6.26 Log_{10}IU/ml (IQR, 5.34-7.54) and 2420.50 IU/ml (IQR, 1083.25-

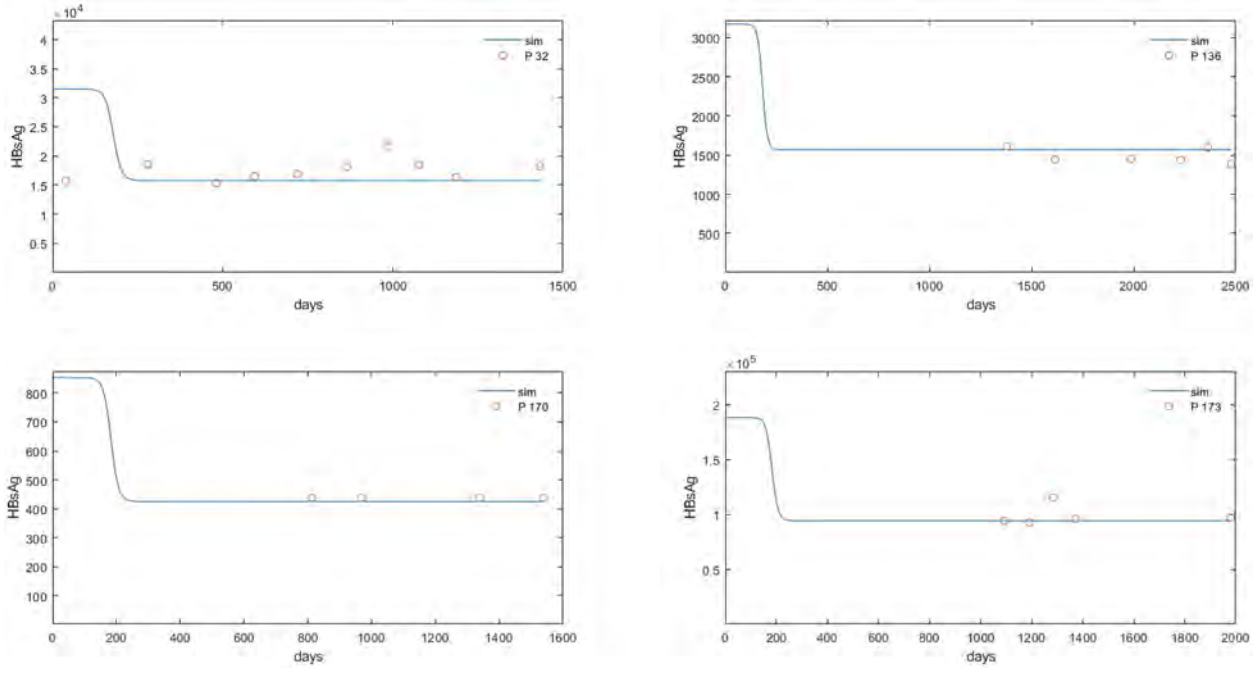

Figure: (abstract: SAT-172)

5342.12), respectively. The model equations for viral and HBsAg dynamics during antiviral treatment were developed as follows, considering i) both cytolytic and non-cytolytic clearance of infected cells, and ii) cccDNA and integrated HBV DNA in the host genome as dual sources of HBsAg:

$dT_1/dt = S\text{-}d_{T1} * T_1 - (1-\eta)\, b * V * T_1$

$dT_2/dt = \alpha * f * I * E\text{-}d_{T2} * T_2 - (1-\eta)\, b * V * T_2 + m_2 * T_2$

$dI/dt = ((1-\eta)\, b * V\, (T_1 + T_2) + m_1 * I\text{-}d_I * I\text{-}\alpha * I * E$

$dV/dt = (1-\varepsilon)\, p * d_I * I\text{-}c * V$

$dE/dt = S_E + b_E * I * E/\, (I + k_E)\text{-}d_E * E$

$sAg = \gamma * T_2/\, (T_2 + k_T) + \delta * I/\, (I + k_I)$

(NOTE. T, target cell; I, infected cells; V, virus; E, immune effectors; sAg, HBsAg; d, death rate; η, treatment efficacy of inhibiting de novo infection; b, de novo infection rate of T; f, calibration coefficient of α for T; m, mitotic production rate of I; α, E-induced clearance rate of I; ε, treatment efficacy of inhibiting viral production; p, viral production rate by I; c, clearance rate of free virions; S_E, production rate of E; b_E, maximum birth rate for E; k_E, Michaelis-Menten type coefficient for E)

Figure 1 demonstrates sample visualization of the HBsAg kinetics with fitted curves using the model equations.

Conclusion: Our novel mathematical model for hepatitis B viral dynamics showed promising results in terms of long-term fitting of HBsAg kinetics. These results need further validation in various clinical settings including discontinuation of NAs.

SAT-173

Global patterns of HBV genotype E epidemic dispersal from Africa determined using a full-genome phylogenetic and phylogeographic approach

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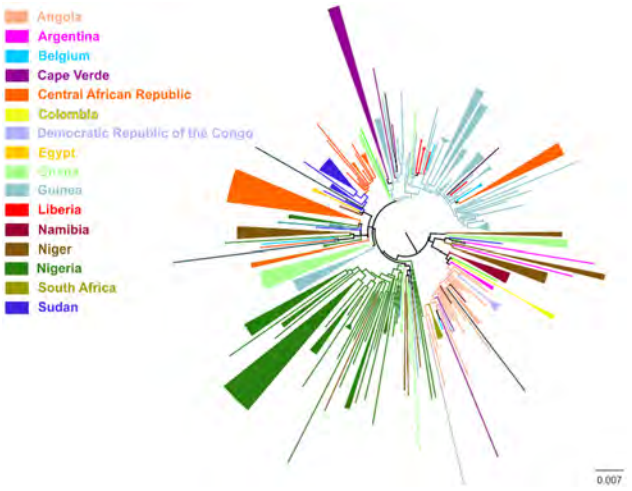
Background and aims: The Hepatitis B virus (HBV) (sub)genotypes circulating in Africa include A1, D3 and E, with E prevailing in W. Africa where HBV is hyperendemic. Unlike subgenotype A1, genotype E is rarely found outside Africa. Despite the wide geographical distribution in Africa, genotype E has a very low genetic diversity. Genotype E has a unique serological subtype ayw4 and a 3-nucleotide deletion in the preS1 region. Our aim was to estimate the levels of regional dispersal of genotype E, in order to shed light on how the virus has been disseminated within different geographic areas.

Method: We analyzed 271 full-length HBV/E sequences available on the HBV database. The number of sequences per geographic region was: W. Africa: 172, C. Africa: 50, E. Africa: 18, America: 9, S. Africa: 8, Europe: 8, N. Africa/Middle East: 5 and Asia: 1. Phylogeny reconstruction was conducted by the maximum likelihood method. We defined as regional dispersal the sequences found within highly supported (bootstrap value > 70%) monophyletic clusters, within which 70% of HBV/E strains share the same geographic area of sampling. Phylogeographic analysis was conducted by the criterion of parsimony.

Results: Analysis revealed that 55% (N = 149) of the HBV/E sequences were found within monophyletic clusters. Country-wise analysis showed that HBV/E sequences form regional clusters at different percentages according to their geographic origin. Specifically, 100% of the sequences from Democratic Republic of the Congo form a single monophyletic cluster. The same pattern was observed for Argentina, Colombia, Egypt and South Africa. High levels of regional dispersal were found for Ghana (79%), Niger (75%), the Central African Republic (71%), Liberia (67%), Namibia (67%) and Sudan (67%). A high number of sequences from Guinea (60%) and Nigeria (54%) were found within 14 and 9 monophyletic clusters, respectively. Sequences from Cape Verde (43%), Belgium (33%) and Angola (11%) revealed the lowest regional dispersal. In addition, we found that sequences from W. Africa were located close to the root of the tree.



Conclusion: Our analysis suggests considerable differences in the patterns of HBV genotype E regional dispersal. Genotype E showed a strong pattern of regional dispersal suggesting that the population movements associated with cross-border transmissions were limited. Genotype E epidemic probably originated in W. Africa and expanded to other regions inside and outside of Africa.

SAT-174

Formation of the occult chronic hepatitis B during antiviral therapy in patients with HIV + HBV + HDV + HCV infection: Clinical cases

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Background and aims: Occult HBV infection can develop in patients after acute hepatitis B, in patients with chronic HBV-infection who have eliminated HBsAg and in seronegative patients infected with small amounts of the virus, insufficient to form an immune response. We observed patients with HIV + HBV + HDV + HCV infection, one of whom (F4 fibrosis stage, HBeAg-negatif) underwent HBsAg seroconversion after the end of therapy with pegylated interferon alpha-2a 180 μg and ribavirin 1200 mg and continued the antiretroviral (HAART) therapy with tenofovir DF 300 mg + lamivudine 300 mg + atazanavir 300 mg/ritonavir 100 mg once daily (OD). In the second patient (F4 fibrosis stage, HBeAg-negatif) seroconversion of HBsAg occurred 6 years after the administration of pegylated interferon alfa-2b and ribavirin 1000 mg with continuing the HAART using lamivudine 300 mg OD till now. Both patients have achieved SVR after treatment of HCV (genotype 1b). In both patients, HBV cccDNA was detected in the liver tissue after HBsAg seroconversion.

Method: The concentration of HBV DNA, HDV RNA, HCV RNA, HIV RNA in blood serum and HBV cccDNA concentration in liver biopsy specimens of two men aged 40 and 49 years was evaluated. There was also performed the qualitative determination of HBsAg, anti-HCV and anti-HDV in blood serum of these patients. The detection of HBV cccDNA in the liver tissue was performed according to Pollicino T. et al., using TaqMan probes for real-time PCR.

Results: Case 1*: Pegylated interferon alpha-2a 180 μg for 96 weeks.

Time period Indicators	Baseline	End of treatment with PIFN	12 Month follow-up	48 Month follow-up
HBsAg	**Posit.**	Neg.	Neg.	**Neg.**
ALT (IU/ml)	53	62	25	15
HBV DNA	**Posit.**	Neg.	Neg.	**Neg.**
cccDNA (copies/ cell)	-	-	-	**0.737**

*Patient is continuing HAART with tenofovir DF 300 mg + lamivudine 300 mg + atazanavir 300 mg/ritonavir 100 mg OD

Case 2*: Pegylated interferon alpha-2b 180 μg for 48 weeks.

Time period Indicators	Baseline	End of treatment with PIFN	12 Month follow-up	72 Month follow-up
HBsAg	**Posit.**	Posit.	Posit.	**Neg.**
ALT (IU/ml)	34	28	11	13
HBV DNA	**Neg.**	Neg.	Neg.	**Neg.**
cccDNA (copies/ cell)	-	-	-	**0.865**

*Patient is continuing HAART with lamivudine 300 mg OD

Conclusion: Seroconversion of HBsAg in these patients is probably the result of effective antiviral therapy. However, the presence of cccDNA in hepatocytes testifies to the formation of occult HBV infection, which requires further careful monitoring of immunological and virological indicators, in view of the possible activation of the infectious process.

SAT-175

Recruitment of HBx on HBV DNA depends on FXR and is inhibited by FXR agonist

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Background and aims: HBV infection and bile acids metabolism are interdependent. HBV infection increases expression of the BA nuclear receptor FXR in infected patients. Reciprocally, FXR is a proviral factor for HBV whose activity is inhibited by FXR agonists, in vitro and in vivo. Presence of FXR favors cccDNA completion as well as viral mRNAs transcription, likely through its binding to two HBV genome sites (FXRE). Since FXR and HBx interact, we aimed at deciphering the respective role of HBx and FXR, and ligand, in controlling HBV transcription.
Method: Expression of FXR was studied in HBV-permissive differentiated HepaRG (dHepaRG) and in hepatocarcinoma cell line Huh7. dHepaRG were infected HBV WT or ΔHBx-HBV. ChIP were realized in Huh7 transfected with Enh2/Cp regulatory region of HBV containing the two FXRE. FXR KO Huh7 cell line was generated through FXR-shRNA to study the impact of HBx on FXR fixation at FXRE. FXR agonist GW4064 (GW) was used at 10μM.
Results: HBV infection with either wild type or ΔHBx-HBV increased FXR expression at the protein level in agreement with in vivo observations, when treatment with FXR agonist decreased this expression. Down regulation of FXR by agonists renders difficult studying the effect of that molecule on FXR binding to FXRE in dHepaRG. On the opposite, agonist increased FXR protein expression and/or stabilization in Huh7. We thus took advantage of this particular FXR expression regulation to perform FXR and HBx-ChIP in Huh7 transfected with Enh2/Cp promoter. FXR-ChIP revealed FXR presence in the Enh2/cp in a dose dependent manner. GW treatment decreased FXR presence at the viral promoter in contrast to FXR stabilization at the BSEP promoter. RXR was also recruited at the Enh2/Cp and released after GW treatment, again at odds with the stabilization at the BSEP promoter. When HBx was cotransfected in Huh7 or shFXR-Huh7 cells with Enh2/Cp region, HBx was recruited to the viral promoter but not in the shFXR-Huh7 cells or in presence of agonist.
Conclusion: Altogether, data suggest that FXR proviral activity depends on its binding to the viral genome at the Enh2/Cp region. Presence of FXR might recruit cellular factors for cccDNA completion and HBx for efficient transcription. Inhibition of FXR proviral activity by agonist might result from repression of FXR expression and of the release of FXR from its viral targets. This later effect seems to be DNA sequence dependent since agonist stabilize FXR on cellular promoter.

SAT-176

The effect of HBV and HCV infection on pregnancy status

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Background: HBV and HCV infections affect 1-7% and 0.2-2.4% pregnant women in Europe. The assessment of impact of these infections on pregnancy is still uncertain.
The aim of study was to assess the course of pregnancy and the condition of a children born by pregnant women infected with HBV or HCV.
Methods: The study included 148 women infected with HBV and 46 with HCV. The control group consisted of 330 healthy pregnant women living in the same region.
Results: All pregnant women infected with HBV were HBeAg negative. HCV infection was caused in 67% by genotype 1b, 20%-3a and 13%-4. Increase of HBV DNA between 6 and 32 week of pregnancy was found in 46%, decrease in 15%, and in 39% remained unchanged. Among both HCV and HBV infected, the incidence of miscarriages was significantly higher than in healthy women (8.6% and 4.1% vs. 1.8%; $p < 0, 05$). In 4 patients infected with HBV who had a miscarriage, HBV viremia was 4.0 log IU/ml and 2 was undetectable. Significantly more frequent premature deliveries were in HCV and HBV infected than in the control group (2.2% and 3.4% vs. 0.6% $p < 0.05$). The duration of pregnancy was shorter, the birthweight of the children was lower and APGAR score was lower among those infected with HCV and HBV compared to children born to healthy mothers. Among newborns born by HCV and HBV infected, the cyanosis (23.9% and 10.8% vs. 6.4%;) and breathing disorders (8.7% and 4, 1% v. 0, 9%; $p < 0.05$) were more frequent.
Conclusions: HCV and HBV infection in pregnancy increase the probability of miscarriages affecting more frequent occurrence of cyanosis, respiratory disorders and lower birth weight of newborns compared to children born by healthy women.

SAT-177

Loss of HBsAg by patients with high levels of HBV-DNA during treatment with nucleoside or nucleotide analogues

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Background: Treatment with pegylated interferon (PEG IFN) in patients with chronic HBV infection and high HBV DNA levels is not recommended. Such patients are usually treated with nucleoside or nucleotide analogues (NUCs).
The aim of this study is to find the factors conducive to the loss of HBsAg during therapy with NUCs among patients chronically infected with high viral load.

Methods: Analysis of patients who cleared HBsAg was carried out among 470 treated with NUCs in two hepatologic centers between 2010 and 2018.
Results: The loss of HBsAg was found in 19 patients, more often in men then women (63% vs. 37%). The time of infection ranged from 1 to 28 years and no relationship between the time of infection and HBsAg clearance was found. In 3 cases HBeAg was present. The mean age of patients was 63 years and only one was below 45 years. The mean viral load before start of therapy was 7 Log IU/ml. No patient was previously treated with PEG IFN, 63% patients received more than one NUCs, and 37% were treated with only one NUC. Elimination of HBsAg was most frequently observed after treatment with Entecavir (58%, mean treatment duration 63 months) less often after Tenofovir (16%, mean treatment duration 44 months) or Lamivudine (16%, mean treatment duration 113 months). In 74% patients anti-HBs antibodies appeared after HBsAg clearance and in 21% after liver transplantation. The advancement of hepatic fibrosis did not affect chance of HBsAg elimination.
Conclusions. Age over 45 years as well as male gender predispose to a more frequent elimination of HBsAg in patients treated with NUCs. The elimination of HBsAg among patients with high levels of HBV-DNA is the most likely during treatment with entecavir. Liver transplantation promotes elimination of HBsAg.

SAT-178

Identification of Hepatitis B virus events in liver and peripheral blood mononuclear cells in individuals with chronic hepatitis B infection

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Background and aims: The Hepatitis B Virus (HBV) can integrate into host genomes with implications towards hepatocellular carcinoma (HCC) development. HBV genomes are found within circulating peripheral mononuclear blood cells (PBMCs), but viral integration and subsequent genetic alterations within the PBMC compartment is unknown. We aim to characterize viral integration in the liver and PBMC of chronic hepatitis B (CHB) carriers with and without HBV-related HCC.
Method: Plasma and PBMC was collected from 16 CHB carriers diagnosed with HBV-related HCC (11 M, median age 62, 14 Asian; 2 African, 13 on nucleos/tide analog therapy [NAT]) in parallel to 14 non-HCC CHB carriers (8 M, median age 48, 10 Asian; 2 African; 2 Caucasian, 9 on NAT). Explant liver tissue from 10 additional cases of end-stage HBV-related HCC (8 M, median age 57, 10 Asian, 9 on NAT) were also collected. HBV-specific regions were amplified from phenol chloroform extracted total DNA derived from liver or plasma and PBMC tissues by nested PCR. Viral-host integration sites in liver and PBMC DNA were identified with AluPCR followed by clonal sequencing of amplicons. Sequences were analysed with MEGA 7 and NCBI blast.
Results: HBV DNA was detected in all patient plasma, PBMC, and liver samples by HBV-specific nested PCR. In the PBMC of the non-HCC and the CHB + HCC cohorts, 44 and 48 HBV-host integration sites were detected, respectively. 13/44 and 17/48 of these sites were present within known coding genes. 110 integration sites were detected in the liver tissues, of which 16 are within known coding genes. HBV integration in genes potentially implicated in oncogenesis, such as SCAI, NECTIN2, and CDKN3, was identified in all cohorts.
Conclusion: Despite long-term NAT, CHB carriers ± HCC show persistent HBV genomes in plasma, PBMC, and liver. Viral integration in known coding genes were identified in both liver and PBMC-derived DNA. Many of these genes have recognized and/or suspected roles in cancer or are components in key signalling pathways which may have oncogenic implications when disrupted.

SAT-179

Human liver organoids culture as a novel in vitro model of HBV infection

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Background and aims: The use of primary hepatocytes as a model of HBV infection is limiting due to rapid dedifferentiation and short lifespan. In an effort to develop a physiological human model of HBV replication we used the method developed by *Huch* to isolate 3D human liver organoids that demonstrate mature hepatocyte function, genetic stability, long-term expansion and importantly they retain the genomic background of the tissue of origin. Our aim was to assess liver organoid culture as a novel *in vitro* model for characterisation of the HBV life-cycle, cellular response and antiviral susceptibility testing.
Method: Human liver organoids were generated following isolation of LGR5+ ductal stem cells from liver resection followed by expansion and differentiation into 3D culture. Hepatocyte differentiation markers (albumin, CYP3A4) and NTCP (bile acid transporter and high affinity HBV receptor) expression were evaluated using qRT-PCR and confocal microscopy. Infection of organoids was performed using HepAD38 cell culture derived HBV (genotype D) at 1000 GE/cell and HBV total RNA harvested and quantified by qRT-PCR at 12 dpi while HBV infected cells (HBsAg, HBcAg) were visualised by immunofluorescence detection.
Results: Differentiation of organoids was confirmed by expression of albumin and CYP3A4 and loss of LGR5 (qRT-PCR and confocal microscopy) and hepatocyte polarisation as assessed by the redistribution of Zona occludens-1 to tight junctions (confocal microscopy). Undifferentiated organoids did not express the HBV receptor, NTCP, while differentiated organoids expressed NTCP at the mRNA level with concomitant expression at the cell surface. Differentiated organoids were successfully infected with HBV as confirmed by an increase in HBV RNA over time and immunostaining for HBcAg and HBsAg by confocal microscopy. No adverse effects on cell or overall organoid viability were noted following infection.
Conclusion: We have successfully generated liver organoid cultures that retain a hepatocyte phenotype that express the NTCP receptor and are permissive to HBV infection. These findings accentuate the utility of human liver organoids as a HBV infection model, with the potential to further dissect HBV replication and the cellular response in a model system that more accurately reflects human HBV infection. Liver organoids also show promise as a personalised antiviral testing platform to guide future HBV cure therapy and to study resistance.

SAT-180

Hepatitis delta genotype 1 and 3 do not replicate after coinfection in the same cell in vivo

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Background and aims: Hepatitis D Virus (HDV) is a single strand circular RNA virus which is classified into eight genotypes. HDV-3 is known to cause severe hepatitis, while patients infected with HDV-1 can develop a wide range of severity. Moreover, it is not known whether sequence and protein diversity between genotype 1 and 3 may allow coinfection and productive replication of both viruses at single cell level. In this study we aimed to investigate the kinetics of coinfection and superinfection of HDV-1 and HDV-3 in vivo both intrahepatically and at single cell level.
Method: Human-liver chimeric mice stably infected with HBV infected were (A) co-infected with HDV-1 and HDV-3 or (B) first infected with HDV-1 and after 9 weeks superinfected with HDV-3 or vice versa. All mice were sacrificed 9 weeks after the last infection. Virological parameters were determined by strain specific qRT-PCR (serum and liver) and using strain specific RNA in situ hybridization (ISH) and immunofluorescence staining of HDAg.
Results: Mice co-infected with HDV-1 and HDV-3 developed viremia for both genotypes; however, HDV-3 was the dominant strain in serum (> 2 log difference) and in the liver, both at RNA and protein levels. Interestingly, ISH revealed the lack of co-existence of anti-genomic HDV1 and HDV3 RNA at single cell level, suggesting strong viral interference. Moreover, the step-wise infection experiments, where stably HDV1 infected mice were superinfected with HDV3, showed that HDV-3 remained below detection in serum. Similarly, dominance of the first virus was determined also when HBV/HDV-3-infected mice were superinfected with HDV-1.
Conclusion: Although HDV3 spread more efficiently and hence appeared dominant, co-infection of HDV1 and HDV3 in the same liver could be detected. However, double infection was never observed at single cell level, indicating that superinfection exclusion in vivo does exist, at last between HDV3 and HDV1. Such coinfection exclusion may allow HDV to evade excessive recombination by incoming viruses. Further studies are needed to analyze whether the inability of delta protein to support replication of distant HDV genotypes is responsible for the observed phenomenon.

SAT-181

Efficacy and safety of glecaprevir/pibrentasvir in patients with severe renal impairment in Japan: A prospective, multicenter study (KTK 49 Liver Study Group)

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Background and aims: In the present analysis of a multicenter study, we evaluated the efficacy and safety of Glecaprevir/Pibrentasvir for chronic hepatitis C Japanese patients with severe renal impairment.
Method: Chronic hepatitis C Japanese patients treated with Glecaprevir/Pibrentasvir between November 2017 and June 2018 were subjected to the present analysis. Patients received Glecaprevir/Pibrentasvir for 8 or 12 weeks according to patient's characteristics. For patients with liver cirrhosis, genotype 3 and patients who failed to achieve SVR with prior DAAs IFN-free treatment, patients were treated with Glecaprevir/Pibrentasvir for 12 weeks. For the remaining patients, the patients such as DAAs naïve, genotype1 and 2, and non-cirrhosis were treated with Glecaprevir/Pibrentasvir for 8 weeks.
Results: Of 1, 003 chronic hepatitis C patients, 142 had CKD stage 4, 5. The patients comprised 107 males and 35 females. The median age was 68 years (range, 38-89 years). Patients with genotype 1b, 2a, 2b and 3 were 30, 59, 28 and 1, respectively. The median eGFR level at baseline was 6.3 ml/min/1.73 m^2; 19.7% (28/142) had CKD stage 4, 80.3% (114/77) had CKD stage 5. Of these, 73.2% (104/142) were undergoing hemodialysis or hemodiafiltration. Of all the patients, 4.2% (6/142) had previously received IFN-free DAAs treatment. The overall SVR rate was 99.3% (141/142). SVR rates in the patients with 8 weeks and 12 weeks were 98.6% (72/73) and 100% (36/36), respectively. Among the 6 patients who failed to achieve SVR with IFN-free DAAs treatment, the SVR rate was 100%. All of the patients with cirrhosis achieved SVR. The SVR rates as per the CKD stage were 100% (24/24) in stage 4, 98.8% (84/85) in stage 5. Almost of all patients undergoing hemodialysis achieved SVR (79/80). Time-course changes in eGFR levels were analyzed in the patients with CKD 4 and 5 without hemodialysis. The most common adverse event was pruritus. In particular, it was frequently observed in patients CKD 5. Multiple logistic regression analysis was performed to clarify the factors associated to the appearance of pruritus. Hemodialysis therapy and hypoalbuminemia were extracted as statistically significant independent factors related to pruritus.
Conclusion: The present analyses of a multicenter, prospective study demonstrated that Glecaprevir/Pibrentasvir is highly effective and safe for chronic hepatitis C Japanese patients with severe renal impairment.

SAT-182

Full length deep sequencing of South African hepatitis B virus isolates reveals increased viral diversity and X-gene deletions in hepatocellular carcinoma patients

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Background and aims: More than 60% of hepatocellular carcinoma (HCC) cases in South Africa are associated with chronic HBV infection. Mutations within the HBV genome have been associated with an elevated risk of HCC development. The aim of this study was to describe the differences in genetic diversity of HBV among South

African adults with HCC and those with chronic HBV infection (CHB) without HCC using deep sequencing.
Method: Blood was collected from 10 patients diagnosed with HBV-associated HCC and 10 patients with CHB. Patients with HIV co-infection and HBeAg positivity were present in both groups. HBV DNA was extracted from plasma and the viral load was quantified by qPCR. Libraries were prepared using a Nextera kit, pooled and then underwent target enrichment with custom-designed pangenotypic HBV probes. Libraries were sequenced on an Illumina Mi-Seq platform and data analysed using a bespoke pipeline.
Results: HBV viral loads were significantly higher in HCC patients ($p = 0.001$). 10/10 HBV HCC and 9/10 CHB samples were successfully sequenced, generating medians of 82196 reads/sample and coverage of 3536 reads/site after deduplication. HBV genotypes A, D and E were identified in both HCC and CHB groups. Resistance mutations L180I and M204I, associated with Lamivudine resistance, were identified at the consensus level in one HCC individual.
Two peaks of diversity were evident within both the HCC and CHB patients, spanning the regions at the end and start of polymerase where only a single gene is encoded. Median within-host viral diversity was significantly higher amongst patients with HCC ($p = 0.03$). X-gene deletions of 8-21 nucleotides (nt) and core deletions of 24-48 nt were identified in the consensus sequences in 3 and 2 HCC patients, respectively, but not in any CHB patients. There was no associations between viral diversity and HIV status, HBeAg positivity or nucleoside analogue therapy.
Conclusion: An unbiased deep sequencing approach specifically enriching for HBV was successfully applied to look for viral differences in HCC vs CHB patients of African origin. Well-described deletions in Core and X-gene were observed in HCC patients infected with genotypes A and E. Continued application of such methods with larger African cohorts will facilitate improved insights into the aetiology of HCC in HBV-infected individuals in the region.

SAT-183

High resolution insight into hepatitis B virus infection and immunity in Africa to inform on intervention strategies

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Background and aims: "Catch-up" HBV vaccination in adults is sometimes employed in working towards the UN 2030 elimination targets. Epidemiological studies and informed interventions for HBV typically only examine the prevalence of hepatitis B surface antigen (HBsAg), a biomarker of active infection. Given the high rates of natural clearance (> 90% in healthy adults), the background of immunity should also inform intervention strategies. We examined the relationship between HBV exposure and active infection in Africa.
Method: We undertook a systematic search of multiple databases in June 2018, using PRISMA criteria to identify studies from adult African populations including data for both anti-HBc and HBsAg prevalence. We used the United Nations geoscheme for Africa to define a list of countries and to sub-divide the region into North (NA), Southern (SA), West (WA), East and Central Africa (CA). Immunity to HBV was defined as HBV core antibody (anti-HBc) positive and HBsAg negative.
Results: We identified 89 studies spanning 37 countries. Across Africa, HBsAg prevalence is positively correlated with total anti-HBc, $p < 0{\cdot}0001$. The prevalence of both HBsAg and anti-HBc positivity are highest in WA, with the lowest exposure and infection rates in NA. There were notable differences in HBsAg prevalence between NA and SA ($p = 0.04$) without any corresponding difference in anti-HBc prevalence ($p = 0.99$). For any given anti-HBc prevalence, the observed HBsAg prevalence in SA was typically two-fold greater than in NA (Fig 1A).
Population exposure to HBV positively correlated with HBsAg prevalence in all regions except CA, where there was no association between HBsAg and anti-HBc ($p = 0.99$, Fig 1B). There were no significant differences in HBsAg or anti-HBc prevalence between HIV positive cohorts ($N = 26$) and other cohorts ($p = 0{\cdot}16$ and $p = 0{\cdot}42$, respectively).

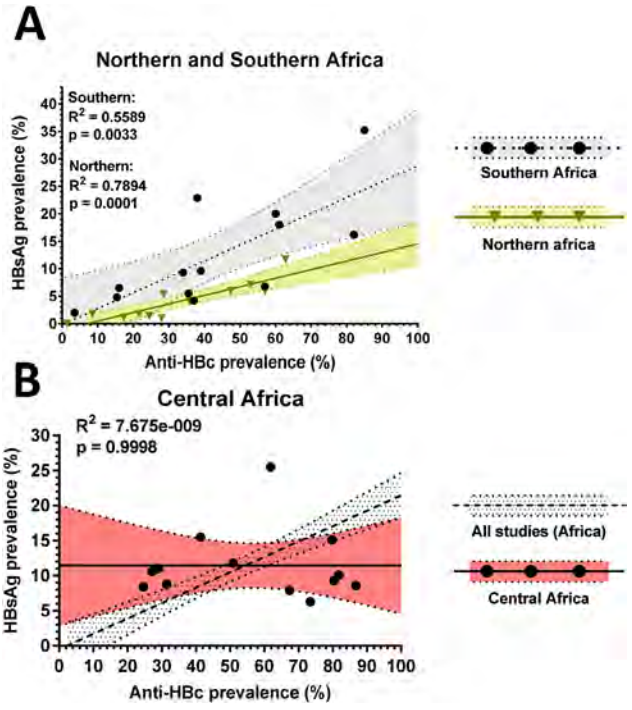

Figure 1: Relationship between anti-HBc (exposure) and HBsAg (active infection) with linear regression analysis in (A) Northern and Southern Africa and (B) Central Africa and all African studies.

Conclusion: We identified distinct regional associations between chronic HBV infection and exposure in Africa. Numerous factors are likely to influence these differences including age at exposure, transmission routes, host genetics and viral genotype.
Population exposure to HBV was ≥ 70% in 24% studies indicating that adult vaccination would benefit < 30% adults, many of whom would clear the infection naturally if exposed. Alternative interventions targeting adults, incorporating diagnosis and treatment, will have considerably more impact in highly endemic populations.

SAT-184

Approximation of the genotype distribution within global chronic hepatitis B virus infections

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Background and aims: Hepatitis B Virus (HBV) is genetically diverse and divided into nine genotypes, A to I, that differ in their primary transmission route, chronicity rate, development of liver cirrhosis and hepatocellular carcinoma and treatment response to Interferon-α. So far, it is not known how many of the 250 million chronic HBV infections are caused by which genotype. This knowledge, however, could assist to specify the HBV disease burden, plan health policies, optimize diagnostic tests, and develop new broadly active antiviral therapies.
Method: We performed a comprehensive literature research on studies reporting HBV genotyping data throughout the world. Over 800 publications were assessed and genotyping data extracted from 194 sources covering 127 countries. Using previously published HBsAg country-estimates and UN population data, we estimated the number of infections with each HBV genotype per country and world-region and the genotype distribution within global chronic HBV infections.
Results: Distinct differences in the genotype distribution between world regions were confirmed in our study. The drastic differences in HBV endemicity and population levels between world-regions strongly influenced the world-wide genotype distribution. Genotypes with frequent appearances in high-endemic areas such as Sub-Saharan Africa and Eastern Asia were found to cause a majority of global HBV infections. We estimated that approximately 96% of global HBV infections are caused by only five (A-E) of the nine genotypes: Genotype C was found to cause most infections (26%), followed by genotype D (22%), E (17%), A (17%) and B (14%). The four remaining genotypes F-I were estimated to cause together less than 2% of global HBV infections.
Conclusion: While alluding to major biases inherent in such studies, our work provides an up to date review of world-wide genotyping results and an initial approach to estimate the genotype distribution within global HBV infections. It furthermore reveals world areas with poor genotyping data which should be addressed in future studies. Besides clinical implications of the HBV genotype distribution, our study highlights the need to expand HBV cell culture and animal models to at least include genotypes A-E to represent the fast majority of global HBV infections.

SAT-185

Is the performance of ultra-sensitive HBsAg Fujirebio assay consistent across HBV genotypes (comparison between CLEIA HBsAg HQ Fujirebio and Abbott Architect assays)

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Background and aims: HBsAg quantification plays an important role in the management of chronic hepatitis B infection. Several testing platform are available, but there is limited data about the assays performance across HBV genotypes in patients with low HBsAg levels. In this pilot study we aimed to compare HBsAg levels tested on using Abbott Architect™ assay (standard of care) vs. Fujirebio an ultra-sensitive chemiluminescent enzyme immunoassay (CLEIA) HBsAg HQ on Fujirebio Lumipulse G600II platform in chronic hepatitis B patients with low HBsAg levels (0-150 IU/ml) across the different HBV genotypes.
Method: Frozen serum samples collected between 2017 and 2018 from 203 chronic hepatitis B (CHB) patients, all HBeAg negative with known level of HBsAg (0.1-150 IU/ml) tested on Abbott Architect were tested using CLEIA HBsAg-HQ assay (Fujirebio). HBV DNA levels were measured by TaqMan (Roche). HBV genotypes were determined by in-house direct sequencing. Bi-variate non-parametric correlations and rank tests were used to compare both assays.
Results: 197 patients (57% males, median age 49 yrs) had HBsAg levels below detection limit of 150 IU/ml of Fujirebio and based on the initial HBsAg levels were stratified into 3 groups: HBsAg 0.1-10IU/ml (n = 72), HBsAg 10-100IU/ml (n = 98) and HBsAg 100-1000 IU/ml (n = 27). There was the following genotypes distribution in our cohort: A (15%), B (23%), C (14%), D (21%), E (26%) and G (1%). 112 patients had not detected HBV DNA at time of this test. Median HBsAg levels were similar between Abbott (18.6, range 0.1-164) and Fujirebio (17.7, 0.1-150IU/ml) and there was a strong bi-variate correlation ($r = 0.977$, $p < 0.001$). When the comparison was made between the individual genotypes the strongest correlation was noted for genotypes E ($r = 0.985$), B ($r = 0.98$) and A ($r = 0.974$) in contrast to genotypes ($r = 0.952$) and D ($r = 0.969$). The assessment according to HBsAg levels revealed strong correlation between tests at levels 0.1-10IU/ml ($r = 0.967$) with gradual decline with increasing HBsAg levels (10-100 IU/ml, $r = 0.86$ and for 100-1000 IU/ml, $r = 0.545$). Median levels differed significantly between Abbott and Fujirebio in genotype C (50.5 vs 68.4IU/ml, $p < 0.01$) and E (17.2 vs. 22.6 IU/ml, $p < 0.01$) patients and patients with HBsAg levels between 10 and 100 IU/ml (27.2 vs. 28.3 IU/ml, $p < 0.05$).
Conclusion: Despite a very strong correlation between HBsAg levels tested by Abbott Architect and Fujirebio CLEIA HQ assay, there are differences in assay performance across HBV genotypes and HBsAg levels. These findings warrant further evaluations in larger cohorts of patients across HBV genotypes and HBV variants.

SAT-186

Pathophysiological impact of HCV on mitochondrial composition and functions

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Background and aims: Hepatitis C virus (HCV) is known to perturb hepatic glucose and lipid metabolism with major patho-physiological consequences including an acceleration of the disease towards liver cancer. However, on the molecular level these processes remain obscure. Mitochondria play a key role in cellular homeostasis. In response to a variety of heterogeneous, external and internal signals such as for example innate immunity, metabolic status and ER/oxidative stress, they adapt cellular metabolism and energy production, activate inflammatory processes or induce apoptosis. This study aims to understand mitochondrial morphological and functional alterations in response to HCV infection and their implication in HCV pathophysiology.
Method: The hepatoma cell line Huh7.5 infected with the HCV JFH1 strain and liver biopsies were used in this study. In order to explore the interactions of HCV with mitochondria and the resulting impact on mitochondrial functions, biochemical fractionation, proximity ligation assays and various functional assays such as mitochondrial respiration, membrane potential, Ca2+ transfer and ROS production were assessed.
Results: Biochemical fractionation revealed the presence of viral proteins at MAMs (Mitochondrial Associated Membranes), the sites of contact between mitochondria and ER, that control metabolic homeostasis, calcium signaling as well as apoptosis. We also observed a modulation in the composition and quantity of MAM resident proteins in HCV infected cells. Genetic ablation by CRISP/Cas9 technology and overexpression of these MAM resident factors in Huh7.5 cells demonstrated that they play pivotal roles in HCV infection and concomitantly impact glucose homeostasis, the central carbon metabolism and respiratory functions in mitochondria.

Finally, we have explored the impact of HCV on mitochondrial functions in more detail, and show that the virus specifically alters activity of respiratory complex 1, with maintained Ca2+ levels in mitochondria albeit the presence of profound ER stress.
Conclusion: Our study advanced our current understanding of the HCV-host interactions. Our data show that HCV associates with mitochondria and MAM, and that infection is associated with changes in mitochondrial functions including increased complex 1 activity, increased superoxide production and maintenance of mitochondrial Ca2+ signaling. These changes may play major role in disease progression. Given that MAM alterations were previously shown to contribute to altered metabolism in liver cancer, our results may also unravel a role of MAM as a driver for HCV-induced liver hepatocarcinogenesis.

SAT-187

Characterization of hepatitis e infection in israel: identification of HEV-7 in camels and high seroprevalence in specific human populations

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Background and aims: Hepatitis E virus (HEV), mainly genotype 1 (HEV-1) and genotype 3 (HEV-3), is a major cause of viral hepatitis worldwide. HEV seroprevalence is ubiquitously age dependent, and is associated with specific population groups. Previously, we have shown that in Israel, HEV-3 is endemic in swine and circulates in sewage however all clinical cases reported were of HEV-1. Recently HEV-7 was shown to infect dromedary camels and cause viral hepatitis in humans. Here, we studied HEV in dromedary camels and in specific populations (Bedouins living in the vicinity of camels, Arabs Muslims, none-Bedouins and Jews), assessed factors associated with anti-HEV seropositivity and determined HEV genotype in camels found to be HEV RNA positive.
Method: Randomly selected serum samples from > 20 years old, Israeli-born Bedouins (n = 305), non-Bedouins Muslim Arabs (n = 320) and Jews (n = 195) collected between 2009 and 2016 were serologically assessed. In addition, serum samples from different age groups dromedary camels (n = 234), collected between 2015 and 2018 were serologically (n = 86) and molecularly (n = 234) assessed. HEV seroprevalence was determined using Wantai IgG ELISA assay and HEV RNA (in camel samples) with Altona real-time PCR assay. HEV ORF2 amplified from HEV RNA positive samples was used for phylogenetic analysis.
Results: Bedouins and non-Bedouin Arabs had significantly higher prevalence of HEV antibodies (21.6% of 305 samples and 15.0% of 320 samples obtained from Bedouins and non-Bedouin Arabs, respectively) compared to Jews (3.1% of 195 samples, p value < 0.05). Seropositivity increased significantly with age in all human populations, reaching 47.6% and 34.8% among ≥ 40 years old, in Bedouins and non-Bedouin Arabs, respectively. 69.8% of the camel serum samples were anti-HEV positive; seropasvity increased with age. Three of 234 camel serum samples (from < 3 years old camels) were HEV RNA positive. Sequencing revealed infection with HEV-7 (Figure 1).
Conclusion: It is possible that HEV-7 is responsible for the high HEV seropositivity in Bedouins. The seropositivty in Muslims, none-Bedouins may result from the endemicity of HEV-3 in Israel. All patients with viral hepatitis should be thoroughly assessed for the possibility of HEV infection.

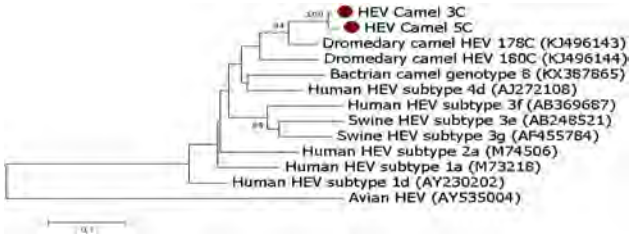

Figure 1: Phylogenetic analysis of partial ORF-2 (180 bp) sequences of HEV genotypes 1-4, 7 and 8.

SAT-188

Expansion and genetic modification of primary hepatocytes to study long-term hepatitis B virus infection

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Background and aims: Primary human hepatocytes (PHHs) are the most physiologically relevant cells for studying HBV infection *in vitro*. Unlike hepatoma cells, they have intact innate immune pathways and maintain important hepatocyte functions. However, working with PHHs also has several challenges: their quantities are limited, they readily de-differentiate and lose hepatocyte functions in culture, and cells from different donors vary with respect to viability, susceptibility to HBV infection, and ability to engraft in liver chimeric mice. In addition, genetic manipulation of PHHs is less efficient than in hepatoma cell lines. Our aim here was to develop a robust primary hepatocyte system for HBV infection studies.
Results: Here we report an HBV infection system based on PHHs freshly isolated and *in vivo* passaged in human liver chimeric mice. This system has several benefits over cryopreserved PHHs. First, expansion in the mouse liver results in ~100 fold more viable hepatocytes that can be used in culture. And in contrast to large donor to donor variability with cryopreserved PHH, human hepatocytes freshly isolated from mice reliably form *ex vivo* cultures that are stable for up to eight weeks. These allow for long-term studies into HBV biology. In addition, *ex vivo* cultures are amenable to gene-specific manipulations, including > 95% lentivirus-based transduction. And finally, lentivirus transduced cultures can be re-transplanted into new chimeric mice to study gene manipulations in the context of HBV infection *in vivo*.
Conclusion: *Ex vivo* human hepatocyte cultures are a flexible system to study hepatocyte biology and long-term HBV infections *in vitro* and genetically altered human grafts in chimeric mice.

SAT-189

GCAC1809-1812TTCT a novel viral quadruple mutation is strongly associated with basal core promotor double mutation and viral load in Hepatitis B e antigen negative chronic hepatitis B virus infected patients

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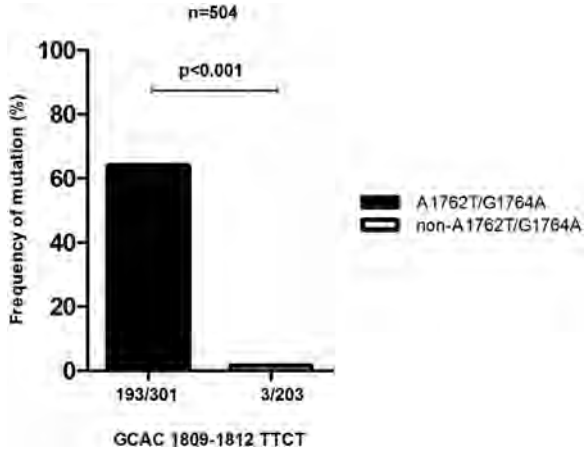
Background and aims: The double mutation A1762T/G1764A in Hepatitis B virus (HBV) basal core promotor (BCP) is associated with

HBeAg negativity and has been described as a prognostic marker for disease progression and disease-related complications of chronic HBV infection. Although an enhancing effect on replication was observed in *in vitro* studies, we observed recently an association of this mutation with lower viral loads in a large European cohort of Hepatitis B e antigen (HBeAg) negative chronic HBV infected patients. In this study, we aimed to identify additional factors related to this observation.

Method: Sera of 504 patients with HBeAg negative chronic HBV infection from the European Albatros trial were analyzed. Parts of the region encoding the core promotor were amplified by nested PCR in two rounds and directly sequenced. A sensitivity level of about 15-20% was assumed.

Results: Overall BCP double mutation was detected in 60% (301/504) of the samples in a genotype specific pattern as recently described. In addition, a novel quadruple mutation (GCAC1809-1812TTCT) in the Kozak sequence preceding the precore start codon was found in 39% of the samples (196/504). Presence of this novel mutation was highly significantly associated with the coexistence of A1762T/G1764A ($p < 0.001$) independent of the HBV genotype (A-E). While this novel mutation was found in samples with A1762T/G1764A in 64% (193/301), in samples without A1762T/G1764A the GCAC1809-1812TTCT was detected only in 1% (3/203). While, GCAC1809-1812TTCT was significantly associated with lower viral loads (2.5 log IU/ml vs. 3.0 log IU/ml; $p < 0.001$), A1762T/G1764A without GCAC1809-1812TTCT was not associated with differences in the viral load. Neither GCAC1809-1812TTCT nor A1762T/G1764A was associated with changes in quantitative HB surface antigen (HBsAg) levels.



Conclusion: In our study the novel quadruple mutation GCAC1809-1812TTCT in the Kozak sequence preceding the precore start codon was found with a high prevalence of 39% in patients with HBeAg negative chronic HBV infection living in Europe. This mutation occurs almost exclusively in coexistence with BCP double mutation A1762T/G1764A (64% in patients with and 1% in patients without A1762T/G1764A) and is associated with lower viral loads. Therefore, our recent observation that A1762T/G1764A is associated with lower viral loads can be explained by the high prevalence of GCAC1809-1812TTCT in patients with A1762T/G1764A.

SAT-190

Specific genetic elements in HBsAg C-terminus profoundly affect HBsAg levels in vivo, hamper HBsAg secretion in vitro and alter HBsAg structural stability in HBeAg-negative chronic HBV genotype D infection

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Background and aims: In eAg-negative chronic infection, HBV genotype D is characterized by lower HBsAg levels. Here, we aim at investigating the correlation of specific mutations in HBsAg C-terminus (critical for a proper HBsAg release) with HBsAg levels *in vivo*, their impact on HBsAg secretion in vitro and on structural stability.

Method: This study includes 228 drug-naïve eAg-negative patients (all genotype D), stratified in HBsAg ≤ 1, 000IU/ml (N = 130) and HBsAg > 1, 000IU/ml (N = 98). Association of mutations with HBsAg ≤ 1, 000IU/ml is assessed by Fisher Exact Test. Association among mutations in C-terminus is assessed by binomial correlation coefficient (phi). The impact of mutations on HBsAg secretion is analyzed by transfecting HepG2 cells with a plasmid encoding wt and mutated HBsAg, linked to a streptavidin-tag (strep-tag). The strep-tagged HBsAg amount in supernatants is quantified by an ELISA recognizing the Strep-tag, not affected by HBsAg antigenicity and thus, capable to identify a defect in HBsAg secretion. I-Tasser is used to predict HBsAg 3-D structures and their stability ($\Delta\Delta G$[wt-mutated] < 0 indicating reduced stability in presence of mutations [Quan, 2016].

Results: Specific mutations in HBsAg C-terminus tightly correlate with HBsAg ≤ 1, 000IU/ml: S204N (33.7% vs 12.1% in HBsAg < 1, 000 vs > 1, 000 IU/ml, P < 0.001), Y206F (16.9% vs 3.3%, P = 0.001) and S210N (6.5% vs 1.3%, P = 0.04).

These mutations lie on divergent pathways involving other mutations in HBsAg C-terminus: S204N with L205P (Phi = 0.36), Y206F with M197T (Phi = 0.32) and S210N with F220L (Phi = 0.40) (p = 0.006-0.002). Notably, each of these pairs of mutations drastically decreases HBsAg titer compared to wt (S204N + L205P: 226[123-394]IU/ml, Y206F + M197T: 284[52-563]IU/ml and S210N + F220L: 335[209-417]IU/ml vs wt: 2791 [1009-8212]IU/ml, P = 0.003-0.02).

In vitro, S204N + L205P determines an 85% decrease in extracellular HBsAg (p < 0.001), while Y206F + M197T and S210N + F220L cause a 32% and 20% decrease compared to wt (p < 0.001).

By structural analysis, these pairs of mutations determine a relevant reduction in the stability of HBsAg C-terminus (ΔΔG[mut-wt] = -1.8 for S204N + L205P, −1.6 for Y206F + M197T and −1.0 for S210N + F220L) and a profound rearrangement of this domain.
Conclusion: Specific clusters of mutations in HBsAg C-terminus correlate with lower HBsAg levels in vivo, hamper HBsAg release in vitro and affect HBsAg structural stability, supporting their detrimental role on HBsAg secretion. Such mutations should be considered for a proper clinical interpretation of HBsAg levels in HBV genotype D chronic infection.

SAT-191

Host genome integration of hepatitis B is prolific and is the primary contributor to viral HBs antigen gene expression

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Background and aims: Genomic integration of Hepatitis B (HBV) promotes liver carcinogenesis, yet the prevalence of viral integration events at single-cell level remains unknown. Our goal was to interrogate the human liver cancer genome data and estimate the number of viral integrations per cell in the liver of chronic HBV infected patients.
Method: We analyzed both whole genome and transcriptome paired-end sequencing data of 192 DNAseq samples (120 tumor and 72 adjacent non-tumor) and 59 non-tumor RNAseq samples from HBV positive hepatocellular carcinoma (HCC) patients (Fujimoto et al. 2016, Sung et al. 2012). Paired-end reads were mapped to the human (GRCh38) and HBV reference genomes. Viral integrations into the human genome were quantified via dual-clustering strategy of chimeric reads accounting for strand polarity as well as viral and human genome coordinates. The viral integration prevalence per cell was calculated by dividing the number of viral integrations by the scaled depth coverage of the genome.
Results: Genome analysis of HBV infected liver tissue revealed 3496 and 1356 viral integrations across 120 and 72 tumor and non-tumor DNA HCC samples, respectively. Although the integrated virus had a preference for fusion breakpoint near the DR1 locus of the viral genome (~23% of total), the integration sites in the human genome were scattered across all chromosomes (Fig 1A). Given the stochastic nature of sequence library preparation, the genome depth coverage can serve as a reasonable surrogate for the number of cells sampled. Following this rationale, we estimated that there are on average 0.86 HBV integrations per diploid cell (median = 0.69, min = 0.044, max = 5.34, Fig 1B). In addition, integrated virus has the potential to be transcribed and possibly obscure the interpretation of clinical biomarker measurements. We used integration-specific genomic feature to quantify the extent of transcripts originating from integrated HBV and found that 82.8% of HBV transcript originated from integrated HBV DNA.
Conclusion: Our data indicate high frequency of HBV integration (avg = 0.86 per cell) in HBV infected HCC patients. This integration frequency is expected to be a conservative estimate for hepatocytes given the cellular heterogeneity in liver tumor tissue samples. To generalize these findings comparative examination of large number of chronic HBV liver samples, particularly via single-hepatocyte sequencing, is warranted.

SAT-192

Targeting the HBx-DDB1-Cullin complex inhibits transcription from HBV covalently closed circular DNA in susceptible hepatoma cells

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Background and aims: More than 200 million people worldwide are suffering from chronic Hepatitis B (HBV) infection without a curative therapeutic regimen available so far. One approach to control HBV replication is silencing transcription from covalently closed circular DNA (cccDNA). Efficient transcription requires the X protein (HBx) as a transcriptional activator, which binds to DNA-damage binding protein 1 (DDB1) and Cullin 4 and induces degradation of the host restriction factor SMC5/6. Therefore, therapeutic interfering with this pathway may silence transcription from cccDNA.
Method: Wild-type (WT), HBx-minus virus that does not encode HBx and an R96E mutant expressing HBx but is deficient in binding DDB1 were generated and tested for infectivity. Lentiviral trans-complementation was established to complement HBx *in trans* in HBx-minus virus infections. Established clones of DDB1 stable knockdown cells were infected. Two stable HepG2-NTCP-HBx (WT) and (R96E) cells supported the study of HBx-DDB1 interaction.

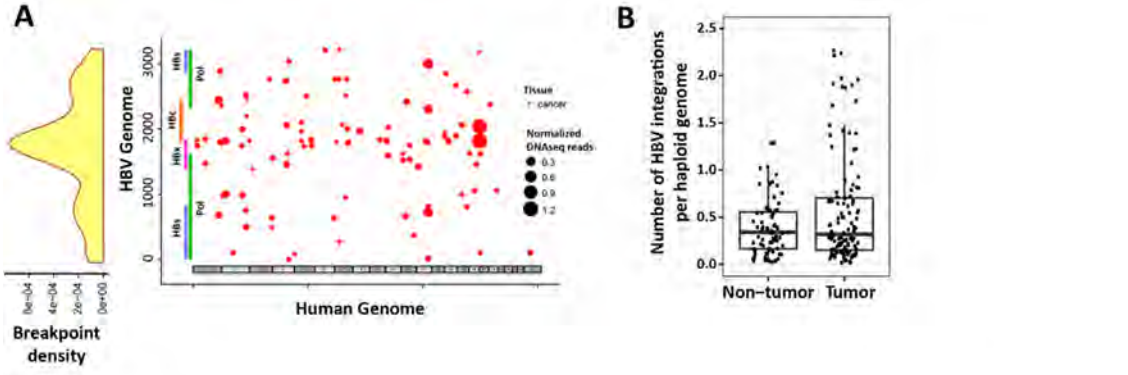

Figure 1
A. Viral-human chimeric paired-end reads were clustered to define viral integration. Each dot represents an independent viral integration event. Size of dot represents number of reads supporting the integration call. Each integration was plotted against the human genomic location (x-axis) and the HBV genome (y-axis). Viral-human fusion breakpoints have a strong preference for the viral region near DR1 but integration spreads out on all human chromosomes. **B.** Estimated viral integration frequency per haploid genome, where each dot represents a sequenced tumor or non-tumor HCC sample.

Figure: (abstract: SAT-191)

Results: Both HBx-minus and R96E viruses expressing DDB1-binding deficient HBx showed lower transcription levels compared to WT virus in infected HepaRG- and HepG2-NTCP cells. Consistently, stable shRNA-mediated knockdown of DDB1 in HepG2-NTCP cells led to reduced transcription from cccDNA. Furthermore, we observed that the reduction degree of HBV transcription is inversely dependent on the level of DDB1 expression.
Besides knockout of HBx and knockdown of DDB1, we identified a small molecule preventing activation of Cullin 4 by prevention of neddylation. Remarkably, this molecule showed inhibitory effects on transcription from cccDNA in all *in vitro* infection models, although it targeted Cullin 4 without affecting HBx expression directly or HBx-DDB1 interaction. We verified that this inhibitor selectively eliminated the enhanced transcription induced by lentiviral HBx transduction in the infection of HBx-minus virus, suggesting dependency on HBx.
Conclusion: Our findings support that the HBx-DDB1-Cullin complex is functionally required for efficient cccDNA transcription and might be targeted using a small molecule to shut down HBV gene expression. To achieve this aim, either depleting HBx, interfering with HBx-DDB1 association, or blocking the function of Cullin 4 result in remarkable inhibition at the transcriptional level.

SAT-193

Evolutionary relationship among hepatitis B virus genotype D in Latin America and Europe

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Background and aims: Hepatitis B Virus (HBV) infects 7 to 12 million people in Latin America. HBV genotype D (HBV/D) has a worldwide distribution and, in Latin America, is associated to European and Middle Eastern migrations. Indeed, some Latin America regions where HBV/D reach higher frequencies, such as Southern Brazil, had received an important flow of Italian migrants in the late 19th century.
Method: In this study, we used phylogenetic and population genetics approaches to compare HBV/D isolates from Latin America, Europe and Middle East and establish evolutionary relationships between viral distribution and historical events associated to HBV spread. Sequences were aligned using the ClustalW algorithm implemented in MEGA v.7. A maximum likelihood (ML) HBV phylogeny was estimated with RAxML v8.2.10 using ten independent searches, and 1, 000 bootstrap replicates to evaluate clade support. We used the fixation index (Φ_{ST}) to quantify the genetic structure among populations. Variation of effective population size through time was estimated using the Bayesian Skyline method.
Results: Our results showed a predominance of HBV/D3 towards southern South America with subgenotype distributions mirroring those present in Italy. On the other hand, the Caribbean and Northeastern Brazil showed a distinct subgenotype distribution, with HBV/D4 reaching high frequencies. At the subgenotypic level, HBV/D3 was more related to Italian migration in Southeast Brazil (BR-SE), and evidenced an older population expansion shared by both populations, which may suggest that BR-SE acted as a source population in Latin America. In addition, we found similarities between Germany and Poland HBV/D3 and other Latin America populations, and also between Germany, Poland and BR-SE for HBV/D2. HBV/D1 showed that while Brazilian populations (BR-S, BR-SE) were closest to NLD, ARG and CUB were closest to LIB + TUR. Finally, HBV/D4 showed a specific population dynamics, with marked genetic differences among localities.
Conclusion: This study highlighted a complex history for HBV/D dispersal across Latin America, in which multiple sources populations contributed to the current HBV/D gene pool in this region.

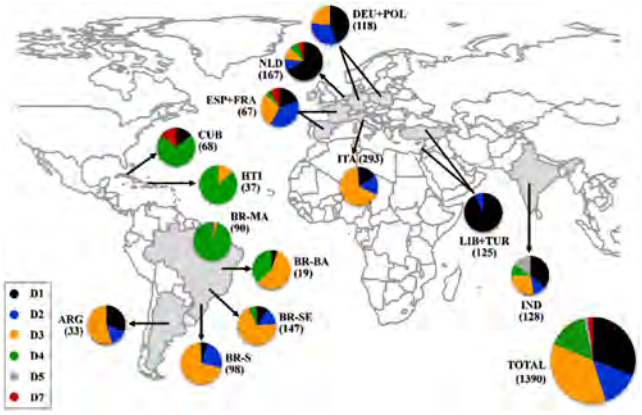

Figure: Geographical distribution of the 1390 HBV sequences belonging to D genotype that were included in this study. Colors indicate the different HBV/D subgenotypes (D1-D5, D7). ARG, Argentina; BR-BA, Brazilian state of Bahia; BR-MA, Brazilian state of Maranhão; BR-S, Southern Brazil; BR-SE, Southeastern Brazil; CUB, Cuba; DEU + POL, Germany and Poland; ESP + FRA, Spain and France; D1, HBV subgenotype D1; D2, HBV subgenotype D2; D3, HBV subgenotype D3; D4, HBV subgenotype D4; HTI, Haiti; IND, India; ITA, Italia; LIB + TUR, Lebanon and Turkey; NLD, Netherlands.

SAT-194

The utility of monomeric HBV genomes for interrogating the HBV cccDNA minichromosome, using in vitro and in vivo models of HBV replication

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Background and aims: The Hepatitis B Virus (HBV) exists as nine distinct genotypes (A-I) which are differentiated by more than 8% difference in the complete nucleotide sequence. These different genotypes generally affect particular demographic groups in discrete geographic regions, with varying severity and treatment response. Differences in their replication efficiencies have also been identified and characterized, but molecular analyses have been hindered by lack of suitable models permitting thorough analysis of the complete replication cycle of HBV, particularly the viral cccDNA nuclear reservoir which is a major source of viral persistence.
Method: Using complete genome PCR, we generated full-length Hepatitis B Virus genomes ("1-mers", genotypes A, C and D), transfection of which induced the complete HBV replication cycle, including establishment of a cccDNA-like intermediate, *in vitro*. We next introduced these plasmid-free monomeric HBV genomes into mice via hydrodynamic tail-vein injection, to investigate their utilization as a novel *in vivo* replication model.
Results: Characterization of HBV replication using cell lysates and murine liver tissue demonstrated production of cccDNA-like episomes via Southern blot, as well as detection of major viral RNA transcripts by northern blot. This was achieved for multiple HBV genotypes.
Conclusion: We have demonstrated the utility of the HBV 1 mer model for the production of a cccDNA like molecule in both *in vitro* and *in vivo* models of HBV replication, across HBV genotypes. This model system will next be used to investigate interactions between

HBV cccDNA and viral and host proteins, to investigate their contributions to HBV replication across genotypes *in vitro* and *in vivo* and gain new insights into cccDNA transcriptional regulatory mechanisms. This may lead to discovery of novel pan-genotypic strategies for curing HBV infection.

SAT-195

The novel HBx mutation F30V correlates with HCC in vivo, hampers HBV replicative efficiency and enhances anti-apoptotic activity of HBx N-terminus in vitro

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Background and aims: HBV X protein (HBx) is critical for viral gene expression and for the initiation of HBV-induced hepatocarcinogenesis. Here, we investigate HBx genetic-elements correlated with HCC and their impact on i) HBV replicative efficiency, ii) HBx-binding to cccDNA, iii) apoptosis and cell-cycle progression, and iv) HBx structural stability.

Method: This study includes 123 HBV-chronically infected patients: 27 with HCC (77.9% genotype-D; 22.1% genotype-A) and 96 without HCC (75%-D; 25.0%-A). HepG2 cells are transfected by *wild-type* (wt) or mutated linear HBV-genome to assess i) the levels of pre-genomic RNA (pgRNA) and intracellular core-associated HBV-DNA by RT-PCR, ii) HBx-binding onto cccDNA by Chromatine Immune-Precipitations-based quantitative assay, and iii) rate of apoptosis and cell-cycle progression by cytofluorimetry. Scansite and Netphos algorithms are used to predict the probability of phosphorylation of a given residue by Serine (Ser) Kinases.

Results: F30V is the only HBx-mutation correlated with HCC in-vivo (18.5% in HCC vs 1.0% in non-HCC, $p = 0.002$). Result confirmed by multivariable-analysis adjusting for patients' demographics, HBV genotype, serum HBV-DNA and ALT (OR[95%CI]:20.0[2.1-195.0], $p = 0.001$).

In-vitro, F30V determines a 40% and 60% reduction in pgRNA and core-associated HBV-DNA compared to wt ($p < 0.05$), paralleling with a 79% decrease of HBx-binding to cccDNA ($p < 0.01$). F30V also decreased the percentage of apoptotic-cells compared to wt (14.8 ± 6.8% vs 19.1 ± 10.1%, $p < 0.01$) without affecting cell-cycle progression.

By structural analysis, F30V is adjacent to HBx-Ser31, whose phosphorylation by PI3-kinase (PI3K), is known to promote HBV anti-apoptotic activity. Interestingly, F30V increases the probability of Ser31-phosphorylation by PI3K respect to wt (F30V:0.54 vs wt:0.48 and F30V:0.76 vs wt:0.72 according to Scansite and NetPhos, respectively), further supporting its anti-apoptotic activity.

Conclusion: F30V tightly correlates with HBV-induced HCC in-vivo, reduces HBV replicative efficiency by affecting HBx-binding to cccDNA and increases anti-apoptotic HBx activity. This suggests that F30V (although hampering HBV replicative-capacity) may promote hepatocytes survival, thus contributing to mechanisms underlying the initiation of HBV-driven hepatocarcinogenesis. Investigation of viral genetic-markers associated with HCC is crucial to identify patients at higher HCC-risk deserving intensive liver monitoring, and/or early anti-HBV therapy.

SAT-196

The integrated use of highly sensitive HBV markers can predict HBV reactivation in HBsAg-negative/Anti-HBc positive patients from oncohematological setting

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Background and aims: To investigate the role of HBV markers in predicting immunosuppression-driven HBV reactivation (HBV-R) in HBsAg-negative/anti-HBc-positive patients (pts) with hematological malignancies.

Method: HBV-R rate is assessed in 111 HBsAg-negative/antiHBc-positive pts (48 receiving rituximab, 36 HSCT, 27 other chemotherapeutics). All pts received lamivudine prophylaxis (median [IQR] duration:29 [22-41] months) and were prospectively monitored every 3 months during and after prophylaxis completion. The role of HBV markers in predicting HBV-R was evaluated in a subset of 30 pts: 5 developing HBV-R and 25 not developing HBV-R. For these pts, a total of 230 serum samples was tested for high sensitive HBsAg, FujiRebio (HS-HBs; lower limit of quantification [LLOQ]:5mIU/ml, vs 50mIU/ml of routinely used HBsAg assays), anti-HBs and HBV-DNA (LLOQ: 20 IU/ml, Roche). HBV-R is defined as serum HBV-DNA > 20 IU/ml (according to Seto WK, 2016).

Results: At baseline, all pts are HBsAg-negative/antiHBc-positive with undetectable HBV-DNA. Among them, 66.7% is positive to anti-HBs [median (IQR): 151 (45-557)mIU/ml]. HBV-R occurs in 10/111 pts with a 4-year cumulative reactivation rate of 22%. At HBV-R, median (IQR) HBV-DNA is 36 (20-522)IU/ml and ALT is > ULN in 6/10 pts with a median of 88 (60-763)U/L. Among 10 pts with HBV-R, 5 develops HBV-R during and 5 after completing the recommended duration of prophylaxis (median [IQR]months after prophylaxis completion:3[1-16]).

Focusing on the 30 pts, an anti-HBs titer < 100mIU/ml at baseline is the only virological marker correlated with a higher risk to develop HBV-R (HBV-R occurs in 55.6% of pts with anti-HBs < 100mIU/ml and never in pts with anti-HBs > 100mIU/ml, $P = 0.046$). The on-monitoring analysis of virological markers shows that the positivity, even at a single time-point, to HS-HBs (detection failed by the routinely used HBsAg assays) and/or to HBV-DNA (below LLOQ) is another risk factor for HBV-R (3/5 pts with HBV-R vs 0/25 pts without HBV-R are positive to HBV-DNA and/or HS-HBs, $P < 0.001$).

Conclusion: In anti-HBc-positive/HBsAg-negative oncohematological pts, HBV-R frequently occurs after completing the recommended course of anti-HBV prophylaxis suggesting the need to reconsider the duration of prophylaxis in the setting of profound immunosuppression. A close monitoring based on an integrated use of HBV markers (including those with high sensitivity) can help in detecting minimal viral replication predictive of HBV-R, allowing early HBV-R diagnosis.

SAT-197

Quality of life measurement using wrist actigraphy in HCV genotype 1 infected, treatment naïve patients suffering from fatigue and receiving ombitasvir, paritaprevir, and ritonavir tablets and dasabuvir tablets (Viekirax/Exviera; 3D regimen)

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Background and aims: Physical and mental fatigue is the most common symptom reported by patients with Hepatitis C Virus (HCV), which highly impacts their overall quality of life. This cardinal symptom presents regardless of the stage of liver fibrosis and is difficult to quantify objectively. Similar to other potential reasons for physical fatigue, increasing evidence suggests a direct viral impact on the central nervous system. Data demonstrating a longitudinal change of debilitating physical fatigue and increased daytime physical activity upon treatment (Tx) with 3D regimen are missing to date. The rationale for this observational study is to observe the impact of 3D regimen on physical activity of HCV+ patients suffering from debilitating fatigue by using wrist actigraphy.
Method: HEMATITE is an observational, prospective, open label, single-arm, Swiss multi-centric, real-life study in HCV+ patients (GT1). The study consists of a Tx preparation phase of 4 weeks (wks), a Tx phase with 3D regimen according to routine clinical practice (12 wks) and a post Tx phase (12 wks) to evaluate Tx response. Fatigue was assessed at every visit using the Fatigue Severity Score (FSS) questionnaire, according to routine clinical care. In addition, physical activity data was collected by providing patients with a wrist-worn activity tracker to be worn for 4 wks before Tx (baseline (BL)) and for 4 wks before each visit.
Results: 40/41 patients reached SVR12. The FSS decreased significantly from BL to post Tx visit week 12 (5.92 ± 0.61 vs. 3.34 ± 1.42 (mean±SD); $p < 0.001$). The physical workday daytime activity data could be analyzed from 37 out of 45 (scale down (sd)ITT). Neither the mean activity nor the change of the mean activity between BL and Tx week 12 showed any significance.
Conclusion: As expected > 97% of the patients achieved SVR12 upon 3D regimen therapy. Moreover, the 3D therapy also reduces fatigue in HCV+ patients, as shown by the FSS, suggesting a causative role of HCV in this extrahepatic manifestation. HCV treatment is therefore effective in reducing/eliminating fatigue.

SAT-198

Full-length 5'RACE analysis discriminates all major intracellular and extracellular viral RNAs during the course of infection

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Background and aims: Covalently closed circular DNA (cccDNA) is the episomal form of the Hepatitis B virus (HBV) genome that stably resides in the nucleus of infected hepatocytes. The amount of cccDNA and its transcriptional activity vary along the natural course of infection and are a main determinant of viral persistence and reactivation. cccDNA is the template for six viral RNAs, i.e. preC- pg-, preS1/2-, S- and HBx-RNA. All viral transcripts share the same 3' end and are all to various degrees subsets of each other. Consequently, transcription of 5' positioned genes obscures the measurement of transcripts starting further downstream, using standard RT and PCR techniques. Especially under infection conditions, it has been difficult to study in depth HBV gene transcription and the differential regulation of each transcript, most importantly that of HBx. Indeed, HBx RNA, whose sequence is common to all viral transcripts, is undetectable by Northern blotting due to sensitivity issues and indistinguishable from the other viral RNAs by qPCR.
Method: We set up an "HBV full-length 5'RACE" technique to specifically measure and characterize the different HBV RNAs. This method takes advantage of anchoring a known sequence at the 5' ends of all HBV transcripts. The different HBV RNAs can then be amplified and resolved by gel electrophoresis according to their molecular weights.
Results: We are able to discriminate all the major HBV RNA species (including HBx RNA) transcribed during the infection cycle in cultured hepatocytes using little starting material. Performing time-course experiments, we confirm HBx to be the first measurable viral RNA after infection of both HepG2-NTCP cells and primary human hepatocytes (PHHs). We find a great diversity in transcription start sites for HBx, giving rise to various HBx transcripts including short HBx transcripts potentially coding for a short version of the X protein. We show that Interferon β treatment leads to the down-regulation of both preC- and pg-RNAs but has no effect on HBx in PHHs. In addition to pg-RNA we find a variety of different HBx transcripts associated with viral particles produced by HepAD38 cells. Finally, apart from pg-RNA and HBx RNA we find at least 2 additional viral RNAs in the plasma of patients.
Conclusion: Our approach should significantly contribute to the understanding of HBV transcription and its regulation during the course of infection and therapy.

SAT-199

Recombinant hepatitis E viruses harbouring tags in the ORF1 protein allow visualisation of the viral replicase

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Background and aims: Hepatitis E virus (HEV) infection is one of the most common causes of acute hepatitis and jaundice in the world. Our current understanding of the molecular virology and pathogenesis of hepatitis E is incomplete, especially due to the limited availability of functional tools. Here, we developed tagged functional HEV genomes to investigate the open reading frame 1 (ORF1) protein representing the viral replicase.
Method: A selectable subgenomic HEV replicon was subjected to random 15-bp sequence insertion using transposon-based technology, followed by selection in a human hepatoblastoma cell line and characterisation of viable insertion sites. Different tags were cloned into viable insertion sites identified in the ORF1 protein and characterised in the context of full-length viral constructs.
Results: Several functional insertion sites were identified in the ORF1 region, with the highest replication efficacy observed for those mapping to the hypervariable region. HEV genomes harbouring a haemagglutinin (HA) epitope tag or a small luciferase (NanoLuc) at these sites were found to be fully functional and to allow for the production of infectious virus. NanoLuc allowed to quantitatively monitor HEV infection and replication by luciferase assay. HA-tagged constructs allowed to localise the site of HEV RNA replication by the simultaneous detection of ORF1 protein by immunofluorescence and of viral RNA by fluorescence *in situ* hybridisation. Candidate HEV replication complexes were found in the cytoplasm at a site which partially overlaps with ORF2 and ORF3 proteins as well as exosomal markers.
Conclusion: Tagged genomes yield new insights into the HEV life cycle, allowing investigation of the subcellular localisation and

composition of viral replication complexes. These efforts may reveal new angles for therapeutic intervention against hepatitis E.

SAT-200

AMPK activation in response to hepatitis E virus infection inhibited viral infection by attenuating autophagy and promoting innate immunity

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Background and aims: Other than hepatitis B or C virus infection, Hepatitis E virus (HEV) infection is generally asymptomatic or leads to acute and self-limiting hepatitis. However, the mechanism of host-cell defence against HEV is unclear. AMP-activated protein kinase (AMPK) activation is crucial for the regulation of cell homeostasis. We thus investigated the role of AMPK in HEV infection.
Method: Huh-7 and HepG2 cells inoculated with infectious HEV viral particle or transfected with *in vitro* generated HEV genome RNA were used to model HEV infection. Viral replication and genes expression were quantified by quantitative real-time polymerase chain in reaction (qPCR). Activation of AMPK and induction of autophagy were assessed by Western Blotting.
Results: We found HEV infection can trigger AMPK activation by phosphorylation of AMPK at threonine 172 by transfecting HEV viral RNA into host cells or inoculating host cells with infectious HEV viral particle. Meanwhile, HEV also induced autophagy. Inhibition of HEV induced AMPK phosphorylation with specific AMPK inhibitor compound C dose-dependently enhanced HEV replication. Conversely, treatment with pharmacological AMPK activator AICAR strongly inhibited HEV replication. These results suggested that AMPK activation is a potent strategy of host cells for HEV clearance. Interestingly, we found inhibition of AMPK efficiently augmented HEV induced autophagy, evidenced by a marked increase in LC3II/I via decreasing mTOR levels, indicating that AMPK activation upon HEV infection can increase mTOR level to supress HEV induced autophagy. Our previous study showed that rapamycin, an activator of autophagy by inhibiting mTOR, has a potent pro-HEV effect. Together, these results suggested that HEV induced AMPK activation can serve to protect HEV infected cells from autophagy and inhibit HEV infection. We also investigated whether HEV-induced AMPK activation affects innate immunity. Interestingly, interference of AMPK activation significantly supressed the expression of a subset of interferon-stimulated genes (ISGs), which are considered the ultimate antiviral effectors. These results indicated that HEV induced AMPK activation also contributes to stimulation of innate immunity, thereby facilitating cell-defence against HEV.
Conclusion: Here we show that HEV infection can activate AMPK phosphorylation, which attenuates HEV-induced autophagy and increases innate immune signalling. Thus the AMPK activation in response to HEV infection is critical in host cells for rapid viral clearance by coordinating autophagic process and establishing persistent antiviral immunity.

SAT-201

Alternation of lipid metabolism and dysfunction of mitochondria might contribute to HCC development in the absence of overt necroinflammation

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Background and aims: Chronic hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC). HBV viral load, necroinflammation, cirrhosis, obesity and diabetes are linked to HCC development. However, HCC also develops in patients with normal or minimally elevated ALT levels. The hepatocarcinogenesis mechanisms in these cases remain unclear. To elucidate the molecular mechanisms in these HCC cases, we have developed a panel of HBV transgenic mice with high liver tumor incidences in the absence of overt immune response mimicking human HCC without severe liver necroinflammation.
Methods: HCC and paired liver tissue samples from these mice were analyzed by microarray and metabolomics, and validated by real-time PCR and Western blotting.
Results: Of note, high viral loads were associated with higher tumor incidence (48/158, 30.4%, vs. 2/73, 2.7%, $p < 0.0001$). The effect of integration sites may also play a role in different liver tumor incidences in lineages B00 vs B13 (57.9% vs 14.3%, $p = 0.0151$) and lineage D11, D14 and D23 (16.7%, 41.9% and 13.7%, $p = 0.0026$). Differentially expressed genes analysis of the microarray data based on 7 HCC of HBV transgenic mice vs 5 normal livers of the background lineage C57BL/6 mice revealed that: 1. Lipid catabolism related pathways were down-regulated (TG breakdown: lipg, mgll, $p < 0.0005$; beta-oxidation: acat1, $p < 0.0001$; acaa1a, acaa2, acadsb, acot8, $p < 0005$; Hsd17b4, $p < 0.0001$). 2. Accumulation of lipid was up-regulated (fatty acid synthesis: acly, $p = 0.0058$ and fatty acid uptake: Fabp4, $p = 0.0165$). The epithelial mesenchymal transition (EMT) related genes such as NID1, CD44, Vim, Ahnak, Col1a2, Col3a1, Col5a2, Msn, Serpine1, Sparc, and Timp1 were significantly up-regulated. Gene involved in Warburg effect such as psat1 was up-regulated. Hepatocellular mitochondrial defects were observed in HBV transgenic mice less than 6 months old by ultrastructural analysis of TEM. In non-target metabolomics analysis of liver of HBV transgenic mice vs C57BL/6 mice, the composition of long-chain saturated fatty acids (C14:0, C16:0, C18:0) were elevated and mono- or poly-unsaturated fatty acids (PUFAs) were reduced (C18:1, C18:2, C20:2).
Conclusion: High HBV viral loads, alternation of lipid metabolism and energy production caused by dysfunction of mitochondria might be important for HCC development. These transgenic mice are of value in the study of hepatocarcinogenesis of human HCC in absence of overt necroinflammation and useful platforms in the development of novel therapy.

SAT-202

Endogenous and exogenous IFN responses suppress HDV persistence during proliferation of hepatocytes in vitro

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Background and aims: Hepatitis B virus (HBV) and D virus (HDV) co-infections cause the most severe form of viral hepatitis. Persistence of both viruses makes it challenging to develop curative therapies. Extracellular spreading pathways are important for persistence of both viruses and can be blocked by the entry inhibitor Myrcludex B. However, HDV can also propagate through cell division (Giersch K, *et al.* Gut. 2017). We recently found that HDV replication induces profound IFN response via MDA5 but is insensitive to the response in resting hepatocytes (Zhang Z, *et al.* J Hepatol. 2018). The aim of this study is to evaluate the effect of the IFN response on HDV persistence during hepatocyte proliferation.
Method: To measure cell division mediated HDV amplification, susceptible innate immune competent and immune deficient cell lines were infected with HDV and splitted (1:6) at day 5 post infection and further splitted every 5 days. Different IFNs were applied during cell proliferation. HDV infected cells and viral markers (HDV RNA and antigens) were quantified using immunofluorescence and RT-qPCR.
Results: Over 6 passages following HDV infection, HDV-specific markers were efficiently amplified in HuH7-NTCP cells which are defective to produce IFNs, but profoundly lost in HepaRG-NTCP cells which are innate immune competent. BrdU labeling of newly

synthesized DNA indicated that HDV replication does not impair HepaRG-NTCP cell division. Blocking of the endogenous IFN response by MDA5 depletion and inhibitors targeting the IFN signaling pathway profoundly promoted HDV amplification by cell division, indicating endogenous restriction of HDV amplification by the "self-induced" IFN response. This finding was in line with the significant suppression of HDV persistence by exogenous IFN-α, -β and -λ1 treatment in HuH7-NTCP cells. In addition to the endogenous IFN effect, exogenous IFN further inhibited HDV persistence during HepaRG-NTCP cell division at low infection levels.

Conclusion: Both exogenously and endogenously induced IFN responses restrict HDV persistence during hepatocyte proliferation. This finding helps to understand the clinical observation of the Myr-203 study demonstrating a strong synergism of combining IFN and the entry inhibitor Myrcludex B. The system also provides a cell culture model for the identification of other synergistically acting immune modulators for future clinical combination therapies.

Viral hepatitis A/E: Clinical aspects

SAT-204

Hepatitis E virus antigen in urine as a useful diagnostic

Background and aims: for monitoring infection and detection of recent infection

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Background and aims: Hepatitis E virus (HEV) infection usually causes a self-limiting infection but can lead to chronicity in immunocompromised individuals. The detection and monitoring of infection relies on evaluation of plasma anti-HEV antibodies or plasma and stool HEV RNA. Recently, an HEV antigen (Ag) ELISA has become commercially available which shows high sensitivity in the detection of infection especially in chronically infected individuals. However, its use in monitoring the clinical course of infection has not been investigated so far.

Background and aims: We retrospectively analysed longitudinal urine, stool as well as plasma samples of 8 patients with either acute or chronic HEV infection. We utilized the Wantai HEV antigen ELISA to detect viral proteins. For inhibition of viral antigen detection in urine, the WHO anti-HEV IgG standard was used.

Results: From the eight analysed patients one died due to acute on chronic liver failure and another patient died from acute liver failure. The others resolved the infection either spontaneously or under treatment. In all patients except of one, HEV RNA decreased over time (plasma/stool). In urines, no viral RNA could be detected. Ag levels in plasma and urine remained detectable even after loss of viral RNA. Thereby, we observed high levels of HEV Ag in the urine with delayed reduction over time as compared to HEV Ag in plasma in all tested individuals. For one chronically infected patient who was treated with ribavirin, HEV Ag was detectable in plasma 2 month and in urine 5 month after achieving RNA negativity (Fig. 1). Dilution of HEV Ag positive samples in HEV Ag negative urine and plasma reveals no unspecific modulation of HEV Ag detection. *In vitro*, addition of the WHO anti-HEV IgG standard to HEV Ag positive urine dose-dependently reduces the HEV Ag ELISA values. In line, anti-HEV IgG positive plasma inhibits the detection of HEV Ag in urine.

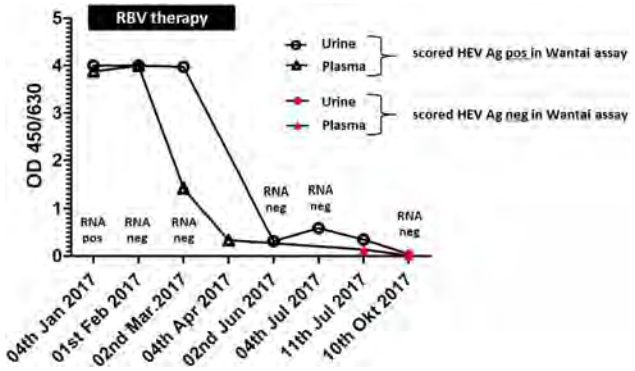

Figure: HEV detection in urine and plasma over time in a chronically infected individual that was treated with ribavirin*
*Off-label use

Conclusion: Collectively, we observed a delayed HEV Ag reduction in plasma and urine of all infected individuals as compared to viral RNA in stool and plasma. Due to the absence of inhibitory anti-HEV IgG antibody, this was more pronounced in urine as compared to plasma in all tested individuals, independent of the clinical course of infection. Evaluation of HEV Ag levels in the urine can be a fast, cheap and easy to perform technique to diagnose as well as monitor HEV infection. The delayed clearance of HEV Ag in urine can be used to determine recent/resolving HEV infections.

SAT-205

Associated risk factors for hepatitis E seroprevalence among liver transplant recipients

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Background and aims: Hepatitis E virus (HEV) is an emerging disease in Europe, especially important among solid organ transplant (SOT) recipients who are at greater risk of developing acute and chronic graft hepatitis with progression to cirrhosis. It is proposed that foodborne transmission is the main route of HEV infection in developed countries. However, risk factors for the acquisition of HEV infection among SOT recipients are incompletely understood. This study aimed to determine exposure of HEV infection and associated socio-demographic risk factors.

Background and aims: In this cross-sectional study, 242 Croatian SOT recipients were screened during routine post-transplant out-patient visits. All participants completed a risk factor assessment questionnaire. Blood samples were tested for anti-HEV IgG using an enzyme immune assay (Mikrogen, Germany) and nucleic acid extracts of whole blood were tested by an in-house real-time reverse-transcriptase polymerase chain reaction assay for HEV RNA.

Results: Anti-HEV IgG seroprevalence in Croatian SOT recipients was 24.38%. No SOT patients had HEV viraemia at time of testing. The median time after transplant was 5 years (range 19 years). The majority of the recipients were male (69.0%) and major indication for

SOT was alcoholic liver disease (50.4%). Older age (OR = 1.05; 95%CI = 1.02-1.09), female gender (OR = 2.61; 95%CI = 1.42-4.81), rural area of residence (AOR = 2.17; 95%CI = 1.10-4.27), and specific factors within a household: a farm (AOR = 2.79; 95% CI = 1.31-5.92), a water-well (AOR = 3.09; 95%CI = 1.11-8.57) and a sewage system connected to a septic tank (AOR = 3.38; 95%CI = 1.64-6.95) were detected as potential risk factors, while highest level of education (AOR = 0.05; 95%CI = 0.01-0.43) and a recent travelling experience (AOR = 0.39; 95%CI = 0.17-0.88) as protective factors. Contrary to initial assumptions, production and/or consummation of cured meat and occupational exposure had no statistically significant strength of association with anti-HEV IgG seropositivity.
Conclusion: Prevalence of anti-HEV IgG in SOT recipients in Croatia is 24.38%. Identified socio-demographic factors associated with the seropositivity set up a platform for further research directions to evaluate sources/routes of transmission and clinical impact of HEV infection after SOT.

SAT-206
The impact of hepatitis E virus infection on the Scottish solid organ transplant population

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Background and aims: Our understanding of HEV infection has evolved with recognition that HEV genotypes 3 and 4 cause autochthonous infection in high-income countries and chronic infection in immunocompromised patients, which may rapidly result in liver cirrhosis. We aimed to assess the impact of HEV infection on the Scottish solid organ transplant (SOT) population.
Background and aims: Patients were identified by the treating physicians and highlighted to the study team; all patients received clinical input from a single hepatologist (KJS). Electronic notes were reviewed and data obtained included patient demographics, type of transplantation, characteristics of HEV infection, treatment and clinical impact of infection.
Results: We identified 27 patients within the Scottish SOT population whose clinical course was affected by HEV infection (renal recipient n = 12, liver recipient n = 9, combined liver/kidney n = 2, simultaneous pancreas/kidney [SPK] n = 2 and live renal donor n = 2). The majority of patients (n = 20) were tested for HEV on the basis of deranged LFTS. The observed consequences of HEV infection are shown below.

Impact/consequence of infection	No. of affected patients	Patient group affected
Iatrogenic infection due to use of grafts from viraemic donors	2	Liver (1), renal (1) recipients
Development of cirrhosis due to chronic infection	2	Renal recipients
Chronic infection requiring treatment	15	Liver, renal, SPK recipients
Infection contributing to need for transplantation	1	Liver cirrhosis
Delay in living organ donation due to donor viraemia	2	Renal living donors (and recipients)

One patient was required to delay IVF treatment due to ribavirin therapy for chronic infection. The patients who developed liver cirrhosis had an episode of decompensation. One of the patients who developed liver cirrhosis died. Two further patients died of unrelated causes. In the patients receiving grafts from viraemic donors, phylogenetic analysis confirmed donor derived transmission via the renal allograft in one patient. In the patient receiving a liver graft from a viraemic donor, the renal recipients from the same donor developed genotype 3c infection with phylogenetic analysis confirming a common source. Both liver and kidney recipients cleared HEV infection without therapeutic intervention.
Fifteen patients required treatment with ribavirin; 3 required treatment with erythropoietin and one patient required admission for blood transfusion.
Conclusion: In Scotland, HEV infection has a wide variety of consequences in the SOT population. Increased awareness of infection and its complications will hopefully lead to increased testing and timely treatment of chronic infection in immunosuppressed populations.

SAT-207
Rabbit HEV in immunosuppressed patients with hepatitis E acquired in Switzerland

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Background and aims: Infection by hepatitis E virus (HEV) genotypes (gt) 3 and 4 has been recognized as a zoonosis in high-income countries. Zoonotic transmission of HEV is believed to result primarily from the consumption of raw pork and game meat. Here, we analyzed HEV sequences in patients who acquired acute or chronic hepatitis E in Switzerland.
Method: HEV genotyping was performed by RT-PCR and Sanger sequencing of plasma samples from 114 patients with PCR-proven acute or chronic hepatitis E likely acquired in Switzerland. Subtype assignment and phylogenetic analyses were performed using the HEVnet genotyping tool (https://www.rivm.nl/en/Topics/H/HEVNet). When indicated, confirmatory RT-PCR amplification of a 289-bp ORF1 region harboring the rabbit-specific 93-nucleotide insertion was performed.
Results: HEV genotyping was successful in 98 of 114 patients, revealing gt 3 in 95 and gt 4 in the remaining three. Sixty-eight of the gt 3 isolates could be assigned to a subtype, including 64 from patients with acute and 4 from patients with chronic infection. Importantly, 76% of these were due to the newly proposed subtype 3 s (Wist V *et al.* Genome Announc 2018). The high frequency of this subtype, identified only in Switzerland so far, indicates that it circulates widely in the country, including in the food chain. Interestingly, three solid organ transplant recipients were found to be infected with rabbit HEV (gt 3ra); two with chronic and one with acute hepatitis E. Phylogenetic analysis revealed that gt 3ra isolates observed in Switzerland cluster with the few isolates previously identified in humans in France (Abravanel F *et al.* Emerg Infect Dis 2017), but also in rabbits from France and Germany. Remarkably, none of the patients with rabbit HEV infection had consumed rabbit meat or been in contact with rabbits, suggesting that this virus has been transmitted through other sources.
Conclusion: Our observations lend support to the recently proposed HEV subtype 3 s circulating and representing the major cause of acute hepatitis E acquired in Switzerland. Rabbit HEV was identified in 2 out of 4 chronically infected individuals while it was identified only in one out of 64 patients with acute hepatitis E of gt 3 which could be subtyped. Although based on a small number of cases, our findings raise interesting questions concerning the source, prevalence, pathogenesis and persistence of the as yet poorly characterized rabbit HEV infection in humans.

SAT-208

Zinc/Ribavirin: A possible treatment option in chronically HEV genotype 3 infected patients without SVR under ribavirin monotherapy

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Background and aims: Chronic hepatitis E virus (HEV) infection is a cause of cirrhosis and of end-stage liver disease in immunosuppressed patients. About 5% of chronic HEV patients do not respond to ribavirin treatment. Inhibition of HEV RNA-dependent RNA polymerase with zinc salts is reported *in vitro* in HEV1 and HEV3 replicons. Therefore, we aimed to study the anti-HEV efficacy of zinc salts in a cohort of chronic HEV patients who did not respond to ribavirin patients.

Method: We evaluated the antiviral properties of zinc salts on Huh-7.5 cell lines expressing a subgenomic replicon of HEV3 (Kernow) or HEV1 (Sar55). Cell viability was determined with MTT assays. Magnesium served as negative control.

We collected retrospective virological data from 8 chronic HEV patients who did not respond to ribavirin treatment and who had received in 2018 either zinc salt monotherapy (n = 5) or zinc salt and ribavirin combination therapy (n = 3) without modifying immunosuppression. Serum zinc levels were measured in 23 patients with acute (n = 2), chronic (n = 11) and asymptomatic (n = 10) HEV infection. All patients gave informed consent.

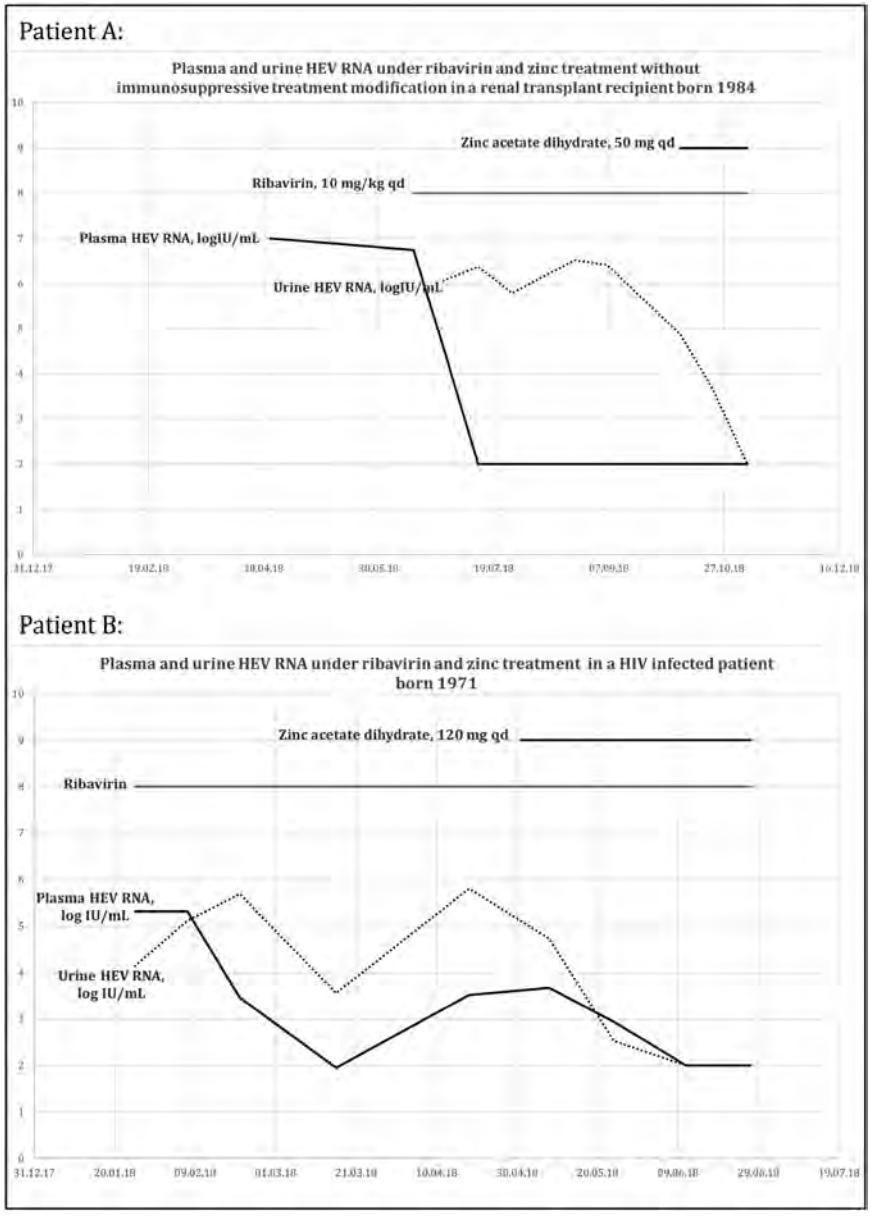

Figure: (abstract: SAT-208): Course viral load in two patients with chronic HEV infection who received zinc/ribavirin treatment

Results: Zinc salts inhibited viral replication *in vitro* with a half maximal inhibitory concentration (IC_{50}) of 130 µM and 115 µM for genotype 3 and 1, respectively. The 50% cytotoxicity concentration (CC_{50}) was 330 µM. Viral clearance was observed in two 2/3 of zinc/ribavirin patients (see figure 1). We did not observe any decrease in viral load among patients who received zinc monotherapy (n = 5). No adverse effect was observed. Serum zinc levels were median 619 mcg/l, 663 mcg/l and 718mcg/l among patients with chronic, acute and asymptomatic HEV infection (chronic vs. asymptomatic: p = 0.049). Serum AST and ALT levels were inversely associated with serum zinc levels (spearman's rho = -0.59; p = 0.006 and –0.42; p = 0.046).
Conclusion: There is a relationship between zinc salt concentration and HEV replication *in vitro and in vivo*.
The potential antiviral effect of zinc/ribavirin treatment should be explored in chronic HEV patients who do not respond to ribavirin treatment. Zinc/ribavirin may be a possible treatment option for patients without SVR under ribavirin monotherapy.

SAT-209
Role of estrogen and its receptors in HEV associated feto-maternal outcomes
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Background and aims: Pregnant women infected with HEV develops adverse pregnancy outcomes like, abortions, intrauterine fetal death, still births, neonatal deaths, preterm delivery and maternal mortality. To correlate estrogen and its receptors ESR1α and ESR2β levels with HEV associated feto-maternal outcomes.
Method: A total of 142 pregnant women with HEV infection and 142 pregnant controls were included in study from Department of Obstetrics and Gynaecology and Department of Medicine, Maulana Azad Medical College (MAMC) and associated Lok Nayak Hospital (LNH), New Delhi. Three ml of blood sample was collected in plain for quantification of estrogen, and its receptors ESR1α and ESR2β using commercially available third generation ELISA kits.
Results: The levels of estrogen, ESR1α and ESR2β were considerably higher in HEV infected pregnant women (20.11 ± 18.19 ng/ml, 10.58 ± 3.27 ng/ml, 10.42 ± 4.71 ng/ml, respectively) than pregnant controls (11.74 ± 6.42 ng/ml, 9.11 ± 1.63 ng/ml, 9.01 ± 1.18 ng/ml, respectively) ($p < 0.0001$). It was found that estrogen levels were significantly higher in pregnant women infected with HEV who had preterm delivery, low birth weight babies and Accepted Article This article is protected by copyright. All rights reserved. fetal loss (19.64 ± 17.60 ng/ml, 19.71 ± 17.63 ng/ml, 33.62 ± 23.20 ng/ml, respectively) than who had full term delivery, average birth weight babies and live babies (11.71 ± 8.77 ng/ml, 11.99 ± 9.44 ng/ml, 16.58 ± 14.98 ng/ml, respectively) ($p < 0.05$). A significant negative correlation was observed between baby birth weight and estrogen levels in HEV infected pregnant women.
Conclusion: The high level of estrogen plays an important role in preterm delivery, low birth weight babies and fetal mortality in pregnant women with HEV infection through placental dysfunction. Moreover, estrogen level is a significant predictor for preterm delivery and maternal mortality and ESR2β levels is a significant predictor for maternal mortality in pregnant women infected with HEV.

SAT-210
Circulation of hepatitis a genotypes in Israel 2017-2018: Environmental surveillance supports clinical findings
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Background and aims: Hepatitis A virus (HAV) is an important cause of acute viral hepatitis worldwide. In Israel, since the introduction of universal toddler vaccination program in 1999, the number of HAV infections has dramatically decreased. However, outbreaks, in vulnerable populations, identified by serological testing, do occur. The last outbreak of HAV in non-vaccinated MSM, which started in the beginning of 2017, triggered the introduction of a systematic molecular investigation of circulating HAV genotypes in all clinical cases and in environmental samples. This study summarizes the impact of this ongoing surveillance on monitoring such an enteric disease.
Method: Sewage samples collected monthly in 2017 (n = 114) and in 2018 (January-June, n = 56) from 11 main sewage treatment facilities located throughout the country and serum samples (n = 80, 2017; n = 43, 2018) from all HAV IgM positive individuals reported to the ministry of health, during the same study period, were included. Total nucleic acids were extracted with NucliSENS EasyMag (bioMérieu, France). Real-time PCR (RT-PCR) and sequencing of the VP1-2A region was performed according to national protocols. Phylogenetic analysis included comparison to reference HAV strains.
Results: 34% (39/114) and 29% (16/56) of all sewage samples collected in 2017 and 2018, respectively, were HAV positive. While 76% (30/39) and 15% (6/39) of the HAV positive sewage samples in 2017 were HAV-1A and HAV-1B positive, respectively, in 2018 6% (1/16) and 81% (13/16) were HAV-1A and HAV-1B positive, respectively. Similarly, 79% and 19% of the positive clinical cases in 2017 were infected with HAV-1A and HAV-1B while the majority of HAV positive cases in 2018 (88%) were HAV-1B and only 9% were infected with HAV-1A (Figure 1). The location of sewage facilities positive for HAV-1A and 1B highly correlated with patients' residence. Other HAV genotypes (HAV-3a/b) were rare (< 3%); 12% (15/143) of all notified patients were HAV RNA negative and therefore not considered hepatitis A cases.

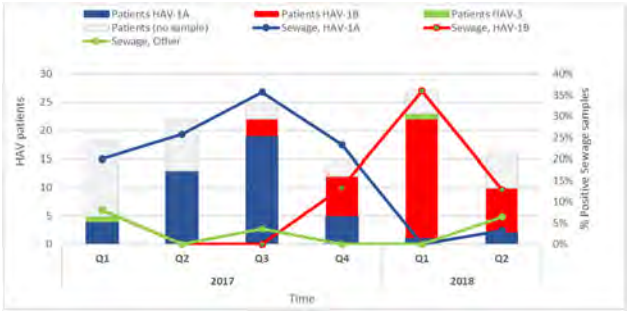

Figure 1: Environmental and clinical HAV surveillance, Israel, January 2017- June 2018

Conclusion: Continuous surveillance of HAV in sewage and confirmation of infection with RNA analysis may assist in correct diagnosis, disease monitoring and identification circulating genotypes in local HAV outbreaks.

SAT-211

HEV infection in Italy: Beyond the hepatic disease

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Background and aims: Hepatitis E virus (HEV) is a RNA virus of Hepeviridae family. In industrialized countries HEV is mainly a zoonosis, spread by pigs, wild boars and deers. In Italy the sero-prevalence reported is 9%, with peak of 49% in the Abruzzo area. Extrahepatic syndromes have been reported.
We describe clinical and virologic features of a population with acute hepatitis in a HEV highly endemic area.
Method: From January 2015 to September 2018, patients admitted to Abruzzo Infectious Disease Departments with elevated liver enzymes and no other acute viral hepatitis were tested for HEV. Acute HEV diagnosis was determined by IgM anti HEV (Wantai®) and HEV-RNA (primers targeting ORF3) presence. Sequencing was carried out by an automated DNA sequencer (Beckman Coulter®). The phylogenetic tree was built using a MEGA 6.06 software. Serologic and virologic analysis were performed at Infectious Diseases Department, National Health Institute, Rome. Anamnestic and clinical data were retrospectively collected.
Results: Out of 97 patients tested, 35 (36%) were diagnosed for acute HEV infection with positive HEV IgM and 32 had detectable HEV-RNA. Genotyping was successful in 24 out of 35 cases and showed all 3 genotype strains (subtypes 3c, 3f, 3e). In the 35 HEV acute cases (85% male, 95% Italian, median age 53 yo), ALT median values were 772 (54-2936) U/L, AST 1282 (95-4312) U/L, Total Bilirubin 5, 08 (0, 44-29.9) mg/dl. HEV-RNA was over 10.000 cp/ml in 44% of patients. Of 32 positive patients in which clinical data were collected, 31% reported onset of gastro-intestinal symptoms, while 40% had extrahepatic symptoms like neurological (arms or legs pain, paresthesia, vertigo, headache), rheumatological (joint pain) or mixed ones, being non-abdominal pain the main clinical feature in 11 patients. Extra-hepatic onset, neurological symptoms, pain and elevated ALT were significantly related to acute HEV infections vs other diagnosis (table 1).

Table 1: Univariate (Chi square test) analysis of clinical variables in HEV-acutely infected population vs other causes of acute hepatitis; other viruses are excluded. OR = Odds ratio; RR = relative risk; CI = confidence interval.

Symptoms	OR/RR	p value	95% CI
Hepatic	0.66	> 0.05	0.25-1.71
Extra-hepatic	16.69	0.0010	1.96-141
Neurologic	14	0.0029	1.62-120.4
Non abdominal pain	1.3043	0.0005	1.0707

Conclusion: In highly endemic area, HEV acute hepatitis represents one third of total acute hepatitis. Extra-hepatic manifestations may be more common than hepatic ones and should raise suspect of HEV aetiology.

SAT-212

Treatment with mTOR inhibitors is an independent risk factor for chronic hepatitis E in transplant patients with increased transaminases levels

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Background and aims: Since the description of the first cases of chronic hepatitis E (CHE) in solid-organ recipients in 2008, many cross-sectional studies have analyzed its prevalence in specific groups such as liver or blood marrow transplantation or HIV-infected subjects. However, there is a lack of prospective analysis in more general populations with high risk of CHE. The aim of this study was to analyze the prevalence of CHE and risk associated factors in a cohort of immunocompromised patients with elevated transaminase levels.
Method: Prospective study including immunocompromised patients (solid-organ or bone marrow transplant (BMT), liver cirrhosis, HIV or undergoing immunosuppressant therapy for dermatological, digestive or rheumatic disorders) with elevated ALT levels ≥ 6 months prior to inclusion. Screening of chronic Hepatitis E virus infection was performed by determination of HEV RNA (PCR Light Cycler 480, Roche).
Results: 207 patients were included: 53% male, mean age 55 ± 16, 90% Caucasian. Underlying disease: 32% transplant (35% BMT, 30% liver, 27% kidney, 8% lung), 31% immunosuppressant therapy, 27% liver cirrhosis, 10% HIV. 22% of recruited patients received at least two different immunosuppressant drugs, including 18% with monoclonal antibodies and 32% corticoids. Overall, anti-HCV was detected in 36%, HBsAg in 4% and anti-HEV IgG in 26%. Median ALT levels were 67 IU/ml (IQR 52-101). The only factor associated with higher HEV seroprevalence was age (> 50 years 16% vs 32%, p = 0.013). HEV seroprevalence was similar in those patients undergoing immunosuppression for transplant than dermatological, digestive or rheumatic disorders (21% vs 27%, p = 0.29). Type of immunosuppression, liver cirrhosis, HIV, HBV or HCV infection did not impact on HEV seroprevalence. Overall, 4 (2%) patients presented CHE with persistently positive HEV RNA, all were solid-organ recipients. Prevalence of CHE in transplantation was 6%: 33% for lung, 17% kidney and 0% in liver and BMT. Both calcineurin and mTOR inhibitors were associated with CHE, though the only independent factor associated with CHE was the use of mTOR inhibitors (OR 32, p = 0.003).
Conclusion: Chronic hepatitis E in a cohort of immunocompromised patients with elevated transaminases levels is not infrequent, especially among transplant population undergoing mTOR inhibitors.
Funding: Instituto de Salud Carlos III (grant ICI14/00367).

SAT-213

Hepatitis E virus prevalence in Flemish blood donors

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Background and aims: Transmission of hepatitis E virus (HEV) through transfusion of blood components has already been reported worldwide. In this study, we assessed the HEV prevalence in Flemish blood donors. Certainly, it is of importance to determine the risk of HEV transmission through blood transfusion, especially for immunosuppressed solid organ transplant patients.

Method: We analysed 38.137 blood donation samples which were collected at the Red Cross Flanders during the period May-June 2015. Previously frozen samples were initially pooled per 6 and screened for the presence of HEV RNA using the cobas® 6800 System (Roche Diagnostics, Pleasanton, CA, USA), which has a limit of detection of 18, 6 IU/ml. In a second phase, RNA reactive pools were deconstructed and analysed individually using the same methodology. Because of volume limitations, individual samples were diluted with an equal volume of PBS. Using a specific ELISA (Wantai, Biological Pharmacy Enterprise, Beijing, China), the presence of HEV IgG was determined in all HEV RNA positive samples, as well as in a selection of 301 randomly chosen samples that scored HEV RNA negative when tested in pool format. HEV-specific IgM (Wantai) was determined in all viraemic samples, as well as in the IgG-positive/RNA-negative samples.

Results: During initial HEV RNA screening, 11 pools reacted positive. After deconstruction, 7 individual blood donations (7/38.137; 0, 02%) were confirmed as HEV RNA positive (range 1, 53 × 102-8, 71 × 103 IU/ml). Serological screening of the RNA positive samples showed that 6 out of these 7 samples were HEV IgM positive, of which 3 donors were also IgG positive. Serological screening was also performed on all samples that constituted the 4 initially HEV RNA reactive pools where RNA positivity was not confirmed on the individual level. This screening showed evidence of IgM and/or IgG seroconversion in 3 out of 4 pools. In the final pool one sample was IgG positive during all analysed time points. These results indicate recent HEV exposure and potentially explains RNA positivity during initial screening. Within 301 randomly selected samples, 27 donations were HEV IgG positive.

Conclusion: Here we show that at least 1:5, 448 of blood donations in Flanders may originate from donors who are actively infected with HEV. Upon transfusion, these donations may pose a major threat towards patients at risk.

SAT-214

Incidence, predictors and prognosis of liver failure in patients with hepatitis E as an acute insult

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Background and aims: Genotype (GT) 3 and GT4 hepatitis E virus (HEV) infection has been recently recognized as an important insult of acute or acute-on-chronic liver failure (A (C)LF), but seldom described before. This study aimed to identify the incidence, predictors and short-term outcomes of GT4 HEV related liver failure (HEV-LF).

Method: All the patients with symptoms of suspected acute viral hepatitis were screened for HEV infection in a tertiary hospital in China. Patients with hepatitis E who developed A (C)LF during hospitalization with HEV as an acute insult between November 2011 and September 2017 were recruited as cases. Hepatitis E patients who did not develop liver failure (HEV-non-LF) from January 2015 through September 2017 were enrolled as controls. Patients with liver failure induced by other acute etiologies were also extracted during the same hospitalized period.

Fig. 1

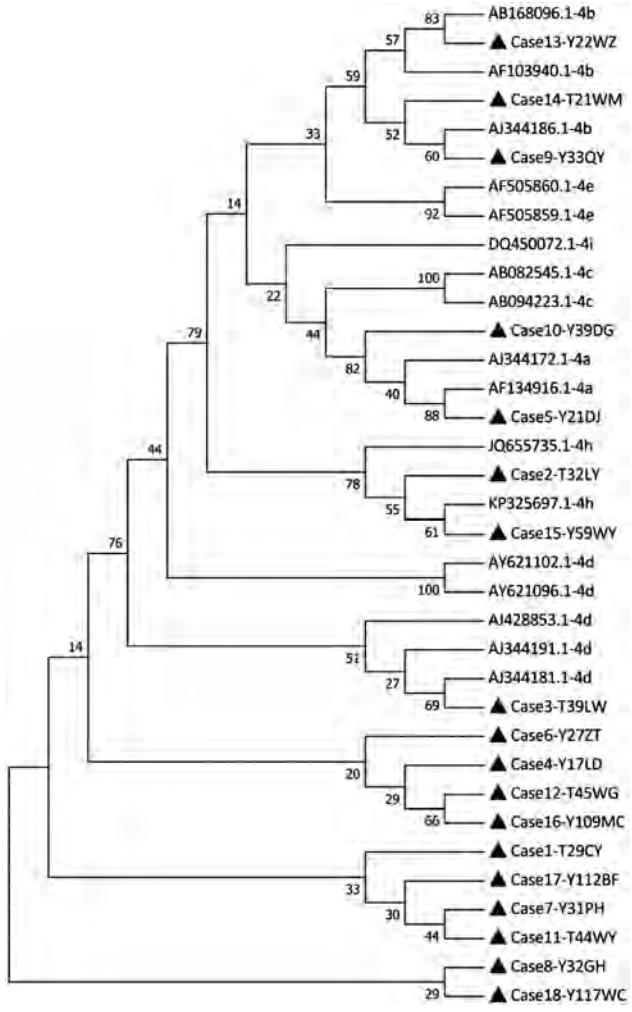

Fig. 2

Results: A total of 737 patients were diagnosed of hepatitis E during the study period, among which 62 (8.41%) developed liver failure with HEV as an acute event. 64.52% HEV-LF patients had chronic liver disease (CLD), significantly higher than HEV-non-LF patients (33.33%). Of note, an overall decline in the number of HEV patients and an increase in the ratio of HEV-LF were observed from year 2012

to 2017 (Fig.1). Sequencing of partial HEV genome has confirmed GT4 HEV strains (Fig. 2). Baseline HEV viral titer is lower in patients who developed A (C)LF than patients who did not ($p = 0.014$), but comparable between HEV-LF patients with favorable and poor outcomes. In the multivariate analysis, electrolyte disturbance (OR 2.4929; $p = 0.029$), ascites (OR 3.9621; $p = 0.003$), spontaneous peritonitis (OR 4.0106; $p = 0.016$), intestines injury (OR 5.2818; $p = 0.049$), lactate dehydrogenase (OR 1.0041; $p = 0.034$), alpha fetoprotein (OR 1.0047; $p = 0.008$) and carbohydrate antigen 125 (OR 1.0047; $p = 0.025$) at inclusion were found to be independent predictors of development of liver failure in short time. Of the 62 HEV-LF patients, 40 (64.52%) became recovered/improved, 20 (32.25%) were failed in response to treatment and 2 (3.23%) died, showing favorable outcomes than A (C)LF induced by other etiologies. Presenting hepatic encephalopathy (OR 6.7218; $p = 0.032$), higher level of glucose (OR 1.9476; $p = 0.005$) and international normalized ratio (OR 8.6245; $p = 0.032$) were independent predictors of poor prognosis of HEV-LF. Cirrhosis is the predominant CLD that associated with development and poor prognosis of A (C)LF in HEV patients compared to alcohol liver disease and chronic hepatitis B.

