

VOLUME 75 Suppl. 2 JULY 2021

ELSEVIER

JOURNAL OF HEPATOLOGY

The Home of Liver Research

THE INTERNATIONAL

LIVER CONGRESS™

BEATING LIVER DISEASE *together*

23-26 June 2021

ABSTRACT

BOOK

www.easl.eu

 **EASL™**
The Home of Hepatology



JOIN THE EASL COMMUNITY

Join us and become an active EASL member, part of the most forward-thinking and dynamic hepatology community in the world.

**Reduced fees to
The International Liver Congress™ and EASL meetings**

- + Journal of Hepatology
- + EASL Schools and Masterclass
- + EASL Fellowships and Mentorship
- + Funding support

Discover more benefits on:

www.easl.eu/join-the-community

JOURNAL OF HEPATOLOGY

The Home of Liver Research

EDITOR IN CHIEF

Paolo Angeli, Italy

DEPUTY EDITOR

Patrizia Burra, Italy

CO-EDITORS

Vlad Ratziu, France | Bruno Sangro, Spain |
Frank Tacke, Germany | Stefan Zeuzem, Germany

ASSOCIATE EDITORS

Alcohol and Drug-Related Liver Diseases

Einar S. Björnsson, Iceland
Alexandre Louvet, France

Cholestasis and Autoimmune Diseases

Tom H. Karlsen, Norway

Complications of Cirrhosis and Liver Failure

Paolo Caraceni, Italy
Javier Fernández, Spain
Constantine Karvellas, Canada

Disease Burden and Public Health

Gregory Dore, Australia

Genetics

Matias Ávila, Spain

Gut-Liver Axis

Bernd Schnabl, USA
Jonel Trebicka, Germany

Hepatic and Biliary Cancer

Jesper Andersen, Denmark
John Bridgewater, UK
Stephen L. Chan, Hong Kong
Jean-Charles Nault, France
Maria Reig, Spain

Imaging and Non-Invasive Tests

Annalisa Berzigotti, Switzerland
Rita Golfieri, Italy
Maxime Ronot, France

Immunology

Barbara Rehermann, USA

Liver Fibrosis

Massimo Pinzani, UK

Liver Surgery and Transplantation

Pierre-Alain Clavien, Switzerland
Julie K. Heimbach, USA
Francesco P. Russo, Italy

NAFLD

Quentin Anstee, UK
Elisabetta Bugianesi, Italy
Jacob George, Australia
Wajahat Mehal, USA

Pathology

Christine Sempoux, Switzerland

Statistics, A.I. and Modelling Outcomes

Anna Chiara Frigo, Italy
Marco Pavesi, Spain
Raphaël Porcher, France

Vascular Liver Diseases

Jordi Gracia-Sancho, Spain

Viral Hepatitis

Thomas Baumert, France
Maria Buti, Spain
Markus Cornberg, Germany
Edward John Gane, New Zealand
Man Fung Yuen, Hong Kong

Consultants

Julius Chapiro, USA
Peter Jepsen, Denmark

SPECIAL SECTION EDITORS

Reviews

Michael Trauner, Austria

Snapshot

Sara Montagnese, Italy
Alexander Ploss, USA

Website/Social Media

Jesus Bañales, Spain
Elliott B. Tapper, USA

EDITORIAL BOARD

Alcohol and Drug-Related Liver Diseases

Raul Andrade, Spain
Michael R. Lucey, USA
Philippe Mathurin, France
Laura E. Nagy, USA
Georges-Philippe Pageaux, France
Mark R. Thursz, UK

Basic Science

Javier Cubero, Spain
José Fernandez-Checa, Spain
Mathias Heikenwälder, Germany
Irene Ng, China
Cecilia Rodrigues, Portugal
Detlef Schuppan, Germany

Cholestatic and Autoimmune Diseases

Ulrich Beuers, Netherlands
Martti Färkkilä, Finland
Michael Heneghan, UK
Gideon Hirschfield, Canada
Pietro Invernizzi, Italy
Verena Keitel, Germany
Ansgar Lohse, Germany
Xiong Ma, China
Aldo J. Montano-Loza, Canada
Atsushi Tanaka, Japan

Complications of Cirrhosis and Liver Failure

Juan G. Abraldes, Canada
Banwari Agarwal, UK
Jasmohan S. Bajaj, USA
William Bernal, UK
Andrés Cárdenas, Spain
Claire Francoz, France
Guadalupe Garcia-Tsao, USA
Pere Ginés, Spain
Thierry Gustot, Belgium
Wim Laleman, Belgium
Mattias Mandorfer, Austria
Sebastian Marciano, Argentina
Salvatore Piano, Italy
Shiv K. Sarin, India

Puneeta Tandon, Canada

Reiner Wiest, Switzerland

Epidemiology/Public Health

Jeffrey Lazarus, Spain
Uwe Siebert, Austria

Genetics

Frank Lammert, Germany
Stefano Romeo, Sweden

Gut-Liver Axis

Sofia Forslund, Germany
Aleksander Krag, Denmark

Hepatic and Biliary Cancer

Ann-Lii Cheng, Taiwan
Laura Dawson, Canada
Peter R. Galle, Germany
Tim Greten, USA
Chiun Hsu, Taiwan
Katie Kelley, USA
Josep Llovet, USA
Tom Luedde, Germany
Tim Meyer, UK
Pierre Nahon, France
Hayato Nakagawa, Japan
Lorenza Rimassa, Italy
Jinil Seong, Republic of Korea
Beicheng Sun, China
Juan Valle, UK

Immunology

Mala Maini, UK
Elsa Solà, Spain

Liver Fibrosis

Scott Friedman, USA
Tatiana Kisseleva, USA
Isabelle Leclercq, Belgium
Robert E. Schwartz, USA
Thierry Tordjmann, France
Holger Willenbring, USA

Liver Surgery and Transplantation

Martina Gambato, Italy
Giacomo Germani, Italy

Vincenzo Mazzaferro, Italy

Rajender K. Reddy, USA
Alberto Sánchez-Fueyo, UK
Gonzalo Sapiochin, Canada
Christian Toso, Switzerland

NAFLD

Leon Adams, Australia
Guruprasad Aithal, UK
Helena Cortez-Pinto, Portugal
Henning Gronbaek, Denmark
Rohit Loomba, USA
Giulio Marchesini, Italy
Phillip N. Newsome, UK
Elizabeth E. Powell, Australia
Manuel Romero-Gómez, Spain
Arun Sanyal, USA
Jörn Schattenberg, Germany
Giovanni Targher, Italy
Luca Valenti, Italy
Grace Wong, Hong Kong
Vincent Wong, Hong Kong
Shira Zelber-Sagi, Israel

Non-invasive Diagnoses and Imaging

Jérôme Boursier, France
Laurent Castera, France
Thierry de Baere, France
Richard (Dick) L. Ehman, USA
Salvatore Petta, Italy
Jordi Rimola, Spain
Riad Salem, USA

Pathology

Karoline Lackner, Austria
Valerie Paradis, France
Peter Schirmacher, Germany
Dina Tiniakos, UK
Achim Weber, Switzerland

Pediatrics

Emmanuel Jacquemin, France
Pietro Vajro, Italy

Statistics, A.I. and Modeling Outcomes

Alex Amoros, Spain
Calogero Camma, Italy

Elisabet García, Spain

Jeremie Guedj, France

Vascular Liver Diseases

Yasuko Iwakiri, USA
Vincenzo La Mura, Italy
Pierre-Emmanuel Rautou, France

Viral Hepatitis

Alessio Aghemo, Italy
Sandra Ciesek, Germany
James Fung, Hong Kong
Jason Grebely, Australia
Ira Jacobson, USA
Patrick Kennedy, UK
Pietro Lampertico, Italy
Darius Moradpour, Switzerland
Jean-Michel Pawlotsky, France
Thomas Pietschmann, Germany
Charles Rice, USA
Jian Sun, China
Robert Thimme, Germany
Stephan Urban, Germany
Heiner Wedemeyer, Germany
Fabien Zoulim, France

EDITORS EMERITUS

Dame Sheila Sherlock†, Founding Editor, UK (1985-1989)
Jean-Pierre Benhamou†, France (1990-1994)
Gustav Paumgartner, Germany (1995-1999)
Juan Rodés†, Spain (2000-2004)
Massimo Colombo, Italy (2005-2009)
Didier Samuel, France (2010-2014)
Rajiv Jalan, UK (2015-2019)

EDITORIAL OFFICE

Manager

Joël Walicki

Coordinators

Jiyeong Adams
Duncan Anderson

Assistant

Kristina Jajcevic

Scientific Illustrator

Pablo Echeverría

EASL GOVERNING BOARD

SECRETARY GENERAL

Philip N. Newsome, UK

VICE SECRETARY

Thomas Berg, Germany

TREASURER

Francesco Negro, Switzerland

SCIENTIFIC COMMITTEE

Tobias Böttler, Germany
Pierre-Emmanuel Rautou, France
Maria Reig, Spain
Emmanouil Tsochatzidis, UK
Luca Valenti, Italy
Saskia van Mil, Netherlands

EDUCATIONAL COUNCILLORS

Ulrich Beuers, Netherlands

EU POLICY COUNCILLOR

Maria Buti, Spain

EASL Office
Journal of Hepatology Editorial Office
7 rue Daubin
1203 Geneva, Switzerland
Tel.: (+41) 22 807 03 67
Fax: (+41) 22 510 24 00
E-mail: jhepatology@easloffice.eu



EASL[™] |

CAMPUS



Open-access eLearning

Interactive training in the fields of
hepatology and liver-related disease

Now EACCME accredited
online modules and courses



Register on

www.easlcampus.eu



 **SCAN ME**

Application for EASL Membership can be done at <https://easl.eu/community/join-the-community/>

© 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

This journal and the individual contributions contained in it are protected under copyright, and the following terms and conditions apply to their use in addition to the terms of any Creative Commons or other user license that has been applied by the publisher and the European Association for the Study of the Liver to an individual article:

Photocopying: Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission is not required for photocopying of articles published under the CC BY license nor for photocopying for non-commercial purposes in accordance with any other user license applied by the publisher and the European Association for the Study of the Liver. Permission of the publisher and the European Association for the Study of the Liver and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

Derivative Works: Users may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions or companies. Other than for articles published under the CC BY license, permission of the publisher and the European Association for the Study of the Liver is required for resale or distribution outside the subscribing institution or company. For any subscribed articles or articles published under a CC BY-NC-ND license, permission of the publisher and the European Association for the Study of the Liver is required for all other derivative works, including compilations and translations.

Storage or Usage: Except as outlined above or as set out in the relevant user license, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the publisher and the European Association for the Study of the Liver.

Permissions: For information on how to seek permission visit www.elsevier.com/permissions.

Author rights: Author(s) may have additional rights in their articles as set out in their agreement with the publisher and the European Association for the Study of the Liver (more information at <http://www.elsevier.com/authorsrights>).

Notice: Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by the publisher or the European Association for the Study of the Liver for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

Publication information: *Journal of Hepatology* (ISSN 0168-8278). For 2021, volumes 74 and 75 are scheduled for publication. Subscription prices are available upon request from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (<http://www.elsevier.com/locate/jhep>). Further information is available on this journal and other Elsevier products through Elsevier's website: (<http://www.elsevier.com>). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of dispatch.

Orders, claims, and journal enquiries: Please visit our Support Hub page <https://service.elsevier.com> for assistance.

Advertising information: Advertising orders and enquiries can be sent to: **USA, Canada and South America:** Elsevier Inc., 360 Park Avenue, Suite 800, New York, NY 10169-0901, USA; phone: (+1) (212) 989 5800. **Europe and ROW:** Robert Bayliss, Pharma Solutions, Elsevier Ltd., 125 London Wall, London EC2Y 5AS, UK; phone: (+44) 207 424 4454; e-mail: r.bayliss@elsevier.com.

Author enquiries: You can track your submitted article at <http://www.elsevier.com/track-submission>. You can track your accepted article at <http://www.elsevier.com/trackarticle>. You are also welcome to contact Customer Support via <http://service.elsevier.com>.

Funding body agreements and policies: Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published by Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies>.

Special regulations for authors: Upon acceptance of an article by the journal, the author(s) will be asked to transfer copyright of the article to EASL. Transfer will ensure the widest possible dissemination of information.

USA mailing notice: *Journal of Hepatology*, ISSN 0168-8278 (USPS 11087) is published monthly by Elsevier B.V. Radarweg 29, 1043 NX Amsterdam, the Netherlands. Airfreight and mailing in the USA by agent named World Container Inc, 150-15, 183rd Street, Jamaica, NY 11413, USA. Periodicals postage paid at Brooklyn, NY 11256.

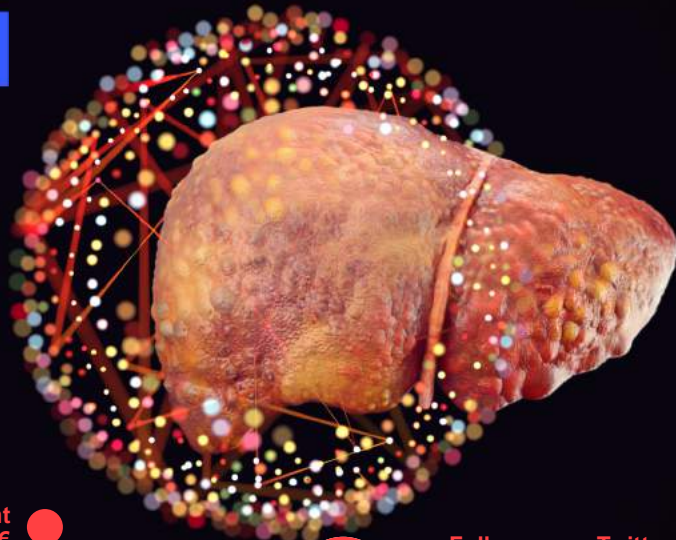
US Postmaster: Send address changes to *Journal of Hepatology*, World Container Inc, 150-15, 183rd Street, Jamaica, NY 11413, USA.

Subscription records are maintained at Elsevier B.V. Radarweg 29, 1043 NX Amsterdam, the Netherlands.

Air Business Ltd is acting as our mailing agent.

© The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Printed by Henry Ling Ltd., Dorchester, UK



kick-off
1st April 2020 ●

project duration
5 ½ years ●

10 countries
21 institutions ●

grant amount
6 million € ●

www.decision-for-liver.eu ●



Follow us on Twitter and LinkedIN:



Decision4Liver



decision-project

The objective of the **DECISION project**

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

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



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



JOURNAL OF HEPATOLOGY

VOLUME **75**, SUPPLEMENT **2**, PAGES **S191–S866**

Abstracts of The International Liver Congress™ 2021
June 23–26, 2021

Publication of this Abstract supplement was supported by the European Association for the Study of the Liver (EASL)

ELSEVIER



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

Discover more on litmus-project.eu



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

JOURNAL OF HEPATOLOGY

VOLUME 75, SUPPLEMENT 2, PAGES S191–S866

CONTENTS

General and Late breaker sessions	S191
General session I	S191
General session II	S197
Late breaker oral presentations	S201
Parallel Sessions	S205
Alcoholic liver disease	S205
Cirrhosis and its complications: ACLF and Critical illness	S208
Cirrhosis and its complications: Experimental and pathophysiology	S212
Cirrhosis and its complications: Other clinical complications except ACLF and critical illness	S212
Cirrhosis and its complications: Portal Hypertension	S215
Fibrosis	S217
Gut microbiota and liver disease	S220
Immune-mediated and cholestatic: Experimental and pathophysiology	S223
Immune-mediated and cholestatic disease: Clinical aspects	S225
Immunology	S230
Liver development, physiology and regeneration	S231
Liver transplantation and hepatobiliary surgery: Clinical aspects	S234
Liver tumours: Clinical aspects except therapy	S236
Liver tumours – Experimental and pathophysiology	S240
Liver tumours – Therapy	S243
Molecular and cellular biology	S248
NAFLD – Clinical aspects except therapy	S251
NAFLD – Diagnostics and non-invasive assessment	S255
NAFLD – Experimental and pathophysiology	S261
NAFLD – Therapy	S267
Non-invasive assessment of liver disease except NAFLD	S270
Nurses and Allied Health Professionals	S271
Public Health	S272

Rare liver diseases (including paediatric and genetic)	S277
Viral Hepatitis A, B, C, D, E: Virology	S281
Viral hepatitis B-D: Clinical aspects except therapy	S284
Viral hepatitis B-D: therapy	S287
Viral hepatitis C: Clinical aspects except therapy	S292
Viral hepatitis C: Therapy and resistance	S292
Posters	S294
Late breaker posters	S294
Acute liver failure and drug induced liver injury	S298
Alcoholic liver disease	S307
Cirrhosis and its complications: ACLF and Critical illness	S325
Cirrhosis and its complications: Experimental and pathophysiology	S334
Cirrhosis and its complications: Other clinical complications except ACLF and critical illness	S343
Cirrhosis and its complications: Portal Hypertension	S362
Fibrosis	S388
Gut microbiota and liver disease	S403
Imaging and drug targeting	S408
Immune-mediated and cholestatic – Experimental and pathophysiology	S417
Immune-mediated and cholestatic disease: Clinical aspects	S423
Immunology	S446
Liver development, physiology and regeneration	S457
Liver transplantation and hepatobiliary surgery: Clinical aspects	S460
Liver transplantation and hepatobiliary surgery: Experimental	S476
Liver tumours: Clinical aspects except therapy	S479
Liver tumours: Experimental and pathophysiology	S497
Liver tumours: Therapy	S512
Molecular and cellular biology	S527
NAFLD: Clinical aspects except therapy	S532
NAFLD: Diagnostics and non-invasive assessment	S556
NAFLD: Experimental and pathophysiology	S587
NAFLD: Therapy	S609
Non-invasive assessment of liver disease except NAFLD	S628
Nurses and Allied Health Professionals	S638
Public Health	S642
Rare liver diseases (including paediatric and genetic)	S677
Viral Hepatitis A, B, C, D, E: Virology	S695
Viral hepatitis A-E: Clinical aspects	S709

Viral hepatitis B-D: Clinical aspects except therapy	S709
Viral hepatitis B-D: therapy	S733
Viral hepatitis C: Clinical aspects except therapy	S763
Viral Hepatitis C: Post SVR and long term follow up	S778
Viral hepatitis C: Therapy and resistance	S791
Author Index	S804
Disclosures: no commercial relationships	S859
Disclosures: commercial relationships	S863
Reviewers list	S865

Registration of Clinical Trials

The *Journal of Hepatology* endorses the policy of the WHO and the International Committee of Medical Journal Editors (ICMJE) on the registration of clinical trials. Therefore, any trial that starts recruiting on or after July 1, 2005 should be registered in a publicly owned, publicly accessible registry and should satisfy a minimal standard dataset. Trials that started recruiting before that date will be considered for publication if registered before September 13, 2005.

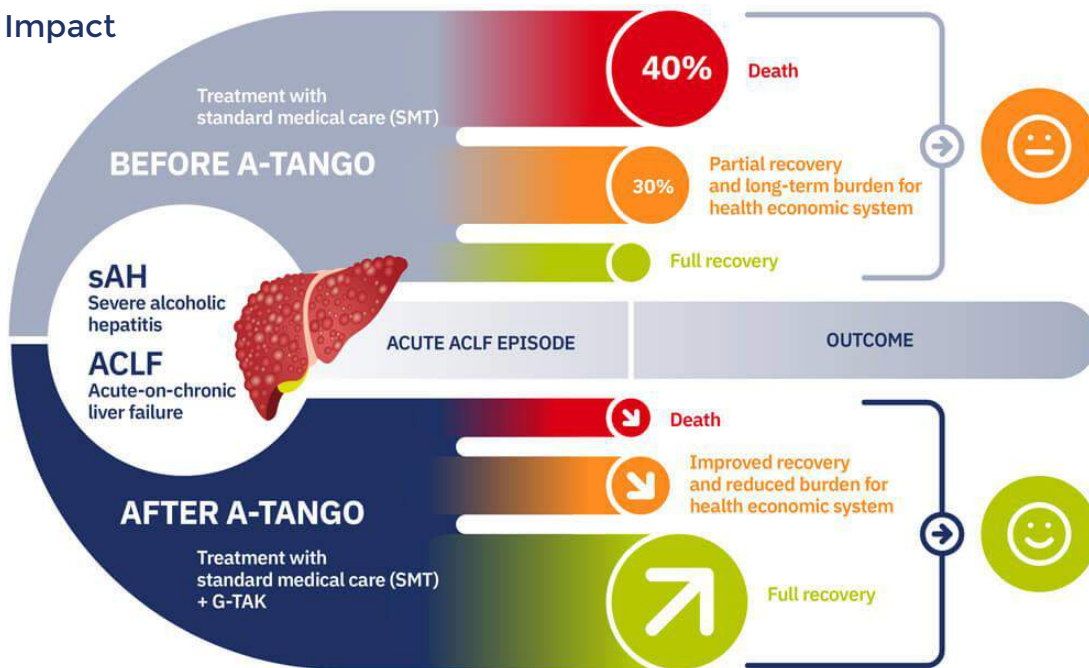
More detailed information regarding clinical trials and registration can be found in *New Engl J Med* 2004; 351:1250–1251 and *New Engl J Med* 2005; 352:2437–2438.

Available online at www.sciencedirect.com


ScienceDirect
 for online access via your library

The A-TANGO project - featuring G-TAK, a novel combinatorial therapy for acute-on-chronic liver failure (ACLF)

Expected Impact



- More than **10 million** people suffer from **decompensated cirrhosis** worldwide.
- Effective treatment of ACLF is an urgent and unmet need.
- A-TANGO performs **Phase II clinical studies of G-TAK**, a novel and innovative therapeutic strategy that aims to **reduce inflammation and improve hepatocyte proliferation**.
- A-TANGO also strives to identify **reliable biomarkers** for better patient stratification and increased survival.

project duration	grant amount	8 countries	kick-off
5.0 years	6.0 million €	14 institutions	1st March 2021

**14 partners, one goal:
Helping cirrhosis patients
in Europe!**



www.a-tango.eu
info@atango.eu



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 945096.



MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response



Project duration
6 1/4 years

Start
01 January 2019

Follow-us on Twitter and LinkedIn:

@MicrobPredict
 MICROB-PREDICT

Grant amount
15 million €

10 Countries
22 Partners

www.microb-predict.eu



will investigate

the human microbiome to identify predictors and mechanisms associated with the development of decompensation of cirrhosis and progression to **acute-on-chronic liver failure (ACLF) and death.**

- New microbiome-based tests for better stratification of cirrhosis patients
- Personalized prediction and prevention of decompensation and ACLF
- Clinical trial to predict response to treatment
- Modern, effective nanobiosensors as clinical tools with improved specificity
- More personalized treatment
- Increased survival times
- Decreased costs for the health systems



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

LIVER SCREEN

Screening for liver fibrosis population-based study across European Countries

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

AIM:

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



General session I

GS-1065**External validation of LCR1-LCR2, a multivariate HCC risk calculator, in patients with chronic hepatitis C**

Thierry Poynard^{1,2}, Jean-Marc Lacombe³, Olivier Deckmyn⁴, Valentina Peta⁴, Sepideh Akhavan², Victor de Lédighen⁵, Fabien Zoulim⁶, Didier Samuel¹, Philippe Mathurin⁷, Vlad Ratziu¹, Dominique Thabut¹, Chantal Housset⁸, Helene Fontaine¹, Stanislas Pol¹, Fabrice Carrat³. ¹Assistance Publique-Hôpitaux de Paris, Hepatology, Paris, France; ²Sorbonne Université, INSERM, Hepatology, Paris, France; ³Institut Pierre Louis d'Épidémiologie et de Santé Publique; ⁴Biopredictive, Research, Pars, France; ⁵Hôpital Haut-Lévêque, Hepatology; ⁶Hospices civils de Lyon, Hôpital Croix Rousse, INSERM, Hepatology; ⁷CHRU Claude Huriez, Lille; ⁸Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine (CRSA), Institute of Cardiometabolism and Nutrition (ICAN), Paris
Email: thierry@poynard.com

Background and aims: Liver cancer risk test algorithm (LCR1-LCR2) is a multi-analyte blood test combining proteins involved in liver cell repair (apolipoprotein A1, haptoglobin), known HCC risk factors (gender, age, GGT), a marker of fibrosis (alpha2-macroglobulin) and AFP a specific marker of HCC. The aim of the present study was to externally validate LCR1-LCR2 in patients with chronic hepatitis C, treated or not with antivirals agent.

Method: Pre-included Patients were from the Hepather cohort, a prospective study in adult patients with chronic HCV infection enrolled from 32 hepatology centers in France. LCR1-LCR2 was assessed retrospectively in the patients with the components and AFP, available at baseline. The co-primary study outcome was the NPV of LCR1-LCR2 at 5-years for the occurrence HCC and survival without HCC according to the predetermined LCR1-LCR2 cutoffs, adjusted for risk covariables and for the response to HCV treatment, quantified using time-dependent Cox proportional hazards models.

Results: A total of 4, 903 patients, 1, 026 (21.9%) with baseline cirrhosis, were included in the study. For a median of 5.7 (IQR 4.2–11.3) years, 3, 788 (77.3%) patients had a sustained virological response, 137 HCC occurred at 5 years and 214 at the end of followup. Twenty-four occurred at 5 years in 3, 755 patients with a low-risk LCR1-LCR2 vs. 113 in 1, 148 with a high-risk LCR1-LCR2. The NPV was 99.4% (95%CI 99.1–99.6). Similar findings (Cox hazard-ratio = 10.8; 8.1–14.3; $p < 0.001$) were obtained after adjustment for exposure to antivirals, age, gender, geographical origin, HCV genotype-3, previous alcohol consumption, and type 2-diabetes.

Conclusion: The performance of LCR1-LCR2 for identifying patients with chronic hepatitis C at very low risk of HCC at 5 years, was externally validated. **NCT01953458.**

GS-1072**Food Insecurity is Associated with All-Cause Mortality in U.S. Adults with Non-alcoholic Fatty Liver Disease and Advanced Fibrosis**

Ani Kardashian¹, Jennifer Dodge^{1,2}, Norah Terrault¹. ¹University of Southern California, Division of Gastrointestinal and Liver Diseases, Los Angeles, United States; ²University of Southern California, Department of Preventive Medicine, Los Angeles, United States
Email: ani.kardashian@med.usc.edu

This abstract is under embargo until the beginning of the press conference it is being presented in on Friday 25 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.



ORAL PRESENTATIONS

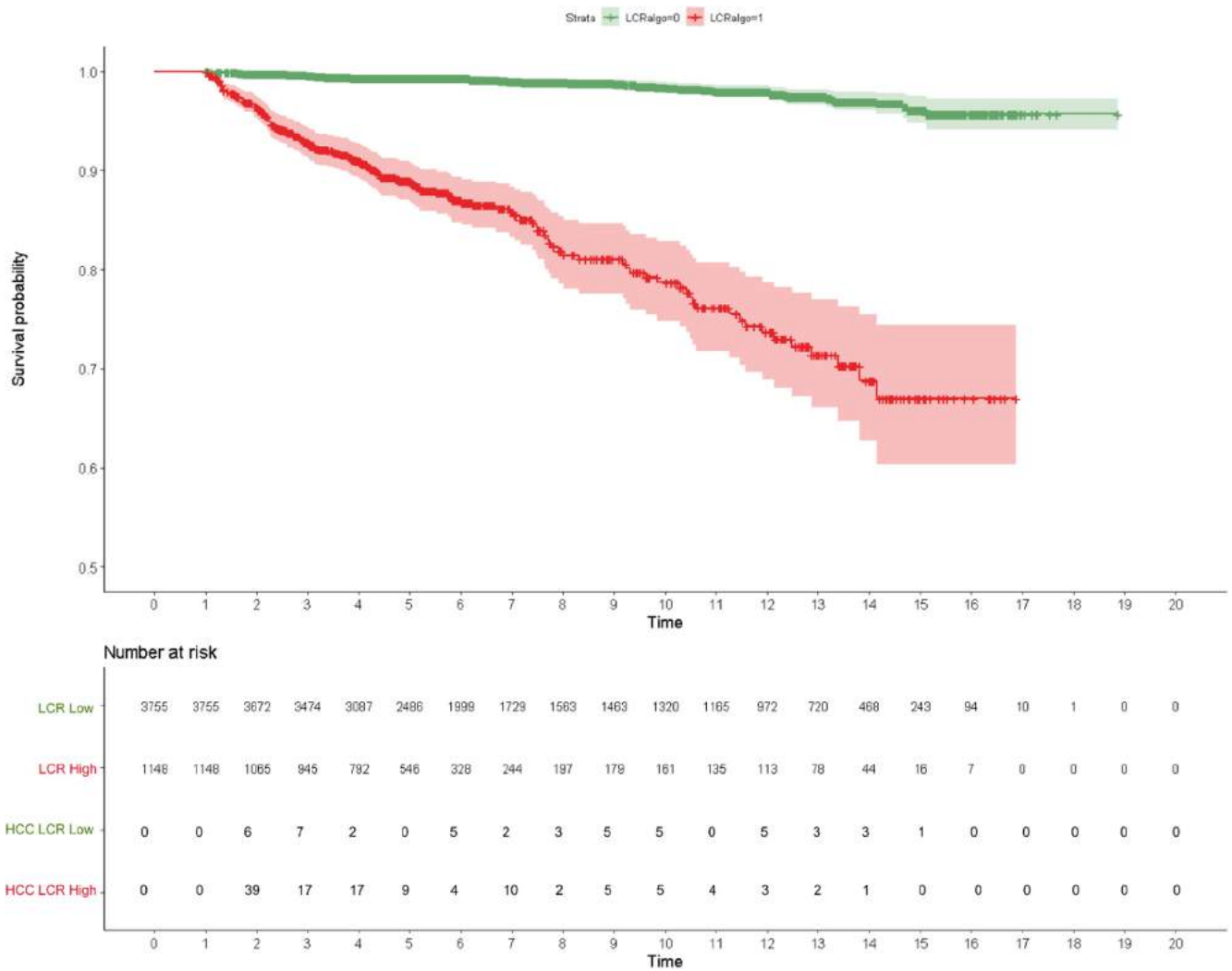


Figure: (abstract: GS-1065)

GS-1213

Multicentre international evaluation of autoimmune hepatitis and liver transplantation: disease recurrence is associated with recipient features, type of immunosuppression and impaired outcomes

Aldo J. Montano-Loza¹, Vincenzo Ronca², Maryam Ebadi¹, Bettina Hansen³, Gideon Hirschfield³, Saleh Elwir⁴, Mohamad Alsaed⁴, Piotr Milkiewicz⁵, Maciej K. Janik⁶, Hanns-Ulrich Marschall⁷, Maria Antonella Burza⁷, Cumali Efe⁸, Ali Riza Caliskan⁹, Murat Harputluoglu⁹, Gökhan Kabaçam¹⁰, Debora Raquel Terrabuio¹¹, Fernanda Onofrio¹², Albert Pares¹³, Laura Patricia Llovet¹⁴, Murat Akyildiz¹⁵, Cigdem Arıkan¹⁶, Michael P. Manns¹⁷, Richard Taubert¹⁸, Anna-Lena Weber¹⁷, Thomas Schiano¹⁹, Brandy Hayde²⁰, Piotr Czubkowski²¹, Piotr Socha²¹, Natalia Oldak²¹, Nobuhisa Akamatsu²², Atsushi Tanaka²³, Cynthia Levy²⁴, Eric F. Martin²⁵, Aparna Goel²⁶, Mai Sedki²⁶, Irena Jankowska²⁷, Toru Ikegami²⁸, Maria Rodriguez²⁹, Martina Sterneck²⁹, Christina Weiler-Normann²⁹, Christoph Schramm²⁹, Maria Francesca Donato³⁰, Ansgar W. Lohse³¹, Raul J. Andrade³², Alan Bonder³³, Vilas Patwardhan³⁴, Bart Van Hoek³⁵, Maaike Biewenga³⁶, Andreas E. Kremer³⁷, Yoshihide Ueda³⁸, Mark Deneau³⁹, Mark Pedersen⁴⁰, Marilyn J. Mayo⁴⁰, Annarosa Floreani⁴¹, Patrizia Burra⁴², Maria Francesca Secchi⁴², Benedetta Terziroli Beretta-Piccoli⁴³, Marco Sciveres⁴⁴, Giuseppe Maggiore⁴⁵, Syed-Mohammed Jafri⁴⁶, Dominique Debray⁴⁷, Muriel Girard⁴⁸, Florence Lacaille⁴⁹, Ellina Lytvyak⁵⁰, Andrew L. Mason¹, Michael Heneghan⁵¹, Ye Htun Oo⁵². ¹Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton, AB, Canada; ²Centre for Liver Research and NIHR Birmingham BRC, University of Birmingham and University Hospital Birmingham NHS Foundation Trust Institute of Immunology and Immunotherapy, University of Birmingham; ³Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Canada; ⁴Baylor University Medical Center, Dallas, USA; ⁵Liver and Internal Medicine Unit, Medical University of Warsaw Poland; ⁶Liver and Internal Medicine Unit, Medical University of Warsaw, Poland; ⁷Sahlgrenska University Hospital, Gothenburg, Sweden; ⁸Department of Gastroenterology, Harran University Hospital, Şanlıurfa, Turkey; ⁹Department of Gastroenterology, İnönü University School of Medicine, Malatya, Turkey; ¹⁰Clinic of Gastroenterology and Liver Transplantation, Guven Hospital Ankara, Turkey; ¹¹Department of Gastroenterology-University of São Paulo School of Medicine, São Paulo, Brazil; ¹²Toronto Centre for Liver Disease, UHN, Toronto, Canada; ¹³Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; ¹⁴Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; ¹⁵University School of Medicine, Department of Gastroenterology and Liver Transplantation Center, Istanbul, Turkey; ¹⁶Koc University School of Medicine Pediatric Gastroenterology and Hepatology, Organ Transplantation Center, Koc University Research Center for Translational Medicine (KUTTAM), Istanbul, Turkey; ¹⁷Hannover Medical School, Hannover, Germany; ¹⁸European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hannover Medical School, Hannover, Germany; ¹⁹Recanati/Miller Transplantation Institute/Division of Liver Diseases, Mount Sinai Medical Center, New York, USA; ²⁰Adult Liver Transplantation, Mount Sinai Medical Center, New York, USA; ²¹Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Childrens' Memorial Health Institute, Warsaw, Poland; ²²University of Tokyo, Japan; ²³Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan; ²⁴University of Miami Miller School of Medicine, Miami, USA; ²⁵Miami Transplant Institute, University of Miami Miller School of Medicine, Miami, USA; ²⁶Stanford University, Stanford, USA; ²⁷Children's Memorial Health Institute, Warszawa, Poland; ²⁸Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; ²⁹UKE Hamburg, Hamburg, Germany; ³⁰Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Liver Transplant

Hepatology Unit, Division of Gastroenterology and Hepatology, Milan, Italy; ³¹University Medical Center, Hamburg, Germany; ³²Gastroenterology Service -IBIMA, University Hospital and CIBERehd, University of Málaga, Spain; ³³Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA; ³⁴Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA; ³⁵Leiden University Medical Center, Leiden, Netherlands; ³⁶Leiden University Medical Center, Leiden, Netherlands; ³⁷Department of Medicine, University Hospital Erlangen and Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; ³⁸Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; ³⁹University of Utah, Salt Lake City, USA; ⁴⁰The University of Texas Southwestern Medical Center, Dallas, USA; ⁴¹Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; ⁴²University of Padova; ⁴³Epatocentro Ticino, Lugano, Switzerland; ⁴⁴UPMC Pediatric Liver Center, Palermo, Italy; ⁴⁵Hepatogastroenterology, Nutrition and Liver Transplant IRCCS Bambino Gesù Pediatric Hospital, Rome Italy; ⁴⁶Henry Ford Health System; ⁴⁷Pediatric Liver Unit, Paris Descartes University and French National Reference center for rare diseases BA and Genetic cholestasis, Hôpital Necker, Paris, France; ⁴⁸Université de Paris, Liver hepatology unit Necker Hospital, and French National Reference center for rare diseases BA and Genetic cholestasis, Paris, France; ⁴⁹Hôpital NECKER, Paris, France; ⁵⁰Department of Medicine, University of Alberta, Edmonton, AB, Canada; ⁵¹King's College Hospital NHS Foundation Trust, London, UK; ⁵²Centre for Liver Research and NIHR Birmingham BRC, University of Birmingham and University Hospital Birmingham NHS Foundation Trust
Email: montanol@ualberta.ca

Background and aims: Autoimmune hepatitis (AIH) frequently recurs after liver transplantation (LT). We evaluated risk factors associated with the recurrence of AIH and its effects on patient and graft survival in a multicentre, international cohort from the International AIH study group.

Method: We included 736 patients (77% female, mean age, 42 ± 1 years) with AIH who underwent LT from January 1987 through June 2020, among 33 centers in North America, South America, Europe and Asia. Patients with overlap syndrome were excluded. Clinical data before and after LT, biochemical data within the first 12 months after LT, and immunosuppression after LT were analyzed to identify patients with a higher risk of recurrence of AIH based on a histological diagnosis. Cumulative probabilities of graft and overall survival after LT were calculated using semi-Markov models.

Results: AIH recurred in 20% of patients after 5 years and 31% after 10 years. Age at LT ≤42 years (HR, 3.01; 95% CI, 1.15–7.89; p = 0.03), use of mycophenolate mofetil post-LT (HR, 3.22; 95% CI, 1.40–7.41; p = 0.006), donor and recipient gender mismatch (HR, 2.68; 95% CI, 1.42–5.06; p = 0.002) and higher IgG pre-LT (HR, 1.03; 95% CI, 1.01–1.06; p = 0.008) were associated with a higher risk of AIH recurrence after adjusting for age at diagnosis, concomitant autoimmune disease, use of tacrolimus, cyclosporine, azathioprine, rejection episodes, living related-LT, Roux-en-Y bile duct anastomosis, bilirubin at 6-month, ALT at 6- and 12- month. In multivariate Cox regression with time-dependent covariate, recurrent AIH significantly associated with graft loss (HR, 9.63, 95% CI 4.73–19.61, p < 0.001) and death (HR, 2.09, 95% CI 1.09–3.99, p = 0.03) after adjusting for confounders. The 5-, 10-, 15- and 20-year probability of graft survival was 78%, 65%, 53% and 53% in patients with recurrent AIH and 96%, 93%, 93%, and 87% in patients without recurrence (Log rank, p < 0.001, Figure 1a). For the overall survival, probability was 81%, 73%, 55%, and 44% in patients with recurrence and 93%, 81%, 75%, and 61% in patients without recurrence (p < 0.001, Figure 1b).

Conclusion: In the largest global cohort study to date we demonstrate that recurrent AIH following liver transplantation is clinically meaningful and associates with younger age at LT, use of mycophenolate mofetil post-LT, gender mismatch and higher IgG pre-LT. Recurrent disease impacts graft and overall survival, highlighting the need for improved management strategies.

ORAL PRESENTATIONS

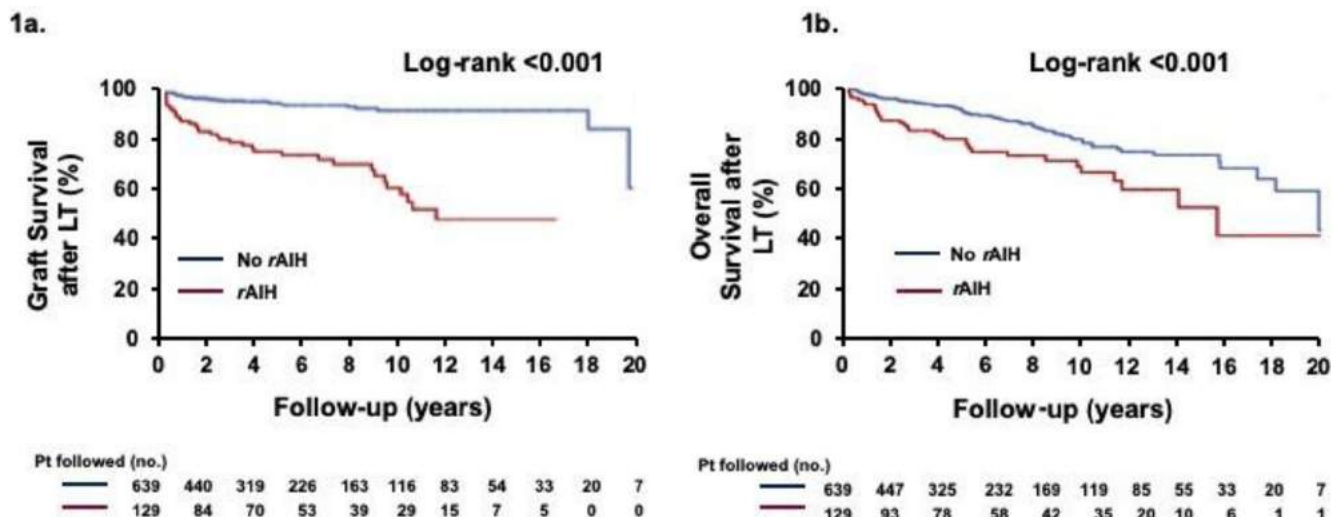


Figure: (abstract: GS-1213)

GS-1587

Chronic liver disease and the risk of mortality after Covid-19: a national, retrospective, cohort study for 2020

Vincent Mallet^{1,2,3}, Pierre Belnou^{1,4}, Samir Bouam^{1,4}, Anais Vallet Pichard^{1,2}, Marion Cororuge^{1,2}, Helene Fontaine^{1,2}, Philippe Sogni^{1,2,3}, Stanislas Pol^{1,2,3}. ¹Assistance Publique-Hôpitaux de Paris, Paris, France; ²Cochin Hospital, Hepatology, Paris, France; ³Université de Paris, Paris, France; ⁴Cochin Hospital, Département d'information médicale, Paris, France
Email: vincent.mallet@cch.aphp.fr

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

GS-1997

A multi-centre, randomized controlled study, to evaluate the safety and performance of the DIALIVE Liver Dialysis Device in patients with Acute on Chronic Liver Failure (ACLF) versus standard of care (SOC)

Banwari Agarwal¹, Faouzi Saliba², Dana Rodica Tomescu³, Rafael Banares Canizares⁴, Daniel Martin⁵, Vanessa Stadlbauer⁶, Gavin Wright^{1,7,8,9}, Mohammed Sheikh¹⁰, Carrie Morgan¹¹, Fausto Andreola⁹, Karl Oettl¹², Katja Waterstradt¹³, Stefanie M. Bode-Böger¹⁴, Rahul Kumar¹⁵, Eman Ibrahim Alabsawy¹⁰, Didier Samuel², Phillippe Ichai², M. Hernández-Tejero¹⁶, Fátima Aziz¹⁶, Michael Hinz^{17,18}, Mihai Popescu³, Maria-Vega Catalina¹⁹, Dr Douglas Corrigan⁷, Jacques Creteur²⁰, Oliver Lheureux²⁰, Francois Durand²¹, Neils Kristian Muff Aagaard²², Aehling Nf²³, Ahmed Elsharkawy²⁴, Sandro Serrano²⁵, Margret Paar²⁶, Sophie-Caroline Sacleux², Gernot Schilcher⁶, Sebastian Koball^{17,18}, Andrada Tudor³, Luis Ibañez⁴, Jaak Minten²⁷, Gema Domenech²⁸, Juan José Aragonés²⁸, Amir Gander¹, Moises Sanchez²⁹, Raj Mookerjee⁹, Andrew Davenport⁹, Daniel Green¹¹, Marco Pavesi³⁰, Jan Stange^{17,18}, Nathan Davies⁹, Vincente Arroyo³⁰, Javier Fernandez^{16,30}, Steffen Mitzner^{17,18}, Rajiv Jalan⁹. ¹Royal Free Hospital, United Kingdom; ²Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ³Carol Davila University of Medicine and Pharmacy, București, Romania; ⁴Complutense University of Madrid, Department of Gastroenterology, Gregorio Marañón General University Hospital, Health Research Institute Gregorio Marañón, Madrid, Spain; ⁵Peninsula Medical School, University of Plymouth, John Bull Building, Plymouth Science Park, United Kingdom; ⁶Medical University of Graz, Department of Internal Medicine, Division of Gastroenterology und Hepatology, Graz, Austria; ⁷Basildon University Hospital, United Kingdom; ⁸King's College London, United Kingdom; ⁹University College London; ¹⁰University College London, UCL Institute for Liver and Digestive Health, London, United Kingdom; ¹¹Yaqrit Ltd; ¹²Otto Loewi

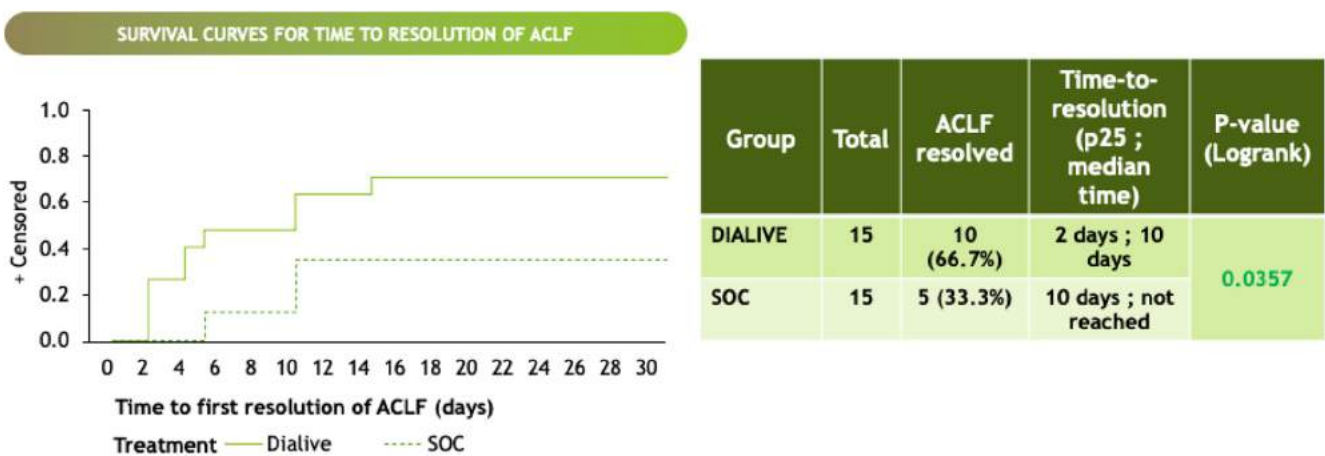


Figure: (abstract: GS-1997): This Kaplan Meier graph shows that significantly greater proportion of patients resolve ACLF with a faster resolution in the DIALIVE group.

ORAL PRESENTATIONS

Research Center, Medical University of Graz, Division of Physiological Chemistry, Graz, Austria; ¹³MedInnovation GmbH, Berlin, Germany; ¹⁴Institut für Klinische Pharmakologie, Magdeburg, Germany; ¹⁵Changi General Hospital, Singapore, Singapore; ¹⁶Hospital Clínic de Barcelona, Liver ICU, Liver Unit, Barcelona, Spain; ¹⁷University Hospital of Rostock, Rostock, Germany; ¹⁸Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany; ¹⁹Gregorio Marañón General University Hospital, Health Research Institute Gregorio Marañón, Department of Gastroenterology, Madrid; ²⁰Hospital Erasme, Dpt of Intensive Care, Bruxelles, Belgium; ²¹Hospital Beaujon AP-HP, Hepatology, Clichy, France; ²²Aarhus University Hospital, Dept of Hepatology, Aarhus, Denmark; ²³Leipzig University Medical Center, Division of Hepatology, Department of Medicine II, Leipzig, Germany; ²⁴Queen Elizabeth Hospital Birmingham, Consultant Hepatologist, United Kingdom; ²⁵IDIBAPS Hospital Clínic de Barcelona, Medical Statistics Core Facility; ²⁶Medical University of Graz, Division of Physiological Chemistry, Otto Loewi Research Center, Graz, Austria; ²⁷De Fakkel Bvba, Landen, Belgium; ²⁸IDIBAPS Hospital Clínic de Barcelona, Medical Statistics Core Facility, Barcelona, Spain; ²⁹IBM Ireland, Dublin, Ireland; ³⁰European Foundation for the study of chronic liver failure, Barcelona, Spain
Email: banwari.agarwal@nhs.net

Background and aims: Treatment of ACLF is an unmet need. DIALIVE is a novel liver dialysis device, that replaces dysfunctional albumin and removes pathogen and damage associated molecular patterns. This randomised study tests the hypothesis that DIALIVE will significantly improve the prognosis of ACLF patients. The primary end point was safety; device performance; clinical and pathophysiological effects.

Method: EUH2020 funded the ALIVER study. Patients with ACLF Grades 1-3a were randomized and the main end points were evaluated at Day 10. A minimum of 3 DIALIVE sessions (max 5) were needed for the patient to be evaluable. No specific hypothesis was to be statistically assessed. 2-populations were defined: *Safety population:* Patients having at least 1 DIALIVE treatment. *Modified-safety (MS) set:* Evaluable patients. A post-hoc inferential Mixed Models for Repeated Measurements analysis was performed to evaluate the statistically significant differences between groups at Days 5 and Day 10. Log-rank tests and Wald test were performed to assess resolution of ACLF.

Results: Study: 32-ACLF patients with alcoholic cirrhosis were randomised either to DIALIVE (N = 17; 13M; age: 49 (12.4); CLIF-OFs: 10.3 (1.6); CLIF-C ACLFs: 48.6 (7.3)) or SOC (n = 15; 13M; age: 49.1 (10.2); CLIF-OFs: 9.9 (1.2); CLIF-C ACLFs: 47 (6.5)). 30 patients (n = 15) comprised the MS set. DIALIVE therapy was administered for a median of 3 sessions (range 1–5) in first 3-days (range 1–6) for a median of 8 hours (hours 7–12) each. Safety: 5-patients died in the DIALIVE group; 4 in SOC group. Serious AEs were seen in 64.7% in DIALIVE and 53.3% in the SOC group. Efficacy: *CLIF-OF score:* Significant improvement in the Liver (p = 0.045) and Brain (p < 0.001) subscores in DIALIVE; and deterioration of Lung subscore (p = 0.002) in the SOC group (Day 10). This resulted in a significant overall treatment effect in CLIF-OFs (p = 0.043). *ACLF Grade:* Significantly more cases reached ACLF 0 (33.3% vs 66.7%) favoring DIALIVE (logrank p = 0.0357) and a 2.8x faster time to ACLF 0 (Wald test p = 0.059) (Fig). *CLIF-C ACLF score:* Difference of means (standard error) between DIALIVE and SOC at Day 10 was -5.4 (2.9) in favour of the DIALIVE group (p = 0.064). *MELD score:* Significantly lower in DIALIVE at both Days 5 (p = 0.049) and 10 (p = 0.028) vs SOC.

Conclusion: DIALIVE is safe and significantly increases proportion of patients resolving ACLF whilst reducing time to resolution. The data justify start of late phase clinical trials.

GS-2069

Claudin-1 is a target for treatment of advanced liver fibrosis and cancer prevention

Houssein El Saghire^{1,2}, Antonio Saviano^{1,2,3}, Natascha Roehlen^{1,2}, Emilie Crouchet^{1,2}, François H.T. Duong^{1,2}, Frank Jühling^{1,2}, Sara Cherradi^{1,2}, Marine Oudot^{1,2}, Victor Gonzalez-Motos^{1,2}, Sarah Durand^{1,2}, Patrick Pessaux^{1,2,3}, Emanuele Felli^{1,2,3}, Christine Thumann^{1,2}, Olga Koutsopoulos^{1,2}, Bryan C. Fuchs⁴, Yujin Hoshida⁵, Greg Elson⁶, Markus Meyer⁶, Roberto Iacone⁶, Tamas Schweighoffer⁶, Mathias Heikenwälder⁷, Laurent Mailly^{1,2}, Mirjam Zeisel^{1,2}, Catherine Schuster^{1,2}, Joachim Lupberger^{1,2}, Thomas Baumert^{1,2,3,8}. ¹Inserm U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France; ²Université de Strasbourg, Strasbourg, France; ³Institut Hospitalo-Universitaire, Pôle Hépatodigestif, Nouvel Hôpital Civil, Strasbourg, France; ⁴Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, MA, United States; ⁵Liver Tumor Translational Research Program, Harold C. Simmons Comprehensive Cancer Center, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX, United States; ⁶Alentis Therapeutics, Basel, Switzerland; ⁷Division of Chronic Inflammation and Cancer, German Cancer Research Center, Heidelberg, Germany; ⁸Institut Universitaire de France, Paris, France
Email: thomas.baumert@unistra.fr

Background: Tissue fibrosis is the key driver of end-stage organ failure, accounting for up to 45% of death in developed countries. Advanced liver fibrosis is the main risk factor for hepatocellular carcinoma (HCC). Despite the urgent medical need, approved antifibrotic therapies are absent and compounds in clinical development have limited anti-fibrotic efficacy. Claudin-1 (CLDN1) is a cell membrane protein mediating cell adhesion, signaling and epithelial-mesenchymal differentiation (EMT). Furthermore, CLDN1 is a cell entry factor and signal transducer of hepatitis C virus, a major cause of liver fibrosis and HCC worldwide.

Aims and Method: Using highly specific humanized monoclonal antibodies (mAbs) targeting non-junctional CLDN1 and a large series of patient-derived cell-based and mouse models combined with loss-of-function studies, we aimed to investigate the role CLDN1 as a therapeutic target for liver fibrosis.

Results: CLDN1 was overexpressed in liver tissues derived from patients with NASH, liver fibrosis and HCC. Targeting non-junctional CLDN1 on the hepatocyte basolateral membrane by highly specific mAbs markedly and significantly inhibited fibrosis and suppressed tumorigenesis *in vivo* in two state-of-the-art NASH fibrosis mouse models including humanized liver chimeric mice. Antifibrotic effects were further confirmed in NASH F3/F4 patient-derived precision-cut liver slices, 3D bioprinted liver tissues and NASH patient-derived liver spheroids. Perturbation studies revealed that CLDN1-targeting mAbs suppress pro-fibrogenic differentiation of liver myofibroblasts and Kupffer cells as well as EMT of hepatocytes by interfering with host cell signaling. Treatment with humanized anti-CLDN1 antibodies is considered to be safe, as administration in non-human primates and mouse models did not reveal any major toxicity even when high doses largely exceeding the therapeutic need were repeatedly applied.

Conclusion: Our results provide robust preclinical proof-of-concept for CLDN1-specific mAbs for treatment of advanced liver fibrosis and prevention of HCC. A key differentiator of CLDN1-targeting approach is the combination of a robust direct anti-fibrotic and HCC preventive effect complementing compounds in clinical development mostly targeting metabolism.

General session II

GS-613

Prophylaxis of recurrent thrombosis by rivaroxaban in patients with non-cirrhotic chronic portal vein thrombosis (PVT): a multicentre randomized controlled study testing rivaroxaban vs no anticoagulation

Aurélie Plessier¹, Odile Gorla², Jean Paul Cervoni³, Isabelle Ollivier-Hourmand⁴, Christophe Bureau⁵, Armelle Poujol-Robert⁶, Anne Minello Franza⁷, Pauline Houssel-Debry⁸, Payance Audrey¹, Scoazec Giovanna¹, Bruno Onorina⁹, Michele Corbic¹⁰, Larbi Boudaoud¹¹, Valerie Vilgrain⁹, Francois Durand¹, Valérie Paradis¹², Deraucourt Emmanuelle¹¹, Pierre-Emmanuel Rautou¹, Carine Roy¹³, Gault Nathalie¹³, Dominique Valla¹. ¹Hospital Beaujon AP-HP, Department of hepatology, DHU Unity, Pôle des Maladies de l'Appareil Digestif, Referral Centre for Vascular Liver Diseases, Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, Université Paris 7-Denis-Diderot, ERN Rare liver Clichy, Clichy, France; ²Hôpital Charles Nicolle, University Hospital of Rouen, Gastroenterology and Hepatology Department, Rouen, France; ³Jean Minjoz Hospital, Department of Hepatology and Intensive Digestive Care, Besançon, France; ⁴Côte de la Nacre Hospital, University Hospital of Caen, Department of Gastroenterology and Hepatology, Caen, France; ⁵Rangueil Hospital, University Hospital of Toulouse, Department of Gastroenterology and Hepatology, Toulouse, France; ⁶Hospital Saint-Antoine Ap-Hp, Department of Hepatology, Paris, France; ⁷Hospital Center University Dijon Bourgogne, Department of Gastroenterology and Hepatology, Dijon, France; ⁸CHU Rennes-Pontchaillou Hospital, Department of Hepatology, Rennes, France; ⁹Hospital Beaujon AP-HP, Radiology, Clichy, France; ¹⁰Private Hospital Des Peupliers-Ramsay Santé, Endoscopy, Paris, France; ¹¹Hospital Beaujon AP-HP, Department of Laboratory Hematology, Clichy, France; ¹²Hospital Beaujon AP-HP, Pathology Department, Clichy, France; ¹³Bichat-Claude Bernard Hospital, Hôpital Bichat, AP-HP Nord, INSERM CIC-EC 1425. AP-HP Nord-Université de Paris F-75018 Paris, Paris, France
Email: aurelie.plessier@aphp.fr

Background and aims: The benefit of long-term anticoagulation on the risk of recurrence of thrombosis in patients with non-cirrhotic chronic portal venous system thrombosis (PVT) is unknown. We aimed to assess the effects of rivaroxaban, compared to no anticoagulation, on thrombosis-free survival in PVT patients without high risk factor for thrombosis.

Method: In this French multicentre, investigator-driven, controlled study, patients with chronic PVT without high-risk factor for thrombosis were randomly assigned to receive either rivaroxaban 15 mg/day or no anticoagulation for a minimum of 2 years planned follow-up. Primary end point was survival free of new occurrence of a venous thromboembolic event in any territory or death.

Results: We included 111 patients: 56 in rivaroxaban arm and 55 in no-anticoagulation arm. An interim analysis was requested by the independent safety monitoring board, which led to discontinuation of enrolment, 28 months after study start and 11.8 months (95% CI [8.8–13.2]) of median follow-up, due to an increased occurrence of thromboses in the no-anticoagulation group. Incidence rate of thrombosis recurrence was 0/100 person-years in rivaroxaban arm and 19.71/100 person-years (95% CI [7.49/100–31.92/100]) in no-anticoagulation arm (3 deep venous phlebitis, 3 pulmonary embolisms, and 4 splanchnic thrombosis in 10 control patients). Recurrent thrombosis-free survival was significantly different between study arms (p = 0.0008) (Figure).

Patients of the no-anticoagulation group were then switched to rivaroxaban 15 mg/d. Monitoring of bleeding and thrombosis events was pursued until the last included patient reached 2 years of follow-up. At the end of the study, after a median follow-up of 30.3 months (95%CI [29.8–35.9]), 3 patients have experienced severe hemorrhage related to portal hypertension, two in patients treated with rivaroxaban and one in a patient without anticoagulant. Three patients were lost to follow-up; and there were no deaths.

Conclusion: In patients with chronic PVT without high-risk factor for thrombosis, rivaroxaban reduces the risk of recurrent venous thrombosis without increasing the risk of severe bleeding.

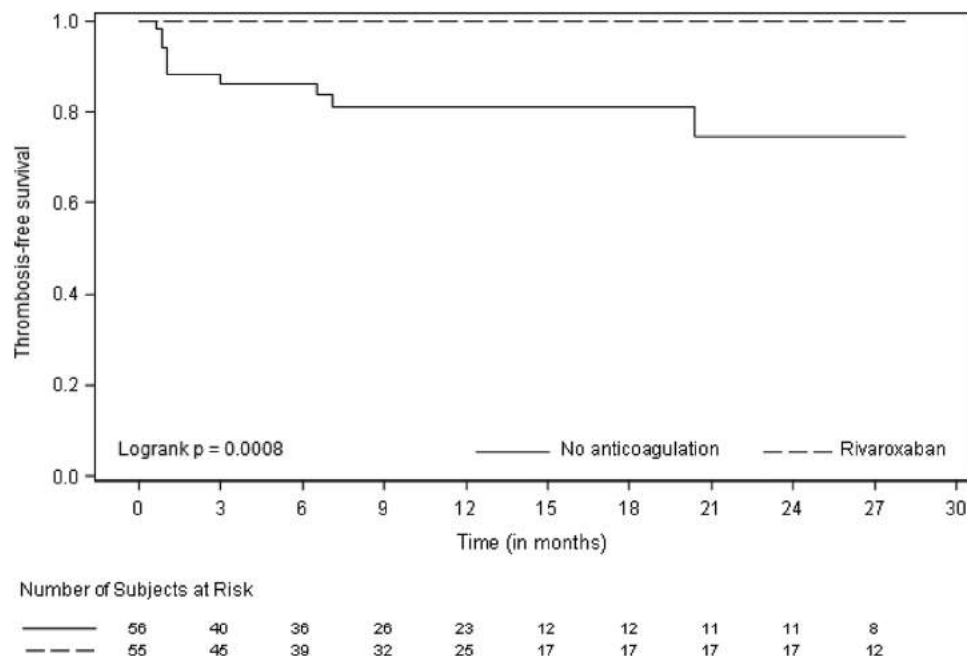


Figure: (abstract: GS-613): Recurrent thrombosis-free survival.

ORAL PRESENTATIONS

GS-945

Radiological and pathological response to neoadjuvant Nivolumab in patients with BCLC A HCC treated by curative percutaneous irreversible electroporation: preliminary report from the NIVOLEP trial (NCT03630640)

Pierre Nahon¹, Olivier Seror¹, Frédéric Oberti², Solohaja Faniha Dimby^{3,4}, Christophe Aubé², Jean-Frédéric Blanc⁵, Hervé Trillaud⁵, Philippe Merle⁶, Agnès Rode⁶, Eric Assenat⁷, Boris Guiu⁷, Mohamed Bouattour⁸, Zohra Talib³, Annick Tibi⁹, Julien Calderaro¹⁰, Marianne Ziou¹, Eric Vicaut³. ¹APHP Avicenne, Bobigny, France; ²CHU Angers; ³APHP Fernand Vidal; ⁴SAMM (EA 4543), Université Paris 1 Panthéon Sorbonne, Paris, France; ⁵CHU Bordeaux; ⁶CHU Lyon; ⁷CHU Montpellier; ⁸APHP Beaujon; ⁹APHP Ageps; ¹⁰APHP Henri Mondor
Email: pierre.nahon@aphp.fr

Background and aims: Irreversible electroporation (IRE) is a percutaneous ablation which induces tumour cells apoptosis. It has been shown to be safe and effective for curative ablation of HCC located near vascular or biliary trunks. The preservation of the tumour microvasculature and extracellular matrix favours infiltration by anti-tumoral immune cells. Given these immunomodulatory changes, neoadjuvant and adjuvant immunotherapy might act in synergy with this non-thermal ablative technique to improve HCC curative management.

Method: The NIVOLEP trial is a French multicentre (n = 6) phase 2 trial aimed at recruiting 50 patients with BCLC A HCC eligible for IRE and high-risk of recurrence (single lesion >3 cm or multiple). Patients consecutively received: (1) 2 neoadjuvant Nivolumab infusions (every 15 days); (2) curative IRE procedure; (3) 12 adjuvant Nivolumab infusions (every 30 days) during one year. All HCC nodules were biopsied at inclusion then during IRE procedure to assess neoadjuvant Nivolumab impact on tumour biology. The present data report preliminary results of the neoadjuvant phase in the first 20 included patients as assessed by sequential radiological and pathological examination before and after 2 Nivolumab infusions.

Results: 37 HCC nodules (uni-nodular 9, bi-nodular 5 and tri-nodular 6 patients, mean size: 31.4 mm) in 20 patients (mean age 69 yrs, males 90%, cirrhosis: 70%, baseline AFP: 56 ng/ml, AFP >50 ng/ml: 10%) were considered. No Grade 3 or 4 adverse events related to

Nivolumab infusions were reported. Following neoadjuvant Nivolumab, radiological response defined by an objective reduction in nodule (s) size (s) was observed in 11 (29%) (complete response in 0 nodules). One patient experienced progression and was ineligible for IRE. The 19 other patients underwent successful curative IRE procedure. Among these 37 nodules, 17 paired pre- and post neoadjuvant Nivolumab HCC biopsies from 15 patients were analyzed. Pathological response pattern was observed in 3/17 nodules (17%), characterized by tumor regression, replaced by fibrosis with mixed inflammatory infiltrate including foamy macrophages and heavy peritumoral and intratumoral lymphocyte infiltration. These 3 nodules also had radiological response. Additionally, significant increase of peritumoral and intratumoral infiltrating lymphocytes, without evidence of tumor regression zone were observed in 4 other nodules. Overall, 9/17 (53%) had either radiological or pathological modification following Nivolumab infusion.

Conclusion: Neoadjuvant Nivolumab in BCLC A HCC patients eligible for IRE was safe and did not delay ablation procedure. Induced radiological and pathological changes were reported in a substantial number of patients suggesting antitumoral and/or immunomodulation effect of neoadjuvant immunotherapy for liver cancer. **NCT03630640.**

GS-1645

SZN-043, a hepatocyte-targeted R-spondin mimetic, promotes robust hepatocyte proliferation and zonal gene expression changes in mice

Russell Fletcher¹, Helene Baribault², Mehaben Patel², Jacqueline Phipps², Shalaka Deshmukh², Darshini Shah², Asmiti Sura², Suhani Gupta², Hui Chen², Jay Ye², Jay Tibbitts², Trudy Vanhove², Wen-Chen Yeh², Yang Li², Chenggang Lu². ¹Surrozen, Inc., South San Francisco; ²Surrozen, Inc., South San Francisco, United States
Email: russell@surrozen.com

Background and aims: Wnt signaling is critical for hepatocyte development and for regeneration after liver injury, and it contributes to the region-specific expression of metabolic genes. R-spondins enhance Wnt signaling via stabilization of Wnt receptors. We tested the effect of repeated dosing of our hepatocyte-targeted

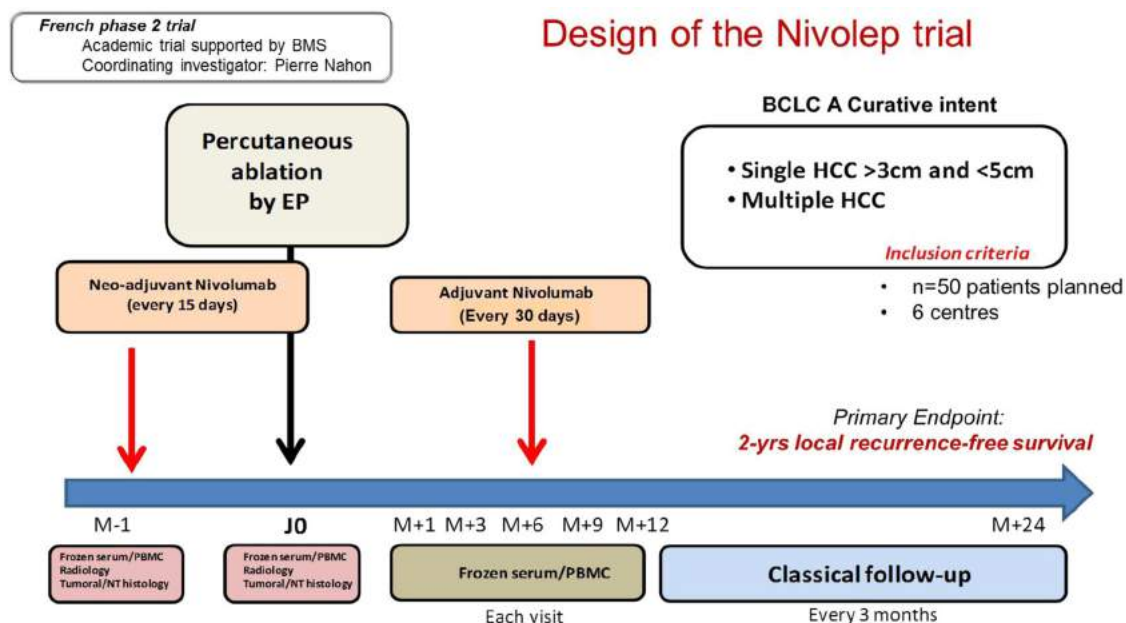


Figure: (abstract: GS-945)

R-spondin mimetic, SZN-043, in mice to understand how SZN-043 impacts hepatocytes and all other cell types and to understand how the liver normalizes upon washout.

Method: C57Bl/6 mice were dosed with either a control antibody (anti-GFP) twice weekly or with SZN-043 at 10 mg/kg intraperitoneally (IP) daily for two weeks. Liver samples were collected at 24 hours after the first dose, 24 hours after the last dose, and at a range of washout timepoints (Day 7, 14, 28, and 56 after the last dose). We perfused livers and performed single cell RNA seq (scRNA-seq) at 24 hours after the first and last dose and 56 days after the last dose. We also examined tissue by immunohistochemistry, RNA in situ hybridization, and/or RT-qPCR at all timepoints.

Results: We detected all known cell types in the liver in our scRNA-seq data, and SZN-043 induced Wnt target gene expression in hepatocytes and promoted hepatocyte proliferation. At 24 hours after the first dose, minimal pharmacologic effects were observed. At Day 14, the expression of central vein-associated metabolic genes was expanded and the expression of periportal vein-associated metabolic genes reduced. In addition, a significantly higher number of proliferating hepatocytes (Ki67+/HNF4 α +) were observed in mice treated with SZN-043 compared to mice administered anti-GFP. The proliferating hepatocytes were located primarily in the periportal area, colocalizing with periportal markers. Both hepatocyte proliferation and changes in zonal-specific gene expression normalized upon 7 days of washout. We did not detect any direct effects of SZN-043 on non-hepatocytes in the liver although we did observe an increase in *Chil3* expression, a gene associated with an anti-inflammatory macrophage state, in a subset of Kupffer cells.

Conclusion: SZN-043 induces a transient increase in the number of proliferating hepatocytes and a transient shift in zonal metabolic gene expression, and both changes normalize within 7 days of dosing cessation. The ability of SZN-043 to target hepatocytes and promote their proliferation suggests its utility as a regenerative therapy for liver diseases.

GS-2283

Long-term Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Children with Chronic Hepatitis B (CHB): Final Results from a Placebo-Controlled Trial

Mei-Hwei Chang¹, Jorge Bezerra², Byung-Ho Choe³, Daniela Pacurar⁴, Sandeep Nijhawan⁵, Jae Hong Park⁶, Rajiv Mehta⁷, Yon Ho Choe⁸, John F. Flaherty⁹, Anh-Hoa Nguyen⁹, Yang Liu⁹, Alexandrina Constantinescu¹⁰, Philip Rosenthal¹¹, Kyung Mo Kim¹², Daniel Hao Bin Leung¹³. ¹National Taiwan University Hospital, Taipei City, Taiwan; ²Cincinnati Children's Hospital, Cincinnati, United States; ³Kyungpook National University; ⁴Grigore Alexandrescu Emergency Clinical Hospital for Children, Institute of Medicine and Pharmacy Bucharest; ⁵Sawai Man Singh Hospital, SMS Medical College; ⁶Pusan National University Children's Hospital; ⁷Surat Institute of Medical Sciences (SIDS); ⁸Sungkyunkwan University School of Medicine; ⁹Gilead Sciences Inc.; ¹⁰Fundeni Clinical Institute; ¹¹University of California, San Francisco; ¹²Asan Medical Center Children's Hospital, Ulsan College of Medicine; ¹³Texas Children's Hospital, Baylor College of Medicine
Email: john.flaherty@gilead.com

Background and aims: TDF was approved in 2018 for treatment of CHB in children ≥ 2 years (y) weighing ≥ 10 kg based on 48-week results from GS-US-174-0144 (NCT01651403); here we report long-term efficacy and safety findings for TDF treatment through 4 years (192 weeks).

Method: Pediatric CHB patients aged 2 to <12 y, ≥ 10 kg body wt. with HBV DNA ≥ 4 log₁₀ IU/ml, ALT $\geq 1.5 \times$ ULN (≤ 30 U/L), and creatinine clearance (eGFR) ≥ 80 ml/min/1.73 m² were randomized (1:1) to TDF 8 mg/kg or matching placebo (PBO) once daily in a double-blind (DB) fashion for 48 weeks (primary end point: % with HBV DNA <69 IU/ml) or 72 weeks, and then eligible for open-label (OL) TDF through Week 192. Viral suppression, serologic and biochemical responses

were serially determined, viral resistance (pol/RT sequencing/phenotyping) was performed yearly (HBV DNA ≥ 69 IU/ml), and safety, including changes in renal and bone parameters was assessed.

Results: 89 patients (TDF 60; PBO 29) were randomized and treated, of which 81 (91%; TDF 56; PBO 25) and 77 (87%; TDF 55; PBO-TDF 22) completed both DB and OL phases. At baseline: mean (range) age and weight were 6 (2–12) y and 24 (10.5–55) kg, with 56% male, 65% Asian, 96% HBeAg-positive; mean (SD) HBV DNA and ALT were 8.1 (0.9) log₁₀ IU/ml and 123 (92) U/L, respectively. Week 192 efficacy (TDF vs PBO-TDF by missing = failure analysis): HBV DNA <29 IU/ml 82% vs 62%; ALT normalization 72% vs 50%; HBeAg loss 54% vs 34%, and HBsAg loss 10% vs 0%. Most adverse events (AEs) during the OL phase were mild-moderate (most common were URIs and GI disorders); no patient had a Grade 3/4 AE or serious AE related to study treatment and none discontinued OL treatment due to an AE. 3 patients (2 TDF; 1 PBO-TDF) had confirmed eGFR <70 but ≥ 50 ml/min/1.73 m². Mean % (SD) BMD increased from baseline which was slightly less in TDF vs PBO-TDF patients: spine: +19.2% [12.28] vs +26.1% [14.26]; whole body: +23.7% [9.82] vs. +27.7% [11.14]. No HBV amino acid substitutions associated with tenofovir resistance were detected through Week 192.

Conclusion: Long-term TDF treatment of CHB in children was associated with a high rate of viral suppression without resistance, while also being safe and well tolerated. Biochemical and serologic responses were comparable to those seen in adults and no patient experienced clinically significant bone or renal toxicity.

GS-2309

Impact of the public health policies and alcohol-associated liver disease in Latin America: An ecological multi-national study

Luis Antonio Diaz¹, Francisco Idalosoaga¹, Eduardo Fuentes-López², Andrea Márquez³, Carolina A. Ramirez⁴, Juan Pablo Roblero⁵, Roberta Araujo⁶, Maria De Fatima Higuera De La Tijera⁷, Luis Toro⁸, Galo Pazmiño⁹, Pedro Montes¹⁰, Nélia Hernandez¹¹, Manuel Mendizabal¹², Catterina Ferreccio¹³, Mariana Lazo¹⁴, Mayur Brahmania¹⁵, Ashwani Singal¹⁶, Ramon Bataller³, Marco Arrese¹, Juan Pablo Arab¹. ¹Pontificia Universidad Católica de Chile, Departamento de Gastroenterología, Escuela de Medicina, Santiago, Chile; ²Pontificia Universidad Católica de Chile, Departamento de Ciencias de la Salud, Facultad de Medicina, Santiago, Chile; ³University of Pittsburgh Medical Center, Center for Liver Diseases, Division of Gastroenterology, Hepatology and Nutrition, Pittsburgh, United States; ⁴Clínica Las Condes, Departamento de Anestesiología, Santiago, Chile; ⁵Universidad de Chile, Sección Gastroenterología, Hospital Clínico Universidad de Chile, Escuela de Medicina, Santiago, Chile; ⁶University of São Paulo, Gastroenterology Division, Ribeirão Preto Medical School, São Paulo, Brazil; ⁷Hospital General de México, Universidad Nacional Autónoma de México, Servicio de Gastroenterología, Ciudad de Mexico, Mexico; ⁸Hepatology and Liver Transplant Unit, Hospitales de San Vicente Fundación de Medellín y Rionegro, Medellín, Colombia; ⁹Pontificia Universidad Católica de Ecuador, Department of Gastroenterology, Quito, Ecuador; ¹⁰Universidad Peruana de Ciencias Aplicadas: Monterrico, Department of Gastroenterology, Lima, Peru; ¹¹Universidad de la República Uruguay, Clínica de Gastroenterología, Hospital de Clínicas, Facultad de Medicina, Montevideo, Uruguay; ¹²Hospital Universitario Austral, Hepatology and Liver Transplant Unit, Buenos Aires, Argentina; ¹³Pontificia Universidad Católica de Chile, Departamento de Salud Pública, Escuela de Medicina, Santiago, Chile; ¹⁴Drexel University, Department of Community Health and Prevention, Dornsife School of Public Health, Philadelphia, Pennsylvania, United States; ¹⁵Western University, London Health Sciences Center, Department of Medicine, Division of Gastroenterology, London, Ontario, Canada; ¹⁶University of South Dakota Sanford School of Medicine, Department of Medicine, South Dakota, United States
Email: jparab@gmail.com

Background and aims: Latin-America has substantial socio-economic disparities between countries. Although alcohol consumption

ORAL PRESENTATIONS

health effects are well-known in Latin-America, alcohol policies' impact are unknown. Therefore, we aimed to assess the association between alcohol policies, alcohol consumption, and cirrhosis in Latin-American countries.

Method: An Ecological multi-national Study including 20 countries in Latin America. We obtained country-level socio-demographic information from the World Bank Open Data source. Alcohol policies data for countries in Latin America were obtained from the World Health Organization (WHO) Global Information System of Alcohol and Health (GISAH). Data analysis included a fixed-effects model to estimate proportions and multiple linear regression models.

Results: We included 20 countries (628, 466, 088 inhabitants). The average \pm SD GINI index in 2016 was 45.9 ± 3.9 , and the mean \pm SD gross domestic product per capita was US\$ 14, 723 \pm 7, 555. The estimated alcohol per capita consumption (APC) among the population 15 years old was 6.84 liters of pure alcohol (5.62 recorded and 1.23 unrecorded). The countries that lead APC were Uruguay (10.8 liters), Argentina (9.8 liters), and Chile (9.3 liters). The prevalence of alcohol use disorder (AUD) was 4.89%. A total of 19 (95%) countries have alcohol-related public health policies. The most frequent alcohol policies were: limiting drinking age and youth focus (90%), alcohol and driving (90%), and government monitoring systems (90%). The presence of alcohol policies in the country was associated with a lower risk of AUD (OR 0.83, 95%CI 0.73–0.94; $p = 0.004$), lower deaths due to traffic injuries (OR 0.84, 95% CI 0.71–0.98; $p = 0.028$), and alcohol-associated cirrhosis (OR 0.18, 95%CI 0.07–0.46, $p < 0.001$).

Conclusion: The current ecological study demonstrates that countries with more alcohol policies have lower alcohol per capita consumption, deaths due to traffic injuries, and alcohol-associated cirrhosis. These results encourage the introduction of alcohol control policies in all countries.

GS-2563

Reduction in Fibrosis and Steatohepatitis Imaging and Biomarkers in a Phase 3 52 Week Resmetirom NASH Trial

Stephen Harrison¹, Naim Alkhoury², Rebecca Taub³, Guy Neff⁴, Seth J. Baum⁵, Ziad H. Younes⁶, Mustafa Bashir⁷. ¹Oxford, Hepatology, United Kingdom; ²Arizona Liver Health, Phoenix, United States; ³Madrigal Pharmaceuticals, Research, Conshohocken, United States; ⁴Covenant Research, LLC, Sarasota, United States; ⁵Excel Medical Clinical Trials, LLC, Miami, United States; ⁶Gastro-One, Memphis, United States; ⁷Duke University Medical Center, Department of Radiology, Durham, United States

Email: rebeccataub@yahoo.com

This abstract is under embargo until the beginning of the press conference it is being presented in on Friday 25 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

Late breaker

The following late-breaker abstracts are under embargo until Saturday 26 June at 12.00 CET.

LBO-2592
ARO-AAT an investigational RNAi therapeutic demonstrates improvement in liver fibrosis with reduction in intra-hepatic Z-AAT burden

Pavel Strnad¹, Mattias Mandorfer², Gourab Choudhury³, Griffiths Bill⁴, Christian Trautwein¹, Rohit Loomba⁵, Dawn Christianson⁶, Natasa Rajcic⁶, Ting Chang⁶, Bruce Given⁶, James Hamilton⁶, Javier San Martin⁶, Jeffrey Teckman⁷. ¹University Hospital, Rwth Aachen, Department of Internal Medicine III, Aachen, Germany; ²Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria;

³University of Edinburgh, Respiratory Medicine, Edinburgh, United Kingdom; ⁴Cambridge University Hospitals NHS Foundation Trust, Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge, United Kingdom; ⁵University of California at San Diego, Division of Gastroenterology, San Diego, United States; ⁶Arrowhead Pharmaceuticals, Inc, Pasadena, United States; ⁷Saint Louis University School of Medicine, Pediatrics, United States
Email: jhamilton@arrowheadpharma.com

LBO-2631
Combination of amoxicillin/clavulanate and prednisolone in severe alcoholic hepatitis: results of the randomized controlled trial Antibiocor

Alexandre Louvet¹, Julien Labreuche², Thong Dao³, Thierry Thévenot⁴, Frédéric Oberti⁵, Christophe Bureau⁶, Thierry Paupard⁷, Eric Nguyen Khac⁸, Anne Minello Franza⁹, Brigitte Bernard Chabert¹⁰, Rodolphe Anty¹¹, Faustine Wartel¹², Nicolas Carbonell¹³, Georges-Philippe Pageaux¹⁴, Leroy Vincent¹⁵, Ludivine Legros¹⁶, Pierre Nahon¹⁷, Camille Potey¹⁸, Alain Duhamel², Philippe Mathurin¹.

¹CHU de Lille, Service des maladies de l'appareil digestif, Lille, France; ²CHU de Lille, Unité de biostatistiques, Lille, France; ³CHU de Caen, Service d'hépatogastroentérologie, Caen, France; ⁴CHU de Besançon, Service d'hépatologie, Besançon, France; ⁵CHU d'Angers, Service d'hépatogastroentérologie, Angers, France; ⁶CHU de Toulouse, Service d'hépatologie, Toulouse, France; ⁷CH de Dunkerque, Service d'hépatogastroentérologie, Dunkerque, France; ⁸CHU d'Amiens, Service d'hépatogastroentérologie, Amiens, France; ⁹CHU de Dijon, Service d'hépatogastroentérologie, Dijon, France; ¹⁰CHU de Reims, Service d'hépatogastroentérologie, Reims, France; ¹¹CHU de Nice, Service d'hépatogastroentérologie, Nice, France; ¹²CH de Valenciennes, Service d'hépatogastroentérologie, Valenciennes, France; ¹³Hôpital Saint-Antoine, Service d'hépatologie, Paris, France; ¹⁴CHU de Montpellier, Service d'hépatogastroentérologie, Montpellier, France; ¹⁵CHU de Grenoble, Service d'hépatogastroentérologie, La Tronche, France; ¹⁶CHU de Rennes, Service des maladies du foie, Rennes, France; ¹⁷Hôpital Jean-Verdier, Service d'hépatogastroentérologie, Bondy, France; ¹⁸CHU de Lille, Unité de pharmacovigilance, Lille, France
Email: alexandre.louvet@chru-lille.fr

LBO-2647

Adeno-associated virus vector mediated gene therapy for Crigler Najjar syndrome: preliminary report of safety and efficacy from the CareCN clinical trial

Lorenzo D'Antiga¹, Ulrich Beuers², Nicola Brunetti-Pierri^{3,4}, Ulrich Baumann⁵, Angelo Di Giorgio¹, Sem J. Aronson², Aurélie Hubert⁶, Roberta Romano⁴, Norman Junge⁵, Piter Bosma², Mariya Pavlyuk⁷, Philippe Veron⁷, Giuseppe Ronzitti^{7,8}, Fanny Collaud⁷, Geraldine Honnet⁷, Nathalie Knuchel-Legendre⁷, Federico Mingozzi⁷, Philippe Labrune⁶. ¹*ASST Papa Giovanni XXIII Hospital, Bergamo, Italy; 2*Amsterdam UMC, locatie AMC, Amsterdam, Netherlands; ³TIGEM, Pozzuoli, Italy; ⁴Federico II University Hospital, Napoli, Italy; ⁵Hannover Medical School, Hannover, Germany; ⁶Hopital Antoine Beclere, Clamart, France; ⁷Généthon, Évry-Courcouronnes, France; ⁸Paris-Saclay University, Univ Evry, Inserm, Integrare research unit UMR_S951, Evry, France
Email: ldantiga@asst-pg23.it

LBO-2764**Repeat dosing of the GalNAc-siRNA AB-729 in subjects with chronic hepatitis B results in robust and sustained HBsAg suppression**

Man-Fung Yuen¹, Elina Berliba², Wattana Sukeepaisarnjaroen³, Simone Strasser⁴, Pisit Tangkijvanich⁵, Jacinta Holmes⁶, Apinya Leerapun⁷, Alina Jucov², Emily P. Thi⁸, Tosh Wattamwar⁸, Michael J. Sofia⁸, Heather Sevinsky⁸, Kevin Gray⁸, Deana Antonello⁸, Timothy Eley⁸, Gaston Picchio⁸, Karen Sims⁸, Edward Gane⁹. ¹Queen Mary Hospital, Hong Kong; ²Arenia Exploratory Medicine, Moldova;

³Sringarind Hospital, Khon Kaen, Thailand; ⁴Royal Prince Alfred Hospital, Sydney, Australia; ⁵King Chulalongkorn Memorial Hospital, Bangkok, Thailand; ⁶St. Vincent's Hospital, Melbourne, Australia;

⁷Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; ⁸Arbutus Biopharma, United States; ⁹Auckland Clinical Studies, Auckland, New Zealand

Email: hsevinsky@arbutusbio.com

ORAL PRESENTATIONS

LBO-2765

Treatment of iron deficiency anemia with intravenous ferric carboxymaltose improves significantly systemic hemodynamics, renal function, and survival in patients with cirrhosis and ascites

Ilias Tsiakas¹, Georgios Kalambokis¹, Maria Christaki¹, Grigorios Despotis¹, Sempastien Fillipas-Ntekouan¹, Lampros Lakkas², Spyridon Tsiouris³, Xanthi Xourgia³, Christina Koustousi¹, Nikolaos Aggelis¹, Chalampos Milionis¹.
¹School of Medicine, University of Ioannina, 1st Department of Internal Medicine, Ioannina, Greece; ²School of Medicine, University of Ioannina, 2nd Department of Cardiology, Ioannina, Greece; ³School of Medicine, University of Ioannina, Laboratory of Nuclear Medicine, Ioannina, Greece Email: gkalambo@uoi.gr

LBO-2800

Efruxifermin (EFX) improved markers of fibrosis, liver injury and metabolism in F4 NASH patients with compensated cirrhosis

Stephen Harrison¹, Peter Ruane², Bradley Freilich³, Guy Neff⁴, Rashmee Patil⁵, Cynthia Behling⁶, Chen Hu⁷, Reshma Shringarpure⁸, Brittany de Temple⁸, Erica Fong⁸, Erik Tillman⁸, Tim Rolph⁸, Andrew Cheng⁸, Kitty Yale⁸. ¹Pinnacle Clinical Research, San Antonio, United States; ²Ruane Clinical Research Group Inc, Los Angeles, United States; ³Kansas City Research Institute, Kansas City, United States; ⁴Covenant Research LLC, Sarasota, United States; ⁵South Texas Research Institute, Edinburgh, United States; ⁶University of California, San Diego, San Diego, United States; ⁷Medpace Inc., Cincinnati, United States; ⁸Akero Therapeutics, South San Francisco, United States
Email: kitty@akerotx.com

Parallel Sessions

Alcoholic liver disease

OS-1293

Neutrophil extracellular traps formation induced by alcohol generates a unique neutrophil subset with defective neutrophil functions causing liver damage in alcoholic hepatitis

Yeonhee Cho^{1,2}, Terence Bukong³, David Tornai⁴, Gyongyi Szabo^{2,5}.
¹University of Massachusetts Medical School, Medicine, Worcester, United States; ²Beth Israel Deaconess Medical Center (BIDMC), Gastroenterology, Boston, United States; ³Armand-Frappier Santé Biotechnologie, Laval, Canada; ⁴University of Debrecen Medical School, Internal Medicine, Debrecen, Hungary; ⁵Harvard Medical School, Boston, United States

Email: ycho3@bidmc.harvard.edu

Background and aims: In alcoholic hepatitis (AH), neutrophil count correlates with poor clinical outcomes. However, it is yet to be

explored why neutrophil count increases and whether increased neutrophils induce inflammation and liver damage in AH. Here, we aimed to explore whether neutrophils contribute to alcohol-induced liver damage through increased neutrophil extracellular traps (NET) formation. We identified a unique neutrophil subset (low-density neutrophils, LDNs) and studied mechanisms and consequences of LDNs increase in AH.

Method: NETs were assessed by NET assays, co-immunofluorescence staining and microscopic analysis with liver specimen from AH patients and mice. LDNs and high-density neutrophils (HDNs) were isolated from AH patients and controls for RNA sequencing. The NIAAA AH model or 4-week chronic alcohol feeding was utilized for in vivo studies in mice.

Results: NET components, including citrullinated histone H3, were significantly elevated in the serum from AH patients, and NET formation was detected in the liver from AH patients and mouse models. Neutrophil depletion in vivo with anti-Ly6G antibody prevented NET formation and reduced alcohol-induced liver damage in mice, supporting the role of NET-mediated liver damage in AH. In patients with AH, we identified low-density neutrophils (LDNs), a unique neutrophil subset, during density separation of blood mononuclear cells. LDNs were present only in AH patients and

ORAL PRESENTATIONS

not in healthy subjects or NASH patients. AH-specific LDNs expressed markers of mature neutrophils with exhaustive phenotypes based on flow cytometry and transcriptomic profile. We discovered that LDNs are generated from HDNs after alcohol-induced NET formation. Moreover, transcriptomic analysis identified significant reduction of the neutrophil homing receptor, CXCR4, expression and increased transpondin-1 (don't eat me signal) in AH HDNs and to a greater extent in LDNs compared healthy subjects suggesting that LDNs are defective in homing back to the bone marrow or clearance by phagocytes such as macrophages.

Conclusion: Alcohol-induced NET formation contributes to prolonged liver damage and generates a novel LDN neutrophil subset that has defects in functions and clearance from circulation and/or liver.

OS-1619

Lung infection impacts short-term survival in severe alcoholic hepatitis treated with steroids: results of a prospective monocenter study

Line Carolle Ntandja Wandji¹, Elise Lemaître¹, Khaldi Marion¹, Massih Ningharhari¹, Pierre Saffers¹, Julien Lollivier¹, Lassailly Guillaume¹, Sebastien Dharancy¹, Philippe Mathurin¹, Alexandre Louvet¹. ¹CHU de Lille, Lille, France
Email: alexandre.louvet@chru-lille.fr

Background and aims: Severe alcoholic hepatitis (AH) is associated with an increased risk of infection but the impact of lung infection has not been specifically analyzed in a dedicated cohort.

Method: All patients admitted for severe AH (Maddrey score ≥ 32) between 2002 and 2020 in our unit were prospectively included. AH was confirmed by liver biopsy. Systematic screening for infection was performed at admission and renewed in case of clinical suspicion during follow-up. If present, infection was treated before steroid initiation and response to steroids was defined using the Lille model.

Results: We included 614 patients with severe AH (males in 60.4% of cases, mean age 49.9 years, median MELD 25.2, bilirubin 18.1 mg/dl), of whom 202 (32.9%) were infected at admission (73 lung infections). In multivariate analysis, encephalopathy (OR 3.9, 95%CI 1.48–10.24, $p=0.006$), MELD score (OR 1.1, 95%CI 1.046–1.155, $p=0.0002$) and tobacco exposure (past: OR 4.29, 95%CI 1.726–10.691, $p=0.002$ or active: OR 3.424, 95%CI 1.462–8.02, $p=0.005$) were independently associated with lung infection at admission. Factors associated independently with death before steroid initiation were encephalopathy (OR, 5.1, 95%CI 1.734–15.044, $p=0.003$), MELD score (OR 1.056, 95%CI 1–1.15, $p=0.05$) and especially lung infection compared to other infections (OR 14.285, 95%CI 3.959–51.541, $p<0.0001$). Thus, patients with lung infection at admission had a lower probability of receiving steroids as compared to those with other infections and those non-infected: 54.8 vs. 88.4 vs. 98.1% ($p<0.0001$). Among the 558 patients who received corticosteroids, 146 developed infection, including 57 (39.04%) lung infections. The risk of lung infection was higher in non-responders to steroids (Lille score ≥ 0.45) than in responders: 13% vs. 7.6%, $p=0.03$. The risk of non-respiratory infection was also higher in non-responders: 27.9% vs. 10.6%, $p<0.001$. Variables independently associated with 2-month death were lung infection (RR 1.76, 95%CI 1.05–2.96, $p<0.0001$), non-response to steroids (RR 10.41, 95% CI 5.33–20.33, $p<0.0001$), MELD score at steroid initiation (RR 1.096, 95%CI 0.53–1.14, $p<0.0001$) while non-respiratory infection was not independently predictive of 2-month death (RR 1.11, 95%CI 0.680–1.81, $p=0.67$).

Conclusion: Lung infection is frequent during severe AH and impacts mortality at admission and after steroid initiation. These results question the need for a systematic chest CT-scan during AH course.

OS-1663

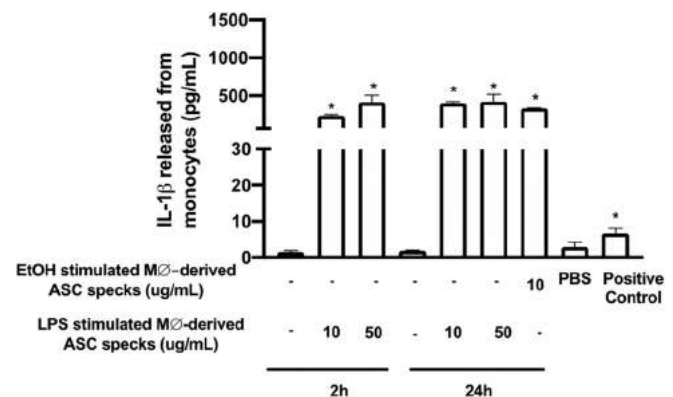
Extracellular inflammasome components perpetuate inflammation in alcoholic hepatitis

Marcelle de Carvalho Ribeiro¹, Mrigya Babuta¹, Charles D. Calenda¹, Christopher Copeland¹, Donna Catalano², Yeonhee Cho^{1,2}, Gyongyi Szabo¹. ¹Beth Israel Deaconess Medical Center (BIDMC), Department of Medicine, Boston, United States; ²University of Massachusetts Medical School, Department of Medicine, Worcester, United States
Email: mribeir1@bidmc.harvard.edu

Background and aims: Nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is activated in Alcoholic Liver Disease (ALD). Upon stimulation, NLRP3 recruits the adaptor protein apoptosis-associated speck-like protein containing CARD (ASC) to oligomerize into specks intracellularly for interleukin (IL)-1 beta release. ASC specks released from pyroptotic cells remain bioactive extracellularly and can activate inflammasomes in neighboring cells. In alcoholic hepatitis (AH), the mechanism for maintaining inflammation even after cessation of alcohol use is yet to be understood. We hypothesized that alcohol induces ASC specks in macrophages (MØs) and hepatocytes, and that these ASC specks propagate inflammation in ALD. Our aim was to investigate how extracellular ASC specks perpetuate inflammation in AH.

Method: Liver and plasma samples from patients with AH and healthy controls were analyzed for ASC aggregates or ASC specks. Transgenic mice expressing fluorescent ASC (ASC-Citrine/Cre+ mice) were evaluated for ASC specks in plasma, liver tissue, MØs, and hepatocytes. The extracellular effect of ASC specks was assessed in HepG2 and THP-1 cell lines. MCC950 was used *in vivo* and *in vitro* to inhibit NLRP3 inflammasome.

Results: Circulating ASC specks and hepatic ASC aggregates were elevated in AH patients compared to healthy controls. Additionally, EtOH binge increased circulating and hepatic ASC specks levels, and induced Kupffer cells pyroptosis and hepatocyte damage in mice. We found that EtOH-treated MØ and hepatocytes released ASC specks via pyroptosis and GSDMD KO mice were protected from EtOH-induced increases in ALT and ASC release in plasma. ASC specks derived from EtOH/LPS-stimulated MØs or hepatocytes triggered significant IL-1 beta release in monocytes, and this was prevented by the NLRP3 inhibitor, MCC950. *In vivo*, MCC950 administration reduced liver ASC specks formation, caspase-1 activation, IL-1 beta production, and steatohepatitis in AH mice.



Conclusion: ASC specks in the circulation and in the liver perpetuate inflammation in AH. Alcohol binge induces the release of ASC specks involving pyroptosis both in hepatocytes and MØs and sustains inflammation. NLRP3 activation, eliciting liver ASC specks formation is responsible for progression of AH, identifying NLRP3 as a potential therapeutic target in ALD.

OS-1726

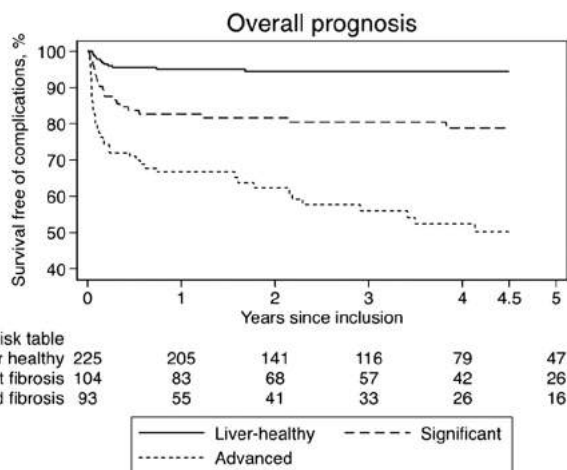
Natural history of alcohol-related liver disease according to biopsy-proven fibrosis in a prospective study of 422 patients and 1,419 patient years

Ditlev Rasmussen¹, Maria Kjærsgaard¹, Katrine Prier Lindvig¹, Mads Israelsen¹, Kathrine Thorhauge¹, Nikkolaj Christian Torp¹, Stine Johansen¹, Sönke Detlefsen², Aleksander Krag¹, Maja Thiele¹.
¹Odense University Hospital, Department of Gastroenterology and Hepatology; ²Odense University Hospital, Department of Pathology
 Email: ditlev.nytoft.rasmussen@regionh.dk

Background and aims: Alcohol-related cirrhosis is associated with high risk of complications and death, but the natural history of different stages of liver fibrosis in asymptomatic, alcohol-overusing patients is unknown. We aimed to describe the natural history of alcohol-related liver disease according to fibrosis stage determined by liver biopsy, and alcohol status at baseline and during follow-up.

Method: We included patients with a history of alcohol overuse but without decompensated liver disease. Based on transient elastography and liver biopsies scored according to Kleiner, we compared liver healthy patients who had a biopsy with F0-F1 fibrosis or transient elastography <6 kPa, patients with significant fibrosis (F2), and advanced fibrosis (F3-4). Ongoing alcohol consumption was an additional predictor. We manually assessed the patients' medical charts for mortality and decompensating events defined as development of overt hepatic encephalopathy, ascites, hepatorenal syndrome, variceal bleeding, or jaundice.

Results: We followed 422 patients for a total of 1,419 patient-years. The median age at baseline was 57 years (IQR 50–64) and 75% were men. During a median follow-up of 43 months (IQR 20–59), 53 patients died. Fifty-one patients experienced a decompensating event, 27 of whom also died. Decompensation-free survival significantly followed disease stage: 13/225 (5.8%) liver-healthy patients died and/or decompensated, compared to 22/104 (21%) with significant fibrosis (hazard ratio, HR 3.8, 1.9–7.5, $p < 0.01$), and 42/93 (45%) with advanced fibrosis (HR 9.6, 5.2–18.0, $p < 0.01$), see figure. At three years, the overall mortality was 3% for liver healthy patients, 12% for patients with significant fibrosis and 22% for patients with advanced fibrosis. Ascites and overt hepatic encephalopathy were the most common decompensating events, followed by variceal bleeding. Periods of excessive drinking during follow-up resulted in poorer decompensation-free survival (HR 1.6, 1.02–2.6), mainly due to decompensation or death in patients with significant or advanced fibrosis. Hospitalizations occurred more frequently in the group of advanced fibrosis, but were comparable for the two remaining groups.



Conclusion: Patients with alcohol-related significant or advanced fibrosis are at high risk of short-term decompensation and death. This

suggests that also patients with moderate fibrosis should be offered combined alcohol rehabilitation and monitoring in liver specialist care.

OS-2028

CXCL12-CXCR4 pathway drives hepatocyte reprogramming in alcoholic hepatitis

Beatriz Aguilar-Bravo¹, Silvia Ariño Mons¹, Elisa Pose², Juanjo Lozano³, Philippe Mathurin⁴, Pere Ginès², Pau Sancho-Bru¹.
¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Cell plasticity and tissue repair, Barcelona, Spain; ²Hospital Clínic de Barcelona, Liver Unit, Barcelona, Spain; ³Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; ⁴Hospital Claude Huriez, Service des Maladies de l'Appareil Digestif, Lille, France
 Email: aguilar@clinic.cat

Background and aims: Hepatocyte reprogramming leading to a loss of cell identity has been previously shown to take place in alcoholic hepatitis (AH) patients. However, the mechanisms and the impact on liver function are poorly understood. The aim of this study was to evaluate the impact of hepatocyte reprogramming and the presence of intermediate hepatobiliary (IHB) cells on the progression of alcohol-related liver disease (ALD) and to dissect the molecular mechanisms regulating this process.

Method: KRT7⁺ hepatocytes (IHB cells) were quantified in liver biopsies from an ALD cohort (n=34). IHB cells, KRT7⁺ ductular reaction (DR) cells and KRT7⁻ hepatocytes were isolated by laser capture microdissection from AH liver sections and used for RNAseq analysis. Transcriptomic analysis was confirmed by immunofluorescence. The protein network interaction of CXCR4 pathway was evaluated by String. CXCR4 and CXCL12 expression was assessed in AH liver sections, and mechanistic studies were performed with primary hepatocytes.

Results: Both IHB and DR cells were increased in AH and decompensated cirrhotic patients, but only IHB cells correlated with poor liver function and reduced synthetic capacity. Transcriptomic profile of IHB cells revealed a transitional phenotype between hepatocyte and biliary cells. Interestingly, hepatocyte transcription factors (TF) and functional markers were reduced in IHB cells suggesting a loss of hepatocyte identity. Functional analysis identified well known pathways involved in hepatocyte reprogramming such as TGFβ, but also novel pathways such as CXCR4 or JAK-STAT. Histologically, CXCR4 protein expression was increased in IHB and DR cells, but it was absent in KRT7⁻ hepatocytes. Importantly, CXCR4 expression was found to negatively correlate with the expression of mature hepatocyte TF and albumin and positively with disease severity in a cohort of AH patients. Mechanistically, primary hepatocytes showed expression of CXCR4 in response to TGFβ, and recombinant CXCL12 promoted hepatocyte reprogramming.

Conclusion: This study shows the association of the loss of hepatocyte identity with ALD progression and poor liver function. Moreover, we identify the CXCL12/CXCR4 pathway as a new driver of hepatocyte reprogramming in AH. Overall, this study suggests that strategies limiting hepatocyte reprogramming and enhancing differentiation may be of interest to improve liver function in advanced ALD.

OS-2158

Interferon lambda 4 is associated with dysfunctional antibacterial immunity during alcohol-related liver disease

Jennifer M Ryan^{1,2,3}, Huyen Li Adams^{1,4,5}, Dhruvi Devshi^{1,4}, Stephen Atkinson⁶, Luke Tyson⁶, Debbie L. Shawcross³, Gavin Wright⁷, Sarah Fairclough⁷, Alex Evans⁵, Marieta Simonova⁸, Krum Katarov⁸, Tanya Hadzhiolova⁸, Slava Pavlova⁸, Jasmohan Bajaj⁹, Andrew Fagan⁹, Mark Thursz⁶, Roger Williams^{1,4}, Andrew McQuillin¹⁰, Marsha Y. Morgan¹¹, Antonio Riva^{1,4},

ORAL PRESENTATIONS

Shilpa Chokshi^{1,4}. ¹Institute of Hepatology-Foundation for Liver Research, Liver Immunology, London, United Kingdom; ²Royal Free Hospital, Department of Hepatology, London, United Kingdom; ³King's College London, Institute of Liver Studies, London, United Kingdom; ⁴King's College London, Faculty of Life Sciences and Medicine, London, United Kingdom; ⁵Royal Berkshire Hospital, Department of Gastroenterology, Reading, United Kingdom; ⁶Imperial College London, St Mary's Hospital, Department of Hepatology, London, United Kingdom; ⁷Basildon and Thurrock University Hospitals, Basildon, United Kingdom; ⁸Military Medical Academy, Department of Gastroenterology, Hepatobiliary surgery and Transplantology, Sofia, Bulgaria; ⁹Virginia Commonwealth University and Hunter Holmes McGuire VA Medical Centre, Richmond (VA), United States; ¹⁰University College London, Molecular Psychiatry Laboratory, Division of Psychiatry, London, United Kingdom; ¹¹University College London, UCL Institute for Liver and Digestive Health, Royal Free Campus, London, United Kingdom
Email: s.chokshi@researchinliver.org.uk

Background and aims: Advanced alcohol-related liver disease (ALD) is associated with defective antibacterial immunity. Consequently, patients face an increased vulnerability to bacterial infection, which may worsen organ failure and increase the risk of death. The interferon lambda family (IFN- λ 1/ λ 2/ λ 3/ λ 4) are important mediators of anti-pathogen immunity, but their role in ALD remains unexplored.

Method: Genetic variants in IFN- λ 1/ λ 2/ λ 3/ λ 4 and their associations with infection were explored in 814 STOPAH participants with severe alcoholic hepatitis (SAH) and >11000 disease and healthy controls. Liver and colon expression of IFN- λ 4 was measured in a public ALD liver microarray dataset and in ALD colonic biopsies. Systemic plasma IFN- λ 4 levels and production of IFN- λ 4 during in vitro bacterial challenge of peripheral blood mononuclear cells (PBMC) in ALD patients and healthy controls (HC) were measured by ELISA. IFN- λ 4 gene expression was assessed in a large PBMC transcriptomics dataset from patients with ALD (30 alcohol-related cirrhosis, ARC; 15 SAH; 12 HC). Finally, the impact of recombinant IFN- λ 4 on antibacterial immune responses in *E. coli* stimulated PBMC cultures from ALD patients and HC was measured by flow cytometry and Luminex.

Results: The only variant associated with bacterial infection in SAH patients at presentation ($p=0.03$) was the loss-of-function rs117648444 in IFNL4. Based on this, we focussed the mechanistic arm of this study on IFN- λ 4 alone. IFN- λ 4 was not expressed in the liver or colon of ALD patients but plasma IFN- λ 4 was lower in these patients compared to HC. PBMC IFN- λ 4 production was lower in ARC patients and undetectable in SAH, compared to HC, and was completely abolished following *E. coli* challenge. In the PBMC transcriptomics dataset, IFN- λ 4 gene expression was lower in ARC and SAH patients compared to HC ($p=0.005$), and in vitro treatment of ALD and HC PBMC with recombinant IFN- λ 4 modulated the antibacterial immunity.

Conclusion: IFN- λ 4 is involved in the immunopathogenesis of ALD and may be a novel attractive target for immunomodulation of antibacterial responses in patients with advanced disease.

Cirrhosis and its complications: ACLF and Critical illness

OS-638

PD-L1 expression of monocytes relates to severity, infection and mortality in acute-on-chronic liver failure

Evangelos Triantafyllou¹, Francesca Trovato², Hannah Husbyn¹, Xiaohong Huang², Sujit Mukherjee¹, Christine Bernsmeier³, Robert D. Goldin¹, Julia Wendon², Lucia Possamai¹, Wafa Khamri¹, Mark Thursz¹, Mark J.W. McPhail². ¹Imperial College London,

Metabolism, Digestion and Reproduction, London, United Kingdom; ²King's College London, Inflammation Biology, School of Immunity and Microbial Sciences, London, United Kingdom; ³University of Basel and University Centre for Gastrointestinal and Liver Diseases, Department of Biomedicine, Basel, Switzerland
Email: e.triantafyllou@imperial.ac.uk

Background and aims: Monocyte dysfunction and bacterial infections are common in cirrhosis and acute-on-chronic liver failure (ACLF) and substantially contribute to the high mortality. We recently identified the importance of the PD-1/PD-L1 checkpoint pathway in regulating macrophage antimicrobial responses in acute liver failure. Here, we sought to explore PD-1/PD-L1 axis in chronic liver failure.

Method: Flow cytometry was used to determine the phenotype of lymphocytes (CD3⁺CD4⁺, CD3⁺CD8⁺ T cells and CD3⁺CD4⁺CD25^{high}CD127^{low} Tregs) and monocytes (CD14⁺HLA-DR⁺) in blood of 10 healthy controls (HC) and patients with stable cirrhosis (SC, n=6), decompensated cirrhosis (DC, n=8) and ACLF (n=24). Plasma cytokine concentrations were measured by Meso-Scale-Discovery (MSD) kit. PD-L1 expression was examined by immunohistochemistry (IHC) in tissue derived from cirrhotic patients and pathological controls. Monocyte *E. coli* phagocytosis was assessed in PBMCs (HC and ACLF, n=5 each) pre-treated with or without anti-PD-1 blocking antibody (10 μ g/ml).

Results: Compared to healthy and disease controls, monocytes in ACLF patients displayed decreased HLA-DR expression (A), as previously established, and significantly increased PD-L1 expression (both % and MFI) (B). Of note, PD-1 expression of CD4⁺, CD8⁺ and Treg cells was not altered among study groups. Importantly, monocyte PD-L1 expression was significantly higher in patients who developed infectious complications or had poor outcome (day 90 mortality) (C). PD-L1 levels correlated with other monocyte anti-inflammatory/pro-restorative markers (CD163 and MerTK), systemic inflammation (e.g., plasma IL-10, IL-8 and IL-6) and disease severity (e.g., MELD, CLIF-SOFA, CLIF-ACLF) (D). Increased hepatic PD-L1 expression was detected in liver tissue from cirrhotic patients, compared to pathological controls. Finally, compared to HC, ACLF patients had decreased monocyte *E. coli* phagocytosis capacity [34663 vs 22722 (MFI); $p=0.0281$] which was improved with in vitro PD-1/PD-L1 blockade (22722 vs 26160 MFI; $p=0.0312$).

Conclusion: We have identified the expansion of an immune-suppressive PD-L1⁺ monocyte population that correlates with disease severity and risk of infections in ACLF. Thus, monocyte PD-L1 may serve as prognostic marker and deserves further evaluation as immunotherapeutic target aimed to prevent the high morbidity and mortality associated with infections in this condition.

OS-845

Treatment of hepatorenal syndrome type 1 with terlipressin reduces need for renal replacement therapy post-liver transplantation

Juan Carlos Q. Velez¹, Seth Sclair², Antonio Sanchez³, Stephen Caldwell⁴, Samuel Sigal⁵, Paul J. Thuluvath⁶, Rohit S. Satoskar⁷, S. Chris Pappas⁸, Khurram Jamil⁹. ¹Ochsner Health System, Department of Nephrology; ²University Hospitals Cleveland Medical Center, Division of Gastroenterology and Liver Disease, Cleveland; ³University of Iowa Hospitals and Clinics, Division of Gastroenterology and Hepatology, Iowa City; ⁴University of Virginia, Gastroenterology and Hepatology; ⁵Montefiore Medical Center, Department of Medicine; ⁶Mercy Medical Center and University of Maryland School of Medicine, Division of Gastroenterology; ⁷MedStar Georgetown University Hospital, Liver Transplantation; ⁸Orphan Therapeutics, Scientific Affairs; ⁹Mallinckrodt Pharmaceuticals, Department of Scientific Affairs
Email: juancarlos.velez@ochsner.org

Background and aims: Hepatorenal syndrome type 1 (HRS-1) is a severe but reversible acute kidney injury in patients with cirrhosis. The need for renal replacement therapy (RRT) posttransplant is

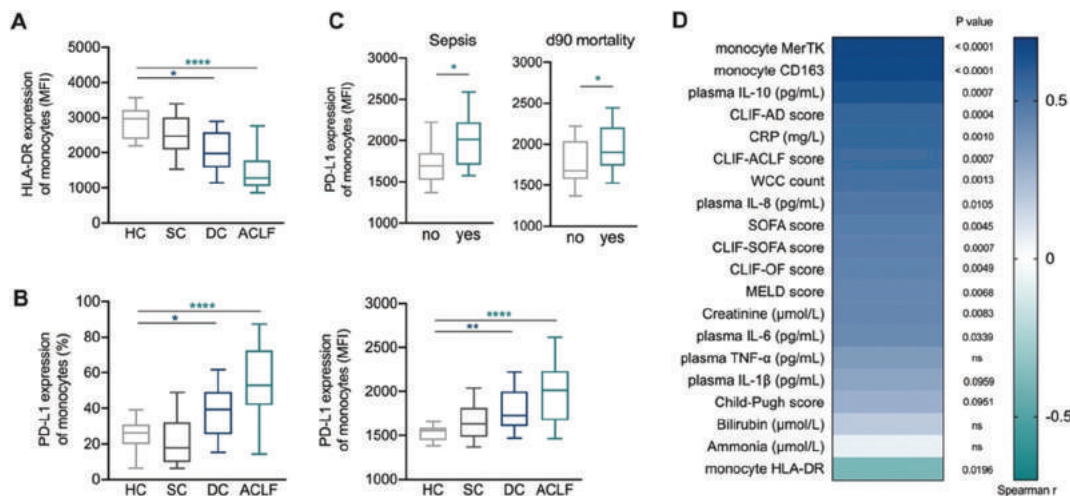


Figure: (abstract: OS-638)

associated with prolonged intensive care unit stays and decreased survival. Recently, a randomized placebo (PBO)-controlled trial (CONFIRM, NCT02770716) demonstrated the efficacy of terlipressin (TERLI) for inducing reversal of HRS-1 and reducing the cumulative need for RRT. This study assessed whether TERLI reduces the rate of RRT following liver transplantation (LT).

Method: CONFIRM was a North American trial (N=300) that compared HRS-1 reversal rates between patients treated 2:1 with albumin plus TERLI (n = 199) or albumin plus PBO (n = 101). In a post hoc analysis, we assessed the rate of RRT post-LT by intention-to-treat analysis through 90 days of follow-up. We also conducted a pooled analysis of the 3 TERLI RCTs in HRS-1 (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to examine 90-day overall and RRT-free survival rates in patients who received LT.

Results: In CONFIRM, 23.1% (46/199) of patients in the TERLI group and 28.7% (29/101) of patients in the PBO group underwent LT. Following LT, the rate of post-LT RRT in patients who received TERLI was significantly lower than that in those who received PBO (19.6% [9/46] vs 44.8% [13/29], respectively; p = 0.036). The overall 90-day survival rate for those transplanted in the TERLI group was 100% (46/46) compared with 93.1% (27/29) in the PBO group (p = not significant). Further, in the pooled analysis of the 3 phase 3 studies, the 90-day survival rates were 98.9% (93/94) and 91.0% (71/78), respectively (p = 0.014). In the pooled analysis of REVERSE and CONFIRM, for transplant-listed patients, 50.0% (46/92) of patients in the TERLI group were alive without RRT at Day 90 compared with 32.2% (19/59) in the PBO group (p = 0.032).

Conclusion: Treatment with TERLI added to albumin for patients with HRS-1 significantly decreases the need for RRT following LT.

OS-2060

Pathophysiological basis of resolution of Acute-on-Chronic Liver Failure (ACLF) induced by the novel liver dialysis device, DIALIVE

Rafael Banares Canizares¹, Faouzi Saliba², Banwari Agarwal³, Dana Rodica Tomescu⁴, Daniel Martin⁵, Vanessa Stadlbauer⁶, Gavin Wright^{3,7,8,9}, Mohammed Sheikh¹⁰, Carrie Morgan¹¹, Fausto Andreola⁹, Karl Oettl¹², Katja Waterstradt¹³, Rahul Kumar¹⁴, Stefanie M. Bode-Böger¹⁵, Sophie-Caroline Sacleux², Gernot Schilcher⁶, Sebastian Koball^{16,17}, Andrada Tudor⁴, Eman Alabsawy¹⁸, Samuel Didier², Philippe Ichai^{2,19}, Maria Hernández-Tejero¹, Fátima Aziz²⁰, Michael Hinz^{16,17}, Mihai Popescu⁴, Maria-Vega Catalina¹, Douglas Corrigan⁷, Jacques Creteur²¹, Margret Paar¹², Sandra Serrano²⁰, Aehling NF²², Ahmed Elsharkawy²³, Niels Kristian Muff Aagaard²⁴, Oliver Lheureux²¹, Francois Durand²⁵, Jaak Minten²⁶, Gema Domenech²⁰, Juan José Aragonés²⁰, Amir Gander³,

Moises Sancez²⁷, Raj Mookerjee¹⁰, Andrew Davenport⁹, Daniel Green¹¹, Marco Pavesi²⁸, Jan Stange^{16,17}, Nathan Davies⁹, Vicente Arroyo²⁸, Javier Fernandez^{28,29}, Steffen Mitzner^{16,17}, Rajiv Jalan⁹. ¹General University Hospital, Health Research Institute Gregorio Marañón, Complutense University of Madrid, Department of Gastroenterology; ²Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ³Royal Free Hospital, United Kingdom; ⁴Carol Davila University of Medicine and Pharmacy, Fundeni Clinical Institute Bucharest, București, Romania; ⁵Peninsula Medical School, University of Plymouth, John Bull Building, Plymouth Science Park, Devon, United Kingdom; ⁶Medical University of Graz, Department of Internal Medicine, Division of Gastroenterology und Hepatology, Graz, Austria; ⁷Basildon University Hospital, United Kingdom; ⁸King's College London; ⁹University College London; ¹⁰University College London, Institute for Liver and Digestive Health; ¹¹Yaqril Ltd; ¹²Medical University of Graz, Division of Physiological Chemistry, Otto Loewi Research Center, Graz, Austria; ¹³MedInnovation GmbH, Berlin, Germany; ¹⁴Changi General Hospital, Singapore, Singapore; ¹⁵Institut für Klinische Pharmakologie, Magdeburg, Germany; ¹⁶University Hospital of Rostock, Rostock, Germany; ¹⁷Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany; ¹⁸ILDH/UCL, London, United Kingdom; ¹⁹Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ²⁰Hospital Clínic, Medical Statistics Core Facility IDIBAPS, Barcelona, Spain; ²¹Hospital Erasme, Dpt of Intensive Care, Bruxelles, Belgium; ²²Leipzig University, Division of Hepatology, Department of Medicine II, Leipzig, Germany; ²³Mindelsohn Way, United Kingdom; ²⁴Aarhus University Hospital, Dept of Hepatology, Aarhus, Denmark; ²⁵Hospital Beaujon AP-HP, Clichy, France; ²⁶De Fakkell Bvba, Landen, Belgium; ²⁷Shelbourne Road, Dublin, Ireland; ²⁸European Foundation for the study of chronic liver failure, Barcelona, Spain; ²⁹Hospital Clínic, Liver ICU, Liver Unit, Barcelona, Spain
Email: rbanares@ucm.es

Background and aims: In ACLF, systemic inflammation (SI) due to pathogen and damage associated molecular patterns (PAMPs and DAMPs), albumin and endothelial dysfunction results in organ failure. DIALIVE, a liver dialysis device replaces dysfunctional albumin and removes PAMPs and DAMPs. In a randomised controlled trial, DIALIVE resolved ACLF faster and in a greater proportion of patients compared with standard of care (SOC). This substudy aimed to evaluate the effect of DIALIVE on pathophysiological processes that are thought to be causally associated with ACLF.

Method: The study included patients with ACLF 1-3a, randomized either to DIALIVE or SOC. End points were evaluated at Day 10. The DIALIVE group received treatments in the first 3-days (range 1-6). Plasma samples were obtained on Days 0, 5 and 10. A post-hoc inferential Mixed Models for Repeated Measurements analysis was performed to evaluate the statistically significant differences

ORAL PRESENTATIONS

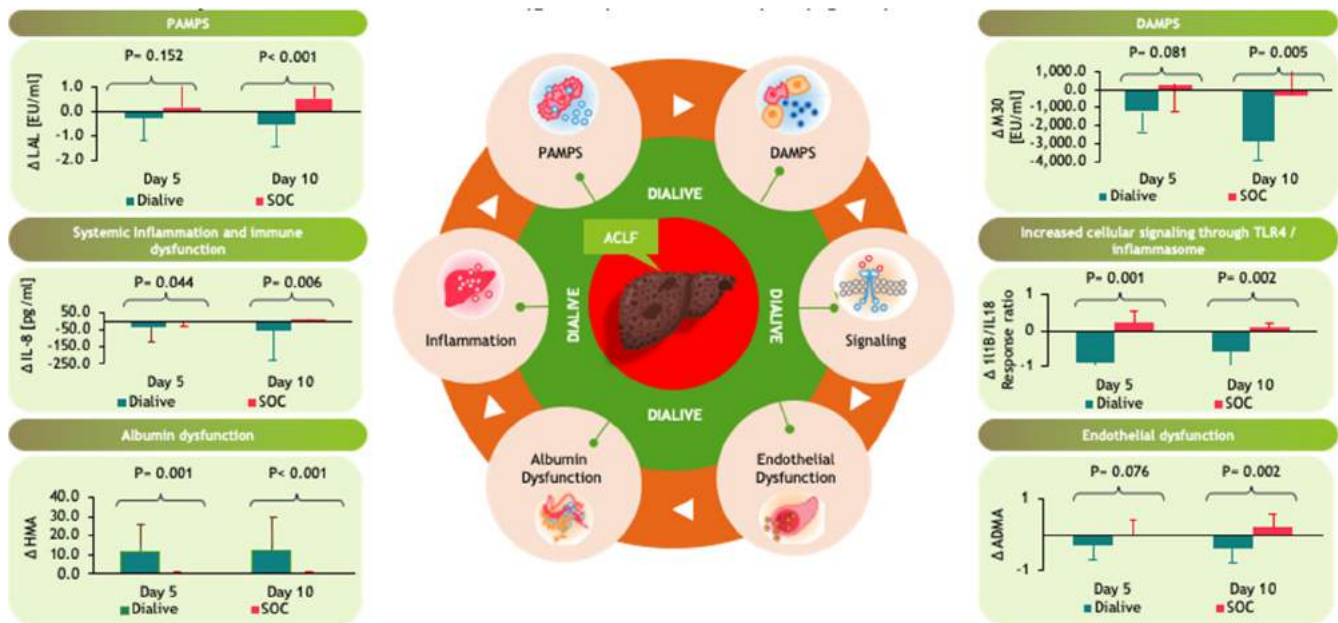


Figure: (abstract: OS-2060): Impact of DIALIVE on the pathophysiological processes deranged in ACLF-change from baseline at Days 5 and 10 for DIALIVE (green) and SOC (red) group.

between groups at the Day 10. Changes in variables from baseline in the groups is shown in the Fig.SAS system v.9.4 used.

Results: 32 ACLF patients were randomised to DIALIVE (N = 17; CLIF-Ofs: 10.3 (1.6)) or SOC (n = 15; CLIF-Ofs: 9.9 (1.2)). 30-evaluable patients (n = 15 each group) comprised this substudy. **PAMPs:** *Endotoxin activity assay:* The patient-level pre-defined reduction goals were 20%. Marked advantage seen for DIALIVE (80%) vs SOC (36.4%) at Day 5. **LAL assay:** Significant reduction in DIALIVE group ($p = 0.001$). **Albumin Function:** DIALIVE increased human mercaptalbumin ($p = 0.001$) and reduced human nonmercaptalbumins 1 and 2 ($p = 0.005$ and $p = 0.017$); improved binding capacity ($p = 0.016$; using EPR spectroscopy) and reduced ischemia modified albumin ratio ($p = 0.009$) vs SOC. **DAMPs:** M30 and M65 components of cytokeratin 18 ($p = 0.005$; $p = 0.029$) and RIPK3 (marker of necroptosis) ($p = 0.486$) were reduced in the DIALIVE group. **SI:** IL-8, IL-18 and TNFa were reduced in the DIALIVE compared with SOC group ($p = 0.006$; $p = 0.636$; $p = 0.053$). **Endothelial function:** ADMA and Factor VIII were markedly reduced in the DIALIVE patients ($p = 0.002$; $p = 0.195$). **TLR4 and Inflammasome ligands:** Incubation of patient's plasma with a 1L1b/IL18 Inflammasome cell line and TLR4 reporter cell line reduced signalling significantly ($p = 0.002$ and $p = 0.030$).

Conclusion: IALIVE impacts significantly on DAMPs, PAMPs, albumin and endothelial function, markers of SI and, reduces TLR4 and inflammasome ligands that collectively contribute to its ability to resolve ACLF.

OS-2142

Comparison of 20% albumin versus crystalloid plasmalyte for fluid resuscitation in cirrhotics with sepsis induced hypotension an open label randomized controlled trial

Abhinav Verma, Dr¹, Rakhi Maiwall¹, Amrish Sahney¹, Lalita Mitra², Shiv Kumar Sarin¹. ¹ILBS, Hepatology, New Delhi, India; ²ILBS, Critical Care, NEW DELHI, India
Email: shivsarin@gmail.com

Background and aims: Sepsis is an inflammatory response to severe infection characterized by hypovolemia and vasodilation requiring treatment with early antibiotics and fluid resuscitation. The choice of fluid to be used in a cirrhotic presenting with sepsis induced hypotension (SIH) is still unclear. We compared the efficacy and

safety of 20% albumin (ALB) versus plasmalyte (PLA) in reversing SIH in critically ill patients with cirrhosis (CICs).

Method: Cirrhotics with septic shock underwent open label randomization to receive either 20% albumin [0.5–1.0 gm/kg over 3 hours; n = 50] or plasmalyte (30 ml/kg over 3 hours, n = 50). Primary outcome was reversal of hypotension. Secondary outcomes included lactate clearance, need for dialysis, length of stay in the intensive care unit (ICU), 28-day mortality and adverse effects of therapy.

Results: The baseline characteristics were comparable between the two groups. The mean baseline arterial lactate (mmol/L) [9.16 ± 3.18 vs 9.38 ± 4.77 , $p = 0.78$], mean arterial pressure [MAP] (mm of Hg) [51.4 ± 6.51 vs. 49.8 ± 4.45 , $P = 0.17$] and SOFA scores [10.8 ± 2.96 vs. 11.1 ± 4.2 ; $p = 0.68$] were comparable in ALB vs. PLA groups, respectively. The most common etiology of cirrhosis was alcohol (39%) and commonest type of sepsis was pneumonia (40%). At 3 hours, there was no difference in the MAP, however a trend towards reduction in norepinephrine dose was noted in ALB vs. the PLA group [$p = 0.05$]. The lactate clearance was noted in both the groups at 3 hours, significantly higher in ALB than PLA ($p = 0.012$). There was no difference in the 28-day mortality in both the groups [ALB (42% vs. PLA 58%, $p = 0.16$) and length of ICU stay [$p = 0.6$]. Patients in the PLA group more frequently required dialysis [58% vs. 44.8%; $p = 0.07$], however, there was no difference in time to initiation of dialysis in both groups [99.67 ± 71.2 vs. 82.12 ± 48.3 hours; $p = 0.26$]. Patients in the ALB group showed significant worsening of lung functions [PaO₂/FiO₂] requiring discontinuation of therapy within 3 hours in 6 (12%) patients.

Conclusion: In cirrhotics with sepsis induced hypotension, Plasmalyte is as effective as 20% albumin in reversing hypotension, restoring the impaired microcirculation and is safe and well-tolerated. Albumin even though achieves rapid lactate clearance, cautious and judicious use of 20% ALB in cirrhotics with hypotension is recommended. **NCT02721238.**

OS-2779

Targeted albumin therapy increases serum sodium in hospitalized cirrhosis patients with hyponatremia at baseline, but has no effect on short term outcome; a sub study from the ATTIRE Trial

Louise China¹, Nicholas Freemantle², Ewan Forrest³, Gavin Wright⁴, Yiannis Kallis⁵, Alastair O'Brien⁶. ¹UCL Institute for Liver and Digestive Health, London, United Kingdom; ²University College London Comprehensive Clinical Trials Unit, University College London, London, United Kingdom; ³Glasgow Royal Infirmary, Glasgow, United Kingdom; ⁴Mid and South Essex NHS Foundation Trust, Basildon and Thurrock University Hospitals NHS Foundation Trust, United Kingdom; ⁵Barts and the London School of Medicine and Dentistry Queen Mary University of London, United Kingdom; ⁶UCL Institute for Liver and Digestive Health, London, United Kingdom
Email: alastair.o'brien@nhs.net

Background and aims: Hyponatremia is negatively associated with outcome in decompensated cirrhosis. Though there is little evidence-based guidance on treatment, data from a large retrospective cohort study indicated that patients treated with intravenous human albumin solution (HAS) saw greater resolution of hyponatremia associated with improved survival. We investigated data from ATTIRE (Albumin to Prevent Infection in Chronic Liver Failure) to determine whether albumin treatment benefited hospitalised decompensated cirrhosis patients with hyponatremia.

Method: ATTIRE was a randomized, multicenter, open-label, parallel-group trial in 777 patients. Patients received targeted 20% HAS infusions for up to 14 days or discharge, to raise albumin >30 g/L, or standard care. Albumin was permitted for paracentesis, spontaneous bacterial peritonitis, or hepatorenal syndrome in standard care. The composite primary end point was new infection, kidney dysfunction,

or death on days 3–15. We examined the interaction between targeted albumin and standard care for the primary end point stratifying by baseline sodium \geq / $<$ 130 mmol/L. Differences in sodium at day 5 between groups were analysed as a mixed model with sodium as response variable.

Results: 568/777 had a sodium \geq 130 and 206 <130 mmol/L at baseline. For <130 mmol/L patients, targeted albumin patients received 239.4 g (SD 129.1) of albumin and standard care 123.2 g (SD 138.4) ($p < 0.0001$). For the composite primary end point, there was a non-linear response according to sodium at baseline with odds ratio rising for low and elevated values (Fig.1A and B). Randomisation to albumin was associated with an overall 1.77 mmol/L increase in sodium, (95% CI 1.04–2.51; $p < 0.0001$) at day 5 which was greater in the hyponatremic group (mean 2.84 mmol/L, CI 1.10–4.57 compared to 1.46, CI 0.67–2.25). There was no interaction between sodium category (hypo or hypernatremia) and treatment group (albumin or standard care) for the composite primary end point, ($p = 0.1002$; Fig. 1C), nor renal dysfunction and death individually ($p = 0.532$ and 0.528). There was a significant interaction for development of new infection ($p = 0.021$).

Conclusion: These prospective data from a randomised trial demonstrate the efficacy of targeted intravenous HAS to raise serum sodium in hospitalized decompensated cirrhosis with hyponatremia at baseline compared to standard care, however, this does *not* improve short-term outcome. There was a significant interaction for new infection but was a combination of improved outcome in targeted albumin hyponatremic patients compared to standard care and improvement in standard care in sodium \geq 130 mmol/L.

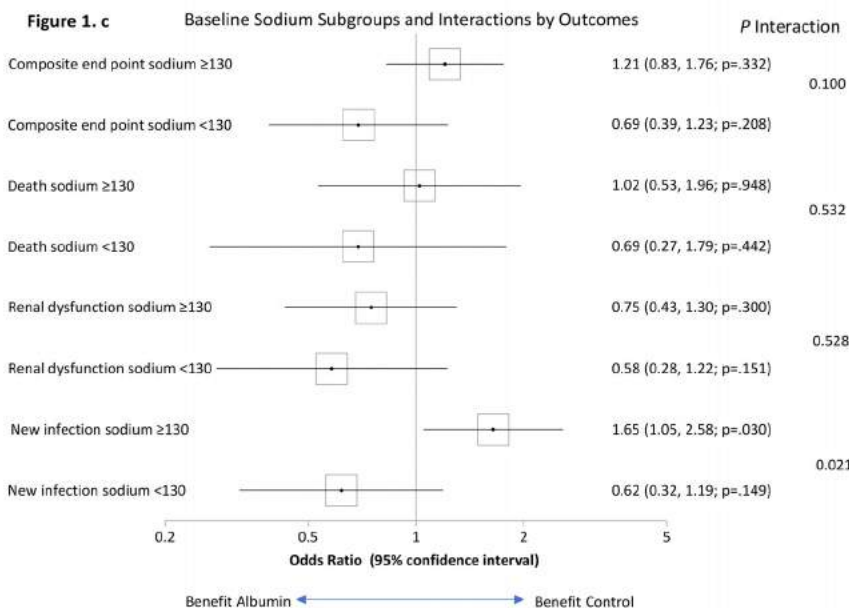
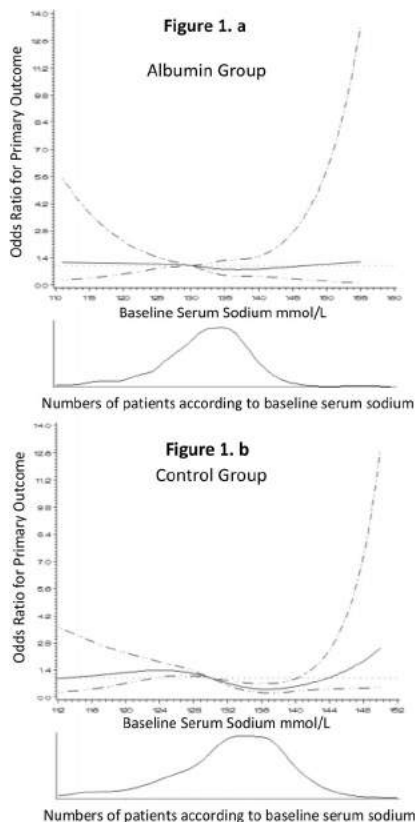


Figure: (abstract: OS-2779): Odds ratio for primary composite outcome according to baseline serum sodium in (a) Albumin and (b) Standard Care treatment groups. (c) Baseline Sodium subgroups and interactions by outcomes.

Cirrhosis and its complications: Experimental and pathophysiology

OS-1491

Hepatocellular carcinoma chemoprevention by inhibition of the angiotensin converting enzyme and EGFR transactivation

Emilie Crouchet¹, Shen Li², Simonetta Bandiera¹, Naoto Fujiwara³, Hussein El Saghire¹, Shijia Zhu³, Tongqi Qian³, Mozhdeh Sojoodi², Stephen Cole Barret², Eugénie Schaeffer¹, Marine Oudot¹, Clara Ponsolles¹, Sarani Ghoshal², Gunisha Arora², Nicolaas Van Renne¹, Joachim Lupberger¹, Kenneth K. Tanabe², Nathalie Pochet^{4,5}, Yujin Hoshida³, Bryan C. Fuchs^{2,6}, Thomas Baumert^{1,7}. ¹Inserm U1110, Institute of Viral and Liver Disease, University of Strasbourg, Strasbourg, France; ²Division of Surgical Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, United States; ³Liver Tumor Translational Research Program, Simmons Comprehensive Cancer Center, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Department of Internal Medicine, Dallas, United States; ⁴Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, United States; ⁵Program in Translational NeuroPsychiatric Genomics, Brigham and Women's Hospital, Harvard Medical School, Boston, United States; ⁶Ferring Research Institute, San Diego, United States; ⁷Institut Hospitalo-Universitaire, Pôle Hépato-digestif, Nouvel Hôpital Civil, Strasbourg, France
Email: thomas.baumert@unistra.fr

Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of death among cirrhotic patients. While new modalities for HCC treatment have been recently approved, HCC chemopreventive strategies for advanced fibrosis are lacking. Identification of candidate compounds for HCC chemoprevention has been hampered by the absence of tractable model systems and the complex cell circuitry driving disease progression. To address these roadblocks, we have recently developed a simple human cell-based system modeling a clinical prognostic liver signature (PLS) predicting liver disease progression and HCC risk (Crouchet et al. ILC 2020). Applying our cell-based discovery system combined with computational screening we identified captopril, an approved angiotensin converting enzyme (ACE) inhibitor, as a candidate compound for HCC chemoprevention. Here we aimed to explore ACE as a therapeutic target for HCC chemoprevention in state-of-the-art preclinical models of advanced fibrosis.