Conclusion: Patients with GT4 hepatitis E were at high risk to develop liver failure, especially in patients with CLD. Different types of CLDs impacted the incidence and prognosis of HEV-LF distinctively. The identified variables shall help to identify HEV patients with high risk of developing liver failure and the risk population with poor outcomes.

SAT-215

Cryoglobulinemia in asymptomatic, symptomatic acute and chronical HEV infections

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Background and aims: Hepatitis E virus (HEV) infections have been associated with numerous extrahepatic manifestations but a causal relationship still needs to be proven. Especially the assumed association with cryoglobulinemia is still under debate. Therefore, we aimed to test a cohort of blood donors with asymptomatic HEV infection, patients with symptomatic acute hepatitis E and immunosuppressed patients with chronic HEV-infection for cryoglobulinemia.

Method: Between 11/2014 and 10/2018 48 individuals with HEV infection, who presented at our outpatient clinic have been tested for cryoglobulinemia. Patient characteristics (age, ALT levels) have been assessed and patients were stratified according to type of HEV infection. Serum levels of total immunoglobulin G (IgG) available in 42 individuals were analyzed.

Results: Out of 48 individuals 12 (25%) had acute hepatitis E (median AST 825U/l), 13 (27%) had chronic hepatitis E (median AST 195 U/l) and 23 (48%) had asymptomatic HEV infection (median AST 35 U/l). 13 patients were female (27%) and median age was 47 years.

4/48 individuals with HEV infection (8%) tested positive for cryoglobulins in serum. All patients with cryoglobulinemia were male and had no clinical signs of cryoglobulinemia. Cryoglobulinemia occurred more frequently in hepatitis E (chronic: n = 3, acute: n = 1) than in asymptomatic HEV infection (n = 0; p = 0.047). Liver enzymes did not differ between patients with and without cryoglobulinemia (ALT, p = 0.21; bilirubin, p = 0.76). We observed a strong trend towards higher total serum IgG levels in patients with cryoglobulinemia compared to those without (median IgG 15 g/l vs. 10.2 g/l; p = 0.06).

Conclusion: While asymptomatic HEV infection was not associated with cryoglobulinemia, presence of cryoglobulins was observed in patients with acute and chronic hepatitis E. However, whether cryoglobulinemia in patients with acute or chronic hepatitis E has impact on the clinical outcome of the infection needs to be further clarified.

Viral Hepatitis C: Post SVR and long term follow up

SAT-217

Effectiveness and safety of sofosbuvir-based regimens in treatment of chronic HCV patients aged 60 years and older, Egyptian single center experience

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Background and aims: Since the introduction of direct-acting antivirals (DAAs), the outcomes of hepatitis C (HCV) treatment have shown an improvement in cure rates with minimal side effects. However, data on the virologic response and tolerability of DAAs in elderly patients are still lacking. Aim: to assess the effectiveness and safety profile of different sofosbuvir-based regimens in a large cohort of HCV patients aged 60 years and older in real-life clinical practice.

Method: This was an observational, retrospective single center study enrolled a total of 11290 chronic HCV patients from Damnhour Viral Hepatitis center, who were treated by different sofosbuvir-based regimens. Patients were divided into two groups: patients aged younger than 60 years (n = 9326) and those aged 60 years and older (n = 1964). Baseline demographics, underlying comorbid conditions such as diabetes and hypertension, prior HCV treatment history, HCV treatment regimen, adverse effects, and interruption or discontinuation of therapy were collected. Sustained virological response (SVR) at 12 weeks after the end of treatment and adverse effects were analyzed according to age.

Results: The overall SVR12 was 98.5%. In terms of by age, 98.5%, and 98.4% of the patients aged < 60, and ≥ 60 years achieved SVR12 respectively. At 12-weeks after the end of treatment (SVR12), levels of ALT, AST and Hemoglobin showed a decline among both groups. However, only the percent change for AST and Hemoglobin levels were significantly higher among patients aged 60 years and older (p < 0.05). Albumin, total bilirubin, total leucocytic counts and platelet count, and INR showed an increase among both groups, however none significant difference was observed between both age groups (p > 0.05). All patients were adherent to the prescribed treatment regimen as well as treatment duration and there were no reported interruptions in therapy because of adverse events (AEs). The most frequent reported AEs were headache, fatigue and insomnia among both groups. About 8.1% of patients reported at least one AE during the treatment period, and their incidence was not significantly different between the younger and elderly groups. There was no decompensating event or other serious adverse events reported and there were no deaths during treatment.

Conclusion: In a real-world setting, compared with younger patients, elderly patients had a similar virological response and tolerance to different sofosbuvir-based regimens.

SAT-218

Impact of sofosbuvir-based therapy on renal functions indices in chronic hepatitis c patients who achieved sustained virological response

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Background and aims: The effect of direct-acting antiviral agents (DAAs) on renal functions in hepatitis C virus (HCV) patients remains controversial. Little data are available on renal toxicity exerted by sofosbuvir (SOF) based therapy in clinical practice. Aim: to evaluate the changes of renal functions indices during and after SOF-based therapy in chronic HCV patients who achieved SVR.
Method: This is a retrospective cohort study of 1004 patients who underwent SOF-based treatment for chronic HCV between 2014 and 2017. Serum creatinine measures before starting DAAs treatment, at end of treatment (EOT) and at12- weeks after EOT (SVR12) were retrieved from patients' database. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients who didn't achieve SVR, had HIV or HBV co-infections, decompensated cirrhosis, transplant recipients and patients with eGFR less than 30 ml/min/1.73m^2 before antiviral therapy were excluded. Comparison of renal functions indices was performed using the Wilcoxon signed-rank test.
Results: 55.7% of our patients were males, with a median age 53 years, 39.7% had cirrhosis, 45.1% had CKD risk factors including diabetes mellitus (24.7%) and hypertension (20.4%) and 97.4% had a baseline eGFR ≥ 60 ml/min/1.73m^2. Ribavirin was used in 69.6% of patients. median serum creatinine was significantly increased at EOT and SVR12 compared to baseline (0.87 (0.7–1), and 0.83 (0.7-1) vs 0.8 (0.7-0.99) (p = < 0.0001, 0.0002 respectively). median baseline eGFR was 112.1 (90.1-137.6), changing to 108.1 (86.1-134.4) at EOT (p = 0.0003) and 109.7 (87.2-134.3) at SVR12 (p = 0.0002). eGFR was improved in 37.6% of patients, remained unchanged in 15%, and worsened in 47.4% at EOT compared to baseline. No significant changes were found between eGFR measures in patients who received sofosbuvir-based therapy without ribavirin at different time points, while for patients who received sofosbuvir-based therapy with ribavirin, median baseline eGFR was 111.9 (89.8-139.1), changing to 106.4 (84.04-130.7) at EOT (p < 0.0001) and 109.8 (87.3-134.4) at SVR12 (p = 0.0001) (figure1).

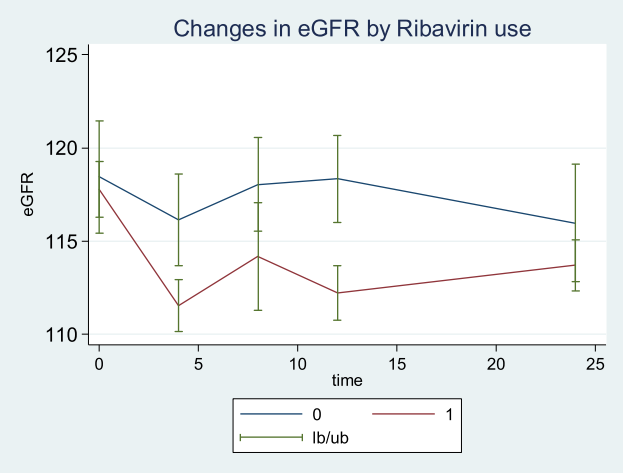

Figure 1: changes in eGFR in chronic HCV patients receiving SOF-based therapy with ribavirin vs without ribavirin.

Conclusion: SOF-based therapy is associated with decreased eGFR among HCV patients who received ribavirin. Renal function should be monitored during and after SOF-based therapy which includes ribavirin.

SAT-219

Effect of treatment of hepatitis C by directly acting antivirals on chronic hepatitis C and B co-infected patients

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Background and aims: Hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infection has a well-known impact on the disease severity and prognosis. The treatment options should be chosen wisely. However, the information concerning many aspects of dual infection, especially reactivation issue during or after completion of directly acting antivirals (DAAs), remains largely incomplete and heterogeneous. We aimed to investigate the risk of HBV reactivation during HCV treatment by DAAs in co-infected patients.
Method: We conducted a prospective cross-sectional cohort study in Al-Mahalla Hepatology Teaching Hospital, Gharbia, Egypt from the period between August 2016 and April 2018. Out of 3689 HCV patients screened for HBV, twenty patients showed co-infection in the age group of 18-70 years old after exclusion of HIV, autoimmune, haematological, and neoplastic disorders. We followed-up the patients for 24 weeks.
Results: Four patients had a negative HBsAg before DAAs treatment, one of them had detectable HBV viral load (occult HBV), with all of the 20 patients had a positive anti-HBc. Eight patients (40%) showed reactivation during DAAs treatment (figure 1). Five males and three females. Three patients with SOF/DAC/RBV regimen, two patients with SOF/DAC regimen, and three patients with SOF/SIM regimen.

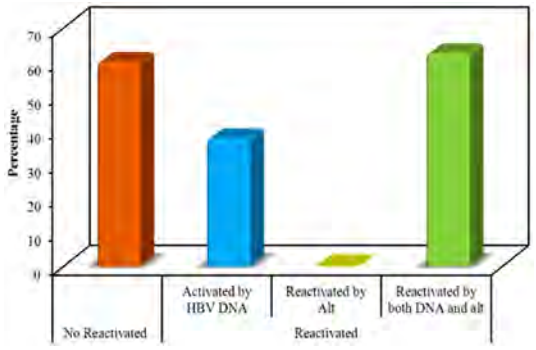

Figure: Distribution of the studied cases according to Reactivation (n = 20)

Conclusion: HBV reactivation during DAA therapy occurred with a respectful number. HBV screening is recommended both before, and during DAAs therapy regardless of the HBV status and the class of DAAs used.

SAT-220

Higher frequency of occult HCV infection in HIV/HCV coinfected patients with advanced liver disease: Post DAAs treatment observation

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Background and aims: Occult hepatitis C virus (HCV) infection (OCI) is defined as the presence of the HCV genome in either hepatocytes or

peripheral blood mononuclear cells (PBMCs) without detection of HCV RNA in serum. One study, analyzing the frequency of OCI both in naïve and DAAs treated patients showed a prevalence of 23% in HCV monoinfected patients. In this study, frequency of OCI resulted significantly higher in cirrhotic patients (73%) than in non-cirrhotic ones (24%, p = 0.0008).We aimed to evaluate the frequency of OCI in HIV/HCV co-infected patients with SVR12 after DAAs treatment and to explore clinical and virological characteristics associated with the presence of OCI.

Method: Fifty-three HIV/HCV co-infected patients with SVR12 after DAAs treatment, attending at Infectious Diseases Division of San Raffaele Hospital, Milan from 2015-2018 with available PBMCs sample at end of treatment and/or at week12 post treatment, were included in the study. In our analysis, OCI was defined as the presence of the HCV genome in PBMCs, determined by qualitative detection of 5' non coding region in this compartment, despite HCV RNA < 12 IU/ml measured in plasma. HCV-RNA negative patients in PBMCs were classified as no-OCI. Clinical and virological data were collected at baseline and provided as median and quartiles. Advanced liver disease (ALD) was defined as liver stiffness, measured by using transient elastography (TE), > 10 kpascal, and by a FIB-4 > 3.25 value. Mann-Whitney non parametric test or Fisher exact test were used to compare clinical and virological variables, as appropriate.

Results: OCI was detected in 43/53 (81%) patients: 30/31 (97%) patients with ALD and 13/22 (59%) patients without ALD (p = 0.0008). Comparison of clinical and virological variables between OCI and no-OCI showed that: liver stiffness [12.3 (6.8-20.6) vs 6.6 (6.2-7.0) kpascal, p = 0.002] and FIB-4 score [2.01 (1.4-4.2) vs 1.49 (0.8-2) (p = 0.009)] were significantly higher in OCI than in no-OCI. Additionally, CD4+ cells count [709 (445-926) vs 816 (743-1023) cells/mmc, p = 0.048] and CD8+ cells count [793 (569-1038) vs 1110 (833-1509) cells/mmc, p = 0.033], were higher in no-OCI patients. ALD resulted associated with a higher risk of OCI both considering liver stiffness (OD 0.048, p = 0.0008) or FIB-4 value (OD 0.15, p = 0.0756).

Conclusion: In our study population of HIV/HCV co-infected patients with SVR12 after DAAs treatment, a high frequency of OCI detected at end of treatment and/or at week12 post treatment, was observed. A less preserved HIV related immunological status and ALD were related with a major probability to maintain HCV infection in PBMCs.

SAT-221

Autoantibodies to apolipoprotein A1 (apoA-1): A new prognostic biomarker in HCV infection

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Background and aims: Chronic HCV infection is associated with an increased risk of atherosclerosis and cardiovascular mortality, despite an ostensibly favourable lipid profile Autoantibodies directed against apoA-1 (AAA-1) are a new biomarker of cardiovascular disease (CVD). High density lipoprotein (HDL) inhibits HCV-neutralizing antibodies by stimulating cell entry via activation of the scavenger receptor BI, an entry factor for HCV and a HDL receptor. ApoA-I is the principal component of HDL and amphipathic helices of apoA-I are critical for its binding to SR-B1. The AAA-1 response is biased towards the C-terminal alpha-helix of the protein.

We reported the presence of AAA-1 in 14/27 patients with advanced HCV and now extend this to 244 individuals: 29 with spontaneous resolution of HCV (SR), HCV RNA negative individuals after sustained virological response (SVR, n = 88) and patients with chronic HCV (CHCV, n = 127).

Method: Serum samples were obtained from HCV Research UK and Hepatology Research Group, Plymouth, UK and assayed for AAA-1 IgG by ELISA and lipids as previously described.

Results: CHCV patients had a high incidence of AAA-1 [59/127 (46.4%), 28/61 (46%) GT1 and 31/66 (47%) GT3]. This was significantly higher (p = 0.004) than HCV SR-5/29 (17%) were positive for AAA-1, similar to the rate in the general population (19.9%). 33/88 (37.5%) SVR sera were AAA-1 positive [n.s compared to CHCV group (p = 0.209)].

CHCV patients had dyslipidaemia with significantly lower total cholesterol, non-HDL-C, triglyceride and apolipoprotein B (p < 0.001) compared to patients with SVR and HCV SR [table]. This impacts on conventional cardiovascular risk factors which lose predictive power in chronic HCV infection.

Biochemical characteristic (median)	Spontaneous resolvers (n=29)	Chronic HCV (n=126)	SVR to antiviral therapy (n= 89)	P value
Total cholesterol (C) (mmol/L)	4.40	3.90	4.40	<0.001
Non-HDL-C (mmol/L	3.35	2.75	3.30	<0.001
Triglyceride (mmol/L)	1.75	1.00	1.50	<0.001
HDL-C (mmol/L)	1.00	1.10	1.00	0.032
Apolipoprotein A1 (g/L)	1.32	1.47	1.37	0.148
Apolipoprotein B (g/L)	0.81	0.76	0.89	<0.001
Triglyceride/HDL-C ratio	1.62	0.91	1.32	<0.001
Cholesterol/HDL-C ratio	4.78	3.46	4.27	<0.001
ApoB/ApoA1 ratio	0.60	0.51	0.66	<0.001

Conclusion: In contrast to spontaneous resolution after HCV infection, there is a high incidence of AAA-1 autoantibodies in CHCV which often persist after SVR. We hypothesise that these autoantibodies facilitate HCV persistence in predisposed individuals. Their role in modulating HCV entry and in CVD in CHCV warrants further study. This novel biomarker may be an independent predictor of CVD in HCV infection after SVR.

SAT-222

Improvement in liver fibrosis among patients with hepatitis C who achieved sustained viral response after direct acting antivirals treatment, in country of Georgia

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Background and aims: Georgia, a country with a large burden of hepatitis C, launched an ambitious hepatitis C elimination program in 2015. The aim of this study was to assess the long-term outcomes among patients with advanced liver fibrosis treated with direct acting antivirals (DAAs) who achieved sustained viral response (SVR).

Method: Four clinics providing hepatitis C diagnostic and treatment services in Georgia as part of national elimination program participated in the study. Patients treated with DAAs as part of the hepatitis C elimination program with advanced liver fibrosis defined

as fibrosis score ≥ F3 by elastography or FIB4 score ≥ 3.25, were treated during May to December 2015, completed a full course of the DAA treatment, and achieved SVR at week 12-24 post treatment were eligible for the study. Follow-up occurred between November 2017 and June 2018. Baseline and post treatment values (at least two years following completion of treatment) for liver fibrosis level (by elastography or FIB4 score), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count (PLT), spleen size and existence of ascites were evaluated among the study participants.
Results: A total of 600 patients were recruited and met the eligibility criteria. Mean age of participants was 52.2 years (range 27-85) and the majority 515/600 (85.8%) were male. Liver stiffness, defined as kpa, decreased a mean of 8.6 kpa (from 23.89 to 15.26) from baseline to follow-up (p <.0001). Among those whose fibrosis was measured by FIB4, the mean decrease was 1.41, from 3.52 to 2.11, (p <.0001). Mean ALT and AST levels decreased from 111.5 to 30.8 (p <.0001) and 89.7 to 30.3 (p < 0.05), respectively. The mean PLT count increased from 159 000 to 182 300 per microliter (p < 0.0001). Mean spleen sizes decreased significantly from 136X56 mm to 132X53 mm (p <.001). Among those with ascites at baseline (n = 17), 10 (58.8%) experienced resolution, while among the 583 patients without ascites at baseline, 9 (1.5%) were noted to have ascites during the follow-up examination.
Conclusion: Significant improvement of liver fibrosis level and clinical and laboratory parameters were observed two years after achieving SVR among patients with advanced liver fibrosis treated with DAAs.

SAT-223

AA genotype of the deSNP rs6726639 of gene MERTK (MER Tyrosine Kinase) is associated with development of hepatocellular carcinoma after hepatitis C virus clearance

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Background and aims: In patients with cirrhosis, the risk for hepatocellular carcinoma (HCC) development after hepatitis C virus (HCV) clearance is not canceled altogether. MERTK (MER Tyrosine Kinase) gene, located in chromosome 2, is a regulator of tumor-associated macrophages (TMA) involved in the modulation of inflammatory responses and angiogenesis. We evaluated the role of the Single Nucleotide Polymorphism (deSNP) rs6726639 of MERTK gene in the development of HCC in patients with a sustained virologic response (SVR) after treatment with Direct Antiviral Agents (DAAs).
Method: All consecutive patients with HCV cirrhosis (90% Child-Pugh class A and 10% Child-Pugh class B) treated with DAAs between March 2015 and December 2016 who obtained a SVR were evaluated for HCC occurrence by Kaplan-Meier curves and variables associated with HCC development were analyzed by Cox regression analysis. Genotyping for rs6726639 deSNP was carried out using the TaqMan SNP genotyping allelic discrimination method (Applied Biosystems, Foster City, CA, USA) on blood samples stored before treatment.
Results: Among 516 patients (mean age 66.9 ± 10.4 years, 57.9% men, 71.5% with esophageal varices) included in this analysis, 93 (18.0%) carried out the AA genotype, 215 (41.6) the AC genotype and 208 (40.4%) the CC genotype of rs6726639 deSNP.
During follow-up (median 25 ± 7 months) 28 patients (5.4%) developed HCC. By multivariate Cox regression analysis, platelet count < 120x 10^9/L (HR 5.72; 95%CI: 1.97-16.63; p = 0.001), Child-Pugh class B (HR: 3.09; 95%CI:1.31-6.89; p = 0.009) and the AA genotype of rs6726639 deSNP (HR 3.04; 95%CI: 1.40-6.62; p = 0.005) were independently associated to HCC occurrence.
Combining the rs6726639 deSNP genotype with clinical factors, we developed a risk profiling model with HCC rates ranging from 0.5% (best risk profile) toward 33% (worst risk profile).
Conclusion: The AA allele of rs6726639 deSNP of MERTK gene is associated with a higher risk of developing HCC in patients with cirrhosis after HCV eradication by DAAs. The identification of risk profiles is an important step forward in establishing prediction models for HCC development.

SAT-224

Design and validation of a risk prediction model for hepatocellular carcinoma development after sustained virological response in chronic hepatitis C patients

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Background and aims: Hepatocellular carcinoma (HCC) can develop after eradication of the hepatitis C virus. We designed and validated a HCC development risk score (HCC-SVR score) based on independent predictors for chronic hepatitis C (CHC) patients after sustained virological response (SVR).
Method: Between 2003 and 2016, 669 CHC patients achieved SVR through antiviral therapy. A new HCC-SVR score was developed based on the multivariate Cox proportional hazards regression model.
Results: After SVR achievement, HCC developed in 19 (2.8%) patients. HCC occurred more frequently in older, male patients and was associated with liver cirrhosis, hypertension, diabetes, lower platelet count, higher alpha-fetoprotein, higher aspartate and alanine aminotransferase, lower total cholesterol, and higher FIB-4 level (all p < 0.05). A multivariate analysis revealed that FIB-4 independently predicted HCC development (hazard ratio [HR] = 1.080), together with male gender (HR = 8.189) and alpha-fetoprotein level (HR = 1.060) (all p < 0.05). The HCC-SVR score based on independent predictors successfully predicted the risk of HCC development (area under receiver operating characteristic curve [AUC] = 0.771 at 2 years, 0.991 at 6 years, and 0.739 at 10 years). When the study population was stratified into three groups according to HCC-SVR risk score (0-2 points as low-risk, 3-7 points as intermediate-risk, and 8-9 points as high-risk), the cumulative incidence rate of HCC was significantly different between the groups (all p < 0.05 by log-rank tests). The accuracy of HCC-SVR score was maintained in a validation cohort (n = 524) (AUC = 0.728 at 2 years, 0.809 at 6 years, and 0.970 at 8 years).
Conclusion: This HCC-SVR score enables the ability to conduct risk stratification for HCC development in CHC patients at the time of SVR.

SAT-225

The risk of hepatic decompensation is reduced, but not abolished after direct-acting antivirals: The role of portal hypertension

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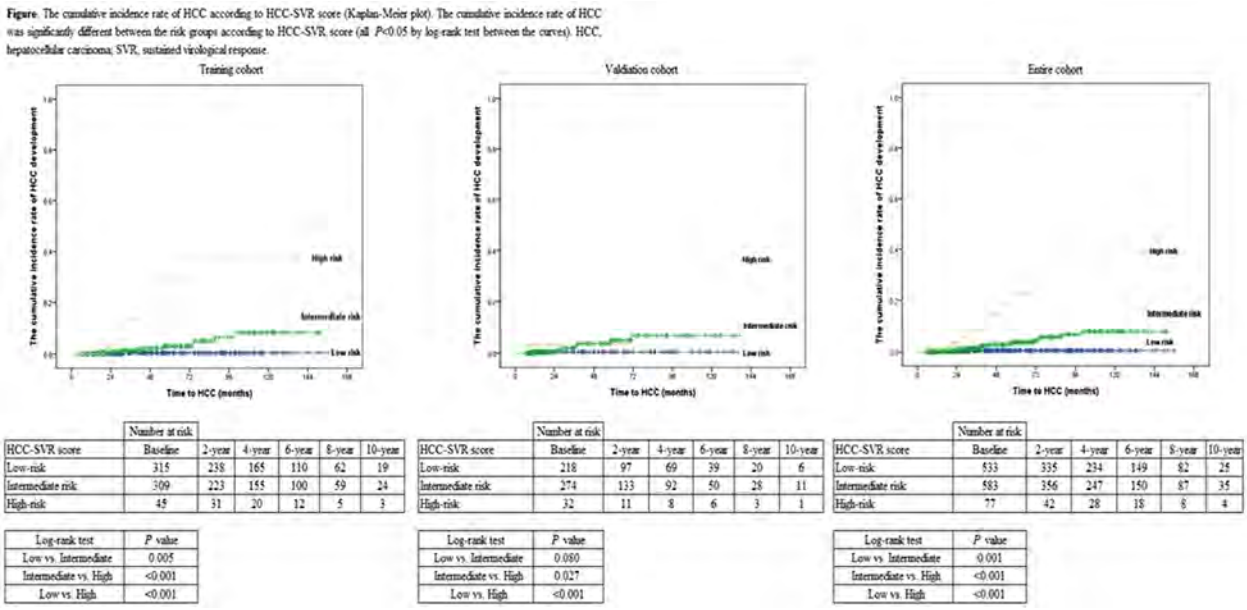
Background and aims: Little evidence is available on the risk of portal hypertension (PH)-related complications, such as hepatic decompensation (HD), after direct-acting antivirals (DAAs) in



	Number at risk					
HCC-SVR score	Baseline	2-year	4-year	6-year	8-year	10-year
Low-risk	315	238	165	110	62	19
Intermediate risk	309	223	155	100	59	24
High-risk	45	31	20	12	5	3

Log-rank test	P value
Low vs. Intermediate	0.005
Intermediate vs. High	<0.001
Low vs. High	<0.001

	Number at risk					
HCC-SVR score	Baseline	2-year	4-year	6-year	8-year	10-year
Low-risk	218	97	69	39	20	6
Intermediate risk	274	133	92	50	28	11
High-risk	32	11	8	6	3	1

Log-rank test	P value
Low vs. Intermediate	0.080
Intermediate vs. High	0.027
Low vs. High	<0.001

	Number at risk					
HCC-SVR score	Baseline	2-year	4-year	6-year	8-year	10-year
Low-risk	533	335	234	149	82	25
Intermediate risk	583	356	247	150	87	35
High-risk	77	42	28	18	8	4

Log-rank test	P value
Low vs. Intermediate	0.001
Intermediate vs. High	<0.001
Low vs. High	<0.001

Figure: (abstract: SAT-224)

patients with HCV-related advanced chronic liver disease (ACLD). Our aims were: a) to evaluate the incidence of HD after DAAs and confront it to a historical cohort of untreated patients; b) to estimate the effect of DAA treatments on HD.

Method: We performed in our tertiary centre a cohort study in 146 ACLD patients treated with DAAs and with available liver (LSM) and spleen (SSM) stiffness measurement both before and 6 months after end-of treatment; the patients were subsequently prospectively follow-up. A historical cohort of 92 consecutively enrolled untreated cirrhotic patients with active HCV-infection was used as a control group. A propensity score stabilized inverse probability weighting approach was used to account for differences between groups. A weighted Cox regression analysis was used to evaluate the predictors of the main outcome.

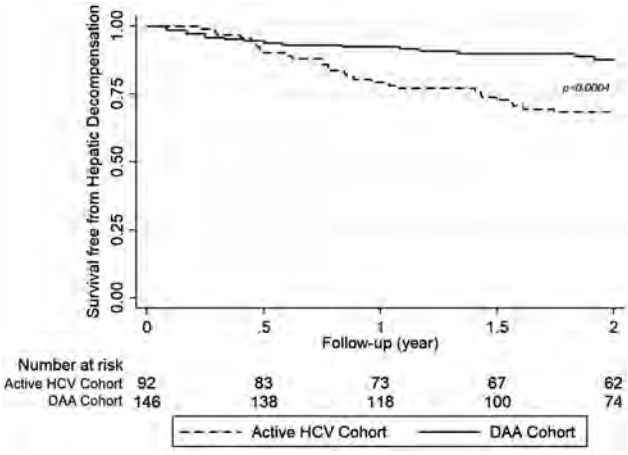


Figure: Kaplan-Meier curves of two-year HD-free survival in the active HCV and the DAA cohort.

Results: Median follow-up in the DAA cohort was 33.5 (22-38) months. The HD incidence in this cohort was 7.07 (4.56-10.96) per 100-person-years (PYs), significantly higher than in the active HCV cohort, 19.75 (13.81-28.25) per 100 PYs. **Figure 1** shows that the 2-year event-free survival was significantly higher in the DAA cohort. (0.004). DAA therapy was an independent protective factor for HD development (hazard ratio [HR], 0.177; 95%Interval-of-confidence [IC], 0.081-0.390), whereas previous HD (HR, 5.982; 95%CI, 2.434-14.702) and higher SSM values (HR, 1.025; 95%CI 1.006-1.045) were associated with a higher risk of the event. HD-free survival statistically differed

Conclusion: The risk of HD is markedly reduced after DAA therapy, but it is not abolished. Patients with severe PH, whether identified by clinical parameters, such as previous HD, or non-invasive approach (SSM), will continue to decompensate independently from etiological treatment, and therefore should be closely monitored.

SAT-226

beneficial effects of DAAs on right cardiac function in hcv patients with low-mild liver fibrosis

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Background and aims: Hepatitis C virus (HCV)-related chronic infection has been associated with a higher incidence of cardiovascular (CV) diseases. Systemic chronic inflammation, specific viral cytotoxicity on either the endothelium or the myocardium or an unexpectedly high prevalence of CV risk factors in HCV patients, may represent etiological factors. In a few studies, a reduced right and left ventricular function and morphology were found in patients affected by HCV hepatitis but the causality of the association is still debated.

Method: Eighty-six non-obese and non-diabetic HCV-patients (59.5 ± 12.0y; males 52%) with fibroscan-documented low-mild liver fibrosis, eligible for virus eradication with DAAs (Direct-Acting Antivirals), were included. Fifty-six of them were compared with 52 control subjects matched for age, sex and CV risk factors at baseline. A transthoracic echocardiography was performed at baseline (T0) in all participants and repeated in all HCV patients after successful eradication (6 months later, T1).

Results: At baseline, no differences in ejection fraction, MAPSE, E/A ratio and indexed Left Ventricular Mass (LVMi) were detected whereas Relative-wall Thickness (RWT) was higher in HCV patients as compared to matched controls. Right indexed atrial volume, basal ventricular diameter and pulmonary pressure were higher in HCV participants. After virus eradication, left atrial volume, tele-diastolic diameter and LVMi were lower as compared to baseline. Indexed right atrial volume, basal ventricular diameter, TAPSE, pulmonary arterial pressure and vena cava diameter decreased significantly.
Conclusion: The study shows a concentric remodelling of left ventricle and structural modifications in the right sections along with a higher pulmonary pressure in HCV subjects. Treatments with DAAs is associated with regression of most cardiac alteration indicating a direct involvement of the HCV virus in cardiac alterations, reversible after etiological treatment.

SAT-227

Clinical but not genetic variables predict the development of hepatocellular carcinoma in hepatitis C cirrhotic patients treated with direct-acting antivirals: A 3-year study in 509 patients

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Background and aims: Several single nucleotide polymorphisms (SNPs) have been associated with increased hepatocellular carcinoma (HCC) risk in viremic and Interferon-cured hepatitis C virus (HCV) cirrhotics, but the role of these genetic predictors in patients treated with direct-acting antivirals (DAA) is still undefined. The study aimed to assess the association between nine SNPs and HCC in a large cohort of DAA-treated patients.
Method: Consecutive HCV cirrhotics receiving DAA between December 2014-2016 in a single Center were enrolled. Cirrhosis was defined clinically, histologically or non-invasively (LSM ≥ 12 kPa). HCC was diagnosed and staged according to international recommendations. Patients were genotyped for 9 genes: TLL1 rs17047200, PNPLA3 rs738409, MBOAT7 rs641738, TM6SF2 rs5842926, IL28B rs12979860, MERTK rs4374383, MERTK rs6726639, EGF rs4444903 and GCKR rs1260326.
Results: 509 patients were analyzed: median age 64 (28-87) years, 58% males, 50% HCV-1b, median LSM 19.4 (12.0-75.0) kPa, 87% CPT-A, 11% with previous HCC. Overall, genotypes distribution was as follows: TLL1 AA (72%), AT (26%), TT (2%); PNPLA3 CC (46%), CG (41%) GG (13%); MBOAT7 CC (29%), CT (49%), TT (22%); TM6SF2 CC (91%), CT (8%), TT (1%); IL28B CC (22%), CT (54%), TT (24%); MERTK rs4374383 GG (37%), GA (48%), AA (15%); MERTK rs6726639 CC (37%), CA (49%), AA (14%); EGF AA (31%), AG (47%), GG (22%); GCKR CC (26%), CT (48%), TT (26%). Demography and clinical features of the patients were similar across SNPs genotypes. After 33 (3-47) months from DAA start, 56 patients developed HCC (3-year estimated cumulative probability of 14%). Male sex (HR 3.78, p = 0.008), diabetes (HR 3.5, p = 0.001) and LSM (HR 1.09, p = 0.001) were baseline independent predictors of HCC. Cumulative rates of HCC were independent of SNPs genotypes (TLL1 p = 0.92, PNPLA3 p = 0.25, MBOAT7 p = 0.69, IL28B p = 0.37, MERTK rs4374383 p = 0.07, EGF p = 0.8, TM6SF2 p = 0.6, MERTK rs6726639 p = 0.09, GCKR p = 0.91). Main HCC features did not differ across SNPs genotypes, such as nodules number (single: TLL1 p = 0.16, PNPLA3 p = 0.47, MBOAT7 p = 0.57, TM6SF2 p = 0.64, IL28B p = 0.68, MERTK rs4374383 p = 0.64, MERTK rs6726639 p = 0.59, EGF p = 0.79, GCKR p = 0.19), and time to HCC onset (TLL1 p = 0.46, PNPLA3 p = 0.14, MBOAT7 p = 0.17, TM6SF2 p = 0.49, IL28B p = 0.87, MERTK rs4374383 p = 0.96, MERTK rs6726639 p = 0.65, EGF p = 0.77, GCKR p = 0.27).
Conclusion: In a large cohort of DAA-treated HCV cirrhotics, clinical but not genetic features predict HCC risk.

SAT-228

Sustained virologic response induced by direct-acting antivirals suppresses skeletal muscle loss in patients with type C liver disease

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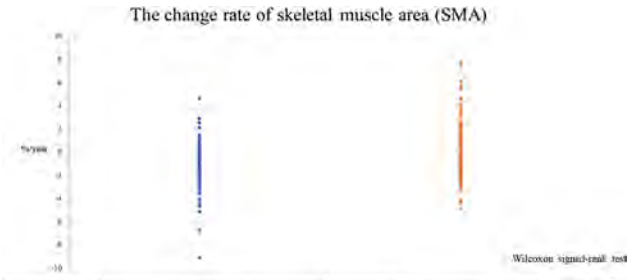
Background and aims: Chronic liver disease is a typical disorder of secondary sarcopenia that adversely affects the quality of life and clinical outcomes of patients. The effect of treatment of the primary disease (hepatitis C virus [HCV] elimination) on skeletal muscle mass has not been clarified. This study aimed to determine whether patients with HCV who achieved sustained virologic response (SVR) by direct-acting antivirals (DAAs) therapy improved skeletal muscle mass.
Method: We selected patients with HCV treated with DAAs therapy between 2014 and 2017. The inclusion criteria for the present study were as follows: (1) achieved SVR 24 by DAAs; (2) observation period evaluable by CT more than 1 year before and after DAAs. The exclusion criteria were as follows: (1) hospitalized for more than 1 month during an observation period; (2) Child-Pugh class B or C. We evaluated the cross-sectional area of the skeletal muscles (cm^2) at the third lumbar vertebra (L3) by abdominal CT. We used an image analysis software (SliceOmatic 5; Tomovision, Canada). The L3 skeletal muscle area was measured thrice: at the initial, start of DAAs, and final during the follow-up period. The Δ skeletal muscle area (SMA)/year (%/y) before the DAAs period was calculated as (SMA at the start of DAAs CT scan – SMA at the initial CT scan/SMA at the initial CT × 100/interval between CT scans (y)). The ΔSMA/y (%/y) after the DAAs period was calculated as (SMA at the final CT scan – SMA at the start of DAAs CT scan/SMA at start of DAAs CT × 100/interval between CT scans (y)). We compared ΔSMA/y (%/y) before and after the DAAs period.
Results: Eighty-six patients were enrolled in this retrospective study. The median age of the patients was 72 years, and 49 (57%) patients were men. In addition, 49 (57%) and 38 (43%) patients were diagnosed with chronic hepatitis (CH) and liver cirrhosis (LC), respectively. HCV genotype and DAA drugs were as follows: 1a:1b:2a:2b = 2:71:9:4, daclatasvir + asunaprevir/ledipasvir + sofosbuvir/sofosbuvir + ribavirin/elbasvir + grazoprevir:34/27/13/12. The median observational periods (CT interval) before and after DAAs were 3.27 and 2.37 years, respectively. SMA measured at the start DAA (second) CT indicated a significant decrease compared with the initial CT values (116.1 cm^2 vs 112.5 cm^2, p < 0.01). In contrast, no significant change was found between start DAAs (second) and final CT values (112.5 cm^2 vs 113.4 cm^2, p = 0.84). The change rate of SMA measured after DAA periods indicated a significant increase compared with that before the DAA periods {–0.03% (– 4.83%-7.66%) vs – 0.89% (– 9.10%-4.67%), p < 0.01}.
Conclusion: Viral eradication by DAAs (SVR) improved liver function, as well as suppressed the decrease in skeletal muscle area in patients with type C liver disease.



n=87	before DAA periods	After DAA periods	P
ΔSMA (%/year)	-0.89 (-9.10 – 4.67)	-0.03 (-4.83 – 7.66)	<0.01

SAT-229

Risk of hepatocellular carcinoma in patients with chronic hepatitis C and stage-3 liver fibrosis after sustained virological response with direct acting antivirals

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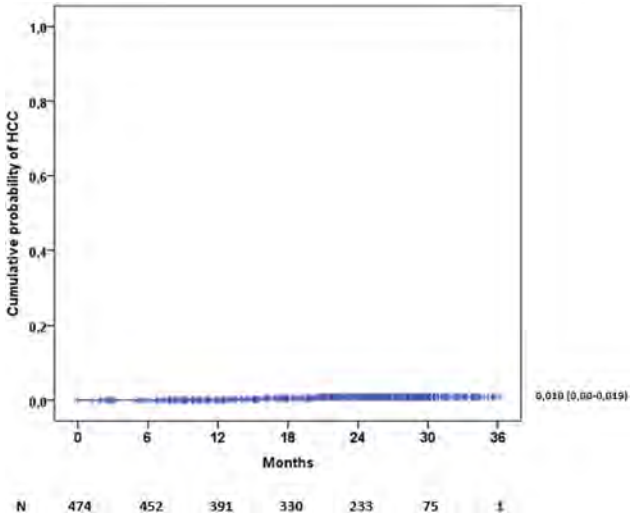
Background and aims: Current guidelines recommend life-long hepatocelullar carcinoma (HCC) surveillance in patients with stage 3 liver fibrosis (F3) after sustained virological response (SVR). However, the real incidence of HCC in this population is not well established and is based on retrospective studies from the Interferon-based treatment era. It also implies a substancial burden for both patients and the Health Systems. We aim to determine the HCC incidence in F3 patients after SVR with direct-acting antivirals (DAA).

Method: multicenter, ambispective, observational study. Inclusion criteria: Chronic hepatitis C; baseline F3 (transient elastography [TE] 9.5-14.5 kPa); SVR after DAA-based treatment from January to December 2015. Exclusion criteria: HCC diagnosed before SVR12; concomitant liver disease, cirrhosis or portal hypertension criteria. Abdominal ultrasounds were performed and HCC diagnosed according to EASL and AASLD guidelines.

Results: 474 patients were eligible for analysis. Median age 56.8 years (P25 51.8; P75 65.9), 60.34% males, 8.72% HCV-genotype 3, 41.41% met criteria of metabolic syndrome (MetS). 35.02% smokers, 13.59% significant alcohol consumption, 19.41% HIV co-infection, 14.95% post-SVR altered liver test. Baseline TE median values were 11.2 kPa (P25 10.2; P75 12.6). Median follow-up was 23.6 months (P75 16; P75 28.4).

Three hepatic tumors were diagnosed: two HCC and one cholangiocarcinoma. None with metabolic syndrome or HIV co-infection. One patient with HCC had genotype 3 and the patient with cholangiocarcinoma consumed alcohol. Baseline TE values of these patients were 11.8, 12 and 10Kpa.

Cumulative HCC incidence was 1% (IC 95% 0-1.9) at 36 months (Figure 1) and the HCC incidence rate 0.35 per 100 patients-year (IC 95% 0.07-1.02).



Conclusion: Patients with chronic hepatitis C and baseline F3 have a very low risk of developing HCC after SVR with DAA, below the threshold considered cost-effective for HCC screening (1, 5/100/year).

SAT-230

HCV re-infection among HIV-infected MSM in New York City

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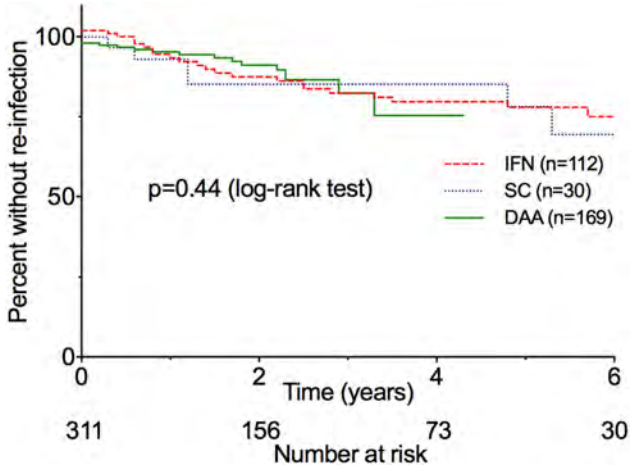
Background and aims: HCV re-infection rates after IFN treatment in HIV-infected MSM in Europe are much higher than primary infection rates, ranging from 3-15%. The primary HCV infection rate in New York City (NYC) was reported by the NYC Department of Health as 0.6/100 person-years (PY), but there are no data on re-infection rates in the United States or NYC, including among those cured with all-oral direct-acting antiviral (DAA) therapy.

Method: We assessed all HIV-infected MSM from our NYC cohort for clearance of HCV. Clearance was defined as SVR 12 if by treatment, or undetectable HCV VL for ≥ 12 weeks if by spontaneous clearance (SC). Re-infection was defined as new HCV viremia after clearance. Clinical onset of re-infection was defined as the date of the 1st-noted ALT elevation or HCV viremia. Observation time was defined as the period between 12 weeks after completion of therapy or SC, and either the clinical onset of HCV re-infection or the last undetectable HCV VL in those not re-infected.

Results: We identified 278 HIV-infected MSM with documented clearance of primary HCV infection and ≥ 4 weeks follow-up. Median age was 45 years; 173 (62%) were white, 44 (16%) black, 59 (21%) Hispanic. Genotypes of the primary HCV infections (n = 267) were 1a in 212 (79%), 1b in 25 (9%), 2b in 19 (7%), 3a in 4 (2%), and 4d in 7 (3%). Median CD4 count was 579 cells/uL; median HIV VL was < 50 copies/ml. We found 46 re-infections among 39 (14%) men between 2006 and 2018, a median of 1.7 (IQR 0.8, 3.3; range 0.2-11.8) years after clearance. Genotypes of the HCV re-infections (n = 41) were 1a in 32 (78%), 1b in 2 (5%), 2a in 5 (12%), 3a in 1 (2%), and 4d in 1 (2%). Including the re-infections, follow-up was available for 311 episodes of HCV clearance among the 113 (36%), 168 (54%), and 30 (10%)

infections cleared with IFN, DAA, and SC, respectively. Median follow-up time was 1.9 (IQR 0.8, 3.5; range 0.1-11.8) years, for a total of 808 PY. The overall HCV re-infection rate was 5.7/100PY (95% CI 4.2, 7.3). Time to HCV re-infection did not differ among the groups (p = 0.44, log-rank test) (Figure).



Conclusion: The HCV re-infection rate in our large cohort of HIV-infected MSM in NYC was almost 10-fold higher than the primary infection rate in NYC, was comparable to Europe rates, and was independent of whether clearance was by IFN or DAA treatments, or by SC. Most HCV re-infections occurred in the first 2 years after clearance, but infections continued for more than 11 years. These data suggest that long-term surveillance is warranted for all HIV-infected MSM after clearance of HCV. Further, strategies to reduce HCV infections and re-infections are needed to meet the goal of eliminating HCV in these men who are at high risk for HCV infection and re-infection.

SAT-231

Impact of the HCV cure with DAAs in the use of concomitant medication and the serum lipid profile: Follow-up data one year after the SVR12

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Background and aims: Patients with chronic hepatitis C (CHC) have several associated comorbidities and concomitant medication (CM). Treatment with direct-acting antivirals (DAA) achieve a sustained virological response (SVR12) in 95% of patients. Recently, it has been reported an increase of cholesterol serum levels (Hernandez-Conde et al., JVH2018) and systemic vascular resistance (Lens et al., Gastroenterology2017) after SVR12. The aim was to evaluate the impact of SVR12 with DAAs in the concomitant medication and the serum lipid profile.
Method: Prospective study of patients with CHC treated with DAAs (January 2015-September 2016) with SVR12. Demographic characteristics, clinical variables, and concomitant medication (CM) were analyzed at baseline and one year after SVR12. The CM was classified according to its anatomical therapeutic chemical classification system (ATC). The differences of the CM between baseline and follow-up were analyzed using the Stuart-Maxwell test and the serum lipid profile with ANOVA test. Patients were categorized according to the increase/decrease in the number of drugs of each ATC and the differences were analyzed by Chi-square test.
Results: We included 226 patients with SVR12 and median age of 59 (25-86): males (55.8%), Charlson index ≥ 4 (54.4%), cirrhosis (48.7%) and HOMA ≥ 3 (45, 7%). A 73.5% of the patients received CM (31% renin-angiotensin system agents, 30.5% antacids, 27.4% diuretics, 19.9% beta-blockers, 16.4% anti-diabetic drugs, 11.5% calcium-channel blockers and 7.1% lipid-lowering agents). A 49.6% were taking at least one drug with antihypertensive effect. During follow-up, total cholesterol serum levels increased from 161 to 179 mg/dL (p < 0.001). A significant increase in the use of lipid-lowering drugs was registered in the global cohort (p = 0, 009) and in patients < 65 (p = 0, 005). A significant trend to the increase of antihypertensive drugs was observed in patients ≥ 65 (p = 0, 06). Patients with an increase in the use of lipid-lowering drugs (n = 12) had a BMI ≥ 30 in a higher proportion (50% vs. 23.8%, p = 0.042). Patients with increased use of antihypertensive drugs (n = 27) presented a greater proportion of age ≥ 65 years (70.4% vs. 37.9%, p = 0.001), Charlson index ≥ 4 (92.6% vs. 49.2%, p < 0.001) and cirrhosis (81.5% vs. 44.2%, p < 0.001). Patients with increased use of antihypertensive drugs presented independently higher Charlson Index (≥ 4) (OR = 6.01, 95% CI: 1.1-32.6, p < 0, 001).
Conclusion: The cure of chronic hepatitis C is associated with a significant increase in cholesterol serum levels and in the use of lipid-lowering drugs, even in young patients, as well as an increase in the use of antihypertensive drugs in patients with comorbidities. However, it would be advisable to evaluate this effect in more extensive cohorts and for a longer period after SVR12 before making a solid recommendation.

SAT-232

Reinfection following successful HCV DAA therapy among people with recent injecting drug use

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Background and aims: HCV direct acting antiviral (DAA) therapy is effective in people who inject drugs however, little is known about HCV reinfection following DAA therapy among people who have recently injected drugs and/or people receiving opioid substitution therapy (OST). The aim of this study was to evaluate HCV reinfection following successful DAA therapy among people with recent injecting drug use.
Method: SIMPLIFY and D3FEAT are phase IV clinical trials of DAA therapy among people with recent injecting drug use (IDU; last six months) or those receiving OST, through a network of 25 international sites (SIMPLIFY: sofosbuvir/velpatasvir for 12 weeks in people with recent injecting; D3FEAT: paritaprevir/ritonavir/dasabuvir/ombitasvir±ribavirin for 12 weeks in people with recent injecting or receiving OST). This analysis assessed HCV recurrence from end of treatment response (ETR) through 24 weeks post-ETR (SVR24).

Results: Overall, 179 participants (72% male, median age 48 years) had an ETR and at least one subsequent follow-up visit in SIMPLIFY (n = 97) and D3FEAT (n = 82). At treatment initiation, 80% (n = 144) reported IDU in the past 6 months, 54% (n = 97) reported IDU in the past month, and 60% (n = 108) were receiving OST. IDU between ETR and follow-up was reported in 70% (n = 125). HCV recurrence was observed in nine participants including three cases of HCV relapse and six cases of reinfection. Over 168 person-years (py) of follow-up, the incidence of reinfection was 3.6/100 py (95% CI 1.6-7.9). There were no cases of reinfection among those who did not report ongoing injecting drug use after ETR. The incidence of reinfection in those with ongoing injecting after ETR (124 py of follow-up) was 4.8/100 py (95% CI 2.2-10.7/100 py).
Conclusion: HCV reinfection can occur following HCV DAA therapy among people with ongoing injecting drug use following DAA therapy, with higher rates of HCV reinfection observed among people with ongoing injecting drug use following therapy.

SAT-233

Hepatitis C virus reinfection following antiviral treatment among people who inject drugs: A systematic review, meta-analysis, and meta-regression

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Background and aims: Among individuals with ongoing injecting drug use (IDU), HCV reinfection following successful therapy can compromise treatment outcome. This systematic review assessed HCV reinfection rate after treatment among people with recent IDU and those receiving opioid substitution therapy (OST).
Method: Bibliographic databases and conference abstracts were searched for studies assessing HCV reinfection rate after treatment among people with recent IDU or those receiving OST. Meta-analysis was used to cumulate reinfection rates and meta-regression to explore factors associated with heterogeneity across studies.
Results: Twenty-two eligible studies were included [total person-years follow-up (PYFU) = 5112], including sub-population data of people with recent IDU (19 studies, PYFU = 4116) and people receiving OST (11 studies, PYFU = 1905). Recent IDU definition varied across studies (IDU during HCV treatment or post-treatment follow-up most commonly used). HCV reinfection rate was 5.4 per 100 PYFU (95%CI: 3.2, 8.9) among people with recent IDU, and 2.7 per 100 PYFU (95%CI: 1.4, 5.4) among those receiving OST. Reinfection rate was comparable between post-interferon-containing therapy (4.6 per 100 PYFU; 95%CI: 2.4, 8.8), and post-DAA therapy (3.4 per 100 PYFU; 95%CI: 2.3, 5.1). In stratified analysis, reinfection rate was 1.3 per 100 PYFU (95%CI: 0.5, 3.2) among people receiving OST with no recent IDU, 3.6 per 100 PYFU (95%CI: 1.5, 9.1) among those with recent IDU who also received OST, and 4.6 per 100 PYFU (95%CI: 2.1, 10.3) among those with recent IDU, not receiving OST. In adjusted meta-regression analysis, longer follow-up was significantly associated with lower reinfection rate [adjusted Rate Ratio (aRR) for each year increase in mean/median follow-up: 0.79 (95%CI: 0.67, 0.92; P = 0.005), while using end of treatment as the start point of time-at-risk of reinfection, compared to 12 weeks post-treatment (SVR12) or later, was significantly associated with higher reinfection rate (aRR: 2.54 (1.28, 5.04; P = 0.011). Diagnosis of reinfection following end of treatment was based on virus sequencing data, or genotype-switch.
Conclusion: Post-treatment HCV reinfection rate was the highest among people with recent IDU, not receiving OST. Higher rate in studies assessing reinfection from the end of treatment and lower rate in studies with longer follow-up suggested higher risk of reinfection early post-treatment. Harm reduction services are required to reduce the reinfection risk while regular post-treatment HCV assessment is required to detect and treat reinfection early.

SAT-234

Risk of hepatocellular carcinoma and efficacy of direct-acting antivirals in patients with concurrent hepatitis C virus

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Background and aims: Direct-Acting Antivirals (DAAs) have enabled us to cure more than 90% of patients with hepatitis C virus (HCV), though recent data suggests that HCV patients are less likely to achieve sustained virological response (SVR) in the presence of hepatocellular carcinoma (HCC). Although it is known that cirrhotic patients with HCV are at risk for HCC development, even in the DAA era, our understanding of HCC risk in non-cirrhotic DAA-cured patients is limited due to the novelty of these agents. We aimed to investigate the histological characteristics and evaluate SVR in patients who developed HCC in the context of DAA-treated HCV.
Method: We retrospectively evaluated 62 patients who underwent liver resection at Mount Sinai Hospital New York for HCV-related HCC, between November 2013 and June 2018 inclusive. The study was approved by the institutional review board. Demographic, clinical and pathological data were collected from our surgical specialty database and medical records where available. Data analysis was performed with Fisher's analysis using GraphPad.
Results: The mean age of our cohort was 65 years (range 49-78 years) and 75.8% [47/62] of these were male. The majority of patients had genotype 1 infection (67.7% [42/62]) and the most common HCV treatment amongst the 55 patients receiving DAA therapy was Ledipasvir/Sofosbuvir (53% [33/52]). The average MELD, platelet count, INR and AFP were 7, 197x10^9/L, 1 and 451 ng/dL respectively. The overall proportion of patients with stage 1, 2, 3, and 4 fibrosis by resection histology were 4%, 21%, 25% and 50% respectively (Fig 1A). The proportion of patients with grade 1 inflammation was significantly higher in patients with undetectable HCV at the time of resection compared to active HCV cases (53.9% [14/26] vs 13.9% [5/36], p = 0.0017) (Fig 1B). The overall SVR rate in DAA-treated patients was 85.5% [47/55]. Patients undergoing DAA treatment post-resection were significantly more likely to achieve SVR compared to those treated prior to resection (72.4% [21/29] vs 100.0% [26/26], p = 0.0048).
Conclusion: HCC continues to be a major complication in patients with HCV in the DAA era. In this study, we demonstrate that a subgroup of DAA-treated patients with minimal liver inflammation and/or liver fibrosis continue to be at risk for HCC. The mechanism behind this, although interesting, is unclear and deserves further investigation. We also show that patients treated with DAAs after HCC resection were more likely to achieve SVR than those treated prior to resection. Although more data is needed regarding the timing of HCC treatment, this supports recent data demonstrating that patients with active HCC are less likely to achieve SVR compared to patients with cured HCC.

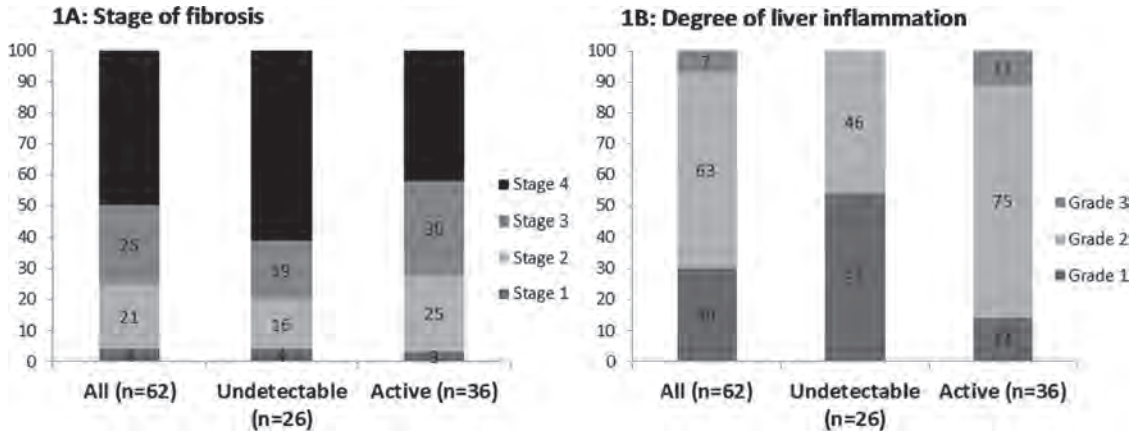

Figure 1: Stage of fibrosis & liver inflammation (Batts-Ludwig score) in cured HCV cases compared with active HCV cases at the time of liver resection.

Figure: (abstract: SAT-234)

SAT-235

Low HCV reinfection incidence following DAA treatment scale-up in people living with HIV in Australia

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Background and aims: Rapid uptake of direct-acting antiviral (DAA) therapy from 2016 in Australia, particularly among people living with HIV (PLWH), provides the opportunity to achieve HCV elimination. HCV reinfection could compromise HCV elimination efforts, especially if risk behavior increases.
Method: The Control and Elimination of HCV from HIV-infected individuals within Australia (CEASE-D) is an ongoing observational cohort study. HIV/HCV (antibody positive) co-infected individuals (≥ 18 years) were enrolled from 14 primary and tertiary clinics in Australia. Participants completed a questionnaire at enrolment (July 2014-March 2017) and first follow-up visit (June 2017-May 2018). We evaluated HCV reinfection incidence, and longitudinal injecting and sexual risk behaviour.
Results: Of 402 HIV/HCV antibody-positive participants (mean age 49 years, gay and bisexual male (GBM) 80%, cirrhosis 13%), 290 (72%) had detectable HCV RNA at enrolment. HCV treatment uptake among those with detectable HCV RNA was 7% in 2014, 10% in 2015, 80% in 2016, and 35% in 2017, and the proportion with detectable HCV RNA declined from 82% in 2014 to 8% in 2018. Reinfection was reported in five participants through follow-up (incidence 0.81 per 100 person years, 95% CI 0.34-1.94), all of whom identified as GBM. At baseline, injecting drug use (IDU) ever was reported by 79%, and current IDU (within six months) by 36%. Amphetamines (30%) were the most common drug injected. During follow-up there was no change in injecting risk, with 35% reporting current IDU (p = 0.715), and injecting frequency and sharing rates also stable. Among GBM, 53% reported condom-less anal intercourse (CLAI) with one or more casual male partners (CMP) and 34% reported group sex at enrolment, compared to 40% CLAI with CMP and 25% group sex at follow-up (p = 0.002 and p = 0.020 respectively). The proportion with detectable HCV RNA declined in all risk sub-populations, including those reporting current IDU (2014: 87%, 2018: 10%) and high risk sexual behavior (2014: 83%, 2018: 10%).
Conclusion: HCV reinfection following DAA therapy was very low, despite ongoing risk behaviour. The probable explanation is rapid and large HCV RNA decline, comparable DAA therapy uptake among high- and low-risk sub-populations, and no increase in injecting or sexual risk behaviour. HCV elimination should be achievable among PLWH in the near future.

SAT-236

Post-treatment fibrotic modifications overwhelm pretreatment liver fibrosis in predicting HCC in CHC patients with curative antivirals

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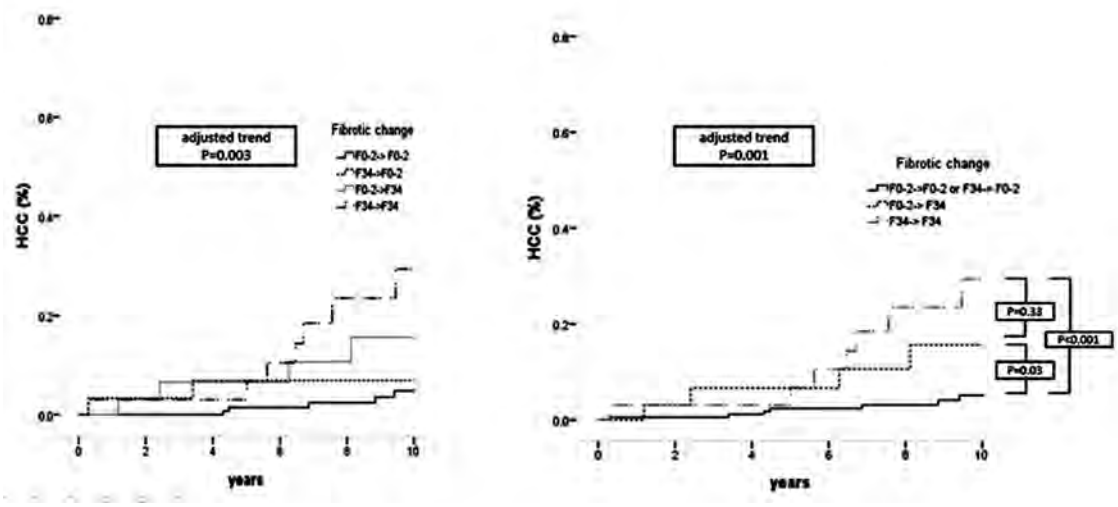
Background and aims: Liver fibrosis determined hepatocellular carcinoma (HCC) occurrence in chronic hepatitis C (CHC) patients with sustained virological response (SVR). We aimed to determine whether post-treatment fibrotic modification overwhelmed pre-treatment fibrotic status in terms of long-term HCC prediction.
Method: 265 SVR patients with paired biopsies before and after antiviral therapy were enrolled for analysis of the association of fibrotic changes with HCC.
Results: Eighteen of the 265 (6.8%) patients developed HCC over 1931 person-years. Cox regression analysis without post-treatment fibrosis as a covariant revealed that factors predicted HCC included age (hazard ratio [HR]/confidence intervals [CI]: 1.07/1.01-1.13, P = 0.01), male gender (HR/CI: 4.57/1.45-14.36, P = 0.009), diabetes (HR/CI: 3.60/1.32-9.85, P = 0.01) and pretreatment advanced fibrosis (HR/CI: 2.73/1.05-7.07, P = 0.039). Advanced fibrosis in post-treatment status replaced pretreatment fibrosis as the most critical determinant of HCC when it was included for analysis (HR/CI: 3.53/1.34-9.30, P = 0.01). The incidences of HCC among patients with fibrotic modification from F0-2 to F0-2, F34 to F0-2, F0-2 to F34 and F34 to F34 were 0.41%, 0.84%, 1.68% and 3.05%, respectively (p = 0.004). Compared to patients whose fibrotic stage remained at F0-2 before and after treatment, the HCC risk decreased and did not differ among those whose fibrotic stage improved from F34 to F0-2. However, HCC risk increased significantly and gradually in patients whose fibrotic stages changed from F0-2 to F34 (HR/CI: 4.13/1.11-15.36, P = 0.035) and



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whose fibrotic stages remained at F34 before and after treatment (HR/CI: 7.47/2.37-23.55, P = 0.001) (trend P = 0.003).
Conclusion: Post-treatment fibrotic modifications overwhelmed pretreatment fibrotic statuses in predicting HCC.

SAT-237

Histological improvement of hepatitis C virus patients after achieving sustained virological response with direct-acting antivirals

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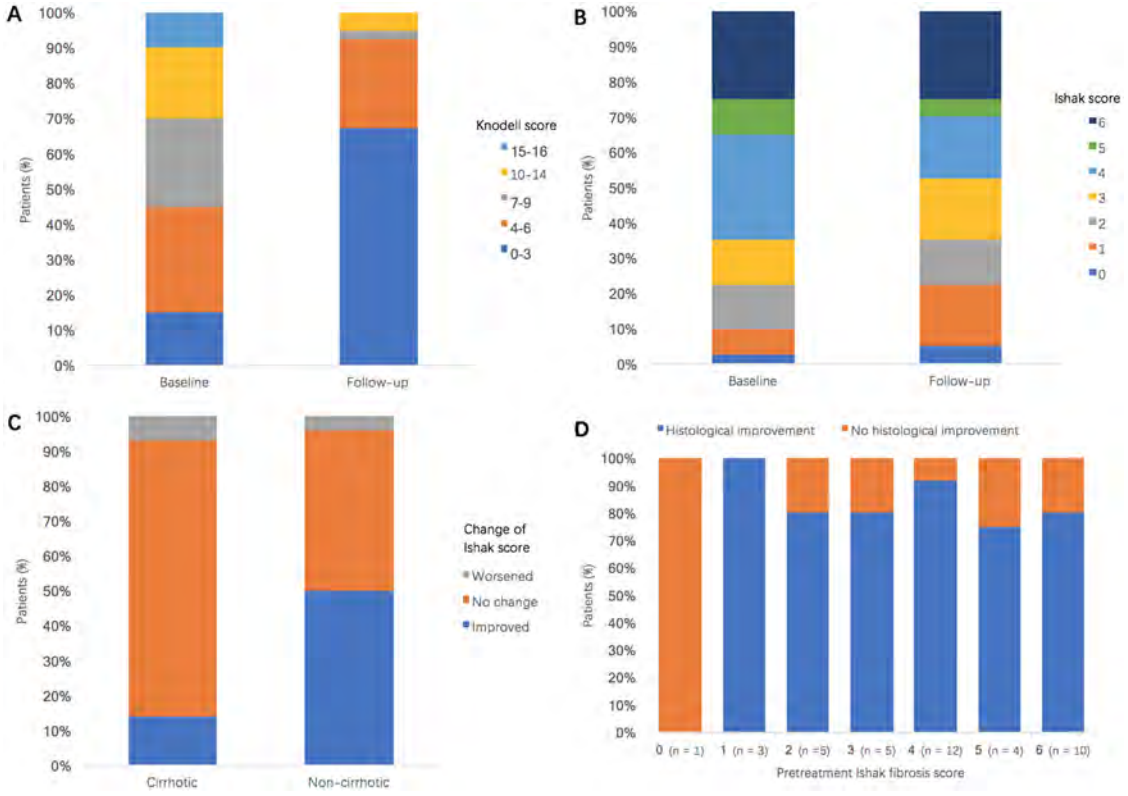
Background and aims: Liver biopsy findings after successful chronic hepatitis C virus (HCV) eradication with direct-acting antivirals (DAAs) has not been well stated. To this end, we collected liver biopsy samples of patients with chronic HCV infection who accepted successful antiviral therapy with DAAs.
Method: Patients with chronic HCV infection with sustained virological response (SVR) after treatment of DAAs were invited. Patients who had both pretreatment and follow-up liver biopsies were evaluated for histological changes. Biopsy slides were assessed by Ishak system. Histological improvement was defined as a



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reduction in Knodell necroinflammation score of ≥ 2 points with no worsening of Knodell fibrosis after end of treatment (EOT). Regression of liver fibrosis was defined as a ≥ 1-point decrease in Ishak score.

Results: 40 patients with available paired liver samples were included into the analysis. Follow-up biopsies were obtained after an average of 6 months from EOT (range: 6-7 months). The mean age was 41.6 ± 14.6 years with 50% (20/40) males. 58% (23/40) patients were genotype 1 and 35% (14/40) patients were diagnosed as cirrhosis. Knodell score were judged as 10-14 and 15-16 in 20% (8/40) and 10% (4/40) patients, respectively. 83% (33/40) patients achieved improvement of HAI ≥ 2 (figure 1A. Distribution of Knodell necroinflammatory scores in 40 patients with results available at each time point, p = 0.000). Periportal interface hepatitis, confluent necrosis, focal lytic necrosis and focal inflammation and portal inflammation were evaluated in the modified HAI grading system. In 40% (16/40) patients the decrease in periportal hepatitis scores was two points or greater. The proportion with no confluent necrosis increased from 70% (28/40) at baseline to 95% (38/40) after EOT (p = 0.000). Respectively, 70% (28/40) and 25% (10/40) patients had a decrease or no change in focal lytic necrosis and focal inflammation score between baseline and follow-up biopsy (p = 0.000). 80% (32/40) patients had decreased portal inflammation scores between pretreatment and follow-up biopsy; 48% (19/40) patients had a decrease of two points or greater. 95% (38/40) patients' fibrosis staging improved or didn't worsen (figure 1B. Distribution of Ishak fibrosis scores in 40 patients with baseline and follow-up liver biopsies, p = 0.547). Overall, regression of liver fibrosis was documented in 38% (15/40) of patients. Change of Ishak scores according to cirrhotic status was shown in figure 1C (Change of Ishak score according to cirrhosis, p = 0.000). 85% (33/39) patients reached the criterion of histological improvement (figure 1D. Histological improvement according to pretreatment Ishak fibrosis score, p = 0.0000).

Conclusion: Significant histological improvement was seen in patients with chronic HCV infection after SVR with DAAs in this paired liver biopies analysis.

SAT-238

The impact of SVR from direct acting antiviral and interferon-based treatments for HCV on hepatocellular carcinoma risk in a large population based cohort

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Background and aims: We evaluated the effect of sustained virologic response (SVR) from direct acting antiviral (DAA) and interferon-based treatments on hepatocellular carcinoma (HCC) risk among those with and without cirrhosis in a large population based cohort in Canada.

Method: We used data from the BC Hepatitis Testers Cohort, which includes ~1.3 million individuals tested for HCV since 1990, linked with data on medical visits, hospitalizations, cancers prescription drugs and mortality. Patients who received DAAs or interferon treatments were followed from the end of treatment to HCC, death or December 31, 2016. We assessed HCC risk among those who did and did not achieve SVR by treatment type using multivariable competing risk proportional hazard models.

Results: Of 12, 776 eligible individuals, 3, 905 received DAAs while 8, 871 received interferon-based treatments and were followed for a median of 1.0[range:0.6-2.7] and 7.9[range:4.4-17.1] years, respectively. 3613 and 6575 achieved SVR with DAAs and interferon based treatments, respectively. Among DAAs treated patients 36 HCC cases were identified, 26 in SVR group. The HCC incidence rate was 6.9 (95%CI: 4.7-10.1)/1000 person-yr (PY) in the SVR and 38.2 (95% CI:20.6-71.0) in the no-SVR group (p < 0.001), with higher rates among those with cirrhosis (SVR: 20.7, no-SVR: 133.5). Among those treated with interferon-based treatments, 340 cases of HCC were identified, 99 in SVR group. HCC incidence rate was 1.8 (95%CI: 1.5-2.2) in the SVR and 13.9 (95%CI: 12.3-15.8) in the no-SVR group (p < 0.001). There was steepest increase in cumulative incidence in those with cirrhosis/no-SVR followed by those with SVR/cirrhosis and no-SVR/no-cirrhosis while increase in incidence among SVR/no-cirrhosis group was a slower and lower (**Figure**). In multivariable model, compared to no-SVR from interferon, SVR from DAA and interferon based treatments resulted in significant reduction in HCC risk (adjusted subdistribution hazard ratio (asHR) DAA = 0.30, 95% CI:0.19-0.48 and asHR interferon = 0.2, 95%CI:0.16-0.26). In model by cirrhosis status, higher reduction in HCC risk was observed among those without cirrhosis (DAA-asHR = 0.28, 95%CI:0.16-0.50/ Interferon-asHR = 0.17, 95%CI:0.13-0.22) compared to those with cirrhosis (DAA-asHR = 0.40, 95%CI: 0.19-0.87/interferon-asHR = 0.56, 95%CI:0.34-0.91).

Conclusion: DAA-related SVR is associated with in 70% reduction in HCC risk. Reduction was lower in those with cirrhosis and among those treated with DAA, related with poor comorbidity profile at treatment. These findings indicate early treatment could further reduce HCC risk.

SAT-239

Real life data on elbasvir/grazoprevir efficacy, safety and drug-drug interaction profile in patients with chronic hepatitis C viral infection: A prospective analysis in the PITER cohort

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Background and aims: In a previous real life study, based on data retrieved by the PITER cohort, it was reported that of HCV chronic infected patients, undergoing direct acting antiviral (DAA) therapy (sofosbuvir-based or paritaprevir/ritonavir, ombitasvir and dasabuvir) and taking comedications, 30% (with mild liver disease stage) and 44% (with moderate to severe liver disease stage), are at risk of potential drug-drug interactions (DDI).

Following the recent introduction of elbasvir/grazoprevir (EBR/GZR) we aimed to evaluate the prospective profile of efficacy and safety combined with real life comedication profile used at the beginning, during and at the end of the DAA therapy in each of treated patient.

Method: Data from patients, who were consecutively enrolled in PITER by 15 clinical centers and were treated with EBR/GZR, with at least three months of follow-up after the end-of-treatment, were evaluated. Comedications profile in terms of no changes, drugs interrupted, or modified as posology, or those added were evaluated and their potential DDI were assigned according to HepC Drug

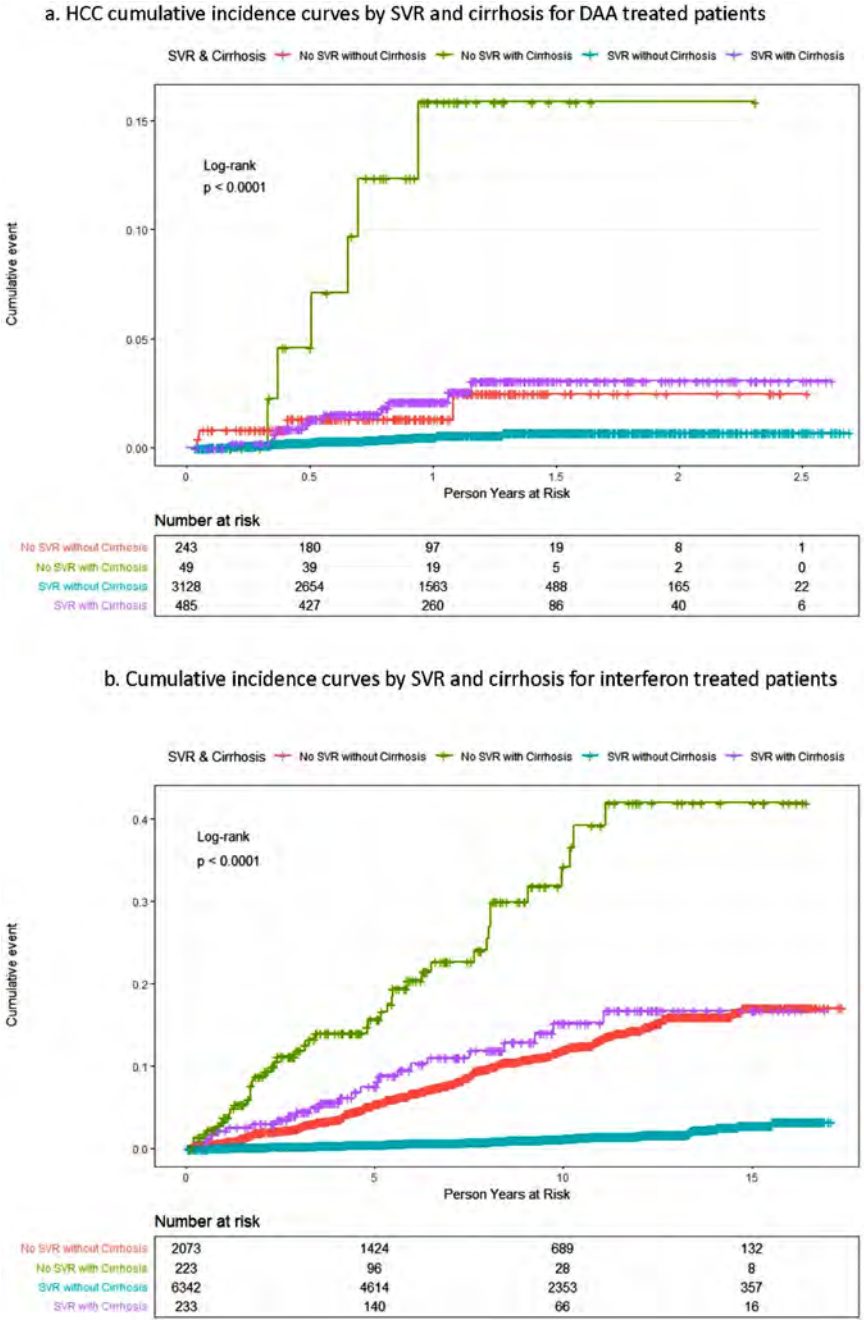

Figure: (abstract: SAT-238) HCC cumulative incidence curves by SVR and cirrhosis status

Interactions (www.hep-druginteractions.org). Overall, 312 patients with at least 12 weeks response following the end of treatment (mean age 63 ± 10 years; 44% male, 90% of genotype 1 of whom 81% HCV GT1b, 85% with Fibrosis stage ≤ F3 and 15% with child A liver cirrhosis) were evaluated.

Results: The 12 weeks Sustained Virological Response (SVR12) was reached in 299 (96%), 13 (4%) of patients failed to reach the SVR12. Gender, age, fibrosis stage, previous interferon therapy, presence of diabetes and fatty liver were not related to failure by logistic regression analysis. Of 312 treated patients, 187 (60%) had at least one comobidity (median: 2 range: 1-6 comorbidities). Follow-up data on comedications used pre, during and at the end of EBR/GZR treatment were available in 182 patients. Of these patients, 21% have taken 1 drug, 24% two drugs, 17% three drugs and the remaining 38% from 5 to 10 drugs. Of 328 comedications used during the DAA therapy, 3% were modified in posology, 2% were interrupted and 3% were new drugs added. None of changes was due to potential DDI. None but statins (in 2% of patients) were reported to require monitoring by HepC Drug Interactions. However, no changes were recorded for the statins, which were used at the lowest dosage recommended during the DAA therapy. Regarding the safety profile, EBR/GZR was well tolerated. An increase in ALT levels were observed in 12 (4%) of treated patients during therapy (with values lower than 2 times of normal levels in 6 patients and lower than 3 times of normal in the remaining 6), all in patients with fibrosis stage lower than F3.

Conclusion: EBR/GZR demonstrated high cure rates and a very good safety profile. No drug-drug interactions were recorded in this real

life cohort of treated patients with different comorbidities and comedications used.

SAT-240

Metabolic liver function improves 12 weeks after successful sofosbuvir-based direct-acting antiviral therapy in patients with chronic hepatitis C and advanced liver disease

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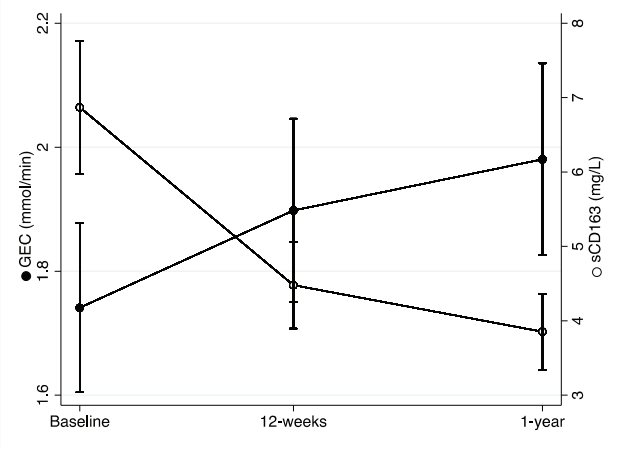
Background and aims: Sofosbuvir-based direct-acting antiviral (DAA)-therapy is very efficient in clearing chronic hepatitis C (CHC) infections, however, the effects on metabolic liver function and the potential rate of recovery are unknown. We aimed to investigate the effects of DAAs on metabolic liver function, macrophage activation, liver stiffness, and continuous reaction time (CRT) in CHC patients with advanced liver disease.

Method: We investigated 71 Danish CHC patients with advanced liver disease (TE > 10kPa) before, during, and after 12-24 weeks of sofosbuvir-based DAA-therapy. Metabolic liver function was estimated by galactose elimination capacity (GEC), macrophage activation by plasma sCD163 and sMR levels (ELISA), liver stiffness by FibroScan or acoustic radiation force impulse (ARFI)-scans, and reaction time as CRT.

Results: All patients achieved sustained virologic response, except one patient with reinfection. Metabolic liver function improved at follow-up (all: 1.74 vs. 1.98 mmol/min) both in patients with cirrhosis ($n = 56$) and those with advanced liver disease ($n = 15$) ($p < 0.0005$). The majority of this effect occurred within 12 weeks post-treatment. The sCD163 and sMR levels decreased rapidly during the study period (sCD163: 6.9 vs. 3.9; sMR: 0.37 vs. 0.30 mg/L) as did liver stiffness (17.8 vs. 12.1 kPa) ($p < 0.0001$, all). The CRT improved at one-year follow-up (1.86 vs. 2.09, $p = 0.05$). sCD163 levels correlated with GEC and liver stiffness at baseline; however, there were no associations between changes in sCD163 or sMR and changes in GEC or liver stiffness during follow-up.



Conclusion: Successful DAA-therapy of CHC proves beneficial in advanced liver disease as metabolic liver function rapidly improves in combination with reduced macrophage activation and liver stiffness.

SAT-241

The dynamics of two plasma markers of type III collagen formation and degradation in the course of chronic hepatitis C viral clearance with direct-acting antiviral therapy

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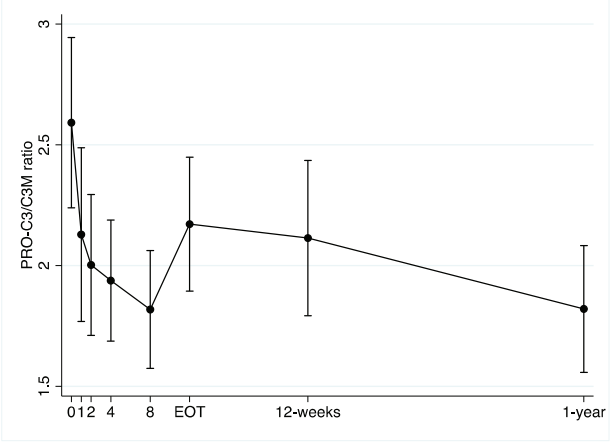
Background and aims: In chronic hepatitis C (CHC) fibrosis and cirrhosis, imbalanced extracellular matrix (ECM) turnover is prominent. ECM turnover generates protein fragments, which reflect liver fibrosis. PRO-C3 is a neo-epitope reflecting type III collagen formation, whereas C3M is a marker of matrix metalloproteinase-9 mediated degradation of type III collagen. It is unknown how ECM turnover is affected after viral clearance with direct-acting antiviral (DAA) therapy. We aimed to assess the dynamics of PRO-C3 and C3M with DAA-therapy in CHC patients with advanced liver disease.

Method: PRO-C3 and C3M were assessed in plasma by competitive ELISAs before, during, and after 12-24 weeks of DAA-therapy in 77 Danish CHC patients; 14 with advanced liver disease (F3) and 63 with cirrhosis. Liver stiffness was evaluated at baseline, end of treatment (EOT), and 12-weeks and one-year post-treatment using FibroScan or acoustic radiation force impulse scans.

Results: At baseline, the level of PRO-C3 was 24.0 ng/ml (95% CI: 21.2-26.8) and it decreased with 22% ((11-32), $p < 0.0001$) during treatment. There was an additional decrease of 16% ((4-27), $p = 0.01$) at follow-up with the PRO-C3 level ending up at 15.6 (13.6-17.5) one-year post-treatment. The PRO-C3 level was not significantly increased in the patients with cirrhosis compared with the patients with advanced liver disease ($p = 0.15$), however PRO-C3 correlated with liver stiffness at baseline, and 12-weeks and one-year post-treatment ($r > 0.39$, $p < 0.02$). The C3M level was 9.3 ng/ml (8.6-10.0) at baseline and the decrease over time was more discrete. The level decreased with 6% ((2-10), $p = 0.001$) from baseline to end of treatment ending at 8.5 (7.8-9.2) at one-year follow-up. The decrease over time was similar for cirrhosis patients and patients with advanced liver disease and the cirrhosis patients had 20% ((1-46), $p = 0.04$) higher C3M levels at all time points. Additionally, C3M correlated with liver stiffness at baseline, at the end of treatment and one-year post-treatment ($r > 0.33$, $p < 0.006$).



Conclusion: PRO-C3 and C3M, two markers of type III collagen formation and degradation, decrease during and after DAA-therapy in CHC patients with advanced liver disease and are associated with liver stiffness at baseline and during follow-up. These results indicate an altered balance between collagen formation and degradation after viral clearance suggesting a potential favourable effect on liver fibrosis.

SAT-242

Liver stiffness measurement is not a predictive factor of HCC in HCV patients with severe fibrosis who achieved SVR by DAA

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Background and aims: Hepatitis C virus (HCV) infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. New direct acting antivirals (DAA) have strongly modified the natural course of HCV. Yet, risk of HCC remains even after sustained virologic response (SVR), specially among patients with pretreatment severe fibrosis. As transient elastography (TE) is one of the leading non-invasive tool to assess liver fibrosis, our aim was to determine whether changes in liver stiffness measurement (LSM) of patients achieving SVR with DAA can help to identify patients at high-risk of HCC.
Method: We reviewed all patients treated for an HCV infection in Saint-Antoine Hospital, Paris, France between November 2013 and January 2018. Inclusion criteria were 1) no prior history of HCC, 2) pretreatment severe fibrosis or cirrhosis, as defined based on liver biopsy, reliable results of LSM (F3 ≥ 9 kPa, F4 ≥ 12 kPa) or on clinical, biochemical and radiologic features of cirrhosis, 3) SVR achievement as defined by undetectable HCV RNA 3 months after the end of treatment (EOT) with DAA only, 4) at least one ultrasound imaging after EOT. Exclusion criteria were HIV infection or any other hepatic comorbidities excepted for excessive alcohol intake and metabolic syndrome. The factors associated with HCC risk were studied using a logistic regression analysis.
Results: A total of 177 patients with severe fibrosis were included (61% male, median age 60 yrs, cirrhosis 65%, median follow-up 2.5 yrs). Pre-treatment, post-treatment, and pre- and post-treatment values of LSM were available in 159, 129 and 111 patients, respectively. There was a significant decrease in LSM with a median of 14.1 kPa in pre-treatment and 10 kPa in post treatment ($p < 0.001$). Seven HCC (4%) occurred in a median time of 2.45 years (range, 1 yr-3, 3 yrs) from EOT. These patients (median age 57 yrs, 100% male) had a median pretreatment value of LSM of 24.8 kPa (range, 12.9 kPa-30.4 kPa). In logistic regression analysis, neither pre- or post-treatment values of LSM, nor its absolute or relative changes after treatment were associated with HCC risk.
Conclusion: In this single center, retrospective study including HCV patients with severe fibrosis who achieved SVR after DAA treatment, pre- and post-treatment values, as well as individual changes of LSM were not predictive of HCC occurrence, suggesting that selection of patients for HCC surveillance program in this specific population should not be based on LSM.

SAT-243

Ledipasvir/sofosbuvir is highly effective and safe in patients with chronic hepatitis B virus and hepatitis C virus coinfection: Final study results

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Background and aims: Patients coinfected with hepatitis C virus (HCV) and hepatitis B virus (HBV) have more rapid liver disease progression and worse outcomes than patients monoinfected with either HBV or HCV. Cases of HBV reactivation during HCV treatment have been reported in the IFN era and with direct acting antivirals (DAAs). This study evaluated the safety and efficacy of an all-oral treatment with ledipasvir (LDV)/sofosbuvir (SOF) for 12 weeks in patients with chronic HCV and HBV coinfection. Here we present the final study results through follow-up week 108.
Method: 111 patients chronically infected with HCV genotype (GT) 1 or GT2 and HBV (positive for serum HBsAg) were enrolled into this open-label study to receive LDV 90 mg/SOF 400 mg (once daily) for 12 weeks. Following treatment, patients were monitored for safety (HBV DNA reactivation) and efficacy for a total of 108 weeks. HBV DNA reactivation is defined as a post-baseline increase from baseline to ≥ LLOQ or > 1 log10 IU/ml in patients that were < LLOQ or ≥ LLOQ at baseline, respectively.
Results: Baseline characteristics included: mean age 55 years, 62% female, 67% treatment naive, 84% without cirrhosis, 61% GT1, and HBeAg negative (99%) with a mean baseline HBV DNA of 2.1 log10 IU/ml. SVR12 was 100% and through week 96 of post treatment follow-up; there were no viral relapses. HBV DNA reactivation occurred in 73% of patients; 12% of whom also had a corresponding ALT increase > 2x ULN. To date, 8 patients have started HBV therapy per Taiwanese treatment guidelines. The majority (86%) of HBV reactivations occurred by post treatment week 12, followed by an additional 11% by the end of Year 1 and 3% by the end of Year 2. 90% of HBV reactivations were asymptomatic with no patient developing clinical symptoms. Through 96 weeks of follow-up, 19 patients had serious adverse events (AEs), 1 patient withdrew consent, and 2 patients died; none were considered drug related. The most common AEs reported (≥ 5% of patients) were headache, fatigue, upper respiratory infection, dizziness, malaise, nephrolithiasis, myalgia and HBV reactivation. Full data through follow-up week108 for all patients will be provided.
Conclusion: In patients with chronic HCV/HBV infection, LDV/SOF for 12 weeks resulted in an SVR12 rate of 100%. Although most patients had an increase in HBV DNA, only 8 patients started HBV therapy. LDV/SOF treatment remains a highly effective, safe and tolerable regimen in patients with HCV/HBV coinfection.

SAT-244

Mixed cryoglobulinemia patients with persisting symptoms after SVR are characterized by B-cell clonality markers

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Background and aims: MC is a HCV-related lymphoproliferative disorder. HCV eradication using IFN-free DAA therapy can improve or heal MC. However, persistence or relapse of the syndrome may be observed in SVR patients. This may be due to the overcoming of point of no-return in the lymphomagenesis cascade with persisting B-cell

clonal expansion or to different, non evolving conditions (e.g. the occurrence of irreversible organ/tissue damage). Consequently, it is conceivable that the evaluation of B-cell clonal expansion may greatly help with a correct clinical, prognostic and therapeutic approach.
Method: We prospectively evaluated consecutive HCV patients treated with DAAs and the following features: Group A: SVR MC patients with complete clinical response; Group B: SVR MC patients maintaining symptoms. B-cell clonal expansion was evaluated by: flow cytometry, Free Light Chains ratio (κ/λ) and t (14;18).
Results: We evaluated 98 patients: 56 group A and 42 group B (mean FU 17 months, range: 3-36). At least one clonality marker was detected in 30/42 (71%) patients with persisting symptoms, including five patients with lymphoma in hematological remission after DAAs. Three patients had systemic symptoms (e.g. itchiness, nocturnal sweating) suggestive of the LPD evolution. Patients negative for B-cell clonality, were generally characterized by persisting arthralgia, sicca syndrome, and neuropathy. κ/λ ratio was altered in 48% of cases, flow cytometry in 16% and t (14;18) in 39%. In 24% of cases more than one marker was detected.
Conclusion: Previous studies showed the association between MC and B-cell clonal expansion. In this study, the detection of B-cell clonality markers was associated with persisting symptoms of MC and with more severe pre-therapy disease, including patients with lymphoma in remission. This suggests the hypothesis of having gone beyond the LPD point of no-return and the rationale for specific treatment (e.g. rituximab). Furthermore, this study strongly suggests that the κ/λ ratio may be a very useful and easy clonality marker in MC patients with persisting symptoms.

SAT-245

Prospective evaluation of the impact of hepatitis C cure on sexual dysfunction

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Background and aims: Hepatitis C virus (HCV) infected patients have a high rate of sexual dysfuntion (SD). Current antiviral therapies with direct acting antivirals (DAA) improve quality of life in cured patients, but there are very few data analyizing changes in sexuality after cure.
Method: Prospective inclusion of patients receiving DAA (April-Dec 2017) recording clinical and demographic variables. Self-reported sexuality was obtained at baseline (BL) pre-DAA and 48 weeks after DAA (FU48) by means of: 1)Changes in Sexual Functioning Questionnaire (CSFQ-14) for assessing SD (< 47 males; < 41 women), comprising dimensions of excitation/orgasme and desire; 2)CSFQ-VAS (analogical scale ranging 0-100 in sexuality); 3)PHQ9 test (assessing major depression[MD] if PHQ9 ≥ 10). Patients were also asked about the fear to transmit HCV to their partner/s and HCV-related limitations in their sexual lifes. Results were expressed in median/IQR (25-75) and n (%), as appropriate. Paired samples were analyzed by means of McNemar and T-tests.
Results: 83% of patients starting DAA in the study period accepted to participate (n = 186); preliminary data of 90 patients cured with DAA and available BL-FU48 data are reported. Median age was 55 (49-61) years; 59% men; 83.1% F0-2. Up to 64.7% of cases presented SD: 58% men and 74% women. Median BL CSFQ-VAS was 50 (20-67.5). 27% of patients reported fear for HCV sexual transmission and 21.1% of cases were limited in their sexual behaviours. At follow-up [43 (37-50) weeks], a significant improvement was observed in the self reported evaluation of sexuality [FU48 CSFQ-VAS 60 (40-80), p < 0.01], together with a significant improvement in CSFQ-14 score (p = 0.03). The latter was explained by improvements in sexual excitation (p = 0.018) and orgasm (p = 0.04).Nevertheless, the overall SD prevalence was not significantly reduced (64.7% vs 53.8%, p = 0.11). SD persistence in FU48 was independently associated with age (OR 1.13 [1.05-1.2], p = 0.001), and major depression coexistance (OR 0.15 [0.04-0.59], p = 0.007)
Conclusion: Sexual dysfuncion is highly prevalent among patients infected with HCV. HCV elimination after treatment was associated with a significant improvement in specific sexual domains (excitation and orgasm). Nevertheless, the prevalence of sexual dysfunction remained high and was independently associated with age and major depression.

SAT-246

Overall survival and incidence of liver-related events in a cohort of cirrhotic patients treated with direct antiviral agents: Results from a multicenter study

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Background and aims: Introduction of direct-acting antiviral agents represented a revolution in HCV management, allowing treatment also in patients with advanced liver disease. Little is known about the long-term effects of antiviral therapy on disease progression, liver-related complications and survival. Aim of our study was to investigate the onset of clinical events and the long-term effects of treatment on surrogate markers of fibrosis and portal hypertension in a large cohort of cirrhotic patients treated at four third-level hospitals in Rome.
Method: The cohort included 352 patients treated with DAA with a median follow-up of 28.5 months from the end-of-treatment. Most patients were males (217/352, 61.6%), with compensated cirrhosis (CPT A 85.4%, MELD score 9.1 ± 3.0) and without clinically significant portal hypertension (61.9%); median age was 63.6 years and genotype 1b was the most frequent (41.5%); 57.5% of patients were naive to previous antiviral treatments. APRI and FIB-4 scores were calculated and paired Student T-test was used to compare markers of advanced disease at baseline and after treatment.
Results: Overall SVR12 was 94.3%, being significantly higher in patients with compensated than decompensated cirrhosis (97.6% vs 76%, p 0.000001). Both APRI and FIB-4 scores significantly decreased after treatment (p = 0.0002 and 0.0003, respectively). During follow-up 42 patients (11.9%) died, 16 underwent liver transplant (4.5%). Cause of death was liver-related in 25 patients (59.5%) and due to extrahepatic diseases in 17 (40.5%), resulting in a liver-related mortality rate of 3%/yr (0.9% for HCC). In the surviving 310 patients, 62 liver-related events were recorded (20%), the most frequent being *de-novo*/recurrent HCC (35, 56.4%), followed by ascites (9, 14.5%), and variceal bleeding (10, 16.1%). The annual incidence were 3.2% and 1.6% for *de-novo* and recurrent HCC respectively, and 3.7% for other liver-related events. At logistic regression analysis, platelet count, clinically significant portal hypertension and a previous history of HCC were independent predictors of liver-related events development.
Conclusion: Despite the high SVR rates and the related improvement of surrogate markers of fibrosis observed after DAA treatment, patients with cirrhosis remain at risk of developing major liver-related complications, thus requiring strict surveillance during the follow-up. HCC still represents the most frequent liver-related event.

SAT-247

The evaluation of the inhibitory effect of oral anti-hepatitis C virus agents on carcinogenesis

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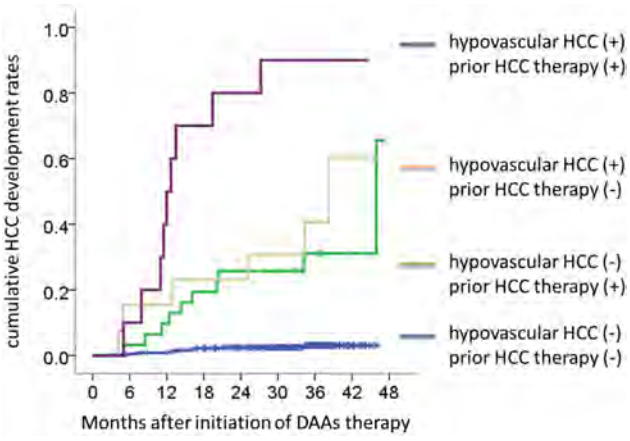
Background and aims: Hepatocellular carcinoma (HCC) occurs as a result of hepatic inflammation and/or changes in the tumor microenvironment. Direct-acting antivirals (DAAs) against hepatitis C virus (HCV) exert high anti-HCV activity and are expected to show anti-inflammatory effects associated with HCV elimination. Furthermore, HCC is known to dedifferentiate from hypovascular tumors, such as dysplastic nodules or well-differentiated HCC, to hypervascular tumors. However, whether or not DAAs prevent carcinogenesis is unclear. We therefore examined whether or not DAAs can suppress the growth and hypervascularization of hypovascular tumors.
Method: Patients with HCV genotype 1 infection were treated with Daclatasvir and Asunaprevir therapy. Hypovascular tumors were diagnosed by contrast-enhanced magnetic resonance imaging or computed tomography before therapy. We analyzed the cumulative incidence of HCC, i.e. the growth or hypervascularization of hypovascular tumors, and compared the findings by the presence of hypovascular tumors.
Results: We enrolled 478 patients, 25 of whom had hypovascular tumors. Forty-eight patients had a history of HCC therapy, and 10 of them (20.8%) had hypovascular tumors. The mean size of hypovascular tumors was 11 mm. The sustained virologic response (SVR) rate was 87.7%. Forty-one patients (8.6%) developed HCC, including 16 of the 25 with hypovascular tumors (64.0%). Among the patients who achieved SVR without prior HCC therapy, the respective cumulative HCC development rates of patients with and without hypovascular tumors were 15.4% and 1.1% per year, 23.1% and 2.5% per 2 years, and 40.7% and 3.1% per 3 years. In contrast, among patients with a history of curative HCC therapy, the respective cumulative HCC development rates in those with and without hypovascular tumors were 40.0% and 9.7% per year, 80.0% and 25.8% per 2 years, and 90.0% and 31.1% per 3 years. A Cox proportional-hazards analysis showed that the history of HCC therapy (hazard ratio: 9.629, 95% confidence interval: 4.334-21.392), presence of hypovascular tumor (7.343, 3.311-16.287), alpha-fetoprotein level at SVR judgment (1.015, 1.009-1.022), and baseline albumin level (0.324, 0.126-0.834) were independent risk factors for developing HCC.



Conclusion: Hypovascular tumors developed into HCC at a high rate despite the elimination of HCV by DAAs. We should confirm the presence of hypovascular tumor before starting DAA treatment.

SAT-248

Patients treated for HCV and listed for LT in a French multicenter study: What happens at 3 years?

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Background and aims: Combinations of DAA have shown excellent results to treat HCV-infection in cirrhotic patient but some issues remain unresolved regarding efficacy in patients awaiting liver transplantation (LT) and impact on access to LT. Our aim is to study the impact of HCV treatment on hepatic function, delisting and outcomes of patients listed for HCC or decompensated cirrhosis.
Method: This is an observational, multicenter, and retrospective analysis from 18 LT centers in France, of patients treated for HCV and listed for LT. Complete clinical and biological response (CBR) to HCV treatment was defined by bilirubinemia < 35 μmol/l, Tp > 50% and absence of ascites or hepatic encephalopathy, partial response by change of Child score class and no response by stability or aggravation.
Results: 183 HCV-positive patients who received antiviral therapy with an IFN-free regimen while awaiting LT between November 2013 and June 2015 were enrolled in this study. The mean follow-up since the end of treatment was 39.6 months (± 1.5). The LT indication was HCC in 106 (58%) patients and decompensated cirrhosis in 77 (42%) patients. Most of the patients were male (145, (79%)) with a median age of 59 years-old (± 2.2). Comorbidities were also collected: diabetes (49, (27%)), alcohol consumption (39, 21%), arterial hypertension (45, (25%)) and dyslipidemia (8, (4%)). Majority of patients were genotype 1 (104, (57%)) treated with DAA plus ribavirin for 99 patients. SVR rate was 83%. At baseline, mean MELD was 12 (6-32) and mean Child B9 for patients listed for decompensated cirrhosis. Among these patients, 10 (16%), 22 (35%) and 31 (49%) had respectively a CBR complete, partial and no response. 40 patients (52%) with decompensated cirrhosis were transplanted, 36 are alive. 37 patients (48%) were not transplanted: 6 are inactive and 26 were delisted (21 for improvement) and 4 developed HCC during the follow-up. Among patients listed for HCC, 80 (75%) were transplanted, 73 are alive. Only 8 patients (7.5%) have been delisted for HCC progression. No case of HCC recurrence has been reported. Predictive factors of delisting will be presented at the meeting.
Conclusion: HCV-treatment in patients awaiting LT allows delisting for improvement in 27% (21/77) of cases. After treatment only 7.5% (8/106) of HCC-patients were delisted for drop out. We did not collect any HCC recurrence post-LT.

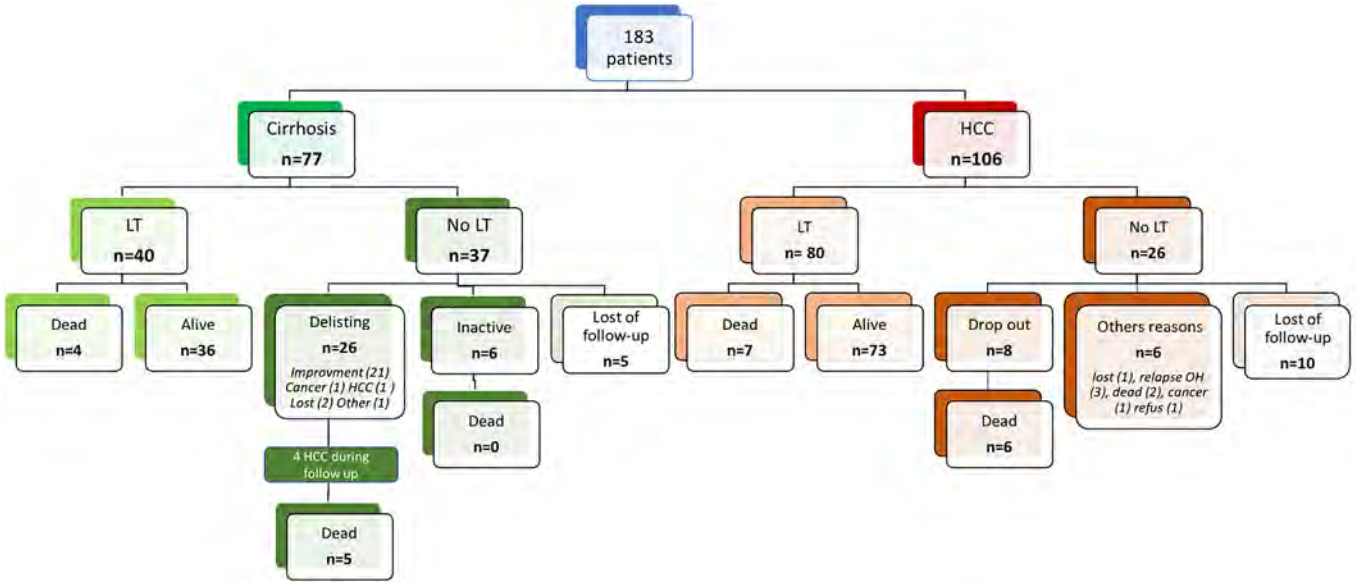

Figure: (abstract: SAT-248) Flow chart patients

SAT-249

Increased cardiovascular risk associated with chronic hepatitis C infection still remains at SVR24

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Background and aims: Chronic hepatitis C infection (HCV) is associated with fatty liver, impaired glucose metabolism and dyslipidemia. When combined with pre-existing obesity due to improper diet, physical inactivity and reduced cardiorespiratory fitness, cardiovascular (CV) risk is a potentially significant cofactor for morbidity post DAA treatment outcomes. This study examined CV risk in patients who had achieving SVR

Method: HCVRNA positive mono-infected patients commencing DAA therapy were recruited from a Hepatology clinic in Dublin, Ireland. Maximal aerobic capacity (VO2max) was used as an indicator of cardiorespiratory fitness and was assessed via a submaximal exercise test using breath by breath gas analysis (Cosmed K4b2). Liver stiffness and liver fat were examined by transient elastography. Blood samples were analysed for levels of fasting plasma glucose, fasting insulin and lipids. Anthropometric measures including blood pressure, height, weight, BMI, body fat %, and waist circumference were also measured. All measures were taken at baseline prior to commencing DAA therapy and were repeated at SVR24. Paired T test were used to assess changes from baseline in normally distributed variables. For non-normally distributed variables, Wilcoxin-signed rank tests were used.

Results: 32 participants (15 female, 17 male, mean age 45 ± 14) were recruited for this study. While reductions in steatosis measures ($p < 0.05$) were observed, mean CAP scores 6-months post SVR remained elevated above 220 $dB.m^{-1}$. Furthermore, mean total cholesterol, HDL, LDL increased from baseline. A significant increase in triglycerides was observed ($p < 0.00$). Maximal aerobic fitness and measures of anthropometry remained similar to baseline, with the exception of waist circumference which was significantly increased at SVR24 ($p < 0.01$). No significant change was noted in cardiorespiratory fitness, and remained below average age and gender norms for the majority of participants at SVR24.

Table 1

	Mean(SD) pre-treatment	Mean(SD) 6 months post SVR	P value
Liver Stiffness (kPa)	5.3 (5.1)	5.6 (4.1)	P < 0.09*
Steatosis (CAP)	254.43 (63.12)	231.16 (48.37)	P < 0.05*
VO2max (ml/min/kg)	31.62 (10.62)	32.38 (10.03)	P = 0.451*
% of n with below average fitness	90	74	
Fasting glucose (mmol/L)	4.90(0.80)	5.00 (0.50)	P = 0.807*
Fasting Insulin (mmol/L)	11.00 (7.90)	9.60 (9.20)	P = 0.522*
Total Cholesterol (mmol/L)	4.42 (1.19)	4.78 (1.10)	P = 0.073*
HDL (mmol/L)	1.46 (0.49)	1.49 (0.50)	P = 0.611*
LDL (mmol/L)	2.61 (0.80)	2.73 (0.93)	P = 0.268*
Triglycerides (mmol/L)	0.87 (0.56)	1.10 (0.68)	P < 0.00**
Systolic Blood Pressure	127 (15)	127 (15)	P = 0.604*
Weight (kg)	78.20 (13.48)	78.28 (14.06)	P = 0.910*
BMI (kg/m2)	27.33 (4.30)	27.38 (4.43)	P = 0.888*
% Body Fat	33.00 (9.91)	33.22 (10.42)	P = 0.659*
Waist Circumference	91.39 (11.75)	93.2 (12.10)	P = 0.011*
Waist-Hip ratio	0.88 (0.08)	0.89 (0.09)	P = 0.310*

*Significant change from baseline

*Paired T test

**Wilcoxon Signed rank test*

Conclusion: This study demonstrates that HCV-associated CV risk persists following SVR, due to elevated cholesterol levels and sustained fatty liver evident at SVR24. Clinical implications include the need for extended monitoring of lipids, anthropometry and steatosis post treatment. Moreover, patients with pre-existing fatty liver may benefit from lifestyle modification programmes targeted at weight loss and increasing physical activity post SVR to mitigate this increased CV risk.

SAT-250

Effects of sustained virological response on the endothelial dysfunction and the cardiovascular risk in hepatitis C after direct antiviral angets treatment: HEPCAR study

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Background and aims: HCV has the ability to cause both metabolic impairments and extrahepatic manifestations, mainly cardiovascular disease. Endothelial (EMPs) and platelets (PMPs) microparticles are novel biological markers of endothelium injury and atherosclerosis. The aim of this study was to analyze the endothelial dysfunction by measuring soluble markers, such as cell free DNA (cfDNA) and the dynamics of apoptotic microparticles, before and after DAAs therapy and their subsequent impact on cardiovascular risk.

Method: Prospective and multi-center study that included 114 patients with hepatitis C treated with DAAs therapy. Baseline, week 12 and one year follow-up after therapy following determinations were performed: (i) Whole lipid profile (ii) adhesion soluble markers and oxidative stress markers in plasma (iii) cellular injury markers including circulating cfDNA and microparticles (MPs), endothelial MPs (EMPs), platelet-derived MPs (PMPs) and total MPs (AV+) by flowcytometry.

Results: Mean age was 53 ± 10 years, 69% (79/114) male, 75% (85/114) genotype 1 and 39% (45/114) cirrhotics. Further, 32% (37/114) suffered from arterial hypertension and 21% (24/114) were diabetics. 60% (68/114) of patients received sofosbuvir-based therapy, ribavirin was added in 37% (42/114) of patients. In patients who reached SVR, total cholesterol (165.9 ± 37.6 mg/dl *vs.* 185 ± 40.6 *vs.* 182.3 ± 36.4 mg/dl; p < 0, 001), LDL (96.6 ± 34.7 mg/dl *vs.* 117.8 ± 38.3 mg/dl *vs.* 110.9 ± 33.1 mg/dl; p < 0.001) and ApoB (89.9 ± 27.5 *vs.* 99.8 ± 31.3 *vs.* 101.7 ± 29.5; p < 0, 001) levels were found to be significantly increased after 12 weeks of treatment and one year compared to baseline. On the other hand, HDL and ApoA levels remained stable after therapy (p = 0.492; p = 0.591). VCAM and e-selectin levels significantly decreased from week 12 after treatment, but oxLDL and oxLDL antibodies were not modified with respect to baseline (p = 0.105; p = 0.589), a trend was seen in VEGF levels (227.8 ± 93 *vs.* 222.9 ± 95.5 *vs.211*±106.9, p = 0.079)). Regarding to cell injury markers, cfDNA did not decrease (p = 0.589), total MPs (AV+), EMPs and PMPs levels were found to be statistically lower one year after treatment than at baseline. Finally, this decrease of total MPs was more evident in non-hypertensive patients (n = 63) (MPs: 19661 ± 136.9 *vs.* 11597 ± 3640 *vs.* 9847 ± 520.1; p = 0.04;EMPs: 478 ± 68 *vs.* 269 ± 39.6 *vs.* 352 ± 78; p = 0.001).

Conclusion: Eradication of hepatitis C virus produces a decrease in VCAM, e-selectin, total MPs, PMPs and EMPs, suggesting an improvement of endothelial function when reaching SVR. These effects are more evident in patients with no or early cardiovascular risk.