Methods: HCC chemoprevention was investigated in the DEN rat cirrhosis model and a diet-based rat model for NASH-induced hepatocarcinogenesis. The mechanism of action was explored using perturbation studies in cellular and patient-derived models combined with integrative RNA-Seq analyses and proteomics. To investigate the clinical translatability, we studied the impact of captopril on the liver cell circuits predicting fibrosis progression to HCC in cirrhotic patients.

Results: In both animal models Captopril markedly and significantly improved liver function, reduced liver fibrosis, and had a pronounced HCC chemopreventive effect as shown by a robust and significant decrease of tumor nodules and burden in the fibrotic or cirrhotic livers. RNA-Seq analysis in cirrhotic rat liver tissues showed that captopril significantly suppressed the expression of pathways mediating fibrogenesis, inflammation and carcinogenesis including

epidermal growth factor receptor (EGFR) signaling. Mechanistic data using gain- and loss-of function studies in cell-based liver disease models uncovered a cross-activation of the EGFR pathway by angiotensin in hepatic cells. Corroborating the clinical translatability, captopril markedly reversed the HCC high risk status of a well-established prognostic liver signature predicting HCC risk in liver tissues of patients with advanced fibrosis.

Conclusion: Captopril prevents fibrotic liver disease progression towards HCC development by targeting the angiotensin converting enzyme and EGFR transactivation. Our study identified the ACE inhibitor captopril as a generic and safe candidate drug ready for clinical assessment and HCC chemoprevention.

Cirrhosis and its complications: Other clinical complications except ACLF and critical illness

OS-31

Branched chain amino acids do not improve muscle mass in patients of cirrhosis with sarcopenia: A double blind randomized placebo controlled trial

Srikant Mohta¹, Sumaira Qamar¹, Abhinav Anand¹, Deepak Gunjan¹, Namrata Singh¹, Sanchit Sharma¹, Samagra Agarwal¹, Anoop Saraya¹. ¹All India Institute of Medical Sciences, Department of Gastroenterology and human nutrition, New Delhi, India
Email: ansaraya@yahoo.com

Background and aims: The role of branched-chain amino acids (BCAA) in alleviating sarcopenia in patients with cirrhosis is presently undefined. We aimed to evaluate the role of BCAA in improving the muscle mass in a randomised controlled trial.

Method: Consecutive patients of cirrhosis with Child Pugh score <10 and sarcopenia were randomized to receive either 12 g/day of BCAA or a placebo for 6 months in addition to a structured home-based exercise program (30 minutes/day) and diet counselling (1–1.2 g/kg/day, daily protein intake). Sarcopenia was defined according to gender specific axial skeletal muscle index (SMI) cut-offs. The primary end point was change in muscle mass based on computed tomography (CT) scan at the 6 months.

Results: Sixty patients [median age:43.5 (IQR = 19.3) years; males (66.6%) of predominantly alcohol related (40%) and viral (31.7%) etiologies] were randomised. Baseline clinical and demographic characters were similar except model for end-stage liver disease (MELD) score (10.2 ± 2.8 vs. 12.2 ± 3.5, p = 0.02) and calorie intake (1838.1 kcal ± 631.5 vs. 2217.5 kcal ± 707.3, p = 0.03), both being higher in the placebo arm. After adjusting for both baseline confounders and protein intake, the change in SMI was similar in both groups [mean adjusted difference (MAD) +0.84, CI –2.9; +1.2, p = 0.42]. The secondary outcomes including change in hand grip strength (MAD +0.49, CI –1.68; +2.67, p = 0.65), 6-meter gait speed (MAD –0.07, CI –0.17; +0.04, p = 0.20), 6-minute walk distance (MAD –11.0, CI –36.4; 14.4, p = 0.39) were similar in both groups. The change in quality of life (chronic liver disease questionnaire) (p = 0.55), plasma ammonia (p = 0.73) and serum myostatin (p = 0.77) levels were also similar. No difference was noted on gender, etiology and severity of liver disease specific subgroup analysis. Four patients had minor adverse events in each group.

Table 1: Outcome measures in both groups at baseline and 6 months of follow-up (unadjusted)

	Baseline			At 6 months		
	BCAA	Placebo	p	BCAA	Placebo	p
Skeletal muscle index (cm ² /m ²)	37.92 ± 5.94	35.23 ± 6.54	0.10	38.93 ± 5.97	37.97 ± 6.43	0.55
Hand grip strength (kg)	22.2 ± 7.3	22.8 ± 7.4	0.73	23.4 ± 7.1	24.0 ± 7.7	0.72
6 m gait speed (m/sec)	0.96 ± 0.20	1.04 ± 0.26	0.14	1.03 ± 0.21	1.15 ± 0.20	0.03
6 minute walk distance (m)	307.3 ± 40.6	326.2 ± 55.0	0.14	342.3 ± 58.0	344.1 ± 64.4	0.21

*values represented as mean ± SD or median (Interquartile range)

Conclusion: Addition of BCAA to standard exercise and dietary counselling does not improve muscle mass in patients with cirrhosis and sarcopenia. (CTRI/2019/05/019269).

OS-513

Algorithm combining fat-free muscle index and total spontaneous portosystemic shunt area identifies high-risk cirrhotic patients

Michael Praktiknjo¹, Jasmin Abu-Omar¹, Anton Faron², Nina Böbling¹, Alois Martin Sprinkart², Ulrike Attenberger², Christian Strassburg¹, Johannes Chang¹, Christian Jansen¹, Jonel Trebicka³, Luetkens Julian².
¹University Hospital Bonn, Center for Cirrhosis and Portal Hypertension Bonn (CCB), Department of Internal Medicine I, Bonn, Germany;
²University Hospital Bonn, Department of Radiology, Bonn, Germany;
³University Hospital Frankfurt, Department of Internal Medicine 1, Frankfurt, Germany
 Email: michael.praktiknjo@ukbonn.de

Background and aims: Sarcopenia and spontaneous portosystemic shunts (SPSS) are common complications of liver cirrhosis and both are associated with higher rates of hepatic encephalopathy (HE) development in these patients. This study aimed to evaluate the simultaneous impact of skeletal muscle mass and spontaneous portosystemic shunting, measured from routine diagnostic computed tomography (CT), on outcome in patients with liver cirrhosis. **Method:** Retrospective analysis of cirrhotic patients. Skeletal muscle mass (including fat-free muscle index (FFMI) as surrogate for sarcopenia) and total cross-sectional spontaneous portosystemic shunt area (TSA) were quantified from CT scans. Primary end point was development of HE, secondary end point was all-cause mortality within 1-year follow-up.

Results: Among 301 evaluations, 156 patients with liver cirrhosis were included. Patients with low (L-) FFMI and large (L-)TSA showed higher rates of HE development. In multivariable analysis, L-FFMI and L-TSA were independent predictors of HE development (L-FFMI HR = 2.69, CI 1.22–5.93; L-TSA HR = 2.50 CI = 1.24–4.72) and 1-year mortality (L-FFMI, HR = 7.68, CI 1.75–33.74; L-TSA, HR = 3.05, CI 1.32–7.04). Simultaneous presence of L-FFMI and L-TSA exponentially increased the risk of HE development (HR 12.79, CI 2.93–55.86) and 1-year mortality (HR 13.66, CI 1.75–106.50). An easy sequential algorithm including FFMI and TSA identified patients with good, intermediate and poor prognosis.

Conclusion: This study is the first to indicate a potential synergy between low skeletal muscle mass and large TSA to predict

exponentially increased risk of HE development and mortality in liver cirrhosis. Simultaneous screening for sarcopenia and TSA from routine diagnostic CT may help to improve identification of high-risk patients using an easy-to-apply algorithm. ClinicalTrials.gov Identifier: NCT03584204.

OS-925

Covered transjugular intrahepatic portosystemic shunt implantation improves renal function in patients with cirrhosis and ascites

Theresa Bucsics^{1,2}, Katharina Schoenhofer¹, Maria Schoder³, Jan Philipp Jonas⁴, David J.M. Bauer^{1,2}, Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, Florian Wolf³, Josef Karner⁴, Franz Karnel⁵, Thomas Grünberger⁴, Michael Trauner¹, Mattias Mandorfer^{1,2}, Thomas Reiberger^{1,2,6}.
¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Department of Internal Medicine III, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ³Medical University of Vienna, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria; ⁴Klinik Favoriten, Department of Surgery, Vienna, Austria; ⁵Klinik Favoriten, Department of Radiology, Wien, Austria; ⁶Medical University of Vienna, Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Vienna, Austria
 Email: thomas.reiberger@meduniwien.ac.at

Background and aims: Guidelines suggest implantation of a transjugular intrahepatic portosystemic shunt (TIPS) in patients with recurrent/refractory ascites—a population at risk for hepatorenal syndrome (HRS). However, data on the course and risk of HRS after TIPS are limited.

Methods: Patients with cirrhosis and ascites undergoing covered TIPS implantation for ascites were included. Serum creatinine (sCr) and blood urea nitrogen (BUN) were recorded prior to TIPS (baseline, BL), within 2–7 days after TIPS, and at 1, 3, 6 and 12 months (M1/M3/M6/M12) after TIPS.

Results: 165 patients were included: male: 75.2%, mean age: 58.4 ± 9.2 years, Child-C cirrhosis: 18.8%, median MELD: 13 (range: 6–30). BUN improved consistently and significantly from median BL 26.9 mg/dL (IQR: 18.0–39.2) to 16.0 (12.2–22.6) mg/dL at M12 (p < 0.0001). Overall, sCr changed from median 1.19 (IQR: 0.91–1.60) mg/dL at BL to 0.92 (0.79–1.20) mg/dL at M12 (p = 0.0048). sCr improved mostly in patients with HRS (i.e. sCr > 1.5 mg/dL; n = 35) from 1.82 (1.52–2.15) mg/dL at BL to 1.22 mg/dL (0.95–1.54) at M3 (p = 0.009) and in patients with BL-sCr of 1.2–1.5 mg/dL to 0.95 (0.85–1.06) mg/dL at M6 (p = 0.024), but remained stable in patients with <1.2 mg/dL at BL (p = 0.424). Overall, renal function improved (sCr decrease by >0.3 mg/dL) in 83.3% of patients with HRS and in 61.8% of patients with a BL-sCr of 1.2–1.5 mg/dL. Diuretic treatment was reduced in 44.8% (60.0% of HRS) at the next clinical visit after TIPS, while 25.5% (32.4% of HRS patients) still required multiple paracenteses. Post-TIPS acute kidney injury was uncommon, and in many cases, non-TIPS related triggers were identified (11/20). BL-sCr and BL-BUN did NOT impact on transplant-free survival (p > 0.05 for both), but TFS was significantly longer in patients who resolved HRS than in those who did not (median 1014 (154–3788) days vs 41 (30–660) days, respectively; p = 0.039).

Conclusion: TIPS implantation significantly improves renal function and ascites control in patients with recurrent/refractory ascites and HRS. Pre-TIPS renal function parameters did not influence transplant-free mortality after TIPS. Acute kidney injury after TIPS was mostly precipitated by non-TIPS related complications.

ORAL PRESENTATIONS

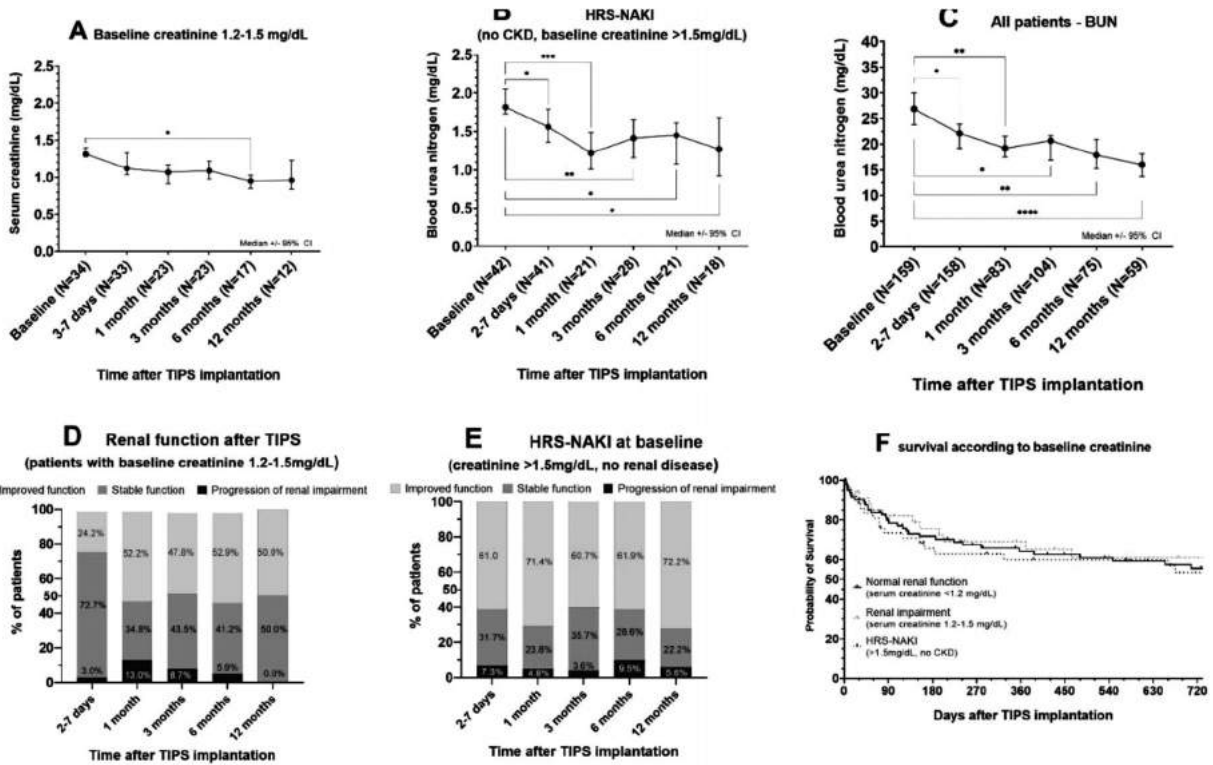


Figure: (abstract: OS-925)

OS-1266

Changes in gas-exchange abnormalities over time in patients with moderate to severe hepatopulmonary syndrome

Xun Zhao¹, Sreelakshmi Kotha², Dhruv Nayyar³, Eric Lui⁴, Xiayi Ma⁴, H el ene Castel⁵, Samir Gupta⁴. ¹Universit e de Montr eal, Medicine, Montreal, Canada; ²Guy's and St Thomas' NHS Foundation Trust, Department of Hepatology, London, United Kingdom; ³University of Toronto, Medicine, Toronto, Canada; ⁴St. Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, Canada; ⁵Centre Hospitalier de l'Universit e de Montr eal (CHUM), Department of Hepatology and Liver Transplantation, Montreal, Canada
Email: xun.zhao@mail.mcgill.ca

Background and aims: Hepatopulmonary syndrome (HPS) is a complication of cirrhosis defined by abnormal oxygenation and intrapulmonary vascular dilatation (IPVD). It carries a poor prognosis but can be treated with liver transplant. Small studies suggest that most patients with HPS experience a progressive decline in oxygenation, however little is known about the rate of this decline and corresponding changes in physiological measures.

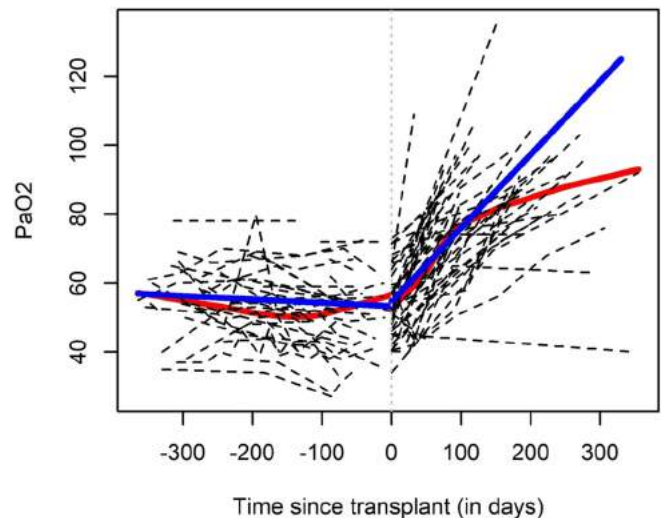
We sought to measure rates of change in oxygenation (PaO₂), diffusion capacity (DLCO), and 6-minute walk distance (6MWD) in patients with HPS, both before/without, and after liver transplant.

Methods: This was a prospective cohort study of Canadian HPS Program patients. We included patients with moderate to very severe HPS, defined as (1) liver dysfunction and/or portal hypertension; (2) IPVDs on contrast echocardiography; and (3) Alveolar-arterial oxygen gradient ≥15 mm and paO₂ <80 mmHg. We used linear mixed-effects models with both random intercept and random slope terms to determine rates of change in PaO₂, DLCO, and 6MWD over time, and a Bootstrap method to compare rates in the first year after transplant to the last year before transplant.

Results: We included 105 patients and 869 clinical visits. PaO₂ declined at a rate of 3.7 mm Hg/year (n = 102) in the first year after diagnosis and increased at a rate of 6.5 mmHg/month (n = 43) in the first year after transplant. The difference in rate of change in the first

year after transplant compared to the last year before transplant was 6.8 mm Hg/month (6.1, 7.5). The 6MWD declined at a rate of 26 m/year after diagnosis (n = 62) and increased at a rate of 190 m/year after transplant (n = 38), with a post- to pre-transplant rate change of 198 m/year (174, 220). The DLCO declined at a rate of 3.3% predicted/year after diagnosis (n = 86) and increased at a rate of 11.0% predicted/year after transplant (n = 34), with a post- to pre-transplant rate change of 11.6% predicted/year (7.6, 15.5).

PaO₂ - 1 year pre- and post-transplant



Conclusion: This is the largest and longest longitudinal follow-up study in HPS. We describe the natural history of physiological decline in this disease and the rate of expected improvement in key variables

after liver transplantation. These data enhance our understanding of the physiological effects of HPS and can aid in prognostication both before and after transplant.

OS-1864

Sex is a major effect modifier on the association between body composition and mortality in patients with cirrhosis assessed for liver transplantation

Amine Benmassaoud^{1,2}, Davide Roccarina², Francesco Arico², Marta Cilla², Rossella Donghia³, Gioacchino Leandro³, Laura Iogna Prat², Mohamed Zuhair², Matthew North², Orla Kearney², John Ryan⁴, Emmanuel Tsochatzis^{2,5}. ¹Division of Gastroenterology and Hepatology, McGill University Health Centre; ²Royal Free Sheila Sherlock Liver Center, Royal Free Hospital, London, United Kingdom; ³National Institute of Gastroenterology, S. de Bellis Research Hospital, Castellana Grotte, Italy; ⁴Translational Gastroenterology Unit, University of Oxford, Oxford, United Kingdom; ⁵UCL Institute for Liver and Digestive Health, University College of London, London, United Kingdom
Email: amine.benmassaoud@mcgill.ca

Background and aims: Body composition predicts increased mortality in patients with cirrhosis. The impact of sex on this association is largely unknown. We studied the impact of sarcopenia, malnutrition and adipose tissue mass on mortality in patients with cirrhosis assessed for liver transplantation (LT) stratified by sex.

Method: We included 628 consecutive patients assessed for elective LT. Nutritional status was assessed using the validated Royal Free Hospital-Global Assessment (RFH-GA). Radiology software was used to calculate muscle and adipose tissue mass data at third lumbar vertebrae, including psoas muscle index (PMI), total (TATI), visceral (VATI) and subcutaneous adipose tissue index (SATI). Sarcopenia PMI was defined as sex-based PMI below 25th percentile.

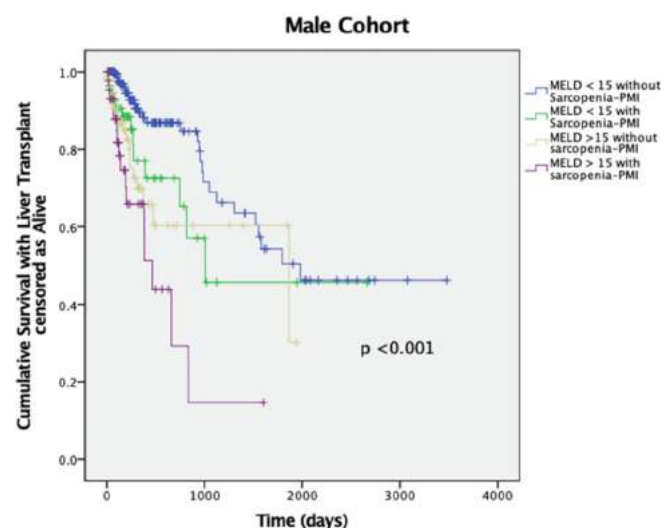


Figure 1: Cumulative survival of male patients with cirrhosis assessed for liver transplantation.

Results: 628 patients were included, of which 429 were males. Median age was 54.5 years, duration of follow-up was 192 days, alcohol misuse was the most common etiology of cirrhosis (30%) and median MELD was 14. Males had more commonly sarcopenia by SMI (male: SMI below 50 cm²/m²; female: SMI below 39 cm²/m² when compared to females (41.3% vs 26.6%, p < 0.001). In the entire cohort, multivariate analysis showed that when adjusted for age and MELD, both RFH-GA (aHR1.39, 95%CI 1.08–1.79) and Sarcopenia PMI

(aHR1.49, 95%CI 1.01–2.21) were independent predictors of mortality. In males, multivariate analysis showed that when adjusted for age and MELD, sarcopenia PMI (aHR 1.74, 95%CI 1.08–2.80) and RFH-GA (aHR1.40, 95%CI 1.03–1.90) remained independent predictors of mortality. Kaplan Meier survival analysis showed that sarcopenic male patients with MELD < 15 did worse than non-sarcopenic male patients with MELD < 15 (p = 0.024), and as poorly as non-sarcopenic male patients with MELD > 15 (p = 0.53) (Figure 1). Sarcopenic male patients with MELD ≥ 15 did worse than sarcopenic male patients with MELD < 15 (p = 0.021), and tended to do worse than non-sarcopenic male patients with MELD ≥ 15 (p = 0.084) (Figure 1). Adipose tissue had no impact on outcomes in males. In females, muscle or adipose tissue parameters did not predict mortality.

Conclusion: This study demonstrates that sex is an important effect modifier on the relationship between body composition and mortality in cirrhosis. Future research in this patient population should minimize sex-related bias, and present data for both groups separately.

Cirrhosis and its complications: Portal Hypertension

OS-755

Relationship between genotype and severe hepatic phenotype in compound heterozygous Cystic Fibrosis patients with one F508del CFTR mutation

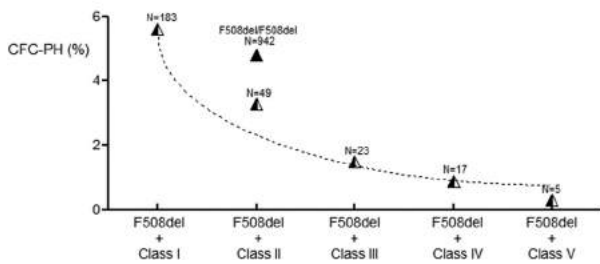
Suzan Duursma¹, Henkjan Verkade¹, Frank Bowedes¹. ¹University Medical Center Groningen, Pediatric Gastroenterology/Hepatology, Groningen, Netherlands
Email: s.duursma@umcg.nl

Background and aims: Cirrhosis with portal hypertension (CFCPH) is the most severe hepatic manifestation of CF. Due to the relatively low incidence of CFCPH, it has remained unclear if the cystic fibrosis transmembrane conductance regulator (CFTR) genotype is associated with the risk of developing CFCPH. F508del is the most prevalent disease-causing CFTR gene mutation in Europe. F508del can occur as a homozygous mutation or in a compound heterozygous combination with a different CFTR mutation. We aimed to study the contribution of the second mutation on the prevalence and mortality of CFCPH in CF patients with one F508del mutation, using the European Cystic Fibrosis Society Patient Registry (ECFSR).

Method: We assessed 37,642 CF patients with at least one F508del mutation with regards to severe liver disease and mortality in the period 2008–2016. We identified 1486 CFCPH patients of which 942 were homozygous for F508del and 544 were compound heterozygous. We stratified the second mutation of compound heterozygous patients based on the functional defect class of the mutation of the CFTR protein (class I–V; TIPS 2007; 8:334–41) and compared.

Results: The prevalence of CFCPH in compound heterozygous patients with one F508del mutation decreased along the class of the second mutation (Fig. 1; p < 0.001). In the study period, CFCPH was associated with increased mortality compared to non-CFCPH patients (11% vs. 5%, p < 0.001). The mortality rate of CFCPH between the different compound heterozygous F508del patients and homozygous F508del did not significantly differ (10% vs. 12%, resp., NS). However, the difference in mortality between CFCPH and non-CFCPH patients within each class stepwise increased from class I (11% vs. 5%, p < 0.001) to class IV (18% vs. 2%, p < 0.001).

Fig. 1. Prevalence of CFCPH in patients with one F508del mutation (▲) in relation to the functional defect classes of the second mutation



Conclusion: The risk of developing CFCPH in compound heterozygous F508del patients is negatively related to the functional defect class of the second mutation. Independent from the functional defect class, CFCPH is associated with increased mortality risk. The characterization of the present genotype-phenotype relationships allows for an early and improved prognostication towards a severe hepatic phenotype in CF patients and may contribute to a more patient-tailored follow-up and treatment.

Acknowledgments: We thank the people with CF, and their families, for consenting to their data being included in the ECFSPR.

OS-1544

Anticoagulation improves overall survival through portal vein recanalization in patients with cirrhosis and portal vein thrombosis: Individual patient data meta-analysis (IMPORTANT study)

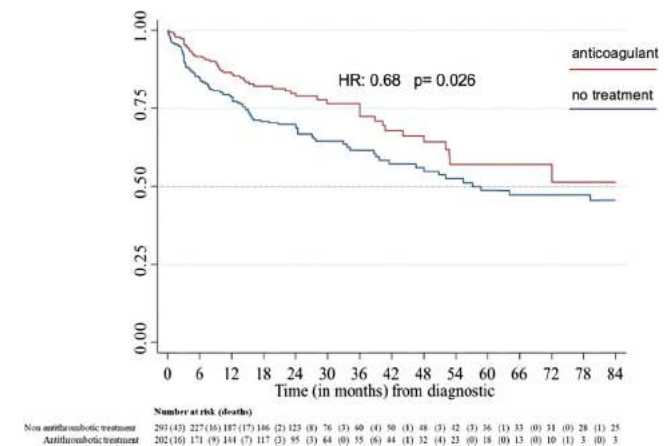
Antonio Guerrero¹, Laura Del Campo², Fabio Piscaglia³, Thomas Reiberger⁴, Guohong Han⁵, Francesco Violi⁶, Carlos Alberto Costa Noronha Ferreira⁷, Tellez Luis¹, Juan Carlos Garcia Pagan⁸, Tomás Artaza Varasa⁹, Dominique Valla¹⁰, Vincenzo La Mura^{11,12}, Angelo Luca¹³, Carol Stanciu¹⁴, Marco Senzolo¹⁵, Lucio Amitrano¹⁶, François Durand¹⁷, Horia Stefanescu¹⁸, Bernhard Scheiner⁴, Stefania Basili¹⁹, Marta Magaz⁸, Filipe Gaio Castro Nery^{20,21,22}, Sylvie Chevret²³, Massimo Primigiani^{11,12}, Irina Girleanu¹⁴, Javier Zamora², Agustín Albillos¹. ¹Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), CIBEREHD, Department of Gastroenterology and Hepatology, Madrid, Spain; ²Hospital Universitario Ramón y Cajal (IRYCIS), CIBER Epidemiology and Public Health (CIBERESP), Clinical Biostatistics Unit, Madrid, Spain; ³Azienda Ospedaliero Universitaria S.Orsola Malpighi, Department of Medical and surgical sciences, Bologna, Italy; ⁴Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Vienna, Austria; ⁵Xijing Hospital, Fourth Military Medical University, Department of Liver Disease and Digestive Interventional Radiology, Xi'an, China; ⁶Sapienza University, Department of Internal Medicine and Medical Specialties, Rome, Italy; ⁷Hospital de Santa Maria-Centro Hospitalar Universitário Lisboa Norte, Serviço De Gastroenterologia e Hepatologia, Lisbon, Portugal; ⁸Institut de Malalties Digestives i Metabòliques, Hospital Clínic-Institut de Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBEREHD, University of Barcelona, Hepatic Hemodynamic Lab, Liver Unit, Barcelona, Spain; ⁹Hospital Universitario de Toledo, Gastroenterology Department, Toledo, Spain; ¹⁰Hôpital Beaujon, APHP, Clichy, and CRI-UMR 1149, Université de Paris and Inserm, Service d'Hépatologie, Clichy, France; ¹¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Milano, Italy; ¹²Università degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Milano, Italy; ¹³Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IRCCS-ISMETT), Radiology Service, Department of Diagnostic and Therapeutic Services, Palermo, Italy; ¹⁴University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania; ¹⁵Padova University Hospital, Multivisceral Transplant Unit, Gastroenterology, Padova, Italy;

¹⁶Ospedale A Cardarelli, Gastroenterology Unit, Naples, Italy; ¹⁷Hospital Beaujon, Hepatology and Liver Intensive Care, Clichy, France; ¹⁸Regional Institute of Gastroenterology and Hepatology "O Fodor", Gastroenterology Department, Cluj-Napoca, Romania; ¹⁹Sapienza-University of Rome, Department of Internal Medicine and Medical Specialties, Rome, Italy; ²⁰Instituto de Ciências Biomédicas Abel Salazar-Universidade do Porto, Porto, Portugal; ²¹Instituto de Saúde Pública da Universidade do Porto, EpiUnit, Porto, Portugal; ²²Centro Hospitalar Universitário do Porto, Serviço de Cuidados Intensivos-Unidade de Cuidados Intermédios Médico Cirúrgica, Porto, Portugal; ²³APHP, Hôpital Saint-Louis, Paris University, HUSLW Service de Biostatistiques et Information Medicale, Paris, France
Email: agustin.albillos@uah.es

Background and aims: The use of anticoagulation in patients with cirrhosis and portal vein thrombosis (PVT) is controversial. Observational series and aggregate-data meta-analysis have proven the safety and efficacy of anticoagulation to yield portal vein recanalization, but it is unknown whether this benefit translates into a survival improvement. Existing aggregated data meta-analysis are limited by the difficulties to adjust by confounders and by their cross-sectional nature. We conducted an individual patient data (IPD) meta-analysis to assess the efficacy of anticoagulation on overall survival and portal vein recanalization in patients with cirrhosis and PVT.

Method: Two review authors performed the literature search up to 1st June 2020. We included studies that compared the efficacy of anticoagulation [low molecular-weight heparin (LWMH)/Warfarin] vs. no treatment in cirrhosis with PVT. We used a one-stage meta-analysis for overall survival and thrombus recanalization. Mortality was analyzed as a time-to-event variable with Hazard Ratios (HR) calculated by a multilevel mixed-effects model with random-intercepts for studies. Thrombus recanalization was analyzed by mixed-effects logistic regression. All analysis were adjusted for age, Child-Pugh, etiology, and PVT location and extension. Survival was described with Kaplan-Meier curves (PROSPERO registration #CRD42020140026).

Results: Five studies with a total of 500 patients assessed the effect of anticoagulants (n = 205) vs. no treatment (n = 295). During a median follow-up of 25.0 months (95%CI 15–52), 115 patients (39%) died in the no treatment group and 53 (25.8%) in the anticoagulant group. Anticoagulation increased overall survival (HR: 0.68, 95%CI 0.48–0.95, p = 0.026) (Figure). Recanalization, partial or complete, was more frequent in patients on anticoagulants (61.4 vs. 37.2%; OR 3.2, 95%CI 2.12–4.88, p = 0.000). Recanalization was independent of the anticoagulation type (LWMH: OR 2.7, 95%CI 1.53–4.77, p = 0.001 and VKA: OR 2.8, 95%CI 1.24–6.34, p = 0.013). The effect of anticoagulation on survival was primarily due to recanalization, as shown by the mediation analysis (recanalization HR: 0.55, 95%CI 0.37–0.81, p = 0.003).



Conclusion: Treatment with anticoagulants increases overall survival in patients with cirrhosis and PVT. The beneficial effect of anticoagulation is largely dependent on portal vein recanalization.

Fibrosis

OS-874

A fully agonistic anti-MET antibody protects hepatocytes against acute and chronic injury, promotes fibrosis regression and restores liver function in cirrhotic mice

Virginia Morello¹, Manuela Cazzanti¹, Luca Rossi^{1,2}, Damiana Sattanino^{1,2}, Torsten Dreier¹, Philippe Wiesel¹, Paolo Michieli^{1,2}. ¹AgomAb Therapeutics, Gent, Belgium; ²University of Torino Medical School, Molecular Biotechnology Center, Torino, Italy
Email: paolo.michieli@agomab.com

Background and aims: Restoring liver function in cirrhotic patients is a high unmet medical need. We have developed a panel of agonistic monoclonal antibodies directed against MET, the high affinity receptor for Hepatocyte Growth Factor (HGF), that mimic the biological activities of the natural ligand. Here we show that 71D6, a fully agonistic anti-MET antibody, displays hepato-protective, anti-inflammatory and anti-fibrotic activity in mouse models of both acute and chronic liver disease.

Method: The hepato-protective activity of 71D6 was tested in BALB-c mice using 3 different models of tetrachloride (CCl₄)-induced liver injury: (1) Acute liver failure: A single CCl₄ administration was followed by a single bolus of antibody. Mice were sacrificed 72 hours post-injection. (2) Chronic liver failure, preventive setting: CCl₄ and antibody were administered 2 times per week for 6 weeks. Mice were sacrificed on week 7. (3) Chronic liver failure, regression setting: Mice were exposed to CCl₄ for 6 weeks and antibody treatment started on week 7 with the same regimen as above. Mice were sacrificed after 2 or 4 weeks of antibody treatment. In all models, liver injury was determined by histology (hematoxylin and eosin) and

immunohistochemistry (picro Sirius red, alpha-smooth muscle cell actin, F4/80). Plasma levels of liver markers was also determined, including aspartate aminotransferase (AST), alanine transaminase (ALT) and bilirubin.

Results: In the acute model, 71D6 inhibited CCl₄-induced AST, ALT and bilirubin increase by 66%, 66% and 57%, respectively. In the chronic preventive model, 71D6 inhibited CCl₄-induced AST, ALT and bilirubin increase by 108%, 76% and 97%, respectively. Collagen deposition was reduced by 87%, myofibroblast activation by 94%, and macrophage infiltration by 77%. In the chronic regression model, 71D6 effectively promoted fibrosis regression already after 2 weeks of treatment. Collagen deposition was regressed by 87%, myofibroblast activation by 78%, and macrophage infiltration by 87%. AST, ALT and bilirubin normalized spontaneously in both arms 2 weeks after CCl₄ discontinuation. In all models, the therapeutic benefits of 71D6 were associated with active hepatocyte regeneration.

Conclusion: These results suggest that 71D6 possesses pro-regenerative, anti-fibrotic and anti-inflammatory activity in mouse models of hepatic injury, and provide proof-of-concept for further 71D6 development.

OS-888

CtsD deficient macrophages display altered proteolytic profile and dysregulated collagen recycling, resulting in increased liver fibrosis

Valeria Pistorio^{1,2}, Paloma Ruiz-Blázquez¹, Maria Fernández-Fernández¹, Susana Núñez³, Carmen García-Ruiz^{1,3,4,5}, Luigi M. Pavone², José Fernández-Checa^{1,3,4,5}, Anna Moles^{1,3,4}. ¹Institute of Biomedical Research of Barcelona, Spanish Research Council (IIBB-CSIC), Barcelona, Spain; ²University of Naples Federico II, Napoli, Italy; ³CiberEHD, Spain; ⁴IDIBAPS, Barcelona, Spain; ⁵USC Research Center for ALPD, Los Angeles, United States

Email: anna.moles.fernandez@gmail.com

Background and aims: Changes in proteolytic activity are essential to liver fibrosis development. Previous reports suggest that macrophages are important effectors for extracellular matrix (ECM)

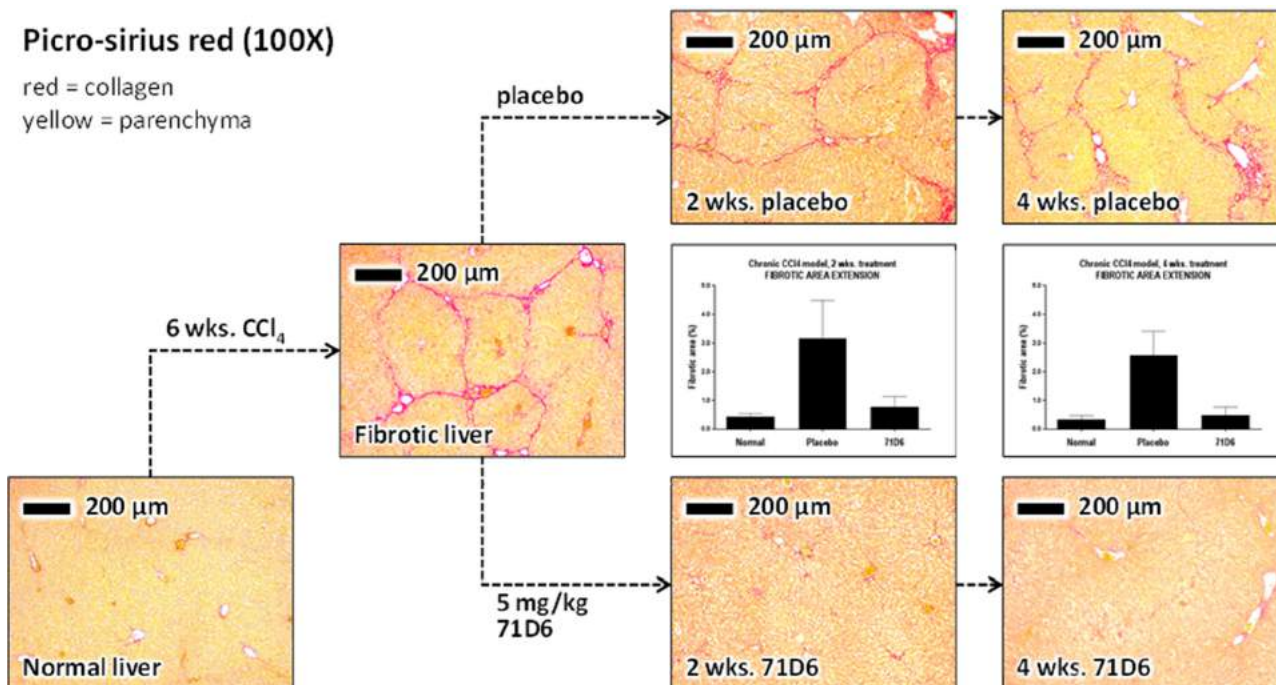


Figure: (abstract: OS-874)

ORAL PRESENTATIONS

remodelling via its phagocytosis and processing within acidic compartments. However, the role of macrophages in ECM remodelling during liver fibrosis is unknown. Thus, the aim of this study was to investigate the proteolytic and degradative pathways associated to macrophages during liver fibrosis.

Method: To study the degradative signals contributing to fibrosis in macrophages we focused our attention on the lysosomal protease cathepsin D (CtsD). We generated and validated a novel macrophage-CtsD knock-out mouse by breeding LysMCre (macrophages) with CtsD floxed mice. Peritoneal macrophage polarization from CtsD^{ΔMyel+/+} or CtsD^{ΔMyel-/-} mice was achieved with LPS for M1 or IL4/IL13 for M2 stimulation. Polarization markers and MMP profile were assessed by RT-PCR. Collagen degradation and endocytosis was studied using DQTM Collagen, type I and 10 kDa Dextran probes respectively, and WB for Endo180 and UPAR. Lysosomal colocalization was determined using LAMP2. Fibrosis was established chronically by CCl₄ (0.5μl/g) in CtsD^{ΔMyel+/+} or CtsD^{ΔMyel-/-} mice and determined by SR staining, α-SMA IHP and Col1 WB as well as RT-PCR.

Results: First, CtsD deletion in macrophages from CtsD^{ΔMyel-/-} mouse was confirmed by WB, CtsD activity in macrophages and dual IHP (F4/80-CtsD) in liver tissue. M1 and M2 polarization of CtsD^{ΔMyel+/+} and CtsD^{ΔMyel-/-} macrophages using LPS (10 and 50 ng/ml) or IL4/IL13 (20 and 50 ng/ml) resulted in similar and significant induction of iNOS (M1) and CD206 (M2) gene expression respectively. However, while M1 downstream effector CCI2 was similarly induced between CtsD^{ΔMyel+/+} and CtsD^{ΔMyel-/-} macrophages after LPS stimulation, IL10 was defectively induced in M2-primed CtsD^{ΔMyel-/-} macrophages. In addition, both, M1 and M2 CtsD^{ΔMyel-/-} macrophages displayed defective induction of MMP-2, -3 and -7 gene expression. CtsD^{ΔMyel-/-} macrophages showed a significant decrease in DQTM Collagen, type I degradation versus CtsD^{ΔMyel+/+} macrophages at 37C. As expected, no degradation was detected at 4C. Collagen degradative profile colocalized partially with LAMP2, indicating that collagen was degraded within the lysosome. Furthermore, Dextran endocytosis in both CtsD^{ΔMyel+/+} and CtsD^{ΔMyel-/-} macrophages remained unaffected. CtsD^{ΔMyel-/-} mice presented enhanced liver fibrosis as shown by an increase in Sirius red staining, alpha-SMA and Col1A1 gene and protein expression with no affectation of the Endo180/UPAR collagen internalization receptors (WB).

Conclusion: Lysosomal cathepsin D is essential for a correct collagenolytic activity displayed by macrophages during liver fibrosis.

OS-1478

HSC-targeted plasmonic hyperthermia treatment reduces liver fibrosis in mice

Jordi Ribera^{1,2}, Clara Vilches³, Vanesa Sanz³, Ignacio de Miguel³, Irene Portolés^{1,2}, Bernat Cordoba-Jover^{1,2}, Wladimiro Jiménez^{1,2,4,5}, Romain Quidant^{3,6}, Manuel Morales-Ruiz^{1,2,4,5}. ¹CIBERehd; ²IDIBAPS, Barcelona, Spain; ³ICFO-Institut de Ciències Fotòniques, The Barcelona Institute of Science and Technology, Castelldefels, Spain; ⁴University of Barcelona, Biomedicine Department, Barcelona, Spain; ⁵Hospital Clínic de Barcelona, Biochemistry and Molecular Genetics Department, Barcelona, Spain; ⁶Nanophotonic Systems Laboratory, Department of Mechanical and Process Engineering, Zurich, Switzerland
Email: mmoralesruiz@ub.edu

Background and aims: Hepatic stellate cells (HSC) are the main responsible cells for fibrosis formation, and PDGF and its receptor (PDGFRb) play a major role in HSC activation. Gold nanorods (GNR) have unique photothermal properties that can be exploited to induce localized near-infrared light-mediated thermal ablation. Therefore, this study aimed to induce thermal ablation of activated-HSC in fibrotic livers of mice using GNR conjugated with PDGFRb antibody (GNR-PDGFRb) and plasmonic photothermal therapy (PPTT).

Method: Fibrosis was induced in mice by intraperitoneal injection of CCl₄. Tissue gold distribution was analyzed by mass spectrometry, and the subcellular location of GNR in the liver was assessed using transmission electron microscopy (TEM). PPTT was performed after 10 days of GNR-PDGFRb treatment (n=15). Liver fibrosis was quantified by Sirius-Red staining, and hepatic macrophage infiltration by immunofluorescence using F4/80 antibody.

Results: Liver and spleen were still the major reservoirs of gold, accounting for the 12–15% and <3% of injected dose, respectively. TEM revealed that GNR-PDGFRb was present in the cytosol of HSC in CCl₄-treated mice. In contrast, GNR-PDGFRb abundance was significantly lower in healthy livers of the control group and accumulated in Kupffer cells. After 5 days from the PPTT, GNR-PDGFRb CCl₄-treated mice showed a significant decrease in hepatic collagen content compared to those who did not receive GNR (2.3 ± 0.2 vs. 4.1 ± 0.5% of fibrotic area per field; p < 0.01). This reduction correlated with a significant decrease in the hepatic macrophage infiltration (p < 0.01) and in the serum concentration of AST and ALT (83.7 ± 8.9 vs. 207.7 ± 61.44 U/L for AST, 22.4 ± 0.9 vs. 28.8 ± 2.6 U/L for ALT; p < 0.05). We also studied the in vivo elimination routes of the GNR and their potential toxic effect in healthy mice. After two months of GNR treatment, the percentage of nanoparticles in the liver decreased using the fecal excretion route preferentially. During this period,

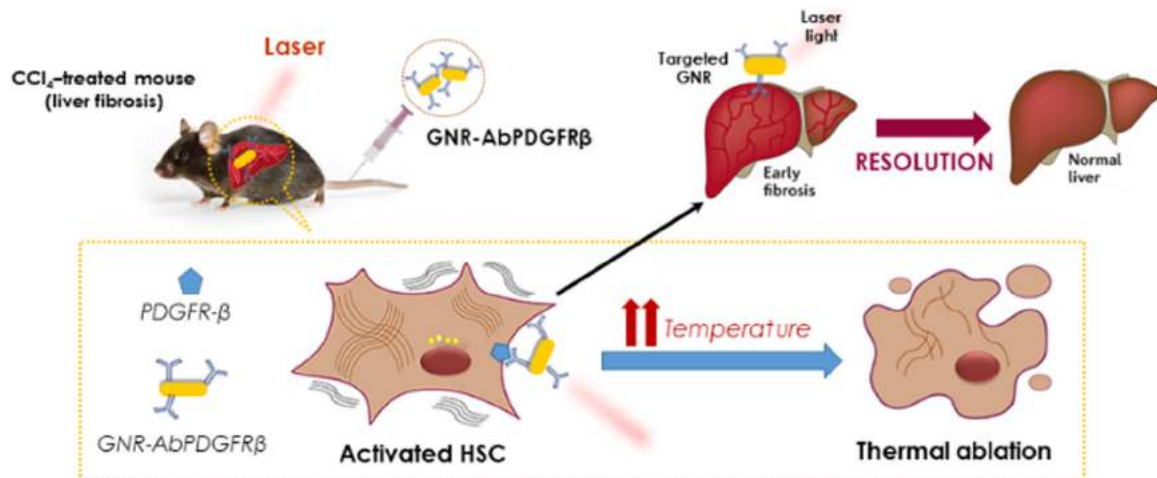


Figure: (abstract: OS-1478)

animals showed no signs of physical discomfort or presence of increased circulating biomarkers for inflammation or tissue injury.

Conclusion: GNR-PDGFRb-mediated photothermal therapy decreases fibrosis, hepatic inflammation, and hepatocyte injury in mice with liver fibrosis, with an optimal biosafety profile without long-term toxicity. This is the first evidence demonstrating the feasibility of applying HSC-targeted PPTT therapy in fibrotic livers.

OS-2754

Liver progenitor cells regulate ductular reaction and induce fibrosis upon severe liver injury via RAGE signaling

Wai Ling Macrina Lam^{1,2}, Dr. Amruta Damle Vartak¹, Simone Jörs³, Nachiket Vartak⁴, Gisela Gabernet⁵, Tanja Poth⁶, Doris Schneller¹, Melanie Sator-Schmitt¹, Georgia Günther⁴, Aurora De Ponti¹, Mathias Heikenwälder⁷, Sven Nahnsen⁵, Jan G. Hengstler⁴, Fabian Geisler³, Peter Angel¹. ¹German cancer research center, Signal transduction and growth control, Heidelberg, Germany; ²Ruprecht Karl University of Heidelberg, Heidelberg, Germany; ³Technical University of Munich, Clinic and Polyclinic for Internal Medicine II, Germany; ⁴Leibnitz Research Centre for Working Environment and Human Factors, System toxicology, Germany; ⁵Eberhard Karls University of Tübingen, Quantitative Biology Center, Germany; ⁶University Hospital Heidelberg, The center for model system and comparative pathology, Germany; ⁷German cancer research center, Chronic Inflammation and Cancer, Germany

Email: m.lam@dkfz-heidelberg.de

Background and aims: Liver fibrosis is characterized by hepatic stellate cell (HSC) activation and extracellular matrix (ECM) deposition upon persistent injury and inflammation, which can impair hepatic function and its ability to regenerate. Ductular reaction is a clinical manifestation observed in response to acute and chronic liver

injury, which involves the proliferation of biliary-like liver progenitor cells (LPCs). The receptor for advanced glycation end products (RAGE) signaling is often associated with chronic inflammation-associated tissue damage and plays an essential role in modulating the tissue microenvironment. Our previous data showed that global deletion of RAGE results in strong reduction in LPC expansion, onset of liver fibrosis and HCC formation (Pusterla et al. Hepatology. 2013). In this study, we seek to delineate the LPC-specific functional and mechanistic role of RAGE activity in response to liver injury.

Method: R26-tdTomato Hnf1b-CreER reporter mouse was utilized as a biliary lineage tracing model, and were crossed with Rage flox/flox mice to generate tamoxifen-inducible LPC-specific RAGE knockout mice. Mice were exposed to a choline-deficient ethionine-supplemented (CDE) diet for three weeks to induce chronic liver damage. RNA-seq of isolated LPCs from CDE-challenged mice, was combined with standard histology analyses and multi-modal 3D architectural staining to investigate the role of RAGE on LPCs and fibrosis formation. *In vitro* co-culture assays combined with live cell imaging were employed to delineate RAGE-dependent crosstalk between LPCs and stellate cells.

Results: Deletion of RAGE in LPCs strongly impairs ductular reaction during chronic liver damage, accompanied by reduction of activated HSCs and bridging fibrosis. RNA-seq data revealed the mechanistic role of LPCs in modulating ECM organization and HSC activation in a RAGE-dependent manner. Classical fibrotic mediators (*Tgfb1*, *Timp1*) and ECM genes (*Col4a1*, *Col16a1*, *Col18a1*) were differentially expressed in the enriched hepatic fibrosis pathways. Indirect co-culture assay showed that *Acta2* and *Col1a1* gene expression in HSC is affected *in trans* by soluble factors from LPCs expressed in a RAGE-dependent manner.

Conclusion: RAGE on LPCs is required for ductular reaction and crosstalk with HSCs in supporting fibrogenesis. Our study provides a

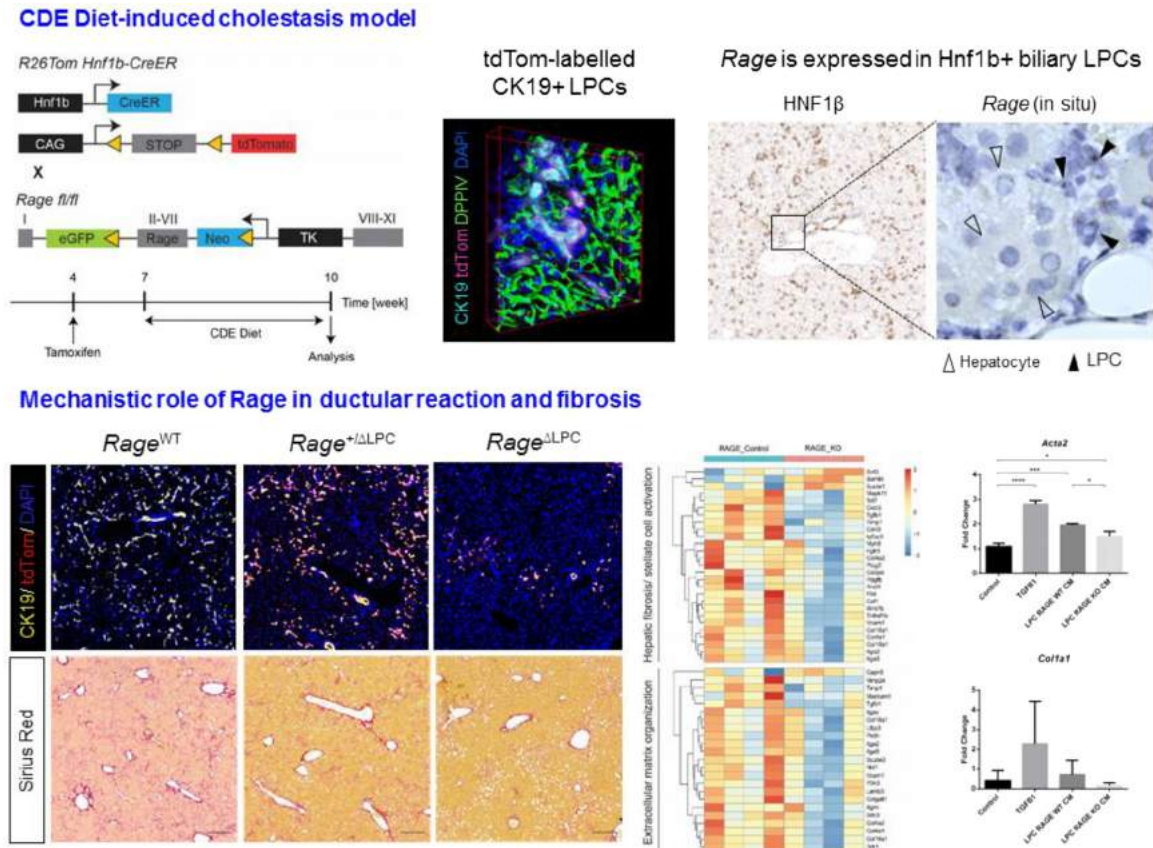


Figure: (abstract: OS-2754)

ORAL PRESENTATIONS

novel insight of RAGE on LPC in shifting the dynamic of ductular reaction to a pro-fibrotic microenvironment upon chronic injury.

OS-2854

Elderly with advanced liver fibrosis had lower response to Pfizer's SARS-CoV-2 vaccine response

David Hakimian¹, Asher Shafir¹, Yael Milgrom¹,
Mohammad Masarwa¹, Wadi Hazou¹, Johnny Amer¹, Rifaat Safadi¹.
¹Hadassah-Hebrew University Hospital, Liver Unit, Jerusalem, Israel
Email: johnnyamer@hotmail.com

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

Gut microbiota and liver disease

OS-119

Virulence factors in gut metagenomics worsen with disease progression and predict outcomes in cirrhosis

Jasmohan S. Bajaj¹, Amirhossein Shamsaddini², Andrew Fagan¹,
Edith Gavis¹, Masoumeh Sikaroodi², Patrick Gillevet². ¹Virginia Commonwealth University and Richmond VAMC, Richmond, United States; ²George Mason University
Email: jasmohan.bajaj@vcuhealth.org

Background and aims: Cirrhosis is linked with altered gut microbiota and higher pathobionts, which can carry several virulence factors (VFs). However, the role of metagenomic VFs in prognosis on patients with cirrhosis is unclear.

Aim: Define change in metagenomic VF abundance with cirrhosis progression and their role in prediction of death and hospitalizations.

Methods: Cirrhotic outpts [\pm hepatic encephalopathy (HE)] and controls underwent fecal collection. Cirrhotics were followed for 1 year for death/hospitalizations. Microbial metagenomics was performed for VF-containing bacteria using the virulence factor database. Comparisons between controls vs cirrhosis, cirrhosis with/without HE were performed. Multi-variable analysis using MAAsLin2 using VF-containing bacteria and clinical factors were performed for death and hospitalizations.

Results: 40 controls and 163 cirrhotics (63 no-HE and 100 HE, Table 1) were enrolled. 44 pts were hospitalized at 90 days and 14 died at 1 year. Cirrhotics had fold change for VFs belonging to *Klebsiella*, *Streptococcus* and *Escherichia* (Fig. A). This burden was even higher in those with HE vs no-HE (Fig. B) with additionally higher *Enterococcus*, *Pseudomonas*, and *Legionella* VF-producing spp. Death: On MaAsLin2, *C.difficile* strains and MELD were linked with death (Table 2).

Hospitalizations: HE, lactulose and MELD and multiple *E.coli* strains that produce VFs were associated with higher hospitalizations (Table 2).

Conclusion: Virulence factors that increase the pathogenicity of *Escherichia*, *Streptococcus*, *C.difficile* and *Klebsiella* are higher in gut microbiome of cirrhosis compared to controls and worsens with cirrhosis progression. VF-containing taxa from *E.coli* and *C.difficile* are linked with hospitalizations and death in independent of MELD, lactulose and HE. Treatments aimed at VF reduction in gut microbiota are needed in cirrhosis.

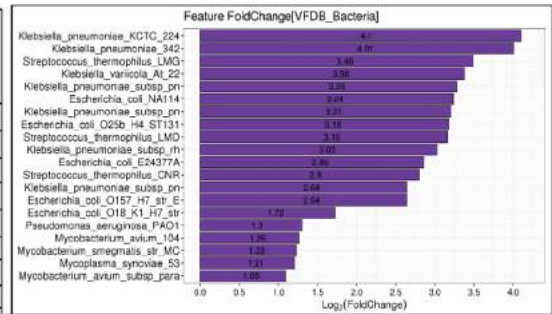
OS-1167

Faecal microbiota transplantation improves intestinal barrier function and modulates mucosal IL-17 immunity in patients with advanced cirrhosis

Lindsey A. Edwards¹, Charlotte Woodhouse¹, Benjamin H. Mullish²,
Thomas Tranah¹, Jesus Miguens Blanco², Victoria Kronsten¹,
Ane Zamalloa¹, Vishal C. Patel^{1,3,4}, Julian Marchesi²,
Simon Goldenberg⁵, Debbie L. Shawcross¹. ¹King's College London,
Institute of Liver Studies, Department of Inflammation Biology, School of Immunology and Microbial Sciences, FoLSM., London, United Kingdom; ²Imperial College London, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, London, United Kingdom; ³King's College Hospital NHS Foundation Trust, Institute of Liver Studies, United Kingdom; ⁴Institute of Hepatology (Foundation for Liver Research), London, United Kingdom; ⁵Guy's and St Thomas' NHS Foundation Trust, Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, London, United Kingdom
Email: lindsey.edwards@kcl.ac.uk

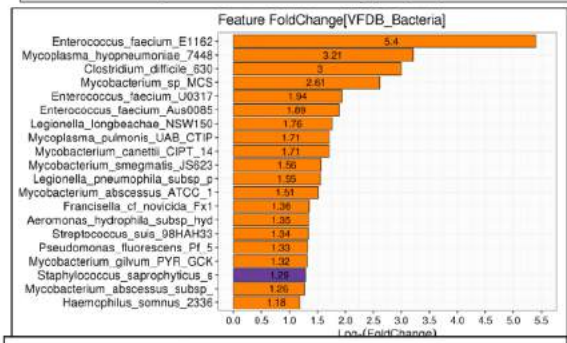
Background and aims: Patients with advanced cirrhosis present with enteric dysbiosis and translocation of bacteria and their products across the gut epithelial barrier. This translocation induces

Table 1: Subject details	Controls (n=40)	All Cirrhosis (n=163)		P value all	P value Cirr-L vs Cirr-LR	
		Comp (N=63)	Decomp (n=100)			
			Cirr-L (n=43)			Cirr-LR (n=57)
Age	58.6±10.3	60.1±7.4	57.9±9.8	61.1±7.6	0.09	0.08
Men	24 (60%)	46 (73%)	34 (79%)	46 (80%)	0.09	0.90
PPI	-	25 (40%)	25 (59%)	41 (71%)	0.002	0.15
Diabetes	-	27 (42%)	12 (23%)	22 (28%)	0.28	0.26
MELD	-	9.3±3.8	13.3±4.7	12.8±4.8	<0.0001	0.60
Alc etiol	-	10 (16%)	22 (51%)	24 (42%)	<0.0001	0.37
α diversity	2.78±0.27	2.56±0.0.35	2.35±0.63	1.70±0.74	<0.0001	<0.0001
Hosp 90 d	-	3 (5%)	24 (56%)	17 (30%)	<0.0001	0.008
Death 1 yr	-	0 (0%)	7 (16%)	7 (12%)	<0.0001	0.56



A: Fold Change ↑VFs in Cirrhosis (purple) vs Controls

Table 2: Multi-variable analysis of VFs with outcomes			
Death at 1 year	Direction	p-value	q-value
<i>Clostridium difficile_630</i>	↑	5.64E-07	0.0003
MELD score	↑	3.18E-05	0.007
<i>Clostridium difficile_CCUG</i>	↑	4.04E-05	0.007
Hospitalizations 90 days	Direction	p-value	q-value
MELD score	↑	3.16E-09	1.76E-06
<i>Escherichia coli_ED1a</i>	↑	1.25E-05	0.001871
<i>Escherichia coli_str_K49</i>	↑	1.34E-05	0.001871
<i>Escherichia coli_ECOR_9</i>	↑	7.19E-05	0.008029
Hepatic Encephalopathy	↑	0.000231	0.018429
On lactulose	↑	0.000225	0.018429



B: Fold Change ↑VFs in HE (orange) vs No-HE (purple)

Figure: (abstract: OS-119)

innate immune dysfunction, which predisposes to infection, and multi-organ failure. We hypothesised that modifying the gut microbiota with faecal microbiota transplant (FMT) may reduce the progression of chronic liver failure. We previously reported FMT reduces the burden of enteric pathogens, known to cause epithelial gut barrier disruption in cirrhosis. Here we investigate further the effects of FMT on intestinal barrier restoration and local luminal mucosal immunity in patients with cirrhosis.

Method: The prospective, randomised, single-blinded, feasibility trial evaluating FMT (n=15) against placebo (n=6) [PROFIT NCT02862249] was completed in late 2019. Patients were administered FMT/placebo into the jejunum within 7 days of baseline. To assess the efficacy in modulating the patient's own microbiome, disease and inflammatory status: stool was collected at days 0, 7, 30 and 90 post-FMT administration. Stool was assessed for cytokine production and barrier integrity markers (electrochemiluminescence/ELISA) and metabolite profile (¹H-NMR).

Results: FMT treatment removed enteric pathogens including *E. faecalis*. Coinciding with a temporary reduction in luminal proinflammatory cytokine IL-17A at day7 (mean -68%, p=0.0037) in contrast with placebo, which increased 30 days post treatment (mean +36%). High levels of IL-17A are known to induce intestinal inflammation via intestinal epithelial cell tight junction permeability; suggestive that FMT initially modulates inflammation towards gut-barrier repair. However, subsequent increases in IL-17A correlated with improved MELD scores 30 days post FMT (p = 0.034) corresponding to levels of endotoxin (p=0.033); indicating restoration to mucosal antimicrobial responses. Similar modulations in cytokines IL-17E/F and IL-21 were observed. Improvement in gut-barrier function and increased butyrate production (p=0.014) were observed post FMT.

Conclusion: These data support FMT as playing an important role in inflammatory restoration at the mucosal barrier and enteric pathogen reduction, promoted by butyrate-induced β-oxidation. Collectively, it may be possible to alter the gut-microbiota to promote barrier repair and to restore immune tolerance in cirrhosis and other systemic inflammatory diseases where the gut-barrier is compromised.

OS-1979

Paneth cells regulate lymphangiogenesis in normal physiology and experimental portal hypertension

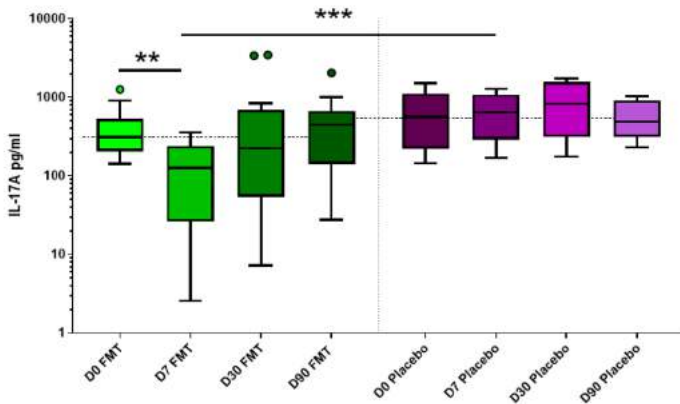
Mohsin Hassan Bhat¹, Oriol Juanola², Andrea de Gottardi^{2,3}, Sheida Moghadamrad². ¹Charité-Universitätsmedizin Berlin, Department of Hepatology and Gastroenterology, Germany; ²Università della Svizzera Italiana, Translational Research Laboratory, Switzerland; ³Ente Ospedaliero Cantonale, Department of Gastroenterology and Hepatology, Switzerland
Email: sheida.moghadamrad@usi.ch

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 (PCs), as part of the intestinal innate immune system, regulate the development of lymphatic vessels and affect portal pressure in response to microbial-derived products.

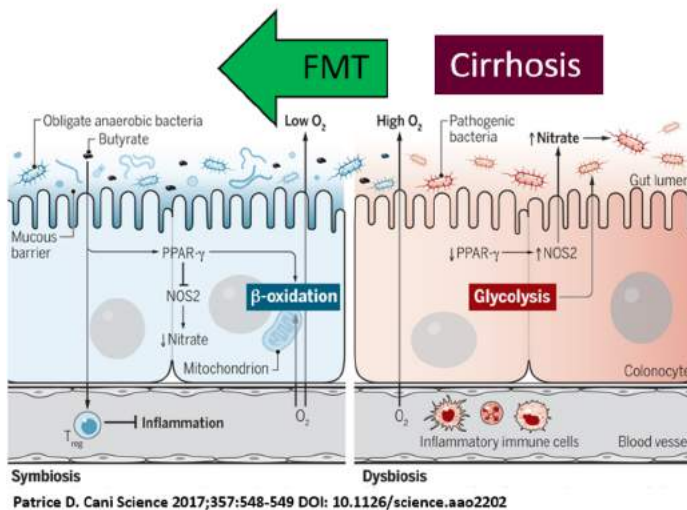
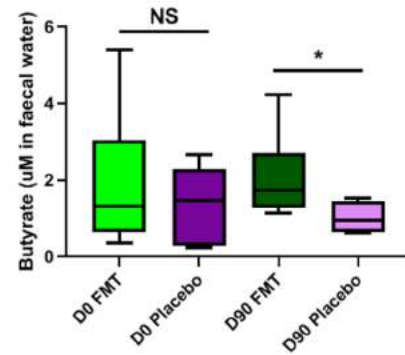
Method: Math1^{lox/lox} VilCreER^{T2} or control mice were injected three doses of tamoxifen to induce depletion of PCs in the intestine. Portal hypertension was induced by partial portal vein ligation (PPVL). After 14 days, portal pressure was measured. Intestinal and mesenteric lymphatic vessels were identified by immunohistochemistry and quantified using Metamorph. The intestinal expression of specific genes involved in lymphangiogenesis was quantified using qPCR. Furthermore, intestinal crypts were isolated to culture organoids from mice with or without PCs. The organoids were then challenged with different microbial-derived products. Then human lymphatic microvascular endothelial cells (LECs) were cultured in the presence of conditioned media (CM). The lymphangiogenic activity of LECs was assessed using the tube formation and wound healing assays. Additionally, we quantified differentially expressed proteins in the CM collected from all different conditions with mass spectrometry-based proteomics and data were analyzed using MaxQuant.

Results: Depletion of PCs resulted in a significantly reduced portal pressure associated with lower density of lymphatic vessels in the intestine and mesentery as compared to PPVL mice with PCs. Several lymphangiogenic genes were significantly downregulated in the

Restoration to mucosal immunity



Enhanced Butyrate (β -oxidation)



Reduction in pathogenic species

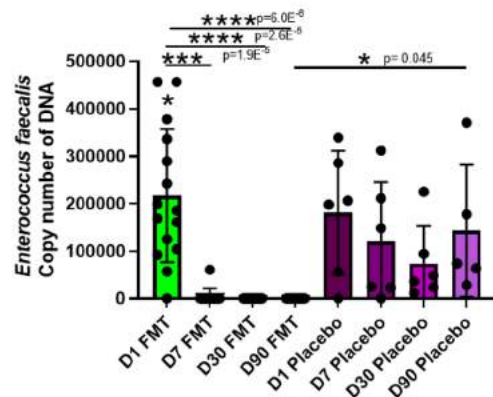


Figure: (abstract: OS-1167)

group of mice without PCs when compared to the control mice with PCs. Tube formation and wound healing responses were significantly decreased in LECs treated with CM from organoids without PC. In the absence of PCs, proteomic analyses revealed a significant down-regulation 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 PCs, intestinal and mesenteric lymphangiogenesis was significantly decreased, and this was associated with an attenuation in portal hypertension. These findings suggest that PCs secrete lymphangiogenic signaling molecules in response to microbial-derived products, thereby regulating intestinal-mesenteric lymphatic vessels proliferation and portal pressure.

OS-2044
In-depth shotgun metagenomic analysis of the gut microbiome identifies striking variations in microbial community structure based on severity and stage of cirrhosis

Sunjae Lee¹, Bethlehem Arefaine², Elizabeth Witherden¹, Neelu Begum¹, Azadeh Harzandi¹, Ane Zamalloa³, Eleanor Corcoran⁴, John Smith⁴, Roger Williams^{2,5,6}, Shilpa Chokshi^{2,5}, Gordon Proctor¹, Adil Mardinoglu^{1,7}, Mathias Uhlen⁷, Saeed Shoaie^{1,7}, Vishal C. Patel^{3,5,8}. ¹King's College London-Guy's Campus, Centre for Host Microbial Interactions, London, United Kingdom; ²Institute of Hepatology, Foundation For Liver Research, London, United Kingdom;

³King's College Hospital, Institute of Liver Studies, United Kingdom; ⁴King's College Hospital NHS Foundation Trust, Department of Critical Care, London, United Kingdom; ⁵King's College London, School of Immunology and Microbial Sciences, London, United Kingdom; ⁶In Memoriam; ⁷Science for Life Laboratory (SciLifeLab), KTH-Royal Institute of Technology, Sweden; ⁸Institute of Hepatology (Foundation for Liver Research), London, United Kingdom
 Email: vishal.patel@nhs.net

Background and aims: Alterations in the gut microbiome in decompensated cirrhosis (DC) and acute on chronic liver failure (ACLF) are recognised as being critical in influencing clinical outcomes (Trebicka *et al.*, Nat Rev Gastroenterol Hepatol, 2020). Knowledge of the oral microbiome is evolving and recognised as important in predisposing to hepatic decompensation (Acharya *et al.*, JCI Insight, 2017). Our aims were to interrogate the gut and oral microbiome by shotgun metagenomic sequencing of faecal and saliva samples, respectively, in well phenotyped cohorts of cirrhosis patients, with healthy and positive disease controls.

Method: 18 healthy controls (HC), 20 compensated cirrhotics (CC), 50 DC, 18 ACLF and 15 with non-liver sepsis (NLS) i.e. severe infection but without underlying CLD were prospectively recruited at a tertiary liver centre in London. DNA extractions were undertaken from faecal samples utilising optimised SOPs, and sequenced on an Illumina NovaSeq 6000 platform to a minimum depth of 20 million reads.

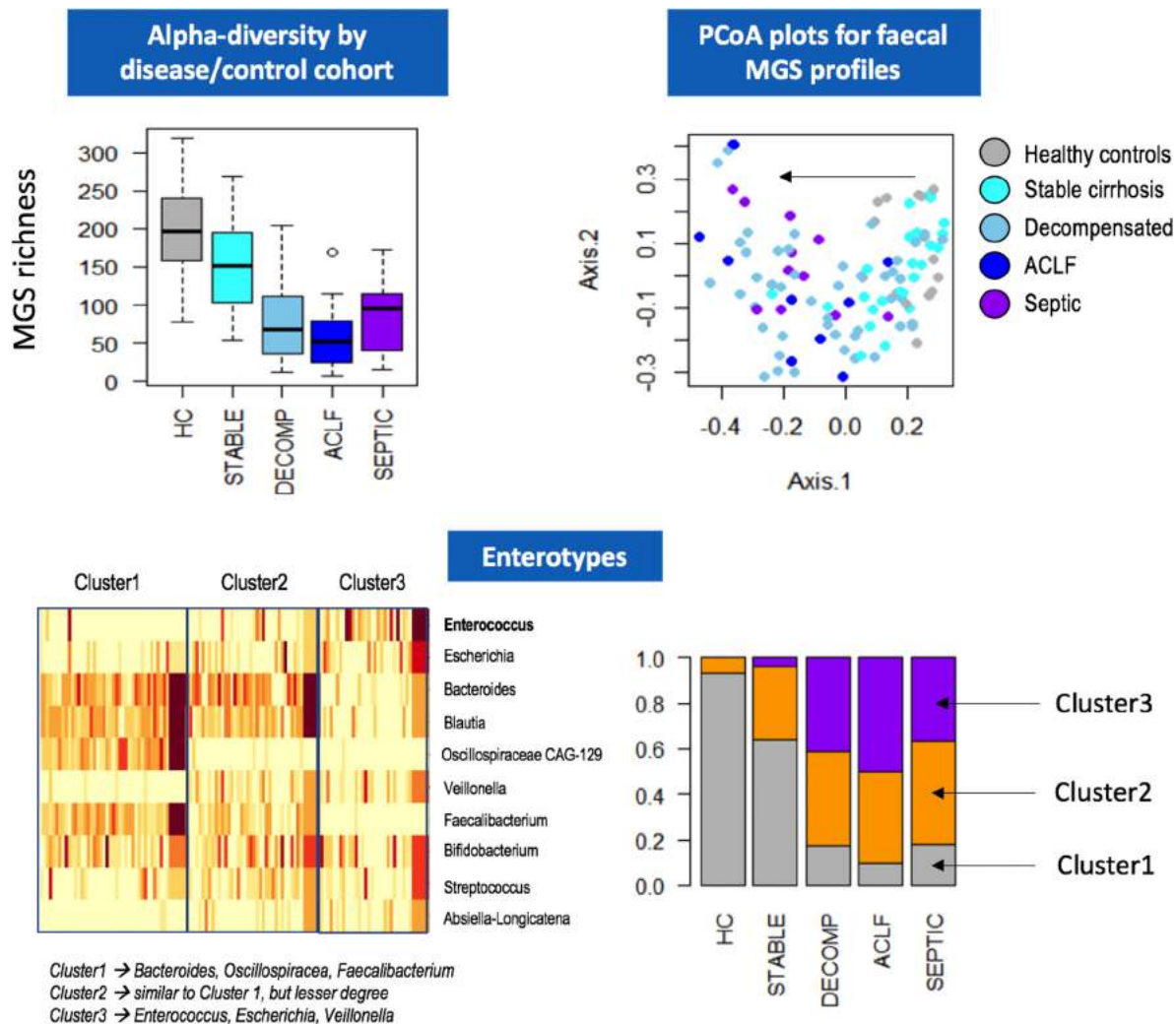


Figure: (abstract: OS-2044)

Filtered and trimmed reads were aligned to a human gut microbiome integrated gene catalogue. Abundance of metagenomic species pan-genomes (MSP) were quantified based on median abundances of 25 markers representing the centroid of gene clusters of MSPs. Enterotypes were calculated by scaling genus profile abundance and clustering by Dirichlet multinomial mixture models.

Results: Faecal DNA was of sufficient quality and quantity in 15 HC, 15 CC, 46 DC, 14 ACLF and 12 NLS. There was a striking decrement in alpha-diversity the sicker the patient cohort vs healthy controls and NLS. Principal coordinate analysis (PCoA) showed discrimination between the groups, with clear shifts from control to sicker patients along the first axis. NLS as a positive disease control group had higher alpha-diversity than DC and ACLF patients, even though all 3 groups received broad-spectrum antimicrobials. Three specific enterotypes were identified based on clustering of genera; Cluster 1 consisted of autochthonous genera, cluster 2 similar to 1 and cluster 3 pathogenic, with significant variation in clusters by disease cohort and control groups.

Conclusion: Gut microbiome profiles differ significantly according to severity and stage of cirrhosis, with specific enterotype clusters reflecting pathogenic potential. DC and ACLF have significantly worse microbial diversity than NLS, despite similar antimicrobial exposure, supporting an additive patho-biological effect of cirrhosis. Comparisons between gut and oral profiles to evaluate the degree of microbiome 'tropism' are underway, with integrations of these data and immuno-metabolic profiles in relation to clinically relevant outcomes.

Immune-mediated and cholestatic: Experimental and pathophysiology

OS-1847

A3907, a novel orally bioavailable inhibitor of the apical sodium-dependent bile acid transporter, improves liver injury in a mouse model of cholestatic liver disease

Peter Akerblad¹, Erik Lindström¹, Jan Mattsson¹, Pal Lundin¹, Sara Straniero², Bo Angelin², Magnus Soholt Larsen³, Thomas Secher³, Michael Feigh³, Jesus Maria Banales⁴. ¹Albireo Pharma, Inc.;

²Karolinska Institutet at Karolinska University Hospital Huddinge;

³Gubra Aps; ⁴Donostia University Hospital

Email: peter.akerblad@albiroepharma.com

Background and aims: Cholestasis is characterised by the intrahepatic accumulation of toxic bile acids (BAs). The apical sodium-dependent bile salt transporter (ASBT) plays an important role in regulation of BA homeostasis by promoting their reuptake in the ileum, bile ducts, and kidney. Thus, ASBT inhibition may block the enterohepatic circulation of BAs and enhance their excretion, leading to beneficial effects on cholestasis and cholangitis. A3907 is a selective ASBT inhibitor with high oral bioavailability and systemic exposure that has potential to modulate BA transport in intestine,

ORAL PRESENTATIONS

kidney, and bile ducts. The objective of this study is to investigate the effect of A3907 on characteristic cholestasis and sclerosing cholangitis developed by *Mdr2* knockout mouse over time.

Method: Male *Mdr2*^{-/-} mice (7–8 weeks old) were treated with A3907 (1–30 mg/kg) or vehicle by oral gavage once daily for 4 weeks. Plasma and liver biochemistry and histology were assessed after sacrifice.

Results: After 4 weeks of A3907 treatment, the concentration of total BAs in plasma was reduced compared with vehicle. Liver transaminases (all A3907 doses $P \leq 0.01$) and alkaline phosphatase (A3907 3–30 mg/kg $P \leq 0.01$) were also reduced. A3907 was associated with dose-dependent reductions in liver and spleen weight vs vehicle (all $P \leq 0.05$), as well as reduced biliary tree volume compared with vehicle (all $P \leq 0.05$). Moreover, A3907 reduced liver inflammation (galectin-3, monocyte chemoattractant protein-1), fibrosis (hydroxyproline and alpha-smooth muscle actin), and expression of the biliary marker cytokeratin 7 compared with vehicle. Pharmacokinetic studies in wild-type mice demonstrated that A3907 can selectively target ASBT in the intestine as well as the bile ducts and kidney.

Conclusion: A3907 improves cholestatic liver injury and the characteristic sclerosing cholangitis of *Mdr2*^{-/-} mice and is a promising new therapeutic tool for cholestatic liver diseases.

OS-1946

CCR2⁺ monocytes induce hepatic accumulation and activation of tissue destructive CD8⁺ T cells in a murine model of checkpoint inhibitor-induced hepatitis

Cathrin L.C. Gudd^{1,2}, Charalambos G. Antoniadis¹, Samra Turajlic³, Martin Gore³, James Larkin³, Mark R. Thursz¹, Wafa Khamri¹, Robert D. Goldin¹, Kevin J. Woollard², Evangelos Triantafyllou^{1,2}, Lucia A. Possamai^{1,2}. ¹Imperial College London, Department of

Metabolism, Digestion and Reproduction, London, United Kingdom; ²Imperial College London, Division of Immunology and Inflammation, London, United Kingdom; ³The Royal Marsden Hospital National Health Service Foundation Trust, Renal and Skin Units, London, United Kingdom
Email: cathrin.gudd@gmail.com

Background and aims: Checkpoint inhibitor-induced hepatitis (CPI-Hep) is a growing clinical challenge with the expanding use of checkpoint inhibitors (CPIs) in cancer immunotherapy. We aimed to better understand the mechanisms underlying CPI-Hep by developing and interrogating a murine model of this condition.

Method: Wild-type (WT) C57BL/6J male mice, 8–12 weeks-old, were dosed with TLR9 agonist (TLR9-L), in combination with anti-CTLA-4/PD-1 (CPI) or PBS for up to 7 days (n=4–8/treatment group). Flow cytometry, histology, immunofluorescence and RT-PCR were used to characterise liver myeloid/lymphoid cell subsets and inflammation. Hepatocyte damage was assessed by measuring plasma cytokeratin-18 (CK-18) and alanine transaminase (ALT) levels. *In vivo* investigations of CPI-Hep were carried out in *Rag2*^{-/-} and *Ccr2*^{trfp/trfp} transgenic mice.

Results: In WT mice, hepatic immune profiling revealed an increased infiltration and formation of inflammatory aggregates of granzyme B⁺perforin⁺CD8⁺ T cells and CCR2⁺ monocytes 7 days post TLR9-L/CPI treatment, compared to TLR9-L/PBS treated or baseline mice. This was accompanied by apoptotic hepatocytes surrounding immune aggregates and elevated CK-18 levels at day 4 and 7 post TLR9-L/CPI treatment and ALT levels at day 4 (Fig.). Increased liver tissue mRNA levels of monocyte/T cell recruitment and inflammation related markers (*Ccl2*, *Cxcl9*, *Cxcl10*, *iNos*, *Tnfa*) were detected. In contrast, TLR9-L/CPI treated *Rag2*^{-/-} mice, lacking mature lymphocytes, were protected from hepatocyte damage and showed significantly reduced CK-18 and ALT levels compared to TLR9-L/CPI treated WT (Fig.).

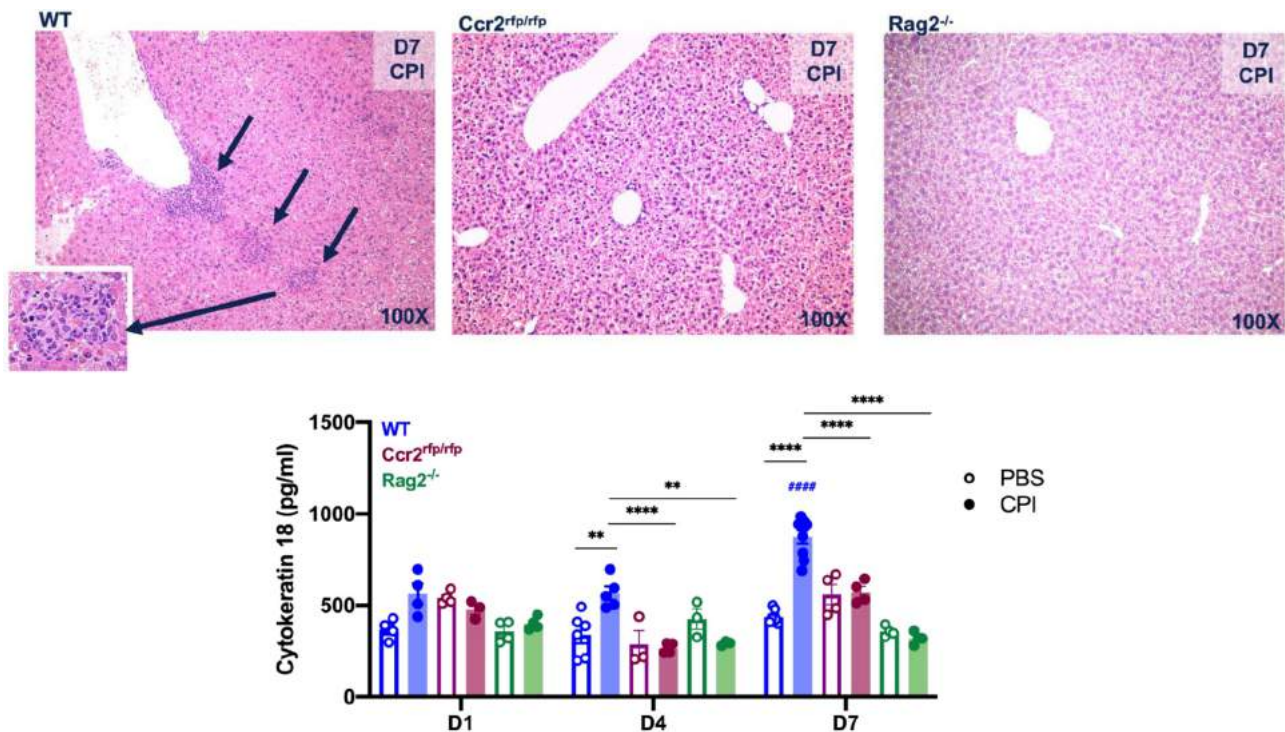


Figure: Representative H&E stained liver sections of CPI treated WT, *Ccr2*^{trfp/trfp} and *Rag2*^{-/-} mice at day 7 of experimental CPI-Hep. Magnification: 100X. Measurement of CK-18 in plasma of WT, *Ccr2*^{trfp/trfp} and *Rag2*^{-/-} mice throughout the time course. Each symbol represents an individual mouse. * represents comparison between groups; # shows comparisons with D1 in the same group. ** $p < 0.01$, **** $p < 0.0001$. D: day.

Figure: (abstract: OS-1946)

CCR2^{flp/rfp} mice, lacking CCR2⁺ monocytes, when treated with TLR9-L/CPI showed a reduced number of granzyme B⁺perforin⁺CD8⁺ T cells compared to TLR9-L/CPI treated WT mice, normal liver histology and significantly reduced CK-18 and ALT levels (Fig.).

Conclusion: Our newly established TLR9-L CPI murine model, which closely resembles human pathology with CD8/macrophage inflammatory aggregates and hepatocyte injury, provides a new platform for *in vivo* mechanistic studies on CPI-Hep. We show that liver infiltration of CCR2⁺ monocytes and their interaction with CD8⁺ T cells are necessary to the pathogenesis of CPI-Hep and hepatocyte injury. This work highlights a potential pathway for therapeutic intervention. Further studies are underway to elucidate the mechanisms of CD8⁺ T cell and monocyte cross talk in driving CPI-induced liver pathology.

OS-2274

Farnesoid X Receptor agonists block macrophage derived IL1beta production, disrupt Th1/Th17 polarization of effector lymphocytes, and ameliorates disease progression in murine sclerosing cholangitis

Astha Malik¹, Annika Yang vom Hofe¹, Brandee Wagner², Alexander Miethke¹. ¹Cincinnati Children's Hospital Medical Center, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati, United States; ²Metacrine, Inc., San Diego, United States
Email: alexander.miethke@cchmc.org

Background and aims: Hepatic monocytes from PSC patients were shown to produce high levels of IL1b upon stimulation with microbes and microbial products (LPS) and to drive pathogenic Th17 responses. We aimed to elucidate the role of FXR in controlling the monocyte-IL1b- Th1/Th17 axis in sclerosing cholangitis (SC).

Method: Wild type (WT), IL1r knockout mice (IL1r^{-/-}) and transgenic mice lacking FXR expression in myeloid cells (FXRdMC) were fed a diet containing 0.1% of the xenobiotic diethoxycarbonyl-1, 4-dihydrocollidine (DDC) to induce cholangiopathy and liver inflammation. M044 was administered at 10 mg/kg by oral gavage following initiation of DDC diet. Liver mononuclear cells (LMNC) were isolated after 7 days of DDC challenge and subjected to treatment with LPS for 16 hours prior to intracellular flow cytometry.

Results: LMNCs isolated from DDC-fed WT mice were treated with 40 ng/ml of IL1Ra antagonist which reduced Ifng expression on macrophages (MP), CD4, and CD8 lymphocytes following LPS stimulation. LMNCs from DDC-fed IL1r^{-/-} mice exhibited decreased IL17a expression in MP, CD4 and CD8 T cells compared with WT mice upon LPS stimulation. End of DDC treatment serum total bilirubin (TB), ALT, and ALP levels were significantly lower in these knockout mice compared with controls. LMNCs from DDC-fed FXRdMC displayed higher levels of Ifng and IL17a expression in MP, CD4, and CD8 cells, higher serum ALT and TB levels, and worse bile duct proliferation by CK19 immunohistochemistry compared with WT controls. To elucidate the role of MP in mediating treatment effects of the FXR agonist M044 in SC, DDC-fed WT and FXRdMC mice were subjected to treatment with M044 or vehicle. Reduction of Th1 and

Th17 responses upon M044 treatment was far less in FXRdMC compared with WT mice (Figure 1). While M044 treatment significantly reduced serum ALT, ALP, and TB levels by 42, 42, and 83%, respectively, in WT mice, no significant reduction of liver biochemistries was observed in identically treated FXRdMC mice. Reduction of %CK19+ area on liver sections was observed in WT mice following administration of an FXR agonist.

Conclusion: Monocyte derived IL1b licenses Ifng and IL17a production by hepatic effector lymphocytes in xenobiotic induced SC. This pathway is critically controlled by FXR in hepatic myeloid cells which mediate the therapeutic effects of FXR agonist therapy in this model of PSC.

Immune-mediated and cholestatic disease: Clinical aspects

OS-706

Blue-collar work increases the risk of developing IgG4-RD of the biliary tract and pancreas

Lowiek Hubers¹, Alex Schuurman¹, Jorie Buijs², Nahid Mostafavi¹, Marco Bruno², Roel Vermeulen³, Anke Huss³, Henk Van Buuren², Ulrich Beuers¹. ¹Amsterdam UMC, Locatie AMC, Department of Gastroenterology and Hepatology, Tytgat Institute for Liver and Intestinal Research, Amsterdam, Netherlands; ²Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ³Utrecht University, Institute for Risk Assessment Sciences, Utrecht, Netherlands
Email: l.m.hubers@amc.uva.nl

Background and aims: IgG4-related disease (IgG4-RD) of the biliary tract and pancreas typically affects men above 50 years of age. The reason for male predominance (~85%) is unclear. Here, we tested our working hypothesis (Hepatology 2014;60:1453) that 'blue-collar work' and occupational exposure to industrial contaminants are risk factors for IgG4-RD of the biliary tract and pancreas.

Method: An age- and sex-matched case-control study was performed in the two largest academic medical centers in the Netherlands. Disease controls were matched 3:1 to cases and consisted of six equally-sized groups with digestive diseases unrelated to occupational risk. The occupational history was surveyed using questionnaires. Jobs were classified by the International Standard Classification of Occupations (ISCO88). The number of years patients were exposed to a selection of industrial compounds were determined using Job Exposure Matrices ALOHA and DOM. Conditional logistic regression was used to assess effects of blue-collar work and exposure to occupational contaminants on developing IgG4-RD of biliary tract and pancreas.

Results: A total of 303 disease controls were matched to 101 patients with IgG4-RD of biliary tract and pancreas. Overall, patients with

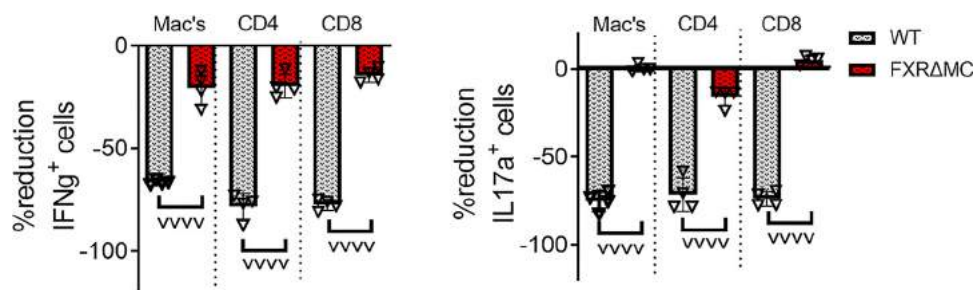
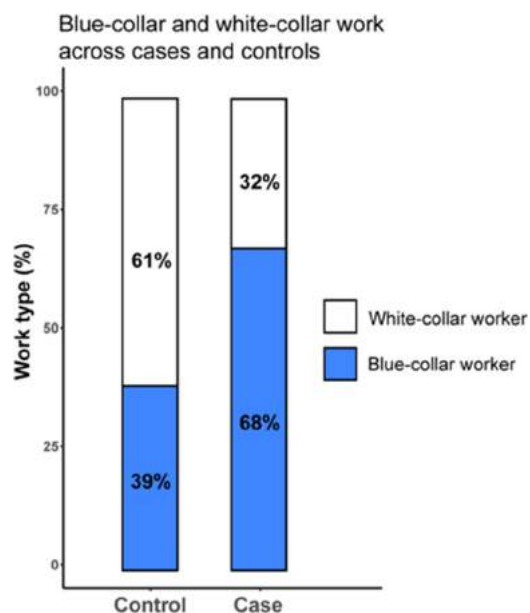


Figure 1: (abstract: OS-2274): **Genetic deletion of FXR from myeloid cells renders immune cells unresponsive to *in vivo* FXR agonist treatment.** WT and FXRdMC were challenged with 0.1% DDC and treated with M044 or vehicle for 7 days. LMNCs were exposed to LPS prior to PMA/Ionomycin restimulation and intracellular flow cytometry. Percent reduction was plotted by comparing each of the treated controls to the average of the vehicle treated mice in each group (n = 4 mice/group).

ORAL PRESENTATIONS

IgG4-RD had a lower education level ($p = 0.001$). 68% of patients with IgG4-RD ($n = 69$) had a history of blue-collar work compared to 39% of controls ($n = 117$, Figure). The odds of developing IgG4-RD among blue-collar workers was 3.66 times higher than among white-collar workers (95% CI 2.18–6.13; $p < 0.001$). Also, long-term exposure (>1 year) to ALOHA (e.g. mineral dust; vapors-dust-gases-fumes) and DOM compounds (e.g. asbestos) increased the odds of developing IgG4-RD (OR = 2.14 (CI 1.26–3.16, $p < 0.001$) and OR = 2.95 (CI 1.78–4.90, $p < 0.001$), respectively).



Conclusion: Blue-collar work increases the risk of developing IgG4-RD of biliary tract and pancreas, presumably through long-term exposure to specific industrial compounds and may explain the striking male predominance among patients.

OS-894

Liver stiffness assessed by Fibroscan is a surrogate end point of outcomes of UDCA-treated patients with PBC: an international follow-up study

Christophe Corpechot^{1,2}, Fabrice Carrat³, Bettina Hansen⁴, Gideon Hirschfeld⁴, Aldo J. Montano-Loza⁵, Ellina Lytvyak⁵, Christoph Schramm^{2,6}, Füssel Katja^{2,6}, Albert Pares^{2,7}, Olivas Ignasi^{2,7}, John Eaton⁸, Karim Osman⁸, Gaouar Farid¹, George Dalekos^{2,9}, Nikolaos Gatselis^{2,9}, Nora Cazzagon^{2,10}, Alessandra Zago^{2,10}, Francesco Paolo Russo^{2,10}, Frederik Nevens^{2,11}, Douglas Thorburn¹², Francesca Saffioti¹², Laszlo Barkai¹², Davide Roccarina¹², Adele Delamarre¹³, Medina-Morales Esli¹⁴, Alan Bonder¹⁴, Vilas Patwardhan¹⁴, Marco Carbone^{2,15}, Pietro Invernizzi^{2,15}, Laura Cristofori^{2,15}, Adriaan Van der Meer¹⁶, Rozanne de Veer¹⁶, Ehud Zigmund¹⁷, Yehezkel Eyal¹⁷, Tony Bruns¹⁸, Karsten Große¹⁸, Georges-Philippe Pageaux¹⁹, Jérôme Dumortier²⁰, Olivier Chazouillères^{1,2}, Victor de Lédinghen¹³. ¹Saint-Antoine Hospital, APHP Sorbonne University, Reference center for inflammatory biliary diseases and autoimmune hepatitis, Paris, France; ²European Reference Network Rare-Liver; ³Pierre-Louis Institute of Epidemiology and Public Health, Saint-Antoine Hospital, APHP Sorbonne University, Public Health Department, Paris, France; ⁴Toronto Centre for Liver Disease, University of Toronto, Division of Gastroenterology and Hepatology, Toronto, Canada; ⁵University of Alberta, Division of

Gastroenterology and Hepatology, Edmondton, Canada; ⁶University Medical Center Hamburg-Eppendorf, Department of Medicine I and Martin Zeitz Center for Rare Diseases, Hamburg, Germany; ⁷Hospital Clínic, University of Barcelona, Liver Unit, Barcelona, Spain; ⁸Mayo Clinic, Division of Gastroenterology and Hepatology, Rochester, United States; ⁹General University Hospital of Larissa, National Expertise Center of Greece in Autoimmune Liver Diseases, Larissa, Greece; ¹⁰University Hospital of Padova, Department of Surgery, Oncology and Gastroenterology, Padova, Greece; ¹¹University Hospitals KU, Division of Hepatology and Liver Transplantation, Leuven, Belgium; ¹²Royal Free Hospital, University College London, Institute for Liver and Digestive Health, London, United Kingdom; ¹³Haut-Lévêque Hospital, University of Bordeaux, Division of Gastroenterology and Hepatology, Bordeaux, France; ¹⁴Beth Israel Deaconess Medical Center, Liver Center, Department of Medicine, Division of Gastroenterology, Boston, United States; ¹⁵Ospedale San Gerardo, University of Milan Bicocca, Division of Gastroenterology and Centre for Autoimmune Liver Disease, Monza, Italy; ¹⁶Erasmus Medical Center, University of Rotterdam, Division of Gastroenterology and Hepatology, Rotterdam, Netherlands; ¹⁷Tel Aviv Sourasky Medical Center, Gastroenterology and Hepatology Institute, Tel Aviv, Israel; ¹⁸RWTH Aachen University Hospital, Department of Internal Medicine III, Aachen, Germany; ¹⁹University Hospital of Montpellier, Division of Gastroenterology and Hepatology, Montpellier, France; ²⁰Edouard Herriot Hospital, Civil Hospices of Lyon, Division of Gastroenterology and Hepatology, Lyon, France
Email: christophe.corpechot@aphp.fr

Background and aims: Liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (Fibroscan) has been shown to predict clinical outcomes in primary biliary cholangitis (PBC), but this finding is based on still very limited single-center data. This study aimed to assess the prognostic value of LSM in a large, multicenter, international cohort of patients with PBC.

Method: Patients with PBC with at least one LSM (Fibroscan) available and a subsequent follow-up ≥ 1 year were included in a multicenter retrospective cohort study. Patients with overlap syndrome were excluded. LSMs with an interquartile/median ratio ≤ 0.3 were considered reliable. All repeated LSMs and associated serum liver function tests were collected. The primary outcome was all-cause mortality or liver transplantation (LT). The secondary outcome was all-cause mortality or liver complication (LC). These outcomes were assessed using a time-dependent, multivariable-adjusted Cox proportional hazards model. The C-statistic was used to assess the predictive performance of LSM. The relationship between the hazard ratio (HR) and LSM was assessed using a cubic spline function.

Results: A total of 5323 reliable LSMs (median value at baseline: 6.8 kPa, IQR 5.3–10.0) was collected in 2736 UDCA-treated patients with PBC (mean age 58; 91% female; 11% cirrhosis; median time between UDCA start and baseline LSM 3.0 years) from 18 centers and 10 countries. The median follow-up from baseline LSM was 4.1 years (range 1.0–16.4). A total of 145 deaths (62 liver-related), 51 LT, and 85 LC with no subsequent death or LT until the last visit was registered. In a time-dependent multivariable analysis adjusted for age, sex, total bilirubin, albumin, ALP, AST, and platelet count, LSM was significantly associated with all-cause mortality or LT (adjusted HR: 1.046 per kPa increase, 95% CI 1.033–1.060) and all-cause mortality or LC (adjusted HR: 1.041, 95% CI 1.028–1.054). Its performance at baseline to predict these outcomes was 0.85 and 0.83, respectively. Within the 5–30 kPa range, the log-HR for all-cause death or LT increased as a linear function of LSM (Figure 1). LSM predicted outcomes independently of the biochemical response to UDCA (regardless of the definition used) and the Globe, UK-PBC, and MELD scores.

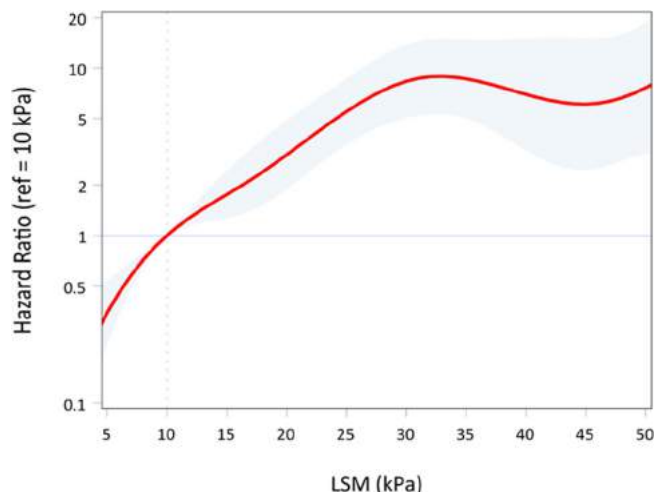


Figure 1: The hazard of all-cause death or LT as a function of LSM at baseline

Conclusion: LSM assessed by Fibroscan can predict clinical outcomes of patients with PBC and might be used as a surrogate end point in clinical trials.

OS-1088

Hepatobiliary malignancy surveillance strategies in primary sclerosing cholangitis associate with reduced mortality

Annika M. Bergquist¹, Tobias Weismüller², Cynthia Levy^{3,4}, Christian Rupp⁵, Deepak Joshi⁶, Jeremy Nayagam⁶, Aldo J. Montano-Loza⁷, Ellina Lytvyak⁷, Ewa Wunsch^{8,9}, Piotr Milkiewicz^{8,9}, Roman Zenouzi¹⁰, Christoph Schramm¹⁰, Nora Cazzagon¹¹, Annarosa Floreani¹², Ingalill Andersson Friis Liby¹³, Miriam Wiestler¹⁴, Heiner Wedemeyer¹⁴, Taotao Zhou², Christian Strassburg², Eirini Rigopoulou¹⁵, George Dalekos¹⁵, Manasa Narasimman⁴, Xavier Verhelst¹⁶, Helena Degroote¹⁷, Mette Vesterhus^{18,19}, Andreas E. Kremer²⁰, Bennet Bündgens²¹, Fredrik Rorsman²², Emma Nilsson^{23,24}, Kristin Jorgensen²⁵, Erik von Seth¹, Martin Cornillet²⁶, Nils Nyhlin²⁷, Harry Martin²⁸, Stergios Kechagias²⁹, Kristine Wiencke¹⁸, Märten Werner³⁰, Benedetta Terziroli Beretta-Piccoli³¹, Marco Marzioni³², Helena Isoniemi³³, Johanna Arola³⁴, Agnes Wefer³⁵, Jonas Söderling³⁶, Martti Färkkilä³⁷, Henrike Lenzen^{14,21}. ¹Karolinska University Hospital, Department of Medicine Huddinge, Unit of Gastroenterology and Rheumatology; ²University Hospital Bonn, University of Bonn, Department of Internal Medicine I, Bonn, Germany; ³University of Miami, Division of Digestive Health and Liver Diseases, Miami, United States; ⁴University of Miami, Schiff Center for Liver Diseases, Miami, United States; ⁵Heidelberg University Hospital, Department of Gastroenterology, Infectious Diseases, Intoxication, Germany; ⁶King's College Hospital London, Institute of Liver Studies, London, United Kingdom; ⁷University of Alberta, Division of Gastroenterology, Department of Medicine, Edmonton, Canada; ⁸Pomeranian Medical University in Szczecin, Translational Medicine Group, Szczecin, Poland; ⁹Medical University of Warsaw, Liver and Internal Medicine Unit, Warsaw, Poland; ¹⁰University Medical Center Hamburg-Eppendorf, Department of Medicine and Martin Zeitz Center for Rare Diseases, Hamburg, Germany; ¹¹University of Padova, Department of Surgery, Oncology and Gastroenterology, Padova, Italy; ¹²Senior University of Padova, Studiosa Senior University of Padova, Padova, Italy; ¹³Sahlgrenska University Hospital, Department of Gastroenterology and Hepatology, Gothenburg, Sweden; ¹⁴Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ¹⁵General University Hospital of Larissa, Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, Larissa, Greece; ¹⁶Ghent University Hospital, Department of Gastroenterology and Hepatology, Ghent, Belgium; ¹⁷Ghent University,

Department of Gastroenterology and Hepatology, Ghent Liver Research Center, Ghent, Belgium; ¹⁸Oslo University Hospital Rikshospitalet, Norwegian PSC Research Centre, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo, Norway; ¹⁹University of Bergen, Department of Clinical Science, Department of Medicine, Haralds plass Deaconess Hospital, Bergen, Norway; ²⁰Friedrich-Alexander-University Erlangen-Nürnberg and University Hospital Erlangen, Department of Medicine 1, Erlangen, Germany; ²¹University Hospital Essen, University of Duisburg-Essen, Department of Gastroenterology and Hepatology, Essen, Germany; ²²University Hospital Uppsala, Department of Gastroenterology and Hepatology, Uppsala, Sweden; ²³Lund University, Department of Clinical Sciences, Lund, Sweden; ²⁴Skåne University Hospital, Gastroenterology Clinic, Sweden; ²⁵Akershus University Hospital, Department of Gastroenterology, Lørenskog; ²⁶Karolinska University Hospital, Department of Medicine Huddinge, Center for Infectious Medicine, Karolinska Institutet, Stockholm, Sweden; ²⁷Örebro University, Department of Gastroenterology, Faculty of Medicine and Health, Örebro; ²⁸University College Hospitals NHS Foundation Trust, Department of Gastroenterology, London, United Kingdom; ²⁹Linköping University, Department of Health, Medicine and Caring Sciences, Unit of Internal Medicine, Linköping, Sweden; ³⁰Umeå University, Department of Public Health and Clinical Medicine, Umeå, Sweden; ³¹Epatocentro Ticino, Lugano, Switzerland; ³²Università Politecnica delle Marche, Ospedali Riuniti-University Hospital, Clinic of Gastroenterology and Hepatology, Ancona, Italy; ³³Helsinki University Hospital, Transplantation and Liver Surgery, Abdominal Center, Helsinki, Finland; ³⁴University of Helsinki and Helsinki University Hospital, Department of Pathology and Huslab, Helsinki, Finland; ³⁵Karolinska University Hospital, 32 Division of Surgery, Stockholm, Sweden; ³⁶Karolinska Institutet, Clinical Epidemiology Division, Department of Medicine, Solna, Stockholm, Sweden; ³⁷University of Helsinki and Helsinki University Hospital, Clinic of Gastroenterology, Abdominal Center, Helsinki, Finland

Email: lenzen.henrike@mh-hannover.de

Background and aims: Patients with primary sclerosing cholangitis (PSC) are at increased risk for hepatobiliary malignancies, especially cholangiocarcinoma. Although many recommend surveillance for malignancy in PSC, different strategies are used by various centers and countries. We aimed to evaluate different surveillance strategies and their effectiveness in PSC with the hypothesis that surveillance imaging improves survival.

Method: We queried centers about surveillance practices and retrospectively collected imaging surveillance data for hepatobiliary cancer in 2, 975 patients with PSC from 28 centers within the International PSC Study Group (IPSCSG). Surveillance strategies were grouped in (i) non-surveillance (no imaging in asymptomatic patients), (ii) magnetic resonance imaging (MRI) and/or ultrasound (US) surveillance (regular imaging regardless of symptoms/labs) and (iii) surveillance including endoscopic retrograde cholangiopancreatography (ERCP)-based (imaging and/or ERCP regardless of symptoms/labs). The primary end point was all-cause mortality. Cox-proportional hazard regression models were used to estimate hazard ratios (HRs).

Results: 65.6% (1953/2975) of patients were male, mean age (SD) at diagnosis of PSC was 35.6 (14.2) years, with concomitant IBD in 71.5% (2127/2973). Hepatobiliary malignancy was found in 175 (5.9%) patients at 7.9 years of follow-up (Figure). Surveillance strategies differed significantly between centers. Of patients undergoing surveillance, 83% were subjected to MRI/MRCP, 49% to US and 28% to ERCP. Deaths were more frequent in the non-surveillance group 23.4% (82/350) than in the surveillance group 8.3% (218/2625). Mortality rate (95% CI) per 1000 person-years was 23.1 (18.1–28.1) in the non-surveillance group (n=350), 12.5 (10.6–14.5) in imaging surveillance with MRI and/or US (n=1897) and 8.4 (6.3–10.5) in surveillance that included ERCP (n=728). The risk of dying was reduced in patients undergoing any type of surveillance (HR 0.53;

ORAL PRESENTATIONS

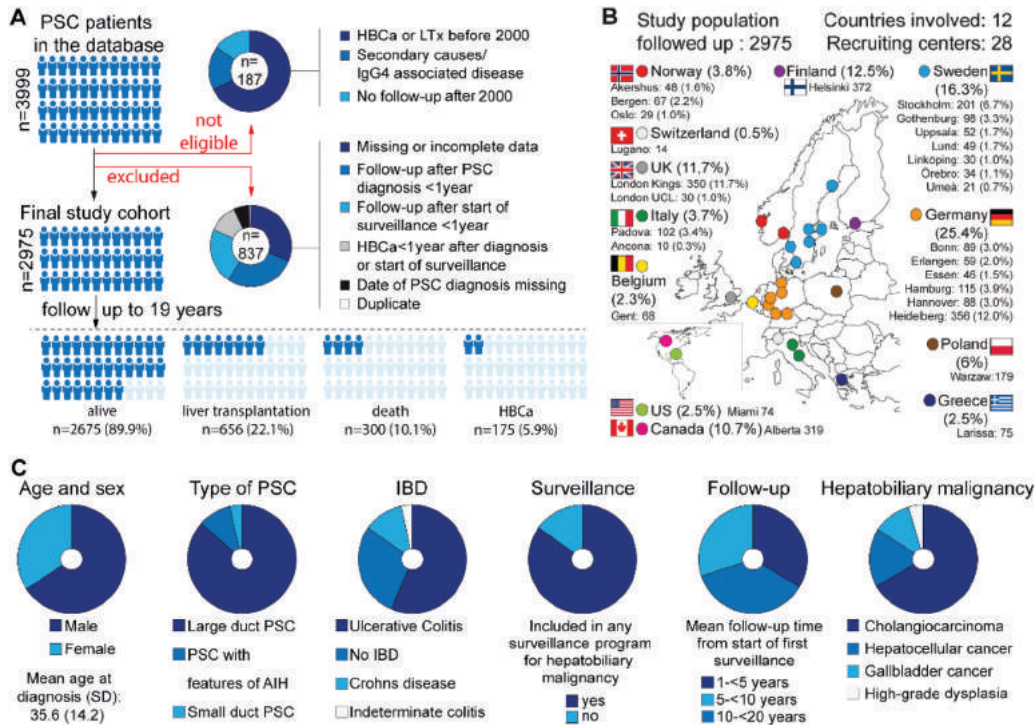


Figure: (abstract: OS-1088)

95% CI: 0.41–0.68) and the reduced risk remained after adjusting for sex, age and start year of follow-up (HR 0.61; 95% CI: 0.47–0.80). **Conclusion:** A broad variety of surveillance strategies across centers are used. Regular surveillance for hepatobiliary malignancy in patients with PSC is associated with improved survival.

OS-1586

Patterns of biochemical response during long-term UDCA treatment in patients with primary biliary cholangitis: association with liver transplant-free survival

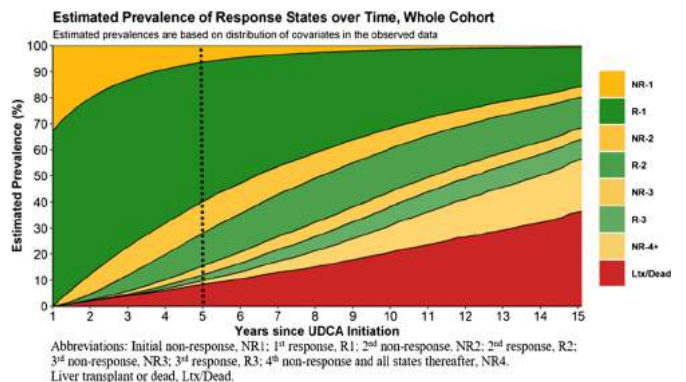
Surain Roberts^{1,2}, Lawrence Worobetz³, Catherine Vincent⁴, Jennifer Flemming⁵, Cynthia Tsien⁶, Karim Qumosani⁷, Mark G. Swain⁸, Dusanka Grbic⁹, Hin Hin Ko¹⁰, Kevork Peltekian¹¹, Nazia Selzner¹², Lusine Abrahamyan¹, Monika Saini¹³, Kattleya Tirona¹³, Bishoi Aziz¹⁴, Ellina Lytvyak¹⁴, Aldo Montano-Loza¹⁴, Gideon Hirschfield^{1,2}, Harry Janssen², Aliya Gulamhusein^{1,2}, Andrew L. Mason¹⁴, Bettina Hansen^{1,2}.
¹University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada; ²University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ³University of Saskatchewan, Medicine, Saskatoon, Canada; ⁴University of Montreal, Medicine, Montreal, Canada; ⁵Queen's University, Medicine, Kingston, Canada; ⁶University of Ottawa, Medicine, Ottawa, Canada; ⁷Western University, Medicine, London, Canada; ⁸University of Calgary, Medicine, Calgary, Canada; ⁹University of Sherbrooke, Medicine, Sherbrooke, Canada; ¹⁰University of British Columbia, Medicine, Vancouver, Canada; ¹¹Dalhousie University, Medicine, Halifax, Canada; ¹²University of Toronto, Medicine, Toronto, Canada; ¹³University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ¹⁴University of Alberta, Medicine, Edmonton, Canada
 Email: surain.roberts@mail.utoronto.ca

Background and aims: Sufficiency of UDCA response is dynamic in PBC, with varied patterns over time. We describe patterns of response and their association with liver transplant-free survival.

Method: Patients with >1 year of UDCA therapy from 8 Canadian sites were assessed; those with a clinical event within 6-mo of diagnosis or

without labs at 1-year (± 6 mo) were excluded. We defined UDCA response as alkaline phosphatase (ALP) < 1.67 \times ULN and total bilirubin (TB) $\leq 1 \times$ ULN. Multistate models estimated dynamic transition through biochemical response states over time, and from each state to transplantation or death (LTx/Death). We adjusted for sex, age, ALP, TB, and FIB-4 ≥ 4.03 at 1-year.

Results: Of 823 patients, median age at UDCA initiation was 53.6 years, 91.0% were female and 86.8% AMA positive. Median follow-up was 6.5 years and 7.0%/11.4%/13.5% had LTx/Death by 5/10/15 years. At 1-year, 67.4% of patients were responders. By 5-years, an estimated 6.4% never responded, 53.6% retained response, and 8.3% had LTx/Death. An estimated 31.8% fluctuated between response states: (i) 15.5% lost response and were non-responders at 5-years; (ii) 14.8% lost but then regained response and were responders at 5-years; (iii) 1.5% had at least five state changes (Figure, dotted line). At any point, patients retaining initial response had significantly lower rates of LTx/Death than those who never responded (0.074-fold, 95% CI 0.015–0.359) or lost response (0.045-fold, 95% CI 0.009–0.219). At any point, regaining response was protective against LTx/Death (transition rates: <0.001 vs 0.037; 0.005 vs 0.064).



Older age at UDCA initiation was associated with increased hazard of responding (HR 1.03/year, 95% CI 1.01–1.04) and of regaining response after loss of initial response (HR 1.04/year 95% CI 1.03–1.05). Response patterns of patients ≤ 40 years at UDCA initiation indicated high risk compared to patients aged 40–60 years: at 1-year, 56.2%/66.3% were responders. By 5-years an estimated 14.8%/6.7% never responded, 53.0%/57.8% retained response, and 4.2%/3.3% had LTx/Death. An estimated 28.0%/32.2% fluctuated between states: 17.9%/15.3% lost response by 5-years while 10.1%/17.0% lost then regained response. Age comparisons are for females, FIB-4 < 4.03, mean ALP and TB at 1-year.

Conclusion: Achievement of response at any time improves liver transplant-free survival regardless of prior non-response. New therapies will be important in improving response patterns, especially for younger patients.

OS-1728

Frequency, clinical features and outcomes of COVID-19 in patients with IgG4-related hepato-pancreato-biliary disease: a collaborative European multi-centre study

Giuseppe A. Ramirez^{1,2}, Marco Lanzillotta^{1,2}, Mikael Ebbö^{3,4}, Andreu Fernandez-Codina^{5,6,7}, Gaia Mancuso¹, Fernando Martínez-Valle^{8,9}, Olimpia Orozco-Galvez^{8,9}, Loren Smith^{10,11}, Nicolas Schleinitz^{3,4}, Lorenzo Dagna¹, Emanuel Della Torre^{1,2}, Emma Culver^{10,11}, ¹IRCCS Ospedale San Raffaele, Unit of Immunology, Milan, Italy; ²Università Vita-Salute San Raffaele, Immunology, Milan, Italy; ³CHU de Marseille-Hôpital de la Timone, Département de Médecine Interne, Marseille, France; ⁴Aix-Marseille University, Internal Medicine, Marseille, France; ⁵Windsor Regional Hospital, General Internal Medicine, Windsor, Canada; ⁶University of Western Ontario, Rheumatology, London, Canada; ⁷Hospital Clinic i Provincial, Emergency Department, Barcelona, Spain; ⁸Universitat Autònoma de Barcelona, Autoimmune Diseases Research Lab, Barcelona, Spain; ⁹Vall d'Hebrón Hospital, Systemic Diseases Unit and Internal Medicine Service, Barcelona, Spain; ¹⁰John Radcliffe Hospital, Oxford Liver Unit, Oxford, United Kingdom; ¹¹University of Oxford, Nuffield Department of Medicine, Oxford, United Kingdom
Email: emmaculver@yahoo.co.uk

Background and aims: The incidence of coronavirus disease 2019 (COVID-19) and of its complications in patients with immune-mediated liver and biliary disease remains unclear. We aimed to assess the frequency and impact of COVID-19 on patients with IgG4-related hepato-pancreato-biliary disease (IgG4-HBD), many of whom are on concurrent immunosuppression.

Method: A European multi-centre retrospective observational study from France, Italy, Spain and the United Kingdom was conducted between February 2020 to January 2021. Phone or in-person interviews were used to evaluate the frequency of COVID-19 infection, clinical presentation, disease course and outcomes in patients with IgG4-HBD. Demographics, comorbidities, organ involvement, current and past treatment, presumed COVID-19 (based on clinical, serological or imaging features: pCOVID) and confirmed COVID-19 (reverse-transcriptase polymerase chain reaction-confirmed: cCOVID). Total pCOVID and cCOVID (totCOVID) were pooled and compared to patients who were not diagnosed with COVID-19. Inter-group comparison of categorical and quantitative variables was performed using chi-square test with Fisher's correction and the Mann-Whitney's test, respectively.

Results: Data were collected for 119 patients [81% males, median age 68 (56–76) years] with IgG4-HBD. The majority (90%) had pancreatic involvement and 50 (42%) had coexisting diabetes mellitus. Fifty-four (45%) were taking corticosteroids (17% >10 mg daily prednisolone for active disease), 32 (27%) were on conventional immunosuppressants (azathioprine n = 17; mycophenolate n = 9; methotrexate n = 3; other n = 2) and 15 were on biological agents (rituximab n = 13). Thirty (25%) were on two or more immunosuppressive drugs for disease

control. Nine totCOVID cases (7 cCOVID, 2 pCOVID) were identified: 5 were hospitalised, 1 in intensive care and 2 died. Having one or more infected family members was a risk factor for COVID-19 in IgG4-HBD (OR = 15.4; p = 0.028). There was no association between adverse outcomes with COVID-19 and higher doses of steroids (>10 mg prednisolone), dual immunosuppression or rituximab.

Conclusion: The prevalence and course of COVID-19 in IgG4-HPB patients are similar to those of the general population of the same age, despite immunosuppressive treatment. There was no evident impact of disease- or treatment-related factors to the basal infectious risk. Effective public health countermeasures should be advocated for patients with IgG4-HBD.

OS-2096

Surrogate markers for bile duct disease progression assessed by sequential ERCP examinations in primary sclerosing cholangitis

Martti Färkkilä¹, Henrik Alftan², Andrea Tenca³, Kalle Jokelainen³, Johanna Arola⁴, Hannu Kautiainen⁵. ¹University of Helsinki, Faculty of Medicine, Helsinki, Finland; ²Helsinki University Hospital, HUSLab, Helsinki, Finland; ³Helsinki University Hospital, Clinic of Gastroenterology, Helsinki, Finland; ⁴Helsinki University Hospital, Department of Pathology, Helsinki, Finland; ⁵University of Eastern Finland, Primary Health Care Unit, Kuopio, Finland
Email: martti.farkkila@hus.fi

Background and aims: Primary sclerosing cholangitis [PSC] is a chronic inflammatory disease of biliary epithelium leading to strictures and eventually to cholestasis and secondary cirrhosis. Several surrogate markers have been developed to predict the disease progression, such as decrease of ALP, IL-8, and ELF and bile calprotectin, using liver cirrhosis, transplantation free survival or death as end points. In recent study, ALP did not associate with disease progression assessed by cirrhosis. Biliary IL8, collected at different stages of PSC demonstrated that it is elevated compared to controls, suggesting an ongoing inflammation driving IL8 production. However, liver cirrhosis, transplantation free survival or death are very late end points and not suitable for monitoring progression of bile duct disease and development of dominant strictures needing dilatations. We evaluated the role of clinical parameters, serum and biliary markers to predict the bile duct disease progression assessed by sequential ERC examinations to find better surrogate markers for PSC progression and drug development.

Method: Patients with suspicion or documented PSC referred for ERC examination to confirm the diagnosis, follow-up of disease progression or dysplasia surveillance were included. ERC findings were scored according to modified Amsterdam score. Based on ERC-score the patients were divided into (1) No progression (n = 259) or (2) Progression \pm need for dilatation (n = 381). Time weight AUC was calculated based on ERC score. Brush cytology was collected from both extra- and intrahepatic ducts. Biliary calprotectin were analysed using ELISA method and IL8 was measured by immune-chemiluminometrics. Optimal cut points, AUC, sensitivity, specificity, positive likelihood ratio (LR+) and PPV were calculated. The study protocol was accepted by HUS Ethical Committee HUS/1566/2020.

Results: 76% had a concomitant IBD, but it had no impact on disease progression, neither did colectomy done before or after diagnosis of PSC, age or sex. None of the liver enzymes levels (P-ALP, P-GT, P-AST, P-ALT) or P-bil demonstrated significant impact on disease progression (AUC 0.55–0.58). Only biliary (Bi-) calprotectin (AUC 0.77 [95% CI 0.73–0.82]), Bi-IL8 (0.81 [0.75–0.86]) or their combination (0.80 [0.75–0.85]) and to less extent S-IL8 (0.60 [0.53 to 0.68]) could significantly predict bile duct disease progression and/or need for dilatation. The LR+ were respectively 2.79 (2.16–3.60), 2.84 (2.07–3.89) and for the combination 3.30 (2.29–4.76).

Conclusion: In this large PSC patient cohort with sequential ERCP regardless of symptoms, liver enzymes or patient demography could not predict bile duct disease progression or need for dilatation. The most sensitive markers with highest LR were Bi-calprotectin and Bi-

ORAL PRESENTATIONS

IL8. The value of serum liver enzymes in assessing bile duct disease progression in PSC seemed to be limited.

OS-2782

Bacterial and fungal colonisation of bile ducts associates with the prognosis of Primary Sclerosing Cholangitis

Ehud Zigmond^{1,2}, Britta Zecher³, Anna-Lena Bartels³, Tomer Ziv², Thomas Rösch⁴, Ansgar Lohse³, Hanno Ehlken^{3,4}, Christoph Schramm^{3,5,6}. ¹Tel Aviv Sourasky Medical Center, Department of Gastroenterology, Tel Aviv, Israel; ²Tel Aviv University, Sackler Faculty of Medicine, Tel Aviv, Israel; ³University Medical Center Hamburg-Eppendorf, Ist Department of Medicine, Germany; ⁴Dept. for Interdisciplinary Endoscopy, Germany; ⁵University Medical Center Hamburg-Eppendorf, Martin Zeitz Center for Rare Diseases, Germany; ⁶University Medical Center Hamburg-Eppendorf, Hamburg Center for Translational Immunology (HCTI), Germany
Email: zigmondu@gmail.com

Background and aims: Primary Sclerosing Cholangitis (PSC) is a rare immune mediated chronic and progressive liver disease characterized by inflammation and fibrosis of bile ducts. Bile ducts in PSC are frequently colonised with bacteria and we have recently described an altered biliary microbiota composition in PSC with a high abundance of *Enterococcus sp.* However, little is known about the impact of these findings on the clinical course of disease.

Method: We here investigated the association of bile fluid culture results obtained routinely during ERCP on major clinical end points in a large single center cohort of PSC patients. Peri-interventional i.v. antibiotics were given as standard after the sampling of bile fluid in our center. Procedures with overt bacterial cholangitis and receiving antibiotic treatment prior to ERCP were excluded.

Results: Microbiological culture results from 591 ERCP were included. Culture results were not associated with the occurrence of cholangiocarcinoma (CCA), which was therefore not included as an end point for further analyses. Positive bile cultures were significantly associated with development of cirrhosis and its complications and survival free of liver transplantation. Bacteria grew in 75% of biliary cultures and in 32% of first time ERCP procedures. Interestingly, amongst the bacterial species, the presence of *Enterococcus faecalis* and/or *faecium* in bile fluid conferred risk of disease progression independent of the presence of fungi in bile with a HR of 2.28 (95% CI 1.32–3.92, $p < 0.005$) for achieving clinical end points and HR of 1.9 (95% CI 1.05–3.41, $p < 0.05$) for survival free of liver transplantation. Fungobilia, present in 20% of cases, was found to strongly associate with disease progression with a HR of 2.39 (95% CI 1.37–4.17, $p < 0.001$) for achieving clinical end points.

Conclusion: Our peri-interventional standard antibiotic regimen and exclusion of patients with overt bacterial cholangitis enabled us to analyze the association of bile duct colonisation with disease course in a large cohort of PSC patients. The strong association of *Enterococcus sp.* and fungi with disease progression highlights the importance of microbiota-mucosal interplay for the pathogenesis of PSC. These results should stimulate further mechanistic studies on the role of microbiota for biliary inflammation in PSC.

Immunology

OS-1171

Non-autonomous induction of endothelial RelA underpins immune-mediated surveillance of premalignant hepatocytes

Kelvin Yin^{1,2}, Daniel Patten³, Aaron Lun², Martijn Schuijjs², Adelyne Chan², Andrew Young², Tim Halim², Shishir Shetty³, Masashi Narita², Matthew Hoare^{2,4}. ¹Helmholtz Pioneer Campus, Helmholtz Zentrum München, Munich, Germany, ²CRUK Cambridge Institute, Cancer Research UK, Cambridge, United Kingdom, ³Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom, ⁴University of Cambridge, Department of Medicine, Cambridge, United Kingdom
Email: chuan-hsin.yin@helmholtz-muenchen.de

Background and aims: Oncogene-induced senescence (OIS) is a tumour suppressor mechanism, with profound effects on the microenvironment (ME) through the senescence-associated secretory phenotype (SASP). Previous studies have shown that OIS hepatocytes are progressively cleared by a SASP-driven CD4+ T-lymphocyte-dependent immune response, termed senescence surveillance; failure of this clearance leads to tumorigenesis. The mechanisms underpinning this surveillance of pre-malignant cells are not well understood. We hypothesised that OIS hepatocytes would regulate immunomodulatory endothelial behaviour, controlling immunocyte recruitment and behaviour in the liver ME.

Method: Using hydrodynamic tail vein injection (HDTV) of NRAS^{G12V}-containing transposons, we generate OIS in murine hepatocytes. To test our hypothesis, we use pharmacological blockade of NF- κ B signalling, as well as inducible endothelial-specific knock-out transgenic mouse model following OIS. LSECs were isolated from dissociated murine livers for characterization by quantitative-PCR. Our observations were validated in two

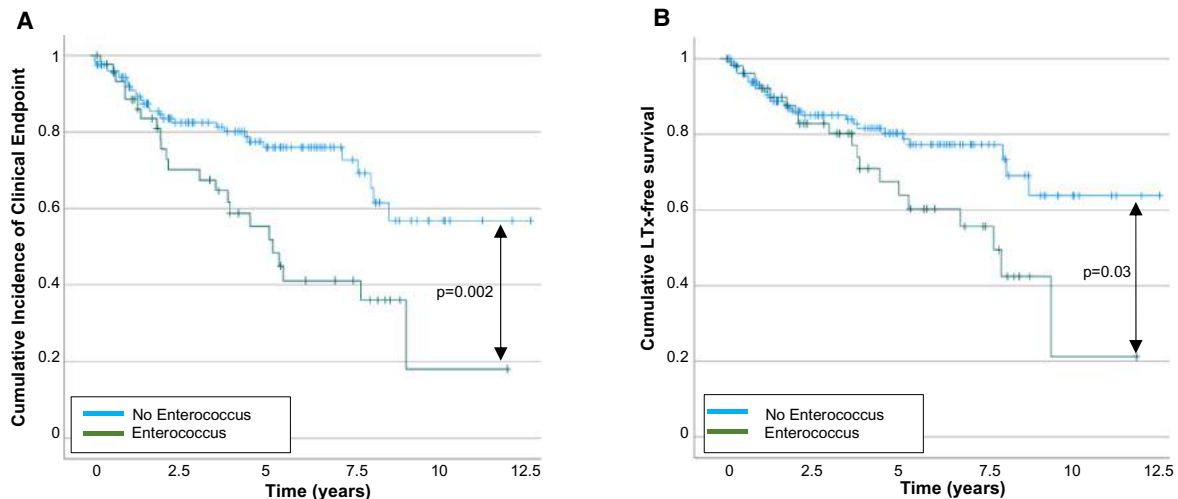
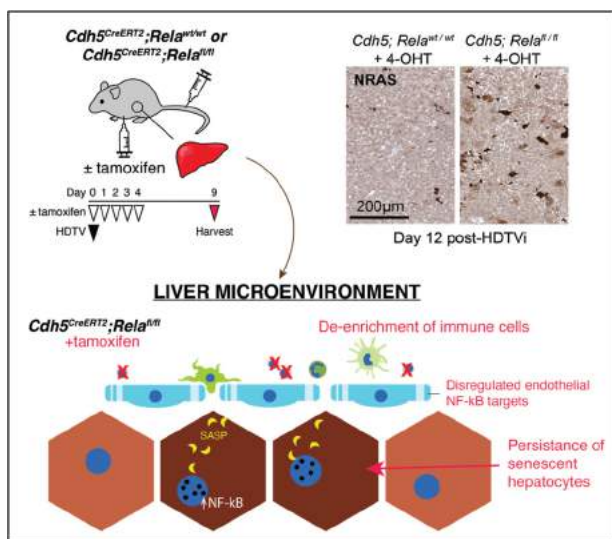


Figure: (abstract: OS-2782)

independent human endothelial cell lines, and in trans-endothelial migration *in vitro* assays using SASP-primed human primary LSECs and lymphocytes. scRNAseq and mass cytometry were used to characterize the hepatic immune landscape in response to OIS.

Results: Using an *in vitro* model of OIS, we have demonstrated a SASP-driven non-autonomous upregulation of NF- κ B-target genes in primary human liver sinusoidal endothelial cells (LSECs). Genetic or pharmacological blockade of NF- κ B signaling in SASP-primed LSECs abrogated lymphocyte trapping and trans-endothelial migration *in vitro*. In the context of *in vivo* studies, we show hepatocyte OIS non-autonomously upregulates multiple NF- κ B-target genes in LSECs, including *Cxcl1* and *Icosl*. Transgenic mouse model of *Cdh5*^{CreERT2}; *Rela*^{fl/fl} provided evidence that endothelial NF- κ B signalling is crucial to senescence surveillance, where loss of endothelial *Rela* leads to persistence of OIS hepatocytes. scRNA-seq suggests that loss of endothelial *Rela* leads to a complete loss of a *Stat1*-expressing CD4+ lymphocyte subset from the liver ME.



Conclusion: Endothelial cells are a target of non-autonomous signalling from senescent cells *in vitro* and *in vivo*. We found that immunomodulatory endothelial behaviour, through non-autonomous induction of endothelial NF- κ B signalling, forms a crucial part of the immune surveillance of premalignant hepatocytes.

OS-1299

Selective depletion of HBsAg-specific B cells in paediatric HBV infection

Sabela Lens^{1,2}, Ida Heiberg³, Thilde Nordmann Winther³, Anna Jeffery-Smith¹, Nikolai Novikov⁴, Simon Fletcher⁴, Birthe Hogh³, Alice Burton¹, Mala Maini¹. ¹Division of Infection and Immunity, UCL, London, United Kingdom, ²Liver Unit, Hospital Clínic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, ³Department of Paediatrics, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark, ⁴Gilead Sciences, United States
Email: m.maini@ucl.ac.uk

Background and aims: Exposure to HBV during vertical transmission or in infancy is associated with a high rate of chronicity, but the immunological mechanisms accounting for this remain unclear. Recent data have highlighted a contribution of B cells to ongoing control of chronic hepatitis B (CHB) and direct *ex vivo* analysis has revealed defects of HBsAg-specific B cells in adults. We therefore characterized the HBV-specific and global B cell compartment (and the T follicular helper cell (Tfh) response that supports it) in children with CHB, comparing with uninfected children or adults with CHB.

Method: 16-colour flow cytometry was used to characterise the composition and phenotype of circulating HBsAg- and HBcAg-

specific B cells (detected using dual fluorochrome-labelled antigen baits), global B cells and circulating Tfh in a cohort of children with CHB (n = 25; age range 5–17 yrs), compared to uninfected children (n = 24) and CHB adults matched by disease phase (n = 35).

Results: HBsAg-specific B cells were strikingly reduced in children compared to adults with CHB. By contrast HBcAg-specific B cells and tetanus-specific B cells were detectable at higher frequencies, comparable in children and adults. These data pointed to a selective depletion of HBsAg-specific B cells in children with CHB, regardless of HBV phase, HBV-DNA level or HBeAg status. HBsAg-specific B cells in children were enriched for the atypical memory phenotype recently described to be a feature associated with the dysfunction of this specificity in adults (atMBC: CD21⁻CD27⁻). AtMBC were also more enriched within global B cells in children with CHB than in adults with CHB or in uninfected children. AtMBC upregulated inhibitory markers (CD22, PD-1) and downregulated homing and signaling molecules (CXCR5, CD80, CD40) compared to their classical memory counterparts. In addition to these defects, we postulated HBsAg-specific B cells received inadequate T cell help; in line with this, HBsAg-specific B cells correlated with frequencies of circulating Tfh, but the latter had reduced CD40L in children with CHB compared to controls.

Conclusion: Children with CHB have a profound and selective depletion of HBsAg-specific B cells compared to adults. Residual HBsAg-specific B cells have a phenotype indicative of dysfunction and may have defective T-B cell interactions. These findings are consistent with the low rate of anti-HBs seroconversion in children and point to pathways for therapeutic intervention.

Liver development, physiology and regeneration

OS-687

A MET-agonistic antibody mimicking hepatocyte growth factor accelerates liver regeneration and improves survival in mice undergoing carbon tetrachloride exposure and partial hepatectomy

Kuai Ma^{1,2}, Weitao Que², Er-li Gu¹, Wen-zhi Guo³, Liang Zhong⁴, Paolo Michieli^{1,5}, Terumi Takahara⁶, Xiao-Kang Li^{2,3}. ¹Central Hospital, Jing'an Branch of Huashan Hospital, Fudan University, Department of Gastroenterology and Hepatology, Shanghai, China; ²National Research Institute for Child Health and Development, Division of Transplantation Immunology, Tokyo, Japan; ³The First Affiliated Hospital of Zhengzhou University, Department of Hepatobiliary and Pancreatic Surgery, Zhengzhou, China; ⁴Huashan Hospital, Fudan University, Department of Gastroenterology, Shanghai, China; ⁵AgomAb Therapeutics NV, Gent, Belgium; ⁶University of Toyama, Third Department of Internal Medicine, Toyama, Japan
Email: ma-kuai@ncchd.go.jp

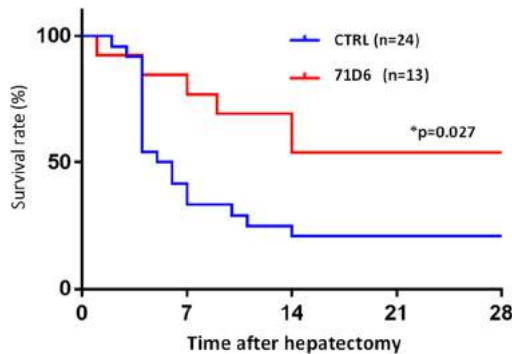
Background and aims: Small for size syndrome (SFSS) is a common complication following partial liver transplantation or extended hepatectomy. SFSS is characterized by postoperative liver dysfunction caused by insufficient regenerative capacity and portal hyperperfusion, and is more frequent in patients with pre-existing liver disease. Hepatocyte growth factor (HGF) possesses potent anti-inflammatory, anti-fibrotic, and regenerative properties, but its very short plasmatic half-life precludes its clinical use. We explored the efficacy of the MET-agonistic antibody 71D6, which mimics the biological activities of HGF, in mice undergoing carbon tetrachloride (CCl4) exposure followed by 70% partial hepatectomy (PHx).