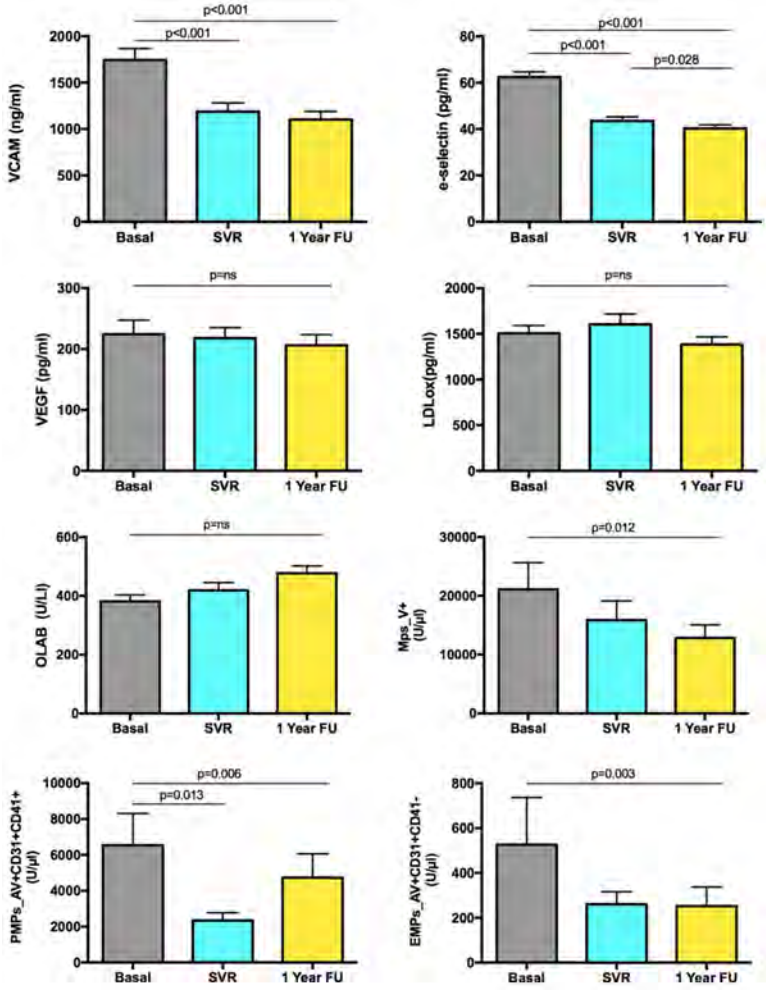

Figure: (abstract: SAT-250)

SAT-251

The association of serum IFN-λ3 levels with liver fibrosis and hepatocarcinogenesis in chronic hepatitis C patients treated with direct-acting antiviral agents

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Background and aims: Although the efficacy of hepatitis C virus (HCV) treatment is improved dramatically by direct-acting antiviral agents (DAAs), the assessment of hepatocellular carcinoma (HCC) remains important even after HCV eradication. IFNL3 polymorphisms are associated with liver fibrosis and inflammation in chronic hepatitis C (CHC) patients, but its impact on carcinogenesis remains controversial and little is known about its effects after viral clearance. To determine the contribution of IFN-λ3 to hepatocarcinogenesis after HCV clearance, we analyzed IFNL3 genotypes and serial serum IFN-λ3 levels in CHC patients who achieved sustained virological responses (SVR).
Method: A total of 201 CHC patients who achieved SVR were enrolled (Peg-IFN/RBV+TVR 13, Peg-IFN/RBV+SMV 21, DCV/ASV 15, LDV/SOF 116, SOF/RBV 36). Serum samples were collected sequentially and IFN-λ3 levels were quantified by chemiluminescence enzyme immunoassay. The IFNL3 polymorphism (rs8099917) was genotyped in 195 patients.
Results: 125 patients were rs8099917 T/T and 70 patients were non-T/T. Serum IFN-λ3 levels did not differ significantly with IFNL3 genotype. Serum IFN-λ3 levels dropped markedly by 1 week and remained at low levels up to 24 weeks after the end of treatment. Pre-treatment IFN-λ3 levels were higher in patients with higher ALT ($p < 0.001$), FIB-4 index ($p < 0.001$) and WFA+M2BP levels (< 0.001), but not related to the histological fibrosis stage ($p = 0.15$). Moreover, Pre-treatment IFN-λ3 levels did not differ regardless of HCC development ($p = 0.932$), either. On the other hand, after HCV eradication, serum IFN-λ3 levels were significantly higher in patients who developed HCC ($p = 0.016$) and were associated with a higher potential for hepatocarcinogenesis, such as a higher frequency of non-hypervascular hypointensive nodules ($p = 0.046$), higher stages of liver fibrosis ($p < 0.001$), and higher post-treatment levels of ALT ($p < 0.001$), FIB-4 index ($p = 0.001$) and WFA+M2BP ($p < 0.001$).
Conclusion: Serum IFN-λ3 levels after HCV clearance are associated with the potential for HCC development. IFN-λ3 may be a helpful clue for elucidating the relationships among immunologic status, liver fibrosis, liver inflammation, and hepatocarcinogenesis, after achieving SVR.

SAT-252

Long-term effect of direct-acting antivirals therapy in patients with hepatitis C-related decompensated cirrhosis: Russian single academic center experience

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Background and aims: Successful direct-acting antivirals (DAAs) therapy have shown early improvement of liver function in patients with decompensated cirrhosis. However, little is known about the long-term benefits of HCV-eradication in these patients. The aim of our study was to assess the follow-up effect of sustained virological response (SVR) on liver function and portal hypertension in decompensated cirrhotic patients.
Method: We conduct a single-center prospective study among 48 patients with HCV-related decompensated cirrhosis successfully treated by DAAs between March 2015 and April 2018. The clinical, laboratory, imaging data were evaluated before treatment (BT), at the time of SVR and last follow-up observation (FU).
Results: The mean patients age was 53.5 ± 10.6 years, 58%-males, 77%-treatment-naïve, 67% had a HCV genotype 1, 81%-Child-Pugh (CP) class B, 85% received sofosbuvir-based therapy, 54%-with ribavirin, for 12 or 24 weeks. The median FU time was 18 (6-36) months. A significant improvement was found in most liver function parameters, among clinical markers of portal hypertension only the presence of ascites showed a significant difference (Table). At last observation 54% of patients switched to a CP class A, 6 (67%) out of 9 patients with CP class C switched to class B, 3 (7.7%) worsened to CP class C. Baseline higher bilirubin (≥ 50 Umol/l, HR 2.82; $p = 0.034$) and lower albumin (< 28 g/l, HR 2.59; $p = 0.026$) and male gender (HR 3.37; $p = 0.03$) were significantly and independently associated with absence of re-compensation at last observation.

Table:

Parameter	BT	SVR	FU	p value
Albumin, g/l, mean ± SD	31.0 ± 3.9	33.6 ± 4.5	35.8 ± 5.6	< 0.001
< 28 g/l, n (%)	11 (23)	5 (10.4)	4 (8.3)	0.002
Bilirubin, Umol/l, mean ± SD	32.9 ± 14.8	30.4 ± 14.6	29.4 ± 14.5	0.098
≥ 50 Umol/l, n (%)	6 (12.5)	5 (10.4)	6 (12.5)	0.779
Prothrombin time, %, mean ± SD	61.6 ± 14.7	62.9 ± 10.1	67.4 ± 11.6	0.002
≤ 60%, n (%)	28 (58.3)	21 (43.7)	13 (27.1)	< 0.001
Platelets count, 10^9/l, mean ± SD	82.5 ± 54.5	84.7 ± 51.3	85.7 ± 52.4	0.802
Ascites, n (%)	33 (68.7)	20 (41.7)	19 (39.6)	< 0.001
Varices F2/F3, n (%)	31 (64.6)	31 (64.6)	31 (64.6)	0.973
Encephalopathy, n (%)	18 (37.5)	15 (31.2)	15 (31.2)	0.307

Conclusion: SVR is associated with improvement of liver function, however, has no significant effect on severity of portal hypertension. Patients with more severe baseline liver decompensation, probably, still remain the candidates of liver transplantation despite HCV-eradication.

SAT-253

Impact of HCV clearance on HCC development and patient survival: Propensity score-matched analysis of an ongoing database of 2173 CHC patients

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Background and aims: With the development of potent direct-acting antiviral agent (DAA) combinations, an almost 100% sustained virological response (SVR) was achieved, even in patients with high risk of developing hepatocellular carcinoma (HCC), but the question of whether the suppressive effect of viral eradication by IFN-free regimens on hepatocarcinogenesis and survival will be equivalent to that obtained by IFN-based regimens has remained to be solved especially for HCC recurrence. The aims of this study were to evaluate the HCC development and patient survival in CHC patients treated with DAAs after antiviral treatment.

Method: This registry study is an ongoing, non-interventional, study, and consists of multicenter observational cohorts of 2173 CHC patients who were treated with IFN-based (n = 1148) or IFN-free (n = 1025) patients that prospectively follows from December 2004 to November 2018. Cumulative de novo HCC and recurrence rates were compared using propensity score-matched analysis by EZR on R commander (Ver. 1.24). Independent factors associated with de novo or recurrence rates of HCC were analyzed using Cox proportional regression analysis using an SPSS software package (version 24).
Results: As for IFN-free therapies, the 3-year incidence of de novo HCC was 3%, and of recurrence was 49.2%. Propensity score-matched analysis showed no significant difference in de novo HCC (p = 0.137) and recurrence (p = 0.150) rates among groups treated with IFN-based or IFN-free therapies. In univariate and multivariate analysis, post-treatment $WFA^{+}M2BP$ level was independently associated with de novo HCC (p = 0.032, HR (95%CI) = 3.367 (0.098-0.902)), and post-treatment AFP level with recurrence after SVR (p = 0.038, HR (95%CI) = 2.907 (0.125-0.943)). Although significant difference was not found so far (p = 0.143), among patients with previous history of HCC, the 3-year survival rate was 92.6% for IFN-based, and 82.4% for IFN-free treatment respectively.
Conclusion: Propensity score-matched analysis showed no significant difference in de novo HCC and recurrence rates among groups treated with IFN-based or IFN-free therapies. Although significant difference was not found so far, among patients with previous history of HCC, the 3-year survival rate was lower in patients treated with IFN-free therapy, so longer-term longitudinal studies about cumulative incidences of survival in larger cohorts are required to reveal the prognostic improvement for CHC patients.

SAT-254

Incidence of hepatocellular carcinoma and mortality after HCV elimination by all-oral DAA therapy: Results from a large-scale, multicenter cohort study

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Background and aims: HCV treatment has become much easier than ever because of short-term, well-tolerated regimens with all-oral DAAs. However, as much data as possible on the de novo and recurrent hepatocellular carcinoma (HCC) are urgently needed to better manage HCC surveillance after HCV elimination. The aim of this study was to evaluate HCC development and mortality among Japanese patients with chronic HCV infection following the achievement of sustained viral response (SVR) by all-oral DAAs.
Method: This large-scale, multicenter cohort study included 2, 847 consecutive patients from 2014 who achieved SVR by all-oral DAAs, divided into groups with (n = 321) or without previous HCC (n = 2, 526). We excluded patients aged < 20 years, 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, related factors of HCC, and mortality.
Results: During the observational period (median: 2.6 years), 195 (7.2%) patients developed HCC. The one- and three-year cumulative rates of de novo HCC were 0.5% and 2.1% for the non-cirrhosis patients, respectively. In contrast, the rates for the cirrhosis group were 4.5% and 10.5%, respectively (log-rank test: p < 0.001). In multivariable Cox analysis, age (OR 1.03, P = 0.033), cirrhosis (OR 2.22, P = 0.045), serum albumin at the end of treatment (EOT) (OR 0.39, P = 0.008), and EOT-alpha-fetoprotein (AFP) level (OR 1.01, P < 0.001) were extracted as predictors of de novo HCC. The one- and three-year cumulative rates of HCC recurrence were 19.7% and 42.4%, respectively. A non-curative procedure with transarterial chemoembolization shortly after HCC treatment (< one year) had a strong impact on the rate of HCC recurrence (two-year cumulative HCC recurrence rate: > 60%). The three-year cumulative mortality rates for non-HCC and previous HCC patients were 0.6% and 10.7%, respectively (log-rank test: p < 0.001). The liver-related complications, mainly HCC, were responsible for approximately three-quarters of all deaths for those with previous HCC.
Conclusion: After HCV elimination, older age, cirrhosis, and a high level of EOT-AFP were strongly associated with the development of de novo HCC. Especially for HCC patients treated with non-curative procedures, HCC recurrence will commonly occur, irrespective of SVR.

SAT-255

Long-term safety and efficacy results in hepatitis C virus genotype 1-infected patients receiving ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in the TOPAZ-I and TOPAZ-II trials

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Background and aims: In phase 3 clinical trials, the triple direct-acting antiviral (3-DAA) regimen consisting of ombitasvir/paritaprevir/ritonavir plus dasabuvir (OBV/PTV/r + DSV)±ribavirin (RBV) (paritaprevir identified by AbbVie and Enanta) had shown high rates of sustained virologic response (SVR) at post-treatment week (PTW) 12 (SVR12) in HCV genotype (GT) 1-infected patients. Here, we report the long-term efficacy, and clinical outcomes in patients receiving 3-DAA ± RBV in TOPAZ-I and TOPAZ-II (TOPAZ) studies.
Method: TOPAZ studies are ongoing, phase 3b, open-label trials. Enrolled patients were HCV GT-1-infected treatment-naïve or interferon-experienced ± cirrhosis and are being evaluated for the long-term suppression and impact of SVR on liver disease progression through 5-years post-treatment. Treatment consisted of OBV/PTV/r +

DSV ± RBV for 12 or 24 weeks, based on HCV GT 1a/b subtype and cirrhosis status as per label. Roche CTM test was used to detect HCV RNA levels. SVR, and liver-related clinical outcomes at PTWs104 and 156 are reported.

Results: 2211 patients were enrolled in the TOPAZ studies. Majority of patients were male (52.8%), white (93.4%), < 65 years of age (88.4%) with 51.7% GT1a and 48% GT1b infection. 55.1% patients were treatment-naïve; 70.6% had high baseline HCV RNA levels (≥ 800, 000 IU/ML); and 16% had compensated cirrhosis (F4). To date, > 99% patients have maintained SVR since PTW12 at both PTWs104 (1904/1909) and 156 (660/662). Clinical outcomes related to progression of liver disease are shown in **Table 1**. Cirrhotic (C) patients showed higher mean reduction in baseline FIB-4 score than non-cirrhotic (NC) patients {PTW104: −0.3 (NC), −2 (C); PTW156: −0.4 (NC), −2 (C)}. Out of 251 patients with F4 at baseline, 164 and 67 improved to ≤ F3 at PTWs104 and 156, respectively (33 and 172 patients had missing METAVIR score at PTWs104 and 156). Mean increase from baseline in platelet count and albumin was 15.4 × 10^9/l and 3.1 g/l, respectively, at PTW104; and 21.8 10^9/l and 2.5 g/l, respectively, at PTW156. Child-Pugh (CP) score decreased from ≥ 6 at baseline to < 6 in 34 patients at PTW104, and in all 5 patients at PTW156.

Table 1: Clinical outcomes

	TOPAZ-I and II (N = 2211) n (%)
All cause death	26 (1.2)
Liver related death	1 (< 0.1)
Hepatic decompensation	
Cirrhotic patients	8 (0.4)
Liver transplantation	
Cirrhotic patients	2 (< 0.1)
Hepatocellular Carcinoma (HCC)	12 (0.5)
Fibrosis stage (F0-F1), n	3
F3	4
F4	5
Composite of any clinical outcomes	42 (1.9)

Conclusion: A high proportion of patients who achieved SVR with 3-DAA ± RBV in the TOPAZ studies showed long-term sustainability of SVR, with improvements in liver disease markers including FIB-4, METAVIR, CP scores, and platelet counts, and a low frequency of clinical outcomes related to long-term progression of liver disease. No new safety signals were detected.

SAT-256

Influence of metabolic syndrome on fibrosis regression regulated by LOXL-2 after SVR

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Background and aims: The potential influence of underlying ALD/NAFLD in fibrosis regression after SVR in HCV infection remains unclear. We aimed to assess the influence of metabolic syndrome (MetS) and alcohol consumption in fibrosis regression (evaluated by elastography, serological scores and biopsy) after 24 months of SVR. Also, we evaluated the relationship with serum and tissue expression of Lysyl oxidase-like-2.

Method: 271 patients treated with DAAs in our hospital from 2015 and who achieved SVR were included. A personal interview with AUDIT questionnaire, physical examination, blood tests, and Fibroscan® were made at baseline (B) and 24-months (24M) after SVR. Hemodynamic studies and transyugular liver biopsy were performed in 13 patients.

Results: At (B) 68 patients were F1 (25, 1%);59 patients were F2 (21, 7%);44 were F3 (16, %) and 100 were F4 (36, 9%).58.4% of patients have a body max index (BMI) ≥ 25 kg/m^2 and diabetes in 13, 1%. At 24M, although elastography improved in absolute value in 82% (n = 222), progressed in 49 cases (17.7%) and 42 remained in F4 (15.4%). At 24M, 48 patients met MetS criteria and patients with BMI ≥ 25 kg/m^2 increase to 59.5% p < 0.001. (B) and 24M BMI ≥ 25 kg/m^2 were risk factors for significant fibrosis or steatosis at 24M (p < 0.05), and progression on liver stiffness (p < 0, 001, Chi^2) as well as B and 24M MetS: OR 4.1IC (1.4-11.7) p = 0.008; and OR 5.4 IC (1.9-15.4) p = 0, 001, respectively. We found a significative correlation of elastography with insulin r = 0.356 and HOMA r = 0.385 p < 0.0001; LDL-cholesterol r = -0.122 p = 0.05, and serological scores APRI r = -0, 165 p < 0, 006; FORNs r-0, 287 p < 0, 0001 and HEPAMET r = 0, 508 p < 0, 001. In multivariable regression analysis, HOMA was the only one that remained significative r = 2.090 p = 0.025. We found correlation among ΔFibroscan, ΔAPRI, ΔForns and Δweight (p < 0.05). We didńt find differences regarding alcohol. 13 liver procedures were performed in cirrhotic patients with mean HVPG 3.7mmHg ± 1.14mmHg. However, we dindńt find a good correlation between Fibroscan® and liver biopsy. There is a great disparity of values (only 6 patients have concordance between them). No patient with METAVIR F1 has a Fibroscan® < 7Kpa and there are 4 patients with > 9Kpa that doń have a compatible biopsy (METAVIR 1 and 2). Interestingly, 3 patients with MetS and non-invasive scores of NALFD, had F3-NASH biopsy. We found statistically significant decrease in LOXL-2 levels at 24M respect B 891.80 ± 1616pg/ml vs 328.0 ± 1415.03pg/ml p < 0.001, with twice serum expression in patients with elastography > 9kPa (p = 0.046). We didńt find correlation with tissue expression or HOMA (p = 0.09).

Conclusion: Regression of elastography is reached in 82%of patients, correlated with serological values of LOXL-2, but not histologically in the subgroup of cirrhotic patients. Metabolic factors and alcohol doń seem to influence the regression of fibrosis in the medium term.

SAT-257

Incidence and predictors of liver outcomes in chronic hepatitis C patients: Comparison of an American and a Chinese cohort

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Background and aims: The prevalence of HCV infection in China is estimated to be 0.7% but outcomes of chronic HCV in China are not well-reported. We compared clinical outcomes among adult chronic HCV patients in the US and China and factors predictive of outcomes.

Method: Prospective study of 2 cohorts of HBsAg-, HCV RNA+ patients recruited in 1 site in the US and 2 sites in China. Data on risk factors and medical history were collected using standardized questionnaire; diagnosis of cirrhosis and HCC was based on predefined criteria. Composite liver outcomes of liver-related deaths, HCC, decompensation, or liver transplant were analyzed using multivariate Cox regression with competing risks and SVR as a time-dependent covariate. Patients were censored at the time of liver transplant or HCC diagnosis.

Results: 795 US and 854 Chinese patients followed for a median of 3.06 and 3.99 years, respectively were analyzed. US patients were significantly more likely to be men (57.4% vs. 48.2%), older (mean 55 vs. 52 years), obese, diabetic, current or past use of alcohol, cigarettes, and coffee, and also had a significantly lower prevalence of anti-HBc (31.2% vs. 46.4%). At enrollment, a significantly higher percent of US patients had cirrhosis (45.4% vs. 16.2%). During follow-up, a similar percent of US and Chinese patients achieved SVR (53.7% vs. 50.6%).

The 5-year cumulative incidence of composite liver outcomes was significantly higher in US than in Chinese patients (25.5% vs. 6.6%, p < 0.0001). Stratification by fibrosis severity at enrollment showed this difference persisted in the subgroup without cirrhosis but not in the subgroup with cirrhosis (Figure). Multivariate analysis showed that baseline liver disease severity, age, and absence of SVR were significant predictors of composite liver outcomes but study site was not. Hazard ratio for outcomes among patients with SVR was 0.32 (95%CI 0.22-0.46) for US and 0.09 (95%CI 0.03-0.28) for Chinese patients.

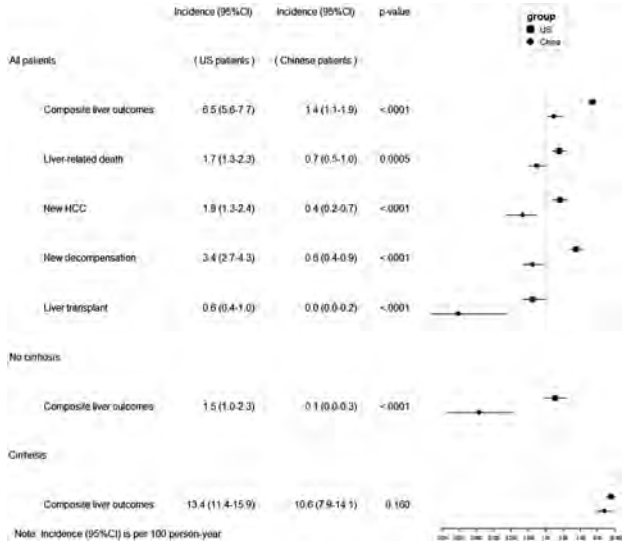

Figure: Incidence of composite liver outcomes in US and Chinese hepatitis C patients

Conclusion: In this parallel cohort study of HCV patients, the incidence of clinical outcomes was significantly higher in the US than in the Chinese patients due to a higher percent of US patients with cirrhosis at enrollment. Achievement of SVR markedly decreased the risk of outcomes in both cohorts. These data strengthen the WHO pledge to eliminate HCV worldwide by 2030 and demonstrate that improved diagnosis and access to treatment can help reduce morbidity and mortality of HCV in both the US and China.

SAT-258

Indocyanine green retention test predicts the risk of portal hypertension-related events after direct-acting antiviral therapy in compensated advanced chronic liver disease patients

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Background and aims: Achieving a Sustained Viral Response (SVR) after treatment with direct-acting antivirals (DAAs) in patients with compensated advanced chronic liver disease (cACLD) HCV-related leads to an improvement in liver function, liver fibrosis and portal hypertension (PH). Currently, the long-term impact in terms of PH-driven complications is still under investigation. Indocyanine green retention test (ICG-r15') is a non-invasive liver test (NIT) correlated with PH and proposed as a predictor of hepatic decompensation in patients with active HCV infection. Thus, we aimed to investigate the changes of ICG-r15' after DAA therapy and evaluate its prognostic role in the development of PH-related events despite successful viral elimination.

Method: We prospectively followed 119 cACLD patients treated with DAAs in our tertiary centre with paired and available ICG-r15' and LSM both before and 6 months after treatment. According to the Baveno VI Criteria, cACLD and clinically significant PH (CSPH) were defined by pre-treatment values of LSM > 10 kPa and LSM ≥ 21 kPa, respectively. Hepatic decompensation (HD), Hepatocellular carcinoma, portal venous thrombosis, liver transplantation and death were considered as PH-related events. The Kaplan-Meier method was used to estimate the HD development during the follow-up. Time-dependent Cox regression models for HD and PH-related events after SVR were applied to account for changes in ICG-r15' and LSM after DAA therapy.

Results: The median follow-up was 26 (15-36) months. ICG-r15' significantly decreased from 17.3% at before treatment to 12.2% at 6 months follow-up. The cumulative incidence rate of PH-related events at 1 year and after 2 years of follow-up were 170.8 (104.7-278.9), 49.5 (15.9-153.3) per 100-Person Years, respectively. The incidence rate significantly differed when compared by previous HD, CSPH status and history of HCC. At the multivariate analysis, previous HD (HR, 6.313; 95%CI 2.201-18.108) and higher ICG-r15' values (HR, 1.025, 95%CI 1.004-1.047) were independently associated with a higher risk of PH-related events development after DAAs treatment. ICG-r15' ≥ 18.5 was significantly associated with a higher risk of PH-related events both at univariate and multivariate analysis.

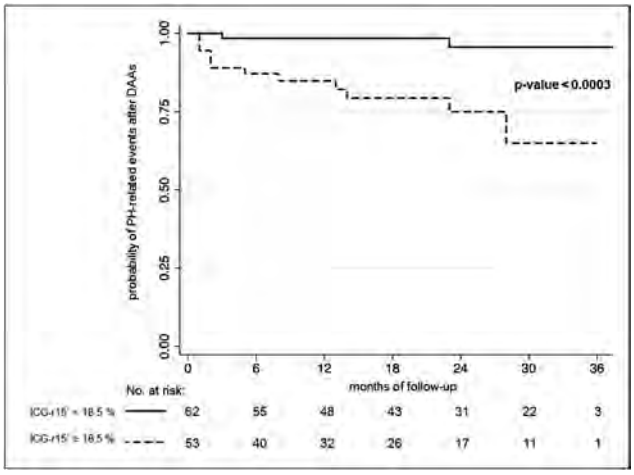

Figure: Kaplan Meier survival curve after DAAs treatment for PH-related events by ICG-r15' cut-off (18.5%) after time-dependent Cox predictive modelling.

Conclusion: ICG-r15', reflecting both liver function and PH, is demonstrated as an accurate predictor of PH-related events after DAAs treatment in HCV patients with cACLD. This predictive tool could help the clinicians to identify the right follow-up timing of ACLD patients after treatment.

SAT-259

Achieving accelerated elimination of hepatitis C virus infection by 2025: A case study in France

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Background and aims: With the introduction of curative therapies for hepatitis C virus (HCV) infection and removal of restrictions on antiviral treatment by fibrosis score, France is on track to achieve

the World Health Organization's (WHO) 2030 targets for HCV elimination. To inform the path towards accelerated elimination, this analysis evaluates the clinical and economic impact of HCV elimination in France by 2025.

Method: A Markov disease progression model was developed to assess the impact of expanding HCV diagnosis and treatment, populated with demographic and epidemiological inputs for France. Historical incidence of HCV was calibrated to match 110, 000 chronically-infected adults (with 40, 000 diagnosed) in 2018. Future incidence was assumed to be proportional to prevalence. Two scenarios were compared: maintaining 15, 000 annual treatments and 4.1 million annual HCV antibody screens ("status quo"), and "accelerated elimination" requiring 13, 700 diagnoses and 18, 650 treatments annually over 2019-2025. Clinical outcomes included cases of decompensated cirrhosis (DC), hepatocellular carcinoma (HC), liver transplants (LTs) and liver-related deaths (LRDs). Economic outcomes included costs of hepatic and extrahepatic complications, screening and treatment, and incremental cost per quality-adjusted life year (ICER; €/QALY).

Results: Compared to the status quo, accelerated elimination in France require screening of two times more people annually, or 28 million additional HCV antibody screens over 2019-2025. This would avert 2, 913 new HCV infections, 32 DC cases, 67 HC cases, 6 LTs, and 50 LRDs while incurring €1, 153 million in additional healthcare costs over 2019-2025 (ICER of €119, 599/QALY). By 2030, the clinical and economic benefits of accelerated elimination would grow and yield cost savings of €159 million (ICER of -€9, 479/QALY).

	Status quo	Accelerated elimination by 2025
Clinical outcomes over 2019-2025, incident cases		
HCV infection	17, 281	14, 368
Decompensated cirrhosis	76	44
Hepatocellular carcinoma	163	95
Liver transplant	15	9
Liver-related deaths	120	70
Economic outcomes over 2019-2025, million €		
Screening	403	754
Antiviral treatment	2, 273	3, 259
Liver-related complications	123	96
Extra-hepatic manifestations	593	436
Total costs	3, 391	4, 545

Conclusion: While France is on track to eliminate HCV as a public health threat by 2030, an expansion of screening to 28 million more people would be necessary to accelerate elimination by 2025. This path would further reduce the clinical and economic burden of HCV and be cost-saving by 2030.

SAT-260

Global timing of hepatitis C virus elimination: estimating the year countries will achieve the World Health Organization elimination targets

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Background and aims: The introduction of highly efficacious therapies for hepatitis C virus (HCV) infection has made the elimination of HCV an attainable goal. This study assessed the progress made in 45 high-income countries and territories towards meeting the 2030 HCV elimination targets by the World Health Organization (WHO) for diagnosis, treatment, incidence, and mortality from chronic HCV infection.

Method: A Markov model was developed to forecast the annual HCV-infected population by stage of liver disease, sex, and age. For each country and territory, the model was populated with reported demographic and epidemiological inputs, and historical incidence was calibrated to reported overall, as well as sex- and age group-specific, prevalence of chronic HCV. Future incidence was assumed to be a linear function of prevalence except when treatment restrictions were in place. With restrictions, incidence was a linear function of the F0 prevalent population. The 2017 levels of diagnosis and treatment were assumed constant over the future. Modelled outcomes were analysed to determine which year countries were projected to meet the four components of the WHO HCV elimination targets for 90% reduction in incidence, 65% reduction in liver-related deaths, 90% diagnosis and 80% of the eligible HCV population treated. The earliest year in which all four targets were met was defined as the year of elimination.

Results: Of 45 high-income countries and territories analysed, only seven (Australia, France, Iceland, Spain, Switzerland, South Korea, and the United Kingdom) are on track towards meeting WHO's HCV elimination targets by 2030. Italy, Japan, and Malta can also reach the targets with expanded screening efforts. 30 countries are off-track by at least 20 years, as they are not projected to achieve HCV elimination before 2050. A 90% reduction in incidence was the most difficult target to achieve, followed by a 65% reduction in liver-related deaths (dependent of screening and treatment). Although many countries have expanded HCV treatment, few have national screening programs that can maintain sufficient number of patients to treat in the future.

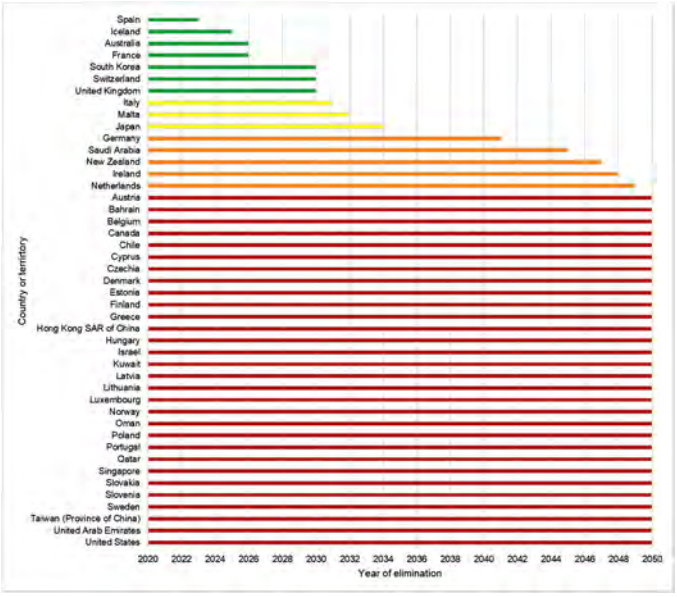

Figure: Year each country/region will meet all four World Health Organization (WHO) elimination targets

Conclusion: Even with the introduction of curative therapies, 84% of high-income countries are not on track to meet the WHO's 2030 targets that would eliminate HCV as a public health threat, and 66% are off-track by at least 20 years. Immediate action to improve HCV screening and treatment is needed globally to make WHO's HCV elimination targets attainable by 2030.

SAT-261

Elevated HCV reinfection rates after cure on spontaneous clearance among HIV-infected and uninfected men who have sex with men

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Background and aims: Increasing rates of hepatitis C virus (HCV) infection associated with ongoing risk activity have been reported after successful cure or viral clearance, particularly among HIV-infected men who have sex with men (MSM). There has been considerably less information on HCV reinfection risk factors in this population. We assessed factors associated with reinfection after treatment-induced or spontaneous clearance (SC) in both HIV-infected and uninfected MSM in British Columbia, Canada.
Method: We identified HIV-infected and uninfected MSM who achieved sustained virologic response (SVR) to HCV treatment or had SC with ≥ 1 subsequent HCV RNA measurement in the British Columbia Hepatitis Testers Cohort. Crude reinfection rates per 100 person-years (PYs) were calculated. Cox regression was used to model adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for reinfection, overall, and by HIV status.
Results: We identified 1, 349 HCV-infected MSM with SVR (n = 856) and SC (n = 493), of which 349 (26%) were HIV-positive. HIV-infected MSM were more likely to have achieved viral clearance through SVR (76% vs. 59%), had histories of injection drug use (IDU; 41% vs. 21%), alcohol use (22% vs. 14%) and mental health disorders (47% vs. 28%), compared to HIV uninfected. A total of 98 reinfections were identified, yielding an overall reinfection rate of 1.9 per 100 PY (1.0 for SVR patients and 2.7 per 100 PY for SC). HIV-infected MSM had higher rates of reinfection (3.1 vs. 1.6 per 100 PY) than HIV uninfected individuals. In multivariable analysis, age < 35 years (HR 3.1, 95% CI: 1.2, 8.1), cure through SVR (HR 0.2, 95% CI: 0.1, 0.4), HIV infection (HR 2.0, 95% CI: 1.3, 3.1), problematic alcohol use (HR 2.0, 95% CI: 1.2, 3.3), IDU (HR 2.7, 95% CI: 1.6, 4.3) and mental health (MH) counseling (HR 0.2, 95% CI: 0.1, 0.4) were independently associated with reinfection, overall. Among HIV-infected, age < 35 years (HR 2.7, 95% CI: 1.0, 7.5) and MH counseling (HR 0.4, 95% CI: 0.1, 0.9) remained associated with reinfection, but IDU (HR 1.9, 95% CI: 0.8, 4.2) was less strongly associated. Among HIV uninfected, alcohol use (HR 3.0, 95% CI: 1.7, 5.7) and IDU (HR 2.7, 95% CI: 1.5, 4.9) remained the largest independent predictors of reinfection.
Conclusion: Rates of HCV reinfection remain elevated among HIV-infected and uninfected MSM. Ongoing substance use is driving reinfection among HIV-negative MSM, while sexual transmission may be more important among HIV-positive MSM.

SAT-262

Long-term liver function outcome and related risk factors in HCV cirrhotic patients treated with direct-acting antiviral therapy: Results from the Navigatore platform in Veneto-Italy

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Background and aims: high efficacy and safety of direct acting antivirals (DAAs) allowed to eradicate also patients with HCV-related advanced liver disease. We aimed to report long-term clinical outcomes from a large real-life multicenter cohort of HCV-infected cirrhotic patients.
Method: all cirrhotic patients starting a DAA regimen with at least 48 weeks (wks) follow-up were included in the study. Data were prospectively entered at sites into a centralized database. Primary outcomes were the modification of Child-Pugh score (CP) at 12 and 48wks after the end of therapy (EOT), and the related risk factors of CP improving or worsening. Multiple linear and logistic regression were used to evaluate the association between the variables considered and the clinical outcomes.
Results: A total of 2232 patients with cirrhosis due to HCV started DAA between January 2015 to September 2018. At baseline, 2046 patients (91.6%) were CPA and 186 patients (8.4%%) were CPB. At 12wks after EOT, 20.3% of patients (n = 452) improved at least 1 point of CP, 75% (n = 1674) remained stable and 4.7% (n = 106) showed liver function worsening. Similar results were showed at 48wks after EOT. At the Univariate analysis, factors associated with statistically significant worsening of CP were:- in CP5-patients: lower level of AST/albumin/PLT and higher level of INR/bilirubin/high stiffness, the presence of obesity, digestive bleeding before treatment (at 12wks after EOT), and HCV-genotype 3, lower level albumin, higher level of INR/bilirubin (at 48wks after EOT)-in CP > 5-patients: higher level of bilirubin (12wks after EOT) and higher level of INR and HCVG2 (48wks after EOT). At the multivariate analysis, baseline bilirubin < 2.5 mg/dL (OR = 0.47), INR < 1.5 (OR = 0.25), Platelets count > 100.000/mm3 (OR = 0.63), older age (OR = 0.98) and sustained virological response (SVR)12 (OR = 0.53), were protective factors of CP worsening at 12wks after EOT, while AST < 100 IU/L (OR = 1.71) was a predictive factor of CP worsening at 12 wks after EOT. Still, INR < 1.5, older age and SVR12 (OR = 0.48), were confirmed to be protective factors for CP worsening at 48wks after EOT. Finally, considering only patients who could improve CP (CP > 5), INR < 1.5 was the only predictive factor of CP improvement (OR = 2.9 12wks EOT and OR = 3.8 48wks EOT).
Conclusion: only 5% of HCV-infected cirrhotic patients showed a worsening of liver function at 12 and 48wks after EOT with DAAs. Liver function tests, coagulation parameters and SVR positively influenced the outcome after EOT.

SAT-263

Immediate versus delayed hepatitis C treatment is cost-saving in the United Kingdom: A pan-genotypic cost-effectiveness analysis

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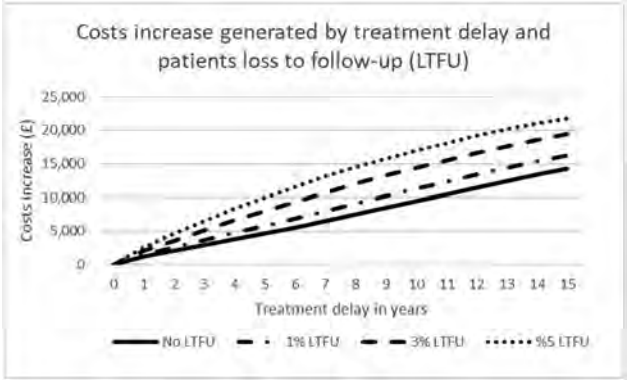
Background and aims: Patients with hepatitis C virus (HCV) face increased healthcare costs due to hepatic and extrahepatic complications. While treatment has been shown to increase health benefits and reduce medical costs, it is often delayed for patients with early stages of liver disease. This study explored the clinical and economic burden of delaying treatment and the cost-effectiveness of immediate versus delayed treatment in the United Kingdom (UK).
Method: A Markov state transition model of the natural history of HCV was developed to forecast liver-related and economic outcomes over a lifetime from the UK National Health Service (NHS) perspective. Treatment attributes were based on clinical trials of glecaprevir (identified by AbbVie and Enanta) and pibrentasvir. Patient demographics as well as hepatic and extrahepatic costs were drawn from UK sources; transition probabilities and health state utilities were based on published literature. The analysis focused on the treatment of patients with HCV genotypes 1-6 and fibrosis stages

F0-F2 immediately versus later. In the base case, there was no patient loss to follow-up (LTFU) due to treatment delay. In scenario analyses, a proportion of the untreated but treatable cohort would be LTFU by 1%, 3% and 5% yearly. Health outcomes included lifetime risks of liver decompensation (DCC), hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related death (LrD). Other outcomes included total costs and quality-adjusted life years (QALYs) valued at £20, 000, and net monetary benefit (NMB), all discounted at 3.5% yearly. Regression analysis was performed to assess the impact of treatment delay and LFTU on NMB.
Results: Delaying treatment with glecaprevir/pibrentasvir increased long-term risks of DCC, HCC, LT, and LrD and total lifetime costs. For example, delaying treatment 5 years would cost £4, 666 more per patient vs immediate treatment, with 71% attributable nto extra-hepatic complications. Immediate treatment was a dominant strategy regardless of time of delay as it delivered more QALYs at lower costs. In regression analysis, NMB would decrease by £4, 236 (95% confidence interval: £4, 063-£4, 409) for every year treatment is delayed and by £3, 303 (£2, 888-£3, 717) per every 1% increase in LFTU.



Conclusion: Immediate versus delayed hepatitis C treatment decreased hepatic and extrahepatic costs and was a dominant strategy in the UK. Immediate treatment avoids the risk and burden of LFTU and maximizes the value of treatment to patients and payers.

SAT-264
Prediction of hepatocellular carcinoma development using liver stiffness after sustained virological responses by magnetic resonance elastography in patients with chronic hepatitis C
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Background and aims: It is unclear whether liver stiffness after sustained virological response (SVR) measured by magnetic resonance elastography (MRE) is useful for hepatocellular carcinoma (HCC) prediction. The aim of this study was to investigate the relationship between liver stiffness at 12 weeks after the end of treatment (SVR12) and subsequent HCC development.
Method: A total of 318 patients with chronic hepatitis C without history of HCC who achieved SVR through direct acting antivirals (DAAs) treatment and had been observed for more than 1 year were included. We initiated observation at the time of MRE measurement (SVR12), continued the observation for subsequent HCC development, and evaluated predictors for HCC development.
Results: Mean age 67.3 ± 10 years, 115 men (33%), 154 (48%) were FIB-4 > 3.25 at the time of DAAs start. 174 patients underwent liver biopsy before DAAs and 65 (37%) were METAVIR fibrosis stage 3/4. The mean observation period was 21.1 ± 6.7 months, and 23 patients developed HCC. For Receiver operating characteristic (ROC) analysis predicting HCC development within 2 years, 3.75 KPa was used as the cutoff value of liver stiffness. Comparing with liver stiffness and fibrosis stage or serum fibrosis markers, area under the ROC curve of liver stiffness, fibrosis stage at the DAA start, WFA+-M2BP at SVR12, and FIB-4 at SVR12 were 0.73, 0.61, 0.68, and 0.63, respectively and area under the ROC was highest in liver stiffness by MRE. The 1-year and 2-year HCC development rates were 6.9% and 13.6% for patients with liver stiffness ≥ 3.75 KPa and were 1.5% and 2.8% for patients with liver stiffness < 3.75 KPa ($p < 0.001$). Univariate analysis revealed that liver stiffness ≥ 3.75 KPa, age every 10 years, AFP ≥ 6.0 ng/ml, and presence of hypovascular nodule were associated with HCC development. In the multivariate analysis, liver stiffness ≥ 3.75 KPa [hazard ratio (HR), 2.97; 95% confidence interval (CI), 1.04-8.62], age every 10 years (HR, 1.97; 95% CI, 1.17-3.29), AFP ≥ 6.0 ng/ml (HR, 2.44; 95% CI, 1.03-5.78), and presence of hypovascular nodule (HR, 3.88; 95% CI, 1.36-11.1) were independent predictive factors of HCC development.
Conclusion: Liver stiffness measured by MRE at SVR12 in patients with chronic hepatitis C who achieved SVR following DAAs treatment is a predictive factor of HCC development. MRE was able to identify patients with high risks of HCC even after SVR was achieved.

SAT-265
Anti-VHC therapy does not increase de risk of developing splanchnic vein thrombosis in patients with cirrhosis
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Background and aims: Splanchnic vein thrombosis (PVT) is a frequent event in the natural history of cirrhosis with an incidence of 4-16% per year. Several factors have been associated with its development such as portal velocity < 15 cm/s or advanced liver disease. Recently, it has been suggested that in patients with HCV cirrhosis, direct-acting antiviral (DAA) oral treatment-induced sustained virological response (SVR) may have an increased risk of PVT associated with a potential overcorrection of the coagulopathy after treatment. Thus, the aim of the study was to evaluate the incidence of PVT in patients with HCV-cirrhosis (active infection and DAA-induced SVR).
Method: 579 cirrhotic patients without PVT followed in our hospital were included: 210 with active HCV infection followed between Dec2010 and Apr2013 and 369 with DAA-induced SVR followed between Oct2012 and Dec2016. 74 patients from the active infection group received antiviral treatment before Apr2013 and were censored from the analysis on the day of its initiation and were not included thereafter in DAA-induced SVR group. All patients underwent an abdominal ultrasound every 6 months for PVT screening. In the DAA-induced SVR group, clinical and biochemical variables included in the analysis were those immediately prior to the start of DAA treatment. Competitive risk analysis was used for the statistical analysis.
Results: Of the 579 patients, 53% were men, mean age 61 ± 10 years, Child-Pugh A/B/C 83/15/2%, MELD 9 ± 3. At inclusion, 20% had presented ascites, 6% hepatic encephalopathy, 48% had esophageal varices (EV), 7% previous upper gastrointestinal bleeding (UGB), 25% were under β-blockers prophylaxis, 7% with previous endoscopic band ligation. The mean follow-up was 2.8 ± 1.2 years. 24 patients presented PVT during follow-up with an incidence of 1.5, 2.3 and 4.1% at 1, 2 and 3 years. Transplant-free survival was 97.4, 95.2 and 89.9% at 1, 2 and 3 years respectively. In a competitive risk analysis in a model adjusted for sex, Child-Pugh, creatinine, platelets, presence of EV, previous UGB, β-blocker treatment and active infection/DAA-induced

SVR, the only independent factor associated with the development of PVT was Child-Pugh (HR 1.37 [1.09-1.71; p = 0.005).
Conclusion: DAA-induced SVR does neither increase nor decrease the risk of PVT during follow-up in HCV cirrhosis. Therefore, despite achieving SVR, patients should be kept on PVT surveillance, especially patients with advance liver disease and deteriorated liver function.

SAT-266

High rates of early HCV reinfections after DAA therapy in active intravenous drug users attended at mobile harm reduction units

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Background and aims: The WHO has recently called for hepatitis C virus (HCV) elimination and has identified injecting drug users (IDU) as a key population. Clinical trials of currently available all-oral regimens have demonstrated a high degree of efficacy in this population. Current HCV reinfections rates in IDU are < 6/100-person years (PY). There is an urgent need to confirm these data in clinical practice.
The aims of this study were to evaluate the efficacy of HCV therapy and the HCV reinfection rate in active drug users followed at low-threshold mobile harm reduction units (LTMHRU).
Method: We included active drug users (persons who smoked or injected heroin/cocaine in the last 6 months) who received HCV treatment and were attended at 2 LTMHRU in Madrid between Jan/2016 and Jul/2018. Sustained virological response (SVR12) was assessed 12 weeks after therapy. HCV reinfection incidence density was defined as the number of reinfections per 100-person years (PY) using person-time of observation and was stratified by drug consumption at initiation of HCV treatment. Cox proportional hazard regression analysis was used to assess factors associated with HCV reinfection.
Results: In the study period 165 drug users started HCV therapy. Intravenous drug use in the last 6 months was reported in 74% of the drug users. Of those who started therapy in abstinence, 65% relapsed drug consumption during follow-up. The overall SVR12 rate was 64.8% (107/165) (ITT, reinfection = failure) and 96.7% (117/121) (mITT). SVR12 was irrespective of the HIV and baseline active consumption status. There were 4 virological failures. The cohort at-risk for reinfection (n = 121) was composed of 44.2% HIV positive and 49.6% drug users who initiated HCV treatment in abstinence. Ten cases (10/121) of HCV reinfection (3 before EOT and 7 after SVR12) were identified and the median time to reinfection was 6.1 (IQR 0.42-1.8) months. Total follow-up time at-risk was 101.1-PY (median 0.6 years, IQR 0.3-1.3). The global reinfection incidence was 9.8 per 100-PY (95% CI 4.7, 18.2). Reinfection incidence was not statistical different according to HIV status: HIV positive [11.0 (95% CI 4.0; 23.9)] and HIV negative [8.6 (95% CI 2.3; 21.9)] per 100 PY; or baseline active consumption: no consumption [9.1 (95% CI 2.9; 21.3)] and consumption [10.8 (95% CI 3.5; 25.2)] per 100- PY; p 0.79. However, the reinfection incidence was higher amongst those who reported injected drug use in the previous six months: 16.7 (95%CI 8.0; 30.7) per 100-PY. In adjusted analysis, the unique factor associated with reinfection was injection drug use in the previous month at baseline (aHR 8.7, 95%CI 1.0-73.6; p 0.04).
Conclusion: HCV treatment was effective in active drug users attended at LTMHRU. We found a very high rate of early HCV reinfections in active IDU in this setting. Surveillance for reinfection at 6–month intervals should be implemented in this population.

SAT-267

Occult hepatitis C in immunocompetent patients who have achieved sustained viral response is associated with persistent histological abnormality

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Background and aims: Whether achieving sustained virological response (SVR) in patients with HCV infection after Direct-acting antiviral agents (DAA) treatment means complete viral eliminationin is uncertain because occult HCV infection (OCI), defined by the presence of HCV RNA in liver tissues or PBMC whose serum is constantly negative for HCV RNA with or without presence of HCV antibodies, may occur. We thus investigated the prevalence and clinical relevance of OCI.
Method: Subjects from three tertiary hospitals who had achieved serum HCV clearance, including 60 of DAA induced SVR, 50 of peg-IFN plus ribavirin (PR) induced SVR, and 30 of spontaneous elimination (SE), were subjected to detect HCV RNA in hepatocytes by RNAscope in situ hybridization assay, and in PBMC by qPCR. All the subjects are immunocompetent. Paired liver biopsies of baseline and post-SVR were evaluated by Ishak scoring system.
Results: Fig.1A is an representative image of RNAscope assay for detecting HCV RNA in liver biopsy of an OCI patient before and after treatment. In total, OCI was detected in 16 subjects (11.4%): nine (15.0%) in the DAA-based group, five (10.0%) in the PR group, and two (6.7%) in the SE group (Fig.1B-E). HCV negative strand were detected in all PBMCs of patients with OCI. Intriguingly, the proportion of OCI was found higher in peg-IFN-free (solely DAA or DAA plus RBV) treated individuals than in patients who received PR treatment with or without combination of DAA (Fig. 1F). The occurrence of OCI is more frequent in patients with HCV genotype 3. No correlation between baseline viral load, interleukin-28B genotype, baseline transaminases, post-SVR transaminases and OCI were found. However, OCI was significantly linked with poor fibrosis status at post-SVR (Fig.2A-B). In addition, we found the fibrosis was significantly improved only in patients without OCI (p < 0.001), but not in OCI subjects (p = 0.385) after adjusted for fibrosis status at baseline, implying a role of OCI in persisting hepatic abnormality. Furthermore, we found only five of 14 (35.7%) OCI patients showed fibrosis regression at post-SVR and the remaining nine OCI patients exhibited either stabilization or worsening of liver fibrosis stage, whereas the frequency of fibrosis regression was 61.0% in non-OCI patients at post-SVR (p = 0.07). Together, these results revealed that patients with OCI reflected a trend towards persisting liver alteration. Importantly, we found HCV relapse in one of the OCI patients at 48 weeks after the end of PR treatment.
Conclusion: HCV RNA can persist in a certain of immunocompetent patients with DAA induced serum resolution of hepatitis C and associated with persistent hepatic abnormality. From a clinical perspective, our findings provide new insights into cure of HCV and could influence the following-up scenario after SVR.

SAT-268

Non-invasive prediction of gastroesophageal varies by serum wisteria floribunda agglutinin positive Mac-2 binding protein and FIB-4 index in chronic hepatitis C

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Background and aims: The aim of this study is to clarify the value of serum fibrosis marker for the non-invasive prediction of

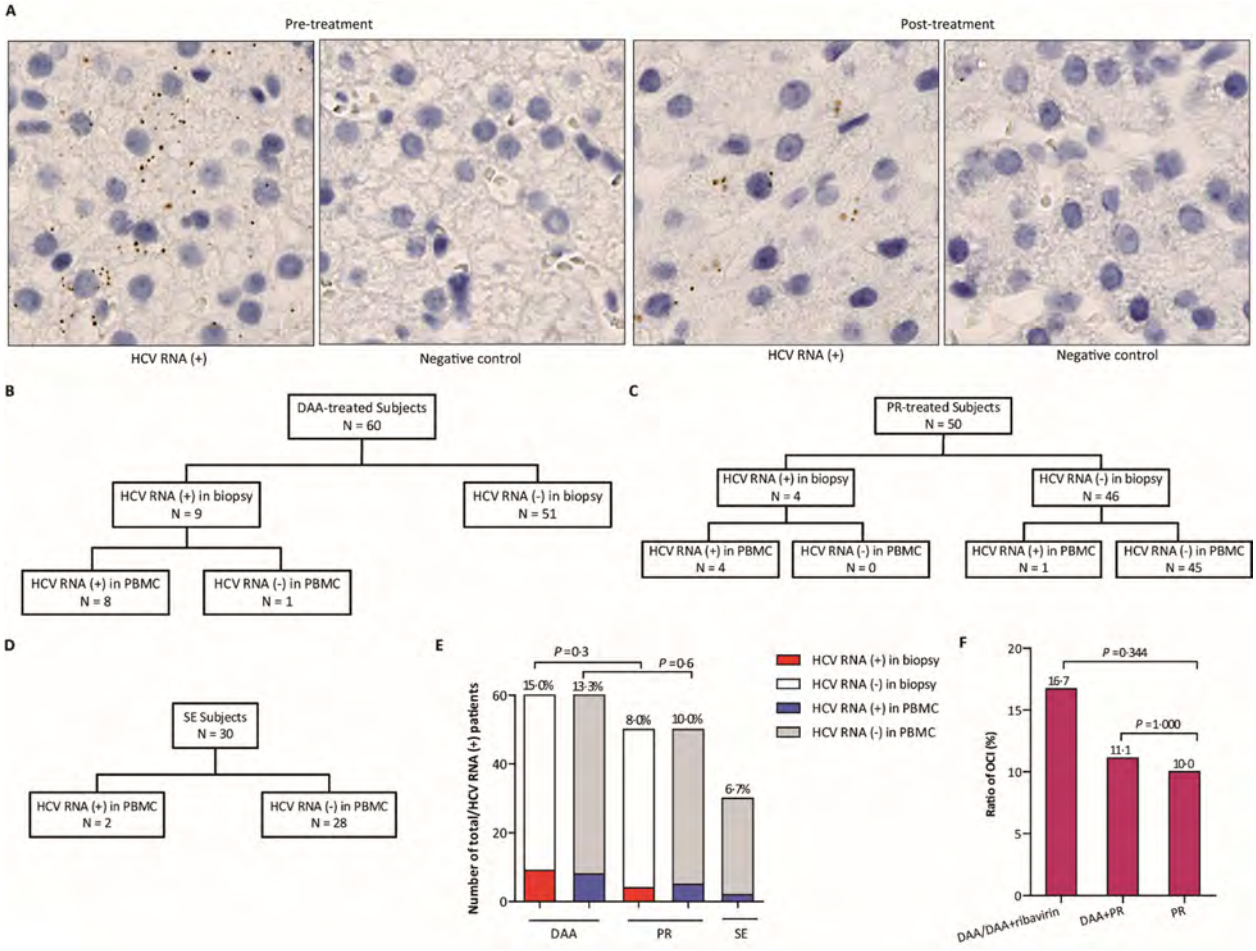

Figure 1: (abstract: SAT-267)

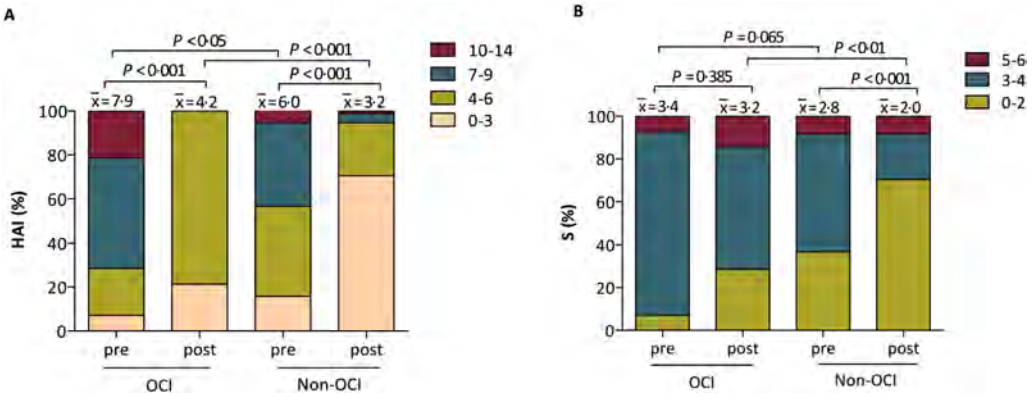

Figure 2: (abstract: SAT-267)

gastroesophageal varices (GEV) in patients with chronic hepatitis C and in those who achieved sustained virological responses (SVR) by direct acting antivirals (DAAs) therapy.

Method: This study involved 166 patients with chronic hepatitis C and 65 patients who achieved SVR by DAAs. Screening of GEV by endoscopy was performed and serum wisteria floribunda agglutinin positive Mac-2 binding protein (WFA+-M2BP), a novel serum biomarker which correlatie with liver fibrosis, was measured along with various laboratory data. The accuracy of serum markers for the prediction of the presence of GEV was examined.

Results: Among chronic hepatitis C, patients with GEV had significantly higher level of serum WFA+-M2BP (3.4 ± 3.0 vs. 10.2 ± 4.7, $p < 0.0001$) and FIB-4 index (4.9 ± 3.3 vs. 10.4 ± 7.2, $p < 0.0001$) compared to those without. The AUROC for the presence of GEV was 0.90 for WFA+-M2BP and 0.86 for FIB-4 index. By using the optimal cut off value of 6.0 for WFA+-M2BP and 6.0 for FIB-4 index, sensitivity and specificity for GEV prediction was 87% and 79% for WFA+-M2BP, and 72% and 79% for FIB-4 index, respectively. Serum WFA+-M2BP increased along with the grade of GEV: 3.4 ± 3.0 in no varices, 7.9 ± 5.1 in small varices, and 11.5 ± 4.1 in large varices ($p < 0.001$). Among

patients after SVR, patients with GEV had significantly higher level of serum WFA+-M2BP (1.6 ± 1.4 vs. 3.0 ± 1.6, p = 0.0007) and FIB-4 index (2.8 ± 1.8 vs. 5.9 ± 3.1, p < 0.0001) compared to those without. AUROC for the presence of GEV was 0.80 for WFA+-M2BP and 0.86 for FIB-4 index, and the optimal cut off value was 1.58 for WFA+-M2BP and 3.35 for FIB-4 index, which was lower compared to the optimal cut off value in chronic hepatitis C. Sensitivity and specificity and positive predictive value for GEV prediction was 76%, 84%, and 82%for WFA+-M2BP, and 82%, 84%, and 83% for FIB-4 index. The positive predictive value was 85% if WFA+-M2BP and FIB-4 index was combined.

Conclusion: Serum WFA+-M2BP and FIB-4 index had satisfactory accuracy to predict GEV, and may be utilized in clinical practice to define patients who need endoscopy. On the other hand, it is important to recognize that the optimal cut off values of these markers are different between patients with on-going hepatitis C infection and those who achieved SVR.

SAT-269

The sustained deleterious impact of viremia on patient reported outcomes in patients with chronic hepatitis C who don't achieve sustained virologic response

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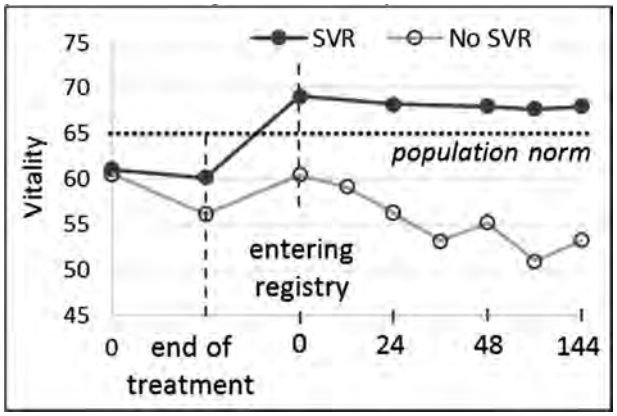
Background and aims: Although improvement of PROs in CHC patients who achieve SVR with direct-acting antivirals (DAAs) has been demonstrated, PROs of CHC patients who failed to achieve SVR with new DAAs have not been documented. AIM: Compare post-treatment PRO scores between CHC patients who did and did not achieve SVR after DAA treatment.

Method: Patients who had completed treatment in a clinical trial were prospectively enrolled in two registries based on treatment outcomes: the SVR Registry and Non-SVR Registry. PRO scores were prospectively collected using the Short Form-36 (SF-36) every 12-24 weeks.

Results: There were 4, 234 patients with SVR and 242 without SVR who were enrolled in these two registries and had pre-treatment PRO data: 54 ± 10 years old, 63% male, 83% white, 65% enrolled in the U.S., 17% with cirrhosis prior to treatment, 12% with coinfection with HIV, and 25% with history of depression. Upon registry enrollment, patients with SVR experienced significant improvement in all their PRO scores in comparison to their own pre-treatment baseline scores (all p < 0.0001) while there was no improvement in any PRO score (all one-sided p > 0.05) and, in fact, a significant decrement in General Health of SF-36 (mean −2.8 points, p = 0.008) in CHC patients without SVR. Furthermore, CHC patients without SVR experienced significant PRO decrements while followed on the registry (up to −7.0 points decrements in 4/8 SF-36 domains at registry week 12; up to −9.2 points in all 8 domains at week 24; up to −8.3 points in 5/8 domains at week 48, and up to −9.0 points in 4/8 domains at week 96 (all p < 0.05). In contrast, patients with SVR experienced sustained improvement of their PRO scores while on the registry (up to +7.0 points at registry week 24, up to +6.9 points at week 48, up to +6.1 points at week 96 (all p < 0.001) (Figure). In multivariate analysis, having achieved SVR was independently associated with superior scores in all SF-36 domains at all registry time points: beta from +4.8 to +14.9 points (all p ≤ 0.01). PRO scores were lower and their decrements were greater in cirrhotics without SVR than non-cirrhotic without SVR (p < 0.05).



Conclusion: These data clearly show the benefit of achieving SVR for patients' well-being which is contrasted to the deleterious impact of viremia (not achieving SVR). These data should inform payers and policy makers to remove any barriers to HCV treatment which could lead to the cure and reduce patients' suffering and PRO impairment.

NAFLD: Diagnostics and non-invasive assessment

SAT-271

Genetic risk factors for advanced alcoholic and non-alcoholic liver disease in the general population

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Background and aims: Several genetic risk variants associated with liver disease have been identified, but their importance in the general population is uncertain. Recent EASL guidelines considered the study of susceptibility genes in alcoholic liver disease a research priority. We analyzed associations of selected genetic variants with incident advanced liver disease in the general population, and separately in non-alcoholic fatty liver disease (NAFLD) and alcohol risk users.

Method: We included individuals participating in Finnish health-examination surveys (FINRISK 1992-2012 or Health 2000) with available genome-wide SNP data. NAFLD was defined as a fatty-liver index > 60 and alcohol use < 30 g/day for men and < 20 g/day for women; alcohol risk use was defined as consumption exceeding these limits. Exclusions were known baseline liver disease or viral hepatitis. Data were linked with national registers for liver-related admissions, mortality, and liver cancer until 2013. Selected genetic variants with reported association with liver disease were individually entered into a Cox regression analysis adjusted for age and sex, with incident advanced liver disease (admission, death, cancer) as the outcome.

Results: The whole study population comprised 32, 939 subjects, 6397 of them with baseline NAFLD and 3336 with alcohol risk use. Carrier frequency of all tested genotypes were similar across these groups. In the whole cohort, PNPLA3 and TM6SF2 genotypes were significantly associated with incident advanced liver disease (Table). In NAFLD subjects, TM6SF2 and the Z allele of α1-antitrypsin (A1AT) deficiency were borderline significant. Among alcohol risk users, only PNPLA3 rs738409 was significant.

	All subjects	NAFLD	Alcohol risk users
Gene variant	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
PNPLA3 rs738409	**1.56 (1.24-1.97)**	1.12 (0.75-1.68)	**1.62 (1.16-2.87)**
TM6SF2 rs58542926	**1.47 (1.07-2.01)**	**1.66 (0.99-2.77)**	1.39 (0.88-2.19)
MBOAT7 rs641738	1.13 (0.94-1.61)	1.29 (0.78-2.12)	1.01 (0.70-1.47)
HFE C282Y rs1800562	0.75 (0.45-1.27)	0.42 (0.13-1.32)	0.83 (0.40-1.69)
HFE H63D rs1799945	0.90 (0.66-1.22)	0.94 (0.56-1.59)	0.80 (0.52-1.23)
A1AT S-allele rs17580	0.27 (0.04-1.92)	too few events	too few events
A1AT Z-allele rs28929474	1.52 (0.90-2.55)	**2.13 (0.99-4.60)**	1.27 (0.56-2.88)

Conclusion: Carriers of the PNPLA3 variant have approximately 50-60% higher risk of incident advanced liver disease than non-carriers. TM6SF2 genotype was significant in all subjects and NAFLD. A1AT Z-allele may be relevant in NAFLD subjects. On a population level, none of the other genotypes tested showed significant impact on the risk for incident advanced liver disease.

SAT-272

A simple algorithm based on electronic medical records to identify NAFLD with advanced fibrosis in patients with Type 2 diabetes

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) remains undiagnosed in the majority of patients even those with advanced fibrosis at highest risk for liver-related morbidity and mortality. With the anticipated approval of potent anti-inflammatory and anti-fibrotic medications, the major barrier to getting patients on effective treatment will be identifying appropriate patients with advanced disease that requires pharmacologic intervention. The aim of this study was to assess the utility of using simple steatosis and fibrosis scores to identify NAFLD-advanced fibrosis in patients with type 2 diabetes (T2DM) within a large electronic medical record (EMR) database.
Methods: All adult patients with a diagnosis of T2DM were identified from EMR using ICD-9 codes. Patients with other causes of chronic liver disease and those on steatogenic drugs were excluded. Baseline demographics, clinical characteristics, and laboratory data were collected. NAFLD was defined as hepatic steatosis index (HSI) > 36. Advanced fibrosis was defined as FIB-4 index > 2.67. A univariable and a multivariable logistic regression analysis were done to further assess which clinical factors are associated with advanced fibrosis. A p value < 0.05 was considered statistically significant.
Results: Of total of 121, 513 diabetic patients were included in the final analysis, 51% were male with a mean age of 62 years, 76% were White and 21% were Black. Overweight or obesity were present in 89% and the mean hemoglobin A1C was at 7.3 ± 4.3% with 26% of patients being on insulin. In total, 12.7% had chronic kidney disease and 64.6% had evidence of dyslipidemia. NAFLD based on HSI > 36 was present in 102, 628 patients or 84% of the total cohort and advanced fibrosis based on FIB-4 index > 2.67 was present in 9%. Factors associated with the presence of advanced fibrosis on multivariable analysis were chronic kidney disease, coronary artery disease, being on insulin, and not being on statins.
Conclusion: By using simple scores that rely on readily available clinical variables, patients with advanced fibrosis related to NAFLD can be identified easily. These strategies should be implemented as screening tools in large EMR databases to prioritize patients for referral and treatment of their liver disease.

SAT-273

Impact of age on routinely available non-invasive tests for the discrimination of advanced fibrosis due to NASH in the phase 3 STELLAR trials of the ASK1 inhibitor selonsertib

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Background and aims: Routinely available non-invasive tests (NITs) have been shown to be able to identify patients with advanced fibrosis due to NASH, but their performance may vary by age. Our aim is to describe the performance of NITs across age groups using the baseline data from the Phase 3 STELLAR studies of the apoptosis-signal regulating kinase 1 (ASK1) inhibitor selonsertib (SEL).
Method: The STELLAR studies (NCT03053050 and NCT03053063) enrolled patients 18-70 years with bridging fibrosis (F3) or compensated cirrhosis (F4) due to NASH (NAFLD Activity Score [NAS] ≥ 3). Baseline liver biopsies were centrally read according to the NASH CRN fibrosis classification and non-invasive markers of fibrosis, including the NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) test, and liver stiffness (LS) by transient elastography (TE; FibroScan®) were measured. The performance of these tests to discriminate advanced (F3-F4) fibrosis in the full study population and in age strata (18-39, 40-64, and ≥ 65 years) was evaluated using AUROCs with 5-fold cross-validation repeated 100x.

Table: AUROCs (95% CI) of NITs to Discriminate Advanced Fibrosis (F3-F4) by Age Group

NIT	Total (n = 3202)	18-39 years (n = 190)	40-64 years (n = 2285)	≥ 65 years (n = 727)
NFS (n = 2417)	0.74 (0.74, 0.74)	0.74 (0.72, 0.74)	0.75 (0.75, 0.75)	0.68 (0.67, 0.68)
FIB-4 (n = 3123)	0.78 (0.78, 0.78)	0.69 (0.68, 0.70)	0.78 (0.78, 0.78)	0.74 (0.74, 0.75)
ELF (n = 3173)	0.80 (0.80, 0.80)	0.74 (0.73, 0.75)	0.79 (0.79, 0.79)	0.76 (0.76, 0.77)
LS by TE (n = 1765)	0.80 (0.79, 0.80)	0.74 (0.73, 0.75)	0.82 (0.81, 0.82)	0.59 (0.53, 0.69)

Results: A total of 3202 patients with evaluable liver histology were screened (median age, 59 years), including 190 aged 18-39 years, 2285 aged 40-64 years, and 727 older than 65 years. The prevalence of advanced fibrosis was71% overall, and varied substantially by age category (18-39: 45%; 40-64: 70%; ≥ 65 years: 80%; p < 0.0001). AUROCs for NITs to discriminate advanced fibrosis were generally similar across age groups except for somewhat lower performance (AUROC < 0.7) for FIB-4 in the 18-39 year old group, and NFS and LS by

TE in subjects ≥ 65 years (**Table**). In general, optimal thresholds for sensitivity and specificity across the total population demonstrated reduced sensitivity in younger patients and reduced specificity in older patients.

Conclusion: In these large, global phase 3 trials of SEL, routinely available NITs demonstrated acceptable diagnostic performance for the discrimination of advanced fibrosis due to NASH, but age-specific thresholds in younger or older patients may be required to optimize sensitivity and specificity.

SAT-274

Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver in children

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Background and aims: Hepatic multiparametric MRI, Liver*MultiScan*™, for quantitative analysis of Proton Density Fat Fraction (PDFF) and iron-corrected T1 (cT1) has been shown to have excellent repeatability and reproducibility in adults. Non-invasive MR-based biomarkers of liver inflammation and fibrosis has shown considerable utility in clinical trials and will have important implications on the delivery of paediatric investigation plans. We test the repeatability and reproducibility of the Liver*MultiScan*™ protocol to measure PDFF and cT1 across field strengths in a cohort of healthy children.

Method: cT1, T2* and Proton Density Fat Fraction (PDFF) maps were acquired from 33 healthy children volunteers (aged 6-18 years, mean 11; 16 male) without a reported history of liver disease. Each participant completed four same-day acquisitions of the Liver*MultiScan*™ protocol that comprised of a scan-rescan on a 1.5 T (Aera, E11C, MyoMaps) and a 3 T (Skyra, E11C, MyoMaps) Siemens scanner (Siemens Healthineers). Participants left the scanner after each scan and the order of scanner was counterbalanced.

Results: There was high reproducibility across different scanner models and field strengths for both cT1 (CoV 2.90%; bias 24.8 ms, 95% LoA of −23.8 ms to 73.4 ms) and PDFF (CoV 22.7%; bias 0.271%, 95% LoA of −1.35% to 1.90%). Bland-Altman analysis of the intra-rater differences also showed good repeatability for cT1 at 3 T (Cov 4.37%; bias 0.0712 ms, 95% LoA of −3.67 ms to 3.82 ms) and 1.5 T (Cov 2.23%; bias −16.9 ms, 95% LoA of −67.7 ms to 34.0 ms). Similar findings were shown in PDFF at 3 T (Cov 15.7%; bias 0.147%, 95% LoA of −1.43% to 1.72%) and 1.5 T (Cov 11.6%; bias 0.0443 ms, 95% LoA of −0.838% to 0.927%).

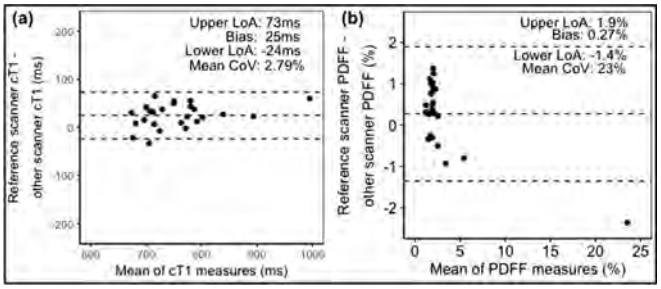

Figure: Bland-Altman plots from in-vivo measurements in children across field strength for (a) cT1 and (b) PDFF.

Conclusion: We demonstrate that multiparametric MRI is a non-invasive, repeatable, and reproducible method for quantifying liver tissue characteristics in children. This has future implications on the clinical utility of non-invasive methods in monitoring of liver disease in children and the delivery of paediatric investigation plans in clinical trials.

SAT-275

Interleukin-32 as a novel NAFLD biomarker in PNPLA3 I148M variant carriers

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Background and aims: Efforts to manage non-alcoholic fatty liver disease (NAFLD) are limited by the absence of accurate non-invasive biomarkers. The rs738409 C > G polymorphism encoding for the I148M variant in Patatin-like phospholipase domain-containing 3 (*PNPLA3*) is the main genetic determinant of NAFLD variability. Aim of this study was to identify novel NAFLD biomarkers and to explore how the presence of *PNPLA3* I148M variant impacts on hepatic gene expression in obese patients at risk of NAFLD.

Method: Transcriptomic analyses were conducted in 125 liver-biopsied obese individuals. "Severe NAFLD" was defined by the presence of steatohepatits, NAFLD activity score ≥ 4, or fibrosis stage ≥ 2. RNA was sequenced using an HiSeq 4000. Reads were aligned and counted by STAR and RSEM. Differential gene and pathways expression were assessed by DESeq2 and GSEA. Plasma IL32 was measured in 71 obese patients by ELISA.

Results: Presence of *PNPLA3* I148M variant was the main feature associated with the two main components of hepatic transcriptome variability and was linked with overexpression of pathways related to inflammation and carcinogenesis. Consistently with impaired lipid turnover in intracellular droplets, the presence of *PNPLA3* I148M variant was also associated with downregulation of lipid metabolism. In patients with severe NAFLD, inflammatory and lipid metabolism pathways were upregulated. At the single gene level, in the severe NAFLD group Interleukin-32 (IL32) was the most robustly upregulated gene (log_2 fold change = 1.36 ± 0.21, adjusted $p = 1*10^{-6}$), and its expression correlated with steatosis severity. Remarkably, the association of IL32 transcript levels with NAFLD was more marked in *PNPLA3* I148M variant carriers.

Plasma IL32 levels were strongly correlated with hepatic gene expression and were associated to both NAFLD and severe NAFLD independently of serum aminotrasferases ($p < 0.01$ both). A combined score encompassing evaluation of IL32-ALT-AST showed a better performance than ALT-AST alone in NAFLD diagnosis (AUC = 0.85 vs. 0.72, p = 0.01). The IL32-ALT-AST classifier tended to perform better in *PNPLA3* I148M variant carriers (AUC = 0.92 vs 0.78, p = 0.06).

Conclusion: These results give insight into the liver transcriptional response associated with NAFLD in obese individuals, underscoring the role of *PNPLA3* I148M variant as a major determinant of transcriptome variability. Moreover, we highlight IL32 as a novel potential biomarker for early NAFLD diagnosis, showing high accuracy in *PNPLA3* I148M variant carriers.

SAT-276

Point shear wave elastography by ElastPQ accurately stages hepatic fibrosis in patients with NAFLD: A prospective, multicentric study

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Background and aims: We face a global epidemic of non-alcoholic fatty liver disease (NAFLD). Vibration-controlled transient elastography (VCTE) represents an accurate non-invasive screening tool for significant fibrosis. Limited evidence for the clinical applicability of point shear wave elastography (pSWE) techniques in NAFLD available.

Method: In this prospective, multicentric study (Vienna, Pavia, Timisoara, Zagreb) we performed liver stiffness measurements (LSM) both by VCTE and by pSWE (ElastPQ®, Philips) in NAFLD patients. Paired LSM were assessed for Pearson correlation and Lin's concordance correlation coefficient (CCC). Diagnostic performance was assessed using VCTE as a reference standard and calculating the area under receiver operator characteristics curves (AUROC) for pSWE. Optimal cutoffs for significant fibrosis (≥ F2) and cirrhosis (F4) were evaluated based on the Youden index. Patients with VCTE = 75kPa were excluded for assessment of linear correlation and CCC.

Results: 280 paired measurements were obtained. While 216 meet the reliability criteria-defined as (VCTE IQR/Median ≤ 30% and ElastPQ IQR/Median ≤ 30%) OR (VCTE ≤ 7kPa AND ElastPQ ≤ 7kPa), n = 6 additional patients with ascites and VCTE = 75kPa but discordantly low (< 1kPa) or high (> 150kPa) ElastPQ results had to be excluded despite meeting reliability criteria.

Among a final cohort of n = 210 patients, median age (IQR) and BMI (IQR) were 59 (18) years and 28.9 (7.0) kg/m^2, respectively. Most patients were male (132, 62.9%), 51 (24.3%) patients had significant

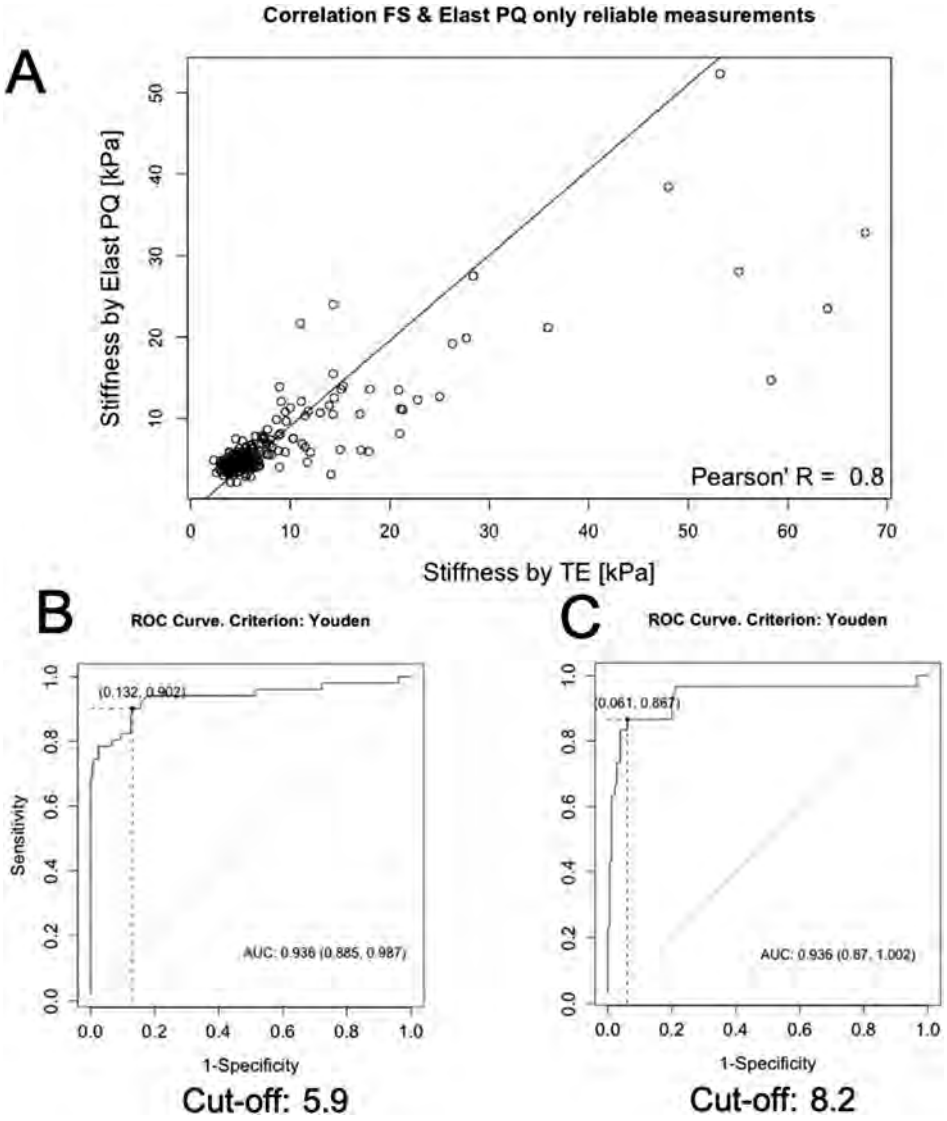

Figure 1: (abstract: SAT-276): A) Correlation of all reliable paired measurements. B) ROC Curve of optimal Youden cut-off for significant fibrosis. C) ROC Curve of optimal Youden cut-off for severe fibrosis

fibrosis (≥ F2, VCTE ≥ 8.5 kPa), while 30 (14.3%) had cirrhosis (F4, VTCE ≥ 12.5kPa). Overall the Pearson correlation between reliable measurements of VCTE and ElastPQ was r = 0.84. The overall CCC was 0.72. We determined an optimal ElastPQ cut-off for significant fibrosis at 6.0 kPa (≥ F2 AUROC 0.936, Se = 0.901, Sp = 0.869) and for cirrhosis at 8.2 kPa (F4 AUROC: 0.94, Se = 0.86, Sp = 0.94). Cutoffs for ruling-in NAFLD-F2 fibrosis and NAFLD-F4-cirrhosis were determined at > 7.5 kPa (PPV: 91%, Se = 0.784, Sp = 0.974,) and at > 10.1 (PPV: 0.78%, Se = 0.833, Sp = 0.956), respectively.

Conclusion: ElastPQ showed an excellent correlation and a high level of concordance with VCTE for staging fibrosis in NAFLD patients. While ElastPQ is very accurate in diagnosing fibrosis and cirrhosis, its concordance with VCTE in advanced liver disease, needs further investigation. Specific ElastPQ cut-offs for NAFLD-associated, significant fibrosis (≥ F2) and cirrhosis (F4) were determined at > 7.5 kPa and > 10.1 kPa, respectively.

SAT-277

Screening diabetic patients at risk for complications of non-alcoholic fatty liver disease: Prospective evaluation of national and international guideline recommendations

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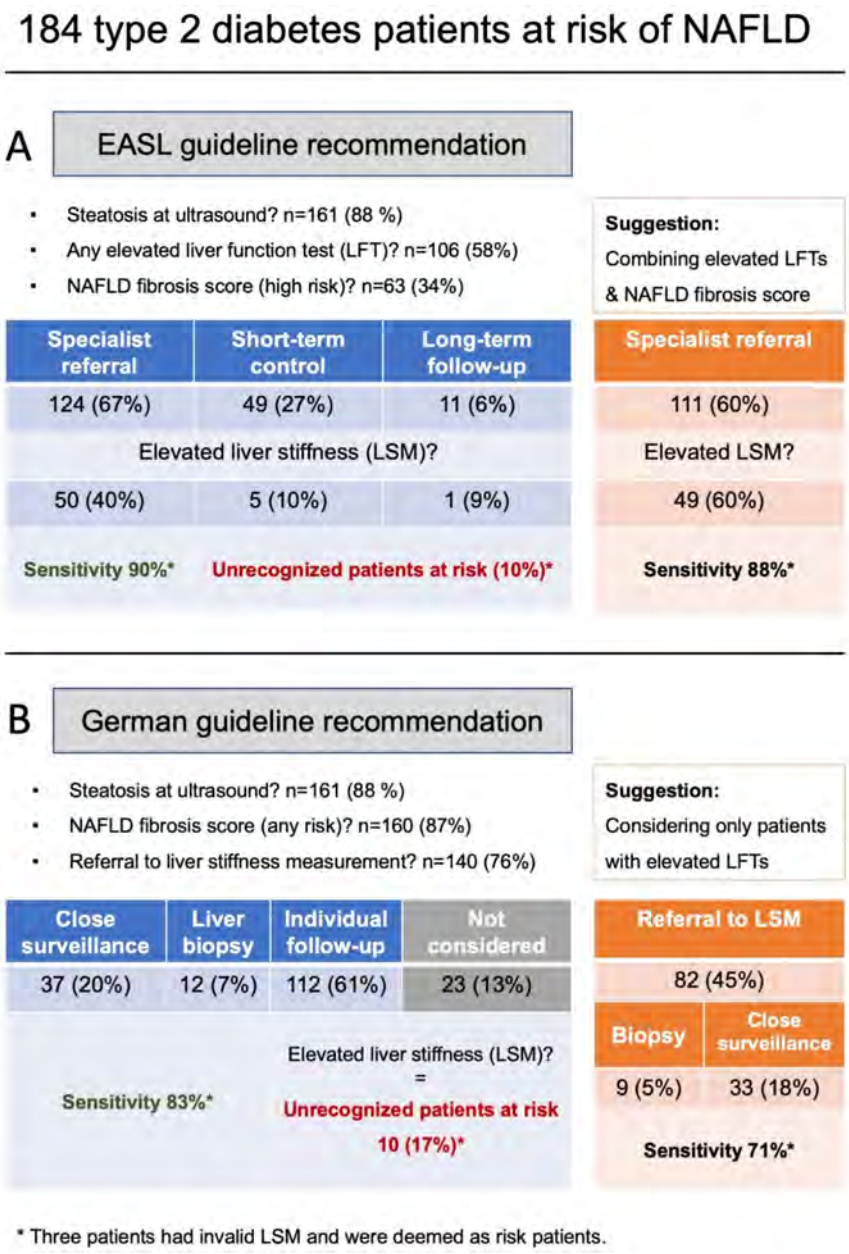

Figure: (abstract: SAT-277)

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver-related morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The high prevalence demands efficient screening strategies to identify patients with advanced liver fibrosis at high risk for complications. Non-invasive fibrosis markers such as liver stiffness measurement (LSM) and serum-based fibrosis scores can guide risk stratification and referral decisions and have recently been implemented in (inter)national guideline recommendations. However, the efficacy of these diagnostic pathways is a matter of ongoing debate.
Method: T2DM patients were invited for NAFLD screening at an academic liver center. Participants were thoroughly evaluated for presence and severity of liver disease including anthropometry, abdominal ultrasound, LSM with transient elastography (TE; M or XL probe as appropriate) and NAFLD fibrosis score (NFS). Patients were then assigned to risk groups according to the current recommendations of EASL-EASD-EASO (E-E-E) and German (DGVS) NAFLD guidelines. Elevated LSM (cut-off 7.9/7.2 kPa for M/XL probe) served as reference for fibrosis risk.
Results: 203 patients with T2DM were recruited, 19 were excluded due to relevant alcohol consumption. The remaining 184 patients (58% female, median age 65 years) showed a high prevalence of obesity (median BMI 31.6 kg/m²: 28% overweight, 60% obese). Hepatic steatosis was observed in 161 (88%) cases. 56 (30%) had elevated LSM.
E-E-E and DGVS recommendations resulted in a high referral rate for hepatological assessment (67% and 76%, respectively; Figure A and B). The E-E-E algorithm identified 90% of cases with increased LSM. DGVS recommendations (sensitivity 83%) did not consider 23 patients without steatosis, of whom 9 (39%) had increased LSM. Additional NFS (E-E-E) or liver function tests (DGVS) based decision steps reduced referral rate (45%) and sensitivity (71%) of the DGVS recommendation, but only moderately influenced the E-E-E efficacy.
Conclusion: Guideline based NAFLD screening of T2DM patients revealed a high prevalence of fibrosis risk and excluded only a minority of patients from referral for further hepatologic assessment. The E-E-E algorithm had a higher sensitivity and a lower referral rate compared to the German DGVS recommendations. Comprehensive NAFLD screening requires optimized risk assessment strategies and reimbursement of non-invasive fibrosis tests.

SAT-278

Integrated analysis of dna methylation and mRNA expression to identify mechanisms of non-alcoholic steatohepatitis

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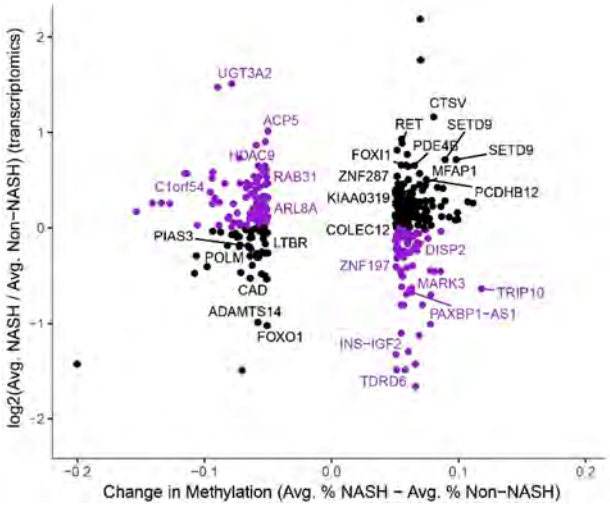
Background and aims: Non-alcoholic steatohepatitis (NASH) in patients with obesity-associated metabolic disorders is a serious and underdiagnosed condition. The lack of non-invasive markers for its diagnosis and follow-up hampers clinical practice and development of novel treatments. Diseased livers undergo abnormal gene expression, and epigenetic mechanisms of gene regulation play a key role in establishing disease gene programs. DNA methylation changes at cytosine residues followed by guanine (CpGs) reprogram the genome at the structural level, coordinating with transcription factors to alter gene expression on a global scale (promoter methylation increase is associated with decreased transcription and vice versa). To identify potential therapeutic strategies for NASH, and to better understand mechanisms of disease, we measured DNA methylation changes directly involved in the gene reprograming that takes place in obese NASH patients.
Method: Patients undergoing laparoscopic sleeve gastrectomy were recruited as a model of obesity-induced NASH in an observational and cross-sectional study. Patient liver samples underwent histological evaluation and clinical stratification based on NASH score. Based on this classification, we systematically measured liver DNA methylation and mRNA expression profiles in NASH and Non-NASH patients (n = 16 each) using the Illumina Infinium Human MethylationEPIC BeadChip and Agilent SurePrint G3 Human Gene Expression 8×60 K v2 platform, respectively.
Results: We identified 2508 differentially methylated CpG sites between NASH and Non-NASH patients, 1640 of which lie within genes. Of those within promoters (TSS1500 or TSS200), we identified 13 genes with significant ($p < 0.05$) negative correlation between promoter DNA methylation and mRNA expression. These genes are involved in processes such as RET signalling (INS-IGF2, MARK3, TRIP10), immunity (DISP2, ARL8A, ZNF197) and gene regulation (HDAC9, RAB31, TDRD6).



Conclusion: Our results reveal 13 genes for stratification of NASH status in obese patients. The detected CpGs in the promoters of these genes are undergoing parallel mechanistic investigation in a separate validation cohort. Manipulation of these CpGs may serve as a locus-specific therapeutic strategy in obese NASH patients. In addition to CpG editing at specific loci, mechanistic study of our candidate genes may open avenues for epigenetic intervention at a broader level.

SAT-279

Comparison of different and new types of non-invasive fibrosis tests in NAFLD

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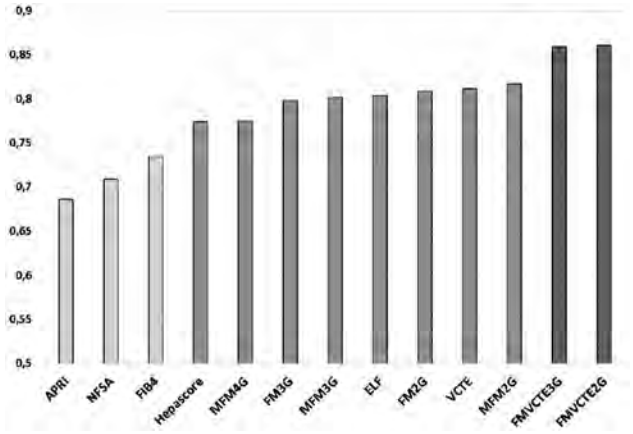
Background and aims: Classical blood tests are monotargeted (usually significant fibrosis) and include indirect (simple tests) and/or direct fibrosis markers (specialized tests). Recently, it has been

shown that non-invasive fibrosis tests developed for chronic viral hepatitis had good accuracy in NAFLD. New tests, like multi-targeted blood test (Hepatol Commun 2018;2:455) or test combining blood markers and liver stiffness measurement (LSM), have shown excellent accuracy in chronic viral hepatis. Thus, our aim was to compare all these types of tests in NAFLD.

Method: 410 patients with NAFLD were included in 2 centers. Their characteristics were: age: 56.5 ± 12.1 yrs, 61.5% males, diabetes: 52.9%, BMI: 32.4 ± 5.7 kg/m², liver biopsy: 29 ± 11 mm, NAS: 3.7 ± 1.6, F Kleiner stages: 0: 8.8%, 1: 22.2%, 2: 27.8%, 3:34.1%, 4: 7.1%. 13 tests were included in 4 categories: specialized blood tests (including direct fibrosis markers): Hepascore (HS), ELF, single-targeted FibroMeterV2G (FM2G including A2M and hyaluronate), FM3G, multi-targeted FM2G (MFM2G), MFM3G (without hyaluronate); LSM by VCTE (Fibroscan); combined tests: FMVCTE2G, FMVCTE3G; simple blood tests: APRI, Fib4, NFSA, MFM4G (multi-targeted FibroMeter without hyaluronate and A2M). Main outcome was advanced fibrosis (F3 + 4).

Results: Spearman's correlation coefficient between tests and Kleiner F ranged from 0.347 (APRI) to 0.672 (FMVCTE2G). AUROcs for advanced fibrosis were by growing order (Figure): APRI: 0.686, NFSA: 0.709, Fib4: 0.735, HS: 0.774, MFM4G: 0.775, FM3G: 0.798, MFM3G: 0.802, ELF: 0.804, FM2G: 0.809, VCTE: 0.812, MFM2G: 0.817, FMVCTE3G: 0.859, FMVCTE2G: 0.861. According to significant differences (by Delong test), tests were merged in 3 sets. 1/Simple blood tests: most (APRI, Fib4, NFSA) were significantly inferior to the 2nd set (except Fib4 vs HS). 2/Direct tests (blood tests and VCTE) + MFM4G; VCTE was not significantly different from other direct blood tests; MFM2G was the only test significantly superior to some other direct blood tests (HS, FM3G). 3/Combined tests: both FMVCTE were the only tests significantly superior to other tests; FMVCTE3G was not significantly different from FMVCTE2G (p = 0.219). We calculated test zones with 90% sensitivity or specificity for advanced fibrosis with grey zone between them. For example, grey zone was reduced from 56.1% for NFSA to 30.0% for FMVCTE2G which was significantly lower than in other tests (p < 0.001, except for FMVCTE3G). AUROCs for cirrhosis ranged from APRI: 0.703 to FMVCTE2G: 0.923.



Conclusion: A multitargeted simple blood test (MFM4G) is as accurate as a monotargeted direct blood test. Among direct blood tests, the most accurate was the multitargeted test MFM2G. Finally, combined blood-elastography tests outperform all other non-invasive fibrosis tests in NAFLD.

SAT-280

Comparison of CAP, MRI-PDFF, Steatotest, FLI and HSI performances for diagnosing NAFLD and NASH in morbidly obese patients undergoing bariatric surgery

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Background and aims: Non-invasive Methods for diagnosing NAFLD and NASH have not been well studied in morbidly obese patients. The aim of the present study was to compare prospectively the performance of MRI-PDFF, CAP, Steatotest (ST), hepatic steatosis index (HSI) and fatty liver index (FLI) for diagnosing NAFLD (steatosis > 5%), grading steatosis and detecting non-alcoholic steatohepatitis (NASH) in morbidly obese patients undergoing bariatric surgery.

Method: Liver biopsy (central reading by PB) was used as reference for steatosis grading (absent, mild > 5%, moderate > 33%, and severe > 66%) and NASH diagnosis (FLIP algorithm). MRI-proton density fat fraction (PDFF) and T2* relaxation rate were measured in an open-bore, vertical field 1.0 T scanner. The controlled attenuation parameter (CAP) was measured using transient elastography (TE, FibroScan, Echosens, France), using the XL probe. Diagnostic performances were measured using area under ROC curve (AUC) and compared using the DeLong Methods.

Results: One hundred and fifty two patients underwent liver biopsy of whom 128 out of 130 had successful MRI (failure rate: 1.5%) and 112 out of 142 had successful CAP and TE (failure rate: 21%; TE vs MRI failure rates p < 0.0001). Finally, 97 patients (mean age 41 ± 10 yrs, female gender 86%, BMI 44.4 ± 5.4) had all tests without fail and available. Histology was as followed: steatosis absent 23; > 5%: 21; > 33% 25; > 66% 28; NASH 31%. Fibrosis: F0 48%; F1 40%; F2 10%; F3 2%. Comparative performances of the 5 Methods are shown in Table 1. MRI-PDFF had significantly better diagnostic accuracy than CAP for moderate (p < 0.003) and severe steatosis (p < 0.002) and NASH (p < 0.006), but not for mild steatosis. MRI-PDFF also outperformed the three biological scores for mild and moderate steatosis. Regarding severe steatosis, MRI-PDFF performed better than HSI and FLI but not better than ST. CAP performance did not differ from those of biological scores.

AUC (95% CI)	MRI-PDFF	CAP	SteatoTest	HSI	FLI
NAFLD (S > 5%)	0.97 (0.94-1.00)	0.82 (0.70-0.94)	0.77 (0.66-0.88)	0.74 (0.62-0.85)	0.74 (0.63-0.86)
S > 33%	0.97 (0.94-1.00)	0.78 (0.69-0.88)	0.77 (0.68-0.86)	0.72 (0.61-0.83)	0.68 (0.57-0.79)
S > 66%	0.93 (0.88-0.98)	0.75 (0.65-0.85)	0.81 (0.72-0.90)	0.72 (0.62-0.82)	0.70 (0.60-0.81)
NASH	0.82 (0.70-0.90)	0.68 (0.57-0.79)	NA	NA	NA

Conclusion: In morbidly obese patients undergoing bariatric surgery, MRI-PDFF is an accurate diagnostic method for grading steatosis and detecting NASH. CAP has performance similar to that of MRI-PDFF for

detecting mild steatosis and could be used as a first-line diagnostic Method for the diagnosis of NAFLD in these patients.

SAT-281

Protease activity sensors for non-invasive monitoring of NASH

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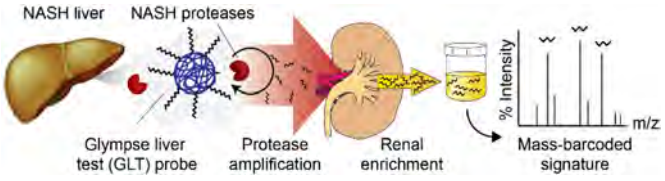
Background and aims: NASH diagnosis is limited by a lack of validated, non-invasive tests. We have developed the Glympse Bio Liver Test (GLT), a multiplexed, injectable diagnostic of protease activity sensors that specifically detects the activity of proteases dysregulated in human fibrosis and NASH to monitor disease progression and regression.
Method: Protease expression was analyzed in liver biopsies from patients undergoing bariatric surgery (78 healthy, 90 NAFL, 144 NASH: 29 F0, 62 F1, 34 F2, 13 F3, 6 F4) using NanoString technology at the Massachusetts Institute of Technology. Peptides and protease sensors were synthesized by solid-phase peptide synthesis. NASH and NAFL were modeled using a choline-deficient high fat diet (CDAHFD) or a high fat diet (HFD) model, respectively, in C57BL/6 mice. Protease sensors were injected retro-orbitally; urine was collected 60-120 min post-injection and analysed by tandem mass spectrometry.
Results: We identified a specific liver protease signature that was upregulated in human NASH (or NASH-associated proteases), from which we selected a subset of 12 proteases in F2-4 (n = 53) vs F0-1 (n = 302) patients. These proteases are linked to relevant biological pathways in the disease (lipogenesis, inflammation and fibrosis) and individual proteases classified F2-4 from F0-1 disease with area under the receiver-operating characteristic curve (AUC) of up to 0.89 (median = 0.62); 12 NASH-associated proteases combined classified disease with AUC = 1.0/0.91. We next designed and synthesized a 19-member peptide substrate probe library to optimally detect the activity of NASH-associated proteases: the GLT. When testing GLT in a pre-clinical model of NASH (with 80% homology in protease signature with humans), we efficiently differentiated healthy (n = 87) or HFD mice (n = 23) from CDAHFD mice (n = 72) with training/validation AUC = 1.00/0.97. Also, GLT accurately identified regressing disease (n = 15) from stable/progressing NASH (n = 15) in mice by urinary fragment accumulation with training/validation AUC = 1.0/0.98. Finally, GLT performed consistently accurate measurements regardless of the circadian cycle or feeding/hydration status of the animals with training/validation AUC greater than 0.86/0.93.



Conclusion: GLT is an exogenously administered cocktail of multiplexed protease sensors that measures the activity of proteases in fibrosis and NASH and monitored NASH progression and regression *in vivo* with marked diagnostic accuracy.

SAT-282

Decrease in HbA1c accounts for the rapid decline in the measurement of liver stiffness by transient elastography in diabetic patients

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Background and aims: Transient elastography (TE) is a reliable technique to estimate the fibrosis of the liver. However, it is intriguing that the measurements of liver stiffness (LS) may change over a short time period in patients with NAFLD. It can not be explained by an improvement in liver fibrosis. We aimed to determine the related parameters with the change of the measurements of LS by TE in diabetic patients over a 3 months period.
Method: Consecutively applied 200 diabetic patients who had been followed up in the outpatient clinic were invited to participate in the study. A hundred and seventeen patients signed the informed consent for the study. The patients with other liver diseases and those who consume alcohol > 20 g/day were excluded. Basal demographic, anthropometric data were recorded and liver biochemistry, CBC, HBA1c, blood insulin level were tested. LS was measured with Fibroscan®, Echosense, France. In accordance with previous studies, it was accepted that, F0 < 5.9 kPa, F1: 5.9-6.5, F2: 6.6-9.7, F3: 9.8-17.4, F4 ≥ 17.5. F3 and F4 were considered as advanced fibrosis. Abdominal ultrasound was used for detection of fatty liver. Anthropometric measurements, blood tests and LS were repeated 3 months later. Associations between basal parameters and LS were investigated. The related changes with the LS alterations were explored.
Results: Of 117 patients with DM, 68 were female, 49 male, mean age was 56 ± 10, mean duration of the illness was 9.2 ± 7.8 years, hypertension diagnosed 45%, peripheral neuropathy 15%. Fatty liver was detected in 80 patients (68%); grade 1: 31%, grade 2: 31%, grade 3: 7%. Metformin was used in 107, insulin in 52 patients. 61 patients took second or third antidiabetic medications. Mean BMI was 30.3 ± 5.3 kg/m^2, HbA1c: 7.7 ± 2.1%, LS: 7.2 ± 6.2 kPa. Among the basal parameters, age, BMI, waist circumference, AST, ALT, GGT, HbA1c, grades of the fatty liver, and insulin use were related to advanced fibrosis. In multivariate logistic regression analysis, BMI, AST, and GGT were found to be related to advanced fibrosis. A hundred patients came to the third-month visit. In these patients, LS decreased from 7.2 ± 6.2 to 6.6 ± 6.2 kPa (p = 0.003). Related parameters with LS decrease or increase at the third month were changes in GGT, ALP, fasted and postprandial blood sugar, and HbA1c levels. In multivariate analysis, the HbA1c change was found to be the single parameter which was related to LS change.
Conclusion: LS may significantly change within a short time in diabetic patients. LS reduction was associated with a better regulation of diabetes mellitus, but not associated with weight loss or reduction in transaminases. As the decline in glycated hemoglobin was related to the decline in LS, it may be speculated that glycated tissue proteins may be related to the liver stiffness.

SAT-283

Plasma acylcarnitines are biomarkers of magnetic resonance imaging-proton density fat fraction response in NASH patients treated with the ACC inhibitor GS-0976

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Background and aims: MRI-PDFF is a reliable imaging modality for assessment of liver fat content and treatment response in NASH studies. However, due to its limited feasibility in clinical practice, simpler non-invasive biomarkers are needed to monitor treatment

response. In this study, we evaluated a novel, targeted panel of plasma AC, markers of fatty acid oxidation, as biomarkers of MRI-PDFF response in a Phase 2 study of the liver-targeted ACC inhibitor GS-0976.

Method: Using fasted plasma samples (baseline [BL], week 1 [W1], W4, and W12) from non-cirrhotic NASH subjects treated with GS-0976 20 mg (n = 49) or placebo (n = 26) orally once daily for 12 weeks (NCT02856555), 24 AC species were quantified with a targeted, LC-MS/MS assay (Metabolon, Morrisville, NC, USA). Changes in AC concentrations were compared according to MRI-PDFF response (MRI-R), defined as a ≥ 30% relative reduction in liver fat content between BL and W12. An optimal AC panel was selected using the Generalized, Unbiased, Interaction Detection and Estimation method, and the AUROC and 95% CI for discrimination of MRI-R were estimated using logistic ridge regression and 100x cross-validation.

Results: BL AC levels were balanced between GS-0976 and placebo groups (except AC5:0, p = 0.02) and did not differ significantly between groups over 12 weeks. Relative changes from BL in AC levels between MRI-R and MRI-non-responders (MRI-NR) in the GS-0976 group were significantly different at W4 and W12 for AC4:0, 12:0, 12:1, 14:0, 14:1, and 16:1 (**Figure**, all p < 0.05). With the exception of AC4:0, these AC increased significantly from BL (p < 0.05) among MRI-NR treated with GS-0976. Correlation of relative change between BL and W12 for AC and MRI-PDFF in the GS-0976 group were highest for AC4:0, 14:0, 14:1, and 16:1 (r = 0.34-0.45; all p < 0.03). For the discrimination of MRI-R among GS-0976-treated patients, the highest AUROCs for individual AC were observed for AC4:0 (AUROC 0.73), 14:0 (0.75), 14:1 (0.73), and 16:1 (0.72) at W12; similar findings were observed at W4. Using multivariate analysis, an optimized panel including 4 AC was derived that demonstrated good discrimination for MRI-R among GS-0976-treated patients (AUROC at W12: 0.77 [95% CI, 0.73, 0.79]).

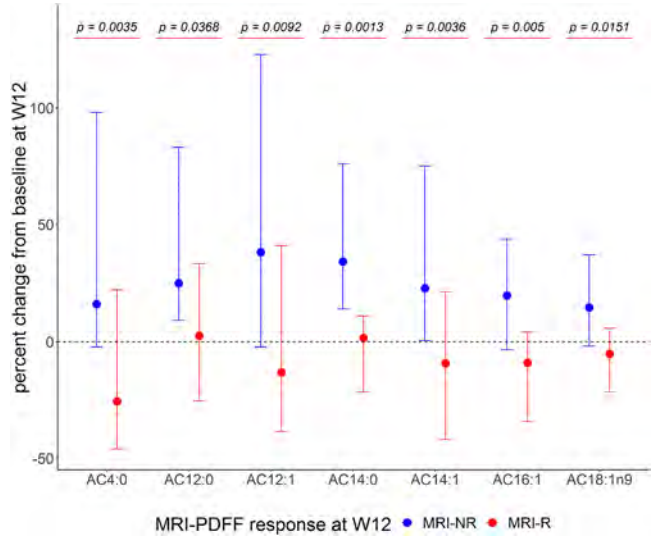

Figure: Relative (% median, IQR) changes from baseline to week 12 in acyl-carnitines among GS-0976-treated subjects according to MRI-PDFF response

Conclusion: Long-chain AC are promising early biomarkers of MRI-PDFF response to GS-0976 treatment in patients with NASH. These findings provide a mechanistic link between ACC inhibition with effects on liver fat content. This AC signature will be validated in future clinical studies of GS-0976 in NASH.

SAT-284

Diagnostic performance of transient elastography on liver fibrosis of patients with non-alcoholic fat hepatitis

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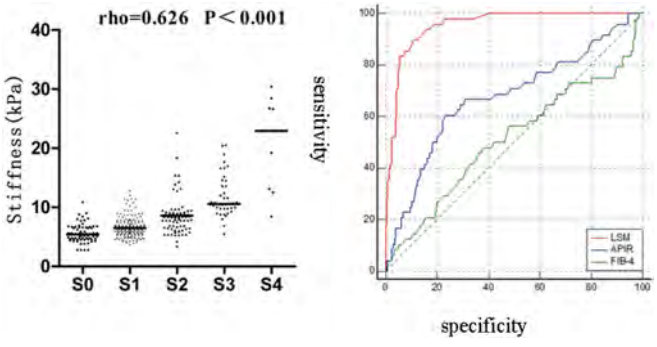
Background and aims: Non -alcoholic fatty liver disease (NAFLD) is an important global public health problem in the 21st century. In the long course of NAFLD, non-alcoholic fat hepatitis (NASH) is a necessary stage of liver cirrhosis in NAFLD. If not timely intervention, it will gradually develop to liver cirrhosis, even liver cancer. Many studies have found that the early effective intervention can effectively control and reverse liver fibrosis. So early diagnosis and correct evaluation is important. This study was to assess the diagnostic performance of transient elastography (TE) on liver fibrosis of patients with NASH.

Method: All patients with NASH were selected from January 2006 to April 2018, were enrolled in the study, and liver stiffness measurement (LSM) by TE was performed within 3 days before liver biopsy. Clinical parameters and the pathological features were analyzed retrospectively. Non-invasive models (APRI and FIB-4) were calculated based on their own formula. The correlations between these 3 non-invasive approaches and liver fibrosis stages were analyzed with Spearman method, the diagnostic performances were analyzed with receiver operating characteristic (ROC).

Results: Of the 470 NASH patients, 346 were male (73.6%). The degree of hepatic fibrosis was detected by liver puncture. The number of patients with S0, S1, S2, S2, S3, S4 was 73, 253, 96, 40, 8 cases respectively. The median value of LSM in each group was 5.4, 6.5, 8.6, 10.7, 22.9 kPa, respectively. Spearman analysis showed that LSM and APRI was positively correlated with the stages of liver fibrosis, and the correlation coefficient were 0.626 and 0.342 (p < 0.001), There was no statistically significant correlation with FIB-4 (rho = -0.120, P > 0.05). ROC analysis showed that the diagnostic value of LSM for different stages of hepatic fibrosis was significantly higher than that of APRI. The AUROC of hepatic fibrosis S1, S2, S3 and S4 in LSM was 0.784, 0.857, 0.953 and 0.986 respectively. The corresponding optimal diagnostic bounds were 5.6, 7.7, 8.8 and 12.3 kPa, respectively.



Conclusion: The value of LSM is positively correlated with hepatic fibrosis stage of NASH and TE is a useful reference for diagnosing the degree of hepatic fibrosis in NASN.

SAT-285

Fibroscan-based score for detection of active nash and significant fibrosis is better than fib-4 in 361 chronic hepatitis B patients with non-alcoholic fatty liver disease

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Background and aims: Chronic Hepatitis B (CHB) combined with Non-alcoholic Fatty Liver Disease (NAFLD) has become a hot research topic in recent years. Our previous study found that more CHB patients combined with Non-alcoholic steatohepatitis (NASH) showed severe fibrosis than those without NASH. Hence, it is particularly important to identify patients who are at high risk of significant disease in CHB-NAFLD patients. So we conducted this study to find a useful non-invasive marker for significant disease in CHB-NAFLD patients.
Method: Naïve-treatment CHB-NAFLD patients performed liver biopsy from April 2013 to October 2017 were enrolled in this study. The demographic, clinical, and pathological data were collected and analyzed to find out the risk factors for significant disease in CHB-NAFLD patients. Significant disease was defined as activity score (NAS) ≥ 4 and Fibrosis stage ≥ 2. Univariate analysis and Logistical regression analysis were used to find risk factors for significant disease. Area under receiver-operator curve (AUC) were used to determine the diagnostic accuracy of the non-invasive marker for significant disease.
Results: A total of 361 CHB-NAFLD patients were enrolled in this study and 139 (38.5%) of them were CHB-NASH patients. The univariate analysis showed that there was no significant difference in gender, age, serum ALT level, HBeAg positive rate and HBV-DNA level between the CHB-NAFLD patients with significant disease (NAS ≥ 4 + F ≥ 2) and those without significant disease. However, the CHB-NAFLD patients with significant disease had higher level of LSM, CAP, BMI, TG, GGT, ALP, glucose and IgG. Furthermore, the logistical regression analysis revealed that LSM and IgG were independent factors for significant disease in CHB-NAFLD patients. Therefore, a score model (Fibroscan-based score) based on the above two factors was established. This score model for active NASH and significant fibrosis resulted in good AUC (AUC = 0.841), which is better than that of FIB-4 (AUC = 0.623, P < 0.05).
Conclusion: The Fibroscan-based score could be used as a useful non-invasive marker for significant disease (NAS ≥ 4 + F ≥ 2) in CHB-NAFLD patients, who shoud be performed liver biopsy.

SAT-286
Application of guidelines for fatty liver in two prospective cohorts of human immunodeficiency virus positive patients

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Background and aims: People living with Human Immunodeficiency Virus (HIV) are at higher risk of non-alcoholic fatty liver disease (NAFLD) than the general population. Recent guidelines from the European Association for the Study of the Liver recommend a diagnostic algorithm to identify HIV-negative NAFLD patients at risk of progressive liver disease. This stepwise algorithm is based on non-invasive screening for NAFLD, followed by fibrosis assessment by the biomarker FIB-4 and ALT. We aimed to apply this algorithm to HIV mono-infected patients.
Method: This was a cross-sectional analysis of two prospective screening programs for NAFLD in HIV-infected persons: the LIVEr disease in HIV (LIVEHIV) Cohort and the Modena HIV Metabolic Clinic (MHMC) Cohort. HIV-infected adults without significant alcohol intake or viral hepatitis coinfection were included. NAFLD was diagnosed in the LIVEHIV Cohort if controlled attenuation parameter (CAP) was ≥ 248 dB/m; and in the MHMC Cohort if liver/spleen HU ratio on abdominal CT was < 1.1. In both cohorts, significant liver fibrosis was defined as FIB-4 > 2.67. Patients with either elevated ALT or NAFLD with significant liver fibrosis were considered at risk for progressive liver disease requiring specialist referral for hepatology consultation. Logistic regression analysis was used to identify predictors of progressive liver disease.
Results: We included 1.228 mono-infected patients (mean age 50, 73% males, time since HIV diagnosis 16 years, CD4 634 cells/mm3; 30% with BMI > 25 kg/m^2). Figure depicts the flowchart from the EASL guidelines applied to included patients. Overall, 31.8% had NAFLD and 25.2% were at risk of progressive liver disease. Among patients without NAFLD, 18.4% had elevated ALT and were considered at risk of progressive liver disease. After adjusting for BMI, hypertension, CD4 cell count and exposure to protease inhibitors, male sex (aOR 1.57, 95% CI 1.08-2.28), diabetes (aOR 1.52, 95% CI 1.04-2.24) and duration of HIV infection (aOR 1.26, 95% CI 1.02-1.58) were independent predictors of risk of progressive liver disease requiring specialist referral, while Black ethnicity was protective (aOR 0.22, 95% CI 0.09-0.52).
Conclusion: According to current NAFLD guidelines for HIV negative patients, a significant proportion of HIV mono-infected patients is at risk of progressive liver disease, requiring dedicated monitoring and referral for specialized care in hepatology.

SAT-287
A novel non-invasive index based on extracellular matrix markers can identify NAFLD patients with active disease and significant fibrosis: analysis of the CENTAUR study

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a burgeoning problem for healthcare providers. Most NAFLD patients

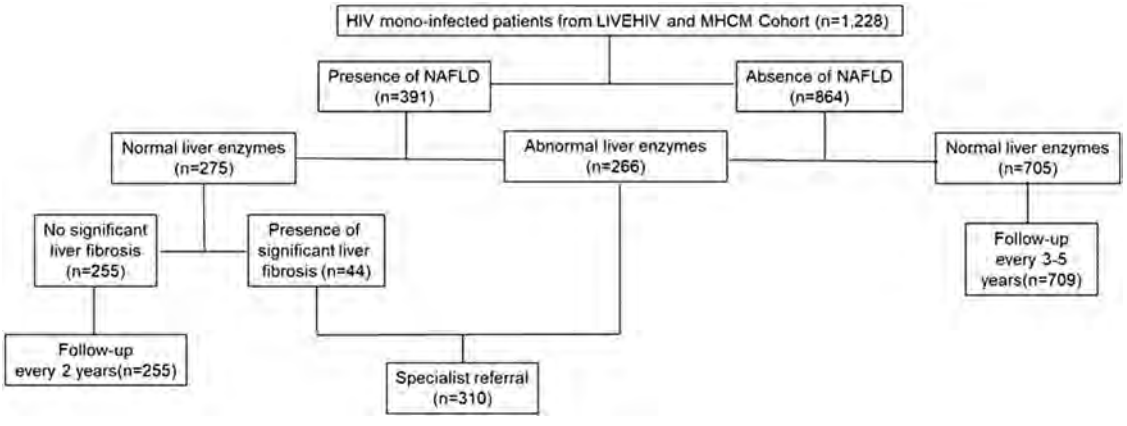

Figure: (abstract: SAT-286)

remain stable; however, those with the progressive phenotype, non-alcoholic steatohepatitis (NASH), are at a greater risk of progressing towards cirrhosis. The early identification of at-risk patients is paramount for timely intervention. We explored the ability of a new non-invasive algorithm based on serological collagen formation markers (PRO-C3 and PRO-C6) to identify subjects with NAFLD and highly active disease; NAFLD Activity Score (NAS) ≥ 5 and significant (F ≥ 2) or advanced fibrosis stage (F ≥ 3) per NASH Clinical Research Network (CRN) scoring in a post-hoc analysis of the Phase 2 CENTAUR study (NCT02217475). PRO-C3, a fibrogenesis marker, is associated with liver fibrosis severity and progression of disease. Endotrophin, a type VI collagen propeptide fragment is quantified by PRO-C6, is associated with metabolic dysfunction and insulin resistance.

Method: CENTAUR evaluated the efficacy and safety of cenicriviroc in adults with NASH (NAS ≥ 4 with ≥ 1 in each component of NAS) and liver fibrosis (NASH CRN Stages 1-3). PRO-C3 and PRO-C6 were assessed by ELISA in EDTA plasma collected at screening. A novel algorithm, developed by multivariate modelling, was applied to identify subjects with NAS ≥ 5 and F ≥ 2 or subjects with NAS ≥ 5 and F ≥ 3. ROC analysis was performed as a measure of diagnostic accuracy; optimal cut-off values for detection of subjects with NAS ≥ 5 and F ≥ 2/F ≥ 3 were identified. Diagnostic performance for the cut-offs (sensitivity, specificity, negative and positive predictive value) was determined.

Results: 406 NAFLD patients with non-missing values were included, 76% had NASH, 55% had F ≥ 2 and 32% had F ≥ 3. The non-invasive-NAS index (NI-NAS) included PRO-C3, PRO-C6, fasting blood glucose, AST and haemoglobin. The AUROC for the detection of subjects with NAS ≥ 5 and F ≥ 2 was 0.77 [0.73-0.82] and the AUROC for NAS ≥ 5 and F ≥ 3 was 0.77 [0.72-0.82]. The optimal cut-off for the identification of subjects with NAS ≥ 5 and F ≥ 2 was 4.89, sensitivity 68% and specificity 77% (PPV 65%, NPV 79%). The optimal cut-off for the identification of subjects with NAS ≥ 5 and F ≥ 3 was 4.95, sensitivity 74% and specificity 72% (PPV 45%, NPV 90%).

Conclusion: NI-NAS is a novel non-invasive serologic score that can aid in identification of NAFLD patients with highly active disease (NAS ≥ 5) and significant fibrosis (F ≥ 2) and patients with NAS ≥ 5 and F ≥ 3.

SAT-288

Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease

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Background and aims: In Non-Alcoholic Fatty Liver Disease (NAFLD), fibrosis is the strongest prognostic factor and can be assessed by non-invasive methods. We evaluated the ability of Liver Stiffness Measurement (LSM) to predict overall survival and liver, cardiovascular and oncologic complications.

Method: We prospectively collected data on 2251 consecutive NAFLD patients (mean age 59 years, male 53%, mean BMI 28 kg/m²) in two centres of non-invasive diagnosis of liver fibrosis. At inclusion all patients had LSM, clinical and biological evaluation. During follow-up, we collected cardiovascular events, cancers, liver complications, liver transplantation, or death. Overall survival was the main end point used to assess the prognostic value of LSM. Survival curves according to LSM were first performed using Kaplan-Meier method for the primary end point, and Aalen-Johansen method for secondary

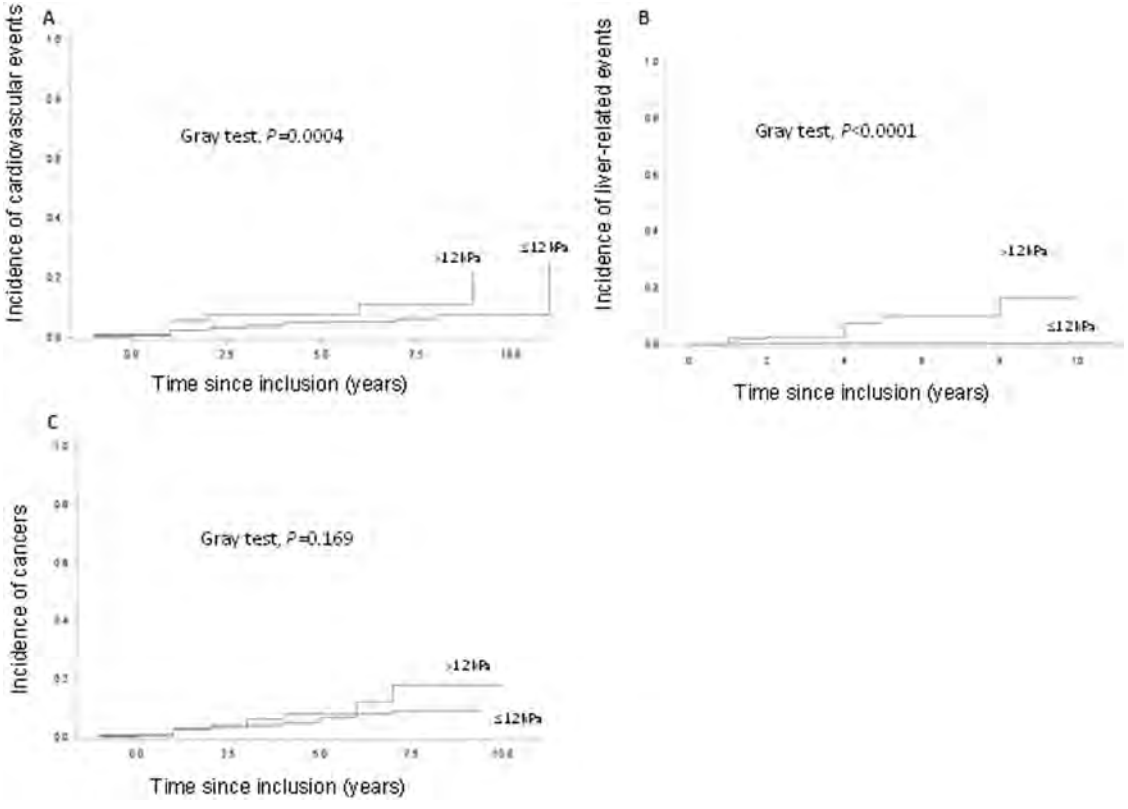

Figure: (abstract: SAT-288): Cumulative incidence of cardiovascular events (A), liver-related events (B), and cancers (C) according to LSM baseline value, taking into account competitive risks by Aalen-Johansen Method (n = 2245).

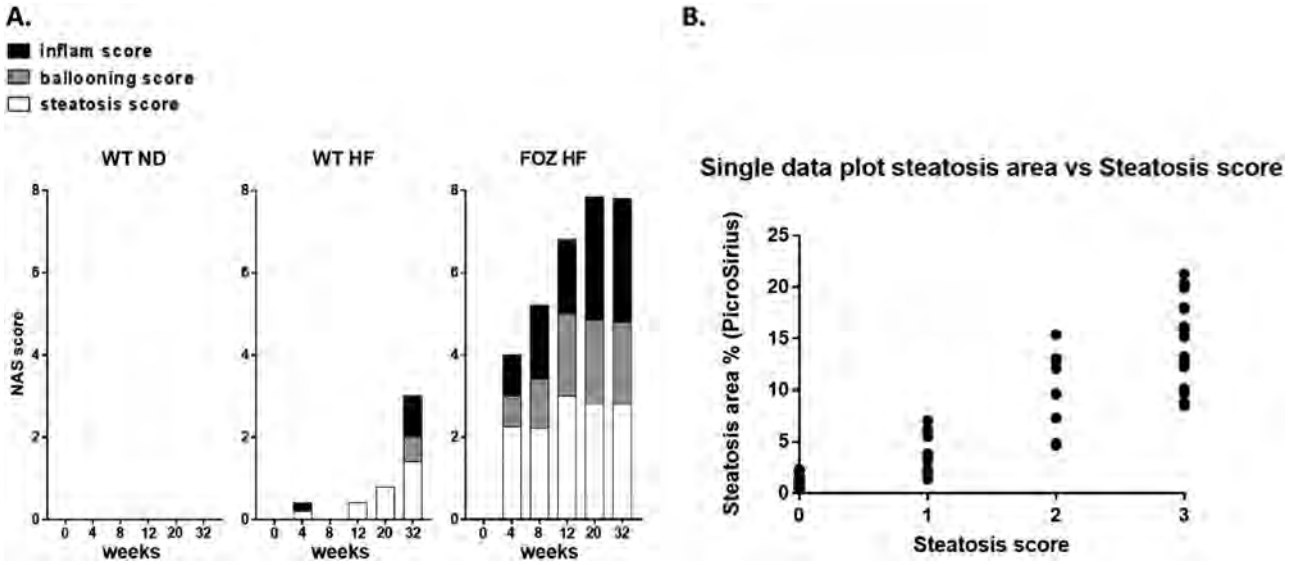

Figure: (abstract: SAT-289)

outcomes to take into account competitive risks. In a second step, a Cox proportional hazard model analysis was done to identify independent predictors of overall survival.

Results: Median follow-up was 27 months [IQR: 25-38]. 55 patients died and three patients had liver transplantation. Twenty-one patients (0.9%) had a liver event, 142 (6.3%) developed cancer (excluding HCC) and 151 (6.7%) had a cardiovascular event during follow-up. Overall survival significantly decreased as baseline LSM increased. Overall, 21 patients (0.9%) had a liver event, 142 (6.3%) developed cancer (excluding HCC) and 151 (6.7%) had a cardiovascular event during follow-up. By multivariable analysis, independent predictors of overall survival were: baseline LSM (adjusted HR (aHR) = 2.85 [1.65-4.92], $P = 0.0002$), age (aHR = 1.11 [1.08-1.13], $P < 0.0001$) and male sex (aHR = 2.05 [1.17-3.57], $P = 0.012$). Patients with elevated LSM presented significantly more cardiovascular and liver events but not other cancers. No cut-off below which HCC did not occur could be identified, but the incidence of HCC increased with baseline LSM (< 12 kPa: 0.32%; 12-18 kPa: 0.58%; 18-38 kPa 9.26% and > 38 kPa: 13.3%).

Conclusion: The prediction of survival, cardiovascular and liver complications should be based on initial evaluation of LSM. Thus, LSM might be a precious tool to decide of a medical treatment of NAFLD, and needs to be validated in clinical trials.

SAT-289

Follow-up of NAFLD/NASH progression using an automated histological image analysis

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Background and aims: Pathologists assess NASH severity using semiquantitative scoring methods, such as NAS or SAF, which are linked to an inherent high variability. Histological scoring assessment provides discrete and not continuous values thus small variations may not translate into a different score. Here we performed a numerical quantification of NASH features, fully automatic, which is of particular interest for accurately monitoring evolution or regression upon therapy.

Method: We followed high fat diet fed foz/foz mice (FOZ HF) known to develop progressive NASH over 32 weeks. We compared them to chow-fed (Ctl) and high fat diet-fed wild type mice (WT HF) (n = 5/group/time point). Automated software image analysis was performed on digital images (20x) from entire liver sections stained with HandE or picrosirius red to quantify steatosis and fibrosis, and on serial F4/80 immunolabelled sections for quantifying inflammation. Data obtained from numerical analysis were compared with NAS score, biochemical quantification and gene expression.

Results: Ctl had normal liver histology at all time-points and WT HF mild steatosis (score 2 at wk32) without inflammation. FOZ HF exhibited macrovesicular steatosis stage 2 to 3 as from wk 4. Inflammation (mean score 1) and ballooning (mean score 1) were present at wk 4 and increased in severity with time such as NAS score was = 5 at wk 8, = 8 at wk 20. Automated assessment of macrovesicular area increased according to histological steatosis score (fig. B) and was strongly correlated with liver lipid content ($r_s = 0.83$, $p < 0.0001$). At each steatosis stage there was a large variation in the total lipid content evidenced by biochemical and macrovesicular area assessment (Fig. B).

The number of inflammatory foci (but not the inflammation score) and the surface of F4/80 crown-like structures, formed by active macrophages, positively correlated with F4/80 mRNA expression ($r_s = 0.68$, $p < 00001$ and $r_s = 0.6$, $p < 0.0001$, respectively). Ctl and WT HF had no fibrosis (sirius red positive area < 1%). In FOZ HF, the fibrogenic gene program was up regulated as from wk 8. A significant sirius red collagen deposits was visible at wk 20 (1.72 ± 0.12%) increasing at wk 32 (3.88 ± 0.29%).

Conclusion: Software-based fully-automated NASH represents a promising accurate and reliable quantitative analysis to rapidly monitor disease activity with high-throughput in large pre-clinical studies.

SAT-290

Association of liver inflammation and fibrosis score with non-invasive biomarkers in non-alcoholic fatty liver disease: Preliminary results from the MAST4HEALTH study

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Background and aims: LiverMultiScan is a non-invasive diagnostic tool which uses multiparametric Magnetic Resonance Imaging to characterize liver tissue. It provides accurate measurements of % Proton Density Fat Fraction (PDFF) and tissue T1-relaxation time, corrected for liver iron (cT1), standardized as the Liver Inflammation and Fibrosis score (LIF). The aim herein was to elucidate the relationship between LiverMultiScan parameters and biochemical and anthropometric markers in a European NAFLD cohort recruited for the MAST4HEALTH study (http://www.mast4health.eu/en/).
Method: We recruited 110 overweight/obese patients (69% males) from three independent cohorts (Greece, Italy, Serbia). Serum lipids, liver enzymes, glucose, insulin and insulin resistance (HOMA-IR) were measured. Anthropometry was recorded. LIF and PDFF were calculated using LiverMultiScan. Our study group was stratified into 4 groups according to LIF (< 1, 1-1.99, 2-2.99, and ≥ 3) and differences between them were assessed. LIF was modeled via linear regression and PDFF via beta regression. Using a variable selection algorithm (*glmulti* R package), all candidate models for LIF and PDFF and the model-average importance of their predictors were assessed.
Results: Age, weight, BMI, HDL, LDL, triglycerides, glucose, ALT, PDFF and liver iron significantly differed between LIF subgroups. Weight, BMI, PDFF and ALT positively correlated with LIF (rho > 0.25; p < 0.01), while AST/ALT negatively correlated with LIF (rho < –0.25; p < 0.01). Based on multi-model inference, BMI (median = 33.4, IQR = 6.8) was the most important predictor for LIF (Figure1A), whereas BMI was the least relevant among the factors shaping PDFF. Instead, AST/ALT (median = 0.7, IQR = 0.3) and serum triglycerides were the factors most related to PDFF (Figure1B). BMI was the only predictor in the model best fitted for LIF (B = 0.04, p = 0.01). The best fitted model for PDFF incorporated triglycerides, glucose, AST/ALT (exp (B) = 1.003, 1.009, 0.396, respectively; p < 0.01) and distinguished patients according to treatment for hyperlipidemia.
Conclusion: In this preliminary survey conducted within the MAST4HEALTH project, the ratio AST/ALT and triglycerides levels were listed as the most important factors associated to PDFF. BMI was the most significant predictor of LIF, while showing least association with liver fat content. This striking contrast may be attributed to different patterns of fat deposition among the study participants.

SAT-291

Identifying NAFLD at the source: A novel approach to capturing non-alcoholic fatty liver disease in a diabetes practice

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Background and aims: Vibration Controlled Transient Elastography (VCTE) is a non-invasive, well validated, and highly reproducible

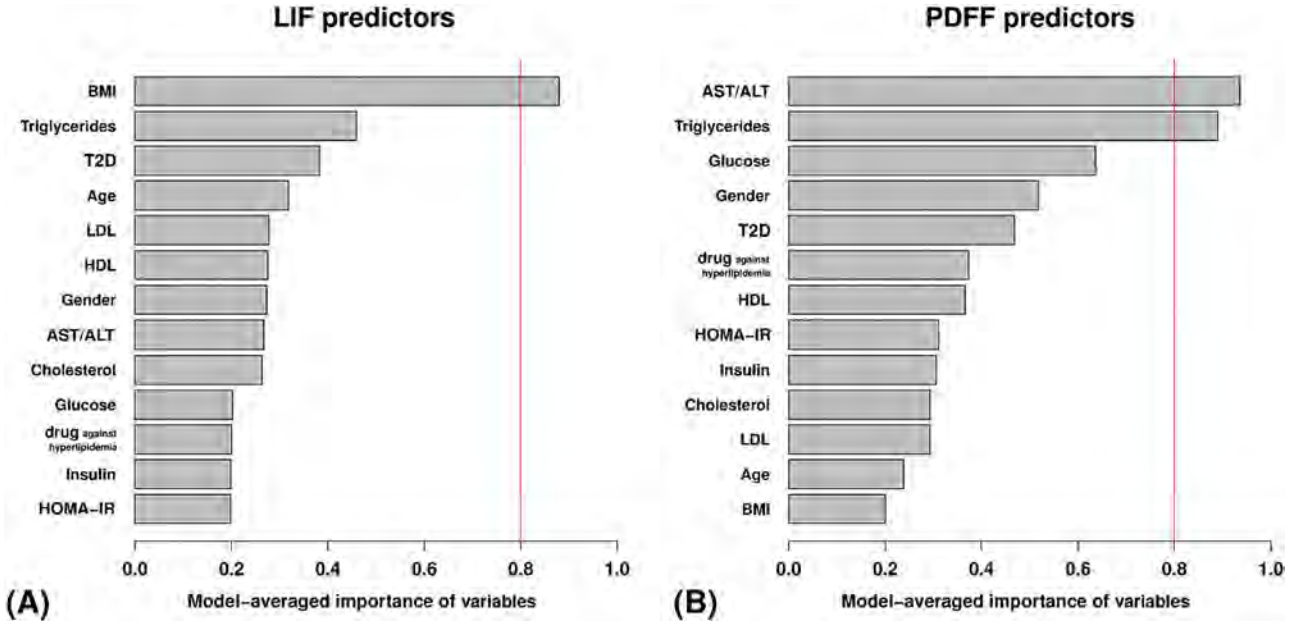
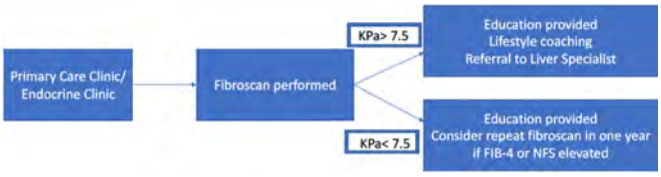


Figure: (abstract: SAT-290)

modality to diagnose NAFLD. Type 2 Diabetes (T2DM) is one of the leading risk factors for the development of NAFLD. Current guidelines recommend risk stratifying T2DM patients for NAFLD utilizing non-invasive tools to measure liver fibrosis. We screened T2DM patients for NAFLD utilizing VCTE after identifying them in two diabetes practices.

Method: T2DM patients > 18 years old were recruited prospectively during their diabetes clinic visits in a tertiary care healthcare system in NYC from September 2017 to September 2018. Features of the metabolic syndrome (MetS) were analyzed using the National Cholesterol Education Program-Adult Treatment Panel III (NCEP III) including waist circumference (with BMI as a surrogate), elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, hypertension, and elevated fasting blood glucose. Having ≥ 3 of these features defined presence of the MetS. Informed written consent was obtained.

Results: A total of 89 patients (51% women, 12% African American, 6% Asian, 18% Caucasian, 44% Hispanic, 10% other), median age 60 (range 32-82) were analyzed. The median liver stiffness was 6.1 kPa (IQR; 2.4, 74.6) with a median controlled attenuation parameter of 296 dB/m (IQR: 100, 400). 51 (57%) patients had FIB-4 score ≤ 1.3, 23 (26%) had FIB-4 > 1.3 and < 2.67, and 3 (15%) had FIB-4 ≥ 2.67. Using NFS scores, 11 (12%) patients had NFS scores < −1.455, 47 (53%) had NFS ≥ -1.455 and ≤ 0.675, and 19 (21%) had NFS > 0.675. All patients had T2DM (89, 100%), 74 (83%) had hypertension, 50 (56%) had hypertriglyceridemia, 40 (45% had reduced HDL and 53 (60%) had a BMI > 30. 70 (82%) of the patients had at least three of these features indicating the presence of metabolic syndrome. Each additional feature of MetS had increased likelihood of KPA > 7.5 (Odd ratio 1.74 (95% CI 1.09, 2.79) for each increase in MetS). There were no statistically significant differences between ethnic groups for FIB-4, NFS or VCTE.



Conclusion: The latest NAFLD guidelines for risk-stratifying patients with type 2 diabetes via FIB-4, NFS or VCTE provide a non-invasive means for identifying patients with NAFLD and advanced fibrosis and are applicable to patients of different ethnicities. Screening for NAFLD in patients with T2DM during routine diabetes clinic visits is feasible, increases diagnoses of NAFLD and linkage to care.

SAT-292

Effectively reducing screen failure rate in non-alcoholic fatty liver disease clinical trial using the FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST

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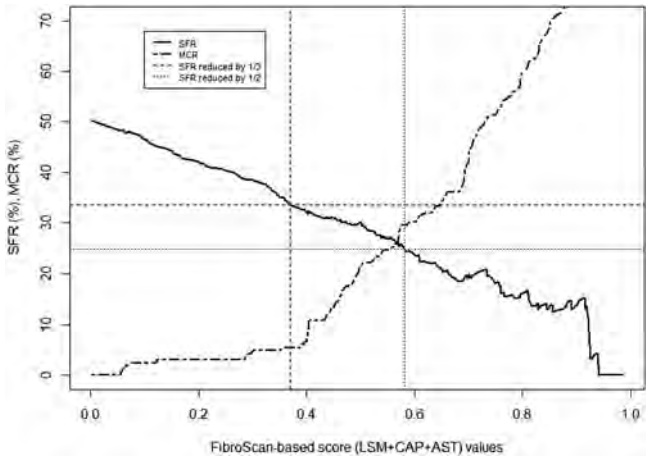
Background and aims: Identifying patients with active NASH (NAS ≥ 4) and advanced fibrosis (F ≥ 2) is a key priority for clinical trials yet current strategies are associated with high screen failure rates. We set out to evaluate the screen failure and missed case rate of a FibroScan based score (TE/CAP/AST) in a UK setting.

Method: Patients were enrolled for undergo FibroScan examination within 2 weeks of a clinically indicated liver biopsy (LB) for suspected NAFLD. Recruitment took place (Mar 2014-Jan 2017) at seven UK centres. LB were scored by two expert pathologists in a blinded manner with consensus using the NASH CRN system and NASH using the FLIP definition. SFR was computed as being 1-positive predictive value for each value of the score. Similarly the missed case rate MCR was calculated as being 1-sensitivity. For each possible value of the score (ranging between 0 and 1), the corresponding SFR and MCR were plotted and used to define optimal cut-offs depending on the study objective. Cut-offs to reduce the SFR by a third and half were calculated as exploratory end points. For comparison SFR/MCR above the higher published cut-offs for Fib4 (3.25) and NFS (0.676) were also calculated.

Results: 335 patients were included in the analysis. AUROC of the FibroScan-based score to detect patients with NASH + NAS ≥ 4 + F ≥ 2 was 0.83 (0.77-0.87). Prevalence of NASH + NAS ≥ 4 + F ≥ 2 was 50% which would have been the SFR if no prior screening of patients was undertaken. Evolution of the SFR as a function of all possible values is shown on Figure 1, together with the evolution of the MCR. At a cut-off value of 0.37, SFR was reduced to 33% with an associated MCR of 5%. At a cut-off value of 0.58, the SFR was reduced to 25% and the MCR was 30%. Taking an in between cut-off value of 0.48 gave a SFR of 30% and an MCR of 17%. Using a 3.25 cutoff for Fib4 yields a SFR of 13% with MCR of 91%. Using a 0.676 cutoff for NFS yields a SFR of 28% with MCR of 86%.



Conclusion: The Fibroscan-based score identified optimal cut-offs to significantly reduce SFR with an acceptable MCR.

SAT-293

Combination of FibroScan and FibroMeter (FibroMeter VCTE) improves identification of patients with advanced fibrosis in patients with NAFLD

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Background and aims: In non-alcoholic fatty liver disease (NAFLD) the presence of fibrosis is predictive of long-term complications. FibroMeter (FM)^{VCTE} is a patented blood test combining blood parameters and FibroScan Liver Stiffness Measurement (LSM) developed in hepatitis C patients which we set out to validate in patients with NAFLD to assess the presence of advanced fibrosis and cirrhosis (F ≥ 3).
Methods: Patients underwent FibroScan and blood collection (analyzed in central lab) within 2 weeks of a liver biopsy (LB) performed due to a clinical suspicion of NAFLD. LB were read in a blinded manner with consensus by two expert pathologists using the NASH CRN scoring system. Advanced fibrosis (F ≥ 3) was ruled out or in using published cutoffs (−1.455 and 0.676 for NFS, 1.30 and 3.25 for FIB4, 6.5 and 12.1 kPa for LSM and 0.385 and 0.715 for FM^{VCTE}). Sensitivity, positive predictive value (PPV) for the high cut-off and specificity (Sp), negative predictive value (NPV) for the low cut-off were calculated. Area under receiver operating characteristics curves (AUC) were assessed and compared using Delong's test.
Results: 356 patients were included. 43% were female, BMI was 34.4 ± 6.5 kg/m² and age 53 ± 12 years. Prevalence of F ≥ 3 was 36%, F4 was 9%. Performance of each test is shown in Table 1. For identifying F ≥ 3, FM^{VCTE} significantly outperformed other tests (AUC = 0.85 (0.81-0.89), P < 0.003). FIB4 had the best PPV = 0.82 with low Se = 0.14 whereas FM^{VCTE} had Se = 0.62 with a PPV = 0.74. FM^{VCTE} had the lowest patients in the grey zone (26%, P < 0.003) and identified 62% of F3/F4 patients vs 14% with FIB4 and 89% of F4 vs 25% with FIB4. For the diagnostic of cirrhosis, AUCs were: NFS 0.79 (0.70-0.87), FIB4 0.84 (0.77-0.90), LSM 0.88 (0.83-0.93) and FM^{VCTE} 0.91 (0.86-0.95). FM^{VCTE} outperformed other tests (p < 0.01).

Table 1:

	AUC (95% CI) for F ≥ 3	P value	Rule out F ≥ 3	Grey zone	Rule in F ≥ 3
*FibroScan **LSM***	0.79 (0.74-84)	$< 10^{-3}$	Sp = 0. 38 NPV = 0.89 N = 98 (28%) F < 3: 87 F = 3: 11 F = 4: 0	N = 152 (42%) F < 3: 110 F = 3: 38 F = 4: 4	Se = 0.59 PPV = 0.70 N = 106 (30%) F < 3: 30 F = 3: 48 F = 4: 28
FM^{VCTE}	0.85 (0.81-0.89)	Reference	Sp = 0.90 NPV = 0.92 N = 154 (43%) F < 3: 141 F = 3: 13 F = 4: 0	N = 93 (26%) F < 3: 57 F = 3: 32 F = 4: 4	Se = 0.62 PPV = 0.73 N = 109 (31%) F < 3: 29 F = 3: 52 F = 4: 28
FIB4	0.78 (0.73-0.83)	0.003	Sp = 0.73 NPV = 0.81 N = 204 (57%) F < 3: 166 F = 3: 33 F = 4: 5	N = 130 (37%) F < 3: 57 F = 3: 54 F = 4: 19	Se = 0.14 PPV = 0.82 N = 22 (6%) F < 3: 4 F = 3: 10 F = 4: 8
NFS	0.74 (0.69-0.80)	$< 10^{-4}$	Sp = 0.55 NPV = 0.85 N = 146 (41%) F < 3: 124 F = 3: 19 F = 4: 3	N = 167 (47%) F < 3: 88 F = 3: 65 F = 4: 14	Se = 0.22 PPV = 0.65 N = 43 (12%) F < 3: 15 F = 3: 13 F = 4: 15

Conclusions: FibroMeter^{VCTE} performs well in the identification of patients with advanced fibrosis without compromising sensitivity.

SAT-294

Automated quantitation of steatosis, inflammation, ballooning and fibrosis using machine learning in routine histological images of liver biopsies of patients with NAFLD

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Background and aims: Histology is the standard to diagnose and stage Non-Alcoholic Fatty Liver Disease. Current scores display high intra and inter-observer variability. We developed an automated method based on machine learning for quantitation of fat, inflammation, ballooning and fibrosis using routine histological images of NAFLD.
Method: We evaluated liver biopsies with NAFLD. Biopsies stained with HandE and Sirius Red were scored for NASH CRN score and digitalized. Fat, inflammation, ballooning and fibrosis were annotated manually for machine learning. Inflammation and ballooning were identified after the analysis of the intensity the nuclei and the texture of the cytoplasm. Results expressed as % (areas divided by the whole biopsy area). Concordance between results and annotations was reported as Interclass Correlation Coefficient (ICC).
Results: We analysed 120 biopsies. As per scores, steatosis was mild in 33, moderate in 65 and severe in 22. Inflammation was 0 in 28, grade 1 in 72, grade 2 in 17 and grade 3 in 2. Ballooning was 0 in 38, 1 in 49 and 2 in 33. Fibrosis was F1-F2 in 47, F3 in 44 and F4 in 14.
As per quantitation, Fat% was 4.1% (IQR 2.1-6.4) in grade1, 11.2% (IQR 8.3-32.4) in grade2, 22.1% (IQR 16.6-44) in grade3. Inflammation% was 1.6% (IQR 0.7-1.9) in score0, 3.7% (IQR2.4-4) in score1, 7.7% (IQR 6.6-9.3) in score2, 9.7% (IQR 7.2-11.3) in score3. Ballooning% was 4.7% (IQR 3.2-6.7) in score0, 12.6% (IQR 10-12.8) in score1, 15.4% (IQR 12-21.9) in score2. CPA was 2.7% (IQR 1.9-4) in F1, 2.1% (IQR 1.3-3.8) in F2, 4.8% (IQR 2.5-8.05) in F3, 12.2% (IQR 6.8-17.2) in F4. ICC was excellent: 0.98 (95%CI = 0.96-0.99, p = 0.0001) for steatosis, 0.95 (95%CI = 0.89-0.98, p = 0.0001) for inflammation, 0.94 (95%CI = 0.87-0.98, p = 0.001) for ballooning and 0.92 (95%CI = 0.88-0.96, p = 0.001) for CPA.

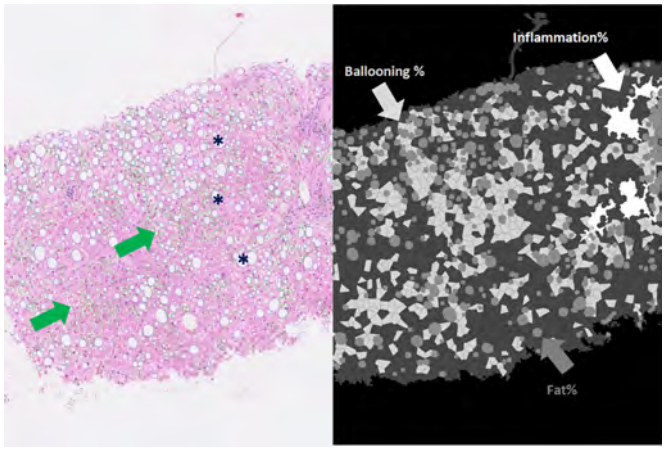

Figure: Fat% 27.7, Inflammation 2.1%, Ballooning 16.6%.

Conclusion: We developed a technique for objective quantitation of histological features in biopsies of NAFLD. This does not require sophisticated equipment and demonstrated reliable results. Given

the key role for histology in clinical trials, these techniques should be considered as end points.

SAT-295

Diagnostic accuracy of non-invasive Methods (NFS Score and FIB-4) for detecting advanced fibrosis: A validation study of NFS score and FIB-4 in a cohort of South Indian patients with NAFLD

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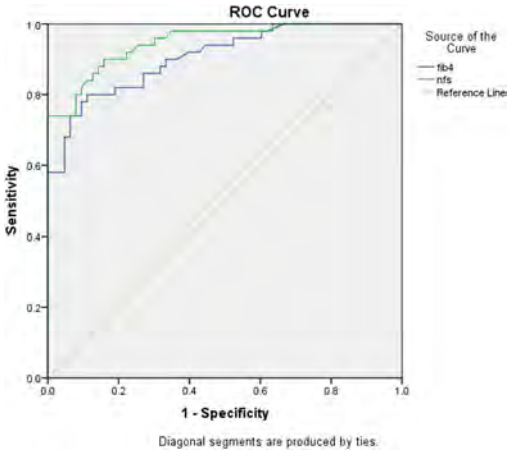
Background and aims: Presence of advanced fibrosis in Non-alcoholic fatty liver disease (NAFLD) increases the risk of HCC as well as liver related and cardiovascular mortality. Liver biopsy is the current goal standard for diagnosing fibrosis in NAFLD but has its own risks. Vibration controlled transient elastography (VCTE) is costly and not easily accessible to all. NAFLD fibrosis score (NFS) and FIB-4 are scoring systems validated in western population for diagnosing fibrosis in NAFLD.

Aim We aimed to assess the accuracy of NFS score and FIB-4 as non-invasive Methods for diagnosis of advanced liver fibrosis in a cohort of south Indian population with NAFLD.

Method: All patients with biopsy proven NAFLD who attended our liver clinic between 1st January 2016 and 30th June 2018 were enrolled. Diagnosis of NAFLD was based on histological criteria for NAFLD by non-alcoholic steatohepatitis clinical research network (NASH CRN). Stages 0-2 were considered as mild/moderate fibrosis and stages 3-4 as advanced fibrosis. NFS score and FIB-4 score were calculated for each patient using an online calculator. An NFS score greater than 0.676 and FIB-4 score more than 2.67 were taken as cut-off to predict advanced fibrosis based on data from previous studies. Statistical analysis was conducted using SPSS 19.0 software (SPSS, Inc., Chicago, IL).

Results: A total of 113 patients [Mean age 49.23 ± 12.07 years; Male: female = 62:51] were studied. Mean BMI was 26.41 ± 3.80 and 72 (63.7%) patients were obese (BMI > 25). 50 (44.24%) patients had advanced fibrosis on liver biopsy. DM was seen in 44 (38.9%) patients and was more common in patients with advanced fibrosis (66% versus 17.5%). Patients with advanced fibrosis were more likely to be older and males. Patients with advanced fibrosis had lower platelet count, higher AST, lower albumin and higher AST/ALT ratio). The NFS score > 0.676 had a sensitivity of 72%, specificity of 100%, PPV of 100%, NPV of 78.46% and accuracy of 86.14% to diagnose advanced fibrosis. FIB-4 > 2.67 had a sensitivity of 70%, specificity of 100%, PPV of 100%, NPV of 70% and accuracy of 82.35% to diagnose advanced fibrosis. Area under ROC curve was 0.948 for NFS and 0.908 for FIB-4 for diagnosing advanced fibrosis (Figure1).



Area Under the Curve

Test Result Variable (s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
fib4	.906	.028	.000	.852	.960
Nfs	.948	.019	.000	.910	.986

The test result variable (s): fib4, nfs has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Conclusion: The NFS and FIB-4 have good accuracy in diagnosing advanced fibrosis in NAFLD patients. These simple, non-invasive tests can substitute liver biopsy as well as guide further investigations and follow-up of patients with NAFLD.

SAT-296

Oxidized LDL is a distinctive biomarker of NASH independently of liver fibrosis in patients with NAFLD

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Oxidized LDL is a distinctive biomarker of NASH independently of liver fibrosis in patients with NAFLD.

Background and aims: To determine the diagnostic capacity of oxidized LDL (oxLDL) in non-alcoholic fatty liver disease (NAFLD) and its role in the physiopathology of the disease.

Method: Multicenter study including 178 patients that underwent liver biopsy due to clinical suspicion of NAFLD: 164/178 (92%) were found to be compatible with NAFLD and 14/178 (8%) showed normal hepatic histology. Epidemiological, biochemical and anthropometrical variables were recorded. Non-alcoholic steatohepatitis (NASH) and liver fibrosis were evaluated by using SAF Score. Levels of oxLDL were measured by ELISA (Mercodia AB, Uppsala, Sweden) following manufacture's instructions.

Results: 53.4% of patients displayed NASH and fibrosis distribution was as follows: F0 27.4% (45/164), F1 37.2% (61/164), F2 25.6% (42/164), F3 6.7% (11/164) and F4 3% (5/164). oxLDL levels in healthy controls were 42.1 + 10.3 U/L. In NAFLD patients, oxLDL was found to be associated with NASH (55 + 15.8 *vs.* 45.1 + 13.7 U/L; p < 0.0001), but not with liver fibrosis (F0 50.7 + 14.8 *vs.* F1 52.7 + 16.5 *vs.* F2 48.6 + 13.8 *vs.* F3 54 + 20.5 *vs.* F4 39.4 + 8.5 U/L; p = 0.299).

Further, association between oxLDL and NASH was found to be maintained independently of obesity [(BMI > 30 kg/m^2 54.5 + 15.1 *vs.* 45.6 + 12.9 U/L; p = 0.0001) (BMI < 30 kg/m^2 65.6 + 27.2 *vs.* 43.8 + 14.3 U/L; p = 0.022)] and *diabetes mellitus* [(DM 55.8 + 15 *vs.* 43 + 12.1 U/L; p = 0.001) (non-DM 54.6 + 16.3 *vs.* 46.2 + 13.8 U/L; p = 0.003)]. In both mild fibrosis (F0-F1) and significant fibrosis (F2-F4), oxLDL levels were found to be significantly higher when displaying NASH

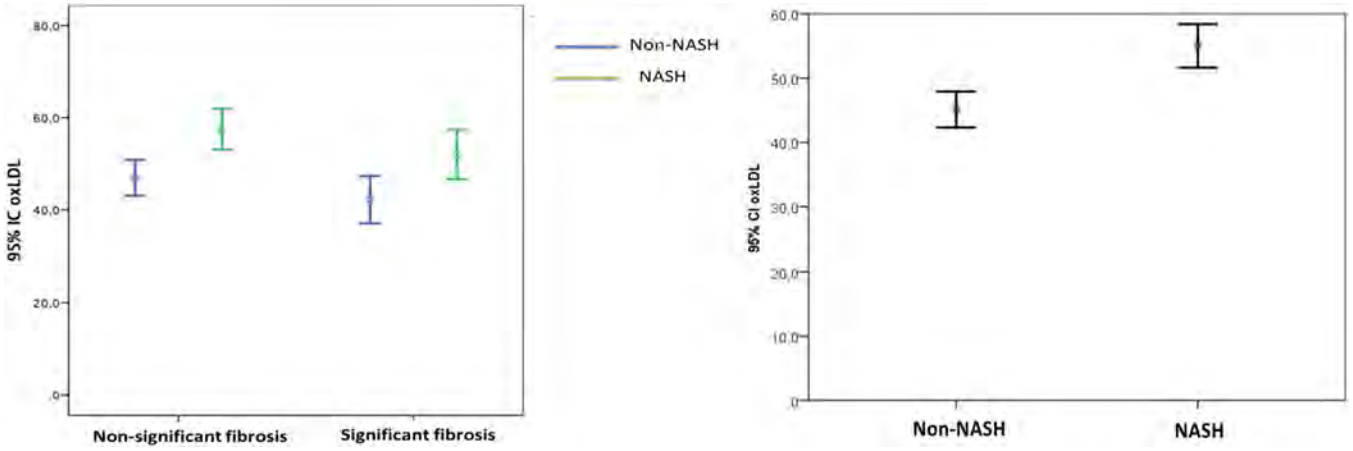

Figure: (abstract: SAT-296)

(Fig 1). BMI, GGT, albumin and total cholesterol were also associated to NASH presence. After multivariate analysis, oxLDL [OR 1.05 (CI95% 1.02-1.08); p = 0.001] and BMI [OR 1.08 (CI95% 1.03-1.13); p = 0.001] remained as independent variables associated to NASH.

Conclusion: oxLDL levels were associated to NASH but not to liver fibrosis. These data may reinforce the role of oxidative stress in NASH, independently of obesity and diabetes, and highlights the interesting role of this molecule linking NASH and cardiovascular risk.

SAT-297

Prediction of incident severe liver disease in the general population using non-invasive scoring systems

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Background and aims: Non-invasive scoring systems can be used to identify persons with a high risk of advanced liver fibrosis in NAFLD. Which score that best predict future liver-related events in the general population is largely unknown.

Method: We used data from the Swedish AMORIS cohort, generated in 1985-1996. The cohort consisted of > 800, 000 persons with laboratory data obtained from routine health check-ups and primary care. Body mass index (BMI) and diabetes status were ascertained by record linkage to national registers and research cohorts. We calculated the following five scores for persons free of baseline cirrhosis or alternative liver diseases than NAFLD: APRI (n = 172, 016), BARD (n = 79, 583), FIB-4 (n = 171, 460), Forns score (n = 164, 861) and the NAFLD fibrosis score (NFS, n = 18, 236). All five scores were possible to calculate in 18, 236 persons. We ascertained incident cases of severe liver disease, defined as diagnoses of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and/or death in liver disease by linkage to high-quality national registers, until 31 December 2011. Cox regression was used to estimate hazard ratios. ROC-curves and C-statistics were used to investigate which score that best predicted incident severe liver disease.

Results: During a mean follow-up period of 17 years, we found an increased incidence of severe liver disease in intermediary as well as high-risk groups compared to low-risk groups. Total number of outcomes, hazard ratios for intermediary and high-risk groups, AUROCs and C-statistics per score are presented in Table 1. Although the negative predictive value for severe liver disease for persons in the low-risk group was > 0.98 for all tested scores, most severe liver disease events occurred in persons with low risk of advanced fibrosis at baseline.

Conclusion: Currently available non-invasive scores predicted incident severe liver disease to a poor extent although subjects in the intermediate and high-risk groups had a clearly elevated risk. Persons with a low risk for having advanced fibrosis per these scores are at a low absolute risk for future cirrhosis, but better prognostic models are needed.

Scoring system	N exposed	N outcomes (%)	HR (95%CI)	AUROC	C-statistics
APRI, low	165, 253	1, 549 (0.94%)	(ref)	0.616	0.631
APRI, interm.	5, 968	265 (4.44%)	5.5 (4.9-6.3)		
APRI, high	795	99 (12.45%)	24.4 (19.9-29.9)		
BARD, low	24, 841	216 (0.87%)	(ref)	0.509	0.511
BARD, interm.	49, 543	329 (0.66%)	0.7 (0.6-0.9)		
BARD, high	5, 199	85 (1.63%)	1.4 (1.1-1.8)		
FIB-4, low	142, 494	1, 218 (0.85%)	(ref)	0.645	0.671
FIB-4, interm.	22, 916	427 (1.86%)	1.4 (1.3-1.6		
FIB-4, high	6, 050	255 (4.21%)	4.3 (3.7-5.0)		
Forns, low	130, 160	996 (0.77%)	(ref)	0.657	0.704
Forns, interm.	33, 121	671 (2.03%)	1.8 (1.7-2.0)		
Forns, high	1, 580	148 (9.37%)	13.3 (11.1-15.9)		
NFS, low	16, 429	125 (0.76%)	(ref)	0.626	0.645
NFS, interm.	1, 698	32 (2.0%)	1.6 (1.1-2.4)		
NFS, high	109	2 (1.83%)			

SAT-298

MR elastography based fibrosis correlates with clinical liver events in patients with non-alcoholic fatty liver disease: A multi-center study

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Background and aims: Liver fibrosis assessed by liver biopsy has been shown to predict clinical liver events in patients with non-alcoholic fatty liver disease (NAFLD) and remains the gold standard in phase 3 trials. MR elastography (MRE) has been shown to be highly correlated with liver biopsy in assessing liver fibrosis and is currently used in phase 2 trials. Data to assess the correlation between MRE and clinical liver events are lacking. We investigated the correlation

between MRE and clinical liver events in a large cohort of NAFLD patients.

Method: This is a multi-center study of NAFLD patients from Texas and California. We investigated liver events in 3 groups of patients, one with MRE ≥ 2.5 kPa (correlated with NASH), one with MRE ≥ 3.62 kPa (advanced fibrosis) and one with MRE ≥ 4.7 kPa (correlated with cirrhosis). Fisher's exact test was used for testing association strength. Univariate logistic regression model was used to predict the events.

Results: Our cohort included 245 patients: 53% female; 47% T2DM; mean BMI 32.3 (6.2) kg/m^2, ALT 55.7 (48.4) U/L, AST 41.6 (29.3) U/L, and ALP 84.4 (33.5) U/L. Patients with MRE ≥ 2.5 kPa and MRE ≥ 3.62 were more likely to be diabetics, have higher ALT, AST and ALP, and lower platelets ($p < 0.05$ for all). NAFLD patients with MRE ≥ 2.5 kPa were more likely to have overall liver decompensation (7.4%% vs 0%; P = 0.003) and ascites (5.2% vs 0%; P = 0.018). Patients with MRE ≥ 3.62 kPa were more likely to have overall liver decompensation (19.2% vs 0%; P < 0.001), ascites (13.5% vs 0%; P < 0.001), hepatic encephalopathy (HE) (9.8% vs 0%; P < 0.001), esophageal variceal bleeding (EVB) (3.8% vs 0%; P = 0.045) and death (3.9% vs 0%; P = 0.043). Patients with MRE ≥ 4.7 kPa were more likely to have overall liver decompensation (26.7% vs 0.9%; P < 0.001), ascites (16.7% vs 0.9%; P < 0.001), HE (17.2% vs 0%; P < 0.001), EVB (6.7% vs 0%; P = 0.015) and death (6.9% vs 0%; P = 0.014). Association of advanced fibrosis estimated by MRE and incidence of clinical liver events using univariate logistic regression is shown in table.

Table:

Events	OR (95%CI)	P value
Decompensation	2.34 (1.64-3.34)	< 0.001
Ascites	1.83 (1.37-2.43)	< 0.001
HE	2.87 (1.62-5.07)	< 0.001
EVB	1.64 (1.18-2.29)	0.003
Mortality	2.47 (1.26-4.85)	< 0.001

Conclusion: MRE is a non-invasive biomarker that has been shown to correlate with histological fibrosis in NAFLD patients. This is the first study to show that MRE may predict clinical liver events and decompensation in NAFLD patients.

SAT-299

Assessment of NIS4 clinical utility for identification of patients with active NASH (NAS ≥ 4) and significant fibrosis (F ≥ 2) in patients at risk of NASH

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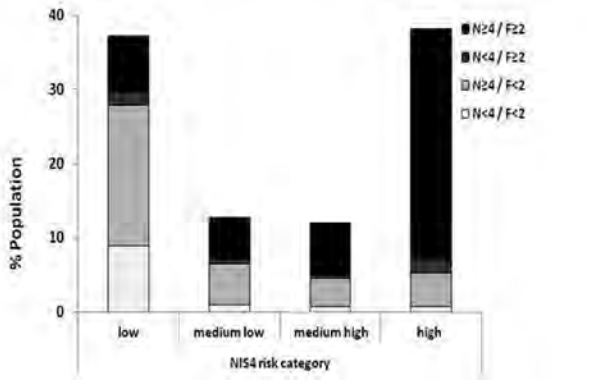
Background and aims: NASH is dramatically under-diagnosed largely because a liver biopsy is needed for diagnosis confirmation. Given the globel burden of NASH, development of new non-invasive tools are needed to identify millions of patients at higher risk of developping liver related outcomes. We recently described a new non-invasive score, NIS4. The aim of this study was to set-up clinically useful cut-offs for NIS4 to efficiently rule-out patients with no or mild disease and rule-in patients with active NASH and significant fibrosis (NAS ≥ 4 with F ≥ 2).

Method: 710 patients were screened for inclusion in GOLDEN and RESOLVE-IT trials. Blood samples and a liver biopsy were collected during the screening periods. Histological diagnosis and scoring were centralized. Each component of NIS4 (i.e. miR-34a, alpha2-macro-globuline, YKL-40 and HbA1c) were measured for calculation of NIS4. A ROC analysis was performed to determine the optimal cut-off for detection of patients with NAS ≥ 4 and F ≥ 2. We then set a low cut-off at 85% sensitivity (Sens) and a high cut-off at 85% specificity (Spec) defining 4 score ranges: low, low-medium, medium-high and high probability of having NAS ≥ 4 and F ≥ 2. Diagnostic metrics (Sens, Spec, negative predictive value and positive predictive value) were derived as well as the % of patients in the 4 score ranges.

Results: Ninety % of patients had signs of liver damage (elevated LFT's) and one or more cardio-metabolic risk factor. The cohort covered the complete histological spectrum of NAFLD (NAS = 0-8 and F = 0-4) and 51% had NAS ≥ 4 with F ≥ 2. The AUROC for detection of these patients was 0.83 [0.80-0.87] for NIS4 vs 0.75 [0.71-0.78] for FIB-4 ($p < 0.001$). At optimal cutoff of NIS4, Sens was 74% [69-78] and Spec was 75% [71-80]. At a low-cut-off set at 85% Sens, Spec was 61% [55-66] while NPV was 80%. 37% of patients (n = 264) had NIS4 values below the low cut-off (Figure1). The vast majority of patients with no or mild histological lesions (80%) were well classified in this low probability range. At high cut-off set at 85% Spec, Sens was 61% [55-66] for NIS4 while PPV was 81%. 38% of patients (n = 271) had NIS4 value above the high cut-off. In this range, almost all patients had histological lesions since 98% of patients had active NASH (NAS ≥ 4) and/or F ≥ 1.

Figure 1: Distribution of patients in NIS4 ranges



Conclusion: Using a large cohort of patients screened for suspicion of NASH, this study illustrates the clinical utility of NIS4 to eliminate patients at low probability of having active NASH and significant fibrosis and to accurately identify those at high probability of progressive disease who should be considered for therapeutic intervention.

SAT-300

Prospective liver biopsy-based prevalence of non-alcoholic fatty liver disease and steatohepatitis among a large middle-aged population utilizing FibroScan, LiverMultiscan and magnetic resonance elastography to guide liver biopsy

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Background and aims: NAFLD prevalence is estimated to be as high as 30-46% in the USA, while the prevalence of NASH is less well delineated. Large prospective studies are lacking correlating demographic, clinical and novel radiographic data to histopathology.
Method: Adult patients were prospectively enrolled predominantly at the time of referral for routine colon cancer screening. They were screened for evidence of NAFLD with FibroScan, LiverMultiScan (LMS), and MR elastography (MRE). A prior history of liver disease or alcohol ingestion greater than the accepted range for NAFLD was considered exclusionary. Patients exceeding pre-specified cut-off values on any imaging test were offered liver biopsy. Liver biopsies were read by two expert pathologists in double-blind with consensus using the Brunt criteria.
Results: 829 subjects were enrolled of which 532 completed all studies and are available for analysis (245 subjects completed liver biopsy; 287 subjects not eligible for liver biopsy based on negative imaging). Mean age: 56.0 ± 6.8 years; mean BMI: 30.6 ± 5.8 kg/m^2; 50.0% male; 14.1% diabetic. The prevalence of NAFLD (defined by a proton density fat fraction (PDFF) of > 5%) among those who completed all radiographic studies was 33.2% (Fig. 1). The prevalence of NASH was found to be 17.7%. PDFF values distributed as follows: 5-10%: 14.7%; 10.1-20%: 14.3%; > 20%: 4.2%. The prevalence of NAFLD/NASH among major ethnic groups were as follows: Hispanics (56.2%/33.1%), Caucasians (39.7%/20.7%), African-Americans (21.9%/4.2%). In the subgroup with biopsies: 22.4% normal, 39.2% Non-NASH NAFLD and 38.4% NASH. Among the NASH patients: 19.1% stage-0 (27.8% diabetic), 45.7% stage-1 (27.9% diabetic), 24.5% stage-2 (47.8% diabetic), and 10.6% stage-3 (70.0% diabetic). Patients with diabetes and NAFLD compared to non-NAFLD had higher FibroScan™ LSM (p = 0.0007), FibroScan™ CAP (p < 0.0001), steatosis grade (p < 0.0001), and fibrosis stage (p < 0.0001). Among those with NASH vs. non-NASH NAFLD mean: FibroScan™ LSM 7.5 ± 3.4 vs. 6.4 ± 2.6 kPa (p = 0.0292); LIF 2.5 ± 0.6 vs. 2.0 ± 0.7 (p < 0.0001); MRE 2.6 ± 0.7 vs. 2.3 ± 0.4 kPa (p = 0.0019), MRI cT1 920.1 ± 53.9 vs. 872.3 ± 55.5 (p < 0.0001).

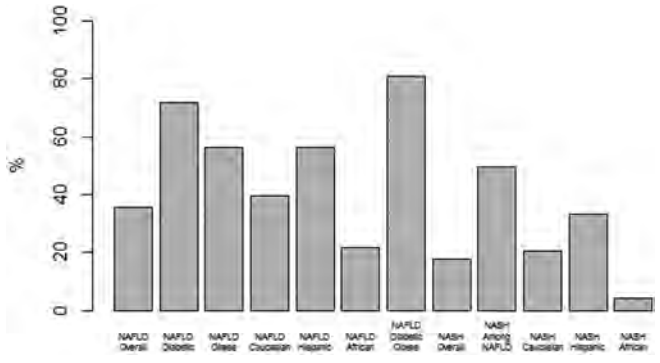

Figure: The prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis using novel radiographic studies and liver biopsy. On the left is the overall NAFLD prevalence distributed by race and ethnicity.

Conclusion: In adult patients without previously known liver disease results from novel radiographic studies and prospective liver biopsy confirm the high prevalence of NAFLD and NASH in middle-aged Americans.

SAT-301

The FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST can efficiently screen for presence of at risk fibrotic NASH: Evaluation in an American cohort of patients screened for NAFLD

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Background and aims: Given the increased need to identify NASH patients with fibrosis in drug development, Echosens has developed a score to identify patients with NASH + NAS ≥ 4 + F ≥ 2. The score combined the FibroScan liver stiffness measurement (LSM), controlled attenuation parameter (CAP) and AST. The objective was to assess its performance in a cohort of patients screened for NAFLD.
Methods: Patients were screened for NAFLD in one American center. Patients with MRI-PDFF ≥ 5% or liver inflammation and fibrosis score (LIF) ≥ 2 or FibroScan LSM ≥ 7kPa or MRE LSM ≥ 3kPa were advised to undergo a liver biopsy (LB). The performance of the score was assessed using area under the receiver operating characteristics (AUC).
Results: 510 patients were included in the analysis: 240 with LB and 270 with no LB (all 4 liver imaging modalities "normal" (below the predefined cutoffs)). 50% of were female, median age was 56 [IQR = 10] years and BMI was 30.3 [7.3] kg/m^2. At LB, 37 (15%) patients had at F ≥ 2, 91 (38%) had NASH and 27 (11%) had a NASH + NAS ≥ 4 + F ≥ 2. Of note, 7 (3%) had F ≥ 2 but no NASH and 3 (1%) had NASH, F ≥ 2 and NAS = 3.
Cutoffs value for a sensitivity (Se) and specificity (Sp) ≥ 0.90 and associated diagnostic metrics are provided in Table 1. AUC for the score to detect NASH + NAS ≥ 4 + F ≥ 2 was 0.88 (0.81-0.94) and significantly outperforming FibroScan LSM (0.77 (0.68-0.86), p = 0.006), CAP (0.71 (0.63-0.80), p < 10-3) and AST (0.76 (0.66-0.86), p = 0.004) alone.
Using the lower cutoff, 97 patients (19% of the population) would have been sent for referral. Among those patients, 26% were NASH + NAS ≥ 4 + F ≥ 2, 69% weren't and 5% had normal imaging modalities. Using the higher cutoff, 38 patients (7% of the population) would have been sent for referral. Among those patients 42% were NASH + NAS ≥ 4 + F ≥ 2, 55% weren't and 3% had normal imaging modalities.
With the hypothesis that patients with normal imaging were not NASH + NAS ≥ 4 + F ≥ 2, prevalence of NASH + NAS ≥ 4 + F ≥ 2 would drop to 5%. Corresponding positive and negative value (PPV/NPV) of the score would be 0.26/99.5 for the lower cutoff and 0.42/97.7 for the higher cutoff.

Table 1:

	Cut-off for Se ≥ 0.90		Cut-off for Sp ≥ 0.90	
In patients with LB	0.205 Se = 0.93/Sp = 0.69 PPV = 0.27/NPV = 0.99		0.425 Se = 0.63/Sp = 0.90 PPV = 0.45/NPV = 0.95	
In all patients	score LSM + CAP + AST < 0.205	score LSM + CAP + AST ≥ 0.205	score LSM + CAP + AST < 0.425	score LSM + CAP + AST ≥ 0.425
Not NASH + NAS ≥ 4 + F ≥ 2 at LB	146	67	192	21
NASH + NAS ≥ 4 + F ≥ 2 at LB	2	25	11	16
Unknown (no LB)	265	5	269	1

Conclusion: A simple score based on FibroScan LSM, CAP and AST can be used to efficiently identify patients eligible for for potential pharmacologic therapy.

SAT-302

Predicting the severity of hepatic steatosis and fibrosis by transient elastography and MRI-based techniques in adults patients with suspected NAFLD

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Background and aims: This ongoing prospective study aimed at evaluating the diagnostic performance of FibroScan- (FS) and magnetic resonance imaging (MRI)-based techniques in predicting the degree of hepatic steatosis, inflammation and fibrosis compared to liver biopsy (LB) in patients with suspected NAFD.
Method: Patients referred for a routine colon cancer screening with no prior history of liver disease or alcohol abuse offered participation in the study. Screening for NAFLD was performed using 5 modalities. 2 FibroScan® (FS) modalities: liver stiffness measurement (FS-LSM) and Controlled Attenuation Parameter (FS-CAP) and 3 MRI-based imaging-based modalities: MR Elastography (MRE-LSM), proton density fat fraction (MRI-PDFF) and liver inflammation fibrosis score (LMS-LIF, Liver MultiScan®). Patients with FS-LSM ≥ 7 kPa, MRE-LSM ≥ 3 kPa, PDFF ≥ 5%, or LIF ≥ 2 were proposed a LB. LB were assessed by two expert pathologists in a double-blind manner with consensus, using the NASH CRN scoring system. Diagnostic performances were assessed using area under receiver operating curve (AUROC). Spearman correlation coefficients were also assessed between modalities.
Results: To date, 829 patients have been screened, of which 232 underwent LB. 22.8% were S0, 37.5% S1, 22.8% S2 and 16.8% S3 steatosis. 53.9% were F0, 30.2% F1, 12.1% F2 and 3.9% F3. 37.9% of patients had NASH. For the prediction of steatosis, respective AUROCs for FS-CAP and MRI-PDFF relative to LB were 0.84 [0.78;0.90] vs 0.93 [0.89;0.97] for S ≥ 1, 0.80 [0.75;0.86] vs 0.96 [0.94;0.98] for S ≥ 2, and 0.76 [0.69;0.83] vs 0.92 [0.88;0.95] for S ≥ 3. For the prediction of fibrosis, respective AUROCs for FS-LSM, and MRE-LSM relative to LB were 0.60 [0.53; 0.68] vs 0.64 [0.57;0.71] for F ≥ 1, 0.78 [0.70;0.86] vs 0.83 [0.75;0.90] for F ≥ 2 and 0.91 [0.86;0.96] vs 0.97 [0.92;1.00] for F ≥ 3. FS-based modalities and MRI-based imaging modalities were available in 595 patients. Correlations coefficients between FS-LSM/MRE-LSM and FS-CAP/MRI-PDFF were.45 and 0.66 respectively. Performance of FS-LSM to predict MRE-LSM ≥ 3 kPa (prevalence 5%) was 0.76 [0.66;0.86]. Performance of CAP to predict MRI-PDFF ≥ 5% (prevalence 37%) was 0.86 [0.83;0.89].
Conclusion: Both FS-CAP/MRI-PDFF and FS-LSM/MRE are very good modalities to non-invasively assess liver fat and liver fibrosis in NAFLD respectively, with a modest advantage for MRI-based imaging modalities for assessment of high grades of steatosis.

SAT-303

Liver fibrosis together with PNPLA3 p.I148M variant affects quality of life in patients with non-alcoholic fatty liver disease: prospective liver stiffness-based study

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) belongs to the most common liver diseases, and the *PNPLA3* gene variant p.I148M is associated with higher hepatic fat contents and liver fibrosis. Here, we investigate if hepatic fibrosis and steatosis as well as the *PNPLA3* variant affect Health-related Quality of Life (HRQoL) in patients with fatty liver diseases.
Method: Prospectively, we recruited individuals with NAFLD/diabetes at our center. All patients filled the battery of HrQoL questionnaires, i.e. SF36, STADI, FIS, PHQ9, and RIS (Regensburg Insomnia Scale). Hepatic steatosis and fibrosis were assessed non-invasively by controlled attenuated parameter (CAP) and liver stiffness measurement (LSM). Patients were stratified using CAP ≥ 248 dB/m, LSM ≥ 9.2 kPa and LSM ≥ 13.0 kPa as cut-offs for significant steatosis, fibrosis and cirrhosis, respectively. The variant *PNPLA3* p.I148M was genotyped using a specific TaqMan assay.
Results: Among 107 patients (57 women, age 60 ± 13 years) 76% presented with significant steatosis, 23% of these showed at least significant fibrosis and 13% cirrhosis. LSM correlated significantly (all $p < 0.05$) with several QoL aspects: physical functioning (SFpfi), physical component summary (SFPCS), anxiety and depression at present (STADI states) and as personal characteristic (STADI traits). Patients with significant fibrosis scored worse in physical scales and often showed characteristics of major depressive disorder (according to PHQ9) (all $p < 0.05$). The differences in HRQoL were most pronounced in patients with cirrhosis, who scored worst in physical and mental health scores. Notably, the *PNPLA3* polymorphism significantly affected patients' quality of life: Carriers of the prosteatotic *PNPLA3* variant were characterized by higher level of physical fatigue (FIS), reported impaired physical functioning in everyday life and during physical activity, felt more often affected by physical pain (Sfpain) and scored worse in SFPCS (all $p < 0.05$).
Conclusion: LSM allows the detection of patients with NAFLD who have impaired life quality, including depressive states. Since not only HRQoL but also treatment success might be affected, special attention should be paid to identify depressive comorbidities in patients with fatty liver. Finally, the *PNPLA3* gene variant might represent the first genetic marker for worse HRQoL in the context of NAFLD.

SAT-304

The association between visceral fat and evolution of patients with non-alcoholic fatty liver disease

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Background and aims: Obesity is a risk factor for non-alcoholic fatty liver disease (NAFLD). However, patients with body mass index (BMI) > 30Kg/m^2 and NAFLD do not always develop advanced fibrosis (AF). The distribution of body fat predicts the risk of AF in patients with NAFLD. This study investigated the association between visceral fat (VF) and the severity of NAFLD.
Method: In this cross-sectional study, 345 patients with liver steatosis detected by ultrasound were included. 36 patients with alcohol consumption > 20gr/day, other liver comorbidities, prior bariatric or ileal surgery, ingestion of drugs known to produce hepatic

steatosis or with malignancy were excluded. All patients underwent an anthropometric evaluation, blood tests and bioimpedance (TANITA DC430PMA). AF was defined by a NAFLD fibrosis score (NFS) > 0.675 and Fibroscan® > 8.7Kpa. Histological diagnosis was obtained in 80 patients

Results: Between September 2017 and August 2018, 309 patients were collected for the study (63.83% male, age 57 years (SD10.4), Metabolic syndrome (MetS) 52.1% and Obesity 53.1%). 32 (10.4%) patients had AF. Age (66 vs. 56 years; p < 0.01), BMI (35 vs 30.8 Kg/m^2; p < 0.01), waist circumference (WC) (118.1 vs. 106.3 cm; p < 0.01), VF (19 vs. 13; p < 0.01), bilirubin (1 vs. 0.7 mg/dl; p < 0.01), FA (95.3 vs. 81IU/L; p = 0.02) and MetS (78.1 vs. 49.1%; p < 0.01) were related to AF. In the multivariate analysis bilirubin (OR 4.7, 95%CI 1.9-11.8; p < 0.01) and VF (OR 1.3, 95%CI 1.2-1.4; p < 0.01) were related to AF. The optimal cutoff point for VF in terms of AF prediction is 16 (Youdeńs index = 0.74) (Se 69% and Sp 78%) and an AUROC of 0.8 (95CI0.7-0.9) (Figure1).

In the cohort of patients confirmed by liver biopsy, 30 (37.2%) patients had AF. Age (63 vs. 53years; p < 0.01), VF (18 vs. 14; p = 0.02), Fibroscan® (23.2 vs 9.2Kpa; p < 0.01), platelets (158.8 vs. 222.2 10F3/microL; p < 0.01) and MetS (100 vs. 55.2%; p < 0.01) were related to AF. The risk of AF was higher in patients with higher VF (OR 1.2, 95%CI 1.1-1.3; p = 0.02) and the optimal cutoff point for VF to predict AF is 14 (Youdeńs index = 0.8) (Se 92% and Sp 61%) and an AUROC of 0.8 (95CI 0.7-0.9)

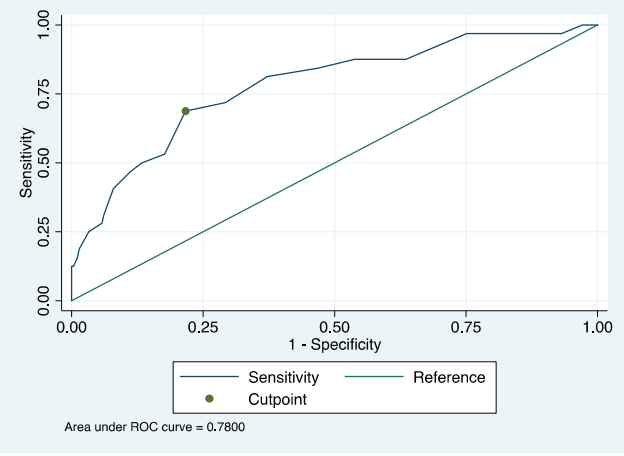

Figure: ROC curve between VF and AF (n = 309)

Conclusion: VF is independently associated with AF in patients with NAFLD. VF is a surrogate marker of visceral obesity and should be measured in all patients with high BMI and NAFLD to predict AF.

SAT-305

Alignment between physician-estimated versus objectively derived fibrosis scores in non-alcoholic steatohepatitis: Real-world evidence suggests clinicians underestimate disease severity in secondary care

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Background and aims: In a real-world setting, physicians do not always have access to or wish to subject patients to the invasive reference standard liver biopsy (LB) diagnostic tool for Non-Alcoholic Steatohepatitis (NASH). Alternative non-invasive tests (NIT) are often relied upon and clinical severity assessment subsequently assigned. This analysis aims to establish the degree of alignment in the real-world with severity staging when comparing physician estimated fibrosis scores to published fibrosis reference points, irrespective of the diagnostic pathway the specialist used to diagnose NASH.

Method: Data were derived from the 2018 5EU Adelphi NASH Disease Specific Programme, a real-world, cross-sectional survey. Physicians completed questionnaires describing five consecutive NASH patients. Diagnosis was via LB or NIT assessment. Physicians reported diagnostic test, stated fibrosis score and Fibroscan reporting. Patients were grouped by fibrosis stage: F0-F2 vs. F3-F4 (Advanced Fibrosis NASH [AF-NASH]). Fibroscan assessment was applied as recommended in two previous studies via both specificity and sensitivity approaches.

Results: 370 physicians (35% hepatologists, 38% gastroenterologists, 27% diabetologists) provided data on 1, 844 NASH patients. Of these, 1, 175 had both a physician-reported fibrosis score and Fibroscan result. Physician-stated fibrosis scores yielded 22% AF-NASH patients. The 1st studies' sensitivity yielded higher proportion of AF-NASH patients vs. specificity (79% vs 61%) as did the 2nd (69% vs 46%). Applying these criteria, NASH patients can have their fibrosis score underestimated by their physician in the real-world (1st study: Specificity 29%, Sensitivity 40%; 2nd study: Specificity 21%, Sensitivity 33%). Of note, the 1st study does state using values with a higher specificity produces more false positive results and conversely a higher sensitivity will produce more false negatives.

Conclusion: In a real-world setting, specialists do not always correctly estimate a NASH patient's fibrosis stage when compared to established Fibroscan reference points. As many as one in four patients may be assigned an incorrect, lower fibrosis score. Underestimation of fibrosis score could result in incorrect patient management and treatment approaches. Further education could help provide physicians with the tools to correctly assign fibrosis classification and enhance optimal patient management approaches.

SAT-306

Autotaxin is a valuable biomarker for predicting liver fibrosis in patients with non-alcoholic fatty liver disease

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Background and aims: Serum autotaxin (ATX) has been reported as a novel fibrosis marker in various chronic liver diseases. In this study we investigated the clinical characteristics of ATX and the diagnostic performance of ATX for liver fibrosis in large cohort sizes of NAFLD subjects.

Method: We compared the usefulness of ATX and other fibrosis markers (hyaluronic acid, type IV collagen 7S, Fibrosis-4 index, and aspartate aminotransferase to platelet ratio index) in 307 biopsy proven NAFLD subjects. In 145 NAFLD subjects, we compared the diagnostic performance of ATX with that of non-invasive imaging methods (vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE)).

Results: There were 307 biopsy proven NAFLD subjects; median age 51.8 ± 14.9 years; 173 males, 134 females. Fibrosis stage was stage 0 for 33 cases (10.7%), stage 1 for 154 cases (50.2%), stage 2 for 52 cases (16.9%), stage 3 for 59 cases (19.2%), stage 4 for 9 cases (3%). Median serum ATX levels in all NAFLD subjects were 0.81 ± 0.32 mg/L. Serum ATX levels in male subjects were significantly lower than in female subjects (0.67 ± 0.21 vs 0.97 ± 0.36, respectively; p = < 0.0001). Serum ATX levels were significantly correlated with fibrosis stage in both male and female NAFLD subjects (Figure). In male NAFLD subjects, the area under the receiver operating characteristic (AUROC) value of ATX for diagnosis of ≧stage 1 was 0.65 and other AUROC values were more than 0.75. In female NAFLD subjects, the AUROC values were all more than 0.81 and that for diagnosis of ≧stage 1 was

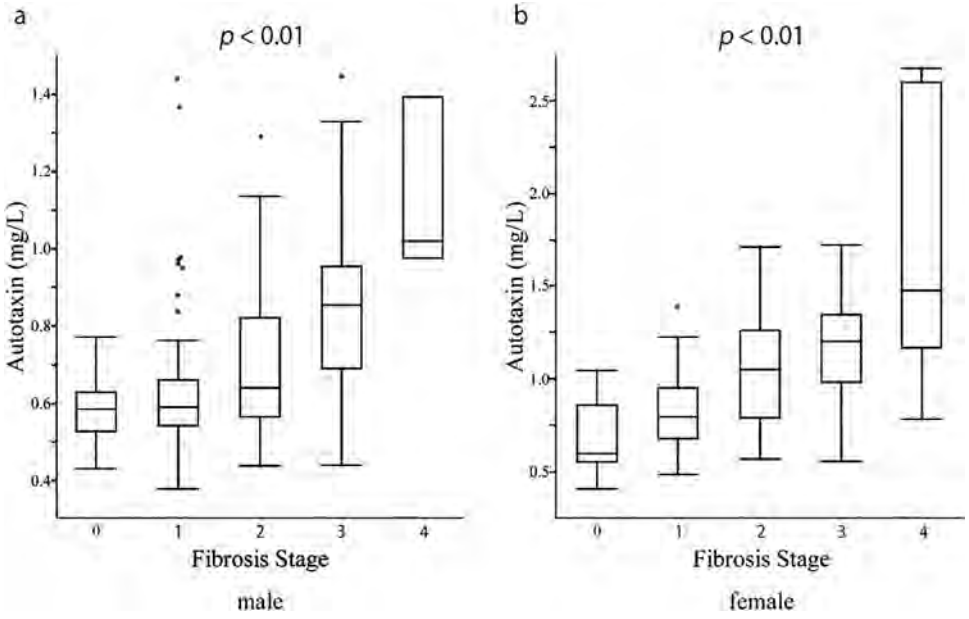

Figure: (abstract: SAT-306)

highest compared with other fibrosis makers. Sensitivities of ATX were highest in diagnosis of ≧stage 2 and ≧stage 3 in both male and female NAFLD subjects. In the comparison between ATX and non-invasive imaging methods, the AUROC levels of MRE were highest in all fibrosis stages.

Conclusion: Serum ATX levels were significantly correlated with fibrosis stage in NAFLD subjects. The diagnostic accuracy of ATX for liver fibrosis was found to be lower than that of MRE, however the diagnostic performance of ATX were comparable with that of other fibrosis markers excluding type IV collagen 7S and sensitivities of ATX in diagnosis of ≧stage 2 and ≧stage 3 were highest. It is supposed that ATX is useful for the selection of patients requiring further examination for liver fibrosis. Further studies must be conducted to explore the usefulness of ATX in NAFLD subjects.

SAT-307

A direct comparative study among magnetic resonance elastography, vibration controlled transient elastography and shear wave elastography in patients with non-alcoholic fatty liver disease

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Background and aims: Non-invasive Methods have been evaluated for the assessment of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). We previously indicated that magnetic resonance elastography (MRE) had higher diagnostic accuracy than vibration-controlled transient elastography (VCTE) in the assessment of each liver fibrosis stage (Gastroenterology 2016). In present study, the diagnostic ability of MRE, VCTE and shear wave elastography (SWE) for liver fibrosis were compared directly in patients with NAFLD.

Method: We performed a cross-sectional study of 119 patients with NAFLD (identified by liver biopsy; mean body mass index, 27.9 kg/m^2). All study subjects were evaluated by MRE using 3.0-T imagers (GE Healthcare), VCTE with the M or XL probe (Fibroscan: EchoSens) and SWE using LOGIQ S8 FS (GE Healthcare). In addition, we aimed to investigate the inter and intraobserver variability of MRE, VCTE and SWE to assess liver fibrosis. Inter and intraobserver variability was assessed by using kappa (κ) statistics.

Results: A rate of reliable measurements of MRE, VCTE and SWE were 98.3%, 93.2% and 86.5%, respectively. The diagnostic accuracy of MRE, VCTE and SWE in detecting liver fibrosis in patients with NAFLD (n = 108) in which all MRE, VCTE and SWE could be performed successfully, are directly compared. MRE, VCTE and SWE identified patients with fibrosis stage > 1, > 2, > 3 and > 4 with an area under the receiver operating characteristic (AUROC) curve value of 0.99 or 0.98 or 0.90, 0.87 or 0.86 or 0.86, 0.87 or 0.85 or 0.86 and 0.90 or 0.85 or 0.88, respectively. The interobserver agreements of MRE, VCTE and SWE were 92%, 85% and 74%, respectively. The intraobserver

Figure: (abstract: SAT-307)

agreement was of MRE, VCTE and SWE was 93%, 88% and 80%, respectively.
Conclusion: MRE had high diagnostic accuracy in the assessment of each liver fibrosis stage relative to VCTE and SWE. In addition, intra and interobserver variability of MRE in evaluation of liver stiffness was excellent compared with VCTE and SWE.
MRE vs VCTE vs SWE

SAT-308

The optimal cut-off points of FIB-4 index for predicting the incidences of HCC and extra-hepatic malignancies in biopsy-proven Japanese NAFLD patients

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Background and aims: The utility of the FIB-4 index, a non-invasive fibrosis marker, used instead of liver biopsy have been reported for predicting the hepatic fibrosis and prognosis in patients with chronic liver diseases. The cut-off points of the FIB-4 index to exclude and diagnose advanced fibrosis in non-alcoholic fatty liver disease (NAFLD) were reported as 1.30 and 2.67, respectively. However, it remains unclear whether these cut-off points of the FIB-4 index are suitable for assessing the outcomes in NAFLD patients, including extra-hepatic carcinogenesis. We therefore aimed to clarify the prognosis in biopsy-proven NAFLD patients based on the FIB-4 index.
Method: A total of 312 patients with Japanese NAFLD diagnosed by liver biopsy were enrolled. We investigated the factors associated with the incidences of hepatic/extra-hepatic malignancies.
Results: The cumulative incidental numbers of hepatocellular carcinoma (HCC) and extra-hepatic malignancies were 11 (3.5%) and 21 (6.7%) during follow-up period (median 7.2 years), respectively. When patients were categorized into three groups based on FIB-4 index; < 1.30 (low, n = 145), 1.30-2.67 (intermediate, n = 100), and ≥ 2.67 (high, n = 67), high FIB-4 group was at the highest risk for HCC (low vs intermediate, P = 0.040; intermediate vs high, P < 0.001). On the other hand, intermediate and high FIB-4 index groups had higher incidental rate of extra-hepatic malignancies compared with low FIB-4 group (p < 0.01). However, there was no significant difference between intermediate and high FIB-4 groups (p = 0.853). Risk factors significantly associated with hepatocarcinogenesis and extra-hepatic carcinogenesis in multivariate analysis were following: liver fibrosis (F3-4) (hazard ratio [HR] 10.539, 95% confidence interval [CI] 2.009-55.286, P = 0.005) and FIB-4 index ≥ 2.67 (HR 3.373, 95% CI 0.803-14.173, P = 0.097) for HCC, and liver inflammation (A2-3) (HR 2.611, 95% CI 1.003-6.797), FIB-4 index > 1.3 and < 2.67 (HR 4.132, 95% CI 1.142-14.949, P = 0.031), and FIB-4 index ≥ 2.67 (HR 3.127, 95% CI 0.770-12.696, P = 0.111) for extra-hepatic malignancies.
Conclusion: Both 1.30 and 2.67 as cut-off points of the FIB-4 index could predict hepatocarcinogenesis with good discriminative ability. Conversely, lower cut-off value of FIB-4 index (1.30), not 2.67, was suitable to predict the incidence of extra-hepatic malignancies. In addition, hepatic inflammation preceding severe fibrosis may be a surrogate marker for the earlier prediction of extra-hepatic carcinogenesis in NAFLD patients.

SAT-309

Prevalence of NAFLD and metabolic syndrome in rural and regional Victoria, Australia

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease in Western communities. Epidemiological data is limited in Australia and frequently extrapolated from overseas studies and culturally distinct ethnic groups. Moreover, there is a paucity of data on the prevalence of NAFLD in rural and regional communities that have poorer health outcomes than metropolitan regions. Thus, we examined the prevalence of NAFLD using non-invasive techniques in rural and regional communities in Victoria, Australia.
Method: We conducted a cross-sectional epidemiological study across four towns in the Goulburn Valley, Victoria, Australia (200 km from Melbourne) as part of a larger population health study-The Crossroads 2 Project. Households were randomly selected from the local government rate payer lists and one adult from each household was randomly selected and invited to a screening clinic. Comprehensive demographic and health related data were obtained. Abnormal ALT was determined as > 1.5 x ULN adjusted for gender (Male < 30U/L and Female < 20U/L). Steatosis was defined as CAp > 250 dB/m. FibroScan® 402 or 530 compact was used. Patients were grouped according to liver stiffness measurement (LSM) < 7.0 kPa, 7.0 ≤ LSM < 12.5 kPa and LSM ≥ 12.5 kPa. Metabolic syndrome was defined according to ATPIII criteria.
Results: A total of 748 participants (Male = 45%, Age 59.6 ± 16 yrs, range 18-92 yrs) completed the clinical assessment. The mean BMI was 28.9 ± 6 kg/m^2 and only 26% had a BMI < 25 kg/m^2. The metabolic syndrome was present in 26% and diabetes mellitus in 10%. Excluding those with an alternative cause for liver disease (n = 57; Alcohol n = 49, HCV Ab + ve n = 8), ALT > 1.5 x ULN consistent with NAFLD was detected in 97/677 (14%). 405 underwent successful assessment with FibroScan (XL probe n = 192) with the mean LSM = 5.7 kPa. LSM ≥ 12.5 kPa or 12.5 > LSM ≥ 7.0 kPa was seen in 9 (2%) and 60 (15%) subjects respectively. The CAP score was available in 79 subjects and was > 250 dB/m in 63%. Severe fibrosis (F3/F4) was suggested in 5% (28/600) by NFS > 0.675 and 2% by FIB4 > 3.25. There was no difference in age or BMI across the LSM groups, but ALT was associated with higher LSM (p < 0.001).
Conclusion: This cross-sectional study in regional Victoria demonstrates high rates of obesity (74%) and the metabolic syndrome (26%). Furthermore there are high rates of hepatic steatosis as determined by CAP (63%). Non-invasive tests indicate advanced fibrosis (F3/4) present in 2-5%. These findings highlight a potential significant burden of metabolic liver disease in rural and regional Victoria.

SAT-310

Real-world evaluation of NASH in US clinical practice: Underutilization of liver biopsy and liver imaging

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Background and aims: NASH requires histologic diagnosis by liver biopsy and the new drug development for NASH requires primary histologic end points (NASH resolution or fibrosis improvement). Hepatology clinical care has moved away from liver biopsy to utilizing non-invasive markers for clinical decision making. The aim of this study was to evaluate the use of liver biopsy and liver imaging in patients with clinical diagnosis of NASH in real world clinical care.
Method: Data were obtained by Trio Health from a national proprietary EMR database containing demographic, medication, lab, diagnosis, and procedure information from academic, hospital, and community care centers in the US. For this study, data were

limited to adult patients from 19 healthcare organizations followed for 3 years (ending in Oct 2018). NAFLD was defined as ICD10 codes K75.81 or K76 and NASH as K75.81. In addition, patients at NASH risk and meeting criteria for evaluation with potential liver biopsy were defined as AGE > 50 years, ALT > 40 U/L + [Type II Diabetes (T2DM) or BMI > 30 kg/m^2] without viral hepatitis or evidence of alcohol abuse/complications. Imaging and liver biopsy were assigned using CPT and ICD-10 codes.

Results: Of the 2, 792, 087 adult patients in the study, 207, 632 (7%) met the predefined criteria of either NASH diagnosis by ICD-10 (N = 8, 010) or at risk of NASH (N = 199, 622). NASH risk was seen in 38% of those diagnosed with NASH (3, 031/8, 010) and 14% with NAFLD (19, 734/137, 495). Despite fulfilling NASH risk criteria, liver biopsy was obtained in only 1-5% of subjects. In contrast, imaging was performed 13-45% of subjects (Table).

Table:

Group	NASH Risk Criteria	Patients	Liver Biopsy	Imaging
NAFLD-K75.81 or K76	All patients-no filters for risk	137495	3327/ 137495 (2%)	31978/ 137495 (23%)
	Age > 50 + ALT > 40 + [BMI > 30 or T2DM]	19734	1027/ 19734 (5%)	8588/ 19734 (44%)
NASH-K75.81 only	All patients-no filters for risk	8010	328/8010 (4%)	2262/ 8010 (28%)
	Age > 50 + ALT > 40 + [BMI > 30 or T2DM]	3031	148/3031 (5%)	1034/ 3031 (34%)
NAFLD-K76 only	Age > 50 + ALT > 40 + [BMI > 30 or T2DM]	16703	879/ 16703 (5%)	7554/ 16703 (45%)
Non-NASH by diagnostic code. Positive risk factors	Age > 50 + ALT > 40 + [BMI > 30 or T2DM]	199622	1492/ 199622 (1%)	26496/ 199622 (13%)

Conclusion: Utilizing well accepted coding and risk factors for NASH, there is almost no utilization of liver biopsy in clinical care in the US with almost a 10-fold higher use of imaging. Novel NASH treatments will either require development of non-invasive diagnostic and outcome surrogates or change current clinical practice in the US.

SAT-311

The PDGFR-beta containing PRTA-score is a novel non-invasive diagnostic algorithm for significant liver fibrosis in patients with viral, alcoholic, and metabolic liver disease

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Background and aims: Diagnosis of liver fibrosis onset and regression remains a controversial subject in the current clinical setting, as the gold standard remains the invasive liver biopsy. Multiple novel non-invasive markers have been proposed but lack sufficient sensitivity and specificity for diagnosis of early stage liver fibrosis. Platelet Derived Growth Factor Receptor beta (PDGFRβ) has been associated to hepatic stellate cell activation and has been the target of multiple therapeutic studies. However, little is known concerning its use as a diagnostic agent. In this study, we analysed the diagnostic potential of PDGFRβ for liver fibrosis in a heterogenous patient population.

Method: The study cohort consisted of 148 patients with liver fibrosis/cirrhosis due to various causes of liver injury (metabolic, alcoholic, viral), and 14 healthy individuals as control population. A validation cohort of 57 patients with metabolic liver disease, who underwent liver biopsy to stage fibrosis, were gathered. Circulating soluble PDGFRβ (sPDGFRβ) levels were determined using a commercial ELISA kit. The diagnostic performance of sPDGFRβ as individual parameter, or in combination with other biochemical and metabolic factors was evaluated, and values were compared to those obtained by the clinical diagnostic algorithms Fib-4, APRI, and AST/ALT ratio.

Results: In the total patient population, sPDGFRβ levels were progressively augmented with increasing fibrosis stage. Circulating sPDGFRβ levels were elevated ($p < 0.0001$) in patients with significant fibrosis ($F \geq 2$), compared to no or mild fibrosis (F0/1), with a discriminative capacity, as quantified by AUC, of 0.7303, which was shown to be higher for this cohort than the AUCs of Fib-4, APRI, and AST/ALT ratio. The accuracy of sPDGFRβ could be increased by combining it with albumin levels and platelet counts into a novel diagnostic algorithm, which we termed the PRTA-score. Using a cut-off value of 7.804; a sensitivity of 77.11% and a specificity of 73.17% could be obtained for the diagnosis of significant fibrosis ($F \geq 2$). AUC values for the prediction of advanced liver fibrosis ($F \geq 3$) and cirrhosis ($F = 4$) were respectively 0.7470 and 0.7995; values which are slightly better, or comparable to Fib-4, APRI, and AST/ALT ratio. The diagnostic value of sPDGFRβ levels and the PRTA score were confirmed in an independent patient cohort, suffering from metabolic liver disease, which were staged for fibrosis by liver biopsy.

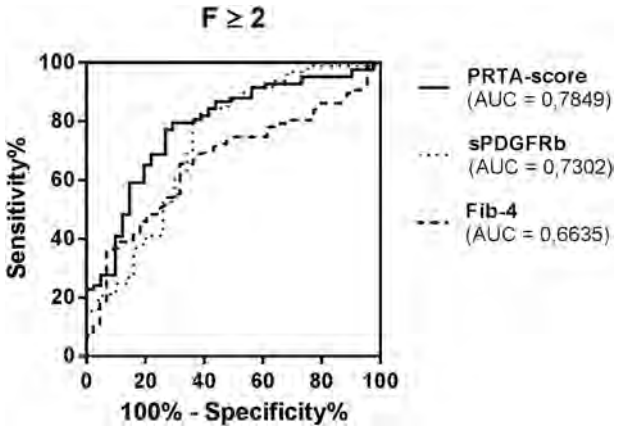

Figure: Comparison of performance of sPDGFRβ, PRTA-score and Fib-4 in the diagnosis of significant liver fibrosis

Conclusion: We put forth the PRTA score as an easy applicable, low cost and accurate scoring for significant liver fibrosis. With validation in larger patient cohorts, this serological test could become an important tool in future non-invasive clinical assessment of liver fibrosis.

SAT-312

Serial liver stiffness and controlled attenuation parameter measurements by transient elastography in patients with type 2 diabetes: A prospective cohort study

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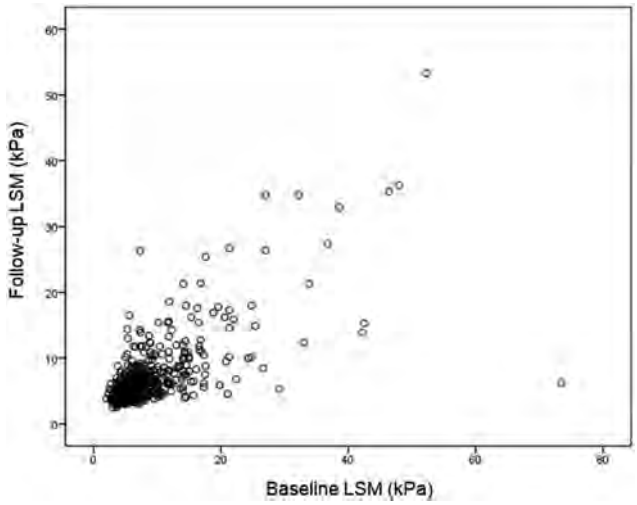
Background and aims: Type 2 diabetes is an important risk factor for non-alcoholic fatty liver disease (NAFLD) and advanced fibrosis. Current European guidelines recommend repeating non-invasive

tests of fibrosis in NAFLD patients at 3-yearly intervals, but data are largely lacking. Here we report the changes in the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) by transient elastography (TE) in patients with type 2 diabetes at 3 years.

Method: We recruited patients with type 2 diabetes from a complication screening facility in Hong Kong in 2013-2014 and repeated the assessment in 2016-2018. The primary end point was the proportion of patients who progressed to compensated advanced chronic liver disease (cACLD) by the Baveno VI criteria (< 10 kPa: unlikely cACLD; ≥ 15 kPa: probable cCALD). The secondary end point was the proportion of patients who experienced a change in the CAP.

Results: A total of 612 diabetic patients with valid LSM (mean age, 61.3 ± 10.8 years; 343 males [56.0%]) were included in this study (573 also had valid CAP). There was a history of hypertension, ischaemic heart disease, and stroke in 53.8% (n = 330), 15.2% (n = 93), and 5.5% (n = 34) of the patients, respectively. Overall, there was moderate correlation between baseline and follow-up LSM (r = 0.689, P < 0.001; Figure). At baseline, 557 (90.9%) patients had an LSM < 15 kPa (487 [79.6%] < 10 kPa), and 15 (2.7%) had follow-up LSM ≥ 15 kPa. Among the remaining 55 (9.0%) patients with LSM ≥ 15 kPa at baseline, 31 (56.4%) had follow-up LSM < 15 kPa (18 [32.7%] < 10 kPa). Among 198/573 (34.6%) patients with CAp < 248 dB/m at baseline, 103 (52.0%) had CAP increased to ≥ 248 dB/m (55 [27.8%] ≥ 280 dB/m suggestive of severe steatosis). Among the 375/573 (61.3%) patients with a CAP ≥ 248 dB/m at baseline, CAP decreased to < 248 dB/m in 49 (13.1%) patients.



Conclusion: The prevalence and incidence of NAFLD in patients with type 2 diabetes are high. While cACLD is common in this population, the incidence of cACLD is relatively low. Our results support one-off fibrosis testing in diabetic patients but not routine 3-yearly assessments in all patients.

SAT-313

Exosomal miRNA analysis for classifying severity of disease in biopsy-proven NAFLD patients

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is becoming leading cause of chronic liver disease. Although determining the exact mechanisms that lead to NAFLD and NASH is important for disease identification, factors that regulate disease progression are largely unknown. In this study, we analyzed serum exosomal miRNA from biopsy-proven NAFLD patients and compared miRNA expression according to disease severity.

Method: Sera were collected from 41 patients with biopsy-proven NAFLD without other chronic liver disease from November 2016 to January 2018. Sera were stored at −20°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.

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-significant fibrosis group (F0-2, n = 25) and significant fibrosis group (F3-4, n = 16). 40 miRNAs expression were significantly increased in advanced fibrosis group comparing with non-advanced fibrosis group. (Figure) Among them, miRNA4668 and miRNA3613 were increased more than 8 times in advanced fibrosis group comparing with non-advanced fibrosis group. Whereas 22 miRNAs expression were significantly increased in non-advanced fibrosis group comparing with advanced fibrosis group. When patients were classified into NASH group (n = 19) and non-NASH group (n = 22), 4 miRNAs showed higher expression comparing with NAFL group, whereas 1 miRNAs showed lower expression in NASH group comparing with NAFL group. In comparison between severe inflammation group (grade 2, 3, n = 25) and mid inflammation group (grade 0, 1, n = 16), severe inflammation group showed higher expression of 1 miRNA and lower expression of 9 miRNAs comparing with mid inflammation group.

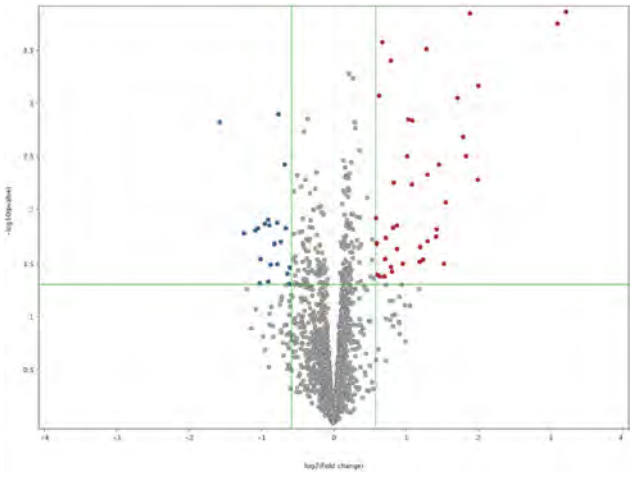

Figure: Volcano plot. F 0, 1, 2 (Blue) versus F3, 4 (Red)

Conclusion: miRNA expression analysis showed significant differences according to status of fibrosis, NASH, and inflammation. These results mean miRNA expression might be important factor for disease progression in NALFD patients. Further validation studies are needed to identify the role of miRNA in disease progression of NAFLD.

SAT-314

Liver fibrosis by FibroScan is highly prevalent in type 2 diabetic patients with NAFLD and fairly normal liver enzymes but increased uric acid

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Background and aims: Type 2 diabetes mellitus (T2DM) is a risk factor for the onset and progression of non-alcoholic fatty liver disease (NAFLD) to liver fibrosis, but this issue is often neglected. Liver biopsy is the gold standard for staging NAFLD, but it is not routinely applicable to wide cohorts of T2DM patients. We aimed at estimating non-invasively prevalence and predictors of NAFLD and fibrosis in a multi-center cohort of T2DM patients.
Method: Three-hundred nineteen T2DM patients attending the diabetes outpatient clinic in five Italian centres were enrolled. Secondary causes of liver disease were excluded. All patients underwent liver ultrasound (steatosis grading 1-3) and FibroScan®. Controlled attenuation parameter (CAP) ≥ 248 Db/m and liver stiffness measurement (LSM) ≥ 8.7 kPa for M probe and ≥ 7.2 kPa for XL probe defined steatosis and advanced fibrosis, respectively.
Results: Among the 319 T2DM patients included (mean age 69 ± 9 years; 49% males; mean HbA1c 7 ± 1.1%), hypertension was present in 78%, dyslipidemia in 84% (mostly treated with statins) and obesity in 32%; 64% of these patients were treated with hypoglycaemic drugs and 36% with diet only; nearly 55% of them had micro-vascular or macro-vascular complications. Elevated levels of AST, ALT and GGT were present only in 3%, 7% and 11% of patients, respectively. The overall prevalence of hepatic steatosis was 89% (severe in 15%), confirmed in 80% of cases by CAP (available in 196 cases). LSM mean values were not significantly different in patients with and without steatosis (5.6 ± 2.7 vs 4.8 ± 1.2 kPa). In patients with steatosis, presence of severe fibrosis (LSM ≥ 8.7/7.2 kPa) was detected in 29 (11%) and correlated in multivariate analysis with elevated serum GGT (OR 1.02; CI 95% 1-1.04; p = 0.04), hyperuricemia (OR 9.8; CI 95% 1.9-50; p = 0.006), BMI (OR 1.2; CI 95% 1-1.05; p = 0.04), severe steatosis (OR 14; CI 95% 2.2-88.7; p = 0.005), and HbA1c > 7% (OR 1.1; CI 95% 1.1-22.2; p = 0.04). LSM, even when considered as continuous variable, did not show any significant association with diabetic complication status, hypoglycaemic treatment and diabetes duration.
Conclusion: NAFLD is highly prevalent in T2DM patients (89%), advanced liver fibrosis is detectable in 11% of them, especially if severe steatosis, obesity and hyperuricemia also coexist. We suggest a non-invasive screening for liver fibrosis in patients with T2DM and NAFLD, irrespective of serum transaminase levels and diabetic complications.

SAT-315

Clinical utility and application of non-invasive tests of fibrosis in the selection of patients with advanced fibrosis due to NASH in the Phase 2 ATLAS trial

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Background and aims: Liver biopsy is a barrier to clinical trial enrollment in NASH. We describe the utility of non-invasive tests (NITs) to enroll patients with advanced fibrosis (F3-F4) due to NASH.
Method: The ATLAS study (NCT03449446) enrolled patients based on: 1) a biopsy showing F3-F4 fibrosis per the NASH CRN classification (the biopsy cohort); or 2) in the absence of a prior biopsy, an ELF test ≥ 9.8 and liver stiffness (LS) by transient elastography (TE; FibroScan) ≥ 14.0 kPa using the XL probe (the NIT cohort). Patients in the NIT cohort had baseline biopsies and were randomized regardless of results. Analyses are based on an interim data cut.
Results: Of the 645 screened patients with evaluable fibrosis stage (median age 59 years, 62% women, 61% with diabetes, median BMI 33.7 kg/m^2), 395 were enrolled. Fifty-five (14%) qualified based on NIT criteria; F3-F4 fibrosis was confirmed in 87% (48/55) (4% F0, 4% F1, 5% F2, 22% F3, 65% F4). Patients in the biopsy cohort with F3-F4 fibrosis had demographics, liver biochemistry, and serum fibrosis markers similar to those in the NIT cohort, but with higher LS by TE (Table). The proportions of patients with NAS ≥ 4 (87% vs 86%) and cirrhosis (65% vs 53%; p = 0.09) did not differ between the NIT and biopsy cohorts. Within the NIT cohort, biopsy length was shorter in patients with F0-F2 vs F3-F4 (1.3 vs 2.2 cm; p = 0.18). Patients with F0-F2 fibrosis also had lower BMI (31.0 vs 34.4 kg/m^2; p = 0.11), less diabetes (43% vs 75%), and less lobular inflammation and ballooning.

Table: Baseline Laboratory and Histological Features

Parameter	Screen Failures F0-F2 (n = 148)	Biopsy Cohort F3-F4 (n = 442)	NIT Cohort* F0-F2 (n = 7)	NIT Cohort* F3-F4 (n = 48)
ALT, U/L	32	42	21	47
FIB-4	1.2	2.0	0.9	2.3
ELF	8.9	10.0	10.1	10.6
LS by TE†, kPa	9.0	14.8	14.4	21.2
Lobular inflammation grade 3	22 (15)	257 (58)	1 (14)	29 (60)
Ballooning grade 2	50 (34)	348 (79)	4 (57)	39 (81)

Data are median or n (%).
* Patients in the NIT cohort are not included in the screen failures or biopsy cohort.
† LS using FibroScan XL probe. Data in n = 123 screen failures, n = 363 with F3-F4 in the biopsy cohort, and all in the NIT cohort.

Conclusion: In this Phase 2 trial of patients with NASH, a combination of ELF and LS by TE identified the target population in 87% of patients. Enrollment based on NITs should be considered for future NASH studies to reduce reliance on biopsy.

SAT-316

Non-invasive assesment of arterial stiffness and carotid intima-media thickness in children with non-alcoholic fatty liver disease

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of cardiovascular disease developing. The increase of local arterial stiffness and carotid intima-media thickness are the earliest structural and functional changes that can be used for instrumental evaluation.
Aim: To study the elastic features of the carotid arteries wall in NAFLD patients and its association with steatohepatitis.
Method: 113 patients aged 8-17 years were examined. Diagnosis of hepatic steatosis was conducted using FibroScan®502touch

(Echosens, Paris, France). Ultrasonic examination of vessels was carried out by Soneus P7 (Kharkiv, Ukraine). The carotid intima media thickness (cIMT) was examined at the standard point at maximum zooming. Patients group distribution was performed according to the presence of obesity/overweight, liver steatosis/steatohepatitis (according to controlled attenuation parameter and ALT level): group 1 consisted of 34 children with simple steatosis and overweight/obesity, group 2-22 children with steatohepatitis and overweight/obesity, group 3-43 children with overweight/obesity without steatosis, (control) group 4-14 children with normal weight.
Results: There was an increase in the pulse wave velocity (PWV), as well as the elastic modulus (EM) in children with NAFLD, with the significant differences of these parameters in patients with simple steatosis. Children with simple steatosis and steatohepatitis differed from the control group by a significant increase in the carotid wall stiffness index (SI) (p < 0, 05). Patients with non-alcoholic steatohepatitis had the highest values of cIMT (0, 051 ± 0, 001) mm, which significantly differentiated these patients from the control group and children with overweight without steatosis (p < 0, 05).
Conclusion: The course of NAFLD in children is accompanied by vascular changes in the form of increased local arterial stiffness and carotid intima media thickness in the case of steatohepatitis.

SAT-317

Fibroscan as a tool to improve cardiovascular disease stratification: Truth or myth?

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. Transient elastography (TE, Fibroscan) with controlled attenuation parameter (CAP) has already been proven as an accurate measure for hepatic fibrosis and steatosis. However, its role in stratifying cardiovascular (CV) risk is unknown.
Method: Cohort, retrospective, single center study, including consecutive NAFLD patients that underwent Fibroscan. Patients were followed at least a year. Co-variables were chosen bearing in mind clinical relevance and literature evidence. The correlation towards the outcome variable (Cardiovascular event) was assessed with univariate and multivariate analysis, using SPSS-p value < 0.05 was considered statistically significant
Results: We assessed 96 patients with NAFLD, of whom 64 (66, 7%) were female, with a mean age of 51, 6 years old, all Caucasian. From our cohort, 55.2% of the patients met criteria for metabolic syndrome. Several variables had statistical significance towards cardiovascular events incidence on the univariate analysis. (Cardiac failure; Hypertension; dyslipidemia, diabetes mellitus, metabolic syndrome, body mass index, CAP higher 290 db/m, Framigham score and some therapeutics, hypocoagulation agents, antiplatelet agents, statins, antihypertension agents.) We report 14 (14, 4%) cardiovascular events during follow-up, the CAP mean in this subgroup was 318, 4 db/m. For CAP values superior to 290 db/m (decibels per meter), the odd of incidence of cardiovascular events were 4, 2 times higher, for each unit of cap increase (Odds ratio crude 4, 250; p value 0.05). Adjusting the regression multivariate model with previous significant variables, the association trend to statistically non-significance. Framingham score was not correlated statistically with CAP values.
Conclusion: We were able to stablish a correlation between CAP and incidence of cardiovascular disease events. Meaning that, a CAP increase is associated with increase of incidence on CV events, mainly in high cap values, over 290 db/m. However, this correlation is diluted adjusting to another CV risk predictor covariables. Fibroscan is easy to apply, safe and a cost-effective Method to evaluate NAFLD. CAP values are related to CV events, nevertheless, further studies are needed to identify properly the subpopulation that would most benefit from this feature.

SAT-318

Comparative accuracy of NAFLD fibrosis score, apri score, and FIB-4 score in predicting significant fibrosis in African Americans and Caucasians with non-alcoholic fatty liver disease

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Background and aims: NAFLD Fibrosis score (NFS), FIB-4 score and APRI scores are non-invasive scoring systems for the staging of liver fibrosis in patients with chronic liver diseases. There is no systematic study that has compared the accuracy of these scores with liver histology in NAFLD among African American and Caucasians. In a large cohort of NAFLD patients we aimed to compare NFS, FIB-4 and APRI score in predicting histologically confirmed significant fibrosis (defined as fibrosis stage ≥ 2) in African American and Caucasian patients using liver biopsy as the gold standard.
Method: A retrospective review of the electronic medical records (EMR) from January 2006 thru December 2016 was performed at a large transplant center using ICD-9/ICD-10 codes to identify NAFLD patients (N = 3, 749). Patients with significant alcohol abuse, HIV, hepatitis B, hepatitis C and ≤ 18 years were excluded. Further manual review of the histological/surgical pathology reports was conducted to confirm NAFLD in these patients to form the final cohort of 904 NAFLD patients: 230 of these were African American and 674 were Caucasian (after exclusion of 25 with other ethnicities).
Results: Of the 904 patients (230 African American and 674 Caucasian) included in the analysis, 480 (53.0%) had liver biopsy prior to or at the time of bariatric surgery, and the remainder (n = 424) had liver biopsy for elevated liver biochemistries, or at the time of non-bariatric abdominal surgeries. Distribution of fibrosis stage in African American vs Caucasian were as follows: stage 0: 92 (40.0%) vs. 205 (30.4%), stage 1: 99 (43.0%) vs. 233 (34.6%), stage 2: 33 (14.3%) vs. 127 (18.9%), stage 3: 6 (2.6%) vs. 56 (8.3%), and stage 4: 0 (0%) vs. 53 (7.9%). In African American, AU-ROC (Area under the Receiver Operating Curve) for NFS in predicting significant fibrosis was 0.60 (95% CI: 0.48-0.71), for APRI score was 0.70 (95% CI: 0.61-0.79), for FIB-4 score was 0.60 (95% CI: 0.50-0.70). In Caucasian, AU-ROC for NFS in predicting significant fibrosis was 0.71 (95% CI: 0.67-0.76), for APRI score was 0.78 (95% CI: 0.74-0.82), for FIB-4 score was 0.79 (95% CI: 0.75-0.83).
Conclusion: In this large cohort of Adult patients with biopsy proven NAFLD, the majority of which were morbidly obese undergoing bariatric surgery, NFS, FIB-4, and APRI scores were all highly predictive of significant fibrosis in the Caucasian population. However, only APRI score can reliably predict significant fibrosis in African American patients with NAFLD. This suggests that ethnicity

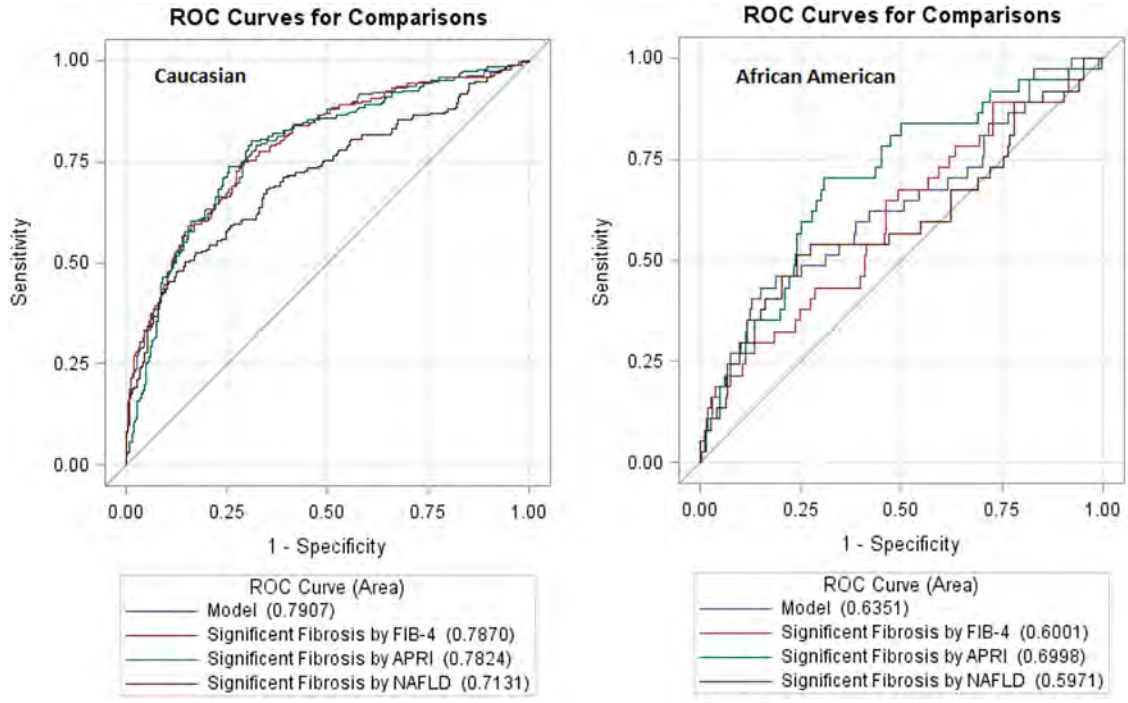

Figure: (abstract: SAT-318)

influences non-invasive fibrosis scoring systems and additional adjustments will be needed so that they can be universally applicable.