Method: 8-week-old mice were administered CCl4 subcutaneously twice a week for 10 weeks, then randomly assigned to receive 71D6 (3 mg/kg) or control IgG, starting 2 weeks before PHx. Livers were

ORAL PRESENTATIONS

harvested at different time points following PHx. The survival rate, body and liver weights, serum albumin, and expression of fibrosis-related and inflammation-related genes were analyzed.

Results: Compared to control IgG, 71D6-treatment in mice undergoing CCL4 and PHx resulted in robust hepatocellular regeneration via activation of extracellular signal regulated kinase (ERK) 1/2 signaling, leading to accelerated recovery of liver function and improved survival 28-day post PHx ($p=0.027$). 71D6 reduced myofibroblast activation and collagen deposition, as shown by reduced alpha smooth muscle cell actin ($p < 0.01$) and picro Sirius red staining ($p < 0.05$), by inhibiting multiple fibrogenic pathways including platelet-derived growth factor, tissue matrix metalloproteinase inhibitor-3, and transforming growth factor- β 1 ($p < 0.01$ for gene expression levels 28 days post-PHx). 71D6 also prevented the development of severe inflammation, as shown by a statistically significant reduction in macrophage infiltration and chemokine/cytokine expression.



Conclusion: Our results demonstrate that mimicking HGF with the MET-agonistic antibody 71D6 promotes liver regeneration, inhibits fibrosis and attenuates immune cell infiltration after PHx in mice with pre-existing liver injury. These results suggest that activating the MET pathway via an HGF-mimetic antibody may be beneficial in patients with SFFS and possibly other types of acute and chronic liver disorders.

OS-943

Single-nucleus RNA-seq2 reveals a functional crosstalk between liver donation and ploidy

Maria L. Richter¹, Ioannis K. Deligiannis¹, Kelvin Yin^{1,2}, Anna Danese³, Ermira Lleshi², Paul Coupland², Catalina Vallejos⁴, Kylie Matchett⁵, Neil C. Henderson^{5,6}, Maria Colome-Tatche^{3,7}, Celia P. Martinez-Jimenez⁸. ¹Helmholtz Zentrum München, Helmholtz Pioneer Campus, Neuherberg, Germany; ²University of Cambridge, CRUK Cambridge Institute, Cambridge, United Kingdom; ³Helmholtz Zentrum München, Institute of Computational Biology, Neuherberg, Germany; ⁴University of Edinburgh, Institute of Genetics and Molecular Medicine, Edinburgh, United Kingdom; ⁵Centre for Inflammation Research, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; ⁶MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom; ⁷TUM School of Life Sciences Weihenstephan, Technical University of Munich, Freising, Germany; ⁸TUM School of Medicine, Technical University of Munich, Munich, Germany
Email: chuan-hsin.yin@helmholtz-muenchen.de

Background and aims: Liver is the largest solid organ, consisting of predominantly parenchymal hepatocytes, which are interspersed in an ordered matrix to provide 'cross-talk' with less common cell types, including liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs)

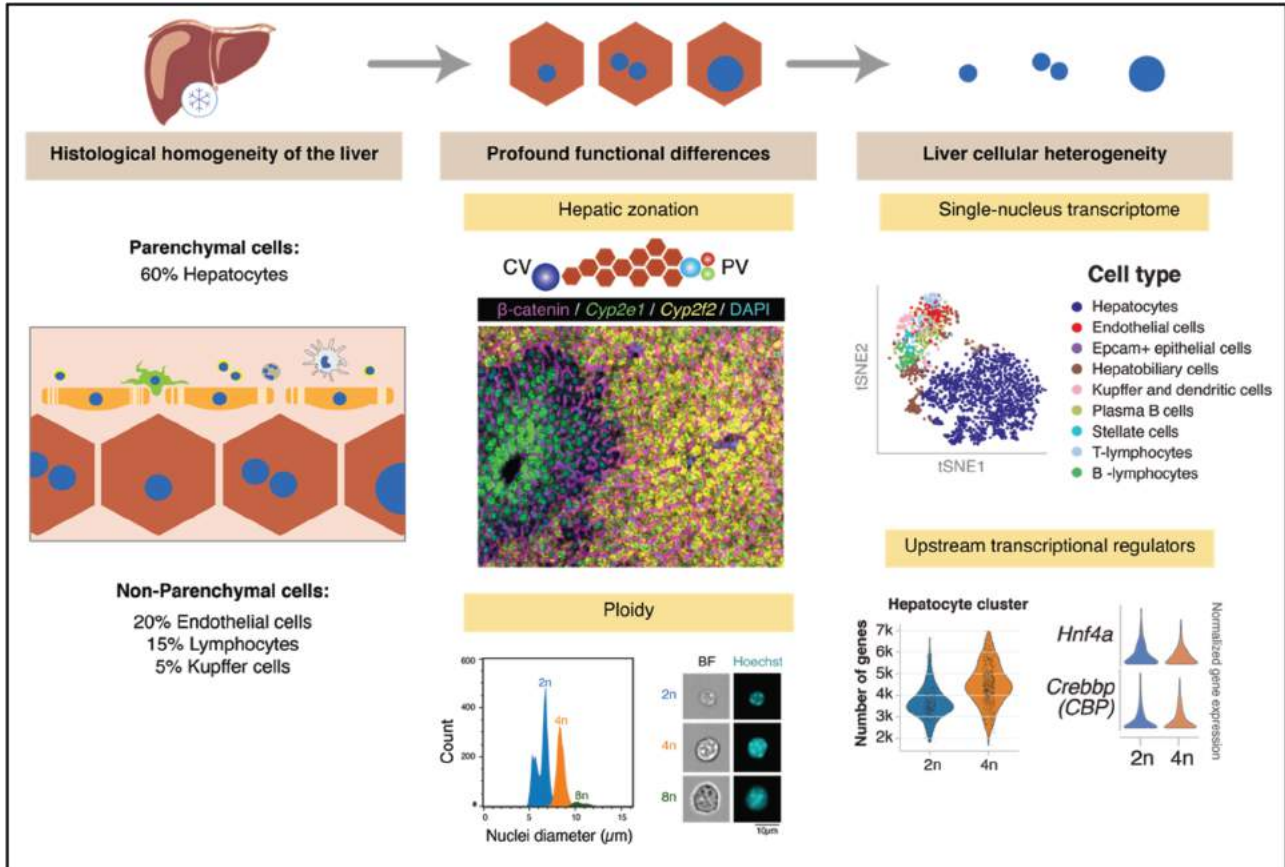


Figure: (abstract: OS-943)

and immune cells. Traditional single-cell RNA-sequencing methodologies require a two-step enzymatic digestion to dissociate liver tissues, leading to the downregulation of liver-specific transcription factors, including *Hnf4a* and *Cebpa*, as well as their downstream target genes. In this context, we have developed a novel single-nucleus RNA-sequencing 2 method (snRNA-seq2) which allows deep characterization of isolated nuclei from frozen samples.

Method: Using flash frozen archived liver samples from 3 months old male C57BL/6J mice, we demonstrate the efficiency of snRNA-seq2, which consists of a modified lysis buffer that efficiently lyses the nuclear membrane. Importantly, snRNA-seq2 utilizes unbiased sorting of single-nuclei, allowing the analysis of differential transcriptional variability between different ploidy levels in hepatocytes. Using pseudotemporal ordering and markers of liver zonation, revealed a functional crosstalk between liver zonation and ploidy. Our observations were validated by immunofluorescence/RNAScope co-detection approach in paraffin embedded liver tissues and in a mouse model of liver fibrosis in which zonation is affected.

Results: SnRNA-seq2 is a highly sensitive method for frozen liver tissue, capable of detecting on average more than 4000 genes per nucleus compared with other single-cell genomic approaches, including MARS-seq, 10x, Smart-seq2 and CELL-seq. SnRNA-seq2 allowed comprehensive characterization of all hepatic cell types, including upstream transcriptional regulators and key metabolic genes. Additionally, tetraploid hepatocytes show extensive co-expression of liver stem cell markers and high capacity for adaptation and regeneration. Importantly, we found that gene expression in hepatocytes is determined by its hepatic metabolic zonation and independent of their ploidy status.

Conclusion: SnRNA-seq2 is a robust and reliable method to investigate the impact of cellular heterogeneity in the development and progression of liver disease using frozen archived samples. We anticipate that changes in the number of 2n and 4n hepatocytes in the overall liver cell composition might lead to the development of chronic liver diseases.

OS-1290

Integrin Alpha FG-GAP Repeat Containing 1 (ITFG1) knockdown enhances liver regeneration and attenuates chronic liver damage related liver fibrosis

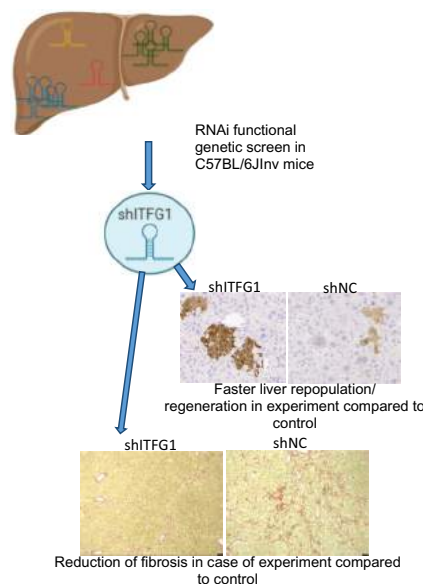
Viktoriia Iakovleva^{1,2}, Anna Potapova¹, Agnes Bee Leng Ong¹, Yock Young Dan², Torsten Wuestefeld^{1,3,4}. ¹Genome Institute of Singapore, Singapore; ²National University of Singapore, Medicine, Singapore; ³National Cancer Centre, Singapore; ⁴Nanyang Technological University, Singapore
Email: iakovlevav@gis.a-star.edu.sg

Background and aims: Chronic liver diseases are one of the major leading causes of death. Moreover, the only current curative treatment for end-stage liver disease is liver transplantation. However, donor organs are limited. Therefore, it is crucial to find alternative strategies to treat such patients. In our research, we established RNAi based *in vivo* functional genetic screens to identify endogenous agents that reverse and hold off end-stage liver disease.

Method: We conducted an RNAi based *in vivo* functional genetic screen in 'wild-type' mice (C57BL/6JInv). We delivered a focused shRNA pool into mouse livers by hydrodynamic tail vein injections (HDTV) together with transposase sleeping beauty 13 (SB13). Then, we applied thioacetamide (TAA) treatment 3 times per week for 8 weeks intraperitoneally to simulate chronic damage of the livers. After that, the abundance of each shRNA was compared to the starting shRNA pool by Illumina based deep sequencing. We followed up enriched candidates. We identified Integrin Alpha FG-GAP Repeat Containing 1 (ITFG1) as a potential regulator of liver regeneration and disease.

We further validated ITFG1, performed *in vitro* and *in vivo* assays. For *in vitro* assays, we generated stable cell lines with ITFG1 knockdown. We tested knockdown efficiency by qPCR. We validated 2

independent shRNAs against ITFG1 to avoid the off-target effect. Stable cell lines with ITFG1 knockdown were used for wound healing assay. For *in vivo* assays, we investigated liver repopulation in FAH^{-/-} mouse model, fibrosis score in chronic liver damage model by using TAA, and fibrosis score in NASH condition by using "Western-Diet" model.



Results: Efficient ITFG1 knockdown accelerated wound healing *in vitro*. Furthermore, faster clonal expansion was observed in the case of ITFG1 knockdown compare to control *in vivo*, using FAH knockout mice. In two chronic liver disease models (TAA and NASH), a significant reduction of fibrosis was observed in the experimental group with ITFG1 knockdown compared to the non-targeting control. **Conclusion:** ITFG1 knockdown accelerates wound healing and liver repopulation, attenuates chronic liver damage related liver fibrosis, protects against NASH related fibrosis.

OS-2656

Cholangiocyte organoids regenerate human bile ducts

Fotis Sampaziotis^{1,2}, Daniele Muraro^{1,3}, Olivia C. Tysoe¹, Stephen Sawiak⁴, Timothy Beach⁵, Edmund Godfrey⁶, Sara Upponi⁶, Brandon Wesley¹, Teresa Brevini¹, Krishnaa Mahbubani⁵, Natalie Lie Berntsen^{7,8,9}, Victoria Mulcahy^{2,10}, Keziah Crick⁵, Corrina Fear⁵, Sharayne Robinson⁵, Lisa Swift⁵, Gareth Corbett¹¹, William Gelson², George Mellis^{2,10}, Susan Davies¹², Irum Amin⁵, Paul Gibbs⁵, Sarah Teichmann³, Andrew Butler⁵, Teik Choon See⁶, Espen Melum^{7,8,9,13,14}, Chris Watson⁵, Kourosh Saeb-Parsy⁵, Ludovic Vallier^{1,5}. ¹University of Cambridge, Cambridge Stem Cell Institute, Cambridge, United Kingdom; ²Addenbrooke's Hospital, Hepatology, United Kingdom; ³Wellcome Trust Sanger Institute, Hinxton, United Kingdom; ⁴University of Cambridge, Clinical Neurosciences, United Kingdom; ⁵University of Cambridge, Surgery; ⁶Addenbrooke's Hospital, Radiology, Cambridge, United Kingdom; ⁷Norwegian PSC Research Center, Oslo University Hospital, Rikshospitalet, Oslo, Norway; ⁸Oslo University Hospital, Research Institute of Internal Medicine, Oslo, Norway; ⁹University of Oslo, Institute of Clinical Medicine, Oslo, Norway; ¹⁰University of Cambridge, Academic Department of Medical Genetics, Cambridge; ¹¹Addenbrooke's Hospital, Gastroenterology, United Kingdom; ¹²Addenbrooke's Hospital, Histopathology, United Kingdom; ¹³Oslo University Hospital, Rikshospitalet, Gastroenterology, Oslo, Norway; ¹⁴University of Oslo, Hybrid Technology Hub-Centre of Excellence, Institute of Basic Medical Sciences, Faculty of Medicine, Oslo, Norway
Email: fotiss@yahoo.com

ORAL PRESENTATIONS

Background and aims: Although organoid technology holds great promise for regenerative medicine, it has not yet been applied to humans. We address this challenge in the context of cholangiocyte organoids and cholangiopathies, which are a leading indication for liver transplantation. We demonstrate that cholangiocytes are plastic and small changes in their transcriptional profile, induced by organoid culture, are reversed when the cells are re-exposed to their natural niche. We exploit this property to inject cholangiocyte organoids in the bile ducts of mice with toxin-induced cholangiopathy and in a novel model for cell transplantation using human organ donor livers perfused *ex situ* and show that organoid transplantation can rescue cholangiopathy in mouse and human.

Method: Primary cholangiocytes were cultured as organoids using published methods. Primary cells and organoids were characterized using droplet encapsulation single-cell RNA sequencing (scRNAseq). Cholangiopathy was induced in immunocompromised mice with 4,4'-methylene dianiline (MDA). The *metra* (OrganOx) normothermic liver perfusion device was used for *ex situ* perfusion of human livers not used for transplantation and organoids were injected in bile duct branches under radiological guidance.

Results: We first demonstrate that different regions of the human biliary tree contain cells with distinct transcriptional profiles. We then show that cholangiocytes lose these differences in organoid culture and become interchangeable, but their *in vivo* identity can be restored using environmental stimuli in culture, suggesting that these cells are plastic. We subsequently transplant human organoids from different regions of the biliary tree in the intrahepatic ducts of mice with MDA-induced cholangiopathy and demonstrate that the cells engraft, they assume an intrahepatic identity and rescue the animals, with resolution of cholestasis in serum samples and resolution of cholangiopathy in histology and MRCP. We repeat this experiment using human livers undergoing *ex situ* normothermic perfusion and show that organoids engraft, rescue cholangiopathy and restore bile parameters (e.g. pH).

Conclusion: Our study validates that cholangiocytes are plastic and interchangeable in organoid culture. Therefore, cholangiocyte organoids derived from any region can repair the entirety of the biliary tree. Moreover, we provide the first proof-of-principle for the efficacy of cell-based therapy using organoids in human organs.

Liver transplantation and hepatobiliary surgery: Clinical aspects

OS-116

Neutralizing antibodies against SARS-CoV-2 in cirrhotic patients waiting for liver transplantation

Margherita Saracco¹, Silvia Martini¹, Francesco Tandoi², Fabrizia Pittaluga³, Antonio Ottobrelli¹, Rossana Cavallo³, Antonio Amoroso⁴, Roberto Balagna⁵, Renato Romagnoli².

¹Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, Torino, Italy; ²General Surgery 2U, Liver Transplantation Center, AOU Città della Salute e della Scienza di Torino, Torino, Italy; ³Microbiology and Virology Unit, AOU Città della Salute e della Scienza di Torino, Torino, Italy; ⁴Regional Transplantation Centre, Piedmont, AOU Città della Salute e della Scienza di Torino; ⁵Anesthesia and Intensive Care Unit 2, AOU Città della Salute e della Scienza di Torino, Torino, Italy
Email: margherita.saracco@gmail.com

Background and aims: The COVID-19 pandemic affected every aspect of healthcare and threatened the availability of liver donors. To limit this phenomenon, the Italian National Transplant Center allowed liver transplantation (LT) from SARS-CoV-2 positive donors to patients with severe liver disease who are SARS-CoV-2 positive or with a previous history of COVID-19. We aimed to ascertain the

prevalence of neutralizing antibodies against SARS-CoV-2 in all our cirrhotic patients on LT waiting list.

Method: From the 25th of November 2020 to the 22nd of January 2021, each patient on the LT waiting list was tested for SARS-CoV-2 neutralizing antibodies (with LIAISON® SARS-CoV-2 S1/S2 IgG test, a quantitative assay for the detection of IgG antibodies against S1/S2 antigens of SARS-CoV-2: ≥ 15 UA/ml positive) and detailed medical history was collected. IgG antibodies were retested 1 month after the first evaluation. COVID-19 asymptomatic patients with positive IgG test underwent immediate SARS-CoV-2 molecular testing using nasopharyngeal swab (NPS, with Simplexa® COVID-19 Direct, DiaSorin Molecular).

Results: At the beginning and at the end of the enrollment period 61 and 73 patients, respectively, were actively on the LT waiting list. During the study period, 17 first adult LTs were consecutively performed in our Center. 80 patients underwent SARS-CoV-2 IgG test, and 17 (21.3%) of them tested positive. 7 out of 17 (41.2%) had a previous documented history of COVID-19; the remaining 10 (58.8%) were asymptomatic and tested negative at NPS. 4 out of those 17 IgG-positive cirrhotics (23.5%) received a graft from a positive SARS-CoV-2 RNA donor. After a median post-LT follow-up of 6.5 weeks: no SARS-CoV-2-related complications occurred. Patient N.8 showed negative SARS-CoV-2 IgG at 1 month, and Patient N.10 showed sole intermittent NPS positivity (Table 1).

Conclusion: In our cohort, 21.3% of cirrhotic patients on the LT waiting list tested positive for SARS-CoV-2 neutralizing antibodies and 58.8% of them did not show a clinical history. This screening allowed a precious expansion of the donor pool by allocating 4 SARS-CoV-2 RNA positive donors to 4 IgG-positive recipients.

Figure: (abstract: OS-116): SARS-CoV-2 S1/S2 IgG-positive cirrhotic patients

Patient	HISTORY OF COVID-19	SARS-CoV-2 IgG T0 (UA/ml)	SARS-CoV2 IgG T1 (UA/ml)	LT	SARS-CoV-2 RNA positive donor	SARS-CoV-2 IgG at 1 month after LT (UA/ml)
1	N	15, 1		N		
2	N	18, 7		N		
3	Y	22, 9	19, 9	N		
4	Y	28, 9	29, 2	N		
5	N	29, 8		N		
6	N	31		Y	N	
7	N	40, 9		Y	Y	48, 4
8	N	48, 5	/	Y	Y	<3, 8
9	N	49, 8	78, 7	N		
10	Y	79, 7		Y	Y	53, 8
11	N	88		N		
12	N	89		N		
13	Y	103		Y	Y	49
14	N	110		N		
15	Y	195	157	Y	N	
16	Y	1310		N		
17	Y	20		N		

OS-161

Radiology-histopathology discordance in Hepatocellular cancer and its impact on post-transplant outcome

Islam Mohamed^{1,2}, Mohamed Ismail^{1,2}, Efstathia Polychronopoulou³, Mahmoud Hashim¹, Ahmed Elkheshen¹, Manal Hassan^{1,4}, Prasun Jalal¹. ¹Baylor College of Medicine, Hepatology, Houston, Texas, United States; ²Ain Shams university Faculty of Medicine, Internal Medicine, Division of Gastroenterology and Hepatology, Cairo, Egypt; ³UTMB Health, Biostatistics, Galveston, United States; ⁴The University of Texas MD Anderson Cancer Center, Epidemiology, Houston, Texas, United States

Email: islam.mohamed@bcm.edu

Background and aims: Multiphasic contrast enhanced cross-sectional imaging is standard in the diagnosis and management of HCC in Society guidelines, replacing the need for histopathology. Milan criteria based radiology is used for selection of HCC patients to liver transplantation (LT). However, radiology-histopathology discordance may lead to improper staging of HCC affecting post-LT outcome. This study aims to assess radiology-histopathology discordance at transplantation in patients with HCC and its impact in the post-LT outcome.

Method: Using OPTN/UNOS database, all adult patients with deceased donor liver-only transplants between April 1, 2012 and December 31, 2017 with HCC exception points based on radiology were analyzed retrospectively. Correctly-staged patients were defined as within Milan by both pre-LT radiology and explant. Under-staged patients were defined as within Milan by radiology and outside Milan by explant. Kaplan-Meier methods and Cox regression analysis were used to evaluate the impact of under-staging on 3-yrs HCC recurrence and post-LT patient survival.

Results: A total of 6842 patients were included in the cohort, of whom 67.7% (n = 4564) were correctly-staged and 32.3% (n = 2278) were under-staged. Post-LT HCC recurrence and death were significantly higher in under-staged patients (p < 0.0001). In adjusted analysis, under-staging is an independent predictor of HCC recurrence (HR 1.88; 95% CI 1.37–2.59) and death (HR 1.31; 95% CI 1.04–1.65).

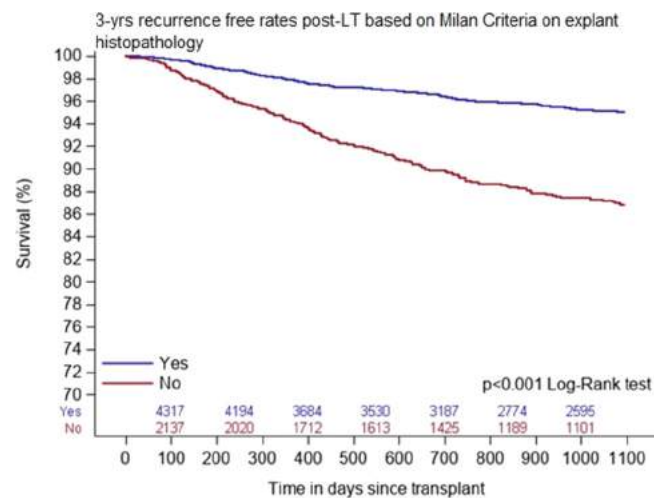


Figure 1: 3-yrs recurrence free rate post-LT.

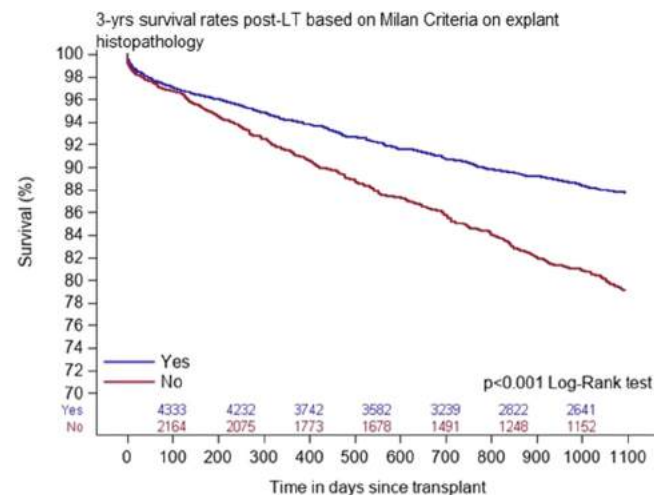


Figure 2: 3-yrs survival rates post-LT based on Milan criteria by explant.

Conclusion: Current practice of pre-LT staging of HCC based on radiology is inadequate and accounts significantly for post-LT HCC recurrence and survival. Improvement in radiological assessment is needed to optimize patient selection to decrease post-LT recurrence and improve survival.

OS-213

Immunological risk stratification of stable long-term liver transplant recipients employing non-invasive tools

Julien Vionnet¹, Juan G. Abalde², Rosa Miquel¹, Jurate Wall³, Elisavet Kodela³, Will Gelson⁴, Joanna Leithead⁴, Phaedra Tachtatzis⁵, Kenneth J. Simpson⁶, James Ferguson⁷, Aileen Marshall⁸, Steven Masson^{9,10}, Frederik Nevens¹¹, Elmar Jaeckel¹², Richard Taubert¹², Pablo Ruiz¹³, Miguel Navasa¹³, Dennis Eurich¹⁴, Eliano Bonaccorsi Riani¹⁵, Alberto Sanchez-Fueyo¹. ¹King's College Hospital, Liver, London, United Kingdom; ²University of Alberta, Liver Unit, Edmonton, Canada; ³King's College London, London, United Kingdom; ⁴Addenbrooke's Hospital, Liver, Cambridge, United Kingdom; ⁵Leeds Teaching Hospital NHS Trust, Liver, Leeds, United Kingdom; ⁶Edinburgh Royal Infirmary, Liver, Edinburgh, United Kingdom; ⁷Queen Elizabeth Hospital, Liver, Birmingham, United Kingdom; ⁸Royal Free Hospital, Liver, London, United Kingdom; ⁹Newcastle Upon Tyne Hospitals NHS Foundation Trust, Liver, Newcastle Upon Tyne, United Kingdom; ¹⁰Newcastle University, Translational and Clinical Research Institute, Newcastle upon Tyne, United Kingdom; ¹¹UZ Leuven, Liver, Leuven, Belgium; ¹²Medizinische Hochschule Hannover, Liver, Hannover, Germany; ¹³Hospital Clinic, Liver, Barcelona, Spain; ¹⁴Charité, Liver, Berlin, Germany; ¹⁵Cliniques Universitaires St-Luc, Liver, Brussels, Belgium

Email: julien.vionnet@chuv.ch

Background and aims: Management of long-term immunosuppression (IS) following liver transplantation (LT) remains empirical. Surveillance liver biopsies in combination with transcriptional profiling has the potential to overcome this challenge by identifying recipients with ongoing alloimmune-mediated liver damage despite normal liver function tests (LFT), but has low applicability. Our aim was to investigate the utility of non-invasive tools in stratifying stable long-term surviving LT recipients according to their immunological risk and need for IS.

Method: We conducted a cross-sectional study of 191 long-term adult LT recipients in whom a liver biopsy was performed between October 2015 and May 2019 as part of the baseline assessment of a multinational immunosuppression withdrawal (ISW) trial (NCT02498977). Participants had normal LFT and had been transplanted for non-autoimmune non-replicative viral liver disease >3 years before inclusion. We conducted histological, immunogenetic and serological studies and assessed the intrahepatic transcript levels of a 11-gene classifier highly specific for T cell-mediated rejection (TCMR). We used logistic regression and classification and regression tree analysis to develop models to predict silent alloimmune damage.

Results: 68/191 recipients (36%) harbored silent fibro-inflammatory liver lesions, which were scored as moderate-to-severe in 42 (22%). The severity of this histological damage was positively associated with TCMR-related transcripts, class II donor-specific antibodies (DSA), ALT and liver stiffness measurements (LSM), and negatively correlated with serum creatinine and tacrolimus trough levels. To assess for the presence of clinically-significant underlying alloimmunity, we stratified the study biopsies according to their TCMR transcript levels using a cut-off derived from liver biopsies with clinically-apparent TCMR. A risk prediction model including ALT and LSM had high discrimination in classifying patients with or without alloimmune damage. A simplified model was developed with classification and regression tree analysis (Figure). Another model with ALT and class II DSA respectively had also good discrimination. This latter model was externally validated in an independent cohort of 156 liver biopsies from pediatric LT recipients with similar

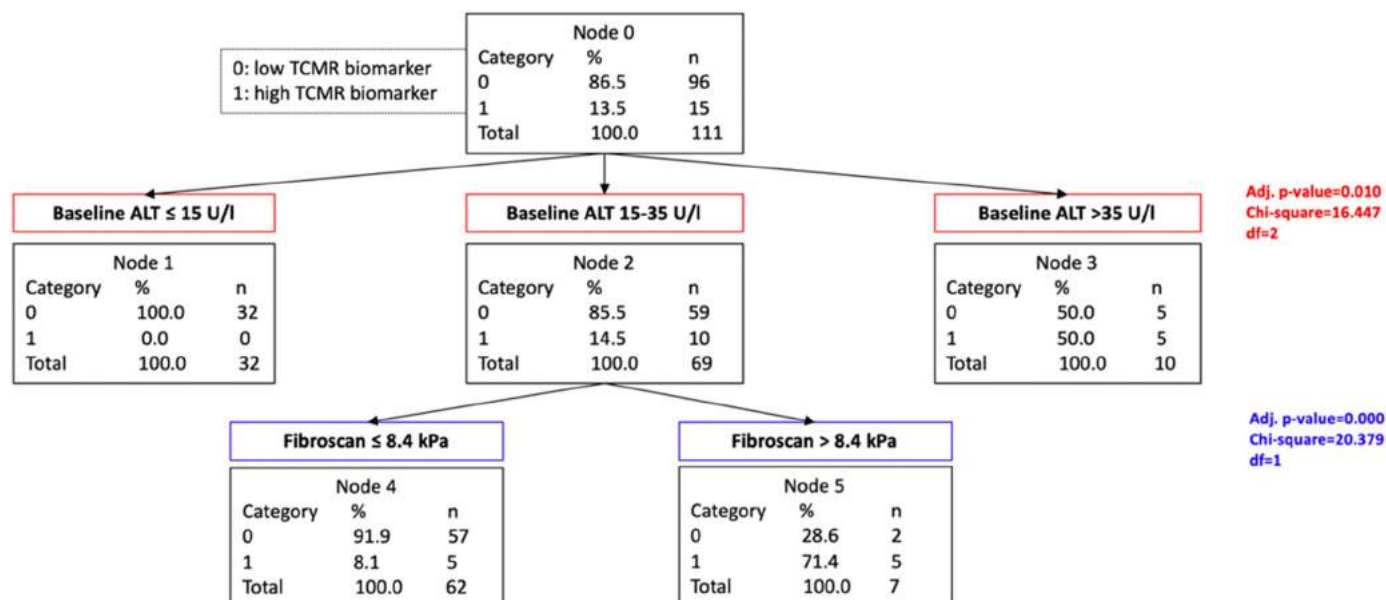


Figure: (abstract: OS-213)

inclusion/exclusion criteria (but without LSM), showing good discrimination (c-statistic 0.72) and excellent calibration.

Conclusion: ALT, class II DSA and LSM are valuable tools to non-invasively identify stable LT recipients without significant underlying alloimmunity, who could benefit from IS minimization.

OS-2792

HLA-A mismatching is associated with an increased risk of hepatic artery thrombosis, sepsis, graft loss and reduced survival following liver transplant

Christopher Bricogne¹, Neil Halliday^{1,2}, Raymond Fernando³, Emmanuel Tsochatzis^{1,2}, Mark Harber⁴, Rachel Westbrook¹. ¹Royal Free London NHS Foundation Trust, Sheila Sherlock Liver Unit, London, United Kingdom; ²University College London, Institute of Liver and Digestive Health, London, United Kingdom; ³Royal Free London NHS Foundation Trust, The Anthony Nolan Research Institute, London, United Kingdom; ⁴Royal Free London NHS Foundation Trust, Kidney Unit, London, United Kingdom

Email: christopher.bricogne@nhs.net

Background and aims: Human leukocyte antigen (HLA) mismatching has an adverse impact on heart, lung and kidney transplant outcomes, however the impact on liver transplant (LT) outcomes is uncertain. As no consistent benefit for HLA matching in LT has been observed it is not routinely performed. Due to this uncertainty, we analysed the impact of HLA mismatches upon LT outcomes.

Method: Historically, donors and recipients at our centre have undergone HLA-A, -B, -C, -DQ and -DR typing at the time of LT, but the results did not influence organ allocation or immunosuppression used. We identified 1165 transplants performed between October 1999 and December 2016 from the hospital transplant registry. 123 were excluded due to missing HLA data. We analysed the influence of mismatching at each HLA locus on graft and patient survival over time and on cause of graft loss.

Results: 1042 LT were included and followed up for a median of 9.16 years. Log rank analysis demonstrated that 1 or 2 HLA-A mismatches were associated with reduced graft (p = 0.004 and 0.012) and patient (p = 0.009 and 0.004) survival, although no consistent effect of mismatches at HLA-B, -C, -DR and -DQ were observed (see figure). One and two HLA-A mismatches were associated with hazard ratios for graft failure of 1.93 (p = 0.004) and 1.77 (p = 0.014), respectively, in

univariate and 1.90 (0.005) and 1.74 (p = 0.018) in multivariate Cox regression analyses. Specific HLA-A mismatches were associated with worse graft survival, including HLA-A2 (p = 0.014), HLA-A1 (p = 0.003) and HLA-A24 (p = 0.014), but no significant differences were seen with HLA-A3 and HLA-A11 mismatch.

Excess graft loss with HLA-A mismatched LT occurred in the 1st 12 months following transplantation; graft loss within 12 months was seen in 6/102 (5.9%) of HLA-A matched LT and 138/940 (14.7%) of those with HLA-A mismatches (OR 2.75, p = 0.015). Analysis of the causes of graft loss revealed that all graft losses due to hepatic arterial thrombosis (n = 31) and sepsis (n = 35) occurred in patients with HLA-A mismatches.

Conclusion: In this large cohort, with long follow up, donor-recipient HLA-A mismatching was associated with a significant reduction in graft and patient survival, and this may be specific to certain HLA-A alleles. We have demonstrated a significant association with the risk of hepatic arterial thrombosis and sepsis, suggesting HLA-A mismatching may influence the risk of these important complications.

Liver tumours: Clinical aspects except therapy

OS-498

Predicting the outcome of patients with hepatocellular carcinoma treated with immunotherapy-the CRAFTY score

Bernhard Scheiner^{1,2,3}, Katharina Pomej^{1,2}, Martha M. Kirstein^{4,5}, Florian Hucke⁶, Fabian Finkelmeier⁷, Oliver Waidmann⁷, Kornelius Schulze⁸, Sandra Koch⁹, Stephan Spahn¹⁰, Iuliana Pompilia Radu^{11,12}, Alexander Siebenhüner^{13,14}, Joachim C. Mertens¹⁵, Nuh N. Rahbari¹⁶, Fabian Kötting¹⁷, Dirk-Thomas Waldschmidt¹⁷, Matthias Ebert¹⁸, Andreas Teufel¹⁸, Sara De Dosso¹⁹, David J. Pinato^{20,21}, Tiziana Pressiani²², Tobias Meischl^{1,2}, Lorenz Balcar^{2,23}, Christian Müller^{1,2}, Thomas Reiberger^{1,3,24,25,26}, Michael Trauner¹, Nicola Personeni^{22,27}, Lorenza Rimassa^{22,27}, Michael Bitzer¹⁰, Jörg Trojan⁷, Arndt Weinmann⁹, Henning Wege⁸, Jean-François Dufour^{11,12}, Marko Peck-Radosavljevic⁶, Arndt Vogel⁴, Matthias Pinter¹. ¹Medical

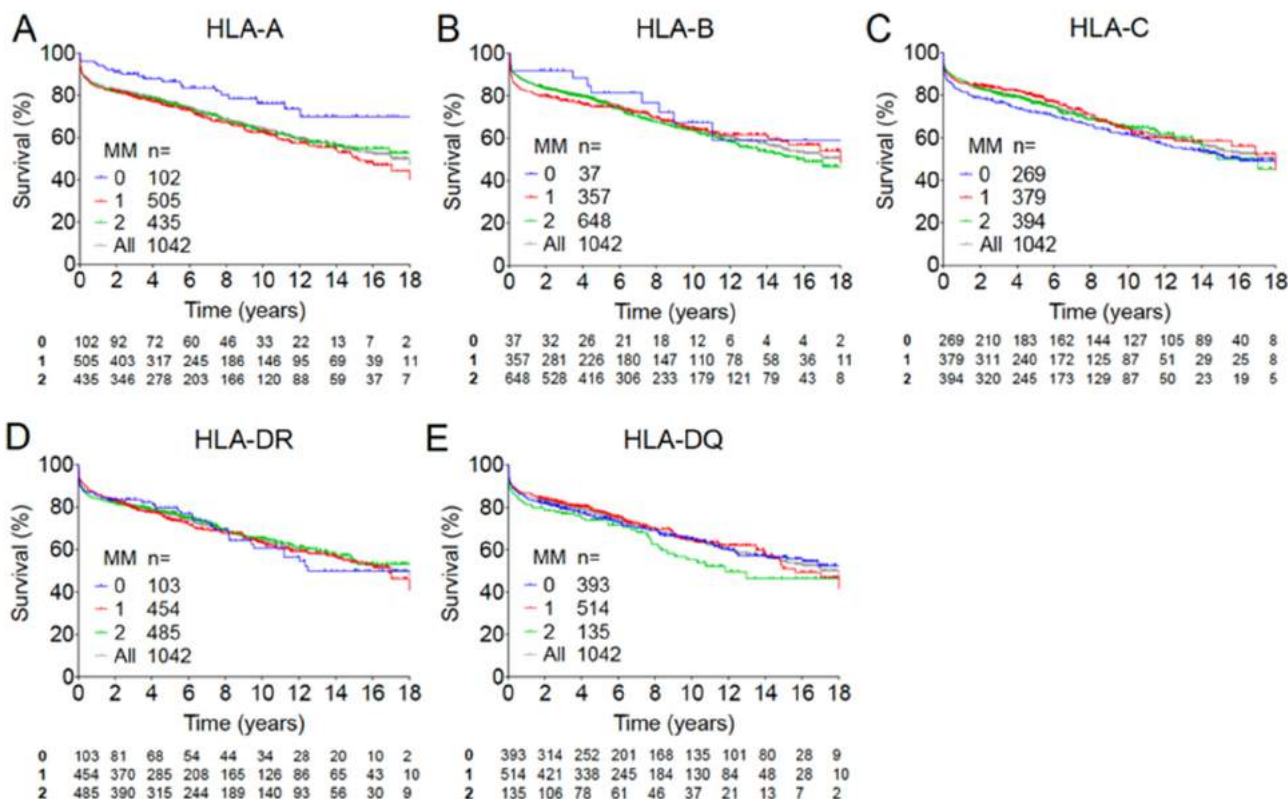


Figure: (abstract: OS-2792)

University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ²Medical University of Vienna, Liver Cancer (HCC) Study Group Vienna; ³Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Austria; ⁴Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Germany; ⁵University Medical Center Schleswig-Holstein, Department of Medicine I, Germany; ⁶Klinikum Klagenfurt am Wörthersee, Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology and Nephrology including Centralized Emergency Department (ZAE), Austria; ⁷University Hospital Frankfurt, Department of Gastroenterology, Hepatology and Endocrinology, Germany; ⁸University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Gastroenterology and Hepatology, Germany; ⁹University Medical Center of the Johannes Gutenberg University Mainz, Department of Internal Medicine I, Germany; ¹⁰Eberhard-Karls University, Tuebingen, Department Internal Medicine I, Germany; ¹¹University of Bern, Hepatology-Department of Biomedical Research, Switzerland; ¹²Inselspital, University of Bern, University Clinic for Visceral Surgery and Medicine, Switzerland; ¹³University Hospital Zurich and University Zurich, Department of Medical Oncology and Hematology, Switzerland; ¹⁴Cantonal Hospital Schaffhausen, Department of Medical Oncology and Hematology, Switzerland; ¹⁵University Hospital Zurich and University Zurich, Department of Hepatology and Gastroenterology, Switzerland; ¹⁶Medical Faculty Mannheim, Heidelberg University, Department of Surgery at University Hospital Mannheim, Germany; ¹⁷University of Cologne, Department of Gastroenterology and Hepatology, Germany; ¹⁸Medical Faculty Mannheim, Heidelberg University, Department of Medicine II, Germany; ¹⁹Faculty of Biomedical Sciences, Università della Svizzera italiana (USI), Lugano, Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ²⁰Imperial College London, Hammersmith Hospital, Department of Surgery and Cancer, Northern Ireland; ²¹Università degli Studi del Piemonte Orientale, Department of Translational Medicine, Italy;

²²Humanitas Cancer Center, Humanitas Clinical and Research Center-IRCCS, Medical Oncology and Hematology Unit, Italy; ²³Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²⁴Medical University of Vienna, Christian-Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Austria; ²⁵Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Austria; ²⁶CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Austria; ²⁷Humanitas University, Department of Biomedical Sciences, Italy
Email: matthias.pinter@meduniwien.ac.at

Background and aims: Immunotherapy with atezolizumab plus bevacizumab represents the new standard of care in systemic front-line treatment of hepatocellular carcinoma (HCC). Biomarkers to predict treatment success are an unmet need.

Method: Patients with HCC treated with PD- (L)1-based immunotherapy between July 2015 and May 2020 in 6 European centers (training set; n = 104) and between August 2015 and February 2020 in 7 European centers (validation set; n=73) were included. We investigated the prognostic value of baseline variables by using a Cox regression model in the training set and developed the CRAFTITY (CRP and AFP in ImmunoTherapy) score. The score was validated in the independent, external cohort.

Results: Baseline serum alpha-fetoprotein (AFP) \geq 200 ng/ml (HR, 2.0; p=0.009) and C-reactive protein (CRP) \geq 1 mg/dl (HR, 2.0; p=0.016) were identified as independent negative prognostic factors in multivariable analysis and were used to develop the CRAFTITY score. Patients who fulfilled none or only one criterion (0–1 point; CRAFTITY-low) had a significantly longer median overall survival (21.8 (95%CI, 13.4–30.2) months) than patients meeting both criteria (2 points; CRAFTITY-high; 5.3 (95%CI, 1.9–8.6) months; p < 0.001). Additionally, they had a significantly better disease control rate (70% vs. 32%; p = 0.001). These results were confirmed in the independent validation set (OS: 14.2 (95%CI, 9.7–18.7) months for CRAFTITY low (n = 52) vs. 8.6 (95%CI, 6.1–11.2) months for CRAFTITY high (n = 21, p = 0.011);

ORAL PRESENTATIONS

DCR: 75% in CRAFITY low patients compared to 41% in CRAFITY high patients ($p=0.013$) and remained significant irrespective of Child-Pugh stage and treatment line.

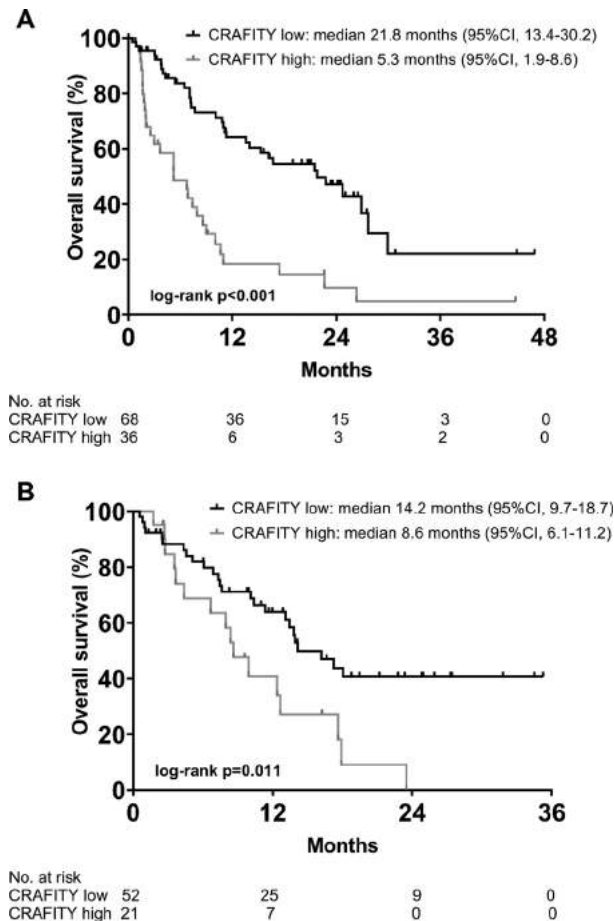


Figure: Kaplan-Meier curves comparing overall survival (OS) between patients with (A) CRAFITY low (0–1 point) versus high (2 points) in the training cohort and (B) according to CRAFITY low (0–1 point) versus high (2 points) in the validation cohort.

Conclusion: The CRAFITY score identifies patients with favorable disease control and survival. The score may help to guide treatment decisions and patient counseling.

OS-1101

Glucose variability and risk of hepatocellular carcinoma in diabetic patients: A nationwide population-based study

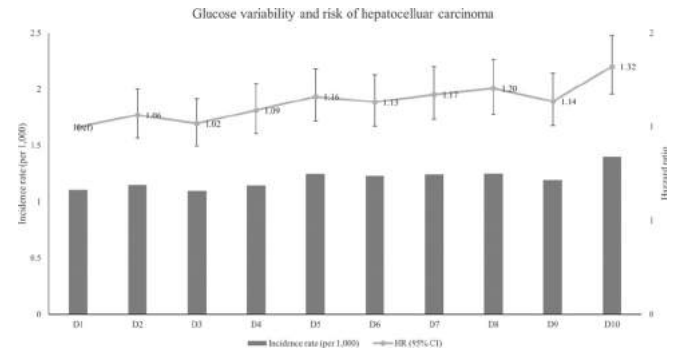
Jeong-Ju Yoo¹, Sang Gyune Kim¹, Young Seok Kim¹. ¹SoonChunHyang University School of Medicine, Internal Medicine, Bucheon, Korea, Rep. of South

Email: puby17@naver.com

Background and aims: Although diabetes is a well-known risk factor for hepatocellular carcinoma (HCC), exactly which metabolic parameters of diabetes are associated with HCC remains unexplored. In this study, we investigated the relationship between glucose variability (GV) and HCC in diabetic patients through a nationwide population-based study.

Method: A population-based cohort study including 674,178 diabetic subjects participating in more than 3 health examinations within 5 years from the index year (2009–2010) were followed until the end of 2017. The coefficient of variation, standard deviation, variability independent of the mean, and average real variability were calculated as GV indices.

Results: During a median follow-up of 6.7 years, there were 5,494 cases of HCC. When classified groups according to glucose level, the highest risk for HCC was observed when the basal blood glucose level was 180 mg/dL or greater [adjusted hazard ratio [aHR] 1.19, 95% confidence interval (CI), 1.08–1.31]. We observed increasing trends for the relationship between GV and HCC in multivariable Cox proportional analyses. The risk of HCC increased by 27% (aHR 1.27, 95% CI, 1.17–1.38) for the highest quartile of GV relative to the lowest quartile. These findings were consistent regardless of the presence of chronic viral hepatitis or cirrhosis, alcohol consumption, or body mass index.



Conclusion: GV is an independent predictor of HCC, even after adjusting for confounding factors. There was a linear relationship between increase in GV and prevalence of HCC. Visit-to-visit GV might be helpful for identifying diabetic patients at high risk of HCC.

OS-1704

Is alcohol only-related hepatocellular carcinoma so frequent? A cluster analysis of 12,841 hepatocellular carcinomas

Charlotte Costentin¹, Mélanie Minoves², Sylvain Kotski², Olivier Farges³, Nathalie Goutte⁴, Thomas Decaens¹, Sébastien Bailly². ¹Grenoble Alpes University Hospital, Hepatology, Gastro-Enterology and Digestive Oncology, Grenoble, France; ²HP2 Laboratory, INSERM U1042, Grenoble Alpes University, Grenoble, France; ³Beaujon Hospital, Hepato-Biliary Surgery Department, Clichy, France; ⁴Paul-Brousse Hospital, Assistance Publique-Hôpitaux de Paris Villejuif, Paris XI University, INSERM UMRS-1193, DHU Hépatinov and centre hépatobiliaire, Villejuif, France

Email: charlotte.costentin.pro@gmail.com

Background and aims: Alcohol-associated hepatocellular carcinoma (AL-HCC) poor prognosis has been mostly attributed to diagnosis at a later stage. However, host factors and specific health trajectories have been associated with severe outcomes in alcohol-associated liver disease. We hypothesize AL-HCC is not an homogeneous condition but encompasses subgroups yielding different outcomes. Our aim was to provide a first attempt at a clinical phenotyping of AL-HCC including host factors, comorbidities and the dynamic course of the underlying liver.

Method: We analyzed data for the calendar years 2007–2013 from the French nationwide administrative hospital database. We selected patients with HCC AL-HCC only, excluding patients with mixed etiologies. Clustering of AL-HCC phenotypes was performed by latent class analysis (LCA).

Results: The study included 12,841 patients with AL-HCC, mainly male (89%), median age 67 years [IQR: 61; 74] of which 68.3% had at least one metabolic comorbidity. Five phenotypes were identified. Only one seemed to be solely related to alcohol (phenotype 1) while others displayed high rates of metabolic comorbidities (diabetes in 40.3% to 53.3% of patients) with history of and/or current complicated underlying liver disease. Phenotype 1 represented only 13% of all AL-HCC and was the youngest group (median age 57 years [IQR: 52; 61]).

	Cluster 1 N=1 632 (12.8%)	Cluster 2 N=6 226 (48.5%)	Cluster 3 N=1 601 (12.5%)	Cluster 4 N=1 389 (10.8%)	Cluster 5 N=1 993 (15.5%)
Age at diagnosis	57	71	62	65	67
Diabetes	1.9	44.8	40.3	53.3	48.8
Arterial hypertension	1.8	65.4	39.8	53.5	61.9
Hist. Anemia	1.2	6.6	28.5	22.2	4
Hist. Ascite	3.4	1.3	85.5	5	11.7
Hist. Liver failure	3.1	1.3	53.8	17.1	7.1
Hist. Portal HT	8.5	2.5	84.3	100	6.5
Co. Ascite	18.1	8.5	78.7	14.4	82.6
Co. Liver failure	10.6	4.2	54.8	18.5	58
Co. Portal HT	18.4	10.6	62.9	77.8	57.8

Figure: (abstract: OS-1704)

In multivariable logistic regression, compared to phenotype 1, probability of death after HCC diagnosis was significantly different for all of the other four phenotypes.

Conclusion: LCA identified five phenotypes of AL-HCC associated with specific survival outcomes. Only one minority phenotype seemed to be solely related to alcohol. Our results provide new perspectives into determinants of HCC prognosis in the setting of alcohol-associated HCC.

OS-2686

International multicenter validation of GES score for HCC risk stratification in CHC patients

Gamal Shiha^{1,2}, Fabrice Carrat^{3,4}, Reham Soliman^{1,5}, Nabel Mikhaïl¹, Azzi Jessica³, Nathalie Ganne-Carrié⁶, Hidenori Toyoda⁷, Haruki Uojima⁸, Akito Nozaki⁹, Koichi Takaguchi¹⁰, Atsushi Hiraoka¹¹, Masanori Atsukawa¹², Hiroshi Abe¹³, Kentaro Matsuura¹⁴, Shigeru Mikami¹⁵, Tsunamasa Watanabe¹⁶, Tsuji Kunihiko¹⁷, Toru Ishikawa¹⁸, Vithika Suri¹⁹, Anu Osinusi¹⁹, Liyun Ni²⁰, JUN Zou²¹, Shiv Kumar Sarin²², Manoj Kumar²², Prasun Jalal²³, Manal Hassan²⁴, Sonia Alonso Lopez^{25,26}, Rafael Bañares^{25,26}, Adriana Ahumada²⁷, Mohamed Eslam²⁸. ¹Egyptian Liver Research Institute and Hospital, Mansoura, Egypt; ²Mansoura University, Faculty of Medicine, Gastroenterology and Hepatology Unit, Mansoura, Egypt; ³Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France; ⁴AP-HP, Sorbonne Université, Hôpital Saint-Antoine, Santé Publique, Paris, France; ⁵Port Said University, Faculty of Medicine, Tropical Medicine, Port Said, Egypt; ⁶Inserm, UMR-1138 « Functional Genomics of solid tumors », Centre de Recherche des Cordeliers, Université de Paris, France, Paris, France; ⁷Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan; ⁸Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Sagami-hara, Japan; ⁹Gastroenterology Center, Yokohama City University Medical Center, Yokohama, Japan; ¹⁰Department of Hepatology, Kagawa Prefectural Central Hospital, Takamatsu, Japan; ¹¹Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan; ¹²Department of Internal Medicine, Division of Gastroenterology and Hepatology, Nippon Medical School, Tokyo, Japan; ¹³Shinmatusdo Central General Hospital, Matsudo, Japan; ¹⁴Nagoya City University, Graduate School of Medical Sciences, Virology and Liver Unit, Nagoya, Japan; ¹⁵smikami@mail.kikkoman.co.jp, Gastroenterology; ¹⁶St. Marianna University School of Medicine, Internal Medicine, Kawasaki, Japan; ¹⁷Teine Keijinkai Hospital, Gastroenterology, Sapporo, Japan; ¹⁸Saiseikai Niigata Hospital, Niigata, Japan; ¹⁹United States, Gilead Sciences, Inc, Foster City, California, United States; ²⁰Gilead Sciences, Inc, Foster City, California; ²¹Gilead Sciences, Inc, Foster City, California, United States; ²²Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India; ²³Division of Abdominal Transplantation Baylor College of Medicine, ²⁴Division of Cancer Prevention and Population Sciences, MD Anderson, Epidemiology, United States; ²⁵Liver Unit, Hospital General Universitario Gregorio Marañón, Instituto De Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain;

²⁶Centro de Investigación Biomédica En Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; ²⁷Hospital General Universitario Gregorio Marañón, Madrid, Spain; ²⁸Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia
Email: g_shiha@hotmail.com

Background and aims: We recently reported the ability of our novel simple predictive model (GES) score for the development of hepatocellular carcinoma (HCC) after direct-acting antivirals (DAAs) [1]. However, our results were restricted to Egyptian patients with HCV-genotype 4. To evaluate the predictive accuracy of our score in mixed populations with various HCV genotypes we aimed at validating our early findings in an independent large sample of multi-ethnic population through our international collaborative activity.

Method: GES score can identify three patients' categories; low risk of HCC ($\leq 6/12.5$), intermediate risk ($>6-7.5/12.5$), and high risk ($>7.5/12.5$) using readily available predictors and thus can be easily calculated in clinical practice, namely, age >54 yrs., male gender, albumin <3.8 , AFP levels >20 ng/ml and fibrosis stage at baseline. We included 11202 patients with chronic HCV from 54 centers from the following countries (France; Japan; India; USA; and Spain). Additional 836 patients were included from Gilead-sponsored RCT cohort from USA, Europe, Canada, and Australia. Total of 12038 chronic HCV patients were analyzed in this study. Descriptive statistics and survival analysis were performed using Kaplan-Meier and Log-rank test. The performance of the GES score was evaluated using Harrell's C-index (HCI).

Results: GES score displayed significant prediction for HCC development in all participants ($p < .0001$), with Harrel C Index range from 0.55 to 0.76 among all cohorts after adjusting for HCV genotyping and ethnicity. GES score was able to stratify all patients successfully into three risk groups, low, intermediate, and high groups (Table 1).

Table 1: GES Risk Scarification by participating site (Validation Assessment)

Countries	N	Low risk	Intermediate risk	High risk	P value	Harrell's C statistic
France	7752	1.23%/5 years	7.39%/5 years	17.69%/5 years	<0.001	0.7688
Japan	2231	2.31%/3 years	4.08%/3 years	6.68%/3 years	<0.001	0.622
India	662	1.50%/5 years	3.06%/5 years	6.35%/5 years	<0.001	0.643
USA	276	1.07%/5 years	0.91%/5 years	5.17%/5 years	0.046	0.666
Spain	181	0.51%/4 years	1.14%/4 years	1.56%/4 years	0.509	0.615
RCT (Gilead)	836	7.46%/3 years	5.88%/3 years	19.61%/3 years	0.0055	0.55
Total	12038					

ORAL PRESENTATIONS

Conclusion: GES score can be used to stratify HCV patients into three HCC risk categories; low, intermediate, and high irrespective of ethnicities or HCV genotypes. This international multicenter validation of a simple, easy to use score based on readily available parameters may pave the way to its use in individualized HCC-risk based surveillance.

References

1. Shiha G, Waked I, Soliman R, *et al.* GES: A validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals. *Liver Int.* 2020;40:2828–2833.

Liver tumours – Experimental and pathophysiology

OS-179

MicroRNA-27a-3p modulates FoxO1 to induce tumor-like phenotypes in CCA

Patricia Munoz-Garrido¹, Lea Duwe¹, Letizia Satriano¹, Monika Lewinska¹, Juan Lafuente-Barquero¹, Dan Høgdall^{1,2}, Awaisa Ghazal¹, Matthias Matter³, Jesus Maria Banales⁴, Colm O. Rourke¹, Jens Marquardt⁵, Jesper Andersen¹. ¹Biotech Research and Innovation Centre (BRIC), Health Science Faculty, University of Copenhagen, Copenhagen, Denmark; ²Herlev and Gentofte Hospital, Copenhagen University Hospital, Department of Oncology, Denmark; ³University Hospital of Basel, Institute of Medical Genetics and Pathology, Basel, Switzerland; ⁴Biodonostia Health Research Institute, Department of Liver Diseases, CIBERehd, Ikerbasque, San Sebastian, Spain; ⁵Johannes Gutenberg University, Department of Medicine I, Lichtenberg Research Group, Mainz, Germany
Email: lea.duwe@bric.ku.dk

Background and aims: Cholangiocarcinoma (CCA) is a clinically and molecularly heterogeneous disease. The ability of microRNAs (miRs) to target multiple signaling pathways links them to tumor heterogeneity. Here, we analyzed the miR landscape in normal livers and tumors in the biliary tree to define their role in orchestrating gene regulation and involvement in CCA development.

Method: We performed miR sequencing (miRseq) of 213 human samples (99 iCCAs, 28 eCCAs, 63 matched adjacent livers and 23 normal livers), including the matched transcriptomes from 196 samples, to study miRs and regulation of target genes in CCA. High throughput screening (HTS) using a library of 2,700 miR mimics was analyzed for their proliferative role in 3 primary normal human cholangiocyte (NHC) cultures. After miRseq-HTS data integration, we performed target prediction and pathway overrepresentation analyses. The main target was confirmed by luciferase reporter assay and characterized by qPCR, immunoblotting and *in situ* hybridization (ISH) in tissue microarrays. To identify the biological role, we generated miR-CRISPR knockout (KO) lines and performed proliferation and wound-healing assays. The oncogenic phenotype *in vivo* was assessed by xenograft experiments in mice.

Results: MiRseq revealed 398 differentially expressed miRs (388 upregulated, 10 downregulated) in CCA compared to controls. Unsupervised hierarchical clustering identified three subgroups, differing significantly based on tumor location, overall survival, tumor microenvironment (i.e., macrophage, hepatic stellate and endothelial cell content) and immune infiltrates (dendritic cells, CD4+ and CD8+ T cells). In HTS, overexpression of 224 miRs increased the NHC proliferation rate, of which 35 miRs were upregulated in CCA. Pathway overrepresentation analysis showed FoxO signaling as the major affected pathway. Further, miR-27a-3p and FoxO1 interaction revealed a strong negative correlation in the CCA cohort, which was independently validated in TCGA-CHOL. This interaction was confirmed *in vitro* by luciferase reporter assay. ISH showed that miR-27a-

3p is highly expressed in tumor cells and vascular smooth muscle. MiR-27a-3p KO CCA cells showed decreased proliferation and migration, highlighting miR-27a-3p as an oncogenic vulnerability in CCA.

Conclusion: MiRs are highly deregulated in CCA. MiR-27a-3p seems to promote CCA, targeting FoxO1 and deregulating FoxO signaling, thus inducing tumor phenotypes.

OS-615

Identification of IGF2 as genomic driver and actionable therapeutic target in hepatoblastoma

Laura Torrens^{1,2}, Jordi Abril-Fornaguera², Juan Carrillo³, Ugne Balaseviciute², Alex Rialdi¹, Philipp Haber¹, Carla Montironi^{1,2}, Nicholas Akers^{1,4}, Catherine E. Willoughby², Miguel Torres-Martín^{1,2}, Marc Puigvehí^{1,5}, Roser Pinyol², Laura Royo³, Montserrat Domingo-Sabat³, del Rio Alvaro³, Stefano Cairo⁶, Marie-annick Buendia⁷, Vincenzo Mazzaferro⁸, Bojan Losic^{1,4}, Ernesto Guccione¹, Daniela Sia¹, Carolina Armengol^{3,9,10}, Josep M. Llovet^{1,2,11}. ¹Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States; ²Translational Research in Hepatic Oncology, Liver Unit, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)-Hospital Clínic, Universitat de Barcelona, Barcelona, Spain; ³Childhood Liver Oncology Group (c-LOG), Health Sciences Research Institute Germans Trias i Pujol (IGTP), Badalona, Spain; ⁴Department of Genetics and Genomic Sciences, The Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, United States; ⁵Hepatology Section, Gastroenterology Department, Parc de Salut Mar, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; ⁶XenTech, Evry, France; ⁷Centre Hepatobiliaire Paul Brousse, Villejuif, France; ⁸Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ⁹CIBERehd, Barcelona, Spain; ¹⁰Program for Predictive and Personalized Medicine of Cancer (PMPPC), IGTP, Badalona, Spain; ¹¹Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain
Email: jmllovet@clinic.cat

Background and aims: Hepatoblastoma (HB), the most frequent pediatric liver cancer, has limited therapeutic options for patients whose tumors are refractory to standard perioperative platin-based regimens, commonly cisplatin. Here, we aimed to identify actionable targets in human HB and assess their response to molecular therapies in experimental models.

Method: Tumor and paired non-tumor (NT) tissues from 32 HB patients were analyzed at the transcriptomic, genomic and epigenomic level using RNAseq, SNP and methylation arrays. The main targetable driver in HB was identified by gene co-expression network analysis (GCN) and its overexpression was confirmed by qRT-PCR. The antitumor potential of inhibiting actionable drivers was assessed *in vitro* (cell lines and PDX-derived organoid model) and *in vivo*.

Results: RNAseq and GCN identified IGF signaling as the top targetable deregulated pathway in HB, and IGF2 was overexpressed in 71% of samples (fold change >4 vs NT), whereas CTNNB1 was the most prevalent non-actionable mutation (~70%). IGF2-high tumors were enriched in progenitor and proliferative gene signatures and CTNNB1 mutations, while IGF2-low tumors were enriched in inflammatory signaling and TGF-beta overexpression. IGF2-high tumors correlated with shorter recurrence-free survival after resection (median 34 months vs not reached for IGF2-low; p = 0.02). Overall, we identified a mechanism of IGF2 overexpression in 86% of IGF2-high tumors: a) overexpression of the fetal IGF2 isoform due to promoter hypomethylation (50%), b) loss of heterozygosity (LOH) in the 11p15 chromosomal region containing IGF2 (57%) and c) overexpression of miR483 (55%), an enhancer of IGF2 transcription. Xentuzumab, a monoclonal antibody against IGF2, significantly reduced proliferation and clonogenic capacity in IGF2-high HB cell lines, whereas in combination with cisplatin in an IGF2-high organoid model was able to increase cisplatin efficacy by 25-fold

and promote apoptosis. *In vivo*, xentuzumab + cisplatin reduced viable tumor volume and extended time to sacrifice (1500 mm³) compared to cisplatin alone (p = 0.04).

Conclusion: IGF2 overexpression associated with promoter hypomethylation, LOH and miR483 overexpression is the main actionable alteration in human HB. In experimental models, IGF2 inhibition with xentuzumab + cisplatin led to a remarkable antitumoral effect, thus providing the rationale for exploring this combination in early trials in patients with IGF2-high HB.

OS-699

Immune classification of hepatocellular carcinoma based on new molecular features: the inflamed class

Carla Montironi^{1,2}, Florian Castet¹, Philipp Haber³, Roser Pinyol¹, Miguel Torres-Martin¹, Agavni Mesropian¹, Huan Wang⁴, Marc Puigvehí^{3,5}, Miho Maeda³, Wei Qiang Leow^{3,6}, Elizabeth Harrod^{3,7,8}, Patricia Taik⁴, Jigjidsuren Chinburen⁹, Erdenebileg Taivanbaatar⁹, Chinbold Enkhbold⁹, Michael Donovan³, Swan N. Thung³, Jaclyn Neely¹⁰, Vincenzo Mazzaferro¹¹, Jeff Anderson¹⁰, Sasan Roayaie¹², Myron Schwartz³, Augusto Villanueva³, Scott Friedman³, Andrew Uzilov^{4,13}, Daniela Sia³, Josep M. Llovet^{1,3,14}. ¹Translational Research in Hepatic Oncology, Liver Unit, Institut D'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)-Hospital Clínic, Universitat de Barcelona, Catalonia, Spain; ²Pathology Department, Hospital Clínic de Barcelona, Barcelona, Catalonia, Spain; ³Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA; ⁴Sema4, Stamford, Connecticut, USA; ⁵Hepatology Section, Gastroenterology Department, Parc de Salut Mar, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Catalonia, Spain; ⁶Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore, National University Hospital; ⁷Royal Surrey County Hospital, Guildford, UK; ⁸University of Surrey, Guildford, UK; ⁹National Cancer Center, Ulaanbaatar, Mongolia; ¹⁰Bristol-Myers Squibb, Princeton, New Jersey, USA; ¹¹National Tumor Institute, Milan; ¹²Department of Surgery, White Plains Hospital, White Plains, New York, USA; ¹³Department of Genetics and Genomic Sciences and Icahn

Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, USA; ¹⁴Institució Catalana De Recerca i Estudis Avançats, Barcelona, Catalonia, Spain
Email: josep.llovet@mssm.edu

Background and aims: Oncogenic mechanisms shape inflamed/non-inflamed microenvironments associated with immune response or immune evasion/resistance, respectively. We aimed to further refine the immune profiles of hepatocellular carcinoma (HCC) by assessing novel molecular features.

Method: We assessed the presence of immune infiltration, performed multiplex immuno-phenotyping for checkpoint molecules, TCR sequencing, RNA and whole-exome sequencing in a new cohort of 240 HCCs balanced according to etiology.

Results: We further characterized the previously described Immune class of HCC (22% of the cohort) (Sia et al. Gastroenterology 2017), which presented higher immune infiltration (52 vs 32%, p=0.05), higher expression of checkpoint molecules (CTLA-4: 58 vs. 29%, p = 0.03; PD-L1: 31 vs 4%, p=0.047) and a more diverse T cell repertoire when compared with the non-inflamed profiles. We identified an Immune-like class (15% of the cohort), that similarly presented high immune infiltration, interferon signaling, cytolytic activity and effector cytokine expression (Figure), but with more CTNNB1 mutations (64 vs 20%, p=0.003) and Wnt-beta catenin activation (54 vs 3%, p<0.001). In order to group all the immune-related subtypes (including active, exhausted and immune-like) in the newly defined inflamed class, we generated a 20-gene signature able to capture >90% of these tumors. In parallel, we characterized the non-inflamed Intermediate and Excluded classes. The Intermediate class was enriched in TP53 mutations (49 vs 29%, p = 0.035), higher broad chromosomal aberrations and deletions in subcytobands harboring immune-related genes (i.e 4q21.1: CXCL9, CXCL10, CXCL11). The Excluded class defined by Wnt-beta catenin activation was enriched in CTNNB1 mutations (93 vs rest 27%, p < 0.001). These Excluded-CTNNB1 mutations induced very high activation of Wnt signaling and were significantly distinct from the immune CTNNB1 mutations that induced weak activation of this cascade. In addition,

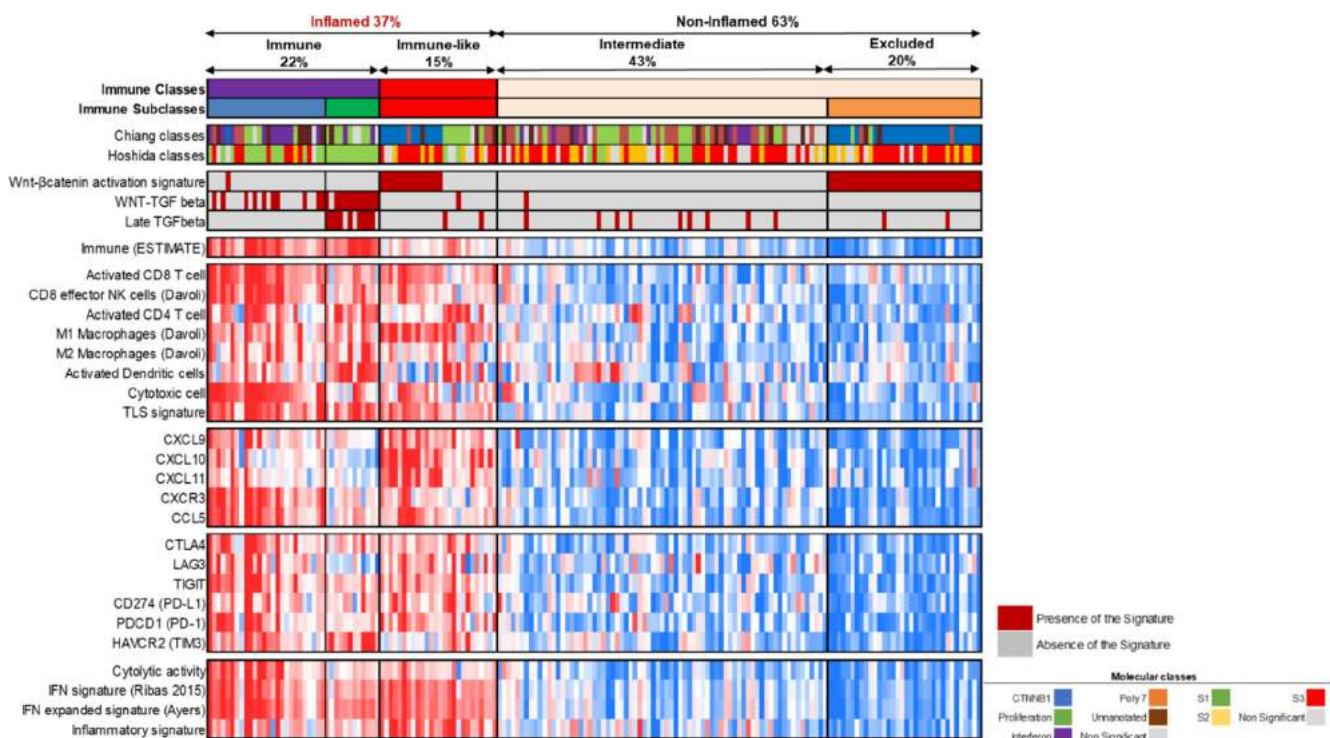


Figure: (abstract: OS-699)

ORAL PRESENTATIONS

tumors with inflamed-*CTNNB1* mutations were associated to over-expression/demethylation of type I antigen presentation genes.

Conclusion: We have defined an inflamed HCC class involving ~35% of tumors and characterized the non-inflamed tumors. In addition, two distinct *CTNNB1* mutation patterns associated with differential pathway activation might explain the role of this oncogene in immune evasion. These features may help to predict response/resistance to immunotherapy in HCC.

OS-906

Molecular plasticity underlies cisplatin resistance and tumor recurrence in hepatoblastoma

Theo Hirsch¹, Jill Pilet¹, Guillaume Morcrette^{1,2}, Amélie Roehrig¹, Benedict Monteiro¹, Laura Molina¹, Quentin Bayard¹, Eric Trépo¹, Lea Meunier¹, Stefano Caruso¹, Victor Renault³, Jean-François Deleuze³, Brice Fresneau⁴, Christophe Chardot⁵, Emmanuel Gonzales⁶, Emmanuel Jacquemin⁶, Florent Guerin⁶, Monique Fabre^{5,7}, Isabelle Aerts⁸, Sophie Taque⁹, Véronique Laithier¹⁰, Sophie Branchereau⁶, Catherine Guettier⁶, Laurence Brugières⁴, Sandra Rebouissou¹, Eric Letouze¹, Jessica Zucman-Rossi¹. ¹Centre de Recherche des Cordeliers, INSERM, Paris, France; ²Hôpital Robert Debré, Paris, France; ³Foundation Jean Dausset, Paris, France; ⁴Gustave Roussy, Villejuif, France; ⁵Hôpital Necker, Paris, France; ⁶Bicêtre Hospital AP-HP, Le Kremlin-Bicêtre, France; ⁷University Hospital Necker Enfants Malades, Department of Pathology, Paris, France; ⁸Institut Curie Hospital, Paris, France; ⁹CHU Fontenoy, Rennes, France; ¹⁰Centre hospitalier régional universitaire de Besançon, Besançon, France
Email: theo.hirsch@polytechnique.org

Background and aims: Hepatoblastomas, the most frequent pediatric liver cancers, are characterized by high histological heterogeneity. Cisplatin-based neo-adjuvant chemotherapy and surgery lead to

>80% long-term survival, however resistance to chemotherapy can occur during the initial treatment or after tumor recurrence, and the molecular determinants of cisplatin resistance are yet to be discovered.

Method: We performed an integrated genomic analysis of 104 hepatoblastoma samples from 65 patients, including 24 patients with multiple samples (pre/post-chemotherapy primary tumors, relapses and metastases), through whole-genome or whole-exome sequencing, RNAseq and methylation analysis. We screened 8 hepatoblastoma cell lines to identify new therapeutic targets and tested one drug in mouse xenograft experiments.

Results: Most hepatoblastomas share driver alterations of *CTNNB1* and the 11p15.5 imprinted locus, but we also identified rare recurrent driver mechanisms, including new targetable genes. Transcriptomic and methylation analysis of spatial and longitudinal heterogeneity showed an important plasticity between 'Hepatocytic', 'Liver Progenitor' and 'Mesenchymal' molecular subgroups. Mutational signature analysis revealed that 'Liver Progenitor' cells specifically accumulate massive loads of cisplatin-induced mutations during chemotherapy, and can later give rise to heavily mutated relapses and metastases (Figure). Among genes overexpressed in 'Liver Progenitor' hepatoblastomas, we selected 3 key targetable genes (*PLK1*, *CHEK1* and *BIRC5*) and showed that hepatoblastoma cell lines are sensitive to their inhibitors even though most are resistant to cisplatin. Finally, we performed mouse xenograft experiments as a proof of concept and showed that the *PLK1* inhibitor BI-2536 can reduce tumor growth *in vivo* compared to cisplatin treatment.

Conclusion: Hepatoblastomas are deadly when they resist to chemotherapy, with limited alternative treatment options. Here, we identified the cellular phenotype at the origin of cisplatin resistance and validated new treatments targeting these molecular features in cell lines and xenografts.

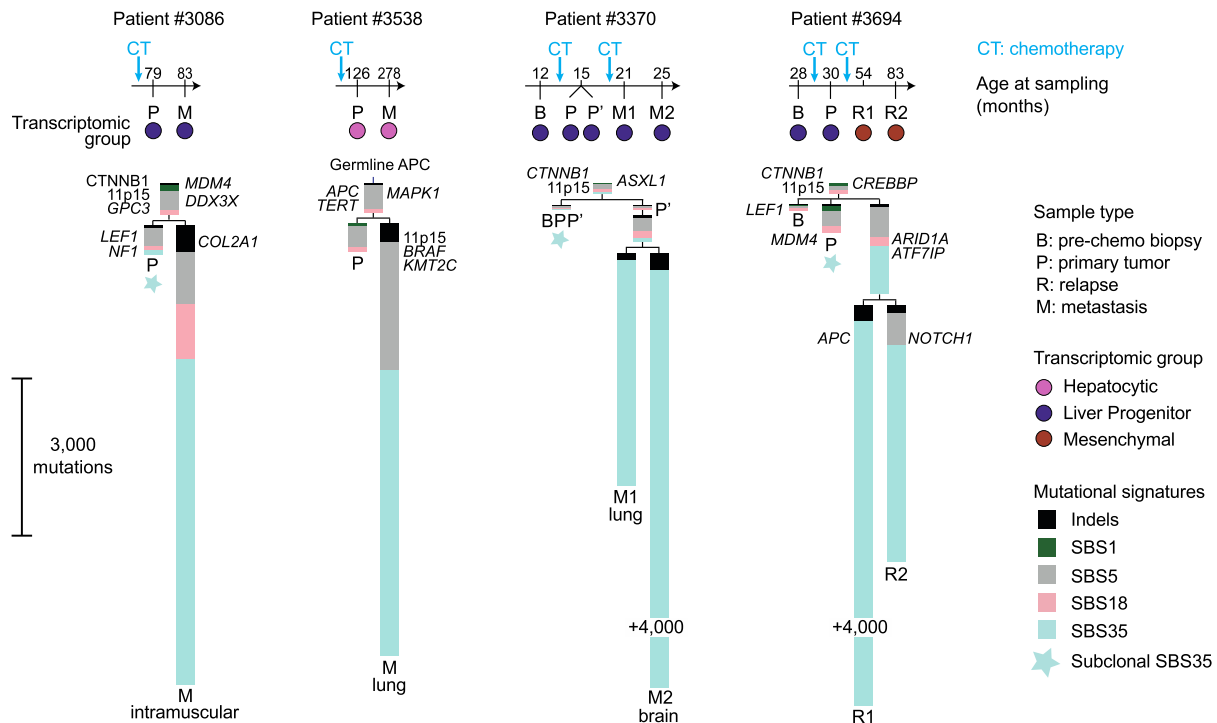
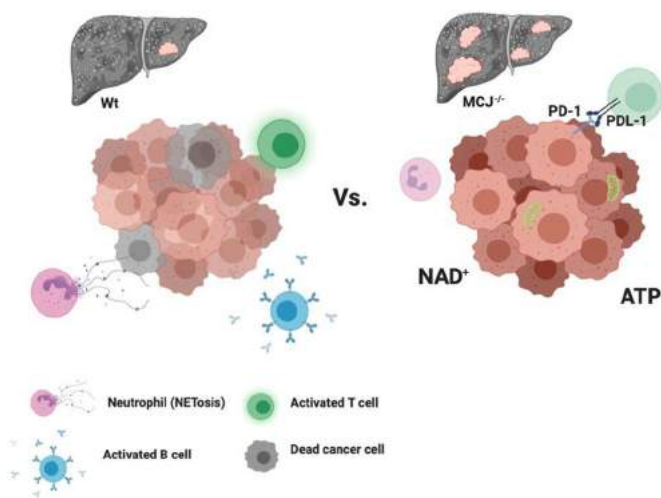


Figure: (abstract: OS-906): Phylogenetic trees reconstructed for 4 patients with primary and recurrent hepatoblastoma analyzed by whole genome sequencing. Driver alterations are indicated. Branch lengths are proportional to the number of clonal mutations, with a color code indicating the contribution of each mutational signature. The cisplatin-related SBS35 signature is already present subclonally in primary tumors with 'Liver Progenitor' phenotype, and SBS35 clonal mutations accumulate in relapse/metastasis.

OS-1948

Metabolic rewiring by increased mitochondrial respiration drives immune evasion in liver cancer

Naroa Goikoetxea-Usandizaga¹, Leire Egia-Mendikute², Marina Serrano-Macia¹, Teresa Cardoso Delgado¹, Iraia Ladero³, Elena Molina³, Sofia Lachiondo-Ortega¹, Rubén Rodríguez Agudo¹, Janire Castelo⁴, Diego Barriales⁴, Begoña Rodríguez Iruretagoyena¹, Silvia Marin^{5,6}, Eva Santamaria⁷, Miren Bravo¹, Maria Mercado-Gómez¹, Irene González-Recio¹, Jorge Simón Espinosa¹, Mercedes Rincón⁸, Matías A. Avila^{7,9}, Marta Cascante^{5,6}, Juan Anguita⁴, Natalia Elguezabal³, Asís Palazón², María Luz Martínez-Chantar¹. ¹Centre for Cooperative Research in Biosciences CIC bioGUNE, Basque Research and Technology Alliance, Liver Disease Lab, Derio, BI, Spain; ²Centre for Cooperative Research in Biosciences CIC bioGUNE, Basque Research and Technology Alliance, Cancer Immunology and Immunotherapy Lab, Derio, BI, Spain; ³NEIKER-Instituto Vasco de Investigación y Desarrollo Agrario, Animal Health Department, Derio, Spain; ⁴Centre for Cooperative Research in Biosciences CIC bioGUNE, Basque Research and Technology Alliance, Inflammation and Macrophage Plasticity Lab, Derio, Spain; ⁵Faculty of Biology, Universitat de Barcelona, Department of Biochemistry and Molecular Biomedicine, Barcelona, Spain; ⁶Instituto de Salud Carlos III, CIBEREHD and Metabolomics Node at INB-Bioinformatics Platform, Madrid, Spain; ⁷CIBEREHD and Instituto de Investigaciones Sanitarias de Navarra-IdiSNA; ⁸University of Vermont, Department of Medicine, Immunobiology Division; ⁹Cima-University of Navarra, Hepatology Program
Email: mlmartinez@cicbiogune.es



Conclusion: Reduced MCJ levels, also visible in HCC patients, increase oxidative respiration and drive a metabolic reprogramming that enables immune evasion, through PD-1/PDL-1 axis. As elevated NAD⁺ and PDL-1 are known to increase sensitivity to anti-PDL-1 treatment, tumor MCJ expression may serve as a predictive biomarker for HCC immunotherapy efficacy.

Background and aims: Recent evidence supporting the need of a mitochondria-based metabolism for tumor growth prompted us to study the role of MCJ, an endogenous negative regulator of mitochondrial complex I, in the context of hepatocellular carcinoma (HCC). The tumor microenvironment imposes various metabolic regulations to hamper the antitumor immunity of infiltrating immune cells, therefore, modulating the metabolic rewiring may help recover the antitumor immune potential. This work aims to study the metabolic reprogramming of cancer cells at different stages, to prove increased malignancy in mitochondria-based tumors, and to analyze the differential immune response driven by metabolic changes.

Method: Wt and *Mcj*^{-/-} mice were injected intraperitoneally with 25 mg/kg body weight of diethylnitrosamine (DENA) at 14 days of age and they were monthly monitored, tumor growth was followed by ultrasound analysis and blood samples were extracted. DENA-treated mice, and the corresponding controls, were sacrificed at 5, 8, and 12 months post injection (a minimum of 5 mice per group). Mortality, tumor number and size, liver metabolism, mitochondrial activity and tumor infiltrating immune cell analysis were then assessed.

Results: The initial *in silico* approach using UALCAN revealed reduced *Mcj* expression in stage IV HCC patients. *In vivo*, lack of MCJ increased both the presence of liver tumors and mortality rate after DENA treatment. Fluxomics analysis using [¹³C]glucose or [¹³C]glutamine will provide information about the metabolic reprogramming during tumorigenesis. A highly oxidative phenotype was confirmed in *Mcj*^{-/-} tumors, as mitochondrial respiration was significantly higher, along with elevated intracellular ATP, NAD⁺ and NADPH levels. We then studied tumor infiltrating immune cells, observing a reduction in effector CD4⁺ T lymphocytes (CD44⁺ CD62L⁻) and neutrophils (GRI1⁺CD11b⁺) in *Mcj*^{-/-} mice 5 months after DENA injection; similar results were also visible at 12 months, including significantly reduced PD-1. Analysis of PDL-1 revealed significantly increased hepatic protein levels in *Mcj*^{-/-} mice, hinting a possible immune evasion. Serum analysis of cytokines highlighted reduced levels of inflammatory IFN-γ and TNF in *Mcj*^{-/-} mice. Besides, highly ROS producing neutrophils were found in DENA-treated Wt mice. Analysis of hepatic cytokines showed increased levels of MCP-1 in Wt mice, a chemoattractant and NETosis facilitator.

Liver tumours – Therapy

OS-295

Checkmate 040 Cohort 5: long-term efficacy and safety of nivolumab in patients with Child-Pugh B advanced hepatocellular carcinoma: associations between baseline biomarker analyses and outcomes

Ana Matilla¹, Bruno Sangro², Anthony El-Khoureiry³, Armando Santoro⁴, Ignacio Melero², Antonio Cubillo Gracian⁵, Mirelis Acosta Rivera⁶, Su-Pin Choo⁷, Ryoko Kuromatsu⁸, Bassel El-Rayes⁹, Kazushi Numata¹⁰, Yoshito Itoh¹¹, Francesco Di Costanzo¹², Oxana Crysler¹³, María Reig¹⁴, Yun Shen¹⁵, Jin Yao¹⁵, Jaclyn Neely¹⁵, Marina Tschaike¹⁵, Masatoshi Kudo¹⁶. ¹Gregorio Marañón Hospital, Madrid, Spain; ²Clinica Universidad de Navarra, Pamplona, Spain; ³USC Norris Comprehensive Cancer Center, Los Angeles, United States; ⁴Humanitas Research Hospital, Rozzano, Italy; ⁵Comprehensive Cancer Center CLARA CAMPAL, Madrid, Spain; ⁶San Juan, Puerto Rico; ⁷Singapore; ⁸Kurume University Hospital, Kurume, Japan; ⁹Winship Cancer Institute of Emory University, Atlanta, United States; ¹⁰Yokohama City University Medical Center, 横浜市, Japan; ¹¹Kyoto Prefectural University of Medicine Hirokoji Campus, Kyoto, Japan; ¹²AOU Careggi, Florence, Italy; ¹³University of Michigan Health System, Ann Arbor, United States; ¹⁴Hospital Clínic de Barcelona, Barcelona, Spain; ¹⁵Bristol Myers Squibb, Lawrence Township, United States; ¹⁶Kindai University, Higashiosaka, Japan
Email: anamatillapena@gmail.com

Background and aims: Patients with Child-Pugh B (CPB) advanced hepatocellular carcinoma (aHCC) have a poor prognosis and are often excluded from clinical trials. In sorafenib-treated patients with CPB, overall survival (OS) is as low as ~4 months. Nivolumab received accelerated approval in the United States for sorafenib-treated patients with aHCC based on the phase 1/2 open-label CheckMate 040 trial (NCT01658878). In patients with CPB (cohort 5), at a median follow-up of 16.3 months, investigator-assessed objective response rate (ORR) was 12%; median OS was 7.6 months (95% CI 4.4–10.5). We report long-term efficacy and safety and new biomarker analyses for

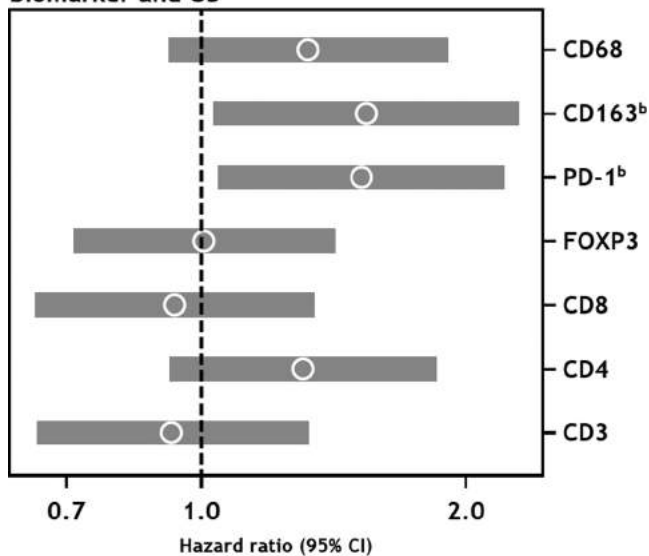
ORAL PRESENTATIONS

this CPB cohort, the first prospective immunotherapy trial in this population.

Method: Patients with CPB 7 or 8 aHCC (sorafenib naive n=25; sorafenib treated n=24) received nivolumab 240 mg intravenously for 30 minutes every 2 weeks until disease progression or unacceptable toxicity. OS was a secondary end point. Baseline tumor samples were assessed for inflammation biomarkers by immunohistochemistry (including CD3, CD4, CD8, PD-1, FOXP3, CD68, CD163). Neutrophil:lymphocyte ratio (NLR) and albumin-bilirubin (ALBI) score were derived from laboratory assessments. Associations between biomarkers and best overall response (BOR), OS, and viral etiology were evaluated. Multivariate analysis was done for each biomarker separately and estimated HR determined for 1 standard deviation difference of each biomarker.

Results: At a minimum follow-up of 33.8 months, median OS was 7.9 months (95% CI 4.4–10.5) for all treated patients; 8.9 months (4.1–13.4) and 7.4 months (1.6–10.5), respectively, in CPB subgroups B7 (n=37) and B8 (n=11); and 8.4 months (4.4–13.3) and 1.6 months (1.4–10.5), respectively, for ALBI score 2 (n=44) and 3 (n=5). 12-month OS rate was 34.7%, and 24-month OS rate was 10.2%. Lower tumor expression of PD-1 and CD163 was associated with longer OS (Fig); however, baseline expression of inflammation biomarkers was not associated with BOR ($p > 0.05$). Baseline NLR of 3 or less vs more than 3 was associated with longer OS ($p = 0.03$). NLR was not associated with response ($p > 0.05$). Safety outcomes were consistent with the primary analysis.

Multivariate analysis: association between biomarker and OS^a



^aCox proportional-hazards regression models with each biomarker as a continuous variable and OS in multivariate models adjusting for gender, age, viral etiology, prior sorafenib, and Eastern Cooperative Oncology Group performance status as covariates. ^bBiomarkers associated with OS. CD, cluster of differentiation; FOXP3, forkhead box protein P3; OS, overall survival; PD-1, programmed death-1.

Conclusion: In patients with CPB aHCC, nivolumab efficacy and safety were maintained at long-term follow-up. PD-1, CD163, and NLR were not associated with BOR. Lower baseline tumor PD-1 and CD163 and lower NLR were associated with longer OS.

OS-777

Real-world outcomes of patients with hepatocellular carcinoma treated with transarterial radioembolization: results from CIRT, a large European prospective observational study

Frank Kolligs¹, Dirk Arnold², Thomas Helmberger³, Geert Maleux⁴, Bora Peynircioglu⁵, Niklaus Schaefer⁶, Rita Golfieri⁷, Thomas Pfammatter⁸, Maxime Ronot⁹, Niels de Jong¹⁰, Bruno Sangro¹¹. ¹Helios Klinikum Berlin-Buch, Internal Medicine and Gastroenterology, Berlin, Germany; ²Asklepios Tumorzentrum Hamburg, AK Altona, Oncology and Hematology, Hamburg, Germany; ³Klinikum Bogenhausen, Department of Radiology, Neuroradiology and Minimal-Invasive Therapy, Munich, Germany; ⁴Universitair Ziekenhuis Leuven, Radiology, Leuven, Belgium; ⁵Hacettepe University, Department of Radiology, School of Medicine, Ankara, Turkey; ⁶Inselspital Hospital Lausanne, Service de médecine nucléaire et imagerie moléculaire, Lausanne, Switzerland; ⁷Sant'Orsola Hospital, University of Bologna, Radiology Unit, Department of Experimental, Diagnostic and Speciality Medicine, Bologna, Italy; ⁸Universitätsspital Zürich, Institut für Diagnostische und Interventionelle Radiologie, Zuerich, Switzerland; ⁹APHP Beaujon, Department of Radiology, Clichy, France; ¹⁰CIRSE-Cardiovascular and Interventional Radiological Society of Europe, Clinical Research, Vienna, Austria; ¹¹Clínica Universitaria de Navarra, IDISNA and CIBEREHD, Liver Unit, Pamplona, Spain
Email: dejong@cirse.org

Background and aims: Transarterial radioembolization (TARE) is a treatment option for patients with hepatocellular carcinoma (HCC). The CIRSE Registry for SIR-Spheres Therapy (CIRT, NCT02305459) was designed to evaluate the clinical outcomes of patients treated with TARE with SIR-Spheres Y-90 resin microspheres in primary and metastatic malignant liver tumours in the multi-institutional real-life clinical setting. The study, which included a large HCC cohort, was conducted by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE).

Method: CIRT was a European-wide prospective multi-centre observational study which enrolled patients between Jan 2015 and Dec 2017. Eligible patients were adults treated with TARE with Y-90 resin microspheres for primary and metastatic malignant liver tumours. This analysis looks at a subset of the larger cohort-HCC patients. Baseline characteristics and treatment-related data were collected with follow-up data every 3 months for 24 months including overall survival (OS), progression-free survival (PFS), hepatic progression free survival (hPFS) and safety data.

Results: 422 patients with HCC were prospectively included from 25 sites in 8 European countries. Median age was 68 (range 22–92) and 80.8% were male. The Barcelona Clinic Liver Cancer (BCLC) staging was A (14.0%), B (51.4%), C (33.4%) or D (1.2%). Portal vein thrombosis (PVT) occurred in 33.1% (segmental 19.4%, lobar 9.0% and main thrombosis 4.7%). 50.2% of the patients received TARE as first-line treatment, 44.8% received locoregional treatments prior to TARE (primarily surgery 17.1%, ablation 14.7% and/or transarterial chemoembolization (TACE) 23.0%). 10.7% received prior systemic treatment. The investigator-assessed treatment intent was predominantly palliative (57.3%) or tumour downsizing (32.5%). Median OS was 16.5 months (95% CI 14.2–19.3), median PFS was 6.1 months (95% CI 5.7–7.0) and median hPFS was 6.7 months (95% CI 5.9–7.6). 36.7% of the patients experience 311 adverse events, with 9.7% of the patients having 41 (13.2%) grade 3 or higher adverse events: abdominal pain 2.1%, fatigue 1.4%, fever 0.5% nausea 0.7%, vomiting 0.5%,

gastrointestinal ulceration 0.2%, radioembolization-induced liver disease 0.7% and other 3.6%. Detailed subgroup analyses are currently being performed. Updated data describing OS, PFS and hPFS for BCLC and PVT, as well as other prognostic factors for OS, PFS and hPFS will be shown.

Conclusion: The results from this large prospective multi-centre observational study show that in the real-world setting, patients with HCC receive TARE as first-line treatment or after alternative locoregional treatments. TARE is well tolerated with low occurrences of severe adverse events.

OS-972

Safety and efficacy of holmium-166 radioembolisation in hepatocellular carcinoma: preliminary results from the HEPAR Primary study

Margot Reinders-Hut¹, Karel J. van Erpecum², Maarten Smits¹, Arthur Braat¹, Joep de Bruijne², Rutger Bruijnen¹, Dave Sprengers³, Robert De Man³, Erik Vegt⁴, Jan Ijzermans⁵, Adriaan Moelker⁴, Marnix Lam¹. ¹University Medical Centre Utrecht, Radiology and Nuclear Medicine, Utrecht, Netherlands; ²University Medical Centre Utrecht, Gastroenterology and Hepatology, Utrecht, Netherlands; ³Erasmus Medical Centre, Gastroenterology and Hepatology, Rotterdam, Netherlands; ⁴Erasmus Medical Centre, Radiology and Nuclear Medicine, Rotterdam, Netherlands, ⁵Erasmus Medical Centre, Surgery, Rotterdam, Netherlands

Email: m.t.m.reinders@umcutrecht.nl

Background and aims: In contrast to Yttrium-90, Holmium-166 (166Ho) is a combined beta and gamma emitter, thus allowing quantitative nuclear imaging with perspective of individualized treatment planning (differentiating between tumour and liver parenchyma). Although transarterial radioembolisation with 166Ho-microspheres has shown promising results in hepatic metastases, no data are available for hepatocellular carcinoma (HCC). Considering their enhanced risk of hepatic decompensation, 166Ho-microspheres are expected to be particularly relevant in this patient group. The primary aim of this prospective clinical phase I/II study was to establish the toxicity profile of 166Ho-radioembolisation in patients with HCC.

Method: Inclusion criteria: HCC without curative options, Child-Pugh (CP) \leq B7 and performance state ECOG \leq 1. Follow-up occurred at 3 and 6 weeks, and (including imaging) 3 and 6 months. The primary end point was the rate of unacceptable toxicity (i.e. total bilirubin increase grade \geq 3 with ascites and low albumin) or any serious adverse event (SAE) that was related to study treatment. Tumour response was scored according to mRECIST.

Results: Thirty-one HCC patients with BCLC stage B (71%) or C (29%) were included, of whom 87% had multifocal disease and 71% had a CP score of A5. Median diameter of the largest tumour was 56 (range 15–195) mm. Patients were treated with an average absorbed dose of 60 Gy. Unacceptable treatment-related toxicity occurred in 3 patients with 4 SAEs (in 2 patients spontaneous bacterial peritonitis occurred and in one patient cholecystitis, bile duct stenosis and biliary fistula). Toxicity included fatigue (71%), back pain (55%), ascites (32%), dyspnoea (23%), nausea (23%) and abdominal pain (23%), mostly grade 1. CP score of 13 patients deteriorated after treatment by 1–4 points, of whom 3 recovered to baseline. At 3 months follow-up, target liver lesions showed complete response (CR) in 16% of the patients, partial response (PR) in 29%, stable disease (SD) in 35% and progressive disease (PD) in 3%, 17% was not evaluable (NE). At 6 months follow-up response was as follows: 23% CR, 29% PR, 10% SD, no PD, 38% NE. Median AFP levels declined with 67% (nadir). Median overall survival is 14.9 months (95% confidence interval 10.4 months–not reached). No significant decline in quality of life was observed.

Conclusion: ¹⁶⁶Ho-radioembolisation toxicity in this study for a selected group of patients with HCC was within the pre-defined limits. Response data support further evaluation. Future individualized treatment planning should allow a reduction of the risk of hepatic decompensation.

OS-1145

A phase Ib study of pembrolizumab following trans-arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): PETAL

David J. Pinato¹, Alessio Cortellini^{1,2}, Cristina Balcells³, Saskia Killmer⁴, Thomas Talbot¹, Robert Thomas⁵, Anwar A. Sayed^{1,6}, Elias Allara^{1,7}, Paul Tait⁵, Paul Ross^{8,9}, Anna Mary Young¹⁰, Tom Cole¹¹, Robert D. Goldin¹², Caroline Ward¹, Ayse Akarca¹³, Jesus Miguens Blanco¹⁴, Teresa Marafioti¹³, Hector Keun³, Alexandros Siskos³, Julian Marchesi¹², Bertram Bengsch⁴, Rohini Sharma¹. ¹Imperial College London, Department of Surgery and Cancer, London, United Kingdom; ²University of L'Aquila, Department of Biotechnology and Applied Clinical Sciences, L'Aquila, Italy; ³Imperial College London, Cancer Metabolism and Systems Toxicology Group, Department of Surgery and Cancer, London, United Kingdom; ⁴University Hospital Freiburg, Department of Internal Medicine, Freiburg; ⁵Imperial College NHS Trust, Interventional Radiology, London, United Kingdom; ⁶Taibah University, Department of Medical Microbiology and Immunology, Medina, Saudi Arabia; ⁷University of Cambridge, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, Cambridge, United Kingdom; ⁸Guy's and St Thomas' NHS Foundation Trust, Department of Medical Oncology, London, United Kingdom; ⁹King's College Hospital NHS Foundation Trust, Department of Oncology, London, United Kingdom; ¹⁰St George's University Hospitals NHS Foundation Trust, Department of Medical Oncology, London, United Kingdom; ¹¹Imperial College London, NIHR Imperial Clinical Research Facility, London, United Kingdom; ¹²Imperial College London, Centre for Pathology, London, United Kingdom; ¹³University College London Hospitals NHS Foundation Trust, Department of Histopathology, London, United Kingdom; ¹⁴Imperial College London, Division of Digestive Diseases, London, United Kingdom
Email: david.pinato@imperial.ac.uk

Background and aims: The efficacy of TACE is secondary to its dual ischaemic and cytotoxic effect, which promotes immunogenic tumour cell death. We hypothesized that TACE will prime adaptive immunity and enhance pembrolizumab efficacy (pembro; anti-PD-1). The aim of this phase Ib study was to evaluate safety, preliminary activity of combination therapy and explore mechanisms of efficacy.

Method: Up to 32 patients (pts) with intermediate-stage HCC were planned to receive up to 2 rounds of TACE followed by pembro 200 mg q3w 30-days post-TACE until disease progression or unacceptable toxicity for up to 1-year. Primary end point was safety with dose-limiting toxicities (DLT) emerging from the combination being evaluated over a 21-day window from commencement of pembro. Secondary end points included progression-free survival (PFS) and evaluation of tumour and host determinants of response in tissue, blood and stool samples.

Results: Of 11 eligible pts, 82% were males, 18% HCV-positive, 55% ECOG PS 0 with a median age of 68 years. Child-Pugh (CP) class was A in 10 pts and B7 in 1 pt. Median tumour size was 4 cm, and median number of tumour nodules was 2. Six pts received pembro after 1 TACE, 5 pts after 2. Pembro yielded no synergistic toxicity with TACE and no DLTs were reported. All-grade adverse events potentially related to treatment (tx) occurred in 90% of pts most commonly skin rash (45%) and fatigue (45%). Median PFS was 9.7 months (95%CI 4.9–14.4) from TACE and 6.1 months (95%CI 3.8–8.3) from pembro initiation. Cause of withdrawal included disease progression (n = 7), adverse events (n = 1) worsening liver failure in the CP B7 pt, non tx-related (n = 1) and withdrawal due to Covid-19 pandemic (n = 2). We document dynamic changes in peripheral T-cell subsets throughout treatment, with significantly higher proportions of Mucosal-associated invariant T (MAIT) cells post-pembro in responding patients. Serum metabolic profiling revealed that TACE plus pembro globally altered the lipid profile of patients, causing significant changes in phosphatidylcholines, acylcarnitines and sphingomyelins. Treatment responders had higher levels of saturated and mono/di-unsaturated

ORAL PRESENTATIONS

phosphatidylcholines, highlighting potential immune-metabolic mechanisms of efficacy.

Conclusion: The TACE plus pembro combination had a tolerable safety profile with no evidence of synergistic toxicity. Alongside emerging efficacy data, this encourages the clinical development of the combination in CP A pts.

OS-1399

Results of the therapeutic cancer vaccine HepaVac-101 clinical trial in HCC patients

Markus Loeffler¹, Francesco Izzo², Stefania Gori³, Andrea Mayer⁴, Alfred Königsrainer¹, Yuk Ting Ma⁵, Bruno Sangro⁶, Sven Francque⁷, Roberto Accolla⁸, Luisa Vonghia⁷, Antonio Avallone², Joerg Ludwig⁴, Diego Alcoba⁴, Katrin Aslan⁴, Regina Mendrzyk⁴, Heiko Schuster⁴, Marco Borrelli², Danila Valmori⁹, Tanguy Chaumette⁹, Regina Heidenreich¹⁰, Cecile Gouttefangeas¹¹, Greta Forlani⁸, Maria Tagliamonte¹², Mercedes Iñarrairaegui⁶, Ulrike Gnad-Vogt¹⁰, Carsten Reinhardt⁴, Toni Weinschenk⁴, Hans-Georg Rammensee¹¹, Luigi Buonaguro¹². ¹Tübingen University Hospital, Tübingen, Germany; ²Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy; ³Ospedale Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy; ⁴Immatics Biotechnologies GmbH, Tübingen, Germany; ⁵University of Birmingham, United Kingdom; ⁶Clínica Universidad de Navarra, Madrid, Spain; ⁷Antwerp University Hospital, Edegem, Belgium; ⁸University of Insubria, Varese, Italy; ⁹University of Nantes, Nantes, France; ¹⁰CureVac AG, Frankfurt am Main, Germany; ¹¹Eberhard Karls University of Tübingen, Tübingen, Germany; ¹²Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Experimental Oncology, Napoli, Italy
Email: l.buonaguro@istitutotumori.na.it

Background and aims: Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer globally with an extremely variable 5-year survival rate. Immunotherapy strategies for HCC may represent a key therapeutic tool to improve clinical outcome in HCC patients. HepaVac-101 (EudraCT Number: 2015-003389-10; NCT03203005), is a single-arm, first-in-man Phase I/II clinical trial evaluating a therapeutic cancer vaccine in patients affected by HCC. It is a highly innovative, novel approach based on a multi-peptide vaccine (IMA970A) combined with the TLR7/8/RIG I agonist CV8102 as an adjuvant.

Method: The IMA970A off-the-shelf vaccine includes 5 HLA-A*24 and 7 HLA-A*02 as well as 4 HLA-DR restricted peptides identified and selected from native human HCC tumor tissue by applying the XPRESIDENT® discovery platform. CV8102 is a novel ribonucleic acid (RNA) based immunostimulatory agent inducing a balanced Th1/Th2 immune response.

HLA-A*02 and/or A*24-positive patients with very early, early and intermediate stage HCCs have been enrolled to be treated with 9 intradermal vaccinations consisting of IMA970A plus CV8102 following a single pre-vaccination infusion of low-dose cyclophosphamide acting as an immunomodulator. Patients have completed standard of care treatments at time of enrolment and received study drugs without concomitant anti-tumor therapy with no evidence of disease reactivation. The primary end points of the HepaVac-101 clinical trial are safety, tolerability, and antigen specific T cell response. Secondary/exploratory end points are additional immunological parameters in blood, infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, disease-free survival/progression-free survival and overall survival.

Results: Patients were enrolled in 6 centers located in 5 European countries i.e. Italy (Naples and Negrar/Varese), Germany (Tübingen), UK (Birmingham), Spain (Pamplona) and Belgium (Antwerp). The end of trial (EOT) was reached on last December 20, 2019. 82 HCC patients have been screened for suitable HLA haplotypes, 22 patients were put on study treatment (i.e. received at least the pre-treatment with cyclophosphamide). The vaccination showed a good safety profile with no major SAE nor AESI reported during the protocol. Immunogenicity data show immune response against at least 1 vaccine class I TAA and 1 vaccine class II TAA in about 70% and 50% of

the vaccinees, respectively. More detailed immunological evaluations will be available at time of the meeting.

Conclusion: The HEPAVAC-101 clinical trial is safe and elicits immune response in HCC patients. This is the achievement of the HEPAVAC Consortium supported by the European Commission's 7th framework program with contract No. 602893 (www.hepavac.eu).

OS-1674

IMbrave150: exploratory efficacy and safety results of atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma (HCC) who had prior locoregional therapy (LRT)

Riad Salem¹, Peter Galle², Richard Finn³, Michel Ducreux⁴, Amit Singal⁵, Alan Nicholas⁶, Sairy Hernandez⁶, Wendy Verret⁶, Philippe Merle⁷, Andrew Zhu^{8,9}. ¹Northwestern University, Chicago, United States; ²University Medical Center Mainz, Mainz, Germany; ³Geffen School of Medicine at UCLA, Jonsson Comprehensive Cancer Center, Los Angeles, United States; ⁴Gustave Roussy Cancer Center, Villejuif, France; ⁵UT Southwestern Medical Center, Dallas, United States; ⁶Genentech, Inc., South San Francisco, United States; ⁷University Hospital La Croix-Rousse, Lyon, France; ⁸Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, United States; ⁹Jiahui Health, Jiahui International Cancer Center, Shanghai, China
Email: r-salem@northwestern.edu

Background and aims: Atezolizumab (atezo) + bevacizumab (bev) has been approved in > 70 countries for systemic treatment (tx)-naive patients (pts) with unresectable HCC, based on IMbrave150 (NCT03434379; Finn RS NEJM 2020). Here, we report post hoc exploratory results of atezo + bev vs sorafenib (sor) in pts who had prior LRT using updated IMbrave150 data with 12 mo of further follow-up from primary analysis (Finn RS ASCO GI 2021).

Method: Pts were randomised 2:1 to atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w or sor 400 mg bid until unacceptable toxicity or loss of clinical benefit per investigator. IMbrave150 enrolled 501 systemic tx-naive pts with unresectable HCC, ≥ 1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and ECOG PS ≤ 1, including pts with prior LRT.

Results: 175, 84 and 77 atezo + bev pts and 80, 44 and 41 sor pts had 0, 1–2 and ≥ 3 prior lines of LRT, respectively. Compared with sor pts, atezo + bev pts had median overall survival (mOS) of 19.4 vs 13.1 mo (HR, 0.61; 95% CI: 0.44, 0.86) in pts without prior LRT, 22.8 vs 10.2 mo (HR, 0.60; 95% CI: 0.36, 1.00) in pts with 1–2 LRTs and 17.4 vs 16.6 mo (HR, 0.83; 95% CI: 0.51, 1.37) in pts with ≥ 3 LRTs. See table for more efficacy data. Grade 3–4 treatment-related adverse events were seen in 79 (46%), 33 (39%) and 31 (41%) atezo + bev pts and 30 (39%), 20 (49%) and 22 (58%) sor pts who had 0, 1–2 and ≥ 3 LRTs, respectively.

Table: Efficacy by no. of prior LRTs

	Atezo + bev			Sor		
	No prior LRT	1–2 LRTs	≥ 3 LRTs	No prior LRT	1–2 LRTs	≥ 3 LRTs
N	175	84	77	80	44	41
mOS (95% CI), mo	19.4 (16.7, 23.7)	22.8 (15.5, NE)	17.4 (14.0, 25.8)	13.1 (7.4, 16.1)	10.2 (7.0, 26.4)	16.6 (12.6, 21.9)
Median progression-free survival (95% CI), mo ^a	6.7 (5.5, 8.3)	9.4 (5.6, 12.9)	6.7 (5.5, 9.7)	4.8 (4.0, 6.7)	4.0 (2.6, 5.5)	4.4 (3.9, 8.6)
Objective response rate, n/N (%) ^a	50/172 (29)	28/79 (35)	19/75 (25)	12/78 (15)	2/41 (5)	4/40 (10)
Complete response	8 (5)	11 (14)	6 (8)	1 (1)	0	0
Stable disease	76 (44)	31 (39)	37 (49)	33 (42)	15 (37)	21 (53)
NE	3 (2)	4 (5)	1 (1)	7 (9)	4 (10)	3 (8)
Missing	9 (5)	1 (1)	4 (5)	7 (9)	8 (20)	3 (8)

Clinical cutoff: 31 Aug 2020. Median follow-up: 15.6 mo. N, no. of pts with measurable disease at baseline; NE, not estimable.

^aIndependently-assessed RECIST 1.1.

Conclusion: Survival benefit with atezo + bev over sor was seen in pts regardless of the number of prior LRTs. Atezo + bev seemed to have more benefit in pts with 1–2 vs ≥ 3 prior LRTs, suggesting an optimal time for switching from LRT to systemic tx.

OS-2190

A humanized Claudin-1 specific monoclonal antibody for treatment of hepatocellular carcinoma

Natascha Roehlen^{1,2}, Sara Cherradi^{1,2}, Marion Muller^{1,2,3}, Nuno Almeida^{1,2}, François H.T. Duong^{1,2}, Emilie Crouchet^{1,2}, Frank Jühling^{1,2}, Houssein El Saghire^{1,2,4}, Sarah Durand^{1,2}, Clara Ponsolles^{1,2}, Marine Oudot^{1,2}, Antonio Saviano^{1,2,5}, Emanuele Felli^{1,2,5}, Patrick Pessaux^{1,2,5}, Gerhard Christofori⁶, Joachim Lupberger^{1,2}, Greg Elson⁴, Markus Meyer⁴, Roberto Iacone⁴, Tamas Schweighoffer⁴, Patrice Laquerriere³, Catherine Schuster^{1,2}, Laurent Mailly^{1,2}, Thomas Baumert^{1,2,5}. ¹Inserm U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France; ²University of Strasbourg, Strasbourg, France; ³CNRS, Institut Pluridisciplinaire Hubert Curien UMR 7178, Strasbourg, France; ⁴Alentis Therapeutics, Basel, Switzerland; ⁵Institut Hospitalo-Universitaire, Pôle Hépato-digestif, Nouvel Hôpital Civil, Strasbourg, France; ⁶University of Basel, Department of Biomedicine, Basel, Switzerland
Email: thomas.baumert@unistra.fr

Background: Hepatocellular carcinoma (HCC) is the fastest rising and third leading cause of cancer death. While new therapeutic modalities have been recently approved, treatment response and survival in patients remain poor. Claudin-1 (CLDN1) is a cell membrane protein mediating cell-cell adhesion, fate and differentiation. Functionality of CLDN1 in solid tumors including HCC has been demonstrated by gain- and loss-of-function studies, yet its impact as a therapeutic target is unexplored.

Aims and Method: Using humanized monoclonal antibodies (mAbs) targeting specifically the extracellular loop of human non-junctional CLDN1 and a large series of patient-derived cell-based and animal model systems we aimed to investigate the role of CLDN1 as therapeutic target for treatment of HCC.

Results: Here we show that humanized monoclonal anti-CLDN1 mAbs robustly and significantly inhibit growth, migration and invasion of tumor cells in cell line-based models of HCC and patient-derived HCC spheroids. Moreover, the robust effect on tumor growth was confirmed *in vivo* in a large series of cell line derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models. Functional studies in patient-derived and cell line-based tumor spheroids revealed that the mAbs perturbed the 3D tumor architecture. Furthermore, CLDN1 mAbs markedly and significantly suppressed epithelial-mesenchymal transition (EMT) and matrix metalloproteinase synthesis in tumor cells. Good treatment response in PDX models correlated with expression of genes that are associated with a fibrotic tumor environment, whereas presence of the angiogenic factor VEGFB predicted low treatment efficacy. Treatment with humanized anti-CLDN1 mAbs is considered to be safe, as administration in non-human primates and mouse models did not reveal any major toxicity even when high doses largely exceeding the therapeutic need were repeatedly applied.

Conclusion: These results provide robust pre-clinical proof-of-concept for humanized CLDN1-specific mAbs for treatment of HCC and pave the way for clinical development of CLDN1-targeting therapies using monoclonal antibodies. The unique and different mechanism of action provides opportunities to break the plateau of limited response and survival offered by currently approved therapies.

OS-2679

Hepatic arterial infusion chemotherapy in combination with PD-1 inhibitor as conversion therapy in locally advanced, potentially resectable hepatocellular carcinoma: A phase II study

Li Xu¹, Yaojun Zhang¹, Minshan Chen¹, Xiaohui Wang¹, Jingyu Hou¹, Zhongguo Zhou¹. ¹Sun Yat-sen University Cancer Center, Liver Surgery, Guangzhou, China
Email: xuli@sysucc.org.cn

This abstract is under embargo until the beginning of the press conference it is being presented in on Thursday 24 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

Molecular and cellular biology

OS-138

Rifaximin regulates nitrogen detoxification in a PXR-independent manner in human small intestinal organoids

Koos de Wit¹, Ulrich Beuers¹, Saskia van Mil², Bart Takkenberg¹.

¹Amsterdam Umc, location AMC, Gastroenterology and Hepatology, Amsterdam, Netherlands; ²UMC Utrecht, Center for Molecular Medicine, Utrecht, Netherlands

Email: k.dewit1@amsterdamumc.nl

Background and aims: The poorly absorbed antibiotic rifaximin-a Pregnane X Receptor (PXR) agonist-prevents recurrent hepatic encephalopathy (HE). Although the pathophysiology of HE is only partly unravelled, ammonia accumulation, systemic inflammation and oxidative stress appear to play a central role. Ammonia is detoxified by formation of glutamine and urea. Due to its poor absorption, rifaximin is considered to exert beneficial effect on HE by acting on the gut microbiome, thereby decreasing bacterial ammonia production. Direct effects of rifaximin on intestinal epithelium have barely been studied. We tested our hypothesis that rifaximin is effective in HE by strengthening the human intestinal mucosal detoxification capacity.

Method: Using lentiviral delivery of short hairpins, we generated a PXR knockdown human small intestinal organoid line and a control line in which a non-target shRNA was introduced. Organoids were cultured for 24 hours with either rifaximin, rifampicin (100 uM each), or DMSO. RNA-sequencing and AccQ-Tag mass spectrometry were performed to investigate effects on gene expression and glutamine metabolism. Rifaximin uptake and secretion were studied by bright field microscopy.

Results: Uptake and apical secretion of rifaximin in human small intestinal organoids was documented using microscopy. In total, 31% of the differentially expressed genes upregulated by rifaximin were overlapping in the PXR knockdown and control organoids. Notably, PXR-independent upregulation of Asparagine Synthetase (Log2FC 2.3, $p < 0.001$) and downregulation of Glutaminase 2 (Log2FC -0.8, $p < 0.001$) are suggestive of increased ammonia detoxification whereas PXR-independent induction of Glutamate-Cysteine Ligase Modifier (Log2FC 1.7, $p < 0.001$) and Glutamate-Cysteine Ligase Catalytic subunit (Log2FC 0.3, $p < 0.001$) are in line with increased glutathione production. Indeed, intracellular concentrations of asparagine and glutathione were increased by rifaximin from 3.6 to 4.0 uM, ($n = 3$, $p = 0.017$) and from 33.3 to 44.6 uM ($n = 3$, $p = 0.047$) while no such effects were seen by rifampicin.

Conclusion: Our findings suggest that rifaximin-after uptake into human small intestinal cells-stimulates nitrogen detoxification and decreases ammonia production in a PXR-independent manner. Luminal intestinal rifaximin excretion may explain the lack of systemic effects of rifaximin.

OS-334

A context-dependent role of c-myc in liver regeneration and hepatocarcinogenesis in chronic liver injury

Silke Marhenke¹, Tiago De Castro², Simon Peter¹, Jan G. Hengstler³, Wei He⁴, Karsten Hiller⁴, Michael Saborowski², Anna Saborowski², Arndt Vogel². ¹Medical School Hannover, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²Medical School Hannover, Gastroenterology, Hepatology and Endocrinology, Hannover; ³Leibniz Research Centre for Working Environment and Human Factors, Toxikologie, Dortmund; ⁴BRICS-Braunschweig Integrated Centre of Systems Biology, Department of Bioinformatics and Biochemistry, Braunschweig

Email: marhenke.silke@mh-hannover.de

Background and aims: c-MYC is frequently dysregulated in human hepatocellular carcinoma (HCC), and is considered to be a driver of

malignant transformation. Despite its well established impact on HCC, the physiological role of c-MYC during acute and chronic liver injury remains enigmatic. We employed two murine liver injury models to explore the consequences of loss of c-MYC on liver damage, regeneration and carcinogenesis.

Method: To investigate the effect of c-Myc in distinct liver disease settings, we crossed conditional c-Myc^{fl/fl} to *Mdr2*^{-/-} and *Fah*^{-/-} mice, respectively, and excised c-Myc by liver-specific Cre recombinase. Mice were monitored longitudinally for biochemical and metabolic parameters and tumor development. Partial hepatectomies (PH) were performed to assess the regenerative response, and bile duct ligations (BDL) to delineate the effects of acute biliary injury.

Results: In line with its role as a driver of hepatocarcinogenesis, loss of c-Myc delayed tumor development in the *Fah*^{-/-} mice. In contrast, tumor development was markedly accelerated in the *Mdr2*^{-/-} model. Biochemical parameters of liver damage were elevated in *Mdr2*/*cmyc*^{Δ/Δ} mice, accompanied by an accelerated fibrosis. The increased liver injury coincided with an impaired regenerative response, likely a direct effect of loss of c-MYC, as indicated by a reduction in Ki67 positive cells in *cmyc*^{Δ/Δ} mice after PH. In contrast, liver regeneration was not impaired in *Fah*/*cmyc*^{Δ/Δ} mice suggesting a context specific role of c-MYC for liver regeneration. *Mdr2*/*cmyc*^{Δ/Δ} displayed an altered energy metabolism reflected by decreased basal ATP-levels, and imbalances in the metabolite profile of the TCA cycle. Moreover, the bile acid composition was severely altered in *Mdr2*/*cmyc*^{Δ/Δ} mice, and transcriptome analysis revealed a strong downregulation of the bile acid transporter *Slco1a1*. Of note, an increased sensitivity to cholestatic injury has been reported for a transgenic *Slco1a1*^{-/-} model. In line with the observation in the *Mdr2*^{-/-} mice, liver injury was markedly increased in *cmyc*^{Δ/Δ} mice following BDL, suggesting c-MYC -regulated *Slco1a1* protects mice from bile acid induced liver injury.

Conclusion: Our results unveil a context-dependent role of c-myc during liver injury and injury-induced tumorigenesis and add a note of caution to the development of MYC-directed therapeutic strategies.

OS-387

Loss of cholangiocyte primary cilia drives reorganisation of the biliary tree and accelerates tumorigenesis

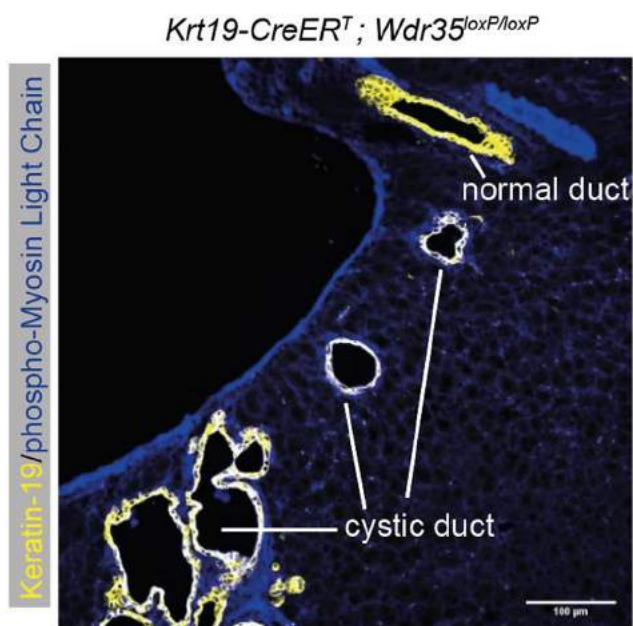
Scott Waddell¹, Yuelin Yao¹, Stephanie Macmaster¹, Kostas Gournopoulos¹, Ava Khamseh¹, Pleasantine Mill¹, Luke Boulter¹. ¹MRC Human Genetics Unit, Edinburgh, United Kingdom
Email: scott.waddell@ed.ac.uk

Background and aims: Primary cilia (PC) are signalling organelles that protrude from most cells to sense the extracellular environment. Cholangiocytes project PC into the bile duct lumen to sense and regulate bile composition. Mutations in genes that result in PC dysfunction have been associated with ductal plate malformations and polycystic liver diseases, though whether loss of cilia function is causative in these pathologies is not entirely clear. In both cholangiopathies and cholangiocarcinoma, the bile duct must mechanically reorganise its structure to form a cyst or cancerous duct, respectively. In this study, we sought to define whether PC loss in bile ducts is sufficient to induce structural reorganisation of the biliary tree and define whether PC loss promotes oncogenesis.

Method: We generated a novel model whereby we can specifically delete PC from cholangiocytes using a *K19Cre;Wdr35*^{loxP/loxP} transgenic mouse in health and in a model of cholangiocarcinoma. We used a combination of approaches including scRNAseq and lineage tracing to characterise the pathological and physical alterations that arise due to PC loss in cholangiocytes.

Results: PC deletion in the healthy adult liver results in the formation of extensive biliary cysts, which have a remarkably low proliferative rate. We found that extensive remodelling of the cholangiocyte cytoskeleton is associated with cystic liver disease. Moreover, when we delete PC in a novel transgenic model of cholangiocarcinoma we

observe increased tumour size and number, suggesting that in patient cholangiocarcinoma PC are lost to promote tumour growth. To understand the molecular changes that are regulated by the PC, we used scRNAseq and whole transcriptome sequencing to identify downstream signals that are deregulated upon PC loss, and immunohistochemistry to characterise physical rearrangements in the cytoskeleton that drive biliary tree reorganisation to generate cysts and promote tumour growth.



Conclusion: Our results show that PC are required to maintain cholangiocyte homeostasis and constrain dynamic reorganisation of the cytoskeleton in the bile duct. Deregulation of actin mediate gross rearrangements of the biliary tract to form extensive cysts in the adult liver, and this process contributes to tumour development. This work highlights the importance of PC in biliary pathophysiology and identifies a potential benefit of targeting actin processing in patients with polycystic liver disease and CCA.

OS-901

A murine model of FGFR2 fusion driven intrahepatic cholangiocarcinoma to delineate mechanism of therapeutic response and resistance to FGFR inhibitors

Gajanan Kendre¹, Silke Marhenke¹, Georgina Lorz¹, Michael Saborowski¹, Arndt Vogel¹, Anna Saborowski¹. ¹Hannover Medical School, Department of Gastroenterology and Hepatology, Hannover, Germany
Email: saborowski.anna@mh-hannover.de

Background and aims: Intrahepatic cholangiocarcinoma (iCC) is an aggressive malignancy with a mOS below 12 months in the palliative setting. Gene fusions involving the *fibroblast growth factor receptor 2* (FGFR2) occur in up to 15% of iCCs, and their therapeutic relevance was confirmed in clinical phase II studies. Despite thus far unparalleled ORRs of up to 35% in second line, several FGFR2 fusion patients do not reach deep responses. Here, we describe a *in vivo* model system for the functional annotation of fusion genes, and delineate how the co-mutational spectrum influences therapy response.

Method: We utilized an *in vivo* electroporation approach to introduce six different FGFR2 fusion cDNAs (or control) into the livers of mice harbouring the latent mutant *Kras* allele (*Kras*^{G12D}), or wildtype (wt) mice, in conjunction with a CRISPR/Cas9 plasmid targeting *Trp53*. The efficacy of FGFR inhibitors was probed both *in vitro* and *in vivo*, and we employ a combination of drug treatment and RNAi technology to

delineate the effect of co-treatment strategies on the sensitivity to FGFR inhibitors.

Results: Following electroporation with a FGFR2-fusion encoding cDNA, tumors developed rapidly in *Kras* mutant, and (with longer latency) in *Kras* WT mice. No tumor development was observed in the controls, indicating that FGFR2 fusions drive malignant transformation. Despite the pre-requisite of the fusion for tumor development, cell lines derived from FGFR2-fusion tumors that harboured a mutant *Kras* allele exhibited an unexpected resistance to FGFR-inhibitors, as determined by dose response assays. A combination of pharmacologic and genetic approaches revealed that, while KRAS knockdown (KD) did not affect the growth of the tumor-derived cell lines, KRAS KD or pharmacologic MAPK/ERK inhibition re-sensitized the cells to FGFR inhibition. Similarly, resistance was also observed following introduction of other MAPK activating mutations (ERBB2, NRAS, BRAF) in *Kras* WT cells.

Conclusion: We present an autochthonous *in vivo* model for FGFR2-fusion driven iCC. Due to its genetic flexibility, this model is highly suited to address mechanisms of primary resistance to clinically relevant FGFR inhibitors, caused by the co-mutational spectrum. Our data suggest that iCC patients with FGFR2 fusions and co-mutations that activate the MAPK-signaling may not benefit from monotherapy with FGFR inhibitors, but that resistance may be overcome by co-treatment strategies.

OS-1355

Hepatic o-glcNacetylated-p53 as a hub integrating the glucose counter regulatory response and insulin-suppressed gluconeogenesis

María J. González Rellán¹, Marcos Fernandez Fondevila¹, Uxia Fernández Paz¹, Amaia Rodriguez², Marta Varela Rey³, Christelle Veyrat Durebex⁴, Samuel Seoane¹, Ganeko Bernardo³, Fernando Lopitz Otsoa³, David Fernandez Ramos³, Jon Bilbao³, Cristina Iglesias¹, Eva Novoa¹, Natalia Lima¹, Begoña Porteiro¹, Timo d Müller⁵, Stephan Herzig⁵, Maria Luz Martinez Chantar³, Roman Perez Fernandez¹, Miguel Lopez Perez¹, Carlos Dieguez¹, Jose Maria Mato³, Oscar Millet³, Roberto Copara⁴, Ashwin Woodhoo³, Gema Frugbeck², Ruben Nogueiras Pozo¹. ¹CIMUS, Physiology, Santiago de Compostela, Spain; ²clinica universidad de navarra; ³cic Biogune, Bilbao, Spain; ⁴University of Geneva, Geneva, Switzerland; ⁵Helmholtz Zentrum München, München, Germany
Email: chusa.gzlz.rellan@gmail.com

Background and aims: Glucose homeostasis is essential for life. The liver is among the key tissues for maintaining an adequate metabolic homeostasis and its alterations are at the root of the pathogenesis of many disease states. A perfect balance between glucose production, mainly at the liver, and glucose consumption in different tissues, is provided by the action of insulin and counterregulatory hormones as glucagon, cortisol or catecholamines. p53 is an intensively studied protein primarily as a tumor suppressor. There is nowadays growing evidence demonstrating that cell cycle regulators have important actions in the metabolic control. In cancer cells, p53 regulates glucose metabolism, opposing the Warburg effect. Nevertheless, the relevance of endogenous hepatic p53 in the physiological fluctuation of gluconeogenesis, as well as the molecular pathways mediating these effects, remains totally unknown.

Method: Either *wild type* (WT) mice or hepatic p53-deficient littermates were subjected to different nutritional conditions to evaluate p53 expression and function. These experiments were also performed *in vitro*, in both THLE-2 cells and HEP3B cells (a hepatic KOP53 cell line). PTT, Gly, GTT and ITT were performed to study glucose homeostasis in WT mice and p53-deficient mice, as well as a clamp to further test their gluconeogenic capacity. Gain-of-function experiments were also performed, over-expressing p53 in the liver. *In vitro* and *in vivo* models were treated with gluconeogenic hormones and insulin, to study the role and function of p53 mediating their hepatic actions. Mutagenesis experiments were also performed to evaluate the relevance of O-GlcNAcylation on p53 gluconeogenic actions.

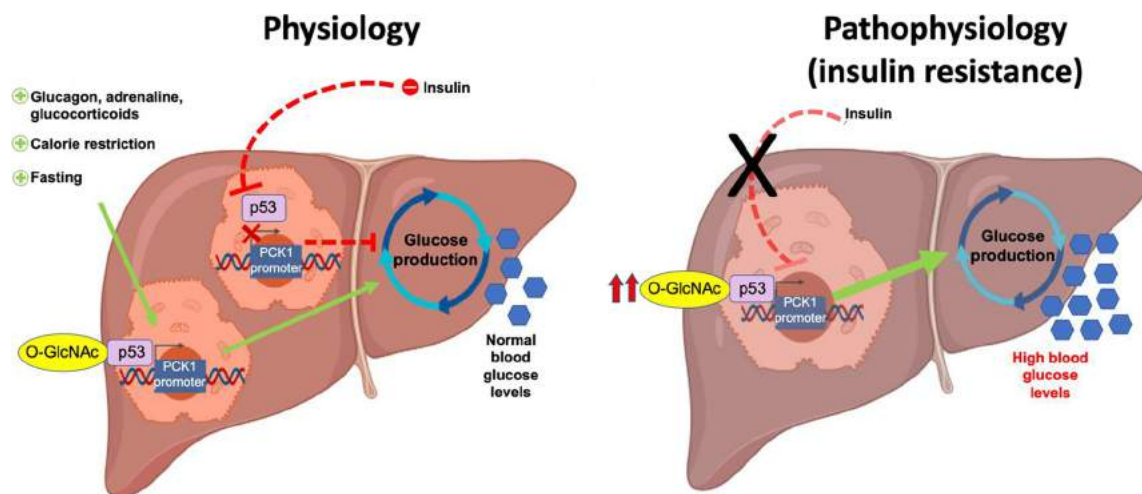


Figure: (abstract: OS-1355)

Results: We show that upon starvation hepatic p53 is stabilized by O-GlcNAcylation, and plays an essential role in the physiological regulation of glucose homeostasis. p53 binds to PCK1 promoter and regulates its transcriptional activation, thereby controlling hepatic glucose production. Mutant p53 that cannot be O-GlcNAcylated is unable to promote PCK1 activity gluconeogenesis. Mice lacking p53 in the liver show a reduced gluconeogenic response during calorie restriction. Glucagon, adrenaline and glucocorticoids augmented protein levels of p53, and administration of these hormones to human hepatocytes and to liver-specific p53 deficient mice fails to increase glucose levels. Moreover, insulin decreases p53 levels, and over-expression of p53 impairs insulin sensitivity. Finally, protein levels of p53, as well as genes responsible of O-GlcNAcylation are elevated in the liver of T2D patients, and positively correlate with glucose and HOMA-IR.

Conclusion: Our results indicate that O-GlcNAcylation of p53 plays an unsuspected key role regulating in vivo glucose homeostasis, with a potential therapeutic target interest.

OS-1414

A hypothalamus-liver axis regulates hepatic glucose homeostasis and lipid metabolism dysfunctions in an intraperitoneal treatment with olanzapine in male mice

Vítor Ferreira^{1,2}, Patricia Rada^{1,2}, María García-Altres^{2,3}, María Guillén⁴, Diana Grajalés^{1,2}, Irma García-Martínez^{1,2}, Rosa Alén^{1,2}, Pilar López-Larrubia⁴, Sebastian Cerdan⁴, Xavier Correig-Blanchar^{2,3}, Angela Martínez Valverde^{1,2}. ¹Instituto de Investigaciones Biomédicas “Alberto Sols”. IIBm (CSIC-UAM), Department of Metabolism and Cell Signaling, Madrid, Spain; ²CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, Madrid, Spain; ³Rovira i Virgili University, Department of Electronic Engineering, Tarragona, Spain; ⁴Instituto de Investigaciones Biomédicas “Alberto Sols”. IIBm (CSIC-UAM), Department of Pathophysiology Endocrine and Nervous System, Madrid, Spain
Email: avalverde@iib.uam.es

Background and aims: Schizophrenia is a chronic and severe mental disorder which is treated with second generation antipsychotics (SGA). Patients under SGAs treatment, including olanzapine (OLA), have higher risk for abnormal weight gain, hyperglycemia and dyslipidemia. Our aim was to understand the molecular mechanisms by which OLA alters insulin sensitivity and hepatic metabolism either directly or mediated through the central nervous system (CNS).

Method: Wild-type (WT) and protein tyrosine phosphatase-1B deficient (PTP1B-KO) mice with hepatic insulin hypersensitivity and protection against obesity, were injected (i.p.) 10 mg/kg/day OLA or vehicle for 8 weeks. Glucose, insulin and pyruvate tolerance tests and tissue insulin signaling analysis were conducted. Body weight and metabolic parameters were monitored. Nuclear magnetic resonance (NMR) was used for metabolomic analysis of hypothalamus. Hypothalamus-liver-axis was corroborated by intracerebroventricular (ICV) OLA injections.

Results: WT mice receiving OLA showed decreased body weight, but insulin and pyruvate intolerance together with insulin resistance in liver and skeletal muscle, key tissue targets of PTP1B. Insulin resistance in OLA-treated WT mice concurred with proinflammatory signals and increased fatty acid synthase in liver. The latter effect paralleled to hypothalamic JNK phosphorylation. By contrast, PTP1B-KO mice were protected against these alterations. OLA ICV injections in WT mice corroborated peripheral molecular alterations in both liver and adipose tissues. OLA-treated WT mice showed lower hepatic ATP levels associated with increased AMPK and acetyl-CoA carboxylase phosphorylation, β -oxidation readouts. As result of these metabolic changes, a futile cycle might occur in the liver of male animals since steatosis was not detected. Analysis of the hypothalamus revealed a decrease of antioxidant metabolites which likely increases reactive oxygen species that are related with JNK activation. These alterations are independent of body weight gain. By contrast, gender differences were found since females were protected against the central effects of OLA regarding the hepatic cross-talk.

Conclusion: We show a hypothalamus-liver crosstalk responsible for OLA hepatic side effects, emphasizing an impact in the CNS and sexual dimorphisms. These results suggest that i.p. administration together with a PTP1B inhibitor might have less metabolic alterations in schizophrenic patients.