SAT-319

Fibroblast growth factor 21 is independently associated with severe hepatic steatosis in non-obese HIV-infected patients

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Background and aims: Severe hepatic steatosis shows a high prevalence and contributes to morbidity and mortality in human immunodeficiency virus (HIV) infected patients. Known risk factors include obesity, dyslipidemia and features of metabolic syndrome. Fibroblast growth factor 21 (FGF-21) is associated with hepatic glucose and lipid metabolism. This study aimed to evaluate FGF-21 as a biomarker for severe hepatic steatosis in non-obese HIV-infected patients.
Method: This is a prospective, cross-sectional, monocentric study including HIV-infected out-patients. Hepatic steatosis was measured via controlled attenuation parameter (CAP) using FibroScan 502 touch (ECHOSENS, France). Peripheral blood samples were collected and analysed for FGF-21. Demographic and clinical characteristics were collected from patient's health records.
Results: In total, 75 non-obese HIV-monoinfected patients were included in this study. Prevalence of severe hepatic steatosis was 37%. Patients with severe hepatic steatosis showed significantly higher levels of FGF-21. Univariate analysis revealed FGF-21, BMI, hyperlipidemia and arterial hypertension as significant, while multivariate analysis showed only BMI and FGF-21 as significant independent risk factors for severe hepatic steatosis.
Conclusion: This study presents FGF-21 as an independent and stronger predictor of severe hepatic steatosis than blood lipids in HIV-infected patients. Moreover, BMI predicts severe steatosis even in non-obese HIV-monoinfected patients. Furthermore, this study supports existing metabolic risk factors and expands them to non-obese HIV-infected patients.

SAT-320

The use of the fatty liver index and fibroscan to determine the prevalence of non-alcoholic fatty liver disease in an Irish population

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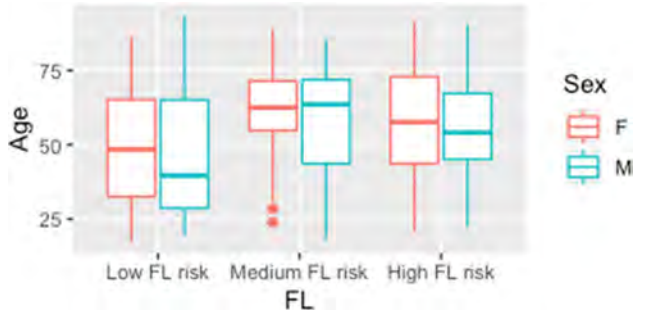
Background and aims: Rates of non-alcoholic fatty liver disease are increasing worldwide. Non-alcoholic fatty liver disease is now the second most common indication for liver transplant in the USA. The Fatty Liver Index has been developed as a non-invasive predictor of fatty liver. This prospective cohort study used the fatty liver index to indicate the prevalence of non-alcoholic fatty liver disease in a population of patients presenting to an Acute Medical Unit in the West of Ireland, and to subsequently perform a fibroscan on those with high FLI scores to assess for the degree of hepatic steatosis and fibrosis in this group.
Method: All patients attending the Acute Medical Unit in a six-month period were invited to participate. Patients with excess alcohol consumption or pre-existing liver disease were excluded. Using established fatty liver index cut-offs; 414 participants were grouped into low (FLI ≤ 30), medium (30 < FLI ≤ 60) and high (FLI >) risk of non-alcoholic fatty liver disease. Patients with fatty liver index scores > 60 were invited to attend a follow-up clinic at which more detailed

examination took place, including fibroscan and controlled attenuation parameter score.
Results: 138 participants were in the low risk group, 92 in the medium risk group and 184 (45%) were in the high risk group. Male sex ($p < 0.0001$) and increasing age ($p < 0.0001$) were associated with higher risk. Patients in the high risk group (N = 184) were invited back for follow-up; of these, 120 attended. Of these 120, 13 participants had an elevated fibroscan score > 7kPa. Higher fatty liver index scores were associated with higher controlled attenuation parameter scores ($p < 0.0001$) but there was no association between fibroscan score and fatty liver index score ($p = 0.53$). Fasting glucose and HbA1c were both found to be associated with higher fibroscan scores, with a 1 mmol/L change in glucose having a 0.604 average increase in fibroscan (95% CI 0.097 to 1.111; $p = 0.021$), while an increase of 1% in HbA1C lead to a mean change of 0.054 in fibroscan (95% CI 0.015 to 0.092; $p = 0.007$).



Conclusion: 44.4% of patients presenting to an Acute Medical Unit were at high risk of non-alcoholic fatty liver disease. Reassuringly despite a large number of people at risk of fatty liver, only 10.8% of the high risk group and 3% of all those recruited were found to have a fibroscan score > 7kPa, i.e. had significant fibrosis or cirrhosis.

SAT-321
Liver fibrosis scores predict mortality in the general population
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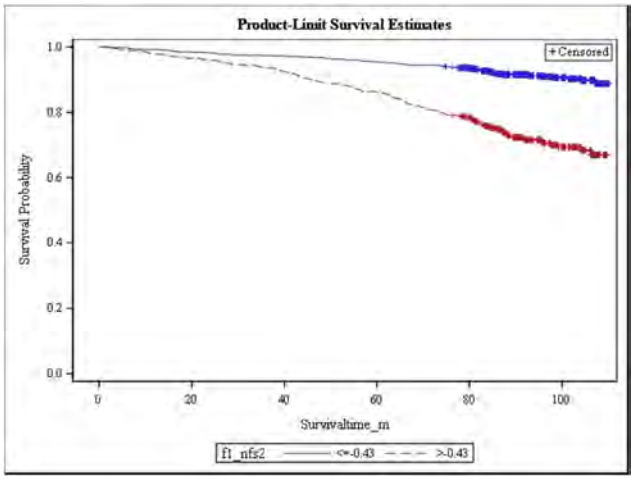
Background and aims: Most studies evaluating non-invasive fibrosis measurement are limited to the hepatological setting. Studies focusing on the general population have been centered on Methods such as transient elastography, which are not available to primary care givers. The aim was to evaluate the association of easily available non-invasive markers of fibrosis in the general population with mortality.
Method: This study is an analysis of the population-based CARLA study evaluating cardiovascular disease risk factors in a population of middle-elderly adults (45-83 yrs) in Germany (Greiser BMC Cardiovascular Disorder 2005) between 2002 and 2006. Two follow-up examinations were performed 2007-2010 and 2013, respectively. Vital status of participants was regulary registered, last time in 2016. The cause of death was defined as specified in the official death certificate. Easily available non-invasive fibrosis scores were calculated (NFS, FIB4, APRI, Lok, GUCI, Forns and BARD) and compared regarding overall mortality, CVD mortality and liver associated mortality with ROC curves. Their independent prognostic value for overall mortality, cardiovascular and liver mortality adjusted by age, CVD risk factors (BMI, diabetes, smoking, arterial hypertension, physical activity), and baseline comorbidities (liver disease and cancer) was evaluated with Cox regression analysis.
Results: 1436 subjects were included in the analyses (mean age 67 (SD 9)years, male 55%, mean BMI 28.4 (SD 4.7)). During follow-up 220 people died, (100 CVD or liver associated). NFS and Forns had the greatest AUC for overall mortality (see table) and cardiovascular/liver related mortality [AUC = 0.78 (95%CI 0.73-0.82) and 0.75 (95%CI 0.70-0.80), respectively]. On multivariate Cox analysis, both were identified as independent predictors of overall mortality [NFS HR 1.60 (95% CI 1.41-1.82), Forns HR.1.17 (95%CI 1.10-1.25)] and cardiovascular and liver disease mortality [NFS HR = 1.99 (95%CI 1.62-2.44); Forns HR = 1.21 (95%CI 1.12-1.32)]. The NFS cut-off –0.43 was the best to predict mortality (Se 72%, Sp 72%). KM curves are shown on figure (log-rank 93.9, $p < 0.001$).

Variable	AUC (95% CI)
NFS	0.732 (0.696-0.768)
FIB4	0.594 (0.554-0.635)
APRI	0.569 (0.526-0.612)
Lok	0.633 (0.591-0.657)
GUCI	0.510 (0.465-0.555)
Forns	0.709 (0.672-0.745)



Conclusion: The non-invasive fibrosis score, NFS, is an independent predictor of overall, cardiovascular and liver mortality in the general population. This easily available score (age, BMI, impaired fasting glucose or diabetes, AST, ALT, platelets and albumin) can be calculated in the primary care setting and select patients that should be referred for specialist care.

SAT-322
Comparison of point shear wave elastography (ElastPQ-pSWE) and FibroScan Transient Elastography (F-TE) for liver fibrosis staging in patients with NAFLD
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Background and aims: ElastPQ is a recently-introduced point shear wave elastography technique used to non-invasively assess liver fibrosis. We compared liver stiffness measured by both ElastPQ and Transient Elastography with Fibroscan (F-TE) in a cohort of

Table: (abstract: SAT-322)

	ElastPQ				FIBROSCAN				
	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC	P value
F ≥ 2	6.9	80	73	0.837	7.9	82	71	0.847	0.5866
F ≥ 3	8.4	87	83	0.881	10.2	77	80	0.847	0.2186
F4	12.4	94	91	0.981	13.5	88	86	0.934	0.04

consecutive patients with NAFLD. We further evaluated the performance of ElastPQ in a subgroup of patients with available 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 (Fibroscan, Echosens, Paris) and ElastPQ (Affiniti 70G, Philips) in all recruited patients.
Results: We enrolled 414 consecutive patients with NAFLD, mean age 55 ± 13y, BMI 31.5 ± 5.7 kg/m^2, waist circumference (WC) 107 ± 15 cm, 59% male, 44% with diabetes, 55% hypertension, 77% hyperlipidaemia.
ElastPQ had a good correlation with F-TE (Spearman's = 0.786, p < 0.001), which was better for mild and moderate stages of fibrosis. A difference ≥ 2 kPa between the two techniques was found in 105 patients. On univariate analysis predictors of such difference were diabetes (p < 0.001), BMI (p = 0.015), WC (p = 0.040), AST (p < 0.001), Hb1Ac (p = 0.003), ALP (p = 0.005), GGT (0.041), Platelets (p = 0.004), INR (p = 0.010) and a liver stiffness ≥ 10 kPa measured by F-TE (p < 0.001). On multivariate analysis the only independent predictor was F-TE ≥ 10 kPa (OR: 6.152, 95% CI 3.247-11.655, p < 0.001).
In the subgroup of 125 patients with available histology, the distribution of fibrosis was as follow: F0 = 15 (12%), F1 = 44 (35%), F2 = 27 (22%), F3 = 22 (18%), F4 = 17 (14%).
The optimal cut-off values of ElastPQ for individual stages of fibrosis were lower than those of F-TE. ElastPQ showed the same good diagnostic performance for F ≥ 2 and F ≥ 3 but a better diagnostic performance for F4 compared to F-TE (Table 1).
Conclusion: ElastPQ and F-TE showed a good correlation in patients with NAFLD, which is better for low values of liver stiffness. The optimal cut-off values of ElastPQ are lower than those of F-TE for individual stages of fibrosis. ElastPQ seems to have a better diagnostic accuracy than F-TE in diagnosing liver cirrhosis but this finding needs to be confirmed in larger cohorts.

SAT-323
Selenoprotein P levels discriminate the degree of hepatic steatosis and are related to the NAS score in patients with non-alcoholic fatty liver disease

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Background and aims: Alterations in glucose and lipid metabolism in the setting of insulin resistance (IR) play an important role in the progression from Non-alcoholic Fatty Liver (NAFL) to Non-alcoholic Steatohepatitis (NASH) via oxidative stress. Selenoprotein P (SeP) is a selenium carrier protein with antioxidant properties that is higher in obese and diabetic subjects but its potential role as biomarker of NASH is not fully elucidated yet. The aim of this study was to assess the usefulness of SeP in discriminating NASH from simple steatosis in a well characterized cohort of biopsy proven NAFLD patients.
Method: We studied 208 subjects with histological diagnosis of NAFLD (145 male). Plasma SeP levels concentrations were measured with a quantitative sandwich enzyme-linked immunosorbent assay (ELISA). Histology was scored according to Kleiner. NASH was diagnosed by the local pathologist according to the joint presence of steatosis, inflammation and ballooning (with or without fibrosis).
Results: Overall, 153 (73.6%) subjects had NASH. Plasma SeP levels were significantly higher in patients with NASH compared to those with simple steatosis (5.3 ± 1.5 *vs* 6.2 ± 2.1, p = 0.0037). Circulating SeP mainly correlated with BMI (r = 0.4, p < 0.0001), visceral obesity by waist circumference (r = 0.2, p = 0.0089), AST (r = 0.3, p = 0.0001) and fasting plasma glucose (r = 0.3, p < 0.0001). Among histological features, plasma SeP showed a stepwise increase according to hepatic steatosis grade (p = 0.0007) and was able to discriminate mild (5-33%) from significant (≥ 33%) steatosis. Furthermore, circulating SeP increased according to the NAS score (p = 0.0131). At univariate logistic regression analysis, the higher SeP tertile (SeP values ≥ 6.3 ug/ml) was associated to NASH and to significant steatosis (≥ 33%) with an OR of 2.3 (95% CI = 1.1-5.0, p = 0.035) and 2.2 (95% CI = 1.2-4.1, p = 0.0095), respectively.
Conclusion: Circulating SeP levels increased in patients with NASH and were associated to both hepatic steatosis and NAS score suggesting its potential role as biomarker in the setting of NAFLD.
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SAT-324
Sonic hedgehog immunohistochemistry is a tissue biomarker of ballooned hepatocytes

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Background and aims: Accurate identification of ballooned hepatocytes (HCs) is important for liver disease categorization (eg, ballooning helps distinguish steatosis from steatohepatitis). Ballooning recognition can be challenging on routine stains. Experimental evidence has confirmed that expression of Hedgehog (Hh) ligand is upregulated by HCs during cellular stress (eg, endoplasmic reticulum stress and lipotoxicity). Sonic Hh (SHh) immunohistochemistry (IHC) can be used to mark ballooned HCs in non-alcoholic fatty liver disease (NAFLD); however, the patterns of SHh IHC have not been fully characterized across a spectrum of liver diseases with ballooning/enlargement and/or cytoplasmic clearing.
Method: Formalin-fixed paraffin-embedded sections from the following liver diseases were retrospectively analysed: adult NAFLD, paediatric NAFLD, NAFLD with glycogenosis, alcohol-related liver disease (ALD), Wilson disease (WD), alpha-1 antitrypsin deficiency (A1AT), acute large duct obstruction (ALDO), chronic hepatitis B (HBV) and neonatal giant cell hepatitis (NGCH). Haematoxylin and eosin, trichrome, and SHh IHC were evaluated.
Results: SHh IHC expression results are detailed in Table 1. Ballooned HCs of adult NAFLD, paediatric NAFLD, ALD, WD, and A1AT show strong cytoplasmic positivity. The following are negative for diffuse

strong SHh IHC: non-ballooned hepatocytes of adult and paediatric NAFLD, ALD, WD, and A1AT. Furthermore, glycogenosis, cholate stasis and the enlarged HCs of NGCH are also negative.

Table 1: Sonic hedgehog IHC marks ballooned hepatocytes

Disease	# of cases	HandE: Cases with ballooned/ enlarged hepatocytes, n (%)	SHh IHC: Ballooned/ cleared hepatocytes	SHh IHC: Non-ballooned/ non-enlarged hepatocytes
Adult NAFLD	15	13 (87%)-ballooned	Positive	Negative
Paediatric NAFLD	9	3 (33%)-ballooned	Positive	Negative
NAFLD with glycogenosis	4	3 (75%)-ballooned	Positive	Negative
		4 (100%)-glycogenosis	Negative	
ALD	9	6 (67%)-ballooned	Positive	Negative
WD	6	1 (17%)-ballooned	Positive	Negative
		2 (33%)-cholate	Negative	
A1AT	6	6 (100%)-ballooned	Positive	Negative
ALDO	5	5 (100%)-cholate	Negative	Negative
HBV	5	3 (60%)-cholate	Negative	Negative
NGCH	6	6 (100%)-giant cells	Negative	Negative

Conclusion: Ballooned HCs, present in a spectrum of liver diseases, show strong cytoplasmic positivity for SHh IHC. Other types of HCs with cytoplasmic clearing and/or enlargement are negative for strong SHh over-expression. SHh IHC is a specific and reliable tissue biomarker of hepatocellular ballooning.

SAT-325

Implementation of a primary care shear-wave elastography-based pathway to identify non-alcoholic fatty liver disease patients with advanced fibrosis in a large North American urban population

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Background and aims: Approximately 24% of adults have NAFLD. Identification of NAFLD patients with advanced fibrosis within the general population is challenging. Therefore, we developed and implemented a 2-D SWE case-identification pathway, driven by primary care physicians, to facilitate referrals of NAFLD patients in primary care with high risk for advanced fibrosis.
Method: Our hepatology and primary care (PCN; primary care networks, covering ~95% of the 1.4 million Calgary population) team co-developed the NAFLD clinical care pathway with a community-based radiology group proficient with SWE. Primary care physicians access the NAFLD pathway for patients with any of the following conditions: overweight, obesity, diabetes mellitus, elevated liver enzymes or fatty liver detected by imaging. Patients with suspected NAFLD (i.e. routine serology excluded other causes of chronic liver disease) were then assessed by SWE. NAFLD patients with liver stiffness by SWE ≥ 8kPa (or an inconclusive result) were referred to hepatology, and those with SWE < 8.0 kPa were managed in primary care using a standardized management pathway. To ensure high quality implementation of the pathway, we completed a training period from Oct 2016-Feb 2018.
Results: Between March-October 2018 we evaluated 1868 patients with suspected NAFLD. NAFLD prevalence by ultrasound was 91.8% (n = 1715). NAFLD patients were more likely women (53.4%) with median age of 54 (IQR: 45-63). Elevated liver enzymes, impaired glucose tolerance or diabetes, and obesity were prevalent (52.1%, 40.5% and 59.7%, respectively). Median SWE was 4.4kPa (3.7-5.5kPa). In our cohort, 1586 NAFLD patients (92.6%) had SWE < 8kPa, not requiring referral to a hepatologist, while 7.4% (n = 127) had either SWE ≥ 8kPa (3.0%) or an inconclusive result (4.4%) and had hepatology referral. Among patients with inconclusive SWE results, liver stiffness by transient elastography ≥ 8kPa was subsequently documented in 79% (59/75) of patients. Compared with non-referred patients, referred patients were older (median age 57 vs 54, P = 0.04), had higher BMI (median 38 vs 32, P < 0.01), and were more likely to have impaired glucose tolerance/diabetes (66.7% vs 45.0%, P = 0.03). In our cohort, FIB-4 and NFS classified 36.5% and 61.4% of NAFLD patients above cut-off of 1.30 and −1.45 respectively. Both FIB-4 and NFS were not correlated with SWE (r = 0.16 and 0.30 respectively). Among referred patients, liver biopsy was obtained (to date) in 27 patients (F0 in 1, F1 in 7, F2 in 7, F3 in 8 and F4 in 4).
Conclusion: The implementation of a primary care-accessible SWE program for NAFLD patients in a large urban population facilitated successful fibrosis risk stratification. The prevalence of advanced fibrosis was 6.4% among patients with risk factors for NAFLD. Serum-based fibrosis scores (i.e. FIB-4, NFS) were not correlated with SWE and would lead to higher referral rates to hepatology.

SAT-326

Influence of NAFLD diagnosed by controlled attenuation parameterin patients of chronic hepatitis B with mildly elevated alt

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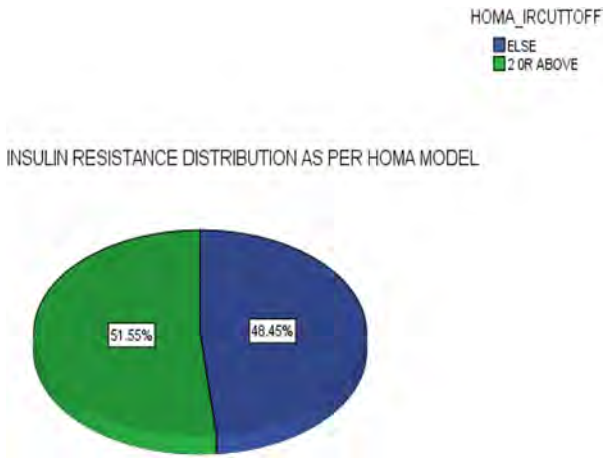
Background and aims: International guidelines vary regarding treating patients with mildly elevated ALT up to 2 times upper limit of normal. Patients with chronic hepatitis B infection may have elevated ALT due to infection itself, NAFLD or both.So it becomes difficult to decide whether to treat or postpone the treatment of hepatitis B.The aim of this ongoing study is to find out the role of NAFLD as a cause of elevated ALT in hepatitis B patients.
Method: The HBsAg positive patients visiting the GI clinic with mildly elevated ALT between up to 2 times upper limit of normal were further evaluated by body mass index (BMI), waist circumference, exclusion of concomitant hepatitis D or C, LFTs, quantitative HBV DNA, HBeAg, and fibroscan. The presence of steatosis was assessed by controlled attenuation parameter (CAP) in decibels/meter (dB/m) and was scaled from 0-3 (0 = 1-4%, 1 = 5-33%, 2 = 34-66%, 3 = 66-100%). The elasticity as an indicator of fibrosis was measured in kilopascals (kPa) and was scored from F0-F4.Significant fibrosis (F2 or more) was considered at ≥ 8 kPa and steatosis at ≥ 225 dB/m. Those patients who had HBV DNA of more than 2000 IU/ml and significant fibrosis were considered for hepatitis B treatment.
Results: Total number of patients evaluated so far in this ongoing study were 150. M:F ratio was 1:2. Mean age 36.4 ± 11.5 years (range 13-69). Mean BMI 28.1 (range 14.2-38.5). Mean waist circumference 95.8 ± 14.8 cm. 20/150 (13%) had diabetes while 6% were hypertensive. There was absence of steatosis in 34 (22.6%) patients according to CAP score, 24 (16%) had grade 1 steatosis, 35 (23.3%) grade II steatosis and 57 (38%) grade III steatosis. 50/150 had significant fibrosis of F2 or more.34/150 (22.6%)had DNA levels of above 2000. Insulin resistance as assessed by HOMA-IR model correlated significantly with the BMI (p = 0.00), waist circumference (p = 0.004), G-gt (p = 0.05) and CAP score (p = 0.00)but not with the HBV DNA levels (p = 0.009) and ALT levels (p = 0.336). Among those with elevated ALT and significant fibrosis, HBV DNA of more than

2000 was seen in 20 patients. Out of these 3 had no fat as per CAP score so increase ALT levels were purely due to HBV. Among those with elevated ALT and HBV DNA of less than 2000, 24 had significant fibrosis of F2 or more suggesting a contribution of NAFLD.



Conclusion: A significant number of HBsAg positive patients with mildly elevated ALT are overweight, have significant steatosis and fibrosis but low HBV DNA levels. This aspect is important while making decision about the treatmentof hepatitis B in the newly diagnosed patients with mildly elevated ALT.

SAT-327

The change of skeletal muscle mass is associated with hepatic steatosis in non-alcoholic fatty liver disease

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Background and aims: We aimed to investigate the association between the change of muscle mass and change of fibrosis and steatosis in NAFLD patients.
Method: We analyzed 2, 893 NAFLD subjects who had health check-up more than twice in St. Vincent′s Hospital between November 2009 and December 2017. NAFLD was diagnosed by ultrasound, and appendicular muscle mass (ASM) was assessed by Inbody 720. Sarcopenia index was calculated as ASM divided by weight (SI%) and ASM divided by body mass index (SI-BMI). Non-invasive markers were used to evaluate the severity of hepatic fibrosis and steatosis; NAFLD fibrosis score (NFS), Fibrosis-4 (Fib-4) score, and Forn′s index for fibrosis, and hepatic steatosis index (HSI) and fatty liver index (FLI) for steatosis.
Results: The mean age was 47.3 ± 10.4 years, and 1956 subjects (67.6%) were male. Diabetes, hypertension, metabolic syndrome were more prevalent in sarcopenic subjects ($p < 0.01$), and non-invasive fibrosis and steatosis markers were higher in sarcopenic subjects ($p < 0.01$). The mean interval between two health check-up was 39.8 ± 21.9 months. There was no significant association between the change of NFS, Fib-4, and Forn's index and the change of SI% and SI-BMI (all $p > 0.1$). However, the changes of HIS and FLI were significantly associated with the change of SI% and SI-BMI (all $P < 0.01$). Multivariate logistic analysis demonstrated the independent association between the change of skeletal muscle mass and the changes of non-invasive steatosis markers after adjusting for other confounding factors (all $p < 0.001$). However, the changes of non-invasive fibrosis markers did not show an independent association with the change of appendicular muscle mass after adjusting for other confounders (all $p > 0.1$)
Conclusion: The change of muscle mass is strongly associated with the change of hepatic steatosis, but not the change of fibrosis.

SAT-328

Controlled attenuation parameter for evaluating liver steatosis in type 2 diabetes patients

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Background and aims: The **aim** of the present study was to assess factors that associate with the severity liver steatosis, in a cohort of type II diabetic patients, using a non-invasive Method: Transient Elastography (TE) with Controlled Attenuation Parameter (CAP).
Method: The study included 284 type II diabetic patients, who were prospectively randomized (every first 6 patients who were referred to the Metabolic Disease Outpatient Clinic on a consultation day), evaluated in the same session by means of CAP (FibroScan EchoSens) to assess liver steatosis. Each patient was evaluated for the presence of viral hepatitis (B, C, D) and an AUDIT-C score was performed to exclude alcohol abuse. Also subjects characteristics, epidemiological data and biochemical tests were recorded. For differentiation between stages of steatosis we used the following cut-off values [1]: S1 (mild)-232.5 db/m, S2 (moderate)-255 db/m, S3 (severe)-290 db/m. Variables tested for the association with steatosis were: body mass index (BMI), abdominal circumference, years after diagnosis, cholesterol, triglycerides, gender, glycemia, glycosylate hemoglobin, oral antidiabetics treatment and insulin treatment. Spearman rank coefficient was used to test correlation between two study variables. Logistic regression was used for multivariate model to assess the association between CAP and other variables.
Results: 284 subjects (112 males and 172 females) were prospectively studied. 29/284 (10.2%) were S0, 17/284 (6%) were S1, 51/285 (17.9%) were S2 and 187/284 (65.9%) were S3 (than 83.8% of diabetic patients had moderate and severe steatosis by CAP). The mean values of CAP were 203 ± 73.5 for S0; 244 ± 14 for S1; 272 ± 24 dB/m for S2, 345 ± 77.7 dB/m for S3. In univariate analysis CAP showed a significant correlation with body mass index (BMI), abdominal circumference, triglycerides and with oral antidiabetics treatment. Multivariate regression analysis confirmed the correlation with oral antidiabetics treatment [OR = 4.4, 95% CI (2.06; 9.52), $p < 0.0001$] and BMI [OR = 1.2, 95% CI (1.09; 1.32); $p = 0.002$], but not with all other variables.
Conclusion: In our group, 83.8% of diabetic patients had moderate and severe steatosis by CAP. Body mass index (BMI), abdominal circumference, triglycerides and with oral antidiabetics treatment were associated with the severity of liver steatosis.

References:

1 Shi KQ *et al.* Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: A meta-analysis of diagnostic accuracy. *J. GastroenterolHepatol* 2014;29 (6):1149–58

SAT-329

Ethyl glucuronide inhair uncovers a high rate of harmful alcohol consumption in patients with presumed NAFLD

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is regarded the most common chronic liver disease worldwide. Yet, distinctive objective features allowing firm exclusion of alcohol-

related liver disease (ALD) are lacking. This study investigated the detection rate of alcohol consumption in patients with NAFLD based on ethyl glucuronide in hair (hEtG).
Method: In this multicentric prospective study, patients with NAFLD and ALD were consecutively included based upon history of alcohol intake assessed by standardized questionnaires (SIAC, AUDIT-C) using a cut-off of 20 g ethanol (EtOH)/d in females, and 30 g/d in males, while ruling out other liver diseases according to standard criteria. EtG (hEtG) as well as the confirmatory fatty acid ethyl ester ethyl-palmitate were measured in hair by gas chromatography-mass spectometry in segments of 0-3 cm and 3-6 cm, allowing a reliable, quantitative proof of alcohol consumption within up to 6 months. Additionally, EtG in urine (uEtG), as well as carbohydrate deficient transferrin (CDT), mean corpuscular volume (MCV) and gamma glutamyl transpeptidase (GGT) were assessed. Results were additionally stratified by BMI.
Results: Of 172 patients, 66.9% (n = 115/172) were primarily classified as NAFLD, and 33.1% as ALD (n = 57/115). In total, 31.4% of hEtG tests, and 51.5% of ethyl-palmitate tests were positive for alcohol consumption. hEtG and ethyl-palmitate indicated excessive alcohol consumption (> 60 g/d) in 14.5%, and 20.9% of patients, respectively. In NAFLD patients, in 20.0% (n = 23/115) excessive alcohol consumption, and in 37.4% (n = 43/115) moderate repeated alcohol consumption (10 to < 60 g EtOH/d) was indicated. In contrast, CDT, MCV, GGT, and uEtG were elevated in only 2.9%, 0.0%, 40.9%, and 10.5% of NAFLD patients. BMI negatively correlated with hEtG levels (r:-0.450, $p < 0.001$), and mean hEtG content was significantly lower in patients with BMI ≥ 30 than BMI < 30 (7.0pg/mg vs. 43.6pg/mg, $p < 0.001$). Within the group of normal to overweight NAFLD patients (BMI < 30) even up to 55% (n = 22/40) showed moderate repeated alcohol consumption, and 25% (n = 10/40) excessive alcohol consumption, whereas in patients with obesity (BMI ≥ 30) moderate repeated alcohol consumption, and excessive alcohol consumption was detected in 18.7% (n = 14/75), and 4.0% (n = 3/75).
Conclusion: hEtG and/or ethyl-palmitate in hair indicated moderate repeated alcohol consumption of 10 to < 60 g EtOH/d in 37.4%, and excessive alcohol consumption ≥ 60 g EtOH/d in 20.0% of NAFLD patients, which could not be detected by commonly used alcohol markers such as CDT, MCV, or GGT. The rate of harmful alcohol consumption was especially high in patients with BMI < 30. Analysis of long-term ethanol metabolites in hair, such as hEtG and ethyl-plamitate may therefore represent an important tool for the differential diagnosis of ALD and NAFLD.

SAT-330

Whole metabolome profiling identifies the combination of an eicosanoid, a bile acid and an androgen as a highly accurate marker of liver fibrosis in patients with non-alcoholic fatty liver disease

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is among the most frequent causes of liver disease and estimates based on imaging and biopsy studies suggest that about 20-30% of adults in the United States and Europe have excess hepatic fat accumulation, and are at risk of developing progressive fibrosis, end-stage liver disease or hepatocellular carcinoma. Liver biopsy is considered the gold standard in the diagnostic evaluation of patients with suspected NAFLD, and fibrosis at index biopsy identifies those at risk of progression. However, liver biopsy is uncomfortable, more expensive than most non-invasive tools and carries a procedure-related risk which together renders it unsuitable for regular screening. This study aims to identify novel non-invasive markers by metabolite profiling that correlate with histological key lesions of progressive NAFLD.
Method: In this multicenter cohort study, 74 patients with biopsy-proven NAFLD (NAFL, n = 42; NASH, n = 32) and 62 healthy blood donors were enrolled. Among the NAFLD patients, 13 had advanced fibrosis (≥ F2) while the remaining 61 showed absent or mild fibrosis (F0-F1). Obtained EDTA plasma samples were subjected to metabolite analysis by the GC-MS- and LC-MS/MS-based MxP® Broad Profiling approach, and by the targeted platforms MxP® Steroids, MxP® Lipids and MxP® Eicosanoids. The metabolic data were statistically analyzed by applying univariate (analysis of variance) as well as multivariate (random forest, elastic net, and linear discriminant analysis) algorithms, and peak signals were compared to key histology lesions of NAFLD, i.e. fibrosis, activity, and steatosis.
Results: A multi-marker panel, consisting of an eicosanoid, a bile acid and an androgen, successfully differentiated the EDTA plasma samples into two main clusters: fibrosis stage ≥ 2 and fibrosis stage < 2 (AUC = 0.95, Sens = 0.92, Spec = 0.90, PPV = 0.225, NPV = 0.997). Thus, our biomarker outperforms the FIB4 index (AUC = 0.80), the ELF score (AUC = 0.82), and plasma levels of caspase-cleaved keratin 18 fragments (AUC = 0.68).
Conclusion: The identified metabolite panel was significantly associated with liver fibrosis stage in NAFLD patients and reveals an excellent test performance to detect early prognostic histological liver lesions. In sum, this biomarker holds high promise to accurately detect fibrosis in NAFLD patients non-invasively in plasma, and thus may serve as a novel non-invasive screening tool in NAFLD patients.

SAT-331

Use of machine learning to predict diagnosis codes for non-alcoholic steatohepatitis in administrative healthcare data

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Background and aims: The use of real world evidence to characterize the long-term consequences of non-alcoholic steatohepatitis (NASH) has been hampered by the absence of a unique code distinguishing it from non-alcoholic fatty liver disease (NAFLD) prior to the adoption of version 10 of the International Classification of Disease (ICD-10) in October 2015. Our study uses machine learning to identify NAFLD patients likely to have a claim for ICD-10 NASH based on claims observed in the ICD-9 era.
Method: In data from the first year of the ICD-10 era (October 2015-September 2016), we identified 10, 717 patients with a NASH diagnosis. A random ~30% sample of patients with no evidence of NASH (N = 90, 214) was selected for comparison. All included patients were enrolled during the final 2 years of the ICD-9 era (October 2013-September 2015) and had a claim for NAFLD during this period. We used the ensemble method Super Learner with 10-fold cross-validation to build a predictive algorithm for ICD-10 NASH based on 12 pre-defined variables (age, sex, and 10 comorbidities known to be associated with NASH/NAFLD including diabetes, obesity and others),

and ICD-9 and medication claim codes agnostically selected by a Bayesian odds ratio (BOR) procedure from a pool of 3, 153 that met defined data sparsity thresholds. The final predictor was validated on a reserved 10% sample of the data. Performance metrics included area under the receiver operating curve (AUC), as well as sensitivity and specificity at a threshold chosen to maximize the Youden index.
Results: The final predictive algorithm, a weighted meta-learner based on 19 discrete base learners, the 12 pre-defined variables, and 60 BOR-selected claim codes, had a validated AUC of 0.76, with a sensitivity and specificity of 0.62 and 0.75, respectively. Using claims data from October 2010 to August 2015, we identified ICD-9-era NAFLD patients with a minimum of 2 years of data to predict claims of ICD-10 NASH. Using the Youden index threshold, we identified 216, 180 additional patients with predicted NASH, bringing the total number of observed NASH patients to 284, 143.
Conclusion: Super Learner combined with BOR variable selection produced a model with a high AUC for identifying patients with predicted ICD-10 NASH during the ICD-9 era. This application of machine learning enables the construction of cohorts spanning ICD-9 and ICD-10 to more fully understand the epidemiology and disease burden of NASH.

SAT-333

Non-alcoholic steatohepatitis significantly decreases microsomal liver function in the absence of fibrosis, which allows the use of the 13C-aminopyrine breath test for its non-invasive detection

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has become the most frequent cause of chronic liver disease in Western countries, with an increasing prevalence. The presence of non-alcoholic steatohepatitis (NASH) can lead to a more aggressive clinical course with fibrosis progression and hepatocellular carcinoma, which necessitates early NASH detection. Currently, the diagnosis of NASH is based on histology, though with the high prevalence of NAFLD, a non-invasive method is needed. The 13C-aminopyrine breath test (ABT) evaluates the function of the cytochrome P450 enzymes of the liver (microsomal liver function) and could be a potential candidate. We aimed to firstly, evaluate a potential change in liver microsomal function in NASH patients; secondly, evaluate the diagnostic power of ABT to detect non-fibrotic NASH (NASH-F0-1); and thirdly evaluate the diagnostic power of ABT to detect fibrotic NASH (NASH-F2-4)
Method: A retrospective analysis was performed on consecutive patients suspected of NAFLD who underwent a liver biopsy and ABT between 2002 and 2018 at the Antwerp University Hospital. Subgroups were created for patients without NASH (noNASH), patients with NASH but without significant fibrosis (NASH-noF) and patients with NASH and significant fibrosis (NASH-F).
Results: 454 patients were included (33% noNASH, 40% NASH-noF, 27% NASH-F). A significant difference ($p < 0.0001$) in ABT was found between noNASH, NASH-noF and NASH-F with a cumulative excretion of 14.6 ± 6.6, 12.8 ± 5.4 and 10.4 ± 5.5%dose, respectively. The cumulative excretion (cABT) proved a better predictor of NASH and fibrosis than peak excretion. The predictive power of cABT as a single test was low for NASH-noF and NASH-F with AUROCs of 0.620 and 0.650, respectively. A predictive model was created adding ALT, C-peptide and age to cABT, which increased the AUROC to 0.775 to detect NASH-noF. A model adding AST to cABT increased the AUROC to 0.796 to detect NASH-F. Cut-off values were determined for optimal accuracy, 90% sensitivity and 90% specificity to predict both NASH-noF and NASH-F.
Conclusion: The microsomal liver function of patients with NASH is significantly decreased even in the absence of fibrosis highlighting the sole impact of steatohepatitis on patients' health. The ABT is a valuable tool in assessing the presence of non-fibrotic and fibrotic NASH; and could therefore be used as a supplementary diagnostic tool in clinical practice.

SAT-334

Liver steatosis in HIV-positive patients with and without HBV coinfection accessing care in a programmatic setting in Africa

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Background and aims: Owing to the success of antiretroviral therapy (ART), non-communicable diseases, including non-alcoholic fatty liver disease (NAFLD), are an emerging concern in HIV care. There is a paucity of data on NAFLD in sub-Saharan Africa, where HIV and HBV infection co-exists. Using controlled attenuation parameter (CAP) readings, this study investigated liver steatosis in a programmatic HIV care setting in Ghana.
Method: Consecutive patients accessing outpatient care over a 2-week period underwent CAP and liver stiffness measurement by FibroScan®. Liver steatosis was graded (S0-S3) using recommended cut-offs (248, 268, 280 dB/m). Patients also underwent clinical examination, laboratory testing, and collection of ART history and demographic, anthropometric, and lifestyle data including alcohol consumption. Metabolic syndrome (MS) was defined using the criteria of the International Diabetes Federation.
Results: Among 330 adults (72% females; median age 48 years), 90/330 (27%) were HBsAg positive. Patients had received ART for a median of 8.9 years and had a median CD4 count of 620 cells/mm^3; 163/330 (49%) had detectable HIV RNA. Overall, 92/330 (28%) were overweight and 41/330 (12%) were obese. Mild, moderate, or severe hypertension was diagnosed in 80/330 (24%), 34/330 (10%), and 27/330 (8%), respectively. Total cholesterol, LDL, and triglycerides were raised in 111/330 (34%), 82/330 (25%), and 68/330 (21%) patients, respectively; 17/330 (5%) had diabetes; 78/330 (24%) had MS. Regular alcohol consumption was reported by 16/330 (5%). CAP readings were S0 in 261/330 (79%) patients, S1 in 26/330 (8%), S2 in 20/330 (6%), and S3 in 23/330 (7%). Liver stiffness was F0-F1 in 280/330 (85%) patients, F2 in 34/330 (10%), F3 in 11/330 (3%), and F4 in 5/330 (2%). In the univariable model, body mass index, central obesity, hypertension, plasmatic lipids, glycated haemoglobin, MS and CD4 count showed a significant association with ≥ S1 steatosis. After adjustment for gender, CD4 count and exposure to stavudine, tenofovir and nevirapine, subjects with MS retained eight-fold higher odds of ≥ S1 steatosis (aOR 8.37, 95% CI 4.43-15.8, $p < 0.01$). There was no effect of HBsAg status.
Conclusion: In this mature HIV cohort, a significant subset had MS (24%) and ≥ S1 steatosis (21%). Whereas a minority (5%) had significant liver fibrosis, the high prevalence of hepatitis B and liver steatosis identify a clear need for diagnosis and management strategies in the region.

SAT-335

A simple biomarker panel predictive of advanced fibrosis in patients with non-alcoholic steatohepatitis

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Background and aims: NASH is an important cause of chronic liver disease. In patients with NASH, histologic stage of fibrosis is an independent predictor of mortality. Given the limitations of liver biopsy, non-invasive biomarkers that can accurately predict significant and advanced fibrosis are highly desirable.
Aim: To use serum from patients with biopsy-proven NASH to develop a biomarker panel to accurately predict advanced fibrosis in NASH.
Method: Serum samples were obtained from our prospective serum bank from patients with histologic NAFLD. All patients had consented before liver biopsy and serum was collected at the time of biopsy and snap-frozen. All liver biopsies were read by the study pathologist with the diagnosis of NASH and the stage of fibrosis being made according to an established protocol. Extensive clinical data were collected at the time of liver biopsy. Serum levels of 58 proteins were evaluated using Luminex Bead-based Multiplex Assays. Univariate Mann-Whitney tests and multivariate logistic regressions were used to determine predictors of significant and advanced fibrosis.
Results: Of 150 NAFLD patients, 100 patients had histologic NASH with 75 having NASH and significant fibrosis (F2-F4 by NASH Clinical Research Network classification). Those with NASH and significant fibrosis were more likely to be diabetic, had higher ALT and AST and lower platelet counts (all p values < 0.05). NASH patients with significant fibrosis also had higher level of serum Cathepsin D, Chitinase 3-Like 1 (CHI3L1)/YKL40, Collagen IV, FAP, ICAM-1/CD54, IGFBP-7, IL-1 beta, MIP-3 beta/CCL19, MMP-7, TIMP-1, and Thrombospondin-2, and lower levels of IGFBP-3, IL-8/CXCL8, and MMP-9 ($p < 0.05$). Using multivariate regression analysis, after stepwise selection of potential predictors among clinico-demographic and biomarker parameters, lower IGFBP-3 (odds ratio (OR): 0.98, 95% CI: 0.97-0.99, p = 0.0003) and higher Thrombospondin-2 (OR: 1.47, 95% CI: 1.28-1.69, p <.0001) were independently predictive of significant fibrosis; the area under the curve (AUC) was 0.86 (0.80-0.92). The same parameters, IGFBP-3 (OR: 0.98, 95% CI: 0.97-0.99, p = 0.0004) and Thrombospondin-2 (OR: 1.35, 95% CI: 1.21-1.51, p <.0001), were also predictive of advanced fibrosis (F3-4); AUC = 0.85 (0.78-0.91).
Conclusions: We have developed a simple biomarker panel able to predict advanced fibrosis in NASH. After external validation, this panel could potentially be used in clinical practice to identify NASH patients with significant and advanced fibrosis.

SAT-336

lLver stiffness measurement: An alternative practical predictor for early kidney dysfunction in patients with non-alcoholic fatty liver disease

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Background and aims: Increasing evidences suggest that non-alcoholic fatty liver disease (NAFLD) is strongly associated with chronic kidney disease. Earlier prediction of early kidney dysfunction (EKD) in NAFLD is pivotal, while the screen method is limited. In this study, we aimed to explore the potential value of liver stiffness measurement (LSM) in EKD.
Method: Biopsy-proved NAFLD patients were included from the First Affiliated Hospital of Wenzhou Medical University and Marmara University School of Medicine, Istanbu. Fibrosis stage was ranged from 0-4, according to the NASH CRN criteria. By transient elastography, LSM with M probe ≥ 8.0 kPa was defined as liver fibrosis. EKD was defined as microalbuminuria and eGFR ≥ 60 ml/min/1.73m^2. OR and 95% confidence intervals for microalbuminuria were calculated using multivariate logistic regression analysis.
Results: A total of 214 biopsy-proved patients were included, of whom 61.2% had liver fibrosis. The prevalence of microalbuminuria significantly increased in liver fibrosis, when compared with no liver fibrosis (22.14% vs. 4.82%). NAFLD patients with microalbuminuria had higher fibrosis stage, mean arterial pressure levels, HOMA-IR values and BMI. After adjustment of traditional confounders including BMI, waist circumference, hypertension, type 2 diabetes and HOMA-IR, liver fibrosis was independently associated with increased risk of microalbuminuria (OR = 5.12, $p < 0.05$). In subgroup analysis with LSM, the trend between liver fibrosis with microalbuminuria was similar. Furthermore, compared with LSM score < 8.0 kPa, LSM ≥ 8.0 kPa had higher prevalence of microalbuminuria.
Conclusion: Liver fibrosis is independently associated with microalbuminuria in NAFLD patients. Higher LSM score may identify NAFLD patients with EKD, which can remind hepatologist to give more intensive surveillance and even treatment to reduce the risk of development of EKD over time.

NAFLD: Therapy

SAT-337

Evaluation of anti-fibrotic properties of OCA and INT-767 in an in vitro system of NAFLD

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Background and aims: An effective treatment for Non-Alcoholic Steatohepatitis (NASH) is still missing. Fibrosis is the most significant predictor of mortality in NASH. FXR agonists have been proposed as anti-fibrotic treatment. In this study, we assessed the anti-fibrotic effect of the FXR agonist obeticholic acid (OCA, INT-747) and the dual FXR/TGR5 agonist INT-767 in a well-established *in vitro* co-culture model reproducing NASH development.

Method: Human hepatoma (Huh7) and hepatic stellate (HSCs, LX2) cells were simultaneously co-cultured (SCC) at a 5:1 ratio and exposed to 1200 µM of free fatty acids (FFAs) without or with OCA or INT-767. Exposure in absence of FFAs was tested for side effects. Working concentrations were selected based on cell viability curves. Expression of ACTA2, Col1a1, FXR and SHP was evaluated at 24, 96, and 144h. Extracellular collagen deposition and metalloproteinase 2 and 9 (MMP2-9) activity were evaluated at 96 and 144h (alphaLISA and Innozyme assay kit, respectively) and compared to the FXR agonists tropifexor and GS-9674.
Results: Based on cell viability, 0.1, 1 and 10 µM were selected for both OCA and INT-767. Exposure to FFAs induced HSCs activation (ACTA2 and Col1a1 ($p < 0.05$)) and extracellular collagen deposition ($p < 0.01$ at 144h) vs. CTRL. Compounds co-treatment did not affect ACTA2 and Col1a1 gene expression, while OCA, and to a lesser extent INT-767, significantly reduced FXR and induced SHP expression.
Interestingly, OCA induced a dose-dependent reduction of collagen at both 96h ($p < 0.05$ and 0.01 vs. FFAs, with 1 and 10 µM, respectively) and 144h ($p < 0.01$ with 10 µM). Similarly, INT-767 induced collagen reduction (1 µM at 96h, $p < 0.05$). Tropifexor was more effective at 0.5 and 0.1µM at 144h ($p < 0.05$), while GS-9674 at 96h ($p < 0.01$) but this effect did not persist over time. Neither OCA nor INT-767 altered collagen deposition in the absence of FFAs.
MMP2-9 activity was reduced at 96h in FFA-treaded cells ($p < 0.05$ vs. DMSO), while OCA counteracted this effect ($p < 0.05$). INT-767 also induced a slight increase in MMP2-9 activity. No significant modulation of MMP2-9 activity was induced by tropifexor or GS-9674.
Conclusion: All FXR agonists tested reduce collagen deposition. OCA exerts a more potent and long-lasting effect (−50% vs. FFAs) compared to INT-767 (−30%), tropifexor (−20%) and GS-9674 (−35%). These effects appear to be related to modulation of the FXR pathway, and to increased extracellular matrix degradation as indicated by enhanced MMP2-9 activity.
This work was supported by Intercept Pharmaceuticals.

SAT-338

Oral arginine supplementation attenuates the progression of steatosis to non-alcoholic steatohepatitis through preventing translocation of bacterial endotoxin

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Background and aims: While being one of the most prevalent liver diseases world-wide, therapeutic strategies of non-alcoholic fatty liver disease still primarily focus on lifestyle interventions frequently associated with low adherence and high relapse rates. Several studies suggest that an oral supplementation of L-arginine (Arg) may prevent the development of liver diseases of various etiologies with protective effects also being associated with a protection of intestinal barrier function. Starting from this background, the aim of the present study was to assess the effects of an oral supplementation of Arg on the progression of a pre-existing diet-induced steatosis and molecular mechanisms involved.
Method: Female C57BL/6J mice (n = 8/group) were pair-fed either a liquid control diet (C) or a fat-, fructose- and cholesterol-rich diet (FFC) for 8 weeks to induce steatosis. For 5 additional weeks mice were fed either C or FFC with or without 2.49 g Arg/kg body weight. In addition, C57BL/6J mice fed FFC or C ± Arg were treated with the arginase inhibitor nor-NOHA (0.01 g/kg body weight). Indices of liver damage and inflammation as well as intestinal barrier function and arginase activity in proximal small intestinal tissue were determined.
Results: Despite similar caloric intake and weight gain after 13 weeks of feeding, liver damage in FFC-fed mice progressed to non-alcoholic steatohepatitis with marked signs of inflammation, e.g. significant higher number of neutrophils and F4/80-positive cells, and macrovesicular fat accumulation while FFC-fed mice receiving Arg for 5 weeks only showed hepatic steatosis. Furthermore, glucose tolerance was significantly disturbed and elevated bacterial endotoxin levels in portal plasma were only found in FFC-fed mice but not in FFC+Arg-fed animals. Moreover, the loss of arginase activity found in proximal small intestine of FFC-fed mice was markedly attenuated in FFC+Arg-fed mice being also associated with lower nitric oxide levels. Furthermore, the treatment with the arginase inhibitor nor-NOHA attenuated the beneficial effects of Arg on bacterial endotoxin levels found in FFC-fed mice.
Conclusion: In summary, our data suggest that an oral supplementation of Arg attenuates the progression of non-alcoholic fatty liver disease in mice through preventing the loss of intestinal barrier function. (DFG FKZ: BE2376/6-3)

SAT-339

Socioeconomic deprivation is associated with non-response to lifestyle interventions in non-alcoholic fatty liver disease

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease globally and affects over 20 million people in the UK. Whilst socioeconomic deprivation has been associated with several risk factors for NAFLD, such as diabetes mellitus and obesity, the association with NAFLD is not well described. The goal of NAFLD treatment is regression of liver fibrosis to reduce all-cause mortality. Therefore, the aim of this study was to assess the likelihood of achieving fibrosis regression by lifestyle modification and the relationship between socioeconomic deprivation, disease severity and outcomes.
Method: All patients attending for Transient Elastography (Fibroscan) with a suspected or confirmed diagnosis of NAFLD at Derriford Hospital (Plymouth) between January 2015 and May 2018 were retrospectively included. Participants were all given lifestyle advice for diet and physical activity modification. Those with missing data or invalid scans (median/IQR ratio > 0.3) were excluded. Follow-up Fibroscan data was recorded where available. Clinically significant regression was defined as a reduction of liver stiffness measurement (LSM) by > 2 kPa. Demographic data was collected and postcode was cross referenced with the English Indices of Deprivation 2015 which ranks levels of deprivation in 32, 844 neighborhoods across England, based on key indicators in seven different domains of deprivation. An overall rank of relative deprivation, the Index of Multiple Deprivation (IMD), is calculated from these domains. A lower rank indicates a greater relative degree of deprivation.
Results: 158 patients with NAFLD underwent Fibroscan during the inclusion period. The median initial LSM was 9 kPa (SD = 9.7). There was no association between IMD and initial LSM severity. 123 patients had a follow-up Fibroscan (median interval 469 days). 40/123 (32%) demonstrated LSM regression > 2kPa. There was a significant difference in IMD between those who had LSM regression (M = 15533, SD = 8826) and no regression (M = 12165, SD = 8367), p = 0.04. The greatest contribution to the difference in IMD was in the domain of barriers to housing. Furthermore, there was a correlation between IMD and LSM regression; r = -.19, p = 0.04, implying social deprivation was associated with non-response to lifestyle intervention, and was more marked in females than males.
Conclusion: This study suggests that socioeconomic deprivation in NAFLD is associated with decreased likelihood of liver fibrosis regression with lifestyle intervention. Given that first-line treatment for NAFLD is lifestyle modification (weight loss, diet and increased activity), deprivation may negatively impact a person's ability to achieve these changes. This has implications for behavioral

interventions and services, which should target populations with socioeconomic deprivation to improve clinical outcomes.

SAT-341

MET409, an optimized sustained FXR agonist, was safe and well-tolerated in a 14-day phase 1 study in healthy subjects

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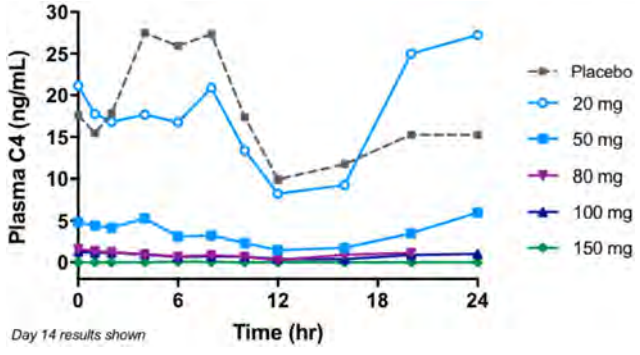
Background and aims: FXR (farnesoid X receptor) agonists for the treatment of non-alcoholic steatohepatitis (NASH) have evolved, although each iteration has had drawbacks. FXR agonists derived from either bile acid/steroidal or non-bile acid core structures have shown increased low-density lipoprotein (LDL) cholesterol levels, as well as moderate to severe pruritus within 14 days of dosing. Non-bile acid FXR agonists that have progressed into clinical development are hampered by transient FXR engagement with once-daily dosing, likely limiting efficacy. Sustained FXR engagement appears key to efficacy based on pre-clinical and clinical studies. MET409 is an optimized next-generation FXR agonist with features of a novel non-bile acid structure, enhanced potency and sustained FXR engagement. We conducted a double-blind, placebo-controlled, single-ascending dose (SAD) and a 14-day multiple-ascending dose (MAD) phase 1 study in healthy subjects to determine the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MET409.
Method: Healthy men aged 18 to 65 years-old were randomized to either MET409 or placebo (6:2 allocation in SAD portion; 8:2 allocation in MAD portion). The primary objective was to assess the safety and tolerability of MET409. The secondary objectives were to establish the PK and PD profiles of MET409, with PD assessed by plasma levels of 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19).
Results: Both single (20-400 mg) and multiple doses (20-150 mg) of MET409 were safe and well-tolerated. There were no serious adverse events, and the severity and frequency of adverse events were comparable between MET409 and placebo. MET409 exhibited sustained PK and PD profiles with once-daily dosing. There were dose-dependent increases in maximum concentration (C_{max}) and exposure ($AUC_{0\text{-}24}$), with elimination half-life ($T_{1/2}$) of ~15 hrs on Day 1 and ~50 hrs on Day 14 at an expected therapeutic level (50 mg). MET409, at ≥ 50 mg, suppressed plasma C4 levels (↓~80-95%) relative to placebo, with suppression observed throughout 24 hours (Figure). Increased FGF19 levels were also observed. MET409 did not increase serum LDL cholesterol, a differentiating attribute relative to other FXR agonists and FGF19 analogs. There were mild, dose-dependent decreases in high-density lipoprotein cholesterol and triglycerides. Mild pruritus, observed only at > 3x exposure above expected therapeutic level, did not require medical intervention or dosing interruption.



Conclusion: MET409, an optimized FXR agonist, demonstrated sustained FXR engagement and an encouraging safety and tolerability profile-including a lack of adverse impact on LDL cholesterol levels – in healthy male subjects.

SAT-342

Morphometric collagen analysis discerns anti-fibrotic effects of INT-767 and OCA in NASH mouse models using second harmonic generation imaging

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent liver disorder that can gradually progress to liver inflammation and fibrosis, including non-alcoholic steatohepatitis (NASH). The farnesoid X receptor (FXR) and transmembrane G protein-coupled receptor 5 (TGR5) regulate bile acid metabolism, inflammation, fibrosis, and inhibit NASH. Here, we assess the anti-fibrotic efficacy of INT-767 (a dual FXR/TGR5 agonist) and obeticholic acid (OCA) (an FXR agonist) in a diet-induced NASH mouse model with a focus on the morphometric quantification of the fibrosis phenotype imaged by Second Harmonic Generation (SHG).
Method: Leptin- deficient ($lep^{ob/ob}$) mice were fed with normal chow or with high-fat diet to induce NASH. Mice were biopsied and confirmed to have steatosis (score 3) and fibrosis (stage 2-3) before treatment (n = 10/group) with vehicle, INT-767 (10 mg/kg), or OCA (30 mg/kg) for 8 wks. Unstained liver histological sections were imaged with Genesis 200® system which uses SHG to produce images specific to collagens I and III. Image analysis of the SHG images quantified morphometric traits of the collagen fibers, including fiber length, width, area, perimeter, tortuosity, and texture. The distribution of each morphometric traits was described by normalized quantitative fibrosis parameters (qFPs). Liver collagen area, density, and reticulation index were also measured. The qFPs were combined to generate a Composite Fibrosis Score (CFS, 0 to 10), a continuous phenotypic quantifier of fibrosis.
Results: INT-767 reduced liver collagen fiber area and fiber density, while OCA decreased it to a lesser degree. This can be expected due to the 3-fold higher potency of INT-767 compared to OCA in FXR activation. Neither drug affected the collagen reticulation structure. The qFPs, reported on heat charts, show highest values for Vehicle, mid values for OCA, and lowest values for INT-767. INT-767 is more effective than OCA in improving fibrosis area, fiber density, qFPs, and Composite Fibrosis Scores (mean CFS ± SEM; Vehicle 6.5 ± 0.5, OCA 6.1 ± 0.3, INT-767 4.5 ± 0.2). Thus, INT-767 has higher anti-fibrotic effects compared to OCA in ob/ob NASH mice.
Conclusion: These data confirm that morphometric analysis of SHG images is an effective label-free method to describe and quantify the severity and progression of liver fibrosis and may differentiate pharmacological agents. These data enrich previous findings obtained using conventional methods.

SAT-343

Alagebrium ameliorates NAFLD progression in mice fed a high advanced glycation end products diet via direct inhibition of Kupffer cells and indirect inhibition of hepatic stellate cell activation

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, affecting up to 30% of the adult population. Although it is a major cause of liver disease related premature illness and deaths, there is no established drug therapy for

this condition. Advanced glycation end products (AGEs), formed when reducing-sugars react with proteins during food processing, have been implicated as a second hit that drives NAFLD progression to liver fibrosis. Therefore, in the present study, we investigated the therapeutic potential of AGE cross-link breaker, alagebrium (Ala), on dietary AGE-induced NAFLD progression.
Method: C57Bl/6 mice were fed a high AGE diet for 40 weeks. They were orally gavaged with Ala for the last 10 weeks. Liver samples were collected to determine gene expressions, oxidative stress and fibrosis. In addition, the effect of Ala on AGE clearance was determined by gavaging labelled AGEs in mice fed the high AGE diet for 4 weeks. Prophylactic and therapeutic effects of Ala (1μM and 100μM) on the expression of proinflammatory cytokines by murine Kupffer cells (KUP5) exposed to AGEs (200μg/ml) were determined. Reactive oxygen species (ROS) generation by these cells was measured using a fluorescent dye. The effect of AGEs on activation of human hepatic stellate cells (LX2) directly or indirectly via Kupffer cells was investigated in the absence or presence of Ala.
Results: Ten weeks of Ala treatment significantly ($p < 0.001$) reduced liver fibrosis which was accompanied by reduced ($p < 0.01$) expression of proinflammatory and profibrotic cytokines compared to high AGE fed mice. Two weeks of Ala treatment improved liver AGE clearance in high AGE fed mice. Oxidative stress, as assessed by 4-HNE immunostaining, which was significantly ($p < 0.0001$) increased by high dietary AGEs was attenuated ($p < 0.001$) by Ala treatment. In support of this, Ala treatment significantly ($p < 0.01$) reduced ROS generation as well as proinflammatory cytokine expression by AGE-treated KUP5 cells. Whilst AGEs applied directly failed to activate LX2 cells, application of AGE-treated KUP5 conditioned media activated LX2 cells, as reflected by increased α-SMA expression. The activation of LX2 cells was however prevented when the cells were incubated with AGEs and Ala treated KUP5 conditioned media, suggesting that Ala likely inhibited AGE-induced cytokine release by KUP5 cells.
Conclusion: AGEs exacerbate NAFLD progression to liver fibrosis by mechanisms involving Kupffer cells which secrete large amounts of ROS and proinflammatory cytokines, leading to activation of hepatic stellate cells. We also conclude that alagebrium increases AGE clearance and has potential to inhibit NAFLD progression to liver fibrosis.

SAT-344
MSDC-0602K targets the mitochondrial pyruvate carrier to treat non-alcoholic steatohepatitis

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Background and aims: MSDC-0602K is an insulin sensitizing thiazolidinedione that binds and inhibits the mitochondrial pyruvate carrier 2 (MPC2). Genetic deletion of Mpc2 in hepatocytes (liver-specific (LS)-Mpc2-/- mice) inhibits stellate cell activation and fibrosis in mice fed a diet that induces NASH (HTF-C diet). MSDC-0602K is now in a clinical trial for NASH. Herein, we evaluated intercellular crosstalk between hepatocytes and stellate cells in response to Mpc2 pharmacologic or genetic inhibition.
Method: Wild-type and LS-Mpc2-/- mice were fed either the HTF-C to induce NASH or low fat (LF) diet. After 4 weeks on plain HTF-C diet, a subset of mice were switched to HTF-C diet including MSDC-0602K. Histologic and gene expression analyses of liver were conducted and plasma miRNA profiled by RNA sequencing.
Results: As expected, treatment with MSDC-0602K reduced histologic and gene expression markers of NASH in liver. In plasma, we found 112 miRNAs that were upregulated and 60 miRNAs that were downregulated by HTF-C diet compared to LF. Compared to plasma from untreated HTF-C diet-fed mice, MSDC-0602K treatment increased 44 miRNAs and decreased 39 miRNAs. Many miRNAs that were increased in HTF-C diet fed mice, were reduced by MSDC-0602K treatment and vice versa. Several miRNAs known to have roles in liver injury or fibrogenesis were affected by MSDC-0602K treatment. We also profiled miRNAs in plasma from WT and LS-Mpc2-/- mice that were fed HTF-C diet in the presence or absence of MSDC-0602K. Only 29 miRNAs were affected by loss of Mpc2 in hepatocytes (compared to wild-type controls). Moreover, the effect of MSDC-0602K was not markedly affected by loss of Mpc2 in hepatocytes, though some miRNA changes were Mpc2-dependent.
Conclusion: MSDC-0602K has potent effects on reducing stellate cell activation, other markers of NASH, and levels of circulating miRNAs. However, the effects of MSDC-0602K on plasma miRNAs were not affected by loss of Mpc2 in hepatocytes. This suggests that MSDC-0602K has hepatocyte-independent effects on miRNA release. The small number of hepatocyte MPC2-dependent miRNAs will be further investigated for effects on stellate cell activation.

SAT-345
Novel mitochondrial pyruvate carrier modulators to treat non-alcoholic steatohepatitis and insulin resistance

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Background and aims: The mitochondrial pyruvate carrier (MPC) has emerged as a novel target for treating non-alcoholic steatohepatitis (NASH). Indeed, a thiazolidinedione derived MPC inhibitor, MSDC-0602, is completing phase 2 clinical trials for NASH in 2019 (EMMINENCE; NCT02784444). MSDC-0602 is a potent insulin sensitizer and it is believed that its beneficial effects on hepatic fibrosis and steatosis are mediated, at least part, by its insulin-sensitizing and other beneficial metabolic effects of modulating hepatic pyruvate metabolism. We sought to identify other small molecules that interact with the MPC that could be new therapeutic leads.
Method: A BRET-based MPC reporter assay system that responds to molecules that interact with the MPC was used to test for direct interaction of candidate compounds with the MPC complex. We also used mice with tissue-specific deletion of the MPC for in vivo drug treatment and for generating isolated mitochondria for ex vivo analyses. Mice were made to be obese and insulin resistant by feeding a high fat diet for 12 weeks prior to acute treatment of MPC inhibitor by oral gavage.
Results: Use of the BRET reporter system confirmed previous reports of MPC interacting drugs, including other thiazolidinediones (pioglitazone and rosiglitazone), zaprinast, an inhibitor of phosphodiesterase 5 (PDE5), and 7ACC2, which was originally purported to be a lactate transport inhibitor. An Asp residue in the MPC complex was shown to be critical for the interaction between the protein complex and thiazolidinediones or zaprinast, but not 7ACC2. Zaprinast and 7ACC2 were investigated further and shown to interact with the MPC with EC_{50}s of nM concentrations. Zaprinast and 7ACC2 also potently inhibited pyruvate-mediated respiration in isolated WT, but not MPC-deficient mitochondria, demonstrating a direct mitochondrial effect and MPC-dependence for this inhibition of pyruvate metabolism. Consistent with a suppression of gluconeogenesis, MPC inhibitors also suppressed glucose production by isolated hepatocytes in an MPC-dependent manner. Lastly, administration of zaprinast or 7ACC2 improved glucose tolerance, insulin sensitivity, and reduced the expression of NASH markers in liver of diet-induced obese mice.
Conclusion: In conclusion, these data provide proof of concept evidence in a mouse model for the efficacy of novel MPC modulators as insulin sensitizing agents and NASH therapeutics. Moreover, despite differing mechanisms for interacting with the MPC complex, both 7ACC2 and zaprinast had similar effects on insulin sensitivity and NASH end points demonstrating a generalization of the MPC inhibitor mechanism of action.

SAT-346

Icosabutate induces a potent reduction in hepatic oxidative stress in rodent models of metabolic stress and fibrosing NASH

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Background and aims: Polyunsaturated fatty acids and their metabolites target multiple signaling pathways regulating hepatic inflammation and metabolism. However, their accumulation into cellular membranes and proneness to peroxidation could potentially reduce their efficacy in conditions associated with increased oxidative stress, such as NASH. Icosabutate is a structurally-engineered eicosapentaenoic acid (EPA) derivative designed to resist both β-oxidation and incorporation into complex cellular lipids, including plasma and mitochondrial membranes. Potent anti-fibrotic effects were observed after icosabutate treatment in diverse rodent models of NASH, whereas no effects were seen with either EPA or the FXR agonist, obeticholic acid (OCA). The potential role of hepatic oxidative stress in mediating these differences was investigated.

Method: Uptake and partitioning of [^{14}C]icosabutate and [^{14}C]EPA into cellular lipids in Huh7 cells was investigated over 24h. Oxidised (GSSG) and reduced (GSH) glutathione were measured in liver samples collected from 3 mouse NASH models: (1) high-fat (31%) diet (HFD) fed mice treated with 0.3mmol/kg icosabutate or EPA; (2) choline-deficient amino acid defined (CDAA) diet fed mice treated with 0.3mmol/kg icosabutate or EPA; (3) *ob/ob* mice with biopsy confirmed NASH fed a diet rich in fat/trans-fat, fructose and cholesterol (AMLN diet) treated with icosabutate (135mg/kg) or OCA (30mg/kg).

Results: In Huh7 cells [^{14}C]icosabutate and its metabolites were almost entirely (< 5% total radioactivity) absent from complex cellular lipids, whereas > 90% of EPA was cell-associated at 24h (45-fold higher conc. of EPA vs. icosabutate in phospholipid fraction). *In vivo*, icosabutate reduced mean hepatic GSSG by 34, 20 and 33% (all $p < 0.001$) which contributed to 29%, 37% (both $p < 0.01$) and 84% ($p < 0.001$) increases in the hepatic GSH/GSSG ratio vs. control in the HFD, CDAA and AMLN mice respectively. In contrast OCA increased GSSG ($p < 0.05$) whilst a significant fall in GSH (−37%) and the GSH/GSSG ratio (−38%) was observed after EPA treatment (both $p < 0.01$). In AMLN mice, hepatic transcript levels of catalase and SOD1/SOD2 and were increased by icosabutate (all $p < 0.001$) whereas glutathione reductase was unchanged. Hepatic GSSG correlated with hepatic Col1A1 transcripts ($p = 0.001$) and collagen (HYP) content ($p < 0.005$) in the CDAA model and with myofibroblast activation (α-SMA), collagen (HYP) content and Col1a1 (%) protein content (all $p < 0.005$) in the AMLN model.

Conclusion: Icosabutate is highly resistant to cellular accumulation and acts as a potent hepatic antioxidant. In both AMLN *ob/ob* and CDAA NASH models, hepatic GSSG concentrations are highly correlated with fibrosis levels. Improvements in hepatic oxidative stress differentiates icosabutate from both EPA and OCA and likely contributes to its anti-fibrotic efficacy in NASH.

SAT-347

MRI-PDFF response in MGL-3196 and placebo treated patients predicts reduction in ballooning and inflammation components of NAS and NASH resolution in a 36-week serial liver biopsy study

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Background and aims: MGL-3196 is a liver-directed, orally active, highly selective THR-β agonist which may reduce NASH by increasing hepatic fat metabolism and normalizing liver function. In a 12-week interim and 36 week final analysis, MGL- 3196 treated patients had reduced liver fat on MRI-PDFF compared with Placebo (pbo) patients and more MGL-3196 (60%) treated than pbo (18%) patients showed at least 30% reduction in hepatic fat (PDFF response) ($p < 0.0001$). NASH resolution was 39% in MGL-3196 patients who were MRI-PDFF responders at Week 12 ($p < 0.001$). We assessed whether response

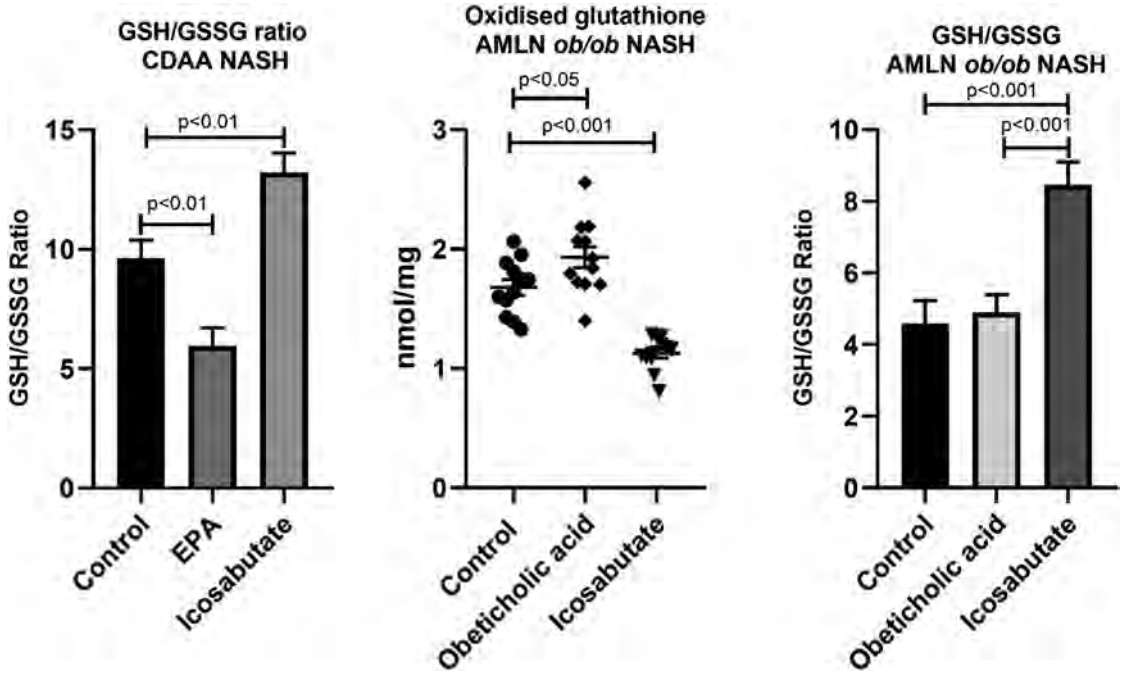

Figure: (abstract: SAT-346)

and magnitude of response on MRI-PDFF at week 12 in pbo or MGL-3196 patients predicted ALT improvement and histologic response on liver biopsy at Week 36.

Method: MGL-3196-05 (NCT02912260) was a 36-week multicenter, randomized, double-blind, pbo-controlled serial MRI-PDFF, paired liver biopsy study in adults with biopsy-confirmed NASH (NAS ≥ 4, F1-F3) and hepatic fat fraction ≥ 10%, assessed by MRI- PDFF. At 36 weeks 107 paired liver biopsies, 73 drug-treated, 34 pbo were assessed. NAS component, correlation and responder analyses were conducted to examine the predictive power of MRI-PDFF response on histologic response of NAS components and ALT reduction in pbo and MGL-3196 patients.

Results: In MGL-3196 patients, week 12 MRI-PDFF response versus non-response predicted NASH resolution at Week 36 (p = 0.001). MGL-3196 PDFF or steatosis responders compared with MGL-3196 non-responders were more likely to show a reduction in other components of NAS (ballooning, inflammation) (OR 8.86, p = 0.0036). In MGL-3196 patients, Week 12 PDFF response correlated with improvement in steatosis (direct relationship), improvement in inflammation and ballooning components of NAS (0.42) and reduction in ALT (0.34). Pbo patients with ≥ 5% weight loss were likely PDFF responders (71%, p = 0.007). In pbo patients PDFF response correlated with weight loss (0.58), which predicted inflammation and ballooning responses (0.58). In pbo patients with < 3% weight loss, ballooning reduction was not correlated with any improvement in steatosis, inflammation, fibrosis or ALT. In MGL-3196 patients, a ballooning reduction without a reduction in steatosis and/or MRI-PDFF response was not associated with improvement in inflammation, fibrosis or ALT.

Conclusion: In both MGL-3196 and placebo treated patients, MRI-PDFF response correlated with reduction in ballooning and inflammation scores on liver biopsy and was associated with NASH resolution. In pbo, but not MGL-3196, patients most of the response was driven by weight loss. These data suggest that reduction of hepatic fat is a critical component of NASH improvement and resolution.

SAT-348

Low frequencies of lifestyle interventions and liver-specific medications in a multicentric prospective real world NAFLD cohort: The fatty liver assessment in Germany (FLAG) study

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Background and aims: Non-alcoholic 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 and physical activity) and the use of available medications that may have a beneficial effects on comorbidities and NAFLD. Cohort studies in a "real life" setting represent a suitable tool to study clinical outcomes in patients with NAFLD and assess 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 University Hospitals 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 profiling are collected. Liver stiffness measurement (LSM) data are included when available. Lifestyle interventions, medications, as well as clinical events are assessed at baseline and followed-up prospectively.

Results: Baseline data from the first 400 Patients with NAFLD were analyzed including 52% men with a mean age of 52 years. By calculating the non-invasive serum score FIB-4 index, 9.4% of patients had advanced fibrosis (F3-F4 fibrosis). Accordingly, those with F3-F4 fibrosis had higher mean LSM (14.1 kPa vs. 8.1 kPa) values as compared to patients with no advanced fibrosis. Type 2 diabetes mellitus (T2DM), arterial hypertension, and a history of cardiovascular events were more frequent in those with F3-F4 fibrosis as compared to patients without advanced fibrosis (47%, 89%, and 19% vs. 19%, 44%, and 14%, respectively; $p < 0.02$ for T2DM and arterial hypertension, respectively). In 17% of the patients, any NAFLD medical intervention was recorded including vitamin E, vitamin D, UDCA, and silymarin, respectively. Nutritional counselling took place in 28% of the patients and 15% of the patients reported physical activity at least 2 time per week.

Conclusion: In this multicentric prospective cohort study, baseline data of patients with NAFLD give insights in the real world patient care in Germany. The prevalence of patients with advanced fibrosis confirms previous estimates. There is a low frequency and heterogeneity in use of available medications that may affect NAFLD outcome. Lifestyle interventions should be strenghtend and their effectiveness will be assessed during prospective data collection

SAT-349

Improvement of hepatic inflammation and fibrosis independently of weight loss from a short, individualized, web-based exercise program in patients with NAFLD

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Pharmacologic therapies for NAFLD are not available and lifestyle modification remains the cornerstone of therapy. The aim of this trial was to evaluate the effects of a short, web-based individualized exercise program on surrogate markers of hepatic steatosis, inflammation and fibrosis.

Method: 44 patients with histological confirmed NAFLD were enrolled into this prospective, interventional single arm study (NCT02526732). The exercise program consisted of combined aerobic and resistance exercise training over 8 weeks, integrated into the patients' daily routine through a web-based platform with weekly bidirectional feedback. A follow-up exam was performed in week 20, 12 weeks after cessation of the individualized program. Changes in liver function tests as well as surrogate markers of hepatic steatosis, inflammation and fibrosis were evaluated.

Results: A total of 41 patients completed the assigned training goal (93.2%). Eight weeks of individualized exercise lead to a small weight loss by 0.9% ($p < 0.01$), nonetheless improvement of ALT (−14.3%, $p < 0.01$) and AST (−18.2%, $p < 0.001$) occurred. Surrogate scores of disease severity including the fatty liver index (FLI) and fibrosis scores (FiB-4 and APRI) were significantly reduced after the intervention. Median liver stiffness determined by transient elastography declined from 7.4 to 6.4 kPa ($p < 0.05$). Inflammatory markers including hsCRP and Ferritin decreased, as well the cytokeratin 18 fragment M30, (baseline: 383.1 U/l to week 8: 318.8 U/l, $p < 0.01$). Pro-coallagen-3 (Pro-C3) decreased significantly at end of follow-up (baseline: 145 ng/ml to week 20: 119 ng/ml, $p < 0.01$), while C4M2, reflecting type IV collagen degradation, increased ($p < 0.05$), suggesting increased collagen turn-over compatible with fibrosis regression.
Conclusion: A short, individualized course of exercise is sufficient to improve surrogate markers of hepatic steatosis, inflammation and fibrosis independently of weight loss.

SAT-350

YH25724, a novel long-acting GLP-1/FGF21 dual agonist, exhibits marked anti-fibrotic effects in different experimental models of liver fibrosis

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Background and aims: YH25724 is a novel long-acting dual agonist consisting of a GLP-1 variant and an FGF21 variant fused to an immunoglobulin Fc region. Due to complementary mechanisms of action, GLP-1 and FGF21 dual agonism may represent an effective therapeutic strategy for the treatment of non-alcoholic steatohepatitis (NASH). In a diet-induced obese mouse model of NASH, YH25724 significantly improved metabolic profiles with anti-steatotic, anti-inflammatory and anti-fibrotic effects. In the current study, we investigated whether YH25724 exerts anti-fibrotic effects in two different rat models.

Method: A choline-deficient, L-amino acid-defined, cholesterol-supplemented (CDAA/chol) diet-induced model and a thioacetamide (TAA)-induced liver fibrosis model were established in Wistar rats. In the CDAA/chol model, rats were fed a CDAA/chol diet over 12 weeks to induce fibrosis and treated with YH25724 subcutaneously during the last 8 weeks. In the TAA model, rats were given 0.03% (w/v) TAA in drinking water for 22 weeks to induce liver fibrosis and treated with YH25724 subcutaneously during the last 8 weeks. In both models, vehicle-treated rats were used as controls. The extent of liver fibrosis was assessed using picrosirius red staining (PSR) or hydroxyproline (HP) content, and liver fibrosis staging was evaluated with semi-quantitative scores. Hepatic alpha-smooth muscle actin (α-SMA) expression was evaluated by immunohistochemistry. Serum fibrosis markers were measured by ELISA.
Results: In the CDAA/chol model, all vehicle-treated rats developed fibrosis after the CDAA/chol diet regimen. PSR staining revealed that the area of fibrosis was significantly reduced in the YH25724-treated group. In the TAA model, all vehicle-treated rats progressed to liver cirrhosis, while fibrosis stage was significantly reduced in the YH25724-treated group. PSR staining, HP content and α-SMA expression were significantly reduced in the YH25724-treated group. Furthermore, serum levels of cytokeratin-18, TGF-β1, Pro-C1, Pro-C3 and hyaluronic acid were significantly decreased in the YH25724-treated group.
Conclusion: YH25724 markedly attenuated the progression of fibrosis in rat models. These data support the general anti-fibrotic potential of this hybrid molecule, which occurs independent of body weight reduction. YH25724 may therefore provide not only metabolic but also strong anti-fibrotic benefits in patients with NASH.

SAT-351

Biomarkers and clinical characteristics associated with non-alcoholic steatohepatitis fibrosis progression in the CENTAUR study

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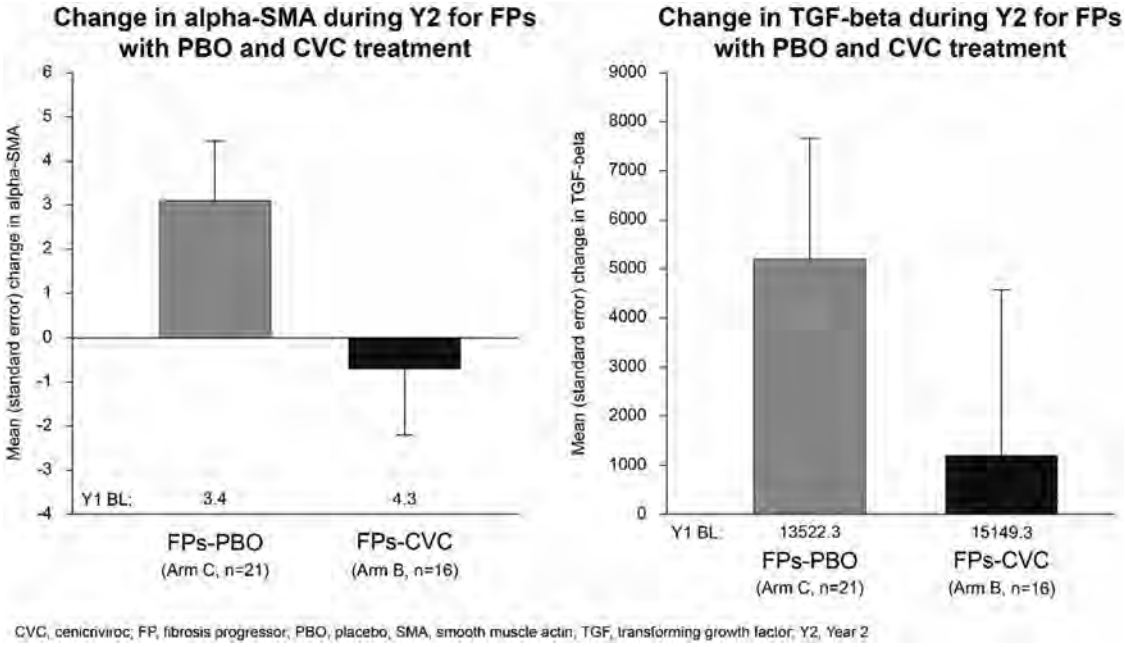

CVC, cenicriviroc; FP, fibrosis progressor; PBO, placebo; SMA, smooth muscle actin; TGF, transforming growth factor; Y2, Year 2

Figure: (abstract: SAT-351)

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Background and aims: Cenicriviroc (CVC) is an oral C-C chemokine receptor type 2/5 antagonist currently being evaluated for the treatment of liver fibrosis in adults with non-alcoholic steatohepatitis (NASH). In the Phase 2b CENTAUR study, CVC treatment resulted in a significant, durable antifibrotic benefit compared with placebo (PBO). The aims of this CENTAUR analysis were to characterise the subpopulation of fibrosis progressors (FPs) initially treated with PBO during Year 1 (Y1) compared to fibrosis non-progressors (FNs), and to evaluate the effect of CVC in FPs on histology and biomarkers of fibrosis during Year 2 (Y2).
Method: Adults with histologically confirmed NASH, non-alcoholic fatty liver disease activity score (NAS) ≥ 4 and liver fibrosis Stages 1-3 (NASH Clinical Research Network) received CVC 150 mg once daily (Arm A) or PBO (Arm C), respectively, for 2 years; Arm B received PBO in Y1 and crossed over to CVC in Y2. FPs were defined as subjects who experienced worsening in fibrosis by ≥ 1 stage from baseline (BL) to Y1 and were identified from the PBO-treated modified intent-to-treat population (N = 126) in Y1 (Arms B and C). Clinical characteristics and serum biomarkers were analysed at BL and over time. Histology was assessed by a central pathologist blinded to treatment assignment. The effect of CVC (Arm B) vs PBO (Arm C) on FPs was assessed during Y2.
Results: Of Y1 PBO-treated subjects in Arms B and C (N = 126), 29% (n = 37) were identified as FPs (mean age: 52.1 years; mean body mass index: 34.1 kg/m^2; NAS ≥ 5: 89%; type 2 diabetes mellitus: 46%). A greater proportion of FPs compared to FNs at BL were female (62% vs 49%), Hispanic/Latino (89% vs 78%) and had higher disease activity (NAS ≥ 5: 89% vs 71%; hepatocellular ballooning grade 2: 65% vs 51%). Considerably more FPs vs FNs had fibrosis Stage 1 (65% vs 20%) and aspartate aminotransferase > 30 U/L (89% vs 74%) at BL. During Y1, increases in serum transforming growth factor (TGF)-beta and tissue inhibitor of metalloproteinase-1 (TIMP-1), and liver biopsy alpha-smooth muscle actin (SMA) staining and collagen proportionate area were observed for FPs vs FNs. During Y2, CVC treatment was associated with a lesser decrease in collagen area, increased TIMP-1, and reduced alpha-SMA staining and attenuated serum TGF-beta concentrations compared to PBO (Figure).
Conclusion: The unique study design of CENTAUR enabled characterisation of NASH FPs during Y1 and evaluation of the antifibrotic effect of CVC in Y2. Female sex, ethnicity and inflammatory disease activity are key characteristics of FPs. In those FPs, CVC treatment was associated with a reduction of some biomarkers of fibrosis (TGF-beta and alpha-SMA) vs PBO in Y2. These findings warrant further investigation.
Writing assistance by Complete HealthVizion.

SAT-352

A combination of the ACC inhibitor GS-0976 and the nonsteroidal FXR agonist GS-9674 improves hepatic steatosis, biochemistry, and stiffness in patients with non-alcoholic steatohepatitis

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Background and aims: Preclinical data suggest that the combination of an ACC inhibitor and FXR agonist is more effective than monotherapy in the treatment of NASH. Here, we describe the combination of the ACC inhibitor, GS-0976, with the nonsteroidal FXR agonist, GS-9674, in patients with NASH.
Method: Twenty patients with NASH diagnosed by a magnetic resonance proton density fat fraction (MRI-PDFF) ≥ 10% and liver stiffness ≥ 2.88 kPa by magnetic resonance elastography (MRE), or historical biopsy consistent with NASH and F2-F3 fibrosis were enrolled. Patients received GS-0976 20 mg and GS-9674 30 mg orally once daily for 12 weeks. Data from two cohorts treated with either GS-0976 20 mg or GS-9674 30 mg daily for 12 weeks are provided for comparison. MRI-PDFF and MRE and serum fibrosis markers were centrally read at baseline (BL) and week 12 (W12). Deuterated water was administered to measure hepatic de novo lipogenesis (DNL).
Results: In the combination cohort, 55% had diabetes and the median BMI was 38.7 kg/m^2. Compared with BL, significant reductions at W12 in combination-treated patients were observed for PDFF (median: 16.4% vs 9.8%; p < 0.001), MRE-stiffness (3.76 vs 3.43 kPa; p = 0.018), serum TIMP-1 (263.4 vs 240.7 ng/ml; p = 0.012), PIII-NP (10.6 vs 8.4 ng/ml; p = 0.003), ALT, and GGT. At W12, a ≥ 30% relative decline in PDFF was observed in 14/19 patients (74%). Compared with monotherapies, combination therapy resulted in greater reductions in hepatic PDFF, ALT, GGT, and hepatic DNL (Table). Combination treatment was safe and well-tolerated with AE rates similar to monotherapies; no patient reported ≥ grade 2 pruritus or discontinued study medications due to AEs.

Table: Median Relative (%) Changes in Imaging, Biochemistry, and Fibrosis Markers at W12

	GS-0976 20 mg (n = 10)	GS-9674 30 mg (n = 10)	GS-0976 20 mg + GS-9674 30 mg (n = 20)
MRI-PDFF	-42.7*	-15.6*	-45.3*
≥ 30% reduction in MRI-PDFF, % (n)	70% (7/10)	0	74% (14/19)
MRE	-8.9	-8.3	-9.0*
ALT	-33.5	-29.7	-37.2*
GGT	-1.6	-19.3*	-32.4*
TIMP-1	-11.6*	6.6*	-7.1*
PIII-NP	-11.9	8.8	-12.1*
DNL	-22.0*	7.5	-30.1*

*p < 0.05 at BL vs W12 using Wilcoxon signed-rank test

Conclusion: The combination of GS-0976 and GS-9674 for 12 weeks was safe and led to improvements in hepatic steatosis, liver stiffness, liver biochemistry, and markers of fibrosis in NASH.

SAT-353

The effect of metformin on hepatic fatty acid partitioning; an investigation using human in vivo and in vitro models

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Background and aims: Many individuals with non-alcoholic fatty liver (NAFLD) disease will be taking metformin, the first-line therapeutic drug for type 2 diabetes (T2D). Whereas rodent models have shown that metformin decreases high-fat diet-induced steatosis, human studies have shown no reduction in liver fat despite increases in hepatic insulin sensitivity and reductions in body weight. The reason for the discrepancy remains unclear. We aimed to determine the effect of metformin on hepatic de novo lipogenesis (DNL) and fatty acid oxidation pathways in humans subjects and in cellular hepatocyte models.
Methods: Ten insulin-resistant, metformin-naïve human subjects underwent 12-weeks metformin treatment (2g/day). Pre- and post-treatment, subjects had magnetic resonance spectroscopy (MRS) to determine liver fat content and underwent metabolic phenotyping including 2-step euglycemic hyperinsulinemic clamp and stable isotope infusions. In vitro, Huh7 cells were cultured in human serum and fatty acids to induce steatosis and subsequently treated with metformin for 48 hrs. Cells were collected and intracellular triglyceride content and markers of fatty acid oxidation were measured.
Results: In human subjects, basal plasma glucose and triglyceride were significantly lower post-metformin treatment. There was no change in plasma non-esterified fatty acid or 3-hydroxybutyrate levels. Hepatic insulin sensitivity and whole body fatty acid oxidation did not change. Liver fat content on MRS was maintained following metformin treatment (15.9 ± 11.6 v 17.1 ± 12.8%) despite 2kg weight loss ($p < 0.05$). DNL tended to increase after metformin treatment and was significantly higher post treatment during the low-dose insulin clamp (AUC $p < 0.05$). In line with the human data, Huh7 cells treated with metformin maintained intracellular triglyceride, and there was no effect on triglyceride secretion or production of 3-hydroxybutyrate.
Conclusion: Our data demonstrate that metformin does not decrease hepatic steatosis in insulin resistant human subjects. De novo lipogenesis was increased following metformin treatment which may have offset any reductions in liver fat conferred by weight loss. Markers of hepatic fatty acid oxidation remained unchanged. This data demonstrates a change in fatty acid partitioning post-metformin and suggests that upregulated DNL may contribute to its glucose lowering effect. Whilst metformin has a role in T2D, we suggest that it does not represent a viable treatment strategy specifically for NAFLD.

SAT-354

Aramchol, SCD1 inhibitor, improves liver glucose homeostasis in NASH

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Background and aims: We have previously shown that Aramchol, an arachidyl cholic acid adduct that targets SCD1 (stearoyl CoA desaturase 1, a key enzyme that catalyzes the first reaction committing fatty acids into triglyceride synthesis), has a unique mechanism of action that targets both the metabolic alterations that characterize NASH (accumulation of lipids, lipotoxicity and oxidative stress) and fibrosis. In a one year study in 247 NASH patients, Aramchol significantly reduced liver fat, improved histology and hepatic biochemistry. At week 52 placebo patients exhibited an increase in HbA1C, while those treated with Aramchol (400 and 600 mg/day) showed a reduction with a dose response pattern. The differences from placebo were statistically significant suggesting Aramchol also targets glucose metabolism. The aim of this study was to elucidate the mechanism by which Aramchol regulates hepatic glucose metabolism using the methionine and choline deficient (MCD) diet mouse model of NASH.
Methods: We collected liver samples from mice fed the MCD diet containing 0.1% methionine (0.1MCD) for four weeks, which developed steatohepatitis and fibrosis, as well as mice receiving a control diet; and the liver metabolomes and proteomes were determined. A group of 0.1MCD fed mice were given Aramchol (5mg/kg/day or 1 mg/kg/day, for the last 2 weeks).
Results: 0.1MCD fed mice developed steatohepatitis and showed a statistically significant reduction 1.5 to 4 fold of liver glucose, glucose 6 phosphate, fructose 6 phosphate and fructose 1, 6 bisphosphate (FBP) as well as altered protein content of a variety of glycolytic/gluconeogenic enzymes, including glucokinase, glucose 6 phosphate isomerase, fructose 1, 6 bisphosphate phosphatase, enolase, pyruvate kinase and phosphoenolpyruvate carboxykinase, as compared to mice fed the control diet. As shown previously, Aramchol treatment improved NASH features reducing lipid accumulation, inflammation and fibrosis. We also found a significant improvement of glycolysis/gluconeogenesis in 0.1MCD fed mice treatd with Aramchol in a dose dependent manner. It is important to note that FBP, the product of the first irreversible step in glycolysis, is a gauge of the cells nutrient status that regulates AMPK, via its interaction with aldolase B, and pyruvate kinase activity. Of note, we found a statistically significant increase in aldolase activity in livers from 0.1MCD fed mice that decreased in Aramchol treated mice.
Conclusions: These results show that Aramchol targets not only the alterations in lipid metabolism that characterize NASH but additionally improves liver glucose homeostasis.

SAT-355

Fatty liver trends in Southern Italy: Mediterranean or Americanized lifestyle habits?

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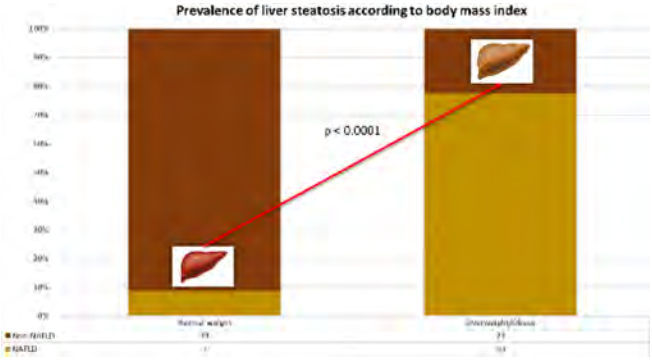
Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, and its current prevalence is estimated to be ≈ 25. Weight loss, with diet and physical activity as main components of healthy lifestyles, is to date the primary therapy for the management of NAFLD. We aimed to assess unhealthy food intake (as "Junk Score") and physical activity frequency with regards to age and liver steatosis, as part of lifestyle habits, in a cohort from Southern Italy.
Method: 1, 124 subjects were enrolled (437 males, mean age 39 ± 0.9 years; 687 females, mean age 39 ± 0.7 years) as young (≤ 30 years, n = 554) and adult (> 30 years, n = 570) individuals, either healthy or as outpatients for gastrointestinal disorders. "Junk Score" was calculated based on the intake of high-fat, high-sugar food (range 0-50). Physical activity frequency was classified in sedentary, low, medium and high (0, 1-2, 3-4 and > 4 times/week, respectively). Liver steatosis was assessed by ultrasound (0 = absent; 1 = present; Noblus Hitachi, Italy).
Results: Mean body mass index was 23 kg/m^2 and 33 kg/m^2 ($p < 0.0001$; without and with NAFLD, respectively). Prevalence of liver steatosis and overweight/obesity (≥ 25 kg/m^2) increased with age (from 6% to 38% and from 17% to 65%; $p < 0.0001$ for both; in subjects ≤ and > 30 years, respectively). "Junk Score" significantly increased with age (from 24.9 ± 0.6 to 34.2 ± 1.3 and from 24.7 ± 0.6 to 35.4 ± 0.7; $p < 0.0001$ for both; in subjects ≤ and > 30 years, without and

with NAFLD, respectively). The prevalence of subjects at each physical activity frequency was 61% vs. 84%, 18% vs. 7%, 16% vs. 5% and 5% vs 4% for sedentary, low, medium and high (without vs. with NAFLD; p < 0.0001 for sedentary vs. low in both groups) respectively. The prevalence of sedentary adults (> 30 years) without NAFLD was lower than those with NAFLD (47% vs. 88%; p < 0.0001).



Conclusion: In the Italian region of Apulia, prevalence of fatty liver is high and rising with age in subjects with no apparent liver disease (23%). Poor quality of diet, reflected by "Junk Score," and number of sedentary subjects are significantly associated with NAFLD, as part of unhealthy lifestyle habits. The "Horizon 2020 Foie Gras" project in Southern Italy is currently investigating educational, feasible and low-cost therapeutic approaches in order to promote healthy lifestyle habits urgently.

SAT-356

Anti-metabolic, anti-inflammatory and anti-fibrotic properties of ART-648, a novel phosphodiesterase 4 inhibitor as a potential clinical candidate for non-alcoholic steatohepatitis

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Background and aims: Phosphodiesterase 4 (PDE4) is ubiquitously expressed in the entire body and plays multiple physiological and pathophysiological roles via increase of intracellular cyclic AMP modulation. Inhibition of PDE4 is a known pharmacological target for inflammatory disorders such as chronic obstructive pulmonary disease and psoriasis. Since PDE4 inhibition is also suggested to improve metabolic and fibrotic disorders, a novel selective PDE4 inhibitor, ART-648, was validated for the treatment of non-alcoholic steatohepatitis (NASH) using in vitro and in vivo models relevant for multiple pathophysiologies underlying the disease.
Method: ART-648 was orally administered to dyslipidemic low-density lipoprotein receptor null (LDLr-/-) mice fed modified choline-deficient diet, in either prophylactic (1, 3, and 10 mg/kg for 7 weeks) or therapeutic modes (4 and 8 mg/kg for 10 weeks). ART-648 (1, 3 mg/kg) was also dosed in diet-induced obese (DIO) mice. Anti-inflammatory and anti-fibrotic effects of ART-648 were evaluated in human and murine whole blood, THP-1 derived macrophages and human primary stellate cells.
Results: ART-648 dose-dependently decreased hepatic fibrosis area ($p < 0.05$), triglyceride content ($p < 0.05$) and gene expression of collagen-I ($p < 0.05$), TNF-α ($p < 0.05$), and TIMP-1 ($p < 0.05$). At the doses with robust anti-fibrotic efficacy, > 50% target engagement with ART-648 over 16 hours per day was simulated. ART-648 significantly decreased body weight ($p < 0.025$), food intake ($p < 0.025$) and fat mass ($p < 0.025$) in DIO mice. A single administration of ART-648 increased oxygen ($p < 0.025$) and energy ($p < 0.025$) expenditure in DIO mice. ART-648 decreased gene expression of TNF-α and αSMA, which were accompanied with intracellular cAMP elevation in THP-1 cells or hepatic stellate cells, respectively. In human whole blood, ART-648 inhibited TNF-α release-induced by LPS in a concentration-dependent manner.

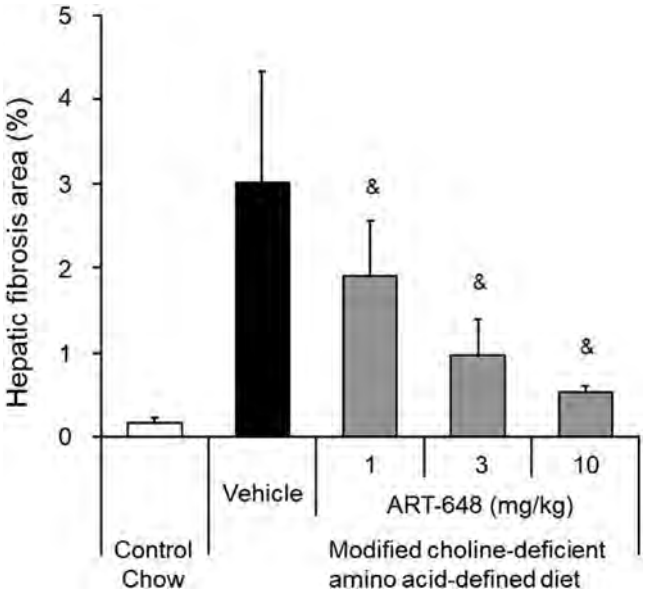

Figure: Prophylactic effects of TAK-648 on hepatic fibrosis area in LDLr -/- mice with modified choline-deficient amino acid-defined diet

Conclusion: Anti-fibrotic, anti-inflammatory and anti-metabolic effects of ART-648 were evident, suggesting potential to be an efficacious pharmacotherapy for NASH pending clinical demonstration of its benefits in NASH treatment.

SAT-357

Tropifexor, a farnesoid X receptor agonist for the treatment of non-alcoholic steatohepatitis: Interim results based on baseline body mass index from first two parts of Phase 2b study FLIGHT-FXR

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Background and aims: Tropifexor (TXR) is a highly potent non-bile acid farnesoid X receptor (FXR) agonist. In single dose Phase 1 trials, the pharmacodynamic response was linear in healthy subjects up to 1, 000 μg/d. In FLIGHT-FXR Parts A and B tropifexor was dosed at 90 μg/d while in the currently ongoing Part C doses up to 200 μg/d are tested.

Method: FLIGHT-FXR (NCT02855164) is a Phase 2 randomized, double-blind, placebo-controlled trial with an adaptive design of 3 sequential parts to assess safety, tolerability and efficacy in NASH patients. Treatment duration in Parts A and B was 12 weeks. Population included 198 patients (47% male) with liver fat, elevated alanine transaminase (ALT) and NASH on either a historical biopsy or phenotype. Pooled results from treatment arms common to Parts A and B (placebo: 46; TXR 60 μg: 37; TXR 90 μg: 85) were assessed in both pre-specified baseline BMI subgroups for target engagement (fibroblast growth factor-19 [FGF19] and 7-hydroxy-4-cholesten-3-one [C4]), changes from baseline in ALT, gamma-glutamyl transaminase (GGT), liver fat (magnetic resonance imaging-proton density fat fraction [MRI-PDFF]) and safety. Statin initiation was not allowed during the trial.

Results: Results in the BMI subgroups are shown in table as geometric mean of percentage changes from baseline to Week 12, except for FGF19 (change 4 hours post dose from pre-dose at Week 6). p values are not shown as hypothesis testing was not done. Effect of TXR on ALT, GGT and PDFF was more pronounced in subgroup of lower BMI. TXR was well tolerated without safety signals of clinical relevance (including pruritus and lipids).

	BMI (kg/m^2) < 35 (Non-Asian) or < 30 (Asian)			BMI (kg/m^2) ≥ 35 (Non-Asian) or ≥ 30 (Asian)		
Stratum	Placebo n = 28	TXR 60 μg n = 21	TXR 90 μg n = 52	Placebo n = 18	TXR 60 μg n = 16	TXR 90 μg n = 33
FGF19	22	360	586	68	277	447
C4	2.8	−33.2	−40.4	37.3	−48.9	−61.8
GGT	−10.8	−47.0	−61.3	−6.8	−38.4	−48.7
ALT	−18.6	−26.0	−26.8	−10.6	−14.8	−19.5
MRI-PDFF	−13.1	−19.9	−18.8	−5.5	−12.9	−11.4
LDL-C	−9.7	10.0	12.7	0.7	8.9	6.9
HDL-C	−4.8	−1.9	−7.7	−3.9	−6.1	−11.9
TG	1.2	1.0	5.7	0.9	−6.7	−2.3
Weight	−0.1	−1.0	−1.1	0.0	−1.2	−1.6

Conclusion: In both BMI subgroups, TXR results provide evidence of target engagement, anti-inflammatory and anti-steatotic effects with favorable safety and tolerability. Consistent trends of lower responses in sub-group receiving lower dosing by body weight support testing higher TXR doses (140 and 200 μg/d) in the biopsy-based Part C, which may provide improved efficacy without jeopardizing safety.

SAT-358

Sodium glucose cotransporter 2 inhibitor, canagliflozin ameliorate liver function in Japanese patients with type 2 diabetes mellitus: Subgroup analyses of clinical trials

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Background and aims: Sodium glucose cotransporter 2 inhibitor (SGLT2I) was developed for the treatment of patients with type 2 diabetes mellitus (T2DM). The aim of this pooled and subgroup analyses was to investigate the efficacy of canagliflozin on liver function and its safety in high alanine aminotransferase (ALT) patients (ALT > 30 U/L).

Method: This post hoc analysis of canagliflozin in T2DM patients was divided into Study 1 (pooled analysis of 12- and 24-week a multicenter, randomized, placebo-controlled, double-blind, parallel-group study in Japanese T2DM patients) and Study 2 (52-week monotherapy/combination therapy study). The canagliflozin 100 mg group data were compared with placebo or baseline ALT subgroup (baseline ALT > 30 or ≤ 30 U/L) data. The primary end point was change in ALT level from baseline. Secondary end points were changes in efficacy-related parameters and adverse events (AEs).

Results: In the high ALT subgroup, the mean ALT change at 12 weeks in canagliflozin group (−10.3 ± 11.7) was significantly greater than placebo group (−3.2 ± 17.6 U/L) (p = 0.0206); while no significant difference was shown in the low ALT subgroup (Study 1). Glycosylated hemoglobin (HbA1c) and body weight were significantly reduced in both ALT subgroups (all P < 0.0001, Studies 1 and 2). In the high ALT subgroup, the mean change in ALT significantly also decreased at 52 weeks (−16.0 ± 18.8 U/L) (p < 0.0001, Study 2). The results of the correlation analysis in the high ALT subgroup showed a negative correlation between the change in ALT and baseline ALT at both 12 weeks (r = -0.605, P < 0.0001) and 52 weeks (r = -0.638, P < 0.0001). The incidence of AEs or serious AEs in the canagliflozin group was the same as those in the placebo group and there was no difference according to ALT level (Studies 1 and 2).

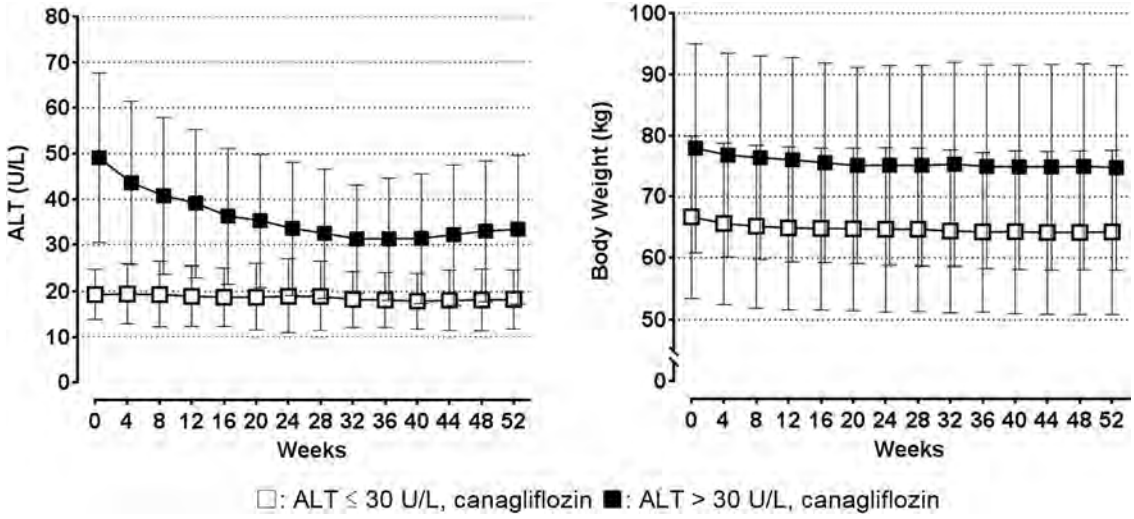

Figure: (abstract: SAT-358): Change in ALT and body weight over 52 weeks (Study 2).

Conclusion: In T2DM patients with impaired liver function, canagliflozin may improve liver function, reduce HbA1c and body weight, and be well tolerated. The treatment with SGLT2I may provide a clinical benefit to type 2 diabetes mellitus patients with NAFLD.

SAT-359

Pharmacokinetics and safety of pegbelfermin (BMS-986036) administered in the abdomen and upper arm to normal, overweight, and obese healthy participants

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Background and aims: Pegbelfermin (BMS-986036), a PEGylated human fibroblast growth factor 21 (FGF21) analogue, improved steatosis, liver injury, and fibrosis biomarkers in a phase 2 study of overweight (OW) and obese (OB) patients with non-alcoholic steatohepatitis (NASH). This phase 1 study evaluated pharmacokinetics (PK) and safety of a single subcutaneous (SC) pegbelfermin dose administered in the abdomen and upper arm to normal, OW, and OB healthy participants (ppts).
Method: MB130-070 was an open-label, fixed-sequence, crossover study in ppts grouped by body mass index (BMI [kg/m^2]; normal, 18.0 ≤ 25.0; OW, > 25.0 ≤ 30.0; OB, > 30.0 ≤ 40.0). Ppts received 20 mg pegbelfermin on Day 1 of successive treatment periods via injection to the abdomen (period 1) and upper arm (period 2). On Days 8, 15, 22, and 29 of each period, serum was collected for PK analysis and safety was assessed.
Results: Thirty ppts received an abdominal injection of pegbelfermin (n = 10/cohort); 29 ppts received pegbelfermin via upper arm injection (normal and OW, n = 10 each; OB, n = 9). Most ppts were male (90%), median age was 31 y. Serum pegbelfermin exposure was up to 30% higher after upper arm vs abdominal administration in normal and OW ppts, but similar between sites in OB ppts (table). Within administration sites, serum pegbelfermin exposure was up to 21% and 67% higher in normal vs OW and OB ppts, respectively. Five ppts reported 6 adverse events (AEs; n = 3 each in OW and OB ppts) after abdominal injection; 12 ppts reported 18 AEs (n = 6, normal; n = 4, OW; n = 8, OB) after upper arm injection. All AEs were of mild to moderate intensity; no serious AEs or deaths occurred. One ppt discontinued due to a non-treatment-related AE; 1 OW ppt was positive for anti-FGF21 antibodies at Days 15 and 29 of period 2.