OS-2934

Identifying patient relevant tumour suppressors that interact with oncogenic KrasG12D in intrahepatic cholangiocarcinoma

Mollie Wilson¹, Luke Boulter¹, Nicholas Younger¹, Alison Meynert¹, Kostas Gournopoulos¹. ¹The Institute of Genetics and Cancer, United Kingdom
Email: s1217700@ed.ac.uk

Background and aims: Intrahepatic cholangiocarcinoma (iCCA), a malignancy arising from the bile ducts, presents with highly

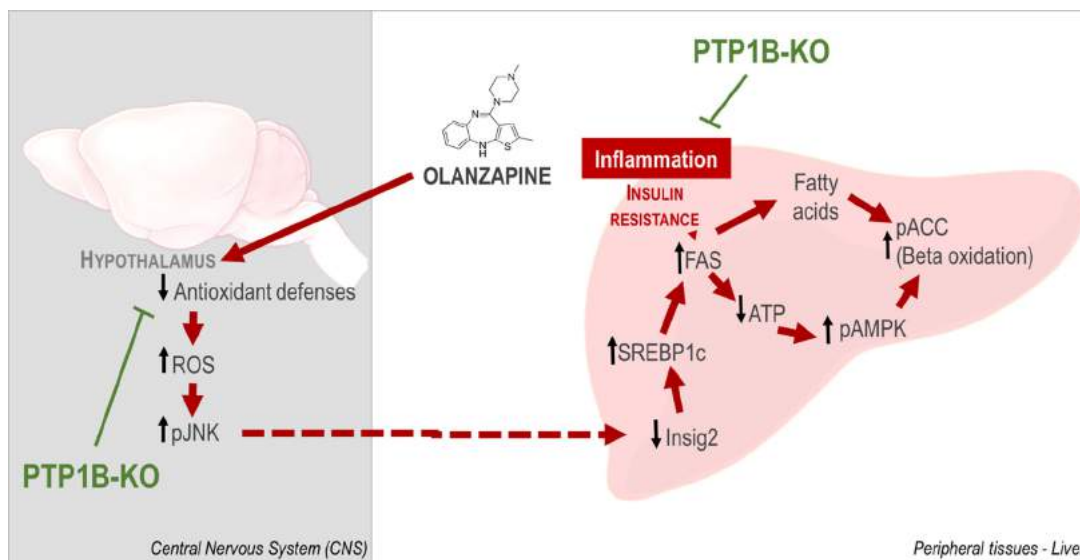


Figure: (abstract: OS-1414)

genetically heterogeneous tumours. The lack of understanding surrounding the genetics of this disease has hampered therapeutic approaches. To address the gap in our understanding of the functional genetics of iCCA we developed a computational screen of patient exome sequencing data to comprehensively identify driver mutations in iCCA, and found that in addition to known drivers of iCCA a large number of infrequently mutated genes typifies iCCAs. Here, we aimed to address whether these infrequently mutated genes are capable of initiating iCCA formation and determine whether rare iCCA mutations are sufficient to enhance, or modify, iCCA growth.

Method: A CRISPR-Cas9 library of loss of function mutations in iCCA was generated using data from patients, which was hydrodynamically injected into immune competent mice to delete iCCA-genes, along with expression of oncogenic Kras^{G12D}. Whole exome and RNA sequencing as well as proteomic approaches were combined to analyse the resulting tumours, to identify mutations that synergise with oncogenic Kras, define the transcriptional signatures that result from these mutations and uncover novel candidate therapeutic pathways.

Results: Computational screening of patient exomes identified a list of mutations in iCCA driver genes. Using this approach, we re-identified canonical mutations in iCCA and >90 mutations in novel genes. To determine which mutations are functional *in vivo*, we performed a CRISPR screen targeting genes found in patient iCCA. Tumours formed that histologically represented human iCCA when the CRISPR-library was co-expressed with Kras^{G12D}. Whole exome sequencing of these tumours identified a number of novel CRISPR-induced mutations that interact with KRas^{G12D} to drive iCCA formation and we identified mutations in neurofibromin 2 (Nf2), a cytoskeletal protein whose encoded protein Merlin is at the apex of many important signaling pathways as a gene of interest. Deletion of Nf2 cooperates with Kras^{G12D} to initiate iCCA formation; moreover, Nf2-loss cooperates with Trp53-loss leading to cancer with a significantly accelerated phenotype and increased lethality. Proteomic analysis of tumour tissue from this aggressive model demonstrated that co-activation of Wnt and PI3K signaling typify these tumours and can be targeted therapeutically to reduce tumour progression.

Conclusion: Our study demonstrates that Nf2 is a rare driver gene of iCCA that acts in a cooperative manner with oncogenic Kras^{G12D} to accelerate tumorigenesis. Using a combination of *in silico* and *in vivo* modelling holds a great deal of promise in unveiling the contribution

of different mutations to iCCA progression and also providing a platform to identify novel therapeutic vulnerabilities.

NAFLD – Clinical aspects except therapy

OS-293

Life expectancy and risk of cardiovascular disease in non-alcoholic fatty liver disease: a population-based cohort study

Ying Shang¹, Patrik Nasr², Linnea Widman³, Hannes Hagström^{4,5,6}.

¹Karolinska Institutet, Neurobiology, Care Sciences and Society, Stockholm, Sweden; ²Linköping University, Department of Gastroenterology and Hepatology, Department of Health, Medicine and Caring Sciences, Linköping, Sweden; ³Karolinska Institutet, Division of Biostatistics, Institute of Environmental Medicine, Stockholm, Sweden; ⁴Karolinska University Hospital, Division of Hepatology, Department of Upper GI, Stockholm, Sweden; ⁵Karolinska Institutet, Department of Medicine, Huddinge, Stockholm, Sweden; ⁶Karolinska Institutet, Clinical Epidemiology Unit, Department of Medicine, Stockholm, Sweden
Email: ying.shang@ki.se

Background and aims: Patients with non-alcoholic fatty liver disease (NAFLD) have a high risk for cardiovascular disease (CVD), but selection bias is common in many previous studies, and there is little data comparing this risk to the general population. It is further unclear if the risk is higher in patients with cirrhosis, differs for fatal and non-fatal events and if patients with NAFLD in general have lower life expectancy compared to the general population. We investigated these questions in a population-based study.

Method: We identified all patients diagnosed with NAFLD from 1970 to 2016 through the Swedish National Patient Register. For each person with NAFLD, up to 10 controls were randomly selected from the general population matched for age, sex, and municipality. The cohort consisted of 9,039 patients with NAFLD, and 91,495 controls with follow-up until 2016. Outcomes on all fatal, non-fatal CVD events and overall mortality were derived from national registers. Cox regression models with cause-specific hazards were used to estimate the risk of NAFLD with these outcomes, accounting for the competing risk of death. Observed and expected life expectancy by age at diagnosis were estimated with relative survival analysis.

ORAL PRESENTATIONS

Results: Over a median follow-up period of 6 years (range 0–46), 1,041 (11.5%) patients with NAFLD and 3,807 (4.2%) controls developed CVD ($p < 0.01$). Patients with NAFLD had a higher risk for all CVD outcomes (aHR = 2.9, 95%CI = 2.6–3.1), primarily for non-fatal CVD (aHR = 3.6, 95%CI = 3.3–4.0) but also for fatal CVD (aHR = 1.3, 95%CI = 1.1–1.5). However, there was no difference in overall mortality after a non-fatal CVD event between patients with NAFLD and controls (aHR = 0.8, 95%CI = 0.5–1.2). In patients with NAFLD, those with cirrhosis had a higher risk for CVD (aHR = 1.6, 95%CI = 1.1–2.3). Moreover, life expectancy was on average 2.5 years for men, and 1.7 years for women, lower than that of controls. Men had 3.2 years and women had 2.1 years lower life expectancy than that of controls when diagnosed in middle age (40–60 years).

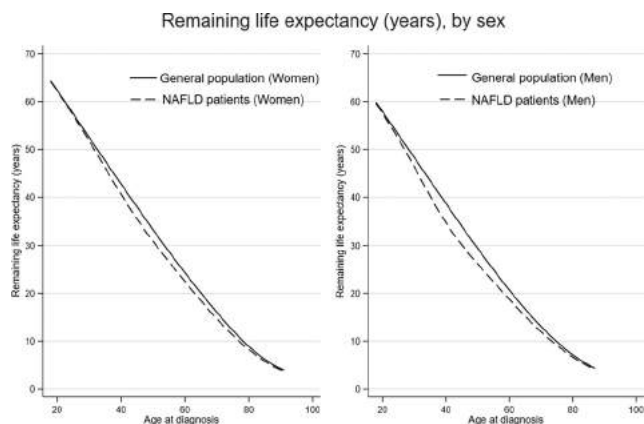


Figure:

Conclusion: In this study of all patients with a diagnosis of NAFLD in Sweden, the risk of fatal and non-fatal CVD was higher than in the general population, and the presence of cirrhosis amplified this risk. Age at diagnosis appears to play a role in survival, which can have implications for when to consider a diagnosis of this common disease.

OS-571

Relationship between hepatic venous pressure gradient and presence of decompensation in non-alcoholic fatty liver disease

Octavi Bassegoda¹, Pol Olivas¹, Laura Turco², Mattias Mandorfer³, Miquel Serra Burriel⁴, Tellez Luis⁵, Wilhelmus Kwanten⁶, Alexia Laroyenne⁶, Oana Nicoara-Farcu⁷, Edilmar Alvarado⁸, Lucile Moga⁹, Elise Vuille-Lessard¹⁰, Jose Ignacio Fortea¹¹, Luis Ibañez¹², Giulia Tosetti¹³, Thomas Vanwollegem¹⁴, Héléne Larrue¹⁵, Diego Burgos-Santamaria⁵, Stefanescu Horia¹⁶, Rafael Paternostro³, Annalisa Cippitelli², Sabela Lens¹, Salvador Augustin¹⁷, Elba Llop¹⁸, Wim Laleman¹⁹, Jonel Trebicka²⁰, Chang Johannes²¹, Helena Masnou²², Alexander Zipprich²³, Francesca Miceli², Georg Semmler³, Xavier Forn¹, Massimo Primignani¹³, Rafael Bañares¹², Angela Puente¹¹, Annalisa Berzigotti¹⁰, Pierre-Emmanuel Rautou⁹, Candid Villanueva⁸, Pere Ginès¹, Juan Carlos Garcia Pagan¹, Bogdan Procopet¹⁶, Christophe Bureau¹⁵, Agustin Albillos⁵, Sven Francque¹⁴, Thomas Reiberger³, Filippo Schepis², Isabel Graupera¹, Virginia Hernandez-Gea¹. ¹Hospital Clínic de Barcelona, Liver Unit. Servei d'Hepatologia, Barcelona, Spain; ²Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy; ³Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Wien, Austria; ⁴University of Zurich, Epidemiology, Biostatistics, and Epidemiology Institute, Zürich, Switzerland; ⁵Hospital

Ramón y Cajal, Department of Gastroenterology and Hepatology, Madrid, Spain; ⁶Hôpital Purpan, Department of Hepato-Gastroenterology, Toulouse, France; ⁷Institutul Regional de Gastroenterologie și Hepatologie Prof. Dr. Octavian Fodor, Cluj-Napoca, Romania; ⁸Hospital de la Santa Creu i Sant Pau, Servei de Patologia Digestiva, Barcelona, Spain; ⁹Hospital Beaujon AP-HP, Service d'Hépatologie, DMU Digest, Clichy, France; ¹⁰Inselspital, Hepatology. University Clinic of Visceral Surgery and Medicine, Bern, Switzerland; ¹¹Marqués de Valdecilla University Hospital, Gastroenterology and Hepatology Department, Santander, Spain; ¹²Gregorio Marañón Hospital, Servicio de Gastroenterología y Hepatología, Madrid, Spain; ¹³Policlinico of Milan, Division of Gastroenterology and Hepatology. Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milano, Italy; ¹⁴Antwerp University Hospital, Department of Gastroenterology and Hepatology Laboratory of Experimental Medicine and Pediatrics (LEMP) Faculty of Medicine and Health Sciences, Edegem, Belgium; ¹⁵Hôpital Purpan, Department of Hepato-Gastroenterology. CHU Toulouse, InSERM U858, University of Toulouse, Université Paul Sabatier Toulouse, France, Toulouse, France; ¹⁶Institutul Regional de Gastroenterologie și Hepatologie Prof. Dr. Octavian Fodor, Hepatology Department and "Iuliu Hatieganu" University of Medicine and Pharmacy, 3rd Medical Clinic, Cluj Napoca, Romania, Cluj-Napoca, Romania; ¹⁷Hospital Universitari Vall d'Hebron, Liver Unit. Department of Internal Medicine, Barcelona, Spain; ¹⁸Puerta de Hierro Majadahonda University Hospital, Universidad Autónoma de Madrid. Liver Unit., Majadahonda, Spain; ¹⁹University Hospital Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium; ²⁰Goethe University Frankfurt, Translational Hepatology. Department of Internal Medicine, Frankfurt, Germany; ²¹Universität Bonn, Department of Internal Medicine, Bonn, Germany; ²²Hospital Germans Trias i Pujol, Universidad Autónoma de Barcelona, Badalona, Spain; ²³Martin-Luther-University Halle-Wittenberg, First Department of Internal Medicine, Halle (Saale), Germany
Email: vihernandez@clinic.cat

Background and aims: Portal hypertension is a key determinant of hepatic decompensation and death in patients with cirrhosis. The hepatic vein catheterization with hepatic vein pressure gradient (HVPG) measurement is the gold standard technique to measure portal vein pressure in patients with cirrhosis. Concerns have been raised about the accuracy of HVPG for determining the portal pressure gradient in patients with non-alcoholic fatty liver disease (NAFLD). We aimed to evaluate the relationship between HVPG and portal hypertension related decompensation in patients with advanced NAFLD (aNAFLD).

Method: We designed a multicenter cross-sectional study including 548 patients with advanced NAFLD and 444 with hepatitis C (HCV-RNA-positive; aHCV) who had detailed portal hypertension evaluation (HVPG measurement, gastroscopy and abdominal imaging). We examined the relationship between etiology, HVPG, and decompensation by logistic regression models. We also compared the proportions of compensated/decompensated patients at different HVPG levels.

Results: Both cohorts, aNAFLD and aHCV, had similar baseline age, gender, Child-Pugh score, and MELD. Median HVPG was lower in the aNAFLD cohort (13 vs 15 mmHg). However, rates of clinical decompensation and high-risk varices were higher in aNAFLD group (32% vs 25%, $p = 0.019$; and 32% vs 27%, $p = 0.103$) than in the aHCV group. Decompensated aNAFLD patients had lower median HVPG (17 mmHg vs 19 mmHg, $p = 0.001$) than aHCV patients. Moreover, the prevalence of decompensation was higher than in the aHCV group for any HVPG threshold.

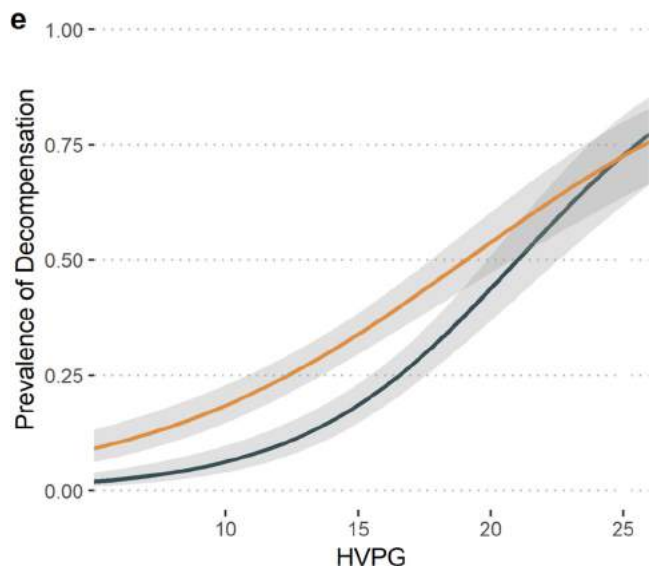


Figure:

Conclusion: Patients with aNAFLD have higher rate of portal hypertension related decompensation at any value of HVPG as compared to aHCV patients. Longitudinal studies aiming to identify HVPG thresholds able to predict decompensation and longterm outcomes in aNAFLD population are strongly needed.

OS-612

Lean NAFLD from the General French Population have more Severe Liver Disease and Poorer Clinical Outcomes (NASH-CO Study)

Oumarou Nabi¹, Nathanaël Lapidus², Karine Lacombe^{3,4}, Jerome Boursier^{5,6}, Philippe Mathurin^{7,8}, Victor de Lédighen⁹, Marie Zins^{10,11}, Marcel Goldberg^{10,12,13}, Lawrence Serfaty¹⁴. ¹Institute Pierre Louis Epidemiology And Public Health, Sorbone Universite, Paris, France; ²Institute Pierre Louis Epidemiology And Public Health, Sorbone Universite, Paris, France; ³Institute Pierre Louis Epidemiology And Public Health, Epidemiology, Paris, France; ⁴Hôpital Saint-Antoine, APH, Infectious Diseases Department, Hôpital Saint-Antoine, Paris, France; ⁵centre hospitalier universitaire d'Angers, Angers, France; ⁶UPRES EA3859, Anger, France; ⁷Chu De Lille, Lille, France; ⁸Inserm U995, Lille, France; ⁹Hospital Center University De Bordeaux, Bordeaux, France; ¹⁰Université Versailles Saint-Quentin-en-Yvelines, Guyancourt, France; ¹¹Inserm UMS 11, Epidemiology en population, Paris, France; ¹²Hôpital Paul-Brousse Ap-Hp, Epidemiology, Villejuif, France; ¹³Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ¹⁴Arlin Alsace Hospitals Academics De Strasbourg, Médecine/Hepatogastroenterology Service, Strasbourg, France
Email: lawrence.serfaty@chru-strasbourg.fr

Background and aims: While obesity is a major risk factor, non-alcoholic fatty liver disease (NAFLD) has also been reported in lean subjects. In this clinical setting, severity of liver injury and clinical outcomes are debated and few studies have been conducted at a general population level. This study aimed to assess prevalence, characteristics and mortality outcomes of lean NAFLD in the French adult population.

Method: The study population consisted of 127, 291 participants from the nationwide CONSTANCES cohort. After exclusion of subjects with excessive alcohol consumption, viral hepatitis or other liver diseases, 110, 120 were analyzed. Non-invasive diagnosis of NAFLD and advanced fibrosis was performed using the combination of Fatty Liver Index and Forns Index. Outcomes analyzed were liver-related events, hepatocellular carcinoma (HCC), cardiovascular disease (CVD), extrahepatic cancer (EHC), chronic kidney disease (CKD), liver transplantation and overall mortality. The median follow-up was 30 months.

Results: The prevalence of NAFLD was 18.1% in overall population and 5.3% in lean subjects, while 16.3% of NAFLD subjects were lean. Compared to non-lean, lean NAFLD were significantly younger and more frequently women, had fewer metabolic risk factors, were more frequently tobacco user and moderate alcohol consumer (all P value <0.001). Prevalence rates of elevated ALT and advanced fibrosis were significantly higher in lean compared to non-lean NAFLD (34.4% vs 20.9%, P<0.001 and 3.6% vs 1.7%, P<0.001, respectively). When adjustment for usual risk factors, NAFLD in lean subjects was associated with increased risk of liver-related events (aHR = 5.48, 95%CI 3.43–8.75), HCC (aHR = 3.35, 1.72–6.55), CVD (aHR = 1.72, 1.25–2.37), EHC (aHR = 2.90, 2.27–3.71), CKD (aHR = 2.11, 1.43–3.11) and overall mortality (aHR = 2.26, 1.76–2.91). Among NAFLD subjects, lean status was associated with increased risk of hepatic events (aHR = 9.10, 95%CI 4.48–18.48), HCC (aHR = 3.86, 1.35–11.03), EHC (aHR = 2.46, 1.78–3.38) and overall mortality (aHR = 3.76, 2.41–5.85), irrespective of usual risk factors.

Conclusion: From a large French community-based cohort, this study confirms the significant prevalence of lean NAFLD and suggests that NAFLD is more severe in terms of advanced fibrosis, liver disease progression and overall mortality in lean compared to non-lean subjects, despite fewer metabolic risk factors. Differences in lifestyle, genetics and microbiota may explain those results.

OS-635

Increased serum ferritin levels predict long-term mortality in patients with NAFLD

Angelo Armandi¹, Ramy Younes², Gian Paolo Caviglia¹, Salvatore Petta³, Luca Miele^{4,5}, Chiara Rosso¹, Grazia Pennisi³, Paolo Francione⁶, Antonio Liguori⁵, Olivier Govaere⁷, Anna Ludovica Fracanzani⁶, Mohammed Eslam⁸, Luca Valenti⁶, Jacob George⁸, Manuel Romero Gomez⁹, Quentin Anstee⁷, Elisabetta Bugianesi¹. ¹Division of Gastroenterology and Hepatology, A. O. Città della Salute e della Scienza di Torino, University of Turin, Department of Medical Sciences, Turin, Italy; ²Boehringer Ingelheim International, Gesellschaft mit beschränkter Haftung, Ingelheim, Germany; ³Sezione di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo, Palermo, Italy; ⁴Area Medicina Interna, Gastroenterologia e Oncologia Medica, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy; ⁵Università Cattolica del Sacro Cuore, Rome, Italy; ⁶Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Unit of Medicine and Metabolic Disease, Department of Pathophysiology and Transplantation, Milan, Italy; ⁷The Newcastle Liver Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, Northern Ireland; ⁸Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Westmead, NSW, Australia; ⁹Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Seville, Spain
Email: angelo.armandi@unito.it

Background and aims: Hyperferritinemia is common in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and correlates with the severity of liver fibrosis. Our aim was to assess the impact of ferritin on long-term outcomes and survival in a large cohort of NAFLD patients.

Method: We included 1247 patients with biopsy-proved NAFLD from tertiary centers in Italy (Turin, Milan, Rome, Palermo), Australia (Sydney), UK (Newcastle) and Spain (Seville). Clinical and biochemical data were collected at the time of liver biopsy. Ferritin levels of 300 ug/L for men and 200 ug/L for women were considered as the upper limit of normal (ULN). Clinical outcomes, including liver-related events (ascites, encephalopathy, variceal bleeding), hepatocellular carcinoma (HCC) and survival, were collected after a median follow-up of 90 months.

Results: The median age of the study cohort was 48 [IQR 38–57] years and 814 (65.3%) patients were male. The overall prevalence of obesity and type 2 diabetes was 45.0% and 28.1%. Overall, hyperferritinemia

ORAL PRESENTATIONS

was found in 373 (29.9%) patients; severe fibrosis (F3-4) was found at liver biopsy in 272 (21.8%) patients. NASH was diagnosed in 756 (60.6%) cases and was similarly distributed between those with normal and high ferritin levels. Serum ferritin $>2 \times$ ULN (32.2% of the total population with hyperferritinemia), significantly associated with F3-4 (OR = 2.10 [95% CI 1.40–3.14], $p < 0.001$). After a median follow-up of 90 months, 24 patients (2.3%) died, while 57 (4.8%) and 18 (1.5%) developed liver-related events and HCC. At univariate analysis, the incidence of liver-related events and mortality varied significantly according to serum ferritin values $>2 \times$ ULN (log-rank test: $p = 0.004$ and $p = 0.001$, respectively). However, at multivariate Cox regression analysis adjusted for age, body mass index, diabetes and fibrosis, ferritin levels $>2 \times$ ULN independently predicted mortality (HR = 3.04 [95% CI 1.16–7.93], $p = 0.023$) but not liver-related events (HR = 1.67 [95% CI 0.90–3.11], $p = 0.105$).

Conclusion: Ferritin levels higher than $2 \times$ ULN are associated with severe liver fibrosis in NAFLD patients and are able to predict long-term mortality.

Funded by:

Horizon2020 under grant agreement: no.634413, EPoS; no.777377, LITMUS.

The Italian Ministry for Education, University and Research (Ministero dell'Istruzione, dell'Università e della Ricerca-MIUR) under the programme "Dipartimenti di Eccellenza 2018–2022" Project code D15D18000410001.

OS-1611

AI-based histologic measurement of NASH (AIM-NASH): A drug development tool for assessing clinical trial end points

Oscar Carrasco-Zevallos¹, Amaro Taylor-Weiner¹, Harsha Pokkalla¹, Maryam Pouryahya¹, Charles Biddle-Snead¹, Ling Han², Ryan Huss², Dinkar Juyal¹, Zahil Shanis¹, Aryan Pedawi¹, Quang Le¹, Kenneth Leidal¹, Victoria Mountain¹, Sara Hoffman¹, Jackie Honerlaw¹, Murray Resnick¹, Rohit Loomba³, Arun Sanyal⁴, Chuhan Chung², Robert Myers², Michael Montalto¹, Andrew Beck¹, Ilan Wapinski¹, Katy Wack¹. ¹PathAI, Boston, United States; ²Gilead Sciences, Inc., Foster City, United States; ³University of California at San Diego, Division of Gastroenterology, San Diego, United States; ⁴Virginia Commonwealth University, School of Medicine, Richmond, United States
Email: katy.wack@pathai.com

Background and aims: Limitations of manual pathology may confound results of NASH clinical trials. Our aim was to develop an AI-based drug development tool (AIM-NASH) that reproducibly calculates NASH Clinical Research Network (CRN) scores.

Method: AIM-NASH machine learning (ML) models were developed using 5923 biopsies from six phase 2b or 3 trials in NASH subjects with F1-F4 fibrosis. Models were trained to identify NASH histologic features and predict ordinal CRN scores using $>100k$ annotations from expert pathologists. Analytic performance was tested in a held-out dataset of 639 HandE- and 633 trichrome-stained biopsy images (NCT02784444; EMINENCE). Agreement between AIM-NASH scores and the consensus of 3 expert hepatopathologists was evaluated using linearly-weighted Kappa (κ) statistics. Histologic end points were retrospectively assessed by AIM-NASH and central reader scores from a separate phase 2b trial (NCT03449446; ATLAS). Comparisons of treatment responses between groups were made using the Mantel-Haenszel test, stratified by diabetes and cirrhosis status.

Results: Agreement between AIM-NASH and consensus reads was higher than that among pathologists [AIM-NASH steatosis $\kappa = 0.71$ (95% CI 0.67–0.74) vs mean pairwise inter-pathologist steatosis $\kappa = 0.60$ (0.56–0.63); lobular inflammation $\kappa = 0.50$ (0.45–0.55) vs 0.33 (0.29–0.37); ballooning $\kappa = 0.58$ (0.53–0.63) vs 0.48 (0.44–0.52); fibrosis $\kappa = 0.58$ (0.54–0.62) vs 0.50 (0.47–0.53)]. In ATLAS, AIM-NASH identified more responders vs the central reader in subjects treated with cilofexor and firsocostat for ≥ 1 -stage fibrosis improvement

without NASH worsening (26% vs 21%), NASH resolution without fibrosis worsening (16% vs 5%), and ≥ 2 -point reduction in NAS (68% vs 38%), and greater improvements in treated subjects vs placebo (Table).

Table: AIM-NASH and Central Reader Assessments of Treatment Response in ATLAS (F3-F4).

End points*	AIM-NASH		P value	Central Reader		P value
	CILO+FIR	Placebo		CILO+FIR	Placebo	
Fibrosis improvement without NASH worsening	26% (16/61)	13% (4/32)	0.142	21% (13/63)	11% (4/38)	0.190
NASH resolution without fibrosis worsening	16% (9/55)	7% (2/27)	0.212	5% (3/63)	0% (0/38)	0.332
≥ 2 -pt reduction in NAS	68% (40/59)	27% (8/30)	<0.001	38% (24/64)	11% (4/38)	0.001

* Sample size for each end point varies due to data availability. CILO, cilofexor; FIR, firsocostat; NAS, NAFLD Activity Score.

Conclusion: AIM-NASH enables automated, and sensitive ML-based CRN scoring, and generates reproducible assessments of disease activity from biopsy samples. AIM-NASH may potentially support standardized evaluation of histologic end points in NASH clinical trials.

OS-1780

Incidence rates of select outcomes among patients with non-alcoholic steatohepatitis (NASH) and evidence of fibrosis or cirrhosis

Monica Bertoia¹, Erik Ness², Thomas Capozza², Lina Titievsky², John D. Seeger¹. ¹Optum Life Sciences, United States; ²Intercept Pharmaceuticals, Inc., New York, United States
Email: monica.bertoaio@optum.com

Background and aims: There are limited epidemiologic data available characterizing patients with NASH using longitudinal data, and rates of rare events require a large patient sample. Electronic health record (EHR) databases represent useful real-world data sources for studying the epidemiology of NASH. This study aimed to systematically estimate incidence rates (IRs) of over 40 a priori outcomes within a cohort of patients with NASH.

Method: Patients with NASH were identified between 2016 and 2019 within Optum's EHR Research Database by structured (diagnosis codes, procedure codes, labs) and natural language processing (NLP) data. Patients with NASH were classified as having cirrhosis or fibrosis using information from the baseline period (the year prior to and including cohort entry). Outcomes were identified in the time following cohort entry using International Classification of Diseases, 10th revision diagnosis codes and lab values. Outcome IRs were estimated among the subset of patients at risk for that particular outcome at the beginning of follow-up (after excluding those with a prior history).

Results: Among 93, 204 patients identified as having NASH, 44, 685 (48%) had evidence of fibrosis and 29, 770 (32%) had evidence of cirrhosis. Patients with NASH were an average of 58 years old, 60% were female, and 81% were white. Estimated IRs of select outcomes are summarized in Table. IRs were highest for NASH patients with cirrhosis. IRs of kidney and cardiovascular outcomes were up to ~2-fold higher for patients with cirrhosis compared to those with fibrosis, and IRs of liver outcomes were several-fold higher.

Table: Incidence rates (95% CIs) per 1, 000 person-years of select outcomes among patients with NASH

	NASH with Fibrosis N = 44, 685	NASH with Cirrhosis N = 29, 770
Chronic kidney disease	98.31 (95.57–102.28)	215.46 (209.41–224.2)
Cerebrovascular accident	15.81 (14.84–17.26)	23.83 (22.3–26.11)
Myocardial infarction	12.08 (11.24–13.34)	26.65 (25.03–29.05)
Liver transplant	0.09 (0.03–0.25)	2.70 (2.22–3.5)
Hepatocellular carcinoma	0.91 (0.69–1.29)	7.31 (6.49–8.58)

Conclusion: This large EHR-based cohort of patients with NASH provides estimated IRs with narrow CIs even for rare outcomes such as liver transplant and hepatocellular carcinoma. These results showing a higher risk of various outcomes with more advanced fibrosis add to the evolving body of literature on the impact of hepatic fibrosis in patients with NASH.

OS-2337

Prevalence estimation of significant fibrosis due to non-alcoholic steatohepatitis combining transient elastography and histology

Jesús Rivera¹, José Luis Calleja², Rocío Aller³, Hugo Gonzalo-Benito³, María Teresa Arias Loste⁴, Paula Ireuzubieta⁴, Javier Ampuero⁵, Ana Lucena⁵, Yolanda Sanchez⁵, Manuel Romero-Gomez⁵, Salvador Augustin¹, Javier Crespo⁴. ¹Vall d'Hebron Hospital Universitari, Liver Unit, Department of Internal Medicine, Barcelona, Spain; ²Hospital Universitario Puerta de Hierro, Majadahonda, Department of Gastroenterology and Hepatology; ³Clinic University Hospital, Department of Gastroenterology; ⁴Marqués de Valdecilla University Hospital, Gastroenterology and Hepatology Department; ⁵University Hospital Virgen del Rocío, Unit of Digestive Diseases and Ciberehd

Email: jesusriveraest@gmail.com

Background and aims: Metabolic associated fatty liver disease (MAFLD) has become a major public health problem, but the prevalence in the general population of fibrosis associated to non-alcoholic steatohepatitis (NASH) is largely unknown. The aim of this study was to provide an updated estimation of the prevalence of NASH fibrosis in Spain.

Method: This is an observational, retrospective, cross-sectional, population-based study. For the prevalence estimations, data was merged from 2 Spanish datasets: a large (N = 12246) population-based cohort (ETHON cohort), including transient elastography (TE) data, and a contemporary multi-centric biopsy-proven NASH cohort with paired TE data from tertiary centers (N = 501).

Results: From the ETHON dataset of patients with valid TE, 5.61% (95% Confidence Interval –95CI- 2.53–11.97) had a liver stiffness measurement (LSM) ≥8 kPa. The proportion attributable to MAFLD (using clinical variables and Controlled Attenuation Parameter data) was 57.3%. The estimated prevalence attributable to MAFLD in the population with LSM ≥8 kPa was 3.21% (95CI 1.13–8.75). In the cohort of patients with biopsy-proven NASH, 389 had LSM ≥8 kPa and among these, 36% did not have significant fibrosis (F2-4). Even at the highest interval (LSM ≥20 kPa), there was a substantial proportion of patients without cirrhosis (39%) in this biopsy-proven cohort. Prevalence for each NASH fibrosis stage in Spain was estimated by crossing TE data from ETHON with histology data from the biopsy-proven cohort and detailed in the table. The estimated prevalence of NASH F2-3 and cirrhosis in Spain's adult population were 1.33% (95CI 0.29–5.98) and 0.70% (95CI 0.10–4.95), respectively.

Conclusion: These estimations provide an accurate picture of the current prevalence of NASH in Spain and can serve as reference point for European populations for dimensioning the therapeutic efforts that will be required as NASH therapies become available.

Figure: Liver fibrosis distribution per LSM threshold and NASH prevalence per fibrosis stages in Spain's general population:

FIBROSIS STAGES	NASH FIBROSIS PREVALENCE (%)				
	LSM ≥8 kPa (%)	LSM ≥8 kPa (95%CI)	SIGNIFICANT FIBROSIS (F2-F4)	TREATABLE STAGES (F2-F3)	CIRRHOSIS (F4)
F0	13.37	0.43 (0.04–4.49)			
F1	23.39	0.75 (0.11–5.04)			
F2	17.99	0.58 (0.07–4.75)	2.03	1.33	
F3	23.39	0.75 (0.11–5.04)	(0.56–7.05)	(0.29–5.98)	
F4	21.85	0.70 (0.10–4.95)			0.70 (0.10–4.95)
TOTAL	100	3.21 (1.13–8.75)			

NAFLD - Diagnostics and non-invasive assessment

OS-243

Comparative diagnostic accuracy of blood-based biomarkers for staging fibrosis in NAFLD: phase 1 results of the LITMUS project

Jenny Lee¹, Yasaman Vali², Jerome Boursier³, Salvatore Petta⁴, Dina Tiniakos⁵, Pierre Bedozza⁵, M. Julia Brosnan⁶, Kevin Duffin⁷, Richard Torstenson⁸, Clifford Brass⁹, Mike Allison¹⁰, Helena Cortez-Pinto¹¹, Jean-Francois Dufour¹², Mattias Ekstedt¹³, Sven Franke¹⁴, Andreas Geier¹⁵, Stephen Harrison¹⁶, Morton Karsdal¹⁷, Diana Julie Leeming¹⁷, George Papatheodoridis¹⁸, Michael Pavlides¹⁹, Jörn M. Schattenberg²⁰, Manuel Romero-Gomez²¹, Vlad Ratziu²², Elisabetta Bugianesi²³, Patrick M. Bossuyt¹, Quentin M. Anstee⁵. ¹Amsterdam University Medical Center, Department of Epidemiology and Data Science, Amsterdam, Netherlands; ²Amsterdam University Medical Center, Department of Epidemiology and Data Science; ³Angers University Hospital, Hepatology Department; ⁴Università di Palermo, Dipartimento Biomedico di Medicina Interna e Specialistica; ⁵Newcastle University, Translational and Clinical Research Institute; ⁶Pfizer, Internal Medicine Research Unit; ⁷Eli Lilly and Company Ltd (LLY), Lilly Research Laboratories; ⁸AstraZenica; ⁹Novartis Pharmaceuticals Corporation; ¹⁰Cambridge NIHR Biomedical Research Centre, Department of Medicine; ¹¹Lisbon University; ¹²University of Bern, Department of Biomedical Research; ¹³Linköping University, Department of Health, Medicine and Caring Sciences; ¹⁴Antwerp University; ¹⁵Wurzburg University Hospital, Department Medicine II; ¹⁶Oxford University; ¹⁷Nordic Bioscience A/S; ¹⁸National and Kapodistrian University of Athens, Gastroenterology Department; ¹⁹Oxford University; ²⁰University Hospital Mainz, Department of Medicine; ²¹Virgen del Rocío University Hospital; ²²Sorbonne University, Assistance Publique-Hôpitaux de Paris; ²³University of Turin, Department of Medical Sciences

Email: j.a.lee@amsterdamumc.nl

Background and aims: Accurate staging of fibrosis in NAFLD is essential for clinical care delivery and trial recruitment. There is a pressing need for robust, comparative analysis on performance of non-invasive tests (NITs). The LITMUS project independently validated NITs that, singly or in combination, enable detection of high-risk NAFLD patients.

Method: Comparative diagnostic accuracy study in the LITMUS Metacohort, including biopsy-proven NAFLD patients in Europe, recruited 2010–18. Fibrosis was staged by the NASH CRN score. Biopsies were locally read. Sixteen NITs, including single markers and

ORAL PRESENTATIONS

combinations were evaluated against liver biopsy for three target conditions: significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$), and cirrhosis (F4). The area under the receiver operating curve (AUC) \pm 95% confidence interval were calculated for each NIT in comparison to FIB-4 in the same patients.

Results: Data from 686 participants (nine centers) were included. Mean age 50 yrs; 57% male; 36% T2DM; mean BMI 35. Fibrosis: 44% $F \geq 2$, 26% $F \geq 3$, and 7% F4. Most combination panels (ELF, MACK-3, FIB3, ABC3D, NFS) had comparable accuracy to FIB-4, while single markers (PRO-C3, CK18, etc.) performed significantly worse. AUCs for $F \geq 2$ ranged from 0.54 to 0.86 with only the SomaScan™ model significantly outperforming FIB-4. For $F \geq 3$ (AUC: 0.53–0.85) SomaScan and ADAPT had significantly better AUC compared to FIB-4. The AUCs for several NITs exceeded 0.80 in detecting F4 (AUC: 0.53–0.90), most of which were combinations (Table 1).

Table 1: Accuracy of NITs in detecting fibrosis compared to FIB-4

NIT.	n.	AUC (95% CI).					
		$F \geq 2$.		$F \geq 3$.		F4.	
		NIT.	FIB-4.	NIT.	FIB-4.	NIT.	FIB-4.
SomaScan	278	0.86 (0.82–0.90)	0.69 (0.63–0.75)	0.89 (0.85–0.93)	0.74 (0.69–0.80)	0.88 (0.80–0.96)	0.81 (0.75–0.88)
ADAPT	417	0.78 (0.74–0.83)	0.74 (0.70–0.79)	0.85 (0.81–0.89)	0.76 (0.71–0.82)	0.90 (0.85–0.95)	0.83 (0.76–0.91)
MACK-3	391	0.79 (0.74–0.84)	0.73 (0.68–0.78)	0.80 (0.75–0.85)	0.77 (0.72–0.83)	0.71 (0.59–0.82)	0.84 (0.76–0.92)
ELF	673	0.69 (0.65–0.73)	0.74 (0.70–0.77)	0.78 (0.74–0.82)	0.78 (0.74–0.82)	0.83 (0.76–0.90)	0.85 (0.79–0.91)
PRO-C3	431	0.67 (0.62–0.72)	0.75 (0.70–0.79)	0.75 (0.69–0.80)	0.77 (0.72–0.82)	0.80 (0.72–0.88)	0.83 (0.76–0.91)

Conclusion: NITs performed well, especially for detecting cirrhosis (F4). For intermediate fibrosis stages ($F \geq 2$, $F \geq 3$), combination panels exhibited the highest AUCs. SomaScan and ADAPT had greater sensitivity than FIB-4 for intermediate stages, while the ELF test offered no advantage over FIB-4. Validation in an expanded cohort is underway.

OS-538

Genome-scale metabolic modeling of human hepatocytes reveals dysregulation of glycosphingolipid pathways in progressive non-alcoholic fatty liver disease

Partho Sen^{1,2}, Olivier Govaere³, Tim Sinioja⁴, Aidan McGlinchey⁵, Dawei Geng⁴, Vlad Ratziu⁶, Elisabetta Bugianesi⁷, Jörn Schattenberg⁸, Antonio Vidal-Puig⁹, Michael Allison¹⁰, Simon Cockell¹¹, Ann K. Daly¹¹, Tuulia Hyötyläinen¹², Quentin Anstee³, Matej Orešič^{2,5}.
¹School of Medical Sciences, Örebro University, Örebro, Sweden; ²Turku Bioscience, University of Turku, Systems Medicine Group, Turku, Finland; ³Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, United Kingdom; ⁴Department of Chemistry, Örebro University, Örebro, Sweden; ⁵School of Medical Sciences, Örebro University, Örebro, Sweden; ⁶Assistance Publique-Hôpitaux de Paris, hôpital Beaujon, University Paris-Diderot, Paris, France; ⁷Department of Medical Sciences, Division of Gastro-Hepatology, Turin, Italy; ⁸Metabolic Liver Research Programm, Department of Medicine, University Hospital Mainz, Mainz, Germany; ⁹University of Cambridge Metabolic Research Laboratories, Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom; ¹⁰Liver Unit, Department of Medicine, Cambridge Biomedical Research Centre, Cambridge University NHS Foundation Trust, Cambridge, United Kingdom; ¹¹Newcastle University, Translational

and Clinical Research Institute, Faculty of Medical Sciences, Newcastle, United Kingdom; ¹²Department of Chemistry, Örebro University, Örebro, Sweden

Email: partho.sen@utu.fi

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver diseases intertwined with the metabolic disorders. The prevalence of NAFLD is rapidly increasing worldwide, while the pathology and the underlying mechanism driving NAFLD is not fully understood. In NAFLD, a series of metabolic changes takes place in the liver. However, the alteration of the metabolic pathways in the human liver along the progression of NAFLD, *i.e.*, transition from non-alcoholic steatosis (NAFL) to steatohepatitis (NASH) through cirrhosis remains to be discovered. Here, we sought to examine the metabolic pathways of the human liver across the full histological spectrum of NAFLD.

Method: We analyzed the whole liver tissue transcriptomic (RNA-Seq)¹ and serum metabolomics data obtained from a large cohort of histologically characterized patients derived from the European NAFLD Registry (n = 206), and developed genome-scale metabolic models (GEMs) of human hepatocytes at different stages of NAFLD. The integrative approach employed in this study has enabled us to understand the regulation of the metabolic pathways of human liver in NAFL, and with progressive NASH-associated fibrosis (F0–F4).

Results: Our study identified several metabolic signatures in the liver and blood of these patients, specifically highlighting the alteration of vitamins (A, E) and glycosphingolipids, and their link with complex glycosaminoglycans in advanced fibrosis. Furthermore, by applying genome-scale metabolic modeling, we were able to identify the metabolic differences among carriers of widely validated genetic variants associated with NAFLD/NASH disease severity in three genes (PNPLA3, TM6SF2 and HSD17B13).

Conclusion: The study provides insights into the underlying pathways of the progressive-fibrosing steatohepatitis. Of note, there is a marked dysregulation of the glycosphingolipid metabolism in the liver of the patients with advanced fibrosis.

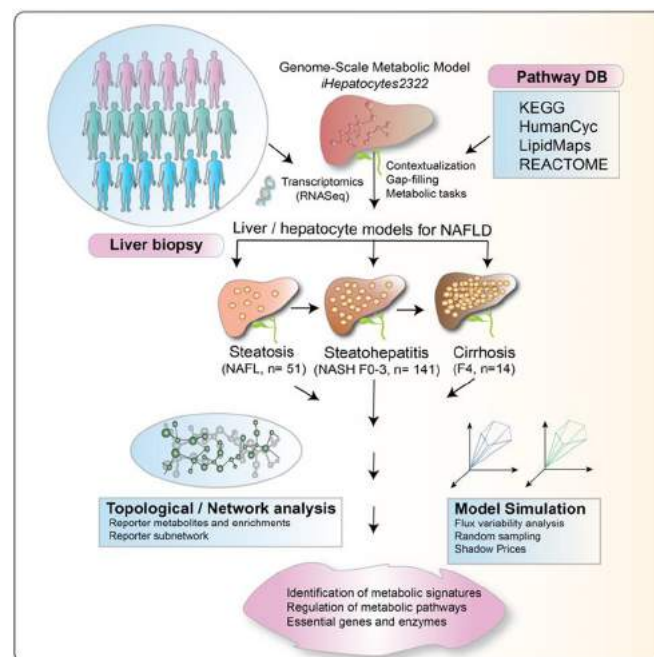


Figure: Study design and schematic illustration.

Reference:

- Govaere *et al.* Transcriptomic profiling across the non-alcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. *Science translational medicine* 12, doi:10.1126/scitranslmed.aba4448 (2020).

OS-555

Development and validation of Agile 3+: novel FibroScan based score for the diagnosis of advanced fibrosis in patients with non-alcoholic fatty liver disease

Zobair Younossi¹, Stephen Harrison², Philip N. Newsome^{3,4,5}, Wah-Kheong Chan⁶, Yusuf Yilmaz^{7,8}, Victor de Lédinghen⁹, Charlotte Costentin¹⁰, Ming-Hua Zheng¹¹, Vincent Wai-Sun Wong¹², Magdy Elkhatab¹³, Ryan Huss¹⁴, Robert Myers¹⁴, Julie Foucquier¹⁵, Labourdette Aymeric¹⁵, Marie Destro¹⁵, Céline Fournier¹⁵, Véronique Miette¹⁵, Laurent Sandrin¹⁵, Jerome Boursier^{16,17}, Arun Sanyal^{18,19}. ¹Inova Health System, Inova Medicine, Falls Church, VA, United States; ²University of Oxford, Radcliffe Department of Medicine, Oxford, United Kingdom; ³Birmingham University Hospital, National Institute for Health Research Biomedical Research Centre, Birmingham, United Kingdom; ⁴University of Birmingham, Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom; ⁵University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham, United Kingdom; ⁶University of Malaya, Department of Medicine, Faculty of Medicine, Kuala Lumpur, Malaysia; ⁷Marmara University, Liver Research Unit, Institute of Gastroenterology, Istanbul, Turkey; ⁸Marmara University, Department of Gastroenterology, School of Medicine, Istanbul, Turkey; ⁹Haut Leveque Hospital, Hepatology, Gastroenterology and Digestive Oncology, Pessac, France; ¹⁰Grenoble Alpes University Hospital, Hepatology, Gastroenterology and Digestive Oncology, Grenoble, France; ¹¹First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ¹²The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China; ¹³Toronto Liver Centre, Toronto, Canada; ¹⁴Gilead Sciences, Foster City, CA, United States; ¹⁵Echosens, Paris, France; ¹⁶Angers University Hospital, Hepato-gastroenterology and Digestive Oncology Department, Angers, France; ¹⁷Angers University, HIFIH UPRES EA3859 Laboratory, Angers, France; ¹⁸VCU Health System, Richmond, VA, United States; ¹⁹on behalf of the NASH Clinical Research Network, NIDDK, NIH
Email: zobair.younossi@inova.org

This abstract is under embargo until the beginning of the press conference it is being presented in on Friday 25 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

OS-1556

Change in FibroScan-aspartate aminotransferase (FAST) score is associated with histological improvement in non-alcoholic steatohepatitis activity

Vincent Wai-Sun Wong¹, Quentin Anstee^{2,3}, Anja Geerts⁴, Mette Kjaer⁵, Steen Ladelund⁵, Louise Nitze⁵, Vlad Ratziu⁶, Adriana Rendon⁵, Jacob George⁷, Philip N. Newsome⁸. ¹The Chinese University of Hong Kong, Hong Kong, China; ²Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom;

ORAL PRESENTATIONS

³Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; ⁴Hepatology Research Unit, Ghent University, Ghent, Belgium; ⁵Novo Nordisk A/S, Søborg, Denmark; ⁶Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France; ⁷Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia; ⁸University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom
Email: wongv@cuhk.edu.hk

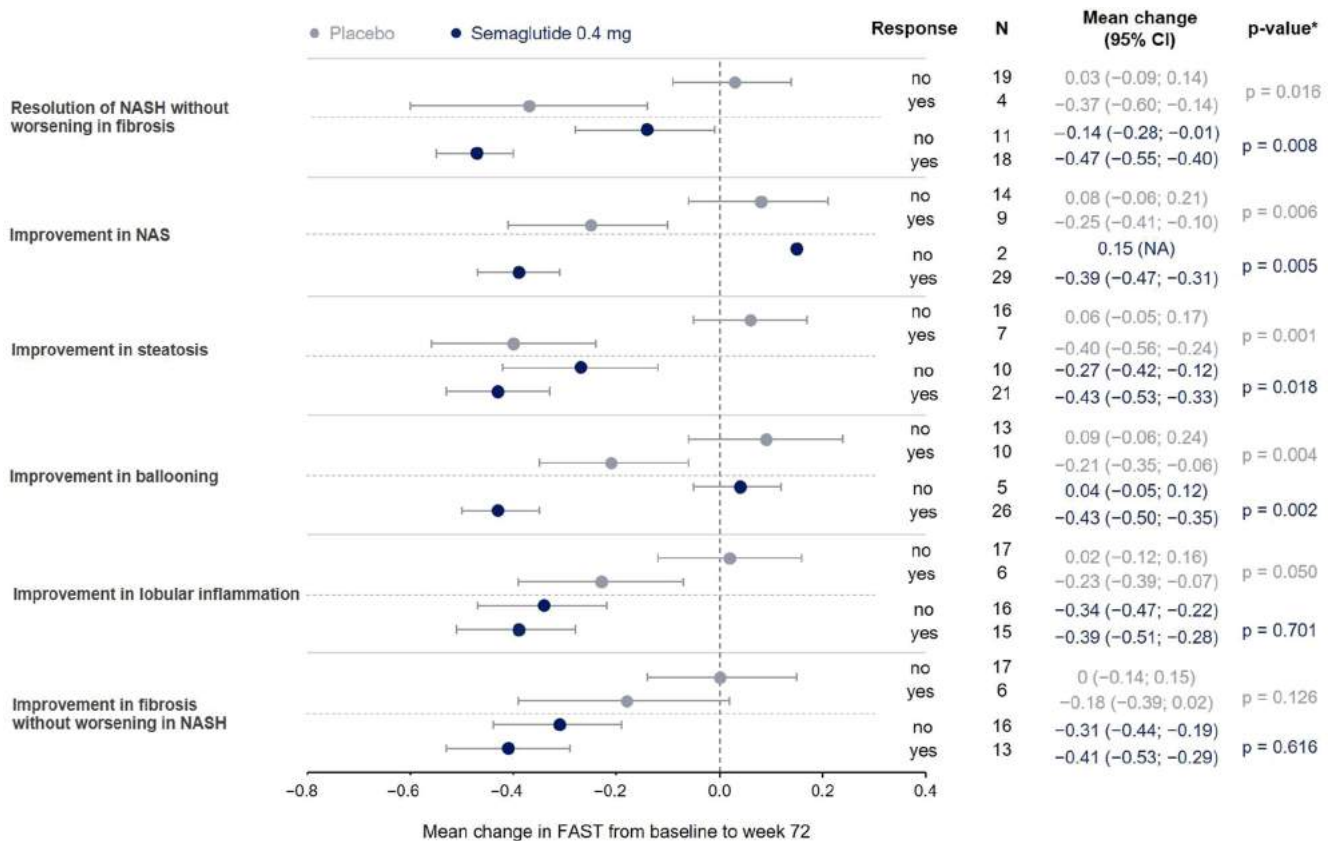
Background and aims: FibroScan® liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) combined with aspartate aminotransferase (AST)-known as FibroScan-AST (FAST)-is a non-invasive method to identify patients with non-alcoholic steatohepatitis (NASH) at risk of progressive disease. Here, we evaluate whether changes in FAST correlate with histological changes in placebo and semaglutide-treated patients with NASH.

Method: In a 72-week phase 2 trial (NCT02970942), 320 patients with NASH and F1-F3 fibrosis were randomised to semaglutide (0.1, 0.2 or 0.4 mg) or placebo. Treatment with semaglutide 0.4 mg showed significant NASH resolution and a non-significant trend for fibrosis improvement vs placebo. This *post-hoc* analysis compared changes in FAST score from baseline to week 72 with histological change in non-alcoholic fatty liver disease activity score (NAS, using

analysis of covariance) and other clinical parameters (Kendall Tau-b correlations) in all randomised patients during the on-treatment period. Biopsies were performed at baseline and at week 72 to determine NAS and fibrosis stage.

Results: In total, 161 patients had FAST scores assessed at baseline and at week 72. Treatment with semaglutide for 72 weeks led to reductions in FAST score and the individual components (LSM, CAP and AST) in a dose-dependent manner. At week 72, mean reductions in FAST score (estimated treatment ratio vs placebo) were 0.7, 0.5 and 0.4 with semaglutide 0.1, 0.2 and 0.4 mg, respectively. Reductions in FAST scores for both placebo and semaglutide 0.4 mg were associated with resolution of NASH without worsening in fibrosis (primary end point), and improvements in NAS, steatosis and ballooning, but not lobular inflammation or improvement in fibrosis without worsening in NASH (Figure). A reduction in FAST score of ≥ 0.2 was identified as the cut-off point for improvement of ≥ 1 point in NAS (Youden's index; odds ratio (95% confidence interval): 25.3 [6.7; 166.9]). A decrease in FAST score of ≥ 0.2 from baseline to week 72 correlated with changes in NASH activity biomarkers (ALT, microRNA-122, interleukin-1 receptor antagonist, cytokeratin [CK] 18 M65, CK18 M30 antigen) and fibrosis biomarkers (Fibrosis-4, AST to platelet ratio index) (range: 0.30–0.64).

Conclusion: FAST score is associated with histological improvement of NASH activity, and may have potential as a non-invasive surrogate end point to monitor disease progression in patients with NASH.



Data are from all randomized patients during the on-treatment period. Response was defined by histology. *p-value for comparisons between responders vs non-responders; CI, confidence interval; FAST, FibroScan-aspartate aminotransferase; N, number of patients; NA, not applicable; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

Figure:

OS-1592

Individual patient data meta-analysis of the diagnostic performance of single and sequentially combined non-invasive tests in detecting advanced fibrosis

Ferenc Mozes¹, Jenny Lee², Emmanuel Selvaraj¹, Arjun Jayaswal¹, Michael Trauner³, Jerome Boursier⁴, Celine Fournier⁵, Katharina Stauffer⁶, Rudolf Stauber⁷, Elisabetta Bugianesi⁸, Ramy Younes⁹, Silvia Gaia⁸, Monica Lupsor-Platon¹⁰, Salvatore Petta¹¹, Toshihide Shima¹², Takeshi Okanoue¹², Sanjiv Mahadeva¹³, Wah-Kheong Chan¹³, Peter Eddowes¹⁴, Philip N. Newsome¹⁵, Vincent Wai-Sun Wong¹⁶, Victor de Lédinghen¹⁷, Jian-Gao Fan¹⁸, Feng Shen¹⁸, Jeremy Cobbold¹⁹, Yoshio Sumida²⁰, Akira Okajima²¹, Jörn Schattenberg²², Christian Labenz²², Won Kim²³, Myoung Seok Lee²⁴, Johannes Wiegand²⁵, Thomas Karlas²⁵, Yusuf Yilmaz²⁶, Guruprasad Aithal¹⁴, Naaventhana Palaniyappan¹⁴, Christophe Cassinotto²⁷, Sandeep Aggarwal²⁸, Garg Harshit²⁸, Geraldine Ooi²⁹, Atsushi Nakajima³⁰, Masato Yoneda³⁰, Marianne Zioli³¹, Nathalie Barget³², Andreas Geier³³, Theresa Tunill³⁴, M. Julia Brosnan³⁴, Quentin Anstee³⁵, Stefan Neubauer¹, Stephen Harrison¹, Patrick Bossuyt², Michael Pavlides¹. ¹University of Oxford, RDM Cardiovascular Medicine, United Kingdom; ²University of Amsterdam, Department of Epidemiology and Data Science, Amsterdam, Netherlands; ³University of Vienna, Austria; ⁴Université d'Angers, Laboratoire HIFIH, France; ⁵ECHOSENS, Paris, France; ⁶University Hospital Bern, Department of Visceral Surgery, Switzerland; ⁷Medical University of Graz, Division of Gastroenterology and Hepatology, Graz, Austria; ⁸University of Turin, Department of Medical Sciences, Torino, Italy; ⁹Boehringer Ingelheim; ¹⁰Iuliu Hatieganu University of Medicine and Pharmacy, Department of Medical Imaging, Cluj-Napoca, Romania; ¹¹University of Palermo, Section of Gastroenterology and Hepatology, Palermo, Italy; ¹²Saiseikai Suita Hospital, Department of Gastroenterology and Hepatology, Suita, Japan; ¹³University of Malaya,

Department of Medicine, Malaysia; ¹⁴University of Nottingham, NIHR Nottingham Biomedical Research Centre, Nottingham, United Kingdom; ¹⁵University of Birmingham, NIHR Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ¹⁶The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, Hong Kong; ¹⁷Bordeaux University Hospital, Centre d'Investigation de la Fibrose Hepatique, Pessac, France; ¹⁸Shanghai Jiaotong University School of Medicine, Department of Gastroenterology, Shanghai, China; ¹⁹University of Oxford, Translational Gastroenterology Unit, Oxford, United Kingdom; ²⁰Aichi Medical University, Department of Internal Medicine, Aichi, Japan; ²¹Koseikai Takeda Hospital, Department of Gastroenterology, Kyoto, Japan; ²²University Medical Center of the Johannes Gutenberg-University, I. Department of Medicine, Mainz, Germany; ²³Seoul Metropolitan Government Boramae Medical Center, Department of Internal Medicine, Seoul, Korea, Rep. of South; ²⁴Seoul Metropolitan Government Boramae Medical Center, Department of Radiology, Seoul, Korea, Rep. of South; ²⁵Leipzig University Medical Center, Department of Medicine II, Leipzig, Germany; ²⁶Marmara University, Department of Gastroenterology, Istanbul, Turkey; ²⁷University Hospital of Montpellier, Department of Diagnostic and Interventional Radiology, Montpellier, France; ²⁸AIIMS, Department of Surgical Disciplines, New Delhi, India; ²⁹Monash University, Department of Surgery, Melbourne, Australia; ³⁰Yokohama City University, Department of Gastroenterology and Hepatology, Yokohama, Japan; ³¹Université Paris, Service d'Anatomie Pathologique et Centre de Ressources Biologiques, Hôpital Jean Verdier, Paris, France; ³²Hopitaux Universitaires Paris Seine-Saint-Denis, Centre de Ressources Biologiques, Bondy, France; ³³University Hospital Würzburg, Division of Hepatology, Würzburg, Germany; ³⁴Pfizer, Internal Medicine Research Unit, Cambridge, United States; ³⁵Newcastle University, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle, United Kingdom
Email: ferenc.mozes@cardiov.ox.ac.uk

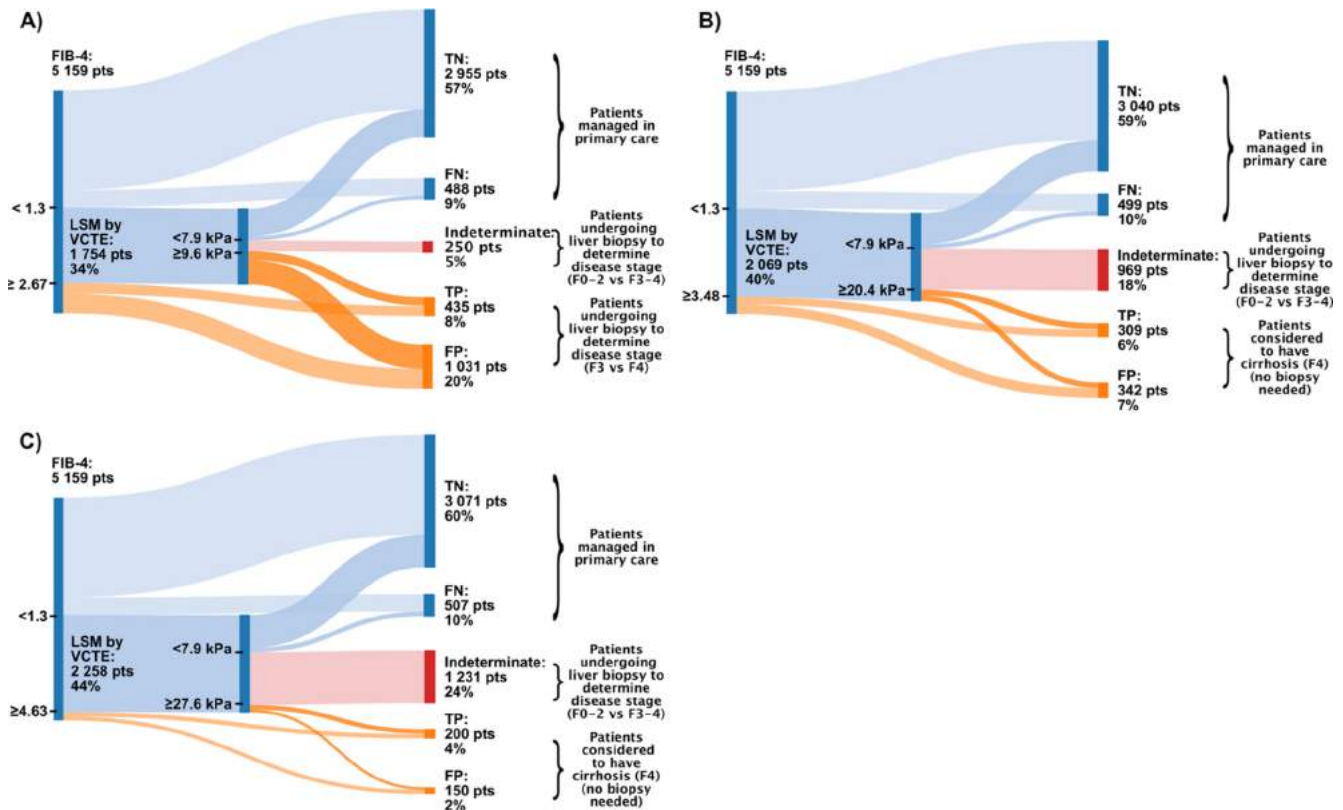


Figure 1: The distribution of the patients in true positive, true negative, false positive, false negative and indeterminate groups for a sequential combination of FIB-4 and LSM by VCTE. The lower cut-offs ruled out advanced fibrosis. The upper cut-off ruled in advanced fibrosis (A) or ruled in cirrhosis with 95% (B) and 98% (C) specificity.

ORAL PRESENTATIONS

Background and aims: Non-invasive tests (NITs) can be used to identify patients with NAFLD at low risk of advanced fibrosis (AF) who can be managed in primary care. However, liver biopsy is still needed in patients where NITs are indeterminate or indicate high risk, to risk stratify and diagnose AF/cirrhosis respectively. Our aim was to perform an individual patient data meta-analysis to evaluate the performance of liver stiffness measurements by vibration controlled transient elastography (LSM-VCTE) and Fibrosis-4 index (FIB-4), and to propose algorithms that reduce the number of liver biopsies.

Method: After a systematic literature search for studies evaluating LSM-VCTE against liver histology, we contacted authors and collected data for LSM-VCTE, demographics, histology and lab parameters. FIB-4 was computed where possible. Diagnostic accuracy of NITs for AF was assessed using the area under the receiver operating curve (AUROC). Cut-offs were selected for 90% sensitivity (Se) and 90% specificity (Sp). Cut-offs from the literature were also evaluated. A strategy of using sequential application of NITs with lower cut-offs to rule out AF and upper cut-offs to rule in cirrhosis with 95% and 98% specificity were also tested.

Results: We included 5735 individual patient data from 37 primary studies (45% female, median age 54 years, median BMI 30 kg/m²; 33% type 2 diabetes; 30% AF, 11% cirrhosis). AUROCs for AF were 0.85 for LSM-VCTE and 0.76 for FIB-4 ($p < 0.001$) and for cirrhosis 0.90 vs 0.80 ($p < 0.001$). Cut-offs to diagnose AF for 90% Se and 90% Sp were respectively, 7.4 kPa (Sp 60%) and 12.1 kPa (Se 55%) for VCTE; 0.88 (Sp 39%) and 2.31 (Se 38%) for FIB-4. Cut-offs for cirrhosis at 95% and 98% Sp were respectively 20.4 kPa and 27.6 kPa for LSM-VCTE and 3.48 and 4.63 for FIB-4. The predefined literature cut-offs for LSM-VCTE (7.9 kPa; 9.6 kPa) and FIB-4 (1.3; 2.67) had Se 84% and Sp 78%, and Se 54% and Sp 91% respectively. Serial combinations of lower literature cut-offs to rule out advanced fibrosis and upper cut-offs to rule in cirrhosis led to a reduction in the number of cases needing liver biopsy from 33% to 18% (Figure 1).

Conclusion: Our results confirm the value of NITs as screening biomarkers to rule out AF. In addition, using upper cut-offs to rule in cirrhosis in sequential test combinations could reduce the number of patients undergoing biopsy in secondary care.

OS-2362

Fibrosis biomarker performance in NAFLD is markedly improved by BMI-specific cut-offs

Sami Qadri^{1,2}, Anni Poikola^{1,2}, Noora Ahlholm^{1,2}, Panu Luukkonen^{1,2,3}, Anne Juuti⁴, Henna Sammalkorpi⁴, Anne Penttilä⁴, Johanna Arola⁵, Kimmo Porthan^{1,2}, Serena Pelusi^{6,7}, Stergios Kechagias⁸, Luca Valenti^{6,7}, Mattias Ekstedt⁸, Hannele Yki-Järvinen^{1,2}. ¹University of Helsinki and Helsinki University Hospital, Department of Medicine, Helsinki, Finland; ²Minerva Foundation Institute for Medical Research, Helsinki, Finland; ³Yale University, Yale School of Medicine, New Haven, United States; ⁴University of Helsinki and Helsinki University Hospital, Department of Gastrointestinal Surgery, Abdominal Center, Helsinki, Finland; ⁵University of Helsinki and Helsinki University Hospital, Department of Pathology, Helsinki, Finland; ⁶Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Translational Medicine-Department of Transfusion Medicine and Hematology, Milan, Italy; ⁷Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy; ⁸Linköping University, Department of Health, Medicine, and Caring Sciences, Linköping, Sweden
Email: sami.qadri@helsinki.fi

Background and aims: Guidelines recommend the use of FIB-4 or NFS for screening of advanced liver fibrosis in NAFLD. Age is known to influence diagnostic cut-offs, but whether obesity affects test performance is unknown. There are no data on the applicability of PRO-C3 derived direct biomarkers of fibrogenesis (ADAPT, FIB3) in patients with obesity.

Method: We studied the impact of obesity on FIB-4 and NFS in 1256 patients with liver biopsy who were eligible for weight-loss surgery or referred to a hepatologist due to NAFLD (378 Finnish, 232 Italian, 646 Swedish, mean age 51 ± 12 years, mean BMI 32.3 ± 7.5 kg/m²). Additionally, we compared the performance of FIB-4, NFS, ADAPT, and FIB3 to diagnose advanced fibrosis in the Finnish cohort (mean age 50 ± 9 years, mean BMI 40.3 ± 7.5 kg/m²).

Results: The AUC of FIB-4 (0.89) and NFS (0.77) for advanced fibrosis were unaffected by BMI. The specificity of NFS, but not FIB-4, deteriorated with higher BMI, decreasing from 83% in lean individuals to 9% in those with BMI over 40 kg/m² (Fig., left panel). We

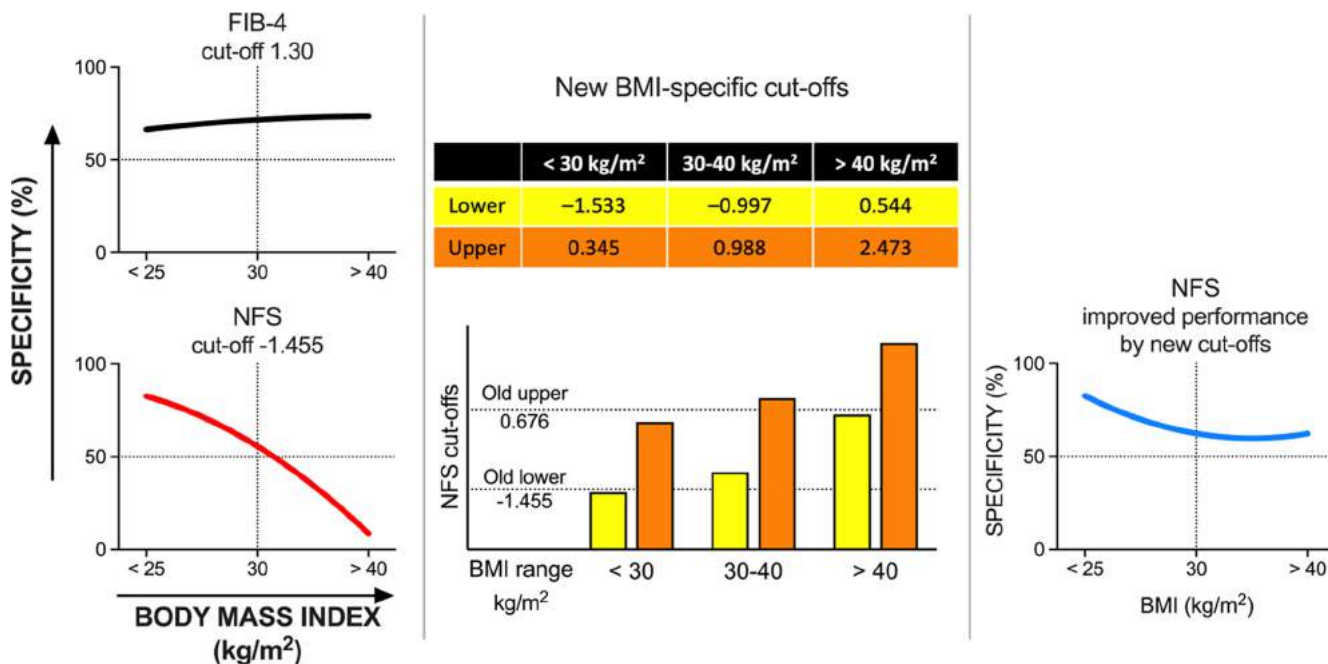


Figure: (abstract: OS-2362)

developed and validated BMI-specific cut-offs for NFS to either rule in ($\geq 95\%$ specificity) or rule out ($\geq 85\%$ sensitivity) advanced fibrosis (Fig., middle panel). New cut-offs significantly improved the performance of NFS, with consistent sensitivity and specificity over the entire BMI range (Fig., right panel). ADAPT (AUC 0.89, sensitivity 79%, specificity 87%) and FIBC3 (AUC 0.86, sensitivity 61%, specificity 84%) performed similarly. They were overall more accurate than NFS and more specific than FIB-4 ($p < 0.05$).

Conclusion: Obesity markedly influences the diagnostic performance of NFS, but not FIB-4. Thus, if using NFS to screen for advanced fibrosis in obese individuals, we recommend applying BMI-specific cut-offs. ADAPT and FIBC3 were marginally superior to FIB-4 in patients with obesity.

NAFLD – Experimental and pathophysiology

OS-297

ATG7 genetic variants predispose to severe fatty liver disease

Guido Baselli¹, Serena Pelusi^{1,2}, Ester Ciociola³, Paola Dongiovanni⁴, Marco Maggioni⁵, Cristiana Bianco¹, Federica Tavaglione³, Annalisa Cespiati⁴, Rosellina Margherita Mancina³, Mahnoosh Ostadreza¹, Monica Miozzo^{2,6}, Roberta D'Ambrosio⁷, Salvatore Petta⁸, Luca Miele⁹, Umberto Vespasiani Gentilucci¹⁰, Alessandro Federico¹¹, Jussi Pihlajamaki^{12,13}, Elisabetta Bugianesi¹⁴,

Anna Ludovica Fracanzani^{2,4}, Helen Reeves^{15,16}, Giorgio Soardo^{17,18}, Daniele Prati¹, Stefano Romeo^{3,19}, Luca Valenti^{1,2}. ¹Translational Medicine-Department of Transfusion Medicine and Hematology-Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ²Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan; ³Department of Clinical and Molecular Medicine, University of Gothenburg, Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; ⁴General Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁵Pathology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁶Scientific direction, Genomic Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁷Division of Gastroenterology and Hepatology, CRC "A.M. and A. Migliavacca" Center for Liver Disease, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁸Gastroenterology and Hepatology, PROMISE, Università di Palermo, Palermo, Italy; ⁹Department of Internal Medicine, Fondazione Policlinico A. Gemelli, Università Cattolica di Roma, Rome, Italy; ¹⁰Department of Hepatology, University Campus Bio-Medico di Roma, Rome, Italy; ¹¹Division of Hepatogastroenterology, Department of Precision Medicine, Università della Campania "Luigi Vanvitelli," Naples, Italy; ¹²Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland; ¹³Department of Medicine, Endocrinology and Clinical Nutrition, Kuopio University Hospital, Finland; ¹⁴Department of Medical Sciences, Division of Gastro-Hepatology, A.O. Città della Salute e della Scienza di Torino, Università di Torino, Turin, Italy; ¹⁵Translational and Clinical Research

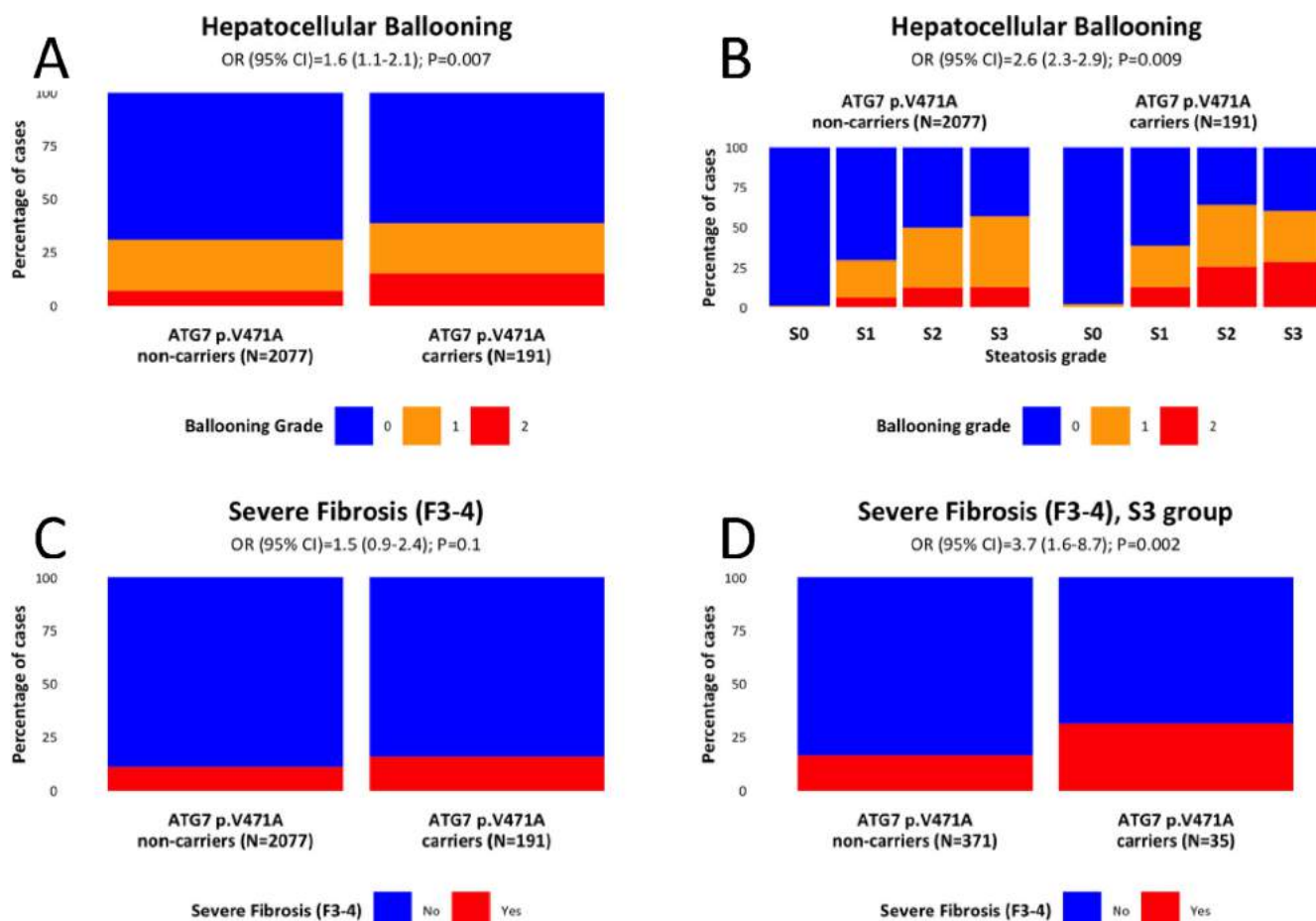


Figure: Impact of p.V471A ATG7 variant on hepatocellular ballooning grade (A) and according to liver steatosis severity (B), and on fibrosis severity in the overall cohort of LBC (C) and in patients with severe steatosis.

ORAL PRESENTATIONS

Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; ¹⁶Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; ¹⁷Clinic of Internal Medicine-Liver Unit, Department of Medical Area (DAME), Università degli Studi di Udine, Udine, Italy; ¹⁸Italian Liver Foundation, Area Science Park, Basovizza Campus, Trieste, Italy; ¹⁹Clinical Nutrition Unit, Department of Medical and Surgical Science, University Magna Graecia, Catanzaro, Italy
Email: biancocristiana.md@gmail.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease and liver-related comorbidity and mortality. NAFLD has a strong inheritable component. The identification of genetic determinants leads to improvements in risk stratification and identification of therapeutic target. The aim of this study was to identify new genes involved in NAFLD pathogenesis.

Method: We performed whole-exome sequencing in 301 patients with NAFLD and severe fibrosis or hepatocellular carcinoma (EPIDEMIC and Perspective cohorts), followed by variant prioritization based on in silico predictors. We replicated the results in the European Liver Biopsy Cohort (LBC, n = 2, 268) and the UK BioBank (UKBB) and we investigated the molecular mechanisms in a Liver Transcriptomic Cohort (LTC) of 125 obese patients.

Results: In the EPIDEMIC cohort vs. the general population, we detected an enrichment of the p.P426L variant (OR = 7.2, 95% c.i. 2–17; p < 0.001) of Autophagy Related Gene 7 (ATG7), a gene involved in lipo-autophagy and steatohepatitis development in mice. We further observed a higher burden of rare (OR = 13.9, 95% c.i. 1.9–611; p = 0.002) and unselected protein-coding mutations (p = 0.027) in the conserved C-terminal ATG7 domain, and an increased frequency of the p.V471A variant (MAF = 0.06 vs. 0.04, OR = 1.7, 95% c.i. 1.2–2.5; p = 0.003). In the UKBB cohort, p.V471A was associated with NAFLD (p = 0.009) and liver disorders (p = 0.004). In the LBC, we confirmed p.V471A association with severe fibrosis, particularly in patients with S3 steatosis (p = 0.002), and those carrying the PNL3A3 p.I148M variant (p = 0.03); p.V471A was an independent predictor of hepatocellular ballooning (p = 0.007). In the LTC ATG7 correlated with suppression of the TNF- α pathway, which conversely was upregulated in carriers of p.V471A. ATG7 protein was expressed in Kupffer cells and predominantly periportal hepatocytes, where the staining was marked around lipid droplets, and more intense in the presence of ballooning.

Conclusion: We identified a novel association of ATG7 variants with severe NAFLD. The mechanism may involve impairment of autophagy and facilitation of hepatocellular ballooning degeneration for the p.V471A variant.

OS-584

auto-aggressive cxcr6+ cd8 t cells cause liver immune pathology in nash

Michael Dudek¹, Dominik Pfister², Sainitin Donakonda¹, Felix Bayer¹, Annika Schneider¹, Philippa Meiser¹, Silke Heegenbarth¹, Percy A. Knolle¹, Mathias Heikenwälder², Jan Boettcher¹, Melanie Laschinger³, Norbert Hueser³, Daniel Hartmann³, Pamela Filpe⁴, Marcial Sebode⁴, Jennifer Wigger⁴, Andrew Bowman⁵, Ron M.A. Heeren⁵, Frank Tacke⁶, Adrien Guillot⁶, Rafael Kaeser⁷, Tobias Böttler⁷, Robert Thimme⁷, Gabriel Seifert⁸, Simon Reider⁹, Herbert Tilg⁹, Friedrich Nolte-Koch¹⁰, Roland Rad¹¹, Rupert Öllinger¹¹, Martina Anton¹, Danijela Heide², Pierluigi Ramadori², Valentina Leone¹², Donato Inverso¹³, Adrian Billeter¹⁴, Beat Müller-Stich¹⁴, Jan-Philipp Mallm¹⁵, Susanne Roth¹⁴, Agnieszka Kabat¹⁶, Edward Pearce¹⁶, Maria Effenberger⁹, Tim Gruber¹⁷, Cristina García-Cáceres¹⁷, Jean-François Dufour¹⁸, Dirk Haller^{19,20}, Dietmar Zehn¹⁹, Peter Murray²¹. ¹Institute of Molecular Immunology and Experimental Oncology, School of Medicine, München, Germany; ²Institute of Chronic Inflammation and Cancer, German Cancer Research Center, Heidelberg, Germany; ³Department of Surgery, University Hospital München rechts der Isar, Munich, Germany;

⁴University Medical Centre Hamburg-Eppendorf, Department of Medicine, Hamburg, Germany; ⁵Maastricht MultiModal Molecular Imaging (M4I) Institute, Division of Imaging Mass Spectrometry, Maastricht; ⁶Charité Universitätsmedizin Berlin, Department of Hepatology and Gastroenterology, Berlin, Germany; ⁷University Medical Center Freiburg, Department of Medicine, Freiburg, Germany; ⁸University of Freiburg, Department of General and Visceral Surgery, Freiburg, Germany; ⁹Medical University Innsbruck, Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology and Metabolism, Innsbruck, Germany; ¹⁰Institute of Molecular Immunology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ¹¹Institute of Molecular Oncology and Functional Genomics, Technical University of Munich, Munich, Germany; ¹²Research Unit of Radiation Cytogenetics, Helmholtz Center Munich, Munich, Germany; ¹³German Cancer Research Center, Division of Vascular Oncology and Metastasis, Heidelberg, Germany; ¹⁴Heidelberg University, Department of General, Visceral and Transplantation Surgery, Heidelberg, Germany; ¹⁵Division of Chromatin Networks, German Cancer Research Center, Heidelberg, Germany; ¹⁶Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany; ¹⁷Institute for Diabetes and Obesity, Helmholtz Zentrum München, Munich, Germany; ¹⁸University Clinic for Visceral Surgery and Medicine, University of Bern, Bern, Germany; ¹⁹Division of Animal Physiology and Immunology, Technical University of Munich, Munich, Germany; ²⁰Chair of Nutrition and Immunology, Technical University of Munich, Munich, Germany; ²¹Max-Planck Institute for Biochemistry, Munich, Germany
Email: michael.dudek@tum.de

Background and aims: Non-alcoholic steatohepatitis (NASH) is a manifestation of systemic obesity-related metabolic disease, characterized by chronic sterile inflammation that causes liver disease. Although it is known that the adaptive immunity drives liver pathology in chronic infectious inflammation, the mechanisms of immune-mediated liver damage in NASH remain incompletely understood. The liver microenvironment is a source of factors as cytokines, nutrients and cell stress molecules that can affect transcriptional networks to balance effector functions in tissue-resident T cells. Here, we identify murine and human Foxo1^{low}CXCR6⁺CD8⁺ T cells as critical tissue-resident T cells causing liver damage in NASH after sequential IL-15 and metabolic activation.

Method: A murine model of NASH (choline-deficient high-fat diet) with antibody intervention studies was used to explore mechanisms of T cell immunopathology *in vivo*. Single-cell and bulk RNA-seq, flow cytometry and cytotoxicity assays were performed to study immunity of murine and human CXCR6⁺CD8⁺ T cells and its dependence on Foxo1 *in vitro* and *ex vivo* studies.

Results: In livers of NASH mice, CD8 T cells accumulated with a phenotype that combined tissue-residency (CXCR6) with effector (Granzymes) and exhaustion (PD-1) characteristics. Liver CXCR6⁺CD8 T cells were characterized by low Foxo1 transcription factor activity and were abundant in mouse and human NASH. Mechanistically, IL-15 induced Foxo1 down- and CXCR6 up-regulation, which rendered CXCR6⁺CD8 T cells tissue-resident and susceptible to local metabolic stimuli in NASH livers, including acetate and extracellular ATP. This collectively triggered MHC-independent CD8 T cell auto-aggression killing hepatocytes through TNF and FasL. Antibodies blocking the activity of TNF, FasL or IL-15 significantly ameliorated liver damage in NASH mice. Importantly, CXCR6⁺CD8 T cells from mouse and human NASH livers had similar transcriptional signatures and showed auto-aggressive killing of cells in an MHC-class-I-independent fashion after signaling through P2X7 purinergic receptors.

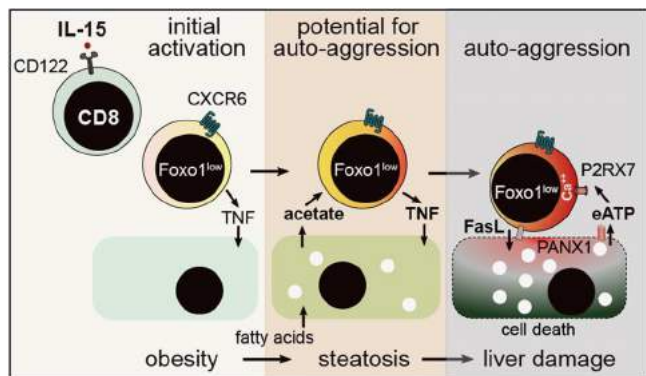


Figure:

Conclusion: We identify a novel pathway of T cell activation and T-cell mediated tissue-pathology that we termed auto-aggression. Distinguishing auto-aggressive from protective T cell immunity will help to design targeted immune intervention therapies for NASH while preserving immune surveillance against infection and cancer.

OS-768

A first-in-class small molecule targeting 17-beta-hydroxysteroid dehydrogenase 13 for the treatment of non-alcoholic steatohepatitis

Ji Won Choi¹, Jin Woo Jung¹, Chanwoo Park¹, Jiyeon Park¹, Hyeim Jo¹, Seong Il Choi¹, Somlee Park¹, Seung-chul Lee¹, Dong-hyun Ko¹, Dong-Kyu Kim¹. ¹HK inno.N Corporation, RandD Center, Icheon-si, Korea, Rep. of South
Email: dongkyu.kim@kolmar.co.kr

Background and aims: Human genetic studies identified an association of single nucleotide polymorphisms in the hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) gene with non-alcoholic fatty liver disease (NAFLD) and HCC development. Recently, the study of human liver lipidome and transcriptome revealed that a loss-of-function variant in HSD17B13 increase hepatic phospholipids, especially phosphatidylcholines and phosphatidylethanolamines, and decrease fibrosis. Thus, we tried to approach to make a HSD17B13 protein (17-beta-hydroxysteroid dehydrogenase 13, 17beta-HSD13) inhibitor, as a first-in-class small molecule, and identified a potent 17beta-HSD13 inhibitor, Compound A.

Method: To determine the in vitro enzyme potency, Compound A was assessed using NAD/NADH-Glo™ assay. In vitro cell efficacy of Compound A were determined by measuring mRNA expression of alpha-smooth muscle actin (alpha-SMA) after treatment with tumor growth factor-beta (TGF-beta) in both normal and HSD17B13-overexpressed LX-2 hepatic stellate cells. C57BL/6 were given either a normal diet or choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for 14 weeks. After 7 weeks of being fed CDAHFD, mice were administered orally with Compound A for 7 weeks. Mice plasma were analyzed by Biochemistry Analyzer and NAFLD activity score (NAS) and liver fibrosis stage were graded by pathologist.

Results: Compound A inhibits the 17beta-HSD13 and significantly decreased mRNA level of alpha-SMA in normal and HSD17B13-overexpressed LX-2 cells. In CDAHFD model, Compound A improved lipid profiling, decreased alanine aminotransferase, lactate dehydrogenase, and liver to body weight ratio. Especially, administration of Compound A dramatically recovered liver morphology and significantly decreased NAS in CDAHFD-fed mice.

◆ CDAHFD model

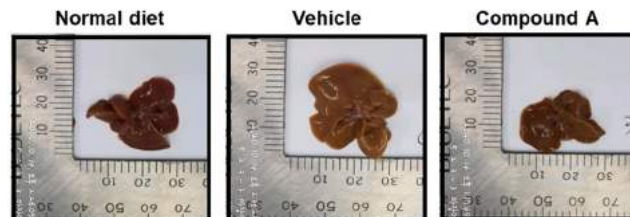


Figure:

Conclusion: Compound A, a first-in-class oral small molecule targeting 17beta-HSD13, decreased the NAS and recovered liver function in CDAHFD model. It is suggested that Compound A could be a potent therapeutic agent for the treatment of non-alcoholic steatohepatitis.

OS-1028

Suppression of insulin-induced gene 1 (INSIG1) function restrains NASH progression by promoting hepatic lipid remodelling

Vian Azzu^{1,2,3}, Michele Vacca^{2,4,5}, Ioannis Kamzolas^{2,6}, Zoe Hall^{5,7}, Jack Leslie⁸, Stefania Carobbio², Samuel Virtue², Susan Davies⁹, Agnes Lukasic², Martin Dale², Mohammad Bohlooly-Y¹⁰, Animesh Acharjee^{5,11}, Daniel Lindén^{12,13}, Guillaume Bidault², Evangelia Petsalaki⁶, Julian Griffin^{5,7}, Fiona Oakley⁸, Antonio Vidal-Puig^{2,14,15}, Michael Allison³. ¹Norfolk and Norwich University Hospital, United Kingdom; ²University of Cambridge, Wellcome Trust/MRC Institute of Metabolic Science, Cambridge, United Kingdom; ³Cambridge University Hospitals NHS Foundation Trust, Hepatology, Cambridge, United Kingdom; ⁴University of Bari Aldo Moro, Clinica Medica Cesare Frugoni, Department of Interdisciplinary Medicine, Bari, Italy; ⁵University of Cambridge, Department of Biochemistry and Cambridge Systems Biology Centre, Cambridge, United Kingdom; ⁶European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Hinxton, United Kingdom; ⁷Imperial College London, Biomolecular Medicine, Systems Medicine, Department of Metabolism, Digestion and Reproduction, London, United Kingdom; ⁸Newcastle University, Newcastle Fibrosis Research Group, Biosciences Institute, Faculty of Medical Sciences, Newcastle upon Tyne, United Kingdom; ⁹Cambridge University Hospitals NHS Foundation Trust, Pathology, Cambridge, United Kingdom; ¹⁰AstraZeneca, Translational Genomics, Discovery Sciences, BioPharmaceuticals RandD, Gothenburg, Sweden; ¹¹University of Birmingham, College of Medical and Dental Sciences, Institute of Cancer and Genomic Sciences, Centre for Computational Biology, Birmingham, United Kingdom; ¹²AstraZeneca, Bioscience Metabolism, Research and Early Development Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals RandD, Gothenburg, Sweden; ¹³University of Gothenburg, Division of Endocrinology, Department of Neuroscience and Physiology, Gothenburg, Sweden; ¹⁴Wellcome Trust Sanger Institute, Hinxton, United Kingdom; ¹⁵Cambridge University Nanjing Centre of Technology and Innovation, Nanjing, China
Email: michael.allison@addenbrookes.nhs.uk

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a silent pandemic associated with obesity and the metabolic syndrome, and is linked to increased cardiovascular- and cirrhosis-related morbidity and mortality. It remains debated whether activation of Sterol Regulatory Element-Binding Proteins (SREBPs) act as a pathogenic drivers of lipotoxicity in non-alcoholic steatohepatitis (NASH), or promote the biosynthesis of protective lipids that buffer excessive lipid accumulation, thus preventing inflammation and fibrosis. We aimed to better understand these adaptive compensatory metabolic programs that modulate NAFLD pathophysiology and NASH progression.

Method: To understand the role of lipid/cholesterol synthesis/remodelling pathways in NASH progression, we employed

ORAL PRESENTATIONS

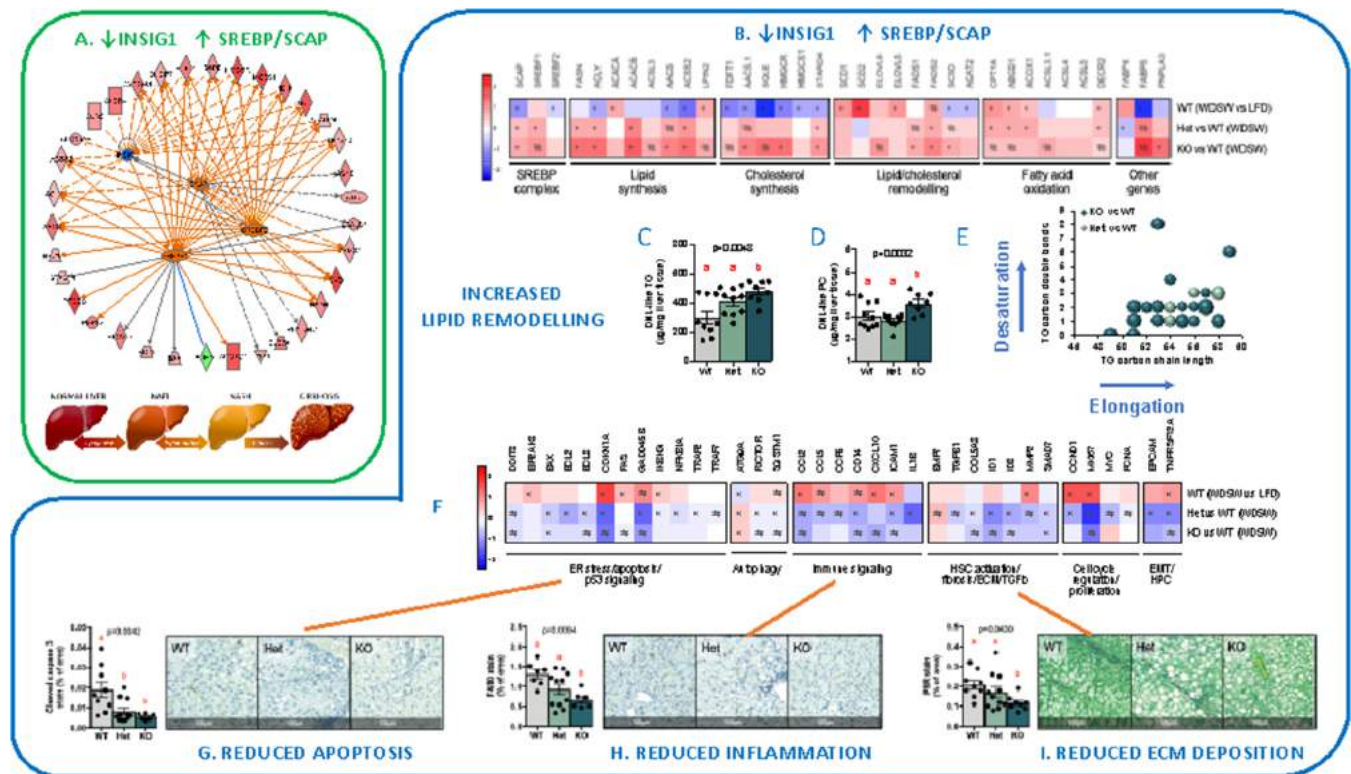


Figure: (abstract: OS-1028): **Upregulation of SREBP metabolic pathways is seen in patients with advanced NASH and mediates hepatic protection from diet induced NASH in mice.** (A) Network-like representation of IPA Upstream Regulator Analysis of human liver transcriptome shows strong SREBP/SCAP pathway upregulation that is associated with predicted INSIG1 downregulation in advancing NASH. (B–H) Mice treated with WDSW: *Insig1* ablation results in upregulation of lipid/cholesterol synthesis (B), shown by *Fasn*-mediated increase in DNL-TG (C) and DNL-PC (D), as well as lipid remodelling shown by desaturation and elongation of carbon chains (E). These lipidome changes correlate with reduced ER stress, apoptosis, inflammation and HSC activation/collagen deposition (F: NGS; G–H: IHC; I: PSR).

transcriptomic analysis of NAFLD patients' liver biopsies coupled with reverse translation in *INSIG1* deficient mice (which display hyperefficient SREBPs activation) challenged with a preclinical murine model of mild NASH (Western Diet Sugar Water, WDSW-12 weeks). Mice were phenotyped with a multiomics systems biology approach.

Results: Clustering the data against NASH progression, Ingenuity Pathway Analysis of hepatic transcriptome showed substantial rewiring of metabolic pathways: SREBPs transcriptional networks and *de novo* lipid/cholesterol synthesis and remodelling were predicted to be activated (Fig. 1A). In WDSW, *Insig1* KO mice had similar systemic metabolism and insulin sensitivity to Het/WT littermates; however, the hyperefficient SREBPs activity in KO mice led to enhanced lipid/cholesterol biosynthesis (Fig. 1B–D) and remodelling (Fig. 1B, E) and restrained NASH progression as a result of decreased apoptotic hepatocellular damage and inflammation, resulting in decreased extracellular matrix deposition (Fig. 1F–I).

Conclusion: Our results suggest that the SCAP/SREBP/INSIG1 trio governs transcriptional programs aimed at protecting the liver from lipotoxic insults in NASH and provides knowledge about NAFLD pathogenesis that may prove useful for the development of new therapeutic strategies.

OS-1524

Acetyl-CoA metabolism drives epigenome change in liver steatosis leading to widespread abnormal transcription, DNA damage and promotion of hepatocarcinogenetic pathways

Gabriella Assante^{1,2}, Aikaterini Tournia^{1,2}, Shilpa Chokshi^{1,2}, Nigel Turner³, J.W.O Ballard³, Margaret Morris³, Neil Youngson^{1,2,3}.
¹Institute of Hepatology, Foundation for Liver Research, London, United Kingdom; ²Kings College London, London, United Kingdom; ³UNSW Sydney, Australia

Email: n.youngson@researchinliver.org.uk

Background and aims: Pathology-associated epigenetic and transcriptional changes in steatotic hepatocytes are currently thought to be caused by programmed cellular responses to lipotoxic processes such as oxidative stress and endoplasmic reticulum stress. However, due to the strong mechanistic links between energy metabolism and epigenetics, we investigated whether genome-wide epigenetic change could be considered an independent pathological process, and thus a novel driver of steatosis-associated transcriptional change and DNA damage.

Method: Genome-wide transcription and epigenetic state was examined in two rodent models of diet-induced fatty liver. To dissect the relationship between metabolism, epigenetics and transcription, steatosis was induced in immortalized human hepatocytes by supplementation with oleic acid. The hepatocytes were also treated with inhibitors of enzymes that produce acetyl-CoA from acetate, pyruvate and beta-oxidation. Imaging of whole genome chromatin state was performed with a DNaseI sensitivity assay, and DNA damage was visualised by gamma H2AX immunofluorescence. Chromatin immunoprecipitation and next-generation sequencing (ChIP-seq) was performed to identify regions of the genome which

are prone to steatosis-associated H4K16 acetylation and gamma H2AX.

Results: Liver triglyceride levels were more than double those of control animals after 6 months of high-fat diet in rats and 8 weeks of high-fructose diet in mice. Transcriptome and histone analysis in livers of rodent models of MAFLD confirmed that steatosis is associated with genome-wide loss of transcriptional repression and increased histone acetylation. *In vitro*, steatosis was associated with relaxed chromatin across the genome and increased gamma H2AX. ChIP-seq revealed that steatosis-associated gamma H2AX was enriched at highly expressed genes in pathways such as fat metabolism, histone acetylation and oxidative stress. Furthermore, known HCC tumour suppressor genes had increases in H4K16 acetylation and gamma H2AX. Finally, steatosis-associated gamma H2AX was reversed through inhibition of acetyl-CoA anabolism.

Conclusion: Our data point to metabolism-driven genome-wide epigenetic change being a new pathological mechanism in liver steatosis which promotes cellular dysfunction and carcinogenesis.

OS-1746

Cilofexor and firsocostat treatment is associated with widespread changes in the hepatic transcriptome in NASH patients with advanced fibrosis

Yevgeniy Gindin¹, Jay Chuang¹, Ling Han¹, Catherine Jia¹, Ryan Huss¹, Chuhan Chung¹, Robert Myers¹, Simone Strasser², Vincent Wai-Sun Wong³, Naim Alkhoury⁴, Kris Kowdley⁵, Mazen Nouredin⁶, Rohit Loomba⁷. ¹Gilead Sciences, Foster City, United States; ²Royal Prince Alfred Hospital and The University of Sydney, Australia; ³Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Department of Medicine and Therapeutics, China; ⁴Arizona Liver Health, Chandler, United States; ⁵Liver Institute Northwest, Seattle, United States; ⁶Cedars-Sinai Medical Center, Fatty Liver Program, Los Angeles, United States; ⁷University of California at San Diego, NAFLD Research Center, United States
Email: yevgeniy.gindin@gilead.com

Background and aims: In the phase 2b ATLAS study, the combination of the ACC inhibitor firsocostat (FIR) and the FXR agonist cilofexor (CILO) led to histologic improvement in patients with advanced fibrosis (F3-F4) due to NASH. We investigated hepatic transcriptomic changes with treatment and associations with histologic responses and serum biomarkers.

Method: FFPE tissue blocks of liver biopsies were obtained from NASH patients with F3-F4 fibrosis in the ATLAS trial (NCT03449446). Fibrosis stage and the NAFLD Activity Score (NAS) were assessed at baseline (BL) and Week 48 (W48) by a central pathologist. Extracted RNA was used to quantify gene expression by RNA-seq. We evaluated gene expression and transcriptome pathway activity (ssGSEA score) at BL and summarized longitudinal changes by treatment group at W48. Transcriptomic pathways were from the Hallmark collection (Broad Institute). Pearson correlations between changes in transcriptome pathways and serum biomarkers were calculated. p values were adjusted using the Benjamini-Hochberg procedure to control the FDR at 0.1.

Results: Compared to BL, CILO+FIR treatment (n=41) for 48 weeks was associated with significant up-regulation of 1015 genes and down-regulation of 320 genes, whereas no changes were observed with placebo (n=20). Placebo-adjusted transcriptome pathway analysis demonstrated 20 significantly affected pathways with CILO+FIR, of which 8 were influenced by CILO treatment, 6 with FIR, and 3 were shared across treatment groups (Figure). The most up-regulated genomic pathway associated with CILO+FIR treatment was related to oxidative phosphorylation, whereas statistically significant changes in pathways or individual genes related to fibrosis (e.g., *COL1A1*, *COL1A2*, *TIMP1*, *ACTA2*, *TGF β* , and *PDGF*) were not observed. Integration of pathway analysis and serum biomarkers revealed significant inverse associations between changes in the bile acid metabolism pathway and serum total bile acids (r= -0.42),

chenodeoxycholic acid (r= -0.41), and primary bile acids (r= -0.41) (all p < 0.05). Changes in the TNF- α signaling pathway, which was reduced by the combination of CILO+FIR, were associated with changes in the NAS (r= 0.39; p < 0.05) and fibrosis stage (r= 0.35; p= 0.1).

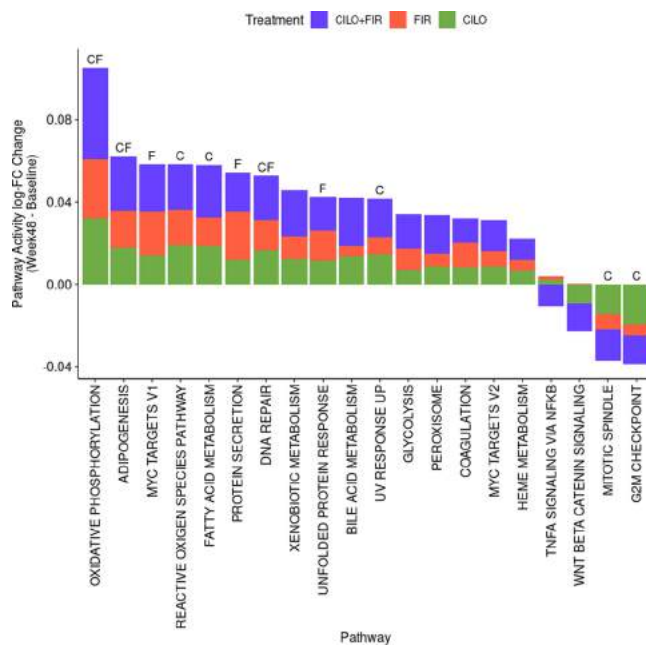


Figure: Each bar, representing log-fold- change (FC) for the pathway activity score, is divided to show the log-FC observed in each group. All depicted pathways are significantly affected by CILO+FIR treatment. Pathways that are also affected by the monotherapies are indicated with C (CILO) and/or F (FIR).

Conclusion: In NASH patients with advanced fibrosis, the combination of CILO+FIR led to widespread changes in hepatic gene expression and transcriptomic pathways. Significant associations were observed between changes in gene expression pathways and bile acid metabolism and inflammation with serum bile acids and changes in the NAS score, respectively.

OS-2450

First in class, orally active Toll-like receptor signaling inhibitor mosedipimod (PLAG) attenuates molecular, biochemical and histological features of non-alcoholic steatohepatitis (NASH) in vitro and in vivo

Jinseon Jeong¹, Young Eun Ko², Su-Hyun Shin³, Kaapjoo Park³, Ki -Young Sohn³, Sun Young Yoon¹, Jae Wha Kim², Michael Charlton⁴. ¹Enzychem Lifesciences, Korea, Rep. of South; ²Korea Research Institute of Bioscience and Biotechnology, Korea, Rep. of South; ³Enzychem Lifesciences; ⁴University of Chicaco, Center for Liver Diseases, Chicago, United States
Email: mcharlton@medicine.bsd.uchicago.edu

Background and aims: There are no currently approved pharmacotherapies for non-alcoholic steatohepatitis (NASH). There is increasing evidence of an important role of the Toll-like receptors (TLRs) in initiation of the fibro-inflammatory cascade in NASH. Attenuating TLR signaling represents an attractive pharmacological strategy to prevent and reverse hepatic fibrosis. The acetylated diacylglycerol 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol (PLAG, chemical name mosedipimod), is an orally active synthetic mono-acetyl-diglyceride that has been shown to attenuate TLR signaling. **Method:** We studied the effects of mosedipimod on molecular, metabolic and histologic facets of NASH in two nutrient-based murine models: a high-fat, high-fructose (HFHF) model of steatosis and inflammation, and the STAM™ model of fibrosing NASH. Effects

ORAL PRESENTATIONS

of PLAG on palmitic acid-induced TLR4 signaling were also studied *in vitro*. In the STAM™ model, effects of PLAG were compared to two agents in advanced clinical trials, obeticholic acid (OCA) and resmetirom (MGL-3196).

Results: Mosedipimod significantly mitigated HFHF diet-induced hepatic steatosis, reducing lipogenesis-associated signaling, as measured by mRNA expression levels of ChREBP, SREBP-1c and FAS ($p < 0.05$ – 0.001), indicating attenuation of *de novo* lipogenesis by mosedipimod. Mosedipimod also reduced surface level expression of TLR4 and decreased TNF- α , IL-6 and MIP-2 levels ($p < 0.05$ – 0.001). Mosedipimod treatment significantly decreased hepatic inflammation (as measured by F4/80), NAFLD activity score (NAS) and fibrosis (Sirius red surface area %, see figure) on end of treatment liver biopsies ($p < 0.05$ – 0.001). PLAG demonstrated similar effects to OCA and resmetirom in reducing hepatic steatosis, inflammation, NAS and fibrosis compared with the vehicle group.

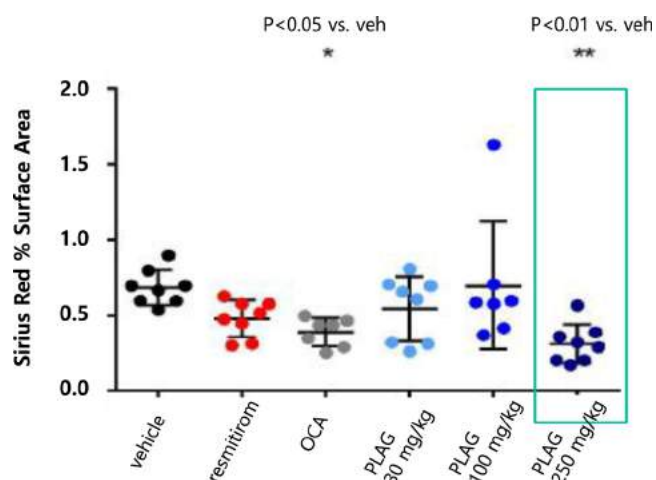


Figure:

Conclusion: Mosedipimod/PLAG mitigates the HFHF diet-induced hepatic injury and inflammatory cytokine production by modulating TLR4-dependent signaling pathways. Mosedipimod also prevents the histological and metabolic effects of NASH to a degree comparable to OCA and resmetirom in a widely utilized preclinical model. Taken together these data identify mosedipimod/PLAG, through a TLR4 signaling dependent mechanism, as a potential therapy for NASH that merits clinical investigation.

OS-2831

Pro-inflammatory hepatic progenitor cell response is associated with progression of human non-alcoholic fatty liver disease

Matthias Van Haele^{1,2}, Ramy Younes^{3,4}, Simon Cockell³, Jeremy Palmer³, Tessa Ostyn¹, Jasper Wouters^{5,6}, Marta Hernández Conde⁷, Timothy Hardy^{3,8}, Jenny Gallacher^{3,8}, Katharine Irvine⁹, Stuart Mcpherson^{3,8}, Michele Vacca¹⁰, Michael Allison¹¹, Michael Drinnan³, Vlad Ratziu¹², Jörn Schattenberg¹³, Alastair Burt³, Anetta S. Hartlova¹⁴, Frank Tacke¹⁵, Baki Topal¹⁶, Ann K. Daly³, Elisabetta Bugianesi¹⁷, Tania Roskams¹, Quentin Anstee^{3,8}, Dina Tiniakos^{3,18}, Olivier Govaere³.
¹KU Leuven and University Hospitals Leuven, Department of Imaging and Pathology, Leuven, Belgium; ²Department of Pathology, Maastricht, Netherlands; ³Newcastle University, Translational and Clinical Research Institute, Newcastle upon Tyne, United Kingdom; ⁴Boehringer Ingelheim International, Ingelheim, Germany; ⁵KU Leuven, Department of Human Genetics, Leuven, Belgium; ⁶VIB KU Leuven, Center for Brain and Disease Research, Leuven, Belgium; ⁷Gastroenterology and Hepatology Department, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; ⁸Newcastle upon Tyne Hospitals NHS Trust, Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne, United Kingdom; ⁹The University of Queensland, Mater Research Institute-UQ,

Brisbane, Australia; ¹⁰Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge Metabolic Research Laboratories, Cambridge, United Kingdom; ¹¹Cambridge University NHS Foundation Trust, Department of Medicine, Cambridge, United Kingdom; ¹²Sorbonne University, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Paris, France; ¹³University Hospital Mainz, I. Department of Medicine, Mainz, Germany; ¹⁴University of Gothenburg, Department of Microbiology and Immunology at Institute of Biomedicine, Gothenburg, Sweden; ¹⁵Charité University Medicine Berlin, Department of Hepatology and Gastroenterology, Berlin, Germany; ¹⁶KU Leuven and University Hospitals Leuven, Department of Abdominal Surgery, Leuven, Belgium; ¹⁷University of Turin, Department of Medical Sciences, Division of Gastro-Hepatology, Turin, Italy; ¹⁸National and Kapodistrian University of Athens, Dept of Pathology, Athens, Greece
 Email: olivier.govaere@ncl.ac.uk

Background and aims: Activation of hepatic progenitor cells (HPCs), observed as ductular reaction, in response to parenchymal tissue damage has been associated with advanced non-alcoholic fatty liver disease (NAFLD) and portal infiltrating immune cells. Yet, the role of HPCs in the progression of NAFLD is still unclear. This study aims to investigate the biological relevance and prognostic value of HPCs in steatohepatitis (NASH) development and fibrosis progression.

Method: A total of 279 patients were included in this study. HPCs and matching hepatocytes were isolated from end-stage NAFLD using laser microdissection and processed for RNA sequencing (RNAseq). Gene signature clustering was performed on a RNAseq cohort of 206 NAFLD patients representing the entire NAFLD spectrum. Cell of origin was determined using publicly available single cell RNAseq and targets were validated using cyclic multiplex immunofluorescence and functionally assessed using ex-vivo human liver slices. In a subgroup of NASH F2/F3 patients with a baseline and a follow-up biopsy at least one year apart, HPC immunophenotype was correlated with clinico-pathological prognostic features. The histological semi-quantitative NASH CRN system was used to score NAFLD biopsies.

Results: High-throughput RNAseq of the HPC niche in end-stage NASH F4 identified 3, 282 differentially expressed genes correlating to a strong pro-inflammatory immune response and tissue remodelling (genes such as *CCR2*, *CCL2*, *CD44*, *SPP1*, *CXCL6*, *S100A6*). Interestingly, this HPC signature stratified the 206 NAFLD patients into distinct clusters characterised by a gradual increase in the presence of NASH, disease activity score (ballooning and inflammation), fibrosis stage and AST levels. Integrated single cell RNAseq analysis and protein level validation showed that HPCs themselves express pro-inflammatory cytokines such as *CCL2* and *SPP1*. Moreover, ex-vivo HPC expansion in human liver slices resulted in an increased release of *CCL2* and *SPP1*. Moreover, comparing baseline and follow-up liver biopsies, the presence of HPCs in the parenchyma at baseline was significantly associated with progression of at least 1 fibrosis stage.

Conclusion: Pro-inflammatory HPCs are associated with disease activity and inflammation, and predict fibrosis progression in NAFLD patients. Further assessment of the HPC phenotype may prove important for both stratifying patients at risk at baseline and for the design of targeted therapies to patients with high likelihood of disease progression.

NAFLD – Therapy

OS-427

Human proof-of-concept in non-alcoholic liver disease (NAFLD) patients with PXL770, a novel first-in-class direct AMP-kinase activator – STAMP-NAFLD Phase 2a trial

Kenneth Cusi¹, Julie Dubourg², David Moller², Sébastien Bolze², Sophie Bozec², Pascale Fouqueray², Stephen Harrison³, Vlad Ratziu⁴.
¹University of Florida, Division of Endocrinology, Diabetes and Metabolism, Gainesville, United States; ²Poxel SA, Lyon, France; ³Summit Clinical Research, San Antonio, United States; ⁴Institute for Cardiometabolism and Nutrition, Paris, France
 Email: kenneth.cusi@medicine.ufl.edu

Background and aims: AMPK activation enhances lipid catabolism, insulin sensitization, and inhibits inflammation and fibrosis. PXL770 is a potent direct allosteric AMPK activator. In rodent models of NASH and type 2 diabetes (T2D) it reduces: steatosis, ballooning, inflammation and fibrogenesis, and improves insulin sensitivity (euglycemic clamp) and normalizes HbA1c. Importantly, endogenous AMPK activity is suppressed in the setting of nutrient overload (including hyperglycaemia); therefore, increased response to an AMPK activator may be predicted to occur in patients with greater metabolic dysfunction. Our aim was to assess the efficacy and safety of PXL770 in a Ph2a study with presumed NASH patients.

Method: This was a 12-week randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of PXL770 in patients with NAFLD. Adults with hepatic fat fraction of at least 10% at baseline (BL) when assessed by MRI-proton density fat fraction (MRI-PDFF) were eligible. Patients were randomly assigned 1:1:1 to receive PXL770 250 mg once-daily (QD), 250 mg twice-daily (BID), 500 mg QD or matching placebo (Pcb). The primary end point was relative change in hepatic fat by MRI-PDFF at week 12. Secondary end points included liver enzymes, glycemic parameters and safety.

Results: 387 patients were screened, and 121 patients were randomized. PXL770 produced a significant mean relative decrease of -18% in liver fat content (LFC, primary end point) from BL in the 500 mg QD dose group (p = 0.0036 vs. -0.7% change in Pcb). A greater proportion of patients who received PXL770 also achieved a >30% relative reduction in LFC compared to Pcb. PXL770 500 mg QD produced significant reductions in mean ALT (BL values 37–41 U/L). In patients with T2D (41–47% of each group), PXL770 treatment resulted in greater mean relative reductions in LFC (-27%; p = 0.004 vs. BL), ALT (-14.9 UI/L; p = 0.02 vs. Pcb) and AST (-9.9 UI/L; p = 0.02 vs. Pcb). In these well-controlled T2DM patients, significant placebo-adjusted decreases were observed in fasting glucose (-21.3 mg/dL) and HbA1c

(-0.64%) along with trends towards improved indices of insulin sensitivity. Adverse events were mostly mild or moderate and were balanced between groups. Safety in T2DM patients appeared similar to the whole trial population.

Conclusion: PXL770 is the first direct AMPK activator to be studied in patients with metabolic or liver disorders. These results support the potential utility of PXL770 in NASH-in particular for the large (~45–50%) subpopulation with coexisting T2DM where the severity and progression of disease is also associated with disproportionately high unmet medical need.

OS-681

Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARM alpha), improves liver stiffness by MRE and serum liver and lipid parameters in NAFLD; a randomized, double-blind, placebo-controlled phase 2 trial

Atsushi Nakajima¹, Yuichiro Eguchi², Kento Imajo¹, Nobuharu Tamaki^{3,4}, Hideki Suganami⁵, Toshiaki Nojima⁵, Ryohei Tanigawa⁶, Yuki Iida⁶, Rohit Loomba⁴.
¹Yokohama City University Graduate School of Medicine, Department of Gastroenterology and Hepatology, Yokohama, Japan; ²Loco Medical General Institute, Kanada Mikatsuki Ogi, Japan; ³Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology, Tokyo, Japan; ⁴University of California San Diego, NAFLD Research Center, La Jolla, United States; ⁵Kowa Company Ltd., Clinical Data Science Department, Tokyo, Japan; ⁶Kowa Company Ltd., Clinical Development Department, Tokyo, Japan
 Email: nakajima-tky@umin.ac.jp

Background and aims: Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARM alpha), has been approved in Japan for dyslipidemia. Pemafibrate reportedly improved non-alcoholic steatohepatitis (NASH) in model mice and serum liver parameters in patients with dyslipidemia. Thus, we aimed to assess the efficacy and safety of pemafibrate in patients with non-alcoholic fatty disease (NAFLD).

Method: This study was a randomized, double-blind, placebo-controlled, multicenter, 72-week, phase 2 clinical trial. The key inclusion criteria were liver fat content of ≥10%, by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF); liver stiffness of ≥2.5 kPa, by magnetic resonance elastography (MRE); and elevated alanine aminotransferase (ALT) level. The patients were randomized to either pemafibrate (0.4 mg/day, BID) or placebo. The primary end point was percent change in liver fat content from baseline to week 24, and the key secondary end points were percent changes in liver stiffness and ALT level from baseline to week 72 and 24, respectively.

Results: Pemafibrate did not significantly alter liver fat content, however, liver stiffness and ALT level significantly decreased in

Table: (abstract: OS-681)

	Placebo (n = 60)			Pemafibrate (n = 58)		
	Week 24	Week 48	Week 72	Week 24	Week 48	Week 72
Liver fat content by MRI-PDFF	-4.2 (-11.6, 3.1)	-0.5 (-7.5, 6.5)	0.2 (-7.2, 7.7)	-5.3 (-12.8, 2.2)	0.5 (-6.7, 7.7)	-4.9 (-12.5, 2.8)
Difference*				-1.0 (-11.5, 9.4)	1.0 (-9.0, 11.1)	-5.1 (-15.8, 5.6)
p value*				0.845	0.840	0.347
Liver stiffness by MRE	-0.7 (-4.0, 2.7)	-3.3 (-7.0, 0.3)	-1.1 (-4.8, 2.6)	-5.0 (-8.5, -1.6)	-9.0 (-12.8, -5.2)	-7.3 (-11.1, -3.5)
Difference*				-4.4 (-9.3, 0.5)	-5.7 (-11.0, -0.4)	-6.2 (-11.5, -0.8)
p value*				0.078	0.036	0.024
ALT	-12.5 (-20.8, -4.1)	-15.8 (-24.3, -7.3)	-10.2 (-19.2, -1.3)	-39.5 (-48.1, -31.0)	-42.5 (-51.3, -33.8)	-43.8 (-53.1, -34.5)
Difference*				-27.1 (-39.1, -15.1)	-26.8 (-39.0, -14.5)	-33.6 (-46.5, -20.7)
p value*				<0.001	<0.001	<0.001

Data shows LS mean (95%CI) for % changes from baseline.

*vs. placebo.

ORAL PRESENTATIONS

pemafibrate compared to placebo (Table). Additionally, pemafibrate significantly improved lipid parameters (e.g., triglycerides, LDL-C). Pemafibrate showed no significant safety issues and it did not affect renal functions (e.g., serum creatinine).

Conclusion: In this proof-of-concept trial, pemafibrate improved liver stiffness by MRE and serum liver and lipid parameters despite not decreasing liver fat content. These results suggest that pemafibrate is a promising therapeutic agent for NAFLD/NASH.

OS-931

Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with lower risk of hepatocellular carcinoma and cirrhotic complications in patients with non-alcoholic fatty liver disease

Xinrong Zhang¹, Vincent Wai-Sun Wong¹, Terry Cheuk-Fung Yip¹, Yee-Kit Tse¹, Yan Liang¹, Vicki Wing-Ki Hui¹, Guanlin Li¹, Huapeng Lin¹, Henry Chan¹, Grace Lai-Hung Wong¹. ¹The Chinese University of Hong Kong, Department of medicine and therapeutics, Hong Kong
Email: wonglaihung@cuhk.edu.hk

Background and aims: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) have been shown to inhibit hepatic stellate cells and liver fibrosis in animal studies. However, data from clinical studies are limited and inconclusive. This study aimed to evaluate the impact of ACEI/ARB use on the risk of hepatocellular carcinoma (HCC) and cirrhotic complications in a territory-wide cohort of NAFLD patients.

Method: We conducted a retrospective cohort study of NAFLD patients aged 18 years or above between January 1, 2000 and December 31, 2014. A propensity score-weighted Cox proportional hazards model was used to balance the clinical characteristics between ACEI/ARB users and non-users. Fine-Gray model was used to adjust for competing risk of death.

Results: We analysed data from 12,494 NAFLD patients (mean age, 54.4 ± 14.5 years; 6,301 men [50.4%]); 7,428 (59.5%) received ACEI/ARB and 5,066 (40.5%) did not. Compared to non-users, ACEI/ARB users were older, more likely to have type 2 diabetes, hypertension and cirrhosis, and had worse renal function. At a median (interquartile range) follow-up of 9.9 (5.4–14.2) years, 268 (3.6%) ACEI/ARB users and 173 (3.4%) non-users developed liver-related events (a composite end point of HCC and cirrhotic complications). After propensity score weighting, ACEI/ARB treatment was associated with a lower risk of liver-related events (weighted subdistribution hazard ratio (SHR) 0.44, 95% confidence interval (CI) 0.33–0.59, $p < 0.001$), HCC (weighted SHR 0.46; 95% CI 0.30–0.72; $p < 0.001$), and cirrhotic complications (weighted SHR 0.42; 95% CI 0.29–0.61; $p < 0.001$).

Conclusion: In this retrospective territory-wide cohort study, ACEI/ARB treatment was associated with a lower risk of liver-related events, HCC and cirrhotic complications in NAFLD patients.

Table 1: Summary of the results of propensity score weighting on the subdistribution hazard ratio (SHR) of liver-related events, HCC and cirrhotic complications in NAFLD patients with or without ACEI/ARB use

	Weighted SHR (95% CI)	P value
Liver-related events	0.44 (0.33–0.59)	<0.001
HCC	0.46 (0.30–0.72)	<0.001
Cirrhotic complications	0.42 (0.29–0.61)	<0.001

OS-1034

The pan-PPAR agonist lanifibranor significantly improves cardiovascular risk biomarkers in patients with NASH

Sven Francque^{1,2}, Michael Cooreman³, Martine Baudin³, Philippe Huot-Marchand³, Lucile Dzen³, Junien Jean Louis³, Pierre Broqua³, Manal Abdelmalek⁴. ¹Antwerp University Hospital,

Gastroenterology and Hepatology, Edegem, Belgium; ²University of Antwerp, Laboratory of Experimental Medicine and Paediatrics, Wilrijk, Belgium; ³Inventiva, Daix, France; ⁴Duke University, Gastroenterology and Hepatology, Durham, United States
Email: sven.francque@uza.be

Background and aims: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with NASH. The panPPAR lanifibranor has shown efficacy on NASH resolution and improvement of fibrosis in non-cirrhotic NASH patients in the phase 2b NATIVE study (Francque et al, AASLD2020). PPAR alpha, delta and gamma signalling improve key mechanisms of atherosclerosis: lipid and carbohydrate metabolism, inflammation and high blood pressure (BP). The aim of this analysis is to assess changes in CVD risk profile in patients with NASH treated with Lanifibranor.

Method: The NATIVE study enrolled 247 patients with SAF activity score 3–4, fibrosis F0–F3, in three arms: Lanifibranor 800 mg/d, 1200 mg/d and placebo for a treatment duration of 24 weeks; 228 patients completed the trial and were included in the analyses. Serum biomarkers that infer increased CVD risk, specifically biomarkers of lipid metabolism (APO-A1 and APO-B (components of HDL and LDL/VLDL particles); APO-C3), insulin resistance (IR) and inflammation were measured at baseline and at end of treatment (EOT). Selected markers were also measured at weeks 4 and 14.

Results: Of the 247, 179 (72%) patients had features of metabolic syndrome (MS): high waist circumference (95%), high triglycerides (TG) (63%), low HDL-cholesterol (47%), type 2 diabetes (T2D) or pre-diabetes (62%), high BP (62%). HDL-cholesterol (HDL-c) significantly increased in both Lanifibranor arms from week 4 to EOT, while values did not change with placebo. APO-A1 and LDL-cholesterol (LDL-c) did not change in any treatment arm. TG, APO-B, APO-C3 and APO-B/APO-A1 (a risk factor for atherosclerosis), mean hs-CRP, fasting glucose and insulin all significantly declined from baseline to EOT with Lanifibranor 800 and 1200 mg/d but not with placebo, independent of diabetes status. Lanifibranor significantly decreased mean systolic and diastolic BP during therapy compared to placebo. Most of the improvements were already observed at week 4 and maintained throughout the treatment period.

Conclusion: Lanifibranor has significant beneficial effects on biomarkers of CVD risk in NASH patients, including dyslipidaemia, IR, inflammation and BP. These data confirm the promising profile of lanifibranor for the treatment of NASH as a manifestation of the broader MS. These effects will be further evaluated in the planned phase 3 study in NASH patients with fibrosis F2/F3.

OS-1044

Lanifibranor therapy improves markers of lipid metabolism, insulin resistance, liver injury and fibrosis in patients with NASH and F2 and F3 fibrosis stages: a subgroup analysis of the phase 2b NATIVE study

Sven Francque^{1,2}, Michael Cooreman³, Martine Baudin³, Philippe Huot-Marchand³, Lucile Dzen³, Junien Jean Louis³, Pierre Broqua³, Manal Abdelmalek⁴. ¹Antwerp University Hospital, Gastroenterology and Hepatology, Edegem, Belgium; ²University of Antwerp, Laboratory of Experimental Medicine and Paediatrics, Wilrijk, Belgium; ³Inventiva, Daix, France; ⁴Duke University, Gastroenterology and Hepatology, Durham, United States
Email: sven.francque@uza.be

Background and aims: In the NATIVE study, Lanifibranor, a pan-PPAR agonist, met the composite efficacy end point of NASH resolution and fibrosis regression in patients with non-cirrhotic NASH. Fibrosis progression is the main predictor of outcomes in NASH. Patients with NASH and significant (F2/F3) fibrosis are expected to have improved outcomes from pharmacological therapy that affects fibrosis and upstream metabolic and inflammatory pathways. We evaluated the effect of Lanifibranor on biomarkers of disease activity and associated risks in the subgroup of patients with F2/F3 fibrosis.

Method: A total of 247 patients were enrolled and randomized, stratified for type 2 diabetes (T2D), to placebo, lanifibranor 800 mg/d or 1200 mg/d for 24 weeks. Primary efficacy end point was a ≥ 2 points reduction of the SAF score (inflammation and ballooning) with no worsening of fibrosis; secondary end points included NASH resolution and fibrosis improvement. Serum markers of lipids, insulin resistance (IR), inflammation, liver injury and fibrosis were assessed at baseline and at end of therapy (EOT); selected markers were also measured at weeks 4 and 14. Data for the patient subgroup with F2/F3 fibrosis were analysed.

Results: Of the 247 patients enrolled, 188 (76%) had fibrosis [F2 (n = 102); F3 (n = 86)]. At baseline, the prevalence of T2D in the placebo (n = 57), lanifibranor 800 mg/d (n = 68) and 1200 mg/d (n = 63) was 47%, 40%, and 46%, respectively; the proportion of patients achieving the composite end point NASH resolution and fibrosis improvement was 7%, 24% (p = 0.012) and 33% (p < 0.001), respectively. Liver tests (ALT, AST, GGT), HbA1c and fasting glucose (FBG) declined significantly by week 4 or 14 in the lanifibranor arms and were maintained or further declined at EOT. Triglycerides (TG) also lowered by week 4, with a continued effect throughout therapy; LDL-C levels remained unchanged; there was a significant increase in HDL-C at week 4 and throughout therapy. Lanifibranor reduced APOB/APO-A1, hsCRP and fibrosis markers MACK-3 and TIMP1/MMP2 at EOT compared to baseline. No significant changes were observed in the placebo arm.

Conclusion: In patients with NASH and F2/F3 fibrosis, lanifibranor improved markers of lipid metabolism, IR, liver injury, inflammation and fibrosis at EOT compared to placebo, supporting previously reported histological efficacy. These findings support the planned phase 3 study of lanifibranor for patients with NASH and F2-F3 fibrosis.

OS-1627

Treatment of NAFLD with intermittent calorie restriction, low-carb high-fat diet or standard dietary advice-a randomized controlled trial

Magnus Holmer¹, Catarina Lindqvist¹, Sven Petersson², John Moshtaghi-Svensson³, Veronika Tillander⁴, Torkel Brismar², Hannes Hagström¹, Per Stal^{1,5}. ¹Karolinska Institutet, Department of Medicine Huddinge, Stockholm, Sweden; ²Karolinska Institutet, Department of Clinical Science, Intervention and Technology, Stockholm, Sweden; ³Godjy AB, Stockholm, Sweden; ⁴Karolinska Institutet, Department of Laboratory medicine, Stockholm, Sweden; ⁵Karolinska Institutet, Dept of Gastroenterology and Hepatology, Stockholm, Sweden
Email: magnus.holmer@ki.se

Background and aims: A reduced caloric intake is central to achieve weight loss and reduced liver fat in non-alcoholic fatty liver disease (NAFLD). Several high-fat diets, such as the Low-Carb High-Fat diet (LCHF), are popular in the public, but the effect on liver steatosis is inconclusive. Diets based on intermittent calorie restriction, such as the 5:2-diet, are popular for weight loss purposes but has not yet been tested specifically as treatment for NAFLD. This trial compared the effects of the LCHF and 5:2 diets compared to standard dietary advice as treatment for NAFLD.

Method: We conducted an open-label randomized controlled trial including 74 patients with NAFLD. Participants were randomized 1:1:1 to a 12-week treatment with either LCHF diet, 5:2 diet or standard of care (SoC). The LCHF diet consisted of a carbohydrate intake of <10% of total energy intake (E%) and fat intake to 50–80 E%. In the 5:2 diet, energy intake was restricted to <500/600 kcal (women/men) on two non-consecutive days per week alternated with days with an intake of 2000/2400 kcal (women/men). The 5:2 and LCHF diets were isocaloric. SoC consisted of advice on a healthy diet with a balanced intake of macronutrients, to eat regular meals and reduce the size of servings. The main outcome was reduction of hepatic steatosis as measured with Magnetic Resonance Spectroscopy.

Results: The LCHF and 5:2 diets were superior to SoC in reducing steatosis (Figure). The LCHF and 5:2 diets were also more effective in

reducing body weight (LCHF -7.3 kg [95%CI = -9.6 to -5.0], 5:2 -7.4 kg [95%CI = -8.7 to -6.0] and SoC -2.5 kg [95%CI = -3.5 to -1.5]). There was no difference between the 5:2 and LCHF arms in reduction of steatosis (p = 0.41) or body weight (p = 0.78). Liver stiffness improved in the 5:2 (-1.8 kPa, p < 0.001) and SoC (-1.5 kPa, p = 0.005) but not in the LCHF group (-0.3 kPa, p = 0.52). In the 5:2 group a significant reduction of LDL-levels was observed (-0.4 mmol/L, p < 0.001). A trend towards higher LDL was seen in the LCHF-group (+0.2 mmol/L, p = 0.075).

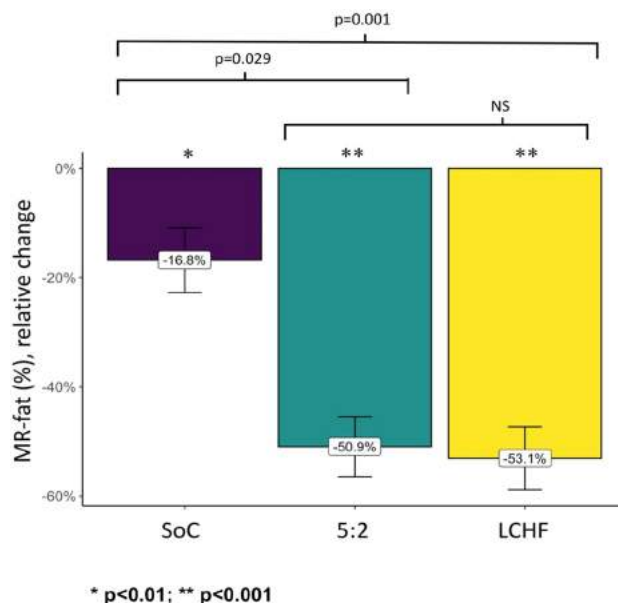


Figure:

Conclusion: The LCHF and 5:2 diets were more effective than SoC in reducing steatosis and body weight in patients with NAFLD. Our findings suggest that dietary advice can be adjusted according to individual preferences. However, coexisting cardiovascular risk factors should be considered since the long-term effect of different diets on blood cholesterol is uncertain.

OS-1769

Interim analysis from a 72 week, double-blind, placebo-controlled, multicenter, paired liver biopsy study of endoscopic sleeve gastroplasty in patients with non-alcoholic steatohepatitis (NASH)

Javier Abad Guerra¹, María Teresa Arias Lose², Diego Burgos Santamaria³, Javier Ampuero⁴, José Luis Martínez Porras¹, Paula Iruzubieta², Rosa Martín-Mateos³, Belén Ruiz Antoran⁵, Álvaro Santos-Laso², Javier Graus³, Adalberto Rincon⁴, Elba Llop¹, Manuel Romero Gomez⁴, Agustín Albillos^{3,6}, Javier Crespo², José Luis Calleja Panero¹. ¹Puerta de Hierro Hospital, Gastroenterology and Hepatology, Madrid, Spain; ²Marques de Valdecilla Hospital, Gastroenterology and Hepatology, Santander, Spain; ³Ramon y Cajal Hospital, Gastroenterology and Hepatology, Madrid, Spain; ⁴Virgen del Rocío Hospital, Gastroenterology and Hepatology, Sevilla, Spain; ⁵Puerta de Hierro Hospital, Pharmacology, Madrid, Spain; ⁶Hospital Ramon y Cajal, IRYCIS, CIBEREHD, Universidad de Alcalá, Madrid, Spain
Email: javiabad83@gmail.com

Background and aims: Life-style intervention losing weight more than 10% promoted NASH resolution in 90% of patients and fibrosis regression, at least one stage, in 80%. However, less than 25% of the subjects achieve this goal with diet and exercise. In recent years endoscopic sleeve gastroplasty with Overstitch® system has emerged as safe and effective option to promote weight loss in patients with obesity. We report the preliminary results of a multicenter,

ORAL PRESENTATIONS

randomized, controlled and double-blind study to evaluate efficacy and safety of endoscopic sleeve gastroplasty in patients with NASH.