	Abdomen			Upper Arm		
	Normal n = 10	Overweight n = 10	Obese n = 10	Normal n = 10	Overweight n = 10	Obese n = 9
C_{max}, ng/ml (%CV)[a]	757 (40)	694 (58) 23[b]	566 (49) —	889 (39)	906 (54) 68[b]	540 (55) —
% increase[b]	34[b]			65[b]		
AUC_{0-T}, h*ng/ml (%CV)[a]	52533 (34)	43507 (47) 25[b]	34767 (58) —	63519 (27)	57260 (39) 51[b]	37963 (56) —
% increase[b]	51[b]			67[b]		

[a]Geometric mean; [b] Relative to geometric mean values for obese ppts.

Conclusion: Pegbelfermin was generally well tolerated when administered SC to the abdomen or upper arm in healthy normal weight, OW, and OB ppts. There was a trend towards increased exposure with decreased BMI. Exposure after abdominal or upper arm administration was generally similar in OB ppts, but up to 30% higher in normal and OW ppts when administered to upper arm relative to the abdomen. A dose-ranging study is underway to evaluate histological and biomarker responses to 10, 20, and 40 mg QW pegbelfermin in patients with NASH.

SAT-360

A phospholipid-based therapeutic perspective for the regression of liver fibrosis: a study on human immortalized hepatic stellate cells

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Background and aims: During liver fibrogenesis, the myofibroblastic transdifferentiation (or activation) of hepatic stellate cells (HSCs) is a reversible key event. Essential phospholipids have shown to exert antifibrotic effects with their polyenylphosphatidylcholine (PPC) fraction and specifically with their phospholipid 1, 2 dilinoleoylphosphatidylcholine (DLPC) playing a major role. However, the mechanism behind it, as well as the exact role of the PPC components, remain still unclear. In this study, novel PPC-based formulations were developed and evaluated for their antifibrotic properties by means of an *in vitro* model based on human immortalized HSCs, LX-2.
Method: LX-2, in their standard activated state, were treated with liposomes either directly or after additional activation for 24 h with TGF-β_1. Liposomes were prepared using 1, 2-dilinoleoyl-*sn*-glycero-3-phosphocholine (DLPC), soy phospholipid with 75% phosphatidylcholine (S80), soy phospholipid 80% with $MgCl_2$ or with $CaCl_2$ (S80 M and S90, respectively), 2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) and DOPC/DLPC (53/47 mol%). Lipid droplets were examined by Oil Red O staining, the scar production was followed with Sirius Red and Fast Green, and the α-SMA by immunocytochemistry. Membrane fluidity variations of adherent LX-2 were studied by means of fluorescence anisotropy of 1, 6-diphenyl-1, 3, 5-hexatriene (DPH) and 1- (4-trimethylammoniumphenyl)-6-phenyl-1, 3, 5-hexatriene *p*-toluenesulfonate (TMA-DPH).
Results: The incubation of LX-2 with DLPC, S80, S80 M, S90, DOPC/DLPC liposomes revealed increased lipid droplets, low content of collagen compared to non-collagenous proteins, and low α-SMA. In contrast as expected, the negative control, DOPC treatment showed opposite features. The anisotropy values of DPH, relative to the inner core of the cell membranes, revealed a low motional order upon treatment with TGF-β_1. On the contrary, all the lipids used, but specifically S80, induced a major increase of the membrane fluidity. The motional order at the interface regions, as measured with TMA-DPH, resulted mostly affected by DLPC, DOPC and DOPC/DLPC direct treatments.
Conclusion: Liposomes of S80, S80 M and S90 showed more promising characteristics as antifibrotic treatments compared to the DLPC ones, used as a positive control for the reported ability to inactivate HSCs. The three PPCs will be further formulated as oral dosage forms and investigated as possible chronic therapy for fibrosis regression.

Immunology except viral hepatitis

SAT-371

Alleviation in NK cells cytotoxicity following inhibitions of Neuroligin-4 (NLG4) receptor by recombinant beta-neurexin involving IL-4 pathway

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Background and aims: Neuroligin-4 receptors (NLG4) are post-synaptic adhesion proteins that control the maturation and function of synapses in the central nervous system (CNS). NK cells from Non-

alcoholic Fatty liver Disease (NAFLD) patients exert high expressions of NLG4 and are thought to interfere with NK cell activity. NLG4 receptor interacts through immune synapse with its ligand β-neurexin (cell-adhesion molecules) and is thought to play an important step in fibrogenesis. We investigated a potential role of recombinant β-neurexin to inhibit NLG4 elevations of NK cells in an *in vitro* co-culture condition.

Method: NK cells isolated form peripheral blood of NAFLD patients lacking metabolic syndrome were pre-incubated with 4 and 10 nM recombinant β-neurexin for 3 hours prior to incubations with hepatic stellate cells (HSCs; LX2- cell line). Following 24 hours, cells were trypsinized and analyzed by flow-cytometry for NK activity by CD107a (Degranulation marker- a marker for NK activation) and LX2 activities (α-smooth-muscle intensities). Interlukine-4 (IL4) expressions were also assessed in NK cells.

Results: LX2 cell line express 75% of β-neurexin. In co-cultures, recombinant β-neurexin significantly decreased the receptor expressions of NLG4 on NK cells and was well correlated with the increase in the recombinant concentrations. In additions, NK cells showed significantly increased lysosomal-associated membrane protein-1 (CD107a, NK activation marker) from 13% to 50% and 53% with the 4 and 10 nM recombinant, respectively ($p < 0.03$). Compared to LX2 mono-cultures, elevations of NK cells CD107a activity was associated with increased LX2 killing; as αSMA mean fluorescence intensities of HSCs decreased from 2948 in cultures without the recombinant to 2552 and 2066 in cultures with the 4 and 10 nM recombinant, respectively, ($p < 0.01$). NK cells pre-treated with the recombinant β-neurexin showed decreased in IL-4 secretion in both the concentrations (2-folds, $P = 0.04$).

Conclusion: β-neurexin-NLG4 recognition mediates HSCs-NK immune synapse to control release of NK vesicles. Recombinant β-neurexin activates NK cells to promote anti-fibrotic effects through increased HSCs killing. These effects were associated with decreased expression in the NLG4 receptor as well as with inhibition of the pro-fibrogenic marker IL4 in the NAFLD NK cells. NLG4 modulation of CD107a activity of NK cells extends the understandment and therapeutic strategies in fatty liver disease.

SAT-372

High prevalence of anti HLA Class II de novo donor-specific antibodies during rejection after liver transplantation

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Background and aims: Anti-HLA donor specific antibodies (dnDSA) after liver transplantation (LT) are currently under investigation. Recent studies show an incidence of dnDSA after LT ranging from 10-25%. However, the prevalence of dnDSA in LT recipients with alloimmune injury (ALO) and non-aloimmune liver injury (non-ALO) is unknown.

Method: Ccase-control cross-sectional study to investigate the prevalence of dnDSA in LT recipients with ALO and non-ALO compared to LT recipients without liver injury (control group, CONT). CONTROL: LT recipients with normal liver tests, normal elastography and no rejection within 6 months. ALO: biopsy-proven T-cell mediated rejection or antibody-mediated rejection lesions, including nodular regenerative hyperplasia (NRH). Non-ALO: liver injury other than ALO. Screening Luminex was performed in all patients and Single Antigen Luminex Assay was performed in those with positive screening. Results are expressed as median (IQR).

Results: The cohort consisted of 83 LR recipients: 20 ALO, 15 non-ALO and 37 CONT. The overall cohort was screened for dnDSA at a median of 30 (300) months after LT (32% < 12 m, 43% 1-5 years, 25% > 5 years). The median age was 57 (47), 29% were female with previous pregnancy in 46%. The pretransplant liver disease was alcohol-related (33%), viral (29%), cholestasic/autoimmune (21%) or other. The immunosupression at DSA assessment was calcineurin inhibitor ± MMF/steroids in 95% of patients and 37% patients had experienced previous episodes of rejection. There were no significant differences regarding age, gender and time since LT between groups. ALO patients had previous rejection more frequently than non-ALO and CONT (61% vs 45% vs 20%, $p = 0.11$, respectively), higher values of ALT (168 (426) vs 138 (471) vs 23 (20) UI/ml), $p = 0.025$) and higher liver stiffness [and 8.2 (12) vs 4.9 (8) vs 5.5 (8) kPa; $p = .010$). The prevalence of positive dnDSA class II was 55% vs 20% vs 8% in ALO vs non-ALO vs CONT ($p = 0.6$ and $p = 0.015$, respectively). All dnDSA in ALO targeted the DQ locus. The median MFI tended to be higher in ALO patient [9445 (23026)] compared to non-ALO and CONT [6026 (19978) vs 1500 (16840, $p = 0.067$)]. Of note, three patients had NRH and focal C4d deposition and high titers of dnDSA class II anti-DQ (median MFI 23500). The prevalence of and dnDSA class I was 0% vs 5 vs 6.3% % in ALO vs non-ALO vs CONT.

Conclusion: Class II dnDSA are common in patients with active alloinmune injury. Further studies are needed to investigate the clinical and histological implications of dnDSA in LT recipients with T-cell mediated rejection.

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Peritoneal mucosal-associated invariant T cells functionally differ from their exhausted circulating counterparts in decompensated cirrhosis

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Background and aims: Mucosal associated invariant T (MAIT) cells are innate-like T cells that are fast-acting using their invariant T cell receptor to recognize microbial riboflavin antigens presented by MR1. Previously, we reported a depletion of MAIT cells in the peripheral blood of patients with cirrhosis alongside a peritoneal accumulation during spontaneous bacterial peritonitis. We now aimed to further compare antibacterial responses and migration properties of circulating and peritoneal MAIT cells.

Method: Mononuclear cells were isolated from peripheral blood and ascitic fluid (AF) from patients with decompensated cirrhosis in the absence or presence of spontaneous bacterial peritonitis (SBP), and mononuclear cells from healthy donors served as a control. Cells were incubated with filtered bacterial culture supernatants. Migration of healthy MAIT cells was investigated using static trans well migration assays. Cells were quantified and phenotyped using flow cytometry.

Results: Filtered AF from patients with SBP was sufficient to activate MAIT cells from healthy individuals in presence of antigen-presenting cells. In contrast to circulating MAIT cells from patients with cirrhosis, which showed impaired TNF and IFN-g production in response to bacterial supernatants or PMA, peritoneal MAIT cells from patients with decompensated cirrhosis released significant amounts of IFN-g after stimulation with *E. coli*. Although peritoneal macrophages expressed higher levels of surface MR1 compared to circulating monocytes, peritoneal MAIT cell activation, was not restricted to MR1 as shown by blocking experiments.

Using migration assays, we observed a preferential migration of activated MAIT cells towards filtered AF from patients with SBP in comparison to patients without SBP. Consistent with their cytokine receptor expression, MAIT cells migrated against gradients of CCL5, CXCL10, and CCL20 as compared to conventional T cells. Interestingly,

the state of peritoneal MAIT cell activation, as indicated by CD69 expression, correlated with the severity of liver disease in the absence of SBP and with markers of inflammation in the presence of SBP.
Conclusion: Our results suggest that MAIT cells are preferentially recruited over conventional T cells to the peritoneal cavity in the context of SBP. In contrast to circulating MAIT cells, peritoneal MAIT cells remain potent producers of inflammatory cytokines, and their activation status indicates more advanced liver disease.

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Interleukin 35 exerts its suppressive function in chronic liver failure through the induction of an immunosuppressive HLA-G+CD4+ regulatory T -cell population

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Background and aims: Infections account for over 50% of hospital admissions of patients with chronic liver disease (CLD) and are the main precipitant for rapid decompensation to Acute-on-chronic-liver failure (ACLF) carrying a mortality rate > 50%. Our data strongly indicate a predominant defect in T cell responses in chronic liver failure. IL-35 is a key mediator of immune suppression and a potent inhibitor of T cell functions. We aim to establish the role of IL-35 in the failure to mount a proper adaptive-immune-mediated response in chronic liver failure
Method: Circulating levels of IL-35 in patients with CLD, ACLF and healthy controls (HCs) were measured using ELISA. Hepatic sinusoidal endothelial cells (HSECs) conditioned in sera from chronic liver failure patients or HCs were assessed for IL-35 secretion and synthesis in supernatants and in cell lysates using ELISA and the Wes^{TM} system, respectively. Multicolour flow cytometry was used to screen for IL-35-secreting T cells from peripheral mononuclear cells using surface and intracellular staining. The suppressive capacity of $CD4^+IL\text{-}35^+$ T cells was tested using flow-based CFSE suppression assays and multiplex cytokine detection platform. We tested the role of circulating IL-35 as well as recombinant cytokines (IL-35, IL-22 and IL-12) in the induction of this suppressive phenotype
Results: IL-35 levels were significantly increased in CLD and ACLF compared to HC (p = 0.01 and P = 0.001, respectively). In liver-failure-conditioned media, HSECs were competent producers of high levels of IL-35. In the peripheral blood, we identified an expanded $CD4^+IL\text{-}35^+$T cell population expressing high levels of the tolerogenic marker HLA-G. We further defined this population to be $CTLA\text{-}4^{high}CD62L^{low}IL\text{-}10^{low}$. Suppression assays demonstrated that $HLA\text{-}G^+CD4^+$T cells from ACLF patients were potent suppressors of PBMC proliferation. However, blockade of cell surface HLA-G and to a greater extent blockade of CTLA-4 abrogated this suppression and restored levels of IFN-γ, IL-2 and TNF-α secretion in PBMCs. Additionally, we have shown that IL-35 as well as IL-22 were potent candidate cytokines for immunomodulation of $CD4^+$T cells into immunosuppressive-$CD4^+IL\text{-}35^+HLA\text{-}G^+$T cells
Conclusion: Our data demonstrate evidence of dysregulation of the adaptive arm of the immune system in chronic liver failure mediated by IL-35. This finding will aid in the identification of novel therapeutic targets to reverse immuneparesis in chronic liver failure

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Therapeutic interleukin 4 modulates monocyte dynamics and accelerates repair and regeneration following acute liver injury

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Background and aims: Acute liver failure has significant mortality, and in its most severe form, the only treatment is liver transplantation. Murine models of acute liver injury are characterised by dramatic changes in the hepatic macrophage compartment, with an initial accumulation of pro-inflammatory $Ly6C^{hi}$ monocytes and loss of Kupffer cells, followed by the dominance of recruited $Ly6C^{lo}$ macrophages that promote liver repair. IL-4 administered prior to injury with carbon tetrachloride (CCl_4) has been shown to be hepatoprotective by directly promoting hepatocyte proliferation. We aimed to assess the effects of therapeutic IL-4 administered following acute liver injury with CCl_4.
Method: Male C57Bl/6 mice were given CCl_4 intraperitoneally to induce an acute liver injury. IL-4 was administered in the form of an immune complex subcutaneously. To investigate the role of IL-4Rα signalling in bone marrow derived cells, whole-body and tissue-protected chimeras were generated with wild type or $IL\text{-}4R\alpha^{-/-}$ donor bone marrow. Results were analysed using immunohistochemistry of tissue sections, serum biochemistry and flow cytometric analysis of leukocytes.
Results: Therapeutic administration of IL-4 following CCl_4 reduced markers of hepatic injury (ALT and necrotic area) and enhanced hepatic regeneration as measured by hepatocyte proliferation. This was paralleled by profound alterations to the monocyte/macrophage pool, with increases in the number of pro-reparative $Ly6C^{lo}$ macrophages but also a significant reduction in the number of pro-inflammatory hepatic $Ly6C^{hi}$ monocytes. Using chimeras, we have shown that $Ly6C^{lo}$ macrophage accumulation required cell-intrinsic, IL-4Rα-dependent proliferation and the loss of hepatic $Ly6C^{hi}$ monocytes was dependent on cell-intrinsic, IL-4Rα signalling. Importantly, analysis of kidney, spleen and blood revealed that the loss of $Ly6C^{hi}$ monocytes secondary to IL-4 treatment was not limited to the liver and occurred systemically. *In vitro* and *ex vivo* assays showed that the reduction in $Ly6C^{hi}$ monocytes in response to administration of IL-4 was due to IL-4Rα-dependent death of circulating monocytes rather than decreased output from the bone marrow.
Conclusion: This novel therapeutic role of IL-4 in causing death of pro-inflammatory $Ly6C^{hi}$ monocytes and an increase in pro-reparative $Ly6C^{lo}$ macrophages could offer potential therapeutic insights not only for acute liver injury but also other inflammatory pathologies characterised by monocytosis.

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Bile acids induce STAT3 and repress FOXP3 expression in hepatic CD4 lymphocytes under cholestatic conditions

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Background and aims: Impaired regulatory T cell (Treg) responses have been identified to predispose to cholangiopathies, including PSC and Biliary Atresia. Immunotherapies targeting Tregs are considered, yet, stability of Tregs in the cholestatic liver is unknown.
Method: Splenic $CD4^+CD25^+Foxp3^+$ Tregs from Foxp3/GFP reporter mice were cultured for 48hrs in presence of either 100 μM Taurocholic acid (TCA) or Taurochenodeoxycholic acid (TCDCA),

αCD3/CD28 and hIL-2 prior to cytometric quantification of Foxp3 expression. $CD4^+CD25^+CD127^{low}$ Tregs separated from PBMCs of healthy donors were cultured with TCDCA and subjected to RNAseq.
Results: Exposure to TCDCA, but not TCA, significantly reduced Foxp3 expression in Tregs and decreased their suppressive capacity when co-cultured with CD8 cells. Quantitative PCR revealed expression of the bile acid (BA) surface receptor S1pr2, but not of Fxr, Pxr, Vdr, or Tgr5. However, blocking S1pr2 with JET-013 did not prevent TCDCA-induced repression of Foxp3. Furthermore, incubation with D4 labelled TCDCA and subsequent mass-spectrometry showed dose dependent intracellular accumulation of BA. Searching for intracellular molecular targets of BA, the role of Stat3 was investigated. TCDCA-treatment increased *Stat3* mRNA expression and pre-treatment of Tregs with the Stat3 inhibitor S31-201 prevented TCDCA effects on Foxp3. Bisulphate sequencing detected hypermethylated CpG sites in the Foxp3 promoter region following TCDCA treatment indicating epigenetic effects of TCDCA/Stat3. Methylation blocker 5-Aza-2'deoxycytidine prevented TCDCA-induced Foxp3 repression in vitro and administration of 20 mg/kg/d for 7 days increased intrahepatic Tregs in cholestatic $Mdr2^{-/-}$ mice (mean ± SEM of % Treg/CD4: 12 ± 1 vs 6.2 ± 1.5 in 5-Aza vs vehicle, $p < 0.01$). Treating $Mdr2^{-/-}$ mice with 10 mg/kg/day of ASBT inhibitor SC-435 for 14 days lowered serum TCDCA-levels (mean: 0.54 vs 45 μM in controls, $p < 0.05$) and expanded hepatic Tregs (#Tregs/100 mg tissue: 1722 ± 208 vs 311 ± 49, $p < 0.01$). RNAseq on human Tregs cultured with TCDCA revealed increased expression of IL17F, IL-17A, AHR and down-regulation of STAT1 and CEBP transcription factors.
Conclusion: TCDCA in concentrations found in the serum of patients with biliary obstruction reduces suppressor function of Tregs via induction of Stat3 and epigenetic silencing of Foxp3. Inhibiting methylation or intestinal BA reuptake restore hepatic Treg responses in murine sclerosing cholangitis. Anti-cholestatic medications may improve the efficacy of Treg-directed immunotherapy for biliary diseases in the future.

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Significant reductions in intrahepatic Mucosal Associated Invariant T cells with increased terminal activation marker expression amongst NAFLD patients following a 12 week aerobic exercise program: a paired liver biopsy study

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Background and aims: Exercise has been shown to improve the cardiometabolic profile and reduce hepatic steatosis amongst NAFLD patients. Aerobic exercise programs can lead to decreases in circulating pro-inflammatory cytokines and alterations in circulating immune cell populations. The aim of this study was to evaluate the effect of an aerobic exercise program on circulating and intrahepatic MAITs.
Method: 25 individuals with biopsy proven NAFLD were enrolled in the study. 16 patients were allocated to an exercise intervention (EI) and 9 patients were recruited as controls. Baseline investigations inclusive of bloods, fibroscans and DEXAs were performed and repeated following completion of EI. The EI consisted of a 12 week aerobic exercise program (two supervised and three unsupervised) with increasing intensity. 13 patients in the EI with steatohepatitis on their initial liver biopsy had repeat liver biopsies to re-assess histological stage. Liver tissue and whole blood samples were stained with antibodies specific for CD45, CD3, CD8, CD161, Vα7.2, CD69 and CD95 and were analysed with multi-colour flow cytometry using a BD FACSCanto II (BD Biosciences) and FlowJo software (Tree Star, Asland, OR). Statistical analysis of paired samples was performed using the Wilcoxon matched pair rank test. Patient characteristics: 52% (n = 13) female, 64% (n = 16) diabetes/IGT, median age 58 *(20-71)*, BMI 35 *(27-48)*, ALT 49 *(14-116)*, AST 30 *(19-63)*, HbA1c 42 *(27-106)*.
Results: Following completion of the EI, there was a significant reduction in BMI ($p = 0.0305$), without any significant changes in ALT, AST or HBA1c. On repeat liver biopsy there were significant reductions in NAS score following the EI ($p = 0.0312$) this was attributable to reductions in the histological grade of ballooning ($p = 0.0078$). No significant reductions were observed in the steatosis, lobular inflammation or fibrosis grade. Review of intrahepatic MAITs demonstrated significant reductions in the percentage of intrahepatic MAITs ($p = 0.0215$), with increased MFI of CD95 ($p = 0.0027$) post EI (See figure 1).

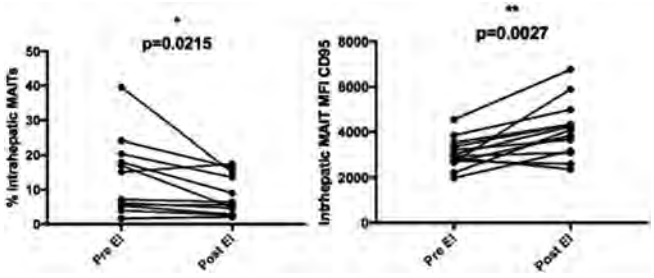

Figure 1:

Conclusion: A 12 week EI resulted in significant improvement in histological NAS score and grade of ballooning. The observed reduction in intrahepatic MAITs combined with increased terminal activation marker may reflect increased MAIT cell apoptosis due to increased oxidative stress and increased FAS signalling.

SAT-378

The NIF mouse as a model for acute, late stage non-alcoholic steatohepatitis

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Background and aims: NAFLD (Non-alcoholic fatty liver disease) is the most common cause of chronic liver disease in the Western world and is a complex spectrum of liver diseases ranging from steatosis to non-alcoholic steatohepatitis (NASH). Therapeutic advances in treatment of NASH have been slow and NASH has been classified as a medical condition with high, unmet therapeutic need. One barrier to therapeutic development is the lack of preclinical models of progressive NASH that recapitulates human disease. We have developed and characterized the novel animal model, the non-obese diabetic inflammation and fibrosis (NIF) mouse, that spontaneously develops chronic inflammation and fibrosis in multiple organs, as a novel animal model of NASH.
Method: The NIF mouse and its littermate controls were analyzed at six different time points through the ages of 3 to 18 weeks, using histology, flow cytometry, qPCR analysis, cell activation and cytokine analysis, immunohistochemistry, hydroxyproline examination and adoptive transfer experiments.
Results: In the liver, the N-IF mouse displays inflammation and fibrosis particularly evident around portal tracts and central veins, and accompanied with evidence of abnormal intrahepatic bile ducts. The extensive cellular infiltration consists mainly of macrophages and granulocytes, particularly eosinophils. This inflammatory syndrome is mediated by a transgenic population of natural killer T cells (NKT) induced in an immunodeficient NOD genetic background and characterized by the combined production of both Th1 and Th2

cytokines. Through upregulation of TGF-β due to the pro-inflammatory factors and the high levels of Th2 cytokines produced by the transgenic NKT cells, the hepatic stellate cells are activated, leading to the development of severe fibrosis, staged at F3. The disease is transferrable to immunodeficient recipients, while polyclonal T cells from unaffected syngeneic donors can inhibit the disease phenotype.

Conclusion: The disease phenotype of the NIF mouse, although lacking the metabolic factor, resembles the late stages of NASH in several pertinent features, including the temporal heterogeneity of the fibrotic lesions, the progressive nature of the disease and, primarily, the preceding chronic inflammation. This in combination with the early on-set, spontaneous nature and reproducibility, makes this novel mouse model a unique tool to gain further insight into the underlying mechanisms mediating transformation of chronic inflammation into fibrosis and to evaluate intervention protocols for treating conditions of fibrotic disorders such as NASH.

SAT-379

Myeloid cells require gp130 signalling for protective anti-inflammatory functions during sepsis

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Background and aims: Abdominal infection is a life-threatening complication, especially in patients with chronic liver disease (CLD). In particular, sepsis may trigger acute-on-chronic liver in patients with liver cirrhosis failure leading to rapid mortality. Therefore, new strategies of immunomodulation may not only be beneficial during sepsis but could also improve survival of patients with liver cirrhosis. While IL-6/gp130 signalling has well-defined roles in hepatocytes, herein, we aimed at exploring the role of gp130 signalling in myeloid immune cells during abdominal sepsis.

Method: We employed an established mouse model of polymicrobial sepsis induced by caecal ligation and puncture (CLP). To interrogate the role of gp130 signalling, we analysed mice with gp130 ablation in haematopoietic cells (bone-marrow transplantation from MxCre $gp130^{flox/flox}$ mice), as well as mice with myeloid cell-specific gp130 deletion (LysCre $gp130^{flox/flox}$ mice).

Results: Here, we show that lack of gp130 signalling in myeloid cells leads to defective M2 macrophage polarisation and elevated expression or secretion of pro-inflammatory cytokines such as IL-1β, TNF-α and IL-12. This triggers enhanced immune cell recruitment to the peritoneum followed by increased mortality during sepsis, while bacterial clearance is not impaired. Moreover, we demonstrate that exogenous IL-10 administration elicits activation of the downstream transcription factor STAT3, thereby restoring responsiveness of gp130-deficient macrophages to an M2 phenotype and improving survival in mice lacking gp130 in haematopoietic cells.

Conclusion: In this study, we identify an essential role for gp130 signalling in myeloid cells during M2 macrophage polarisation. Our data provide new insights into the molecular basis of M1/M2 phenotypic dichotomy and identify gp130 as a key regulator of immune homeostasis during sepsis. In addition, our results suggest that IL-10 and gp130 pathways redundantly converge to enhance IL-4-induced M2 polarisation and to counterbalance the profound inflammatory response that occurs in sepsis. Hence, these are also relevant in patients with liver cirrhosis to prevent acute-on-chronic liver failure.

SAT-380

Liver-resident memory CD8 T cells do not egress into hepatic venous blood

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Background and aims: Emerging evidence suggests that the immunological landscapes of liver tissue and peripheral blood are distinct. Populations of T cells and NK cells have been described that are adapted to the liver microenvironment, remain resident within liver tissue and are therefore absent from the circulation. One example is the highly functional tissue-resident memory CD8 T cell (T_{RM}), recently identified in the human liver. CD8 T_{RM} are characterised by co-expression of tissue retention molecules CD69 and CD103, and are associated with control of chronic HBV infection *(Pallett LJ, et al. J Exp Med 2017)*. Here we sought to provide more definitive evidence for complete sequestration of this population in human liver by excluding low-level egress that would only be detectable by sampling the hepatic vein. We also aimed to investigate whether gut T_{RM} can transit to the liver by sampling portal venous blood.

Method: We isolated mononuclear cells from heparinised blood samples obtained from 13 patients undergoing hepatic vein catheterisation (transjugular liver biopsy or hepatic venous pressure gradient measurement), and 3 patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures. Hepatic and peripheral venous blood samples were obtained from all patients, and portal venous blood samples from the 3 TIPS patients. CD8 T cells were interrogated by multiparametric flow cytometry for the expression of tissue-retention signals.

Results: Sampling hepatic venous blood (with or without balloon inflation), failed to reveal a population of CD8 T cells co-expressing CD69 and CD103; CD8 T_{RM} were essentially undetectable, as in peripheral blood (< 1%). The overall T cell composition as assessed by CD4/CD8 ratio was reflective of the circulation rather than the liver, with a strong intra-donor correlation between the frequencies of CD8 and CD4 T cells in hepatic and peripheral venous blood. Preliminary data also showed no detection of CD8 T_{RM} transiting in portal venous blood from gut to liver. Expression of the prototypic exhaustion marker PD1 and cytotoxic potential (granzyme B expression) of CD8 T cells was similar in all venous blood compartments.

Conclusion: By sampling the human liver vasculature we provide evidence in support of tissue-specific retention of human T_{RM}. This has direct implications for monitoring and targeting these highly functional organ-specific memory CD8 T cell sentinels.

SAT-381

TAA-specific CD8+ T-cell responses are inefficiently induced in hepatocellular carcinoma

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Background and aims: In hepatocellular carcinoma (HCC), CD8+ T-cell responses targeting tumor-associated antigens (TAA) are considered to be beneficial. However, the molecular profile of TAA-

specific CD8+ T cells in HCC is not well defined due to their low frequency.
Method: By applying peptide/MHCI tetramer-based enrichment, a method of high sensitivity, we now could define the heterogeneity of TAA-specific CD8+ T cells targeting AFP, glypican-3, NY-ESO-1, MAGE-A1 and MAGE-A3.
Results: In this study, we demonstrate that TAA-specific CD8+ T-cell responses are not efficiently induced in HCC patients as supported by the following observations: First, in HCC patients, frequencies of TAA-specific CD8+ T cells were not increased compared to healthy donors or patients with liver cirrhosis. Second, a remarkable proportion of TAA-specific CD8+ T cells exhibited were naive despite the presence of antigen within the tumor tissue. Third, transarterial chemoembolization (TACE) did not enhance TAA-specific CD8+ T-cell responses. In addition, we observed that antigen-experienced TAA-specific CD8+ T cells lack the characteristic transcriptional regulation of exhausted CD8+ T cells, namely $Eomes^{hi}Tbet^{dim}$, and express inhibitory receptors only on a minor proportion of cells. This suggests restricted antigen recognition and further supports the hypothesis of inefficient induction and activation.
Conclusion: Our comprehensive analysis reveals that TAA-specific CD8+ T cells are not properly induced in HCC thereby unravelling new and unexpected insights into TAA-specific CD8+ T-cell biology in HCC. This clearly highlights severe limitations of these potentially anti-tumoral T cells that may hamper their biological and clinical relevance in HCC.

SAT-382
Crosstalk between liver NKT cells and liver sinusoidal endothelial cells
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Background and aims: The liver is known for its tolerogenic microenvironment and organ-resident antigen-presenting cell populations. It also harbors a large number of innate lymphocytes out of which NKT cells constitute a substantial population. While NKT cells are known to exert potent effector functions upon CD1-restricted antigen presentation, it has remained largely unclear which local cell populations in the liver are capable of activating NKT cells in an CD1-specific fashion and whether such antigen-activation of NKT cells is involved in the orchestration of hepatic CD8 T cell immunity. The aim of this study was to characterize the ability of liver sinusoidal endothelial cells as antigen presenting cells to orchestrate NKT cell immunity.
Method: Methods used in this study include high-purity isolation of primary liver cell populations to study their cognate interaction with lymphocytes *ex vivo* using flow cytometry and bead-array based detection of cytokines released upon antigen-specific stimulation.
Results: We isolated primary cell populations from the liver, i.e. liver sinusoidal endothelial cells (LSECs), Kupffer cells and hepatocytes to study which of these cell populations engaged in CD1-restricted antigen presentation to NKT cells. LSECs showed highest CD1 expression that was even further increased upon contact with pro-inflammatory mediators. Dose kinetic studies revealed that LSECs cross-presented minute concentrations of the alpha-galactosyl-ceramide in a CD1-restricted fashion to primary NKT cells. Such cognate interaction resulted in upregulation of activation markers and preferential induction of IL-2 and Interferon gamma from activated NKT cells. Compared with splenic dendritic cells, LSECs proved to be more efficient in CD1-restricted activation of NKT cells. Importantly, cognate interaction between LSECs and NKT cells initiate polyclonal activation of CD8 T cells.
Conclusion: Our results reveal efficient CD1-restricted activation of NKT cells by antigen-presenting LSECs as initiating event in broad local CD8 T cell that may be instrumental in anti-viral immunity in the liver.

SAT-383
Human mesenchymal stem cells-derived exosomes attenuate liver ischemia/reperfusion injury by up regulation of notch-1-related autophagy in CD4 T cell
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Background and aims: Mesenchymal stem cell (MSC)-derived exosomes administration has been identified as a novel and effective cell-free therapeutic tool for several liver diseases through cell-contacted communication. The present study was aimed to investigate the role of umbilical cord MSC (UC-MSC) derived exosome (UC-MSC-Exo) in the treatment of hepatic ischemia-reperfusion injury and further explore the potential mechanisms.
Method: UC-MSC-Exo were utilized to the liver I/R injury mice through intravenous transfusion and their effects were assessed by serum hepatic enzyme and liver histopathologic analysis. Furthermore, the number of CD4+Foxp 3 + regulatory T cells (Tregs) in liver was detected by flow cytometry, and total CD4+ T cells were isolated from the liver of each group to evaluate their changes of autophagy by flow cytometry and transmission electronic microscope (TEM). In order to elucidate the mechanisms of UC-MSC-derived exosomes in CD4+T cells, CD4+T cells were isolated from C57BL/6 spleen and co-cultured with UC-MSC-Exo. The activation of Notch-1 and autophagy-related proteins in CD4+ T cells were determined by Western blot analysis, respectively. The exosomes from Jagged-1-knockdonwded UC-MSCs (UC-MSC-$Exo^{Jagged\text{-}1\text{-}KD}$) were contributed to further confirming the role of Jagged-1 in UC-MSC-Exo-based therapy.
Results: UC-MSC-Exo administration remarkably attenuated I/R-induced liver injury as determined by decreased serum hepatic enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)] and hepatic inflammatory microenvironment as well as improved hepatocellular apoptosis and hepatic pathologic changes. Further investigations showed that UC-MSC-Exo not only increased the ratio of T-reg cells but also upregulated autophagy in CD4+ T cells. Furthermore, Jagged-1, which can enhance autophagy by targeting the Notch-1 signaling pathway, abundantly expressed on UC-MSC-Exo. While the therapeutic roles of UC-MSC-$Exo^{Jagged\text{-}1\text{-}KD}$ on liver I/R injury were remarkably weakened as they could not availably activate Notch-1-related autophagy and suppress inflammatory activation in CD4+ T cells in vitro and in vivo.
Conclusion: Expression of Jagged-1 on exosomes plays an important role in UC-MSC-Exo therapy for liver I/R injury by targeting the Notch-1 signaling pathway and upregulating autophagy in intrahepatic CD4+ T cells. UC-MSC-Exo-based therapy may be considered as a beneficial approach for upregulating autophagy to alleviate inflammatory liver diseases.

Molecular and cellular biology

SAT-385
Production and characterization of human liver extracellular matrix hydrogels for in vitro culture of distinct human primary liver cell populations
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Background and aims: The study of human primary liver cell biology is largely hampered by the lack of adequate *in vitro* culture systems that allow the maintenance of the cells' viability and physiologic phenotype for prolonged periods of time. In this context, a growing interest for liver decellularization and for the use of liver extracellular matrix (ECM) in cell culture and tissue engineering applications emerged over the past five years. Whereas several publications describe detailed procedures for animal liver decellularization and ECM-based hydrogel production, few is known about the composition and properties of isolated human liver ECM. In this study, we analyzed the composition of human liver ECM and derived hydrogels, and we further addressed the question of the potential benefits of a liver ECM protein-coated surface for the culture of primary human liver cells.
Method: A combination of thermic and osmotic shock, enzymatic digestion and detergents has been used to decellularize human liver fragments unsuitable for transplantation. Liver ECM was partially digested with pepsin for coating purposes and characterized by histology and mass spectrometry. Primary human liver cells, including hepatocytes, hepatic stellate cells (HSC) and endothelial cells (EC) were seeded on liver-coated culture dishes. Adhesion (2 h), viability (24 h), proliferation (7 days) and phenotypic properties were evaluated and compared to a surface of reference (CellBIND or rat tail collagen coating).
Results: Our protocol led to a residual amount dsDNA below decellularization standards. Coating derived from liver ECM showed no toxicity for primary human liver cells. Mass spectrometry revealed the abundance of type I and type III fibrillar collagen components (COL1A1, COL1A2, COL3A1) as well as elastin in liver ECM hydrogels used for coating. Preliminary results further suggest the benefits of human liver ECM on human primary liver cell properties in 2D culture as compared to surfaces of reference.

Conclusion: Our study provides a first detailed characterization of human liver ECM and derived hydrogels, easily and reproducibly isolated from small human liver fragments. Our results further open the way for the use of human liver ECM as a coating for the culture of primary human liver cells in 2D. In a near future, 3D applications will be developed.

SAT-386

Insulin resistance in NK cells of F4 fibrosis inhibit mTOR expressions and are associated with decreased F-actin and killing ability in NASH patients

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Background and aims: In humans, two NK-cell subsets have been characterized according to the cell-surface density of CD56 and expression of CD16. $CD56^{+}CD16^{+}$ NK cells (more cytolytic and produce significant amounts of cytokine when their activating receptors are engaged) compose approximately 90% of circulating NK cells; $CD56^{++}CD16^{-}$ NK cells (Bright NK cells) constitute approximately 10%. We investigated a potential role of NMDAR (an insulin responding *N*-Methyl-D-Asparate Receptor) to modulate NK responses in Non-alcoholic-Fatty-Liver-Disease (NAFLD) progressions.
Method: Flow cytometry analysis was performed in peripheral-blood-lymphocytes from healthy and histology documented NAFLD cases with low and advanced fibrosis.
Results: The NK cytolytic $CD56^{Dim\ (CD16+)}$ showed to be the dominant populations in all studied samples. NAFLD NK^{dim} population had lower insulin receptors ($NK^{dim}\ IR^{low}$), mainly in advanced fibrosis ($p < 0.05$). These patients showed higher HOMA-score while their NK^{dim} population showed lower F-Actin and mTOR expressions. NAFLD $CD56^{Dim}$ CD107a (NK-granzymes-activation marker) tend to increase in low fibrosis NAFLD cases ($p = 0.06$) but was unchanged in advanced fibrosis. In cultures, insulin exposure unleashed the CD107a to increase NK killing. However, insulin resistance of NAFLD NK cells showed lower responses and decreased killing ability. On the other hand, insulin up-regulation of the NMDAR showed to depresses mTOR activity.
Conclusion: NAFLD NK cells exert insulin resistance, mainly the $CD56^{Dim}$ cytolytic population. The NMDAR unit regulates NK activity as a result of metabolic modifications; via an mTOR dependent pathway. It stimulated F-Actin accumulations and NK granzymes complex; indicating a new cellular pathway through which NK cells contribute to the NAFLD progression.

SAT-387

Pharmacological inhibition of P2X7 receptor ameliorates liver injury in nonhuman primates by reducing liver inflammation and fibrosis

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Background and aims: Activation of the inflammasome complex has been identified as a major contributor to hepatocyte damage, immune cell activation, and amplification of liver inflammation in non-alcoholic steatohepatitis (NASH). The purinergic receptor (P2X7 receptor) is an ATP-gated ion channel responsible for the activation of the inflammasome complex and the release of IL-1β. Although P2X7 receptor has been suggested to regulate inflammation and fibrosis in murine models, whether it can serve as a therapeutic target for NASH remains unknown.
Method: We have analyzed P2X7 receptor in NASH patients and examined the effects of P2X7 receptor pharmacological inhibition in human primary hepatocytes, Kupffer cells, and hepatic stellate cells *in vitro* and in a chemically-induced fibrosis model in nonhuman primates.
Results: We found that livers from NASH donors showed increased P2X7 receptor expression compared to livers from NAFLD and healthy donors. In addition, P2X7 receptor pharmacological inhibition blocked IL-1β release from human primary Kupffer cells and PBMCs, leading to reduced hepatocyte damage and fibrogenesis in human primary hepatic stellate cells. We also found that

pharmacological inhibition of P2X7 receptor resulted in a marked protection against inflammation and fibrosis in monkey in a chemically-induced model of liver injury.
Conclusion: Taken together, these findings indicate that pharmacological inhibition of P2X7 receptor has the ability to reduce inflammation and fibrosis in both human in vitro primary cells and nonhuman primates. Thus, P2X7 receptor is a promising molecular target for treating liver diseases, including NASH.

SAT-388
How to infuse heterologous human adult liver-derived progenitor cells safely?
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Background and aims: Mesenchymal stem cell (MSC) infusions are currently evaluated in numerous clinical trials, but therapy-induced thrombi have been described in several patients. Most MSCs in fact express a procoagulant activity (PCA) linked to tissue factor (TF) expression. The aim of this study was to optimise infusion protocols using Heterologous Human Adult Liver-derived Progenitor Cells (HHALPC) without inducing a thrombogenic risk after the infusion. We studied infusions of high cell doses in metabolic patients and low cell doses in cirrhotic patients, known to a have rebalanced haemostasis.
Method: First cell dose escalation was studied using a xenotransplant animal model (healthy Wistar rat, with or without anticoagulants). Then the crucial role of TF in PCA was confirmed using flow chambers (shear stress model). Finally, we characterized disseminated intravascular coagulation (DIC) induced by HHALPCs *in vitro* and investigated how to control the induced thrombotic and haemorrhagic risks in whole blood of healthy and cirrhotic patients (by fibrin generation model and tubing loops, mimicking blood flow).
Results: *In vivo* we showed that the thrombogenic risk induced by HHALPC infusions is dose dependent. High cell doses such as 50×10^6 cells/kg induced DIC 1 h after transplantation with a significant decrease in platelets ($p < 0.01$), fibrinogen ($p < 0.001$), and coagulation factors II, V and VIII ($p < 0.01$) compared to control rats infused only with PBS. Infusions of lower cell doses, such as 5×10^6 cells/kg did not activate the coagulation cascade. Adding anticoagulants during infusions of high cell doses, such as heparin (300 I.U./5×10^6 cells) or a combination of heparin (10 I.U./5×10^6 cells) and bivalirudin can control the thrombogenic risk. By tubing loop model we showed that HHALPCs activate the coagulation cascade in a less explosive way in decompensated cirrhotic patient's blood compared to healthy volunteers. HHALPCs only induce a significant decrease in platelets ($p < 0.01$) and fibrinogen ($p < 0.01$) and not in coagulation factors.
Conclusion: Low doses of MSCs (5×10^6 cells/kg) expressing TF do not induce a thrombogenic risk, and could thus be used in future clinical trials treating acute decompensated cirrhotic patients while monitoring platelet and fibrinogen levels. The thrombogenic risk induced by infusions of higher cell doses can be controlled by adding anticoagulants and could therefore be used to treat metabolic patients.

SAT-389
Obeticholic acid reduces matrix metalloproteinases activity via iNOS modulation in hepatic ischemia/reperfusion injury
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Background and aims: We have previously shown that the Farnesoid×Receptor (FXR) agonist obeticholic acid (OCA) decreases inducible NOS (iNOS) content in ischemia/reperfusion (I/R)-treated rats (Ferrigno A et al., 2018). iNOS is known to regulate the activity of matrix metalloproteinases (MMPs) in liver I/R injury (Hamada T et al., 2009). In this study, we evaluated the effects of OCA on MMP-2 and MMP-9 gelatinase activity in liver, bile and serum after hepatic 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 bile flow was quantified, and serum, bile and tissue samples were collected for MMP-2 and MMP-9 analysis by zymography. Serum levels of AST and ALT as well as biliary levels of LDH, γGT and glucose were quantified. Liver morphology was evaluated by HandE staining as well as Western blot analysis of iNOS.
Results: I/R induced increase in both iNOS expression ($p<0.01$) and MMP-2 and MMP-9 activity ($p<0.005$ and $p<0.01$, respectively) in the liver. OCA administration reduced MMP-2 and MMP-9 in liver ($p<0.009$ and $p<0.05$, respectively) and bile ($p<0.03$ and $p<0.01$, respectively); the same trend, although not significant, was observed in serum samples. OCA did not change liver morphology, while less pyknotic cells in liver specimens from OCA-treated rats were found. Although not significantly, OCA administration reduced hepatic serum enzyme levels in the I/R group. Biliary levels of LDH, γGT and glucose were significant lower in I/R rats treated with OCA compared with I/R group treated with vehicle ($p<0.05$, $p<0.008$ and $p<0.05$, respectively). No difference in bile flow were detectable in I/R groups.
Conclusion: In liver submitted to I/R a reduction in MMPs activity by OCA administration was found. For the first time, we have shown an MMPs biliary content that was modulated by the treatment with OCA. These data are also associated with lower levels of biliary markers of cholangiocyte injury and biliary reabsorption of glucose, this last index of cholangiocyte function (Tabibian JH et al., 2013). The present data suggest that OCA is involved in the reduction of bile duct injury by the MMPs activity modulation and the decrease of hepatic gelatinase activity observed using this FXR agonist appears to be mediated by iNOS.

SAT-390
Dengue virus protein NS3 activates hexokinase activity in hepatocytes to support virus replication
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Background and aims: Viruses modulate central carbon metabolism in the infected cell but the underling molecular mechanisms are poorly described. We have previously demonstrated that NS5A of hepatitis C virus directly interacts with the first glycolysis enzyme hexokinase and increases its activity to support HCV replication (ramiere et al, 2014). To test if this was a common mechanism shared by flaviviruses, we looked whether dengue virus (DENV) proteins were capable of modulating hexokinase activity. Because clinical evidences point to a more pronounced infection of the liver in the

severe forms of infection, we analyzed the dependence of DENV to glycolysis and hexokinase activity in relevant hepatocyte models.
Method: Interaction between DENV proteins and the four hexokinase isoenzymes was studied by protein-complementation assays and coimmunoprecipitation. Like virtually all cancer cells, the hepatocarcinoma cell line Huh7 express the "cancer-type" HK2 isoenzyme whereas in vivo hepatocytes express the HK4 isoenzyme (or Glucokinase, GCK). Therefore, we invalidated HK2 expression in Huh7 cells by CRISPR-Cas9 and restored the expression of the hepatocyte-specific hexokinase isoenzyme, GCK. Dependence of viral replication to glycolysis was evaluated in the two cell models.
Results: We showed that DENV-NS3 interacts with all hexokinase isoenzymes, suggesting a potential impact of DENV-NS3 on the glycolytic activity of infected cells. Expression of DENV-NS3 enhanced glucose consumption and lactate secretion in both Huh7-HK2 and Huh7-GCK and in the none hepatic cell line A549 expressing HK1. In cellular homogenates we analyzed the modulation of catalytic parameters of the enzyme by DENV-NS3. We observed that DENV-NS3 decreased the apparent Km of GCK and abolished the normal allosteric activity of the enzyme. DENV infection was drastically increased in Huh7-GCK compared to Huh7-HK2. Interestingly, using the subgenomique DENV-GFP+ replicon we observed that GFP expression was dependant of glucose concentration in culture medium confirming the direct impact of glycolysis activity on viral replication. Moreover, stimulating GCK activity by direct synthetic activators resulted in an increased replication of the replicon and GFP expression.
Conclusion: DENV controls hepatic glycolysis through the interaction between NS3 and Glucokinase. This interaction modifies the catalytic parameters of the enzyme and favours replication of the virus. This observation suggests that liver infection by DENV is highly dependent on the control of glycemia in vivo.

SAT-391
The influence of Caveolin-1 on hepatocyte metabolism

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Background and aims: The membrane protein caveolin-1 (CAV1) has been associated with metabolism in hepatocytes, adipocytes, cancer-associated fibroblasts, and is thought to contribute to cancer progression by altering biochemical pathways. However, the impact of CAV1 expression on metabolic profile is still poorly understood. Here, we aimed to determine novel metabolic gene alterations altered by CAV1 in murine hepatocytes and whole liver.
Method: Freshly isolated murine hepatocytes were transfected with siRNA to knock down CAV1 expression, followed by microarray profiling. The differentially altered genes were used for functional annotation analysis (DAVID, GSEA bioinformatics platforms), to predict molecular functions, biological processes and cellular components altered by CAV1. In addition, we evaluated consistency of altered genes by *in vivo* profiling of *Cav1-/-* mice liver.
Results: Knockdown of CAV1 significantly altered ~1350 genes, topmost of which were *Ifit3*, *Ly6a*, *Zbp1* (upregulated) and *Tnc*, *Nes*, *Fhl1, and Cav1 (as proof of principle),* (downregulated). Pathway annotation analysis revealed that loss of CAV1 induced upregulation of a plethora of metabolic processes and the downregulation of cancer-related pathways. We observed a similar annotation pattern in a dataset of *Cav1-/-* mice liver. Interestingly, 229 of the altered genes were specifically metabolic genes had not been previously associated with CAV1. The novel CAV1-altered genes belong mostly to amino acid metabolism (e.g. *Gcat, Scly*), fatty acid metabolism (e.g. *Acad11, Acadvl*), glycan metabolism (e.g. *Alg6, Galnt7*), nucleotide metabolism (e.g. *Nme5, Nt5c2*), or ion/small molecule transporters (e.g. *Ndufb8, Atp7a*).
Conclusion: Our data reveals that CAV1 affects many metabolic processes in hepatocytes. These changes may have significant implications in liver pathophysiology.

SAT-392
Dickkopf-1 from hepatocellular carcinoma cells promotes the angiogenic potential of endothelial cells by activating the VEGFR-2 signaling pathway

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Background and aims: Dickkopf-1 (DKK-1) is an antagonist of Wnt signaling. Several reports have shown an association between the elevated expression of DKK-1 and tumor angiogenesis. However, the biological function of DKK-1 in angiogenesis of hepatocellular carcinoma (HCC) is not well documented. We investigated the phenotypical changes of vascular endothelial cells after interactions with HCC cells expressing DKK-1 using two-dimensional (2D) and three-dimensional (3D) co-culture systems.
Method: The cell lines Huh7 and Hep3B, with low and high DKK-1 expression, respectively, were selected. The tetracycline-inducible DKK-1 expression cell line (Tet-on Huh7) and a DKK-1 knockout cell line using CRISPR/Cas9 (KO Hep3B) were established. The angiogenic potential of human umbilical vein endothelial cells (HUVECs) was investigated using wound scratch, transwell, and tube formation assays. HUVECs were co-cultured with Tet-on/off Huh7, or KO Hep3B for 3D spheroid models, where cells were seeded in a 10:1 ratio (HCC cells:HUVECs) in non-adhesive, round-bottom 96-well plates. After 3 days, spheroids were harvested for quantitative polymerase chain reaction, western blotting, and immunohistochemistry staining.
Results: The angiogenic potential of HUVECs significantly increased after being treated with human recombinant DKK-1. When HUVECs were treated with Tet-on/off Huh7 and KO Hep3B-conditioned media in an indirect 2D co-culture system, Tet-on Huh7 increased the angiogenic potential of HUVECs, which was not increased with Tet-off Huh7 and KO Hep3B. When 3D spheroids were constructed to mimic the in vivo environment, spheroids with HUVECs and Tet-on Huh7 were constructed faster and more packed than those mixed with Tet-off Huh7. When HUVECs in spheroids were stained, HUVECs mixed with Tet-on Huh7 cells exhibited greater viability than those mixed with Tet-off Huh7 cells (Figure). The biological morphology of spheroids with KO Hep3B was similar to those with Tet-off Huh7. Furthermore, the expression levels of vascular endothelial growth factor receptor 2 (VEGFR-2) signaling factors significantly increased when HUVECs were mixed with Tet-on Huh7 cells in 3D spheroids.
Conclusion: We confirmed that DKK-1 from HCC cells promoted the angiogenic potential of HUVECs by activating the VEGFR-2 signaling pathway. Thus, further studies should determine whether blockade of DKK-1 may represent a novel therapeutic target for HCC treatment.

SAT-393
Melatonin attenuates dysregulation of the circadian clock pathway in liver fibrosis and progression to hepatocarcinoma

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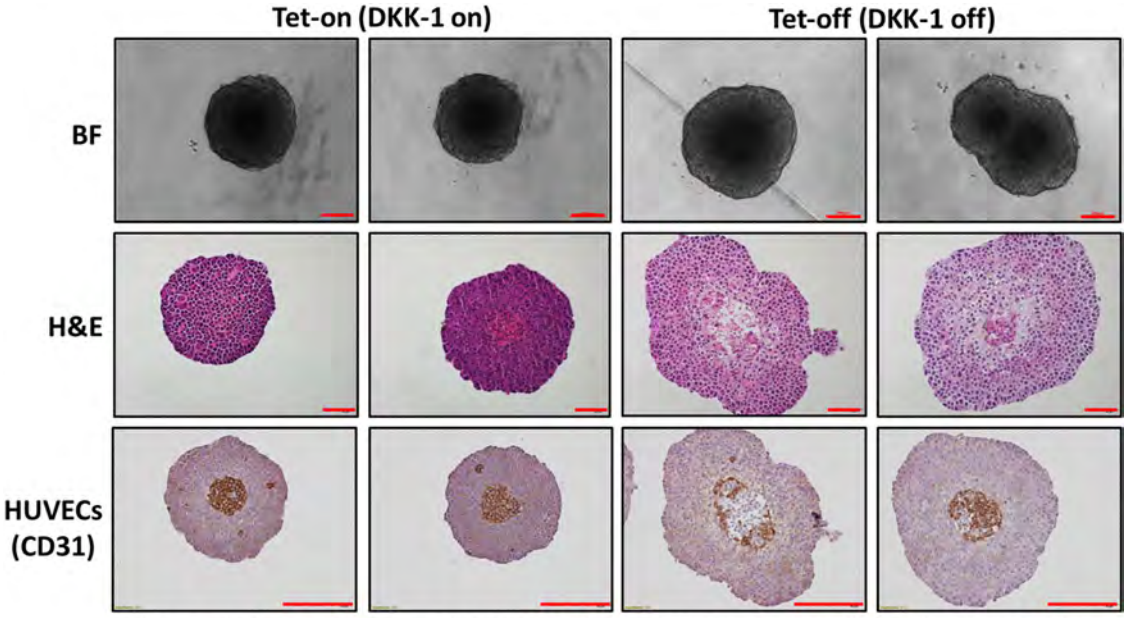

DKK-1, dickkopf-1; Tet, tetracycline; BF, bright-field; H&E, hematoxylin and eosin; HUVECs, human umbilical vein endothelial cells. Scale bar indicates 200 μm.

Figure: (abstract: SAT-392)

Background and aims: Disruption of circadian rhythm, which is regulated by Clock genes, results in pathological processes including fibrosis and progression to hepatocarcinoma (HCC). Melatonin exhibits antifibrotic and oncostatic features, but it is unknown if these effects are mediated by the regulation of Clock genes.
Method: Fibrosis was induced in C57BL/6J mice with CCl4 twice a week for 4 or 6wk; melatonin was given at 5 or 10 mg/kg/day i.p. beginning 2wk after the start of CCl4 administration. HCC was induced in ICR mice receiving DEN once a week for 8wk; melatonin was given (5 or 10 mg/kg/day i.p.) 4wk after the onset of DEN administration and ending at 10, 20, 30 and 40wk. We investigated whether melatonin has its effect through the modulation of the nuclear receptor REV-ERB, using the agonist SR9009, in human stellate cells LX2 and Hep3B cells. Cells were exposed to SR9009 (10 μM for 24 h) and treated with melatonin (0.1-0.5 mM and 0.5-1 mM respectively). To study the effect of melatonin on the pathway, BMAL1 was silenced in Hep3B cells, treated or not with the indole (0.1 and 0.5 mM), for 24 h after silencing. The expression of fibrosis markers, proliferation, apoptosis and Clock genes were analyzed by Western-blot, qRT-PCR, immunohistochemistry and cell proliferation assays.
Results: The expression of the main Clock genes, BMAL1 and CLOCK, the transcriptional repressors, PER and CRY, and the nuclear receptors, REV-ERB and RORα, were disrupted in both animal models from the first time-periods reaching higher differences at 6 and 40wk, respectively. Melatonin prevented these altered expressions dose-dependently. To aim if the melatonin antifibrotic and oncostatic effects were through the modulation of REV-ERB, LX2 and Hep3B cells were exposed to SR9009. The ligand was able to modulate the pathway in a similar way to that observed after melatonin administration in LX2 cells, and potentiating melatonin effects in Hep3B cells. The elevated expression of fibrosis markers α-SMA and COL1 were reduced in LX2 cells after SR9009 exposure. BMAL1 silencing resulted in a decreased cell proliferation and an increased expression of the apoptotic markers Bax, cleaved caspase 3 and PARP1/2. Pro-apoptotic and antiproliferative melatonin effects were attenuated in BMAL1-depleted cells.
Conclusion: Melatonin modulates the expression of dysregulated Clock genes, and this could contribute to its beneficial effects in liver fibrosis and the progression to HCC.

SAT-394
Genetic Features Associated with 18F-FDG uptake in intrahepatic cholangiocarcinoma
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Background and aims: In intrahepatic cholangiocarcinoma (iCCA), genetic characteristics on ^{18}F-FDG-PET scans are not yet clarified. If they are evaluated, we can predict molecular features based on the FDG uptake. We analyzed RNA sequencing in iCCA patients to evaluate gene expression signatures associated with FDG uptake patterns.
Methods: We performed RNA sequencing of 22 cases iCCA who underwent preoperative ^{18}F-FDG- PET, and analyzed the clinical and molecular features according to the maximum standard uptake value (SUVmax). Genes and biological pathway which are associated with SUVmax were analyzed.
Results: Patients with SUVmax higher than 9.0 (n = 9) had poorer disease-free survival than those with lower SUVmax (n = 13, P = 0.035). Genes related to glycolysis and gluconeogenesis, phosphorylation and cell cycle were significantly correlated with SUVmax (| r | ≥ 0.5). RRM2, which is related to the toxicity of Gemcitabin was positively correlated with SUVmax, and SLC27A2 which is associated with Cisplastin response was negatively correlated with SUVmax. Cell cycle, hypoxia and metabolism-related pathways were enriched in high SUVmax patients.

Conclusion: The genomic features of gene expression and pathways can be predicted by FDG uptake features in iCCA. Patients with high FDG uptake have enriched cell cycle, metabolism and hypoxic pathways, which may lead to a more rational targeted treatment approach.

SAT-395

Bone marrow-mesenchymal stem cells of cirrhosis patients show insulin resistance and bioenergetic exhaustion

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Background and aims: Autologous bone marrow MSC therapy in cirrhotics has shown varied clinical response. Cirrhosis is a state of chronic inflammation and metabolic stress which can adversely affect the BM and stem cell population. We hypothesized that chronic liver injury may result in metabolic dysfunction of BM-MSCs and compromise their therapeutic potential.
Method: We isolated MSC from BM of cirrhotic patients (n = 10) and compared with matched healthy BM (n = 8). All the cells were characterized for MSCs as per criteria of International Society Cell and Gene Therapy (ISCT). Global-transcript profiles of cells were done by Next Generation Sequencing (NGS). Bioenergetics was studied using Seahorse Extracellular Flux Analyzer. Cellular glucose uptake was measured using Glucose Uptake Assay kit.
Results: In isolated cells from both cirrhotic and healthy BM fulfilling the minimal criteria for MSCs, mRNA sequencing showed significant upregulation of genes linked to insulin resistance, TNF signaling and down regulation of genes linked to oxidative phosphorylation, glutathione metabolism, longevity and nucleotide excision repair (fig 1a). In comparison to healthy BM-MSCs, cirrhotic BM-MSCs showed significant decrease in both baseline glycolysis ($p < 0.001$) (fig 1b) and glycolytic reserve ($p < 0.001$). In NGS data, though cirrhotic BM MSCs showed increased expression of Glycolytic genes they showed significant decrease in glucose uptake ($p < 0.001$) (fig 1c). Further analysis of oxidative phosphorylation showed significant decrease in baseline respiration, ATP production and spare respiratory reserve capacity in cirrhotic BM-MSCs in comparison to control (fig 1d). Cirrhotic BM-MSCs also showed decreased expression of genes associated with oxidative phosphorylation (fig 1a) and showed significant increase in mitochondrial ROS ($p < 0.01$) in comparison to control (fig 1e), suggesting compromised oxidative phosphorylation and mitochondrial dysfunction in cirrhotic BM-MSCs.
Conclusion: Cirrhotic BM-MSCs have impaired metabolic profile characterized by compromised glycolysis and oxidative phosphorylation due to insulin resistance. This might adversely affect their therapeutic potential and requires attention and modulation in ex-vivo cultures.

SAT-396

Heat activation of hepatocytes is sufficient to account for post radiofrequency ablation induced tumorigenesis

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Background and aims: Radiofrequency ablation (RFA) is an image-guided minimally invasive treatment commonly used to treat a wide range of focal primary and metastatic tumors in the liver, lung, kidney, bone, and other sites. Yet, RFA in some cases can also cause increased cancerous effects. Thus, RFA induced tumor progression remains a substantial barrier to clinical efficacy due to the poorly characterized mechanism of periablational and distant effects.
We have previously demonstrated in an in vivo rodent model that RFA of normal liver can induce growth of distant tumor. Moreover, following liver ablation an increased inflammatory response has been observed including cellular recruitment of neutrophils, macrophages, and activated myofibroblasts to the ablated zone. Additionally, several cytokines with potential pro-tumorigenic properties, including IL-6, HGF, STAT-3, and VEGF, are increased following RFA. These and additional factors may be expressed and secreted either by liver parenchymal or non-parenchymal cells. Yet, the main mechanistic pathway that drives RFA's pro-oncogenic effects has yet to be fully elucidated. Therefore, our purpose is to determine the role of the heat damaged hepatocytes in this process.
Method: In order to identify mechanisms of tumor recurrence and progression post RFA, we established an in vitro model to determine which parenchymal and recruited/non-parenchymal cells within the periablational zone activate pro-tumorigenic pathways post RFA.
Results: Our results demonstrate that primary hepatocytes subjected to moderate hyperthermia induce accelerated cell growth of several cancer cell lines (R3230 rat mammary adenocarcinoma, CT26 and MC38 mouse colorectal cancer, BNL.CL2 mouse hepatoma) that can be reduced by the c-Met inhibitor, PHA. Protein microarray of heated hepatocytes medium indicated secretion of proteins implicated pathways involved in tumor progression and immune system activation including multiple members of the fibroblast growth factors family, VEGFC, and CSF-1. Significant upregulation in mRNA expression of HSP70, IL-6, STAT3 and HGF were detected in the heated hepatocytes.
Conclusion: These results may indicate that heat damaged hepatocytes in the ablated zone by themselves can induce proliferation of tumor by releasing pro-tumorigenic factors post RFA. Elucidation of these pathways may allow us to uncover methods to eliminate these unwanted secondary effects of an otherwise robust clinical therapy.

SAT-397

HIC-5 and GARP expression is upregulated by hydrogen peroxide and TGF beta in primary human hepatic stellate cells cultured on decellularized human liver 3D ECM scaffolds

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Background and aims: Transforming growth factor beta (TGFb) plays a crucial role in the activation of hepatic stellate cells (HSC). This study aims to investigate the expression of three TGFb1-modulated proteins, namely Hydrogen peroxide Inducible Clone-5 (HIC-5), NADPH oxidase 4 (NOX4) and Glycoprotein A Repetitions Predominant protein (GARP), in primary human HSC cultured in a novel 3D model based on decellularized healthy and cirrhotic human liver extracellular matrix (ECM) scaffolds.
Method: Decellularized human liver 3D scaffolds were repopulated with primary human HSC ($0.25*10^6$) for 10 days. HSC were exposed to H_2O_2 (10uM-100uM) and TGFb1 (5 ng/ml) for 24 h, w/wo pre-treatment of H_2O_2/TGFb1. HSC engraftment/proliferation was assessed histologically and by immunohistochemistry and viability was quantified by PrestoBlue. 2D and 3D experiments were

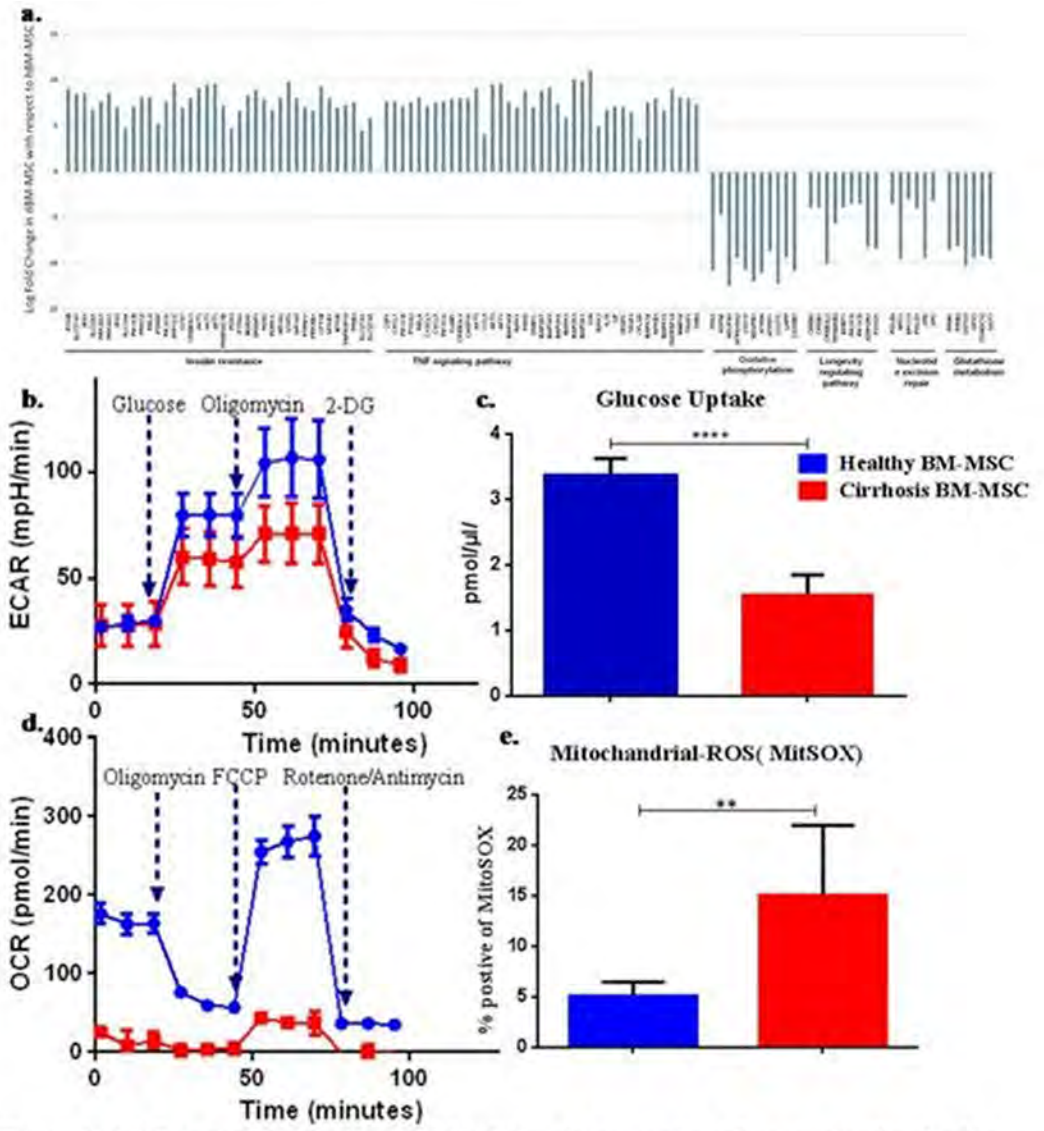

Figure 1: (a.) Bar graphs showing log fold change in expression of genes associated with Insulin Resistance, TNF signaling , Oxidative Phosphorylation , Longevity Regulating, Nucleotide Excision Repair and Glutathione Metabolism pathway in cirrhotic BM-MSCs with respect to healthy BM-MSCs. (b.) Graph showing real time changes in ECAR of starved healthy and cirrhotic BM-MSCs after treatment with Glucose, Oligomycin and 2-DG (c.) Bar graph showing glucose uptake by healthy and cirrhotic BM-MSCs (d.) Graph showing real time changes in OCR of healthy and cirrhotic BM-MSCs after treatment with Oligomycin, FCCP and Rotenone/Antimycin (e.) Bar graph showing percent MitoSOX positive BM-MSCs from healthy and cirrhotic patients

Figure: (abstract: SAT-395)

performed in parallel to compare pro-fibrogenic and pro-inflammatory gene expression as assessed by qPCR.

Results: Engraftment/proliferation in healthy 3D scaffolds were demonstrated histologically and with Ki67 and PDGFB-R IHC staining. Prestoblue assay showed that H_2O_2 did not affect HSC viability. HIC-5 mRNA expression in HSC cultured on healthy 3D scaffolds was induced upon exposure to H_2O_2 (50um and 100um). In contrast, H_2O_2 exposure did not affect the mRNA expression of NOX-4, GARP, TGFb1, TGFbR1. When comparing 3D with 2D cultures, HIC-5 mRNA expression was significantly upregulated in 3D indicating a specific 3D ECM-induced effect. Moreover, HIC-5 mRNA expression was further increased upon TGFb1 exposure in 3D in contrast to the corresponding 2D model. NOX4 and GARP were upregulated by TGFb1 in both models, however the effect of TGFb1 on gene expression was greater in HSC cultured in 3D compared to 2D. HSC in 3D healthy scaffolds pre-treated with TGFb1 and exposed to H_2O_2 induced significantly HIC-5, GARP and Col1a1 mRNA expression in comparison to simultaneous treatment with H_2O_2/TGFb1. This indicated a TGFb1 positive feedback as was shown by TGFb-R1 upregulation. NOX4 was not affected by pre-treatment with H_2O_2/

TGFb1. Experiments using HSC cultured in cirrhotic 3D scaffolds are ongoing.
Conclusion: Primary human HSC express differently HIC-5, NOX-4 and GARP when cultured in 3D ECM scaffolds derived from healthy human liver in comparison to 2D culture. Human tissue-specific 3D scaffolds offer a more realistic pathophysiological model to further define the specific role and modulation of the TGFb1 signalling pathway in hepatic fibrogenesis.

SAT-398

Pterostilbene reduces liver steatosis associated with obesity

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Background and aims: Excessive fat accumulation within the liver is known as simple hepatic steatosis, the most benign form of non-alcoholic fatty liver disease. Our aim was to determine whether pterostilbene, a phenolic compound belonging to the group of stilbenes, improves this hepatic alteration in a rodent model of genetic obesity.
Method: Zucker (*fa/fa*) rats were distributed in 2 experimental groups. Rats in the pterostilbene group were orally given this compound at a dose of 15 mg/kg/d through an orogastric catheter for 6 weeks. Histological liver analysis was carried out. Enzyme activities were assessed by spectrophotometry or fluorimetry, gene expression by RT-PCR and protein expression by western blot.
Results: Obese Zucker rats showed a grade 2 steatosis, according to Brunt scale, and pterostilbene partially reduced this to grade 1. No effects were observed in pterostilbene-treated rats in the activity of *de novo* lipogenesis enzymes. In contrast, an increase was observed in carnitine palmitoyltransferase 1a (CPT-1a) and microsomal triglyceride transfer protein (MTP) activities in PT group. Gene expression of the transporter *cd36* was decreased by pterostilbene and that of respiratory electron transport chain complex IV (*cox-2*) was increased. Pterostilbene administration did not modify protein expression of sterol regulatory element-binding protein-1 (SREBP-1c), but increased that of peroxisome proliferator-activated receptor α (PPARα) and mitochondrial transcription factor A (TFAM), and decreased that of diacylglycerol O-acyltransferase 2 (DGAT2).
Conclusion: Pterostilbene is a useful molecule to reduce liver steatosis. Its delipidating effect is due, at least in part, to reduced fatty acid availability and triacylglycerol synthesis, as well as increased very low density lipoprotein assembly and increased fatty acid oxidation.

SAT-399

The profile on intracellular gangliosides correlates with the malignant phenotype of cholangiocarcinoma cells and modulates cells adhesion

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Background and aims: Identification of cancer stem cell (CSC) has opened the way to the design of innovative diagnostic and therapeutic strategies in neoplastic diseases. Gangliosides (GS) a family of sialic acid-containing glycosphingolipids, have been associated with malignant phenotype of several cancers (i.e. breast, melanoma, glioblastoma, ovary). In particular, GD2, a complex GS, has been proposed as a novel CSC-marker. Nonetheless, limited information is available for many tumor types including human cholangiocarcinoma (CCA). This study aims to obtain a GS profiling of human CCA stem-like subset and their parental cells.
Method: Stem-like compartment was enriched by sphere culture (SPH) in two lines of established human intrahepatic CCA cells (HUCCT1, CCLP1). CCA GS composition was performed by chromatographic analytical techniques and revealed by resorcinol-HCl reagent. GD2 detection as well as its co-expression with CD133 CSC-marker was carried out by FACS analysis. The role of the GM3 GS on cell adhesion was investigated using D-threo-1phenyl-2-palmitoylamino-3-N-morpholine-1-propanol (PPMP), a GM3 synthase inhibitor.
Results: In contrast to parental cells grown as adherent monolayers (MON), CCA-SPH showed strong expression of GD2. The time course of SPH-growth revealed a remarkable GD2 expression along with CD133 levels just few days after plating. Overall, CCA-SPH showed a GM1/GM2 reduction in parallel with an increase in GM. Notably, a cell-line specific GS profile was revealed. MON-CCA exhibited high levels of simple GS such as GM3 and GM2 in HUCCT1 and in CCLP1, respectively. Moreover, HUCCT1 showed a GM3-dependent adhesion capacity on fibronectin. Remarkably, since GM2 and GD2 biosynthesis is driven by the enzyme beta-1, 4 N-acetylgalactosaminyltransferase-1 (B4GALNT1) and GD3 by alpha-N-acetylneuraminide alpha-2, 8-sialyltransferase (ST8SIA1), mRNA expression of both enzymes were analyzed by transcriptomic data from surgically resected CCA samples. Both B4GALNT1 and ST8SIA1 were significantly increased in tumor samples compared to paired non-tumoral liver tissue. Strikingly, B4GALNT1 expression considerably correlated with recurrence, perineural invasion and presence of satellite nodules in CCA patients.
Conclusion: We show for the first time that the GS composition is modulated in the CCA stem-like subset. GD2 should be explored as a candidate biomarker for CCA. GS composition may affect pivotal characteristics of CCA cells such as adhesion.

SAT-400

IL-1 beta-mediated macrophage-hepatocyte crosstalk upregulates hepcidin under physiologic low oxygen levels

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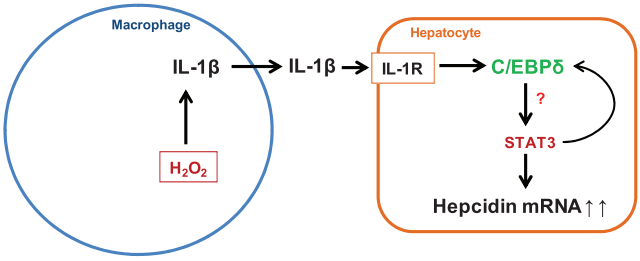
Background and aims: Liver-secreted hepcidin is the systemic masterswitch of iron homeostasis and its dysregulation leads to iron accumulation in most of chronic liver diseases. Hepcidin is strongly upregulated by iron, inflammation or H_2O_2 but the role of monocyte-derived macrophages on hepcidin regulation under (patho)physiological conditions is poorly understood. We here investigate the cellular crosstalk involved in hepatic hepcidin regulation by using macrophage/hepatocytes co-cultures mimicking physiological cell ratios and oxygen levels.
Method: Huh7 cells and THP-1 monocytes differentiated into macrophages were co-cultured at different physiological cell ratios (10:1 or 4:1) under normoxia (21% O_2) or hypoxia (1 or 5% O_2). The exposure of Huh7 cells to macrophage-conditioned medium was also investigated. Hepcidin, IL-1β, IL-6 and C/EBPδ mRNA level were assessed by qRT-PCR and the expression of STAT3 and SMAD proteins was analyzed by western blot. A cytokine array identified several macrophage-secreted cytokines, however studied using IL-1 receptor antagonist evidenced the role of IL-1β. Signaling pathways involved in hepcidin regulation were studied by using truncated hepcidin promoter constructs and siRNA-mediated knockdown of STAT3 or C/EBPδ.

Results: We demonstrated that the presence of macrophages leads to significantly increased hepatic hepcidin mRNA levels. This effect was even potentiated when co-cultures were maintained under 1 or 5% O_2. Interestingly, hepcidin was also upregulated in Huh7 cells exposed to macrophage-conditioned medium under 1% O_2 suggesting the role of a secreted factor in mediating hepatic hepcidin induction. Western Blot analysis, as well as studies with truncated hepcidin promoter constructs suggested the involvement of the STAT3 but not BMP signaling pathway. Among all the secreted cytokines analyzed, IL-1β was identified as important mediator of macrophage-induced hepcidin upregulation and found to act independent of IL-6. Moreover, we demonstrate an involvement of C/EBPδ in mediating IL-1β-STAT3 signaling with subsequent hepcidin induction.



Conclusion: Our findings underscore the importance of the hepatocyte/macrophage crosstalk for hepatic hepcidin regulation including IL-1β as macrophage-released cytokine, which is rapidly expressed during acute or chronic liver injury. We highlight the induction of hepcidin by IL-1β via STAT3, independent of IL-6-mediated signaling, which may result in hepatic iron accumulation in chronic liver disease.

SAT-401

Necroptosis signaling molecules regulate hepatic stellate cell activation via MLKL oligomerization-cell death independent pathway

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Background and aims: Necroptosis, a type of regulated cell death, is dependent on kinase activities of receptor interacting proteins (RIPs). We evaluated the role of necroptosis in hepatic stellate cells regulation via cell death independent pathway, and as well as its potential for target in hepatic fibrosis.
Method: Up-regulation of mixed lineage kinase domain like pseudokinase (MLKL) was evaluated in In-vitro liver fibrosis model. Morphology of stellate cells activation were analyzed by immunofluorescence and TEM. Necroptosis molecules and MLKL oligomerization was confirmed by immuno-blotting.
Results: Necroptosis stimulation with TNF-α and zVAD treatment on stellate cells caused stellate cell activation, and fibrosis markers including α-SMA, collagen1 and TIMP1 were significantly increased after necroptosis stimuli. Contrary, MLKL inhibitor (necrosulfonamide) reduced stellate cells activation markers including α-SMA, vimentin, and collagen1α. However, necroptosis stimulation or overexpression of MLKL did not lead to cell survival and number of stellate cells unexpectedly. MLKL phosphorylation, oligomerization, and cell membrane rupture of stellate cell did not observe after necroptosis stimulation. Our results show that the hepatic stellate cells did not form necrosome in the necrosome formation stage, unlike other cells (ex. hepatocyte). Instead, necroptosis stimulation regulated ICAM-1, VCAM-1, and chemokine C-X-C motif ligand-1/2 expression in hepatic stellate cell.
Conclusion: Necroptosis pathway activates hepatic stellate cell. But MLKL oligomerization and necroptotic cell death did not develop in stellate cell. Necroptosis stimulation seems to be differently act on stellate cell via oligomerization-cell death independent pathway.

SAT-402

Hepamine 2.0: Visualization and data-mining resource for liver disease

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Background and aims: Throughout the past two decades, numerous gene expression profiling data on literally all liver diseases were generated and stored in public databases. These data are thought to contain deep insights into the molecular development of liver diseases, support the development of molecular diagnostics and ultimately promote precision medicine in hepatology. However, once published the majority of these data remain idle. Only very few data were used for additional analyses or comparative projects by the hepatology research community. This may mostly be due to the limited bioinformatics knowledge on how to obtain and analyze the stored raw data by most biomedical research personnel. In order to overcome this barrier and to support an easy translation of bioinformatics data into translational hepatology research, we created Hepamine, a liver disease microarray database, visualization platform and data-mining resource.
Method: Microarray data were obtained from the ArrayExpress Archive of Functional Genomics Data (http://www.ebi.ac.uk/arrayexpress). Pre-analysis of expression data was performed using R statistical software and microarray analysis packages from the Bioconductor repository (https://www.bioconductor.org). Expression data were stored locally in a MySQL database.
Results: We have generated Hepamine, a web-based repository of pre-analyzed microarray data for various liver diseases. Among these are HCC, CCC, liver fibrosis/cirrhosis, chronic hepatitis, autoimmune liver disease, fatty liver disease and many more. Further development was influenced by optimization the access and visualization of the data. By restructuring the frontend, the data access is know more comfortable. Filtering and visualization of the data are know configure able separately. Genes may be searched on the basis of specific expression patterns across diverse samples. We also provide predefined gen sets to select pathways from KEGG and wikipathways. Results are furthermore visualized in simple three color tables indicating up-, down-, or no differential expression in multiple experiments. To enlarge the scope of the Hepamine, all data were linked to common functional and genetic databases, in particular offering information on the respective gene, signaling pathway analysis and evaluation of biological functions by means of gene ontologies.
Conclusion: Hepamine provides comprehensive data and easy access to various hepatologic gene expression data. It will open this widely unused resource particularly to hepatologists without bioinformatics or microarray profiling experience and substantially facilitate the translation of these data to molecular hepatology research. Hepamine is accessible at: http://www.hepamine.de.

SAT-403

Polycyclic aromatic hydrocarbons can trigger a hepatocyte release of cytotoxic extracellular vesicles

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Background and aims: Extracellular vesicles (EVs), membrane enclosed nanostructures released by cells into the extracellular environment, have been described as mediators in several pathogenic processes including liver diseases. In regards to xenobiotic liver injury, EVs emerge as potential actors of DILI (Drug Induced Liver Injury), but nothing is known concerning TAFLD (Toxicant-Associated Fatty Liver Disease) and TASH (Toxicant-Associated SteatoHepatitis) progression. Therefore the aim of this work was to study the impact of polycyclic aromatic hydrocarbons (PAHs) on hepatocyte-derived EV production with a special attention to hepatocyte death, as a key characteristic of TASH. PAHs are major environmental pollutants formed during incomplete combustion of organic materials and can be found in cigarette smoke and contaminated food, the main exposure in non-smokers.
Method: WIF-B9 and primary rat hepatocytes were treated by three different PAHs at a concentration of 100 nM : benzo (a)pyrene (BP), dibenzo (a, h)anthracene (DBA) or pyrene (PYR). They were selected based upon their various affinities for the AhR (Aryl hydrocarbon Receptor) and their various concentrations in common food. Then, EVs were isolated from extracellular medium by differential ultracentrifugation.
Results: PAHs were able to increase the release of EVs and to induce apoptosis of both types of hepatocytes. EVs released were mainly composed of exosomes. EV production, as well as cell death, involved oxidative stress, CYP metabolism and activation of cytosolic transcription factors such as AhR (Aryl hydrocarbon Receptor) or CAR (Constitutive Androstane Receptor), depending on the PAH type. Moreover, PAHs changed exosome protein marker expression in WIF-B9 hepatocytes. In addition, changes in membrane fluidity of EVs occurred with all tested PAHs, but bulk cellular membrane fluidization was only involved in BP- or DBA-induced EV release and cell death. PAHs modified also cholesterol levels both in cells and EVs, but only the cholesterol depletion due to BP or DBA was implicated in EV release and cell death. Finally, EVs released by PAH-treated hepatocytes were internalized by untreated hepatocytes causing cell death.
Conclusion: PAHs caused release of exosomes by hepatocytes in the extracellular environment that could participate in the process of hepatocyte death.

SAT-404

Discordant NS5a but not NS3 RASs profile in liver and plasma compartments of HIV/HCV genotype 1a/4d infected patients

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Background and aims: Naturally occurring resistance-associated substitutions (RASs) in the NS3 and NS5a DAAs target regions may be present in liver, the major site of HCV replication, irrespective of un detectability in plasma compartment. This finding may have implication for the response to treatment with direct acting antivirals (DAAs). We evaluated the RAS profile of NS3 and NS5a in liver and plasma of HIV/HCV coinfected patients (pts) harboring genotype (GT) 1a/4d.
Method: Twenty-one HIV/HCV coinfected pts naïve to anti-HCV treatment who performed liver biopsy for diagnostic purposes were included in the study. Fourteen pts harbored HCV GT1a and 7 pts harbored GT4d. Median age was 41 years (inter quartile-range, IQR 38-43); 14 were males and 7 females; median alanine amino transferase (ALT) and aspartate amino transferase (AST) values were 66 IU/L (IQR 41-200, normal values < 59 IU/L), 65 IU/L, (IQR 49-137, normal values < 35 IU/L), respectively. CD4 cells count was 486 (IQR 443-614) HCV-RNA load was 5.6 Log IU/ml (IQR 5.5-6). The study was conducted in accordance with ethical principles stated in the Declaration of Helsinki and the patients gave written informed consent. NS3 and NS5a RASs profile was investigated by viral population sequencing in liver tissues and plasma, according to Lontok, 2015, Sarrazin, 2016 and Carrasco, 2018.
Results: RASs in the NS3 were detected in 9/21 (43%) coupled liver tissues and plasma samples. NS3 mutated strains in GT1a exhibited Q80 K in plasma and liver. In GT4d infected pts, NS3 protease region resulted conserved in plasma and liver. The analysis of the NS5a domain showed RASs in 10/21 (47.6%) liver tissues and 6/21 (28.5%) corresponding plasma samples; in GT1a, 3/14 sequences from liver had RASs [M28R/Q30P/L31R in 1 pt, Q30R/L31R in one other pt, H58E in the remaining pt] while RASs were not revealed in the corresponding plasma. Interestingly, in GT4d 7/7 (100%) liver tissues and 6/7 plasma samples (85.7%) showed the amino acid substitution T58P at site of resistance.
Conclusion: We detected a different profile of RASs in the compartments explored concerning the NS3 and NS5a target regions. So, in particular for GT1a the liver compartment could be responsible for the emergence of resistant variant not detected in the corresponding plasma sample by viral population analysis. This finding may have implication especially for GT1a patients with virological failure and absence of RASs in plasma sample at re-treatment.

SAT-405

Genomic expression in circulating PBMCs of patients with hepatocellular carcinoma: Effect of ablative treatment

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Background and aims: Genomic profiling of HCC has a significant clinical and prognostic role and novel correlations with clinical features, therapeutic response, survival and follow-up are expected. The aims of the work are: to find out the role of the analysis of gene expression profile of PBMCs as a surrogate approach for the assessment of local HCC-infiltrating mononuclear inflammatory cells and its main clinical features; To find out whether ablative treatment of HCC may affect the genomic expression in circulating PBMCs.
Methods: 30 patients affected by HCC, classified on the basis of Child Class and staged by BCLC criteria; all of them underwent to ablative treatment (radiofrequency 16, chemoembolization 14); the effect of treatment has been evaluated by mRECIST criteria. Blood samples have been collected at time 0, before treatment, and at time 1 (three months after the ablative procedure). RNA profiling: microarray expression profiling on PBMCs has been performed in order to identify upregulation and down-regulation of specific gene expression pathways at the basis of the phenotypic identity card of the individualized patient. Experiments have been performed on high-throughput iSCAN illumina facility using the HumanHT-12 v3 Expression BeadChip Kit; PCR Quantitative Real Time (RT-qPCR);

RTqPCR primers were designed using Primer Express software (Applied Biosystems, Foster City, CA).
Results: The genomic evaluation by microarrays analysis on circulating PBMCs has been completed on all subjects (11 with complete response, CR; 12 with partiale response, PR; 7 stable or progression disease, SD, PD).
After preliminary microarrays analysis, the RTqPCR identified the following significant ($p < .05$) variations of genes expression in the comparison between time 0 and time 1 (data are expressed as relative mRNA, M+SEM):
Down-regulated genes: KLF9 in all (0.96+0.07 vs 0.74+0.04) and RP (1.27+0.21 vs 0.78+0.04); in RC subjects CCDC88C (1.07+0.04 vs 0.87+0.01), CORO7 (0.99+0.01 vs 0.22+0.04), LTBR4 (1.54+0.31 vs 0.35 +0.13), PREX1 (1.11+0.06 vs 0.72+0.07);
Up-regulated genes: in RC subjects: EAF2 (0.91+0.10 vs 1.59+0.07).
Furthermore, in the comparison RC vs RP at time 0, ENTPD1 (0.91 +0.08 vs 1.31+0.07) and ICOS (2.11+0.55 vs 0.92+0.16) resulted different.
Conclusions: Finding of down and up-regulation of genes in circulating PBMCs in HCC patients after ablative procedure represents a novel result with possible diagnostic and prognostic implications.

SAT-406

Elevated biliary cholesterol in spite of hepatic ABCG5/G8 deficiency: Biliary lipid secretion in conditional knock-out mice

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Background and aims: Gallstone disease is one of the most common gastrointestinal diseases worldwide. It results from biliary cholesterol supersaturation, which is the necessary condition for the nucleation of cholesterol crystals that grow into mature gallstones. Cholesterol is transported across the hepatocanalicular membrane in an ATP-dependent, regulated manner by the heterodimer ABCG5/G8. Besides its function in the liver, *Abcg5/g8* is also expressed in enterozytes, where it transports plant sterols and cholesterol back into the intestinal lumen. The aim of this study was to analyze the biliary lipid composition when the transporter is inactivated selectively in the liver but not the intestine.
Method: Using BAC-based recombineering, we have generated conditional *Abcg5/g8* knock-out mice that allow tissue-specific deletion of the first 2 exons of *Abcg5* and the first exon of *Abcg8*, respectively, by cre-mediated recombination. *Abcg5/g8* flox mice were crossed to albumin-cre mice expressing cre in the liver under the control of the albumin promoter (*Abcg5/g8*-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 hour of the acute bile fistula. In addition, expression analyses of cholesterol metabolism regulating genes were performed.
Results: All animals developed normal, were fertile and showed no gross abnormalities. Total biliary lipids in hepatic bile were significantly reduced in the knock-out mice compared to wild-type controls (1.1 ± 1.0 g/dl vs. 1.5 ± 1.0 g/dL), and the cholesterol saturation index (CSI) was significantly elevated (2.3 ± 0.3 vs. 0.9 ± 0.1). Analysing bile consumption during the first hour of the acute bile fistula, we demonstrated that bile acid output was significantly decreased (66.95 ± 6.8 vs. 124.6 ± 18.7 µmol/hr/kg), while both cholesterol and phospholipids were elevated (10.26 ± 1.2 vs. 4.8 ± 0.8 µmol/hr/kg and 33.1 ± 4.6 vs. 27.7 ± 3.7 µmol/hr/kg, respectively). Expression of *Abcg5* and *Abcg8* was not detectable in the liver but unaffected in the intestine. The alternative cholesterol transporter *Abcg1*, which is expressed in endothelial cells, macrophages and monocytes, was significantly induced.
Conclusion: Our results show that the liver-specific deletion of *Abcg5/g8* does not protect against gallstone formation, rather it leads to supersaturation of cholesterol in bile and a markedly increased CSI in the conditional knock-out mice. These changes occur in the setting of decreased bile acid and total lipids, all of which increase gallstone susceptibility. Further studies need to determine the mechanistic changes of biliary lipid secretion at the level of the hepatocanalicular membrane as well as adaptive responses.

SAT-407

The Wilson's disease mouse (Atp7b-/-) has profound alterations in the hepatic metabolome and improved insulin sensitivity

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Background and aims: Inactivating mutations in the copper transporter Atp7b result in Wilson's disease (WD). The *Atp7b*$^{-/-}$ mouse develops hallmarks of WD, including elevated hepatic copper accumulation preceding pathology, high urinary copper excretion, and development of necrosis, inflammation, steatosis, and bile duct proliferation. We previously reported that hepatic metabolic nuclear receptor activity is disrupted in *Atp7b*$^{-/-}$ mice and WD patients, suggesting an unexpected mechanism for WD pathology. Hepatic nuclear receptors, in particular FXR and PPARα, are critical for maintaining metabolic homeostasis, and activity of these nuclear receptors is decreased in the Atp7b$^{-/-}$ mice. Therefore, we hypothesized that decreased nuclear receptor activity in *Atp7b*$^{-/-}$ mice correlates with altered glucose and lipid homeostasis.
Methods: Following 10 weeks on either a chow or Western diet (40% kcal fat), body and liver weights, lean and fat mass, glucose sensitivity (glucose tolerance testing), insulin sensitivity (insulin tolerance testing), and gluconeogenesis (pyruvate tolerance testing) were assessed in *Atp7b*$^{-/-}$ mice and wild-type (WT) littermate controls. Hyperinsulinemic-Euglycemic clamp was also performed to further assess insulin sensitivity. Hepatic glycolytic, TCA, and amino acid metabolites were measured by LC-MS. Microarray analysis was performed with GeneChip Mouse 430 2.0 (Affymetrix), and gene mRNA expression was measured by real-time PCR.
Results: Body, liver, and lean mass were not different between WT and *Atp7b*$^{-/-}$ mice on chow diet, whereas, fat mass was 50% less in *Atp7b*$^{-/-}$ mice on chow diet. Unlike WT mice, *Atp7b*$^{-/-}$ mice did not exhibit Western diet induced increases in body, liver, or fat mass. *Atp7b*$^{-/-}$ mice showed decreased gluconeogenesis and had improved insulin sensitivity on chow or Western diet compared with WT mice. Hepatic glucose, pyruvate, and lactate levels were decreased in *Atp7b*$^{-/-}$ mice; however, the glycolytic intermediates glucose-6 phosphate, 3 phosphate-glycerate, and phosphoenolpyruvate were significantly increased. TCA metabolites citrate, fumarate, malate, and oxaloacetate were increased, whereas α-ketoglutarate was decreased. Interestingly, concentrations of asparagine, proline, methionine, and glutamic acid were increased; however, glutamine concentration was decreased in *Atp7b*$^{-/-}$ mice. Metabolite-gene associated changes were identified from the microarray analysis, indicating an association between changes in gene expression and metabolite enrichment.
Conclusions: *Atp7b*$^{-/-}$ mice exhibited changes in glucose and insulin sensitivity that accompanied complementary alterations in hepatic metabolites and metabolic gene expression. Taken together, these significant metabolic changes are likely due to copper-mediated dysfunctional nuclear receptor activity in *Atp7b*$^{-/-}$ mice.

Non-invasive assessment of liver disease except NAFLD

SAT-409

Hepatic vein arrival time assessed by contrast-enhanced ultrasound in the non-invasive evaluation of portal hypertension

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Background and aims: There is a growing interest in the non-invasive assessment of hepatic venous pressure gradient (HVPG) due to its invasiveness and limited accessibility. Transient elastography (TE) is the most used technique, with good results determining clinically significant portal hypertension (CSPH: HVPG ≥ 10 mmHg), nevertheless it yields worse results with higher HVPG cut-offs (> 12 mmHg: bleeding risk portal hypertension [BRPH]). Intrahepatic shunts developed in cirrhosis with portal hypertension leads to hemodynamic changes that correlate with disease severity, and are worse assessed by TE. Measurement by other techniques, such hepatic vein arrival time (HVAT), could be clinically useful.
Method: Prospective, single-center study. Inclusion criteria: liver cirrhosis, clinical need for HVPG measurement. Exclusion criteria: portal vein thrombosis, prehepatic hypertension, cardiopathy. On the same day, and prior to the HVPG, TE and ultrasound measurement (Toshiba Aplio 500, Japan) of HVAT from the cubital vein was performed (10% increase in hepatic vein signal compared to baseline after injection of contrast [Sonovue®, Bracco, Italy]). Beta-blocked patients had their medication withdrawn five days before testing. The reliability of HVAT and TE in the prediction of CSPH and BRPH was evaluated by determining the areas under receiver operating characteristic curves (AUROC) and the percentage of correctly classified patients.
Results: 56 patients were included. 6 were excluded from analysis of HVAT because of poor echo window and 10 of TE due to invalid results (89% vs 82% applicability) In the 50 patients with HVAT (medians): 61 years, 70% male, BMI 26.6 kg/m^2, Child-Pugh A/B/C 70/28/2%, MELD 10, 87% varices, 14% ascites. Linear correlation (Pearson) of HPVG with HVAT: –0.55 (p < 0.001).
The AUROC of CSPH by TE was 0.86 (95%CI: 0.72–1; p = 0.008) with optimal cut-off (OC) of 15.2 kPa (Se 91.4%, Sp 80%, PPV 97%, NPV 57%) and by HVAT was 0.94 (95%CI: 0.85–1; p = 0.001) with OC of 17 seconds (Se 93%, Sp 66%, PPV 95%, NPV 57%). The AUROC of BRPH by TE was 0.74 (95%CI 0.58–0.89; p = 0.013) with OC of 22 kPa (Se 65.4%, Sp 71.4%, PPV 81%, NPV 52.6%) and by HVAT was 0.8 (95%CI 0.67–0.93; p = 0.001) with OC of 14 seconds (Se 82%, Sp 62%, PPV 82%, NPV 62%). For HVPG ≥ 12 mmHg, TE correctly classified 67.5%, HVAT 76% and sequential use (HVAT > TE) 85% of patients.
Conclusion: HVAT assessed by contrast-enhanced ultrasound is an excellent non-invasive method to evaluate the existence of CSPH, and superior to TE in the assessment of BRPH.

SAT-410

Higher spleen iron content estimated by MRI T2* signal is associated with lower insulin-resistance in patients with dysmetabolic iron overload syndrome

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Background and aims: Dysmetabolic Iron Overload (DIOS) is the most common cause of liver iron overload. It is defined as moderately increased hepatic and body iron stores with at least one feature of the metabolic syndrome without other cause of iron overload. The significance of a predominant parenchymal or mesenchymal distribution of iron overload in this context is discussed. Abdominal T2* MRI is the gold standard to quantify Liver Iron Content (LIC). It also allows estimation of Splenic Iron Content (SIC) which may provide insight on iron overload distribution. The goal of this study is to evaluate the clinical relevance of SIC estimated by MRI in patients with DIOS.
Method: MRI of patients with DIOS included in our center in a prospective randomized trial evaluating the benefit of bloodletting (Laine Hepatology 2017), were reviewed to estimate SIC at inclusion. Patients with diabetes were excluded. SIC was estimated by T2* MRI similarly to LIC (d'Assignies Eur Radiol 2018), and T2* signal converted in µmol/g to ease understanding. Clinical and biological data were collected in the prospective study. Association between LIC and SIC was assessed by Spearman correlation. Factors associated with SIC were studied by univariate and multivariate analysis, with SIC divided in two classes according to median value.
Results: 101 patients were included. Mean age was 56.6 (± 9.5) years, 87% were men, and mean BMI was 27.7 (± 2.7). Mean serum ferritin (Frt) was 813 (± 290)µg/L, mean LIC 88.9 (± 42.5) µmol/g and mean SIC 57.2 (± 42.7)µmol/g. The mean HOMA index was 2.1 (± 1.3).
In univariate analysis SIC was correlated to LIC (r = 0.33, p < 0.001), transferrin saturation (TSat) (r = -0.18, p = 0.08), and mean corpuscular volume (MCV) (r = -0.32, p < 0.01). SIC ≥ 50µmol/g was associated to higher LIC (p = 0.01), higher alkaline phosphatases (ALP) (p = 0.04), lower fasting insulin (p = 0.04), lower HOMA index (p = 0.05), and high blood pressure (HBP) (p = 0.04).
In Multivariate analysis SIC ≥ 50µmol/g was associated to LIC ≥ 100µmol/g (OR = 7.0; IC:2.0–24.8), HOMA ≥ 2.4 (OR = 0.20; IC:0.06–0.60), HBP (OR = 3.1; IC:1.0–9.0), ALP > 70UI/L (OR = 4.8; IC:1.6-13.8), Frt > 650 µg/L (OR = 3.2; IC:1.0-9.7), TSat ≥ 35% (OR = 0.32; IC:0.11-0.95), and MCV ≥ 95fL (OR = 0.19; IC:0.06-0.63)
Conclusion: In patients with DIOS spleen iron content estimated by T2* MRI may identify patients with lower insulin resistance, suggesting differential toxicity of iron overload depending on its localization. The relevance of SIC to the clinical management of these patients should be further investigated.

SAT-411

Clinical comparison and conversion of international normalized ratio and prothrombin index

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Background and aims: Coagulation tests are often used in hepatology. The main test is Quick time (QT) expressed as INR or prothrombin index (PI, % vs normal). Our first aim was to compare the

clinical performance of PI and INR. Our second aim was to develop a direct conversion between INR and PI since intermediate variables (QT or ISI) are often unavailable.
Method: Evaluation was performed in three steps detailed in results.
Results: ***First step***: clinical comparison. In a 1st study, we evaluated the accuracy for Metavir F staging by liver biopsy in 949 patients with chronic liver disease (CLD) of various etiologies. PI was superior to INR in 12 out 13 judgement criteria. For example, the mean values between F2 vs F1 were significantly different for PI (p = 0.001) and not for INR (p = 0.110). In a 2nd study, we evaluated the prognosis for survival in 2387 patients with CLD of various etiologies (follow-up: 9.9 ± 5.9 years). PI was more predictive (Harrell C-index: 0.727) than INR (0.726). Then, we evaluated AUROC for large esophageal varices (EV) in 487 patients: PI: 0.704, INR: 0.695. The reproducibility, tested by intra-class correlation coefficient (ICCC), between 17 laboratories in 20 CLD was, PI: 0.92, INR: 0.83. Thus, in almost all comparisons, PI was superior to INR. Finally, INR and PI interacted for the diagnosis of fibrosis or EV. The PI/INR ratio solved this interaction and increased the accuracy for fibrosis or EV. ***Second step***: conversion. In a 1st study performed in 29.690 patients with various pathologies, we developed 2 mathematical formula of conversion between PI and INR. We provide the results for the conversion from INR to PI that includes 8 terms. ICCC was 0.9998 between measured PI (mPI) and estimated PI (ePI) by INR. The formula was validated in other 6185 patients with various pathologies and different ISI (ICCC: 0.9995) or in 1674 patients with CLD (ICCC: 0.9942) or in 1574 patients with various pathologies from another center with different ISI and 4 analyzers (ICCC: 0.9933). ***Third step***: clinical validation of conversion formula. This was evaluated with accuracy of a fibrosis test (FibroMeter V2G) in the 1st population with 949 CLD. AUROCs of FibroMeters were, respectively calculated with mPI and ePI for F ≥ 2: 0.8168 vs 0.8169, for F ≥ 3: 0.8277 vs 0.8271, for F = 4: 0.8751 vs 0.8753.
Conclusion: PI is superior to INR in terms of liver fibrosis or EV diagnosis, prognosis and reproducibility in CLD. The PI/INR ratio is useful by increasing accuracy. Conversion formula between PI and INR (freely available on a calculator) provide excellent accuracy.

SAT-412

The utility of the enhanced liver fibrosis test in alcoholic liver disease

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Background and aims: Alcohol is the main cause of chronic liver disease (CLD) in the UK, the third commonest cause of death in 18-65 year-olds. Liver fibrosis severity correlates with prognosis. The Enhanced Liver Fibrosis (ELF) test is a serological biomarker able to stratify fibrosis severity in CLD, however its utility in alcoholic liver disease (ALD) warrants further validation. We assessed the diagnostic and prognostic performance of ELF in ALD.
Method: Paired ELF tests and liver biopsies from 786 patients were assessed. Results were compared between ALD (n = 81) and non-ALD aetiologies (n = 705). Prognostic data were available for 70 ALD patients for a median of 5.9 years. ELF cut-offs of < 8.3, ≧9.8, ≧10.5 and ≧11.3 were assessed and area under receiver operator characteristic (AUROC) curves used to determine diagnostic utility in histologically staged moderate fibrosis (Ishak F≧3) and cirrhosis (F≧5). Survival data were assessed using Cox Proportionate Hazard Ratios (HR) adjusted for age, sex and treatment centre; and logistic regressions adjusted for age and sex.
Results: Median age in the ALD cohort was 50. Biopsies staged as; F0: 5, F1: 7, F2: 6, F3: 4, F4: 5, F5: 10, F6: 44. ELF identified cirrhosis and moderate fibrosis in ALD independently of inflammation, AUROCs = 0.895 and 0.923 respectively, and was non-inferior to non-ALD aetiologies (Figure 1A and B). The overall diagnostic accuracy of ELF was assessed using the Obuchowski Method: AUROC in ALD = 0.934; non-ALD = 0.907. Using ELF < 9.8 to exclude and ≧10.5 to diagnose cirrhosis, 87.7% of ALD cases could have avoided biopsy, with a sensitivity of 91% and specificity of 85%. A unit increase in ELF was associated with a 2.6 times greater risk of a liver related event (LRE) at 6 years. ELF ≧11.3 was associated with a Cox HR of 8.6 for LREs compared to ELF < 9.8.
Conclusion: ELF accurately stratifies liver fibrosis in ALD independently of inflammation. Its use may improve detection of alcoholic cirrhosis in primary and secondary care. Prognostically, ELF performs as well as biopsy in ALD with performance similar to that observed in other aetiologies of CLD.

SAT-413

Selected cytokines associated with chronic hepatitis b histological activity and fibrosis: A 78-week prospective study

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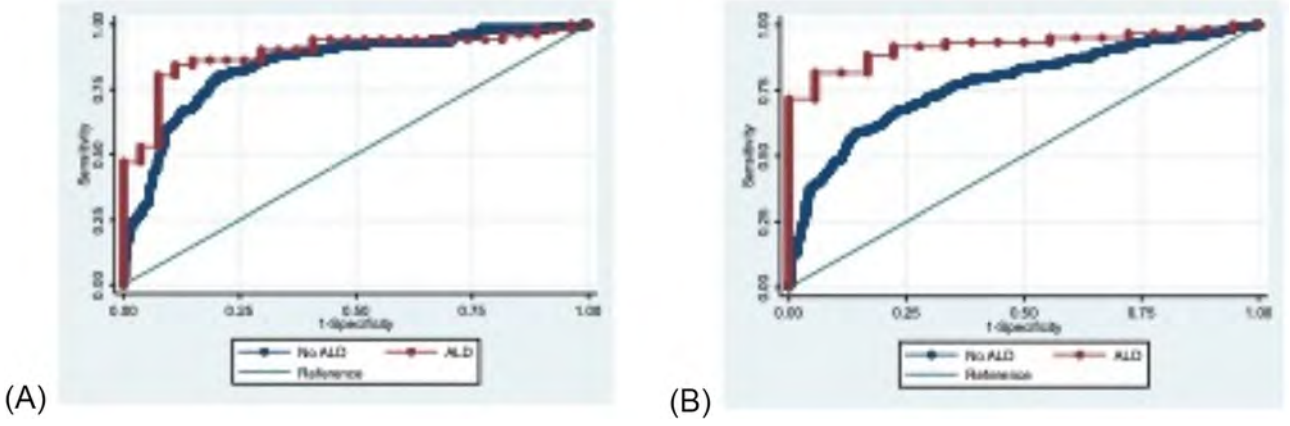

Figure 1: (abstract:SAT-412): AUROC for ALD (red) and non-ALD (blue) for (A) cirrhosis and (B) moderate fibrosis. AUROC for cirrhosis was 0.895 (95% CI: 0.823-0.968) in ALD and 0.846 (95% CI: 0.807-0.885) in non-ALD aetiologies (p = 0.307). AUROC for moderate fibrosis was 0.775 (95% CI: 0.739-0.811) in non-ALD and 0.919 (95% CI: 0.859-0.980) in ALD (p < 0.001).

Background and aims: Previous studies of small cohorts have revealed that several circulating cytokines are involved in the progression of chronic hepatitis B (CHB). And little reliable data is available about these cytokines for liver fibrosis monitoring in CHB patients on antiviral therapy. We aimed to investigate associations between circulating cytokines and liver histopathological activity and fibrosis in a large cohort, and explore the performance of selected cytokines in monitoring liver histopathology change following 78-week antiviral treatment in CHB patients.

Method: Based on Ishak system, we prospectively assessed liver biopsies from 734 CHB patients and serially in 233 patients before and after 78-week enticavir-based treatment. Circulating cytokines were measured by Luminex screening system. Univariate and multivariate analyses were conducted to analyse data. The detailed clinical trial protocol has been registered (NCT01962155 and ChiCTR-DDT-13003724).

Results: Before treatment, anti-hepatitis B virus core antibody (anti-HBc) ($p = 0.000$), Collagen IV alpha 1 (COL4A1) ($p = 0.028$), Hyaluronic Acid (HA) ($p = 0.040$), Interferon- gama -inducible T-cell alpha chemoattractant (I-TAC) ($p = 0.004$) and Angiopoietin-like protein 2 (Angptl2) ($p = 0.049$) were independently associated with at least moderate inflammation (Histology activity index ≥ 5), and Interferon-gama-inducible protein-10 (IP-10) ($p = 0.000$), COL4A1 ($p = 0.033$), HA ($p = 0.004$), Laminin (LN) ($p = 0.006$), and Angptl2 ($p = 0.011$) independently correlated with significant fibrosis (Ishak fibrosis score ≥ 3). After 78-week antiviral therapy, the decline of COL4A1, HA, IP-10 and LN were much greater in patients with inflammation improvement, and greater decline of HA, IP-10 and LN in patients with histological improvement was also observed (Figure). Further analysis found that change in COL4A1, HA, I-TAC, Angptl2, IP-10 and LN were correlated with change in liver histological necro-inflammatory activity, but not with the change in liver fibrosis after 78-week antiviral therapy.

Conclusion: Anti-HBc and I-TAC were independently associated with at least moderate inflammation, COL4A1, HA and Angptl2 were independent markers of at least moderate inflammation and significant fibrosis, whereas IP-10 and LN were independent indicators of significant fibrosis. Changes in these selected cytokines, which could be related to change in liver inflammation, were unreliable to reflect fibrosis change after 78-week antiviral treatment.