Method: This interim analysis was conducted when 21 out of 40 planned subjects included reached in week 72. Inclusion criteria included biopsy proven NASH with NAS \geq 3 and fibrosis stage from F1 to F3 Patients were randomized 1:1 to endoscopic sleeve gastroplasty (ESG) (n = 11) with OverStitch® system (Apollo Endosurgery, Austin, TX, USA) plus lifestyle modification versus endoscopic simulated intervention (ESI) (n = 10) with a diagnostic upper endoscopy plus lifestyle modification. We evaluated changes from baseline in body weight, liver test, Fibroscan and histological features (baseline biopsy and week 72 biopsy).

Results: A significant reduction in body weight were observed in 9 out of 11 ESG group with an average of 9.7% weight reduction vs 4 out of 11 in ESI group with an average of 4% (p < 0.05). Only patients in the ESG group achieved more than 20% of their body weight.

ALT, AST and ferritin levels improved significantly in ESG group vs ESI group (-42.7 vs 1.6 p < 0.017; - 32.4 vs 1.3 p < 0.045; - 39.8 vs 57.7 p < 0.032). We observed a reduction in Fibroscan values of - 5.80 (8.3) Kpa in ESG group vs +2.01 (7.3) Kpa in ESI group (p < 0.05).

Patients that achieved weight loss showed a significant improvement in the NAS score (p < 0.001). 70% of them were from the ESG group. The magnitude of the improvement was significantly higher in those patients with a weight reduction >10% (p < 0.001). ESG was well-tolerated and just mild adverse events were reported in 5% in ESG group vs 1% in ESI.

Table 1:

HISTOLOGICAL BY WEIGHT CHANGES (n)	No weight loss (8)	Weight loss (13)	p
NAS score (SD)	0.00 (1.07)	-3.00 (1.96)	0.001
Steatosis (SD)	-0.13 (0.64)	-1.38 (0.77)	0.001
Lobulillar inflammation (SD)	0.13 (0.83)	-0.54 (0.78)	0.080
Ballooning (SD)	0.00 (0.53)	-1.08 (0.86)	0.005

HISTOLOGICAL BY WEIGHT CHANGES (n)	Weight loss <10% (14)	Weight loss >10% (7)	p
NAS score (SD)	-0.57 (1.45)	-4.43 (0.53)	<0.001
Steatosis (SD)	-0.43 (0.65)	-1.86 (0.69)	<0.001
Lobulillar inflammation (SD)	0.07 (0.83)	-1.00 (0.00)	0.003
Ballooning (SD)	-0.21 (0.70)	-1.57 (0.53)	<0.001

Conclusion: Endoscopic sleeve gastroplasty is an effective and safe method to promote weight reduction associated with significant improvement in liver function test, stiffness and histological parameters compared to life-style intervention alone.

Non-invasive assessment of liver disease except NAFLD

OS-507

Von Willebrand factor for outcome prediction within different clinical stages of advanced chronic liver disease

Bernhard Scheiner^{1,2}, Lorenz Balcar^{1,2}, Rafael Paternostro^{1,2}, Benedikt Simbrunner^{1,2}, Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, David J.M. Bauer^{1,2}, Georg Semmler^{1,2}, Albert Stättermayer^{1,2}, Matthias Pinter¹, Prof. Peter Quehenberger MD³, Michael Trauner¹, Thomas Reiberger^{1,2}, Mattias Mandorfer^{1,2}. ¹Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ³Medical

University of Vienna, Department of Laboratory Medicine, Vienna, Austria

Email: mattias.mandorfer@meduniwien.ac.at

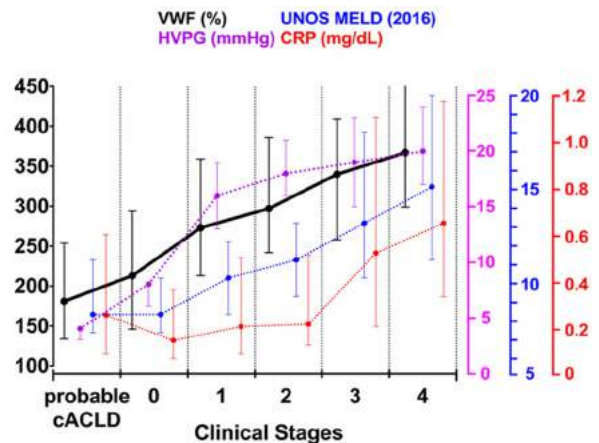
Background and aims: Although von Willebrand factor (VWF) levels have been reported to predict hepatic decompensation and mortality, the specific prognostic value of VWF in distinct clinical stages (CS) has not been systematically assessed. We (i) compared changes in prognostic biomarkers throughout the clinical spectrum of ACLD and (ii) established CS-specific VWF cut-offs for risk prediction.

Method: Patients undergoing HVPG-measurement at the Vienna Hepatic Hemodynamic Lab with evidence of ACLD were considered. CS were defined as follows: **Probable compensated ACLD (cACLD):** LSM \geq 10kPa and HVPG < 6 mmHg; **0:** cACLD and 6-9 mmHg; **1:** cACLD and HVPG \geq 10 mmHg; **2:** decompensated ACLD (dACLD) with bleeding; **3:** dACLD with non-bleeding decompensation; **4:** \geq 2 decompensations.

Results: 923 patients were included. As illustrated in the Figure, we observed a steady step-wise increase of VWF with CS progression. In contrast, HVPG levelled off in dACLD with only modest numerical differences between CS 2-4, whereas MELD showed only minor changes in early CS and CRP did not increase until CS 3, i.e., non-bleeding decompensation.

cACLD patients with VWF levels above the stage-specific 75th percentile (\geq 342%) had a more than four times increased risk of decompensation/death (HR: 4.17 (95%CI: 2.20-7.90), p < 0.001). In dACLD patients, VWF levels above the 75th percentile (\geq 418%) were associated with a 67%-increased risk (HR: 1.67 (95%CI: 1.28-2.19), p < 0.001), while having values below the 25th percentile (<268%) nearly halved the risk (HR: 0.57 (95%CI: 0.42-0.78), p < 0.001) of decompensation/death.

Importantly, even in a fully adjusted model (age, etiology, HVPG, MELD, albumin, and CRP), VWF was independently associated with hepatic decompensation/death in cACLD. In dACLD, VWF remained independently predictive after adjusting for MELD, but not when adjusting for additional variables.



N for VWF	302	418
75 th VWF percentile	342	418
Hazard ratio (HR)	4.17	1.67
95%CI	2.20-7.90	1.28-2.19
p-value	<0.001	<0.001
Median	259	348
25 th VWF percentile	-	268
Hazard ratio (HR)	-	0.57
95%CI	-	0.42-0.78
p-value	-	<0.001

Figure:

Conclusion: Among the investigated parameters, VWF was the only prognostic indicator that steadily increased throughout all CS of

ACLD. Its prognostic implications are particularly pronounced in cACLD patients, in whom VWF $\geq 342\%$ identify those who are at a 4-fold increased risk of hepatic decompensation/death. In dACLD, VWF cut-offs $<268\%$ and $\geq 418\%$ identify low- and high-risk populations. The proposed stage-dependent VWF cut-offs are easily applicable in clinical routine and may help to broaden the use of VWF—a highly versatile and readily available biomarker—for risk stratification and treatment individualization.

OS-1954

Real-world assessment of the non-invasive ratio of exchangeable copper (REC) as a marker of Wilson's disease in a multicentric cohort of pediatric and adult patients.

Cristina Molera Busoms^{1,2}, Zoe Mariño³, Jesús Quintero Bernabeu^{4,5}, Juan Moreno-García⁶, Mauricio Larrarte King⁷, María Margaret Mercadal⁷, Javier Martín de Carpi^{8,9}, Alicia Isabel Pascual Pérez¹⁰, Javier Juampérez Goñi⁷, Celia Badenas¹¹, Rafael Artuch Iriberrí¹². ¹Hospital Sant Joan de Deu, Barcelona, Pediatric Gastroenterology, Hepatology and Nutrition Service, Esplugues de Llobregat, Spain; ²Hospital Sant Joan de Deu and Hospital Vall d'Hebron, Comprehensive unit of complex hepatology and pediatric liver transplantation, Barcelona, Spain; ³Hospital Clínic, CIBERehd and IDIBAPS, University of Barcelona, Liver Unit, Barcelona, Spain; ⁴Hospital Vall d'Hebron, Pediatric Gastroenterology, Liver Transplantation and Nutritional Support Unit, Barcelona, Spain; ⁵Hospital Vall d'Hebron and Hospital Sant Joan de Deu, Comprehensive Unit of Complex Hepatology and Pediatric Liver Transplantation, Barcelona, Spain; ⁶Institut de Recerca Sant Joan de Deu, and CIBERER, Clinical Biochemistry Department, Barcelona, Spain; ⁷Hospital Vall d'Hebron, Pediatric Hepatology and Liver Transplant Unit, Barcelona, Spain; ⁸Hospital Sant Joan de Deu, Barcelona, Spain; Department of Pediatric Gastroenterology, Hepatology and Nutrition, Barcelona, Spain; ⁹Hospital Sant Joan de Deu and Hospital Vall d'Hebron, Comprehensive Unit of Complex Hepatology and Pediatric Liver Transplantation, Barcelona, Spain; ¹⁰Hospital Sant Joan de Deu, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Barcelona, Spain; ¹¹Hospital Clínic, CIBERER and IDIBAPS, University of Barcelona, Biochemistry and Molecular Genetics Unit, Barcelona, Spain; ¹²Institut de Recerca Sant Joan de Deu and CIBERER, Clinical Biochemistry Department, Barcelona, Spain
Email: cmolera@sjdhospitalbarcelona.org

Background and aims: Wilson's disease (WD) is a rare disease with high diagnostic and follow-up challenges, due to high phenotypic variability and biomarkers drawbacks. Exchangeable copper and relative exchangeable copper ratio (REC) have shown to be promising diagnostic tools but its use in clinical practice is limited. Our aim was to assess the usefulness of REC in a real-world multicentric cohort of patients with WD.

Methods: This is a cross-sectional study where pediatric and adult patients with confirmed WD (by genetic diagnosis and/or Leipzig score ≥ 4) were included. Serum samples were obtained at diagnosis or follow-up. Exchangeable copper and REC were measured by Inductively plasma coupled to mass spectrometry (ICP-MS). Demographic, clinical and laboratory data were collected. A control group of non-WD individuals was included. Quantitative/categorical variables were expressed as median-IQR₂₅₋₇₅/n (%); comparisons between groups were done by Chi-Square or U-Mann Whitney/Kruskal-Wallis, as appropriate; correlations were assessed by Spearman test.

Results: Forty-two WD patients were included (33 adults, 9 children): 52.4% male, mean age at sample extraction 28.5 years (IQR: 19–42); 88% were in the follow-up phase [median time from diagnosis: 13 years (IQR: 5–23)]; 71.4% compound heterozygosis; 61.9% with chronic liver phenotype; 50% under zinc salts and 52.4% classified as adherents. The control group consisted in 34 non-WD individuals with significantly lower age at sample extraction ($p < 0.001$). REC was significantly higher in WD patients compared to controls (33.5% vs 3.9%, $p < 0.001$), confirming its accuracy to detect

high values even during the follow-up phase. REC negatively correlated with ceruloplasmin levels ($\rho = -0.51$, $p = 0.002$) and positively with ALT ($\rho = 0.35$, $p = 0.021$) but no correlation with age was found. No significant differences of REC were found between time of evaluation (diagnosis vs follow-up), genotype, phenotype, time of follow-up or treatment adherence. REC was significantly higher in patients with abnormal ALT levels compared to those with normal ALT (40.3% vs 23%, $p = 0.002$).

Conclusion: REC showed to be promising tool for WD diagnosis in this real-world cohort of adults and children, even during the follow-up phase. Despite REC was statistically associated with ceruloplasmin and ALT levels, its utility for follow-up monitoring and adherence deserves further evaluation.

Nurses and Allied Health Professionals

OS-686

Suffering from the unpredictable illness in liver cirrhosis

María Hjorth^{1,2}, Ann Karin Svanberg³, Daniel Sjöberg², Fredrik Rorsman¹, Elenor Kaminsky⁴. ¹Uppsala University, Department of Medical Sciences, Uppsala, Sweden; ²Dalarna County Council, Center of Clinical Research in Dalarna, Sweden; ³Dalarna University, School of Education, Health and Social Studies, Sweden; ⁴Uppsala University, Department of Public Health and Caring Sciences, Uppsala, Sweden
Email: maria.hjorth@regiondalarna.se

Background and aims: Mental reactions following chronic illnesses may be explained by suffering. According to Morse's theory suffering, the first phase, *enduring*, means suppressing emotions to preserve energy (Figure). When suffering proceeds to *emotional suffering*, there is a demand of energy due to overwhelming emotions. Gradually, one may experience *acceptance* or *hope*. The expression of feelings during the suffering process may fluctuate. The end of suffering, *self-reformulation*, means new insights about life arise. The lack of knowledge of suffering in liver cirrhosis (LC) hampers feasible nursing interventions to improve patients' health. Hence, Morse theory of suffering was used in this study to characterise suffering in LC.

Method: Purposive sampling of 20 informants (men = 10, age 25–71) with confirmed LC (range 0.5–10 years) resulted in twenty semi-structured interviews from 2016 to 2017. Inductive qualitative content analysis was performed of interview transcripts. Morse theory of suffering was used to discuss the study results.

Results: Coherent to Morse (Figure), all informants confirmed suffering. To avoid distress, informants *endured* by (I) remaining silent, (II) focus on anything but the illness or (III) constantly monitoring the illness, anxious that complications may arise (Figure, Box 1). In this phase, informants were uninterested of knowledge about the disease and preferred to be left alone. When *emotional suffering*, informants experienced sadness and grief (Figure, Box 7). Having someone to entrust then gave comfort and relief. Fluctuating between *enduring* and *emotional suffering* occurred. After suppression of anxiety, informants could suddenly broke out in tears or scream (Figure, Box 4–6). Sometimes acceptance of changes in life emerged (Figure, Box 8). *Hope* was expressed as a desire of improved health, or to be fortunate enough to be liver transplanted (Figure, Box 9). *Self-reformulation* was rare. One informant considered life with LC to be an educative process (Figure, Box 10).

Conclusion: Morse theory of suffering, facilitated the understanding of how suffering in LC may be experienced. The absence of self-reformulation, may be explained by the threat of unexpected and serious complications. Future interventions may target how nursing may relieve and support persons through different stages of suffering in LC.

ORAL PRESENTATIONS

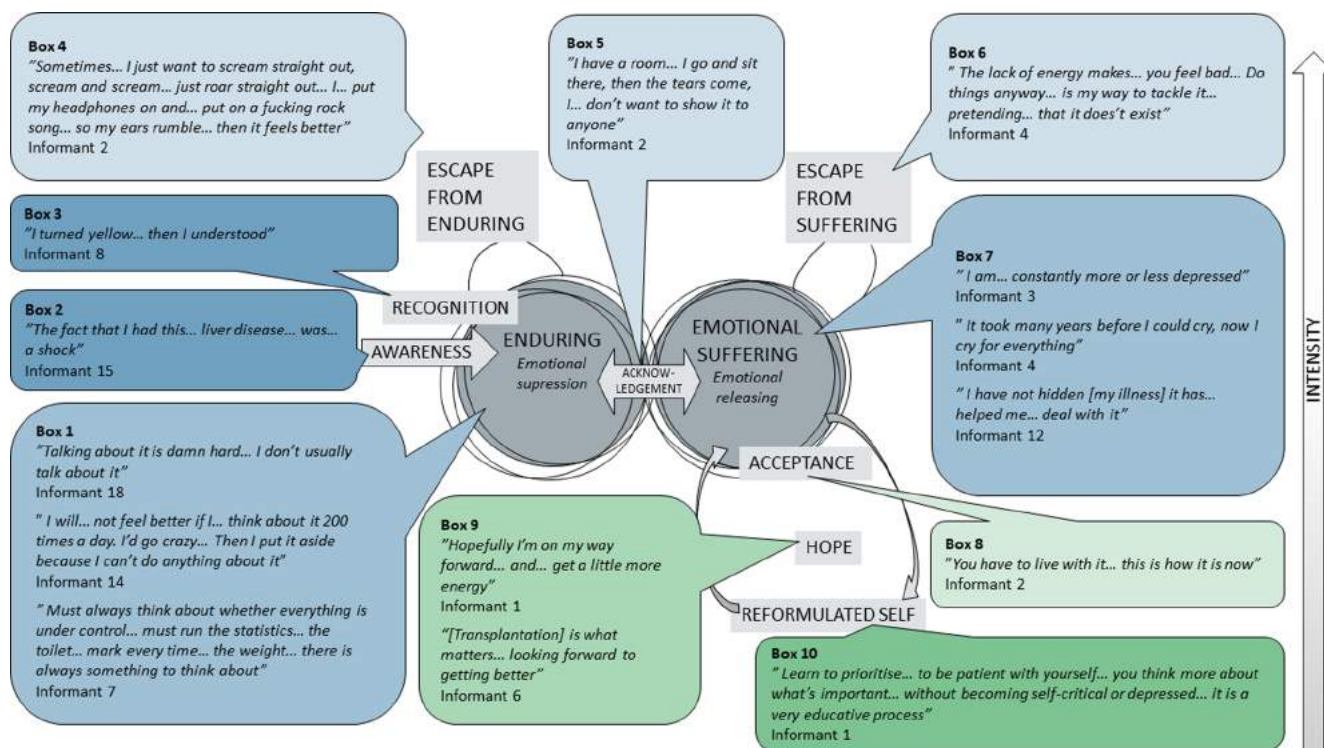


Figure: (abstract: OS-686): Morse's suffering process with informant's citations, describing experiences of suffering due to liver cirrhosis.

OS-798

The impact of intervention by dedicated nurse upon the treatment of patients post DAA treatment for HCV

Evelin Oxtrud¹, Yael Harif¹, Orly Sneh Arbib¹, Michal Cohen-Naftaly¹, Erika Waiss¹, Amir Shlomai¹, Marius Braun¹, Assaf Issachar¹. ¹Rabin Medical Center, Liver Institute, Petah Tikva, Israel
Email: assafissa@gmail.com

Background and aims: Chronic HCV infection may lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). The most important risk factor for disease progression is the degree of liver fibrosis. Treatment with DAA eradicates HCV infection in more than 98% of the patients. Cure is defined as SVR (sustained virological response, e.g., undetectable viral RNA 12 weeks after therapy). Despite achieving SVR, patients with advanced fibrosis remain at risk of liver deterioration and HCC, therefore follow-up and screening for HCC is recommended. We observed significant non-compliance with follow-up.

Aims of the study: To evaluate whether a phone call by a dedicated hepatology nurse providing detailed instructions might increase follow-up compliance to a greater degree than scheduling appointments only by mail, regarding attendance and performance of necessary tests.

To evaluate the patient perception regarding the value of instruction by dedicated nurses.

Method: 200 HCV patients treated with DAA between 2014–2019 in Rabin Medical Center who did not attend follow-up visits were randomly divided to two groups: group A-patients received a letter with a scheduled appointment and a request for blood tests and abdominal US and group B- patients received a phone call by nurse to explain the importance of the appointment and an appointment by mail. The patients who showed up were asked to complete a questionnaire about the added value of nurse instruction.

Results: There were no differences between the groups regarding age and gender. 140 patients (70%) showed up. The attendance was significantly higher in the phone intervention group (79 vs 61

respectively, $p < 0.005$). There was no difference in compliance with having the tests done in time. 119 had complete results and 16 partial. During the appointment 5 patients were found to have significant lesions (3 liver lesions, 1 suspicious pancreatic cyst and 1 RCC). 74/140 patient (52.8%) completed the questionnaire about the value of the dedicated nurse intervention. All patients were satisfied with the professionalism of the team. 90% of the patients thought that the phone call contributed to their adherence with follow-up and 85% of the patients felt that the explanation provided by the nurse during the appointment contributed to their understanding of their medical situation.

Conclusion: Explanation by dedicated nurse by phone call in addition to scheduling appointments by mail can increase the compliance of patients post HCV treatment with follow-up. Clinically significant findings were diagnosed. The patients pointed the added value of nurse explanations and instructions for better understanding of the disease and the importance of follow-up. Intervention by dedicated nurses improves the communication and compliance.

OS-1756

Increased hospital presentations with alcohol-related disorders during the COVID-19 crisis in the United Kingdom

Michelle Layton¹, Michael Luciw¹, Nasima Ali¹, Jeremy Cobbold¹, Francesca Saffioti¹. ¹Oxford Liver Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
Email: fsaffioti.83@gmail.com

Background and aims: The social restrictions and increased psychological distress triggered by the COVID-19 pandemic have led to a change of the individual alcohol consumption patterns in the UK. General population survey data show variable behavioural changes in alcohol intake; increased alcohol misuse has also been documented. There are concerns about reduced visibility of an increased alcohol-related harm due to a general reduction of the healthcare utilisation during the COVID-19 crisis. Data on admission episodes for alcohol-

related conditions during the pandemic are lacking. We aimed to analyse the pattern of hospital presentations with alcohol-related disorders in the COVID-19 era.

Method: The number of presentations with “alcohol-related liver disease” [ALD], “drug overdose with alcohol intoxication” and “mental and behavioural disorders due to use of alcohol” [MBDA] (including acute intoxication and alcohol withdrawal seizures with and without delirium) at the Oxford University Hospitals NHS Foundation Trust was retrieved using the diagnosis codes for the periods April-August 2019 (pre-COVID era) and April-August 2020 (COVID era). The comparison of figures between the two periods was performed by Chi-square test.

Results: Compared with the pre-COVID era, in the COVID era there was a 48.7% increase in the presentations with drug overdose with alcohol intoxication (80 vs 119, $p = 0.005$) and a 32.6% increase in the number of presentations with MBDA (1838 vs 2438, $p < 0.0001$). In particular, the number of presentations with alcohol withdrawal seizures with (22 vs 64, $p < 0.0001$) and without delirium (221 vs 411, $p < 0.0001$) increased by 191% and 86%, respectively.

There was a 47.5% increase in the presentations with ALD (781 vs 1152, $p < 0.0001$). Notably, there was a 77% increase of presentations with alcoholic hepatic failure (96 vs 170, $p < 0.0001$) and a 34% increase of presentations with alcohol-related cirrhosis (444 vs 595, $p < 0.0001$). There was also a remarkable 207% increase in diagnoses of alcoholic hepatitis between the two periods (68 vs 209, $p < 0.0001$).

Conclusion: Our local data demonstrate a significant increase of hospital presentations with alcohol-related disorders, in particular acute alcoholic hepatitis and withdrawal syndrome, in the context of the COVID-19 crisis. Close integration and reinforcement of clinical and alcohol services both in the community and in hospital are urgently needed, including an improvement of alcohol counselling services and psychological support.

Hospital presentations with alcohol-related liver disease

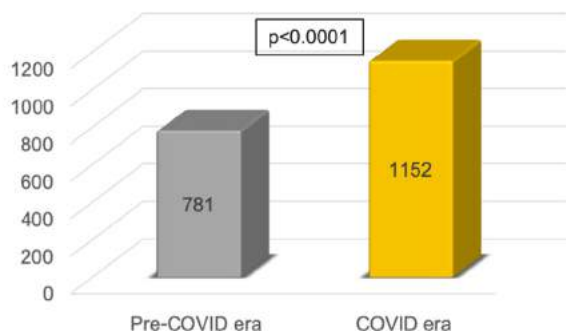


Figure:

Public Health

OS-183

Exploring the relationship between maternal pre-pregnancy BMI and outcomes of NAFLD in young adulthood: a parental negative control study

Kushala Abeysekera^{1,2}, James Orr², Gwen Fernandes¹, Paul Madley-Dowd¹, Luisa Zucculo^{1,3}, Fiona Gordon², Deborah Lawlor^{1,3,4}, Jon Heron¹, Matthew Hickman^{1,3}. ¹University of

Bristol, Population Health Sciences, United Kingdom; ²Bristol Royal Infirmary, Department of Liver Medicine, Bristol, United Kingdom; ³University of Bristol, MRC Integrative Epidemiology Unit, Bristol, United Kingdom; ⁴University of Bristol, Bristol NIHR Biomedical Research Centre, Bristol, United Kingdom
Email: k.abeysekera@bristol.ac.uk

Background and aims: The importance of the maternal-infant dyad in the genesis of non-alcoholic fatty liver disease (NAFLD) is of increasing interest. Murine models suggest an obesogenic in utero environment can “prime” the liver to develop NAFLD. The Avon Longitudinal Study of Parents and Children (ALSPAC) showed that at age 24, 1 in 5 had NAFLD measured by controlled attenuation parameter (CAP) during transient elastography. Our aim was to investigate the association between maternal pre-pregnancy BMI and offspring NAFLD in young adulthood, building on previous analyses from the Raine birth cohort which found maternal pre-pregnancy obesity more than doubled odds of NAFLD in adolescent offspring.

Method: 4021 offspring participants attended clinic for FibroScan and CAP measurement using the Echosens 502 Touch®. 440 participants with Alcohol Use Disorders were excluded. Offspring of 100 non-singleton pregnancies were excluded. 2961 valid CAP measurements for NAFLD were analysed. The exposure of interest was maternal pre-pregnancy BMI, categorized into BMI <math>< 25</math> kg/m², overweight (25 to <math>< 30</math> kg/m²) and obese (>math>\geq 30</math> kg/m²). Multivariable logistic regression models estimated the odds of NAFLD at 24 years by level of the exposures. Confounders included maternal age, smoking in pregnancy and social class. A paternal negative control test was used to explore the potential for residual shared confounding in the analyses of pre-pregnancy BMI. Paternal and maternal BMI were mutually adjusted for to account for bias secondary to assortative mating.

Results: Maternal and paternal pre-pregnancy BMI was available for 2869 and 2316 participants respectively. Offspring of mothers with obesity had three times higher odds of NAFLD following adjustment for confounders (OR 3.06 [95% CI 2.11–4.42]; $p < 0.0001$). However, offspring whose fathers had obesity were also at higher odds of NAFLD (crude OR 1.85 [1.26–2.72; $p = 0.002$]).

The negative control design, provided evidence of a specific maternal effect which could not be explained by the shared confounding structure, having compared effect size estimates between maternal and paternal BMI categories after mutual adjustment.

Conclusion: We found evidence of higher maternal pre-pregnancy BMI influencing NAFLD development, having accounted for shared parental confounding. This suggests early life exposures could be compounding existing environmental factors that perpetuate NAFLD development. Ultimately this supports the role of the maternal-infant dyad in NAFLD pathogenesis, reflective of the obesogenic environment our patients live in.

OS-199

Get Tested LeEDs: Clinical impact and cost-effectiveness of opt-out emergency department testing for bloodborne viruses (BBVs)

Elizabeth Smout¹, Jack Williams², Alec Miners², Khine Phyu³, Lee Parker³, Amy Evans³, Joscelyne McLaren³, Mark Aldersley³, Gareth Hughes¹, Murad Ruf⁴, Emma Page³. ¹Public Health England, Field Service, National Infection Service; ²London School of Hygiene and Tropical Medicine, Department of Health Services Research and Policy; ³Leeds Teaching Hospitals Trust; ⁴Gilead Sciences Ltd, Medical Department
Email: elizabeth.smout@nhs.net

Background and aims: Innovative testing approaches and care pathways are required to meet global HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) elimination goals. Routine testing for BBVs within emergency departments (EDs) is recommended by European Centre for Disease Prevention and Control (ECDC) but paucity of supporting evidence is highlighted. We evaluated the introduction of

ORAL PRESENTATIONS

integrated, opt-out testing for HIV, HBV and HCV infections in EDs at Leeds Teaching Hospitals NHS Trust, UK.

Method: From October 2018–July 2019, HBV (HBV surface antigen [HBsAg]), HCV (HCV antibody [anti-HCV] and reflex HCV-RNA) and HIV antibody testing were opportunistically offered, on an opt-out basis through electronic record modification, to all ED attendees aged 16–65 years who had a routine blood test for urea and electrolytes. Linkage to care (LTC) was attempted for patients who were newly diagnosed or who had disengaged from care.

We analysed testing uptake, BBV seropositivity and LTC at six months following diagnosis and developed an economic model to evaluate hepatitis screening cost-effectiveness from a UK NHS perspective.

Results: Over 9 months, 16, 053/28, 178 (57.0%) ED attendees were tested for ≥ 2 BBVs. 299 active BBV infections were identified: 73 HBsAg-positive (0.5% seroprevalence), 156 HCV-RNA (1.0%) and 70 HIV-positive (0.4%) ED attendees.

Nearly all (94.9%, 148/156) HCV-RNA positive individuals required LTC. A smaller but substantial proportion of HBsAg-positive (53.4%, 39/73) and HIV-positive (24.3%, 17/70) individuals required LTC. 69.3% (27/39) of HBsAg-positive and just 39.2% (58/148) HCV RNA-positive individuals were successfully linked to care, with 25.0% (37/148) commencing treatment. Nearly all (94.1%, 16/17) of eligible HIV-positive individuals were successfully linked.

Testing for HCV and HBV was highly cost-effective, with incremental cost-effectiveness ratios of £6, 024 and £16, 812, respectively.

Conclusion: Integration of routine BBV testing within the ED was feasible, effective and sustainable, identifying a large number of active BBV infections requiring LTC. Our integrated approach achieved good LTC rates although further work is necessary, particularly for HCV.

Our findings support utility of opt-out BBV testing in EDs in line with the ECDC guidance and demonstrate cost-effectiveness of routine hepatitis testing in the UK at much lower seroprevalence than that stated in the guidelines.

OS-551

The effect of COVID-19 on the progress of the hepatitis C elimination program in Georgia

Amiran Gamkrelidze¹, Alexander Turdziladze¹, Maia Tsreteli¹, Vladimer Getia¹, Ana Aslanikashvili¹, Sophia Surguladze¹, Lia Gvinjilia², Tinatin Kuchuloria², Irina Tskhomelidze², Shaun Shadaker³, Paige A. Armstrong³. ¹National Center for Disease Control and Public Health Georgia, Tbilisi, Georgia; ²The Task Force for Global Health, Tbilisi, Georgia; ³National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC, Division of Viral Hepatitis, Atlanta, United States
Email: a.gamkrelidze@ncdc.gov

Background and aims: Georgia, with a population of 3.7 million, has an estimated 150,000 adults living with chronic hepatitis C virus (HCV) infection. The country initiated the world's first national HCV elimination program in 2015, with free screening and treatment available to all citizens. Despite great progress, the COVID-19 pandemic has created new challenges for the program. This analysis describes the progress made in HCV screening since program initiation and the impact of the COVID-19 pandemic on testing.

Method: A national database was created to collect screening data for the HCV program, for the purpose of surveillance and program monitoring and evaluating. This analysis uses data from the national HCV screening registry and treatment databases linked by individuals' national IDs, and the 2014 general population census.

Results: As of January 23, 2021, 2, 100, 693 adults have been tested for antibody to HCV (anti-HCV) (73.4% of the adult population), of whom 157, 515 (7.5%) were anti-HCV positive. Overall, 113, 315 (71.9%) of anti-HCV positive individuals received follow-up viremia testing, and 90, 498 (79.9%) were found to have chronic HCV infection.

The COVID-19 pandemic has led to a decline in testing in the national HCV elimination program. Screening rates dropped after restrictions

were imposed in March, 2020, from as high as 87, 997 in February, to just 37, 010 in April. Testing briefly increased in the summer, with 113, 658 tests performed in July, due in part to relaxed restrictions and intensified integrated screening programs (HCV, tuberculosis, and HIV). Overall, the number of individuals tested in 2020 decreased by 51% (288, 343) compared to 2019 (584, 987).

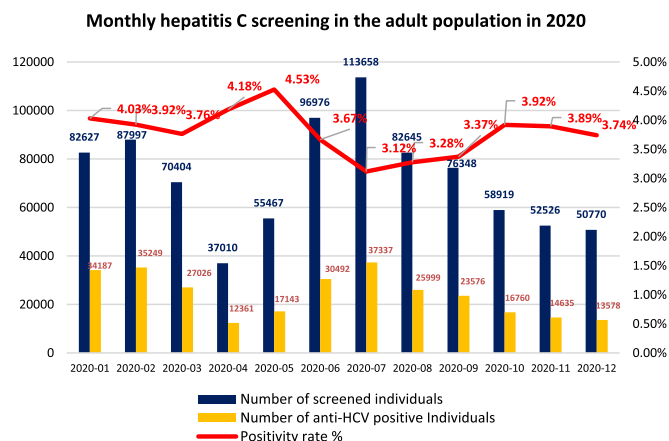


Figure:

Conclusion: Although the program has made significant progress toward HCV elimination, the ongoing pandemic has led to a decline in testing rates. In response, Georgia intends to increase integrated screening, and seek active approaches to link patients to care. The lessons learned and impact on the program demonstrate how a pandemic can prove challenging for public health programs, and highlights the need to employ innovative strategies to avoid loss of progress.

OS-1381

Effect of COVID-19 on alcohol use disorder among hospitalised patients: a retrospective cohort control study

Mohsan Subhani^{1,2}, Abhishek Sheth³, Stuart Unitt², Joanne Morling^{3,4}, Guruprasad Aithal^{1,3}, Stephen Ryder^{2,3}.

¹Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham; ²Nottingham University Hospitals NHS Trust, NIHR Nottingham Biomedical Research Centre, Nottingham, United Kingdom; ³Nottingham University Hospitals NHS Trust and the University of Nottingham, NIHR Nottingham Biomedical Research Centre, Nottingham, United Kingdom; ⁴Nottingham University Hospitals NHS Trust and the University of Nottingham, Division of Epidemiology and Public Health, Nottingham
Email: subhani@doctors.org.uk

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

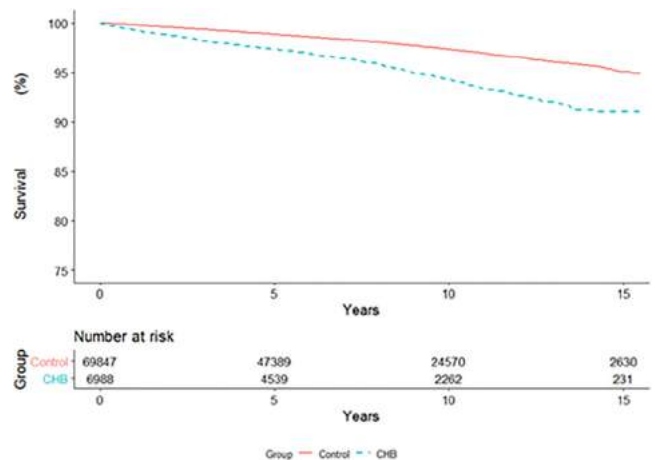


Figure: Kaplan Meier plot of survival after inclusion in study in persons with chronic hepatitis B and controls.

Conclusion: This study showed an increased all-cause mortality in persons with chronic hepatitis B in comparison with the general population which remained after adjustment for several confounding factors. Excess death was mainly related to liver disease. However, rates of death from neoplasms (excluding HCC), endocrine disease, genitourinary disease and external factors were also increased in persons with CHB.

OS-2202

Mortality and cause of death in people with chronic hepatitis B-a nationwide register-based cohort study

Signe Bollerup¹, Sofie Hallager¹, Frederik Engsig¹, Amanda Mocroft², Peer Brehm Christensen³, Jan Gerstoft⁴, Nina Weis¹. ¹Copenhagen University Hospital, Hvidovre, Department of Infectious Diseases, Hvidovre, Denmark; ²Copenhagen University Hospital, Rigshospitalet, Centre of Excellence for Health, Immunity and Infections (CHIP) and PERSIMUNE, Copenhagen, Denmark; ³Odense University Hospital, Department of Infectious Diseases; ⁴Copenhagen University Hospital, Rigshospitalet, Department of Infectious Diseases, Copenhagen, Denmark

Email: signe.bollerup@regionh.dk

Background and aims: In this nationwide cohort study, we aimed to determine adjusted all-cause mortality and cause of death in persons with chronic hepatitis B compared with the general population in a setting with low prevalence of chronic hepatitis B.

Method: We used several nationwide registries to identify persons aged ≥ 18 diagnosed with chronic hepatitis B in 2002–2016 in Denmark and included 10 age- and sex matched controls from the general population for each person with chronic hepatitis B. The study population was followed from six months after first chronic hepatitis B registration until death, emigration or December 31, 2017. Mortality rate ratios adjusted for age, sex, employment, region of origin and comorbidity were calculated using Poisson regression. Unadjusted cause specific mortality rate ratios with 95% confidence intervals were calculated assuming a Poisson distribution.

Results: A total of 6,988 persons with chronic hepatitis B and 69,847 controls were included in this study. During a median follow-up of 7.7 years (range 0.0–15.5), 315 (5%) persons with chronic hepatitis B and 1,525 (2%) without chronic hepatitis B died. The figure shows a Kaplan Meier plot of survival starting at 6 months after chronic hepatitis B diagnosis. The adjusted all-cause mortality rate ratio was 1.5 (95% CI 1.2–2.0). Persons with chronic hepatitis B had increased mortality due to liver disease (mortality rate ratio 12.3 [8.6–17.7]), neoplasm except hepatocellular carcinoma (HCC) (mortality rate ratio 1.6 [1.2–2.0]), endocrine disease (mortality rate ratio 3.2 [1.8–5.4]), genitourinary disease (mortality rate ratio 3.2 [1.2–7.6]) and external causes (mortality rate ratio 3.3 [2.5–4.7]).

OS-2750

Estimating the contribution of viral hepatitis and other etiologies to the burden of cirrhosis: a worldwide systematic review

Catharina Alberts¹, Gary Clifford¹, Francesco Negro², Yvan Hutin³, Catherine de Martel¹. ¹International Agency for Research on Cancer, World Health Organization, Lyon, France; ²University Hospitals, Divisions of Gastroenterology and Hepatology and of Clinical Pathology, Geneva, Switzerland; ³World Health Organization Regional Office for the Eastern Mediterranean, Department for Universal Health Coverage/ Communicable Diseases, Cairo, Egypt

Email: demartelc@who.int

Background and aims: The International Agency for Research on Cancer estimated that, worldwide, the fraction of hepatocellular carcinoma (HCC) attributable to hepatitis B virus (HBV) and hepatitis C virus (HCV) were 56% and 20%, respectively (2015). Currently, estimates for cirrhosis are lacking. We conducted a systematic review to estimate the prevalence of HBV and HCV among cirrhotic patients worldwide.

Method: We included studies published between 1993 and 2019 with case series of cirrhotic patients that reported on the prevalence of both HBV and HCV infection in at least 20 adults. We excluded studies using first-generation assays for HCV. We extracted available information on the prevalence of HBV and HCV infection, heavy alcohol consumption, non-alcoholic fatty liver disease (NAFLD), or on the etiology of HCC cases, and calculated prevalence stratified by UN region.

Results: In total, 507 studies from 73 countries included over 1 million cases of cirrhosis. In most European and American regions, HCV was more prevalent among cirrhosis cases (ranging between 17–25% and 33–35%, respectively) compared to HBV (4–17% and 3–13%). In Asian and African regions, both HBV and HCV were prevalent with combined HBV and HCV prevalence $>50\%$, albeit with large variations between sub-regions e.g. with highest prevalence of HBV in Eastern Asia and sub-Saharan Africa (see Figure). Heavy alcohol consumption (395 studies) varied from $<10\%$ in Northern Africa and Western Asia to 40–50% in South America, Oceania and Western Europe. Only 112 studies reported the prevalence of NAFLD ranging from 15% in North America to 1% in sub-Saharan Africa. In the 69 studies reporting etiology for both cirrhosis and HCC, the prevalence

of viral infections was greater among HCC than in cirrhotic patients, and this effect was stronger for HBV than for HCV.

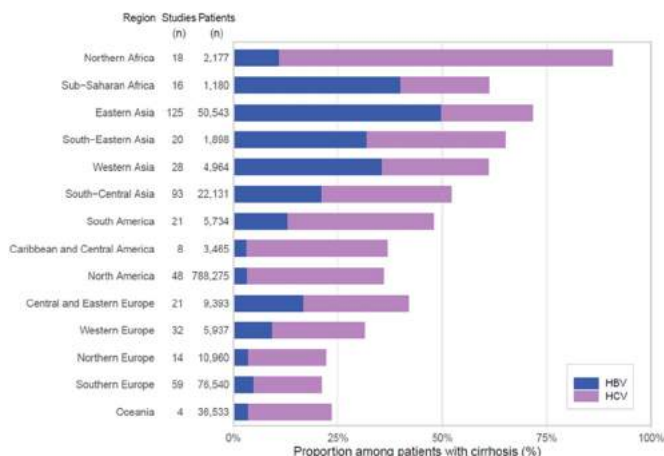


Figure:

Conclusion: Similar to HCC, HBV and HCV prevalence varies worldwide and is an important cause of cirrhosis, yet, the combined fraction of HBV and HCV is lower than for HCC. Limited data on heavy alcohol consumption and NAFLD prevalence also suggests major geographical variations. This review provides much needed country-level, regional, and global data on the etiological fractions of cirrhosis to help set priorities for liver disease prevention, especially for viral hepatitis in Asian and African regions. Systematic, ongoing collection of representative data on the etiology of cirrhosis and HCC is required to evaluate progress towards hepatitis elimination.

Rare liver diseases (including paediatric and genetic)

OS-1172

Liver transplant for porto-sinusoidal vascular disease (psvd): long-term outcome

Marta Magaz¹, Heloïse Giudicelli-Lett², Oana Nicoară-Farcău³, Neil Rajoriya⁴, Ashish Goel⁴, François Durand², Lena Smets⁵, Karlien Raymenants⁵, Sophie Hillaire², Gonzalo Crespo⁶, Luis Téllez⁷, Laure Elkrief⁸, Constatino Fondevila⁹, Lara Orts¹, Filipe Nery¹⁰, Akash Shukla¹¹, Hélène Larrue¹², Xavier Verhelst¹³, Helena Degroote¹³, Victoria Aguilera¹⁴, Elba Llop¹⁵, Anna Baiges¹, Fanny Turon¹, José Luis Calleja¹⁵, Christophe Bureau¹², Agustín Albillos⁷, Frederik Nevens⁵, Virginia Hernandez-Gea¹, Dhiraj Tripathi⁴, Pierre-Emmanuel Rautou², Juan Carlos Garcia Pagan¹, For Valdig, an EASL consortium¹⁶. ¹Hospital Clínic, Hemodinámica Hepática, Barcelona; ²Service d'Hépatologie, Centre de Référence des Maladies Vasculaires du Foie, DHU Unity, Pôle des Maladies de l'Appareil Digestif; ³Regional Institute of Gastroenterology and Hepatology "Octavian Fodor, Hepatology Department and "Iuliu Hatieganu" University of Medicine and Pharmacy; ⁴University Hospital Birmingham NHS Foundation Trust, Birmingham, Liver Unit; ⁵University Hospital KU Leuven, Department of Gastroenterology and Hepatology; ⁶Hospital Clínic, Liver Transplant Unit; ⁷Hospital Universitario Ramón y Cajal, Department of Gastroenterology and Hepatology; ⁸Hôpitaux Universitaires de Genève, Service d'Hépatogastroentérologie; ⁹Hospital Clínic, Department of Surgery, Division of Hepatobiliary and General Surgery, Institut de Malalties Digestives I Metabòliques (IMDiM); ¹⁰Hospital do Porto, Hospital Sto Antonio, Liver Unit; ¹¹Lokmanya Tilak Municipal General Hospital and Lokmanya Tilak Municipal Medical College, Department of Gastroenterology; ¹²Ranguel

Hospital, CHU Toulouse, Department of Hepatology; ¹³Ghent University Hospital, Ghent; Department of Gastroenterology and Hepatology; ¹⁴Hospital Universitari i Politècnic La Fe, Hospital Universitari i Politècnic La Fe; ¹⁵Hospital U, Puerta de Hierro, Liver Unit
Email: martamagazm@gmail.com

Background and aims: PSVD is a rare disease usually with preserved liver function. Yet, some patients develop complications of portal hypertension or liver failure and require liver transplantation (LT). Data regarding LT are limited. The objective was to describe indications and outcome of LT in patients with PSVD.

Method: Retrospective VALDIG network multicentre study, 80 PSVD patients who underwent LT between 1996 and 2019: 51 came from a prospective international cohort of 587 patients and 29 additional were transplanted with the misdiagnosis of cirrhosis. Those patients without an underlying-disease or that have a similar life-expectancy to healthy patients, ie autoimmune hypothyroidism, were classified as mild underlying-disease. The remaining with potentially associated disorders with reduced life-expectancy, such as severe lupus were classified as severe.

Results: Indications for LT were 24 (30%) refractory ascites, 16 (20%) hepatic encephalopathy, 13 (16%) hepatopulmonary syndrome, 8 (10%) liver failure, 4 (5%) spontaneous bacterial peritonitis, 2 (2%) hepatorenal syndrome, 2 (2%) hepatocellular carcinoma, 1 (1%) recurrent portal hypertension related bleeding and other indications 10 (12%). Patients were categorized according to severity of the underlying-disease, 48 had a mild underlying-disease, the remaining 32 severe. Mean post-LT follow-up was 60 ± 60 [1–265] months. Twenty-four patients died after a median of 44 ± 70 [1–235] months, eight due to hepatic related conditions and 16 due to the underlying-disease. Post-LT cumulative survival was 82%, 81% and 69%, at 1, 2, 5 years. Post-LT survival was significantly better in patients without a severe underlying-disease (p = 0.05) (Figure).

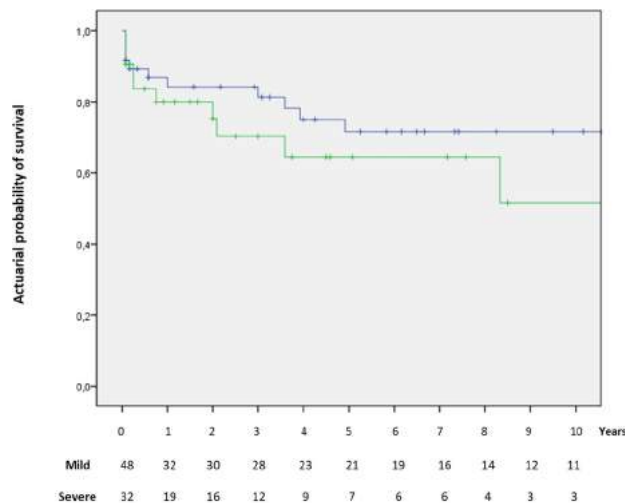


Figure:

Six patients (7.5%) required a new LT (hepatic artery thrombosis n = 2, acute liver failure n = 2, graft loss n = 1, and unresolvable biliary complication n = 1). Consequently, overall graft survival was 81%, 78% and 66%, at 1, 2, 5 years respectively. Seventeen patients (21%) experienced acute rejection, and two developed chronic rejection. There were no reports of de novo post-transplant neoplasia.

Conclusion: The present large series, shows that when required, LT is associated with a good long-term outcome provided PSVD is not associated with a severe underlying-associated disease. Therefore, the severity of the underlying-disease must be taken into account when considering LT for these patients.

ORAL PRESENTATIONS

OS-1396

cJun N-terminal kinase signaling prevents biliary cyst formation through a Caspase-8-dependent function of receptor-interacting serine/threonine kinase 1 during aging

Katrin Mueller¹, Hanna Honcharova-Biletska², Christiane Koppe¹, Anne Schneider¹, Lap Kwan Chan², Fabian Geisler³, Thomas Longerich⁴, Mathias Heikenwälder⁵, Achim Weber², Mihael Vucur⁶, Tom Luedde⁶. ¹RWTH Aachen University Hospital, Clinic for Gastroenterology, Metabolic Disorders and Internal Intensive Medicine, Aachen, Germany; ²University Hospital Zürich, Institute for Pathology and Molecular Pathology, Zürich, Switzerland; ³University Hospital rechts der Isar, Technical University Munich, Internal Medicine II, Munich, Germany; ⁴University Hospital Heidelberg, Institute for Pathology, Heidelberg, Germany; ⁵German Cancer Research Center, Chronic Inflammation and Cancer, Heidelberg; ⁶University Hospital Düsseldorf, Department of Gastroenterology, Hepatology and Infectious Diseases, Düsseldorf, Germany
Email: tom.luedde@med.uni-duesseldorf.de

Background and aims: The c-Jun N-terminal kinase (JNK) signaling pathway mediates adaptation to stress signals and has been associated with cell death, cell proliferation and malignant transformation in the liver. However, up to now its function was

experimentally studied mainly in young mice. The long-term effects of JNK deficiency in the liver have remained unclear.

Method: For this study we have been using multiple genetic mouse models, including different cre-recombinase approaches (LPC-KO and Sox9-creERT2) and genetic subcrossings. Furthermore, we performed cell death analyses, a three-dimensional reconstruction method of the intrahepatic bile duct system in mice, an in vitro kinase activity array for the investigation of the protein interaction processes, and immunohistochemical stainings in human liver samples.

Results: We show here that aging JNK1/2^{LPC-KO} mice (LPC: liver parenchymal cells) spontaneously developed large biliary cysts. 3D reconstruction of serial biliary stainings as well as genetic subcrossing to biliary-specific cre-lines versus hepatocyte-specific cre-lines demonstrated that these cysts originated from biliary cells, arguing against a trans-differentiation defect of hepatocytes in JNK-deficient livers. Mechanistically, we could show that cyst formation in livers of JNK1/2^{LPC-KO} mice was depending on a Caspase-8-dependent function of receptor interacting protein kinase 1 (RIPK1), a known regulator of programmed cell death, namely apoptosis and necroptosis. An unbiased kinase-substrate-array in cholangiocytes suggested that JNK-deletion might trigger overactivation of the kinases MK-2/3, resulting in the putative over-phosphorylation of RIPK1 and

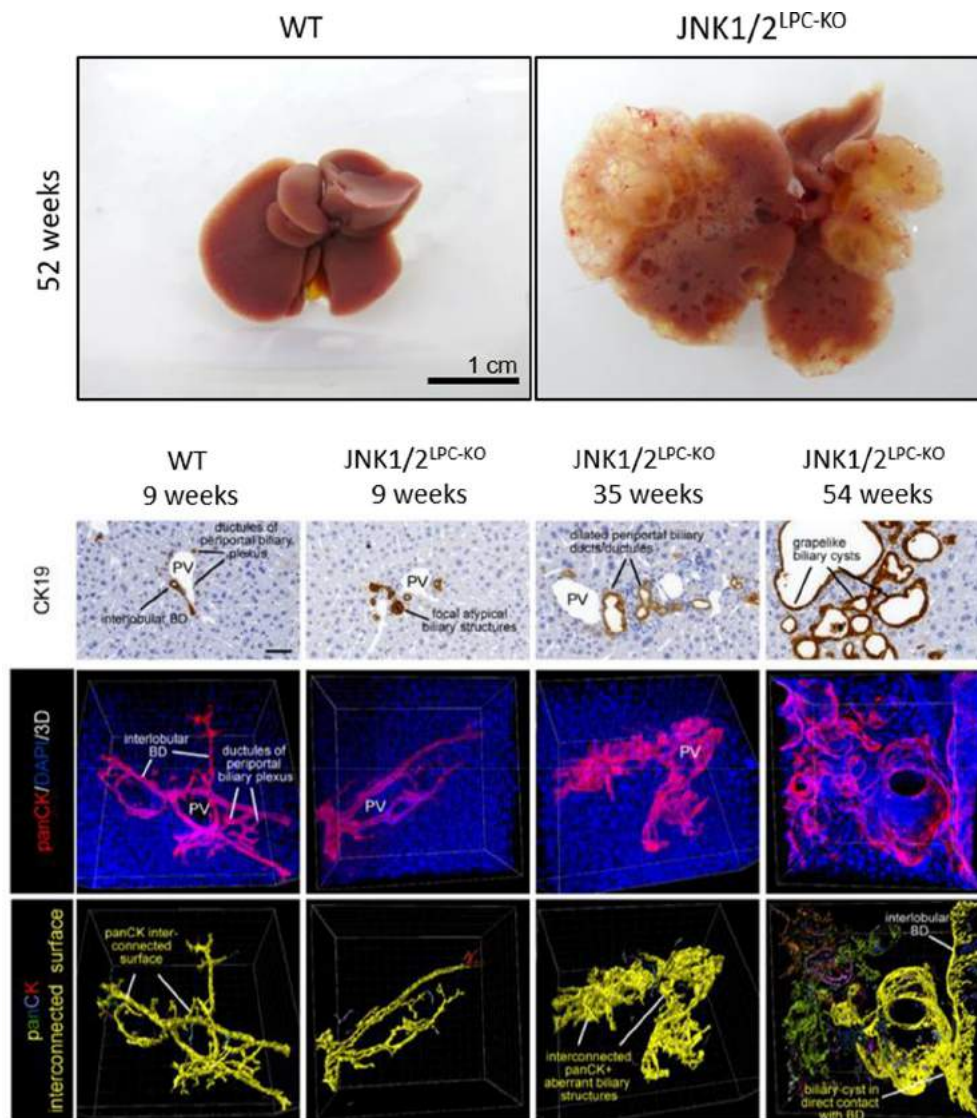


Figure:

subsequent inhibition of cell death of biliary cells during aging. In line, we showed that RIPK1 was overexpressed in human cyst epithelium of a subset of patients with polycystic liver disease.

Conclusion: Collectively, these data reveal a previously unrecognized functional interaction between JNK signaling and RIPK1 in age-related progressive biliary cyst development. Thus, they provide a novel functional linkage between stress-adaption and programmed cell death (PCD) in the maintenance of liver homeostasis during aging and a potential hub for a new molecular targeting of human polycystic liver disease.

OS-1554

Rapid and durable effect of odevixibat on clinical and biochemical parameters of cholestasis in children with progressive familial intrahepatic cholestasis

Richard Thompson¹, Lorenzo D'Antiga², Binita M. Kamath³, Lise Kjems⁴, Quanhong Ni⁴, Mohammad Ali Shagrani⁵, Eyal Shteyer^{6,7}, Nisreen Soufi⁸, Patrick Horn⁴. ¹Institute of Liver Studies, King's College London, London, United Kingdom; ²Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; ³Hospital for Sick Children and the University of Toronto, Toronto, Canada; ⁴Albireo Pharma, Inc., Boston, United States; ⁵King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; ⁶Hebrew University of Jerusalem, Faculty of Medicine, Jerusalem, Israel; ⁷Shaare Zedek Medical Center, Juliet Keidan Department of Pediatric Gastroenterology, Jerusalem, Israel; ⁸Children's Hospital Los Angeles, Los Angeles, United States
Email: patrick.horn@albireopharma.com

Background and aims: Odevixibat, an ileal bile acid transporter inhibitor, is in development to treat cholestatic liver diseases. Here, we describe a pooled analysis on the timing and magnitude of effects of odevixibat on serum bile acids (sBAs), pruritus, and biochemical

markers from the phase 3 PEDFIC 1 (P1) and PEDFIC 2 (P2) studies in children with progressive familial intrahepatic cholestasis (PFIC).

Method: In P1, children with PFIC1 or PFIC2 were randomized to oral placebo (Pbo) or odevixibat 40 or 120 µg/kg/day for 24 weeks. P2 is an ongoing, 72-week, open-label extension study enrolling patients from P1 or new patients with any type of PFIC; all P2 participants receive odevixibat 120 µg/kg/day. Currently, 69 patients have received treatment in P2. This pooled analysis covers 48 weeks of combined data from these studies. Primary outcomes assessed were proportion of patients with sBA response (ie, ≥70% reduction from baseline or sBAs ≤70 µmol/L) and change in pruritus based on a patient's proportion of positive pruritus assessments (PPAs) over time (ie, scratching score ≤1 or a ≥1-point drop from baseline on the PRUCISION® instrument). Mean changes in autotaxin (linked to cholestatic pruritus intensity) and plasma 7α-hydroxy-4-cholesten-3-one (p-C4; marker of bile acid synthesis) levels were also summarized.

Results: Overall, 77 patients received odevixibat. This included 19 who received Pbo in P1 and rolled into P2, 42 who received odevixibat in P1 (of these, 34 rolled into P2), and 16 newly enrolled patients in P2. Treatment with odevixibat was associated with rapid improvement in sBAs, pruritus, autotaxin, and p-C4 levels (ie, by week 1–4), with clinical benefits sustained through 48 weeks of treatment (Figure, panels A-D, respectively). Overall, 61 of 77 patients (79%) experienced any treatment-emergent adverse event (TEAE), incidence comparable to that in patients treated with placebo in P1 (17/20 [85%]). Eight patients reported severe TEAEs, and none had serious adverse events deemed related to treatment.

Conclusion: In this pooled analysis of children with PFIC, treatment with odevixibat was generally well tolerated and was associated with

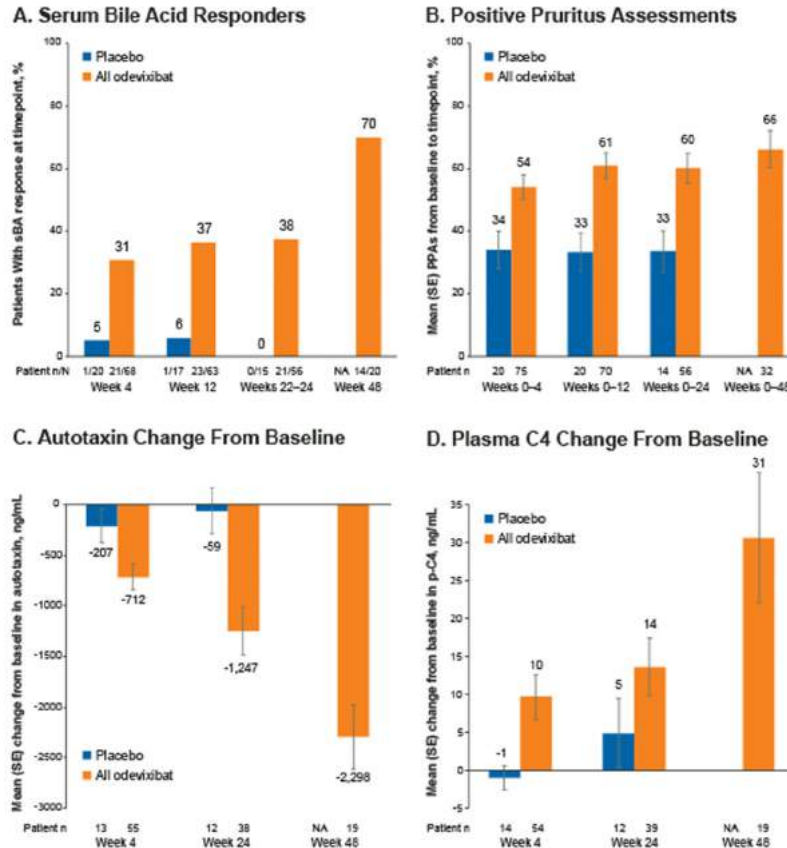


Figure:

ORAL PRESENTATIONS

rapid control of biochemical and clinical markers of cholestasis, with durable effects over time.

OS-1921

Factors related to liver impairment during SARS-CoV-2 infection

Lidia Canillas^{1,2}, Giulia Pagano¹, Teresa Broquetas^{1,2}, Judit Romero^{1,2}, Esther Garrido^{1,2}, Ana Viu^{1,2}, Jose A. Carrión^{1,3}, Nuria Cañete Hidalgo^{1,2}, Susanna Coll^{1,2}, Xavier Bessa^{1,2}, Montserrat Garcia-Retortillo^{1,2}, Marc Puigvehí^{1,2}. ¹Hospital del Mar, Barcelona, Spain; ²IMIM, Barcelona, Spain; ³Universitat Autònoma de Barcelona, Bellaterra, Spain
Email: mpuigvehi@psmar.cat

Background and aims: Abnormal liver function tests (LFTs) have been reported in 22–53% of patients with SARS-CoV-2 infection. LFTs impairment has been suggested to be related with greater severity of respiratory disease, use of hepatotoxic treatments, and higher mortality. We aimed at evaluating factors related to LFTs abnormality during SARS-CoV-2 infection.

Method: Retrospective observational study including the first consecutive 600 patients admitted with coronavirus disease (COVID-19) in our tertiary center (Hospital del Mar, Barcelona, Spain). Sociodemographic data, comorbidities (including chronic liver disease -CLD-), SARS-COV-2 infection severity (defined by PaFi < 200 or organ dysfunction leading to intensive care unit -ICU-admission), laboratory tests, treatments received, and mortality data were collected. LFTs abnormality grade (absent to grade 4) was defined using aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin levels (TBIL), using the common terminology criteria for adverse events. Patients were further divided into mild (absent or grade 1 LFTs abnormality), and severe (grade 2/3/4 LFTs abnormality).

Results: A total of 595 patients were evaluated: median age 62 years, 361 (60.7%) males and 45 (7.6%) had CLD, of which 5 (11.1%) with cirrhosis. COVID-19 was severe in 250 (42%) patients. LFTs abnormality was found in 366 (61.5%) patients: 228 (38.3%) grade 1, 70 (11.8%) grade 2, 61 (10.3%) grade 3 and 7 (1.2%) grade 4. Patients with severe LFTs abnormality had a variable liver profile on admission: 89 (64.5%) and 49 (35.5%) showed mild and severe LFTs abnormality at the time of admission, respectively. Median time from the onset of symptoms to maximum LFTs impairment was 12 [IQR 9–16] days (4 [IQR 1–7] days from hospital admission). In a multivariate analysis [OR (CI 95%)], severe LFTs abnormality was independently related with PaFi < 200 [2.47 (1.18–5.14), $p = 0.016$], and higher interleukin-6 [1.63 (1.01–2.62), $p = 0.046$] and ferritin [2.68 (1.64–4.37), $p < 0.001$] levels on admission. Global mortality was 10.3%: 9% and 14.5% in patients with mild and severe LFTs abnormality, respectively ($p = 0.061$). Worsening of LFTs during admission ($n = 89$) was independently related with ICU admission [5.34 (3.08–9.28), $p < 0.001$] and use of immunomodulatory drugs [2.57 (1.50–4.39), $p = 0.001$], but not antibiotic drugs. Patients with CLD didn't show greater LFTs abnormality, more severe COVID-19 infection, admission to ICU, neither mortality (all $p = ns$).

Conclusion: Liver impairment appeared during the first days of admission, and was related with COVID-19 severity. The worsening of LFTs during COVID-19 was related with immunomodulatory but not antibiotic treatment. Patients with CLD did not present a more severe LFTs abnormality, greater severity nor mortality from COVID-19.

OS-2590

Trientine tetrahydrochloride for the treatment of patients with Wilson Disease

Karl Heinz Weiss¹, Anna Czlonkowska², Massimo Giovanni Zuin³, David Cassiman⁴, Aurelia Poujois⁵, Peter Ott⁶, Koenraad D'Hollander⁷, C. Omar Kamlin⁸, Michael Schilsky⁹. ¹Salem Medical Center, Dept. of Internal Medicine, Heidelberg, Germany; ²Institute of Psychiatry and Neurology, Neurology, Warsaw, Poland; ³University of Milan, Division of Internal Medicine and Liver Unit, Milan, Italy; ⁴KU Leuven, Department

of Clinical and Experimental Medicine, Leuven, Belgium; ⁵Fondation Hospital Rothschild, Neurologie, Paris, France; ⁶Aarhus University Hospital, Medical Dept LMT Hepatology and Gastroenterology, Aarhus, Denmark; ⁷IDDI, Biostatistics, Louvain-la-Neuve, Belgium; ⁸Orphan SA France, Medical Affairs, London, United Kingdom; ⁹Yale University, New Haven, United States
Email: omar.kamlin@orphanal.uk

This abstract is under embargo until the beginning of the press conference it is being presented in on Thursday 24 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

Viral Hepatitis A, B, C, D, E: Virology

OS-595

Preclinical antiviral profile of AB-836, a potent, highly selective hepatitis B virus capsid inhibitor

Nagraj Mani¹, Andrew G. Cole¹, Steven G. Kultgen¹, Andrzej Ardzinski¹, Tim Chiu¹, Andrea Cuconati¹, Bruce D. Dorsey¹, Kristi Fan¹, Ingrid Graves¹, Ju-Tao Guo², Troy O. Harasym¹, Zhanying Hu², Rose Kowalski¹, Jeevan Kunta¹, Angela M. Lam¹, Amy C.H. Lee¹, Boya Liu¹, Eugen Mesaros¹, Cornelis Rijnbrand¹, Holly M. Steuer¹, Kim Stever¹, Sunny Tang¹, Xiaowei Teng¹, Emily P. Thi¹, Michael J. Sofia¹. ¹Arbutus Biopharma Inc, Warminster, United States; ²Baruch S. Blumberg Institute, Doylestown, United States
Email: nmani@arbutusbio.com

Background and aims: The global prevalence of chronic hepatitis B infection imposes tremendous healthcare burden with treatments limited to nucleos(tide) analogs (NAs) and pegylated interferon-alpha. HBV antivirals with better curative potential are needed. Capsid inhibitors have demonstrated encouraging results in clinical trials. The aim of the study was to evaluate the *in vitro* and *in vivo* anti-HBV activities of AB-836, a novel HBV capsid inhibitor.

Method: HepDE19 cells were used for efficacy and mechanism of action studies. HBV genotypes (Gt) and core- and NA-resistant variants were evaluated in a HepG2/plasmid DNA transfection system. The effect on cccDNA establishment was determined in HBV-infected HepG2-hNTCP cells and primary human hepatocytes (PHH). X-ray crystallography data of the AB-836 chemotype bound to core protein (Cp-Y132A) was used for *in silico* docking of AB-836. Pharmacokinetic (PK) properties were assessed in rodent and non-rodent species. A hydrodynamic injection (HDI) mouse model of HBV was used for *in vivo* efficacy studies.

Results: AB-836 inhibited HBV replication with an EC₅₀ of 0.01 μM, with no significant cytotoxicity (CC₅₀ >25 μM). The presence of 40% human serum caused a slight reduction in potency (2.3-fold). AB-836 induced formation of empty capsid particles devoid of pgRNA and rcDNA. In a *de novo* HBV infection system, AB-836 inhibited cccDNA establishment and HBsAg production with an EC₅₀ of 0.18 μM and 0.20 μM, respectively. AB-836 showed pan-genotypic activity against isolates from Gt A to H. AB-836, docked into the Cp-Y132A X-ray structure, showed a unique binding mode characteristic of its chemotype. Core variants Y38F, I105V, and T109M showed no significant decrease in potency (≤2 fold); L30F and I105T showed modest decrease in potency (<10-fold); while L37Q and T33N/Q resulted in greater reductions (20 to 65-fold). NA-resistant variants remained fully susceptible to AB-836. PK results showed low systemic clearance with oral bioavailability of 30–100% in rats, dogs, monkeys, and mice. In a HDI mouse model of HBV, oral administration of AB-836 at 3 and 10 mg/kg once daily resulted in a dose-dependent antiviral effect with up to 2.5 log₁₀ reductions in serum HBV DNA after 7 days of treatment.

Conclusion: AB-836 is a novel class II capsid inhibitor that showed potent, selective inhibition of HBV *in vitro* and *in vivo*, with a unique binding mode to core protein, and a favorable preclinical profile for clinical advancement.

OS-1021

Immunogenicity and cytokine patterns of newly identified CD4 T cell epitopes within the three open reading frames of the hepatitis E virus

Benedikt Csernalabics¹, Stefan Marinescu¹, Katharina Wild¹, Lars Maurer², Katharina Zoldan¹, Marcus Panning³, Maïke Hofmann¹, Christoph Neumann-Haefelin¹, Bertram Bengsch¹, Robert Thimme¹, Viet Loan Dao Thi², Tobias Böttler¹. ¹University Hospital Freiburg,

Department of Internal Medicine II, Freiburg, Germany; ²University Hospital Heidelberg, Department of Infectious Diseases and Virology, Heidelberg, Germany; ³University Hospital Freiburg, Institute of Virology, Freiburg, Germany
Email: tobias.boettler@uniklinik-freiburg.de

Background and aims: The roles of virus specific CD4 T cells in shaping the neutralizing antibody repertoire and facilitating viral clearance in response to viral infections are well accepted. However, little is known about their specificity and dynamics in the context of acute and resolved Hepatitis E Virus (HEV) infection. Therefore, we aimed to identify HEV-specific CD4 T cells targeting different regions of the viral polyprotein, unravel their differentiation fate and correlate their presence and function with neutralizing antibodies targeting naked and quasi-enveloped virions in patients with acute and resolved HEV-infection.

Method: HEV-specific T cell epitopes for the open reading frames (ORF) 1 and 2 were predicted *in silico* using the IEDB analysis resource consensus tool and epitope candidates were confirmed *in vitro* by flow cytometric intracellular cytokine staining after antigen-specific expansion of PBMCs from 33 HLA-typed individuals with HEV-infection (rHEV) and 7 acutely infected (aHEV) patients. ORF3-specific CD4 T cells were analyzed by stimulation with an overlapping peptide (OLP) library spanning the entire ORF 3 and subsequent intracellular cytokine staining. Antibodies targeting naked and quasi-enveloped virions were determined in a neutralization assay.

Results: Strong and multi-specific CD4 T cell responses were identified in all aHEV patients and in 23 out of the 33 rHEV donors. In these individuals, a total of 21 different HEV epitopes, originating from ORF1 and 2 were identified. 6 out of 21 HEV epitopes were restricted by the HLA alleles DRB1*01:01, DRB1*04:01, DRB1*07:01 or DRB1*15:01. Preliminary results indicate a strong positive correlation between the total magnitude of IFN γ -producing HEV-specific CD4 T cells targeting the capsid-protein and titers of neutralizing antibodies against naked HEV virions. While ORF 1 and ORF 2 epitopes induce strong CD4 T cell responses in HEV patients, we detected fewer ORF 3-specific CD4 T cell responses. Overall, stronger and broader T cell responses were observed in aHEV, comparing to rHEV patients.

Conclusion: Our results provide important insights into the role of HEV-specific CD4 T cells during and after HEV infection and suggest a solid maintenance of CD4 T cells specific for ORF 1 and 2-derived epitopes and implicates them in the generation of neutralizing antibodies. In contrast, ORF 3-derived epitopes seemed less immunogenic, inducing only weak HEV-specific CD4 T cell responses.

OS-1024

Recapitulating hepatitis e virus-host interactions and facilitating antiviral drug discovery in human liver organoids

Pengfei Li¹, Yunlong Li², Jiaye Liu¹, Yang Li², Ruyi Zhang¹, Monique Versteegen³, Yining Wang¹, Zhongren Ma⁴, Denis Kainov⁵, Yijin Wang⁶, Marco Bruno², Robert De Man², Luc Van De Laan³, Maikel Peppelenbosch², Qiuwei Pan². ¹Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Netherlands; ²Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ³Erasmus MC-University Medical Center, Department of Surgery, Netherlands; ⁴Northwest Minzu University, Biomedical Research Center, China; ⁵Norwegian University of Science and Technology, Department of Clinical and Molecular Medicine, Norway; ⁶Southern University of Science and Technology, School of Medicine, China
Email: p.li@erasmusmc.nl

Background and aims: Hepatitis viruses naturally have narrow host and tissue tropisms, which is a fundamental impediment for the development of robust experimental models. The advent of organoid technology provides a unique opportunity for moving the field forward. Compared to 2D cultured cancer cell lines, organoids are

ORAL PRESENTATIONS

much better in recapitulating the architecture, composition, diversity, organization and functionality of cell types of the origin tissue/organ. We aim to establish human liver organoid-based hepatitis E virus (HEV) models for mapping virus-host interactions and discovering new therapeutics.

Method: Human fetal and adult intrahepatic organoids were isolated and cultured from different donor tissues. Full-length genotype 3 (GT3) HEV genome, variant harboring an RdRp mutation G1634R, subgenomic GT3 and GT1 HEV replicon coupled with a *Gaussia luciferase* reporter gene and HEV replication defective replicon were used. The genome-wide transcriptomic analysis was performed. A library of 94 safe-in-man board-spectrum antiviral agents were screened.

Results: We demonstrate that 3D cultured organoids from fetal and adult human liver with cholangiocyte-like phenotype, are highly permissive to the replication of GT1 and GT3 HEV. Liver organoids, further differentiated towards hepatocyte-like phenotype, are also permissive to HEV replication. By inoculation with infectious HEV particles, staining of viral proteins and replicating double-strand viral RNA, and testing the infectivity of produced viral particles, we demonstrate that liver organoids support the full life cycle of HEV infection. Genome-wide transcriptomic analysis reveals a robust host response triggered by HEV replication, in particular type I interferon signaling. This may explain the self-limiting nature of *de novo* HEV infection in liver organoids, which highly resembles acute HEV infection in healthy individuals. Moreover, we successfully screened a library of safe-in-human broad-spectrum antiviral agents and identified bequinar and homoharringtonine as potent HEV inhibitors, which are also effective against the ribavirin resistance variant harboring G1634R mutation in liver organoids.

Conclusion: We successfully established innovative HEV models using organoids cultured from fetal and adult human liver. With this, the understanding of HEV-host interactions is catalyzed and antiviral drug discovery is boosted.

OS-1062

Identification and characterization of neutralizing human monoclonal antibodies against Hepatitis E virus

Katja Dinkelborg¹, George Ssebyatika², Lucas Hüffner¹, Prossie Lindah Nankya², Luisa J. Ströh³, Heiner Wedemeyer^{4,5}, Thomas Pietschmann^{1,5,6}, Thomas Krey^{2,3,5,6,7}, Patrick Behrendt^{1,4,5}.
¹Twincore, Zentrum für Experimentelle und Klinische Infektionsforschung GmbH, Hannover, Germany; ²University of Lübeck, Institute of Biochemistry, Center of Structural and Cell Biology in Medicine, Lübeck, Germany; ³Institute of Virology, Hannover Medical School, Hannover, Germany; ⁴Medizinische Hochschule Hannover, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ⁵German Center for Infectious Disease Research (DZIF), Partner Sites Hannover-Braunschweig and Hamburg-Lübeck-Borstel-Riems, Germany; ⁶Excellence Cluster 2155 RESIST, Hannover Medical School, Hannover, Germany; ⁷CSSB, Center for Structural Systems Biology, Hamburg, Germany

Background and aims: Hepatitis E virus (HEV) is the leading cause of viral acute hepatitis worldwide. Although healthy patients can recover spontaneously from HEV infection, it poses a serious threat to patients with pre-existing liver disease, immunosuppressed patients and pregnant woman. Despite the high prevalence, no specific therapy is available to date. Even though HEV circulates as pseudo-enveloped virus, HEV vaccine studies demonstrated that antibodies protect from viral infection. Of note, Hepatitis A virus (HAV), which also exists in such a pseudo-enveloped state, can be efficiently neutralized by specific antibodies.

The aim of this study is to investigate the antibody response against HEV and identify human neutralizing antibodies that can be used as new therapeutic option for the treatment of HEV infection.

Method: Fluorescently labeled parts of HEV's ORF2 capsid protein were used in multi-color FACS to isolate antigen-specific memory B

cells from PBMCs of convalescent individuals. Single cell sequencing of the isolated B cells facilitated the identification of paired heavy and light chain B cell receptor sequences and the expression of antibody fragments in insect cells. The expressed antibody fragments are currently analyzed for antigen binding and their ability to neutralize viral infection in a GT3 based cell-culture infection model.

Results: We identified ~5000 sequences of ORF2 capsid-specific antibodies from two convalescent patients. We expressed 92 selected antibodies in form of single chain variable fragments (scFvs) and observed pronounced differences in their binding capacity to ORF2. Preliminary analysis of the neutralizing activity of these scFv in an *in vitro* infection model revealed a dose-dependent inhibition of HEV infection (an example is shown in the figure). In total, six out of the 42 scFvs tested to date reduced viral titers at least by 50% at a concentration of 10 µg/ml, three of them by over 90%.

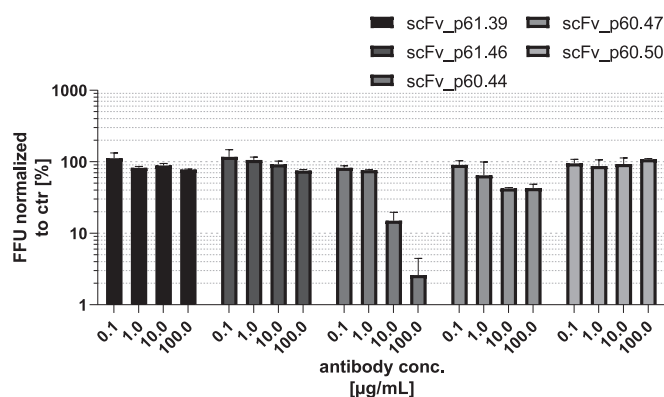


Figure:

Conclusion: We have identified and expressed antibody fragments derived from B cells of convalescent patients that potentially neutralize HEV infection. We will evaluate our best candidates as intact IgG molecules. Based on recent experiences gained with other pathogens, e.g., SARS-CoV-2 or Ebola virus, such human monoclonal antibodies constitute a promising novel therapeutic option that could facilitate treatment of HEV infection *in vivo*.

OS-1742

IFN response blocks cell division-mediated HDV spread and suppresses HDV persistence when combined with antivirals abrogating *de novo* infection

Zhenfeng Zhang¹, Tobias Walther¹, Florian Lempp¹, Yi Ni^{1,2}, Stephan Urban^{1,2}. ¹University Hospital Heidelberg, Department of Infectious Diseases, Heidelberg, Germany; ²German Center for Infection Research (DZIF)-Heidelberg Partner Site, Heidelberg, Germany
Email: stephan.urban@med.uni-heidelberg.de

Background and aims: HBV/HDV co-infection causes the most severe form of viral hepatitis. HDV exploits HBV envelope proteins for dissemination and *de novo* entry into hepatocytes. However, HDV can also spread through cell division which challenges the HDV-eliminating efficiency of antivirals targeting either *de novo* infection, e.g. Hepcludex/bulevirtide (formerly Myrcludex B) or assembly (e.g. Lonafarnib). Here we investigated the effect of the HDV-induced IFN response and the administration of IFNs on cell division-mediated HDV spread. Furthermore, we determined the synergistic effects of co-treatments *in vitro*.

Method: HDV infected cells were split to allow cell division following reseed. The effect of IFN response was evaluated by blocking the PRR-mediated endogenous IFN response or by application of IFNs. H7NB2.7 cell line stably expressing the HBV envelope proteins and the viral receptor NTCP was generated to support both HDV spreading pathways. The anti-HDV effects of mono- or co-treatment with Hepcludex, Lonafarnib, IFN-alpha, and IFN-lambda1 was measured in H7NB2.7 cells.

Results: Cell division-mediated HDV spread was profound in HuH7-NTCP cells (deficient for IFN production), but limited in HepaRG-NTCP cells (IFN competent). Exogenous IFN treatment significantly suppressed this spread during HuH7-NTCP cell division but had little effect on the HDV replication in resting cells. Blocking IFN signaling or infecting with low HDV titers (weak IFN activation) also favored cell division-mediated HDV spread in HepaRG-NTCP cells. Consistently, the effect of IFN treatment was more pronounced when virus-induced IFN response was low. In H7NB2.7 cells, all inhibitors showed the expected antiviral effects when applied individually. However, co-treatments targeting both spreading pathways (e.g. Hepcludex plus IFN-alpha) showed synergism.

Conclusion: Both virus-induced IFN response and IFN treatment efficiently restricts cell division-mediated HDV spread. IFN treatment under conditions with low virus-induced IFN responses is accordingly more profound. Combination of inhibitors targeting different spreading pathways suppresses HDV persistence synergistically. The findings unveil a novel mode-of-action of IFN (independent from activation of cellular immune responses), confirm the clinical observation of the Myr-203 study demonstrating a strong synergism of Myrcludex B and peg-IFN-alpha, and help to design future combination therapies.

OS-2482

Decrease of intrahepatic cccDNA and HBV integration in chronic hepatitis B patients with functional cure

Weiqiang Gan¹, Na Gao¹, Lin Gu¹, Zhishuo Mo¹, Xiuqing Pang¹, Ziyang Lei¹, Zhiliang Gao¹. ¹The Third Affiliated Hospital of Sun Yat-Sen University, Department of Infectious Diseases, Guangzhou, China
Email: ganweiq@mail.sysu.edu.cn

Background and aims: The present study aimed to explore the level of intrahepatic cccDNA and HBV integration, its relationship with virological markers and its value in predicting virological relapse in CHB patients with functional cure.

Method: A total of 90 patients were included in the study, including 40 CHB patients with functional cure, 40 treatment naïve CHB patients for positive control and another 10 CHB patients for HBV integration analysis. The patients with functional cure were followed up for 24 weeks to see whether relapse happened after drug cessation. The level of intrahepatic cccDNA and synchronous serum virological markers were detected. 10 CHB patients for HBV integration analysis were composed of seven treatment naïve CHB patients and 3 CHB patients with functional cure. We used deep whole genome sequence to search for HBV integration.

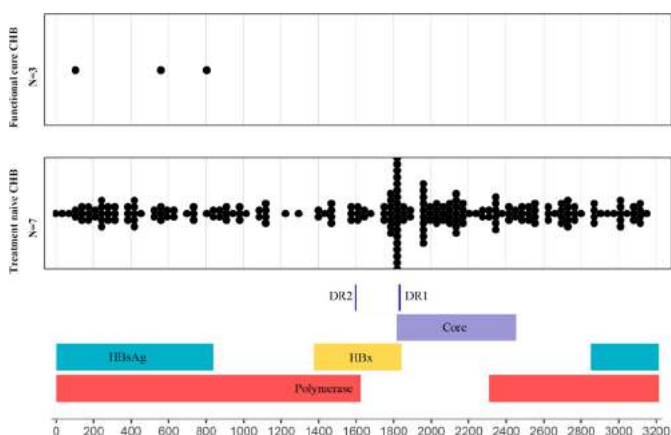


Figure 1: Distribution of HBV break points across the HBV genome. This figure included sites from genotype B and C of HBV. Viral junctions determined from chimeric reads. The locations of the genes encoding HBV polymerase (red), core protein (violet), HBsAg (blue) and HBx (yellow) are shown.

Results: Ten out of 40 functional cure patients had undetectable cccDNA. The intrahepatic cccDNA and serum HBcrAg level were significantly lower in the functional cure group than that in CHB group. Only one patient had virological relapse during the followup. For HBV integration analysis, the numbers of integration sites were 398, 1558 and 4 in HBeAg positive CHB group, HBeAg negative CHB group and functional cure group respectively. 42.85% of integration sites were located in protein coding gene and integration sites preferentially located in CpGs ($p = 0.001$, $X^2 = 10.57$), exon ($p < 0.001$, $X^2 = 12.766$), promoter ($p = 0.016$, $X^2 = 5.817$) compared to the expected.

Conclusion: The intrahepatic cccDNA level was significantly decreased in CHB patients with functional cure. Patients with functional cure had a very low risk of virological relapse. HBV integration in functional cure patients was apparently lower than CHB patients.

OS-2826

Profiling anti-HBs; immune complex peaks, epitope occupancy, ADCC phenotype and neutralization profiles associated with functional cure in a genotype A chronic hepatitis B cohort.

Hui Xu¹, Stephen Locarnini¹, Darren Wong², Danni Colledge¹, Rachel Hammond¹, Thao Huynh¹, Tim Shaw¹, Sally Soppe¹, Peter Revill¹, Alexander Thompson³, Anuj Gaggar⁴, Renae Walsh⁵, Nadia Warner¹. ¹The Peter Doherty Institute for Infection and Immunity, Melbourne, Australia; ²Austin Repatriation, Heidelberg West, Australia; ³St. Vincent's Hospital Melbourne, Fitzroy, Australia; ⁴Gilead Sciences, Inc., Foster City, United States; ⁵Clear B Therapeutics, Boston, United States
Email: nadia.warner@mh.org.au

Background and aims: The presence and functionality of antibodies specific to HBV surface antigen (anti-HBs) during CHB has been poorly defined, due to anti-HBs binding to the excessive decoy SVPs rendering anti-HBs undetectable using traditional approaches. The aim of this study was to develop and utilise a set of assays designed to specifically examine anti-HBs, in free and HBs-bound form, to further understand anti-HBs responses associated with functional cure (FC).

Method: Longitudinal serum samples from 25 genotype A CHB patients undergoing nucleos(t)ide analogue (NA) treatment were examined; 14 of these patients achieved functional cure (FC) while 11 patients remained infected (non-FC). HBsAg/anti-HBs Immune complexes (HBs-IC) were quantified using a modified diagnostic assay. FcγRIIIa dimer binding (NK cell target) of anti-HBs within convalescent sera was detected using ELISA. Epitope-specific anti-HBs responses were detected using a 19-plex assay, and neutralization efficacy of anti-HBs was measured using an *in vitro* HBV infection model.

Results: HBs-IC peaks were detected prior to HBs-loss in 10/14 FC patients. These HBs-IC peaks overlapped with either an ALT flare (8/10 patients), or a rise in ALT (2/10 patients). HBs-IC peaks were detected in 7/11 non-FC patients, but were not associated with an ALT flare.

FcγRIIIa binding was detected in 9/14 FC patients, independent from detection of overlapping HBs-IC/ALT peaks.

FC patients had stable HBsAg epitope occupancy across the study, whereas non-FC patients had a reduction in HBsAg epitope occupancy within the first 12–24 weeks of NA treatment.

Convalescent sera from FC patients recognised more HBsAg epitopes and neutralized HBV infection more potently than anti-HBs derived from vaccines. Neutralisation potency appeared to increase post HBs-loss in 4/5 FC patients examined.

Conclusion: Using this toolbox of complementary anti-HBs assays, combined with biochemical data, we were able to identify key anti-HBs profiles associated with either FC, or failure to achieve FC.

ORAL PRESENTATIONS

These findings shed light on some of the anti-HBs-mediated immunological mechanisms that may be occurring in the liver during and post-FC. Further investigation may inform the development of biomarkers predictive of disease outcome, or the development of antiviral approaches to induce these mechanisms.

OS-2864

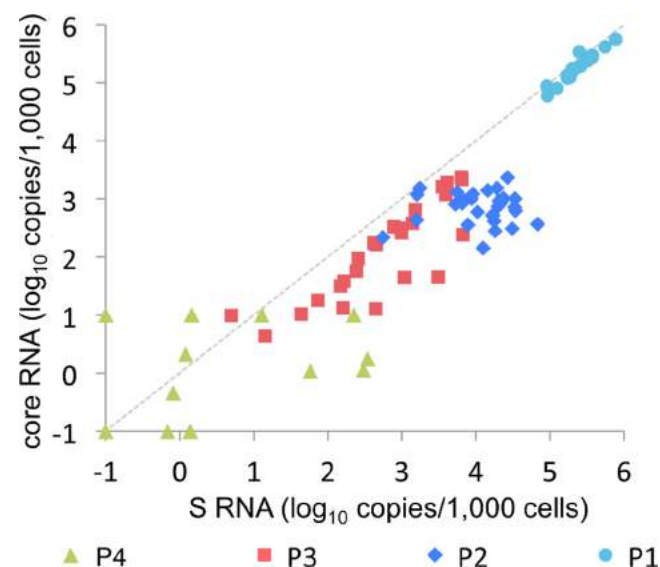
Quantification of viral RNA in multiple pieces of liver tissue shows distinct focal differences of hepatitis B infection

Gustaf Rydell¹, Kasthuri Prakash¹, Simon B. Larsson¹, Catarina Skoglund², Johan Ringlander¹, Maria Andersson¹, Maria Castedal², Heléne Norder¹, Magnus Lindh¹. ¹University of Gothenburg, Department of Infectious Diseases, Gothenburg, Sweden; ²University of Gothenburg, Department of Surgery, Gothenburg, Sweden
Email: gustaf.rydell@gu.se

Background and aims: Hepatitis B virus (HBV) induces immune responses that may cause liver damage or clear the infection. It is not known to what extent immune clearance is focal, if it changes the balance between so-called covalently closed circular DNA (cccDNA) and HBV DNA integrated into chromosomal DNA, or changes the expression of these templates. We addressed these questions by analyzing multiple pieces of liver tissue.

Method: HBV DNA and RNA were quantified by droplet digital PCR assays in 20–30 tissue pieces from each of four liver explants with cirrhosis caused by HBV.

Results: The within-patient variability of HBV RNA levels between pieces was up to tenfold in highly active HBV infection, and up to thousand fold in cases with low HBV replication, reflecting uneven distribution of cccDNA and integrations, and of their expression. Core RNA and S RNA levels were similar and correlated strongly when replication was high, supporting transcription from cccDNA. By contrast, enhanced expression of S RNA relative to cccDNA and core RNA was observed when replication was medium-high or low.



Conclusion: Immune clearance results in large focal differences in the distribution of HBV infection. Enhanced expression of S RNA relative to cccDNA and core RNA supports that HBV surface antigen can be expressed mainly from integrated HBV DNA.

Viral hepatitis B-D: Clinical aspects except therapy

OS-654

VALIANT: A targeted long-read approach to study translocation and mRNA isoforms associated with HBV integration

Cameron Soulette¹, Ricardo Ramirez¹, Nicholas Van Buuren¹, Dong Han¹, Vithika Suri¹, Patrick Marcellin², Maria Buti³, Neeru Bhardwaj^{1,4}, Anuj Gaggar¹, Li Li¹, Hongmei Mo¹, Becket Feierbach¹. ¹Gilead Sciences, Inc., Foster City, United States; ²Hospital Beaujon AP-HP, Clichy, France; ³Hospital Universitari Vall d'Hebron, Barcelona, Spain; ⁴Foundation Medicine Inc, Cambridge, United States
Email: becket.feierbach@gilead.com

Background and aims: Hepatitis B virus (HBV) infects an estimated 260 million people worldwide and is associated with the development of hepatocellular carcinoma (HCC). Integration of HBV DNA into the host genome may be a key driver of HCC oncogenesis. Standard sequencing approaches are unable to capture the complete architecture of HBV DNA insertions and underestimate the contribution of integrated HBV to viral mRNA production. We present a method for detecting VirAL Integrations AND Translocations (VALIANT): a quantitative workflow that uses targeted long-read sequencing to determine the structure of HBV DNA integrations and full-length HBV RNA transcripts.

Method: DNA and RNA were isolated from 42 fresh frozen liver biopsies collected within the GS-US-174-0149 clinical trial. A pan-genotypic panel of biotinylated oligos was developed to enrich for HBV sequences from sheared genomic DNA (~7 kb) and full-length cDNA from poly-adenylated RNA. Samples were sequenced on the PacBio long-read platform and analyzed with VALIANT.

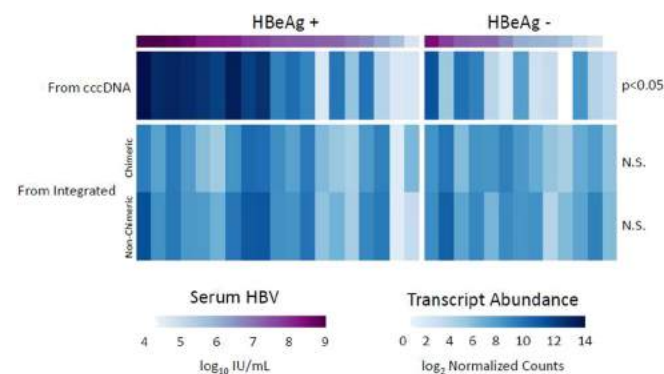


Figure:

Results: HBV-targeted long-read DNA sequencing generated high coverage data that spans entire integrations, resulting in the detection of thousands of chimeric HBV-host sequences in each patient. Strikingly, 13 of 42 samples (31%) contained HBV sequences flanked by two different chromosomes, indicating a chromosomal translocation associated with HBV integration. Chromosomal translocations were unique to each biopsy sample, suggesting that each originated randomly, and in some cases had evidence of clonal expansion. From our HBV-targeted cDNA sequencing, we identified transcriptional activity from HBV integrations, including fusion transcripts associated with inter-chromosomal translocations. By inspecting the 3' ends of HBV RNAs, we determined that nearly 95% of HBV transcripts from HBeAg positive patients originate from cccDNA, whereas HBeAg negative patients expressed mostly HBsAg from integrations. In both groups, we detected non-chimeric HBV transcripts from HBV integrations within host genes, which utilize

a non-canonical polyA site in the X ORF. These transcripts would not be properly classified by standard RNA-Seq.

Conclusion: Our VALIANT workflow is a powerful tool for studying HBV integration architecture and expression. The existence of multiple unique HBV-associated inter-chromosomal translocations in non-HCC CHB patient liver biopsies suggests a novel mechanism with mutagenic potential that may contribute to progression to HCC.

OS-887

HDV RNA replication is linked with higher serum concentrations of HBV cccDNA transcriptional activity markers-HBcrAg and pre-genomic HBV RNA

Ivana Carey¹, Mark Anderson², Christiana Moigboi¹, Bo Wang¹, Gavin Cloherty², Geoffrey Dusheiko¹, Kosh Agarwal¹. ¹King's College Hospital, Institute of Liver Studies, London, United Kingdom; ²Abbott Diagnostics, Department of Infectious Diseases, Abbott Park, United States

Email: ivana.kraslova@kcl.ac.uk

Background and aims: Persistent HDV infection requires help from HBsAg for the assembly, envelopment, propagation, and entry of HDV into the hepatocytes. HBsAg originates from both cccDNA and integrated HBV DNA encoded transcripts and levels may vary between patients with active HDV replication (HDV RNA positive) and patients with positive anti-HDV antibodies, but persistently negative HDV RNA (non-active HDV). The presence or absence of novel markers of cccDNA transcriptional activity-pre-genomic HBV RNA (pgRNA) and hepatitis B core-related antigen (HBcrAg)-may indirectly differentiate the derivation of virion and subviral HBsAg from cccDNA vs. integrated genomes. We aimed to quantify whether active cccDNA transcription, imputed by testing for pgRNA and HBcrAg, indicate a relative influence of HBsAg derivation, from cccDNA transcription (and hence HBV replication), on persistent HDV infection.

Method: We studied serum samples of 120 treatment naïve HBsAg positive, anti-HDV positive patients (70 males, median age 40 years): 53 patients were HDV RNA positive (in-house real-time PCR assay, LLQD = 640 copies/ml) and 67 were persistently HDV RNA negative. We compared HBsAg levels (Abbott Architect [IU/ml]), HBV DNA concentrations (TaqMan Roche [IU/ml]), HBcrAg (CLEIA Fujirebio [\log_{10} U/ml]) and pgRNA (real-time PCR Abbott Molecular Diagnostic assay (LLQD = 1.65 \log_{10} U/ml) between HDV RNA positive and negative cohorts.

Results: There was no difference in the numbers of HBeAg+ patients (2 patients in each group, $p = 0.81$), or median HBV DNA concentrations (27 vs. 22 IU/ml) between HDV RNA positive vs. negative patients. HBsAg levels were significantly higher in HDV RNA positive patients (median: 8068 vs. 1479 IU/ml, $p < 0.01$). HBcrAg concentrations were significantly higher in HDV RNA positive patients (median: 3.6 vs. 2.0 \log_{10} U/ml, $p < 0.01$) as were pgRNA levels (median: 1.99 vs. 1.67 \log_{10} U/ml, $p < 0.01$). Only 5.6% and 3.7% of HDV RNA positive patients did not have detectable pgRNA or HBcrAg respectively.

Conclusion: In this study we observed higher concentrations of markers of HBV transcriptional activity in HDV RNA positive versus negative patients. These data suggest that although integrant derived envelope proteins may support assembly of HDV, independently of HBV replication, the spreading cycle of HDV in patients with low serum concentrations of HBV DNA is favoured by ongoing cccDNA transcriptional activity, and hence replication-derived HBsAg. Further studies focusing on the relative fraction of HBV RNAs encoding envelope proteins, that are generated from viral integrants versus progeny virus, (and of HBsAg composition), are needed to understand the maintenance of HDV infection. The apparent facilitation of HDV persistence in patients showing ongoing HBV replication has implications for the design of therapeutic interventions to reduce HBsAg levels and cure HDV infection.

OS-900

Current and past infection of hepatitis B virus do not increase mortality in patients with COVID-19: a territory-wide cohort of 5,639 patients

Terry Cheuk-Fung Yip^{1,2,3}, Vincent Wai-Sun Wong^{1,2,3}, Chung Yan Grace Lui^{1,2,4}, Yee-Kit Tse^{1,2,3}, Henry Chan^{1,2,3}, Grace Lai-Hung Wong^{1,2,3}. ¹The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, Hong Kong; ²The Chinese University of Hong Kong, Medical Data Analytics Centre (MDAC), Hong Kong, Hong Kong; ³The Chinese University of Hong Kong, Institute of Digestive Disease, Hong Kong, Hong Kong; ⁴The Chinese University of Hong Kong, Stanley Ho Centre for Emerging Infectious Diseases, Jockey Club School of Public Health and Primary Care, Hong Kong, Hong Kong
Email: wonglaihung@cuhk.edu.hk

Background and aims: We compared the risk of acute liver injury and death in coronavirus disease 2019 (COVID-19) patients with current, past, and no hepatitis B virus (HBV) infection.

Method: This was a retrospective cohort study using a territory-wide database in Hong Kong. COVID-19 patients virologically diagnosed from 23 January 2020 to 1 January 2021 were identified. Patients with hepatitis C or no hepatitis B surface antigen (HBsAg) results were excluded. Current HBV infection was defined by positive HBsAg. Past HBV infection was defined by negative HBsAg with positive hepatitis B core antibody and/or antibody to HBsAg if patients were born before the launch of universal neonatal vaccination program, i.e. year 1988. Acute liver injury was defined as alanine aminotransferase (ALT) or aspartate aminotransferase $\geq 2x$ upper limit of normal (ULN) (i.e. 80 U/L), with total bilirubin $\geq 2x$ ULN (i.e. 38 μ mol/L) and/or international normalised ratio ≥ 1.7 . The primary outcome was COVID-19-related death.

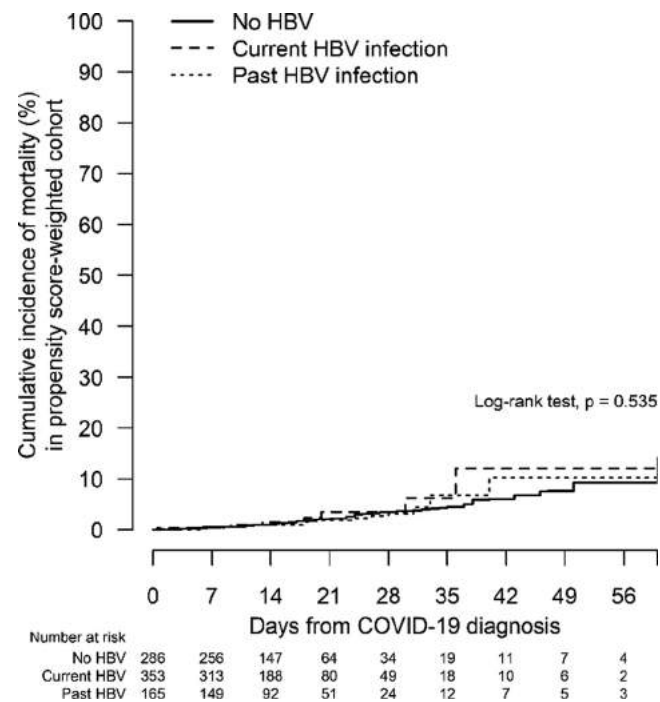


Figure:

Results: Of 5,639 patients (mean age 51 years, 49% male) included, 353 (6.3%) and 359 (6.4%) had current and past HBV infection, respectively. Compared to patients without known HBV exposure, current HBV-infected patients were older, and more likely to have cirrhosis, higher ALT, lactate dehydrogenase (LDH), and lower platelets. Among the three groups, past HBV-infected patients were the oldest, and more had diabetes and cardiovascular disease, higher creatinine, LDH, and neutrophil-to-lymphocyte ratio. At a median

ORAL PRESENTATIONS

follow-up of 14 (9–20) days, 138 (2.4%) patients died; acute liver injury occurred in 58 (1.2%), 8 (2.3%), and 11 (3.1%) patients with no, current, and past HBV infection, respectively. After adjusting for demographics, comorbidities and laboratory parameters, acute liver injury (adjusted hazard ratio [aHR] 2.45, 95% CI 1.52–3.96, $p < 0.001$), but not current (aHR 1.29, 95% CI 0.61–2.70, $p = 0.507$) or past HBV infection (aHR 0.90, 95% CI 0.56–1.46, $p = 0.681$), was associated with death. Similar results were shown after propensity score weighting (Figure). Corticosteroid, antifungals, ribavirin, and lopinavir/ritonavir use (adjusted odds ratio [aOR] ranged from 2.55–5.63), but not current (aOR 1.93, 95% CI 0.88–4.24, $p = 0.102$) or past HBV infection (aOR 1.25, 95% CI 0.62–2.55, $p = 0.533$), were associated with acute liver injury.

Conclusion: Current or past HBV infection were not associated with more acute liver injury and death in COVID-19.

OS-1892

The artificial intelligence-driven model for prediction of hepatocellular carcinoma development in chronic hepatitis B patients: Derivation and validation using 11, 111 patients from Asian and Caucasian cohorts

Hwi Young Kim¹, Pietro Lampertico², Joon Yeul Nam³, Hyung-Chul Lee⁴, Seung Up Kim⁵, Eun Sun Jang⁶, Han Ah Lee⁷, Soo Young Park⁸, Yeon Seok Seo⁷, Young-Suk Lim⁹, George Dalekos¹⁰, Ramazan Idilman¹¹, Vana Sypsa¹², Thomas Berg¹³, Maria Buti¹⁴, José Luis Calleja Panero¹⁵, Ioannis Goulis¹⁶, Spilios Manolakopoulos¹⁷, Harry Janssen¹⁸, Yun Bin Lee³, Eun Ju Cho³, Su Jong Yu³, Yoon Jun Kim³, Jung-Hwan Yoon³, George Papatheodoridis¹⁹, Jeonghoon Lee³. ¹Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea; ²Division of Gastroenterology and Hepatology, CRC “A. M. and A. Migliavacca” Center for Liver Disease, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; ³Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; ⁴Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Republic of Korea; ⁵Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; ⁶Departments of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea; ⁷Department of Internal Medicine, Korea University Anam Hospital, Korea University College; ⁸Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University

Hospital, Daegu, Republic of Korea; ⁹Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Centre, Seoul, Korea; ¹⁰Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece; ¹¹Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey; ¹²Department of Hygiene, Epidemiology and Medical Statistics, Medical School of National and Kapodistrian University of Athens, Athens, Greece; ¹³Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; ¹⁴Hospital General Universitario Vall Hebron and Ciberehd, Barcelona, Spain; ¹⁵Hospital U Puerta de Hierro, IDIPHIM CIBERhd, Madrid, Spain; ¹⁶4th Department of Internal Medicine, Aristotle University of Thessaloniki Medical School, General Hospital of Thessaloniki “Hippokratio,” Thessaloniki, Greece; ¹⁷2nd Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens “Hippokratio,” Athens, Greece; ¹⁸Toronto Western and General Hospital, University Health Network, Liver Clinic, Toronto, ON, Canada; ¹⁹Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens “Laiko,” Athens, Greece
Email: pindra@empal.com

Background and aims: Several risk scores have recently been developed to predict hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). Our aims were to develop and validate an artificial intelligence (AI)-assisted prediction model for HCC risk, and to compare the utility of our model with previous models.

Method: Using Gradient Boosting Machine (GBM), a model was developed from 6, 051 chronic hepatitis B patients on entecavir or tenofovir therapy from 4 tertiary hospitals in Korea. Two external validation cohorts were independently established: Asian cohort (3, 420 patients from 3 Korean centers) and Caucasian PAGE-B cohort (1, 640 from 11 Western centers). The primary outcome was HCC development. The performance of PLAN-B model was compared to previous models using Harrell’s c-index.

Results: In the derivation cohort and two validation cohorts, mean ages were 48.6–52.8 years and 60.2–70.6% were male. Cirrhosis was present in 26.9–50.2% at baseline. A total of 595 patients (9.8%) developed HCC during a median 5.2 years of follow-up in the derivation cohort. A model using 10 parameters at baseline was derived and showed a good prediction performance (c-index, 0.79). This model was designated as the PLAN-B model and consisted of the

Fig. 1A

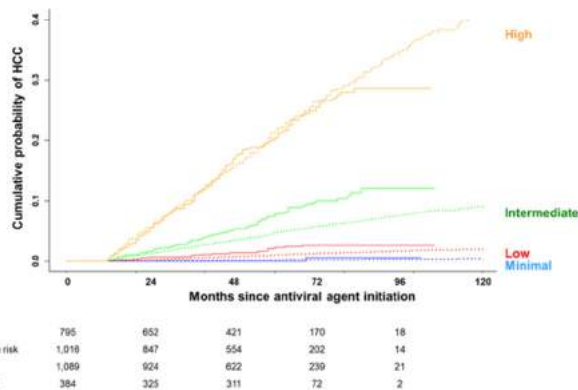


Fig. 1B

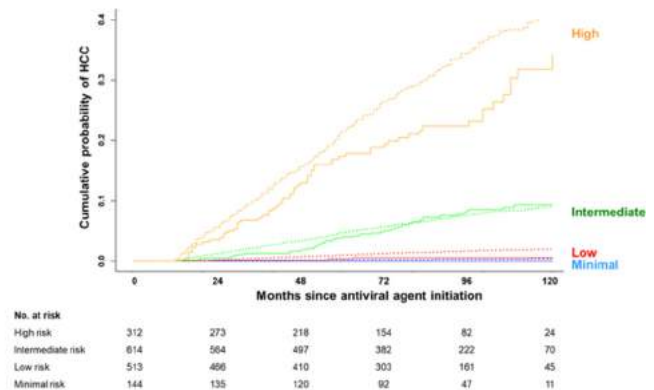


Figure 1. The expected versus the observed HCC development according to PLAN-B model in the (A) Asian and (B) Caucasian validation cohorts. Thick lines represent the observed HCC development and dotted lines represent the expected HCC development.

Figure:

presence of cirrhosis, age, platelet count, antiviral agent (tenofovir or entecavir), baseline serum levels of HBV DNA, alanine aminotransferase, and bilirubin, and HBeAg status, which are listed in order of importance according to Shapley values. PLAN-B showed significantly better predictive power than previous models (PAGE-B, modified PAGE-B, REACH-B, and CU-HCC) in both Asian (c-index, 0.79 vs. 0.64–0.74; all $p < 0.001$) and Caucasian validation cohorts (c-index, 0.81 vs. 0.57–0.79; all $p < 0.05$ except modified PAGE-B [$p = 0.22$]). When the patients were grouped into 4 groups using a probability result from GBM algorithm, respective groups showed significantly different risk of HCC development from other groups in both Asian (Fig. 1A) and (Fig. 1B) cohorts and there was good correlation between expected and observed risk (Fig. 1A and 1B). Specifically, the group with the minimal risk group (11.2% of Asian cohort and 8.8% of Caucasian cohort) showed <1% of HCC risk during 10 years of follow-up.

Conclusion: This AI-based PLAN-B model provides the best prediction power for HCC risk in Asian as well as Caucasian patients with CHB under entecavir or tenofovir treatment.

OS-2225

Predictive Immune Biomarkers of Persistent HBV DNA Suppression and Low Replicative State After Treatment Discontinuation in CHB Patients

Henry LY Chan¹, Scott Fung², Ed Gane³, Maria Buti⁴, Diana Chen⁵, Ruidong Li⁵, Vithika Suri⁶, Jeffrey Wallin⁶, John F. Flaherty⁶, Anuj Gagar⁶, Patrick Marcellin⁷, Jorg Peterson⁸, Sang Hoon Ahn⁹, Thomas Berg¹⁰. ¹Chinese University of Hong Kong, Hong Kong; ²Toronto General Hospital Research Institute, Canada; ³University of Auckland, New Zealand; ⁴Vall d'Hebron University Hospital, Spain; ⁵Gilead Sciences Inc., United States; ⁶Gilead Sciences Inc., Foster City, United States; ⁷University of Paris, Paris, France; ⁸University of Hamburg, Hamburg, Germany; ⁹Yonsei University, Seoul, Korea, Rep. of South; ¹⁰University Hospital Leipzig, Leipzig, Germany
Email: vithika.suri@gilead.com

Background and aims: Current international guidelines recommend stopping nucleos (t)ide analogue (NA) therapy in a select group of patients with the aim of promoting sustained off treatment response. However, numerous reports suggest that NA treatment discontinuation results in recurrence of HBV viremia in the majority of patients with low rates of HBsAg loss or maintenance of inactive carrier state. Therefore, the ability to predict outcomes prior to discontinuation would be an asset for safe and effective treatment discontinuation. Here we aimed to identify biomarkers at the end of treatment that can predict off treatment HBV response.

Method: Patients (n = 359) from GS-US-174-0102/0103/0149 were used to identify predictive biomarkers for HBV DNA suppression (HBV DNA <29 IU/ml) and low- replicative states (LRS) (HBV DNA <2000 IU/ml and ALT \leq ULN) 24 weeks after TDF \pm Peg treatment discontinuation in HBeAg positive and negative patients. We profiled 182 relative expression levels in serum or plasma proteins at end of treatment (or last visit prior to treatment withdrawal), using Olink Proteomics. Wilcoxon-Mann-Whitney test was used to compare differences in protein expression, and multiple comparisons were adjusted using Benjamini-Hochberg method, at significant levels of 0.05 for adjusted p values. Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were conducted.

Results: In patients with HBV DNA suppression (n = 25) at treatment free follow-up Week 24 (TFFU-24), levels of 29 proteins were found to be significantly higher vs those without suppression (n = 334). These proteins included myeloid cell markers (e.g., CD164, CLEC5A, IL-33, CD1c), leukocyte trafficking chemokines (e.g., CCL4, CXCL5, CCL17), NK markers (i.e., KLRD1), and extracellular matrix (ECM) and/or

ECM-associated proteins (e.g., ANGPT1, MMP12, PDGF8, SERPINB8). Pathway analyses show enrichment for ECM remodeling, innate immune response to virus and immune regulation in the DNA suppressed group. For LRS (n = 111), CD8a expression levels trended higher in subjects with LRS compared to those without LRS (n = 247) at TFFU-24. Feature selection and assessment of predictive performance of the identified biomarkers is ongoing.

Conclusion: The results suggest HBV DNA suppression and maintenance of inactive carrier state following treatment discontinuation is associated with higher levels of certain innate and T cell immune responses during treatment.

Viral hepatitis B-D: therapy

OS-44

Safety and antiviral activity of VIR-2218, an X-targeting RNAi therapeutic, in participants with chronic hepatitis B infection: week 48 follow-up results

Edward Gane¹, Young-Suk Lim², Daniel Cloutier³, Ling Shen³, Andrea Cathcart³, Xiao Ding³, Phil Pang³, Stephen Huang⁴, Man-Fung Yuen⁵. ¹University of Auckland, Auckland Clinical Studies, Auckland, New Zealand; ²Asan Medical Center, University of Ulsan College of Medicine, Gastroenterology, Seoul, Korea, Rep. of South; ³Vir Biotechnology, San Francisco, United States; ⁴Alnylam Pharmaceuticals, Cambridge, United States; ⁵Queen Mary Hospital, The University of Hong Kong, Medicine, Hong Kong
Email: dcloutier@vir.bio

Background and aims: VIR-2218 is an investigational GalNAc-conjugated small interfering ribonucleic acid (siRNA) therapeutic in development for functional cure of chronic hepatitis B virus infection (CHB). VIR-2218 was created using Enhanced Stabilization Chemistry Plus, which retains *in vivo* potency while reducing off-target effects. VIR-2218 targets a conserved region of the X gene and is designed to silence all major HBV transcripts, from both cccDNA and integrated DNA, across all 10 HBV genotypes as a single siRNA. We present final safety and antiviral activity data from a Phase 2 trial of VIR-2218 in participants with CHB.

Method: Non-cirrhotic, virologically suppressed participants received 2 subcutaneous doses of VIR-2218 or placebo on Day 1 and Day 29 (Week 4). HBeAg- participants received 20, 50, 100 or 200 mg, and HBeAg+ participants received 50 or 200 mg. Cohorts included 4 or 8 participants randomized 3:1 to VIR-2218 or placebo. Assessments included safety, HBsAg levels and other viral markers, with 12 weeks of follow-up after the 2nd dose for all participants and an additional 32-weeks follow-up for participants achieving pre-specified HBsAg declines.

Results: Twenty-four CHB participants received VIR-2218 (18 HBeAg-; 6 HBeAg+). Maximum mean HBsAg log₁₀ IU/ml declines in HBeAg- participants receiving 20, 50, 100, and 200 mg of VIR-2218 were 1.03, 1.23, 1.50, and 1.65, respectively. For the HBeAg+ participants receiving 50 and 200 mg of VIR-2218, the maximum mean HBsAg log₁₀ IU/ml declines were 1.16 and 1.57, respectively. Most participants achieved maximum HBsAg decline by week 16. Most participants had levels of HBV DNA and HBV RNA <LOQ at baseline, and significant changes were not detected. Declines in qHBeAg and HBcrAg were observed in HBeAg+ subjects receiving 200 mg VIR-2218. No participants discontinued due to an adverse event (AE), and the majority of treatment emergent AEs were mild in severity. No clinically significant ALT elevations were observed.

ORAL PRESENTATIONS

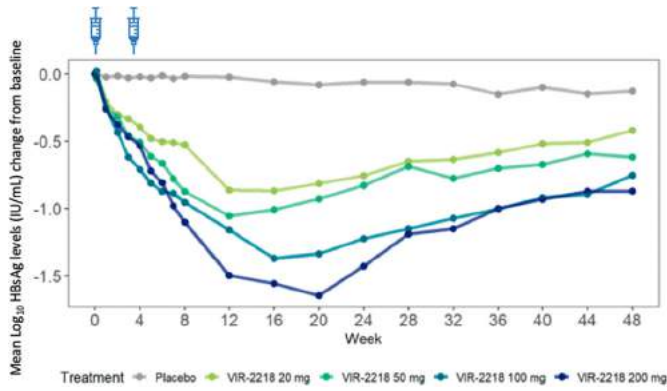


Figure:

Conclusion: Two doses of VIR-2218 at 20–200 mg given 4 weeks apart were well tolerated in CHB participants. Substantial reductions in HBsAg were observed in both HBeAg- and HBeAg+ participants across all dose levels, suggesting that VIR-2218 may silence transcripts from both cccDNA and integrated DNA. The antiviral activity of VIR-2218 demonstrated in this study support continued development as part of combination regimens targeting functional cure.

OS-211

A phase 1 study evaluating the neutralizing, vaccinal monoclonal antibody VIR-3434 in participants with chronic hepatitis B virus infection

Kosh Agarwal¹, Man-Fung Yuen², Heiner Wedemeyer³, Daniel Cloutier⁴, Ling Shen⁴, Andre Arizpe⁴, Phil Pang⁴, Chin Tay⁴, Sneha V. Gupta⁴, Andrea Cathcart⁴, Edward Gane⁵. ¹Institute of Liver Studies, Kings College Hospital, London, United Kingdom; ²Queen Mary Hospital, The University of Hong Kong, Medicine, Hong Kong; ³Hannover Medical School (MHH), Dpt. of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ⁴Vir Biotechnology, San Francisco, United States; ⁵University of Auckland, Auckland Clinical Studies, Auckland, New Zealand
Email: kosh.agarwal@nhs.net

Background and aims: VIR-3434 is a fully human, monoclonal antibody in development for the treatment of chronic hepatitis B virus (HBV) infection with three distinct modes of action: 1) entry inhibition via neutralization of all 10 HBV genotypes in vitro, 2) reduction of circulating HBsAg-containing particles in vivo, and 3) potential therapeutic vaccination via Fc engineering. In the Phase 1a part of this study, single doses up to 3,000 mg were well tolerated in healthy participants (see Gupta et al., EASL 2021). We report here the preliminary safety and HBsAg reduction data from a Phase 1b study evaluating VIR-3434 in participants with chronic HBV infection.

Method: This is an ongoing randomized, double-blind, placebo-controlled Phase 1 single ascending dose study evaluating VIR-3434 in healthy volunteers (Part A) and participants with chronic HBV infection who are receiving nucleos (t)ide reverse transcriptase inhibitor (NRTI) therapy (Parts B-C). In Part B, non-cirrhotic, virally suppressed, HBeAg-negative participants with HBsAg <1,000 IU/ml are randomized 3:1 to receive a single dose of VIR-3434 or placebo administered subcutaneously. Participants are followed for safety, tolerability, pharmacokinetics, and viral biomarkers. Preliminary blinded safety and HBsAg reduction results through Day 29 for the first cohort evaluating a single dose of 6 mg are presented herein. Dose escalation to 18 mg, 75 mg, and 300 mg single doses is planned and ongoing.

Results: In this blinded trial, eight participants were enrolled. Six received a single dose of 6 mg of VIR-3434, and two received placebo on Day 1. Among the six participants who responded, a mean HBsAg reduction of 1.3 log₁₀ IU/ml was observed (Figure). One Grade 1 adverse event was reported. No clinically significant changes in safety

laboratory parameters were observed. No participant developed clinical or laboratory evidence of immune complex disease.

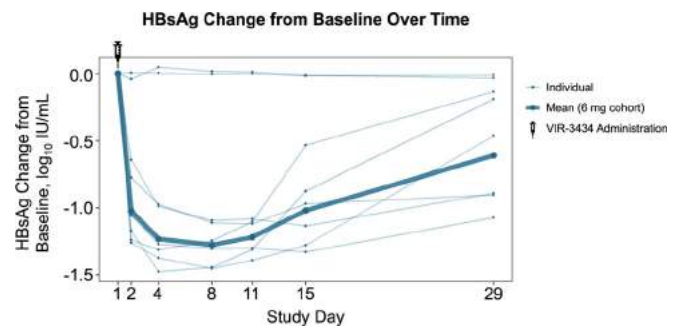


Figure:

Conclusion: A single low dose of 6 mg of VIR-3434 resulted in rapid reductions in HBsAg that were maintained through 2 weeks after dosing. Having observed no safety signals with doses up to 3,000 mg in healthy volunteers, this substantial HBsAg reduction in patients supports the potential for VIR-3434 to have a meaningful role in the functional cure of chronic HBV infection. Additional data from this ongoing study, including the effect of higher doses of VIR-3434, will be presented.

OS-691

Nucleos (t)ide analogue treatment is associated with lower risk of extrahepatic malignancy in chronic hepatitis B patients: A landmark study using nationwide claim data

Donghyeon Lee^{1,2}, Sungwon Chung¹, Goh Eun Chung^{1,3}, Boram Yang^{4,5}, Joon Yeul Nam¹, Misook Kim⁴, Yun Bin Lee¹, Eun Ju Cho¹, Su Jong Yu¹, Yoon Jun Kim¹, Jung-Hwan Yoon¹, Jeonghoon Lee¹. ¹Seoul National University College of Medicine, Department of Internal Medicine and Liver Research Institute, Seoul, Korea, Rep. of South; ²Seoul Metropolitan Government Seoul National University Boramae Medical Center, Department of Internal Medicine, Seoul, Korea, Rep. of South; ³Seoul National University Hospital, Department of Internal Medicine Healthcare System Gangnam Center, Seoul, Korea, Rep. of South; ⁴Seoul National University Hospital, Medical research collaborating center, Seoul, Korea, Rep. of South; ⁵Chungnam National University, College of Pharmacy, Daejeon, Korea, Rep. of South
Email: pindra@empal.com

Background and aims: Epidemiologic studies suggested that chronic hepatitis B virus (HBV) infection is a risk factor for various primary extrahepatic malignancy as well as liver cancer. Although nucleos (t)ide analogues (NAs) against HBV could reportedly reduce the risk of hepatocellular carcinoma (HCC), whether NAs could reduce the risk of extrahepatic malignancy is still unclear.

Method: We conducted an 18-month landmark study using the nationwide claim data from the National Health Insurance Service of Korea. Patients who were diagnosed with chronic hepatitis B (CHB) in 2012–2014 (n = 90,944) and age, sex, socioeconomic status, and areas of habitat matched-controls from general population (n = 685,436) were included. CHB patients were further classified into NA-treated (n = 6,539) or NA-untreated CHB groups (n = 84,405). Washout period was established two years prior to the cohort entry date. The inverse probability treatment weighting analysis was applied for balancing study groups. The primary outcome was the development of overall extrahepatic malignancy. The development of liver cancers (HCC and intrahepatic cholangiocarcinoma) and death were considered as competing events. We additionally analysed extrahepatic malignancy incidence with different landmark points (12-month and 24-month) as a sensitivity analysis.

Results: During the study period (median = 47.4 months), 30,413 patients (3.9%) developed extrahepatic malignancy. The NA-untreated CHB group had significantly higher risk of overall extrahepatic malignancy than both the NA-treated CHB group

(adjusted sub-hazard ratio [aSHR] = 1.27, 95% confidence interval [CI] = 1.11–1.45, $p = 0.003$) and the control group (aSHR = 1.22, 95% CI = 1.18–1.26, $p < 0.001$), while there was no difference between the NA-treated CHB group vs. the control group (NA-treated vs. control, aSHR = 0.96, 95% CI = 0.84–1.09, $p = 0.55$). In both 12-month and 24-month landmark analyses, the NA-untreated CHB group had significantly higher risk of overall extrahepatic malignancy than both the NA-treated CHB group (aSHR = 1.22, $p = 0.002$; aSHR = 1.22, $p = 0.002$, respectively) and the control group (aSHR = 1.24, $p < 0.001$; aSHR = 1.20, $p < 0.001$, respectively), while there was no difference between the NA-treated CHB group vs. the control group (aSHR = 1.01, $p = 0.85$; aSHR = 0.98, $p = 0.76$, respectively).

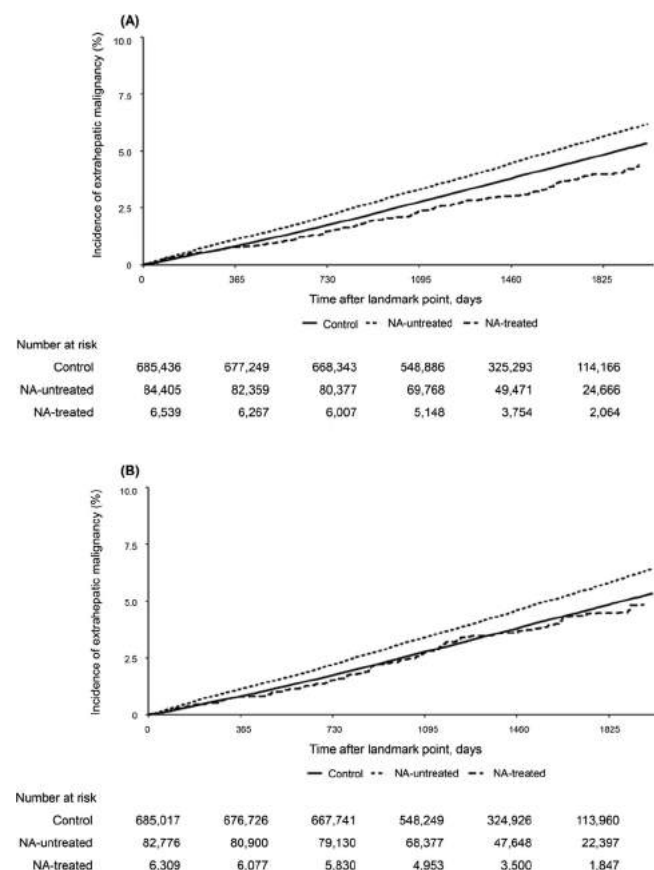


Figure: Cumulative incidence of extrahepatic malignancy (18-months landmark) (A) Before inverse probability treatment weighting (IPTW) analysis, (B) after IPTW analysis.

Conclusion: CHB patients without NA treatment have higher risk of extrahepatic malignancy, which can be attenuated with NA treatment.

OS-865

Immunoglobulin-free alternative strategy to prevent HBV mother to child transmission in Cambodia: preliminary results of the ANRS 12345 TA PROHM study

Olivier Segeral¹, Bunnet Dim², Christine Durier³, Sovann Nhoueng², Kearena Chhim⁴, Say Tiv⁵, Polinn Sar⁵, Sothy Pech⁶, Bunthoeun Nem⁷, Kay Hout⁸, Chanlina Vong⁹, Song Yin², Saren Sovann², Julia Guillebaud¹⁰, Boraneath Nang², Denis Laurent¹¹, Chantana Yay¹¹, Samsorphea Chhun⁹, Laurence Borand². ¹University of Health Sciences, ANRS, Phnom Penh, Cambodia; ²Institut Pasteur du Cambodge, Epidemiology and Public Health Unit, Phnom Penh, Cambodia; ³Inserm SC10/USO19, Essais thérapeutiques et maladies infectieuses, Villejuif, France; ⁴Calmette Hospital, Hepatology, Phnom Penh, Cambodia; ⁵Jayavarmen VII Hospital, Maternity, Krong Siem Reap, Cambodia; ⁶National Maternal and Child Health Center, Phnom Penh, Cambodia;

⁷Kampong Cham Hospital, Maternity, Krong Kampong Cham, Cambodia; ⁸Maternity Department, Takeo Referral Hospital, Takeo, Cambodia; ⁹Calmette Hospital, Maternity, Phnom Penh, Cambodia; ¹⁰Institut Pasteur du Cambodge, Virology, Phnom Penh, Cambodia; ¹¹Kantha Bopha Children's Hospitals Jayavaraman VII, Krong Siem Reap, Cambodia
Email: oliseg@hotmail.com

Background and aims: In Cambodia, HBsAg prevalence among pregnant women, young children and infants of HBsAg-positive mothers is 4.39%, 0.56% and 10.11%, respectively. Intervention to prevent mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is limited to childhood vaccine, for which national coverage is 88.7% (45% for timely birth-dose).

The objective of the TA-PROHM study was to evaluate the effectiveness of an immunoglobulin-free (HBIg) alternative strategy to prevent HBV MTCT in Cambodia: 1/Use of HBsAg/HBeAg rapid diagnosis tests and ALT to decide tenofovir disoproxil fumarate (TDF) prophylaxis 2/TDF initiation, for those eligible, from 24 weeks of amenorrhea and "test and treat" strategy for those seen later 3/early vaccination for all infants at birth.

Method: Positive HBsAg pregnant women aged ≥ 18 yo were enrolled in a multicenter interventional non-randomized prospective study. Women HBeAg-positive or, following a protocol amendment, HBeAg-negative and ALT ≥ 40 IU/L received TDF from 24 weeks of amenorrhea to 6 weeks postpartum. Infants received hepatitis B vaccine at birth in delivery room (<2 hours) and at 6, 10 and 14 weeks of age. HBIg were not recommended but could be done if accessible. The primary end point was the proportion of infants with plasmatic HBs Ag positivity confirmed by HBV DNA at 6 months of life.

Results: From 2017 to 2019, we screened 21, 251 women for HBsAg and 1, 339 (6.3%) were positive. We enrolled 1, 194 women and 338 (28.3%) were eligible for TDF prophylaxis. At enrollment, median age was 29 years and median gestational age 23 weeks. The median HBV DNA level was 7.9 log₁₀ IU/ml for TDF-eligible women and 2.5 log₁₀ IU/ml for non TDF-eligible women. The proportion of eligible women starting TDF was 94.1%. At birth, 86.5% of infants received the first dose of vaccine ≤ 2 hours of life, 95.5% ≤ 24 hours of life and 15.4% received HBIg. Overall, 4/317 infants (1.26%, 95% CI 0.34–3.20) were infected in the TDF group and 7/711 infants (0.98%, 95% CI 0.4–2.02) in the non TDF group. For infants not receiving HBIg, 4/271 (1.48%, 95% CI 0.40–3.74) were infected in the TDF group and 6/565 (1.06%, 95% CI 0.39–2.30) in the non TDF group. Transmission rate for women treated by TDF for ≥ 1 month (N = 259) was 0% (95% CI 0–1.41). In the non TDF group, all mothers of infected infants were HBeAg negative and ALT <40 U/L but 6 of them had an HBV DNA >5.3 Log₁₀ IU/ml at enrollment.

Conclusion: A free-HBIg strategy with maternal use of TDF and early vaccination at birth could be effective to reduce HBV MTCT, specifically if TDF is administered for ≥ 1 month prior delivery. For women with low-level viremia, an early vaccination without HBIg could be enough to reduce HBV MTCT.

OS-1430

Short interfering RNA JNJ-3989 combination therapy in chronic hepatitis B shows potent reduction of all viral markers but no correlate was identified for HBsAg reduction and baseline factors

Edward Gane¹, Stephen Locarnini², Tien Huey Lim³, Simone Strasser⁴, William Sievert⁵, Wendy Cheng^{6,7}, Alexander Thompson⁸, Bruce Given⁹, Thomas Schlupe⁹, James Hamilton⁹, Michael Biermer¹⁰, Ronald Kalmeijer¹¹, Maria Beumont-Mauviel¹¹, Oliver Lenz¹⁰, Filip De Ridder¹⁰, Gavin Cloherty¹², Danny Ka-Ho Wong¹³, Christian Schwabe¹, Kathy Jackson², Carlo Ferrari¹⁴, Ching Lung Lai¹³, Robert G. Gish¹⁵, Man-Fung Yuen¹³. ¹Auckland Clinical Studies, Auckland, New Zealand; ²Victorian Infectious Disease Reference Laboratory, Victoria, Australia; ³Middlemore Hospital, Auckland, New Zealand; ⁴Royal Prince Alfred Hospital, Sydney, Australia; ⁵Monash Health and Monash University, Melbourne, Australia; ⁶Royal Perth

ORAL PRESENTATIONS

Hospital, Perth, Australia; ⁷Linear Clinical Research, Perth, Australia; ⁸St. Vincent's Hospital, Melbourne, Australia; ⁹Arrowhead Pharmaceuticals, Pasadena, United States; ¹⁰Janssen Pharmaceutica NV, Beerse, Belgium; ¹¹Janssen RandD, Titusville, United States; ¹²Abbott Diagnostics, Abbott Park, United States; ¹³The University of Hong Kong, Hong Kong, China; ¹⁴University of Parma, Parma, Italy; ¹⁵Hepatitis B Foundation, Doylestown, United States
Email: edgane@adhb.govt.nz

Background and aims: Short RNA interference (siRNA) therapy with JNJ-3989 includes both S and X triggers which silence all HBV RNA transcripts. In AROHBV1001 (phase 2a; NCT03365947), JNJ-3989 (3 monthly doses 25–400 mg) + a nucleos(t)ide analogue (NA) demonstrated antiviral activity in patients (pts) with chronic hepatitis B (CHB). Here we assessed baseline factors associated with HBsAg reduction and compared the effect of JNJ-3989 against the viral markers HBsAg, HBeAg, HBcrAg and HBV RNA.

Method: Data from NA experienced or naïve, HBeAg±ve CHB pts who received 3 s.c. JNJ-3989 doses (days 1, 27, 57) of 100 (n=8), 200 (n=8), 300 (n=16) or 400 mg (n=8) were used. Pts started/continued with an NA on day 1 and continued throughout the study to Day 392. HBsAg, HBeAg, HBV RNA, HBcrAg was assessed using standard assays.

Results: Treatment with JNJ-3989 + an NA resulted in mean (range) HBsAg reductions from baseline at nadir of 1.93 (0.73, 3.84) log₁₀ IU/ml with 39/40 pts (98%) achieving >1log₁₀ IU/ml reduction. Baseline HBsAg levels and other viral markers, treatment status (naïve vs NA suppressed) and BMI had no impact on HBsAg reduction. A trend for greater reduction in HBsAg was seen in HBeAg +ve vs HBeAg -ve pts mainly driven by a few (n=4) HBeAg +ve females who showed the greatest HBsAg response (>2.5 reduction at nadir). Impact of race IL28B status could not be assessed since the majority of pts were Asians with IL28B CC genotype. HBV genotype had no impact on HBsAg reduction but a limited number of pts had data available. Pronounced reductions in HBeAg, HBcrAg and HBV RNA were observed, although HBeAg and HBcrAg reductions were generally smaller than for HBsAg. In pts with baseline levels >1log above LLOQ of the respective marker, the mean (SE, N) reduction at day 113 for HBeAg were -1.47 (0.12, 12) vs -2.12 (0.21, 12) for HBsAg, for HBcrAg -1.20 (0.17, 18) vs -1.97 (0.16, 18) for HBsAg, and -1.93 (0.14, 21) for HBV RNA vs -1.86 (0.15, 21) for HBsAg. Generally, the reductions of the different markers correlated within pts, but individual differences were observed.

Conclusion: JNJ-3989 (100–400 mg, Q4W) achieved potent reduction of all viral markers, with trends for more pronounced reductions in HBsAg than other markers, and in HBeAg +ve compared to HBeAg -ve pts. Reductions in HBeAg, HBcrAg and HBV RNA generally correlated with reductions in HBsAg. These findings are being evaluated in larger Phase 2b studies with JNJ-3989 + NA in CHB pts.

OS-2299

Second generation Hepatitis B Virus core inhibitors ABI-H2158 and ABI-H3733 have enhanced potency and target coverage for both antiviral inhibition and covalently closed circular DNA establishment activities

Dawei Cai¹, Marc Evanhcic¹, Ran Yan¹, Renuka Kumar¹, Yuhua Zong¹, Qi Huang¹, Richard Colonna¹, Luisa Stamm¹, William Delaney¹.

¹Assembly Biosciences, Inc., South San Francisco, United States
Email: wdelaney@assemblybio.com

Background and aims: Core inhibitors are a novel class of HBV antivirals with potential to increase treatment responses and cure rates. We currently have 3 core inhibitors in clinical development: vebicorvir (VBR, Phase 2), ABI-H2158 (2158, Phase 2) and ABI-H3733 (3733, Phase 1). Core inhibitors have multiple mechanisms of action (MOAs) including 1) inhibition of pgRNA encapsidation, which reduces virion formation (antiviral activity) and 2) premature disruption of incoming capsids which inhibits the generation of new covalently closed circular DNA (cccDNA prevention). Core

inhibitors exert their greatest antiviral activity against viral replication, yet both MOAs may be important for optimal responses. Here we determined the human plasma and estimated liver concentrations of VBR, 2158, and 3733 relative to protein-adjusted (pa) EC₅₀s for each MOA.

Method: Plasma concentrations of VBR, 2158 and 3733 including C_{min} 24 hr post QD dosing were measured in Phase 1a/b studies. EC₅₀s for antiviral activity (HBV DNA end point) and cccDNA prevention (HBeAg end point) were measured in primary human hepatocytes. pa factors were determined in HepAD38 cells cultured in 2%, 20%, or 40% human serum and extrapolating to 100%. Liver concentrations relative to plasma were estimated from nonclinical PK studies.

Results: The C_{min} of VBR, 2158, and 3733 at steady-state dosing using 300 mg QD are shown in Table 1 along with their EC₅₀s, pa factors and liver enrichment factors. VBR, 2158, and 3733 achieve C_{mins} 3-fold, 19-fold, and 28-fold, above their antiviral paEC₅₀s respectively. In contrast, C_{mins} for VBR, 2158, and 3733 were 0.2-fold, 4-fold, and 6-fold over their respective paEC₅₀s to inhibit cccDNA generation. Concentrations of all three core inhibitors are predicted to be enhanced in the liver by 18-fold, 5-fold, and 6-fold, respectively.

Table 1: Key PK and Antiviral Properties of VBR, 2158, and 3733

Parameter	VBR 300 mg QD	2158 300 mg QD	3733 300 mg QD
C _{min} (nM)	3102	5852	2454
Antiviral EC ₅₀ (nM)	154	41	12
cccDNA EC ₅₀ (nM)	2210	204	62
pa (fold)	8	8	7
Plasma C _{min} /paEC ₅₀ (antiviral)	3	19	28
Plasma C _{min} /paEC ₅₀ (cccDNA)	0.2	4	6
Liver:plasma ratio	18	5	6
Liver C _{min} /paEC ₅₀ (antiviral)	48	95	170
Liver C _{min} /paEC ₅₀ (cccDNA)	3	19	33

Conclusion: VBR, 2158, and 3733 achieve plasma concentrations significantly above EC₅₀ and paEC₅₀ for antiviral activity. The second generation compounds 2158 and 3733 show enhanced potency and exposures that cover cccDNA prevention activity at significant multiples of paEC₅₀ at C_{min}.

OS-2478

VRON-0200, A therapeutic HBV vaccine with an intrinsic checkpoint inhibitor elicits broad CD8+ T cell responses and sustained antiviral declines in preclinical studies

Mohadeseh Hasanpourghadi¹, Andrew Lubert², Colin Magowan², Xiang Zhou¹, Hildegund Ertl¹. ¹The Wistar Institute, Philadelphia, United States; ²Virion Therapeutics, Newark, United States
Email: aluber@viriontx.com

Background and aims: HSV-1 glycoprotein D (gD) acts as a checkpoint inhibitor of early T cell activation. Here we describe the immunogenicity and efficacy of a therapeutic HBV vaccine that includes select antigens of both HBV polymerase (N- and C-terminus) and core fused into gD (gD-HBV2; VRON-0200).

Method: Groups of C57Bl/6 mice were injected i.v. with an AAV8–1.3HBV vector. At week 4, after high levels of circulating HBV genomes were established, they were vaccinated (n=5–10/group) with a single i.m. dose of 1 × 10¹⁰ vp of chimpanzee adenoviral vectors expressing sequences of the N-terminus of polymerase within gD (gDPoIN), polymerase and core within gD (gDHBV2), polymerase and core without gD (HBV2) or nothing (controls). Lymphocytes were tested periodically after immunization for frequencies and epitope specificities of IFN-γ producing vaccine-insert-specific CD8⁺ T cells. HBV genome copy numbers in sera were assessed before and after vaccination.

Results: Vaccination induced CD8⁺ T cell responses to the vaccine inserts in blood and spleen and gD enhanced responses. In AAV8-1.3HBV injected mice immunization with the gD containing vaccines caused ~2–3 log₁₀ sustained declines in HBV genome copies while naïve mice showed ~ 0.5 log₁₀ increases (Figure). Frequencies of circulating vaccine-insert-specific CD8⁺ T cells were inversely correlated with HBV viral loads (r = -0.77; p < 0.0001).

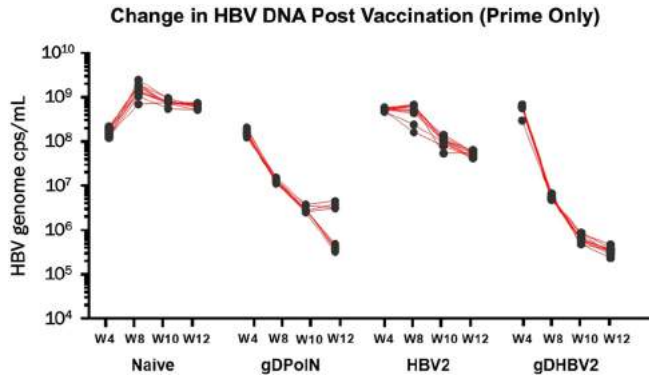


Figure:

Conclusion: The inclusion of gD into a therapeutic HBV vaccine enhances CD8⁺ T cell responses and is necessary for the observed sustained efficacy of the vaccine to reduce viral loads in the AAV8-1.3HBV mouse model. Mice vaccinated with the gDHBV2 vector showed better viral control than those immunized with gDPOIN stressing the importance of a broad-based immune response. A Phase 1b study of VRON-0200 is in planning.

OS-2717

Safety and efficacy of bulevirtide monotherapy and in combination with Peginterferon alfa-2a in patients with chronic hepatitis delta: 24 weeks interim data of MYR204 Phase 2b study

Tarik Asselah¹, Sorin Stefan Arama², Pavel Bogomolov³, Marc Bourliere⁴, Hélène Fontaine⁵, George Sebastian Gherlan^{6,7}, Vladimir Gorodin⁸, Marie-Noëlle Hilleret⁹, Stefan Lazar¹⁰, Nina Mamonova¹¹, Morozov Viacheslav¹², Victor Pantea¹³, Gheorghe Placinta¹³, Jérôme Gournay¹⁴, Francois Raffi¹⁵, Vlad Ratzu¹⁶, Christiane Stern¹⁶, Olga Sagalova¹⁷, Didier Samuel¹⁸, Tatyana Stepanova¹⁹, Vladimir Syutkin²⁰, Adrian Streinu-Cercel², Fabien Zoulim²¹, Dominique Roulot²². ¹Hôpital Beaujon APHP, Université de Paris, INSERM, Clichy, France; ²Matei Bals National Institute of Infectious Diseases, Bucharest, Romania; ³Moscow regional research-clinical institute, Moscow, Russian Federation; ⁴Hôpital Saint Joseph Marseille, Marseille, France; ⁵Hôpital Cochin - Unité d'Hépatologie Pavillon Achard, Paris, France; ⁶“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania; ⁷Dr. Victor Babes Foundation, Bucharest, Romania; ⁸State budgetary institution of health care “Specialized Clinical Infectious Diseases Hospital”, Krasnodar, Russian Federation; ⁹Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; ¹⁰Dr. Victor Babes Foundation - Infectious and Tropical Diseases Hospital, Bucharest, Romania; ¹¹National Research Medical Centre for Phthisiopulmonology and Infectious Diseases, Moscow, Russian Federation; ¹²LLC Medical Company “Hepatolog,” Samara, Russian Federation; ¹³Infectious Clinical Hospital “T. Ciorba” - Medical University Department of Infectious Diseases, Chisinau, Moldova; ¹⁴Nantes University Hospital (CHU de Nantes Hôtel-Dieu), Nantes, France; ¹⁵Nantes University Hospital (CHU de Nantes Hôtel-Dieu), Nantes, France; ¹⁶CH Pitié-Salpêtrière, Paris, France; ¹⁷Southern Ural State Medical University, Chelyabinsk, Russian Federation; ¹⁸Centre Hépatobiliaire - Hôpital Paul Brousse, Université Paris Saclay, Villejuif, France; ¹⁹Limited liability company “Clinic of Modern Medicine,” Moscow, Russian Federation; ²⁰Institute of Emergency Medicine n.a. NV Sklifosovsky, Liver Surgery and Transplantation, Moscow, Russian Federation; ²¹Hospital Croix Rousee, Service Hépatologie, Lyon, France;

²²Hopital Avicenne, APHP, Université Sorbonne Paris Nord, Bobigny, France
Email: tarik.asselah@aphp.fr

Background and aims: Bulevirtide (BLV) is a first-in-class entry inhibitor used for the treatment of chronic hepatitis delta virus (HDV) infection. Combination therapy of BLV and Peginterferon alfa-2a (pIFN) showed strong synergistic effects on HDV RNA and Hepatitis B surface Antigen (HBsAg) levels in MYR203 trial.

We present here the 24 weeks interim on treatment data of the MYR204 phase 2b trial in HBV/HDV co-infected patients receiving BLV as monotherapy or in combination with pIFN.

Method: 175 patients with chronic HDV infection were randomized in a 1:2:2:2 ratio to receive (see Figure): arm A: pIFN; arm B: BLV 2 mg/day and pIFN; arm C: BLV 10 mg/day and pIFN for 48 weeks followed by BLV monotherapy for additional 48 weeks or arm D: BLV 10 mg/day monotherapy. The primary endpoint is undetectable HDV RNA (<LoD) at week 24 after end of treatment; main secondary endpoints include HDV RNA decline by ≥2log₁₀ IU/ml, ALT normalization, combined response (undetectable HDV RNA or decrease by ≥2log₁₀ IU/mL from baseline and ALT normalization) and HBsAg decrease.

Results: Safety: In the first 24 weeks of treatment, 998 AEs were reported by 151 patients (86.8%), being mostly mild (536) or moderate (296). 181 of 998 AEs were judged as possibly related to BLV and 724 AEs to pIFN. Overall, 7 SAEs (judged as not related to BLV) were reported, one of which (anaplastic astrocytoma, judged as non-related to BLV nor pIFN) reported in a patient in arm B led to death.

Efficacy: At week 24, the proportion of patients with HDV RNA decline of ≥2log₁₀ IU/mL from baseline was 37.5%, 86.0%, 90.0%, and in 72.0% of patients in arms A-D, respectively.

Undetectable HDV RNA was demonstrated in 12.5%, 24%, 34% and 4% of patients at week 24 in arms A-D, respectively.

Both, ALT and combined response had a higher proportion of responders in arm D, followed by arm B, arm C and arm A (Figure 1). HBsAg response (decline by ≥1log₁₀ IU/ml) was observed in 10 patients receiving combination therapy with BLV and pIFN (12% in arm B and 8% in arm C) and 1 patient in arm A.

Study design. Baseline and 24 weeks interim data	Baseline - levels			Results at week 24 - % of patients with response			
	HDV RNA (log ₁₀ IU/ml) Mean (SD)	ALT (U/ml) Mean (SD)	Compensated cirrhosis (% of patients)	HDV RNA decrease from baseline ≥2 log ₁₀ IU/mL	ALT normalization	Combine response	HBsAg decrease >1 log ₁₀ from baseline
arm A (n=25) pIFN week 0 week 48 week 96 Follow Up	5,197 (1.064)	121.5 (95.9)	33.3%	37.5%	12.5%	12.5%	4.2%
arm B (n=50) 2 mg BLV + pIFN / 2 mg BLV week 0 week 48 week 96 week 144 Follow Up	5,268 (1.355)	107.5 (77.0)	34.0%	86.0%	30.0%	30.0%	12.0%
arm C (n=50) 10 mg BLV + pIFN / 10 mg BLV week 0 week 48 week 96 week 144 Follow Up	5,090 (1.343)	112.6 (98.6)	36.0%	90.0%	24.0%	24.0%	8.0%
arm D (n=50) 10 mg BLV week 0 week 48 week 96 week 144 Follow Up	5,448 (1.098)	118.4 (108.1)	34.0%	72.0%	64.0%	50.0%	0

Figure: Study design. 24 weeks interim data

Conclusion: BLV monotherapy and in combination with pIFN is safe and well tolerated through 24 weeks of therapy. Combination therapy and BLV monotherapy resulted in high rates of HDV viral decline, while BLV monotherapy resulted in the highest rate of ALT normalization. Ongoing analysis of safety, ALT normalization and HDV viral suppression on therapy at weeks 48, 96 and SVR 24 will be performed.

Viral hepatitis C: Clinical aspects except therapy

OS-728

Late presentation for HCV care: time to target people with diabetes and/or hazardous alcohol use (ANRS CO22 HEPATHER cohort)

Camelia Protopopescu¹, Melina Santos¹, Elizabeth Delarocque-Astagneau^{2,3}, Marc Bourliere^{4,5}, Ventzislava Petrov-Sanchez⁶, Vincent Di Beo¹, Dominique Larrey⁷, Mael Baudoin¹, Dorival Celine⁸, Morgane Bureau¹, Hélène Fontaine^{9,10}, Fabrice Carrat^{8,11}, Fabienne Marcellin¹, Stanislas Pol^{9,10}, Carrieri Patrizia¹. ¹Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France; ²Université Paris-Saclay, UVSQ, Inserm, anti-infective evasion and pharmacoepidemiology, CESP, 78180, Montigny, France; ³AP-HP, GHU Université Paris Saclay, Hôpital Raymond Poincaré, Département Hospitalier d'Epidémiologie et de Santé Publique, 92380 Garches, France; ⁴Department of Hepatology and Gastroenterology, Hôpital Saint Joseph, Marseille, France; ⁵Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and; ⁶ANRS (France Recherche Nord and Sud Sida-HIV Hépatites), Unit for Basic and Clinical Research on Viral Hepatitis, Paris, France; ⁷Service des maladies de l'appareil digestif, Hôpital Saint Eloi, IFR-, Inserm Montpellier, Montpellier, France; ⁸Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, Paris, France; ⁹Département d'Hépatologie, AP-HP, Hôpital Cochin, Paris, France; ¹⁰INSERM U1223, Institut Pasteur, Université Paris Descartes, Paris, France; ¹¹Hôpital Saint-Antoine, Unité de Santé Publique, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
Email: pmcarrieri@aol.com

Background and aims: Late presentation for care of hepatitis C virus (HCV) infection-defined as having severe liver fibrosis (\geq F3 Metavir score) when consulting a healthcare specialist for HCV treatment for the first time-increases morbidity and mortality risks in HCV-infected patients. Identifying the socio-behavioural profile of late presenters is essential to improve HCV screening strategies and optimize the global HCV cascade of care. We investigated clinical and socio-behavioural correlates of late presentation for HCV care in HCV mono-infected individuals.

Method: This study included chronic HCV mono-infected patients participating in the French national prospective cohort ANRS CO22 HEPATHER which started in 2012. The correlates of late presentation for HCV care were estimated using a Heckman selection probit model, which enabled us to take into account possible selection bias due to missing data in the outcome.

Results: Among the 9, 174 study patients, 1, 236 had available data on liver fibrosis stage at first presentation for HCV care. Of the latter, 591 (47.8%) were late presenters. In a multivariable analysis adjusted for age, sex, and HCV genotype, having diabetes (adjusted coefficient [95% confidence interval]: 0.55 [0.30; 0.80]), current hazardous alcohol use (defined as consuming at least two standard drinks (each containing 11–14 g of alcohol) per day for women or three for men) (0.36 [0.03; 0.69]), and current abstinence but past hazardous alcohol use (0.42 [0.19; 0.64]) (vs. abstinence with no past hazardous use) were all independently associated with late presentation for HCV care.

Conclusion: As late presentation severely affects the HCV cascade of care, our findings bring important new evidence about the need to promptly identify and target people with diabetes and/or past or current hazardous alcohol use for HCV screening and treatment, within the wider context of the WHO goal to eliminate HCV by 2030.

OS-1390

Automated Liver Function Testing in Identifying "Hard to Reach" Hepatitis B and C Patients

Callum Livingstone¹, Iain Macpherson¹, Jennifer Nobes², Elizabeth Furrrie², Michael Miller¹, Ellie Dow², John Dillon¹. ¹University of Dundee, Gut Group, United Kingdom; ²NHS Tayside, Blood Sciences, United Kingdom
Email: c.r.livingstone@dundee.ac.uk

Background and aims: In Europe, 13.3 million and 15 million people are estimated to be living with chronic HBV and HCV, respectively. Many remain undiagnosed, increasing their likelihood of fibrosis, cirrhosis, hepatocellular carcinoma and ultimately death.

Automated testing of abnormal LFTs for HBV and HCV may aid find undiagnosed patients. Intelligent liver function testing (iLFT) was developed and is now routine in Tayside, Scotland, where all abnormal LFTs are reflex tested for HBV and HCV. Our aim was to assess if iLFT increased case finding in "hard to reach" populations.

Method: Retrospective cohort analysis of patients who initiated iLFT, triggered at an ALT value above 30, from August 2018 to August 2020 and received an HBV or HCV outcome.

Results: For HCV, 49 patients out of 6791 (0.7%) were confirmed to be HCV antibody positive. 29 antibody positive patients (59%) had detectable HCV RNA levels, predominantly Genotype 3 (34%), suggestive of an active infection. 28/29 patients (97%) commenced treatment on average 65 days from the iLFT request date (95% CI 55.4–74.6 days) and 1 patient failed to attend.

26/28 patients (93%) completed their treatment, 1 experienced side-effects and 1 was lost to follow-up. An intention-to-treat analysis demonstrated 21 patients (75%) to have a sustained viral response (SVR). 19 SVR patients (90%) were discharged or due for discharge and 2 continued under review due to the presence of fibrosis and/or cirrhosis.

Patients who underwent HCV treatment were on average 52-years-old, predominantly declared to having never injected drugs (75%) and primarily resided in more affluent areas (75%).

For HBV, iLFT identified 2 chronic active and 4 inactive carrier HBV infected patients. The 2 chronic active patients were initiated on treatment and all 6 patients remain under review. 1 chronic patient was also found to be Delta antigen positive.

The average age of the 6 HBV patients was 52-years-old and all 6 patients (100%) lived in more affluent areas.

Conclusion: iLFT successfully identified patients with HBV and HCV infections, providing an opportunity for cure and/or continued follow-up. Of note, most patients treated for HCV had no overt risk-factors; no history of injecting drugs and residing in more affluent areas. NHS Tayside has already identified approximately 90% of prevalent HCV cases. By utilising iLFT, Tayside now has the potential to identify the remaining 10% "hard to reach" HCV patients, thus offer a cure.

Viral hepatitis C: Therapy and resistance

OS-795

Peer support in a national hepatitis C elimination program-pseudo-randomised analysis of impact in 30, 729 patients

Davina Jugnarain¹, Pantelis Samartsidis², Rachel Halford³, Stuart Smith³, HCV ODNs Clinical Leads⁴, Graham Foster¹. ¹Queen Mary University of London, United Kingdom; ²MRC Biostatistics Unit, Cambridge Biomedical Campus, Cambridge, United Kingdom; ³Hepatitis C Trust, United Kingdom; ⁴NHS England, United Kingdom
Email: g.r.foster@qmul.ac.uk

Background and aims: Hepatitis C (HCV) is prevalent in people injecting drugs (PWIDs), around 90% of infections in England. Peer

supporters are individuals with lived experience of a disease who can motivate patients. Previous studies using peer supporters for HCV have been small and did not show unequivocal benefits. As part of NHS England's aim to eliminate HCV ahead of the World Health Organisation's target of 2030, peers have been deployed in treatment networks. We examined the effect of peer supporters on HCV treatment uptake using the English registry.

Method: Peer support workers were centrally trained by The Hepatitis C Trust, and introduced to 17 out of 22 regional networks at different times. Time of peer introduction depended on funding and operational readiness. Hence this was a pseudorandomised stepwise implementation of peers to different networks. For patients receiving antiviral therapy, demographic and treatment outcome data were derived from the national registry. Statistical analysis was conducted using a Bayesian Poisson random effects and a Binomial random effects model. We explored the effects of peers immediately and 2 months after deployment.

Results: 30,729 patients were treated in the 17 networks during the study period. An increase in numbers starting treatment (OR 1.12; 95% confidence interval [CI], 1.02 to 1.21; $p = 0.006$) and completing treatment (OR, 2.45; 95% CI, 1.49 to 3.84; $p = 0$) was observed. No significant changes were seen in drug service referrals, PWIDs initiating treatment, numbers treated in drug services, completion of adequate treatment, attendance at follow-up nor viral clearance. For the delayed analysis, similar results were observed. However, drug service referrals (RR, 1.15; 95% CI, 0.99 to 1.33; $p = 0.0355$) and numbers treated in drug services exhibited a mild increase (OR 1.19; 95% CI, 1.00 to 1.44; $p = 0.023$).

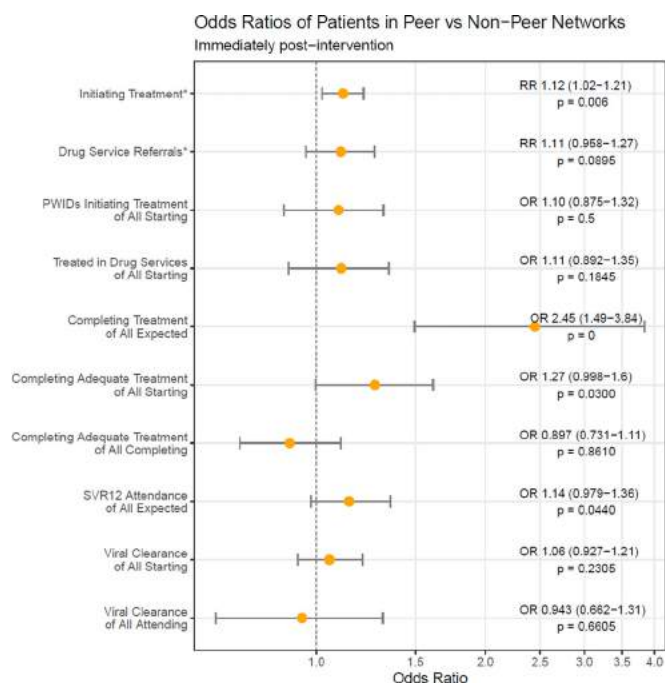


Figure:

Conclusion: Peer support workers appear to be immediately effective in improving initiation and completion of treatment. Although the proportion of people with drug use as a risk factor for infection did not change, peers appear to increase referrals and treatment within drug services. Broadly, this suggests that peer support workers are effective in engaging at-risk groups for HCV and could accelerate attainment of eradication targets.

OS-2306

DAA therapy in HCV-infected Egyptian children: real-life model from a multicentre program supported by an NGO

Manal Hamdy El-Sayed^{1,2}, Dr Khaled Kabil², Fatma Ebeid¹, Wafaa El-Akel³, Ashraf Abou-Taleb⁴, Gihan Bebars⁵, Amel Mahfouz⁶, Shereen Galal⁷, Shreen El-Zainy⁸, Mohamed Rabea⁹, Wahid Doss^{2,3}.
¹Faculty of Medicine, Ain Shams University, Paediatrics and Clinical Research Centre (MASRI-CRC), Cairo, Egypt; ²Egyptian Liver Care Society, Cairo, Egypt; ³Faculty of Medicine, Cairo University, Endemic Medicine and Hepatogastroenterology, Cairo, Egypt; ⁴Faculty of Medicine, Sohag University, Pediatrics, Sohag, Egypt; ⁵Faculty of Medicine, Minia University, Minia, Egypt; ⁶Faculty of Medicine, Alexandria University, Pediatrics, Alexandria, Egypt; ⁷Faculty of Medicine, Assiut University, Pediatrics, Assiut, Egypt; ⁸Faculty of Medicine, Mansoura University, Pediatrics, Mansoura, Egypt; ⁹National Hepatology and Tropical Medicine Research Institute, Pediatrics, Cairo, Egypt
 Email: manalhelsayed@yahoo.co.uk

Background and aims: DAAs for chronic HCV in children aged 3 years and above had been approved but evidence from real-world experience is needed for brand and generic medicines to inform global policies and fast-track elimination. This project assessed safety and efficacy of generic DAAs in treating Egyptian children with HCV-infection in a multicentre program supported by the Egyptian Liver Care Society (ELCS), an NGO supporting patients with liver disease.

Method: The program enrolled 535 children >35 kg with chronic HCV-infection between March 2019 and December 2020 from 7 specialised centres in 6 Egyptian Governorates. The ELCS fully equipped dedicated sites for the HCV-Free Child project, trained physicians, nurses and IT personnel. All children received generic sofosbuvir 400 mg/ledipasvir 90 mg once daily for 12 weeks. Recruited children were sampled for CBC, liver functions, renal functions and HCV-RNA (RT-PCR) at baseline, 4, 8, 12 and 24 (sustained virological response; SVR) weeks of therapy. In addition to baseline ultrasound and Fibroscan. Personal care items and awareness booklets were provided to children during awareness sessions with attending parents at 12 and 24 weeks. The ELCS provided sites with protective equipment and sanitizers to protect personnel and patients during COVID-19 crises and medication was dispensed for 12 weeks while tele-communication was provided for follow-up and awareness.

Results: A total 264 children completed their SVR follow-up to-date. Median age of treated patients is 16 years (range:11.5–17.5 years; M/ F:1.4/1). On intention-to-treat basis, SVR was reported in 249 (94%) patients; while 13 (5%) lost follow-up and 2 (1%) had discontinued therapy for medical causes. SVR on Per protocol was 100%. Comorbidities were reported in 21 (8%) patients; hemophilia (n = 4), lymphoma (n = 3), thalassemia (n = 3) and cardiac disease (n = 2). Fifty-one (19%) children and adolescents were cancer survivors. Clinical findings were mostly hepatomegaly in 26 (10%), splenomegaly in 3 (1%) patients and splenectomy in 3 (1%) patients. Seventeen patients (6%) were previously treated with Interferon therapy. Maternal history revealed 97 mothers (37%) with known HCV infection and Vaginal delivery in 79 (74%) patients. Risk factors of treated patients were; circumcision or injection by an informal health care provider in 44 (17%), 132 (50%) respectively. Multiple injections (>10 times) were reported in 222 (84%) patients. Most patients (92%) attended at hospital (s), and 123 underwent surgery (47%) and 133 patients underwent dental procedures. Blood transfusion was reported in 85 (32%) patients.

Conclusion: Generic DAA therapy is safe and effective therapy in adolescents real-life. NGOs can fulfil unmet needs providing a successful model of service delivery for treatment of children and adolescents to achieve the 2030 elimination goal.

Late breaker posters

LBP-2580

ARO-HSD reduces hepatic HSD17B13 mRNA expression and protein levels in patients with suspected NASH

Edward Gane¹, Christian Schwabe², Ki Tae Yoon³, Jeong Heo⁴, Russell Scott⁵, Jeonghoon Lee⁶, Jung Il Lee⁷, Young Oh Kweon⁸, Martin Weltman⁹, Stephen Harrison¹⁰, Brent Tetri¹¹, Kenneth Cusi¹², Rohit Loomba¹³, Dawn Christianson¹⁴, Natasa Rajjic¹⁴, Javier San Martin¹⁴, James Hamilton¹⁴, Lung Yi Loey Mak¹⁵, Man-Fung Yuen¹⁵. ¹University of Auckland, Auckland, New Zealand; ²New Zealand Clinical Research, Auckland, New Zealand; ³Pusan National University Yangsan Hospital, Yangsan, Korea, Rep. of South; ⁴Pusan National University and Medical Research Institute, Busan, Korea, Rep. of South; ⁵Lipid and Diabetes Research, Christchurch Hospital, Christchurch, New Zealand; ⁶Seoul National University Hospital, Seoul, Korea, Rep. of South; ⁷Gangnam Severance Hospital, Seoul, Korea, Rep. of South; ⁸Kyungpook National University, Daegu, Korea, Rep. of South; ⁹Nepean Hospital, Penrith, Australia; ¹⁰Pinnacle Clinical Research Center, San Antonio, United States; ¹¹Saint Louis University School of Medicine, St. Louis, United States; ¹²University of Florida, Gainesville, United States; ¹³NAFLD Research Center, UCSD, La Jolla, United States; ¹⁴Arrowhead Pharmaceutical's, Inc, Pasadena, United States; ¹⁵Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong Email: jhamilton@arrowheadpharma.com.

This abstract is under embargo until the beginning of the press conference it is being presented in on Friday 25 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

LBP-2730

Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study

Heiner Wedemeyer¹, Soo Aleman², Pietro Andreone³, Antje Blank⁴, Maurizia Brunetto⁵, Pavel Bogomolov⁶, Vladimir Chulanov⁷, Natalia Geyvandova⁸, Gudrun Hilgard⁹, Nina Mamonova¹⁰, Uta Merle⁴, Morozov Viacheslav¹¹, Olga Sagalova¹², Tatyana Stepanova¹³, Julian Schulze zur Wiesch¹⁴, Sergey Zotov¹⁵, Stefan Zeuzem¹⁶, Pietro Lampertico^{17,18}. ¹Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover, Hannover, Germany; ²Karolinska University Hospital/Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden; ³Internal Medicine, University of Modena and Reggio Emilia, Italy; ⁴University Hospital Heidelberg, Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany; ⁵U.O. Epatologia-Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; ⁶State budgetary institution of health care of Moscow region "Moscow regional research clinical institute after M.F. Vladimirov", Moscow, Russian Federation; ⁷Federal Budget Institute of Science "Central Research Institute for Epidemiology" of Federal Service on Consumers Rights Protection and Human Well-Being Surveillance, Moscow, Russian Federation; ⁸Stavropol Regional Hospital, Stavropol, Russian Federation; ⁹Universitätsklinikum Essen (AöR), Klinik für Gastroenterologie und Hepatologie, Essen, Germany; ¹⁰FSBI National Research Medical Center for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; ¹¹LLC Medical Company "Hepatolog," Samara, Russian Federation; ¹²Federal state-funded institution of higher education "Southern Ural State Medical University of Ministry of Health of the Russian Federation" of Ministry of Health of the Russian Federation, Chelyabinsk, Russian Federation; ¹³Limited liability company



“Clinic of Modern Medicine,” Moscow, Russian Federation; ¹⁴Universitätsklinikum Hamburg-Eppendorf Medizinische Klinik Studienambulanz Hepatologie, Hamburg, Germany; ¹⁵State budgetary institution of health care “Specialized Clinical Infectious Diseases Hospital” of Ministry of Health of Krasnodar Region, Krasnodar, Russian Federation; ¹⁶University Hospital Frankfurt, Department of Medicine, Frankfurt am Main; ¹⁷Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; ¹⁸CRC “A. M. and A. Migliavacca” Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy
 Email: wedemeyer.heiner@mh-hannover.de

This abstract is under embargo until the beginning of the press conference it is being presented in on Thursday 24 June 2021 at 09:00 EDT/15:00 CET.
 It will be uploaded to the conference website once the embargo has lifted.

LBP-2814
Modeling HCV elimination recovery following the COVID-19 pandemic in the United States: Pathways to regain progress
 Sarah Blach¹, Chris Estes¹, Homie Razavi¹. ¹CDA Foundation, Lafayette, United States
 Email: sblach@cdafound.org

Background and aims: As of 2019, the United States (US) was not on track to achieve the WHO targets for elimination, due to increasing incidence and barriers to treatment. In 2020, the COVID-19 pandemic disrupted HCV services globally, with the US experiencing multiple waves of infections and restrictions. As COVID-19 vaccinations

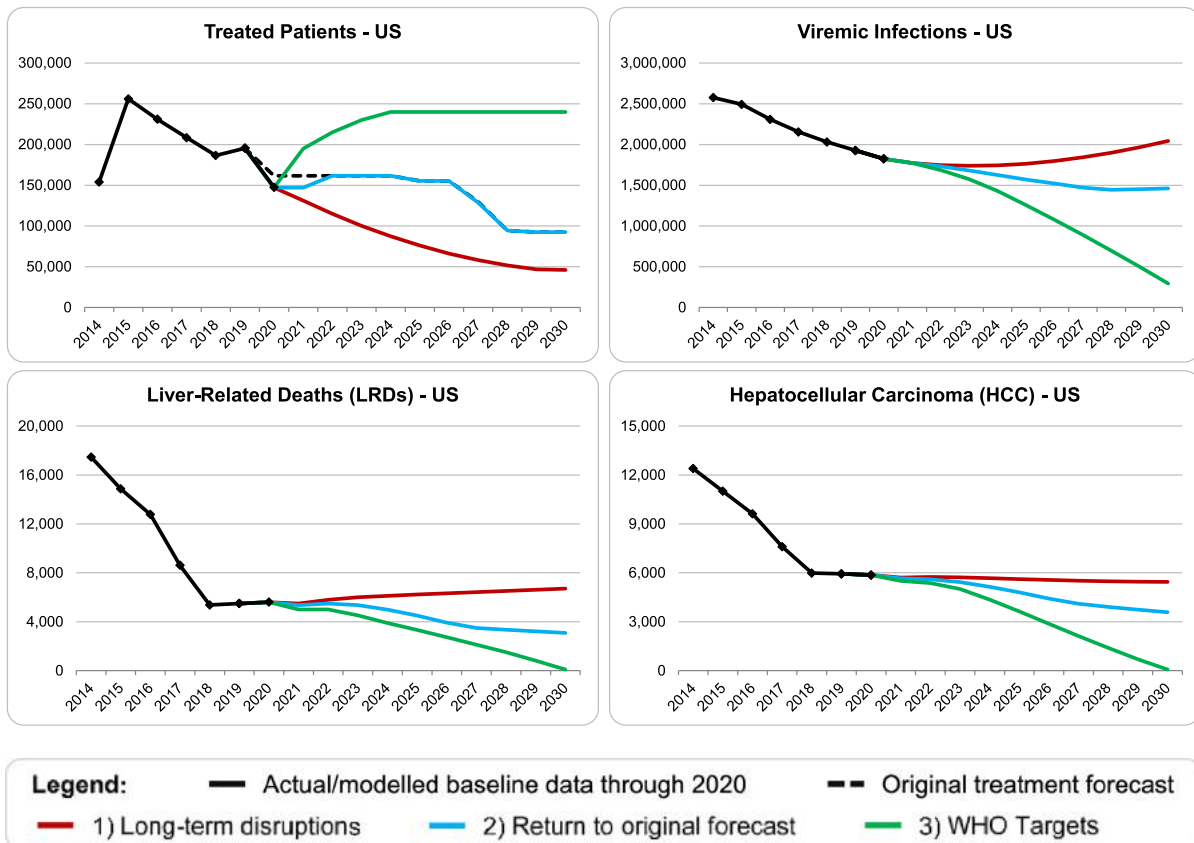


Figure: (abstract: LBP-2814)

POSTER PRESENTATIONS

become commonplace and healthcare services normalize, there is an urgent need to reassess the country's progress toward HCV elimination and evaluate scenarios for recovery.

Method: We updated a previously validated Markov model to estimate HCV-related morbidity and mortality in the US. HCV epidemiological data were based on published data, with annual treatment data from industry reports through 2020. Three scenarios were developed to bookend possible outcomes for HCV recovery in the wake of the pandemic. These included (1) long-term treatment disruptions; (2) return to pre-COVID-19 treatment forecasts; (3) Achieve WHO targets through increased treatment and harm reduction.

Results: From 2014–2019, ~1.2 million patients were treated for HCV, leading to >50% reduction in hepatocellular carcinoma (HCC) cases and >65% reduction in HCV liver-related deaths (LRDs) in 2019 relative to 2014. In 2020, 25% fewer patients were initiated on treatment than in 2019. In the modeled scenarios, between 780, 000 and 2.3 million patients (cumulative) would be initiated on treatment from 2021–2030. WHO Targets (scenario 3) could be achieved in the US by treating at least 240, 000 patients per year and increasing access to harm reduction programs. Compared to scenario 1, scenarios 2 and 3 could avert 19, 400 LRDs and 9, 500 HCC cases and 33, 200 LRDs and 24, 900 HCC cases, respectively.

Conclusion: The US has made strides toward HCV elimination, but these gains could easily be lost in the wake of the pandemic if we become complacent. There is time to regain momentum and avert more than 33, 000 deaths while reducing the viral pool to prevent new infections. This requires a swift and coordinated effort from the entire HCV community—including government, industry, patient groups and providers. Political will for HCV elimination is increasing (demonstrated through the endorsement by AASLD, US CDC and USPTF of a one-time universal screening for all adults); however, to prevent further morbidity and mortality, all new or previously diagnosed patients should be immediately linked to treatment, without restriction (EASL, AASLD/IDSA).

LBP-2886

LPCN 1144 improves body composition in biopsy-confirmed NASH patients

Shadi Mehraban¹, Benjamin Bruno², Kilyoung Kim³, Kongnara Papankorn³, Nachaippan Chidambaram³, Mahesh Patel⁴, Anthony DelConte⁵. ¹Lipocine Inc., Clinical Affairs, Salt Lake City, United States; ²Lipocine Inc., Clinical Development, Salt Lake City, United States; ³Lipocine Inc., Product Development, Salt Lake City, United States; ⁴Lipocine Inc., Salt Lake City, United States; ⁵Saint Joseph's University, Philadelphia, United States
Email: sm@lipocine.com

Background and aims: Non-alcoholic Steatohepatitis (NASH) is a common cause of liver disease and rapidly rising to be the leading indication for liver transplantation. Sarcopenia, loss of muscle mass, occurs in 20–60% of patients with liver disease and reduces survival of cirrhotic patients. There is an unmet need for addressing adverse body composition (BC) in advanced NASH. A decrease in free testosterone (T) and increase in Sex Hormone Binding Globulin (SHBG) are reported with progression of NASH. LPCN 1144, an oral prodrug of endogenous T, is currently being investigated in an ongoing randomized, double-blind, paired biopsy, placebo-controlled, phase 2 study in men with NASH (LiFT, NCT04134091). Here, we present topline BC results post 20 weeks (w) of treatment.

Method: Biopsy-confirmed NASH (F1-F3) males were randomized 1:1:1 to three arms; (1) Treatment A: oral T twice daily (BID), (2) Treatment B: oral T with d-alpha tocopherol BID, and (3) oral matching placebo (PL) BID. BC parameters, including appendicular lean muscle mass (APLM), whole body fat mass (WBFM) and whole body lean mass (WBLM), were evaluated using Dual Energy X-ray Absorptiometry (DEXA) scan at baseline and w20. Other key outcomes measured were changes in SHBG, hepatic fat fraction,

alanine aminotransferase (ALT), and aspartate aminotransferase (AST) at w12.

Results: APLM was significantly elevated with LPCN 1144 treatment compared to PL ($p < 0.05$). Additionally, treatment with LPCN 1144 resulted in a significant reduction of WBFM compared to PL ($p < 0.01$). Favorable BC changes, defined as a decrease in WBFM and an increase in WBLM, were observed in 64% of the subjects receiving LPCN 1144 compared to 15.4% in the PL arm ($p < 0.01$). Furthermore, LPCN 1144 reduced progression of adverse muscle composition (AMC); 4% in the treatment arm vs 46.2% in the PL arm had an increase in WBFM and a decrease in WBLM ($p < 0.01$). Treatment with LPCN 1144 significantly decreased SHBG from baseline compared to PL ($p < 0.001$). Liver fat, ALT, and AST were also significantly reduced in both treatment arms compared to PL ($p < 0.001$, < 0.05 , and < 0.05 , respectively).

Table:

Group	Relative Change from Baseline (%)			Percentage of Subjects with Favorable Body Composition Post Therapy	Percentage of Subjects with Adverse Muscle Composition Post Therapy
	Appendicular lean muscle mass	Whole body fat mass	Whole body lean mass		
Placebo (N = 13)	-1.65	3.24	-0.47	15.4	46.2
LPCN 1144 Treatment (N = 25)	2.43	-5.07	2.40	64.0	4.0
P Value vs placebo	0.0111	0.0018	0.0473	0.0064	0.0035

Conclusion: LPCN 1144 significantly improved BC in biopsy-confirmed NASH male subjects. The forthcoming w36 data in the ongoing LiFT trial is expected to further elucidate the effects of LPCN 1144 on changes in BC. This significant impact of LPCN 1144 on BC can be beneficial in cirrhotic subjects. Larger longitudinal investigations may be required to study this potential effect in advanced liver disease.

LBP-2891

Artificial intelligence and digital single-operator cholangioscopy: automatic identification of papillary projections in patients with indeterminate biliary strictures

Tiago Ribeiro^{1,2,3}, Miguel Mascarenhas^{1,2,3}, João Afonso^{1,2,3}, João Pedro Sousa Ferreira^{4,5}, Filipe Vilas-Boas^{1,2,3}, Marco Parente^{4,5}, Renato Natal Jorge^{4,5}, Pedro Pereira^{1,2,3}, Guilherme Macedo^{1,2,3}. ¹Centro Hospitalar Universitário de São João, Gastroenterology, Porto, Portugal; ²WGO Gastroenterology and Hepatology Training Center, Porto, Portugal; ³Faculty of Medicine of the University of Porto, Porto, Portugal; ⁴Faculty of Engineering of the University of Porto, Mechanical Engineering, Porto, Portugal; ⁵Institute of Science and Innovation in Mechanical and Industrial Engineering, Porto, Portugal
Email: tiagofcribeiro@outlook.com

Background and aims: Digital cholangioscopy revolutionized the diagnostic workup of patients with indeterminate biliary stenosis. The visual impression of these lesions is highly sensitive for the diagnosis of malignancy. Morphologic characteristics such as masses, tumor vessels or papillary projections are common findings in those with malignant biliary strictures. Nevertheless, the specificity and interobserver variability in the detection of these findings are significant limitations. The application of artificial intelligence (AI) tools to a wide range of endoscopic techniques has provided promising results. The application of these systems for automatic characterization of biliary lesions has not been explored. The aim of this study was to develop a deep learning algorithm for automatic detection of papillary projections in D-SOC images.

Method: An AI algorithm based on a convolutional neural network (CNN) was constructed for automatic detection of *papillary projections* in D-SOC images. A total of 3920 were extracted from a pool of 85 cholangioscopy exams using the *Spyglass™ DS II system* (Boston Scientific, Marlborough, MA, USA). Each frame was classified by two endoscopists with experience in D-SOC for the presence or absence of *papillary projections*. This pool of images was split in two distinct datasets for training (80%) and validation (20%) of the CNN. The performance of the model was measured by calculating the area under the receiving operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).

Results: After the optimization of the architecture of the CNN for automatic detection of papillary projections, our network showed a sensitivity of 99.7%, a specificity of 97.1%, a PPV of 96.2% and a NPV of 99.8%. The overall accuracy of our CNN was 98.2%. The AUC was 0.99 (Figure 1). The image processing speed was of 15 ms/image.

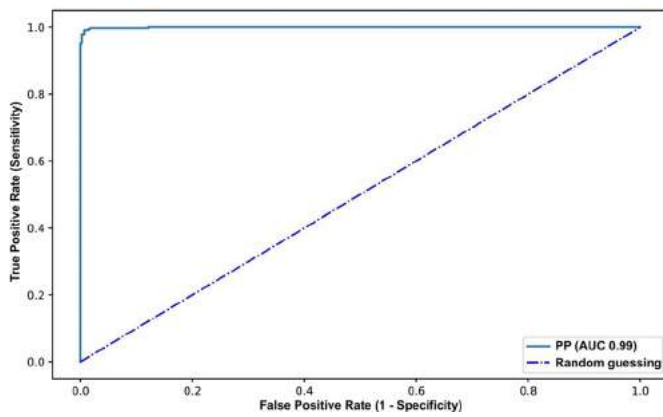


Figure 1: ROC analysis of the network's performance in the detection of papillary projections associated with malignant biliary strictures. ROC-receiver operating characteristic. PP-papillary projections.

Conclusion: Our *deep learning* algorithm detected papillary projections, a finding frequently associated with malignant biliary strictures, with high accuracy. The development of AI tools for may positively impact the diagnostic yield of cholangioscopy, potentiating a timely diagnosis and treatment, which may ultimately translate into prognostic gains.

LBP-2907

Icosabutate, a novel structurally engineered fatty acid, significantly reduces relevant markers of NASH and fibrosis in 16 weeks: interim analysis results of the ICONA trial

Stephen Harrison¹, Nadege T. Gunn², Muhammad Y. Sheikh^{3,4}, Madhavi Rudraraju⁵, Anita Kohli⁶, Guy Neff⁷, Patrick Round⁸, David A. Fraser⁸, Carine Beysen⁸, Stephen Rossi⁸, Arun Sanyal⁹.

¹University of Oxford, Radcliffe Department of Medicine, Oxford, United Kingdom; ²Pinnacle Clinical Research, Austin, United States; ³Fresno Clinical Research Center, Fresno, United States; ⁴Fresno Clinical Research Center, Fresno, CA, United States; ⁵Pinnacle Clinical Research, San Antonio, United States; ⁶Arizona Liver Health, Chandler, United States; ⁷Covenant Clinical Research, Sarasota, United States; ⁸Northsea Therapeutics, Amsterdam, Netherlands; ⁹Virginia Commonwealth University, Richmond, United States

Email: stephen.rossi@northseatherapeutics.com

This abstract is under embargo until the beginning of the press conference it is being presented in on Friday 25 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

Posters

Acute liver failure and drug induced liver injury

PO-443

SZN-043, a hepatocyte targeted R-spondin mimetic, induces hepatocyte proliferation in acute acetaminophen-induced liver injury model

Mehaben Patel¹, Maureen Newman¹, Vincent Meador², Haili Zhang¹, Wen-Chen Yeh¹, Trudy Vanhove¹, Jay Tibbitts¹, Helene Baribault¹.

¹Surrozen, South San Francisco, United States; ²Pacific Tox Path, LLC, Seattle, United States

Email: meha@surrozen.com.

Background and aims: Wnt signaling plays a central role in hepatocyte expansion during development and tissue repair. R-spondins (RSPOs) amplify Wnt signaling via stabilization of Frizzled and LRP co-receptors and their function depends on the presence of Wnt ligands, which are upregulated in injured tissue. The APAP-induced liver injury model in mice reproduces all important clinical features of adverse events and toxicity observed with APAP overdose in humans. To test the efficacy of SZN-043 in an acute liver injury model, we tested the ability of SZN-043 to repair APAP-induced liver damage.

Method: SZN-043 efficacy was tested in C57BL/6J (B6) mice which were randomized based on body weight. Mice were fasted overnight to ensure that all animals had an initial, homogeneous, low level of glutathione. Mice then received a single i.p. dose of APAP (300 mg/kg) and were returned to their cage with food. One control group received a single i.p. dose of saline. Two hours later, mice were administered a single dose of negative control anti-GFP (10 mg/kg), SZN-043 (10 mg/kg) or positive control N-acetyl cysteine (1200 mg/kg). Blood and liver tissue samples were collected at 24, 48 and 72 hours. To measure the effect of SZN-043 on hepatocyte proliferation, maturation and zonation, liver tissue markers were analyzed respectively using RT-qPCR. Clinical chemistry included ammonium, ALT, AST and total bilirubin levels. Hepatocyte specific proliferation was analyzed by immunofluorescence staining of Ki67 and Hnf4-alpha. Histopathology was done using hematoxylin and eosin staining.

Results: Serum chemistry analysis showed that SZN-043 had no effect on ALT or AST levels but showed a trend towards bilirubin reduction. Compared to anti-GFP, both NAC and SZN-043 significantly reduced the levels of circulating ammonia. As expected, SZN-043, but not NAC, induced Wnt activation as shown by a significant increase of the direct Wnt target genes, *Axin 2* and *Ccnd1* mRNA. Notum, a physiologic negative regulator of Wnt signaling was also significantly induced in response to SZN-043. SZN-043 induced Ki67 positive nuclei specifically in HNF4-alpha-expressing hepatocytes in immunofluorescence, suggesting that SZN-043 induced hepatocyte expansion and maturation to HNF4-alpha positive cells after APAP-induced liver injury. Histopathological analysis at 72 hr after APAP treatment showed large regions of diffuse necrosis in the pericentral regions of the liver samples in mice treated with anti-GFP. In contrast, livers from mice treated with NAC and particularly SZN-043 displayed reduced necrosis.

Conclusion: These results provide supporting evidence that SZN-043 can induce hepatocyte specific regeneration in response to APAP overdose. This approach may be beneficial for the treatment of liver diseases.

PO-537

Protective effect of GOLM1 on acute liver failure in mice

Linlan Qiao¹, Junzhou Zhao¹, Mengyun Ke¹, Tingyao Chen¹, Jian Dong¹.

¹The First Affiliated Hospital of Xi'an Jiaotong University, Department of Hepatobiliary Surgery, Xi'an, China

Email: dongjiandoctor01@xjtu.edu.cn.

Background and aims: Acute liver failure (ALF) is a life-threatening disease with a high mortality rate. However, the pathogenesis of ALF is still unclear. Golgi Membrane Protein 1 (GOLM1), a protein involved in the trafficking of proteins through the Golgi apparatus, plays an important role in anti-apoptosis. Furthermore, some previous studies demonstrated that Growth differentiation factor-15 (GDF15) had protective effect on ALF. Therefore, we tried to explore the role of GOLM1 and GDF15 in ALF.

Method: Immunohistochemistry, q-PCR, and western blot analysis were performed to evaluate GOLM1 levels in D-GalN/LPS induced liver failure wild mice tissue samples and normal mice tissue samples at 3 and 6 hours, respectively. Meanwhile, 6 wild type (WT) mice and GOLM1- transgene (TG) mice were selected to establish D-GalN/LPS induced liver failure models. The effect of GOLM1 in the process of liver failure was investigated by HE staining, detection of liver function, the level of inflammatory cytokines, and comparison of survival rate between the GOLM1-TG group and WT group. Serum GDF15 levels and liver GDF15 mRNA levels were detected by ELISA and q-PCR. SPSS (Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis, and p value <0.05 was considered statistically significant.

Results: The level of GOLM1 mRNA in liver failure wild mice tissues was lower at 3 h and 6 h than the level in control group. Western blot showed that the level of GOLM1 protein in liver failure wild mice tissues was also lower than the level in control group at 3 h and 6 h. The expression of GOLM1 protein in liver failure wild mice tissues was still lower than that in control group at 3 h and 6 h through IHC. HE staining of liver tissue in WT mice and TG mice showed that liver necrosis was more serious in WT mice. Liver function test showed that the liver function of TG mice was less damaged and the level of inflammatory cytokines was lower than control group. The survival rate of TG mice was significantly higher than that of WT mice. IHC detection showed that the expression of GDF15 in GOLM1-TG group liver tissue was significantly higher than that in WT group. ELISA and q-PCR detection showed that the serum GDF15 level and liver GDF15 mRNA level in TG group were significantly higher than those in the control group.

Conclusion: GOLM1 may play a protective role in acute liver failure by upregulating the expression of GDF15.

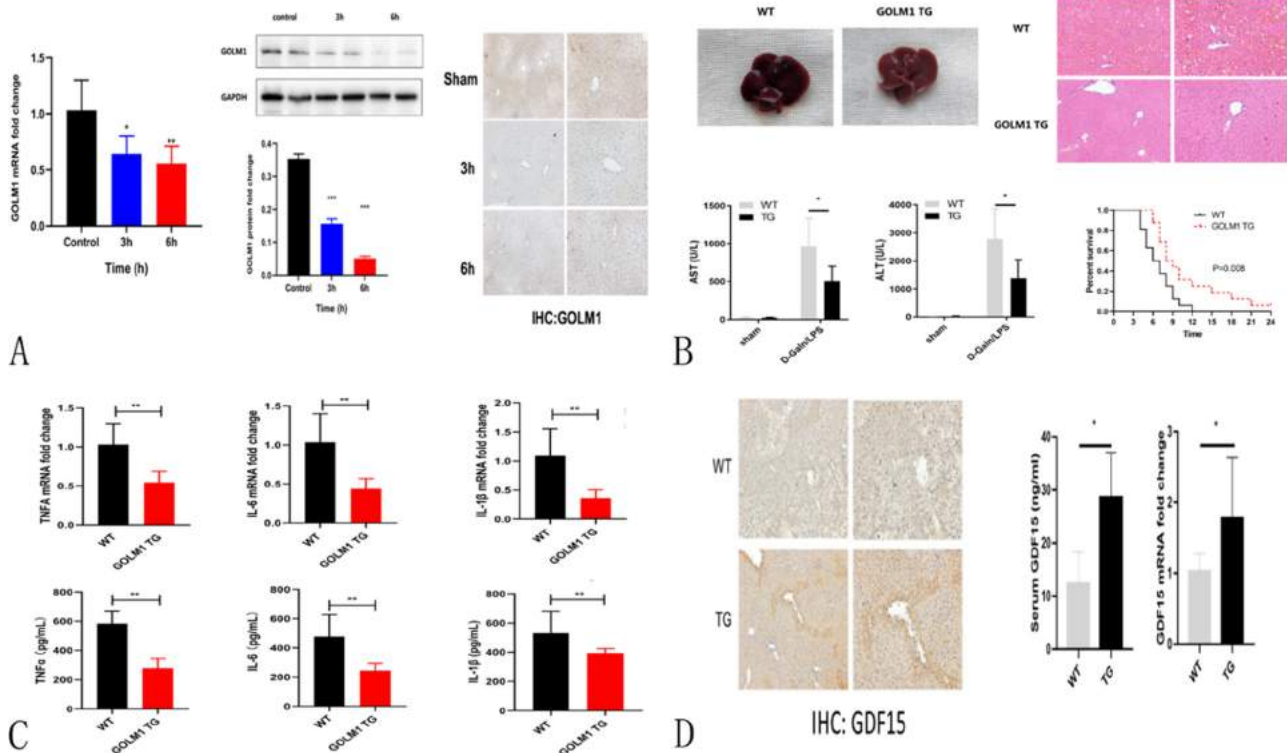


Figure (abstract: PO-537): A. The level of GOML1 mRNA and the expression of GOML1 protein in 3 h and 6 h between D-GalN/LPS induced ALF mice and control mice. B. The gross specimen, HE staining, liver function, and survival rate between GalN/LPS induced liver failure GOML1-TG mice and GalN/LPS induced liver failure WT mice. C. The level of inflammatory cytokines in GOML1 TG mice and WT mice, respectively. D. The expression of GDF15 in liver tissue of GOML1-TG and WT mice in IHC. The serum GDF15 level and liver GDF15 mRNA level of TG group and WT group.

PO-559
Chemokine receptor CCR5 and its corresponding chemokines contribute to virus-induced liver injury via conventional NK cells recruitment

Zhongwei Zhang¹, Zhongyuan Yang¹, Weiming Yan¹, Qiuyu Cheng¹, Yunhui Liu¹, Tao Chen¹, Qin Ning¹. ¹Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department and Institute of Infectious Disease, Wuhan, China
 Email: qning@vip.sina.com.

Background and aims: Our previous study demonstrated that conventional natural killer (cNK) cells migrate into liver from peripheral organs and exert cytotoxic effects on hepatocytes post murine hepatitis virus strain 3 (MHV-3) infection in BALB/cj mice, however the mechanisms of migration was not reported yet. This study aimed to investigate the role of chemokine receptors and their corresponding chemokines in the migration of cNK cells in virus-induced liver injury.

Method: Mice were injected intraperitoneally with MHV-3 to induced fulminant hepatic failure (FHF), In the Pharmacological inhibition of CCR5 experiment, mice received maraviroc by oral gavage daily.

Results: Gene expression analysis indicated that chemokine (C-C motif) receptor 5 (CCR5) in cNK cells own the highest expression comparing with other receptors including CCR1, CXCR3 and CXCR4 after MHV-3 infection in BALB/cj mice. By flow cytometry, the

number of hepatic CCR5+ cNK cells increased and reached peak at 48 hours post MHV-3 infection, while the number of hepatic resident NK cells (rNK) declined steadily. Moreover, its corresponding chemokines macrophage inflammatory protein (MIP)-1 α , MIP-1 β and regulated on activation, normal T cell expressed and secreted (RANTES) multiplied throughout the whole course of infection. In vitro, the transwell migration assay displayed a decreased migration of splenic cNK cells towards infectious hepatocyte after blocking CCR5 on cNK cells, and individual neutralization of CCR5 ligands MIP-1 β and RANTES but not MIP-1 α decreased cNK cells migration. In vivo, pharmacological inhibition of CCR5 (by the inhibitor, maraviroc) reduced cNK cells infiltration in liver and virus-induced liver injury after MHV-3 infection in mice. Meanwhile, CCR5 knockout (KO) mice displayed reduced infiltration of cNK cells in liver post MHV-3 infection, this was accompanied with attenuated liver injury and improvement of survival time. Adoptive transfer experiments in CCR5 KO mice verified that cNK migrating into liver aggravate liver injury during MHV-3-induced FHF.

Conclusion: These results indicated that CCR5 and its ligands MIP-1 β , RANTES play a critical role in the hepatic recruitment of cNK cells in MHV-3-induced liver injury, and the CCR5 inhibitor might bear therapeutic potential to ameliorate liver damage during virus-induced FHF.

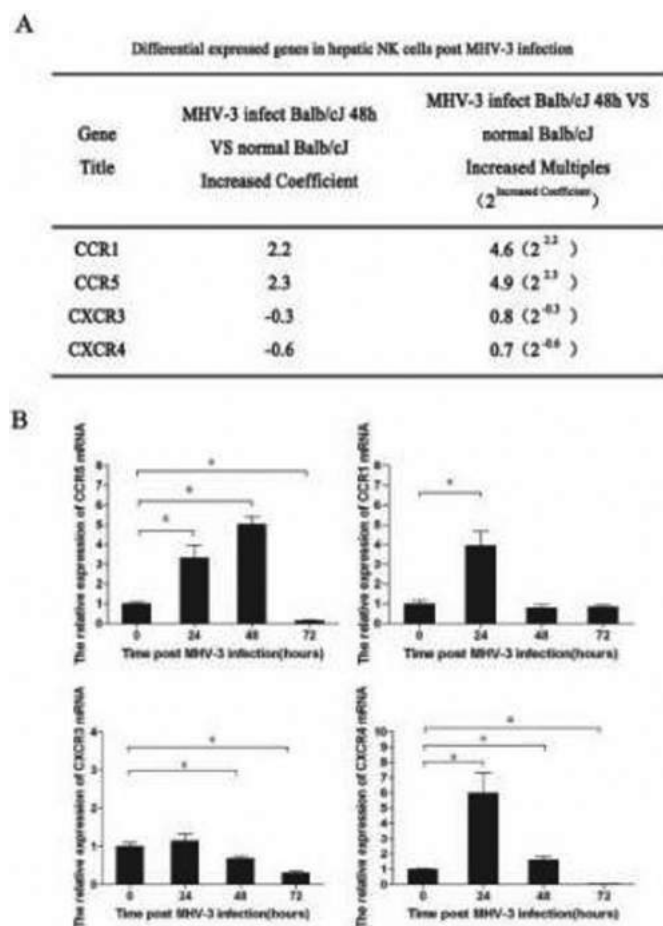


Figure: (abstract: PO-559)

PO-679
Development and validation of a non-invasive algorithm to predict significant fibrosis in patients with chronic drug-induced liver injury

Dong Ji¹, Zhong-bin Li¹, Guofeng Chen¹. ¹5th Medical Center of Chinese PLA General Hospital, Department of Liver Diseases, Beijing, China
 Email: jidg302@126.com.

Background and aims: Currently, there are no satisfactory non-invasive methods for the diagnosis of fibrosis in patients with chronic drug-induced liver injury (DILI). Our goal was to develop an algorithm to improve the diagnostic accuracy of significant fibrosis in this population.

Method: Consecutive patients with biopsy-proven chronic DILI from January 2013 to December 2017 were retrospectively enrolled. An algorithm was developed by using multivariate logistic regression, receiver operator characteristic (ROC) curves, and decision curve analysis (DCA) to diagnose significant fibrosis in the training cohort, and the algorithm was subsequently validated in the validation cohort.

Results: Totally, 1,130 patients were enrolled and randomly assigned into a training cohort (n=848) and a validation cohort (n=282). Based on the multivariate analysis, LSM, CHE, and APRI were independently associated with significant fibrosis. A novel algorithm, LAC, was identified with the AUROC of 0.81, which was significantly higher than LSM (AUROC 0.78), CHE (AUROC 0.73), and APRI (AUROC 0.68), alone. The best cutoff value of LAC in the training cohort was 5.4. When the LAC algorithm was used to diagnose advanced fibrosis and cirrhosis stages, the optimal cutoff values were 6.2 and 6.7, respectively, and the AUROC values were 0.84 and 0.90 in the training cohort and 0.81 and 0.83 in the validation cohort.

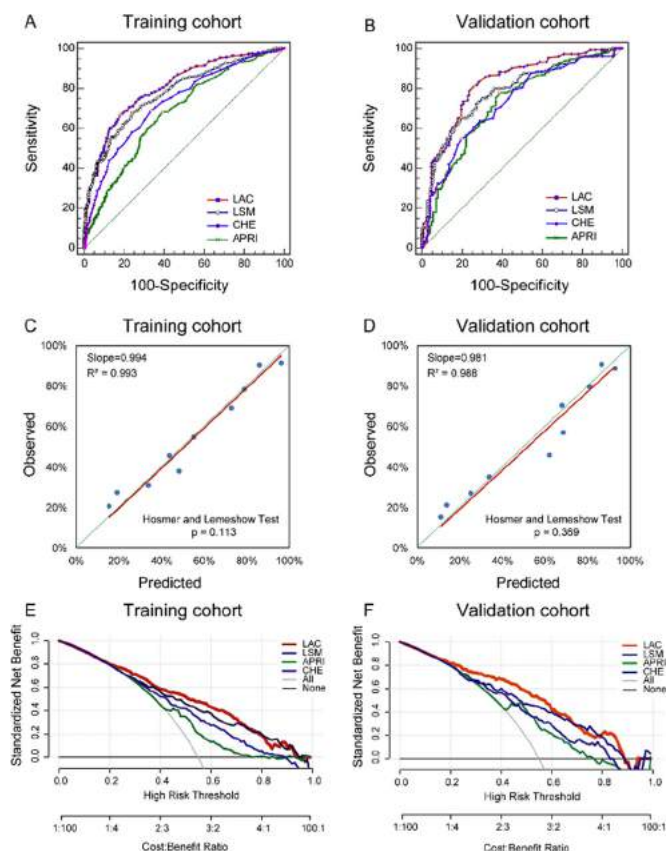


Figure: (abstract: PO-679)

Conclusion: The LAC algorithm shows a better performance than LSM, APRI, or CHE alone in predicting significant fibrosis, thus contributing to the accurate assessment of high-risk disease progression and the establishment of optimal treatment strategies for patients with chronic DILI.

PO-712
Fibrinogen-like protein 2 promotes fulminant hepatitis by inducing neutrophil activation and neutrophil extracellular traps formation

Xitang Li¹, Junjian Hu¹, Suping Hai¹, Hongwu Wang¹, Qin Ning¹, Xiaojing Wang¹. ¹Department and institute of infectious diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, Department and institute of infectious diseases
 Email: qning@vip.sina.com.

Background and aims: we aim to investigate the role of fibrinogen-like protein 2 (fgl2) in regulating neutrophil and neutrophil extracellular traps (NETs) in fulminant hepatitis (FH).

Method: Neutrophil amount and NETs formation were detected in serum and liver of wild type and fgl2^{-/-} mice following murine hepatitis virus-3 (MHV-3) infection. Bone marrow-derived neutrophils were stimulated with MHV-3 in vitro to investigate the underlying mechanism of NETs formation.

Results: Concomitant with histopathology lesions and increased ALT and AST, abundant neutrophil accumulation and NETs formation were observed in mice following MHV-3 infection. NETs depletion significantly improved the survival rate (from 4% to 28%) of infected mice, implying that NETs contribute to FH progression. Fgl2^{-/-} mice showed remarkable reduction of myeloperoxidase levels, along with improved histopathology damage, decreased liver enzymes and expression of inflammatory cytokines. The expression of fgl2 on neutrophils was upregulated post MHV-3 infection. Fgl2 destruction reduced neutrophil accumulation in liver of the infected mice, and

downregulated expression of hepatic ICAM-1, CXCL1, CXCL2 and CXCR2. Both in vivo and in vitro studies revealed that fgl2 promoted NETs generation through the ROS-dependent PAD4 pathway. Moreover, fgl2 directed fibrin deposition in NETs area, aggravating the following coagulation cascade and tissue lesions.

Conclusion: Fgl2 promotes FH progression partially via boosting hepatic neutrophil accumulation as well as facilitating NETs formation and subsequent liver injury. Thus, fgl2 might serve as a potential therapeutic target in FH.

PO-1107

Acute liver injury among patients with COVID-19 in a tertiary hospital

Henry Winston Li¹, Janus Ong¹. ¹Philippine General Hospital, Gastroenterology, Manila, Philippines
Email: winolps2488@gmail.com.

Background and aims: The COVID-19 disease primarily affects the respiratory system with principal symptoms including fever, cough, dyspnea and malaise. However, liver involvement has been demonstrated on prior studies with abnormalities seen from 14 to 53% of cases. The prevalence of liver injury was also believed to be associated with increased disease severity and mortality among infected patients. The aim of the study was to determine the clinical characteristics and risk factors for acute liver injury (ALI) among COVID-19 patients admitted in our local setting and to identify potential association of ALI on significant health outcomes.

Method: This was a retrospective study of adult patients with COVID-19 admitted at Philippine General Hospital. Acute liver injury was defined as ALT >ULN-mild ALI (up to 2× ULN), moderate ALI (2–5× ULN), severe ALI (>5× ULN). Descriptive analysis was conducted accordingly. Univariate and multivariate analyses of predictors of ALI were performed. Impact of ALI on health outcomes was determined and adjusted for known predictors including age, gender, co-morbidities and FIB-4.

Table 1: Multivariable Predictors of ICU Admission by Category of ALT elevation among patients

Predictors	Univariable		Multivariable.	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
ALT Category				
Normal	1.00		1.00	
1-<2× UL	1.11 (0.83–1.49)	0.49	1.13 (0.81–1.58)	0.46
2–5× UL	1.22 (0.85–1.75)	0.29	1.19 (0.79–1.79)	0.41
>5× UL	2.26 (0.94–5.45)	0.07	2.62 (0.97–7.08)	0.06
Age	1.05 (1.04–1.06)	<0.01*	1.06 (1.05–1.07)	<0.01*
Sex				
Female	1.00		1.00	
Male	1.74 (1.35–2.23)	0.01*	1.86 (1.40–2.47)	0.01*
Co-morbid Conditions				
	1.73 (1.35–2.21)	0.01*	0.89 (0.66–1.20)	0.43
Hypertension				
Diabetes mellitus	1.57 (1.19–2.07)	0.01*	1.09 (0.80–1.50)	0.58
Malignancy	2.17 (1.28–3.67)	0.01*	1.91 (1.06–3.47)	0.03*
FIB-4 Levels	1.11 (1.06–1.17)	<0.01*	1.02 (0.99–1.05)	0.11

Results: A total of 1, 086 patients satisfied inclusion criteria with mean age of 54, M:F ratio 1.2:1. 425/1086 (39%) had ALI-mild ALI 258 (24%), moderate ALI 146 (13%), severe ALI 21 (2%). Chronic liver disease (CLD) (OR: 2.52; p = 0.01), critical COVID-19 (OR: 4.94; p = 0.02), increased AST (OR: 1.04; p = <0.01) and increased ferritin (OR: 1.03; p = 0.01) were all associated with moderate to severe ALI. Although there was a trend towards higher rates of ICU admission with increasing severity of ALI [severe ALI, OR 2.26 (0.94–5.45, p =

0.07), moderate ALI, OR 1.22 (0.85–1.75, p = 0.29), mild ALI, 1.11 (0.83–1.49, p = 0.49), this was not statistically significant. (Table 1) There was a similar but likewise not statistically significant trend in rates of intubation, need for renal replacement and mortality with increasing severity of ALI.

Conclusion: ALI occurred commonly among patients admitted for COVID-19 and was associated with CLD, critical COVID-19, AST, and ferritin. Severity of ALI showed a trend towards higher adverse outcomes.

PO-1185

Magnesium homeostasis by Cyclin M4: a novel therapeutic mechanism in Acetaminophen-induced liver damage

Irene González-Recio¹, Jorge Simón Espinosa^{1,2}, Naroa Goikoetxea-Usandizaga¹, Marina Serrano-Macia¹, Maria Mercado-Gómez¹, Rubén Rodríguez Agudo¹, Sofia Lachiondo-Ortega¹, Claudia Gil-Pitarch¹, Carmen Fernández-Rodríguez¹, Donatello Castellana³, Maria U. Latasa⁴, Leticia Abecia^{5,6}, Juan Anguita^{2,5}, Teresa Cardoso Delgado¹, Matías A Avila^{2,4}, Cesar Martin^{7,8}, Ute Schaeper⁹, Michel LTremblay^{10,11}, James Dear¹², Steven Masson¹³, Misti McCain¹⁴, Helen L. Reeves^{13,14}, Raul J. Andrade^{2,15}, Maria Isabel Lucena^{2,16}, Daniela Buccella¹⁷, Luis Alfonso Martinez-Cruz¹, María Luz Martínez-Chantar^{1,2}. ¹CIC bioGUNE, Liver disease Lab, Derio, Spain; ²Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; ³CIC bioGUNE, Research and Development, Derio, Spain; ⁴CIMA, Hepatology Programme, Pamplona, Spain; ⁵CIC bioGUNE, Inflammation and Macrophage Plasticity Laboratory, Derio, Spain; ⁶Facultad de Medicina y Enfermería, Departamento de Inmunología, Microbiología y Parasitología, Leioa, Spain; ⁷Biofisika Institute (UPV/EHU, CSIC); ⁸Universidad del País Vasco, Dpt. Of Biochemistry and Molecular Biology; ⁹Silence Therapeutics GmbH, Berlin, Germany; ¹⁰Mc Gill University, Rosalind and Morris Goodman Cancer Research Centre; ¹¹Mc Gill University, Department of Biochemistry; ¹²University of Edinburgh, Pharmacology, Toxicology and Therapeutics, Centre for Cardiovascular Science; ¹³Newcastle-upon-Tyne Hospitals NHS Foundation Trust, The Liver Unit; ¹⁴The Medical School, Newcastle University, Northern Institute of Cancer Research; ¹⁵Hospital Universitario Virgen de la Victoria, Unidad de Gestión Clínica de Enfermedades Digestivas, Instituto de Investigación Biomédica de Málaga-IBIMA; ¹⁶Hospital Universitario Virgen de la Victoria, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA; ¹⁷New York University, Department of Chemistry
Email: mlmartinez@cicbiogune.es.

Background and aims: Drug-induced liver injury (DILI) is the main cause of acute liver failure (ALF) in the Western World. Acetaminophen (APAP), the most available pain medication in USA, accounts for 50% of ALF in USA and Europe. N-acetylcysteine, routinely used for early stages of idiosyncratic DILI and APAP abuse, has limited effect after 20 hours of overdose. Therefore, additional therapeutic approaches are necessary in this pathology. Cyclin M4 (CNNM4) has a key role in magnesium transport across cell membranes. Here, we investigated if CNNM4 and dysregulated magnesium homeostasis could play a functional role in DILI.

Method: Hepatic CNNM4 expression and magnesium levels were assessed in human samples and in mice. Mice were treated with APAP 360 mg/kg by intraperitoneal injection and 24 h thereafter *Cnnm4* siRNA or an unrelated control (siCtrl) were administered via tail vein injection and compared to control group. Mice were sacrificed 48 hours after APAP overdose. Primary hepatocytes treated with GalNAc conjugated *Cnnm4* siRNA or control siRNA were exposed to APAP and mitochondrial ROS and ER stress were evaluated.

Results: Patients with APAP overdose and idiosyncratic DILI presented an upregulation of hepatic CNNM4 expression and disturbances in magnesium serum levels. In the liver, we showed that

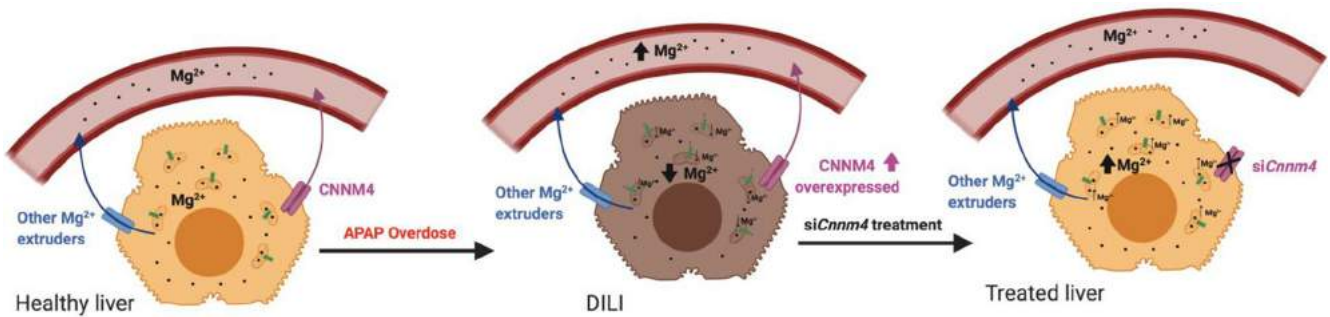


Figure: (abstract: PO-1185)

CNNM4 overexpression coincides with ER stress and mitochondrial dysfunction, affecting ATP production and ROS generation. Silencing *Cnm4* expression in the liver with nanoparticle- or in hepatocytes with GalNAc-conjugated siRNA protects from APAP-induced liver injury and restores cellular magnesium homeostasis. **Conclusion:** CNNM4 appears as a new therapeutic approach to treat DILI with the added value of ameliorating mitochondrial dysfunction and ER stress that NAC does not provide.

PO-1335
Metabolomic predictive models in the diagnosis of drug-induced liver injury

Daniel E. Di Zeo-Sánchez¹, M. Robles-Díaz^{1,2}, Ibon Martínez-Arranz³, Inmaculada Medina-Caliz¹, Aida Ortega-Alonso¹, Miren Garcia Cortes^{1,2}, Jose Pinazo Bandera¹, J. Sanabria-Cabrera¹, Enrique del Campo Herrera¹, Rocio González-Grande⁴, Miguel Jiménez⁴, Maria Isabel Lucena^{1,2}, Raul J. Andrade^{1,2}. ¹UGC Aparato Digestivo, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; ²Centro de investigación biomédica en red en el área temática de enfermedades hepáticas y digestivas (CIBERehd), Madrid, Spain; ³OWL Metabolomics, Derio, Bizkaia, Spain, Spain; ⁴Servicio de Aparato Digestivo, IBIMA, Hospital Universitario Regional de Málaga, Málaga, Spain, Málaga, Spain
 Email: danielizeo9@hotmail.com.

Background and aims: Due to the lack of biomarkers, the diagnosis of drug-induced liver injury (DILI) currently relies in the exclusion of other liver disorders and the interpretation of causality scores, which usually have low sensitivity and poor inter-observer reproducibility. We aimed to develop a new predictive algorithm tool that could help clinicians to effectively distinguish DILI from liver injury of other aetiologies.

Method: The study sample comprised 26 Spanish DILI cases -mostly due to anti-infective drugs- and 34 with non-DILI acute liver injury (ALI) -mostly viral hepatitis-. Clinical data (sex, age, BMI, severity and biochemical tests) and serum metabolomic profiles (UHPLC-MS analysis), were used to design different predictive models: Logistic regression, Random Forest, Support Vector Machine and K-NN. These models were developed to find the best methodology to classify the patients. A selection of significant features was applied to each model, first features with low variance were removed and then a univariate selection was performed ($p < 0.05$). In order to avoid bias in the models, the cohort was split into two subcohorts (50%/50%): training and validation

Results: Two clinical parameters (AST and ALT) and 17 metabolites were selected for inclusion in the predictive models. Among the metabolites, 47% were fatty acids, 21% were glycerophospholipids, 10.5% amino acids, 5% bile acids and 5% peptides. Specifically, the AST and ALT transaminases and the amino acid tryptophan stood out for their higher statistical significance ($p < 0.009$). Most of the fatty acids used to discriminate between DILI and ALI were polyunsaturated species ($p < 0.05$). PE (20:4/0:0) was the glycerophospholipid that

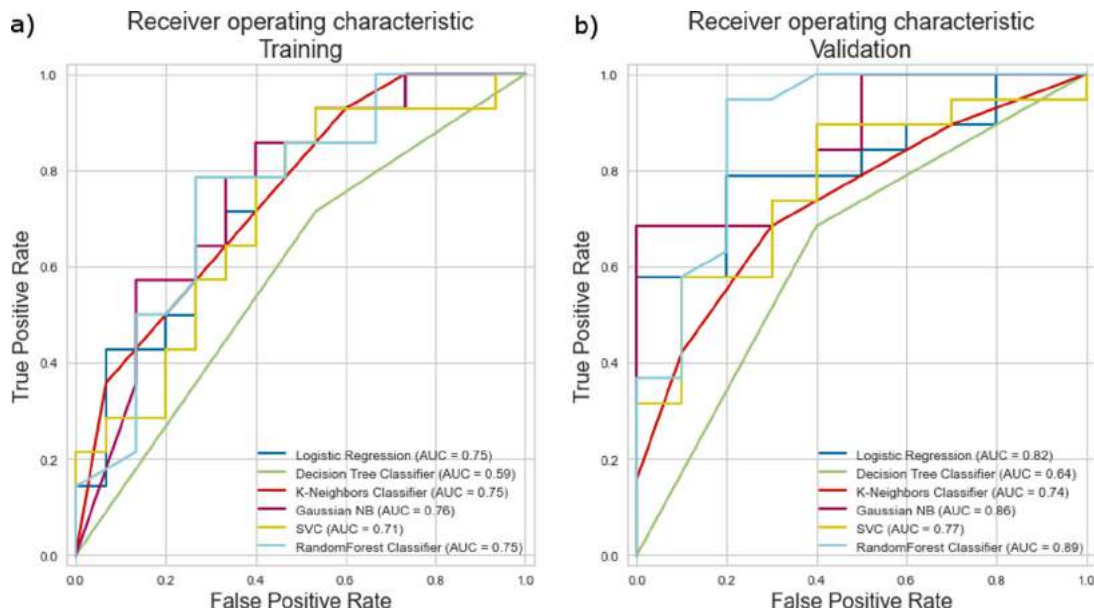


Figure: (abstract: PO-1335)

reached the highest statistical significance ($p < 0.02$), and Phe-Phe was the only dipeptide included in the model ($p < 0.03$). Based on these variables, Logistic regression, K-NN classifier and Random Forest models were selected as the best choice for classifying the patients in the training cohort, all of them with an area under the receiver operating characteristic curve (AUC) over 0.75 (Figure 1a). The highest AUCs were obtained for the Random Forest Classifier (AUC = 0.89) and the Logistic Regression (AUC = 0.82) in the validation cohort (Figure 1b).

Conclusion: A metabolic signature capable of discriminating DILI vs ALI patients with an AUC over ~0.75 has been identified. Further refinement of this model and the development of other mathematical approaches could support a more accurate diagnosis of DILI. Funding: CIBERehd, ISCiii-FEDER PI18/00901, PI19/00883.

PO-1379

CXCR3pos CD27pos CD161pos NK cells in autoimmune and drug induced liver injury position around lectin like transcript-1 expressing Kupffer cells and CD70pos dendritic cells

Amber Bozward^{1,2,3}, Stuart Astbury^{4,5}, Edmond Atallah^{4,5}, Grace Wootton^{1,2,3}, Jane Grove^{4,5}, Poulam Patel⁶, Ankit Rao⁷, Yukting Ma⁸, Pankaj Punia⁸, Guruprasad Aithal^{4,5}, Ye Htun Oo^{1,2,3}.
¹Centre for Liver and Gastroenterology Research, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom; ²European Reference Network Centre-Rare Liver, Centre for Rare Disease, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ³Liver Transplant and Hepatobiliary Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ⁴Nottingham Digestive Diseases Centre, School of Medicine, Nottingham, United Kingdom; ⁵National Institute for Health research Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University Of Nottingham, Nottingham, United Kingdom; ⁶Division of Cancer and Stem Cells, School of Medicine, Nottingham, United Kingdom; ⁷Nottingham University Hospitals NHS Trust, Oncology Department, Nottingham, United Kingdom; ⁸UHB NHS Foundation Trust, Oncology Department, Birmingham, United Kingdom
 Email: amber@bozward.com.

Background and aims: Autoimmune hepatitis (AIH) and drug-induced liver injury (DILI) present with acute hepatitis and share many clinical features. We hypothesised that the innate immune response to activate the adaptive immune system is key to the pathogenesis of both conditions. However, underlying innate immune subsets involved, their recruitment and cellular crosstalk in liver immunopathology remain unexplored.

Method: We performed immunophenotyping of peripheral blood immune cells from patients with AIH (n = 13), on-going DILI (n = 8) and compared with healthy controls (n = 4). Expression of lectin like transcript-1 (LLT-1), CXCL10 on liver tissue was explored with immunohistochemistry. CD70 expression was examined with flow cytometry on liver lymphocytes. CXCL10 secretion on human hepatocytes and biliary epithelial cells (BEC) was analysed by ELISA.

Results: Compared to healthy controls, both AIH and DILI were associated with an increased number of NK cells. AIH patients have significant (29.9 ± 5 vs 5.7 ± 1.2 ; $p \leq 0.03$) and DILI patients have high-level expression (15.6 ± 3.1 vs 5.7 ± 1.2 ; $p = 0.056$) of liver-homing chemokine receptor CXCR3 compared to control. CXCR3 ligand, CXCL10 expression was observed on hepatocytes and BEC in AIH. TNF α and IFN γ stimulated human hepatocytes (702 vs 75; $p \leq 0.05$) and BEC (648 vs 5.7; $p \leq 0.05$) to secrete significant amount of CXCL10 chemokine. NK cells have significant expression of CD27 in AIH (9.0 ± 1.8 vs 1.2 ± 0.4 ; $p \leq 0.05$) and high-level of CD27 (5.8 ± 2.3 vs 1.2 ± 0.37 ; $p = 0.01$) in DILI compared to controls. CD27 ligand, CD70 was observed on CD1c⁺ CD11c⁺ (54.9 ± 20.1) and CD123⁺ CD303⁺ ($50.5\% \pm 22.9$) dendritic cells. In addition, there was a high level of CD161 expression on NK cells in both AIH (50 ± 9.7 vs 34 ± 4) and DILI (45 ± 4.7 vs 34 ± 4) compared to controls. Multi-colour immuno-staining in

AIH demonstrated CD161 ligand, LLT-1 expression on intrahepatic CD68^{positive} Kupffer cells.

Conclusion: We have reported for the first time the presence of CXCR3^{positive}, CD27^{positive}, CD161^{positive} circulating NK cells in patients with AIH and ongoing DILI. CXCR3^{positive} NK cells and CXCL10 expression on hepatocytes and biliary epithelium support NK cells positioning around hepatocytes and BEC. These CD161^{positive} CD27^{positive} NK cells interact with LLT-1 expressing Kupffer cells and CD70 expressing dendritic cells in AIH and DILI contributing to pathogenesis.

PO-1389

Effect of corticosteroids in the outcome of drug-induced liver injury: a propensity score matched study

Hao Niu¹, Ismael Alvarez-Alvarez^{1,2}, Inmaculada Medina-Caliz¹, Elvira Bonilla¹, Zeus Perez-Valdes¹, Mercedes Robles-Díaz^{2,3}, Miren Garcia Cortes^{2,3}, Judith Sanabria-Cabrera^{1,4}, Raul J. Andrade^{2,3}, Maria Isabel Lucena^{1,3,4}.
¹Servicio de Farmacología Clínica, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga-IBIMA, Universidad de Málaga, Málaga, Spain; ²UGC Aparato Digestivo, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga-IBIMA, Universidad de Málaga, Málaga, Spain; ³Biomedical Research Network Center for Hepatic and Digestive Diseases (CIBERehd), Carlos III Health Institute, Madrid, Spain; ⁴Platform for Clinical Research and Clinical Trials IBIMA, Plataforma ISCiii de Investigación Clínica, Madrid, Spain
 Email: andrade@uma.es.

Background and aims: There is no specific therapy approved for idiosyncratic drug-induced liver injury (DILI) treatment. Previous data show that corticosteroids are often empirically used in DILI patients although its benefit-risk balance remains controversial. We aimed to evaluate the effects of corticosteroids in DILI patients using non-experimental data through propensity score matching (PSM).

Method: All cases of idiosyncratic DILI entered in the Spanish DILI registry from 1994 to November 2020 were retrieved (N = 979). The primary outcome was the development of acute liver failure (ALF) that went on to liver-related death/liver transplantation. Patients treated with corticosteroids were compared to those who did not receive any treatment. A nearest neighbor propensity score matching (1:1) was used to reduce confounding factors (age, sex, total bilirubin, alkaline phosphatase, type of liver injury and Model for End-stage Liver Disease score). Matching without replacement was performed using a caliper width of 0.25 on the propensity score scale. Crude and adjusted odds ratio (OR) along with its 95% confidence interval (CI) were estimated.

Results: A total of eligible 548 patients, 78 treated with corticosteroids, 2 of them also treated with ursodeoxycholic acid, and 1 with ursodeoxycholic acid and MARS (mean age 54 ± 18 years, 58% women), and 470 who did not receive any treatment (54 ± 18 years; 48% women), were enrolled. Hepatocellular injury was more frequent in both groups (63% and 66%, respectively). Among patients who received corticosteroids 6.4% developed ALF, compared to 1.9% who did not receive any treatment ($p = 0.036$), and risk of ALF was significantly increased in patients who received corticosteroids (crude OR = 3.50; 95% CI 1.14–10.76, $p = 0.028$). After PSM, 55 well-balanced pairs were matched. Baseline characteristics were no longer significantly different between the treatment and control group. Corticosteroids use was not associated with an increased risk for developing ALF (adjusted OR = 1.71; 95% CI 0.30–9.89; $p = 0.548$). Sensitivity analysis excluding drug-induced autoimmune hepatitis cases (N = 29) showed consistent findings (adjusted OR = 0.99; 95% CI 0.19–5.07, $p = 0.987$).

POSTER PRESENTATIONS

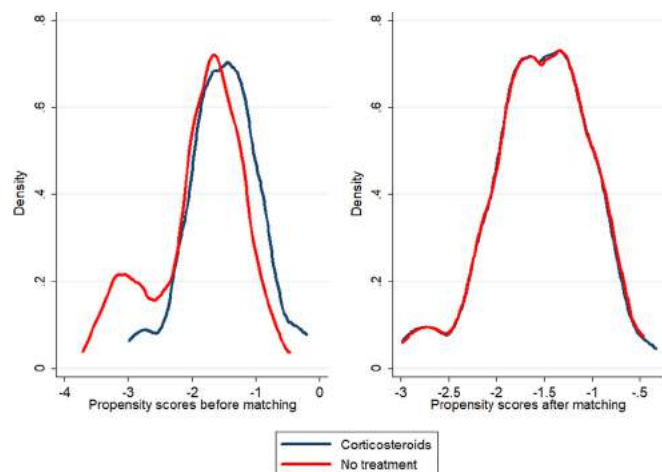


Figure:

Conclusion: This PSM study evidenced that corticosteroids administration in DILI patients was not associated with an increased risk of progression to ALF in DILI patients. Further collaborative studies to validate these findings are clearly needed.

PO-1406

Comparison of gut microbiota composition between patients with drug-induced liver injury, other forms of liver injury and healthy controls

Alejandro Cueto-Sanchez¹, M. Robles-Díaz^{1,2}, Aida Ortega-Alonso¹, Miren Garcia Cortes^{1,2}, J. Sanabria-Cabrera¹, Jose Pinazo Bandera¹, Enrique del Campo Herrera¹, Rocio González-Grande³, Miguel Jiménez³, Maria Isabel Lucena^{1,2}, Camilla Stephens^{1,2}, Raul J. Andrade^{1,2}. ¹UGC Aparato Digestivo, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; ²Centro de investigación Biomédica en red en el área temática de enfermedades hepáticas y digestivas (CIBERehd), Madrid, Spain; ³Servicio de Aparato Digestivo, IBIMA, Hospital Universitario Regional de Málaga, Málaga, Spain
Email: andrade@uma.es.

Background and aims: The gut microbiota may play a role in drug-induced liver injury (DILI) due to its effect on drug metabolism and the immune system. We aimed to compare gut microbiota composition between patients with DILI, non-DILI acute liver injury (ALI) and healthy liver controls (HLC).

Method: DNA was extracted from faecal samples obtained within the first week of presentation of 13 DILI and 22 ALI patients (10 viral hepatitis, 5 autoimmune hepatitis and 7 others) and 58 HLC. DNA was also extracted from a second sample (≥ 1 month from onset) of 10 DILI and 9 ALI patients. Microbiota composition was determined by 16S ribosomal RNA sequencing using Illumina MiSeq system and BaseSpace Application 16S Metagenomics v1.0 to classify the reads. A statistical analysis was performed using STAMP.

Results: A total of 18,345,256 reads were obtained from the 112 faecal samples. Two phyla, Firmicutes and Bacteroidetes, dominated in all groups (DILI: 46%/44%; ALI: 44%/46%; HLC: 49%/41%). 5 families (Clostridiaceae3, Nocardiaceae, Clostridiaceae4, Christensenellaceae, Proteinivoraceae; $p < 1.64E-04$), 5 genera (Coprococcus, Parasporobacterium, Gp3, Sporobacter, Christensenella; $p < 3.95E-05$) and 5 species (*Blautia producta*, *Parasporobacterium paucivorans*, *Senegalia massiliensis*, *Coprococcus eutactus*, *Sporobacter termitidis*; $p < 2.13E-05$) had significantly less reads in DILI compared with HLC. The species all belong to the order Clostridiales. No differences were detected between DILI and ALI. No noteworthy differences in number of reads were seen in most of the above groups in the second DILI samples. Significant differences in bacterial richness were detected ($p < 0.002$) with DILI presenting the lowest number of mean species

(321), followed by ALI (381) and HLC (402). Of the DILI cases, 62% were caused by antibacterial drugs and 32% of the ALI patient had taken antibiotics within 30 days from the episode. Number of species increased in DILI in the second sample, but not in ALI. No significant difference was detected in Shannon diversity between the three groups.

Conclusion: The bacterial composition in DILI differed from that of HLC, but less from ALI. These differences included mainly bacteria belonging to Clostridiales, which are involved in maintenance and overall gut function. Further studies are required to determine if decreased bacterial richness and reduced levels of commensal Clostridiales are risk factors for DILI. Funding: PI16/01748, PI19/00883, CIBERehd-ISCIII.

PO-1885

ALKBH5-modified HMGB1-STING activation contributes to radiation-induced liver disease via innate immune response

Genwen Chen¹, Qianqian Zhao¹, Baoying Yuan¹, Zhaochong Zeng¹. ¹Zhongshan Hospital Fudan University, Radiation Oncology, Shanghai, China
Email: zeng.zhaochong@zs-hospital.sh.cn.

Background and aims: Radiation therapy (RT) is vital for the therapy of primary liver cancer, but inevitable liver injury limits the implement of RT. N6-methyladenosine (m6A) methylation is involved in many molecular functions; however, its role in radiation-induced liver diseases (RILD) remains unknown. Hence, we intend to investigate the role of m6A methylation in RILD.

Method: Methylated RNA-immunoprecipitation sequencing (MeRIP-seq) and RNA transcriptome sequencing (RNA-seq) were used to reveal the methylation pattern of human hepatic stellate cells with exposure to irradiation. C3H/HeN mice and STING-deficient mice underwent X-ray irradiation of 24 Gy in three fractions. The m6A methylation of HMGB1 transcript was validated using MeRIP, RIP, luciferase assay and mRNA decay assays.

Results: Human hepatic stellate cells shown significant difference of methylation pattern after 8 Gy of X-ray irradiation. Irradiation recruits ALKBH5, an eraser of m6A methylation, and then demethylated HMGB1 transcript at m6A residues in the 3'UTR, following activation of STING-IRF3 signaling. Inserting of the HMGB1 3'UTR into a luciferase reporter resulted in regulation of luciferase activity by ALKBH5 knockdown, which was lost after m6A residue mutation. Strikingly, ALKBH5 deficiency or HMGB1 silencing both attenuated type I interferon production, resulting to less hepatocyte apoptosis. *In vivo* depletion of ALKBH5 abolished the upregulation of HMGB1-mediated STING signaling, leading to slightly liver inflammation, which was consistent to STING^{-/-} mice in response to irradiation. Notably, the m6A reader protein YTHDF2 directly binds to m6A-modified site of HMGB1 transcript, which consequently promotes its degradation.

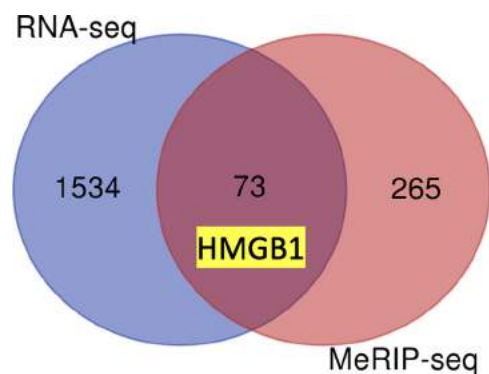


Figure:

Conclusion: ALKBH5 demethylates m6A-modified HMGB1 transcript through YTHDF2-mediated degradation, resulting in RILD via innate immune response.

PO-1947

Etiology and clinical characteristics of acute hepatitis in South Korea: A prospective, multicenter Study

Gwang Hyeon Choi¹, Eun Sun Jang¹, Byung Seok Lee², Young Seok Kim³, Youn Jae Lee⁴, In Hee Kim⁵, Sung Bum Cho⁶, Jaehyun Yoon⁷, Kyung-ah kim⁸, Dae Hee Choi⁹, Woo Jin Chung¹⁰, Hyun Chin Cho¹¹, Seong Kyun Na¹², Sook-Hyang Jeong¹. ¹Seoul National University Bundang Hospital, Seoul National University College of Medicine, Internal Medicine; ²Chungnam National University Hospital, Internal Medicine, Korea, Rep. of South; ³Soonchunhyang University Bucheon Hospital, Internal Medicine, Korea, Rep. of South; ⁴Inje University Busan Paik Hospital, Internal Medicine, Korea, Rep. of South; ⁵Jeonbuk National University Hospital, Internal Medicine, Korea, Rep. of South; ⁶Chonnam National University Hwasun Hospital, Internal Medicine, Korea, Rep. of South; ⁷Chonnam National University Hospital, Internal Medicine, Korea, Rep. of South; ⁸Inje University Ilsan Paik Hospital, Internal Medicine, Korea, Rep. of South; ⁹Kangwon National University Hospital, Internal Medicine, Korea, Rep. of South; ¹⁰Keimyung University Dongsan Hospital, Internal Medicine, Korea, Rep. of South; ¹¹Gyeongsang National University Hospital, Internal Medicine, Korea, Rep. of South; ¹²Jeju National University Hospital, Internal Medicine, Korea, Rep. of South
Email: jsh@snuh.org.

Background and aims: The etiology of acute hepatitis is dynamically changing according to public health improvement and lifestyle alteration. Therefore, continuous monitoring of profiles of acute hepatitis is required to control the hepatitis disease burden and establish the preventive strategies. The aim of this study is to investigate the etiology and clinical characteristics of current acute hepatitis in South Korea.

Method: We prospectively enrolled 214 with acute hepatitis diagnosed by AST >200 IU/L without history of underlying chronic hepatitis. in 12 university hospitals from March 2020 to November 2020. Clinical data as well as a detailed questionnaire survey results on the risk factors for acute hepatitis were collected and entered into the common case report forms. We also collected serum and stool samples from the patients diagnosed non-A, B, C hepatitis, including hepatitis E, toxic and cryptogenic hepatitis.

Results: The causes of acute hepatitis were viral hepatitis (n = 79, 36.9%), toxic hepatitis (n = 71, 33.2%), cryptogenic (n = 53, 24.8%), and autoimmune hepatitis (n = 11, 5.0%). There was only one cryptogenic hepatitis patient who received transplantation, and no patient died. Among the patients with viral hepatitis, hepatitis A virus (HAV) was attributable to 75.9% (n = 60), HBV 2.5% (n = 2), HCV 3.8% (n = 3), HEV 10.8% (n = 7), Epstein-Barr virus (EBV) 7.7% (n = 5), and Cytomegalovirus 2.5% (n = 2). Therefore, HEV was the 2nd most common cause of acute viral hepatitis. Among the patients with toxic

hepatitis, the most common causative substances were oriental medicine (n=26, 36.1%) followed by diet pills (n=7, 9.7%). Interestingly, there were substantial proportion of patients classified as cryptogenic hepatitis. Compared to viral hepatitis group, the cryptogenic group showed significantly lower maximal ALT level (843 vs 2231 U/L, p<0.001), and higher albumin (4.3 vs 3.8 mg/dL, p=0.038) and platelet count (207 vs 85 ×1, 000/mm³, p=0.015), suggesting milder form of hepatitis. However, compared to toxic hepatitis group, the cryptogenic group showed similar characteristics except significantly older age (40.2 vs 53.1 years, p<0.001).

Conclusion: In viral hepatitis, HAV was the most common etiology followed by HEV. The most common causes of toxic hepatitis were oriental medicine and diet pills. Cryptogenic hepatitis were clinically similar to toxic hepatitis, which warrant further study.

PO-2122

Decreased Overall Mortality and Mortality without Liver Transplantation with N-Acetylcysteine in Non-acetaminophen-induced Acute Liver Failure: A Systematic Review and Meta-Analysis

Adrian Alick Bonghanoy¹, John Mark Torres¹, Janus Ong¹, Eric Yasay¹, Jonathan Luzano², Amiel Villanueva². ¹Philippine General Hospital, Division of Gastroenterology, Manila, Philippines; ²Philippine General Hospital, Department of Internal Medicine, Manila, Philippines
Email: adrianalick1987@gmail.com.

Background and aims: To date, there is no established treatment for non-acetaminophen-induced acute liver failure (NAI-ALF) other than liver transplantation. N-acetylcysteine (NAC) is an effective drug for ALF caused by acetaminophen; but its use in NAI-ALF remains uncertain. The study aims to determine the effect and safety of NAC in decreasing mortality among patients with NAI-ALF.

Method: A comprehensive literature search of PubMed, EMBASE, Google Scholar, Cochrane, NEJM, Chinese Biomedicine Database and Science Citation Index Expanded was done. Two reviewers independently selected studies, assessed quality, extracted and pooled outcomes including overall mortality and mortality without liver transplantation (MWO_{LT}). All selected studies have low risk for bias based on Cochrane risk of bias assessment tool.

Results: Four studies in adults and one study in pediatric patients, with a total of 287 patients receiving treatment with NAC and 277 patients in the placebo group, were included in the meta-analysis. No statistical difference was identified between NAC and placebo for overall mortality [OR 0.78 (0.54–1.13), 95% CI; p = 0.19] however, there was a trend showing decreased overall mortality with NAC. In a subgroup analysis excluding the pediatric study, statistical differences were demonstrated between NAC and placebo in overall mortality [OR 0.56 (0.36–0.88), 95% CI; p = 0.01]. In terms of MWO_{LT}, there was a significant difference between NAC and placebo, showing NAC decreasing MWO_{LT}. [OR 0.35 (0.24–0.50), 95% CI; p = <0.00001]. The identified common side effects of NAC include dyspepsia,

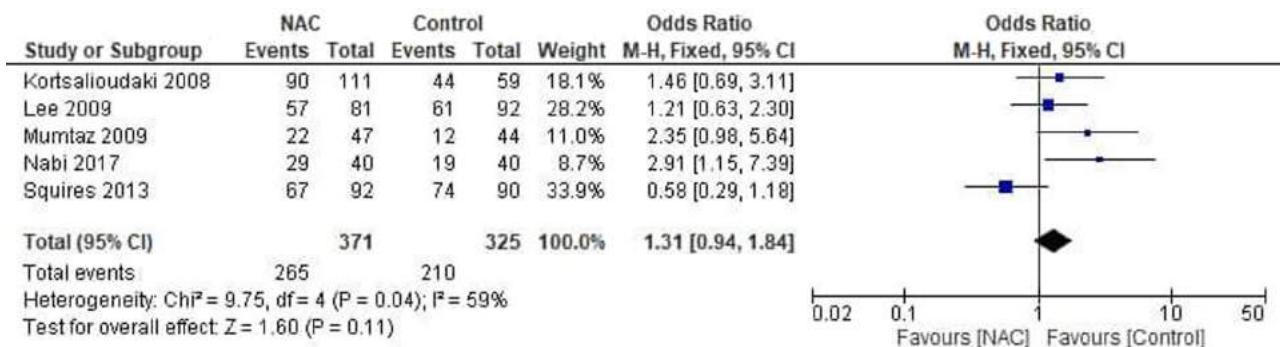


Figure (abstract: PO-2122): Forrest plot on the effect of NAC vs placebo in OVERALL SURVIVAL among adult and pediatric patients

POSTER PRESENTATIONS

vomiting, and rashes. Otherwise, NAC was well-tolerated among patients.

Conclusion: NAC is safe and can decrease overall mortality and MWoLT among adult patients with NAI-ALF.

PO-2178

Low baseline cortisol but not delta cortisol relates to 28-day transplant-free survival in acute liver failure syndromes

Sofia Roth¹, Emilio Flint¹, Lea Ghataore², Vishal C. Patel³, Arjuna Singanayagam^{3,4}, Royce P. Vincent², Evangelos Triantafyllou^{3,4}, Yun Ma³, William Bernal³, Georg Auzinger³, Michael Heneghan³, Mark McPhail³, Charalambos Antoniadis^{3,4}, Mirjam Christ-Crain⁵, David R. Taylor², Julia Wendon³, Christine Bernsmeier^{1,3}. ¹University of Basel and University Centre for Gastrointestinal and Liver Diseases, Department of Biomedicine, Basel, Switzerland; ²King's College Hospital NHS Foundation Trust, Department of Clinical Biochemistry (Viapath), London, United Kingdom; ³King's College London, King's College Hospital, Liver Intensive Therapy Unit and Institute of Liver Studies, London, United Kingdom; ⁴Imperial College London, St. Mary's Hospital, Hepatology Department, London, United Kingdom; ⁵University Hospital Basel, Department of Endocrinology, Diabetes and Metabolism, Basel, Switzerland
Email: sofia.roth@unibas.ch.

Background and aims: Adrenal insufficiency (AI) has been reported in patients with acute liver failure syndromes, yet, its definition, clinical and prognostic significance remains controversial. We sought to determine the diagnostic value of cortisol measurement and the benefit of glucocorticoid (GC) treatment in patients with acute (ALF) and acute-on-chronic liver failure (ACLF).

Method: We studied 28-day transplant-free survival (TFS) in relation to previously described different definitions of AI and GC treatment in patients with ALF (n = 29) and ACLF (n = 34) admitted to Liver Intensive Therapy Unit at King's College Hospital. Admission corticosteroid hormone concentrations at baseline (BL) and following short synacthen test (SST, 250 µg) were assessed by chemoluminescence immunoassay (CLIA) and compared to liquid chromatography-mass spectrometry (LC-MS). Clinicians retrieved cortisol results, yet their decision on GC treatment was independent. In addition, we assessed phenotypic and functional characteristics of circulating monocytes in relation to cortisol concentrations.

Results: In ALF, patients with AI defined by BL cortisol <275 and <450 nmol/L had higher TFS compared to patients without AI. BL cortisol concentrations <399 nmol/L predicted TFS (sensitivity 82%, specificity 60%). GC treatment improved TFS only in patients with AI defined by BL cortisol <450 nmol/L. In ACLF, detection of AI did not affect TFS, yet BL cortisol <392 nmol/L correlated with TFS (sensitivity 80%, specificity 61%). Benefit from GC treatment was observed only in patients with AI defined by BL <275 nmol/L albeit low numbers. In both, ALF and ACLF, TFS did not differ when AI definition was based on delta cortisol using SST results. Low levels of distinct corticosteroids (cortisone, 11-deoxycortisol, androstenedione) measured by LC-MS affirmed an association with TFS. High BL cortisol in ALF and ACLF correlated with low HLA-DR expression on monocytes.

Conclusion: Baseline cortisol levels may serve as a prognostic factor in liver failure patients given values <399 nmol/L indicated TFS. The finding was supported by the correlation of cortisol with low HLA-DR expression on monocytes, previously associated with poor outcome. Furthermore, ALF patients with BL <450 nmol/L and ACLF patients with BL <275 nmol/L benefited from GC treatment suggesting cortisol assessment can be applied for treatment guidance. Conducting an SST was dispensable.

PO-2203

Diagnostic role of liver biopsy in patients with acute liver failure or acute liver injury

Peter Hunyady¹, Eva Herrmann², Jörg Bojunga¹, Mireen Friedrich-Rust¹, Anita Pathil¹, Stefan Zeuzem¹, Ulrike Mihm¹. ¹University Hospital Frankfurt, Department of Internal Medicine 1, Frankfurt am Main, Germany; ²Goethe-University, Institute of Biostatistics and Mathematical Modelling, Frankfurt am Main, Germany
Email: mihm@med.uni-frankfurt.de.

Background and aims: Severe acute liver injury (ALI) is characterized by jaundice, coagulopathy and elevation of transaminases in patients without underlying liver disease. If complicated by hepatic encephalopathy, the criteria for acute liver failure (ALF) are fulfilled. To determine the etiology of the ALF or ALI in a patient, liver biopsy may be considered. The present study evaluated how often liver biopsy results affected clinical management in patients with ALF or ALI.

Method: All patients with ALF or ALI who had undergone liver biopsy from January 2010 to May 2020 at University Hospital Frankfurt, Germany, were enrolled. Patients were identified by electronic search

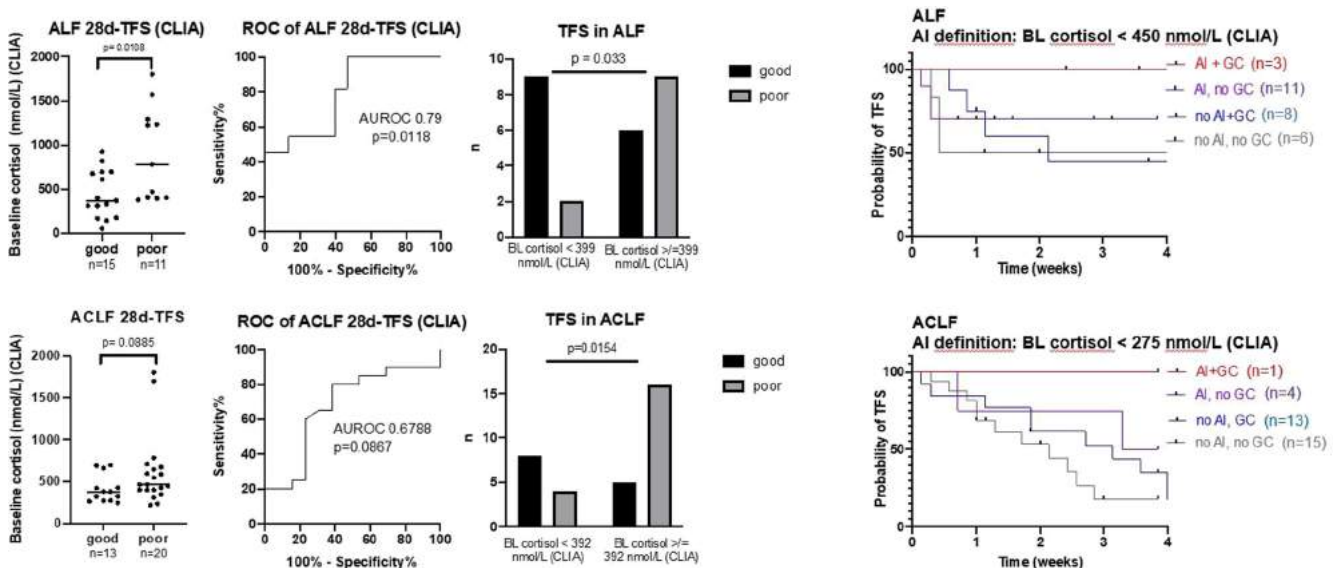


Figure: (abstract: PO-2178)

of the institution's patient database. Data were collected retrospectively of the initial event of ALF/ALI and also of follow-up visits in the institution's outpatient clinic.

Results: 66 patients with liver biopsy during ALF/ALI were identified. In 47/66 patients (71%) liver biopsy results did not affect clinical management. In 15/66 patients liver biopsy allowed for investigation of liver involvement by a pre-existing extrahepatic chronic disease (2 patients with AIDS and disseminated tuberculosis; 13 patients with a known hematologic malignancy). In 4/66 patients (6%) the suspected diagnosis was confirmed by the histopathological findings (2 patients with drug-induced liver injury (DILI), 2 patients with autoimmune hepatitis (AIH)).

Postprocedural bleeding occurred in 1/13 patients with a transjugular and in 1/53 patients with a percutaneous liver biopsy. During follow-up in the institution's outpatient clinic, the initial diagnosis was revised in 5 patients, mainly taking into account patient development after corticosteroid withdrawal. So, finally 14 patients were diagnosed with AIH and 33 patients with DILI. In only 2 patients of each group, the initial histopathology had been conclusive for AIH (2/14) or DILI (2/33), respectively.

During ALF/ALI IgG levels were significantly higher in patients with AIH than with DILI (2238 ± 809 mg/dl vs. 1096 ± 264 mg/dl, $p < 0,00001$). An IgG cut-off-value of 1550 mg/dl was able to distinguish between AIH and DILI with a sensitivity of 92, 9% and specificity of 100% in the study cohort.

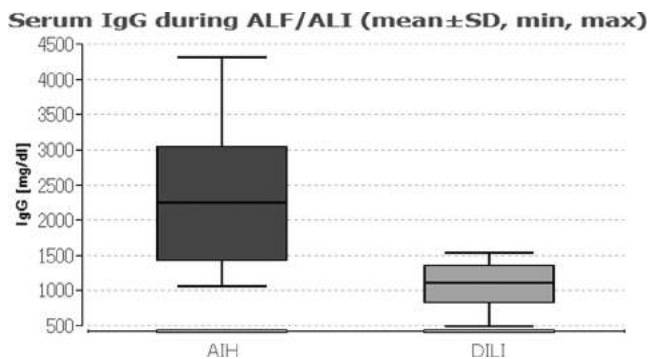


Figure:

Conclusion: In the present study liver biopsy results did not affect clinical management in the majority of patients with ALF or ALI. Serum IgG levels during ALF/ALI discriminated well between AIH and DILI.

PO-2888

New insights in CCl4 induced acute liver injury in the presence and absence of Ripk1

Huma Hameed^{1,2,3}, Muhammad Farooq^{1,2,3},
 Melanie Simoeseugenio^{1,2,3}, Marie-therese Biotrel^{1,2,3},
 Claire Piquet Pellorce^{1,2,3}, Jacques Le-seyec^{1,2,3}, Michel Samson^{1,2,3}.
¹University of Rennes 1, Rennes, France; ²IRSET, Rennes, France; ³Inserm, Paris, France
 Email: michel.samson@univ-rennes1.fr.

Background and aims: Liver disease is one of the global health problems, in particular, acute liver injury is associated with high mortality rates. The pathogenesis of acute liver injury is known to involve a complex interplay of oxidative stress, apoptosis, autophagy, and necrosis. Carbon tetrachloride (CCl₄)-induced acute liver injury in mice is a classic experimental model sharing some similarities with human acute liver pathogenesis. Our team and others have shown that RIPK1 is a kinase that is involved in both cell survival and cell death pathways in certain cases of acute hepatitis involving molecular death factors. In the present study, we aim to investigate its role during hepatocyte death induced by a specific hepatotoxic agent, CCl₄.

Method: Two different mouse lines, either deficient (1) for *Ripk1* specifically in liver parenchymal cells (*Ripk1*^{LPC-KO}) or (2) for the kinase activity of RIPK1 (*Ripk1*^{K45A}) plus their respective wild-type littermates (*Ripk1*^{fl/fl}, *Ripk1*^{WT}) were exposed to a high dose of CCl₄ that induce severe acute hepatitis. Further, Etanercept (TNF- α receptor decoy) was injected prior and after CCl₄ administration to explore the role of TNF- α and anti-FasL antibody (FasL antagonist) were injected prior CCl₄ administration to explore the respective role of FasL in CCl₄ induced hepatitis. Different clinico-pathological investigations (liver transaminase measurement, liver histology, cleaved-caspase 3 staining, anti-CD45 IHC, qPCR analysis) were conducted to analyse the challenged animals.

Results: While inactivation of the RIPK1 kinase activity had no impact on CCl₄ induced hepatotoxicity, its deficiency in liver parenchymal cells potentiated CCl₄ induced hepatotoxicity by massive apoptosis. More oxidative stress and immune infiltration were found in the liver of CCl₄-injected *Ripk1*^{LPC-KO} mice compared to *Ripk1*^{fl/fl} mice. Administration of ETA further increased liver damage by apoptosis only in *Ripk1*^{LPC-KO} mice. Interestingly; FasL mRNA was only upregulated in CCl₄-injected *Ripk1*^{LPC-KO} mice and over-induced in presence of ETA. Thus, pre-administration of anti-FasL antibody partly reduced liver injury in *Ripk1*^{LPC-KO} mice. Notably, the anti-FasL antibody pretreatment had an opposite impact on CCl₄-injected *Ripk1*^{fl/fl} mice, which displayed more liver damage. We hypothesized that, in this last experimental condition, anti-FasL partly prevented the described protective property of soluble FasL against apoptosis.

Conclusion: Our study highlighted the protective role of RIPK1 in CCl₄ induced acute liver injury which prevent hepatocytes from death by apoptosis independent of TNF- α . The enhanced hepatic immune cell infiltration, oxidative stress and FasL expression detected in the absence of *Ripk1* promoted apoptosis of hepatocytes. Overall, this study provides a deeper understanding of mechanisms that could occur during acute liver hepatitis.

Alcoholic liver disease

PO-48

Alcohol-related liver disease phenotype impacts survival after an acute variceal bleeding episode

Ares Villagrasa¹, Virginia Hernandez-Gea^{2,3},
 Meritxell Ventura-Cots^{1,4}, Ramon Bataller⁵, Alvaro Giraldez-Gallego⁶,
 Bogdan Procopet⁷, Lucio Amitrano⁸, Candid Villanueva^{3,9},
 Dominique Thabut¹⁰, Luis Ibañez^{3,11}, Gilberto Silva-Junior²,
 Agustin Albillos^{3,12}, Christophe Bureau¹³, Trebicka Jone^{14,15,16,17},
 Elba Llop^{3,18}, Wim Laleman¹⁹, Jose María Palazon²⁰,
 José Castellote Alonso²¹, Susana G. Rodrigues²², Lise Lotte Gluud²³,
 Carlos Noronha Ferreira²⁴, Nuria Cañete²⁵,
 Prof. Dr. Manuel Rodríguez²⁶, Arnulf Ferlitsch²⁷, Jose Luis Mundi²⁸,
 Henning Grønbaek²⁹, Manuel Hernandez-Guerra³⁰,
 Romano Sassatelli³¹, Alessandra Dell'Era³², Marco Senzolo³³,
 Juan Abraldes³⁴, Manuel Romero Gomez³⁵, Alexander Zipprich³⁶,
 Meritxell Casas³⁷, Helena Masnou³⁸, Massimo Primignani³⁹,
 Aleksander Krag⁴⁰, Marcel Tantau⁴¹, Guardascione Maria⁸,
 Edilmar Alvarado^{3,9}, Marika Rudler⁴², Rafael Bañares^{3,43},
 Javier Martinez¹², Marie-Angèle Robic¹³, Christian Jansen⁴⁴,
 José Luis Calleja Panero^{3,45}, Frederik Nevens¹⁹, Jaime Bosch^{2,3,46},
 Juan Carlos Garcia Pagan^{2,4}, Joan Genesca^{1,4}. ¹Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Liver Unit, Barcelona, Spain; ²Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, IMDIM, Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Barcelona, Spain; ³Instituto Carlos III, Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas, CIBEREHD, Madrid, Spain;

POSTER PRESENTATIONS

⁴Instituto Carlos III, Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas, CIBEREHD, Barcelona, Spain; ⁵Pittsburgh Liver Research Center, University of Pittsburgh, Center for Liver Diseases, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Pittsburgh, United States; ⁶University Hospital Virgen del Rocío, Clinical Management Unit of Digestive Diseases, Seville, Spain; ⁷University of Medicine and Pharmacy, 3rd Medical Clinic, Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Hepatology Department and "Iuliu Hatieganu", Cluj-Napoca, Romania; ⁸Ospedale A Cardarelli, Gastroenterology Unit, Naples, Italy; ⁹Hospital of Santa Creu and Sant Pau, Autonomous University of Barcelona, Hospital Sant Pau Biomedical Research Institute (IIB Sant Pau), Department of Gastroenterology, Barcelona, Spain; ¹⁰Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France; ¹¹Hospital Universitario Gregorio Marañón. IISGM, Servicio de Medicina de Aparato Digestivo Gregorio Marañón, Madrid, Spain; ¹²Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá, Department of Gastroenterology, Madrid, Spain; ¹³Purpan Hospital, CHU Toulouse, France; INSERM U858, University of Toulouse, Department of Hepato-Gastroenterology, Toulouse, France; ¹⁴University of Bonn, Department of Internal Medicina I, Bonn, Germany; ¹⁵European Foundation for the Study of Chronic Liver Failure (EF-Clif), Barcelona, Spain; ¹⁶Institute for Bioengineering of Catalonia, Barcelona, Spain; ¹⁷Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; ¹⁸Hospital Universitario Puerta de Hierro, Universidad Autónoma de Madrid, Liver Unit, Madrid, Spain; ¹⁹University of Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium; ²⁰Hospital General Universitario de Alicante, Alicante, Spain; ²¹Hospital Universitari de Bellvitge, IDIBELL, Universitat de Barcelona, Gastroenterology Department, Hepatology Unit, Barcelona, Spain; ²²Centro Hospitalar Sao Joao, Gastroenterology and Hepatology Department, Porto, Portugal; ²³University Hospital of Hvidovre. Faculty of Health and Medical Sciences, University of Copenhagen, Gastronit, Medical Division, Copenhagen, Denmark; ²⁴Hospital de Santa Maria-Centro Hospitalar, Serviço de Gastreenterologia e Hepatologia, Lisboa Norte, Portugal; ²⁵Hospital del Mar, Universitat Autònoma de Barcelona, IMIM (Hospital del Mar Medical Research Institute), Liver Section, Gastroenterology Department, Barcelona, Spain; ²⁶Hospital Central de Asturias, Department of Gastroenterology, Oviedo, Spain; ²⁷Medical University of Vienna, Department of Internal Medicina III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²⁸University Hospital San Cecilio, Department of Gastroenterology, Granada, Spain; ²⁹Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; ³⁰University Hospital of the Canary Islands, Gastroenterology Department, La Laguna, Tenerife, Spain; ³¹Arcispedale Santa Maria Nuova-IRCCS, Unit of Gastroenterology and Digestive Endoscopy, Reggio Emilia, Italy; ³²University of the Studies of Milan, Gastroenterology Unit, ASST Fatebenefratelli Sacco, Department of Clinical and Biomedical Sciences, Milan, Italy; ³³University Hospital of Padua, Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; ³⁴University of Alberta, Cirrhosis Care Clinic, Division of Gastroenterology (Liver Unit), CEGIIR, Edmonton, Canada; ³⁵UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Sevilla, Spain; ³⁶Martin Luther University Halle-Wittenberg, First Department of Internal Medicine, Halle (Saale), Germany; ³⁷Parc Taulí University Hospital, Institut d'Investigació i Innovació Parc Taulí I3PT, Autonomous University of Barcelona, Liver Unit, Gastroenterology Department, Sabadell, Spain; ³⁸Hospital Universitari Germans Trias i Pujol, Universitat Autònoma Barcelona, Badalona, Spain; ³⁹IRCCS Ca' Granda Maggiore Hospital Foundation, University of Milan, Division of Gastroenterology and Hepatology, Milan, Italy; ⁴⁰Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; ⁴¹University of Medicine and Pharmacy, 3rd Medical Clinic, Regional Institute of Gastroenterology and Hepatology "Octavian Fodor," Hepatology Department and "Iuliu Hatieganu," Cluj-Napoca, Romania; ⁴²Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France;

⁴³Hospital General Universitario Gregorio Marañón. IISGM, Servicio de Medicina de Aparato Digestivo Gregorio Marañón, Madrid, Spain; ⁴⁴Institute for Bioengineering of Catalonia, Barcelona, Spain; ⁴⁵Hospital U. Puerta de Hierro. Universidad Autónoma de Madrid, Liver Unit, Madrid, Spain; ⁴⁶Inselspital, Bern University, CH, Department of Biomedical Research, Bern, Switzerland
Email: jgenesca@vhebron.net.

Background and aims: Alcoholic hepatitis (AH) is a distinct clinical entity characterized by a recent onset of jaundice in the context of heavy alcohol use. We aimed to assess the prevalence of AH in patients admitted for acute variceal bleeding (AVB) and to compare clinical outcomes and survival of AH patients with patients with alcohol-related liver disease (ALD) and viral cirrhosis.

Method: Ancillary study of the preemptive TIPS cohort, a multicenter, observational study with data from 2138 consecutive patients with cirrhosis and AVB collected from October 2011 to May 2015. 916 patients were selected under the next categories regardless of whether they received or not a p-TIPS: patients with AH clinical criteria (as defined by NIAAA guidelines), ALD cirrhosis actively drinking at the time of AVB (d-ALD) (n = 285), ALD cirrhosis abstinent from alcohol (a-ALD) (n = 227) and viral cirrhosis (n = 305). Main exclusions were related to other or mixed etiologies, and incomplete data. Survival was assessed by the Kaplan-Meier method and log-rank Mantel-Cox test and subanalysis according to CLIF-C AD (acute decompensation score of the CLIF Consortium) was performed.

Results: AH patients accounted for 10.8% of the 916 patients included in the study and 16% of the 611 ALD patients. AH patients were younger, had worse prognostic severity scores, and the highest frequency of infections and active bleeding at baseline. The best survival rates were seen in the d-ALD group at all time points (Figure). AH and a-ALD patients presented the lowest survival rates at 42 and 90 days after AVB. A-ALD patients exhibited the worse survival rate at 1 year (65.5%-Figure). Among patients with a CLIF-C AD > 55 the worst survival was observed in the a-ALD group across all time points, while patients from the d-ALD group presented the best survival rates. When focused on patients with CLIF-C AD < or = 55 those with AH exhibited the worst outcomes at any time point.

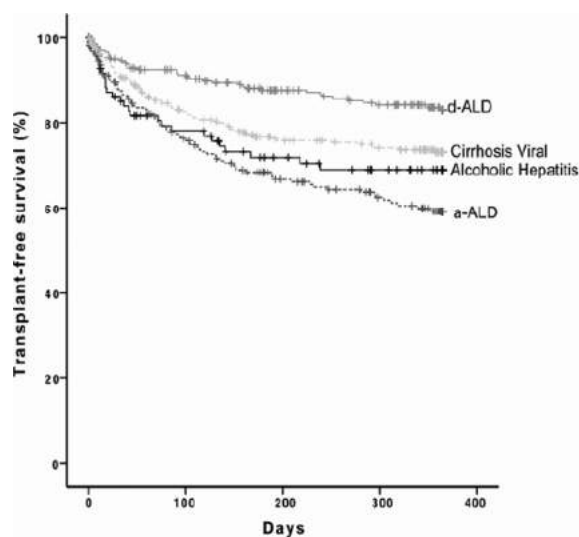


Figure. Transplant-free survival was 83.8%, 93.3%, 86.3% and 90.4% among AH, ALD cirrhosis active drinkers, ALD cirrhosis abstinent and viral cirrhosis groups at 42 days. At 90 days transplant free-survival was 79.8%, 93%, 79.6% and 84.8% again with statistical significant differences only between AH and ALD active drinkers groups. At 365 days transplant free-survival was 72.7%, 86%, 65.5% and 76.6%. At all time points statistical significant differences were found between d-ALD and the other groups.

Alcohol-related liver disease, ALD; ALD cirrhosis actively drinking, d-ALD; ALD cirrhosis abstinent from alcohol, a-ALD

Figure:

Conclusion: The underlying etiology and ALD phenotype have an impact on survival after an AVB. AH patients present the worst short-term outcome, while abstinent ALD patients had the worst long-term survival.

PO-94

Automated quantitation of histological features could predict mortality in patients with severe alcoholic hepatitis

Luke D. Tyson^{1,2}, Roberta Forlano¹, Edagul Ulucay¹, Nikhil Vergis^{1,2}, Nikolaos Giannakeas³, Alexandros Tzallas³, Mark Thursz^{1,2}, Robert Goldin^{1,2}, Stephen Atkinson¹, Pinelopi Manousou^{1,2}. ¹Imperial College London, Department of Metabolism, Digestion and Reproduction, London, United Kingdom; ²Imperial College Healthcare NHS Trust, Department of Hepatology, London, United Kingdom; ³Technological Educational Institute of Epirus, Άρτα, Greece
Email: luke.tyson@nhs.net.

Background and aims: Alcoholic hepatitis (AH) is characterised by acute jaundice and liver dysfunction in patients misusing alcohol. A liver biopsy demonstrating steatohepatitis is often considered necessary for a definitive diagnosis. Presently, biopsies are interpreted according to the Alcoholic Hepatitis Histologic Score (AHHS), which is designed to predict 90-day mortality. As a semi-quantitative score, AHHS carries low reproducibility, even between expert pathologists. The lack of reliability of such scores may affect the power of clinical trials. We have developed a high-throughput machine learning based quantitation of histological features in non-alcoholic fatty liver disease. This methodology estimates the percentage of fat, inflammation, ballooning and fibrosis with higher intra- and interobserver variability than conventional histological assessment. As these histological features are also seen in AH, we applied the same method to liver biopsies from patients with AH aiming to identify features predictive of mortality.

Method: Biopsies obtained from 80 patients with severe AH recruited to STOPAH (STeroids Or Pentoxifyline for Alcoholic Hepatitis) were digitalized. Biopsies were obtained between 15 days pre- to 7 days post-treatment. Fat proportionate area (FPA), inflammation percentage (IP), ballooning percentage (BP) and collagen proportionate area (CPA) were expressed as percentage of the whole tissue area. Quantitation results were evaluated against clinical outcomes including mortality by binary logistic regression and Kaplan-Meier survival analysis.

Results: IP was inversely associated with mortality at day 90 (OR 0.91, 95% CI 0.84–1.00, p = 0.050). FPA, BP and CPA were not. However, when IP was corrected for CPA (IP/CPA) the association with mortality became stronger (OR 0.01, 95% CI: 0.00–0.48, p = 0.019) than IP alone. Treatment with prednisolone did not affect survival nor IP. Neither the AHHS score, nor the individual components of the score, were predictive of mortality. Youden's index analysis revealed that an IP cut-off of 10% allowed patients to be classified into low-risk (IP > 10%) and high-risk groups (figure, p = 0.017).

Conclusion: In severe AH increased inflammation on liver biopsy may be associated with improved survival at day 90, particularly for patients with less fibrosis. This association was not observed for the AHHS score. Quantitation may improve prediction of clinical outcomes in patients with AH.

PO-117

Sulfated Steroids and Bile Acids and Dopamine Metabolites are Associated with Favorable Outcomes after Fecal Transplant in Alcohol Use Disorder

Jasmohan S. Bajaj¹, Phillip Hylemon¹, Andrew Fagan¹, Genta Kakiyama¹, William Pandak¹, Masoumeh Sikaroodi², Huiqing Zhou², Patrick Gillevet². ¹Virginia Commonwealth University and Richmond VAMC, United States; ²George Mason University, Manassas, United States
Email: jasmohan.bajaj@vcuhealth.org.

Background and aims: AUD pts have altered gut microbiota that worsens in cirrhosis. In a RCT, fecal microbial transplant (FMT) improved craving and cognitive function compared to placebo in cirrhotic AUD pts. AUD cirrhotic pts have higher toxic BAs and men show feminization. Sulfation is a key step towards detoxification of bile acids (BA) and can inactivate sex steroids, which are modulated by the gut-liver axis. which can worsen outcomes. *Aim:* Define metabolomic correlates of improvement in outcomes with FMT vs placebo in cirrhotic pts with AUD.

Method: Cirrhotic men with AUD underwent Phase 1 RCT with FMT vs placebo with f/u for 15 days (Fig A). Safety evaluation, alcohol craving (ACQ) and consumption (Etg), plasma and feces collection were performed at baseline and day 15 for both groups. Metabolomics for aromatic amino acid (AA, putative neurotransmitters and intestinal barrier affecting metabolites), lipidomics,

Kaplan-Meier survival curves for patients with severe alcoholic hepatitis classified as low or high risk based on their inflammation percentage computed using an automated machine-learning based algorithm

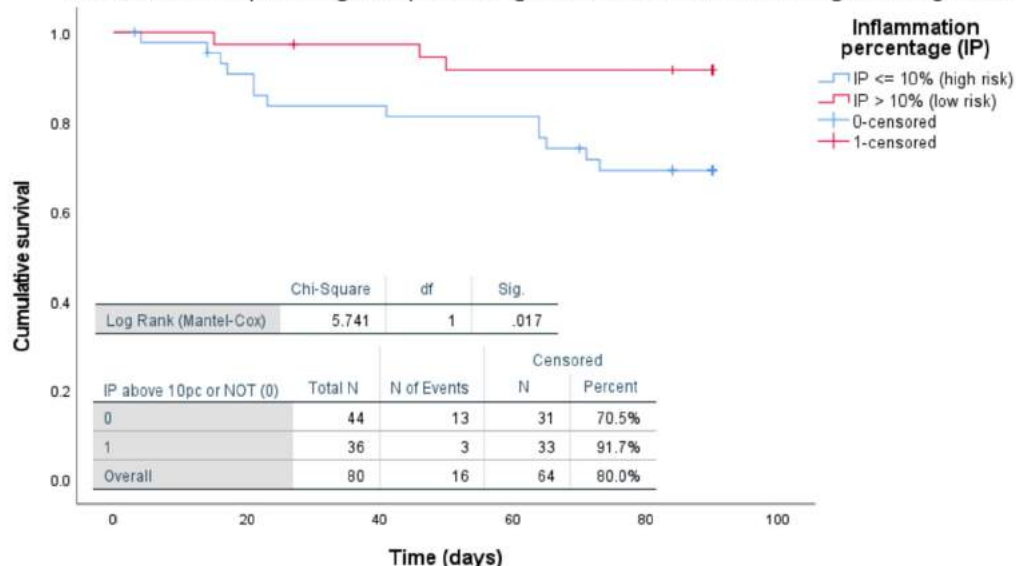


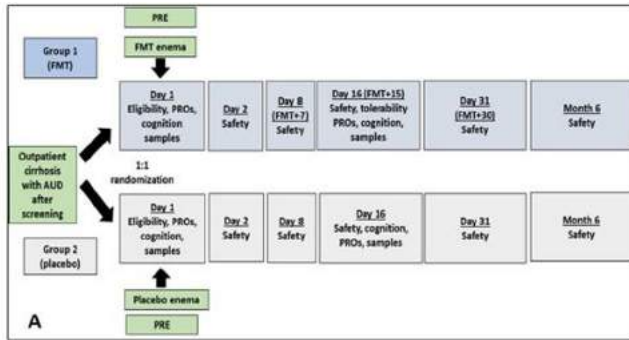
Figure: (abstract: PO-94)

POSTER PRESENTATIONS

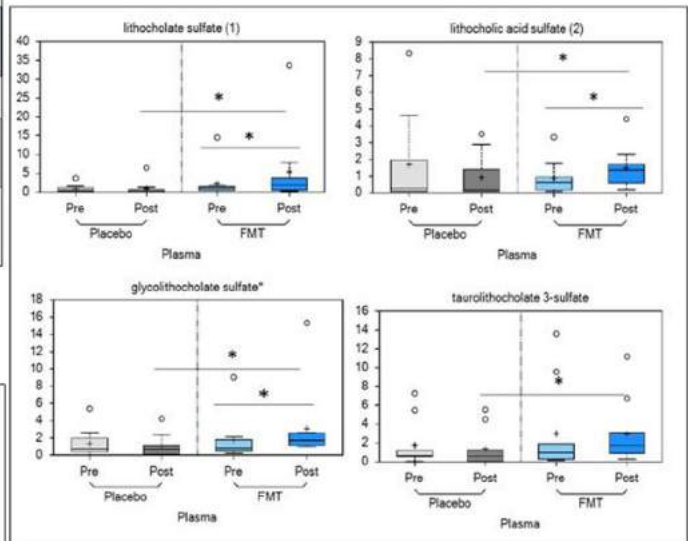
including BAs were performed and fold-change in ANOVA values pre/post-FMT and post-placebo vs post-FMT states were performed.

Results: Trial: 20 men with AUD-cirrhosis [65 ± 6.4 years, MELD 8.9 ± 2.7] were included. Groups were comparable with respect to demographics, cirrhosis, and AUD severity at baseline. Liver function and safety labs were stable over time. Craving reduced significantly in 90% of FMT-assigned versus 30% in placebo (p = 0.02). This was

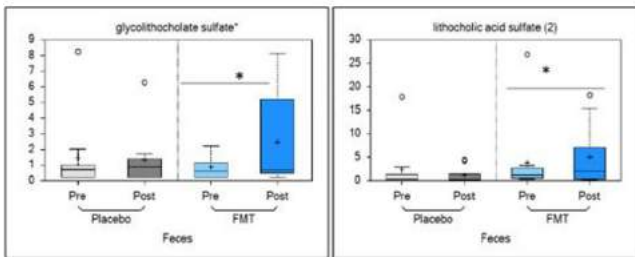
accompanied by ↓ urinary Etg (p = 0.03) and improved intestinal barrier (↓LBP and IL-6). These were not seen in the placebo pts. **Metabolomics:** Unsulfated BAs: no changes were seen in plasma/feces. **Sulfated BAs:** Plasma ↑ litho and glycolithocholate sulfate moieties post-FMT vs pre-FMT and vs post-placebo. Also, we found ↑ plasma sulfated glycocholate and glycoUDCA increased only post-FMT vs pre-FMT and ↑ deoxy-cholate 12-sulfate and tauroolithocholate



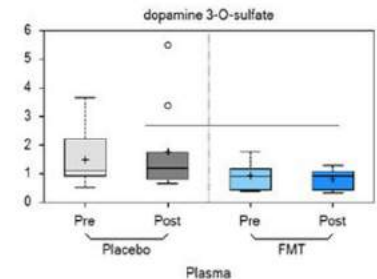
B. Plasma Sulfated Lithocholate Moieties ↑ Post-FMT



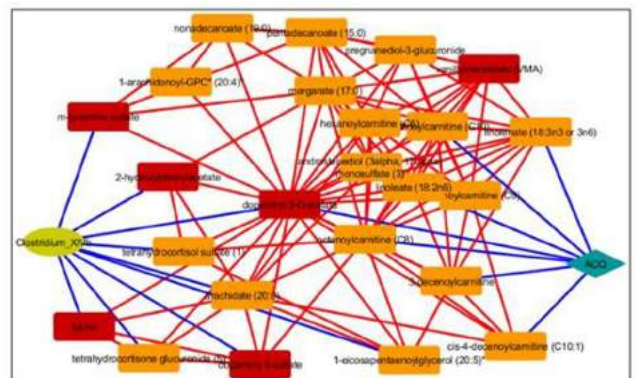
C. Fecal Sulfated Lithocholate Moieties ↑ Post-FMT



E. Plasma Dopamine Sulfate ↓ post-FMT



F. Plasma Dopamine Sulfate negatively linked to ACQ & positive with beneficial bacteria & sex steroids post-FMT



D. Plasma Sulfated Progesterone hormones Increase post-FMT Vs Baseline

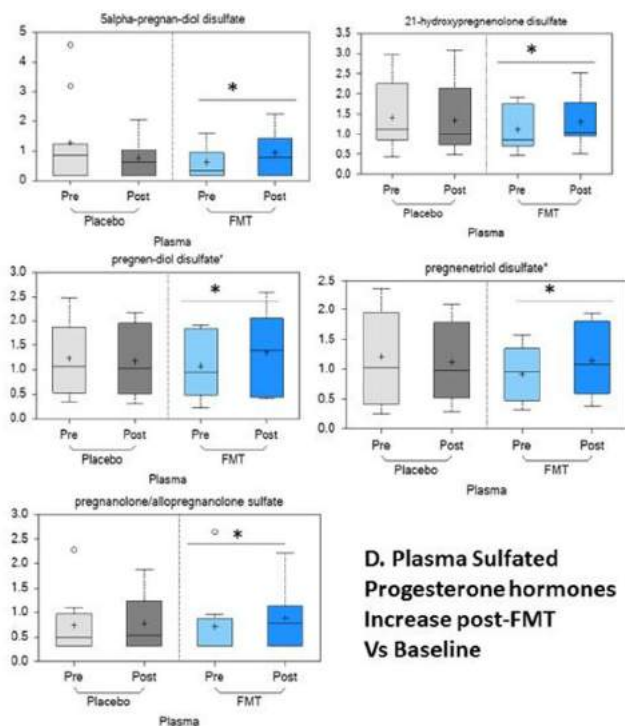


Figure: (abstract: PO-117)

3-sulfate post-FMT vs placebo (Fig. B). Feces ↑sulfated lithocholate moieties post-FMT (Fig. C). **Sex steroids:** In plasma, vs pre-FMT, we found ↑fold change of sulfated progesterone precursors (Figure D), which makes them inactive. No changes in feces were seen. **Lysophospholipids:** Only in plasma we found ↑ lysophospholipids, which are useful for membrane integrity post-FMT vs baseline. **Aromatic AA metabolites:** Plasma dopamine 3-O-sulfate, a neurotransmitter involved in alcohol craving, reduced post-FMT vs placebo (Fig E). Dopamine sulfate also negatively correlated with Post-FMT ACQ indicating the linkage with craving and with beneficial Clostridia post-FMT (Figure F).

Conclusion: FMT in AUD men with cirrhosis increases sulfation of toxic secondary BAs, and of progesterone steroids (reducing activity and thus, feminization), increases lysophospholipids that indicating membrane stability, and reduces dopamine, which links with craving and beneficial bacteria. Therefore, there is a multi-faceted effect on the gut-liver-brain axis with FMT in men with cirrhosis and AUD.

**PO-302
Pharmacokinetics, Pharmacodynamics, and toxicology of SZN-043, a hepatocyte-targeted Wnt potentiator, in nonhuman primates**

Jay Tibbitts¹, Maureen Newman², Jay Ye², Peter Stathis², Trudy Vanhove². ¹Surrozen, South San Francisco, United States; ²Surrozen, South San Francisco, United States
Email: jtibbitts@surrozen.com.