SAT-414

Baveno VI principle for non-invasive assessment of high risk varices is also applicable with shear wave elastography

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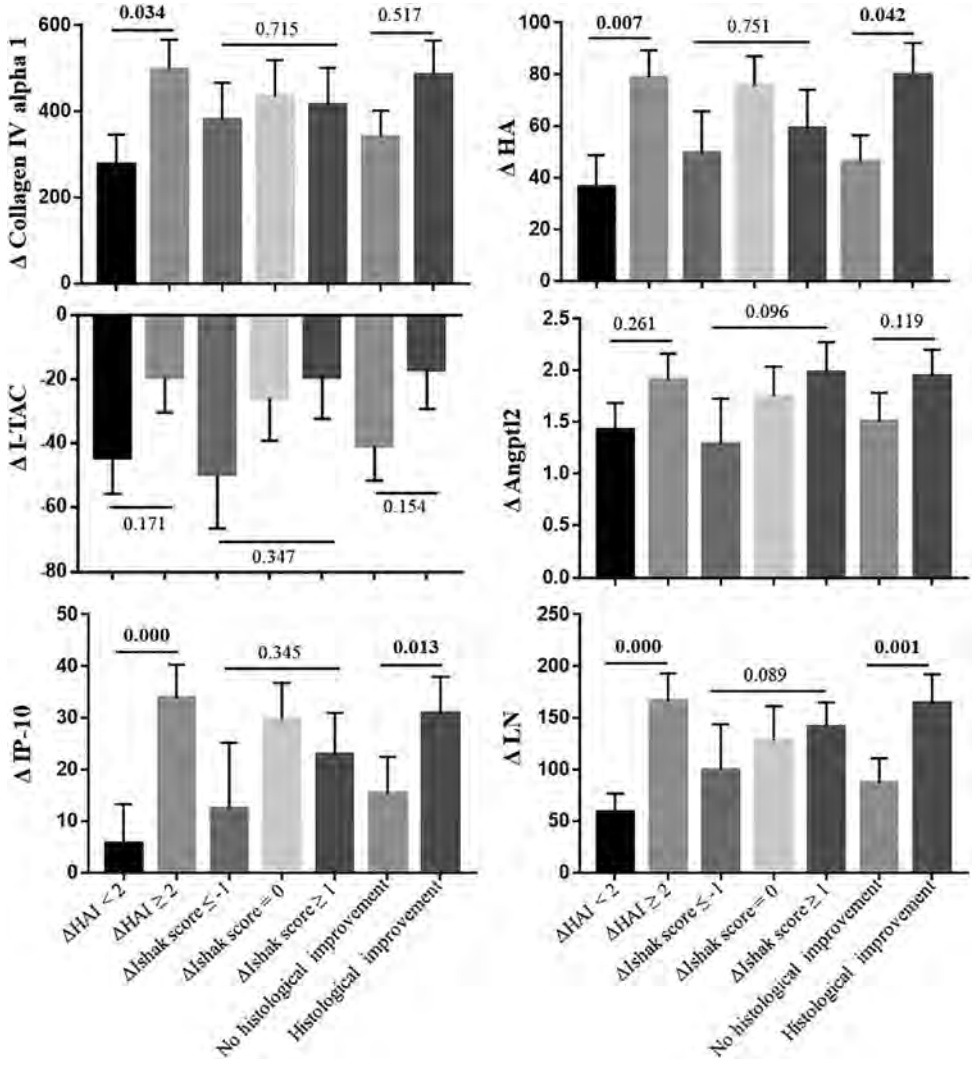

Figure: (abstract:SAT-413)

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Background and aims: Baveno VI criteria state that high risk esophageal varices (HRV) can be safely ruled-out if liver stiffness (LS) by transient elastography (TE) is < 20 kPa and platelets count (PLT) is > 150×10^3. However, TE's applicability is limited in some patients. Realtime shear-wave elastography (2D-SWE) is a novel ultrasound-based technique that estimates LS. Our group recently demonstrated the good performance of 2D-SWE from General Electric (2D-SWE.GE) to estimate clinically significant portal hypertension: for a cut-off 11.3 kPa, the diagnostic accuracy is > 80% for HVPG ≥ 10 mmHg.
The aim of this study was to test and validate the performance of LS estimated by 2D-SWE.GE to predict the presence of HRV, alone or in association with PLT.
Method: In this bicentric study, all consecutive cirrhotic patients due to various etiologies were enrolled in a training (center 1) and a validation set (center 2). All patients underwent in the same day LS assessment by both TE and 2D-SWE.GE and usual lab test, including PLT. All patients also had endoscopy within 6 months from inclusion for assessment of variceal status (HRV-grade II and III varices, or grade I with red signs or Child-Pugh C cirrhosis).
Results: In the training set [n = 103; median age = 56 (20-74) years; 41.7% prevalence of HRV] LS was feasible by TE in 97/103, while by 2D-SWE.GE in all patients. Mean LS values by 2D-SWE.GE were higher in patients with HRV (16.79 vs. 13.15 kPa, p = 0.008). AUC for the prediction of HRV was 0.76 (95%CI:0.65-0.86) for TE and 0.65 (95% CI:0.53-0.76) for 2D-SWE.GE, (deLong test p = ns) and the proportion of correctly classified patients was 57/93 (61.3%) and 58/98 (59.2%), respectively. The best cut-off for 2D-SWE.GE-LSM was again 11.3 kPa, with 0.8 Se and 0.45 Sp. By using together 2D-SWE.GE-LS < 11.3 kPa and PLT > 150×10^3, the missed HRV rate is 5% (1/18) and the spared endoscopies rate is 29.3% (17/58). The classic Baveno VI criteria, however, showed a higher rate of missed HRV (1/14, 7%) and lower rate of spared endoscopies (13/56, 23%).
In the validation set [n = 82; median age = 60 (38-75) years; 25.6% HRV prevalence] the AUC of 2D-SWE.GE-LS for predicting HRV was 0.68 (95%CI: 0.55-0.81) vs. 0.73 (95%CI: 0.61-0.85) for TE-LS, deLong test p = ns. The combination between 2D-SWE.GE-LS < 11.3 kPa and PLT > 150×10^3 had a 0% (0/12) missed HRV rate and 19.7% (12/61) spared endoscopy rate. The original Baveno VI criteria had similar performance: 0/15 missed HRV rate and 15/61 (24.5%) spared endoscopies rate.
Conclusion: LS by 2D-SWE.GE can predict the presence of HRV in patients with cirrhosis. The best cut-off (which also predicts CSPH) has modest diagnostic accuracy, but used in conjunction with PLT, in a Baveno VI approach, leads to better performance, low missed HRV rates and good proportion of spared endoscopies. Therefore, 2D-SWE.GE is a good and alternative for TE for LS assessment in patients with advanced liver diseases.

SAT-415
High levels of basement membrane remodelling (C4M) and low activity of wound healing (FPA) reflect fibrosis in alcoholic liver disease

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Background and aims: Alcoholic liver disease (ALD) is characterized by a long symptom free phase which is difficult to diagnose. If undetected, development of liver fibrosis may lead to liver-related complications and mortality. Thus, there is a need for non-invasive diagnostics to evaluate dynamics of liver fibrosis and progression at an early stage of disease. One approach may be assessment of neo-epitopes released from extracellular matrix or wound healing. We assessed whether fibrosis stage was associated with serological levels of fibrinopeptide a (FPA), a peptide fragment released when fibrinogen is converted to fibrin, together with C4M, a marker of MMP mediated type IV collagen degradation of the basement membrane.
Method: In this study 302 asymptomatic, compensated ALD patients were recruited prospectively. FPA and C4M were measured in serum by competitive ELISAs. We used liver biopsy as reference, with central scoring of fibrosis (Kleiner stage F0-4) and non-alcoholic fatty liver disease (NAFLD) Activity Score: ballooning 0-2, lobular inflammation 0-3 and steatosis 0-3. The association between C4M or FPA and clinical, demographic and liver histologic data was evaluated by Mann Whitney test, Kruskal Wallis tests and Receiver operating characteristics (ROC) analysis.
Results: C4M levels were 35% higher in patients with hepatocyte ballooning scores of 2 compared to 0 ($p < 0.001$), 36% higher in patients with lobular inflammation score 3 compared to 0-1 ($p = 0.004$) and 16% higher in patients with portal inflammation than in those without ($p = 0.003$). In contrast, FPA was 36% lower in patients with hepatocyte ballooning score 2 compared to 0 ($p = 0.001$), 34% lower in patients with a lobular inflammation score 3 compared to 0 ($p < 0.001$) and 22% lower in patients with portal inflammation than in those without ($p = 0.003$). C4M concentrations were 45% higher and FPA levels were 38% lower in patients with a fibrosis score 4-5 compared to 0-1 (both $p < 0.0001$). ROC analyses revealed that C4M was able to discriminate between F0-1and F3-4 with an AUC of 0.69, for FPA the AUC was 0.71 whereas C4M and FPA combined improved the AUC to 0.80.
Conclusion: The present findings suggest that degradation of basement membrane in the presence of decreased wound healing capacity is highly associated with fibrosis stage, inflammation and ballooning in early stage alcoholic steatohepatitis. Basement membrane damage in the absence of relevant wound heling may lead to increased fibrogenesis.

SAT-416
Transient elastography in normal pregnancies: A prospective cohort study

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Background and aims: Transient elastography is a valuable tool to detect liver fibrosis by estimation of liver stiffness. Results can be falsely high when blood flow to the liver is increased. A normal material of transient elastography results during a normal pregnancy, when blood flow from the abdomen is high in late stages is currently not available.
Method: We recruited 28 women with normal singleton pregnancies in a prospective cohort study. Women with an abnormal elastography result (> 7.9 kPa), signs of liver disease prior to conception or a BMI > 25 kg/m^2 at the first trimester were excluded. All women underwent transient elastography during the first, second and third trimester, and additionally three months postpartum. There were complete and reliable data from all four visits on 24 women on liver stiffness, this group was used as the analytical sample.
Results: Mean age at baseline was 30.6 years (SD 4.1), and mean BMI was 22.3 kg/m^2 (SD 1.9). 14 women (58%) were nulliparous. All

women underwent a normal pregnancy without signs of preeclampsia or gestational diabetes. Mean gestational length was 284 days (SD 7.1). Mean liver stiffness increased from 3.8 kPa during the first trimester to 5.9 kPa during the third trimester (p = 0.002). At the third trimester, 2 women (8%) had an elastography measurement of > 7.9 kPa. At the final examination, results were normalized (5.9 to 3.8 kPa, p = 0.002), with no woman with more than 7.9 kPa at elastography (Figure 1). Likewise, mean CAP increased from 186 dB/m in the first trimester to 215 dB/m in the third trimester (p = 0.01) and then fell postpartum (215 to 193 dB/m, p = 0.03). All pregnancies ended with normal results.

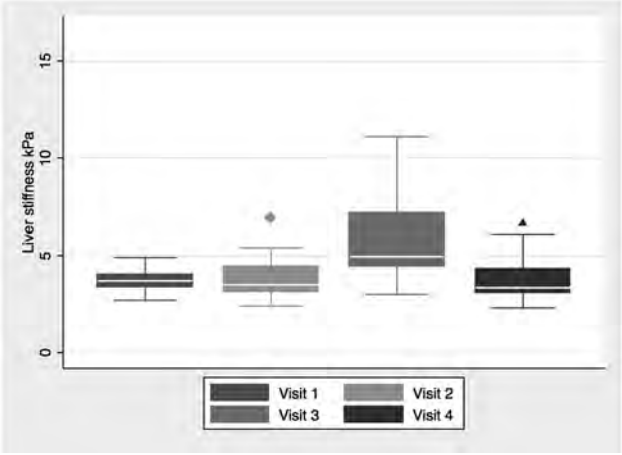

Figure 1. Results from transient elastography measurements in 24 normal pregnancies.

Conclusion: Transient elastography can be pathologic during the third trimester in normal pregnancies but slightly elevated levels can be considered a normal finding.

SAT-417

Serum levels of keratin 19 fragments (CYFRA 21-1) are elevated in advanced liver disease and predict poor survival

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Background and aims: Keratins (Ks) are tissue-specifically expressed proteins. Among them, K18 is produced in hepatocytes while K19, the most widely used ductular reaction (DR) marker, is found in cholangiocytes and progenitor cells of the liver. While the K18-based serum fragments M30/M65 are commonly used liver disease predictors, K19 fragments as detected via CYFRA 21-1 (fragments of cytokeratin 19) are established tumor markers but their usefulness in liver disease remains unknown. Therefore, we systematically evaluated K19 in different liver disease settings.
Method: Hepatic expression of DR markers was analyzed in liver biopsies of 63 patients with chronic liver disease. Serum CYFRA 21-1 levels were measured in: (i) 52 German alcohol misusers prior and after detoxification therapy, (ii) 280 German patients with decompensated cirrhosis, (iii) 231 French patients with alcoholic cirrhosis.
Results: Hepatic K19 levels were comparable in F0-F3 (no/intermediate fibrosis stages), but significantly increased in F4 (cirrhosis). Hepatic K19 mRNA correlated strongly with expression levels of other DR-specific keratins (i.e. K7/K23). In active alcohol misusers, CYFRA 21-1 levels were increased in patients with higher liver stiffness (i.e. LSM ≥ 15 kPa; a surrogate of advanced liver disease) compared to patients with LSM < 15 kPa (3.71 (2.20-4.53) vs. 1.42 (0.23-2.33) ng/ml, p = .002). Similar CYFRA 21-1 levels were seen before and after alcohol detoxification therapy (median duration 7 days). The strong correlation between both values (r = .744, p <.0001) indicated that CYFRA 21-1 constitutes a rather stable parameter. In patients with decompensated cirrhosis, serum CYFRA 21-1 predicted 90-day transplant-free survival (HR = 2.97 [1.92-4.60], p <.0001) and its diagnostic accuracy was comparable to the composite scores MELD and ACLF (AUROC 0.64, 0.70 and 0.68, respectively). CYFRA 21-1's usefulness was confirmed in patients with alcoholic cirrhosis, where elevated serum CYFRA 21-1 prognosticated liver-related death (HR = 2.59 [1.64-4.09], p <.001) and HCC occurrence (HR = 1.74 [1.02-296], p = .039).
Conclusion: Hepatic K19 and serum CYFRA 21-1 levels rise in cirrhotics. In the latter, increased CYFRA 21-1 levels associate with a poor prognosis. Hence, CYFRA 21-1 constitutes a novel, DR-related prognostic marker in advanced liver disease.

SAT-418

Splenic stiffness measurement using the ultrasound-fusion method

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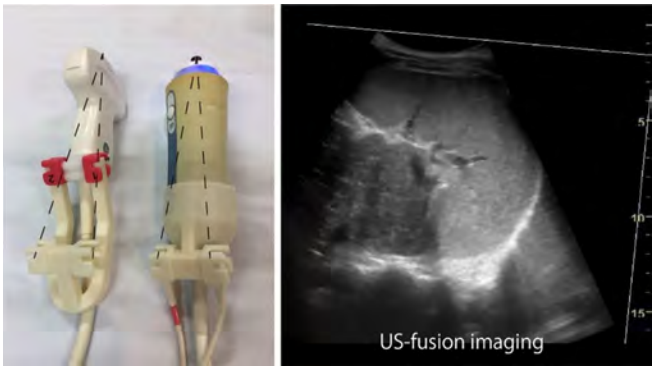
Background and aims: Recently, it has been recognized that spleen stiffness measurement can be used to stratify the degree of portal hypertension and rule out high-risk varices. However, performing spleen stiffness measurement adequately by transient elastography with A- and M-mode images is difficult. Thus, we developed a new method of transient elastography with B-mode images. We aimed to assess the diagnostic performance of spleen stiffness measurement using our method.
Method: We enrolled 60 patients (mean age, 66.9 ± 10.8 years; male: female, 42:18) and 18 healthy volunteers without hepatic venous pressure gradient measurements in this study and performed transient elastography and esophagogastroduodenoscopy. The hepatic venous pressure gradient was measured in patients with chronic liver disease. To perform transient elastography with virtual B-mode images using the ultrasound-fusion method, new attachments printed on a 3D-printer were used (shown as picture). Using these attachments, the distance between the top of the convex probe and the position sensors was made equivalent to the distance between the top of the transient elastography probe and sensors. First, the 3D-ultrasound volume was determined by scanning the spleen in a manual sweeping manner, using the convex probe with the new attachment and sensor, in the magnetic field. Second, the sensors were replaced with the transient elastography probe's attachment, and transient elastography was performed. The diagnostic accuracy in the presence and absence of the attachments was assessed.
Results: The median volume of the spleen was 170 ml (range 70-1727ml). The median success rates of transient elastography were 76.9% with the new attachment and 55.6% without the new attachment (p < 0.001). Especially in patients without splenomegaly (< 100 ml), the median success rates of transient elastography were 76.9% and 35.0% with and without the new attachment, respectively (p < 0.001). Correlation coefficients for spleen stiffness measurement

and hepatic venous pressure gradient were better with (r = 0.72, p = 0.007) than without (r = 0.62, p = 0.014) the new attachment. To predict ERV, the area under the receiver operator characteristic curve was 0.921 and 0.858 with and without the new attachment, respectively (p = 0.043). The positive likelihood ratios were 5.4% and 3.4% with and without the new attachment, respectively. Cut-off values of spleen stiffness measurement were 53.3 and 45.0 kPa with and without new attachment, respectively.



Conclusion: In conclusion, the spleen stiffness could be measured easily by virtual B-mode imaging using the new attachment. Moreover, the potential for ERV detection improved.

SAT-419

Endotrophin, a fragment of collagen type VI formation (PRO-C6) is associated with progression free survival and mortality in patients with hepatocellular carcinoma

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Background and aims: Hepatic fibrosis develops in response to chronic injury and is characterized by excessive accumulation of extracellular matrix (ECM) proteins. Injury may lead to cirrhosis and progress further to hepatocellular carcinoma (HCC). Small fragments of ECM proteins, known as neo-epitopes are generated during liver injury and released into the circulation. Collagen type VI (COL6) is known to be over-expressed in progressive fibrosis and cancer. PRO-C6 is a COL6 fragment which reflects formation of COL6 and was recently proposed to be a pro-fibrotic signaling molecule, endotrophin, that induces fibrosis directly through fibroblasts. We investigated PRO-C6 as a diagnostic and prognostic biomarker of HCC.
Method: PRO-C6 was measured in plasma from 86 biopsy-proven HCC patients, age and sex-matched cirrhotic (n = 86), non-cirrhotic HBV (n = 86) patients, and healthy controls (n = 86). Demographic data, liver parameters and AFP were gathered. The HCC patients were followed for up to 17-years after diagnosis. Progression free survival (PFS) were defined as time from diagnosis to objective tumour progression or death. Associations between PRO-C6 levels for progression and mortality in HCC patients was assessed by Kaplan-Meier and Cox Regression analysis.
Results: PRO-C6 was able to separate healthy controls, non-cirrhotics and cirrhotics from HCC patients (p < 0.0001, p < 0.0001 and p = 0.007 respectively). Within a 17-year follow-up period, seventy-five (75%) of 82 patients experienced disease progression. PRO-C6 levels above the median was significantly associated with PFS time (p = 0.011), whereas AFP was borderline significant (p = 0.051). PRO-C6 was included in the final model for prediction of whether the patient had an event (HR [95% CI]; 1.06 [1.01-1.11], p = 0.020). Both PRO-C6 and AFP were significantly associated with overall survival (p = 0.003 and p = 0.006, respectively), and both were included in the final model for prediction of mortality (PRO-C6: HR [95% CI]; 1.08 [1.02-1.13], p = 0.007; AFP: HR [95% CI]; 1.00 [1.00-1.00], p = 0.017).
Conclusion: The novel biomarker PRO-C6 was shown to be a marker of disease severity in patients with hepatic fibrosis and HCC. PRO-C6 was independently associated with progression and overall survival, superior to AFP. The role of PRO-C6 and its potential as a prognostic biomarker for HCC should be further investigated, as well as the role of Endotrophin in hepatic fibrosis progression and conversion into HCC.

SAT-420

The value of liver stiffness to platelet ratio and liver stiffness to spleen diameter to platelet ratio score compared with hepatic venous pressure gradient to predict the portal hypertension in patients with alcoholic and viral cirrhosis

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Background and aims: The hepatic venous pressure gradient (HVPG) well reflects portal hypertension but its measurement is relatively invasive. Transient elastography (TE) is a non-invasive method for evaluating liver stiffness (LS), but the readings are higher in those with alcoholic than viral liver cirrhosis, rendering it difficult to predict the HVPG.. Here, we explored whether the HVPG could be deduced from the LS to platelet ratio (LPR) and the LS to spleen diameter-to platelet ratio score (LSPS) in patients with alcoholic and viral liver cirrhosis.
Method: Between January 2008 and March 2017, 556 patients who underwent HVPG and TE were consecutively enrolled at three Korean tertiary medical centers. HVPG and TE were performed within 1-month intervals. The causes of liver cirrhosis, and the cutoffs of TE, the LPR, and the LSPS were analyzed for all patients.
Results: All non-invasive methods for evaluating LS afforded significantly lower sensitivities and specificities when the HVPG value was ≥ 16mmHg; this was also true of the LPR and LSPS. However, at HVPG values ≥ 6, ≥ 10, and > 12mmHg, the cutoffs facilitated estimation of HVPG values. Unlike what was found using TE, when the LPR and LSPS were used to calculate cutoffs, these were significant in patients with viral liver cirrhosis (for HVPG values ≥ 6, ≥ 10, and > 12 mmHg; all TE cutoffs were 18.0; but were 0.09, 0.32, and 0.40, respectively, for the LPR, and 1.04, 4.47, and 4.65 for the LSPS).
Conclusion: TE, LPR, and LSPS usefully predicted HVPG levels except when the HVPG was > 16 mmHg. HVPG estimation via the LPR and LSPS was useful for patients with either viral or alcoholic liver cirrhosis; this was not true of TE.

SAT-421

A novel score to select patients for treatment in chronic hepatitis B: Results from a large Ethiopian cohort

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Background and aims: Modern treatment guidelines for chronic hepatitis B (CHB) require viral load measurement and liver fibrosis assessment to determine treatment eligibility, but such tools are rarely available in low- and middle-income countries. Recently, a simple score (TREAT-B), based on alanine aminotransferase (ALT) and hepatitis B e-antigen (HBeAg), was suggested as an alternative tool to determine treatment eligibility in resource-limited settings. The aim of the present study was to evaluate the diagnostic performance of TREAT-B in a large cohort of CHB patients in Ethiopia.
Method: Out of 1303 CHB patients enrolled at a public hospital in Addis Ababa, 964 treatment-naïve patients aged 18 years and older were included in this analysis. Patients with hepatitis C/D and HIV co-infections, hepatocellular carcinoma, pregnancy or decompensated cirrhosis were excluded. All patients underwent a standardized evaluation at recruitment, including blood tests and transient elastography (Fibroscan 402, Echosense, France). The most recent guidelines from the European Association for the Study of the Liver (EASL) was considered the "gold standard," using a Fibroscan result > 7.9 kPa to define significant fibrosis and > 9.9 kPa to define cirrhosis. The diagnostic accuracy of the TREAT-B score was estimated by calculating the area under the receiver operating characteristics curve (AUROC). A TREAT-B score of 2 and above (HBeAg positive and ALT ≥ 20 U/L, or HBeAg negative and ALT ≥ 40 U/L) was used as the treatment threshold.
Results: One-hundred-and-ninety-seven patients (20.4%) were eligible for treatment based on the EASL 2017 guidelines and 220 (22.8%) based on the TREAT-B score. The AUROC of the TREAT-B score was 0.72 (95% confidence interval 0.68-0.77), yielding a sensitivity, specificity, positive predictive value and negative predictive value of 52.8, 84.9, 47.3 and 87.5%, respectively. By applying a TREAT-B score of 3 and above to determine treatment eligibility, the specificity increased to 97.0% but at the cost of a reduced sensitivity at only 26.9%.

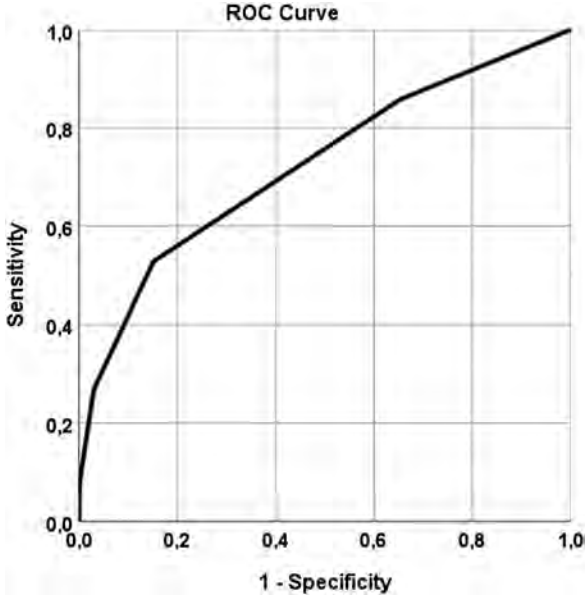

Figure: Receiver operating curve for TREAT-B to determine treatment eligibility in patients with chronic hepatitis B in Ethiopia

Conclusion: The performance of the TREAT-B score was only modest in a large CHB cohort in Ethiopia.

SAT-423

Spleen extracellular volume fraction and platelet count/spleen volume ratio are accurate non-invasive markers of portal hypertension

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Background and aims: Non-invasive markers of portal hypertension are needed. In portal hypertension, splenic venous congestion and fibrosis may increase splenic extracellular water content. Whilst a magnetic resonance imaging (MRI) measure of total spleen water content, spleen cT1, correlates with hepatic venous pressure gradient (HVPG, r = 0.68), specific measures of splenic extracellular water content have not been tested. This multicentre study explores markers of portal hypertension including splenic extracellular fluid volume fraction (ECV).
Method: Twenty healthy volunteers and 122 patients with cirrhosis of mixed aetiologies had spleen MRI with gadoxetic acid contrast and blood assessment. All patients with cirrhosis had endoscopy within median 31 days (IQR 12-93) of MRI. Portal hypertension was defined as the presence of varices, ascites or HVPG > 5 mmHg. MRI was analysed for spleen ECV, native T1, native cT1 and size. Spleen ECV was calculated as (1-haematocrit)*ΔR1spleen/ΔR1blood, where ΔR1 = 1/T1native-1/T1post gadoxetic acid. Diagnostic accuracy for portal hypertension was assessed by area under the receiver operator curve (AUROC).

Table 1: Diagnostic accuracy of non-invasive markers for the identification of portal hypertension in 122 patients with cirrhosis

	AUROC (95% CI)	p	Cut off	Sensitivity (%)	Specificity (%)
Candidate MR markers					
Spleen ECV	0.79 (0.71-0.87)	< 0.001	0.36	78	72
Native spleen T1 (ms)	0.71 (0.62-0.80)	< 0.001	1332	63	79
Native spleen cT1 (ms)	0.73 (0.63-0.82)	< 0.001	1274	73	73
Spleen volume (ml)	0.77 (0.69-0.86)	< 0.001	480	77	67
Platelet/spleen volume ($x10^9$/l/ml)	0.79 (0.71-0.87)	< 0.001	0.28	74	71
Platelets ($x10^9$/l)	0.73 (0.64-0.81)	< 0.001	117	55	84
Spleen diameter (mm)	0.74 (0.65-0.83)	< 0.001	152	58	82
Platelet/spleen diameter ($x10^9$/l/mm)	0.76 (0.68-0.85)	< 0.001	0.71	53	94

Abbreviations: AUROC, area under the receiver operator curve; ECV, extracellular volume fraction.

Results: Patients had median age 61 years, 78% were male and 65% had portal hypertension. Healthy volunteers had median age 56 years and 60% were male. Median spleen ECV was higher with portal hypertension (0.402 (IQR 0.364-0.457)) than without (0.343 (IQR 0.319-0.368), p < 0.001) in patients with cirrhosis, and similar between healthy subjects (0.338 (IQR 0.324-0.352)) and patients with cirrhosis without portal hypertension (p = 0.302). In patients

with cirrhosis, spleen ECV and platelet/spleen volume ratio identified portal hypertension with the highest accuracy (AUROC 0.79 each, table 1) of all measures tested.
Conclusion: Spleen ECV and platelet/spleen volume ratio can identify portal hypertension accurately and non-invasively.

SAT-424

Spleen transient elastography and suprahepatic vein dumping index can be useful to identify patients without acute and chronic response to beta-blockers

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Background and aims: Monitoring of acute (AR) or chronic (CR) response to beta-blockers in patients with liver cirrhosis is based on the measurement of the hepatic venous pressure gradient (HVPG). Our aim was to evaluate AR and CR to beta blockers with non-invasive techniques.
Method: Prospective observational study. Consecutive patients with indication of primary or secondary prophylaxis of variceal bleeding were included. Patients with multicentric hepatocellular carcinoma, complete portal vein thrombosis, active alcohol consumption or active viral hepatitis were excluded. AR (> or equal 10% decrease in HVPG after e.v. propranolol) and CR (> or equal 20% or GPVH < 12mmHg after 3 months of treatment) were evaluated. Baseline and after AR and CR hepatosplenic measurements of transient elastography (TE) and ARFI and Doppler ultrasound with contrast were obtained.

	Baseline measurements (n = 41)
HVPG (mmHg)	17 (6)
Righ atrial pressure (mmHg)	3.9 (2.6)
Inferior cava vein pressure (mmHg)	7.5 (3.5)
Free suprahepatic vein pressure (mmHg)	9.2 (4.7)
Wedge suprahepatic vein pressure (mmHg)	25.9 (6.6)
SBP/DBP (mmHg)	136.3/76.3 (24.5/12.5)
HR (bpm)	74.3 (9)
Liver TE (KPa)	38.3 (18.6)
Spleen TE (KPa)	65.0 (19.4)
Liver ARFI (m/s)	2.7 (0.7)
Spleen ARFI	3.3 (0.5)
Portal vein diameter (mm)	13.1 (2.6)
Portal vein speed (cm/s)	19.3 (5.3)
Hepatic artery speed (cm/s)	74.2 (40.0)
Resistance index	0.7 (0.2)
Suprahepatic contrast wash time (s)	21.6 (6.6)
Dumping index (> 0.6) (n;%)	16 (42.1%)

Results: From June 2015 to May 2018, 55 patients (14 with exclusion criteria) were included. We analyzed 41 patients, mean age 57 (SD8), 82.9% males, alcohol 43.9%, Child A/B/C 78%/17.1%/4.9% and 87.8% on primary prophylaxis. In all AR was performed and in 68.3% (CI 55%-85%) was positive. The CR was performed in 30 (73.2%) and was positive in 36.7% (CI18%-55%). The baseline measurements are shown in Table 1. Basal measurements related significantly with AR were: spleen TE (STE) (responders (R) 58.4 (SD 23.0) KPa vs non-responders (NR) 75 (SD0) KPa; p = 0.04) and suprahepatic vein dumping index (SHVDI) (> 0.6 greater flattening) (R30.8% vsNR63.6%, p = 0.06), and with CR, the STE (R58.1 (SD21.4) KPavsNR73.2 (SD5.5) KPa; p = 0.02) and SHVDI (R18.2% vs NR58.8%, p = 0.03). A STE > or equal to 74KPa showed 100% sensitivity and 60% specificity for AR, and 88% sensitivity and 70% specificity for CR (AUC 0.8 and 0.8). The SHVDI (> 0.6) showed an AUC of 0.7 in AR and 0.8 in CR. AR was not observed in 6 (66.7%) vs 3 (33.3), p = 0.01 patients with STE > or equal to 74KPa and SHVDI > 0.6. CR was not observed in 9 (100%) vs 0 (0%), p = 0.03 patients with STE > or equal to 74KPa and SHVDI > 0.6.
Conclusion: STE and SHVDI identify a subgroup of patients without AR or CR to beta-blockers.

SAT-425

Serum metabolites as diagnostic biomarkers for cholangiocarcinoma, hepatocellular carcinoma and primary sclerosing cholangitis

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Background and aims: Early and differential diagnosis of intrahepatic cholangiocarcinoma (iCCA) and hepatocellular carcinoma (HCC) by non-invasive methods represents a current clinical challenge. The analysis of low-molecular weight metabolites by new high-throughput techniques is a novel strategy for identifying biomarkers. Here, we have investigated whether serum metabolome can provide useful biomarkers in the diagnosis of iCCA and HCC and could discriminate iCCA from HCC. Since primary sclerosing cholangitis (PSC) is a risk factor for CCA, serum metabolomic profiles of PSC and CCA have also been compared.
Method: Chloroform/methanol and methanol extracts obtained from the serum of patients with PSC, iCCA, or HCC and healthy individuals were analyzed using ultra-performance liquid chromatography coupled to mass spectrometry (UHPLC-MS).
Results: The analysis of the levels of lipids and amino acids in the serum of patients with iCCA, HCC, PSC and healthy individuals (n = 20/group) showed differential profiles. Several metabolites presented high diagnostic value for iCCA vs control, HCC vs control, and PSC vs control, with areas under the receiver operating characteristic curve (AUC) greater than those found in serum for the non-specific tumor markers carbohydrate antigen 19-9 (CA19-9) and alpha-fetoprotein (AFP), commonly used to help in the diagnosis of iCCA and HCC, respectively. The development of an algorithm combining glycine, aspartic acid, SM (42:3) and SM (43:2) permitted to accurately differentiate in the diagnosis of both types of tumors (biopsy-proven). The proposed model yielded 0.890 AUC, 75% sensitivity and 90% specificity. Another algorithm by combination of PC (34:3) and histidine accurately permitted to differentiate PSC from iCCA, with an AUC of 0.990, 100% sensitivity and 70% specificity. These results were validated in independent cohorts of 14-15 patients per group and compared with profiles found in NAFLD/NASH patients.

Conclusion: Specific changes in serum concentrations of certain metabolites are useful to differentiate iCCA from HCC or PSC, and could help in the early diagnosis of these diseases.

SAT-426

Abnormal liver function tests: Current waiting times and comparison to iLFTs

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Background and aims: At present patients referred to secondary care with abnormal LFTs are seen at a nurse-led pre-assessment clinic, where a serological liver screen and Fibroscan are performed. They are then discussed at a Multi-Disciplinary Team (MDT) meeting and discharged or appointed to a consultant-led clinic. "Intelligent Liver Function Tests" (iLFTs) provide a diagnostic pathway, stratifying referrals to primary or secondary care. If referrers provide data on alcohol intake, BMI and comorbidities, those with abnormal LFTs have reflex tests without further venepuncture or clinical interview. We aimed to identify how long the current process takes, and how iLFTs could impact this.
Method: A retrospective analysis of 135 cases discussed at MDT from February-August 2018 was performed. Time from abnormal LFTs to referral; and times from referral to completion of serological liver screen and discussion at MDT were recorded. The diagnosis recorded at MDT was compared to the diagnosis and outcome had iLFTs been used.
Results: 93 of the 135 patients were referred due to abnormal LFTs. Figure 1 shows the timescales involved. The median time from identifying deranged LFTs to referral was 15 days (range 1-32). The median time from referral to completion of liver screen was 83 days (range 0-264). The median time to MDT discussion was 95 days (range 23273).
6 patients did not attend pre-assessment. 3 (50%) did not require referral if the iLFT protocol was followed.
37 patients (39.9%) were discharged by the MDT. MDT diagnosis matched iLFTs diagnosis in 30 cases (81%). 23 patients (24.7%) would not have been referred if iLFTs were used.
50 patients were referred for review at a consultant clinic. In 41 cases (82%), the diagnosis proposed at MDT was the same if the GP had used iLFTs. Only 2 (2.1%) patients would not have been referred if iLFTs had been used: one diagnosed as NAFLD with low fibrosis risk, and one with NAFLD with F3 fibrosis whom iLFTs would have diagnosed as ARLD with low fibrosis risk.

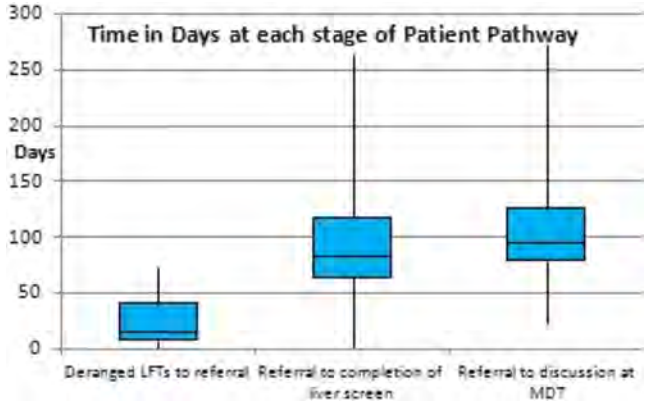

Figure: Duration of each stage of the pathway

Conclusion: iLFTs rapidly and safely identify patients with elevated liver enzymes requiring referral to secondary care. If iLFTs were used by referrers, the time to completion of the liver screen would be reduced by 83 days on average. In addition 24.7% of patients would not require referral to secondary care. This represents a substantial cost saving in terms of clinic appointments and unnecessary investigations.

SAT-427

The role of liver and spleen stiffness measurement in predicting hepatic decompensation after HCV eradication with direct antiviral agents therapy

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Background and aims: To date few evidences are available on the risk of hepatic decompensation (HD) related to portal hypertension (PH) after therapy with new direct-acting antivirals (DAAs) in patients with HCV-related advanced chronic liver disease (ACLD). Furthermore, the predictive role of non-invasive markers of PH, such as liver (LSM) and spleen (SSM) stiffness measurement after DAA therapy is still debated and should be clarified. We previously reported that SSM ≥ 54 kPa was able to predict HD in untreated HCV patients, better than LSM. Our aim was to assess the role LSM and SSM in HD prediction after sustained virologic response (SVR).
Method: A cohort study in 146 ACLD patients treated with DAAs and with available LSM and SSM both before and 6 months after end-of treatment (EOT) was performed in our centre. Patients were prospectively followed up from EOT and PH related events were registered. Time-dependent models for HD prediction after SVR were applied to account for changes in LSM and SSM after DAA therapy.

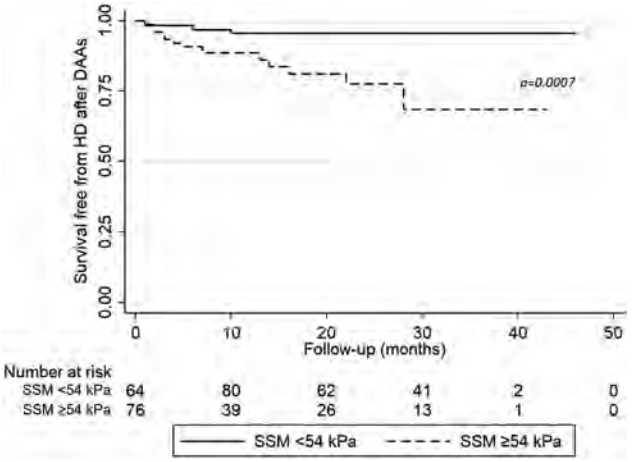

Figure 1: Kaplan Meier HD-free survival curves by SSM cut-off (54 kPa) after time-dependent predictive modelling.

Results: During a follow-up of 33, 5 months a total of 20 (13.7%) patients developed at least one episode of HD (among these, 3 presented a second HD event). The first decompensating event was ascites in the majority (17/20, 85%) of patients. Three patients developed a second episode of HD. Besides HD development, 18 (12.3%) patients developed hepatocellular carcinoma after DAA therapy; 3 (2.1%) developed portal vein thrombosis, 4 (2.7%) underwent high-bleeding risk varices prophylaxes, 3 (2.1%) underwent liver transplantation and 7 (4.8%) patients died. At the multivariate analysis, previous HD (HR, 8.065; 95%CI 2.806-23.180)

and SSM ≥ 54 kPa (HR, 4.678; 95%IC 1.307-16.744) were independently associated with a higher risk of HD development after DAAs treatment. Kaplan-Meier curves were estimated and drawn by the SSM cut-off of 54 kPa (Figure 1); in term of survival, the difference between the two curves was statistically significant (p = 0.0007). The time-dependent model including SSM values at baseline and at 6 months after EOT predicted post-SVR HD development better than the models including LSM and its changes after therapy.
Conclusion: SSM is confirmed to be an accurate surrogate of portal hypertension also after SVR achieved with DAA therapy. Moreover, SSM is able to stratify for the risk of HD development after DAA therapy more accurately than LSM.

SAT-428
Prediction of liver stiffness by serum indexes in HCV-infected patients with or without HIV coinfection
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Background and aims: Assessment of liver stiffness (LS) prior to therapy is recommended in HCV-infected patients, mainly with the aim of identify those with advanced fibrosis/cirrhosis. As transient elastography (TE) is not available in all settings, this could be a barrier for achieving the goal of HCV elimination. Our aim was to analyse the diagnostic accuracy of serum indexes for the prediction of liver stiffness.
Method: Cross-sectional retrospective study conducted in 6 hospitals and a prison program of health in Spain (2017-2018). Patients were included provided they met the following inclusion criteria: a) Chronic hepatitis C (with or without HIV infection); b) Undergoing a LS assessment by TE as part of pre-treatment evaluation; and c) Availability of routine blood test by the time of TE examination. Liver cirrhosis was diagnosed by a LS ≥ 12.5 kPa and advanced fibrosis was considered if LS was ≥ 9.5 kPa. The predictive accuracy of APRI and FIB4 indexes was assessed by means of AUROC curves and the diagnostic accuracy was determined by estimating the sensitivity, specificity and the negative (NPV) and positive (PPV) predictive values.
Results: 1391 patients (25% HIV-coinfected; 53% previous injection drug users; 13% incarcerated) were included. Median (Q1-Q3) time between blood test and TE was 0 (−4; +4) days. 557 (40%) patients had a LS ≥ 9.5 kPa and 351 (25%) patients had a LS ≥ 12.5 kPa. The AUROC (95% CI) for APRI and FIB for predicting a LS ≥ 12.5 kPa was 0.83 (0.81-0.85) and 0.84 (0.82-0.87), respectively. The respective figures for predicting a LS ≥ 9.5 kPa were 0.78 (0.76-0.81) and 0.79 (0.77-0.82). APRI < 0.5, present in 595 (43%) individuals, had a 95% NPV for excluding cirrhosis. The combination of a FIB4 < 1.45 with an APRI < 0.5, present in 467 (34%) patients, had an 87% NPV for excluding a LS ≥ 9.5 kPa. The combination of APRI > 2 with FIB4 > 3.25, present in 134 (10%) patients, had an 89% PPV for a LS ≥ 9.5 kPa. Globally, this approach could avoid the need of TE in 53% patients, with only 5% of cirrhotic patients incorrectly classified as non-cirrhotic. Accuracy of the proposed cut-off values was not influenced by HIV-coinfection.
Conclusion: Simple serum indexes confidently identify the absence of cirrhosis and the presence of advanced fibrosis in HCV infected patients with or without HIV. Our diagnostic approach could avoid the need for TE assessment prior to starting therapy in a half of the patients. As HIV coinfection does not impact on the diagnostic yield of serum indexes, the same algorithm can be adopted when evaluating these patients.

SAT-429
Von Willebrand factor a non-invasive serum biomarker of portal pressure in cirrhosis: Evidence in human and rodent
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Background and aims: Endothelial dysfunction and inflammation-associated markers has been shown to correlate significantly with portal pressure and the increase level of them is associated with poor outcomes in patients with cirrhosis. However, there is still no evidence on whether these serum biomarkers correlate with portal pressure in cirrhotic experimental animal models. Therefore, we aimed to assess the correlation between serum biomarkers and portal pressure in both cirrhotic patients and rodents.
Method: This prospective multicenter trial (ClinicalTrials.gov ID: NCT03713606) included cirrhosis patients scheduled to undergo transjugular hepatic venous pressure gradient (HVPG) measurement in 4 centers of China between September 2018 and November 2018. Plasma levels of the nineteen serum biomarkers (Fas, VCAM-1, von Willebrand Factor [vWF], heat shock protein 70 [HSP70], sCD163, T cell immunoglobulin and mucin domain-3 [TIM-3], CD28, CD137, CD27, CD152, herpesvirus entry mediator, indoleamine 2, 3-dioxygenase [IDO], lymphocyte-activation gene 3, B and T lymphocyte attenuator, glucocorticoid-induced tumor necrosis factor receptor [GITR], CD80, PD-1, PD-L1, and PD-L2) that were previously reported to associate with liver cirrhosis in other studies were detected. The correlation between HVPG and the abovementioned markers was analyzed. For the animal experimental study, plasma levels of VCAM-1, vWF, and HSP70 were detected in cirrhotic rats and mice (n = 78 and 37, respectively) induced by carbon tetrachloride to study the correlation with portal venous pressure (PVP).
Results: A total of 74 eligible patients with cirrhosis were recruited with 40 of them were HBV-related cirrhosis patients. There were significant correlations between HVPG and VCAM-1, vWF, HSP70, TIM-3, CD28, CD137, CD152, IDO, GITR, CD80, and PD-L2 (all p < 0.05). Notably, in HBV-related cirrhosis sub-group, vWF had the strongest correlation with HVPG (r = 0.571, p < 0.001) (Figure 1A) among the 19 biomarkers. Additionally, in cirrhotic rodent animal models, only vWF presented a significant correlation with PVP in rats and mice groups (r = 0.608 and 0.405, respectively, both p < 0.001) (Figure 1B and 1C). Besides, the expressions of vWF in cirrhotic liver tissue were obviously higher than that of the healthy tissues of rats and mice (Figure 1D).

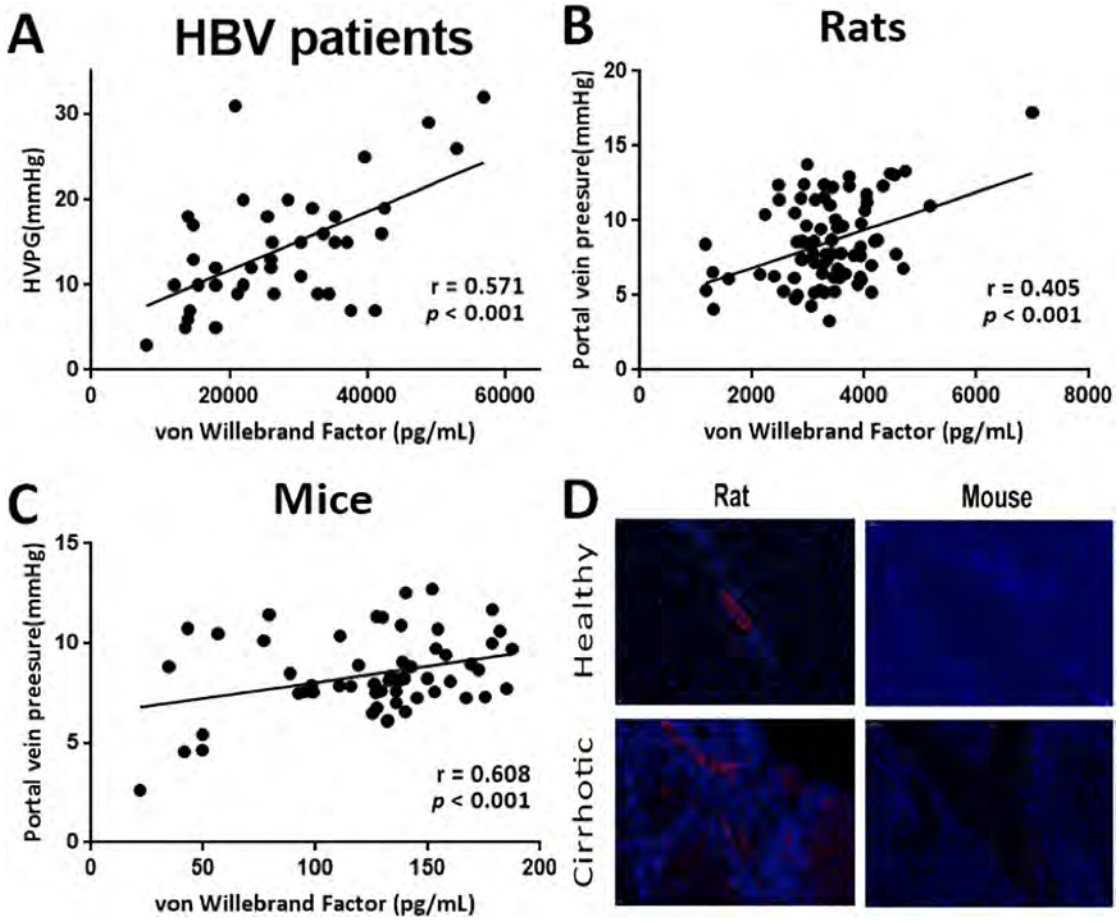

Figure: (abstract:SAT-429)

Conclusion: vWF had the potential to serve as a non-invasive cross-species predictor for diagnosis and monitoring of portal pressure in cirrhosis.

SAT-430

Spleen stiffness measured with ElastPQ point shear wave elastography has a good performance in predicting clinically significant portal hypertension in patients with primary sclerosing cholangitis

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Background and aims: Large efforts have been made to identify non-invasive surrogates as markers of clinically significant portal hypertension (CSPH), defined as the presence of gastro-oesophageal varices on upper endoscopy. The correlation of spleen stiffness measurement (SSM) with portal hypertension (PH) as measured by hepatic venous pressure gradient has been reported, but data regarding its reliability are still controversial. We assessed the performance of liver stiffness measurement (LSM) and SSM as performed by point-shear wave elastography (pSWE) in detecting the presence of CSPH in primary sclerosing cholangitis (PSC).

Method: Predictors of CSPH were investigated in 46 PSC patients who underwent an upper-GI endoscopy within 12 months of the elastographic assessment. Demographics, biochemistry and ultrasonographic data were prospectively collected. Fibroscan transient elastography (F-TE), liver and spleen pSWE were obtained on the visit date. Receiver operating characteristics (ROC) curves were constructed to establish the performance of elastographic techniques in predicting CSPH.

Results: Mean age 47 ± 16y, 74% male, CSPH was detected in 18 cases (1 at high-risk of bleeding). Variables significantly associated with CSPH on univariate analysis were: cirrhosis, Child-Pugh, MELD and Mayo risk score, spleen area and length, platelet, albumin, bilirubin, AST, GGT, INR, F-TE, liver and spleen ElastPQ, LSPS (LSM*spleen diameter/platelet). SSM remained the only independent predictor of CSPH on multivariate models (OR 1.13; 95% CI 1.02-1.25; p < 0.025). F-TE and ElastPQ LSM showed a good performance [AUROC, 95%CI, Sensitivity (Se) and Specificity (Sp)]: 0.82, 0.68-0.96, 92% and 64%, and 0.83, 0.70-0.97, 92% and 68%, respectively. Best cut-off was 18.5 and 21.1 kPa, respectively. However, Sp was < 70% for both tests. ElastPQ SSM showed a better performance in predicting OVs (0.87, 0.76-0.99, 92% and 77%), cut-off 40.2 kPa. However, the best diagnostic performance was obtained by combining ElastPQ SSM, spleen diameter and platelet count (0.92, 0.83-1.00, 92% and 81%) which was better than LSPS (0.90, 0.81-0.99, 94% and 67%) (**Fig1**). ElastPQ SSM was superior to BavenoVI and Expanded BavenoVI criteria (Se 92%, for both; Sp 54% and 59%, respectively).

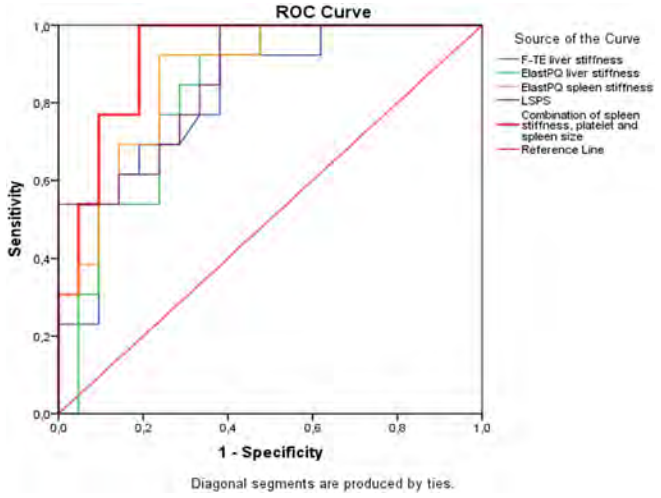

Figure 1: Receiver operating characteristic analysis of the ability of the non-invasive tests to predict the presence of oesophageal varices. Abbreviations: F-TE, transient elastography performed by Fibroscan; LSPS, liver stiffness X spleen diameter/platelet count.

Conclusion: We provide evidence that ElastPQ SSM, particularly in combination with spleen diameter and platelet count, can be used as a reliable tool for the non-invasive diagnosis of CSPH in patients with PSC.

SAT-431

Spleen stiffness measurement with ElastPQ point shear wave elastography has an excellent performance in predicting the presence of clinically significant portal hypertension in primary biliary cholangitis

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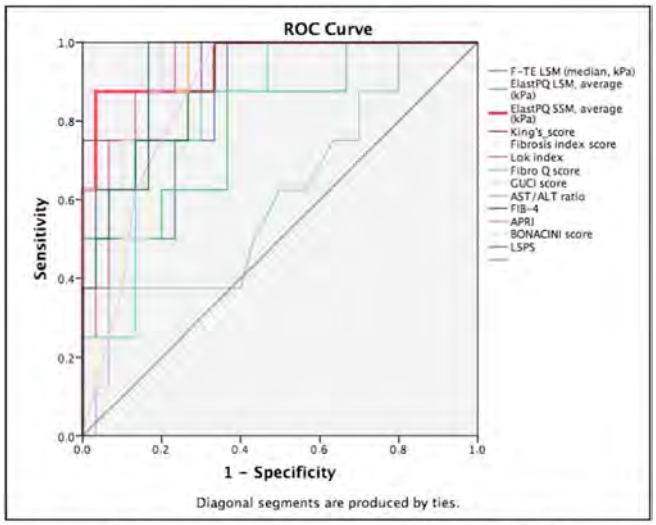
Background and aims: There is an ongoing effort to identify non-invasive surrogates for staging liver disease and detecting clinically significant portal hypertension (CSPH), defined as the presence of gastro-oesophageal varices on endoscopy. The correlation of spleen stiffness measurement (SSM) with portal hypertension measured by hepatic venous pressure gradient has been reported, but data regarding its reliability are controversial. We assessed the ability of liver stiffness measurement (LSM) and SSM performed by point-shear wave elastography (pSWE) to detect CSPH in primary biliary cholangitis (PBC).
Method: Predictors of CSPH were evaluated in 53 PBC patients who had an upper-GI endoscopy within 12 months of the elastographic assessment. Demographics, biochemical and ultrasonographic data were prospectively collected. Transient elastography (Fibroscan, Echosens) [F-TE], liver and spleen pSWE (ElastPQ, Philips Affiniti70G), and the most common clinical fibrosis scores were obtained. ROC curves were constructed to establish the performance of elastographic techniques and fibrosis scores in predicting CSPH.
Results: Mean age 57 ± 12 years, 91% female. OVs were detected in 12 (23%) cases (4 at high-risk of bleeding). Variables significantly associated with CSPH at univariate analysis were: diagnosis of cirrhosis, Child-Pugh, MELD and Mayo risk score, spleen area and longitudinal diameter, platelets, albumin, ALT, INR, F-TE, ElastPQ LSM and SSM, LSPS (LSM*spleen diameter/platelets). SSM remained the only independent predictor of CSPH in all the multivariate models (OR 1.101; 95%CI 1.14-1.20; p < 0.022). F-TE and ElastPQ LSM showed good AUROCs (95%CI): 0.85 (0.72-0.99) and 0.80 (0.62-0.98), with best cut-off 14.3 and 13.8 kPa, respectively. However, specificity (Sp) was < 70% for both tests. ElastPQ SSM showed the best performance in predicting CSPH (AUROC 0.95, 95%CI 0.87-1.00, sensitivity (Se) 88%, Sp 97%), with optimal cut-off 50.1 kPa (PPV 0.89, NPV 0.97), followed by GUCI, King's score and LSPS [AUROC (95%CI): 0.94 (0.87-1.00), 0.94 (0.85-1.00), 0.93 (0.85-1.00), respectively] (**Fig. 1**). In this cohort, the diagnostic performance of ElastPQ SSM in detecting CSPH was superior to the recently validated Baveno VI and Expanded Baveno VI criteria, which showed good Sp (77% and 87%, respectively) but low Se (67%, for both).



Abbreviations: F-TE, transient elastography performed by Fibroscan; LSM, liver stiffness measurement; SSM, spleen stiffness measurement; GUCI, Göteborg University Cirrhosis Index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index, AST to Platelet Ratio Index; LSPS, liver stiffness X spleen diameter/platelet count.

Figure 1: Receiver operating characteristic analysis of the ability of the non-invasive tests of liver fibrosis, liver and spleen elastography to predict the presence of oesophageal varices.

Conclusion: We provide evidence that transient elastography, in particular ElastPQ SSM, can be used as a reliable tool for the detection of CSPH in PBC.

SAT-432

The CT1 multi-parametric MRI value is more sensitive and reliable than transient elastography for the non-invasive monitoring of intra-hepatic inflammation/fibrosis response to DAA therapy in CHC patients

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Background and aims: The eradication of HCV infection is supposed to resolve intra-hepatic inflammation and to ameliorate fibrosis, metabolic alterations and steatosis. Nevertheless, accurate non-invasive methods for liver inflammation/fibrosis/steatosis quantification remain a major unmet need. We investigated the impact of DAAs on systemic metabolic alterations, liver inflammation/fibrosis and steatosis assessed by new multi-parametric magnetic resonance (MRI)

Method: 45 consecutive genotype 1b chronic hepatitis C patients (M: F = 22:23, median age 56 ± 28, 75; F0-F2:35; F3-F4:10) received 12-week PAR/OMB/DAS (41)or SOF+VEL (3)or SOF+LED (1) according to the Italian-Drug-Regulatory-Agency-criteria and were enrolled in an observational pilot study.Assessments at baseline (BL) and 6 months after end of treatment follow-up (FU) were: HCV-RNA, AST, ALT, GGT, p-glucose, Insulin, HOMA-index, total-cholesterol, LDL, HDL, triglycerides, Transient Elastography (TE, Fibroscan®);liver inflammation/fibrosis quantification [MRI (corrected T1, cT1) and steatosis (Proton Density Fat Fraction, PDFF) LiverMultiscan™, Perspectum Diagnostics, Oxford, UK]. Wilcoxon test was applied to analyse significant BL/FU modifications (significant if $p < 0.05$).
Results: All patients showed week-12-SVR.Significant reduction from BL to FU was observed for AST ($p < 0.01$), ALT ($p < 0.01$), GGT ($p < 0.01$), p-glucose ($p = 0.04$), HOMA ($p = 0.023$), TE ($p = 0.004$), cT1-MMR ($p = < 0.01$).On the contrary total-cholesterol ($p < 0.01$)and LDL ($p < 0.01$) increased. PDFF values remained stable ($p = 0.48$).Overall median cT1 values declined significantly from BL to FU [811 (663-1133) Vs 791 (652-960) $p < 0.01$]. cT1 values decline significantly in 35 patients ($p < 0.01$] in whom TE presents a significant decrease ($p = 0.002$). Whilst in 10 patients cT1 BL/FU increase significantly (0.005); in this subgroup TE does not change significantly ($p = 0.678$).Overall TE median levels showed a BL/FU significant reduction ($p = 0.004$). TE did not decrease (Δ BL/FU < 1 kPa) in 24 patients in whom cT1 declined significantly ($p = 0.008$).Their BL TE values were significantly lower than those of 21 patients with TE decline [4.8 (3.4-9.3) vs 9.2 (4.9-14) kPa, $P < 0.001$]. Overall TE and cT1 correlated at BL ($p = 0.032$ $r = 0.320$), but not at FU. ($p = 0.503$ $r = 0.104$)
Conclusion: Multi-parametric MRI cT1 appears more accurate than TE in detecting the reduction of liver inflammation/fibrosis after DAAs SVR, that shows a positive impact on glycemic profile but causes a significant increase of total cholesterol and LDL

SAT-433

Portal venous velocity and platelet count as a simple non-invasive tool to rule out the presence of varices needing treatment in patients with compensated cirrhosis

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Background and aims: Esophagogastroduodenoscopy (EGDS) is the main tool to evaluate the risk of bleeding in cirrhotic patients. Recently a combination of non-invasive methods (transient elastography and platelet count) has been proposed as a simple way to rule out the presence of varices needing treatment (VNT) in patients with liver cirrhosis. We investigated whether portal venous velocity (PVV) can predict the presence of VNT in patients with compensated liver cirrhosis.

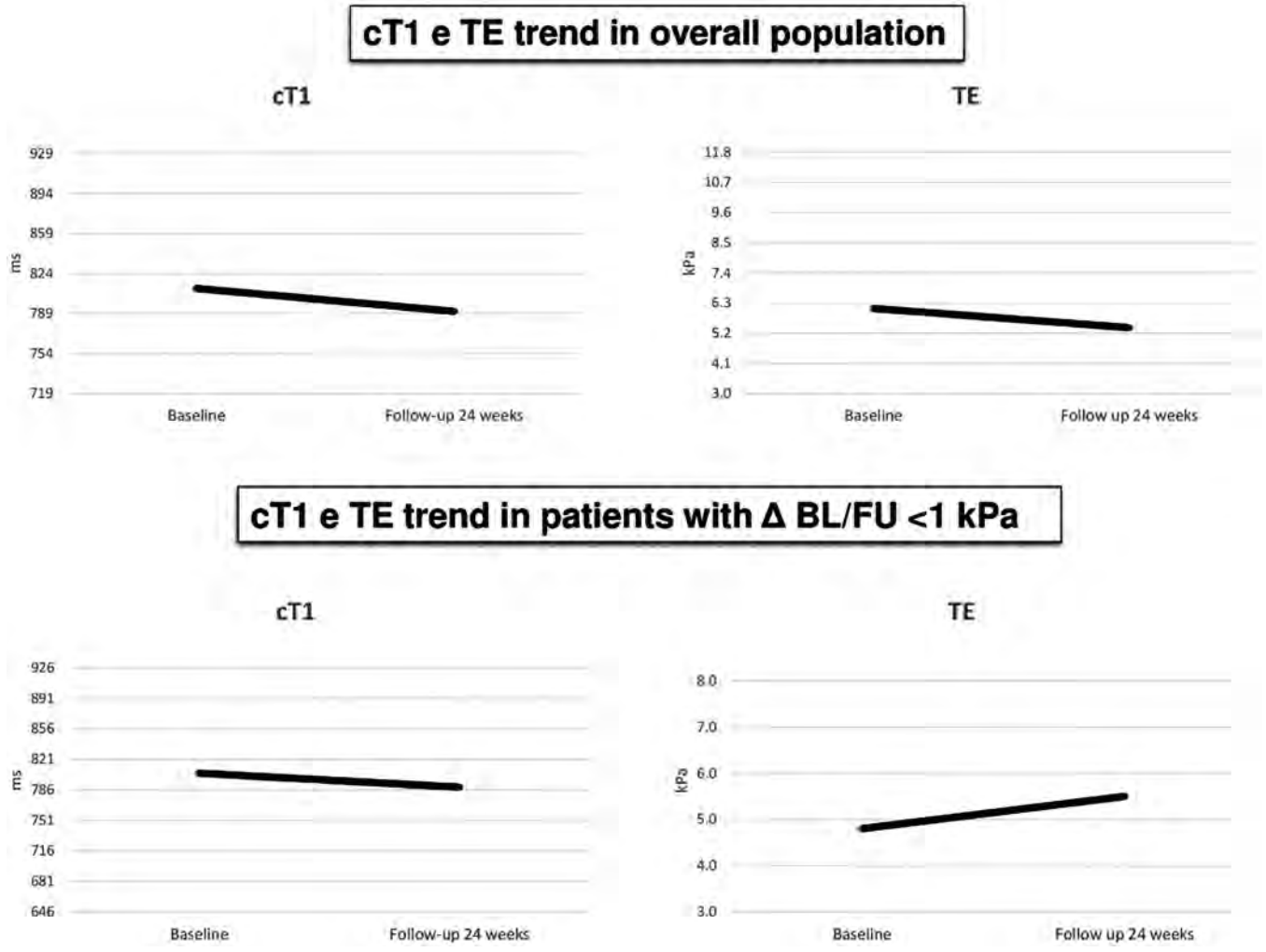

Figure: (abstract: SAT-432)

Method: We retrospectively assessed 246 patients (mean age 60.3, 77.6% males) with compensated liver cirrhosis who had EGDS performed within 6 months from a Doppler ultrasound examination of the portal system. Liver cirrhosis was virus-related in 128 (52%), alcohol-related in 52 (21.1%), NASH-related in 46 (18.7%) and multifactorial in 20 (8.1%). Portal venous velocity (PVV), estimated by Doppler ultrasound, was measured in cm/s. All EGDS and Doppler ultrasound examinations were performed by an expert hepatologist with at least 10 years of experience in a single tertiary center. We also measured platelet count within 6 months of Doppler examination.
Results: VNT were present in 46.6% of patients (122/246). No difference in age, sex and etiology were found between patients with or without varices. Patients with VNT had lower PVV (15.65 cm/s vs 23.53 cm/s; $p < 0.00001$) and lower platelet count (72, 000/cc vs 122, 000; $p < 0.00001$) compared to those without VNT. At logistic regression analysis, PVV ($p < 0.00001$) and platelet count ($p = 0.00001$) were significantly associated with the presence of VNT. Using ROC curves analysis, a cut-off levels of 20 cm/s for PVV and 125, 000 platelets had the highest predictive accuracy for the presence of VNT (AUROC: 0.82). In our cohort 49 of 246 (19.7%) patients met the above criteria (platelets count > 125000 and PPV > 20 cm/s) and none had VNT.
Conclusion: In the present study, a combination of PVV and platelet count measurement allowed to identify a subgroup of patients with compensated cirrhosis (approximately one fifth of the whole cohort) who may avoid undergoing EGDS with a 100% of accuracy. We speculate that a combination of PPV and transient elastometry could be an even better non-invasive tool to rule out the presence of VNT in compensated cirrhosis.

SAT-434

Liver stiffness measurement by transient elastography for the prognosis of hepatic carcinoma, decompensation, and death in patients with chronic liver diseases: A systematic review and meta analysis

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Background and aims: Liver stiffness measurement (LSM) by transient elastography (TE), a non-invasive method, has been assessed for the evaluation of clinical relevant outcomes in patients with chronic liver diseases (CLD) while with variable results. This systematic review and meta-analysis aims to study the relationship between baseline live stiffness (LS) measured by TE and the development of clinical relevant outcomes.
Method: The systematic review identified eligible cohorts reporting the association between baseline LSM by TE and risk of hepatic carcinoma (HCC), hepatic decompensation (HD), all-cause and/or liver-related mortality and liver-related events (LREs) in CLD patients. Summary relative risks (RRs) with 95% confidence intervals (CIs) were estimated using a random-effect model. The dose-response association was evaluated by generalized least squares trend estimation and restricted cubic splines. Commands of GLST, MKSPLINE, MVMETA were applied for statistical analysis.
Results: 62 observational cohort studies were included in the final analysis. Compared with the lowest category, subjects with a highest category of baseline LS were associated significantly with risk of HCC (n: 14 studies; RR: 5.31; 95%CI: 3.76-7.51), all-cause mortality (n: 8 studies; RR: 4.30; 95%CI: 2.85-6.50), HD (n: 11 studies; RR: 7.33; 95% CI: 3.84-14.00), or LREs (n: 11 studies; RR: 9.16; 95%CI: 4.14-20.30), thus suggesting for further dose-response analysis. For one kPa increment in baseline LS, the pooled RR (95%CI) was 1.08 (n: 16 studies; 95%CI: 1.05-1.11) for HCC, 1.08 (n: 7 studies; 95%CI: 1.06-1.11) for all-cause mortality, 1.11 (n: 6 studies; 95%CI: 1.05-1.17) for liver-related mortality, 1.08 (n: 17 studies; 95%CI: 1.06-1.10) for HD and 1.07 (n: 13 studies; 95%CI: 1.04-1.09) for LREs, respectively. Evidence of a non-linear association was found between baseline LS and HCC, all-cause mortality, HD, LREs as well as a composite of all these outcomes ($p < .05$). The non-linear dose-response meta-analysis showed that a significant increase in the risk of corresponding clinical relevant outcomes turned to a stable increase or a slight decrease with increasing baseline LS.
Conclusion: The dose-response meta analysis presents a combination between the levels of baseline LS and RRs for each clinical relevant outcome. TE, which is non-invasive, might be a novel strategy for risk stratification and identification of patients at high risk of developing these outcomes.

SAT-435

Quantitative MRCP imaging (MRCP+): Accuracy, repeatability and reproducibility evaluation in healthy and liver disease patients

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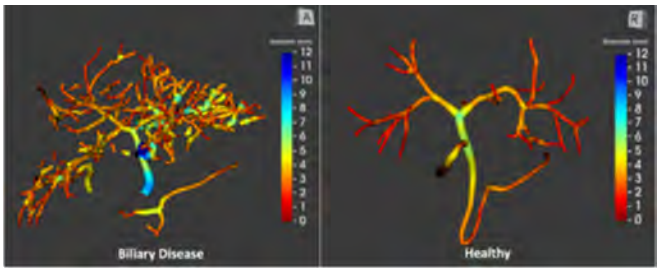
Background and aims: Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique for the evaluation of biliary disease. Despite its widespread use there remain limitations, including variable quality bile duct depiction and subjective assessment. We report the first, groundbreaking, application of quantitative MRCP imaging and demonstrate the robust performance profile for its application to a cohort of healthy and liver disease subjects.
Method: For *in vivo* performance assessment, liver disease patients (n = 10 biliary disease, n = 10 parenchymal disease) and health subjects (n = 20) were recruited for repeated heavily T2-weighted MRCP imaging on Siemens Prisma 3 T, Siemens Avantofit 1.5 T, GE Discover 3 T and GE Optima 1.5 T scanners, followed by processing with MRCP+, that combines multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms. Accuracy was assessed using digital synthetic 3D printed phantoms. Reference intervals were calculated for all reported metrics to inform interpretation.
Results: Performance profiles were demonstrated for tree volume (95% LoA for repeatability of –3.5-3.4 ml and reproducibility of –1.5-2.8 ml), gallbladder volume (95% LoA for repeatability of –9.4-4.4 ml and reproducibility of –8.0-12.0 ml), and duct diameter measures for the common hepatic (CBD), left-hepatic (LHBD), right hepatic (RHBD), pancreatic (PD) and cystic ducts (CD) with a CoV of 13%, representative. MRCP+ duct measurement accuracy was within ± 0.8 mm of ground-truth. Normal reference intervals were estimated at 1-9 ml and 7-40 ml for tree and gallbladder volumes, and 2.6-6.4 mm, 1.3-4.7 mm, 2.3-5.2 mm, 1.4-4.2 mm, 2.3-5.3 mm for CBD, CD, LHBD, PD and RHBD median diameter, respectively.



Conclusion: We report the inaugural assessment of biliary tree measures and performance profile charateristics determined using groundbreaking quantitative MRCP imaging. MRCP+ provides reliable measures with significant potential for applications in biliary disease diagnosis, stratification and monitoring in clinical practice.

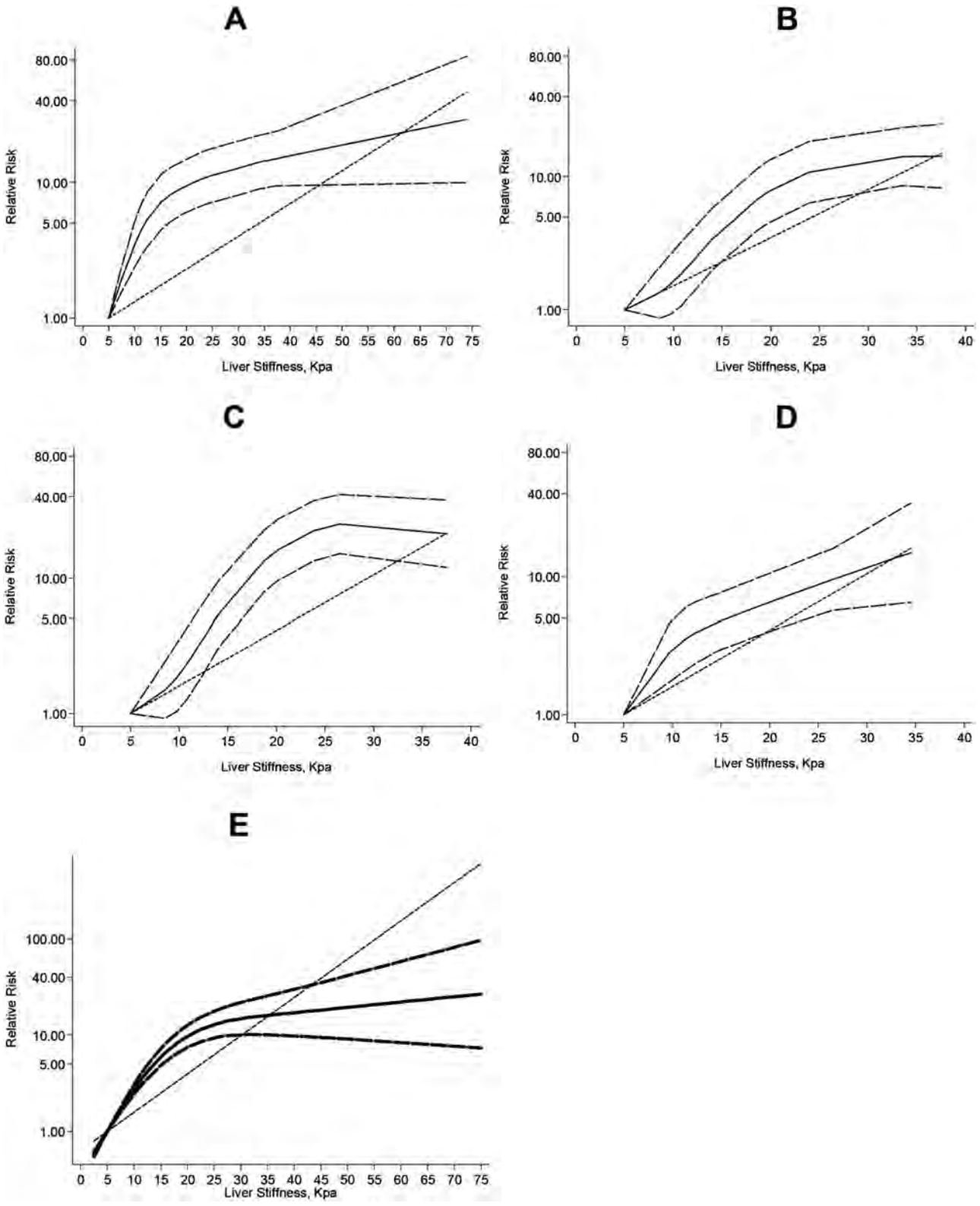


Figure: (abstract: SAT-434): Dose-Response Analysis. The dose-response relationship between baseline LS and risk of (A) hepatic carcinoma, (B) all-cause mortality, (C) hepatic decompensation, (D) liver-related events, (E) composite outcomes. The short dash line represents the linear relationship. The solid line and the long dash line represent the estimated RR and its 95% CI for the spline model. The value of 5 kPa served as referent.

Liver transplantation and hepatobiliary surgery: Experimental

SAT-436

Inhibition of autophagy prolongs recipient survival through accelerating CD8+ T-cell apoptosis in a rat liver transplantation model

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Background and aims: In liver transplantation (LT), acute rejection (AR) remains a common complication that significantly shortens recipient survival although various immunosuppressors have been used in clinical practice. In recent years, manipulating immune tolerance has been regarded as one of the promising solutions. Autophagy, an evolutionarily conserved protein degrading system, has been reported to be involved in the immune rejection and may become a target to establish immune tolerance. However, its role in AR after LT has not been elucidated.
Method: Human liver tissues from patients with AR and control individuals were obtained to evaluate autophagy specific protein LC3 expression. Acute rejection model was established in rats to analyze the exact role of autophagy in AR. In addition, the underlying mechanism of autophagy participated in AR were further explored by ex vivo study.
Results: The autophagy of $CD8^+$ T cell was strongly enhanced in patients with AR and autophagy level was positively correlated with the severity of rejection. Similar findings were observed in the acute rejection rat model. Furthermore, administration of autophagy inhibitor 3-methyladenine (3-MA) significantly prolonged graft survival through inhibiting autophagy of $CD8^+$ T cell, which resulted in decreased viability and function of $CD8^+$ T cell. In addition, inhibition of autophagy of activated CD8+ T cells largely reduced the stabilization of intact mitochondria and subsequently increased the production of mitochondrial superoxide (MitoSOX) in vitro.
Conclusion: We firstly showed inhibiting autophagy significantly prolongs liver allograft survival by accelerating apoptosis of CD8+ T cells, which will provide a novel strategy for immune tolerance induction.

SAT-437

An mTor-based immunosuppression reduces the antiviral efficacy of NS3/4A and NS5A inhibitors for HCV genotype 1b treatment in vitro

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Background and aims: With the approval of direct-acting antivirals (DAAs), the success of HCV therapy has been considerably improved. However, in the context of HCV therapy after LT, the influence of mTOR Inhibitors for immunosuppressive therapy (IS) after LT on the efficacy of DAAs is not thoroughly investigated.
Method: Subgenomic HCV replicons of different genotypes (GT) were treated with different IS (mTOR Inhibitors: Everolimus (EVR), Sirolimus (SRL); Calcineurin Inhibitors (CNI): Cyclosporin A, Tacrolimus) alone and in combination with Daclatasvir (DAC), Elbasvir (ELB), Ledipasvir (LDV), Simeprevir (SIM) and Grazoprevir (GRZ). The HCV replication activity was determined by qRT PCR (GT1b) or luciferase assay (GT2a/GT3a/GT4a).
Results: The combination of NS3/4A inhibitors with mTOR inhibitors does significantly reduce antiviral efficiency against HCV GT1b. The efficacy of the Protease Inhibitor (PI) GRZ, is reduced by 14% (EVR: $p \leq 0.05$) or 20% (SRL: $p \leq 0.005$), whereas mTOR inhibitors completely eliminate the antiviral effect of the PI SIM (EVR: $p \leq 0.005$; SRL: $p \leq 0.01$). The combination of NS5A inhibitors (DAC, ELB, LDV) with EVR or SRL also results in a 10-20% lower antiviral effect in GT1b compared to DAA treatment alone ($p \leq 0.05$). In contrast, HCV GT2a and 3a replication activity does significantly decrease upon combination of NS3/4A and NS5A inhibitors with EVR/SRL ($p \leq 0.01$). Upon administration of Calcineurin Inhibitors antiviral activity of DAAs was not compromised in either genotype.
Conclusion: The combination of an NS3/4A or NS5A inhibitor with an mTOR inhibitor-based IS leads to a significant reduction of DAA efficiency in GT1b, suggesting that post LT, IS should abandon mTOR inhibitors during antiviral treatment. In GT1b patients, CNI-based IS appears to be more suitable, whereas mTOR-based IS would be a rather beneficial treatment option in patients with GT2a or GT3a.

SAT-438

Effect of chondroitin sulfate in the rat liver cold ischemia and warm reperfusion injury

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Background and aims: Liver transplantation is the effective treatment for severe liver disease. The primary dysfunction and initial malfunction of the graft is related to the ischemia-reperfusion injury (IRI). IRI is characterized by an initial event of sinusoidal endothelial cell necrosis followed by a late phase of hepatocyte apoptosis. Strategies have been done to minimize cell death. We recently verified that chondroitin sulfate (CS) increased cell regeneration and decreased apoptosis in the bile duct ligation model. So, the aim was to investigate the effect of CS in the cold ischemia and warm reperfusion injury model.
Method: Wistar rats (6-8 weeks) were submitted to cold liver ischemia (4°C) in University of Wisconsin solution for 24h and warm reperfusion (37°C) with Krebs solution for 20 or 40 min. CS (120 mg/kg body weight) was added at ischemia (I) and/or reperfusion (R) period; none was added in the control. Liver viability was evaluated by glucose production, BSP clearance and bile secretion. Trypan blue-positive cells (necrosis) and apoptotic bodies were counted on hematoxylin–eosin stained liver slides. Cathepsin B (CB), catalase (CAT) and superoxide dismutase (SOD) activity were measured in liver homogenate. Nitric oxide (NO) was measured using NO analyzer (Sievers). Results were analyzed by GraphPad Prism and expressed as mean ± SEM.
Results: CS did not change all the liver viability parameters studied. In the 20 min-R groups, CS decreased (ANOVA, $p < 0.0001$) the number of necrotic cells (cells.$10^{-3}/\mu m^2$) when added in R (2.2 ± 0.1) or IR (2.2 ± 0.1), but not in I (3.2 ± 0.1) compared to the control group (2.6 ± 0.2). In the 40 min-R group, CS did not affect the necrosis level. In relation to apoptosis, we found more apoptotic bodies and an increased CB activity in the 40 min-R group when CS was added in the R compared to control and to the CS added to IR. We did not observe any difference in CAT and SOD activity level in all groups. However, CS decreased (ANOVA, $p = 0.0259$) the concentration of NO (µM) when added in the I (13.4 ± 0.8) compared to control group (17.5 ± 0.2).

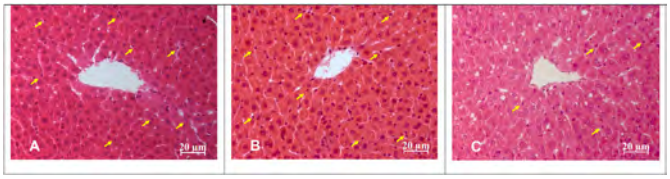

Figure: Hematoxylin-eosin liver specimens (40x total magnification) of control (A), Chondroitin sulfate added to ischemia (B) and to the reperfusion period (C).

Conclusion: Our data suggest that CS protects liver from necrosis in the early stage of IRI. However, at the late stage, it seems that CS did not have effect in relation to apoptosis.

SAT-439

Identification of new drug targets to prevent ischemia-induced bile toxicity using a human biliary organoid model

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Background and aims: The study of bile duct biology and disease has been hampered by the lack of a good cell culture model of cholangiocytes. With the establishment of the human liver-derived organoid (LDOs) culture platform, it has become possible to long-term expand cells which exhibit cholangiocyte-like properties. The aim of this study is to investigate the role of cystic fibrosis transmembrane conductance regulator (CFTR) in hypoxia induced bile duct injury. It has been hypothesized that (transplantation-related) liver hypoxia leaves cholangiocytes vulnerable for bile toxicity due to an insufficient protection by CFTR-related bicarbonate (NH_3) secretion. There for we investigated if liver-derived organoids have functional cholangiocyte-transport channels and can be used for drug-discovery purposes.
Method: LDOs, cultured from donor livers reserved for LT, were analyzed on the genetic and protein level for cholangiocyte-specific transporters (CFTR and AE2). Functionality of these channels was analyzed using an Ussing-chamber assay in 2D-grown organoids (n = 42). Forskolin (cAMP-activator) added to the apical side of the cells, initiated CFTR activation which was specifically inhibited by GlyH. Hypoxic conditions were achieved by nitrogen gas ($95\%N_2/5\%CO_2$) exposure. To study bile-related toxicity, undiluted bile was added under oxygen and hypoxic conditions and cell death was analyzed. Finally, compounds were tested for the ability to abrogate the hypoxic-induced inhibition of CFTR.
Results: CFTR was expressed in all liver organoid cultures on both gene (qPCR) and protein (Western blot) level. Moreover CFTR could be functionally activated by Forskolin in the Ussing chamber set-up. CFTR activity was significantly lower when measured under hypoxic conditions compared to oxygenated conditions (1.66 ± 0.45 vs. 4.18 ± 0.48, p = 0.005). Furthermore, a significant decrease in activity was observed when the same 2D-organoids were switched from oxygenated to hypoxic conditions (8.00 ± 1.19 vs. 5.89 ± 1.26, p = 0.02). Further experiments showed that bicarbonate is the driving factor when CFTR is activated in LDOs, suggesting that under hypoxic conditions less bicarbonate is excreted into the bile. When 2D-grown LDO were exposed to bile, it resulted in more cell death in hypoxic versus oxygen conditions (31.2% ± 4.32 vs. 19.18 ± 4.81, p = 0.04). Most importantly, addition of compound C (cAMP-inhibitor) was able to rescue transporter activity under hypoxic conditions.
Conclusion: LDOs provide an excellent model to study cholangiocyte-transporters. We demonstrate that hypoxia inhibits CFTR-related bicarbonate secretion and cAMP-inhibitor compound C can restore this. This encourages further clinical studies to test whether cAMP-inhibitors can prevent hypoxia-related biliary injury during graft preservation and after LT.

SAT-440

Molecular fingerprint of T cell-mediated and antibody-mediated rejection after human liver transplantation

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Background and aims: The long-term outcome of patients after liver transplantation has not been improved over the past three decades. Up to 50% of patients show refibrosis in 5 year biopsies and side effects of chronic immunosuppression determine the morbidity and quality of life after liver transplantation. As histology long-term after liver transplantation is less precise in distinguishing between harmful and non-harmful findings, we employed molecular analysis to better characterize various rejection types (molecular microscope).
Method: We conducted next generation sequencing of mRNA isolated from 71 cryo-conserved liver allograft biopsies with no histological rejection (NHR; n = 20), subclinical TCMR (subTCMR; n = 25), clinical TCMR (cTCMR; n = 10) or possible cAMR (pcAMR; n = 16). Pathway analysis was performed with Ingenuity Pathway Analysis (IPA, QIAGEN) for transcripts with $p < 0.05$, false discovery rate < 0.05 and with > 2fold change in expression.
Results: In the principal component analysis NHR and subTCMR exhibited quite similar intrahepatic gene expression patterns indicating no major inflammation in the graft. In contrast cTCMR and pcAMR were quite different from NHR on the molecular level. Next, each rejection type (subTCMR, cTCMR, pcAMR) was compared pairwise to NHR and the overlap of these three comparisons was determined. Only two transcripts, PRDM1 and RGCC, were consistently regulated in all three rejection types compared to NHR. On the other hand cTCMR and pcAMR were significantly different from NHR. Both rejection types shared 200 transcripts mostly involved in regulation of the T cell compartment, dendritic cell maturation, leucocyte migration and cell cycle control including proliferation and DNA repair. However, not all of these 200 transcripts were homogenously up or down regulated in cTCMR and pcAMR: 516 pcAMR specific transcripts were mostly involved in similar pathways as those shared by cTCMR. 341 cTCMR specific transcripts were mostly involved in cell cycle control, potentially reflecting tissue response to more severe and more acute tissue damage during cTCMR compared to subTCMR and pcAMR. There was only a minimal overlap between our 341 cTCMR specific transcripts and the published 13 TCMR specific transcripts (two of 13 transcripts: CCL19, TOP2A) that were determined by microarray.
Conclusion: On the molecular level subTCMR is nearly indistinguishable from NHR ruling out any relevant graft inflammation. In contrast pcAMR is rather a resembling TCMR thereby showing substantial graft injury and tissue repair. Molecular profiling will help to identify patients with relevant graft inflammation thereby potentially providing a chance for individualized immunosuppression.

Liver tumours: Clinical aspects except therapy

SAT-451

Gallbladder disease in the absence of cirrhosis is a significant risk factor for hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is the most common primary Liver cancer with a five-year survival rate of less than 5%. Gallbladder disease (GBD) is defined as the presence of cholelithiasis or cholecystitis. Both cholelithiasis and cholecystitis have been reported as risk factors in the development of gastrointestinal cancers, such as biliary tract and pancreatic cancers. Moreover, patients with GBD tend to develop chronic liver diseases which may progress to cirrhosis. However, the role of GBD in the development of non-cirrhotic related HCC has not been elucidated. We aimed to investigate the role of GBD and the risk of HCC development in absence of cirrhosis and after adjustment for potential confounders.
Method: We conducted a case-control study at The University of Texas M.D. Anderson Cancer Center. Cases were defined as pathologically confirmed HCC. Controls were healthy individuals without prior history of cancer, who are spouses of other cancer patients seen at MD Anderson. All subjects are USA residents. Participants were personally interviewed for prior history of GBD and for several HCC risk factors (environmental, behavioral, chronic medical conditions, and family history of cancer). Blood samples of all participants were tested for markers of hepatitis B and C viruses. We reviewed the pathology and radiology records of HCC patients to assess presence and absence of cirrhosis. Multivariable logistic regression analysis was conducted to estimate the adjusted odds ratio (AOR) and 95% confidence interval (CI) for the association between GBD and HCC in absence of cirrhosis and adjustment for potential confounders.
Results: Between 2000 and 2017 a total of 1333 cases and 1104 controls were enrolled in the study; 347 HCC patients showed no evidence of cirrhosis and were eligible for this analysis. The prevalence of GBD based on the participants' recall during personal interview was 22.7% in the cases. Upon further assessment by review of medical records, the prevalence of GBD was 40.3% in the cases. Individuals with GBD were two times more likely to develop HCC than individuals with no history of GBD (AOR = 2.0; 95% CI: 1.4–2.8). The estimated AOR did not meaningfully change when we rely on the prevalence of GBD recalled by cases (27%) versus the prevalence of GBD obtained from medical records. The association between GBD and HCC continue to be significant in absence of viral hepatitis, through a restricted analysis among non-viral non-cirrhotic population after controlling for age, sex race, alcohol use, cigarette smoking, diabetes and family history of cancer.
Conclusion: We conclude that GBD is a significant risk factor for HCC development in absence of cirrhosis. Future research aiming at investigating the underlying mechanism of GBD-induced HCC in absence of cirrhosis should be warranted. In addition, patients with GBD should be screened for evidence of cirrhosis.

SAT-452

Analysis of intrahepatic sarcomatoid cholangiocarcinoma compared with intrahepatic adenocarcinoma

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Background and aims: Most malignant tumors in the intrahepatic bile duct are adenocarcinoma which are commonly referred to as cholangiocellular carcinoma (CCC). In contrast, intrahepatic sarcomatoid cholangiocarcinoma (s-CCC) is an extremely rare, accounting for less than 1% of hepatobiliary malignancies. In this study, we investigated the clinical, imaging, and histopathologic features of s-CCC compared with those of CCC.
Method: From January 2001 to June 2018, a total of 228 patients with intrahepatic cholangiocarcinoma (IHCC) diagnosed via surgery or US-guided liver biopsy at Dong-A University Hospital were screened. Among them, 11 patients were diagnosed with s-CCC and 2 patients showed mixed histopathologic features of HCC and s-CCC.

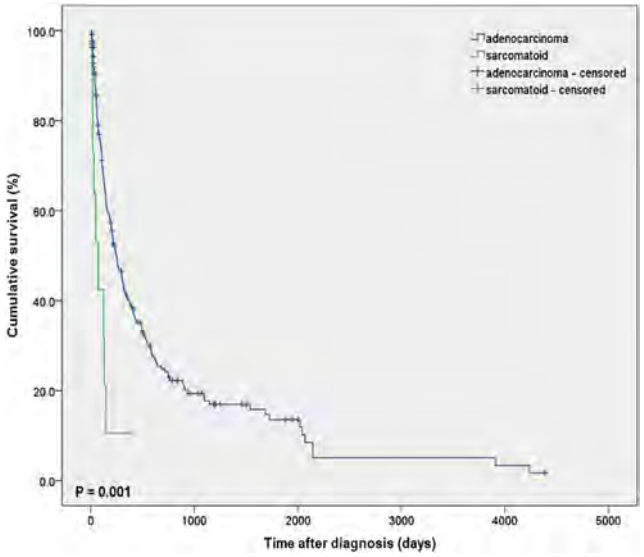

Figure: Comparison of cumulative survival rates

Results: Among 11 patients diagnosed with s-CCC, 9 (81.8%) were men and 2 (18.2%) were women. The median age was 61 years. Compared with 216 patients with CCC, fever, past history of chronic viral hepatitis, and LC were more common in patients with s-CCC. The incidence of abdominal pain was more likely to be significantly high in patients with s-CCC (10 cases, 90.9%). CEA and AFP levels were with normal range in most cases, which were not helpful in the diagnosis of s-CCC. The initial radiologic impression obtained via abdominal US and CT scan was very variable as IHCC, HCC, lymphoma, and hepatic abscess. None of the 11 patients were not clearly diagnosed with s-CCC at the first imaging study. In immunohistochemical findings, IHC study had shown that cancer cells expressed CK8, CK19 and vimentin, but not HSA and AFP. A larger mass size, more frequent distant metastasis, and more advanced stage were more likely to be observed in patients with s-CCC than those with CCC. The mean survival time of patients with s-CCC was significantly shorter than that of patients with CCC. (Figure 1)
Conclusion: Intrahepatic s-CCC of the liver is an extremely rare disease, and it characterized by non-specific symptoms and commonly diagnosed at an advanced stage. In addition, the prognosis is

extremely poor due to the rapid progression of the disease. Early diagnosis and appropriate treatment are important. Because clinical, serologic, and imaging findings are not helpful in distinguishing s-CCC from CCC, biopsy should be performed to accurately diagnose and predict prognosis. There has been no fully established treatment thus far, but, surgical resection is usually prioritized.

SAT-453

Effects of sorafenib on pancreatic volume and their clinical implications in patients with hepatocellular carcinoma

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Background and aims: Sorafenib is the frontline therapy for advanced hepatocellular carcinoma (HCC). Pancreatic toxicity, from asymptomatic elevation of pancreatic enzymes to overt acute pancreatitis, is a common adverse even. Pancreatic atrophy has been reported as a relatively infrequent event. However, the actual prevalence of sorafenib-induced pancreatic atrophy, its clinical impact and its possible prognostic role remain elusive. Our aim to prospectively asses the pancreatic volume at the baseline and six months after the start of sorafenib. We also looked for correlations between pancreatic volume reduction, prevalence of sorafenib-related diarrhoea, and overall survival (OS).
Method: We evaluated 52 consecutive patients who started sorafenib for hepatocellurar carcinoma in our outpatient clinic. As part of the routine clinical examinations, these patients underwent a thorax-abdomen-pelvis computed tomography: a) within 2 weeks before the start of sorafenib; b) every two months after the first dose (± 2 weeks). Pancreatic volume and response to sorafenib were evaluated at each examination. Clinical evaluations were performed a week after each CT. Clinicians were blinded to the results of pancreatic volume assessment.
Results: Pancreatic volume was significantly lower 6 months after the start of sorafenib compared to the baseline ($p < 0.01$). In detail, 29 patients (55.8%) had a volume loss > 10%. The prevalence of diarrhoea was similar in patients with and without volume loss > 10% (48.2 vs 30.7%, $p = 0.403$). A significant volume loss was not associated with an higher rate of lipase elvation (34.5 vs 34.6%, $p = 1.000$). Either, there were no correlation with the median average daily dose of sorafenib or with the OS (median 9.6 vs 9.0 months, $p = 0.435$).
Conclusion: Reduction of pancreatic volume is a relatively common event in sorafenib-treated patiens, however it has no significant clinical implications.

SAT-454

Management of hepatocellular carcinoma in a real life multinational, longitudinal, observational study (TARGET-HCC)

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Background and aims: Over the past two years, there has been an expansion of systemic therapy options including tyrosine kinase inhibitors and immune checkpoint inhibitors for hepatocellular carcinoma (HCC). The aim of this study was to characterize clinical characteristics and HCC treatments in a contemporary cohort of HCC patients across diverse practice settings.
Method: TARGET-HCC, a multinational observational study, includes participants followed by hepatology and oncology investigators from academic and community sites in the US and Europe. In a combined retrospective/prospective design, medical records including provider narratives, laboratory, pathology, and imaging data are abstracted into a centralized database. Interventions for HCC, adverse events, and disease progression are longitudinally assessed.
Results: We identified 1198 pts enrolled across 47 sites who were diagnosed with HCC within 3 years of enrollment (median time from diagnosis to enrollment = 7 months). Most pts (76%) were male; white (73%), had underlying hepatitis C (61%), and most had Child Turcotte Pugh A (63%) or B (29%) cirrhosis. Distribution of Barcelona Clinic Liver Cancer (BCLC) tumor stage at diagnosis and initial treatment within 6 months of diagnosis are shown in Table 1. Only 38% of BCLC 0-A pts (n = 674) underwent curative treatment with ablation, resection, or transplant, with many (37%) instead undergoing non-curative locoregional therapy (LRT) and 3% undergoing systemic therapy (ST). Non-curative LRT was the most common type of treatment (63%) for BCLC-B pts (n = 258), although 24% were able to undergo curative treatment approaches whereas 9% were treated with ST. Surprisingly, only 23% of BCLC-C pts (n = 101) underwent ST with a large proportion (42%) still undergoing non-curative LRT. BCLC-C pts treated with LRT had less vascular invasion than those without LRT (31% vs 49%, respectively). For BCLC-C pts with follow-up of ≥ 6 months (n = 30), 11% received ST (primarily kinase inhibitors and/or immunotherapies) and 3% had radiation as second line treatment.

Figure: First Line Therapy Within 6 Months of Initial HCC Diagnosis by BCLC Stage at Diagnosis

First Line Therapy	BCLC-0 (N = 114)	BCLC-A (N = 560)	BCLC-B (N = 258)	BCLC-C (N = 101)	BCLC-D (N = 10)
LRT	67%	64%	72%	48%	40%
Ablation	42%	22%	16%	6%	10%
TACE	25%	36%	48%	26%	30%
Other Embol.	7%	13%	14%	18%	0%
Other LRT	2%	1%	0%	0%	0%
Resection	4%	15%	9%	13%	0%
Transplant	1%	0%	0%	0%	0%
External Radiation	2%	5%	3%	11%	20%
Systemic	1%	4%	10%	23%	10%
Treatment pending	29%	20%	14%	19%	30%

During a median follow-up of 11 months from diagnosis, 12% of all pts (n = 143) have died. Long-term follow-up is ongoing.

Conclusion: In a diverse cohort of patients with HCC in clinical practice, LRTs are frequently applied to pts with late stage disease, which may be discordant with current guidelines. Further evaluation of treatment paradigms and long-term outcomes is ongoing.

SAT-455

Efficacy of sorafenib and lenvatinib for hepatitis status: a network meta-analysis of phase III trial

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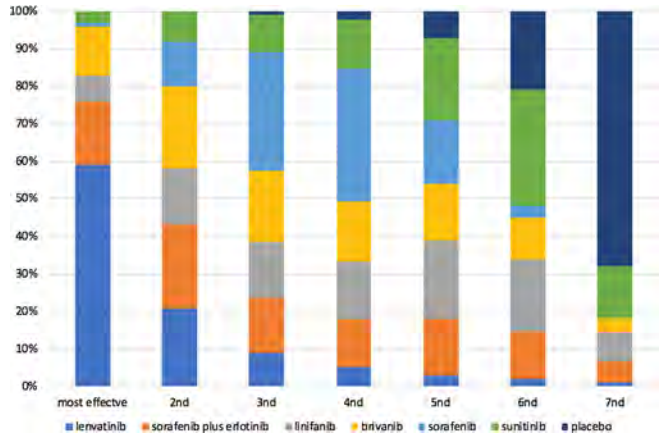
Background and aims: To date, there are no validated prognostic nor predictive markers of response to sorafenib in HCC, although hepatitis status seems to be a potential candidate.
For this reason, we conducted an NMA to evaluate whether the virus etiology could be used to determine which patients may benefit from either lenvatinib or sorafenib.
Method: Data were extracted from the publications or estimated as proposed by Parmar et al.[28]. Treatment effects were estimated by posterior means and 95% credible intervals (CrIs) using random

effect, identity link function and non-informative prior distributions (uniform and normal). We performed 25, 000 iterations with burn-in number of 5, 000 iterations and a thin interval of 20 to obtain the posterior distributions of model parameters. Convergence was assessed using the Brooks-Gelman-Rubin method. Posterior distributions were used to assess the probability of each treatment to be the best, second best and so on. Inconsistency and heterogeneity were assessed using node-split models, I2 and Cochran Q tests. Significant heterogeneity was considered to be present for I2 > 50% or p value > 0.10. Der Simonian and Laird method and random effect were used. All the analyses were made with the R packages "Metaphor" and "Gemtc" (https://www.r-project.org/).

Results: The NMA was performed on a total of 1, 788 patients on six study, of these 1160 patients were HCV-positive or HBV-positive. Of these, 251 (21.6%)HBV-positive patients and 91 (7.8%) HCV-positive patients received lenvatinib, whereas 390 (33.6%)HBV-positive patients and 229 (19.7%) HCV-positive patients received sorafenib. A total of 114 (9.8%)HBV-positive patients and 85 7.3%) HCV-positive patients received placebo. In the overall population no difference was observed between lenvatinib and sorafenib, despite if a slight trend towards a greater efficacy of lenvatinib (HR 0.92, 95% CrI0.61-1.36). Both lenvatinib and sorafenib were significantly better than placebo. When we restricted the analysis to HBV-positive patients, a significant benefit in terms of OS was estimated for sorafenib (HR 0.78 95% CrI 0.62-0.97) with respect to placebo; for HBV-positive patients there was a clear trend in favor of lenvatinib over sorafenib (HR 0.82 95% CrI 0.60-1.15).



For HCV-positive no differences between lenvatinib and sorafenib were observed (HR 0.91 95% CrI 0.41-2.01). I2, Cocran's Q and node-split models showed no evidence of heterogeneity nor inconsistence, strengthening the results of the NMA.

The rankogram in Fig. 1 reports the probably best approach for these patients. The rankogram show that Lenvatinib was probably the best approach for HBV-positive patients

Conclusion: Our data from NMA highlighted that lenvatinib has a greater activity in HBV-positive patients.

SAT-456

New multi inflammation indicators in advanced hepatocellular carcinoma patients receiving sorafenib

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Background and aims: Several inflammation and immune-based prognostic scores, such as lymphocyte count, neutrophil-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), have been developed to predict survival and recurrence in cancers, including HCC.

We evaluated the potential role of new multi inflammation indicators (MII) as predictors of outcome in HCC patients treated with sorafenib.

Method: 170 patients with HCC (24 BCLC B and 146 BCLC C) consecutively treated with sorafenib between March 2008 and August 2018 were enrolled. Information on neutrophil, lymphocyte and platelet counts was obtained from blood tests carried out the week before the start of treatment. The MII-1 was calculated as the ratio between the absolute neutrophil count and the lymphocyte count (NLR) x high sensitivity protein C reactive (hs-PCR); MII-2 was calculated as the ratio between the absolute platelet count and the lymphocyte count (PLR) x hs-PCR; MII-3 was calculated as platelet count × NLR (SII) x hs-PCR.

PFS and OS were estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics (age, gender, etiology, ECOG performance status) were calculated using the Cox proportional hazards model.

We also conducted landmark analyses to reduce possible confounding by time on treatment by assessing the impact of change in SII; NLR and PLR at 1 month landmark time on survival outcomes. X-tile 3.6.1 software (Yale University, New Haven, CT) was used to determine the cutoff value for baseline levels of each II.

Results: Median overall survival (OS) was 12.4 months (95% CI 9.6-15.4) and 8.9 months (95% CI 6.9-9.7) for patients with low (< 25) and high (≥ 25) MII-1 values, respectively (HR = 1.74, 95% CI 1.21-2.51, p = 0.003).

Median OS was 12.6 months (95% CI 9.6-16.2) and 8.9 months (95% CI 6.9-9.7) for patients with low (< 1424) and high (≥ 1424) MII-2 values, respectively (HR = 2.14, 95% CI 1.44-3.20, p = 0.0004).

Median OS was 12.6 months (95% CI 9.8-16.0) and 8.9 months (95% CI 6.9-9.6) for patients with low (< 6068) and high (≥ 6068) MII-3 values, respectively (HR = 1.91, 95% CI 1.98-2.90, p = 0.0005).

Multivariate analysis showed that MII-1, MII-2 and MII-3 were the only independent prognostic factors for OS and they outperformed NLR.

Conclusion: These news immune inflammation indicators represent potential prognostic indicator in patients with advanced HCC treated with sorafenib.

SAT-457

Sarcopenia determines post-progression outcomes in advanced hepatocellular carcinoma after sorafenib failure

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Background and aims: Sarcopenia, an objective surrogate for performance status, is associated with the degree of liver fibrosis, outcomes of patients with cirrhosis and hepatocellular carcinoma (HCC). In patients with advanced HCC after sorafenib treatment, most of the patients had poor ECOG performance status. Whether muscle mass still a prognostic factor after sorafenib failure was unclear. In this study, we aimed to determine the role of sarcopenia in advanced HCC patient after sorafenib treatment.

Method: From August 2012 to March 2017, 515 consecutive patients who received sorafenib treatment for advanced HCC in Taipei Veterans General Hospital were retrospectively reviewed. Among them, 381 patients who experienced radiology-proved progressive diseases (PD) and had complete clinical data were enrolled into the

analyses. Sarcopenia was defined as transverse psoas muscle thickness per height less than 16.8 mm/m.
Results: The prevalence of sarcopenia was 64.8% (247/381) at the time of PD after sorafenib treatment. Sarcopenia was female predominant and was associated with lower body mass index, chronic hepatitis C infection, larger tumor size, prolonged prothrombin time, lower serum albumin level, more ascites formation, and higher grade of albumin-bilirubin (ALBI) grade. Patients with sarcopenia had significantly shorter post-progression survival (PPS) compared with the counterparts (median PPS 3.9 vs 5.8 months, p = 0.005). In multivariate analyses, large tumor size (> 10 cm), high alpha-fetoprotein level (> 400 ng/ml), ALBI grade, early progression within 4 months, presence of new extrahepatic metastasis, and sarcopenia were independent risk factors to post-progression mortality. After adjustment of other factors, sarcopenia remained a significant predictor to a poor PPS in sorafenib-failed HCC (hazard ratio [HR] = 1.30, p = 0.029).
Conclusion: Sarcopenia significantly differentiates PPS and is an independent prognostic factor to determine mortality in sorafenib-failed HCC. Building muscle mass is important for advanced HCC patients after sorafenib failure before entry into second-line systemic therapy to prolong survival.

SAT-458

Subtraction arterial images of hepatocyte-specific contrast-enhanced MRI: Added value for the diagnosis of hepatocellular carcinoma in the liver imaging reporting and data system v2018

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Background and aims: Arterial-phase image of hepatocyte-specific contrast-enhanced magnetic resonance image (MRI) has not been satisfactory due to weak arterial hyperenhancement, despite its higher sensitivity for diagnosing hepatocellular carcinoma (HCC). We investigated the clinical effect of arterial subtraction images of gadoxetate-enhanced MRI in diagnosing HCC using natural history cohort.
Method: We retrospectively analyzed 372 hepatic nodules (273 HCCs, 18 other malignancies, and 81 benign nodules) 3.0 cm or smaller of 258 patients at risk of HCC who underwent hepatocyte-specific contrast-enhanced MRI in 2016. Final diagnosis was assessed histopathologically or clinically (marginal recurrence after treatment or change in lesion size on follow-up imaging). We compared the detection rate of arterial hyperenhancement between ordinary arterial-phase image and subtraction arterial image and assessed effect of subtraction arterial images in diagnosing HCC using the Liver Imaging Reporting and Data System (LI-RADS) v2018.

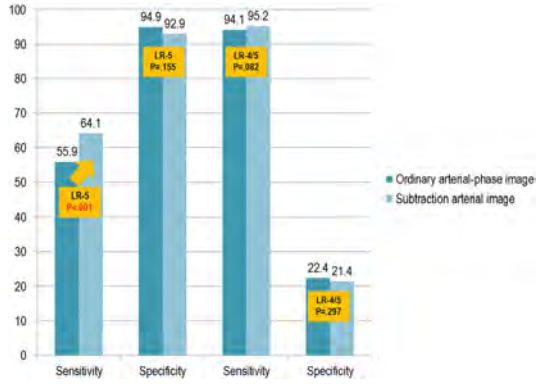

Figure 1: Comparison of Diagnostic Performance for HCC According to the LI-RADS between the Ordinary Arterial-Phase Image and Arterial Subtraction Image for 368 Hepatic Nodules. NOTE. After excluding four LR-TIV nodules from whole 372 nodules, 368 hepatic nodules were used for the analysis.

Results: Subtraction arterial images had a significantly higher detection rate of arterial hyperenhancement than ordinary arterial-phase images for all hepatic nodules (72.3% vs. 62.4%, p <.001) and HCCs (91.9% vs. 80.6%, p <.001; Fig. 1). Compared with ordinary arterial-phase images, subtraction arterial images significantly increased sensitivity of LI-RADS category 5 for diagnosing HCC (64.1% vs. 55.9%, p <.001, Fig. 1), without a significantly decreasing specificity (92.9% vs. 94.9%, p = .155). For histopathologically confirmed lesions, subtraction arterial images significantly increased sensitivity to 68.8% from 61.3% of ordinary arterial-phase images (p <.001) with a minimal decrease in specificity to 84.8% from 89.1% (p = .151).
Conclusion: Subtraction arterial images of hepatocyte-specific contrast-enhanced MRI can significantly improve sensitivity for diagnosing HCC, without a significantly decreasing specificity.

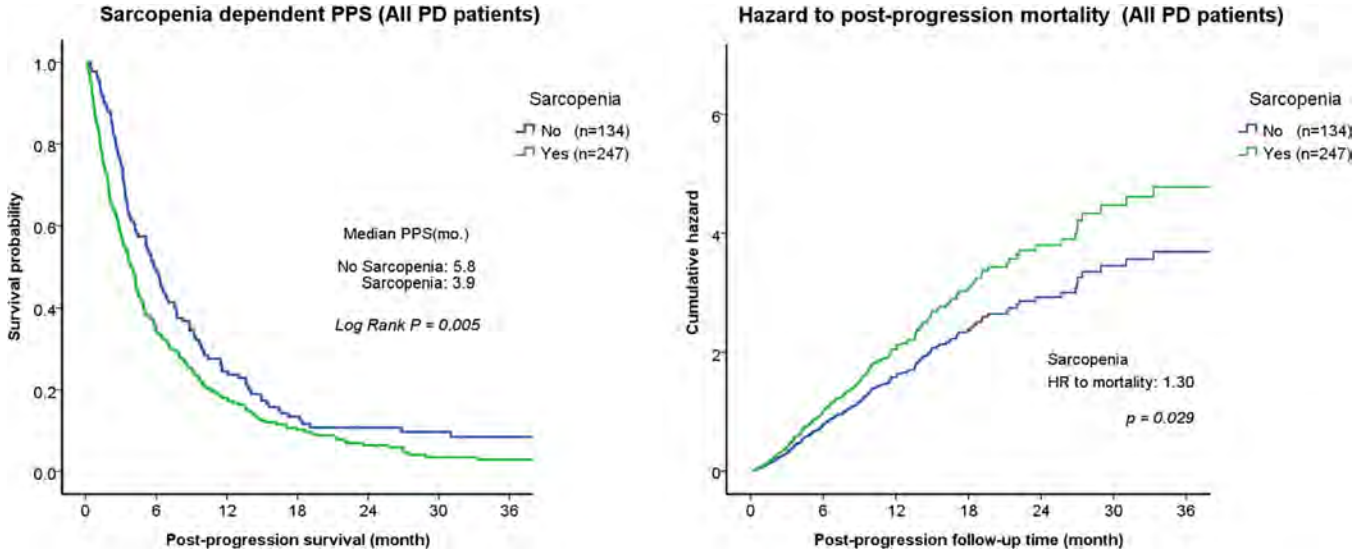

Figure: (abstract: SAT-457)

SAT-459

NASH as a risk factor for intrahepatic cholangiocarcinoma and its prognostic role: Case-control study

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Background and aims: The prevalence of intrahepatic cholangiocarcinoma (ICC) is rising worldwide. The current epidemics of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) might be partly responsible for this trend.
Method: Case control study investigating the prevalence of histology-confirmed NASH in peritumoral liver of resected ICC patients and controls (pre-explant biopsies of liver donors). Controls were matched for age and sex in a 2:1 fashion. Correlates between NASH, tumor characteristics and overall survival (OS) were also explored in the ICC cohort.
Results: Between 2006 and 2017, 84 ICCs were resected in our Institution. Sixty-two (74%) had no apparent risk factors for ICC. Amongst this group, the prevalence of NAFLD and NASH was 45.2% and 24.2%, respectively, compared to 44.3 and 8.9% in the 124 matched liver donors ($p = 1.000$ and $p = 0.007$, respectively). The 5-year OS rate was 20.0% in NASH and 57.4% in ICC without either NASH and other risk factors ($p = 0.017$). Main tumor size, sex and NASH (hazard ratio 2.618, 95% confidence interval 1.140-6.013, $p = 0.023$) were independent predictors of the OS at the multivariate Cox regression.
Conclusion: NASH (but not NAFLD) acts as a risk factor for ICC and may affect its long-term outcome. A collaborative multicenter approach could confirm and strengthen these data.