Background and aims: Wnt/β-catenin signaling plays an important role in liver homeostasis and is critical to hepatocyte regeneration following liver injury. In severe liver diseases, there is a deficiency of functional hepatocytes and, in chronic patients, often underlying fibrosis caused by activated hepatic stellate cells. Therefore, a hepatocyte-specific molecule that enhances Wnt signaling specifically in hepatocytes, but not in stellate cells, would be desired. SZN-043 is an RSPO-mimetic bispecific fusion protein specifically targeted to hepatocytes through binding to the Asialoglycoprotein Receptor (ASGR1). In preclinical animal models of liver injury and fibrosis, SZN-043 has been shown to amplify Wnt signaling, promote hepatocyte proliferation, demonstrate functional improvement and reduce fibrosis.

Method: To inform the potential clinical use of SZN-043, toxicology and pharmacokinetic studies were conducted in non-human primates (NHPs). In a dose-range finding toxicology study in cynomolgus monkeys, SZN-043 was administered intravenously twice weekly at 0, 12.5, 37.5 and 125 mg/kg/dose for two weeks. Main study animals were terminated one day after the last dose and a subgroup of animals were followed for recovery. Assessments included clinical observations, clinical pathology, pharmacodynamics, toxicokinetics, and gross and histopathology. The pharmacokinetics and pharmacodynamics of SZN-043 in NHP were evaluated following a single IV bolus dose of 0.5, 2, or 5 mg/kg or two doses of 12.5 mg/kg separated by 3 days. Serum concentrations of SZN-043 and a biomarker for ASGR1 occupancy (serum alkaline phosphatase, ALP) were measured for up to 25 days using qualified assays following initiation of dosing, and noncompartmental pharmacokinetic parameters calculated.

Results: Administration of SZN-043 to NHPs was well-tolerated with no drug-related adverse effects observed, including histopathology. Dose-related increases in ALP due to reduced clearance by ASGR1 were observed, but were expected and not considered adverse. Drug exposure and pharmacodynamic effect were confirmed, with full occupancy of ASGR1 observed. The PK of SZN-043 in NHP was consistent with an IgG-like molecule with evidence of target-mediated drug disposition, whereby exposure increased more than proportional to dose, providing further evidence of occupancy of ASGR1.

Conclusion: The data from these studies indicate that SZN-043 can be safely administered to NHPs, with PK suitable for use in humans, and support further investigation of this molecule in settings of

severe hepatocyte loss where SZN-043 may have a rapid impact on hepatocyte regeneration, as well as in cirrhosis.

**PO-345
Alcoholic foamy degeneration: a singular clinical entity that mimics alcoholic hepatitis and may be distinguished by serum triglyceride levels**

Jordi Gratacós-Gines¹, Emma Avitabile², Martina Perez^{1,2}, Alba Díaz^{2,3,4}, Marta Cervera^{1,2}, Marta Carol², Ana Belén Rubio², Núria Fabrellas^{2,4}, Octavi Bassegoda¹, Laura Napoleone^{1,2}, Ann Ma², Adria Juanola^{1,2}, Isabel Graupera^{1,2,4}, Elisa Pose^{1,2,4}, Pere Ginès^{1,2,4}. ¹Hospital Clínic de Barcelona, Liver Unit, Barcelona, Spain; ²Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ³Hospital Clínic de Barcelona, Pathology, Barcelona, Spain; ⁴University of Barcelona, Barcelona, Spain
Email: EPOSE@clinic.cat.

Background and aims: alcoholic foamy degeneration (AFD) is a variant of alcohol related liver disease (ArLD) with a similar clinical presentation than alcoholic hepatitis (AH) but with a specific histological pattern and a dramatically different treatment and prognosis. Since AFD was described in 1983, only case reports or short series have been reported. The aim of the study was to assess the real prevalence of this disease, its natural history and long-term prognosis.

Method: retrospective study that reviewed all cases of clinical suspicion of AH in the last 11 years (2010–2020) in Hospital Clínic of Barcelona, and the results of the liver biopsies performed. Liver biopsies were analyzed for the presence of histological criteria of AH, AFD or others (cirrhosis, steatosis, etc.). Patients were characterized at a clinical, histological and prognostic level. Patients with AFD were compared with a control group of 90 patients with diagnosis of AH confirmed by histology. Clinical criteria of AH from the NIAAA were reviewed.

Results: of 271 cases of clinical suspicion of AH, 201 (74%) underwent liver biopsy. Of those, 164 (82%) met histological criteria for alcoholic steatohepatitis, 20 (10%) had AFD and 15 (8%) had other findings. Thirteen patients with AFD had portal hypertension and 5 had ascites at diagnosis. Median MELD score at diagnosis was 17 (11–20). The ratio of patients who met clinical NIAAA criteria for AH was similar in the AFD vs HA group (59 vs 63%, p = ns). Patients with AFD presented higher levels of transaminases, cholesterol and triglycerides. Triglyceride levels of 162 mg/dL had an AUROC of 0.88 (0.80–0.96) to differentiate AFD from AH. All patients with AFD had a rapid and spontaneous improvement of liver function from admission, with a median MELD of 9 (8–11) at hospital discharge. In the long-term, 1 (5%) patient died in the AFD group compared to 34 (38%) patients in the AH group (p = 0.02).

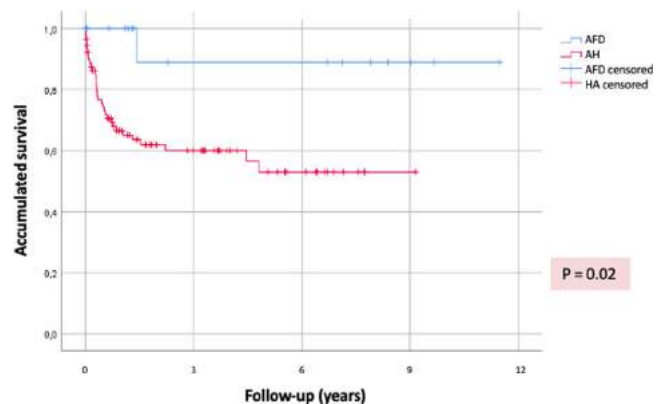


Figure:

Conclusion: one out of ten patients with clinical suspicion of AH has AFD. AFD is a little-known entity that is frequently misdiagnosed as

POSTER PRESENTATIONS

AH when liver biopsy is not performed. Moreover, NIAAA criteria, widely used for clinical diagnosis of AH, are not useful to differentiate AFD from AH. Differential diagnosis is relevant because AFD prognosis is markedly better. Although definitive diagnosis is based on histology, high levels of triglycerides should raise suspicion of AFD.

PO-433

Drivers of outcome in compensated alcohol-related cirrhosis: a prospective study

Alexandre Louvet¹, Cendrine Chaffaut², Jérôme Gournay³, Frédéric Oberti⁴, Laure Elkrief⁵, Thong Dao⁶, Christophe Moreno⁷, Jean-Charles Duclos-Vallée⁸, Dominique Roulot⁹, Romain Moirand¹⁰, Eric Nguyen Khac¹¹, Sylvie Chevret², Nathalie Ganne-Carrié⁹. ¹Hôpital Huriez, Lille, France; ²SBIM Hôpital Saint-Louis, Paris, France; ³CHU de Nantes, Nantes, France; ⁴CHU d'Angers, Angers, France; ⁵CHU de Tours, Tours, France; ⁶CHU de Caen, Caen, France; ⁷Hôpital Erasme, Brussels, Belgium; ⁸Hôpital Paul-Brousse, Villejuif, France; ⁹Hôpital Avicenne, Bobigny, France; ¹⁰CHU de Rennes, Rennes, France; ¹¹CHU d'Amiens, Amiens, France

Email: alexandre.louvet@chru-lille.fr.

Background and aims: The deleterious impact of heavy alcohol relapse is established in patients with alcohol-related cirrhosis despite a limited body of evidence based on old studies. However, drivers of long-term outcome are still poorly investigated.

Method: All patients with biopsy-proven compensated alcohol-related cirrhosis who were included in the CIRRAL cohort (Ganne-Carrié et al. *J Hepatol* 2018) were evaluated prospectively. Primary end point was 5-year survival. Prognostic variables of survival and event-free survival were assessed using Cox models with stepwise selection on AIC criteria. The prognostic impact of alcohol relapse during follow-up was assessed using a time-dependent covariable. Liver events were defined as transplantation (LT), decompensation (ascites, gastrointestinal bleeding or encephalopathy) or hepatocellular carcinoma (HCC).

Results: From 2010 to 2016, 650 patients with compensated alcohol-related cirrhosis were included in 22 centers. At baseline, main characteristics were the following (medians with IQR or percentage): age 58.4 (51.2–64.3) years, male gender 67.4%, BMI 27.5 kg/m², Child-Pugh score A 98.3%, past history of liver decompensation 65.3%, alcohol cessation at inclusion 69.2%. At 5 years, cumulative incidence of any alcohol relapse was 51.4%. We observed 153 deaths during the follow-up, among which 41.8% were related to cirrhosis and 11.8% to hepatocellular carcinoma and 5-year survival was 74.6%. Multivariate analysis identified the following factors at baseline as independently associated with survival: platelet count HR 0.996 (0.993–0.998, $p = 0.002$) and Child-Pugh score >5 HR 2.189 (1.529–3.133, $p < 0.001$) while there was a trend toward significance for age, male gender, coffee consumption and low alcohol consumption at baseline. The following variables at baseline were associated with event-free survival: age HR 1.017 (1.002–1.033, $p = 0.02$), male gender HR 1.413 (1.051–1.901, $p = 0.02$), coffee consumption HR 0.632 (0.464–0.86, $p = 0.004$), platelet count HR 0.995 (0.993–0.998, $p < 0.001$), Child-Pugh score >5 HR 1.941 (1.409–2.673, $p < 0.001$), low alcohol consumption at baseline (1–6 units/week) HR 1.612 (1.132–2.294, $p = 0.008$); alcohol consumption at baseline ≥ 7 units/week HR 1.372 (0.962–1.956, $p = 0.08$) was close to significance. Alcohol consumption during the follow-up, regardless of the amount, was associated with a lower survival (HR 1.55, 95%CI 1.12–2.15, $p = 0.0009$) and a lower event-free survival (HR 1.67, 95%CI 1.27–2.24, $p = 0.0003$).

Conclusion: This prospective study performed in patients with compensated alcohol-related cirrhosis identifies coffee consumption at baseline as a protective factor of long-term survival while alcohol consumption during the follow-up negatively impacts outcome. Further analysis is required to determine if a “safe” modest alcohol consumption during follow-up exists.

PO-442

SZN-043, a Hepatocyte-targeted-R-spondin mimetic, stimulates hepatocyte proliferation in an acute alcoholic hepatitis model

Trevor Fisher¹, Tiej Le¹, Mehaben Patel¹, Maureen Newman¹, Wen-Chen Yeh¹, Trudy Vanhove¹, Jay Tibbitts¹, Helene Baribault¹. ¹Surrozen, South San Francisco, United States

Email: trevor@surrozen.com.

Background and aims: Wnt signaling plays a central role in hepatocyte expansion during development and tissue repair. R-spondins (RSPOs) are known enhancers of Wnt signaling, via stabilization of Frizzled and LRP co-receptors. SZN-043 is a bispecific fusion protein and hepatocyte-specific R-spondin mimetic that induces hepatocyte-targeted Wnt signaling and hepatocyte proliferation in normal mice. Severe alcoholic hepatitis (AH) is characterized by reduced hepatocyte proliferation and impaired hepatic regeneration. Since improved hepatocyte proliferative capacity has been linked to increased survival in AH, therapies that can stimulate hepatocyte proliferation may have substantial benefits in these patients. We therefore tested the effect of SZN-043 on hepatocyte expansion and liver function in a commonly used AH-induced liver injury model.

Method: 11-month-old female C57BL/6J mice were fed the control Lieber-DeCarli diet ad libitum for 5 days to acclimatize them to liquid diet and tube feeding. Afterward, EtOH-fed groups were allowed free access to a Lieber-DeCarli diet containing 5% (vol/vol) EtOH for 7 weeks, and control groups were pair-fed with an isocaloric control diet. In the second week, and for the remainder of the EtOH feeding, EtOH-fed and pair-fed mice were gavaged twice weekly with EtOH (5 g/kg body weight) or isocaloric maltose dextrin, respectively. Mice were then returned to the control liquid diet, randomized and injected intraperitoneally with either SZN-043 at 30 mg/kg daily for 7 days or an anti-GFP control (10 mg/kg twice weekly). Blood and liver tissue samples were collected at Days 0, 3 or 7 of treatment and analyzed for serum chemistry, gene expression, immunostaining and histopathology.

Results: SZN-043 induced Wnt signal activation in the liver as shown by the increase in the Wnt target gene, Axin2, mRNA expression and the induction of proliferation markers, cyclin D1 and Mki-67 (Ki67). This was confirmed by an increase of 2 serum biomarkers of Wnt activation, leukocyte cell-derived chemotaxin-2 (LECT2) and angiogenin. SZN-043 also reduced the mRNA expression of markers of hepatic inflammation, IL1b and IL6. ALT was modestly increased after SZN-043 treatment and AST was greatly reduced when compared to control at Day 3 resulting in a substantial reduction in AST/ALT ratio. Circulating ammonia was significantly decreased at Day 3, when compared to control. No differences were seen between treatment groups in bilirubin, albumin or triglyceride levels.

Conclusion: These results show that SZN-043 can stimulate hepatocyte-specific cell regeneration in this commonly used AH-induced liver injury model. SZN-043 may have meaningful clinical benefit in human disease states where hepatocyte proliferation is impaired, such as in severe AH.

PO-487

Binge drinking induces an acute release of markers of hepatic fibrogenesis

Nikolaj Torp^{1,2}, Mads Israelsen^{1,2}, Mette Juul Nielsen³, Claus Philip Åstrand^{1,2}, Pernille Juhl^{3,4}, Stine Johansen^{1,2}, Camilla Dalby Hansen^{1,2}, Bjørn Stæhr Madsen^{1,2}, Ida Villesen³, Diana Leeming³, Torben Hansen⁵, Morten Karsdal^{3,6}, Aleksander Krag^{1,2}. ¹Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; ²University of Southern Denmark, Institute of Clinical Research, Odense, Denmark; ³Nordic Bioscience A/S, Herlev, Denmark; ⁴Copenhagen University, Department of Biomedical Sciences, København, Denmark; ⁵Copenhagen University, Novo Nordisk Foundation Center for Basic Metabolic Research, København, Denmark; ⁶University of Southern Denmark, Department of Molecular Medicine, Odense, Denmark
Email: nikolaj.christian.torp@rsyd.dk.

Background and aims: Binge drinking increases the risk of alcohol-related cirrhosis. The fibrogenesis, leading to cirrhosis, is a long-standing process of collagen deposition in the hepatic extracellular matrix (ECM). However, fibrogenic activity is highly dynamic and the acute effects of binge drinking on ECM turnover are largely unknown. We aimed to investigate hepatic fibrogenesis and fibrolysis following a binge drinking episode.

Method: We performed a pathophysiological intervention study in 39 participants (16 with \geq F2 fibrosis, 13 with F0-F1, and 10 healthy controls). To mimic binge drinking, participants with alcohol-related liver disease, non-alcohol related liver disease and healthy controls received 2.5 ml of 40% ethanol per kg body weight, infused over 30 minutes via a nasogastric tube. At eight time points within three hours after alcohol infusion, we sampled venous blood simultaneously from the hepatic and right external jugular vein. Additionally, peripheral venous blood was sampled 24 hours after alcohol infusion. Markers of hepatic fibrogenesis (PRO-C3 and PRO-C8) and fibrolysis (C3M) were measured with competitive ELISA assays.

Results: The blood alcohol concentration was 0 ± 0 mmol/L at baseline, 34 ± 4 mmol/L at one hour, and declined to 21 ± 3 mmol/L after three hours. Baseline level of peripheral PRO-C3 was 12.6 ng/ml (IQR 9.8; 16.2) and increased by +1.2 ng/ml ($p < 0.001$) after 24 hours, with no difference between the groups ($p = 0.661$). Increasing baseline PRO-C3 was associated with a hepatic PRO-C3 increase of +0.03 ng/ml/h (95% CI 0.01; 0.05, $p = 0.005$) and a systemic PRO-C3 decrease of -0.04 ng/ml/h (95% CI -0.05; -0.02, $p < 0.001$) during the first three hours. The hepatic level of C3M did not change within three hours ($p = 0.829$), nor the peripheral PRO-C3 after 24 hours ($p = 0.911$). Peripheral PRO-C8 at baseline was 3.3 ng/ml (IQR 1.9; 5.5) and did not increase significantly after 24 hours (+0.3 ng/ml, IQR 0.0; 1.1, $p = 0.068$). However, in the subgroup of participants with elevated PRO-C8 after 24 hours, the increasing trend was seen during the first three hours (+0.22 ng/ml/h, 95% CI 0.08; 0.37, $p = 0.003$).

Conclusion: Binge drinking induces an acute burst release of fibrogenic markers in healthy individuals and in patients with fatty liver disease. Fibrosis degradation C3M is not correlated to fibrosis formation PRO-C3, indicating that even a single episode of binge drinking promotes hepatic fibrogenesis.

PO-488

Has the 5-year mortality of patients with alcoholic cirrhosis changed during the last 20 years?

Edeline Kaze¹, Jean Henrion¹. ¹Jolimont Hospital, Gastroenterology and Hepatology
Email: kazeedeline@gmail.com.

Background and aims: Patients with alcoholic cirrhosis have a poor short-term prognosis. The aim of this study was to determine whether the 5-year mortality of alcoholic cirrhosis has changed over the past two decades.

Method: From January 1995 to December 2014, 932 cirrhotic patients who attended the hepatology outpatient clinic of our institution were consecutively listed in a registry. From this registry, 565 patients had alcoholic cirrhosis (61%). 16 patients were excluded because they were lost to follow-up and 114 patients were excluded because the diagnosis of cirrhosis was made more than 2 years before the inclusion in the registry. We separated the 435 remaining patients into two cohorts 10 years apart: the cohort C1 (C1), patients included in the registry between 1995 and 2004 ($n = 206$) and the cohort C2 (C2), patients included from 2005 to 2014 ($n = 229$). Epidemiologic data and 5-year mortality were retrospectively compared between both cohorts.

Results: The sex ratio was similar between both cohorts (C1: male 68% vs C2: male 71%) as well as the Child Pugh score at inclusion in the registry (C1: 7.28 vs C2: 7). By contrast, the mean age at diagnosis of cirrhosis was significantly higher in the cohort C2 than in the cohort C1 (C1: 52.8 ± 11 years vs C2: 56.5 ± 9.3 years, $p < 0.0001$). From the 206 patients in the cohort C1, 80 died within 5 years after diagnosis of cirrhosis compared to 83 patients from the 229 patients in the cohort C2 (C1: 39% vs C2: 36%, $p = 0.6$). When the circumstances of 5-year mortality were compared between the 80 patients from the cohort C1 (Group A) and the 83 patients from the cohort C2 (Group B), the liver-related mortality rate was similar between both groups (Group A: 64 of 80 patients (80%) vs group B: 65 of 80 patients amongst whom the cause of death was known (81%), $p = 0.8$). Among those patients who died from their cirrhosis, liver-related mortality by end-stage liver disease without precipitating event was not statistically different between both groups (Group A: 36% vs Group B: 29%, $p = 0.4$). However liver-related mortality precipitated by an acute event was different according to the underlying precipitating event. Patients in Group A died more often from gastrointestinal bleeding than patients in Group B (Group A: 30% vs Group B: 9%, $p = 0.003$). Patients in Group A died less by sepsis than patients in Group B (Group 1: 1.5% vs Group 2: 14%, $p = 0.009$). There were no statistically differences concerning liver-related death precipitated by alcoholic hepatitis (Group 1: 17% vs

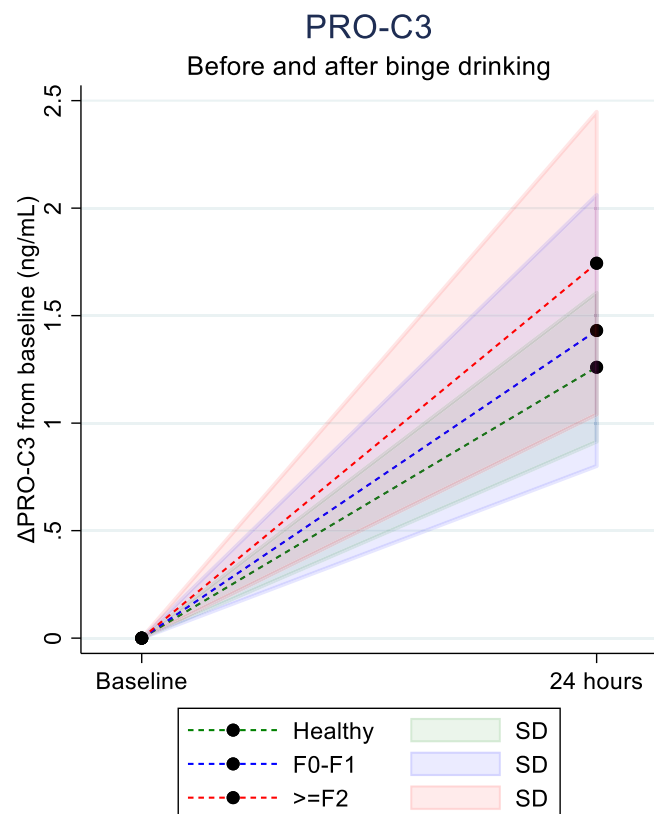


Figure:

POSTER PRESENTATIONS

Group 2: 18%, $p = 0.8$) or hepatocellular carcinoma (Group 1: 9% vs Group 2: 15%, $p = 0.3$).

Conclusion: Our study demonstrated that the 5-year mortality rate in patients with alcoholic cirrhosis has not changed. However, the type of precipitating events which lead to liver-related death has changed with a rarefaction of mortality provoked by acute gastrointestinal bleeding, but an increase of mortality by sepsis.

PO-607

Acamprosate for the treatment of alcohol use disorder may be safer than baclofen in patients with cirrhosis

Luke D. Tyson^{1,2}, Alexandra Cheng², Charles Kelleher², Kirstin Strathie², James Lovendoski², Zebib Habtemariam², Heather Lewis². ¹Imperial College London, The Department of Metabolism, Digestion and Reproduction, London, United Kingdom; ²Imperial College Healthcare NHS Trust, Department of Hepatology, London, United Kingdom
Email: luke.tyson@nhs.net.

Background and aims: Patients with alcohol use disorder (AUD) and liver cirrhosis benefit from stopping alcohol intake. Baclofen has been trialled for AUD in cirrhotic patients and appears safe. However, in patients without cirrhosis, acamprosate is safer and more efficacious. There are concerns about acamprosate use in cirrhosis, for example that it may precipitate hepatic encephalopathy (HE). The only published report of acamprosate use in cirrhotic patients was for 24 hours in a controlled setting. Our centre uses both medications in selected cirrhotic patients with AUD. We performed an audit to compare the safety of acamprosate to baclofen.

Method: We retrospectively reviewed the electronic records of all patients prescribed acamprosate or baclofen in our NHS Trust between 01/04/17 and 31/03/20 to identify cirrhotic patients taking acamprosate or baclofen for AUD. We recorded disease severity, hepatic decompensations, length of treatment, side effects, adverse events, hospital admissions, and abstinence at last follow-up. Data was compared by Student's t-test, Mann-Whitney U test or Chi-squared test as appropriate.

Results: 92 patients met inclusion criteria: 48 took acamprosate (median 84 days, range 2–524); 44 baclofen (median 247 days, 8–910). No baseline differences were observed between groups: 41% had Childs-Pugh B or C cirrhosis; 37% had evidence of hepatic decompensation at baseline. There were no significant differences in abstinence, side effects or new decompensation events between groups. However, more patients taking baclofen were admitted to hospital during treatment (figure) and the mean number of admissions per patient was significantly higher (1.6 admissions vs 0.6, $p = 0.032$). Sub-group analysis revealed increased admissions in actively-drinking patients prescribed baclofen to achieve abstinence (mean 2.4 vs 0.6, $p = 0.020$) including when normalised for time on medication (0.9 per 100 days on baclofen vs 0.3 admissions per 100 days on acamprosate, $p = 0.035$). Admissions did not differ when medication was prescribed to maintain abstinence (mean 0.9 vs 1.1, $p = 0.812$). There was an increased number of admissions due to confusion or HE in the baclofen group, although this did not reach significance (14/90 admissions vs 1/34, $p = 0.055$).

Conclusion: We describe, for the first time, acamprosate use in cirrhotic patients in clinical practice. Acamprosate may be safer than baclofen, although prospective confirmation is required.

PO-832

Prevalence of steatosis and fibrosis in individuals with high-alcohol consumption assessed by FibroScan: real-world cohort study from the US population

Naim Alkhoury¹, Fady Tanios², Birol Emir², Deepa Malhotra², Euan McLeod³, Katherine Hoover², Mazen Nouredin⁴. ¹Arizona Liver Health, Chandler, United States; ²Pfizer Inc, New York, United States; ³Pfizer Ltd, Tadworth, Surrey, United Kingdom; ⁴Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, United States
Email: naim.alkhoury@gmail.com.

Background and aims: Steatosis is a hallmark of both non-alcoholic and alcoholic fatty liver disease, which can each progress to fibrosis. This analysis aimed to determine prevalence of fibrosis assessed by

Figure 1: Response to treatment, side effects, adverse events and hospital admissions in patients with cirrhosis taking acamprosate or baclofen for alcohol use disorder

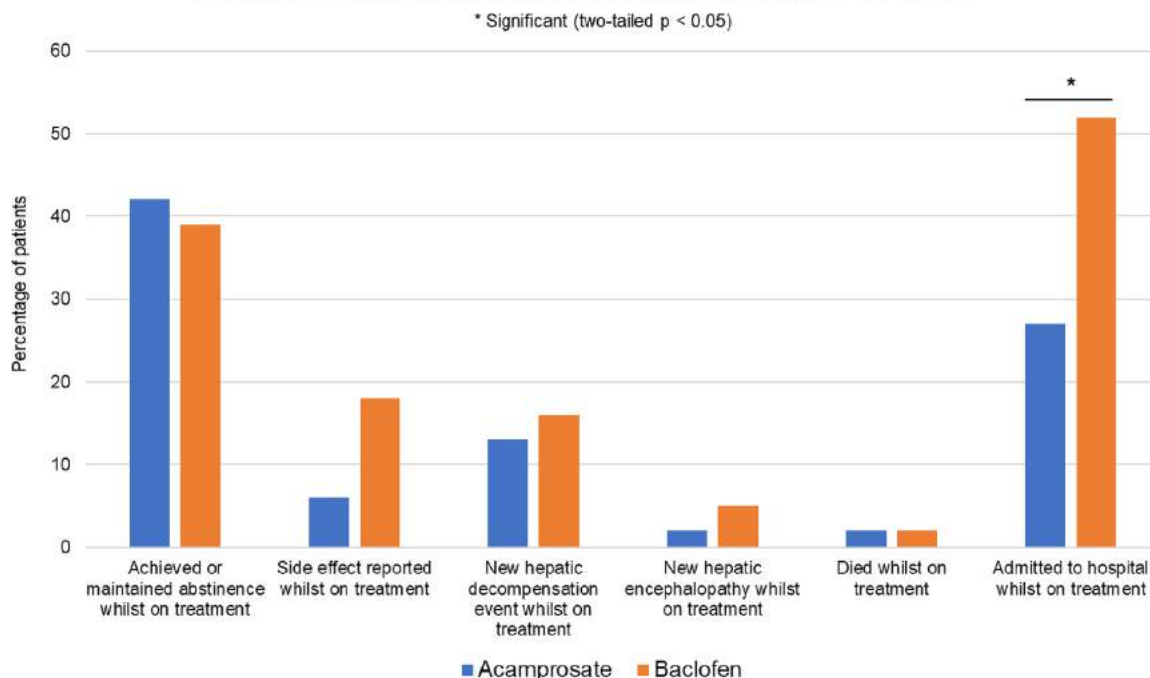


Figure: (abstract: PO-607)

transient elastography (FibroScan®) and comorbidities in the US population with hepatic steatosis and heavy alcohol consumption.

Methods: Adult subjects in the National Health and Nutrition Examination Survey (NHANES) database (2017–2018) with valid FibroScan® measurements were included (N = 4, 471). Prevalence of liver fibrosis was predicted for the US population with steatosis and heavy alcohol use (>20 or >30 g/day for women or men, respectively). Steatosis was assessed using controlled attenuation parameter (CAP), and fibrosis stage was assessed based on liver stiffness. CAP cutoff of 290 dB/m determined NAFLD; liver stiffness cutoffs were <9.0, <12.1, <18.6 and ≥18.6 kPa for F0-F1, F2, F3 and F4, respectively. Clinical characteristics and comorbidities were evaluated.

Results: Overall, 470 subjects (10.5%) had high-alcohol consumption in the eligible FibroScan® cohort (after excluding subjects with viral hepatitis and HIV). Of these, 364 (77.4%) had steatosis. Most subjects (unweighted) had F0-F1 fibrosis (42.6%), followed by F2 (2.5%), F3 (1.4%) and F4 (1.6%). Age-adjusted rates and means of demographics, clinical characteristics and comorbidities were generally similar between high- and low-/no-alcohol consumers with or without steatosis; however, fibrosis stages F2-F3 in high-alcohol consumers were associated with elevated BMI, hypertension, diabetes and elevated liver enzymes (Table 1).

Table 1: Age-adjusted characteristics and comorbidities

	High alcohol	
	Steatosis/ non-steatosis	Fibrosis F2-F3/F0-F1
% of subjects	78/22	4/34*
Characteristics		
Age, years, mean	48/46	46/47
Male, %	53/36	82/62
BMI ≥ 30 kg/m ² , %	51/12	83/61
Alanine aminotransferase, U/L, mean	25/17	68/31
Aspartate aminotransferase, U/L, mean	23/20	42/28
Comorbidities, %		
Hypertension	34/20	65/35
Diabetes	17/7	25/16
Hypercholesterolaemia	37/30	46/39
Ischaemic heart disease	6/5	17/8

*Remainder F4 (1%), cryptogenic cirrhosis (0.3%), fibrosis and moderate steatosis (60%).

Conclusion: This analysis estimated that the majority of the US population with steatosis and high-alcohol consumption have fibrosis, as indicated by real-world FibroScan® data. These results demonstrate the high incidence of metabolic-related comorbidities in subjects with steatosis, fibrosis and high-alcohol consumption.

PO-1099

The alarming impact of COVID-19 pandemic on alcohol-related liver disease: a population-based Canadian study

Abdel-Aziz Shaheen¹, Stephen Congly¹, Mark G. Swain¹, Kristine Kong², Carla Coffin¹, Kelly Burak¹, Samuel Lee¹, Matthew Sadler¹, Meredith Borman¹, Juan G. Abralde³. ¹Cumming School of Medicine, University of Calgary, Gastroenterology and Hepatology Division, Department of Medicine, Calgary, Canada; ²Alberta Health Services, Calgary, Canada; ³University of Alberta, Edmonton, Canada

Email: azshaheen@me.com.

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

POSTER PRESENTATIONS

PO-1215

Cell specific roles of MLKL in alcohol-associated liver disease

Xiaoqin Wu¹, Megan McMullen¹, Xiude Fan¹, Tatsunori Miyata¹, Emily Huang¹, Laura Nagy¹. ¹Cleveland clinic
Email: nagy13@ccf.org.

Background and aims: Hepatocellular fate in response to death receptor activation depends on the cellular environment. Recent work has investigated the role of mixed lineage kinase like (MLKL)-mediated necroptotic pathway in alcohol- (ALD) and non-alcohol-associated (NAFL/NASH) liver diseases. MLKL is differentially activated in ALD/AH compared to NAFL/NASH in both murine models and patients. *Mkl1*^{-/-} mice are protected from liver injury in a Western-diet induced model of obesity, associated with the regulation of hepatocellular autophagy. However, *Mkl1*^{-/-} mice are not protected from Gao-binge and chronic ethanol-induced liver injury, despite a normalization of ethanol-induced increases expression of *Tnf-α*, *Il-1β* and *Mcp-1* mRNA in *Mkl1* deficient mice. These findings indicate that MLKL likely functions via cell-specific mechanisms in ALD.

Method: Bone marrow transplants between *Mkl1*^{-/-} mice and littermate controls were conducted. Mice were then challenged with the Gao-binge (acute on chronic) ethanol model to distinguish potential myeloid vs non-myeloid cell-specific roles of MLKL in ALD. Liver tissue from patients with alcoholic hepatitis (AH) was used for immunohistochemical staining and Western blot.

Results: Immunohistochemical staining of liver biopsies from patients with AH revealed that MLKL was localized to both hepatocytes and immune cells. MLKL was expressed in isolated hepatocytes and non-parenchymal cells (NPCs) from the liver of control mice. Interestingly, in chimeric mice expressing MLKL in non-myeloid cells (*Mkl1*^{-/-}→WT), hepatic injury and steatosis were exacerbated by Gao-binge ethanol exposure. In contrast, chimeric mice not expressing MIF in non-myeloid cells (WT→*Mkl1*^{-/-}) had similar phenotype as WT→WT mice in response to ethanol. In addition, in response to Gao-binge ethanol, *Mkl1*^{-/-}→WT mice had elevated numbers of circulating neutrophils, and a more robust infiltration of neutrophils and monocytes into the liver, assessed by NIMP-R14⁺ and Ly6C⁺ staining, compared to WT→WT mice. *Mkl1* deficiency in myeloid cells also exacerbated ethanol-induced increases in expression of *Il-1β* and *Cxcl5* mRNA in liver.

Conclusion: Taken together, these data indicate that myeloid cell-specific MLKL restricts liver injury and inflammation in response to Gao-binge ethanol, associated with an increased accumulation of immune cells in the liver.

Figure: None.

PO-1375

Self-reported interest in decreasing alcohol use in patients with alcohol-related liver disease: a national health survey

Anna Kann^{1,2,3}, Peter Jepsen³, Lone Madsen¹, Colin Crooks^{4,5}, Kate Fleming^{6,7}, Anne Illemann Christensen⁸, Cathrine Lau², Joe West^{5,9}, Gro Askgaard^{1,2,3}. ¹Zealand University Hospital, Medical Department, Section of Gastroenterology and Hepatology, Køge, Denmark; ²Bispebjerg and Frederiksberg Hospital, Centre for Clinical Research and Prevention, Frederiksberg, Denmark; ³Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; ⁴University of Nottingham, Nottingham Digestive Diseases Centre, School of Medicine, Nottingham, United Kingdom; ⁵Nottingham University Hospitals NHS Trust and the University of Nottingham, NIHR Nottingham Biomedical Research Centre (BRC), Nottingham, United Kingdom; ⁶University of Liverpool, Department of Public Health Policy and Systems, Institute of Population Health, Liverpool, United Kingdom; ⁷University of Liverpool, Liverpool Centre for Alcohol Research, Liverpool, United Kingdom; ⁸University of Southern Denmark, National Institute of Public Health, Copenhagen, Denmark; ⁹University of Nottingham, Division of Epidemiology and Public Health, School of Medicine, Nottingham, United Kingdom
Email: annaemiliekann@gmail.com.

Background and aims: Heavy drinking is frequent in patients with alcohol-related liver disease (ALD). We examined the association of being interested in decreasing alcohol use with clinical variables in patients with ALD. We then examined whether interest in decreasing alcohol use was associated with initiation of alcohol treatment later.

Method: We linked information from the Danish National Health Surveys 2010–2017 with national registries to identify participants diagnosed with ALD and their initiation of alcohol treatment within 2 years after the survey. The health survey included a question regarding interest in decreasing alcohol use (yes/no/don't know). We calculated adjusted relative risks (RR) of being interested in decreasing alcohol use according to alcohol problems (CAGE questionnaire), health-related quality of life (SF-12), and severity of liver disease (cirrhosis or not). We used competing risk regression to calculate the cumulative incidence of alcohol treatment after the health survey.

Results: Of 674 patients with ALD of whom 58% had cirrhosis, 41% drank more than 14 drinks per week and 35% were abstainers. Among the 436 alcohol drinkers, 132 (30%) were interested in decreasing use. A larger amount of alcohol, more severe alcohol problems, and low mental quality of life were all associated with being interested in decreasing alcohol use. For example, compared to 1–13 drinks per week, the RR for being interested in decreasing alcohol use was 3.6 (95% CI 2.0–6.4) for 14–27 drinks per week, 5.7 (95% CI 3.2–10) for 28–41 drinks per week and 6.0 (95% CI 3.5–10) for ≥42 drinks per week. Physical quality of life and severity of liver disease were not associated with being interested in decreasing alcohol use. The cumulative incidence of alcohol treatment within 2 years was 30% (95% CI 22–37) for those who reported being interested in decreasing use in the health survey and 6.5% (95% CI 3.2–9.8) for those who reported no interest (figure).

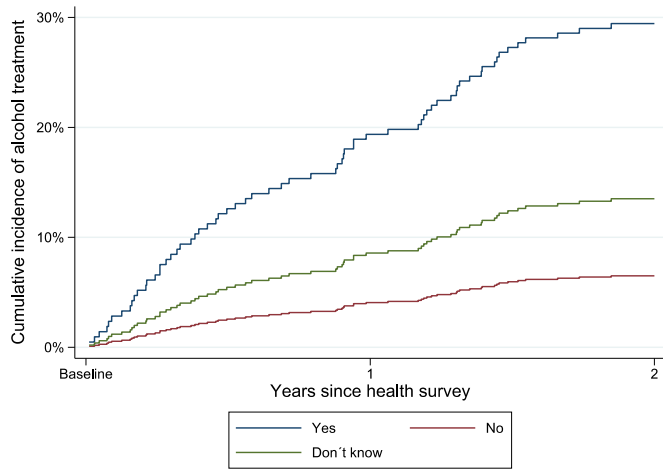


Figure: Cumulative incidence (%) of alcohol treatment in ALD patients according to interest in decreasing alcohol use in the Danish National Health Survey 2010–2017, n = 436.

Conclusion: Being interested in decreasing alcohol use among patients with ALD was associated with the presence of alcohol problems, low mental quality of life, but not with severity of liver disease. Self-reported interest in decreasing alcohol use was associated with likelihood of initiation of alcohol treatment later.

PO-1541
Potential underlying mechanisms in the immune response to COVID in obese heavy drinkers

Marti Ortega-Ribera^{1,2}, Adam Kim¹, Megan McMullen¹, Annette Bellar¹, Vai Pathak¹, Laura Nagy^{1,3,4}. ¹Lerner Research Institute-Cleveland Clinic, Department of Inflammation and Immunity, Cleveland, United States; ²IDIBAPS, Liver Vascular Biology Research Group, Barcelona Hepatic Hemodynamic Unit, Barcelona, Spain; ³Cleveland Clinic, Department of Gastroenterology and Hepatology, Cleveland, United States; ⁴Case Western Reserve University, Department of Molecular Medicine, Cleveland, United States
 Email: nagy13@ccf.org.

Background and aims: Alcohol abuse has a harmful effect on the innate and adaptive immune response and is associated with increased susceptibility to several respiratory syndromes such as pneumonia or tuberculosis. In the current COVID-19 pandemic, a recent analysis of UK BioBank data by our group revealed that frequent drinking, and especially heavy drinking, is associated with higher risk of death in COVID-19 patients who are also obese. The molecular mechanisms underlying this interaction remains unexplored.

Method: Peripheral blood mononuclear cells (PBMC) from lean (BMI < 25) or obese (BMI > 30) heavy drinkers (HD; AUDIT >16, n = 3 each) were treated with a dsRNA homopolymer (pl:C) for 2 h or 24 h to mimic a viral infection *ex vivo*. Additionally, a subgroup of cells was treated with 10 ng/ml LPS (last hour during pl:C treatment). PBMCs from healthy patients were used as controls. Plasma proteomics [Data provided by the MGH Emergency Dept COVID-19 Cohort (Filbin, Goldberg, Hacohen) with Olink Proteomics] from COVID-19 patients were also analyzed. Results were considered as significant when $p < 0.05$.

Results: Early (2 h) PBMC response to pl:C showed a significant increase in TNF gene expression in lean HD patients (+92%) while the response was significantly higher in the obese HD group (+158%). TNF expression further increased upon LPS stimulation (+1811% lean and +1916% obese). As expected, after 24 h, responses were attenuated, with no induction of TNF in response to pl:C and a mild upregulation after LPS treatment (+47% lean and +22% obese). Analysis of the plasma proteome from COVID-19 patients revealed significant differences in expression of antiviral-related molecules when

comparing lean (n = 41) versus obese (n = 123) patients. Obese patients had increased interferon (IFN) gamma (+35%) and IFN lambda 1 (+19%) production with a significant reduction in the expression of their respective receptors IFNGR1 (-19%) and IL10RB (-7%) when compared to lean patients. Moreover, the dsRNA sensor DDX58 (+10%), its downstream transcription factor ATF2 (+86%) and IFN-induced cytokines, e.g. CXCL10 (+7%) and IL-1beta (+46%) were also increased in obese compared to lean COVID-19 positive patients. **Conclusion:** Our results suggest that heavy drinking patients with obesity have an impaired innate immune response to viral insults (e.g. COVID-19). Current scRNAseq analysis will better delineate the implicated immune populations and molecular pathways involved in this disrupted response.

PO-1563
Longer-term Outcome from Alcoholic Hepatitis: survival, re-admission rate and out-patient attendance after discharge

Murray Foster¹, James Knight¹, Ewan Forrest². ¹University of Glasgow, Glasgow, United Kingdom; ²Glasgow Royal Infirmary, Gastroenterology, Glasgow, United Kingdom
 Email: ewanforrest@hotmail.com.

Background and aims: Alcoholic hepatitis (AH) has a high short-term mortality. Few studies have looked at the longer-term outcome of AH patients, although achievement of abstinence from alcohol is associated with better survival. The aim of this study was to review the long-term outcome of patients with AH and their subsequent use of medical services.

Method: All patients recruited to the STOPAH trial between March 2011 and February 2014 from hospitals within NHS Greater Glasgow and Clyde were assessed. For those who survived their STOPAH admission, subsequent gastroenterology/hepatology out-patient clinic (OPC) and in-patient episodes were recorded. Kaplan-Meier, Spearman's correlation and Odds Ratio analyses were undertaken: results are presented as medians and 95% confidence intervals. Censorship was until 1/10/2020 for survivors.

Results: 140 patients were recruited, with a median follow-up of 667 days (390–1195) until censorship or death. 108 (77%) survived their index STOPAH admission for whom subsequent information was available in 106; the median follow-up until censorship was 1261 days (823–1883). Their survival was 28%. 92% of index admission survivors had a further hospital admission (64% liver-related). Median time to readmission after discharge was 101.5 days (56–161). 59% of readmitted patients did so prior to an OPC consultation. 79 (74%) patients attended at least one OPC appointment, the first being a median of 86 days (68–108) after discharge. Correspondence from the first OPC after index admission indicated no alcohol use in 56%, continued alcohol use in 24% and no record of alcohol intake in 20%. Those attending $\leq 50\%$ OPC appointments had a lower survival (19%) compared with those attending $>50\%$ (38%; $p = 0.02$; Figure). There was a correlation between time to first OPC appointment and subsequent attendance rate with those attending sooner after discharge more likely to attend ($\rho = -0.367$; $p = 0.0009$).

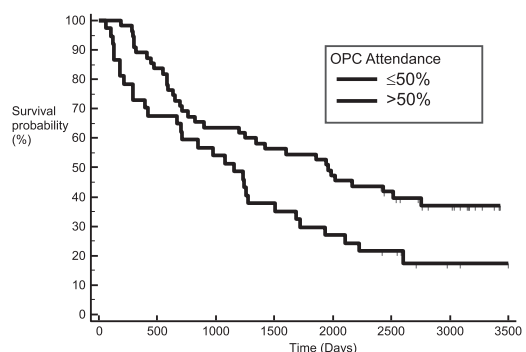


Figure:

POSTER PRESENTATIONS

Conclusion: With long-term follow-up, the mortality of AH patients who survive their index admission is high. Most patients were readmitted prior to an OPC consultation, but those who did attend >50% of offered OPCs had a better outcome. Documentation of alcohol use at OPC review was inadequate in a fifth of cases. Prompt and more assertive OPC follow-up might benefit this cohort of patients to improve long-term survival.

PO-1623

Treatment of alcohol withdrawal syndrome in patients with alcohol-related liver disease

Alexander Doyle¹, Katherine Duncan², William MacKey², Sardar Chaudhary², Ewan Forrest^{1,2}. ¹University of Glasgow, Glasgow, United Kingdom; ²Glasgow Royal Infirmary, Gastroenterology, Glasgow, United Kingdom
Email: ewanforrest@hotmail.com.

Background and aims: Management of alcohol withdrawal syndrome (AWS) in patients with alcohol-related liver disease (ArLD) is poorly studied. Variable metabolism of benzodiazepines (BZDs) and risk of encephalopathy in ArLD patients presents a challenge. We have established a guideline to manage AWS in ArLD using a symptom triggered (ST) approach with the Glasgow Modified Alcohol Withdrawal Score (GMAWS) and prescription of lorazepam. We have reviewed the management of these patients.

Method: The medical records of all patients discharged from the Gastroenterology/Liver wards at GRI in the fourth quarter of the years 2015–2019 were reviewed. Patients presenting with or with known ArLD who had been drinking within 1 week of admission were identified. Admission data were collected retrospectively: BZD use calculated as diazepam (mg) equivalent. Alcohol Use Disorder (AUD) was assessed with the FAST score (abbreviated AUDIT: ≥ 8 associated with increased BZD use). Severe AWS defined as more than 80 mg BZD/day and/or need for parenteral sedation. MELD-Na scores were determined for all patients.

Results: 188 ArLD patients were identified, 128 of whom had a FAST score recorded. BZD use in the first 96 hours of admission correlated with FAST score ($p < 0.0001$; ρ 0.371) and initial GMAWS score ($p < 0.0001$; ρ 0.539), but not with MELD-Na. There was an inverse correlation with FAST score and MELD-Na ($p = 0.0053$; ρ -0.250). 114 patients had a FAST ≥ 8 taking a median of 27 units of alcohol/day (range 4.6–80) and median BZD use of 47.5 mg (range 0–520) in the first 96 hours of admission. 29 (25%) did not require any BZD; 28 (24%) had severe AWS. Logistic regression identified initial GMAWS score ($p < 0.0001$; OR 1.83, 1.36–2.47) and baseline neutrophil-to-lymphocyte ratio ($p = 0.048$; OR 1.08, 1.00–1.18) as associated with severe AWS. There was no association with markers of liver dysfunction. 60 (53%) received diazepam initially, but only 17 (15%) continued this after 24 hours. 93 (82%) received ST treatment initially increasing to 99 (87%) after 24 hours.

Conclusion: AWS in ArLD is not associated with markers of liver disease. The need for treatment is unpredictable with about a quarter not needing any BZD treatment, and a further quarter experiencing severe AWS. High FAST score and severity of initial AWS symptoms are most indicative of AWS. AWS in ArLD can be managed effectively using a lorazepam-based ST approach with GMAWS.

PO-1651

Histological lesions can predict response to corticosteroids in patients with severe alcohol-related steatohepatitis

Horia Stefanescu¹, Marion Jager², Rautou Pe², Adelina Horhat¹, Davies Susan³, Helmut Denk⁴, Hans-Peter Dienes⁵, Viviane Gnemmi⁶, Maria Guido⁷, Rosa Miquel⁸, Valérie Paradis⁹, Ioana Rusu¹⁰, Peter Schirmacher¹¹, Luigi Maria Terracciano¹², Rudolf E. Stauber¹³, Annette Gouw¹⁴, Dina Tiniakos¹⁵, Carolin Lackner⁴. ¹Regional Institute of Gastroenterology and Hepatology, Liver Unit, Cluj-Napoca, Romania; ²Université de Paris, Hôpital Beaujon, Service d'Hépatologie, Paris, France; ³Cambridge University Hospitals NHS Foundation Trust, Department of Histopathology, Cambridge, United Kingdom; ⁴Medical University of Graz, Institute of Pathology, Graz, Austria; ⁵Medical University of Vienna, Department of Pathology, Vienna, Austria; ⁶Université Lille, CHU Lille, Service de Pathologie, Lille, France; ⁷University of Padova, Department of Medicine, Padova, Italy; ⁸Kings College Hospital, Liver Histopathology Laboratory, London, United Kingdom; ⁹Hôpital Universitaire Beaujon, Service d'Anatomie et de Cytologie Pathologiques, Paris, France; ¹⁰Regional Institute of Gastroenterology and Hepatology, Department of Pathology, Cluj-Napoca, Romania; ¹¹University Hospital Heidelberg, Institute of Pathology, Heidelberg, Germany; ¹²University Hospital Basel, Institute of Pathology, Basel, Switzerland; ¹³Medical University of Graz, Internal Medicine, Graz, Austria; ¹⁴University Medical Center Groningen, Department of Pathology and Medical Biology, Groningen, Netherlands; ¹⁵Newcastle University, Transitional and Clinical Research Institute, Newcastle upon Tyne, United Kingdom
Email: rudolf.stauber@medunigraz.at.

Background and aims: Liver biopsy is useful to confirm alcohol-related steatohepatitis (ASH) in patients with alcohol-related liver disease (ALD) and clinically suspected alcoholic hepatitis (AH). Current EASL guidelines recommend prednisolone for the treatment of severe AH with Maddreys discriminant function (MDF) ≥ 32 . However, steroid treatment may lead to severe side effects like sepsis. Therefore, treatment response is assessed at day 7 using the Lille model and steroids are discontinued in non-responders to limit the risk of unnecessary steroid exposure. The aim of our study was to investigate the potential utility of histologic features of ALD for early prediction of response to corticosteroids as per Lille score in patients with AH in order to avoid the risk of a 7-days steroid exposure for those unlikely to benefit.

Method: We analyzed data of a multinational cohort of patients with severe AH and MDF ≥ 32 . All patients underwent liver biopsy for the confirmation of clinically suspected AH and were treated with prednisolone. Morphological features of ALD including steatosis, activity (contributed by hepatocellular ballooning, Mallory Denk bodies and lobular neutrophils), canalicular and ductular cholestasis as well as fibrosis stage were assessed using the recently developed ALD-specific SALVE grading and staging system. Association of histological variables with response to steroids (Lille score < 0.45) was analyzed by Chi-square test. Logistic regression was performed to ascertain the effects of histological variables on the likelihood of response to steroids.

Results: Complete data were available in 119 patients. A Lille score of < 0.45 indicating response to steroids was observed in 72 patients and was associated with steatosis grade ($p = 0.037$) and ductular cholestasis ($p = 0.029$) but not with SALVE fibrosis stage or activity. Logistic regression analysis revealed presence of ductular cholestasis ($p = 0.016$, OR 2.8) and steatosis grade < 2 ($p = 0.047$, OR 2.2) as histologic predictors of a Lille score of ≥ 0.45 indicating non-response to steroids.

Conclusion: Liver biopsy may thus be used not only to confirm ASH but also to achieve early prediction of steroid efficacy thus sparing high-risk AH patients from potentially life-threatening side effects of steroid exposure.

PO-1654

Changes in alcohol-related liver disease admissions over the time of minimum unit pricing of alcohol: the GRI Q4 study

Sardar Chaudhary¹, William MacKey¹, Katherine Duncan¹, Ewan Forrest¹. ¹Glasgow Royal Infirmary, Gastroenterology, Glasgow, United Kingdom
Email: sardar.chaudhary2@nhs.scot.

Background and aims: Minimum unit price (MUP) of 50 pence per unit of alcohol was introduced in Scotland on the 1st of May 2018. This was one of several measures which hoped to reduce alcohol harm and alcohol-related liver disease (ArLD) in particular. Standard discharge coding for ArLD is not sufficiently accurate to determine differences between variable clinical presentations. We assessed ArLD admissions to Glasgow Royal Infirmary (GRI) before and after the introduction of MUP.

Method: The medical records of all patients discharged from the Gastroenterology/Liver wards at GRI in the fourth quarter (Q4) of the years 2015–2019 were reviewed (pre-MUP 2015–17; post-MUP 2018–19). All patients with ArLD were identified and admission data were collected retrospectively detailing clinical features of liver disease, blood test results and recent drinking history. Over this time there has been no change to the placement of ArLD patients in GRI. The National Institute of Alcohol Abuse and Alcoholism definition for alcoholic hepatitis (AH) was used. MELD scores were determined for all patients. Active drinking was defined as alcohol use within 8 weeks of admission. The 90-day mortality and readmission rates were assessed.

Results: In total 1875 inpatient episodes were reviewed (1164 pre-MUP; 711 post-MUP) of which 319 were with ArLD (212 pre-MUP; 107 post-MUP). Overall, the mean number of ArLD in-patient episodes fell (80.3 pre-MUP; 68 post-MUP) with a similar fall in the individual patients in each quarter (70.7 pre-MUP, 53.5 post-MUP). The proportion of active drinkers was lower post-MUP (64.7%) compared with pre-MUP (70.5%). There were no differences in the proportion of patients presenting with ascites (45.2% cf. 47.8%) encephalopathy (21.2% cf. 24.3%) or AH (18.3% cf. 19.1%) pre- and post-MUP. However there was a reduction in presentations with acute upper GI bleeding (AUGIB): 15.8% cf. 7.4%; $p = 0.02$; odds ratio 0.42. The overall severity of liver disease remained unchanged (mean MELD 16 for both time periods). The 90-day mortality (12.4% cf. 13.2%) and readmission (48.5% cf. 54.4%) rates were not significantly different pre- and post-MUP.

Conclusion: Since the introduction of MUP there has been a reduction in the absolute numbers of ArLD in-patient episodes and number of individual patients involved at GRI. However the pattern of clinical presentation was largely unaffected other than a reduction in the proportion of patients presenting with AUGIB. The overall ArLD severity, readmission rates and 90-day mortality were similar pre- and post-MUP.

PO-1708

Hallmarks of neutrophil extracellular trap (NET) components in the course of alcoholic liver disease

Anna Rycyk¹, Beata Kasztelan-Szczerbinska¹, Agata Surdacka², Jacek Rolinski², Agata Michalak¹, Mariusz Szczerbinski³, Halina Cichoż-Lach¹. ¹Medical University of Lublin, Department and Clinic of Gastroenterology with Endoscopy Unit, Lublin, Poland; ²Medical University of Lublin, Department and Clinic of Clinical Immunology, Lublin, Poland; ³Independent Public Clinic Hospital No. 4 in Lublin, Gastroenterology Clinic, Lublin
Email: aniryck@op.pl.

Background and aims: Neutrophils release neutrophil extracellular traps (NETs) as a defense strategy in response to broad-spectrum infections, but also to sterile triggers. NETs consist of a DNA scaffold decorated with antimicrobial peptides (AMPs) including cathelicidin (LL37) and α -defensins (HNP1-3), and enzymatically active proteases including peptidyl arginine deiminase type 4 (PAD-4). Damage-

associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), stimulate NET formation. Susceptibility to infections and inflammatory dysregulation are hallmarks of alcoholic liver disease (ALD).

Method: We aimed to investigate the systemic concentrations of NET components such as LL37, HNP1-3, and PAD-4, and the NET promoter HMGB1 in patients with ALD. 62 patients with ALD were prospectively recruited and assigned to subgroups based on their 1/gender, 2/severity of liver dysfunction according to Child-Pugh and Model of End-Stage Liver Disease (MELD) scores, and modified Maddrey's Discriminant Function (mDF) 3/presence of ALD complications. 24 age- and sex-matched healthy volunteers served as the control group. Correlation coefficients between their blood concentrations and (i) markers of systemic inflammation [the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), white blood cell (WBC) and neutrophil (NEUT) counts], (ii) liver dysfunction severity scores, and (iii) ALD complications were calculated.

Results: Systemic concentrations of HNP1-3, PAD-4, and HMGB1 were significantly increased in patients with ALD in comparison with controls. HNP1-3 levels correlated with MELD and mDF scores. ALD subgroups with MELD > 20 and mDF > 32 presented with significantly higher HNP1-3 concentrations. HNP1-3 levels revealed a good predictive AUC for the hepatic encephalopathy and ascites development (0.81 and 0.74, respectively), and for the survival (0.87) in patients of above 40 years of age. PAD-4 levels correlated with standard markers of inflammation (CRP, WBC, NEUT) and revealed a good predictive AUC (0.76) for the survival in the whole ALD group. **Conclusion:** Our results reveal that systemic blood levels of NET components and the NET promoter are elevated in ALD patients and support the value of HNP1-3 and PAD-4 as biomarkers in the ALD assessment. PAD-4 seems to be an inflammatory mediator, while HNP1-3 the disease severity indicator. HNP1-3 and PAD-4 may be potentially applied as predictors of the patients' survival in ALD.

PO-1932

Results of a screening program of liver fibrosis with transient elastography in subjects with alcohol use disorder

Elisa Pose^{1,2}, Emma Avitabile¹, Jordi Gratacós-Gines^{1,2}, Martina Perez², Marta Cervera¹, Ana Belén Rubio¹, Marta Carol¹, Ana Lopez Lazcano³, Anna Lligoña³, Hugo Lopez³, Lluisa Ortega³, Alba Díaz⁴, Núria Fabrellas⁵, Octavi Bassegoda^{1,2}, Laura Napoleone^{1,2}, Ann Ma¹, Adria Juanola², Isabel Graupera², Pere Ginès^{1,2,5}. ¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Chronic liver disease, Barcelona, Spain; ²Hospital Clínic of Barcelona, Hepatology, Barcelona, Spain; ³Hospital Clínic of Barcelona, Psychiatry, Barcelona, Spain; ⁴Hospital Clínic of Barcelona, Anatomopathology, Barcelona, Spain; ⁵University of Barcelona, Barcelona, Spain
Email: EPOSE@clinic.cat.

Background and aims: Transient elastography (TE) is a non-invasive method used for the assessment of liver fibrosis (LF) through liver stiffness measurement (LS). There is some evidence from population-based studies that patients with alcohol use disorder (AUD) are at high risk for LF. However, to date few studies have evaluated the performance of a screening program for diagnosis of LF in subjects with AUD. The aim of this study was to assess the prevalence of significant LF in subjects with AUD through a screening program based on TE.

Method: Consecutive subjects with AUD attending the Addictions Unit of the Hospital Clinic of Barcelona were included prospectively. Those with previously known liver disease were excluded. The presence of significant LF, defined as $LS \geq 8$ kPa, was evaluated through TE. Liver steatosis was assessed through the controlled attenuation parameter (CAP) and defined as $CAP \geq 290$ dB/m. Liver biopsy was proposed in all patients with high values of LS to evaluate LF through Metavir scale.

Results: 160 patients were screened and 140 included. Main reason for exclusion was lack of informed consent. The majority were men

POSTER PRESENTATIONS

with a median age of 52 y/o. Median alcohol consumption was 84 SD/week and mean LS value was 4.8 kPa. Thirteen (9%) patients presented $LS \geq 8$ kPa and all of them underwent liver biopsy. Liver biopsy assessment confirmed the presence of significant LF in 6 (46%). None of the subjects with $LS < 10$ kPa presented significant LF at liver biopsy. The group with $LS \geq 8$ kPa was older, presented higher prevalence of metabolic comorbidities and higher values of transaminases. There were no differences in terms of quantity and duration of alcohol consumption. Age was the only factor associated with the risk of presenting high LS values at the multivariate analysis. Median CAP was 245 dB/m (203–289) and 34 (24%) subjects had steatosis. Factors associated with steatosis at the Multivariate analysis age, waist circumference, and FIB-4.

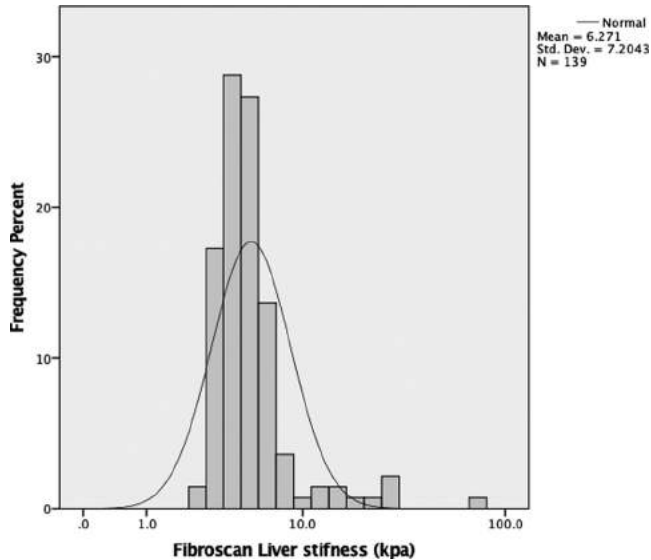


Figure: Distribution curve of liver stiffness values

Conclusion: the prevalence of LF in subjects with AUD assessed with a screening program based on TE was of 9%, approximately twice as much as the prevalence reported in previous screening studies in the general population. Only older age was associated with a higher risk

of LF in subjects with AUD. These data reveal a high prevalence of undiagnosed liver fibrosis in this specific population of subjects and call for the implementation of programs of non-invasive assessment of fibrosis in these subjects.

PO-2043

The role of miR-873-5p in Alcohol-related Liver Disease

Rubén Rodríguez Agudo¹, Naroa Goikoetxea¹, Marina Serrano-Macia¹, Irene González-Recio¹, Pablo Fernández Tussy¹, Delia Blaya², Jose Maria Herranz³, Sofia Lachiondo-Ortega¹, Maria Mercado-Gómez¹, Claudia Gil-Pitarch¹, Carmen Fernández-Rodríguez¹, Álvaro Eguileor¹, Petar Petrov¹, Miren Bravo¹, Pau Sancho-Bru², Matías A. Avila³, Luis Alfonso Martínez-Cruz¹, Teresa Cardoso Delgado¹, Jon Mabe⁴, Jorge Simón Espinosa¹, María Luz Martínez-Chantar¹. ¹CIC bioGUNE-Centro de Investigación Cooperativa en Biociencias; ²Hospital Clínic de Barcelona; ³CIMA (Center for Applied Medical Research) University of Navarre; ⁴Fundación Tekniker
Email: mlmartinez@cicbiogune.es.

Background and aims: Alcohol-related liver disease (ALD), the most prevalent type of chronic liver disease has become a major public health problem worldwide, and a leading cause of morbidity and mortality. One of the unmet needs to address ALD is the lack of effective therapies. Just cutting off alcohol intake is presented as effective therapy. Going deeper, alcohol abuse promotes a disbalance in lipid homeostasis that subsequently, induces liver injury and inflammatory response. During this pathological process, sirtuins play a key role, and SIRT1 is the most extensively studied. Increasing evidence suggests the relevance of microRNAs (miRNAs) as therapeutic targets for ALD. Previously, our lab demonstrated the relevance of miR-873-5p as a suitable target for liver diseases, such as NAFLD and fibrosis by modulating among different targets the expression of the gene Glycine-N-Methyl transferase (GNMT), key modulator of One Carbon Metabolism pathway. Considering the unmet need to develop new therapies against ALD, miR-873-5p appears as a suitable candidate to ameliorate the damaged induced by alcohol in the liver. **Method:** MiR-873-5p levels were measured in paired patient liver samples affected by alcoholic hepatitis vs healthy biopsy (n = 16). As a readout to analyze the effect of miR-873-5p, Gnm1 mRNA expression was studied in human tissue from patients with different alcoholic

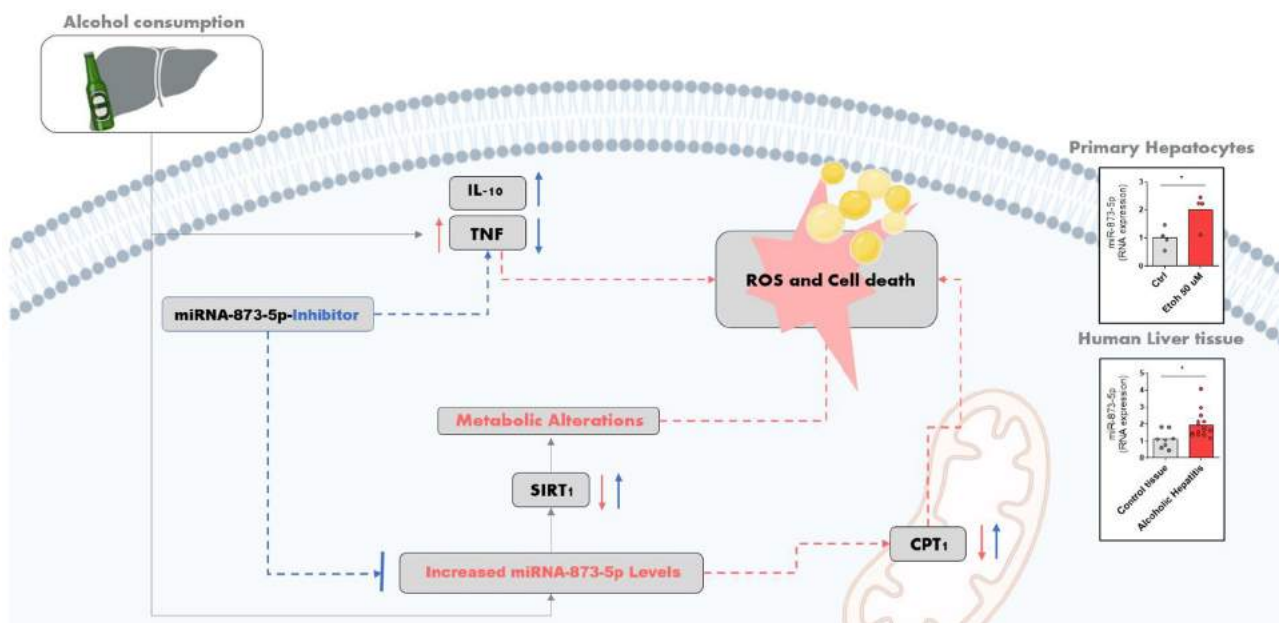


Figure: (abstract: PO-2043)

disturbances (n = 63). The expression levels of MiR-873-5p and Gnm1 were further tested in different mice models (BASH and N1IA). In vitro assays in primary hepatocytes were performed in the presence of anti-miR-873-5p, anti-miR-Control or mimic-miR-873-5p under 12 h of ethanol exposure (50 mM). Cell death rate by TUNEL assay, mitochondrial ROS production, seahorse analysis as well as diverse signaling pathways were evaluated in these conditions.

Results: Raised levels of miR-873-5p were found in ALD patients. Accordingly, Gnm1 levels were downregulated in unrelated cohorts of patients with different alcoholic disease stages. These results were consistent in primary hepatocytes and mice models. Hepatocytes transfected with anti-miR-873-5p showed minor TUNEL cell death in situ and less ROS production measured by MitoSOX compared with anti-miR-Control under ethanol exposure. The negative modulation of miR-873-5p renders higher levels of SIRT1 and CPT1 in primary hepatocytes with a concomitant reduction of S6 Ribosomal Protein (Ser235/236) phosphorylation. Also, the inhibition of miR-873-5p in primary hepatocytes under ethanol treatment, modulates the inflammatory process, with higher levels of IL10 and a reduction of TNF expression.

Conclusion: Targeting miR-873-5p is a valuable therapeutic tool for ALD mediated by SIRT/mTOR regulation.

PO-2185

Human Precision Cut Liver Slices as a model of Alcohol-related Liver Disease: recapitulating disease progression in a dish.

Elena Palma^{1,2}, Nicola Harris^{1,2}, Una Rastovic^{1,2}, Tsin Shue Koay^{1,2}, Ewald Doornebal^{1,2}, Sandra Phillips^{1,2}, Antonio Riva^{1,2}, Daren Ure³, Rosa Miquel⁴, Melissa Preziosi⁴, Andreas Prachalias⁴, Krishna Menon⁴, Nigel Heaton⁴, Roger Williams^{1,2}, Shilpa Chokshi^{1,2}.

¹Institute of Hepatology, Foundation for Liver Research, London, United Kingdom; ²King's College London, Faculty of Life Sciences and Medicine, United Kingdom; ³Hepion Pharmaceuticals, Edison, United States;

⁴Institute of Liver Studies, King's College London, London, United Kingdom

Email: e.palma@researchinliver.org.uk.

Background and aims: The canonical experimental models (i.e. cell culture and rodents) for the study of Alcohol-related Liver Diseases (ALD) present limitations which impede the advancement of novel therapies, particularly the difficulty in recapitulating the spectrum of pathological manifestations associated with the development/progression of ALD in humans including steatosis, inflammation, hepatotoxicity, fibrosis and cirrhosis. The need to overcome this barrier to drug development underpins the current study. We describe the development of an immunocompetent ex-vivo human model of ALD based on the culture of Precision Cut Liver Slices (PCLS) and their direct application for the assessment of the therapeutic effects of the cyclophilin inhibitor, CRV431.

Method: Tumour-free liver specimens ('healthy' or cirrhotic) were collected from patients (n=22) undergoing resection of liver metastasis. PCLS were made from the resected tissue, cultured for up to 5 days, and exposed to hepatotoxic insults: ethanol 50–250 mM, oleic/linoleic acids 0.1 mM, and LPS 10 µg/ml. The therapeutic effects of 5 µM CRV431 were studied for the duration of the culture. Viability and cell death were evaluated by histology, cytokeratin 18 release, and ATP content. Steatosis was evaluated by Oil-Red-O staining. Fibrosis was measured by gene expression, secretion and histology. Inflammatory cytokines were quantified by luminex. Mitochondrial fitness was evaluated by functional and morphological assays.

Results: The exposure of PCLS to ethanol for increasing time periods (up to 5 days) could mimic the clinical features of ALD. Early ethanol exposure was characterised by low overall cell death but increased mitochondrial alterations. The addition of fatty acids and an acute inflammatory hit (LPS) promoted steatohepatitis, inflammatory cytokine production and fibrosis. The cirrhotic PCLS were used to investigate tissue architecture and fibrotic processes in the context of

late stage chronic disease. PCLS treated with CRV431 maintained good viability, mitochondrial function, and low apoptosis over the culture duration. CRV431 also tempered inflammation in the presence of LPS and induced a dramatic decrease in gene expression and deposition of Collagen and Timp-1.

Conclusion: In summary, we have developed a versatile immunocompetent platform which can reliably recapitulate the clinical features of ALD and have shown that it can be effectively employed to assess the efficacy of novel immunomodulatory and anti-fibrotic therapeutic agents.

PO-2331

Past hospital contacts due to alcohol do not predict fibrosis stage in alcohol-related liver disease. A study of alcohol diagnoses and morbidity in 18 years leading up to biopsy-proven liver fibrosis in 462 patients

Ditlev Rasmussen¹, Maria Kjærgaard¹, Katrine Prier Lindvig¹, Mads Israelsen¹, Kathrine Thorhauge¹, Nikkolaj Christian Torp¹, Stine Johansen¹, Sönke Detlefsen², Aleksander Krag¹, Maja Thiele¹.

¹Odense University Hospital, Department of Gastroenterology and Hepatology; ²Odense University Hospital, Department of Pathology, Denmark

Email: ditlev.nytoft.rasmussen@regionh.dk.

Background and aims: Decompensated alcohol-related liver disease is preceded by several years of excessive drinking. Hospital contacts for alcohol problems are potential opportunities for early detection of cirrhosis. We aimed to investigate whether patients with biopsy-proven severe fibrosis and cirrhosis had more past hospital contacts due to alcohol than alcohol-overusing patients with significant or minimal fibrosis.

Method: Liver-healthy patients had a liver stiffness below 6 kPa assessed by transient elastography or a biopsy of F0-F1 fibrosis. Patients with significant fibrosis and advanced fibrosis had liver biopsies with F2 and F3-4 fibrosis, respectively. All patients had a history of alcohol overuse but no decompensations. We linked patient's fibrosis stage to registry data of ICD-10 diagnosis codes for the patients' hospital contacts in the 18 years leading up to liver biopsy. In order to observe changes over time, we split the 18-year period into the first, the second and the last 6-year period before fibrosis assessment. We distinguished between Intoxication (ICD-10 code F10.0), harmful use of alcohol (F10.1) and alcohol dependency (F10.3-F10.5).

Results: We studied the past medical record of 462 patients, 261 liver-healthy, 107 with significant fibrosis, and 94 with advanced fibrosis. During the 18 years, 45% of all patients had one or more alcohol-related hospital contacts, with no difference between groups (43%, 50%, and 44% respectively, P=0.57 for difference). The proportion of patients who had at least one alcohol-related contact was similar between the groups throughout the 18-year-period, and this proportion increased for all groups in the last 6-year-period, see figure. The type of alcohol diagnosis through the three six-year periods for the individual patient was not stable over time in any of the groups. A past diagnosis of polyneuropathy was four times as common for patients with advanced fibrosis, and ulcers were more than twice as common.

POSTER PRESENTATIONS

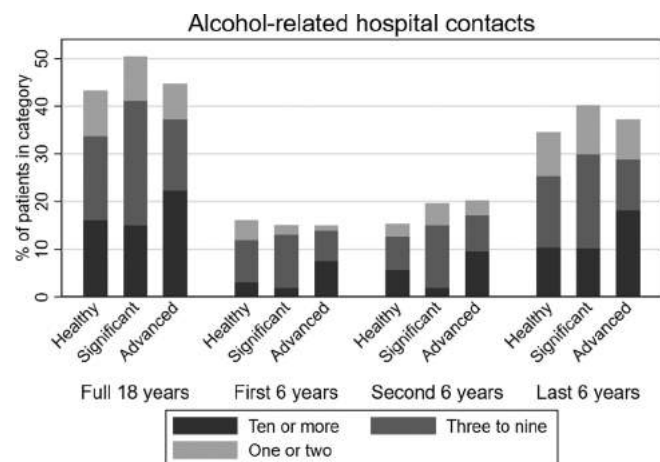


Figure:

Conclusion: More than half of patients who progress to severe alcohol-related fibrosis and cirrhosis do not have any hospital contact with a diagnosis of alcohol use disorder, and the frequency of hospital contacts due to alcohol cannot be used to predict who will experience fibrosis progression within two decades.

PO-2341

High oxidative stress in T cells and monocytes correlates with mortality from alcoholic hepatitis

Huey Tan¹, Paula Boeira¹, Euan Yates¹, Matthew Cramp¹, Ashwin Dhandra¹. ¹University of Plymouth, Faculty of Health: Medicine, Dentistry and Human Sciences, Plymouth, United Kingdom
Email: hueytan@nhs.net.

Background and aims: Multiple mechanisms including immune dysfunction drive poor outcomes from alcoholic hepatitis (AH) although the role of oxidative stress in immune cells remains unknown.

Method: Patients from University Hospitals Plymouth with AH (discriminant function [DF] > 32); and healthy volunteers (HV) were recruited. Disease severity was scored using Model for end stage liver disease (MELD) and DF. 2'-7'-dichlorofluorescein diacetate (DCFH-DA) staining (fluoresces on oxidation) was assessed by flow cytometry to measure oxidative stress directly in peripheral blood T cells (CD3+) and monocytes (CD14+) and after ex-vivo exposure to tert-butylhydroperoxide (TBH) to simulate maximal oxidative stress with results presented as percentage maximal oxidative stress.

Results: 7 HV (4 male, mean age 36) and 34 AH patients (18 male; Mean age 53; Mean MELD 23, DF 81.5) were studied. Samples from AH patients were obtained at baseline before treatment with corticosteroids. 8 AH patients died within 90 days (2 male; mean age 55, mean MELD 29.8, DF 161.8).

Percentage maximal oxidative stress in AH patients was significantly higher than in HV in CD14+ (60.1% vs 41%, $p = 0.001$), but not in CD3+ (54.4% vs 49%; $p = 0.24$). Within AH patients, percentage maximal oxidative stress was significantly higher in non survivors compared to survivors in CD3+ (76.9 vs 47.4%; $p < 0.05$) and CD14+ cells (73.9% vs 55.9%; $p < 0.05$). No correlation was found between MELD or DF scores and percentage maximal oxidative stress in either CD3+ or CD14+ cells.

Figure legend: NS-Not significant, **- $p < 0.01$.

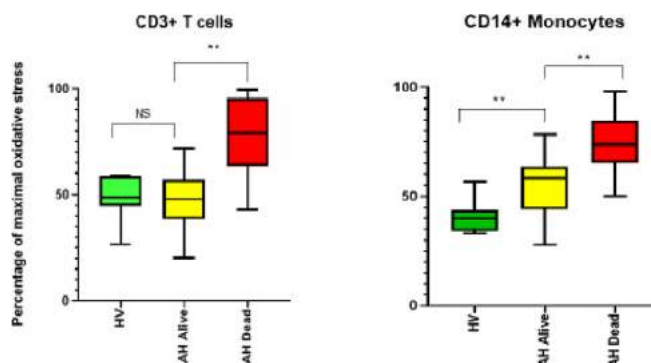


Figure:

Conclusion: In patients dying from AH, both T cells and monocytes showed close to maximal levels of oxidative stress. The role of oxidative stress in the pathogenesis of AH requires further investigation and may represent a novel therapeutic target.

PO-2389

Hospitalization Outcomes of Acute Alcoholic Hepatitis with Protein Energy Malnutrition-A nationwide Analysis

Adnan Malik¹, Muhammad Malik², Umer Farooq³, Khadija Naseem⁴, Mahum Nadeem⁵, Waseem Amjad⁶. ¹Loyola University Medical Center, Maywood, United States; ²Airedale General Hospital, Steeton, United Kingdom; ³MacNeal Hospital, Berwyn, United States; ⁴Charleston Medical Center, Charleston, United States; ⁵OU Health-University of Oklahoma Medical Center, Oklahoma City, United States; ⁶Albany Medical Center, Internal medicine
Email: adnanmalik892@hotmail.com.

Background and aims: Acute Alcoholic Hepatitis (AAH) is the severest form of Alcohol Liver Disease (ALD). It is a significant cause of morbidity, mortality, and healthcare resource utilization in the United States. Protein-energy malnutrition (PEM) is one of the adverse sequelae of alcohol consumption. This study examined the demographic characteristics and hospitalization outcomes, including mortality, length of stay (LOS), and total expenditure in hospitalizations for acute alcoholic hepatitis with protein malnutrition.

Method: This retrospective study utilizes Nationwide Inpatient Sample (NIS) 2016–2018 employing International Classification of Diseases, Tenth Revision (ICD-10) codes for adult patients with a primary diagnosis of acute alcoholic hepatitis secondary diagnosis of protein malnutrition. In-hospital mortality was the primary outcome, while secondary outcomes included length of stay (LOS) and hospital charges. To adjust for confounding variables, multivariate logistic and linear regression analyses were used.

Results: Of 84,693,310 discharges in the NIS 2016-18 database, 1360 hospitalizations were for AAH (Table 1), and 272 (20%) had a concomitant diagnosis of Protein Malnutrition. AAH hospitalizations with protein malnutrition had significant 9.2% mortality (adjusted OR 7.85, 95% CI (1.86–33.08), $P = 0.005$) (Table 2). AAH hospitalizations with PM had 8.65 days increase in adjusted mean LOS (adjusted OR 13.81, 95% CI (0.61–27.02), $P = 0.04$) and a statistically significant average adjusted total hospital cost increase by 27889.5 (OR, with 95% CI (2724.80–53054.31), $P = 0.030$).

Conclusion: AAH is a syndrome associated with high mortality and morbidity. Good nutritional status is essential in reducing poor outcomes. Our analysis results emphasize the importance of protein-energy malnutrition being associated with significant mortality and increased length of stay, and total cost of hospitalization. Both enteral feeding and micronutrient supplementation may play an essential role to improve these poor outcomes of PEM with AAH.

Table 1: (abstract: PO-2389)

Outcomes	AAH: (n = 1360)		Adjusted OR/ Adjusted Difference	p value
	Protein Malnutrition: (n = 72) Unadjusted	Without Protein Malnutrition: (n = 1088) Unadjusted		
Outcome				
Mortality, total, n	39.99 (12.27–67.72)	25.0 (3.11–46.88)	7.85	0.005
Mean LOS, days (95% CI)	5.31 (4.47–6.14)	13.96 (5.48–22.43)	13.81	0.04
Total Cost, mean, USD	10, 026 (7889–12163)	33560 (9808–57312)	27, 889	0.03

n:total number, AAH: Acute Alcoholic Hepatitis OR: Odds Ratio, CI: Confidence Interval, LOS: Length of Stay, USD: United States Dollar

PO-2417

Impact of COVID-19 pandemic on liver transplantation and alcohol-associated liver disease in the United States

Karthik Goli¹, Abbas Rana², Fasiha Kanwal¹, George Cholankeril¹.
¹Baylor College of Medicine, Section of Gastroenterology and Hepatology, Houston, United States; ²Baylor College of Medicine, Division of Abdominal Transplantation, Houston, United States
 Email: gcholankeril@gmail.com.

Background and aims: The recent surge in unhealthy alcohol use during the COVID-19 pandemic may have detrimental effects on the already rising burden alcohol-associated liver disease (ALD) has placed on liver transplantation (LT) in the United States (U.S.). We aim to evaluate temporal trends in LT during the pandemic and the impact ALD has placed on it.

Method: Utilizing data provided by United Network for Organ Sharing registry, we analysed trends and outcomes on waitlist additions, waitlist death, and liver transplant surgeries performed in the U.S. from through November 30, 2020. Patients listed or transplanted after April 1, 2020 was defined as COVID-19 era. Interrupted time-series analyses and Cox hazards models were constructed to compare the rate of LT between eras and aetiologies adjusting for waitlist dropout.

Table 1: Hazard rates for liver transplant within 90 days of listing prior to and during COVID-19 pandemic

	Hazard Ratio [95% C.I.]	p value
Overall^a		
Non-ALD	Reference	
ALD	1.39 [1.33–1.45]	<0.001
Overall within ALD only^b		
ALD: Pre- Pandemic	Reference	
ALD: During Pandemic	1.86 [1.73–2.01]	<0.001
Overall within non-ALD only^b		
Non-ALD: Pre-pandemic	Reference	
Non-ALD: During Pandemic	1.06 [0.99–1.14]	= 0.100
During Pandemic only		
Non-ALD	Reference	
ALD	1.74 [1.62–1.87]	<0.001

^aAdjusted for waitlist removal due to death and era prior to and during COVID-19 pandemic

^bAdjusted for waitlist removal due to death

Results: Waitlist additions and liver transplant had recovered to pre-pandemic volume from May 2020 onwards. Monthly waitlist dropout (death or clinical deterioration) was observed to be lower during the pandemic. In a time-series analysis, the pandemic was associated with a significant monthly increase in the proportion of liver transplants due to ALD (pre-COVID-19 era rate: -0.138 [0.129–0.147] % per month, COVID-19 era rate: -0.162 [0.159–0.165] % per month, p < 0.001). The monthly rate in liver transplants due to hepatitis C virus infection and non-alcoholic steatohepatitis declined

during the pandemic. Median MELD-Na at listing increased for ALD during the pandemic (pre-COVID-19 era: 22 vs. COVID-19 era: 24; p < 0.001), with a higher percentage listed with a high MELD (MELD-Na ≥ 25). ALD patients listed during the pandemic had a 74% higher rate for 90-LT (HR, 1.74, 1.62–1.87, P < 0.001) than non-ALD patients.

Conclusion: ALD patients have presented with a higher acuity of illness necessitating LT during the pandemic. An unintended consequence of the pandemic may be the further prioritization of ALD for LT. Collective efforts are urgently needed to curtail the effect ALD will have on the healthcare system even after the pandemic has subsided.

PO-2704

The Alcohol-Associated Liver Disease Paradox in Chile: An Assessment with data from the National Health Survey 2016–2017

Juan Pablo Roblero¹, Juan Pablo Arab^{2,3}, Pablo Roblero^{4,5}, Francisco Idalsoaga³, Luis Antonio Diaz³, Gianfranco Oneto^{6,7}, Jaime Poniachik⁸. ¹Hospital Clínico Universidad de Chile, Sección de Gastroenterología, Departamento de Medicina., Santiago-RM, Chile; ²Hospital Clínico de la Universidad Católica de Chile, Departamento de Gastroenterología, Santiago-RM, Chile; ³Hospital Clínico de la Universidad Católica de Chile, Departamento de Gastroenterología, Santiago, Chile; ⁴Pontificia Universidad Católica de Chile, Sociología, Chile; ⁵Pontificia Universidad Católica de Chile, Departamento de Sociología, Santiago, Chile; ⁶Hospital San Borja Arriarán, Departamento de Gastroenterología, Santiago, Chile; ⁷Hospital San Borja Arriarán, Gastroenterología, Santiago, Chile; ⁸Hospital Clínico Universidad de Chile, Sección de Gastroenterología, Departamento de Medicina., Santiago, Chile
 Email: jproblero@gmail.com.

Background and aims: It has been observed that people with a low-income level (<IL) have greater liver injury due to alcohol consumption (AC), even when their consumption levels are lower or equal to those with a high-income level (>IL). The aim of this study was to evaluate alcohol-associated liver disease (ALD) paradox in Chile.

Method: The 2016–2017 NHS was a nationally representative cross-sectional study of the population aged 15 years and older, which included blood tests performed on a random subsample (N = 3700). We used the results of these test for persons aged 25–64 years (N = 2190) to evaluate the ALD paradox in Chile. We constructed a logit regression model that estimated the dangerous AC effect (defined as AUDIT ≥ 8 points) on the probability of presenting ALD (defined as GPT ≥ 40 U/L). We controlled for IL, presence of metabolic syndrome (MS), type 2 diabetes mellitus (DM2), obesity and tobacco.

Results: The average AC was 39 g of alcohol per week (13 g women <IL; 23 g women >IL; 64 g men, without differences by IL). In women, hazardous AC only increased ALD among those >IL who presented with obesity or MS in combination with T2DM (+36% obesity + MS + T2DM; p < 0.01). In men, hazardous AC only increased ALD among those with <IL (16% without comorbidities, 17% with tobacco, 22% with MS, 26% with obesity, and 28% with all; p < 0.05).

POSTER PRESENTATIONS

Conclusion: ALD paradox can be observed in Chile among men, but not among women. The evaluated associated comorbidities increased the effect of hazardous AC on ALD. It is necessary to investigate how the IL determines the patterns of AC and comorbidities stratifying by sex. Among men, <IL is likely to be associated with more harmful drinking patterns and a greater presence of comorbidities. Among women, >IL is likely associated with higher AC and more harmful consumption patterns.

PO-2749

The combination of ABIC+ELF as a single marker outperforms ABIC alone in predicting 90-day survival in alcoholic hepatitis.

Freya Rhodes^{1,2}, Nikhil Vergis³, Mark Thursz³, Rachel Westbrook^{1,2}, Alison Rodger⁴, Sudeep Tanwar^{1,5}, William Rosenberg^{1,2}. ¹UCL, Institute for Liver and Digestive Health; ²Royal Free NHS Foundation Trust, Hepatology; ³Imperial College, London, Hepatology; ⁴UCL, Institute for Global Health; ⁵Barts Health NHS Trust, Gastroenterology and Hepatology

Email: Frhodes@doctors.net.uk.

Background and aims: Tests predicting mortality could improve management of patients with Alcoholic Hepatitis (AH). Maddrey's Discriminant Function, MELD, ABIC and GAHS were found to predict

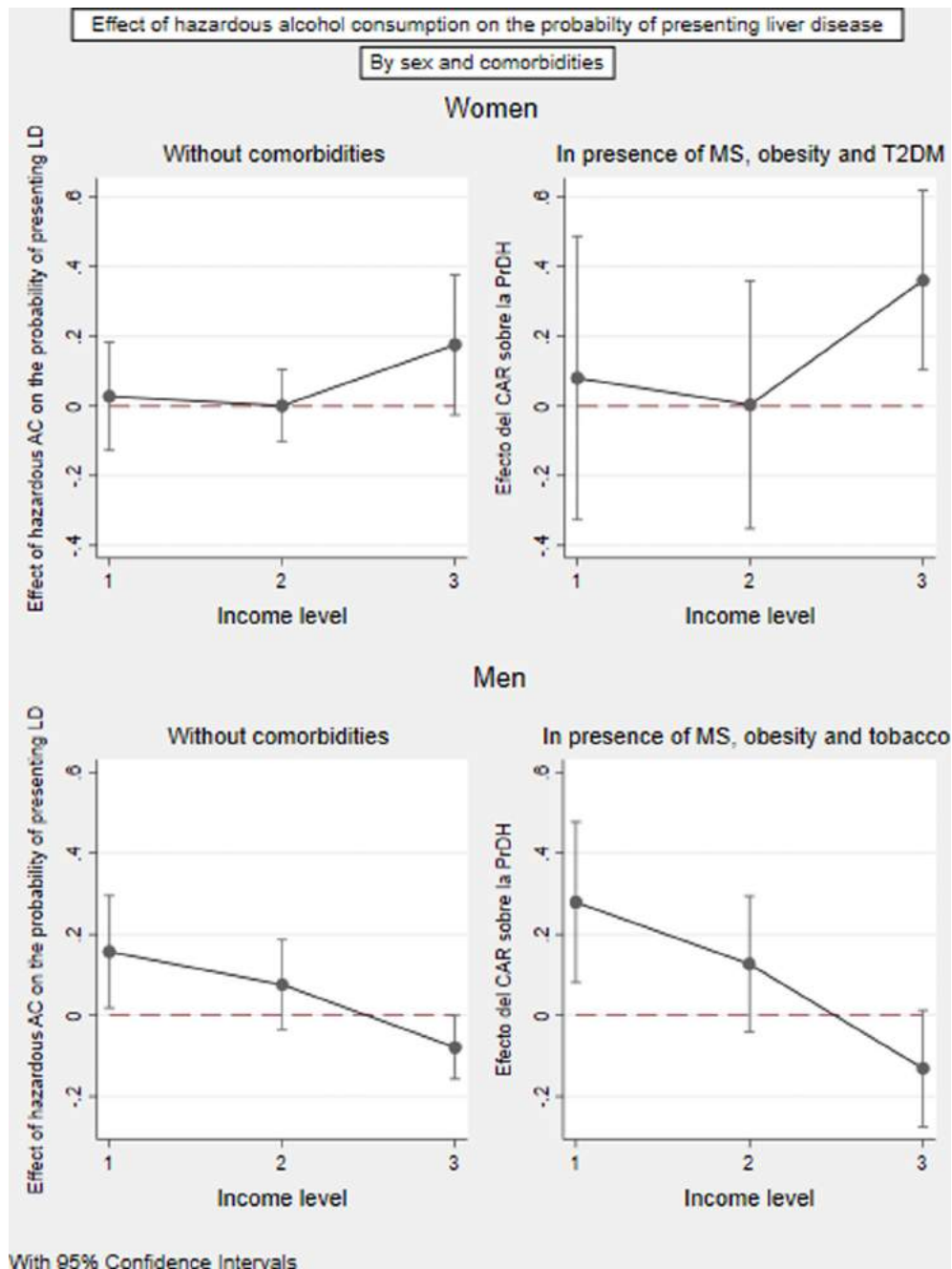


Figure: (abstract: PO-2704)

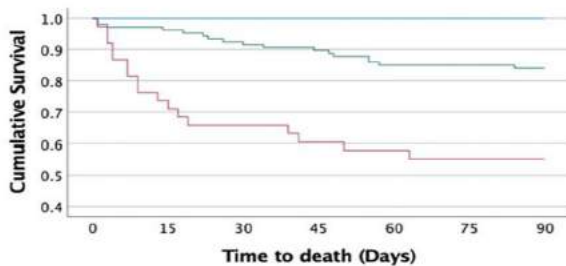
Cirrhosis and its complications: ACLF and Critical illness

mortality in AH in the STOPAH trial, but with sub-optimal scores (90-day AUCs of 0.670, 0.704, 0.726 and 0.713 respectively). The Enhanced Liver Fibrosis (ELF) test is a good prognostic marker for Chronic Liver Disease but has not been studied in AH. We aimed to evaluate the prognostic performance of ELF alone and in combination with other scores in AH.

Method: ELF measured in 179 baseline STOPAH serum samples on an Advia Centaur XP, was compared to baseline STOPAH data. Prognostic performance predicting mortality at 28/90/120 days was assessed using logistic regression, AUROC and Kaplan Meier for ELF, ELF components, MELD, GAHS, ABIC, Neutrophil-to-Lymphocyte-Ratio (NLR). FIB4 and Lille were evaluated in sub-analyses.

Results: All scores were available for 162/179 participants. ELF ranged from 11.97–21.68, (median = 15.9; IQR 14.9–16.9). ELF predicted mortality at 28/90/120 days; 90-day mortality OR = 1.7 (95% CI 1.3–2.2, $p < 0.001$), AUROC 0.72 (95% CI 0.63–0.81). AUROCs for other markers were not statistically different (ABIC = 0.74; NLR = 0.70; GAHS = 0.75; MELD = 0.74). ELF was positively correlated with CRP ($\rho = 0.51$, $p < 0.001$) and AST ($\rho = 0.35$, $p < 0.001$), but was not associated with infection ($p = 0.55$) or variceal bleeding ($p = 0.56$). Logistic regression revealed that an optimal algorithm combining ABIC+ELF predicted 90-day mortality; AUC = 0.81, (95% CI 0.73–0.89), significantly better than ABIC alone ($p = 0.01$). Both low-ABIC (<6.71) and low ELF (<16.78) predicted 100% 90-day survival-rate ($n = 17/17$), compared to 55% survival for high ABIC/high ELF ($n = 21/38$) ($p < 0.01$). Those with High ABIC/high ELF and Lille <0.45 had a 90-day survival-rate of 90% ($n = 9/10$), compared to 46% (6/13) survival in those with Lille ≥ 0.45 ($p = 0.047$). Survival rates were 59% in 17 with sepsis compared to 89% in 83 without sepsis ($p = 0.001$) amongst 100 with high ABIC/low ELF.

Kaplan Meier Survival curve for combined ABIC+ELF at 90-day mortality end-point.



Combined ABIC + ELF categories
 — ABIC < 6.71 and ELF < 16.78
 — ABIC < 6.71 and ELF ≥ 16.78 OR ABIC ≥ 6.71 and ELF < 16.78
 — ABIC ≥ 6.71 and ELF < 16.78
 — ABIC ≥ 6.71 and ELF ≥ 16.78

ABIC + ELF survival groups	Total N	N of deaths (Survival %)
ABIC < 6.71 and ELF < 16.78	17	0 (100)
ABIC < 6.71 and ELF ≥ 16.78 OR ABIC ≥ 6.71 and ELF < 16.78	107	17 (84)
ABIC ≥ 6.71 and ELF ≥ 16.78	38	17 (55)
Overall	162	34

Kaplan-Meier survival probability for patients stratified by a combination of ELF with ABIC at 90-day censored study end-point. ABIC threshold of 6.71 taken from published optimum threshold. ELF threshold of 16.78 derived from Youden's (J) index. ABIC = Age, Bilirubin, INR, Creatinine.

Figure:

Conclusion: The prognostic performance of ABIC+ELF (AUROC = 0.81) exceeded ABIC alone in STOPAH patients with AH. The addition of Lille allowed further refinement of survival-rates. Validation of ABIC-ELF may establish wide applicability of this test for prognosis in AH.

PO-552

The landscape of mitochondrial dysfunction in circulating leukocytes of patients with acute-on-chronic liver failure is characterized by altered mitochondrial metabolism and structure

Ingrid Wei Zhang^{1,2}, Anna Curto², Cristina López-Vicario^{1,2}, Mireia Casulleras^{1,2}, Marta Duran-Güell^{1,2}, Roger Flores-Costa^{1,2}, Ferran Aguilar², María Hernández-Tejero³, David Toapanta³, Javier Fernandez^{2,3}, Vicente Arroyo², Joan Clària^{1,2,4}. ¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ²European Foundation for the study of chronic liver failure, Barcelona, Spain; ³Hospital Clínic de Barcelona, Liver ICU, Barcelona, Spain; ⁴University of Barcelona, Department of Biomedical Sciences, Barcelona, Spain

Email: IWZHANG@clinic.cat.

Background and aims: Patients with acute decompensation (AD) of cirrhosis progressing to acute-on-chronic liver failure (ACLF) present a systemic hyperinflammatory response associated with increased levels of small molecule metabolites in the circulation. To investigate whether these alterations reflect inadequate cell energy output, we assessed mitochondrial morphology and central metabolic pathways with special emphasis on the tricarboxylic acid (TCA) cycle in peripheral leukocytes from AD patients with and without ACLF.

Method: Mitochondrial ultrastructure of circulating leukocytes from patients with AD cirrhosis and ACLF was visualized by transmission electron microscopy and compared to healthy subjects. Cytosolic and mitochondrial metabolic fluxes were determined in these cells by plate-based assays measuring NADH and FADH₂ production from various substrates.

Results: Mitochondrial ultrastructure in patients with AD cirrhosis was distinguished by cristae rarefaction and swelling. The number of mitochondria per leukocyte was higher in patients, accompanied by a reduction in their size. The severity of these morphological changes peaked in patients with ACLF. Mononuclear leukocytes from both AD and ACLF patients showed increased utilization of carbon and nitrogen sources to meet, preferentially through extra-mitochondrial pathways, the high-energy demand of inflammatory cells. In mononuclear leukocytes from ACLF patients, mitochondrial flux analysis uncovered two break-points in the TCA cycle at the isocitrate dehydrogenase and succinate dehydrogenase level, which were bridged by anaplerotic reactions involving glutaminolysis and nucleoside metabolism.

Conclusion: Our findings provide evidence at the organelle and biochemical level that severe mitochondrial dysfunction in leukocytes is a hallmark of patients with AD cirrhosis progressing to ACLF.

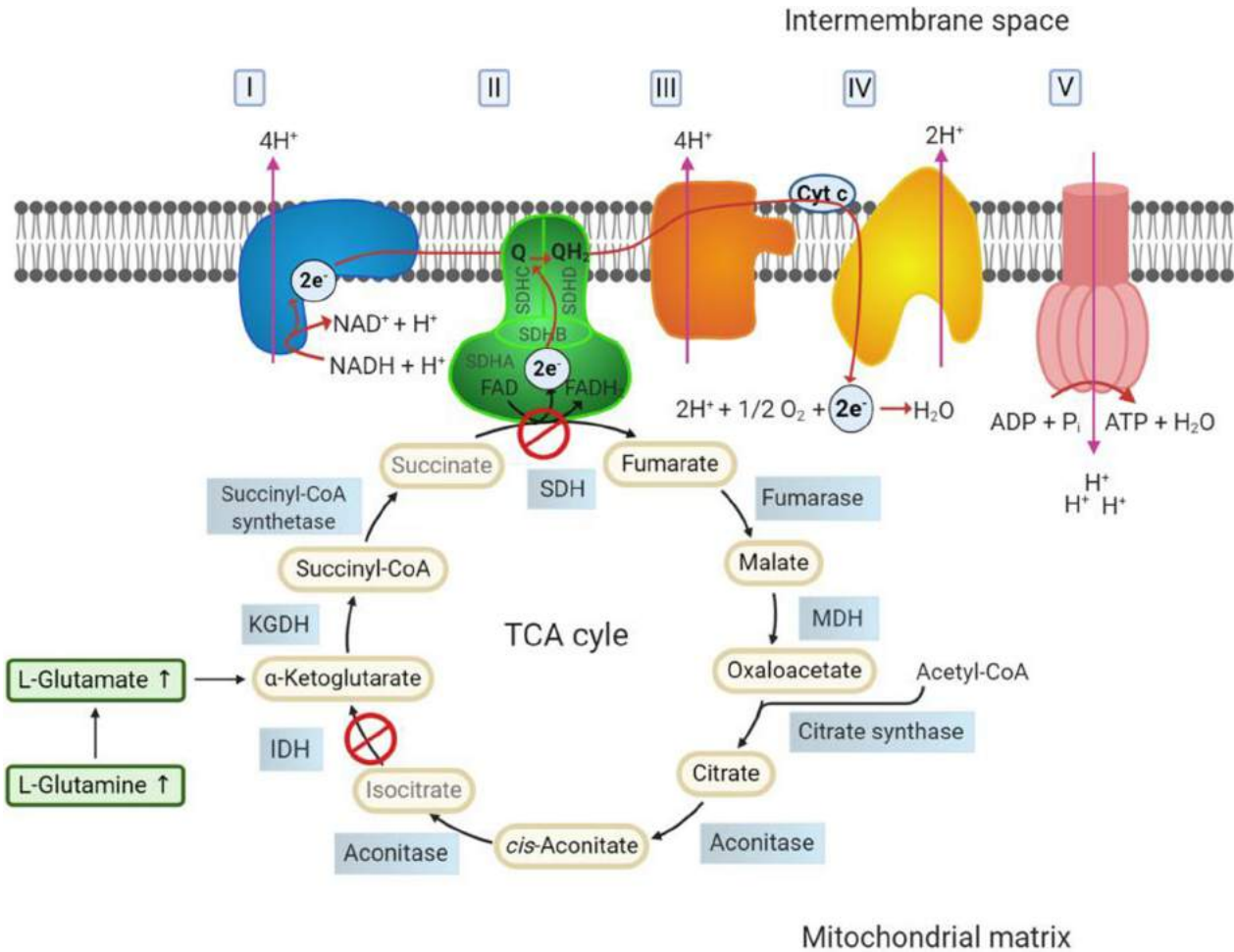


Figure: (abstract: PO-552)

PO-675
Increased incidence of respiratory failure with terlipressin use in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure

Florence Wong¹, Chris Pappas², Rajender Reddy³, Hugo E. Vargas⁴, Michael Curry⁵, Khurram Jamil⁶, Arun Sanyal⁷. ¹University of Toronto, Medicine, Toronto, Canada; ²Orphan Therapeutics, Lebanon, United States; ³University of Pennsylvania, Medicine, Philadelphia, United States; ⁴Mayo Clinic, Transplant Hepatology, Phoenix, United States; ⁵Beth Israel Deaconess Medical Center, Gastroenterology, Boston, United States; ⁶Mallinckrodt Pharmaceuticals, Critical Care Division, Bedminster, United States; ⁷Virginia Commonwealth University, Internal medicine, Richmond, United States
 Email: florence.wong@utoronto.ca.

Background and aims: The North American CONFIRM study (NCT02770716) for HRS1 suggests an increased incidence of respiratory failure (RF) in very ill patients with HRS1 treated with terlipressin. This study was to assess the incidence and predictive factors of RF in such patients treated with terlipressin vs. placebo.

Method: 300 patients with HRS1 in the CONFIRM study were randomized in 2:1 ratio to terlipressin vs. placebo, 1–2 mg 6 hourly by bolus injection both with albumin. At enrollment, all patients were assessed for organ failure (OF) per EASL-CLIF criteria (Moreau et al. Gastroenterology 2013) and then classified into grades of acute-on-chronic liver failure (ACLF). All patients had at minimum grade 1 ACLF due to the presence of HRS 1; grades 2 and 3 ACLF represent 2 or 3 OFs respectively. This post-hoc analysis divided patients into grade ≤2

and grade 3 ACLF subgroups; the effects of terlipressin vs. placebo on the incidence of RF between these subgroups were compared.

Results: 200 patients received terlipressin and 99 received placebo (1 patient was not dosed) with a group mean age of 53.8 ± 11.5 yrs, 60% male, median baseline serum creatinine 3.3 mg/dL, and median MELD 33. There were 49.7% vs. 40.6% with grade 1 ACLF, 30.2% vs. 40.6% with grade 2 ACLF, and 20.1% vs. 17.8% with grade 3 ACLF for the terlipressin and placebo arms respectively. The Table shows the incidence of RF between the treatment arms in the ACLF subgroups. The predictors of RF with terlipressin use were baseline INR (odds ratio or OR: 1.81, p = 0.011, baseline mean arterial pressure (OR: 1.037, p = 0.037) and baseline SpO₂ (OR: 0.835, p = 0.014). There was no difference in 90-day survival between the terlipressin and placebo arms for the ACLF grade ≤2 group (55.5% vs. 56.6% respectively).

Table: RF and death incidence by ACLF grade (*p < 0.05 terlipressin vs. placebo)

	ACLF grade ≤2		ACLF grade 3	
	Terlipressin n = 160	Placebo n = 81	Terlipressin n = 40	Placebo n = 18
Any SAE	98 (61.3%)	48 (59.3%)	32 (80%)	12 (66.7%)
RF as SAE	15 (9.4%)	5 (6.2%)	12 (30%)*	0 (0%)
Death in 30 days	56 (35%)	31 (38.3%)	27 (67.5%)	9 (50%)
Dear from RF in 30 days	8 (5%)	1 (1.2%)	9 (22.5%)*	0 (0%)

For patients with ACLF grade 3, 90-day survival was significantly worse with terlipressin (27.5%) vs. placebo (50%), mainly related to RF. **Conclusion:** Terlipressin should be used with extreme caution in patients with HRS1 and ACLF grade 3, especially in those with compromised oxygen saturation, as they are at risk for RF and increased mortality.

PO-968

Terlipressin improves renal replacement therapy-free survival in hepatorenal syndrome type 1

Juan Carlos Q. Velez¹, Alex Befeler², Ira Kurtz³, Juan Gallegos-Orozco⁴, Hugo E. Vargas⁵, John M. Vierling⁶, S. Chris Pappas⁷, Khurram Jamil⁸. ¹Ochsner Health System, Department of Nephrology; ²Saint Louis University, Division of Gastroenterology and Hepatology; ³UCLA Medical Center, Division of Nephrology; ⁴University of Utah, Division of Gastroenterology; ⁵Mayo Clinic, Division of Gastroenterology and Hepatology; ⁶Baylor College of Medicine, Section of Gastroenterology and Hepatology; ⁷Orphan Therapeutics, Scientific Affairs; ⁸Mallinckrodt Pharmaceuticals, Department of Scientific Affairs
Email: juan-carlos.velez@ochsner.org.

Background and aims: Hepatorenal syndrome type 1 (HRS-1) is an ominous form of acute kidney injury in patients with decompensated cirrhosis. Recently, the results of the randomized placebo (PBO)-controlled trial (RCT) CONFIRM demonstrated that terlipressin (TERLI) is effective in reversing HRS-1 and in reducing the cumulative need for renal replacement therapy (RRT). However, whether TERLI reduces the need for RRT among survivors has not been determined. **Method:** CONFIRM (NCT02770716) was a North American RCT (N = 300) that compared HRS-1 reversal rates between patients treated with albumin plus TERLI (n = 199) vs. albumin plus PBO (n = 101) (2:1). We conducted a post hoc intention-to-treat analysis to assess the incidence of RRT among CONFIRM survivors to assess longer term benefit. We also conducted a pooled analysis of the 3 TERLI RCTs in HRS-1 (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to examine 90-day RRT-free survival rates.

Results: In CONFIRM, the cumulative incidences of need for RRT for TERLI at day 14, 30, and 90 were 23%, 26%, and 29% compared with 35%, 36%, and 39% for patients assigned to PBO (p = 0.03, 0.07, and 0.1, respectively). Among survivors, significantly fewer TERLI-treated patients remained dependent on RRT at day 14, 30, and 90 (22%, 26%, and 30%, respectively) compared with PBO (39%, 43%, and 46%; p < 0.01, p = 0.03, and p = 0.05, respectively). The 90-day RRT-free survival rate was 35% in the TERLI group vs 30% in the PBO group (p = 0.08), with a numerically longer median number of days in the TERLI group (20 vs 11). Pooled analysis of the 3 RCTs revealed a greater 90-day RRT-free survival rate for TERLI-treated (n = 352) compared with PBO-treated (n = 256) patients (37% vs 29%, p = 0.03; OR [95% CI], 1.47 [1.04, 2.07]).

Conclusion: Treatment with TERLI plus albumin decreased the rate of RRT and improved RRT-free survival in survivors with HRS-1. This is the first pharmacological intervention proven to reduce the need for RRT in patients with HRS-1. Because of the significant impact of RRT on quality of life and risk of infections, this observation expands the clinical benefit of TERLI and enhances the reported efficacy of TERLI in inducing HRS-1 reversal.

PO-984

Hepatopulmonary Syndrome is related with the Development of Acute-on Chronic Liver Failure and Poor prognosis in Cirrhotic patients

Han Seul ki¹, Moon Young Kim¹, Seong Hee Kang¹, Soon Koo Baik¹. ¹Wonju Severance Christian Hospital, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Weonju, Korea, Rep. of South
Email: baiksk@yonsei.ac.kr.

Background and aims: Hepatopulmonary syndrome (HPS) is characterized as a defect in arterial oxygenation caused by pulmonary vascular dilatation in the setting of chronic liver disease. The long-term prospective data for hepatopulmonary syndrome (HPS) including large number of patients is lacking especially in Asian. We evaluated the long-term prognosis of HPS, especially the development of acute-on chronic liver failure (ACLF) in HPS and related factors.

Method: A total of 142 patients with cirrhosis who had been undertaken saline agitated contrast echocardiography to diagnose HPS were enrolled and observed prospectively. The cohort based on our previous study who were followed until December, 2019. All events related with cirrhosis including liver transplantation were recorded and monitored.

Results: Median follow-up period was 27 months. 59 patients (41%) were diagnosed as HPS (grade 1 = 24, grade 2 = 23, grade 3 = 12). There were 38 cases of mortality in HPS group and 37 cases were in Non-HPS group (p < 0.01). 5-year survival rate was 47% in HPS group and 62% in non-HPS group. During the study period, 9 patients in non-HPS and 8 patients in HPS were not followed. 5 patients of HPS and 4 patients of non-HPS underwent liver transplant.

In Cox proportional hazards model, HPS and Modified End stage Liver Disease (MELD) score above 18, Child-Turcotte-Pugh (CTP) class B/C were statistically significant risk factors of mortality after adjusting other risk factors (HPS Hazard ratio (HR) = 1.9, p = 0.01; MELD ≥ 18 HR = 2.3, p < 0.01; CTP class B/C HR = 2.9, p < 0.01). In HPS group, CTP class B/C and MELD score above 18 were independent risk factors of mortality (CTP B/C HR = 1.5, 95% CI = 0.5–4.3, p = 0.45; MELD ≥ 18 HR = 2.68, 95% CI = 1.3–5.4, p < 0.01). In additional analysis, the development of ACLF during follow-up was significantly higher in patients with HPS (p < 0.01) and there was more frequent lung involvement of ACLF in HPS group (p = 0.03).

Conclusion: In long-term follow-up cohort, patients with HPS showed a poor prognosis compared to non-HPS patients. HPS is a risk factor for the ACLF development independently with hepatic dysfunction and the lung involvement was more common.

PO-1161

Impact of INFECTIONS on the post-operative survival of ACUTE-ON-CHRONIC LIVER FAILURE patients undergoing LIVER TRANSPLANTATION

Elina Lam¹, Antonella Putignano¹, Valerio Lucidi², Desislava Germanova², Antonia Lepida¹, Trépo Eric¹, Nathalie Boon¹, Lukas Otero-Sanchez¹, Mohamed Zerriouh¹, Elisa Brauns³, Degré Delphine¹, Christophe Moreno¹, Thierry Gustot¹. ¹CUB Hospital Erasme, Gastroenterology, Hepato-Pancreatology and Digestive Oncology, Bruxelles, Belgium; ²CUB Hospital Erasme, Digestive and Hepatobiliary Surgery, Bruxelles, Belgium; ³CUB Hospital Erasme, Internal Medicine, Bruxelles, Belgium
Email: putignano.anto@gmail.com.

Background and aims: The prevalence of infections in patients with acute-on-chronic liver failure (ACLF) is high (Fernandez *et al*, Gut 2018), however the role of sepsis on the outcome of ACLF patients undergoing liver transplantation (LT) is currently unknown. In this single center, retrospective study, we investigated the role of infections and septic shock on post-LT outcome of patients with ACLF.

Method: Consecutive ACLF patients transplanted in a tertiary Belgian center between 2007 and 2017 were included (EASL-Clif definition).

POSTER PRESENTATIONS

To evaluate the outcomes, patients were stratified according with the presence of an active but controlled infection 24 hours before LT, defined as an infection treated by antibiotics since at least 48 hours and with stable or improving vasopressors doses in case of shock. Kaplan Meier analysis (Log Rank) was used to estimate cumulative survival and Cox Regression for univariate analysis.

Results: Ninety-six patients with ACLF were transplanted (female N = 35, age 54 ± 9.9), 26 ACLF-1, 25 ACLF-2 and 45 ACLF-3. Forty-three patients (44.8%) had an infection before LT, 1 ACLF-1 (3.8%), 12 ACLF-2 (48.0%) and 30 ACLF-3 (66.7%). Patients with pre-LT infections had longer post-LT ICU in-stay (7 days, IQR 7) compared to non-infected ones (4 days, IQR 4, $p = 0.028$). The post-LT survival rate of patients with and without infection was 88.4% and 100% at 28-day ($p = 0.011$), 81.4% and 96.2% at 90-day ($p = 0.016$), 72.1% and 88.5% at 1-year ($p = 0.033$) post-LT, respectively. The causes of 90-day post-LT mortality were septic shock (30%), hemorrhagic shock (20%), invasive aspergillosis (10%), cardiac arrest (10%), other cause (20%) and unknown (10%). Risk factors for 90-day mortality in patients with infection at LT were pre-surgical bilirubin level (HR 1.08, CI 1.02–1.14, $p = 0.009$), MELD score (HR 1.10, CI 1.02–1.19, $p = 0.01$), arterial lactates (HR 1.3, CI 1.0–1.6, $p = 0.017$), CLIF-C ACLF score (HR 1.08, CI 1.01–1.17, $p = 0.033$), septic shock (HR 5.32, CI 1.27–22.29, $p = 0.22$), Quick-SOFA score (HR 2.95, CI 1.27–6.86, $p = 0.012$). However, length of antibiotic treatment before LT and MDR bacteria or fungi infections or colonization during the 6 months before LT were not associated with higher mortality.

Conclusion: Patients with active but controlled infection at LT show an increased short- and medium-term mortality. However, mortality risk factors are related both to sepsis and to ACLF severity and should be considered to avoid LT futility.

PO-1387

Plasma Soluble CD14 predicted development of hospital acquired infection in decompensated cirrhosis patients from the ATTIRE trial

Louise China¹, Natalia Becares¹, Thais H. Tittanegro¹, Camilla Rhead¹, Alastair O'Brien¹. ¹University College London, United Kingdom
Email: louise.china@ucl.ac.uk

Background and aims: Patients with decompensated cirrhosis hospitalised with acute complications have high incidences of hospital-acquired infection (HAI), often with multi-drug resistant organisms (MDRO) leading to high mortality. Empiric/prophylactic antibiotics in the absence of positive microbial culture results can reduce infection and death in certain settings, e.g. variceal bleeding, yet indiscriminate prescribing increases risk of MDROs. A balance is needed, but current antibiotic strategies for decompensated patients are homogenous, leading to overprescribing to mitigate risk of missing infection. However, decompensated cirrhosis is heterogeneous and a precision-approach based on individualised risk could be beneficial. We tested whether serological biomarkers of infection could identify patients at high risk of HAI to aid antimicrobial stewardship. Using samples from the ATTIRE trial we compared the ability of selected serological biomarkers to predict development of HAI in these acutely unwell patients.

Method: HAI, defined as new infection >48 hr after trial entry, was diagnosed according to site clinicians' judgement with infection case report forms containing clinical, biochemical, microbiological and radiological data was blindly scrutinized by 3 independent physicians. 135 randomly selected patients (76 without and 59 with new infection) had plasma samples analysed at trial days 1 and 5 using a luminex multiplex assay with WCC and CRP measured at site.

Results: Patients were mostly male with alcoholic cirrhosis, mean MELD score 20.2 (SD 7.0) and median age 53.9 years. Overall 177 new infections were diagnosed from 828 randomisations with respiratory infection most commonly diagnosed. Only 44/177 (24.9%) of these new infections were culture positive with only 6/55 (10.9%) of respiratory infections being culture positive. The mean trial treatment day on which patients developed a new infection was 6 (SD 2.5).

Plasma soluble CD14 and WCC was significantly higher at day 5 in patients that were diagnosed with HAI during the trial compared to those not (13, 596 ng/ml vs 5746 ng/ml, $p = 0.0094$, CI 1975–13, 727 ng/ml and $11.4 \times 10^9/L$ vs $8.9 \times 10^9/L$, $p = 0.0361$, CI 0.1608–4.743). Conversely, there were no significant differences in Procalcitonin, plasma Calprotectin, Lipopolysaccharide Binding Protein, CRP, CD163 or CCL8 between patients that received HAI diagnosis or not when day 1 or 5 samples were compared.

Conclusion: Only increasing plasma soluble CD14 values during hospitalisation, which mediates immune responses to Lipopolysaccharide via monocyte and macrophage activation, and WCC were able to predict decompensated cirrhosis patients at high risk of developing HAI and could be used to aid appropriate antibiotic prescribing.

PO-1501

Ascitic fluid lactic acid is an accurate predictor of mortality in patients with spontaneous bacterial peritonitis

Ilianna Mani¹, Alexandra Alexopoulou¹, Theodoros Alexopoulos¹, Larisa Vasilieva¹, Emilia Hadziyannis¹, Danaï Agiasotelli¹, P. Spyridon Dourakis¹. ¹Medical School, National and Kapodistrian University of Athens, 2nd Department of Internal Medicine and Research Laboratory, Athens, Greece
Email: ilianamani@windowslive.com

Background and aims: Elevated blood lactic acid was found to predict accurately mortality in severely ill patients with cirrhosis, especially in acute-on-chronic liver failure (ACLF). In the present study, ascitic fluid lactic acid (AFlac) was evaluated as potential predictor of short-term mortality in patients with spontaneous bacterial peritonitis (SBP).

Method: Sixty-three consecutive patients with SBP (SBP group), 50 patients without SBP but with acute event (AD/ACLF group) and 12 with decompensated cirrhosis without acute event (DC) (control group) were prospectively studied. AFlac was measured in the first paracentesis of AF on admission using GEM Premier 3500 analyzer (Instrumentation Laboratory, Lexington, USA).

Results: Characteristics of SBP group were: 68.3% male, median age 60 (IQR 54–72) years, MELD score 17 (12–29), ACLF 34.9%. AFlac levels were higher in SBP group compared to AD/ACLF or control group ($p < 0.001$ or $p < 0.001$, respectively). In SBP group, ROC curve for 30 days showed that AFlac value of 3.5 mmol/ml was associated with the best prediction of mortality [c-statistic = 0.894, 72% sensitivity, 89.5% specificity, 81.8% positive predictive value (PPV), 82.9% negative predictive value (NPV)]. In Kaplan-Meier curve, patients with high AFlac (≥ 3.5 mmol/ml) had a poor prognosis in 30 days compared to those with low values (< 3.5 mmol/ml) (log-rank $P = 0.001$). In 90 days, prognostic accuracy of AFlac was further enhanced (c-statistic 0.927) with the optimal value at 2.25 mmol/l (93.9% sensitivity, 83.3% specificity, 86.1% PPV, 92.6% NPV).

In multivariate analysis for 30 days, only AFlac [hazard ratio (HR) 1.443, (95% confidence interval -CI 1.146–1.817), $P = 0.002$] and NLR [HR 1.075 (95%CI 1.027–1.125), $P = 0.002$] were independent predictors of mortality after adjusting for age, sex, MELD score and C-reactive protein. The same parameters [HR 1.503 (95%CI 1.193–1.893), ($p = 0.001$) and HR 1.078 (95%CI 1.032–1.127), ($p = 0.001$), respectively] emerged again at 90 days as independent predictors of mortality.

Conclusion: Ascitic fluid lactic acid was increased in patients with SBP and was an accurate predictor of short-term mortality. Ascitic fluid lactic acid and NLR were independently associated with mortality in spontaneous bacterial peritonitis.

PO-1585

Potential mechanisms underlying the protective effect of long-term albumin infusion in cirrhosis

Qianwen Zhao^{1,2}, Abeba Habtesion¹, Fausto Andreola¹, Nathan Davies¹, Jane Macnaughtan¹, Rajiv Jalan¹. ¹University College London, Institute for Liver and Digestive Health, London, United Kingdom; ²Department of Gastroenterology and Hepatology, West China Hospital, Sichuan University, Chengdu, China
Email: r.jalan@ucl.ac.uk.

Background and aims: The mechanisms preventing hepatic decompensation and mortality (Lancet 2018;391:2417) following long-term albumin infusion in cirrhosis is unknown. Increased hepatocyte expression of TLR4 in cirrhosis sensitises patients to the 'second hit' resulting in acute on chronic liver failure (ACLF). The aims of this study were to determine (i) whether analbuminaemic (NAR) rats have greater liver injury and sensitivity to LPS (ii) whether albumin infusion is protective in NAR rats (iii) the impact of analbuminaemia and albumin infusion on the gut-liver interface and hepatic TLR4 signaling.

Methods: 10 groups of NAR and SD rats were studied (n=4-7 in each group); Naïve, cirrhosis (4-w after bile duct ligation (BDL) and ACLF models (induced by lipopolysaccharide (LPS) to BDL) were studied. BDL groups: ±LPS, ±albumin infusion (1.5 g/kg i.p. for 2 weeks). Markers of liver injury: plasma ALT level and TUNEL staining; markers of gut integrity and permeability: DAB immunohistochemistry ZO-1 expression in ileum and colon tissue; Hepatic TLR4 immunohistochemistry and related pathway genes RT² PCR profiler were studied.

Results: *Liver injury:* ALT levels and TUNEL positive areas were significantly higher in NAR compared with SD rats (p = 0.01 and p = 0.01), which were corrected with albumin infusion (p = 0.02, p = 0.047). *Effect of LPS administration:* coma-free survival was higher in SD rats than NAR rats (80% vs 40%). *Effect of albumin administration:* Administration of albumin to BDL rats reduced severity of liver injury and mortality after LPS administration [p = 0.001; 40% vs 100%, p = 0.04]. *Markers of gut permeability:* In NAR rats, the histopathological examination of the ileum and colon revealed severe distortion and reduction in ZO-1 expression, which was restored with albumin supplementation (Fig). *Hepatic expression of TLR4 and associated pathways:* Cirrhotic NAR animals had greater hepatic TLR4 expression which was reduced by albumin administration. Hepatic TLR4 gene array confirmed the activation of TLR4 dependent pathways in the cirrhotic NAR animals, which was abrogated by albumin infusion.

Conclusion: NAR animals have significantly greater liver injury, increased sensitivity to LPS and mortality which is prevented by albumin administration. Our data show for the first time that the mechanism of the protective effect of albumin is consequent upon restoration of gut junctional proteins and reduction of hepatic TLR4 expression.

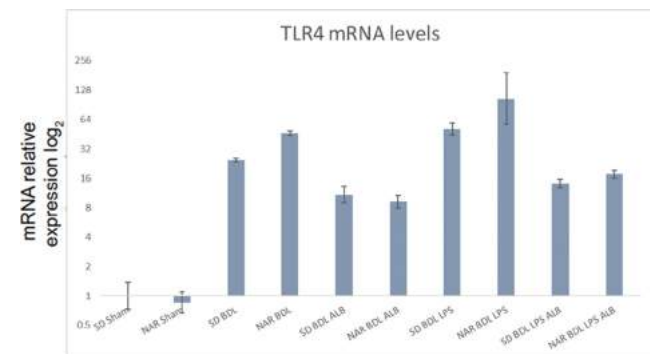


Figure 1: TLR4 qPCR data.

TLR4 qPCR was performed and its relative expression was studied using the DDCT method and delineated in a log₂ scale. TLR4 was

upregulated in cirrhotic and ACLF NAR groups compared to SD controls. Albumin administration reduced TLR4 expression in cirrhotic and ACLF groups, in both NAR and SD species.

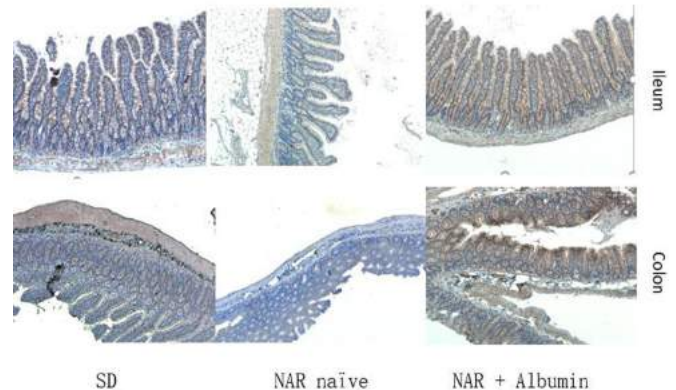


Figure 2: Gut ZO-1 immunohistochemistry showed ZO-1 was downregulated in NAR naïve group. Albumin infusion restored ZO-1 expression.

PO-2058

Stem Cell Transplantation in patients with cirrhosis and acute-on-chronic liver failure: A randomized, double-blind placebo control trial

Enric Reverter¹, Adria Juanola^{1,2}, Verónica Prado¹, Jordi Gratacós-Gines¹, Pedro Marin³, Enrique J. Andreu⁴, Fatima Aziz¹, Octavi Bassegoda^{1,2}, Isabel Graupera^{1,2,5,6}, Elisa Pose^{1,2,5}, Javier Fernandez¹, Pere Ginès^{1,2,5,6}. ¹Hospital Clínic de Barcelona, Liver Unit, Barcelona, Spain; ²Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ³Hospital Clínic de Barcelona, Hematology Department, Barcelona, Spain; ⁴Clinica Universidad de Navarra, Cell Therapy Area, Pamplona, Spain; ⁵Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; ⁶Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain
Email: pginès@clinic.cat.

Background and aims: Acute-on-chronic liver failure (ACLF) is associated with high mortality and does not have a specific treatment beyond transplantation. Administration of Mesenchymal Stem Cells (MSCs), with immunomodulatory and pro-regenerative properties, could be a potential treatment for ACLF. The present study evaluates the efficacy and safety of MSCs administration in patients with ACLF. **Method:** Double-blind, placebo-controlled, randomized clinical trial (1:1) evaluating the effects of MSCs infusion in patients with ACLF. 2 × 10⁶ MSCs/kg weight were administered on days 1, 4, 11 and 18. Changes in liver function, organ failure according to specific scales (CLIF-OF, CLIF-C ACLF, MELD), inflammatory cytokines and safety of MSCs infusion were assessed. Patients were followed 1-year.

Results: Twenty-three patients (78% men, mean age 54 years) with predominant alcohol etiology (69%) were included. Causes of admission were alcoholic hepatitis (57%), infection (22%), hemorrhage and others (21%). Eleven (48%) patients had grade I ACLF, 8 (35%) grade II and 4 (17%) grade III, with predominance of liver failure (96%), coagulation (35%) and renal failure (26%). The baseline CLIF-OF and MELD scores were 10 (10–12) and 32 (29–35). Fourteen (61%) patients received MSCs and 9 (39%) placebo. No differences in liver score changes (CLIF-OF, CLIF-C ACLF or MELD) were observed at days 7, 14, 18 or 28. No significant differences in leukocyte count or CRP were observed between groups at days 7, 14, 18 and 28. There were 5 infections in 3 patients (33%) of the control group and 8 in 6 patients (43%) of the MSCs group. Survival was not different between groups at 28 days (MSCs 50% vs. placebo 56%), 90 day (21% vs 44%) and 365 days (MSCs 21% vs. placebo 33%). Adverse events were similar between groups and mostly attributable to cirrhosis.

POSTER PRESENTATIONS

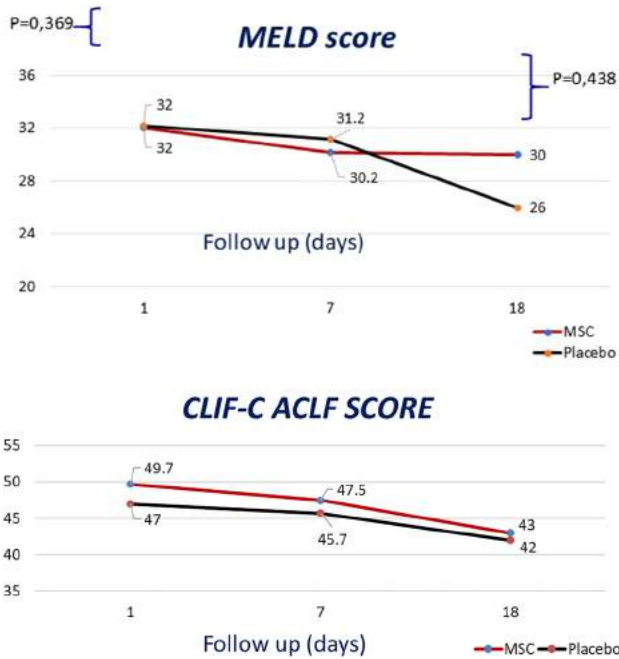


Figure:

Conclusion: In this pilot study, the administration of MSCs in patients with ACLF compared to placebo did not show an improvement in parameters of hepatic dysfunction or severity of ACLF. The infusion of MSCs was a safe and well tolerated intervention.

PO-2147

Intestinal epithelial cell signalling and cell death in Cirrhosis and Acute-on-Chronic Liver Failure

Stijn Aaron den Daas^{1,2}, Ugo Soffientini^{1,2}, Abeba Habtesion³, Bethlehem Arefaine^{1,2}, Roger Williams^{1,2}, Sukriti Sukriti⁴, Rajiv Jalan³, Shilpa Chokshi^{1,2}, Vishal C. Patel^{1,2,5}, Gautam Mehta^{1,2,3}. ¹Institute of Hepatology, Foundation for Liver Research, London, United Kingdom; ²King's College London, Faculty of Life Sciences and Medicine, London, United Kingdom; ³UCL Institute for Liver and Digestive Health, London, United Kingdom; ⁴Institute of Liver and Biliary Sciences, New Delhi, India; ⁵Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom
Email: s.dendaas@researchinliver.org.uk.

Background and aims: The precipitating event that drives the progression from cirrhosis to acute-on-chronic liver failure (ACLF) remains unidentified in around a third of cases (Moreau *et al.*, 2013). Endogenous mechanisms, such as translocation of gut-derived products, have been suggested to play a role in these cases but the molecular mechanisms remain unknown. Recent work has highlighted intestinal epithelial cell-derived extracellular vesicles (EVs)

(Bulek *et al.*, 2020), and intestinal epithelial cell death (Zheng *et al.*, 2019), as key steps in propagating intestinal inflammation and permeability. The aim of this study was to investigate EV signalling and cell death in intestinal epithelial cells, in response to bacterial LPS and ACLF patient faecal samples.

Method: Intestinal organoids were derived from healthy female C57BL/6J mice and cultured in mouse intestinal organoid medium as described (Sato *et al.*, 2011). Two experiments were undertaken: (i) organoids (n = 4/group) were treated with 100 µg/ml LPS, or control media, for 3 hours; (ii) organoids were treated with 10% human faecal samples from healthy controls (HC, n = 4), ACLF patients (n = 4, median ACLF grade = 3 IQR = 1–3), or control media (n = 4) for 3 hours. Supernatants from experiment (i) were analysed for EV release using Zetaview Nanoparticle Tracking Analyser. Samples from (ii) were analysed for lytic cell death, measuring supernatant LDH (Promega LDH-Glo) and by immunofluorescence [HOECHST, propidium iodide (PI)].

Results: (i) Treatment of mouse intestinal organoids with 100 µg/ml LPS for 3 hours causes a significant increase in EV release compared to control ($5.73 \times 10^9 \pm 1.89 \times 10^9$ vs $1.23 \times 10^{10} \pm 7.20 \times 10^9$ particles/ml, n = 4, p = 0.025); (ii) treatment of organoids with 10% ACLF faecal samples for 3 hours causes a significant increase in LDH release compared to 10% HC (650.9 ± 190.2 vs 259.9 ± 91.6 , n = 4, p < 0.05). Immunofluorescence demonstrates increased PI staining in 10% ACLF group compared with control (figure).

Conclusion: These data present potential mechanisms for propagation of intestinal inflammation, intestinal cell death and consequently gut-liver signalling of PAMPs and DAMPs in cirrhosis and ACLF. Future studies will delineate the specific inflammasome and cell death pathways involved in these responses. These findings pave the way for targeted molecular therapies to mitigate intestinal inflammation and onset of ACLF in cirrhosis.

PO-2313

IL-1Ra, IL-18 and TREM-1 circulating factors and CD+ve HLADR-low TIM3+ve suppressive monocytes predict development of sepsis within 3 days in patients with acute on chronic failure

Pushpa Yadav¹, Rakesh Kumar Jagdish², Rashi Sehgal¹, Rakhi Maiwall², Vijayraghavan Rajan², Ravinder Chaudhary¹, Mojahidul Islam¹, Sukriti Sukriti¹, Deepanshu Maheshwari¹, Anupam Kumar¹, Gayatri Ramakrishna¹, Nirupma Trehanpati², Shiv Kumar Sarin². ¹Institute of Liver and Biliary Sciences, Molecular and Cellular Medicine, New Delhi, India; ²Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India
Email: shivsarin@gmail.com.

Background and aims: Acute on Chronic Liver Failure (ACLF) patients with systemic inflammatory response (SIRS) have high probability to develop sepsis due to immune dysregulation. There are no early biomarkers of development of sepsis in setting of ACLF. We aimed to investigate dynamics of new circulating biomarkers and monocyte functions overtime in patients with ACLF.

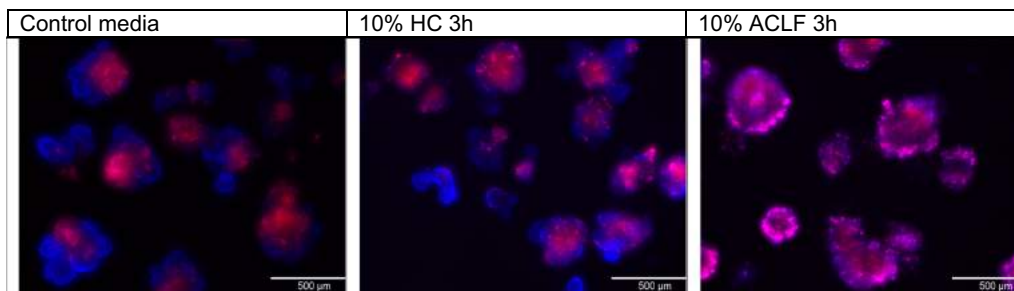


Figure: (abstract: PO-2147): Immunofluorescent staining of mouse intestinal organoids treated with faecal samples. Mouse intestinal organoids were treated with control media, 10% healthy control faecal sample, or 10% ACLF faecal sample for 3 hours. Organoids were washed and incubated for another 24 hours before HOECHST (blue) and propidium iodide (red) staining. Representative images shown.

Method: Ninety eight ACLF patients; without clinical SIRS [Group I: (n=25)] with SIRS but no sepsis [Group II: (n=35)] and with sepsis [Group III: (n=38)] and healthy controls (Group IV, n=15) were included. Patients were closely followed from admission and studied at baseline, 6 and 24 hr, day 3 and 7. We measured 40 plasma cytokines using cytokine bead assay and studied HLA-DR expression, phagocytosis, oxidative burst capacity and METosis in monocytes. Monocyte-T cell co-culture assays were done to explore the PD-L1, PD-L2, TIM-3+ve suppressive monocytes regulating T-cells functionality. Clinical correlations of immune dysregulation were determined.

Results: ACLF patients (aged 57 ± 6 yr, 70% males, 94% with alcoholic cirrhosis) had MELD of 28 median with range 14–47). At admission, HGF, IL-6, IL-8, MIF, MIP3a and MMP7 was significantly increased (p < 0.01) in Gr.I compared to healthy; Gr.II had increased IL-8, MIP-3a,

MCP-1, VEGFa, compared to Gr.I (p < 0.05). Gr. III had significantly raised (p < 0.001) levels of IL-1Ra, IL-18, and TREM1. Out of 25, 5 patients from Grp. II, developed sepsis within 2–3 days and showed raised levels of IL-1Ra (from 1203 to 35,000 pg/ml), IL-18 (48 to 114 pg/ml), and TREM1 (1273 to 4865 pg/ml) within 1224 hrs of admission. Circulating monocytes showed reduced HLA-DR expression at admission and during hospitalisation till Day 7 but significantly gained the suppressive phenotype with PDL1 and Tim3 expression (p < 0.05) and increased METosis in SIRS and sepsis patients.

Conclusion: This prospective study suggests that elevated levels of IL-1Ra, IL-18, TREM1, and TIM3+positive suppressive monocytes can be used as hallmark of sepsis within 12–24 hrs to discriminate ACLF SIRS from sepsis.