SAT-460

Influence of sustained virological response in diagnostic performance of alpha-fetoprotein for hepatocellular carcinoma in patients with HCV-cirrhosis

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Background and aims: The usefulness of alpha-fetoprotein (AFP) for hepatocellular carcinoma (HCC) surveillance has been limited by its low sensitivity (sen.) and specificity (spe.), mainly in patients with viral cirrhosis. The aim of this study was to know AFP behavior in patients with HCV-cirrhosis included in an HCC surveillance program, comparing patients with sustained virological response (SVR) and viremic patients (VIR).
Method: 349 patients with HCV-cirrhosis, without HCC, follow-up ≥ 18 months and > 3 AFP determinations (det.) (223 SVR/126 VIR), enrolled in a surveillance program based in biannual US/AFP were analyzed. 105 additional patients with HCV-cirrhosis who developed HCC within the program were also included (with AFP at HCC diagnosis and 6 months earlier). 2141 AFP det. in patients without HCC were collected (median: 6/patient; 1305 in SVR and 836 in VIR). ROC curves were used for the analysis of sen./esp., considering the first AFP det. in patients without HCC and the one at diagnosis in those with HCC.
Results: Most patients without HCC were male (65.3%), age 54 years, genotype 1 (79.3%) and CHILD-Pugh A (91.1%). In 83% SVR was obtained with DAA. The proportion of AFP det. > 10, > 15 y > 20 ng/ml in SVR and VIR patients was 4.3% vs 45%, 0.45% vs 28.7% y 0.22% vs 21.1% ($p < 0.001$). No SVR patient had det. > 20 ng/ml and more than twice the previous det., while this fact was present in 2, 75% in VIR patients ($p < 0.001$). Patients with HCC were mainly male (75.2%), genotype 1 (69.5%). Among them, 18 (17%) had developed HCC after SVR. The proportion of patients with AFp > 10, > 15 y > 20 ng/ml at HCC diagnosis was 60, 9%, 59% y 49, 5% respectively, without differences between SVR and VIR patients ($p > 0.5$). 28, 5% of patients had AFp > 20 ng/ml and more than twice the previous det. Area under the ROC curve of AFP for HCC diagnosis was 0, 77 (IC95%:0.71-0.83) in the global series, 0.65 (IC95%:0.57-0.73) in VIR patients and 0.75 (IC95%:0.59-0.92) in SVR. The value with higher diagnostic efficacy was 15 ng/ml in VIR patients (sen.58.6%; spe.73.4%) and 10 ng/ml in those SVR (sen.66.7%; spe.94.2%; VPP 48%, VPN 97.2%).
Conclusion: In HCV-cirrhosis, SVR leads to a normalization of AFP value, lowering the proportion of false positives. SVR also allows to reduce the value with most discriminative ability, increasing sensibility. As a consequence, diagnostic performance of AFP substantially improves after SVR. These results open the door to re-evaluate AFP role in HCC screening in patients with HCV-cirrhosis.

SAT-461

HCC recurrence after DAA treatment in HCV patients

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Background and aims: The present real-life multicenter, prospective study aims to investigate the effects of DAAs IFN-free therapies in HCV patients with a previous successfully treated HCC, in terms of neoplastic recurrence and SVR rates.
Method: From March 2015 to March 2017, all consecutive HCV patients with a previous successfully treated HCC and underwent to DAAs therapy were enrolled. The baseline clinical, biochemical and radiological data were registered. The assessment of neoplastic recurrence was used as primary outcome, while a secondary outcome was the evaluation of patients characteristics predicting HCC recurrence. Cumulative probabilities of recurrence were extracted from time-to-event curves based on Kaplan-Meier product limit method Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were estimated using univariate and multivariable Cox regressions.
Results: Eighty-three percent of patients were in Child-Pugh class A, and 89% had a history of HCC BCLC stage 0/A, while 35% of patients had a prior HCC recurrence. Ninety-one percent of the patients achieved SVR. The median time between the HCC 1st diagnosis and DAAs-starting was 17.2 months (range 10.1-37.2), while the median time from the last successful HCC treatment to DAAs starting was 10 months (range 5.8-16.6). Thirty-one HCC recurrences were observed from DAAs-starting in a median observational follow-up of 31.7 months. The incidence rate of recurrence was 20.5/100 person-year (95% C.I. 13.9-29.0). The 6-, 12- and 24-months HCC recurrence rates from the last HCC treatment were 1%, 8.9% and 25.6%, respectively. Higher BMI (HR 1.20, 95% C.I. 1.01-1.42, $p = 0.020$), higher levels of Total Bilirubin (HR 2.54, 95% C.I. 1.04 to 6.19, $p = 0.041$) and of AFP (HR 1.02, 95% C.I. 1.001-1.03, $p = 0.019$) and DAA treatment failure (HR 5.68, 95% C.I. 1.63 to 19.80) (fig. 1) were significantly associated with

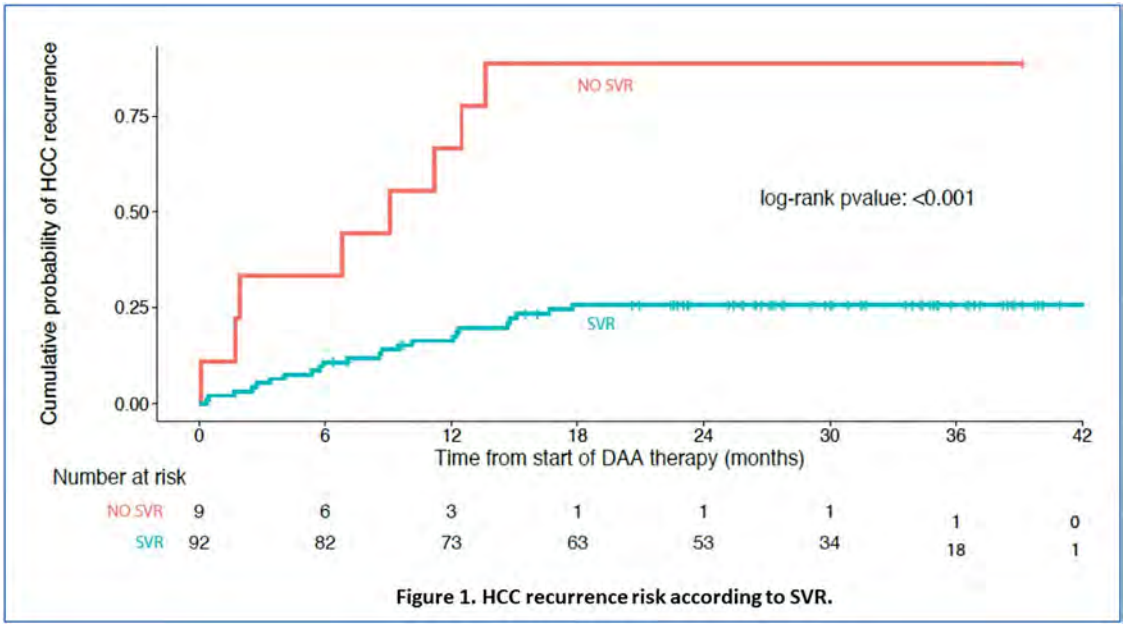

Figure 1. HCC recurrence risk according to SVR.

Figure: (abstract: SAT-461)

higher risk of HCC recurrence, both at univariate and at Cox multivariable analysis.

Conclusion: Patients with lower risk of HCC recurrence are characterized by lower BMI, lower bilirubin and AFP levels and higher SVR rate. These data suggest that the absence of well-known HCC risk factors reduces the HCC recurrence rate also in patients underwent DAAs.

SAT-462

Current non-invasive liver reserve models do not predict histological fibrosis severity in hepatocellular carcinoma

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Background and aims: The Ishak scoring system has been used to stage liver fibrosis. Ten non-invasive liver reserve models were proposed to assess the severity of liver fibrosis, but their performance in hepatocellular carcinoma (HCC) is unknown. We aimed to evaluate the correlation between these models and severity of fibrosis in patients with HCC.

Table 1: Performance of 10 non-invasive liver functional reserve models in predicting cirrhosis (Ishak score 5 or 6)

Non-invasive liver reserve models	AUROC	95% CI	p
ALBI	0.594	0.542-0.647	< 0.001
APRI	0.706	0.658-0.753	< 0.001
CDS	0.729	0.682-0.775	< 0.001
CTP	0.561	0.506-0.615	0.028
FIB-4	0.708	0.660-0.756	< 0.001
GUCI	0.711	0.664-0.759	< 0.001
MELD	0.565	0.513-0.618	0.018
Lok index	0.703	0.655-0.751	< 0.001
PALBI	0.467	0.414-0.521	0.233
King's score	0.709	0.661-0.756	< 0.001

AUROC, area under receiver operating curve

Table 2: Correlation of non-invasive liver reserve models and stage of fibrosis in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

Non-invasive liver reserve models	HBV (n = 209)		HCV (n = 76)	
	Coefficient	p	Coefficient	p
ALBI	0.141	0.410	0.323	0.004
APRI	0.066	0.343	0.464	< 0.001
CDS	0.340	< 0.001	0.546	< 0.001
CTP	0.145	0.036	0.233	0.042
FIB-4	0.120	0.083	0.591	< 0.001
GUCI	0.076	0.276	0.459	< 0.001
King score	0.093	0.179	0.468	< 0.001
Lok's index	0.277	< 0.001	0.546	< 0.001
MELD	0.166	0.016	0.106	0.361
PALBI	-0.113	0.105	0.186	0.109

Method: A total 464 patients with HCC undergoing surgical resection were retrospectively analyzed. Multivariate logistic regression analysis was performed to determine independent factors associated with advanced fibrosis (Ishak score 4 or higher).

Results: There were no significant correlations between all non-invasive models and severity of fibrosis in HCC (p for trend all > 0.1). In subgroup analysis, cirrhosis discriminant index (CDS) and Lok's index in hepatitis B-, and fibrosis index based on 4 factors (FIB-4), CDS and Lok's index in hepatitis C-associated HCC, best correlated with the severity of liver fibrosis. Low platelet count, prolonged prothrombin time, hepatitis C and multiple tumors were independently associated with advanced fibrosis. Among the 10 models, CDS was the best model to predict cirrhosis.

Conclusion: Currently used non-invasive liver reserve models do not well correlate with severity of histological fibrosis in HCC. New non-invasive models are required to improve the predictive accuracy of liver fibrosis in HCC.

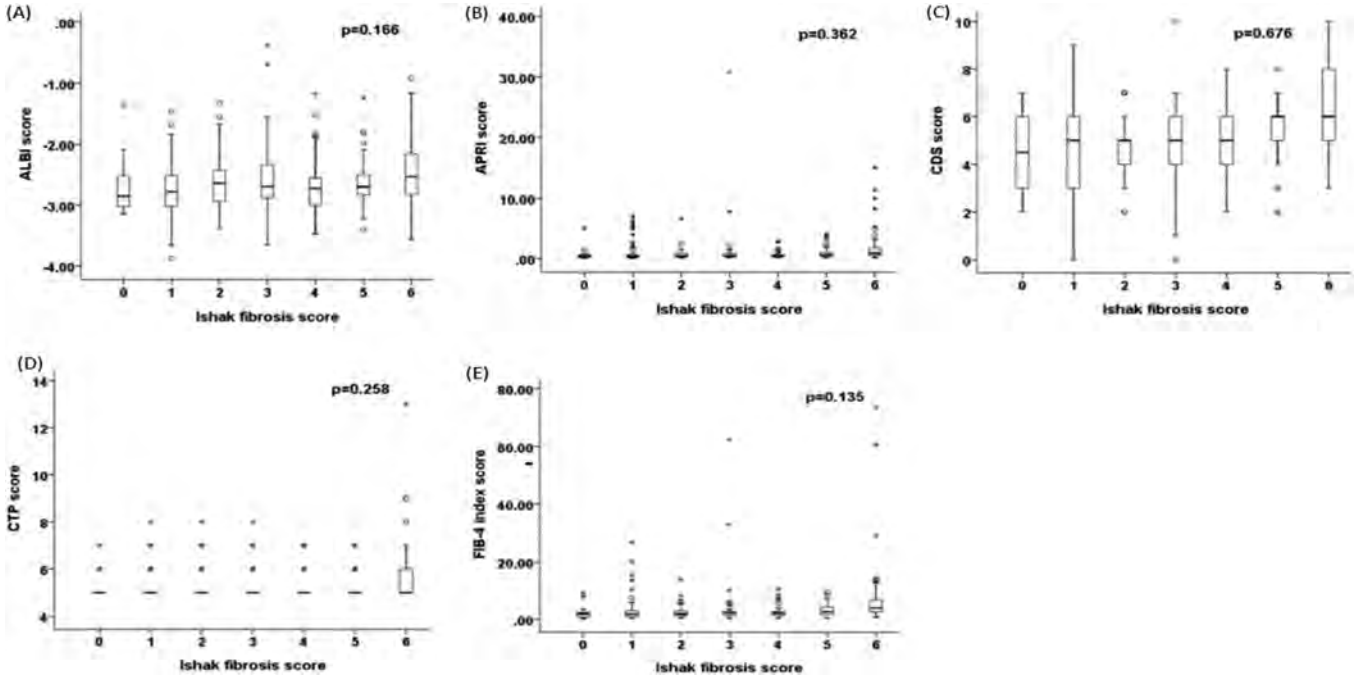

Figure 1: (abstract: SAT-462)

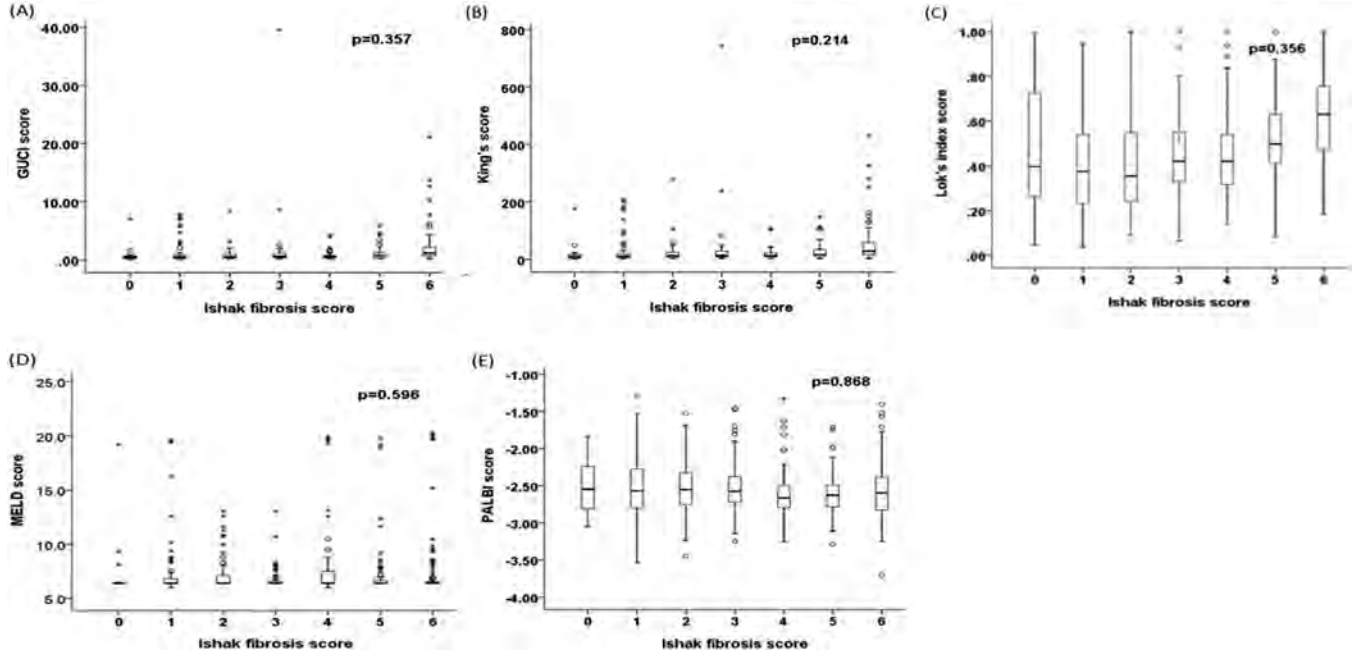

Figure 2: (abstract: SAT-462)

SAT-463

Albumin-bilirubin grade-based nomogram to predict tumor recurrence in patients with hepatocellular carcinoma

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Background and aims: Tumor recurrence after curative resection is common in hepatocellular carcinoma (HCC), but large-scale long-term prediction on an individual basis has seldom been reported. We aimed to construct an albumin-bilirubin (ALBI) grade-based nomogram to predict tumor recurrence in patients with HCC undergoing surgical resection.

Method: A total 1, 038 patients with newly diagnosed HCC undergoing curative resection between 2002 and 2016 were enrolled. Baseline characteristics, tumor status and severity of liver functional reserve were collected. The Cox proportional hazards model was used to predict tumor recurrence and construct the nomogram. The performance of the nomogram was evaluated by the discrimination and calibration tests.

Results: After a mean follow-up time of 30 months, 510 (49%) patients developed tumor recurrence. The cumulative recurrence-free survival at 1, 3, 5, and 10 years were 79%, 51%, 38% and 26%, respectively. In the Cox multivariate model, ALBI grade 2-3, multiple tumors, tumor size equal or large than 2 cm, serum α-fetoprotein level equal or greater than 20 ng/ml and total tumor volume equal or larger than 227 cm^3 were independent risk factors associated with tumor recurrence. A nomogram was constructed based on these five variables. Internal validation with 10, 380 bootstrapped sample sets had a good concordance of 0.607 (95% of confidence interval: 0.587-0.627). The calibration plots for 1-, 3- and 5-year recurrence-free survival well matched the idealized 45-degree line.
Conclusion: ALBI is a feasible marker for tumor recurrence. This easy-to-use ALBI grade-based nomogram may predict tumor recurrence for individual HCC patient undergoing surgical resection.

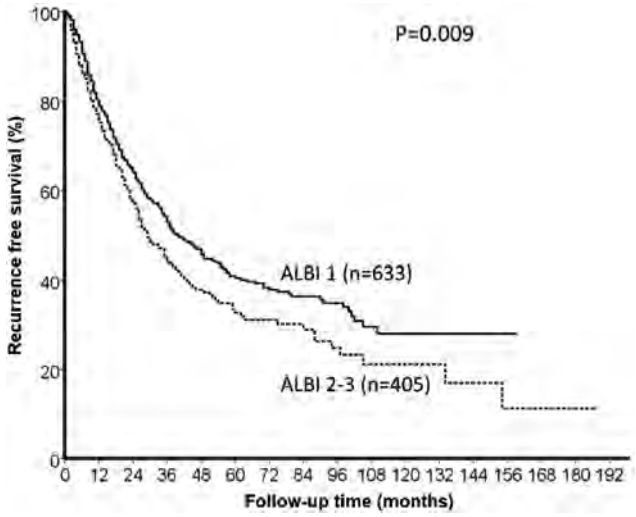

Figure 1: Recurrence-free survival distribution according to albumin-bilirubin (ALBI) grade.

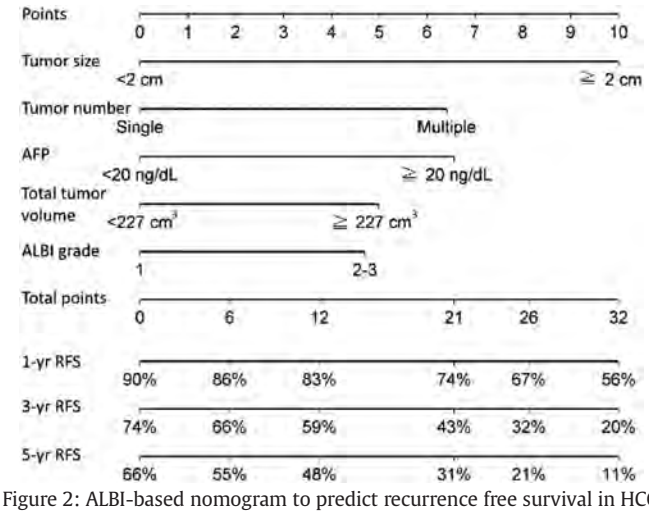

Figure 2: ALBI-based nomogram to predict recurrence free survival in HCC

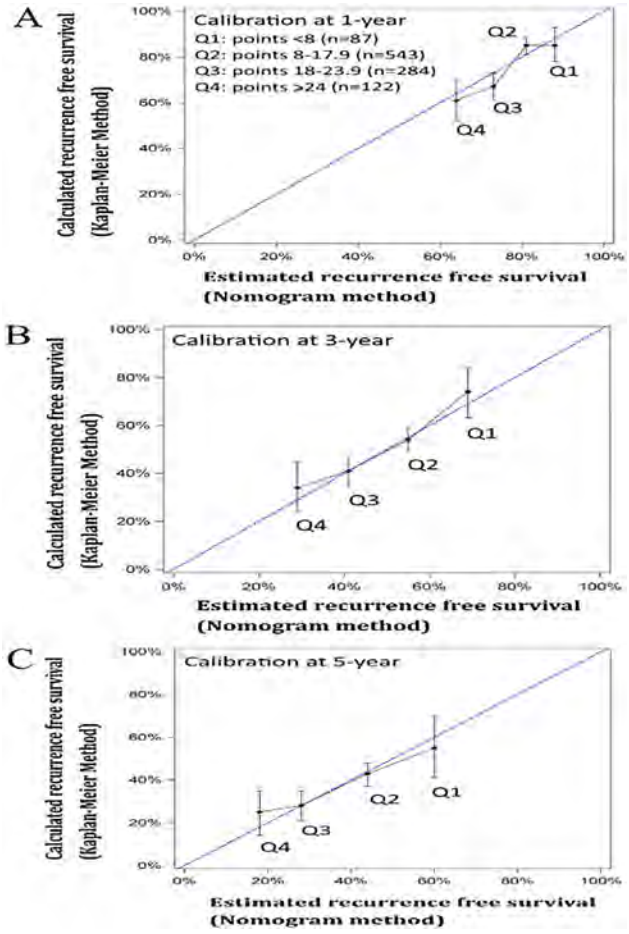

Figure 3: The calibration of nomogram for 1-, 3-, 5-year recurrence-free survival prediction

SAT-464

Predictive value of pretreatment neutrophil-to-lymphocyte ratio in survival of patients with hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is inflammation-related cancer because nonresolving inflammation contributes to the development and progression of HCC. The neutrophil-to-lymphocyte ratio (NLR) has been shown to be associated with prognosis in various types of cancer. The present study aimed to investigate the utility of NLR in the prognosis after diagnosis of HCC.
Method: We retrospectively analyzed data regarding peripheral blood inflammatory cells, patient and tumor characteristics from HCC patients who diagnosed with HCC between November 2008 and December 2017. Baseline data were recorded before treatment. The relationships between overall survival (OS) and the variables including the NLR were assessed.
Results: A total of 1, 688 patients who diagnosed with HCC were included. In multivariate analysis elevated NLR, multiple tumors, large tumor size, underlying liver cirrhosis, vascular invasion, extrahepatic metastases, high tumor markers, low albumin and high bilirubin were found as independent indicators of poor overall survival. The NLR rose in association with advancing the BCLC stage ($p < 0.001$). An NLR ≥ 1.9 was a significant predictor of poor overall survival ($p < 0.0001$).
Conclusion: We have demonstrated that an elevated pretreatment NLR is associated with a poor overall survival in patients for HCC.

SAT-465

The NIACE Score: A prognostic indicator in Hepatocellular carcinoma

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Background and aims: The Barcelona Clinic Liver Cancer (BCLC) classification is the reference system to stage and prognosticate hepatocellular carcinoma (HCC). The NIACE (tumour nodularity, infiltrative nature of the tumour, serum alpha-fetoprotein level, Child-Pugh score, and ECOG performance status) score uniquely considers tumour characteristics, although is yet to be validated in an Australian context. It is suggested that the NIACE score may offer prognostic clarity in some BCLC classes, which encompass heterogenous tumours matched with single management options. We aimed to compare the prognostic value of the NIACE score within the BCLC staging system

Method: We retrospectively analysed data from a cohort of 2202 patients with HCC, across six metropolitan hospitals in Victoria, Australia from the period January 2000-August 2018. Patients were included in the study if all markers were available to calculate prognostic scores including: tumour nodularity (0 if < 3, 1 if ≥ 3), tumour infiltration (0 if no, 1.5 if yes), serum AFP (0 if < 200, 1.5 if ≥ 200 ng/ml), Child-Pugh score (0 if A, 1.5 if B) and ECOG status (0 if 0, 1.5 if ≥ 1). Baseline characteristics including age, sex, country of birth, ethnicity, aetiology of chronic liver disease, and presence cirrhosis were recorded. Survival time was measured from date of diagnosis to date of death (or censored at last follow-up). Transplant-free survival (TFS) was used as the end point for analysis.

Results: A total of 366 patients (M/F = 86%/14%; median age at diagnosis = 63 ± 12 yrs; Australian born 103 (28.1%)) were included in the analysis. Aetiology of liver disease was HBV = 64 (17.4%), HCV = 157 (42.8%), alcohol = 143 (39.0%), and other = 108 (29.4%). The mean serum AFP level for the cohort was 7839 ng/ml. During a median follow-up time of 16 mths, 185 patients (50.4%) had deceased. The median TFS for BCLC 0 (n = 21), A (n = 108), B (n = 82), C (n = 113) and D (n = 39) were; 64, 29, 24, 12 and 4 months respectively (p < 0.001). The Transplant-free survival for NIACE score < 2.5 (n = 169) vs ≥ 2.5 (197) was 34 ± 3mths vs 12 ± 2mths, p < 0.001. Furthermore, NIACE had prognostic value within BCLC subclasses with the TFS of patients within BCLC-A (36 ± 7mths vs 20 ± 3mths, p < 0.01) and BCLC-B (31 ± 7mths vs 19 ± 4mths, p < 0.005) being significantly different for scores of < 2.5 vs ≥ 2.5 respectively. There was no significant discriminating ability amongst later stage BCLC C or D.

Conclusion: The NIACE score is a relatively easy-to-calculate prognostic score that distinguishes 2 subgroups with different prognosis within BCLC A and B stage HCC. This is the first validation of the score in an Australian population. Further prospective validation of the NIACE score in HCC patients and comparison with other simple scores such as ALBI grade is warranted to confirm its prognostic value and use in guiding decision making in conjunction with the BCLC staging system.

SAT-466

A meta-analysis of risk factors for intrahepatic and extrahepatic cholangiocarcinoma

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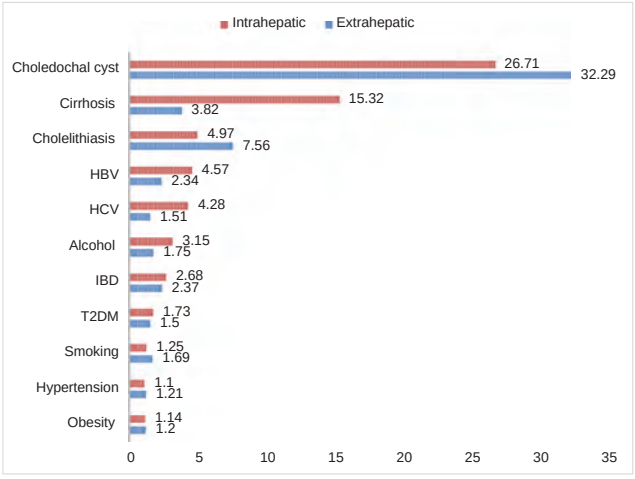
Background and aims: Cholangiocarcinoma (CCA) carries a poor prognosis. Multiple studies report an increasing incidence of CCA, particularly intrahepatic CCA, globally. This systematic review and meta-analysis analysed the association of previously inconclusive or unexplored risk factors, as well as those previously reported, for both iCCA and extrahepatic CCA (eCCA).

Method: A literature search of case-control studies was performed to identify potential risk factors for CCA. Revman 5.3 was used to calculate pooled odds ratios (OR) with 95% confidence intervals. Heterogeneity was assessed with the Cochrane Q test. A random effects model was utilised when there was significant heterogeneity. Funnel plots were used to assess for publication bias.

Results: 25 studies were identified from seven countries and 11 risk factors selected for meta-analysis. Choledochal cysts infer the greatest risk of both ICC and ECC: pooled ORs 26.71 (95% CI, 15.80-45.16) and 32.29 (95% CI, 26.90-38.78), respectively. Cirrhosis inferred significant risk, stronger for ICC than ECC (OR 15.32 and 3.82, respectively). Hypertension was associated with least risk of ICC with a pooled OR of 1.10 (95% CI, 0.89-1.37) and obesity was found to infer the least risk of ECC with a pooled OR of 1.20 (95% CI, 0.84-1.70). There was no evidence of publication bias.



Conclusion: This is the most comprehensive meta-analysis of risk factors for CCA to date. Multiple studies report increasing trends in some of these risk factors which may partially explain the increasing incidence of iCCA.

SAT-467

Pathologic identity of indeterminate hepatic nodules on dynamic computed tomography images of cirrhotic patients undergoing liver transplantation: A potential bias in evaluating suitability for transplantation

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Background and aims: There has been no consistent practical guidance on whether to do biopsy or to wait and see for indeterminate hepatic nodules (IDNs) not meeting diagnostic criteria for hepatocellular carcinoma (HCC) by the combination of arterial hyper-enhancement and portal/delayed wash-out in cirrhotic patients. The aim of this study based on explant pathology of cirrhotic patients is to investigate histological identities for differently-enhanced lesions considered to be IDNs on dynamic computed tomography (CT) images before liver transplantation (LT).

Method: This study included 239 cirrhotic patients who primarily underwent LT and had dynamic CT images within two months before LT at Asan Medical Center. All patients had at least one hepatic nodule ≥ 1 cm in diameter on CT, which were definitely not benign lesions such as hemangioma and cyst; and ≤ 4 measurable nodules. IDNs on CT were histologically classified by correlating with corresponding

explant pathology. Parameters predicting malignant potential of IDN were examined.
Results: Most of included patients were infected with hepatitis B (68%) with a median age of 54 years. A total of 316 nodules in all 239 patients were identified: 112 classified as HCC and 204 as IDN by CT. Eighty-seven percent of IDNs were measured ≤ 3 cm in size. Analyses of radio-pathological correlation of IDNs revealed that 123 out of 204 IDNs (60%) were proved to be malignant tumors with 115 HCCs, 1 cholangiocarcinoma (CCA), and 1 combined HCC-CCA. Non-malignant IDNs in the explant livers were mostly dysplastic nodules (75%). Arterial iso- and portal/delayed hypo-attenuation was the enhancement pattern with the highest possibility of malignant IDNs (73%:43/59), followed by hyper- and iso- (60%:59/99), hyper- and hyper- (57%:8/14), hypo- and hypo- (48%:12/25), and iso- and hyper-attenuation (25%:1/4). There were no malignant IDNs with hypo- and hyper-attenuation or hypo- and iso-attenuation. Most of radiological HCCs (90.2%) were correctly confirmed on explant examination. No clinical, radiological, and temporal factors including serum alpha-fetoprotein level, size of nodule, arterial and portal/delayed patterns, and interval change of the nodule were significantly associated with malignant IDNs (Ps < 0.05). In our series, 43 patients within Milan by pre-LT CT turned out to be beyond Milan by explant pathology in which malignant IDNs could be calculated.
Conclusion: Our study indicates that a considerable number (60%) of small hepatic nodules considered indeterminate on dynamic CT images of LT patients with cirrhosis contained primary malignancies, mostly HCC in a HBV-endemic country. Biopsy-based evaluation of IDNs may be preferred in clinical practice, and careful assessment of the eligibility for LT is required in cirrhotics with IDNs.

SAT-468
Prognostic value of post-treatment liver stiffness in hepatocellular carinoma with histologically confirmed cirrhosis
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Background and aims: Severity of liver fibrosis can be non-invasively evaluated by measuring liver stiffness (LS) using transient elastography, and patients with cirrhosis may undergo dynamic changes in LS measurements (LSM) after antiviral therapy. This study aimed to evaluate the value of achieving low LSM after curative resection in hepatocellular carcinoma (HCC) patients with histologically proven liver cirrhosis.
Method: Total 192 (n = 146, newly started antiviral therapy [AVT]; n = 46, previously started AVT) patients that received curative surgery for HBV related HCC at Barcelona Clinic Liver Cancer stage 0-A, and had METAVIR fibrosis 4, were investigated.
Results: The follow-up LSM significantly decreased in newly started AVT group (New AVT) (p = 0.002) whereas no significant changes were noticed in previous AVT (Previous AVT) group (p = 0.062). Achieving low LSM (≤ 8 kiloPascal [kPa]) had no predictive value in early recurrence in both groups (p = 0.520 and *P* = 0.898, respectively). However, low LSM (≤ 8 kPa) during the follow-up suggested reduced risk of late recurrence (> 12 months) (Hazard Ratio [HR], 0.519; 95% Confidence Interval [CI], 0.307-0.877; *P* = 0.014) in New AVT group whereas no predictive value was found for in Previous AVT group (p = 0.375). Late recurrence suggested increased risk of mortality in New AVT group (HR, 14.80, 1.894-115.718; *P* = 0.010) along with having low APRI score during the follow-up (HR, 0.234, 0.066-0.831; *P* = 0.025). No significant predictors were detected in Previous AVT group.
Conclusion: Among those with HCC occurred without concomitant antiviral therapy, achieving low LSM (≤ 8 kPa) after antiviral therapy might be a good prognostic marker for late recurrence after surgery even with histologically confirmed cirrhosis.

SAT-469
Frequency of TP53, CTNNB1, and TERT promoter mutations in patients with hepatocellular carcinoma from Southern Italy
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Background and aims: Mutations in TP53 and CTNNB1 genes as well as in TERT promoter are considered drivers for hepatocellular carcinoma (HCC) development. They show variable frequencies in different geographic areas, possibly depending on liver disease etiology and environmental factors.
Method: We investigated TP53, CTNNB1, and TERT genetic mutations using direct Sanger sequencing technique in tumor and non-tumor liver tissues from 67 patients with HCC (43 HCV or HBV related; 24 non-virus related) as well as in liver tissue specimens from 30 subjects with non-alcoholic fatty liver as control. All studied subjects were from Southern Italy. TERT expression was assessed by quantitative RT-PCR in duplicate using TaqMan (Applied Biosystems) gene expression assay.
Results: No CTNNB1 mutation or TP53 R249S substitution were detected in any case. The homo- or heterozygous TP53 R72P polymorphism was found in 10/67 (14.9%) tumors, in 0/67 (0%) non-tumor tissues (p = 0.001), and in 0/30 controls (p = 0.02) analyzed. Two TERT gene promoter mutations were found in 33/67 (49.2%) tumor tissues examined. None of the non-tumor tissues and of the liver specimens from control subjects carried these mutations. The most frequent mutation was the known hot spot located at −124 bp from the ATG start site of TERT (−124G > A, 28 cases, 41.8%; P < 0.001). The other mutation-never described before-was located in the promoter at −300 bp from the ATG (−300G > C, 5 cases, 7.5%; P = 0.02). This mutation creates a typical TFII-I binding sequence (CTGTCC), and was found alone (2 cases) or in combination (3 cases) with the −124 bp mutation. Neither TP53 R72P polymorphism nor the two TERT gene promoter mutations were associated with viral or non-viral etiology.
Real-time PCR experiments showed that mutations at −124 bp and −300 bp induced a 20-fold and 4-fold increase of TERT expression, respectively. When both mutations were present in the promoter, expression of TERT was increased more than 100-fold.
Conclusion: CTNNB1 mutations are uncommon in patients with HCC in our geographic area, whereas the TP53 R72P substitution and TERT promoter mutations at −124 bp and −300 bp are significantly associated with HCC. The combination of mutations at −124 bp and at −300 bp strongly induces TERT promoter activity.

SAT-470
Circulating levels of soluble urokinase plasminogen activator receptor (suPAR) predict outcome after resection of cholangiocarcinoma
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Background and aims: While surgical resection has remained the only potentially curative therapy for patients with cholangiocarcinoma (CCA), 5-year survival rates after tumor resection are still below 30%, corroborating the urgent need for better preoperative stratification tools to identify the ideal surgical candidates. The soluble urokinase plasminogen activator receptor (suPAR) has evolved as a prognostic marker for various clinical conditions but its role in the context of CCA has remained unknown. In this study, we evaluated

circulating levels of suPAR as novel biomarker in patients undergoing resection of CCA.
Method: Tumor expression of uPAR, the membrane bound source of circulating suPAR, was analysed by IHC in 108 CCA samples. Serum levels of suPAR were measured by ELISA in a trainings and validation cohort comprising a total of 117 CCA patients as well as 76 healthy controls and 11 patients with primary sclerosing cholangitis (PSC).
Results: High tumoral uPAR expression was associated with an impaired outcome after CCA resection. Moreover, circulating levels of suPAR were significantly elevated in CCA patients compared to PSC patients and healthy controls. Importantly, patients with initial suPAR levels above the ideal prognostic cut-off value of 3.72 ng/ml had a significantly impaired long-term survival in the trainings and validation cohort. The prognostic relevance of circulating suPAR was further confirmed by uni- and multivariate Cox regression analysis. Finally, high pre-operative suPAR levels were indicative for acute kidney injury after tumor resection.

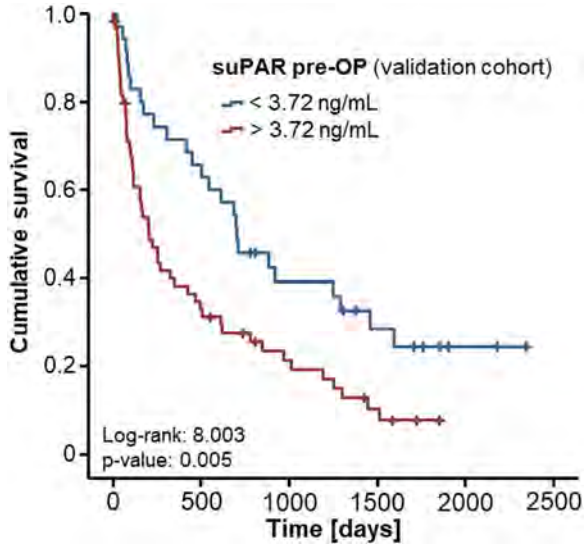

Figure 1: **Overall survival after tumor resection**. Patients with preoperative suPAR serum levels above the optimal cut-off value of 3.72 ng/ml show a significantly impaired long-term survival after tumor resection.

Conclusion: Circulating suPAR represents a previously unrecognized biomarker in patients with resectable CCA which might help to preoperatively identify the ideal candidates for extended liver resection.

SAT-471

Hepatic adenomatosis increases risk of hepatic adenoma bleeding

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Background and aims: Known risk factors for hepatic adenoma (HA) bleeding are size > 5 cm, Beta-catenin mutated and Sonic hedgehog activated adenomas. The objective of this study is to determine additional clinical risk factors for HA bleeding.
Method: Retrospective analysis of patients diagnosed with HA by MRI at a single-center academic hospital. Demographics, clinical data, and data from initial and latest MRIs were collected. Number of lesions and largest three lesion sizes were recorded for patients with multiple HAs. Complications and treatments delivered were followed.
Results: 187 patients were reviewed. 94% were women, the mean age was 47.7 ± 13.7 years and median follow-up time was 386 days (IQR 172, 1142). Of the 132 patients who had clinical follow-up and follow-up MRIs, 17.6% (all women) experienced bleeding from HA. Bleeding was not significantly higher in patients with specific race, ethnicity, type 2 diabetes, obesity, or tobacco and alcohol use. In univariate analysis, risk of bleeding was increased in patients with oral contraception (OCP) use (OR = 2.38; CI: 0.97-5.8, p = 0.057), larger HAs (OR = 1.48 per 1 mm increase; CI: 1.2-1.8, p < 0.0001), and multiple HAs (> 10 lesions) (OR = 4.03; CI: 1.4-11.9, p = 0.058). In the multivariate adjusted analysis, only size remained statistically significant (OR = 1.44, CI: 1.4-1.2, p < 0.0001).
Most patients who had HA bleeding were resected (88%), but some underwent multiple embolizations (4%), embolization followed by resection (12%), radiofrequency ablation (4%) and liver transplant (6%). The median size of unifocal lesions in bleeding patients was 7.50 cm (IQR 5.30, 11.8) compared to 2.30 cm (IQR 1.2, 4.10) in non-bleeding patients. The smallest lesion that bled was 1.8 cm. In patients with > 10 lesions who bled, the median lesion size for the largest three lesions was 6.5 cm (IQR 4.7, 9.05), 4.4 cm (IQR 2.2, 5.6) and 1.45 cm (IQR 1.3, 1.6) compared to 3.60 cm (IQR 2.3, 5.4), 2.70 cm (IQR 2, 3.1) and 2.20 cm (IQR 1.7, 2.8) in non-bleeding HA patients. In patients with > 10 HAs, 40% of patients did not bleed from their largest lesion.
Conclusion: There is an increased risk of bleeding with larger HA, multiple HAs, and OCP use. In the adjusted multivariate analysis, size was more predictive of HA bleeding, but this could be related to a smaller population of patients with multiple HAs. Patients with > 10 HAs should be considered for prophylactic therapy. Larger multi-center prospective studies are needed to confirm these observations.

SAT-472

Massive sequencing of circulating DNA as a potential tool for diagnosis and follow-up in patients with hepatocellular carcinoma

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Background and aims: Tumor biopsy is the usual source of molecular information in cancer. Analysis of plasma cell free DNA (cfDNA) could be a non-invasive tool, having clinical applications in terms of diagnosis and prognostic estimation in patients with hepatocellular carcinoma (HCC). We aim to evaluate correlation between mutations detected in HCC and those detected in cfDNA, and the prognostic value of their evolutive changes.
Method: Patients undergoing surgical resection for HCC in our center were prospectively included in the study. 4 samples were analyzed on each: 1) fresh frozen tumor tissue (HCC), 2) adjacent non-tumoral tissue (NT), 3) peripheral blood mononuclear cells (PBMC) and 4) plasma. cfDNA was extracted from 1 ml of plasma using the MagMAX Cell-Free DNA Isolation kit from Thermo fisher. Samples were

subjected to high-depth sequencing for the detection of mutations in 5 of the most relevant/prevalent genes in HCC on the Illumina MiSeq platform. Sequences with coverage of more than 10, 000 readings were analyzed and only mutations with a frequency higher than 1% were accounted for

Results: 12 patients have been analyzed to date. 75% men (9/12), average age of 62 years. 100% had single HCC, median size of 4.05 cm. 50% (6/12) were HCV positive. 18 mutations were detected in HCC tissue: TERT (11/12), TP53 (2/12) and CTNNB1 (5/12) and 16 mutations in the cfDNA: TERT (10/12), TP53 (3/12) and CTNNB1 (3/12). 12/18 mutations detected in HCC, were detected in the corresponding sample of cfDNA, (75% agreement). 4 mutations detected in cfDNA were not in their tumor tissue, suggesting that cfDNA captures information not obtained by conventional biopsy due to tumor heterogeneity. Follow-up samples after more of 20 months from resection in 2 patients with no evidence of recurrence, did not detect mutations in cfDNA. Analysis of samples collected 10 months before HCC diagnosis in one patient, detected a TERT mutation at 8% of frequency (10% at the time of resection)

Conclusion: Analysis of mutations in cfDNA by massive sequencing identifies most of tumor somatic mutations of HCC patients; moreover, other mutations detected in cfDNA were not present in the tumor, suggesting it could overcome tumor heterogeneity. Its detection could have relevant implications in early diagnosis and its follow-up over time, could have prognostic implications in early detection of recurrence, optimizing clinical management of HCC.

SAT-473

Transition to the era of direct-acting antiviral changes in the prognosis of patients with hepatitis C virus-related hepatocellular carcinoma

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Background and aims: Since the usage of direct-acting antivirals (DAAs) in the Japanese field practice in 2014, the numbers of patients whose hepatitis C virus (HCV) was eradicated not only before the occurrence of HCC but also after receiving curative therapies have dramatically increased. In this study, we evaluated the impact of DAAs in patients with HCV-related HCC using 3 different time-period cohorts.

Method: Between 2003 and 2016, we retrospectively identified HCV-related early stage HCC patients who received curative therapies (either resection, percutaneous ethanol injection [PEI], or radio-frequency ablation [RFA]) from the database of our institution and divided them into 3 cohorts (group A: 2003-2006, group B: 2007-2011, and group C: 2012-2016).

Results: Of the 453 HCV-related early stage HCC patients, 128, 161, and 164 patients belonged to groups A, B, and C, respectively. The median ages of groups A, B, and C patients were 68 years [range: 46-84], 71 years [range: 39-86], and 71 years [range: 45-85], respectively. The resection rates were similar in all 3 groups (group A: 23.4%, group B: 21.7%, and group: 23.1%). Of the 128 patients in group A, 4.7% and 4.7% patients achieved sustained virological response (SVR) before and after the occurrence of HCC, respectively. Both the rates were significantly increased in groups B and C (9.3% and 13.0% in group B and 20.7% and 36.5% in group C, respectively; $p < 0.0001$). The 5-year survival rate in group C were significantly higher than in groups A and B (group A: 55.6%, group B: 61.7%, group C: 73.6%; $p = 0.0015$). Similarly, of the 400 patients who did not eradicate HCV at the time of occurrence, the 5-year survival rate of group C was significantly higher than that of groups B and C (group A: 55.0%, group B: 58.7%, group C: 71.4%; $p = 0.0070$).

Conclusion: The prognosis of HCV-related HCC receiving curative therapies significantly improved during the era of "DAAs."

SAT-474

Misdiagnosis of focal liver lesions by means of CEUS

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Background and aims: Contrast Enhanced Ultrasound (CEUS) has become the method of choice for many practitioners for the evaluation of Focal Liver Lesions (FLL) detected by standard ultrasound. In real life though some lesions may not follow the classical enhancement pattern described by EFSUMB guidelines. The **aim** of this paper is to assess the FLL's that were misdiagnosed or inconclusive in CEUS in our monocentric cohort.

Method: The analysis was performed on 979 FLL's that were evaluated by CEUS by 4 ultrasound experts. All FLL's were judged according to EFSUMB-CEUS guide lines (1) and had a second line imaging method (CT, MRI) or histology as a refference method. Using the refference method for the final diagnosis we highlighted the most frequent lesions that were misdiagnosed or inconclusive and the issues that may lead to misdiagnosis in CEUS.

Results: from the 979 FLLs, 123 (12.5%) FLL's were misdiagnosed and 227 (23.1%) inconclusive for the CEUS final diagnosis. From the misdiagnosed lesions the most frequent were: 31.7% HCC; 24.3% Metastasis; 17.8% Hemangioma; 8.9% FNH; From the 227 inconclusive lesions, 115 were classified as benign or malignant, the rest of 112 lesions were considered fully inconclusive at CEUS. The most frequent inconclusive lesions were: 37% HCC, 5.2% dysplastic nodules, 4.8% cholangiocarcinoma, 13.6% metastasis, 11.8% hemangioma. The size of the lesions and the age of the patients did not influenced the correct CEUS diagnosis [size: 4.3 ± 3.2 cm (350 lesions) vs. 4.5 ± 3 cm (629 lesions) P = **0.3293**], [age: 59.1 ± 13 years vs. 60 ± 12.3 years, **p = 0.2902**]. From the 350 FLL's (misdiagnosed or inconclusive), 42.8% (150/350) were present on advance liver fibrosis while only 29.4% (185/629) from the FLL's that were corectlly diagnosed by CEUS were detected on advance liver fibrosis. (**p < 0.0001**)

Conclusion: In our cohort, 12.5% of the FLL's were misdiagnosed by CEUS. The misdiagnosis was not influenced by the size of the lesions or by the age of the patient but was influenced by advance liver fibrosis.

SAT-475

Clinical validation of the role of contrast-enhanced ultrasound in the EASL guidelines for the diagnosis of hepatocellular carcinoma

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Background and aims: Contrast-enhanced ultrasound (CEUS) of liver nodules after an inconclusive CT/MRI was endorsed in the 2018 EASL guidelines for the management of hepatocellular carcinoma (HCC), but no validation of this flowchart exists to verify whether using CEUS as second diagnostic line is useful or a waste of resources. Thus, this observational study aims to validate the role of CEUS in the diagnosis of HCC in real clinical practice.

Method: During a 6 months period, we prospectively enrolled patients at risk of HCC with liver nodules submitted to CEUS for the characterization of liver lesions. Exclusion criteria: CEUS performed to study treatment outcome, portal vein thrombosis or to choose target lesion, CT/MRI performed ≥ 3 months apart from CEUS. The theoretical impact of CEUS on the clinical decision was then assessed.

Results: A total of 43 patients (mean age 64y) with conditions at risk for HCC underwent CEUS to characterize 64 liver nodules (median diameter 19 mm, range 6-91 mm). A total of 12 lesions were excluded as not receiving CT/MRI within < 3months from CEUS (none with a pattern of HCC). A total of 20 of the 52 remaining nodules received a diagnosis of HCC by CT/MRI. CEUS showed no case of LRM class (which would suggest a non-hepatocellular malignancy prompting biopsy), thus provided no additional benefit in this setting (in keeping with the guidelines). Conversely CEUS showed an HCC pattern in 4/32 (12.5%) nodules (4/16 patients, 25%) without a diagnosis of HCC at first CT/MRI. Of the remaining 28 cases one was LRM (and confirmed metastasis at histology), while no other showed the HCC pattern. Of these 4 typical HCC nodules 1 was diagnosed as such by biopsy, 1 by MRI after an inconclusive CT, 1 by repeating MRI in 2 months, 1 was not biopsied because of poor clinical conditions with ascites, but exams showed AFp > 250.000 ng/ml.
Conclusion: The present observational prospective study validates the effectiveness of CEUS according to the diagnostic flowchart of the 2018 EASL guidelines for HCC. In particular using CEUS in second line after an inconclusive CT or MRI investigation was shown to be able to provide a correct diagnosis of HCC in 12.5% of cases missed by CT or MRI.

SAT-476
Discordance between clinical judgement and genetic differentiation of intrahepatic metastasis and multicentric occurrence in multinodular HCC

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Background and aims: It is important to differentiate between IM and MC in multinodular HCC for its treatment strategy. The differentiation has been dependent on image finding or pathological observation of each tumor, while the criteria remains obscure. The **AIMs** of the present study were to elucidate genetic alterations in multinodular HCCs for differentiation between IM and MC, and to examine the accuracy of conventional criteria.
Method: Forty HCC patients (30 solitary and 10 multinodular, 99 lesions) were genetically investigated. Microdissected samples were analyzed employing a next generation sequencer (NGS). We performed targeted sequencing covering 72 SMGs reported to be associated with HCC in TCGA or ICGC. **Intra nodules analysis:** As a validation analysis, genetic clonality among pathologically distinct components within each HCC nodule (13 nodules, 33 lesions) was analyzed. **Inter nodules analysis:** Multinodular HCCs were tested whether each tumor possesses common genetic alterations (IM) or not (MC) (10 patients; 27 nodules). The results of genetic differentiation were compared with conventional clinical judgement.
Results: Intra nodular validation analysis revealed that pathologically distinct components within HCC nodule possessed common trunk mutations, such as *TERT* promoter, *TP53*, or *CTNNB1*, implying their monoclonal origin despite pathological heterogeneity. In inter nodular analysis, MC was identified in 2 cases without common genetic alterations, and IM was diagnosed in 7 cases. In a case with 4 nodules, 2 nodules had common mutations, while others not, being mixture of IM and MC. Intriguingly, in a MC case with 3 neighboring nodules, who was diagnosed as IM on image analysis, no common genetic mutation was detected among those moderately differentiated HCCs. The concordance rate between genetic differentiation and conventional clinical judgement was about 50%.
Conclusion: There is limitations in conventional diagnosis criteria for IM or MC in multinodular HCCs. Elucidation of genetic clonality in each tumor is critical for better understanding of pathophysiological features of multinodular HCCs.

SAT-477
Impact of skeletal muscle quality and quantity on outcomes following curative therapy of hepatocellular carcinoma

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Background and aims: The quality and quantity of skeletal muscle are important in patients with malignant tumors to predict prognosis. In this study, we investigated the impact of skeletal muscle quality and quantity on outcomes after curative therapy in patients with Hepatitis C Virus (HCV)-related hepatocellular carcinoma (HCC).
Method: We investigated 223 patients (mean age 72 years, 131 liver cirrhosis) who underwent first hepatic resection or radiofrequency ablation for HCV-related HCC between January 2004 and December 2013. The quantity and quality of skeletal muscle, indicated by psoas muscle mass index (PMI) and intramuscular adipose tissue content (IMAC), were measured in pre-therapeutic computed tomography images at the L3 level by manual tracing. Overall survival (OS) and recurrence-free survival (RFS) rates were compared according to PMI and IMAC, and prognostic factors were assessed.
Results: The OS rate in patients with low PMI and high IMAC was lesser than in those with high PMI and low IMAC ($p = 0.010$), with a mean survival time of 6.0 and 9.8 years, respectively. The RFS rate in patients with high IMAC was lesser than in those with low IMAC ($p = 0.036$). In multivariate Cox hazard analysis, liver cirrhosis (hazard ratio, 3.336; $P < 0.001$), low PMI and high IMAC (hazard ratio, 2.088; $P = 0.007$) and des-γ-carboxy prothrombin level (≥ 40 mAU/ml) (hazard ratio, 1.880; $P = 0.016$) were significant prognostic factors of poor OS, and hepatic resection (hazard ratio, 1.844; $P = 0.016$) and high IMAC (hazard ratio, 1.656; $P = 0.042$) were significant prognostic factors of poor RFS.
Conclusion: Loss in the quality and quantity of skeletal muscle is closely related to mortality and recurrence in patients with hepatocellular carcinoma.

SAT-478
Comparison of prediction models for hepatocellular carcinoma development in treatment naive chronic hepatitis B patients with cirrhosis

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Background and aims: There are various predictiction models for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB), but the prediction model for HCC in treatment naïve CHB patients is insufficient. Moreover, there's lack of studies on cirrhotic patients.
Method: This study enrolled 602 treatment naïve chronic hepatitis B patients with cirrhosis, who were treated with nucleoside/nucleotide (NUC : Entecavir or Tenofovir disoproxil fumarate). To identify the most favorable model for predicting the HCC development, we compared the areas under the receiver operating characteristic curve (AUROCs) of previous HCC prediction models and non-invasive predictive scores. And then we used the method of Delong et al. for the calculation of the standard error of the AUROC and of the difference between two AUROCs.
Results: After excluding patients developed HCC within 1 year NUC treatment or have missing data, 582 patients were enrolled. FIB-4 and modified PAGE-B showed higher predictive value than others (CU-HCC: 0.604, GAG-HCC: 0.612, REACH-B: 0.577, PAGE-B: 0.619, modified PAGE-B : 0.678, APA-B: 0.553, THRI : 0.58, FIB-4 : 0.61, FIB-4 after 1year treatment : 0.648, GPR : 0.608, APRI : 0.461).
Conclusion: In treatment naïve cirrhotic CHB patients, modified PAGE-B model and FIB-4 showed the highest predictive power, but their accuracy was poor. A new model for patients with cirrhosis is needed.

SAT-479

Analysis of the relationship between serum creatinine/cystatin C ratio and muscle mass in patients with hepatocellular carcinoma

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Background and aims: Sarcopenia is defined as a loss of skeletal muscle mass and strength, and its influences on various diseases has been one of the latest controversial research topics. It is strongly correlated with prognosis of patients with hepatocellular carcinoma (HCC). The ratio between blood creatinine (Cre) and cystatin C (CysC) values has been recently determined to have a potential role in screening sarcopenia. Therefore, this study aimed to investigate the relationship between serum Cre/CsyC ratio and muscle mass in patients with HCC using a large cohort.
Method: Among patients who underwent treatment for newly diagnosed HCC in our hospital from June 2009 to December 2016, those with available data for both Cre and CysC at the same time were identified. The skeletal muscle index at L3 level (L3-SMI) (cm^2/m^2) was calculated to evaluate muscle mass using CT imaging in patients with HCC. A correlation between Cre/CysC and L3-SMI was analyzed.
Results: Among the 622 patients with available Cre and CysC data, 435 (69.9%) were men, the median age was 71 years, and the mean body mass index was 23.9 ± 4.0. The number of each Child-Pugh classification was 496 (79.7%) in A, 121 (19.5%) in B, and 5 (0.8%) in C. Regarding HCC staging based on the Barcelona Clinic Liver Cancer stage, 376 (60.5%) were in the early, 144 (23.2%) in the intermediate, and 102 (16.4%) in the advanced stage. Cre/CysC was 0.66 ± 0.21, and L3-SMI was 42.35 ± 9.09, showing that Cre/CysC was significantly correlated with L3-SMI ($r = 0.186$, $p < 0.001$). A total of 522 patients had serum Cre level lower than the normal upper limit, indicating a stronger correlation between Cre/CysC and L3-SMI ($r = 0.352$, $p < 0.0001$); however, no significant correlation was observed in patients with serum Cre level higher than the normal upper limit ($r = -0.026$, $p = 0.788$).
Conclusion: This study confirmed that Cre/CysC can potentially be used as a simple marker associated with muscle volume. Additional validation studies should be conducted.

SAT-480

Long-term survivors in patients with hepatocellular carcinoma: An ITA.LI.CA report

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Background and aims: Hepatocellular carcinoma (HCC) is characterized by a poor prognosis but some patients reach a quite long survival, the predictors of the event not being fully elucidated. The aim of our study was to compare a long-term survival group (≥ 5 yrs) to a control group (< 5 yrs) to identify parameters associated with good prognosis.
Method: To conduct this retrospective case-control study a group of HCC patients with survival ≥ 5 years (cases, n = 568) and a control group of equal size (n = 568) with survival < 5 years were selected from the ITA.LI.CA. database, now including 6991 patients.
Results: Compared to controls, cases were less frequently cirrhotics (89.8% vs. 93%, $p = 0.04$) with less frequent portal hypertension (36.8% vs. 53.9%, $p < 0.0001$) and had at diagnosis better residual liver function (Child A in 82.7% vs. 69.5%, $p < 0.0001$). Moreover, they had their diagnosis more frequently during surveillance (80.1% vs. 71.4%, $p = 0.0007$), with less advanced HCC (in the majority of cases monofocal, whit a diameter ≤ 3 cm and in stage BCLC 0-A). The long-term survivors had been treated in 80.8% of cases with at least one curative therapy (resection or ablation) in their clinical history, against 56.6% of controls ($p < 0.0001$). At a multiple logistic regression analysis, variables significantly associated with survival were: surveillance, ECOG-PS, portal hypertension, tumor aspect (monofocal/multifocal), diameter of the largest liver lesion, AFP levels and BCLC stage. The discriminant analysis identified diagnosis under surveillance, main treatment and BCLC stage as the variables with better discriminant capacity between the two groups, correctly classifying 77.2% of the cases, overall.
Conclusion: Preserved liver function, early stage at diagnosis and radical treatment are associated with good prognosis. Surveillance confirms its usefulness being in this study a sound predictive factor of long-term survival.

SAT-481

Intratumoral mast cell infiltration and recurrence of hepatocellular carcinoma in patients undergoing orthotopic liver transplantation

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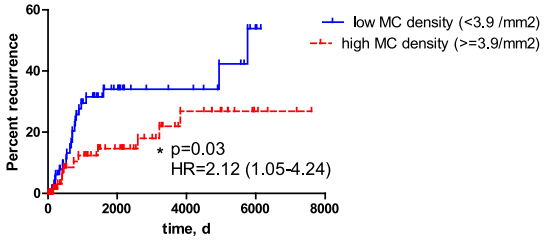
Background and aims: Tumor-infiltrating immune cells are highly relevant for prognosis as well as for discovery of immunotherapy targets in hepatocellular carcinoma (HCC). Recently, we provided evidence for altered mast cell infiltration and activation in tumor tissue of HCC patients by CIBERSORT immune cell profiling in combination with immunohistochemical (IHC) staining for the mast cell marker tryptase. Here, we retrospectively investigated the relevance of mast cells for HCC recurrence in an Austrian cohort of patients who underwent orthotopic liver transplantation (OLT).
Method: The Austrian HCC patient cohort included 172 patients (21 females, 151 males, 55.2+7.9 years, tumor staging 28/121/23 T1/T2/T3) who underwent OLT at the Medical University of Vienna. The underlying HCC etiologies comprised HCV infection (n = 70), alcoholic liver disease (n = 49), HBV (n = 16), and others (n = 22). Tissue microarrays (TMAs) from tumors and corresponding surrounding tissues were IHC-stained for tryptase. The TMA core diameter was 2 mm. Two cores per tumor and one core per surrounding tissue were analyzed for each patient. Tryptase-positive cells were quantified by tissue morphometric analysis and correlated with HCC recurrence.
Results: Mast cells were detected in 93% of HCC tumors (160/172) and in 100% of available surrounding liver tissues (n = 149). A low density of intratumoral mast cells (median mast cell density cut-off: 3.9 cells/mm^2) correlated significantly with a higher HCC recurrence rate (Fig.1, hazard ratio: 2.12, 95% confidence interval: 1.1-4.2; log-rank Mantel-Cox test p = 0.03) and was associated with a larger tumor size (Spearman correlation coefficient $r^2 = 0.237$, p = 0.001). Moreover, the mean number of tumors was significantly increased in patients with low density of intratumoral mast cells (2.7+0.2 cm vs. 2.2 +0.1 cm; p = 0.04 unpaired t-test, Welch correction).

Fig. 1. Intratumoral mast cell density and HCC recurrence (172 patients)



Conclusion: OLT-HCC patients with low mast cell density in tumor tissue have a higher risk for HCC recurrence, which is of prognostic importance. The underlying mechanisms and the impact of MCs on HCC biology require further investigation.

SAT-482

Incidence of hepatocellular carcinoma after hepatitis C cure with DAA in a cohort of patients with advanced liver disease: Results from a prospective screening program

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Background and aims: Although HCV cure with DAA (> 95%) is associated with a reduced risk of disease progression, the impact of DAA on hepatocellular carcinoma (HCC) occurrence is controversial. The aim of this study was to estimate HCC incidence after DAA in a cohort of patients with advanced liver disease by a prospective screening program.
Method: Prospective study including HCV-infected patients with cirrhosis or advanced fibrosis (F3, TE ≥ 9.5Kpa), without previous history of HCC, cured after DAA; patients should have a US imaging in < 30 days from inclusion excluding the presence of HCC or non-characterized nodules. All patients were evaluated every 6 months. Follow-up (FU) time was censored at the moment of event (HCC) or September 2018. HCC incidence was expressed in 100/patients-year (100PY) (IC95%). Adherence to screening was assessed.
Results: 275 patients signed inform consent; 90 patients were excluded (mainly due the absence of pre-DAA US in < 30 days); 185 patients were analysed: 52.4% men, age 65.1 [55.1-72] years. 34% (n = 63) patients were F3 (TE 11.5[10.1-12.1] KPa) vs 122 (65.9%) patients with cirrhosis (TE 18[14.3-26.6] Kpa): 87.7% Child-A, 17.2% history of decompensation, 40.9% varices in endoscopy, 39.3% TE ≥ 21Kpa. Adherence to screening program was 98.4% and 7 incident HCC were detected after a median clinical and radiological time of 27.5[24.7-33.9] and 23.9[23.4-24] months, respectively. Median time from SVR to HCC diagnosis was 24.5[17.3-30.7] months. Overall incidence of HCC was 2.01/100PY [IC95%: 0.9-4.2]. All HCC cases occurred in cirrhotic patients (incidence: 3.04/100PY [IC95%: 1.4-6.3]) with TE ≥ 21KPa (incidence in subgroup: 5, 93/100PY [IC95%: 2.9-11.8]. The 7 HCC cases [BCLC-0 (n = 3)/A (n = 3)/C (n = 1)] received specific treatment [percutaneous (n = 4), surgery (n = 1), TACE (n = 1); sorafenib (n = 1)]; 2 patients presented recurrence/HCC progression after 2.3 and 2.04 months of oncologic treatment. During FU, 7 patients died (3.78%), one due to HCC progression.
Conclusion: Risk of HCC persists in cirrhosis even if SVR is achieved with DAA (3.04/100PY). In this cohort, we did not identify any HCC in F3 patients (although the number of patients is limited). Moreover, in this specific cohort of patient without non-characterized nodules at baseline we did not find a time-association of HCC and DAA. Altogether, screening programs to rule out HCC are necessary in patients with cirrhosis achieving SVR; this risk should be further investigated in larger cohorts of F3 patients.

SAT-483

Hepatic epithelioid hemangioendothelioma: An international multicenter study

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Background and aims: Hepatic epithelioid hemangioendothelioma (HEHE) is a vascular neoplasm, more frequent in women than in man and usually arises in a non-cirrhotic liver. This is a very rare tumor (0.1-1/100, 000 person) and no prospective study on this population is available until today. The aim of this study is to describe the HEHE patients profile and the treatment of patients with this orphan condition.
Method: We performed an international (Sao Paulo, Salvador de Bahia and Barcelona-Clínic), retrospective and multicentric study which registered the baseline clinical, biochemical radiological and pathological features and all the evolutionary events that were available in the patient file. The images were centralized and pathologic samples were revised by three pathologists (MS, VA and CM) with more than 10 years of experience in liver cancer.
Results: From 1994 to 2016 we identified 27 patients with HEHE diagnosis in the patient reports but complete baseline clinical and laboratory data were available in 25 patients. One patient was diagnosed of a hepatic angiosarcoma at the moment of liver transplantation (LT) and finally excluded from this analysis. Median age was 38.7 years, the majority of patients were females (64%), without underlying chronic liver disease (76%). In 17 patients the diagnosis was incidental while 7 patients were symptomatic. Of the 24 included patients, 66.7% had multinodular disease and 50% presented extrahepatic disease at the diagnosis, all of them presenting at least lung involvement. Interestingly, 71% of the patients received a specific treatment such as chemotherapy (n:6), resection (n:7) or LT (n:4). The pathology revision was possible in 20 patients and the central radiologic evaluation only in 13 patients. The most frequent radiologic pattern, was a progressive central contrast uptake in 6 patients, followed by stable nperipheral enhancement without changes through the phases and persistent minimal uptake through all phases in 4 and 3 patients in each pattern, respectively. Median follow-up in the whole cohort was 80.2 months [IQR; 51.7 to 154.3], survival rate at 5- and 10-years were 91.5% and 51.9%, respectively. Eleven patients of the whole cohort developed progression and 7 died.
Conclusion: This multicentric study reflects the need of a better characterization and understanding of the natural history of this hepatic neoplasm. Active research through larger international consortia should define the molecular pathways involved in its development and allow an optimal treatment approach.

SAT-484

CEUS pattern of hepatocellular carcinoma: Prognostic implication

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Background and aims: American College of Radiology (ACR) has released the Liver Imaging Report And Data System (LI-RADS) scheme, which categorizes nodules in patients at risk for hepatocellular carcinoma (HCC) according to the degree of risk of nodules to be HCC as LR-3, LR-4, LR-5 (definitely HCC) and LR-M (probable malignancy not specific for HCC). EASL guidelines recommend biopsy for nodules not meeting the LR-5 class whereas LI-RADS policy, adopted by AASLD, largely include only imaging follow-up.
Aim of this study was to test whether HCC showing the CEUS pattern of indeterminate nodules (LR-3 and LR-4) are associated with better prognosis in terms of *Overall Survival* (OS) and *Recurrence-Free Survival* (RFS) than LR-5 (which could support LI-RADS/AASLD policy) or not (which would mandate EASL policy).
Method: Among 472 consecutive cirrhotic patients with liver nodules referred to our Centre (January 2005-December 2016), we retrospectively enrolled 98 patients with first diagnosis of single HCC according to 2012 AASLD guidelines (CT/MRI if typical or histology if CT/MRI were inconclusive) for whom a complete CEUS pattern, categorized according to the CEUS LI-RADS policy, was available.
Results: Median size of HCC lesions was 2.5 cm (range 1-7.2 cm). According to CEUS LI-RADS classification, 8 (8%) patients were in LR-3, 31 (32%) in LR-4, 54 (55%) in LR-5 and 5 (5%) in LR-M. Patient and nodule characteristics were not statistically different between LI-RADS classes. At univariate analysis CEUS LI-RADS class was not found to be a predictor of survival but statistically related to RFS (p = *0.029)*, since LR-M had shorter RFS than other classes. Also the LR-4 had shorter RFS than LR-5.
Conclusion: HCC showing the CEUS LI-RADS classes LR-3 and LR-4 have no better clinical outcome than typical HCC, therefore conclusive diagnostic investigation of indeterminate nodules up to liver biopsy is promptly requested to avoid leaving aggressive HCC not timely treated.

SAT-485

European cholangiocarcinoma (EU-CCA) registry: An initiative to broaden awareness on the second most common primary liver cancer

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Background and aims: Cholangiocarcinomas (CCAs) are classified into intrahepatic (iCCA), perihilar (pCCA) or distal (dCCA). Their etiologies are mostly unknown and their pathogenesis is poorly understood. Large international registries of CCA patients with demographic, biochemical, clinical and histopathological information are missing and necessary to better understand this disease and improve its management.
Method: The European CCA Registry is an international multicenter initiative supported by EASL (Registry Award 2016) that includes patients with CCA from 8 institutions and 4 countries in the secure online platform REDCap. Clinical data was retrospectively (2010) and prospectively (2016) collected by experts in the field.
Results: A total of 1, 011 records are entered, including 48% iCCAs, 23% pCCAs, 28% dCCAs and 1% CCA-HCC mixed tumors. Mean age at diagnosis was 65.6, and the male/female ratio 1:0.76. The most

common known risk factors were cirrhosis (6.4%), viral hepatitis (3.1% HCV; 1.8% HBV), diabetes (20.5%), obesity (15.2%), alcohol (17.2%) and presence of primary sclerosing cholangitis (PSC: 1.3%). Serum levels (mean; IU/L) of biochemical markers of cholestasis (GGT: 417; ALP: 313) and liver injury (ALT: 74.1; AST: 60.8), as well as non-specific tumor markers (CA19.9: 5, 138 UI/ml; CEA: 163 ng/ml) were altered. These biomarkers were considered for diagnosis together with imaging (53.1%: MRI, CT, USG, ERPC) and pathological (34.5%: biopsy/cytology) approaches. Tumor staging (TNM; AJCC 7th Edition) at diagnosis revealed that 39.7% of cases had stages I-III, 39.9% stage IV, and 20.4% unknown. Moreover, 38.9% of patients underwent surgical resection (R0-R1) (81.0% I-III; 12.2% IV; 6.8% unknown) with an overall survival (OS) of 18 months (IC95: 16-22). On the other hand, 61.1% of the tumors were unresectable: 70% (16.8% I-III; 59.7% IV; 23.5% unknown) received chemo- or locoregional therapies, and 30% did not receive treatment (10.2% I-III; 57.2% IV; 32.5% unknown). Chemo- or locoregional therapies provided an OS of 10 months (IC95: 9-11), whereas non-treated patients exhibited an OS of 4 months (IC95: 3-6).

Conclusion: This international initiative shows the current management of patients with CCA, and demonstrates the need of international collaborations to improve diagnosis, staging and treatment. The European CCA Registry, which also includes biological samples, emerges as a unique and extraordinary platform for future collaborative studies.

SAT-486

Short- and long-term effects of transarterial chemoembolization on portal hypertension in patients with hepatocellular carcinoma

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Background and aims: Transarterial chemoembolization (TACE) affects hepatic perfusion, and might impact on portal pressure in patients with hepatocellular carcinoma (HCC). However, the significance of these transient changes is unclear, since data on the impact of TACE on portal hypertension (PHT) and associated complications is limited.

Method: We report the secondary outcome "hepatic hemodynamics" from the AVATACE trial, a prospective randomized, placebo-controlled trial on the efficacy of TACE in combination with bevacizumab or placebo. Hepatic venous pressure gradient (HVPG) was measured at baseline (prior to 1st TACE), within 9 days ("acute effects"), 2 months ("intermediate effects"), and 6 months ("long-term effects") after 1st TACE.

Results: 28 patients with mainly intermediate stage HCC (BCLC B: n = 24, 86%) were included. N = 20 (71%) had clinically significant portal hypertension (CSPH, HVPG ≥ 10mmHg) at baseline (median HVPG 12 (IQR 9-19) mmHg). TACE neither had "acute effects" on HVPG (median after 2 days: 16 (IQR 7-20) mmHg p = 0.822) nor "intermediate effects" (median after 2 months/3 TACE, HVPG: 14 (IQR 6-18) mmHg, p = 0.223). However, in 13 patients with available HVPG measurement at month 6, there was a significant increase in HVPG (10 (IQR: 5-12) mmHg vs. 16 (IQR: 11-19) mmHg, p = 0.007). Changes in HVPG did not correlate with changes in MELD (Spearman's ρ = 0.305, p = 0.310). PHT-related complications exclusively occurred in patients with CSPH (8 (40%) vs. 0). Survival was not statistically significantly different between patients with vs. without CSPH at baseline (10 (95%CI: 4-16) vs. 15 (0-43) months, p = 0.201).

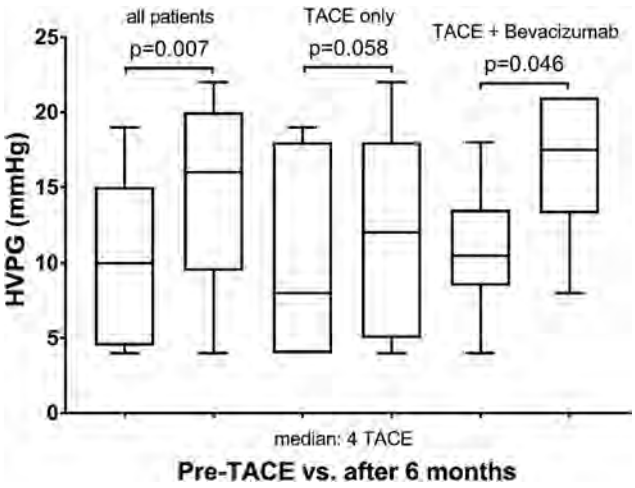

Figure: Long-term effects of repeated TACE (median: 4 procedures) on hepatic venous pressure gradient

Conclusion: Repeated TACE was associated with a significant long-term increase in HVPG. This finding should be considered when deciding whether to continue with TACE or switch to systemic treatment, since CSPH drives the development of complications.

SAT-487

Reliability of a single biopsy in evaluating immune tumor microenvironment of hepatocellular carcinoma

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Background and aims: Tumor heterogeneity has been repeatedly reported in hepatocellular carcinoma (HCC). Therefore, the reliability of a single tumor biopsy in evaluating immune tumor microenvironment (ITME) is often questioned. We conducted a prospective study to analyze the similarity of ITME from different parts of a single tumor.

Method: With patients' consent, multi-region random sampling was done from freshly resected tumors. The ITME was evaluated by conventional immunohistochemical staining as the composition of 8 immune cell types (CD4+ T, CD8+ T, CD20+ B, Foxp3+ Treg, CD68+ macrophage, MPO+ myeloid, DC-LAMP+ dendritic and NKp46+ NK cells). The density of immune cells (number/mm^2) was determined by whole-slide counting under 100X-fields. The similarity of ITME within a single tumor was evaluated by a multivariate Mahalanobis distance analysis, which measured the distance of a given point to the center of the dataset by taking both variance and covariance into account. Similarity in ITME of random samples within a tumor was defined as a distribution of distance within 0-10.

Results: Thirteen tumors were collected from 12 patients. The median diameter of tumor is 9 cm (range: 3-16 cm). A median of 6 samples (range: 3-12) were obtained from each tumor. Seventy-three samples were adequate for IHC analysis. The mean (range) immune cell densities per sample (/mm^2) were 175.9 (0.2-1213) for CD8+ T cells, 72.5 (0-326.7) for CD4+ T cells, 10.0 (0-58.2) for D20+ B cells, 30.8 (0-190.8) for Foxp3+ regulatory T cells, 286.1 (7.0-778.6) for CD68+ macrophages, 38.5 (0-420.7) for MPO+ myeloid cells, 1.4 (0-7.7) for DC-LAMP+ dendritic cells and 1.1 (0.1-6.6) for NKp46+ NK

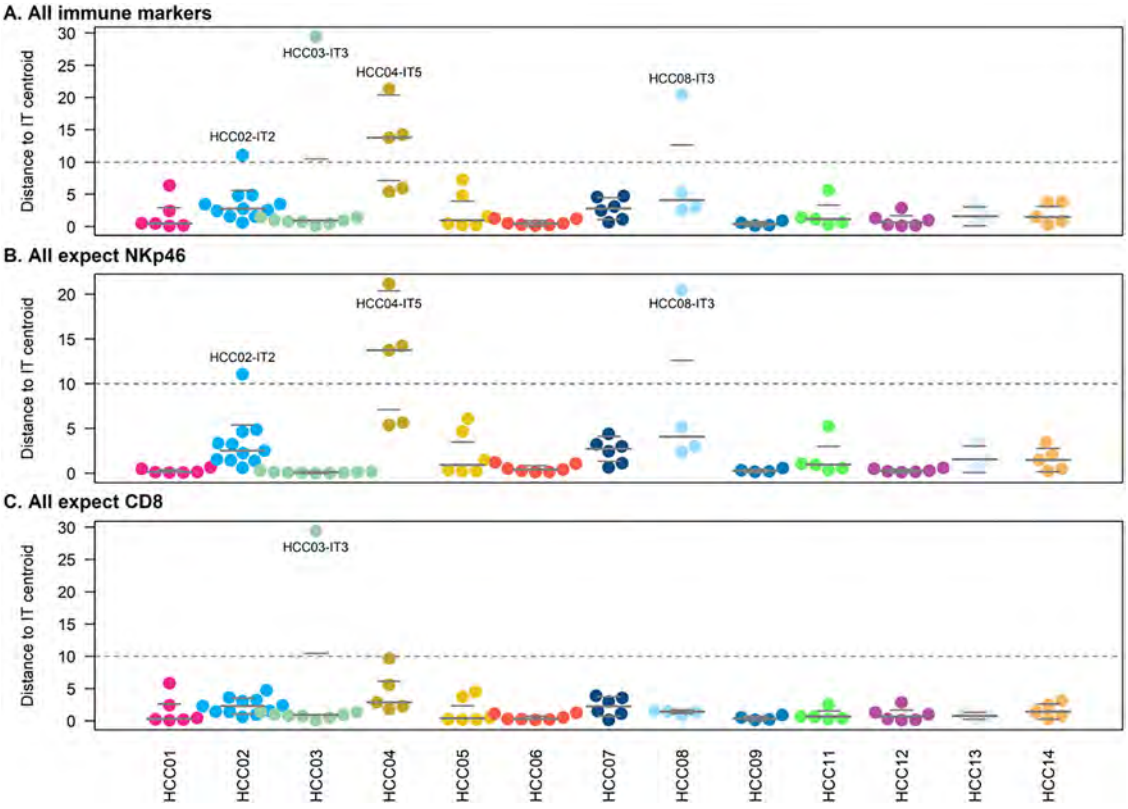

Figure: (abstract: SAT-487): Multivariate analysis of ITME of HCC by using Mahalanobis distance.

cells. Ignoring the rarest NKp46+ subpopulation, 10 out of 13 tumors (77%) showed similarity in ITME of the random samples within the tumor. The CD8+ T cell is the major contributor of dissimilarity in ITME of the rest 3 tumors (No. 2, 4, 8).
Conclusion: Random biopsy from a given HCC for quantification of tumor-infiltrating immune cells is adequate in the majority of patients.

SAT-488
Both ALBI/delta ALBI grade are good predictive parameters for prognosis in chc/hcc patients with transarterial chemoembolization treatment

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Background and aims: The prognosis of patients with hepatocellular carcinoma (HCC) is influenced by both the anatomic extent of cancer and liver reserve function. The Albumin-Bilirubin (ALBI) grade is a new index for liver function evaluation using only albumin and total bilirubin level. Its predictive role on outcome of HCC patients undergoing TACE is still undetermined. This study aimed to investigate the application of ALBI grade and dynamic change of ALBI grade (delta ALBI grade) after first TACE for prognosis prediction in CHC-HCC patients.
Method: From January 2005 to December 2015, freshly diagnosed naïve CHC-HCC patients that were treated with TACE as the initial treatment at the Chang Gung Memorial Hospital, Linkou Medical Center were retrospectively recruited. The pre-treatment host factors, tumor status and non-invasive markers were collected. The Cox regression model was used to identify independent predictors of overall survival.
Results: Among 613 treatment-naïve CHC-HCC patients, most (74.9%) were grade II/III at baseline. The median follow-up duration was 31.7 (range 3.0-129.0) months. 430 patients died after repeated TACE that more than half due to liver failure (n = 241, 56.0%) during median follow-up 26.9 months. Complete remission after repeated TACE occurred in 46.2% patients. 208 patients (33.9%) had tumor recurrence after complete remission with median recurrence free interval 8.5 months. By Cox regression analysis, ALBI grade II/III (aHR: 1.451, p = 0.005) and increased delta ALBI grade during treatment (aHR: 1.436, p = 0.006) were predictive factors while achieving complete response after repeated TACE (aHR: 0.373, p < 0.001) was a protective factor of mortality. The 2- and 5-year survival rate was lower in ALBI grade II/III (67.3%, 34.2% vs. 77.2%, 46.8%) and in increase delta ALBI grade patients (67.8%, 20.0% vs. 73.4%, 39.6%) (Log rank test, p = 0.023 and 0.039 respectively). Furthermore, ALBI grade II/III (aHR: 1.088, p = 0.035) and increased delta ALBI grade (aHR: 1.456, p = 0.029) were independent predictive factors related to tumor recurrence. The 1- and 2-year HCC recurrence rate was higher in ALBI grade II/III (54.3%, 74.3% vs. 43.9%, 61.7%) and in increase delta ALBI grade patients (71.1%, 86.8% vs. 52.0%, 72.0%) (Log rank test, p = 0.042 and 0.026 respectively).
Conclusion: Both ALBI and delta ALBI grade are independent parameters to predict survival and tumor recurrence of CHC-HCC patients receiving TACE treatment.

SAT-489
Efficacy and safety of thermal ablation in patients with hepatocellular carcinoma and high comorbidity

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Background and aims: Radiofrequency (RF) is the ablative method of choice in HCC BCLC-0/A not candidates for resection or transplantation. Microwave ablation (MW) is potentially more effective by avoiding the heat sink effect and achieving greater ablation volume. There is little evidence comparing RF vs MW (specially in Caucasian patients) and also about the prognosis in patients (pat.) with high comorbidity (hc). Describe the efficacy and safety of thermal ablation in pat. with hc (Charlson index > 3) with HCC.
Method: This is a retrospective observational unicentric study on pat. with HCC and high comorbidity who received RF/MW as initial treatment, decided on a multidisciplinary committee (MC). Visits were made at baseline, one more post-RF/MW and every 4 months if evidence of a complete response (mRECIST criteria), deciding the follow-up schedule in MC. Baseline variables (comorbidity, liver function, tumour burden), type of treatment, adverse effects, and clinical-analytical-radiological changes of each visit were recorded. RF was performed with cool-tip RF Ablation System (Medtronic) and MW with Solero MTA System (AngioDynamics) under deep sedoanalgesia.
Results: From Jan 2014 to July 2018, 163 pat. were treated and 86 met the inclusion criteria (44 RF/42 MW): 70 males, median age 69, range 50-85 years; 74 cirrhosis (66 Child-A, 8 Child-B7); Charlson index: median 8, range 4-14. Etiology: 39 alcoholic, 34 HCV, 6 NAFLD. Staging: 19 BCLC-0/67 BCLC-A; 70 uninodular, 50 subcapsular, median tumour diameter 25 mm (P25- P75 19-33). Complete response to the first ablation was observed in a 65.9%, being the most frequent recurrence adjacent to the ablation margin (73, 04%). There were 14% complications (decompensation of cirrhosis 2.3%), 1 death after colon perforation. Baseline characteristics, tumour burden and evolution were similar in RF vs MW, except basal platelets (RF: $128x10^3$vs MW: $131x10^3$, p = 0.006) and n° nodules [RF: 1 (n = 29), 2 (n = 11), 3 (n = 2) vs MW: 1 (n = 41), 2 (n = 3), 3 (n = 0), p = 0.012]. No differences were found in the complete response rate (p = 0.203) or in complications (p = 0.412). Median follow-up was 19 months, 12 transplanted, 16 deceased (10 due to comorbidity). The median overall survival, OS (n = 86) was 40 months, 95% CI 37.4-42.6, without differences between RF/MW (p = 0.234). The baseline factors associated with OS in the univariate analysis were age (p = 0.024), platelets (p < 0.01), serum creatinine (p < 0.01), Charlson index (p = 0.008), BCLC (p = 0.096) and AFP (p < 0.01); and in the multivariate BCLC (p = 0.022, HR 4.090, 95% CI 1.230-13.597), the Charlson index (p = 0.014, HR 0.104, 95% CI 0.017-0.635) and the AFP value (p = 0.012; HR 1.005; 95% CI 1.001-1.009).
Conclusion: Thermal ablative treatments are safe and effective in patients with high Charlson index. In our series, there were no differences in the complete radiological response rate or in the adverse events between RF and MW.

SAT-490

No impact of direct-acting antivirals on recurrent hepatocellular carcinoma tumour growth in the ANRS CO22 Hepather Cohort

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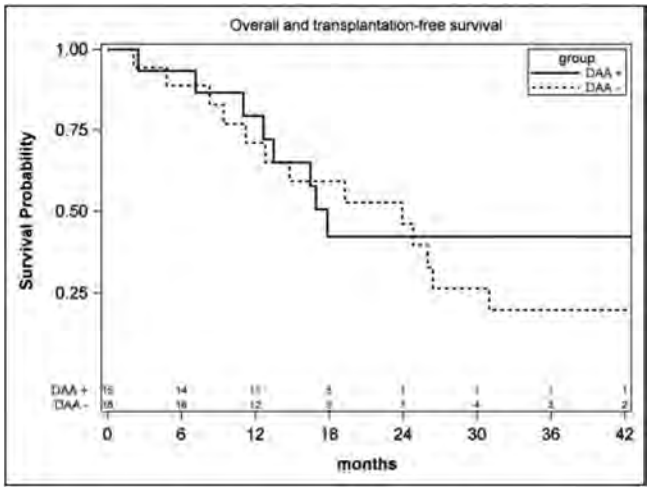
Background and aims: If a significant risk of hepatocellular carcinoma (HCC) associated with direct-acting antiviral (DAA) in HCV-infected patients has now been excluded, a putative effect of DAAs on tumor growth is still debated. We performed a blinded comparison of the kinetics of HCC recurrence after HCV treatment with DAAs (DAA+) or no treatment (DAA-).
Method: Blinded radiological re-evaluations (CT scan and/or MRI) of the 40 HCV-infected patients with HCC recurrence (J Hepatol 2016), 6 months before the HCC recurrence, at the time of recurrence and in the follow-up. Seven patients (17.5%) were excluded because the "curative" treatment was not confirmed (incomplete hepatic response in 6 and parietal HCC spreading). Thirty of the 33 patients were Interferon-experienced.
Fifteen DAA^+ patients (3 with PEG-IFN) before HCC recurrence (occurring 9 (0.3-33) months after treatment) were compared to the 18 DAA^- patients among whom 4 initiated DAA after HCC recurrence. The median (IQR) follow-up was 17 (13-23) in DAA^+ and 28 months in DAA^- (11-51) (p = 0.11).
Results: They were 24 men, with a median age of 62 (57-71) years and 31 (94%) had cirrhosis. The DAA^+ in comparison with DAA^- patients had a lower MELD score (7.5 vs 10.1, p = 0.03). The median delay of HCC recurrence (time between the date of curative treatment and diagnosis of recurrence) was not different (21 vs 17 months) (p = 0.28) between DAA^+ and DAA^-. There was no difference in the rate of unifocal recurrence (47 vs 33%, p = 0.85), of nodular (vs infiltrative) form (93 vs 100%, p = 0.45), in the median diameter of the largest nodule (14 vs 19 mm, p = 0.40), in the rate of portal invasion (6.7 vs 5.6%, p = 0.99).
Seven patients died in each group; 1 and 7 liver transplantations were performed in the DAA^+ and DAA^- groups, respectively without difference of the overall survival and (/or) transplantation-free survival (median 17.8 vs 23.9 months, respectively, p = 0.98) (Figure). There was no difference between the groups for the occurrence of new hepatic nodules (p = 0.78), and RECIST time to progression (p = 0.81).



Conclusion: This blinded analysis of HCC recurrence after curative treatment does not evidence a significant impact of DAA therapy on the delay, severity or progression of HCC. Despite it does not impact overall survival, it suggests that DAA treatment should be initiated in all cirrhotic patients, including those with prior history of HCC.

SAT-491

Assessment of liver function by 13C methacetin breath test may help to predict liver function deterioration after selective transarterial chemoembolisation of hepatocellular carcinomas

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Background and aims: Transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC) is associated with a risk of deterioration of liver function. The maximum liver function capacity test (LiMAx®) is a dynamic breath tests based on ^{13}C methacetin metabolism that reflects the hepatic functional mass. The aim of our study was to assess the potential of LiMAx to give more accurate information on decrease of liver function following TACE as compared to currently used routine parameters.
Method: Transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC) is associated with a risk of deterioration of liver function. The maximum liver function capacity test (LiMAx®) is a dynamic breath tests based on ^{13}C methacetin metabolism that reflects the hepatic functional mass. The aim of our study was to assess the potential of LiMAx to give more accurate information on decrease of liver function following TACE as compared to currently used routine parameters.
Results: Before the first TACE, LiMAx results revealed normal liver function, limited hepatic or significant hepatic impairment in 9, 18 and 10 patients. LiMAx results correlated intermediately with CPS (r = -0.54) and weakly with BCLC (r = 0.13) scores. At day 14 after TACE, all patients were still under observation including two with newly developed and one with shift from mild to moderate ascites, 3 with increase in CPS score, 3 and one with newly developed fatigue or pruritus, respectively, all of which had shown either limited or severe hepatic impairment by LiMAx ($^{13}CO2$ < 275 µg/kg/h) before TACE. Four patients with previously normal liver function by LiMAx had shifted to limited hepatic and one from limited to severe hepatic impairment.
Conclusion: Assessing liver function by ^{13}C methacetin metabolism may represent a novel tool for the early identification of patients developing deterioration of liver function after TACE. Our results need to be confirmed in larger cohorts and for different interventional treatments for HCC.

SAT-492

Associating spleen volume and liver stiffness measurements improves prediction of persistent post-hepatectomy decompensation after resection of hepatocellular carcinoma

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Background and aims: Liver Stiffness Measurement (LSM) by Transient Elastography (TE) could be useful for predicting persistent post-hepatectomy decompensation (PHD) with thresholds around 22kPa (ref). However, there is a so-called "gray zone" (15 to 22kPa) where prediction of outcomes remains challenging and this might condition the use a composite score including another factor. Spleen volume, a parameter associated to portal hypertension, could improve patient selection in association with LSM.
Method: Patients who underwent hepatectomy at our tertiary center were included in a prospective database, all patients operated for HCC between august 2014 to December 2017 were considered for inclusion in the study. Follow-up results were analyzed beyond three months. Spleen volume was measured using dedicated software and Liver Stiffness Measurements were obtained with Transient Elastography. Morbidity/Mortality was defined accoding to Clavien-Dindo classification. Post-hepatectomy liver failure was defined by the "50:50 criteria" and PHD if ascites, jaundice or encephalopathy were present after three-month follow-up.
Significant preoperative variables were included for multivariate analysis and bootstrapped at 1, 000 to determine independent factors for PHD. ROC curves were performed to determine LSM and SV cut-off points and diagnostic ability. Thereafter, a theoretical decision tree model was created and compared the diagnostic ability with and without the presence of SV in the algorithm.
Results: One hundred and sixteen patients were analyzed. The median of number of lesions was 1 (1-9) and the tumor size was 3.5 cm (0.7-45). Laparoscopic resections were made in 35% of patients. PHD was found in 9.5% (n = 11). Mortality rate was 4.3% (n = 5). LSM had a cut-off point of 11.6kPa (AUROC 0.71 CI 95% 0.71-0.88) with a sensitivity of 89%, specificity of 47% with a PPV of 14% and a NPV of 98%. The SV showed a cut-off point of 380 cm^3 (AUROC 0.77 CI 95% 0.77-0.93) with a S: 55%, Sp: 91%, PPV 38.5% and NPV 96%. SV and LSM did not have a correlation above the threshold of 11.6kPa (r = 0.156 p = 0.152).
A theoretical decision tree model was created using LSM with or without SV. ROC curves were obtained. If SV was retained, there was an increase in Sensitivity (from 61.5% to 96.7%) and NPV (from 96.4 to 100%) but also a decrease in Specificity (From 96.7 to 93.4) and PPV (from 64 to 59.1%) (p = 0.0034).
In the cohort, 8.6% of the patients with LSM > 11.6kPa developed PHD; however 36% of patients with both LSM > 11.6 and SV > 380cm^3 presented it. None of the patients without any of the conditions had PHD.
Conclusion: Associating SV to LSM improves prediction of PHD. Given the non-invasive nature of these tests, they can be used for selection of patients with HCC who are fit for liver resection.

SAT-493

Prevalence and clinical significance of intrahepatic cholangiocellular carcinoma with radiological enhancement pattern mimicking hepatocellular carcinoma

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Background and aims: Non-invasive diagnosis of hepatocellular carcinoma (HCC) in patients with cirrhosis requires demonstration of wash-in and wash-out on contrast imaging. Recent studies reported misclassification with intrahepatic cholangiocarcinoma (ICC). To analyze the radiological enhancement patterns of ICC and their association with prognosis, with particular interest to lesions mimicking HCC.
Method: We retrospectively evaluated all consecutive patients affected by ICC undergoing surgery between 2007 and 2017. Patients with mixed HCC-ICC were excluded. Two expert radiologists reviewed the arterial and portal/late phases of preoperative CT and

MRI. Full-nodule hyper-enhancement in arterial phase and hypo-enhancement in portal/late phase was classified as "HCC-like pattern." Imaging of ICCs with HCC-like pattern was reviewed by an additional radiologist blinded to clinical data.

Results: We reviewed imaging of 92 patients (mean age 68 years; males 49%; cirrhosis 18%) including multiphase CT in all and MRI in 85 (92%). Sixty-six (72%) tumors showed arterial hyper-enhancement, categorized as: full-nodule (12/66, 13%), > 25% of nodule (20/66, 22%) and peripheral (34/66, 37%). The remaining ICCs were either iso-enhancing (4%) or hypo-enhancing (24%). Among 12 ICCs with full-nodule arterial enhancement, 4 were hypo-enhancing in portal/late phase (HCC-like pattern), including 1 cirrhotic patient.

Overall, 4/92 (4%) ICCs (4/45 cirrhosis/hepatitis, 9%) showed a HCC-like pattern accounting for misclassification as HCC on imaging review. HCC-like ICCs accounted for 9% of single tumors ≤ 50 mm. All HCC-like ICCs arose on liver cirrhosis or hepatitis (100% vs. 47% for non-HCC-like ICCs, p = 0.053).

After a median follow-up of 29 months, 3-year survival was 62%. All patients with HCC-like ICCs are alive and disease-free (median 64 months), whereas peripheral rim enhancement was associated with a shorter 3-year survival (48% versus 70%).

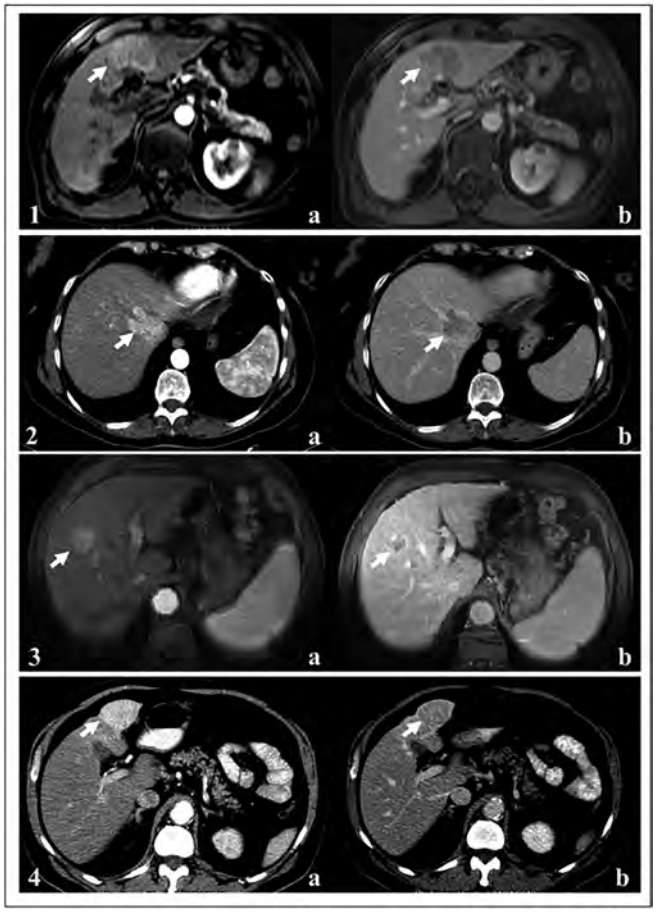

Figure: ICC with a full-nodule wash-in (a) and wash-out (b) pattern at CT or MRI contrast-enhanced imaging, mimicking typical features of HCC.

Conclusion: ICC can be misdiagnosed as typical HCC in 4% of cases, 9% of single tumors ≤ 50 mm or of tumors on cirrhosis/hepatitis. HCC-like ICCs show a favorable survival compared to ICCs with peripheral rim enhancement. The risk for misdiagnosis should be considered before treatment planning.

SAT-494

Global hepatocellular carcinoma mortality trends: An analysis of the world health organization cancer mortality database

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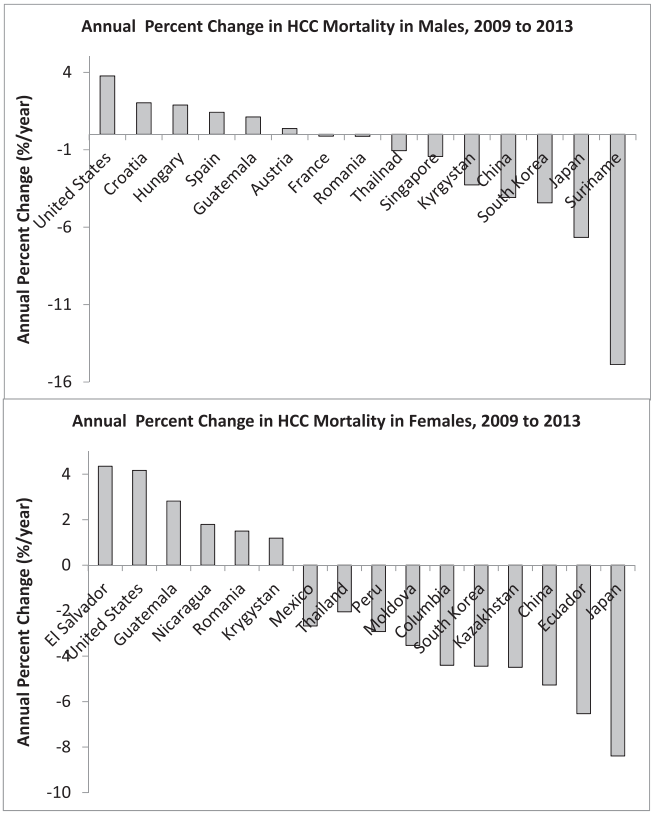
Background and aims: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide. HCC mortality is influenced by multiple factors including etiology of liver disease, successful implementation of HCC surveillance, and access to HCC therapies, among which there is significant variation across world regions. Identifying regions with persistently high HCC mortality can help target public health resources to those in need. We aim to evaluate country-specific disparities in HCC mortality trends using World Health Organization's (WHO) Cancer Mortality Database.

Method: We retrospectively evaluated 2004-2013 WHO cancer mortality data to identify adults (age 35-74 years) with histologically confirmed HCC across 58 countries. Age-standardized sex-specific mortality rates were calculated based on country-specific population data and presented as mortality rate per 100, 000 persons. Annual percent change (APC) in HCC mortality was evaluated using a simple regression model to the log of the adult survival rate.



Results: Overall HCC mortality among men was highest in South Korea (63.56 per 100, 000 persons) and Thailand (63.31 per 100, 000 persons), both significantly higher than the country with the next highest HCC mortality, China (43.36 per 100, 000 persons, p < 0.001). HCC mortality in women was highest in Thailand (22.77 per 100, 000 persons) and Guatemala (22.39 per 100, 000 persons), both significantly higher than the country with the next highest mortality, South Korea (14.55 per 100, 000 persons). Within each country, HCC

mortality was significantly higher in men compared to women. For example, HCC mortality in men was nearly 4 times higher than women in a high HCC mortality region such as South Korea (63.56 vs. 14.55 per 100, 000 persons, p < 0.001), with similar observations in a lower HCC mortality region such as Spain (14.88 (men) vs. 3.83 (women) per 100, 000 persons, p < 0.001). While South Korea, Thailand, and China had the highest HCC mortality among men, all three countries reported overall declining mortality from 2009 to 2013 (APC: South Korea, 4.43% decline; Thailand, 1.06% decline; China, 4.08% decline). While Thailand, Guatemala, and South Korea had the highest HCC mortality rates among women, only Thailand (APC, 2.95% decline) and South Korea (APC, 4.44% decline) demonstrated decreasing mortality from 2009-2013, whereas HCC mortality increased in Guatemala (APC, 4.17% increase).

Conclusion: Significant country-specific and sex-specific disparities in worldwide HCC mortality were observed. While HCC mortality rates have declined in many world regions, countries with rising HCC mortality require greater attention to identify potential gaps in the HCC care cascade so that quality improvement programs can be implemented to improve global HCC outcomes.

SAT-495

Incidence and risk factors of hepatocellular carcinoma in patients with hepatitis C in China and the US

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Background and aims: Hepatitis C virus (HCV) infection is the main cause of HCC in the US and an increasingly common cause of HCC in China. We aimed to evaluate the incidence and risk factors of HCC in HCV patients in China and the US.

Method: HCV RNA+, HBsAg- patients without HCC were prospectively recruited from 2 centers in China and 1 center in the US using a standardized protocol. Diagnosis of HCC was based on predefined criteria and radiology/pathology reports. Competing-risk Cox regression was used to identify risk factors for HCC with SVR as time-dependent covariate.

Results: 795 US and 854 Chinese patients followed for a median of 3.06 and 3.99 years, respectively were analyzed. US patients were significantly more likely to be men (57.4% vs. 48.2%), older (median 57 vs. 53 years), have cirrhosis (45.4% vs. 16.2%), diabetic, have current or past use of alcohol, cigarettes and coffee, and lower prevalence of anti-HBc. 45 US patients and 13 Chinese patients developed HCC. Cumulative incidence of HCC at 5 years was significantly higher in the US than in the Chinese cohort, 7.6% vs. 1.8% (p < 0.0001), which was driven by the higher prevalence of cirrhosis in the US patients. None of the patients with APRI < 0.5 or FIB-4 < 1.45 developed HCC. In the 10 patients without cirrhosis at enrollment who developed HCC, the median APRI was 2.03 and FIB-4 4.49 compared to 0.55 and 1.67, respectively in those who did not develop HCC. 53.7% of US and 50.6% of Chinese patients achieved SVR. HCC developed in 8 patients with cirrhosis but none of the patients without cirrhosis, after achieving SVR. Multivariate analysis showed that age, gender, cirrhosis and APRI were predictors of HCC while study site and SVR were not. SVR was associated with significantly lower incidence of HCC when analyzed as binary variable with hazard ratio of 0.16 (0.08-0.33) overall, and 0.22 (0.11-0.46) for cirrhosis patients.

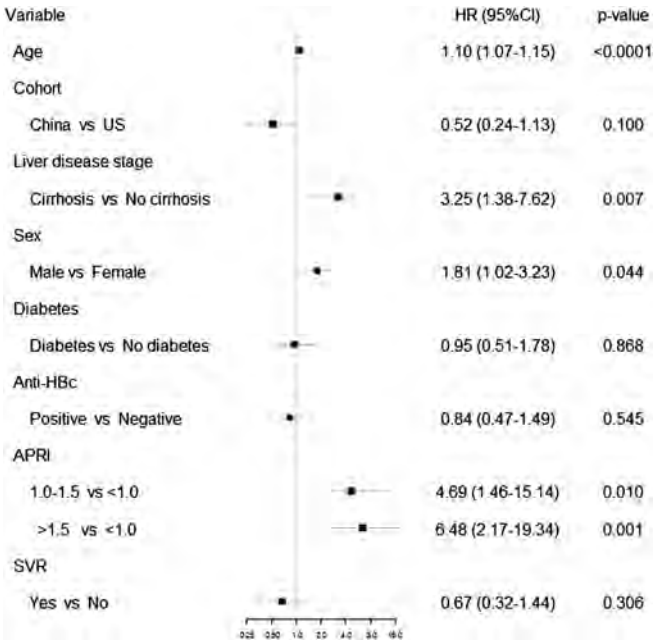

Figure: Multivariate Cox regression analysis of predictors of HCC

Conclusion: In this study of HCV patients, HCC incidence in the Chinese cohort was lower than in the US cohort, due to lower proportion of Chinese patients with cirrhosis. APRI and FIB-4 can identify risk of HCC among patients not diagnosed to have cirrhosis. Incidence of HCV-related HCC in China and the US will continue to increase unless patients are treated prior to cirrhosis development.

SAT-496

Circulating cell-free HBV-human chimera DNA as new marker for HCC recurrence and clonality after curative resection

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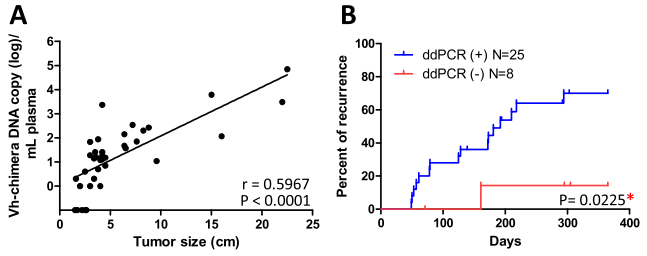
Background and aims: Early stage hepatocellular carcinoma (HCC) is treated by curative therapies, such as surgical resection or RFA. However, about 20-50% of patients develop tumor recurrence within the first year, indicating the frequent presence of minimal residual HCC after curative therapies. Alpha-fetoprotein (AFP) is the only biomarker currently used in clinical diagnosis for residual HCC but with limited sensitivity and specificity, and a better biomarker is an unmet need. This study examined the HBV-human chimera DNA (vh-DNA), generated from junctions of HBV integration in HCC chromosome and released into blood, as a potential circulating biomarker in HBV-related HCC. As more than 90% of HBV-related HCC contain integrated HBV DNAs which randomly distribute in chromosomes, the vh-DNA becomes a signature biomarker for monitoring the presence and clonality of recurrent HCC in majority of cases.

Method: We established a capture-next generation sequencing (NGS) platform to identify the HBV integration sites in 42 resected HCC tissues. For individual HCC, the most dominant junction of HBV integration was chosen to design specific primer pairs for droplet digital PCR (ddPCR). The ddPCR was used to detect and quantify the HCC specific vh-DNA in plasma samples collected just before surgery and 2 months after surgery. Levels of vh-DNA were then correlated with HCC recurrence in one-year follow-up.

Results: We succeeded in detecting HBV integrations in the HCC from 38 out of 42 HBV-related HCC patients (~91%), matching the performance of whole genomic sequencing. One specific signature vh-chimera was chosen from individual HCC of 38 cases, for detection

of circulating vh-DNA in the plasma (1 ml). The copy number of vh-DNA in plasma at surgery correlated well with the size of HCC, with the detection limit at 1-2 cm (Fig. 1A). Among the plasma collected at 2 months after surgery, two-thirds of samples contained the same signature vh-DNA as baseline plasma, indicating a possible residual HCC. Consistently, they suffered HCC recurrence more frequently than those without vh-DNA (Fig. 1B) in one year. The detection of same signature vh-DNA during HCC recurrence confirmed majority of recurrence within one year originated from the residual HCC escaping the surgical resection.



(A) Correlation between tumor size and plasma vh-DNA (copy number / mL plasma). (B) Recurrence analysis stratified by (+) or (-) of plasma vh-DNA detected by ddPCR.

Conclusion: This study supported vh-DNA as a new circulation marker for detecting minimal residual HCC in HBV-related HCC after surgery and for monitoring recurrence within one year of surgical resection. The marker warrants more investigations for clinical use.

SAT-497

Individual surveillance using PAGE-B score-based hepatocellular carcinoma risk in chronic hepatitis B patients under potent antiviral therapy

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Background and aims: Current guidelines for chronic hepatitis B (CHB) patients are to undergo surveillance for hepatocellular carcinoma (HCC) with ultrasonography (US) every 6 months. However, sensitivities of US to detect early stage HCC are suboptimal in cirrhotic patients. We aimed to compare detection rates of very early stage HCC based on the Barcelona Clinic Liver Cancer stage (BCLC 0) between two groups: group A under 6-monthly US surveillance vs. group B under 6-monthly alternate dynamic 4-phase computed tomography (CT) and US surveillance. In low-risk patients, detection rates of HCC within BCLC 0 were compared between patients under 6-monthly US and 12-monthly US surveillance.

Method: We examined 2,151 CHB patients under entecavir/tenofovir therapy in multicenter cohorts from 2007 to 2016. In intermediate- and high-risk patients based on the PAGE-B score, detection rates of HCC within BCLC 0 were compared between group A and B. In low-risk patients, detection rates of HCC within BCLC 0 were compared between patients under 6-monthly US and 12-monthly US surveillance. Primary end point was proportion of HCC within BCLC 0 in each group. Cox proportional hazards model was used to assess effect of surveillance modality on detection of HCC within BCLC 0 after balancing between the comparison groups using frequency matching.

Results: During a median follow-up of 4.3 years in the high-risk group (n = 584), 5-year cumulative HCC incidence rates in group A were 15.0% not significantly different from 18.2% in group B (p = 0.17). However, detection rates of HCC within BCLC 0 were significantly higher in group B than those in group A (p < 0.001). In multivariable analysis for detection of HCC within BCLC 0, surveillance modality using CT showed a significant association with detection of HCC within BCLC 0 (adjusted hazard ratio [HR] 3.89, 95% confidence interval [CI] 2.03-7.44, P < 0.001). In intermediate-risk patients (n = 1,063), 5-year cumulative HCC incidence rates in group A were 5.3% not significantly different from 5.8% in group B (p = 0.30). Detection rates of HCC within BCLC 0 between A and B were not significantly different (p = 0.22). In multivariable analysis for detection of HCC within BCLC 0, surveillance modality using CT did not show a significant association (HR 1.61, 95% CI 0.75-3.47, P = 0.23). In low-risk patients (n = 504), 5-year cumulative HCC incidence rates in patients under 6-monthly US surveillance were 0.7% not significantly different from 0.5% in patients under 12-monthly US surveillance (p = 0.80). All of patients were diagnosed with HCC within BCLC 0 irrespective of surveillance intervals.

Conclusion: In CHB patients at high risk, surveillance using alternate dynamic CT and US resulted in significantly higher detection rates of very early HCC as compared to continuous US surveillance. The PAGE-B scores enable clinicians to provide more individualized surveillance recommendations.

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26-28 Sep 2019

NAFLD Summit 2019

EASL meetings
Sevilla, Spain

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October 2019

EASL - AASLD ALD Endpoints

EASL meetings
USA

05-06 Oct 2019

December 2019

05-07 Dec 2019

EASL-AASLD Masterclass

EASL Courses, Schools & Masterclasses
Amsterdam, Netherlands

January 2020

Viral Hepatitis

EASL meetings
Athens, Greece

23-25 Jan 2020

February 2020

Feb 2020

Liver Cancer Summit 2020

EASL meetings
Prague, Czech Republic

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