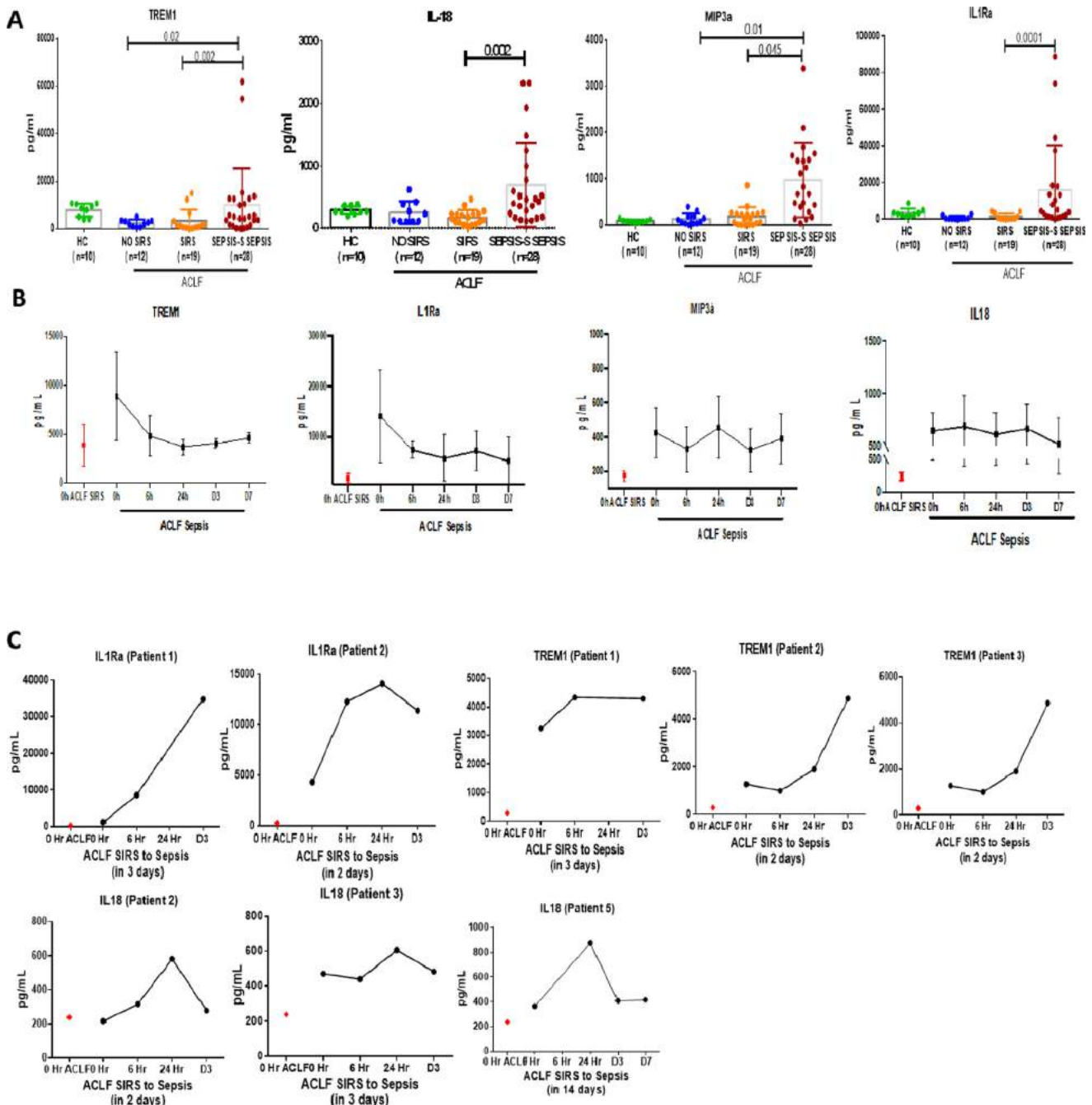


Figure: (abstract: PO-2313)

POSTER PRESENTATIONS

PO-2358

Modification of the CLIF-C ACLF score improves the predictive accuracy by adjusting for risk factors mechanical ventilation and pulmonary failure

Martin Schulz¹, Jan Mengers¹, Philip Ferstl¹, Frank Uschner², Nora Ackermann², Georg Guttenberg², Wenyi Gu², Alexander Queck², Maximilian Brol², Christiana Graf², Anna-Lena Laguna de la Vera², Stoffers Philipp², Cremonese Carla², Hans-Peter Erasmus², Martin-Walter Welker², Achim Grünewaldt², Jörg Bojunga², Stefan Zeuzem², Kai Hendrik Peiffer³, Christoph Welsch², Gernot Rohde², Jonel Trebicka². ¹Universitätsklinikum Frankfurt am Main, Medizinische Klinik 1, Frankfurt am Main, Germany; ²Universitätsklinikum Frankfurt am Main, Medizinische Klinik 1, Frankfurt am Main; ³Medizinische Klinik 1, Frankfurt am Main
Email: martin.schulz2@kgu.de.

Background and aims: Adequate risk stratification is essential in ACLF patients, since ACLF is associated with high short-term mortality. The CLIF-C ACLF score is the superior prognostic model to predict short-term mortality in ACLF patients. This study aims to evaluate, if its predictive accuracy can be improved by adjusting for pulmonary impairment.

Method: Retrospectively, data from 498 patients with cirrhosis, admitted to IMC/ICU between March 2015 and June 2019 were collected. ACLF was defined according to EASL-CLIF criteria. To better dissect the role of pulmonary impairment, we performed a 1:1:1 propensity score matching of 147 patients with ACLF either combined with mechanical ventilation (MV), pulmonary failure (PF, PaO₂/FiO₂ < 200 mmHg) or unimpaired ventilation, adjusting for CLIF-C ACLF score and sex. Cox regression and ROC analysis were performed to evaluate predictive performances of scores.

Results: In the whole cohort (n=498) MV and PF (PaO₂/FiO₂ < 200mmHg) were identified as independent risk factors of mortality. Already 28-day mortality rates were significantly higher in ACLF patients with PF (83.7%) or MV (67.3%) compared to matched ACLF-noMV/noPF (38.8%). ROC analysis confirmed superior predictive accuracy of the CLIF-C ACLF score (28d AUROC=0.8; n=489) but showed poor prediction in patients with ACLF-PF (AUROC=0.49) or ACLF-MV (AUROC=0.66). We adjusted the CLIF-C ACLF score for presence/absence of MV/PF (CLIF-C ACLF-R score), resulting in an improved predictive performance not only in ACLF-patients (AUROC = 0.84 vs. 0.77), but also in cirrhosis overall (AUROC = 0.87 vs. 0.81, see Figure 1).

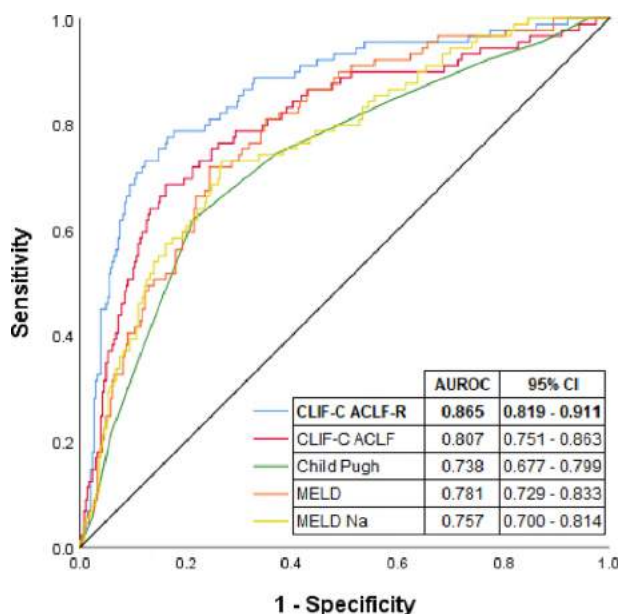


Figure:

Conclusion: While CLIF-C ACLF score underestimates the risk of mechanical ventilation and pulmonary failure in ACLF patients, adjusting for pulmonary impairment can improve the overall predictive accuracy of the CLIF-C ACLF score. Although the modified CLIF-C ACLF score needs to be independently validated, it may be useful to stratify care in decompensated cirrhosis.

PO-2547

CLIF-SOFA accurately predicts in-hospital mortality in patients with cirrhosis and bacterial infection

Minjong Lee¹, Ji Hyun Kim², Baek Gyu Jun³, Tae Suk Kim², Seong Hee Kang⁴, Ki Tae Suk⁵, Moon Young Kim⁴, Young Don Kim⁶, Gab Jin Cheon⁶, Soon Koo Baik⁴, Dong Joon Kim⁵, Dae Hee Choi². ¹College of Medicine, Ewha Womans University, Korea, Rep. of South; ²Kangwon National University School of Medicine; ³Sanggye Paik Hospital; ⁴Wonju Severance Christian Hospital; ⁵Chuncheon Sacred Heart Hospital; ⁶Gangneung Asan Hospital
Email: minjonglee2@naver.com.

Background and aims: Sepsis-3 criteria and the quick Sequential Organ Failure Assessment (qSOFA) have been advocated to define sepsis in the general population. However, these criteria may have certain limitations that fail to reflect liver failure in patients with cirrhosis. We aimed to compare Sepsis-3 criteria and Chronic Liver Failure-SOFA (CLIF-SOFA) scores as predictors of in-hospital mortality in patients with cirrhosis and bacterial infections.

Method: Overall, 1,622 consecutive Asian patients with cirrhosis and bacterial infections were assessed for retrospective analysis, examining demographic, laboratory, and microbiologic data at diagnosis of infection. The primary endpoint was in-hospital mortality. Predictive performances of baseline CLIF-SOFA, SOFA, and qSOFA for in-hospital mortality were assessed.

Results: CLIF-SOFA proved significantly better for discriminating in-hospital, 1-month and 3-month mortality (area under receiver operating characteristic curve [AUROC]: 0.80, 0.77, 0.67, respectively) (all, $p < 0.001$). CLIF-SOFA scores (adjusted hazard ratio [aHR] = 1.12; $p = 0.001$) and CLIF-C-AD score (aHR = 1.02, $p = 0.001$) were independent predictors of in-hospital mortality with CLIF-SOFA scores showing a significant linear relation with in-hospital mortality. Sepsis-3 criteria and positive qSOFA were not significant risk factors for in-hospital mortality. At CLIF-SOFA scores ≥ 6 , in-hospital mortality was $>10\%$ which is originally suggested cutoff for definition of sepsis.

Conclusion: CLIF-SOFA scores showed better predictive performance for mortality than both Sepsis-3 criteria and qSOFA scores in Asian patients with cirrhosis and infections and can be a simple, one-time useful tool of accurately risk stratification in Asian patients with cirrhosis who need timely intervention for infection.

PO-2609

Geographic variability in rates of intensive care unit admission in patients with chronic liver disease and critical COVID-19: international registry data

Thomas Marjot¹, Andrew Moon², _COVID-Hep/SECURE-Liver Contributors³, Matthew Armstrong⁴, A. Sidney Barritt², Eleanor Barnes¹, Gwilym Webb⁵. ¹Oxford University Hospitals NHS Foundation Trust, University of Oxford; ²University of North Carolina, Chapel Hill; ³COVID-Hep/SECURE-Liver Contributors; ⁴Queen Elizabeth Hospital Birmingham; ⁵Cambridge University Hospitals, Addenbrooke's Hospital
Email: thomas.marjot@ndm.ox.ac.uk.

Background and aims: The COVID-19 pandemic has provided a unique opportunity to evaluate global intensive care unit (ICU) admission practices for a common indication. Patients with chronic liver disease (CLD) and cirrhosis may also have limited or variable access to ICU. We aimed to describe international ICU admission rates and outcomes in patients with CLD and critical COVID-19.

Method: Data were combined from two international registries (COVID-Hep and SECURE-Liver) for patients with CLD and COVID-19 deemed severe enough to require ICU by the reporting clinician. Rates of ICU admission or decline, and respective outcomes were compared by country.

Results: Between 25th March 2020 and 3rd February 2021, 319 patients with CLD and COVID-19 from 27 countries were judged to require ICU. The proportion of patients ultimately accepted to ICU varied according to country (Fig. 1A), although mortality following ICU admission was similar by country (Fig. 1B). To explore this further, we compared cases from the USA and UK, the two greatest contributing countries. Rates of ICU admission differed significantly between the USA and UK [77/79 (95%) vs. 22/77 (29%); $p < 0.001$]. However, there were no differences in mortality after being admitted to ICU (42/75 [56%] vs. 10/22 [45%]; $p = 0.468$; Fig. 1B), or after receiving invasive ventilation (29/59 [49%] vs. 9/17 [53%]; $p = 1.000$). There were also no differences in age, sex, Charlson Comorbidity Index, or baseline liver disease severity between countries, both in those requiring and admitted to ICU. This included comparable rates of cirrhosis (53/79 [67%] vs. 56/77 [72%]; $p = 0.723$). Only four USA patients were declined ICU admission of whom 2 (50%) died, whereas 55 UK patients were declined ICU admission of whom 51 (93%) died. Baseline factors associated with being declined ICU admission in the UK were older age, alcohol-related liver disease, and decompensated cirrhosis. In both USA and UK cohorts, the reason for not admitting patients to ICU was due to this being deemed inappropriate by the responsible clinician, except for one case in both countries where no ICU bed was available. Notably, information relating to patient wishes, long-term outcomes in survivors, and granular detail regarding organ support requirements were not available.

Conclusion: Patients with CLD and critical COVID-19 were over 3-times more likely to be admitted to ICU in the USA than the UK despite having similar baseline characteristics. However, the rates of mortality following ICU admission were comparable between the two countries. The differing thresholds for escalation to ICU but similar post admission outcomes warrants further discussion.

PO-2870

Methylation state of circulating cell-free DNA as a prognostic marker for early to late stage chronic liver disease and acute on chronic liver failure

Aikaterini Tourna¹, Marilena Stamouli¹, Bethlehem Arefaine¹, Guido Alessandro Baselli², Luca Valenti³, Shilpa Chokshi^{1,4}, Neil Youngson^{1,4}, Vishal C. Patel^{1,4,5}. ¹Institute of Hepatology London, Foundation for Liver Research, London, United Kingdom; ²Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Translational Medicine-Department of Transfusion Medicine and Haematology, Milano, Italy; ³Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milano, Italy; ⁴King's College London, School of Immunology and Microbial Sciences, London, United Kingdom; ⁵King's College Hospital NHS Foundation Trust, Institute of Liver Studies, London, United Kingdom
Email: k.tourna@researchinliver.org.uk.

Background and aims: We recently demonstrated circulating cell-free DNA (cfDNA) is present in critically ill patients with chronic liver disease (CLD) as a consistent predictor of mortality. Cirrhotic patients can develop acute-on-chronic liver failure (ACLF) with superimposed organ failure. We now extend this work by identifying cfDNA sources and examine potential to identify organ-specific damage, prior to onset of organ failure. CLIF-C-ACLF score defines ACLF with criteria for liver-kidney-brain-circulatory-respiratory and/or coagulation systems.

Method: We generated an extensive biobank from patients with varying severities of liver disease and controls. Spectrum of liver disease covers metabolic-associated fatty liver disease, compensated and decompensated cirrhosis, and ACLF. We developed assays to identify cfDNA origin, utilising organ-specific methylation profiles of genomic regions. Plasma-derived cfDNA underwent enzymatic modification and PCR amplification of organ-specific methylation regions. Amplicons underwent next-generation sequencing (NGS); methylation status was correlated with clinical data. NGS data were validated with targeted methylation-specific quantitative PCR assays.

Results: These novel assays can identify six organ system failures relevant to the CLIF-C-ACLF score. cfDNA assays for organ systems not measured by the CLIF score but known to be involved in ACLF (adrenals, gut, pancreas, vascular epithelium) were also developed. Initial data demonstrates liver-specific cfDNA methylation levels

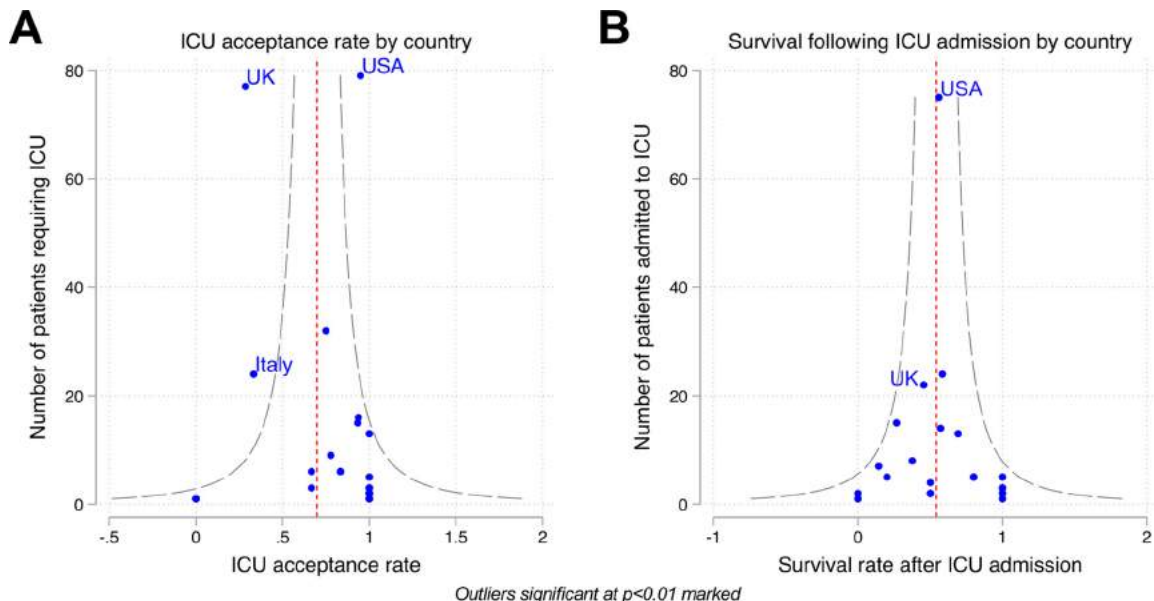


Figure: (abstract: PO-2609)

POSTER PRESENTATIONS

being distinguishable from healthy controls and early MAFLD, rising consistently with increasing CLD severity.

Conclusion: Circulating cfDNA shows promise for CLD stratification and predicting organ failure in ACLF. Vital organs not measured by the CLIF-C-ACLF score can also be interrogated based on their cfDNA signatures, providing novel patho-biological insights into ACLF.

Cirrhosis and its complications: Experimental and pathophysiology

PO-134

Genetic variation in the mitochondrial glycerol-3-phosphate acyltransferase is associated with liver injury

Aaron Hakim¹, Matthew Moll², Joseph Brancale³, Jianguan Liu², Jessica Su², Edwin Silverman², Silvia Vilarinho³, Z. Gordon Jiang¹, Yered Pita-Juarez¹, Ioannis Vlachos¹, Xuehong Zhang², Fredrik Åberg⁴, Nezam Afdhal¹, Brian Hobbs², Michael Cho². ¹Beth Israel Deaconess Medical Center (BIDMC), Boston, United States; ²Brigham And Women's Hospital, Boston, United States; ³Yale School of Medicine, New Haven, United States; ⁴University of Helsinki, Helsinki, Finland
Email: remhc@channing.harvard.edu.

Background and aims: In contrast to many common metabolic disorders, few genetic associations have been identified for chronic liver disease. This highlights the need for studies with increased sample size and the exploration of novel liver-related endophenotypes. We sought to identify novel genetic loci that modulate the risk of liver injury.

Method: We performed genome-wide association studies (GWAS) on circulating levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin across 312, 671 White British participants in the UK Biobank. We focused on variants associated with elevations in all four liver biochemistries at genome-wide significance ($p < 5 \times 10^{-8}$) and that replicated using Mass General Brigham Biobank in 19, 323 European ancestry individuals. We also analyzed single-cell RNA sequencing data from healthy human livers to determine cell sub-populations expressing identified target genes.

Results: We identified 58 distinct genetic loci associated with both ALT and AST, 18 associated with both ALP and total bilirubin, and 5 associated with ALT, AST, ALP and total bilirubin at genome-wide significance in UK Biobank. A genetic locus in the mitochondrial glycerol-3-phosphate acyltransferase (*GPAM*; rs10787429) associated with increased levels of ALT, AST, ALP and total bilirubin and replicated in Mass General Brigham Biobank. This common genetic variant was also associated with an increased risk of alcoholic liver disease (OR 1.34, $p = 2.6 \times 10^{-5}$) and fatty liver disease (OR 1.18, $p = 5.8 \times 10^{-4}$) by ICD-10 codes. We identified significant gene-environment interactions between *GPAM* rs10787429 and elevated body mass index in association with ALT and AST (p -interaction = 7.1×10^{-9} and 3.95×10^{-8} , respectively), as well as between *GPAM* rs10787429 and weekly alcohol consumption in association with ALT, AST, and alcoholic liver disease (p -interaction = 5.2×10^{-3} , 1.2×10^{-2} and 4.2×10^{-2} , respectively). Unlike previously described genetic variants that are associated with an increased risk of liver injury but confer a protective effect on circulating lipids, *GPAM* rs10787429 was associated with an increase in total cholesterol ($p = 2.0 \times 10^{-17}$), LDL cholesterol ($p = 2.0 \times 10^{-10}$), and HDL cholesterol ($p = 6.6 \times 10^{-37}$). Single-cell RNA sequencing data demonstrated hepatocyte-predominant expression of *GPAM* in cells that co-express genes related to VLDL production ($p = 9.4 \times 10^{-103}$).

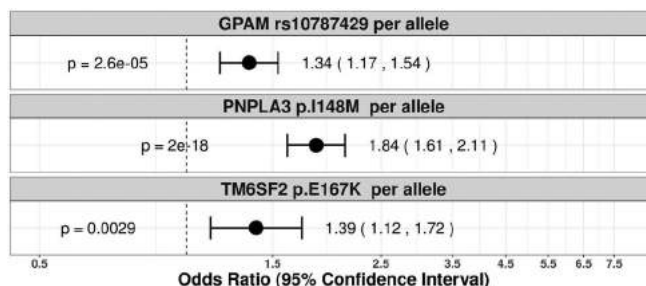


Figure:

Conclusion: Genetic variation in *GPAM* is associated with susceptibility to liver injury. *GPAM* may represent a new therapeutic target in chronic liver disease.

PO-624

Transcriptomic profiling of liver sinusoidal endothelial cells during cirrhosis progression reveals stage-specific secretory signature

Nicolò Manicardi¹, Anabel Fernández Iglesias^{2,3}, Laia Abad^{2,3}, Félix Royo^{2,4}, Mikel Azkargorta⁴, Martí Ortega Ribera³, Ana Martínez-Alcocer³, Felix Elortza⁴, Amelia Hessheimer^{2,5}, Constantino Fondevila^{2,5}, Juanjo Lozano², Juan Carlos Garcia Pagan^{2,5}, Jaime Bosch⁶, Francisco Javier Cubero⁷, Agustín Albillos^{2,8}, Javier Vaquero^{2,9}, Juan Falcon-Perez^{2,4}, Jordi Gracia-Sancho^{2,3,6}. ¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Liver Vascular Biology, Barcelona, Spain; ²CIBEREHD; ³Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Liver Vascular Biology, Spain; ⁴Center for Cooperative Research in Biosciences (CIC bioGUNE); ⁵Hospital Clinic de Barcelona; ⁶University of Berne, Hepatology; ⁷Universidad Complutense Madrid; ⁸Ramon y Cajal Hospital; ⁹Gregorio Marañón Research Institute
Email: jordi.gracia@idibaps.org.

Background and aims: The poor prognosis of chronic liver disease (CLD) generates the need to investigate the evolving mechanisms of disease progression, thus disclosing therapeutic targets before development of clinical complications. Considering the central role of the liver sinusoidal endothelium in advanced CLD pathophysiology, the present study aimed at investigating the progression of CLD from a liver sinusoidal endothelial cells (LSECs) holistic perspective. **Method:** RNAseq was applied to define the transcriptome of primary LSECs from healthy and cirrhotic (alcoholic aetiology) human livers, and from rats with acute liver injury, mild liver fibrosis and cirrhosis (due to carbon tetrachloride [CCl₄] or thioacetamide [TAA] administration). At each stage of the disease the effects of LSECs secretome on neighbouring cells were determined. Proteomic analysis of LSECs-derived extracellular vesicles (EVs) was performed.

Results: 1374 genes were differentially expressed in human cirrhotic LSECs compared to healthy, sharing greater homology with CCl₄-than TAA-cirrhotic rat LSECs. Pathway enrichment analysis of deregulated genes in human cirrhotic LSECs and in rat LSECs isolated during liver cirrhosis progression, revealed predominance of genes related with cellular communication processes and EVs biogenesis. Crosstalk experiments between fibrotic and cirrhotic LSECs secretome subfractions (complete secretome, soluble factors, large EVs and small EVs) and neighbouring hepatic stellate cells and macrophages confirmed activation effects, revealing endothelial EVs as potent angiocrine effectors. Finally, proteomic analysis of LSECs EVs showed stage-specific signatures, including significant over-expression of tropomyosin-1 (TPM-1) in liver cirrhosis progression. Proof-of-concept experiments treating cirrhotic HSCs and *in vitro* activated HSCs with recombinant TPM-1 showed down-regulation of *Col1 (alpha)1*, *(alpha)Sma* and *Rock1* suggesting potential de-activating effects.

Conclusion: Through a comprehensive characterization of LSECs transcriptome and secretome across cirrhosis, our study shows

dominance of pathways involved in cellular secretory machinery during disease progression. Our data provide the basis for discovering novel biomarkers and therapeutic targets for new disease-modifying treatments for patients with advanced CLD.

PO-698

Characterizing sensory thresholds and autonomic dysfunction in cirrhotic patients with minimal hepatic encephalopathy

Dalia Rega¹, Mika Aiko², Juan José Gallego¹, Alessandra Fiorillo¹, Franc Casanova¹, María Pilar Ballester-Ferré^{1,3}, Cristina Ipiens⁴, Nicolás Peñaranda², Carla Giménez-Garzó⁵, Amparo Urios¹, Desamparados Escudero-García³, Joan Tosca³, Cristina Montón³, José Ballester³, Paloma Lluch⁶, María Pilar Ríos⁷, Lucía Durbán⁷, Salvador Benlloch⁷, Paula Cases², Vicente Felipo⁵, Carmina Montoliu^{1,8}. ¹INCLIVA Institut d'Investigació Sanitària, València, Spain; ²Hospital Clínic Universitari, Servicio de Neurofisiología, València, Spain; ³Hospital Clínic Universitari, Unidad de Digestivo, València, Spain; ⁴Hospital Públic Universitari de la Ribera, Alzira, Spain; ⁵CIPF Centro de Investigación Príncipe Felipe, Laboratorio de Neurobiología, Valencia, Spain; ⁶Unidad de Digestivo, Hospital Clínico Universitario de Valencia, Spain; ⁷Hospital Arnau de Vilanova, Servicio de Digestivo, València, Spain; ⁸University of Valencia, Departamento de Patología, València, Spain
Email: cmontoliu@incliva.es.

Background and aims: Hepatic encephalopathy (HE) associated to cirrhosis is a complex neuropsychiatric syndrome. Near 40% of cirrhotic patients have minimal hepatic encephalopathy (MHE) with mild motor and cognitive impairments that can affect daily life activities.

Cirrhotic patients may have alterations in the peripheral nervous system such as disorders in sensory perception. The awareness of cold and heat pain is mediated by A-delta nerve fibers (myelinated, small diameter) and non-myelinated C fibers, respectively. Whilst vibration is transmitted by larger myelinated fibers (A-alpha). The alteration of these fibres is determined as small fibre neuropathy (SNP). Which includes autonomic and sensory symptoms such as, dysesthesia and allodynia. Consequently, it can produce an alteration of thermal and pain sensibility as well as sudomotor function. Alterations in thermal sensitivity have been described in patients with HE, which have been correlated with the degree of HE and with attention deficits.

The aim of this study is the evaluation and characterization of thermal sensitivity, vibration and heat-pain in addition to sudomotor function in cirrhotic patients and healthy controls, as well as to assess whether there are alterations associated to MHE.

Method: Fifty-eight cirrhotic patients were included in the study, 38 without MHE (NMHE) and 20 with MHE, according to the PHES score (Psychometric Hepatic Encephalopathy Score) and 39 healthy controls. Selective and sustained attention were assessed using the Stroop and d2 tests. The evaluation and characterization of sensory thresholds was performed by quantitative sensory testing using a CASE IV device. The following sensory thresholds were measured: vibration, heat pain and cooling both on the hand and foot. Sudomotor function was explored through cutaneous sympathetic response (CSR) conducted by the Synergy UltraPro S100.

Results: Results show that the thresholds were higher in NMHE patients compared to controls in all modalities except heat-pain 5.0. Patients with MHE showed higher thresholds than NMHE patients in cooling detection and heat pain when the foot was the test site. The proportion of patients in which over half the tests were outside the normal range was higher in MHE (67%) than in NMHE patients (26%). This hyposensitivity correlates with attention deficits. The amplitude of SSR was significantly reduced in patients with MHE compared to controls and NMHE while latency was significantly higher in both patient groups compared to controls.

Conclusion: Patients with MHE have a general decrease in cognitive and sensory abilities as well as alterations in autonomic functions such as thermoregulation. Quantitative sensory tests and SSR could

be used as an indicator of MHE and would allow studying the effects on the sensory system before and after a treatment.

PO-709

Multi-omic analysis unveils biological pathways in peripheral immune system associated to minimal hepatic encephalopathy appearance in cirrhotic patients

Teresa Rubio¹, María-Pilar Ballester-Ferré^{2,3}, Juan José Gallego Roig², Alessandra Fiorillo², Franc Casanova², Sonia Tarazona⁴, Carla Giménez-Garzó¹, Amparo Urios², Paloma Lluch⁵, Desamparados Escudero-García³, Juan Tosca³, Cristina Montón³, José Ballester³, María Pilar Ríos⁶, Lucía Durbán⁶, Ana Conesa⁷, Vicente Felipo¹, Carmina Montoliu^{2,8}. ¹CIPF Centro de Investigación Príncipe Felipe, Valencia, Spain; ²INCLIVA Institut d'Investigació Sanitària, Valencia, Spain; ³Hospital Clínic Universitari, Unidad de Digestivo, Valencia, Spain; ⁴Polytechnic University of Valencia, Departamento de estadística e investigación operativa aplicadas y calidad, València, Spain; ⁵Hospital Clínic Universitari, Unidad de Digestivo, València, Spain; ⁶Hospital Arnau de Vilanova, Servicio de digestivo, València, Spain; ⁷University of Florida, Microbiology and Cell science department, Gainesville, United States; ⁸University of Valencia, Departamento de Patología, València, Spain
Email: cmontoliu@incliva.es.

Background and aims: Patients with liver cirrhosis may develop minimal hepatic encephalopathy (MHE) which affects their quality of life and life span. It has been proposed that a shift in peripheral inflammation triggers the appearance of MHE. However, the mechanisms involved in this immune system shift remain unknown. In this work we studied the broad molecular changes involved in the induction of MHE with the goal of identifying (1) altered genes and pathways in peripheral blood cells associated to the appearance of MHE, (2) serum metabolites and cytokines with modified levels in MHE patients and (3) MHE-regulated immune response processes related to changes in specific serum molecules.

Method: We adopted a multi-omic approach to profile the transcriptome, metabolome and a panel of cytokines of blood samples taken from cirrhotic patients with or without MHE.

Results: Transcriptomics analysis support the hypothesis of alternations in the Th1/Th2 and Th17 lymphocytes cell populations as major drivers of MHE. Cluster analysis of serum molecules resulted in 6 groups of chemically similar compounds, suggesting that functional modules operate during the induction of MHE. Finally, the multi-omic integrative analysis suggested a relationship between cytokines CCL20, CX3CL1, CXCL13, IL-15, IL-22 and IL-6 with alteration in chemotaxis, as well as a link between long-chain unsaturated phospholipids and the increased fatty acid transport and prostaglandin production.

Conclusion: We found altered immune pathways that may collectively contribute to the mild cognitive impairment phenotype in MHE. Our approach is able to combine extracellular and intracellular information, opening new insights to the understanding of the disease.

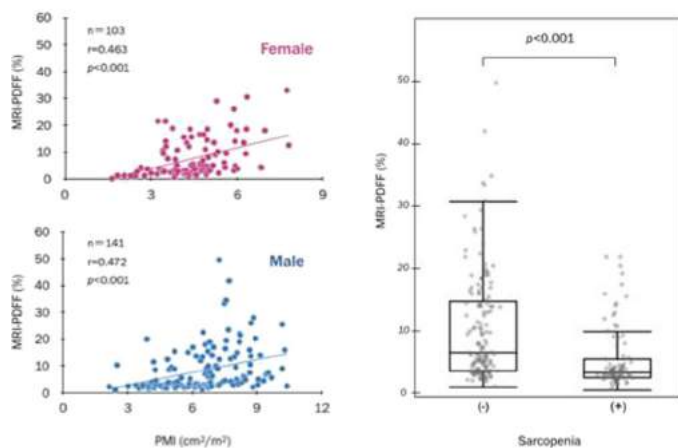
PO-994

Hepatic fat loss in cirrhosis: Evaluation of malnutrition using MRI proton density fat fraction (MRI-PDFF)

Atsushi Nakamura¹, Takeshi Ichikawa¹. ¹Kawasaki, Japan
Email: naka2722@gmail.com.

Background and aims: Fatty acids are the largest energy storage in the body, and the liver acts as a central hub for fatty acid metabolism. In LC, protein-energy malnutrition (PEM) increases in relation to the severity of the disease, and fatty liver presents as “burn out” NASH with loss of fat droplets. MRI-PDFF has been used as an alternative to liver biopsy as a non-invasive and accurate method for quantifying liver fat content. In this study, we investigated the relationship between MRI-PDFF and malnutrition.

1) Relationship between muscle mass and PDFF



2) Kaplan-Meier survival curve in liver cirrhosis

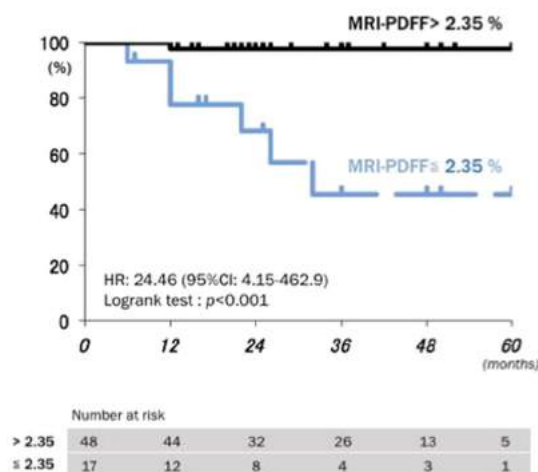


Figure: (abstract: PO-994)

Method: A total of 389 patients with chronic liver disease (M/F: 365/239, 61 ± 14 y) underwent MRI examination. By etiology, HBV/HCV: 103/111, NAFLD: 121, PBC/AIH: 35, unknown 19. 65 LC (Child A/B/C: 45/14/6) and 33 HCC were included. PDFF (%) and LSM (liver stiffness measurement: kPa) were analyzed by MRI. Nutritional status was assessed by CONUT (controlled nutritional status) score, and sarcopenia was diagnosed by measuring PMI (psoas muscle index) from CT images (244 cases) in the same period.

Results: (1) PDFF in CLD: There was no gender difference in PDFF (%), 12.8 ± 8.3 and 5.4 ± 5.1 for NAFLD and non-NAFLD groups ($p < 0.01$). Univariate analysis of PDFF correlated with age, BMI, and was associated with liver inflammation (AST, ALT, γ GTP, ferritin) and nutrient metabolism (alb, TC, TG, HbA1c, TLC) ($p < 0.05$). There were also significant differences between LC and non-LC, and between ± HCC ($p < 0.05$).

(2) Malnutrition and PDFF: CONUT score correlated with LSM ($r = 0.531$, $p < 0.01$) and PDFF ($r = -0.324$, $p < 0.01$), and both NAFLD and non-NAFLD groups showed an association between severity of CONUT and decrease in PDFF ($p < 0.05$). On the other hand, PDFF was also correlated with PMI ($p < 0.01$), and the PDFF of sarcopenia patients (38%) was significantly lower (5.0 ± 5.0% vs. 10.0 ± 8.7%, $p < 0.01$).

(3) PDFF in LC: Nine patients died during the observation period (30 ± 18M), and Child Pugh score (HR: 1.374, 95% CI: 1.075–1.744, $p < 0.05$) and PDFF (HR: 0.913, 95% CI: 0.843–0.974, $p < 0.01$) were prognostic factors in Cox proportional hazards model. ROC analysis showed that PDFF ≤ 2.35% (AUC: 0.89, $p < 0.01$) was predictive of mortality, and BMI (odds ratio: 0.619) and alb (0.086) were independently associated with hepatic fat loss in LC ($p < 0.01$).

Conclusion: Decreased PDFF was associated with malnutrition and sarcopenia in CLD, and decreased liver fat mass in LC was a prognostic factor independent of liver function. MRI-PDFF may be a powerful indicator of nutritional status in cirrhosis.

PO-1051

Systemic and hepatic endothelial cell activation biomarkers expression are associated with inflammation and disease progression in patients with cirrhosis

Jelte Schaapman¹, Tessa Ostyn², Danny van der Helm¹, Matthias Van Haele², Johannes van der Reijden¹, Frederik Nevens³, H.W. Verspaget¹, Tania Roskams², Minneke Coenraad¹. ¹Leiden University Medical Center (LUMC), Hepatology, Leiden, Netherlands; ²University Hospitals KU Leuven, Imaging and Pathology, Leuven, Belgium; ³University Hospitals KU Leuven, Hepatology, Leuven, Belgium. Email: j.j.schaapman@lumc.nl.

Background and aims: Vascular endothelium is involved in several pathological processes in cirrhosis, including fibrogenesis and inflammation. Decompensated cirrhosis is characterized by chronic inflammation and molecular activation patterns. Aim of this study was to evaluate circulating and hepatic endothelial cell (EC) activation, inflammation and adhesion markers in cirrhotic patients in relation to systemic inflammation and disease severity.

Method: 150 cirrhotic patients and 18 healthy controls were included. Circulating inflammatory and EC biomarkers were measured using a multi-array assay. 80 explanted cirrhotic and 11 control liver tissue specimens were available for immunohistochemical analysis for markers of ECs (CD31, CD34, LYVE-1), EC activation (ICAM-1, VCAM-1, P-selectin, thrombomodulin) and apoptosis (Caspase 3). Marker expression was assessed separately for liver portal and sinusoidal ECs (LSECs) by two pathologists.

Results: Median MELD score of cirrhotic patients was 15 (IQR 11–21). Serum concentrations of CRP, ICAM-1, VCAM-1 and thrombomodulin were significantly elevated in patients compared to controls (table). CD31, CD34, LYVE-1, VCAM-1 and thrombomodulin in portal venous ECs and ICAM-1 and LYVE-1 in LSECs were almost universally expressed in both groups. Expression of ICAM-1, P-selectin, Caspase 3 in portal venous ECs and of CD31, CD34, VCAM-1, P-selectin, thrombomodulin and Caspase 3 in LSECs was significantly more frequent in cirrhotic patients compared to controls (table). Circulating ICAM-1, VCAM-1, thrombomodulin levels and ICAM-1 and P-selectin in portal ECs were correlated with MELD score (all $p < 0.004$). In addition, P-selectin expression in portal ECs and LSECs was correlated with CRP (both $p < 0.05$).

Conclusion: Circulating EC activation biomarkers are significantly elevated in cirrhotic patients. In addition, the increased expression of several EC activation markers in cirrhotic patients but not controls

indicate EC molecular activation patterns with hepatic inflammation, adhesion and apoptosis, in association with systemic inflammation and clinical disease progression.

Table:

Circulatory inflammation marker	Controls (n = 18)	Cirrhosis (n = 150)	p value
CRP	2.0 (0.4–3.6)	12.4 (4.5–34.6)	<0.001
Circulatory endothelial markers			
ICAM-1	0.4 (0.3–0.4)	1.4 (1.2–2.1)	<0.001
VCAM-1	0.5 (0.4–0.6)	2.5 (1.7–3.5)	<0.001
P-selectin	73.4 (65.0–91.3)	78.4 (58.1–99.8)	0.667
Thrombomodulin	4.2 (3.6–4.7)	8.2 (6.4–10.6)	<0.001
Tissue endothelial markers			
CD31 (s)	0%	100%	<0.001
CD34 (s)	0%	100%	<0.001
ICAM-1 (p)	0%	58.8%	<0.001
VCAM-1 (s)	0%	82.5%	<0.001
P-selectin (p)	27.3%	81.3%	<0.001
P-selectin (s)	0%	49.9%	0.002
Thrombomodulin (s)	0%	97.5%	<0.001
Caspase 3- (p)	0%	78.8%	<0.001
Caspase 3- (s)	0%	100%	<0.001

Median (IQR), s = sinusoidal, p = portal

PO-1222

PNPLA3-associated cirrhosis: HSD17B13 and MBOAT7 variants as modulators of chronic liver injury

Matthias Reichert¹, Robin Greinert², Alexander Zipprich^{2,3}, Cristina Ripoll², Marcin Krawczyk^{1,4}, Frank Lammert^{1,5}. ¹Department of Medicine II, Saarland University Medical Center, Saarland University, Homburg, Germany; ²First Department of Internal Medicine, Martin-Luther University Halle-Wittenberg, Halle, Germany; ³Department of Internal Medicine IV, Friedrich-Schiller-University Jena, Jena, Germany; ⁴Laboratory of Metabolic Liver Diseases, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland; ⁵Hannover Medical School, Hannover, Germany
Email: marcin.krawczyk@uks.eu.

Background and aims: Carriers of the adiponutrin (PNPLA3) p. I148M variant, and in particular homozygous patients, have an increased risk for cirrhosis. The hepatoprotective splice variant of HSD17B13 reduces, in turn, liver injury (Abul-Husn *et al.* N Engl J Med 2018), whereas a variant in the MBOAT7 gene aggravates liver damage. Our aim was to investigate the modulation of the risk of advanced cirrhosis in homozygous carriers of the PNPLA3 variant by the HSD17B13 and MBOAT7 variants.

Method: In total, 998 patients with cirrhosis were screened for the PNPLA3 variant. Clinical, laboratory and imaging data were collected. Hepatic decompensation was defined as the presence of ascites, history of variceal bleeding, hepatic encephalopathy, or jaundice (i.e., serum bilirubin ≥3.0 mg/dl). Within this cohort, the MBOAT7 (rs641738) and HSD17B13 (rs72613567) polymorphisms were genotyped by PCR-based allelic discrimination assays, and genotype-to-phenotype correlations were analyzed.

Results: Overall, 148 patients (15%) were homozygous carriers of the PNPLA3 p.148MM risk genotype (64% men, age range 30–81 years). Aetiology of cirrhosis resembled a typical European cohort (59% alcoholic, viral 14%, NASH 9%, 14% other). Two thirds of the patients were in the decompensated stage of the disease. When comparing patients according to the presence or absence of the protective HSD17B13 variant, 56% of the patients in the compensated stage were carriers versus 36% in the decompensated stage (p = 0.025). Similarly, MELD scores (13.1 versus 10.9; p=0.04), Child-Pugh scores (7.6 versus 7.1; p=0.23) and bilirubin concentrations (3.3 versus 1.7 mg/dl, p=0.035) were significantly higher when the HSD17B13 protective

variant was absent. None of these parameters was influenced by the MBOAT7 alleles.

Conclusion: The risk of progressive cirrhosis is increased in homozygous carriers of the PNPLA3 variant p.148MM. Notably, the presence of an HSD17B13 allele mitigates, at least in part, the harmful effects conferred by PNPLA3 homozygosity. As both PNPLA3 and HSD17B13 exert their functions in hepatocellular lipid droplets, the interaction of the metabolic pathways at this intracellular localization should be investigated in the future studies.

PO-1643

Nutritional supplementation with B-Hydroxy-B-methylbutyrate (HMB) in malnourished cirrhotic patients

Silvia Espina¹, Vanesa Bernal Monterde¹, Alejandro Sanz Paris², Javier Fuentes Olmo¹, Eva Fernandez Bonilla¹, Yolanda Gonzalez Irazabal³, Beatriz Garcia Rodriguez³, Maria Pilar Garcia Sobrevela⁴, Jose M. Arbones Mainar⁴. ¹Hospital Universitario Miguel Servet, Gastroenterology and hepatology, Zaragoza, Spain; ²Hospital Universitario Miguel Servet, Endocrinology, Zaragoza, Spain; ³Hospital Universitario Miguel Servet, Biochemistry, Zaragoza, Spain; ⁴Translational Research Unit, Hospital Universitario Miguel Servet, Instituto Aragonés de Ciencias de la Salud (IACS), Instituto de Investigación Sanitaria Aragón (IIS-Aragón), Adipocyte and Fat Biology Laboratory (AdipoFat), Zaragoza, Spain
Email: silesipina@gmail.com.

Background and aims: HMB is derivative of the BCAA (branched-chain amino acid) leucine. BCAA supplementation in cirrhosis has shown positive effect only on encephalopathy and muscular strength. HMB supplementation increase muscle mass and strength during resistance exercises but there are no data in cirrhosis. The aim was to investigate the effects of oral HMB supplementation on changes in body composition and liver status in patients with cirrhosis and malnutrition.

Method: This is a double-blind placebo-controlled trial (NCT03285217). 43 individuals were randomized to receive for 12 wk oral supplementation twice a day with either 220 ml of Ensure® Plus Advance (HMB group, n = 22) or with 220 ml of Ensure® Plus High Protein (HP group, n = 21). Inclusion criteria was liver cirrhosis of any aetiology with at least 1 previous decompensation and clinical malnutrition class B or C screened by Subjective Global Assessment (SGA). Longitudinal and treatment-specific changes were assessed by mixed models.

Results: 34 patients completed the clinical trial. Both treatments, with no differences, improved liver function (MELD score, p=0.02) and increased fat mass index (p=0.014) while reduced serum concentrations of LDL cholesterol (p=0.002) and apolipoprotein B (p=0.001). None of the two treatments changed the skeletal muscle mass index (SMI) or appendicular skeletal muscle mass (ASMM). However, we observe in the HMB group an upward trend in hand grip strength and a downward trend in minimal hepatic encephalopathy (MHE).

Conclusion: Oral supplementation for 12 weeks, with no differences between treatments, was significantly associated with an increase in fat mass and improved liver function without benefit on muscle mass.

POSTER PRESENTATIONS

Table 1: (abstract: PO-1643)

	HMB Group			HP Group		
	T0	T1	T2	T0	T1	T2
FMI (kg/m ²)	4.85 [1.25;7.15]	6.35 [3.92;8.40]	6.20 [1.95;7.50]	5.30 [2.20;7.20]	6.05 [4.67;7.47]	6.10 [3.75;8.10]
ASMM (kg)	24.4 [19.3;28.2]	23.4 [16.5;27.4]	23.5 [16.4;26.6]	22.2 [19.2;27.2]	21.5 [19.6;25.2]	20.8 [19.8;24.3]
Hand grip (Kg)	26.5 [23.2;34.0]	29.5 [24.8;35.2]	30.0 [24.5;33.0]	32.0 [28.0;40.0]	33.0 [26.5;38.0]	33.0 [25.5;37.0]
MELD score	11.5 [7.75;15.8]	11.0 [8.00;16.0]	10.5 [9.00;18.0]	12.0 [9.00;17.0]	10.0 [7.25;12.8]	10.0 [8.00;13.0]
MHE	8 (36.4%)	4 (26.7%)	3 (20%)	4 (19%)	4 (21%)	4 (21.1%)

T1: 6 wk, T2: 12 wk. Data in bold correspond to statistically significant variations

Conflict of interest: Abbot provided the nutritional supplements at a discounted price but had no part in the study.

PO-1684

Low-grade hyperammonemia induces severe neuronal mitochondrial dysfunction in cellular and animal models of hepatic encephalopathy

Annarein Kerbert¹, Plamena Stroh², Abeba Habtesion¹, Andrey Abramov², Rajiv Jalan¹. ¹University College London, Institute for Liver and Digestive Health, United Kingdom; ²University College London, Institute of Neurology, United Kingdom
Email: a.kerbert@ucl.ac.uk.

Background and aims: In liver cirrhosis, hyperammonemia plays a key role in the pathophysiology of hepatic encephalopathy (HE). The astrocytes are traditionally believed to be the principal target of ammonia neurotoxicity. The role of neuronal dysfunction in HE is not clear. In this study, we aim to explore the impact of hyperammonemia on mitochondrial function in different brain cell types and in acute brain slices, by using live cell imaging.

Method: *In vitro*: to primary co-cultures of astrocytes and neurons, concentrations of 1 μ M and 5 μ M ammonium chloride were applied. Cell viability was measured by the use of membrane-impermeable fluorescent dye propidium iodide that stains cells with damaged cell membranes in combination with Hoechst 33342 for assessment of the total cell number. *In vivo*: In a rat model of liver cirrhosis and minimal HE (4 weeks post bile duct ligation (BDL), 3 groups were studied: sham (n = 5), BDL (n = 3) and BDL + the ammonia scavenger Ornithine Phenylacetate (OP; n = 2) 0.3 g/kg i.p. twice daily for 5 days. After sacrificing, the brain was placed in artificial cerebrospinal fluid and immediately sliced at 100 μ m. Fluorescence measurements of changes in mitochondrial membrane potential (MMP), reactive oxygen species (ROS) production and rate of lipid peroxidation (LP) were performed using a confocal microscope.

Results: *In vitro*: Neuronal cultures, treated with ammonia (1 μ M and 5 μ M), exhibited reduced cell viability (27.8 \pm 2.3% and 41.5 \pm 3.7%, respectively) compared to untreated cultures (15.7 \pm 1.0%, both p <

0.0001). *In vivo*: Ammonia (umol/L) levels were: sham (56 \pm 3), BDL (141 \pm 4) and BDL+OP (60 \pm 2). BDL led to increased lipid peroxidation (p = 0.0003; Figure) and cytosolic ROS generation (p < 0.0001) in the brain, which was restored by OP (both p < 0.0001). Mitochondrial function was severely compromised in BDL, resulting in hyperpolarization of mitochondrial membranes (p < 0.0001) with consequent overconsumption of ATP and augmentation of mitochondrial ROS production rates (p < 0.0001). Administration of OP in BDL animals, restored mitochondrial membrane potential (p < 0.0001). Neuronal loss was prominent in CA1 areas of the hippocampus in BDL.

Conclusion: Our results elucidate for the first time that low-grade hyperammonemia can severely impact on brain mitochondrial function in liver cirrhosis. Besides astrocyte swelling, profound neuronal injury was observed in hyperammonemic rats. These data point towards a novel mechanism of HE development.

PO-1761

Sleep study with actigraphy in patients affected by cirrhosis with and without minimal hepatic encephalopathy

Cristina Ipiens¹, Juan José Gallego², Alessandra Fiorillo², Franc Casanova², María Pilar Ballester², Rut Victorio³, Dalia Rega², Mika Aiko³, Nicolás Peñaranda³, Carla Gimenez-Garzo⁴, Desamparados Escudero-García⁵, Joan Tosca⁵, Paula Cases³, Amparo Urios², Vicente Felipo⁴, Carmina Montoliu^{2,6}. ¹Hospital Universitario de La Ribera, Valencia, Spain; ²Fundación Investigación Hospital Clínico de Valencia. Instituto de Investigación Sanitaria-INCLIVA, Valencia, Spain; ³Servicio de Neurofisiología, Hospital Clínico Universitario de Valencia, Spain; ⁴Laboratorio de Neurobiología. Centro Investigación Príncipe Felipe. Valencia, Spain; ⁵Unidad de Digestivo, Hospital Clínico Universitario de Valencia, Spain; ⁶Departamento de Patología, Facultad de Medicina, Universidad de Valencia, Spain
Email: cmontoliu@incliva.es.

Background and aims: Sleep disorders are frequently associated with hepatic encephalopathy (HE) and might be some of its first clinical findings, observable even in minimal hepatic encephalopathy (MHE). They are also common in patients with cirrhosis and other

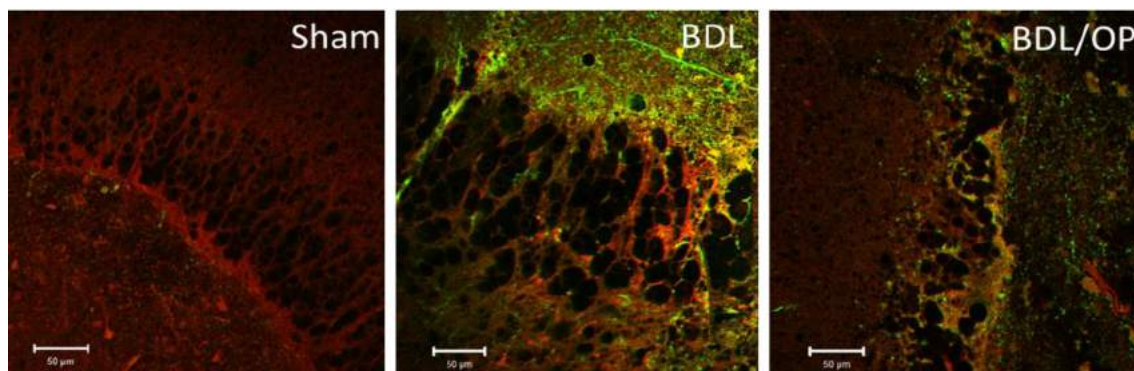


Figure (abstract: PO-1684) Lipid peroxidation in acute hippocampal slices of sham, BDL and BDL+OP treated rats. Red: not oxidized, green: oxidized.

liver conditions without defining signs of HE. Currently, polysomnography is the gold standard for sleep studies, but requires a high consumption of hospital resources and the recording is usually only one-night long. Actigraphy devices offer the chance of making longer ambulatory studies. Sleep-wake patterns are estimated from periods of activity and inactivity reflected by the movements of the patient.

Method: An analytical, observational cohort study has been done to analyze the macrostructure of sleep and the wake-sleep cycle using an actigraphy record for 14 days. It was carried out in a sample of 68 individuals from the Hospital Clínico Universitario de Valencia (Spain), grouped into three categories: MHE, cirrhosis without MHE and healthy control subjects. The differences between these three groups were analyzed in terms of time spent in bed, sleep latency, percentage of sleep, interleaved arousals, and sleep fragmentation index, as well as time in bed and sleep of the patient during the day.

Results: It is observed that, during the night, patients with pathology, either with cirrhosis or with cirrhosis with MHE, stay longer in bed, have a higher sleep latency, a higher sleep fragmentation index and a lower percentage of sleep, which generally represents a worse quality of night rest. This aspect may be related to the greater immobility and frequent drowsiness that is shown in the daytime record. It is also observed that patients with cirrhosis, with or without MHE, have a significantly higher risk of presenting greater sleep fragmentation, and a risk close to the statistical significance of presenting a longer sleep time during the day.

Conclusion: Patients with liver disease might present sleep disturbances and these be the first clinical manifestation in the neurological sphere. This has been observed both in patients with diagnosed MHE and cirrhosis without MHE, which suggests that patients with cirrhosis might present subclinical neurological alterations. The actigraphy record proves to be a useful tool for the diagnosis, while it is a test that stimulates its ambulatory use, consumes few professional resources, and allows a prolonged record while respecting the daily life of patients.

PO-1787

Markers of neutrophil extracellular traps are elevated in patients with Child-Pugh B and C liver cirrhosis or large hepatocellular carcinomas

Robin Zenlander^{1,2,3}, Sebastian Havervall⁴, Maria Magnusson^{5,6}, Anna Ågren^{7,8,9}, Charlotte Thålin⁴, Per Stal^{3,10}. ¹Department of Clinical chemistry, Karolinska University Hospital, Stockholm, Sweden; ²Department of Laboratory Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; ³Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; ⁴Division of Internal Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden; ⁵Division of Paediatrics, CLINTEC, Karolinska Institutet, Stockholm, Sweden; ⁶Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden; ⁷Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; ⁸Coagulation Unit, Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; ⁹Department of Clinical Sciences, Danderyd Hospital, Stockholm, Sweden; ¹⁰Division of Hepatology, Department of Upper GI diseases, Karolinska University Hospital, Stockholm, Sweden
Email: robin.zenlander@ki.se.

Background and aims: Liver cirrhosis is a procoagulant condition despite concomitant thrombocytopenia or reduced production of coagulation factors. Neutrophil extracellular traps (NETs) are web-like structures extruded from neutrophils and composed of DNA and histones, which trap and neutralize invading pathogens. Markers of NETs are elevated in thrombus formation, inflammatory conditions and cancer¹. However, the role of NETs in the increased thrombosis risk seen in liver cirrhosis and hepatocellular carcinoma (HCC) is unknown. We asked if plasma levels of two NETs markers, MPO-DNA and H3Cit-DNA^{2,3} were elevated in liver cirrhosis and HCC, and if they

were associated to clinical parameters or correlated to thrombin-antithrombin complex (TAT).

Method: H3Cit-DNA, MPO-DNA and TAT were measured with ELISA in plasma from 95 patients with liver cirrhosis, 82 patients with HCC, and 50 healthy controls. Clinical parameters and laboratory data were collected from medical files. Levels of NETs markers were correlated to clinical and laboratory data.

Results: H3Cit-DNA and TAT were both significantly elevated in plasma of liver cirrhosis and HCC patients compared to healthy controls (H3Cit-DNA median 66.4 ng/ml for liver cirrhosis, 63.8 ng/ml for HCC, 31.8 ng/ml for controls; TAT median 3.1 µg/ml for liver cirrhosis, 3.7 µg/ml for HCC, 0.0 µg/ml for controls). MPO-DNA was elevated in liver cirrhosis patients compared with both other groups (0.53 O.D. for liver cirrhosis, 0.33 O.D. for HCC, 0.33 O.D. for controls). H3Cit-DNA was significantly higher in Child-Pugh B and C patients compared to Child-Pugh A and controls and correlated positively with MELD score. H3Cit-DNA was increased in patients with underlying non-alcoholic steatohepatitis (NASH) vs. hepatitis C aetiology, and in HCC patients with tumour burden >8 cm. H3Cit-DNA and MPO-DNA were not higher in patients with previous thrombosis development compared with those without history of thrombosis.

Conclusion: Plasma markers of NETs are elevated in liver cirrhosis with reduced liver function. HCC itself is not associated with increased plasma markers of NETs formation, except for larger tumours. Underlying NASH associates to increased levels of NETs in plasma. Our results indicate a potential role of NETs in the development of a procoagulant state in decompensated liver cirrhosis, but further studies are needed.

References

Thålin C, et al. *Arterioscl. Thromb Vasc Biol.* 2019;39(9):1724–1738.
Kaltenmeier CT, et al. *HPB* 2020 Aug 15:S1365–182X(20)31095-9
van der Windt DJ, et al. *Hepatology.* 2018;68(4):1347–1360.

PO-2098

GLAST redistributes, clusters and forms homomultimers at the plasma membrane

Joana Patrícia Ventura Pereira¹, Boris Goerg², Stefanie Weidtkamp-Peters³, Verena Keitel², Dieter Häussinger², Christoph Roderburg², Tom Lüdde², Markus Jördens². ¹Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital of the, Düsseldorf, Germany; ²Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital of the Heinrich Heine University, Düsseldorf, Germany; ³Center of Advanced Imaging, Heinrich Heine University, Düsseldorf, Germany
Email: joana.venturapereira@med.uni-duesseldorf.de.

Background and aims: In hepatic encephalopathy (HE), high levels of NH₄Cl in the brain lead to an alteration of glutamate homeostasis but the mechanism involved is not completely known. Since L-glutamate/L-aspartate transporter (GLAST) contributes to glutamate homeostasis, we studied the effect of hyperammonia on GLAST, concretely receptor clustering, membrane translocation and multimerization.

Method: We transfected primary rat astrocytes with GLAST tagged with eYFP or/and mCherry. Using living cells before and after exposition to 5 mM NH₄Cl we (i) performed epifluorescence microscopy to investigate the formation of GLAST clusters in the presence of putative inhibitors/inducers of glutamate exocytosis (ii) studied the alteration of GLAST distribution recurring to Total Internal Reflection Microscopy (TIRFM) (iii) investigated multimerization of GLAST using Fluorescence Resonance Energy Transfer-Fluorescence Life Time microscopy (FRET-FLIM).

Results: GLAST redistribution and clustering occurred in cultured rat astrocytes in the presence of NH₄Cl (n = 18 cells) and Glutamate (n = 5) (Figure). Furthermore we could observe GLAST clustering was

POSTER PRESENTATIONS

induced by the NO-donor DEANOONOate (n = 10) and prevented by LNMTA (inhibitor of NO-Synthetase) (n = 4), indicating an involvement of reactive nitrogen oxide species (RNOS) in the clustering process. In addition clustering by NH₄Cl was absent when the cells were pretreated with a Ca²⁺-chelator (BAPTA) (n = 4) or an inhibitor of the Cyclooxygenase (Indomethacin (n = 6)/Diclofenac (n = 4)). Using TIRF microscopy, a statistically significant increase of eYFP-GLAST (n = 7) and GLAST-eYFP (n = 7) particles was observed in the plasma membrane after 30 sec stimulation of cultured rat astrocytes with NH₄Cl. We analyzed 39 single-cells by FRET-FLIM microscopy and on 23 cells we detected a significantly decrease in fluorescence lifetime of GLAST-eYFP upon exposure to NH₄Cl, suggesting a shorter distance between GLAST molecules.

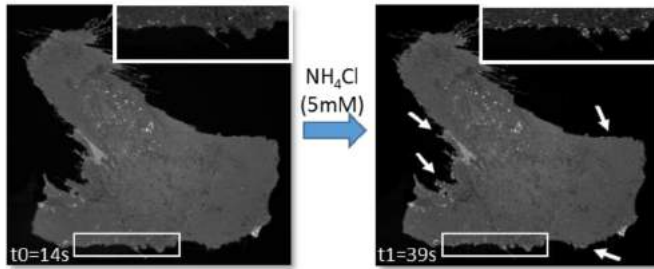


Figure: Redistribution of eYFP-GLAST molecules and their accumulation at the pericytoplasmic regions of the cell (clustering) upon exposure to NH₄Cl.

Conclusion: Our study shows that NH₄Cl induces rapid GLAST clustering in cultured rat astrocytes. The NH₄Cl-induced clustering seems to be dependent on calcium, Cyclooxygenase and NO

Synthase. NH₄Cl causes the redistribution of GLAST in the plasma membrane and seems to induce GLAST multimerization. Next experiments are focus on anisotropy analysis to confirm the formation of GLAST multimers. We also plan to knockout GLAST using CRISPR-Cas9 to investigate the influence of hyperammonia on the functionality of the transporter.

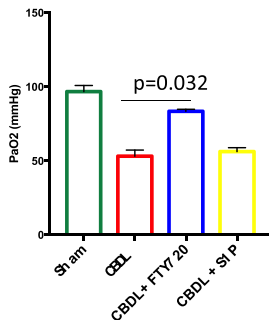
PO-2213

Fingolimod Represents a Novel Therapy in Experimental Model of Hepatopulmonary Syndrome

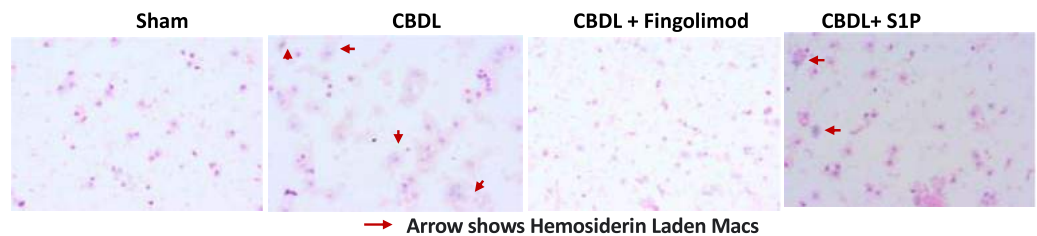
Sukriti Sukriti¹, Anupama Kumari¹, Preeti Negi¹, Arvind Tomar¹, Swati Thangariyal¹, P. Debishree Subudhi¹, Chitranshu Vashistha¹, Chhagan Bihari¹, Rakhi Maiwall¹, Shiv Kumar Sarin¹. ¹Institute of Liver and Biliary Sciences, New Delhi, India
Email: shivsarini@gmail.com.

Background and aims: Hepatopulmonary syndrome (HPS) is a serious complication of cirrhosis and is characterized by pathological vasodilation of the pulmonary vasculature resulting in arterial oxygenation defects. There are no effective treatment options. Fingolimod, a functional agonist of sphingosine-1-phosphate (S1P) maintains the vascular tone by reducing nitric oxide production, which represents an attractive therapy for HPS. We aimed to investigate if Fingolimod, is an effective agent to target pathological vasodilation and improvement in an experimental model of HPS.

Method: HPS model was developed in mice by common bile duct ligation (CBDL). After 2 weeks of CBDL, the hypoxemia and intrapulmonary shunting on a background of liver fibrosis were seen. Group A (n = 10) received S1P (1 μM/g), Group B (n = 10) fingolimod (100 μM/g) and Group C (n = 10) normal saline, twice a week intraperitoneally for next 3 weeks and were compared with Group D; (n = 10) sham operated. Animals were assessed for PaO₂



Bronchioalveolar Lavage



Liver Histology

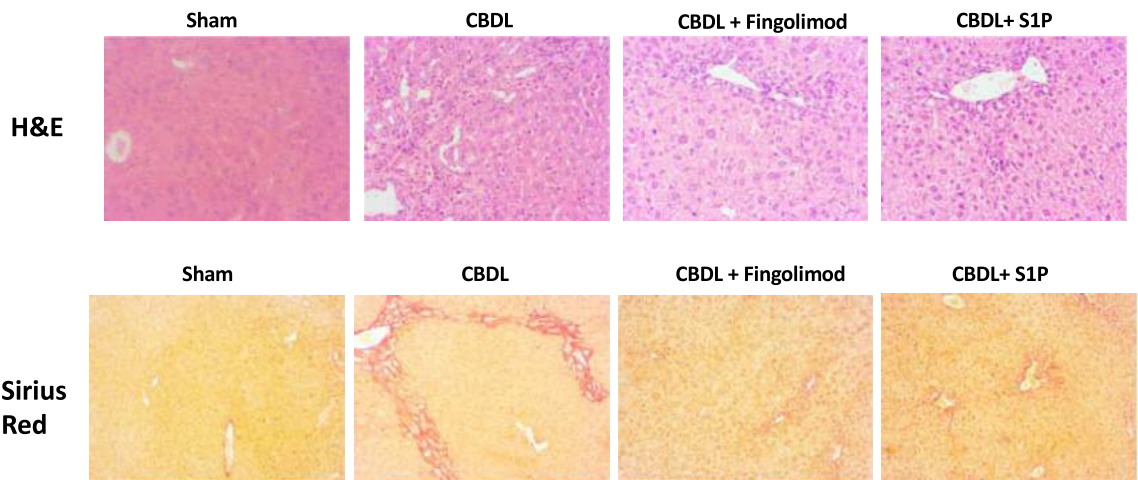


Figure: (abstract: PO-2213)

(mmHg), vessel formation using 6 µm microspheres, trans-endothelial albumin influx, lung wet-dry ratio, liver histology, hepatocyte proliferation. Bronchioalveolar lavage (BAL) was analysed for alveolar macrophages activation, S1P, nitric oxide levels. mRNA levels for genes of iNOS, eNOS, SPHK1/2, S1P receptors.

Results: In CBDL HPS model, after 3 weeks of treatment, animals in Gr.B had significantly improved gas exchange with increased PaO₂ levels (p = 0.032), significantly less intra-pulmonary shunting and trans-endothelial albumin influx (p = 0.023) than Gr. C. Whereas, Gr. A also showed reduction but could not achieve significance. The lung wet to dry ratio showed significant reduction in both the Gr. A and B (p = 0.042; 0.048) than Gr. C. Upon BAL analysis, hemosiderin laden macrophages/20× field showed significant reduction in Gr. B than C (12 ± 5 vs 84 ± 26; P = 0.002). Also, the NO levels in BAL decreased in Gr. B but not in Gr. A. The lung iNOS, eNOS genes were reduced <8-fold in Gr. A and B than C (p < 0.00). Among S1P receptors, S1PR-3 was 2-fold upregulated in Gr. B than Gr. A (p < 0.001). The liver histology showed reduction in ductal proliferation and inflammation, while no morphological changes in Gr. D was observed. The Sirius red staining showed reduction in fibrosis grade from F3 to F1 in Gr. B, F3 to F2 in Gr. A. The PCNA showed significant increase, depicting hepatocytes proliferation in Gr. B than A, C (p < 0.001). Upon follow-up for 8 weeks, Gr. B significantly improved survival than Gr. C (p = 0.042).

Conclusion: CBDL in mice induces HPS, which is mediated by excessive NO production. Administration of fingolimod after development of HPS is a novel potential drug for reducing the intrapulmonary shunting, inflammation and fibrosis in HPS. Fingolimod treatment improves experimental HPS by counteracting vasodilation and potentiates an attractive therapeutic strategy for human HPS.

PO-2279

Obese-induced brain sphingolipid dysregulation in bile-duct ligated rats accelerates and exacerbates hepatic encephalopathy

Rafael Ochoa-Sanchez^{1,2}, Mélanie Tremblay¹, Christopher F. Rose^{1,2}.
¹Centre de recherche du CHUM (CRCHUM), Montreal, Canada;
²Université de Montréal, Medicine, Montreal, Canada
 Email: rochoa.sanchez@gmail.com.

Background: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome observed in chronic liver disease (CLD/cirrhosis). With an increasing prevalence of obesity-induced cirrhosis and evidence linking blood-derived lipids and brain lipid alterations to neurological impairment, we hypothesize that obese-induced brain lipid dysregulation increases the progression of HE in bile-duct ligated (BDL) rats. Aim: Study the impact of obesity on brain sphingolipids and the development of neurological impairment in a rat model of CLD and obesity.

Method: CLD and HE model: 5-week BDL rats and Sham-controls, were used. Groups: Obese-BDL (O-BDL) and Obese-Sham (O-Sham) received high-fat diet (HFD) for 25-days pre-BDL surgery and then proceeded with high-carbohydrate diet (HCD) for 5 weeks post-BDL; Lean-BDL (L-BDL) and Lean-Sham (L-Sham) received regular-diet (RD) pre-BDL surgery and then HCD post-BDL. Body weight (BW), fat-mass, behavior, plasma liver markers and brain hippocampal sphingolipids were measured at 0 (pre-BDL), 3 and 5 weeks post-BDL.

Results: Pre-BDL, HFD lead to increased BW and fat mass vs RD which was sustained with HCD in O-BDL vs L-BDL at 3 and 5 weeks. Ammonia, albumin, AST, ALT, ALP and bilirubin were impaired in O-BDL and L-BDL vs Shams at 3 and 5 weeks. High-density (HDL) and low-density (LDL) lipoprotein levels were detected in pre-BDL rats which persisted in O-BDL and L-BDL vs controls at 3 and 5 weeks. LDL and total-cholesterol were higher in O-BDL vs L-BDL at 5 weeks.

Short- and long-term (LTM) memory were impaired in both BDL groups at 5 weeks, whereas at 3 weeks, LTM impairment was found solely in O-BDL. Furthermore at 3 weeks, motor coordination was reduced in O-BDL, but not in L-BDL. At 5 weeks, motor coordination decreased in both BDL groups, with worse performance in O-BDL vs L-BDL. At 3 and 5 weeks, skill learning improved in L-Shams and L-BDL, but not in O-Shams and O-BDL. Muscle-strength was reduced in L-BDL but not in O-BDL vs Shams. Hippocampal sphingomyelin lipids were increased in O-BDL vs L-BDL rats at 0, 3 and 5 weeks, while ceramides were only reduced at 5 weeks.

Conclusion: CLD-obesity rat model is characterized by increased fat mass and hyperlipidemia pre- and post-BDL. Neurological decline in O-BDL rats developed earlier and was more severe vs L-BDL rats. In addition, different neurological impairments developed in O-BDL vs L-BDL. Brain sphingolipid alteration in obese-cirrhotic rats may contribute to accelerate/worsen HE.

PO-2382

Role of sex on the development of sarcopenia and ammonia metabolism in bile-duct ligated rats

Mariana M. Oliveira^{1,2}, Alexis Monnet Aimard³, Tremblay Mélanie¹, Christopher F. Rose^{1,2}.
¹Centre de recherche du CHUM (CRCHUM), Montréal, Canada; ²Université de Montréal, Medicine, Montréal, Canada; ³Institute of Neuroscience of la Timone, Marseille, France
 Email: marianaoliveira39@yahoo.com.br.

Background and aims: In chronic liver disease (CLD) loss of muscle mass (sarcopenia) is highly prevalent which leads to an increased risk in hepatic encephalopathy (HE). Muscle plays a compensatory role during liver disease in clearing ammonia since it contains glutamine synthetase (GS). Therefore, diminished muscle mass leads to a further reduced capacity to remove ammonia. Loss of muscle mass has been described in male rats with CLD but has not been explored in female CLD rats. Our aim was to identify whether sex has an effect on muscle mass and blood ammonia levels.

Methods: Five weeks after either BDL (n = 8) or Sham (n = 8) surgery in male and female rats, the following were assessed; markers of liver injury and function, HE (open field test for anxiety, rota-rod test for motor coordination and night-time activity), body parameters (weight, composition (MRI) and gastrocnemius muscle weight/circumference and grip strength). In addition, muscle GS activity and muscle ammonia clearance as well as glutamine generation (femoral venous-arterial difference) were evaluated in female vs male BDL rats.

Results: Female and male BDL rats had similar levels of impaired liver markers (ALP, AST, bilirubin and albumin (p < 0.001)) and both developed HE (motor-coordination and night activity (p < 0.05)) when compared to respective Shams. Male BDL rats experienced loss of lean mass, muscle weight and strength (p < 0.01) while no differences were found in female BDL vs Sham rats. Male and female BDL rats had similar ammonia clearance and glutamine production by muscle, while GS activity was lower in female vs. male BDL rats (p < 0.01).

Discussion: Our results demonstrate that following BDL surgery, female rats develop CLD and HE comparable to male rats. However, contrary to males, female BDL rats did not develop sarcopenia compared to respective controls. Preserved muscle mass in female BDL did not result in lower blood ammonia (higher ammonia clearance) whereas muscle mass loss in male BDL rats was accompanied with an upregulation in GS which may explain the similar blood ammonia levels found in both male and female BDL rats.

POSTER PRESENTATIONS

PO-2420

Impact of a loss-of-function variant in HSD17B13 on hepatic decompensation and mortality in cirrhotic patients

Antonio Gil-Gomez¹, Javier Ampuero^{1,2}, Sheila Gato Zambrano¹, Rocío Montero-Vallejo¹, Rocio Munoz Hernandez¹, Douglas Maya¹, Rocío Gallego-Durán¹, Angela Rojas Alvarez-Ossorio¹, Rubén Francés³, German Soriano⁴, Manuel Romero Gomez^{1,2}. ¹SeLiver Group at Institute of Biomedicine of Seville (IBiS), Virgen del Rocio University Hospital/CSIC/University of Seville, Spain; ²UCM Digestive Diseases, Virgen del Rocio University Hospital, Seville, Spain; ³Instituto de Investigación Sanitaria y Biomédica de Alicante. Dpt. Clinical Medicine, Miguel Hernández University, Alicante, Spain; ⁴Department of Gastroenterology Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. Email: mromerogomez@us.es.

Background and aims: A common splice variant in HSD17B13 (rs72613567:TA) was recently found to be associated with a reduced risk of developing chronic liver disease (NAFLD/ALD) and its related fibrosis and cirrhosis (Abul-Husn *et al.*, NEJM 2018). By contrast, recent data showed worse outcomes in patients with advanced chronic liver disease carrying the mutation (Scheiner *et al.*, Liver Int, 2020). In this study, we aimed to evaluate the prognosis of cirrhotic patients harbouring this variant.

Method: We performed a retrospective analysis in 442 prospectively recruited cirrhotic patients from three different hospitals in Spain followed-up for 5 years. Clinical, demographical and biochemical data was collected, and we performed a genotyping analysis for common variants previously associated to liver disease risk.

Results: The majority of patients were male (68.1%), mean age of 59.4 with predominance of alcoholic etiology (48%) over viral hepatitis (43%). Liver function was MELD 12.4 ± 5.3, Child A/B (87.1%). 268 (60.6%) patients harbored the wild-type T- of rs72613567, 130 (29.4%) were heterozygous and 44 (10.0%) homozygous for the variant TA. Surprisingly, patients homozygous for the TA-allele had higher MELD (p = 0.041), Child-Pugh score (p = 0.014), INR levels (p = 0.047), as well as decreased albumin (p = 0.007) at baseline. After multivariate analysis, we found that patients with the “low-risk” variant had indeed increased risk of hepatic decompensation (aOR 2.533; 1.071–7.373, p < 0.05) and liver related mortality (aOR 2.184; 1.015–4.698, p < 0.05). Specifically, these patients had increased risk of developing ascites (Log-R 8.7, p < 0.05), hepatic encephalopathy (Log-R 5.5, p < 0.05) and higher mortality (Log-R 4.5, p < 0.05) at 5 years of follow-up. However, no differences were found in the frequency of HCC (24.5% in T-TA vs 18.2% TA/TA, p = 0.232). No association was found for the variant rs738409 in PNPLA3.

Conclusion: These findings suggest that the variant rs72613567: TA HSD17B13 has no protective effect, but indeed increases the risk of decompensation and death in patients with advanced chronic liver disease. Further studies focusing on the effects of HSD17B13 genotypes in patients with different stages of liver disease are needed.

PO-2833

Early and late changes in the phenotype of liver sinusoidal endothelial cells (LSECs) along the development of heart failure

Kamila Wojnar-Lason^{1,2}, Agnieszka Kij¹, Patrycja Kaczara¹, Agnieszka Jasztal¹, Stefan Chlopicki^{1,2}. ¹Jagiellonian Centre for Experimental Therapeutics (JCET), Kraków, Poland; ²Jagiellonian University Medical College, Faculty of Medicine, Chair of Pharmacology, Kraków, Poland
Email: kamila.wojnar-lason@jcet.eu.

Background and aims: Heart failure (HF) is one of the leading causes of death worldwide. During the development of heart failure the hepatic circulation may be impaired, that consequently leads to the tissue hypoxia and alternations in liver function. The aim of the study was to characterize the changes in the phenotype of LSECs during the progression of HF in the unique murine model of this disease

represents by Tgαq*44 mice, which importantly mimics all the typical characteristics of HF in humans.

Method: LSECs and livers were isolated at early (4-month-old mice) and late stage (12-month-old mice) of HF development from Tgαq*44 female mice (n = 6). Organs were fixed and stained by HandE and PSR. LSECs were cultured overnight in medium under hypoxia conditions, and were subsequently used to assess phenotype changes related to HF progression—the expression level of endothelial markers (immunocytochemistry), eicosanoid biosynthesis (UPLC-MS/MS) and changes in cellular metabolism (Seahorse) were investigated.

Results: Livers obtained from 12-months old Tgαq*44 mice did not display fibrosis but were characterized by wider sinusoids as compared with age-matched FVB mice. In the early stage of the development of HF in Tgαq*44 mice, LSECs were characterized by lower expression of COX-1, eNOS and pro-inflammatory markers, whereas the iNOS expression remained unchanged. The decreased biosynthesis of COX-dependent eicosanoids (PGI₂ measured as 6-keto-PGF_{2α}PGE₂, PGF_{2α}) was also observed in LSECs in the early phase of HF. Furthermore, LSECs isolated from young Tgαq*44 mice displayed increased biosynthesis of anti-inflammatory and vasoprotective EETs, that was reflected by increased level of their metabolites (8, 9-, 11, 12- and 14, 15-DHET). Interestingly, the biosynthesis of 12- and 15-HETE was decreased in Tgαq*44 mice LSECs independently of the phase of HF. Additionally, the late phase of HF was associated with changes in the bioenergetics of LSECs towards activation of glycolysis pathway. Mitochondrial stress test (MST) and glycolytic stress test (GST) revealed that LSECs isolated from 12-month-old Tgαq*44 mice were metabolically more active than age-matched FVB mice.

Conclusion: In the early phase of HF LSECs were characterized by endothelium-derived NO deficiency along with decreased expression of COX-1 and a shift in eicosanoid biosynthesis from COX-dependent prostanoids to CYP-450-dependent EETs. Taking into account, that EETs are considered as vasoprotective mediators the activation of EET-dependent may represent a compensatory mechanism in response to decreased bioavailability of NO related to HF development. The late stage of heart failure was dominantly featured by the overactivation of glycolysis pathway and an increased ATP production in LSECs.

Taking together, HF development induces alterations in LSEC phenotype, that may contribute to the liver dysfunction of HF.

PO-2851

In vitro skeletal muscle cell atrophy and mitochondrial dysfunction after exposure to human serum from patients with ESLD and NAFLD

Sophie Allen^{1,2}, Alex Seabright¹, Jonathan Quinlan^{1,2}, Amritpal Dhaliwal^{2,3,4}, Felicity Williams^{2,3,4}, Nick Fine⁵, David Hodson^{5,6}, Yu-Chiang Lai^{1,5,7}, Matthew Armstrong^{2,4}, Ahmed Elsharkawy^{2,4}, Carolyn Greig^{1,2,7}, Janet Lord^{2,3,7}, Gareth Lavery^{2,5,6}, Leigh Breen^{1,2,7}. ¹University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences, Birmingham, United Kingdom; ²National Institute for Health Research, Birmingham Biomedical Research Centre at University Hospitals Birmingham, Birmingham, United Kingdom; ³University of Birmingham, Institute of Inflammation and Ageing, Birmingham, United Kingdom; ⁴Queen Elizabeth Hospital Birmingham, Liver Unit, Birmingham, United Kingdom; ⁵University of Birmingham, Institute of Metabolism and Systems Research, Birmingham, United Kingdom; ⁶Birmingham Health Partner, Centre for Endocrinology, Diabetes and Metabolism, Birmingham, United Kingdom; ⁷University of Birmingham, MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research, Birmingham, United Kingdom
Email: l.breen@bham.ac.uk.

Background and aims: Sarcopenia, defined as a loss of muscle mass, strength and function is a common complication associated with End Stage Liver Disease (ESLD). Despite its clinical importance, the mechanisms which contribute to the development of sarcopenia in

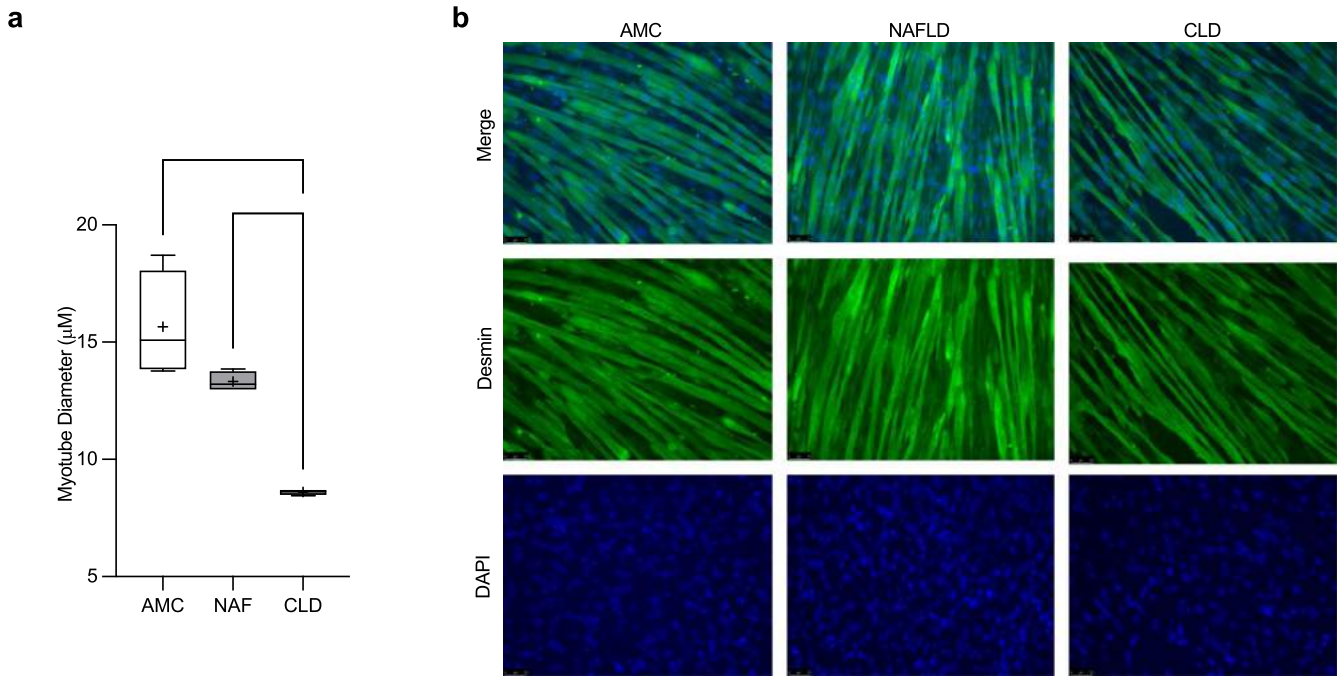


Figure: (abstract: PO-2851)

ESLD remain unclear. Therefore, we aimed to investigate the mechanistic drivers of sarcopenia in ESLD through the use of an in vitro model utilising ex vivo human serum from ESLD and non-alcoholic fatty liver disease (NAFLD) patients.

Method: Fasted blood samples were obtained from 4 age-matched control (64.7 ± 10.0), 4 non-cirrhotic NAFLD (61.8 ± 7.6) and 4 decompensated ESLD (60.5 ± 1.7) patients. C2C12 myotubes were serum and amino acid starved for 1 hour and subsequently conditioned with serum from control, NAFLD and ESLD patients for 4 or 24 hours. After 4 hours C2C12 myotubes were treated with 5 mM leucine for 30-minutes. Myotube diameter was assessed using fluorescent microscopy. Mitochondrial function was measured through: (1) respiration, utilizing a mitochondrial stress test on a XFe24 Seahorse Analyser; (2) mitophagy, assessed using a C2C12 mitoQC cell line. Muscle protein synthesis (MPS) was determined using the surface sensing of translation (SUnSET) technique and signaling markers of anabolic and catabolic pathways was measured via Western blotting.

Results: Myotube diameter was reduced in myotubes treated with serum from ESLD patients in comparison to both control (45%) and NAFLD (35%) patients ($p < 0.001$ for both). A reduction in maximal mitochondrial respiration, coupling efficiency and mitophagy was identified in myotubes conditioned with both NAFLD and ESLD serum in comparison to controls ($p < 0.05$ for both). No difference in mitochondrial protein content was identified. MuRF-1, a catabolic protein, was elevated in myotubes treated with ESLD serum in comparison to control serum ($p = 0.03$). Leucine treatment did not alter muscle protein breakdown (MPB) signaling in any group. No change in MPS or anabolic signaling markers was identified within or between groups, in the presence or absence of leucine treatment.

Conclusion: We show myotube atrophy in cells conditioned with ex vivo human serum from ESLD patients in comparison to control and NAFLD patients, which may be caused through mitochondrial dysfunction and an increase in MPB. This work provides an experimental platform to further probe mechanisms of sarcopenia within ESLD and to develop potential therapeutic targets to mitigate sarcopenia.

Cirrhosis and its complications: Other clinical complications except ACLF and critical illness

PO-187

Non-malignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus

Ellen Driever¹, Fien von Meijefeldt¹, Jelle Adelmeijer¹, Robbert J. de Haas², Marius C. van den heuvel³, Chandrasekaran Nagasami⁴, John W. Weisel⁴, Robert J. Porte¹, Anabel Blasi⁵, Nigel Heaton⁶, Stephen Gregory⁷, Pauline Kane⁷, William Bernal⁶, Yoh Zen⁶, Ton Lisman¹. ¹University Medical Center Groningen, Surgery, Groningen, Netherlands; ²University Medical Center Groningen, Radiology, Groningen, Netherlands; ³University Medical Center Groningen, Pathology and Medical Biology, Groningen, Netherlands; ⁴Perelman School of Medicine at the University of Pennsylvania, Cell and Developmental Biology, Philadelphia, United States; ⁵Hospital Clinic, Anesthesiology, Barcelona, Spain; ⁶King's College Hospital, Institute of Liver Studies, London, United Kingdom; ⁷King's College Hospital, Radiology, London, United Kingdom
Email: e.g.driever@umcg.nl

Background and aims: Portal vein thrombosis (PVT) is a common complication of cirrhosis. The exact pathophysiology remains largely unknown and treatment with anticoagulants only lead to recanalization of the portal vein in a proportion of patients. A better insight in the structure and composition of portal vein thrombi may assist in developing a more rational treatment approach.

Method: Eight prospectively and 63 retrospectively collected non-malignant portal vein thrombi from cirrhotic patients who underwent liver transplantation were included. Histology, immunohistochemistry and scanning electron microscopy were used to assess structure and composition of the thrombi. Most recent CT scans were reanalysed for thrombus characteristics. Clinical characteristics were related to histological and radiological findings.

POSTER PRESENTATIONS

Results: All prospective and retrospective samples showed a thickened, fibrotic tunica intima. Fibrin-rich thrombi were present on top of the fibrotic intima in 4/8 prospective cases and in 21/63 retrospective cases. A minority of the fibrotic areas stained focally positive for fibrin (ogen) (fg, 16% of the cases), Von Willebrand Factor (VWF, 10%) and CD61 (platelets, 21%), while most of the fibrin-rich areas stained positive for those markers (fg, 100%; VWF, 77%; CD61, 100%). No associations were found between clinical characteristics including estimated thrombus age and presence of fibrin thrombi.

Conclusion: Here we demonstrated that PVT in cirrhotic patients consists of intimal fibrosis with an additional fibrin-rich thrombus in only a third of the cases. These results suggest that the majority of portal vein thrombi in cirrhotic patients are unlikely to recanalise by anticoagulant therapy.

PO-342

Improved survival and reduced risk of hospital admissions after 12-weeks of resistance training in patients with cirrhosis—a three year follow-up from randomization

Luise Aamann^{1,2}, Gitte Dam¹, Peter Jepsen¹, Hendrik Vilstrup¹, Niels Kristian Aagaard¹. ¹Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; ²Copenhagen University Hospital Hvidovre, Gastro Unit, Medical division, Denmark
Email: luise.aamann@gmail.com

Background and aims: Cirrhosis is a serious condition that causes frequent acute admissions to the hospital and may shorten life expectancy. Physical activity provides a remarkable variety of health benefits, and exercise may extend lives—even in patients with chronic diseases.

We followed participants from a clinical trial over a period of three years after randomization. The intervention was supervised resistance training for 12 weeks. Our aim was to estimate the effect of resistance training on overall survival estimates and the risk of the first acute hospitalization after three years.

Method: 39 participants with cirrhosis Child-Pugh stage A/B were randomly assigned to either a group performing 12 weeks of supervised resistance training or a control group. Regardless of cause, all deaths and acute admissions to the hospital were registered during the three-year follow-up.

Here we present an intention-to-treat analysis including all participants from randomization. We used Cox regression for survival analysis and Fine and Gray regression to analyze time to first admission with death before hospitalization as a competing risk. Both analyses were adjusted for Child-Pugh A or B at randomization.

Results: Baseline values were similar between groups. During the follow-up 1 exerciser and 6 controls died. After three years (1095 days), we found a statistically and clinically significant difference in survival in favor of patients randomized to resistance training: adjusted hazard ratio 0.12 (95% CI: 0.01–0.96; $p = 0.046$).

All through the follow-up 9 exercisers and 15 controls were acutely hospitalized at some point. The risk of an acute admission to the hospital three years after randomization was reduced in exercisers compared to controls: adjusted subdistribution hazard ratio 0.40 (95% CI: 0.17–0.92; $p = 0.032$).

Conclusion: Twelve weeks of supervised resistance training may increase survival and reduce the risk of acute hospitalization three years after exercise.

However, these data are based on a secondary outcome of a randomized clinical trial and larger studies with survival and hospital admission as primary end points are required to confirm the effect of resistance training.

PO-485

Baveno-VI criteria to predict variceal bleeding and liver decompensation in compensated cirrhosis patients

Yu Jun Wong^{1,2}, Martin Putera¹, Francis Teh¹. ¹Changi General Hospital, Gastroenterology and hepatology, Singapore; ²Duke-NUS Medical School, Singapore
Email: eugene.wong.y.j@singhealth.com.sg

Background and aims: Hepatic venous pressure gradient (HVPG) is an invasive approach to identify compensated cirrhosis patients with clinically significant portal hypertension and at risk of liver decompensation. The Baveno-VI criteria can safely omit screening esophagogastroduodenoscopy (EGD) in compensated cirrhosis patients. Beyond the exclusion of high-risk varices, it was uncertain if Baveno-VI criteria could predict the clinically meaningful end points such as variceal bleeding and liver decompensation in compensated cirrhosis patients. We aim to compare the performance of the Baveno-VI and expanded Baveno-VI criteria to predict the risk of liver decompensation among compensated cirrhosis patients.

Method: Compensated cirrhosis patients with liver stiffness measurement (LSM) performed from 2013 to 2018 in our institution were prospectively included in a database for analysis. All subjects had paired EGD with LSM. Patients with prior liver decompensation were excluded. All patients were followed-up until the occurrence of liver decompensation (variceal bleeding, ascites and hepatic encephalopathy).

Results: We included 304 compensated cirrhosis patients. Median follow-up was 36 (IQR: 22–50) months. Mean age and MELD score were 55 ± 11 and 8 ± 3 , respectively. 14 (4.6%) patients had HRV.

The expanded Baveno-VI criteria spare more EGD than the Baveno-VI criteria (57% vs 28%, $p < 0.001$) without missing more high-risk varices (2.3% vs 1.2%, $p = 0.25$). Patients with favourable Baveno-VI status had a lower rate of missed gastroesophageal varices at baseline (3.5% vs 14.1%, $p < 0.001$) and a lower risk of liver decompensation during follow-up (1.2% vs 5.2%, $p = 0.008$) compared to those with favourable expanded Baveno-VI status.

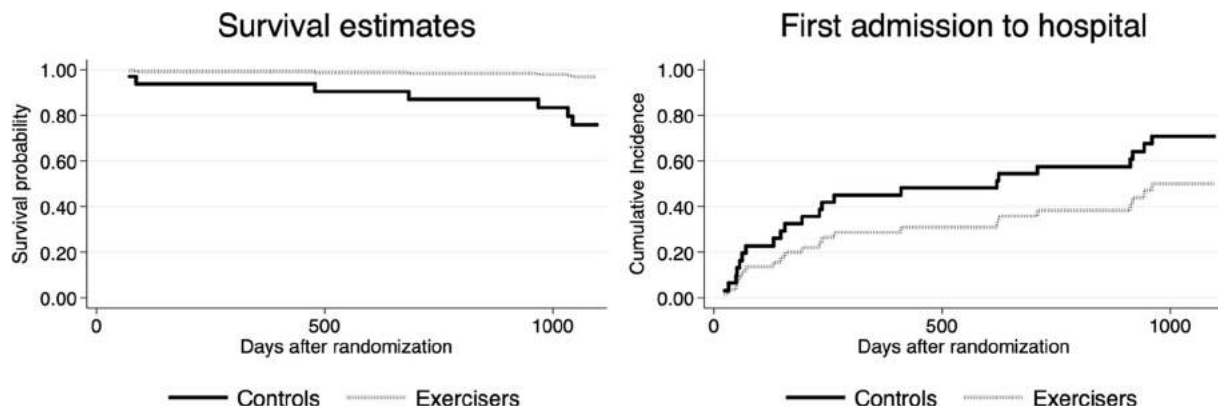


Figure: (abstract: PO-342)

Both criteria had similar risk of developing variceal bleeding (1.2% vs 3.4%, $p = 0.063$), ascites (0% vs 2%, $p = 0.250$) or HE (0% vs 2%, $p = 0.250$) during the follow-up. The Baveno-VI criteria also have a higher sensitivity and negative predictive value to predict liver decompensation than the expanded Baveno-VI criteria (sensitivity: 96% vs 68%, specificity: 31% vs 60%, positive-predictive value: 12% vs 15% and negative predictive value: 99% vs 95%).

Conclusion: The Baveno-VI criteria is superior to the expanded Baveno-VI criteria to identify compensated cirrhosis patients at risk of liver decompensation. As HPVG is invasive and not widely available, the Baveno-VI criteria may be a non-invasive alternative to identify compensated cirrhosis patients with clinically significant portal hypertension for early treatment.

PO-714

Prognostic impacts of the change in muscle mass on patients with cirrhosis

Tae Hyung Kim¹, Young Kul Jung¹, Hyung Joon Yim¹, Young-Sun Lee¹, Sun Young Yim¹, Ji Hoon Kim¹, Yeon Seok Seo¹, Jong Eun Yeon¹, Kwan Soo Byun¹, Soon Ho Um¹. ¹Korea University College of Medicine, Internal medicine, Seoul, Korea, Rep. of South
Email: 93cool@hanmail.net

Background and aims: Sarcopenia has a negative impact on the prognosis of patients with cirrhosis. Although muscle mass changes are also expected to be an important factor, available data are limited yet.

Method: Adults with cirrhosis were included from the prospective cohort who received the abdomen CT annually for HCC surveillance. L3 skeletal muscle index (SMI) was adopted as a proxy of skeletal muscle mass, and we calculated a change of SMI between baseline and one-year (Δ SMI/yr).

Results: Among a total of 155 patients, 113 and 21 had sarcopenia and Child-Pugh class B/C decompensation, respectively. During a median follow-up of 36 months, five patients died and 19 had undergone complications of cirrhosis. Multivariate Cox regression analyses showed 1% decrease in Δ SMI/yr was associated with a 1.15–1.19-fold increased risk of complication occurrence even adjusted for Child-Pugh or MELD score. In addition, Δ SMI/yr showed good prediction of aggravation of liver function (Child-Pugh score at 2 years after baseline), especially in female patients ($n = 46$), with a cut-off of -2.5% (sensitivity 57.1%, specificity 94.9%).

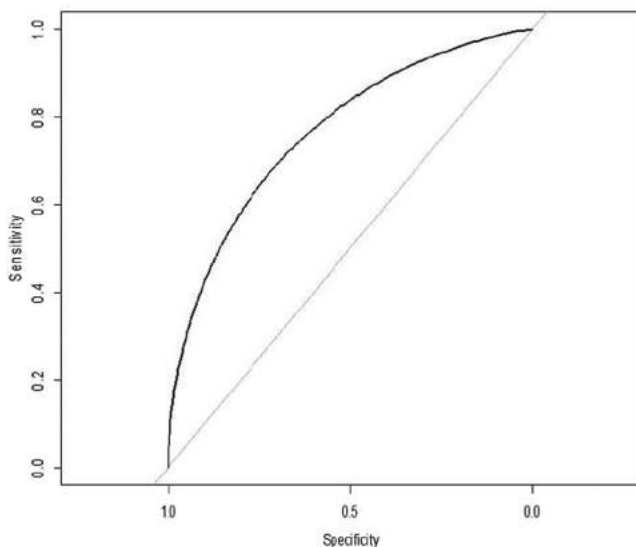


Figure:

Conclusion: Δ SMI/yr was significantly associated with prognosis of patients with cirrhosis independent of baseline Child-Pugh and MELD scores.

PO-835

Safety of 11, 043 paracentesis in patients with liver cirrhosis with and without anticoagulant treatment. Large, retrospective, unicentric study

Jordi Vives Moreno¹, Eduard Brunet¹, Cristina Solé¹, Gemma Solé², Meritxell Casas¹, Mireia Miquel^{1,3}, Jordi Sánchez-Delgado^{1,3}, Montserrat Gil¹, Jose Alberto Ferrusquia¹, Oliver Valero⁴, Mercedes Vergara^{1,3}. ¹Corporació Sanitària Parc Taulí, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain; ²Corporació Sanitària Parc Taulí, Laboratory and analysis service, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell; ³Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid; ⁴Universitat Autònoma de Barcelona, Applied Statistics Service, Universitat Autònoma de Barcelona, Cerdanyola del Vallès
Email: jordivivesm@gmail.com

Background and aims: Paracentesis is a diagnostic and therapeutic procedure frequently used in patients with liver cirrhosis (LC). Patients with LC have a complex coagulation disorder with alteration in coagulation parameters that poorly correlate with bleeding risk. Moreover, some of these patients receive antiplatelet (APT) or anticoagulation (ACT) treatment. There is no consensus about the use of these therapies during paracentesis. The aim of this study is to evaluate the safety of the paracentesis and the incidence of paracentesis-related haemorrhagic complications (PHC) in patients with LC particularly in those patients receiving APT or ACT.

Method: Retrospective, unicentric, and observational study. All paracentesis performed in adult patients with LC in our centre from January 1998 to December 2018 were identified by clinical history registers. PHC were identified by ICD-9-CM codes.

Results: A total of 11, 043 paracentesis in 1, 137 patients with LC were identified. The mean age was 65 ± 12.2 years. A 2.4% ($n = 273$) of paracentesis were performed under AP: 1.6% ($n = 182$) treated with acetylsalicylic acid, 0.8% ($n = 89$) with clopidogrel and 0.0002% ($n = 2$) with ticagrelor. And 6.3% ($n = 698$) of paracentesis were performed under AC: 4.5% ($n = 494$) treated with acenocoumarol, 1.8% ($n = 202$) with heparin and 0.006% ($n = 4$) with apixaban. PHC occurred in 36 (0.3%) of all paracentesis performed. In those patients, 78% ($n = 28$) received red blood cells transfusion, 31% ($n = 11$) needed arterial embolization, and 28% ($n = 10$) required plasma transfusion. One (2.8%) patient died because of a severe paracentesis-related bleeding. Variables associated with the development of PHC in the univariate analysis were the use of ACT (8 (1.1%) vs 27 (0.3%); $p < 0.001$) and a higher INR (1.6 vs 1.4; $p < 0.03$), bilirubin (1.9 vs 1.5; $p < 0.04$), urea (73 vs 61; $p < 0.03$) and MELD (17 vs 15; $p < 0.012$) values. APT or heparin treatment, number of platelets and creatinine were not associated with bleeding events. Finally, ACT (OR: 3.23 (1.15–9.09); $p = 0.027$), INR (OR: 6.75 (2.32–19.68); $p = 0.001$) and urea (OR: 1.72 (0.94–3.15); $p = 0.079$) were independently associated in the multi-variate analysis.

Conclusion: Paracentesis is an extremely safe procedure with only 0.3% of bleeding complications. Slightly higher risk was observed in patients under AC and those with worse liver function. More studies are needed to confirm these results.

PO-864

Further analysis of simvastatin safety trial in patients with decompensated cirrhosis provides promising information about improving liver function and reducing cirrhosis severity

Alberto Muñoz¹, Florencia Pollarsky¹, Mónica Marino¹, Mariano Cartier¹, Carlos Míguez¹, Horacio Vázquez², Daniel Alvarez³, Pablo Salgado⁴, Gustavo Romero¹. ¹Hospital Dr. Carlos B. Udaondo, Hepatology Section, Buenos Aires, Argentina; ²Hospital Dr. Carlos B. Udaondo, Clinical Unit, Buenos Aires, Argentina; ³Fundación Favaloro, Ultrasound Service, Buenos Aires, Argentina; ⁴Facultad de Odontología, Universidad de Buenos Aires, Instituto de Investigaciones en Salud Pública, Buenos Aires, Argentina
Email: aemunoz@intramed.net

Background and aims: There is some evidence concerning the beneficial effects of statins in decompensated cirrhosis (DC) in the clinical research setting. In this regard, the chronic administration of simvastatin to DC patients was associated with reducing Child-Pugh class and Child-Pugh score at the end of a safety trial (EST). We assessed whether chronic simvastatin treatment could avoid liver function deterioration and decrease cirrhosis severity in these DC patients by further analyzing the safety trial.

Method: The safety phase IIa trial was conducted on 30 DC patients (Child-Pugh class A [n=6], B [n=22], and C [n=2]), who received simvastatin for up to one year. The primary end points of this further analysis were liver function and cirrhosis severity. The secondary end points were health-related quality of life (HRQOL), hospital readmissions by cirrhosis complications, and survival.

Results: Liver function improved at the EST compared to baseline, serum albumin concentration 3.3 ± 0.6 g/dL versus 2.9 ± 0.5 g/dL (p = 0.003); ascites 36.7% versus 63.3% (p = 0.008); and serum sodium concentration 135 ± 4 mEq/L versus 133 ± 4 mEq/L (p = 0.025). Cirrhosis severity reduced at the EST compared to baseline, (Child-Pugh class A: 53.3% versus 20.0%), (Child-Pugh class B: 40.0% versus 73.3%), and (Child-Pugh class C: 6.7% versus 6.7%) (p = 0.012), and Child-Pugh score 6.7 ± 1.7 versus 7.3 ± 1.3 (p = 0.041). Besides, 12 patients (40%) who at baseline were Child-Pugh class B became Child-Pugh class A at the EST. Serum albumin concentration was the only Child-Pugh variable showing a statistically significant difference in all comparisons carried out between Child-Pugh class A (n = 15) and Child-Pugh class B/C (n = 15) at the EST (p = 0.036). The physical component summary and its domains of HRQOL upgraded from baseline to the EST (p < 0.040). The hospitalizations for cirrhosis complications decreased from 76.7% (the year before the safety trial) to 26.7% (the year of the safety trial) (p = 0.002), and the survival rate reached 90%.

Conclusion: Chronic simvastatin treatment in DC patients has a promising prospect since improving liver function and reducing cirrhosis severity would improve HRQOL, it would in turn decrease hospital readmissions -by cirrhosis complications- and have a positive impact upon survival rate.

PO-918

Low myocardial mechano-energetic efficiency is an independent predictor of prognosis in patients with advanced chronic liver disease

Maurizio Cesari¹, Anna Chiara Frigo², Salvatore Piano¹, Paolo Angeli¹. ¹Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padua, Italy, Department of Medicine, Padova, Italy; ²Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy, Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy
Email: maurizio.cesari@unipd.it

Background and aims: We aimed at investigating if a low myocardial mechano-energetic efficiency (MEE) with energy waste could be a feature of cirrhotic cardiomyopathy and predictive of poor prognosis.

Method: We retrospectively interrogated a large data set of 115 cirrhotic patients followed up for 6 years and compared with 50

healthy controls. Echocardiographic and haemodynamic parameters were assessed at baseline according with current guidelines. MEE was estimated by echocardiographic stroke volume (z-derived)/ (heart rate × 0.6).

Results: Cirrhotic patients presented low peripheral vascular resistance, a compensatory hyperdynamic syndrome with increased cardiac work, left atrial and left ventricular (LV) dimension and mass. Systolic parameters and MEE were similar between patients and controls. Patients with cirrhosis and refractory ascites showed significantly lower MEE compared with both patients with treatable ascites and patients without ascites (1.68 ± 0.47 vs 1.98 ± 0.64 and 1.80 ± 0.37 ml/s respectively, p < 0.05). Increased age and heart rate and reduced BSA, cardiac dimension and work significantly correlated with lower MEE, mostly in non-alcoholic as compared with alcoholic cirrhosis (1.65 ± 0.42 vs 1.95 ± 0.56 ml/s respectively, p = 0.002). Among the cardiovascular parameters increased early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio (E/e') was significantly associated to death; left atrium enlargement and reduced MEE were independent predictors of death (see table below).

Conclusion: In advanced chronic liver disease LV performance is blunted due to an energetically inefficient cardiac mechanical work which correlates with a poor prognosis. Therefore, the simple basal assessment of myocardial mechano-energetic efficiency can identify patients with a worse prognosis which requires a close follow-up.

Table: Parameters associated with death during follow-up (multivariate Cox's regression analysis)

Predictors	SHR (95% CI)	P
MELD	1.11 (1.07–1.15)	<0.0001
Age (years)	1.06 (1.02–1.09)	0.001
LA volume (ml/m ²)	1.03 (1.01–1.06)	0.006
MEE (ml/s)	0.57 (0.33–0.98)	0.04
BSA (Kg/m ²)	0.27 (0.04–1.66)	0.16

E/e' early diastolic transmitral and myocardial velocity on TDI ratio; LA, left atrium; MEE, myocardial mechano-energetic efficiency.

PO-932

Prevalence and prognostic value of cirrhotic cardiomyopathy as defined according with the new proposed classification

Maurizio Cesari¹, Anna Chiara Frigo², Salvatore Piano¹, Paolo Angeli¹. ¹Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padua, Italy, Department of Medicine, Padova, Italy; ²Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy, Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy
Email: maurizio.cesari@unipd.it

Background and aims: The prevalence and prognostic relevance of cirrhotic cardiomyopathy (CCM), as defined according with the new core criteria proposed in 2019, is still unknown. We investigated this relevant issue in a large cohort of cirrhotic patients in different stages of liver disease.

Method: We retrospectively interrogated a data set of 162 collected cirrhotic patients followed up for at least 6 years, which at baseline underwent standard Doppler echocardiography and were compared with 46 healthy subjects. Left ventricular (LV) geometry, systo/diastolic function, global longitudinal strain and the main hemodynamic parameters were assessed according with current guidelines. Systolic dysfunction was diagnosed if LV ejection fraction ≤50% and/or GLS <18% or >22%.

Results: Adequate echocardiographic images permitting speckle tracking analysis were available in 83 patients. No patient presented LV ejection fraction ≤50%; GLS <18% or >22% was evident in 25%; advanced diastolic dysfunction was evident in 10%. Overall the prevalence of CCM was 29%. Patients with and without CCM presented similar clinical, biochemical, hemodynamic and

echocardiographic features at baseline and similar incidence of death after 6 years follow-up (see table below).

Table: Clinical, demographic and biochemical features of cirrhotic patients with and without CCM

Variable	CCM present (n 24)	CCM absent (n 59)	P	Healthy subjects (n 46)
Age (years)	60 ± 12	56 ± 10	NS	55 ± 10
Gender (Male %)	79	70	NS	48
Alcolic etiology (%)	50	43	NS	0
MELD	12 ± 7	12 ± 5	NS	0
Presence of ascites (%)	25	14	NS	0
Dead after 6 yrs FW (%)	38	36	NS	0
BMI (Kg/m ²)	26 ± 3	26 ± 4	NS	25 ± 5
QTc	452 ± 32	453 ± 27	NS	410 ± 21
MAP (mmHg)	93 ± 11	96 ± 13	NS	97 ± 7
Heart rate (bpm)	71 ± 11	69 ± 10	NS	67 ± 10
Creatinine (µmol/L)	89 ± 37	96 ± 80	NS	NA
Aldosterone (ng/dL)	59 (32–86)	66 (48–84)	NS	NA

The data are reported as mean ± SD or median (and interquartile range) as appropriate. MAP, mean arterial pressure; NA, not available

Conclusion: According with the new criteria CCM is detected in 29%, mainly due to altered GLS at rest, but without prognostic relevance and therefore useless for the clinical management of cirrhotic patients.

PO-974

Evaluation of cardiac function in cirrhosis across different prognostic stages; A focus on plasma biomarkers of fibrosis

Jolanta Zuwała-Jagiello¹, Monika Pazgan-Simon², Ewa Grzebyk¹, Joanna Gorka-Dynysiewicz¹, Jacek Jagas³, Simon Krzysztof⁴. ¹Wrocław Medical University, Department of Pharmaceutical Biochemistry, Wrocław, Poland; ²Wrocław Medical University, Clinic of Infectious Diseases, Liver Diseases and Acquired Immune Deficiency, Wrocław, Poland; ³Cardiology Department County Hospital, Wrocław, Poland; ⁴Wrocław Medical University, Clinic of Infectious Diseases, Liver Diseases and Acquired Immune Deficiency, Wrocław, Poland
Email: jolanta.zuwala-jagiello@umed.wroc.pl

Background and aims: As myocardial fibrosis might be an important contributor to the association of liver cirrhosis with diastolic dysfunction and latent form of cirrhotic cardiomyopathy, we investigated the profile of some cardiac biomarkers, fibrosis, and proinflammatory biomarkers in patients with cirrhosis across different prognostic stages.

Method: Overall, 69 patients with liver cirrhosis were included, of whom 22 (32%) patients have compensated cirrhosis with portal hypertension and no varices, and 29 (42%) did not have any decompensating events but conducted regular follow-up and/or prophylactic endoscopic variceal treatment and 18 (26%) had decompensating event, gastrointestinal hemorrhage. We retrospectively screened the cirrhotic patients who had undergone the evaluation of laboratory data regarding plasma cardiac biomarkers [N-terminal pro-B-type natriuretic peptide (NT-pro BNP), high-sensitivity cardiac troponin T (hs-cTnT)], fibrosis biomarkers [carboxy terminal peptide of procollagen type I (PICP), amino terminal propeptide of procollagen type III (PIIINP), matrix metalloproteinase-degraded type III collagen (C3M), tissue inhibitor of matrix proteinase-1 (TIMP-1) and pentraxin-3], various proinflammatory biomarkers (TNFα, IL-1β, IL-6, IL-8, IL-18) and pentraxin-3 (provides information reflecting the integrated effects of fibrosis, injury, and inflammation). All patients underwent transthoracic echocardiography.

Results: Cirrhotic patients with gastrointestinal hemorrhage had higher values of LV volumetric parameters, indexed parameters of LV myocardial mass (LVMM), and higher concentrations of NT-proBNP

(all p < 0.01). The concentrations of pentraxin-3 were greater in patients with varices and gastrointestinal hemorrhage compared to patients with compensated cirrhosis (p < 0.01 and p = 0.02, respectively). PICP and PICP/PIIINP ratio were greater in cirrhotic patients with gastrointestinal hemorrhage compared to patients with varices (p < 0.043 and p < 0.033, respectively). In all patients with cirrhosis, a relationship was found between pentraxin-3 and LVMM/body surface area (r = -0.42, p = 0.01), PIIINP, TIMP-1, and LV end-diastolic volume (r = -0.56 and p = 0.001 and r = 0.35 and p = 0.01, respectively).

Conclusion: The dynamics at different prognostic stages of the liver cirrhosis in the plasma fibrosis biomarkers may reflect an increase in fibrotic and decrease in antifibrotic processes already at the latent form of cirrhotic cardiomyopathy. At the same time, the changes found in the circulating procollagen levels may indicate an important role of type I collagen in the development of myocardial structural changes in cirrhosis. Ongoing inflammation has a significant role in the progression of cirrhosis affecting not only the liver but also leading to the development of structural and functional cardiac changes.

PO-1045

A Double Blind, Randomised, Placebo-Controlled Study To Assess Safety and Tolerability of Oral Enterosorbent Yaq-001 In Cirrhotic Patients (CARBALIVE Consortium)

Jane Macnaughtan¹, Agustin Albillos², Annarein Kerbert¹, Víctor Manuel Vargas Blasco³, Francois Durand⁴, Pere Ginès⁵, Lindsey A. Edwards⁶, Simon Eaton⁷, I. Jane Cox⁸, Fausto Andreola¹, Amir Gander⁹, Javier Martinez², Giacomo Zaccherini¹⁰, Gautam Mehta¹, Cesar Jimenez³, Kathrin Husi¹¹, Catalina Toledo³, Maurizio Baldassarre¹², João Vasques¹³, Marites Aban¹⁴, Tellez Luis², Gavin Wright^{15,16,17,18}, Miguel Ángel Rodríguez-Gandía², Joan Vila¹⁹, Susan Sandeman²⁰, Roberto Elosua¹⁹, Alicia Navarro²¹, Caroline Morgan²², Daniel Green²², Karen Church²², Lynda McConaghy²², Nathan Davies¹, Marco Pavesi²³, Raj Mookerjee²⁴, Vicente Arroyo²⁵, Helena Cortez-Pinto²⁶, Reiner Wiest¹¹, Paolo Caraceni¹⁰, Rajiv Jalan²⁴. ¹UCL Institute for Liver and Digestive Health, Hepatology, London; ²Hospital Ramón y Cajal, Hepatology, Madrid, Spain; ³Hospital Vall d'Hebron, Hepatology, Barcelona, Spain; ⁴Hospital Beaujon, Clichy, Hepatology, Paris, France; ⁵IDIBAPS, Hepatology, Barcelona, Spain; ⁶Institute of Liver Studies, Inflammation Biology, London, United Kingdom; ⁷Institute of Child Health, UCL, London, United Kingdom; ⁸Institute of Hepatology London, Foundation for Liver Research, London, United Kingdom; ⁹Department of Surgery, Royal Free Hospital, London, United Kingdom; ¹⁰University of Bologna, Hepatology, Bologna, Italy; ¹¹University Hospital Bern, Gastroenterology, Switzerland; ¹²Centre for Applied Biomedical Research, University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; ¹³Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; ¹⁴Royal Free Hospital, London, United Kingdom; ¹⁵Mid and South Essex NHS Foundation Trust, Basildon and Thurrock University Hospitals NHS Foundation Trust, United Kingdom; ¹⁶Royal Free Hospital, London, United Kingdom; ¹⁷University College London, London, United Kingdom; ¹⁸King's College London, London, United Kingdom; ¹⁹Datarus, Barcelona, Spain; ²⁰University of Brighton, United Kingdom; ²¹Alpha Bioresearch, Madrid, Spain; ²²Yaqrit, Ledbury, United Kingdom; ²³EF-CLIF, Barcelona, Spain; ²⁴UCL Institute for Liver and Digestive Health, London, United Kingdom; ²⁵EF-CLIF, Barcelona, United Kingdom; ²⁶Universidade de Lisboa, Lisbon, Portugal
Email: j.macnaughtan@ucl.ac.uk

Background: Yaq-001 is a non-absorbable, synthetic carbon with high adsorptive capacity for bacterial products including lipopolysaccharide (LPS) and pro-inflammatory cytokines. Studies in cirrhotic rats showed reduced endotoxemia, improvements in end-organ dysfunction and reduced sensitisation to LPS. The aims of this study were to evaluate the safety and tolerability of Yaq-001 in

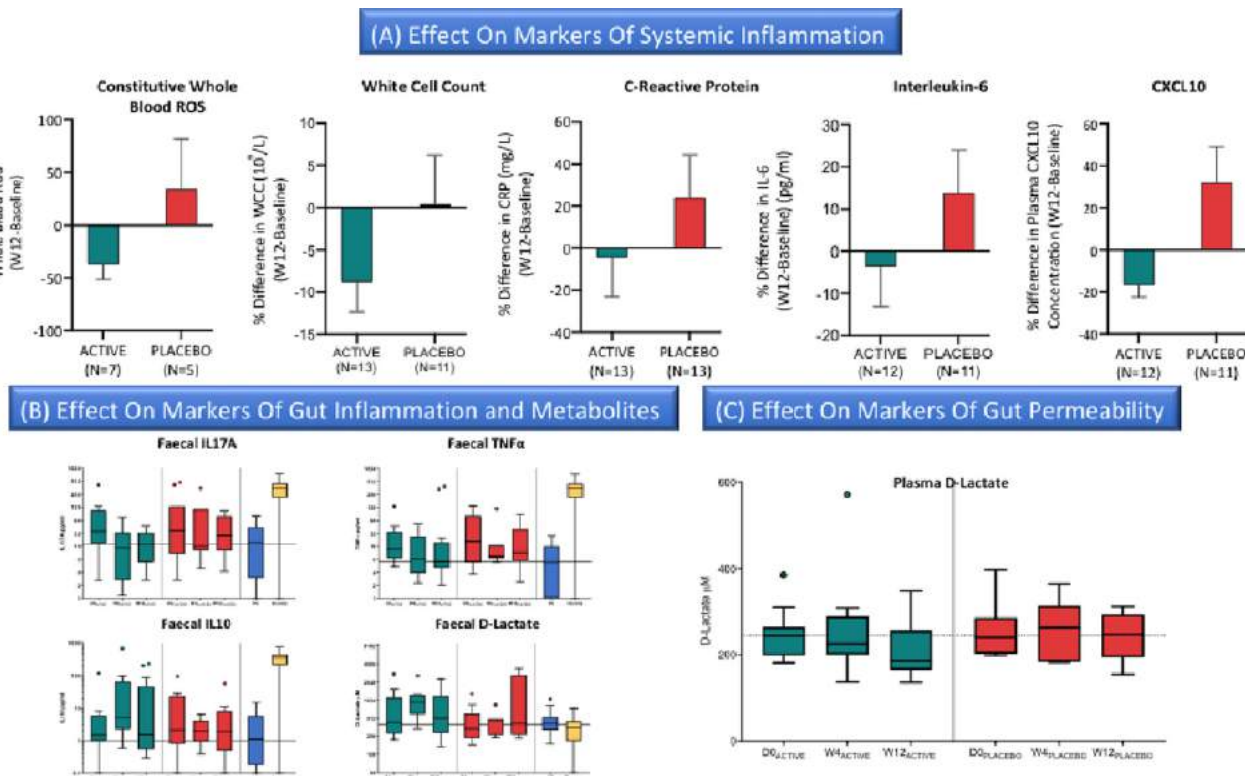


Figure 1: (abstract: PO-1045): Effect of Yaq-001 treatment on indices of systemic (A) and gut (B) inflammation and (C) gut permeability (SD ± SEM). HC and Decomp values from PMID: 32838247

decompensated cirrhotic (DC) patients and characterise immunological and metabolic effects.

Methods: This EU-funded H2020 study (CARBALIVE:634579) recruited patients with diuretic-responsive cirrhotic ascites. 28-patients from 8-EU centres were randomised to receive 4g of Yaq-001 (Y) or placebo (P) for 12-weeks. Safety assessments were performed at baseline, weeks 1, 4, 8 and 12. Endotoxin activity assay (EAA, data used for analysis: CV < 20%), organ function, nutrition, markers of systemic and gut inflammation, gut permeability, urinary ¹HMRS, and next generation sequencing of stool were evaluated at baseline, W4 and W12. Data were summarized by group and visit as means (SD) with select efficacy parameters modeled using MMRM.

Results: 14-patients were randomised to each group (Y: Age: 57.8 ± 7yrs, M:71%, MELD:12.4 ± 0.9; P: Age: 57.3 ± 10, M:75%, MELD:13.9 ± 1). **Safety:** Yaq-001 was well tolerated with no SAEs, stable MELD score, decompensation events and nutritional status. Compliance:93% (Y) 67% (P). **Endotoxemia:** Trends to reduction in EAA ratio (Y:-2.4% vs P:29.6%) and constitutive whole blood ROS (Y:-37.3% vs P:+34.3%) were observed in the active group. **Systemic inflammation:** Reductions in WCC, CRP, IL6 and CXCL10 in the active group were observed compared with placebo (Y (%): -8.8, -4.3, -3.6, -16.7; P (%) +0.4, +23.9, +13.8, +31.8). **Gut inflammation/permeability:** Improvements in faecal cytokines in Yaq-001 patients trended towards published values for healthy control. Reduction in plasma D-lactate was observed in Yaq-001 compared to placebo suggestive of an improvement in gut barrier integrity. **Metabolism:** Yaq-001 reduced stool ammonia with a trend to increased urinary hippurate. **Microbiome:** No change in bacterial diversity was observed.

Conclusion: Yaq-001 was safe and well tolerated. The data suggest proof of mechanism that Yaq-001, modulates systemic endotoxemia and inflammation by impacting gut inflammation and its permeability.

PO-1102

Epidemiology of spontaneous bacterial peritonitis and bacterascites in patients with cirrhosis in Queensland, Australia from 2008 to 2017

Isanka Ratnasekera¹, Amy Johnson^{2,3}, Elizabeth Powell^{2,3}, Andrew Henderson^{4,5}, Katharine Irvine¹, Patricia Valery⁶. ¹The University of Queensland, Mater Research Institute, Brisbane, Australia; ²Princess Alexandra Hospital, Department of Gastroenterology and Hepatology, Brisbane, Australia; ³The University of Queensland, Centre for Liver Disease Research, Brisbane, Australia; ⁴Princess Alexandra Hospital, Infection Management Services, Woolloongabba, Australia; ⁵The University of Queensland, Centre for Clinical Research, Saint Lucia, Australia; ⁶QIMR Berghofer Medical Research Institute, Herston, Australia

Email: amy.louise.johnson28@gmail.com

Background and aims: Spontaneous bacterial peritonitis (SBP), a common infection in patients with cirrhosis and ascites, is associated with high morbidity and mortality. The aim of this study was to investigate the longitudinal epidemiology of ascites fluid infections in an Australian population.

Method: A retrospective, population-based study of patients with cirrhosis admitted to public hospitals in Queensland during 2008–2017 was performed, linking demographic/clinical and microbiology data.

Results: Among 103, 165 hospital admissions of patients with cirrhosis, ascites was present in 16, 550 and in 60% (9, 977) a sample of ascitic fluid was tested. SBP was diagnosed in 770 admissions (neutrophil count >250/ml) and bacterascites in 552 (neutrophil count <250/ml with positive culture). The number of admissions with an ascites fluid infection increased by 76% from 2008 to 2017, paralleling an 84% increase in cirrhosis admissions. Patients with SBP had a longer hospital stay (median 15.7 vs 8.6 days from patients without SBP, p < 0.001) and higher in-hospital mortality,

although this decreased from 39.5% in 2008–2010 to 24.8% in 2015–2017 ($p < 0.001$). Common Gram-positive isolates included *Coagulase negative Staphylococci* (37.9%), *Viridans group Streptococci* (12.1%), and *Staphylococcus aureus* (7.2%). Common Gram-negative isolates included *Escherichia coli* (13.0%), *Klebsiella pneumoniae* (3.1%) and *Enterobacter cloacae* (2.6%). The prevalence of antibiotic resistance was $< 10\%$.

Conclusion: SBP remains associated with high in-patient mortality and long hospital stays. Typical skin and bowel pathogen were common; therefore, empirical antibiotic therapy should target these pathogens. This study provides evidence informing infection management strategies in this vulnerable patient population.

PO-1165

Cirrhocare-a pilot study of digital home-monitoring of advanced cirrhosis to determine feasibility and utility to diagnose new decompensation events

Konstantin Kazankov^{1,2}, Devnandan Amor Chatterjee¹, Simone Novelli¹, Alexandra Phillips¹, Anu Balaji³, Maruthi Raja³, Rajiv Jalan¹, Ravan Boddu³, Ravi Kumar³, Raj Mookerjee^{1,2}. ¹Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom, Liver Failure Group, University College London (UCL), London, United Kingdom; ²Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus N, Denmark; ³CyberLiver Limited, Middlesex, United Kingdom
Email: r.mookerjee@ucl.ac.uk

Background and aims: Patients discharged from hospital following acute decompensation are at high risk of new complications and need close follow-up, limited currently by the growing burden of cirrhosis and impact of COVID-19. Specialist hepatology care in the community is an urgent unmet need, to reduce hospital exposure and manage new decompensation events.

Method: We included 20 patients with cirrhosis and recent acute decompensation. Commercially available devices and a smartphone were given to all patients for daily recording of ECG, blood pressure, weight, and % body-water (bioimpedance), Stroop test (hepatic encephalopathy (HE) assessment), as well as self-reported well-being and food/fluid/alcohol intake. Data was Blue-toothed to the Cirrhocare-App, which also had 2-way patient-physician communication. Clinical hepatologists evaluated daily data and facilitated interventions by phone/text messages on the app as required. A propensity matched control cohort ($n = 20$) with advanced cirrhosis, screened after study recruitment closed, was followed as per monitored patients.

Results: Patient demographics: Mean age 59 ± 10 years, 14 male, main etiology alcohol (75%); 75% Child-Pugh class B. Fifteen patients (75%) showed good compliance (≥ 4 readings/week), 2 had moderate compliance (2–4/week), and 3 had poor compliance (< 2 /week). In a usability questionnaire scored 1–10, the median score was ≥ 9 for any given question.

Median follow-up was 10.1 (IQR 9–12) weeks. One patient died and 1 received a liver transplant (OLT). Besides the planned OLT admission, 8 liver-related admissions occurred in 5 different patients, including one patient who died: 2 admissions due to HE, 1 due to acute kidney injury (AKI), 1 due to both AKI and HE, and 3 in the same patient due to rectal bleeding. The median admission lasted 5 (IQR 4–11) days, and none was > 14 days. Except for the acute bleeds, we identified signs of decompensation in all cases, e.g. failed Stroop test, hypotension or reduction/gain in weight and body fluid, and facilitated 2 short hospitalizations of the 8 total admissions.

Based on early signs of decompensation, we contacted patients on 16 other occasions, revealing new events and guiding intervention such as advice on fluid intake, diuretics and laxatives.

No control died or received OLT, and there were 11 liver-related admissions in 7 patients, lasting a median of 5.5 (IQR 3–12) days with two admissions > 14 days. Controls had 5 unplanned paracenteses compared to 1 in monitored patients.

Conclusion: Cirrhocare's novel, multimodal, home-monitoring in patients with advanced cirrhosis is feasible, with good compliance, and prompts early diagnosis of decompensating events and their intervention; and hospital admissions are fewer and shorter in duration than in a control group. We propose Cirrhocare as a tool for managing cirrhosis patients at-risk of acute decompensation, at-home.

PO-1462

Efficacy and safety of albumin infusion for treatment and prevention of hepatic encephalopathy: a systematic review and meta-analysis

Francis Teh¹, Jing Hong Loo², Steve Yew-chong Tam³, Yu Jun Wong^{1,4}. ¹Changi General Hospital, Gastroenterology and hepatology, Singapore; ²National University of Singapore, Yong Loo Lin School of Medicine, Singapore; ³Singapore General Hospital, Education resource center, Medical board, Singapore; ⁴Duke-NUS Medical School, Singapore
Email: eugene.wong.yj@singhealth.com.sg

Background and aims: The efficacy and safety of albumin infusion for the treatment and prevention of hepatic encephalopathy (HE) among decompensated cirrhosis patients were controversial. We aim to systematically review the existing literature on the efficacy and safety of albumin infusion for prevention and treatment of HE.

Methods: We performed a systematic search of 4 electronic databases (PubMed, EMBASE, Scopus and Web of Science) up to 15th January 2021. Including free text and MESH term, studies on albumin infusion for treatment and prevention of HE in cirrhosis patients were screened and selected. Primary outcome was the resolution of clinically overt HE. Secondary outcomes were inpatient mortality, length of stay and albumin-associated adverse events. We assessed the pooled relative risk (RR), pooled mean differences (MD), 95% confidence interval (CI) and heterogeneity (I^2) using Review Manager Version 5.3.

Results: A total of 12 studies (4 treatment studies, 8 prevention studies) from 951 subjects fulfilling our inclusion criteria were identified among 1382 citations. Mean MELD score ranged from 8 to 26. Among cirrhosis patients with HE, treatment with albumin infusion was associated with a lower pooled relative risk of HE (RR = 0.56, 95%CI: 0.41, 0.77; $I^2 = 20\%$). Among cirrhosis patients without HE at baseline, prevention with albumin infusion was associated with a lower pooled risk of developing clinically overt HE (RR = 0.61, 95%CI: 0.41, 0.90; $I^2 = 63\%$). Albumin infusion was associated with a lower pooled relative risk of inpatient mortality (RR = 0.44, 95%CI: 0.28, 0.67; $I^2 = 0\%$) and shorter length of stay (MD = -5.5, 95%CI: -14.1, -3.0; $I^2 = 100\%$). No significant difference in albumin-related adverse events (RR = 1.06, 95%CI: 0.75, 1.51; $I^2 = 0\%$) and overall survival were observed.

Conclusion: Albumin infusion is a safe option to treat and prevent HE among cirrhosis patients. Well-powered randomised trial is required to confirm the benefit of albumin infusion for the prevention and treatment of hepatic encephalopathy in decompensated cirrhosis patients.

POSTER PRESENTATIONS

PO-1471

Myostatin is associated with sarcopenia and in combination with creatinine phosphokinase or albumin may be used as a screening tool of sarcopenia in liver cirrhosis

Theodoros Alexopoulos¹, Larisa Vasilieva¹, Meropi Kontogianni², Roxani Tenta², Alexandra Georgiou², Evangelia Stroumpoulis³, Ilianna Mani¹, Alexandra Alexopoulou¹. ¹Medical School, National and Kapodistrian University of Athens, 2nd Department of Internal Medicine and Research Laboratory, Athens, Greece; ²School of Health Sciences and Education, Harokopio University, Department of Nutrition and Dietetics, Athens, Greece; ³Hippokraton General Hospital, Department of Radiology, Athens, Greece
Email: thoalex@windowolive.com

Background and aims: Sarcopenia is a syndrome affecting muscle mass, strength and function. In patients with liver cirrhosis (LC), sarcopenia is correlated with more frequent complications and increased mortality. Myostatin, a myokine, is produced by muscle cells and adipocytes and is considered a biomarker of skeletal mass and/or sarcopenia. The aim was to evaluate the diagnostic utility of myostatin in LC.

Method: Muscle mass and quality measured by computed tomography at L-3 using specialized software (Tomovision, Sliceomatic), muscle strength evaluated by hand dynamometry and physical function assessed by the Short Physical Performance Battery were used to diagnose sarcopenia according to latest EWGSOP-2 criteria. Serum myostatin was measured by ELISA (GDF-8/Myostatin Immunoassay, RandD Systems Europe, Ltd.).

Results: 115 consecutive patients with LC [72.2% male, median age 59-years (IQR 52–67), MELD 12 (8–16), 28.7% with compensated LC] were included. Sarcopenia was diagnosed in 34.8% and in 21.7% of total patients it was severe. Serum myostatin was lower in patients with sarcopenia compared to those without ($p < 0.001$) and even lower in severe sarcopenia ($p < 0.001$). In the multivariate model, with sarcopenia as the dependent variable, age [OR 2.406 (95%CI 1.396–4.149), $p = 0.002$] and myostatin concentrations [OR 0.516 (95%CI 0.334–0.795), $p = 0.003$] were independently associated with the presence of sarcopenia after adjustment for sex, MELD score, creatine phosphokinase (CPK) and albumin. In ROC curve analyses, ratios of \log_{10} myostatin (pg/ml) to CPK (IU/L) and albumin to myostatin showed good diagnostic accuracy to differentiate sarcopenic from non-sarcopenic patients (AUROC 0.731 and 0.728, respectively). The cut-off value of 0.0448 of the \log_{10} myostatin to CPK ratio showed 85% sensitivity and 52.1% specificity whereas the cut-off value 2.206×10^7 of albumin to myostatin ratio showed 85% sensitivity and 49.3% specificity. In patients with more severe liver disease (MELD score

≥ 15), ratios \log_{10} myostatin to CPK and albumin to myostatin showed even better diagnostic accuracy to differentiate sarcopenic from non-sarcopenic patients (AUROC 0.829, $p = 0.001$ and 0.802, $p = 0.001$, respectively).

Conclusion: Myostatin was proved to be an important emerging biomarker independently associated with sarcopenia, and in combination with CPK or albumin can be used as a screening tool for sarcopenia in clinical practice.

PO-1549

Circulating microRNAs profiling in acute decompensation of liver cirrhosis

Yasmina Chouik^{1,2}, Fanny Lebossé^{1,2,3}, Marie-Laure Plissonnier², Teresa Antonini¹, Kerstin Hartig-Lavie¹, Miroslava Subic-Levrero¹, Clothilde Miaglia¹, Camille Boucheny⁴, Domitille Poinot¹, Francois Villeret^{1,3}, Dr Guichon Céline⁵, Fabien Zoulim^{1,2,3}, Massimo Levrero^{1,2,3}. ¹Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Hepatology, Lyon, France; ²Cancer Research Center of Lyon (CRCL), INSERM U1052, CNRS UMR5286, Lyon, France; ³University of Lyon Claude Bernard 1 (UCLB1), Lyon, France; ⁴GHN, Hospices Civils de Lyon, Clinical Research Center, Lyon, France; ⁵Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Department of Anesthesiology and Intensive Care, Lyon, France
Email: yasmina.chouik@inserm.fr

Background and aims: Acute decompensation (AD) represents a major cause of hospital admission and mortality in cirrhotic patients but refers to different conditions with distinct clinical characteristics and prognoses. MicroRNAs (miR) are small non-coding RNAs involved in the post-transcriptional regulation of gene expression. Circulating miR are stable molecules and can be used as non-invasive diagnostic or prognostic biomarkers. Recently, serum miR profiles that differentiate between AD in cirrhosis and healthy controls or between AD with or without ACLF have been reported but the direct comparison of carefully selected patients with AD and compensated cirrhosis has not been explored. We aimed at profiling circulating miR in AD and identifying AD subgroups defined by differential circulating miR signatures.

Method: We prospectively included 76 patients with alcohol, dysmetabolic or post-hepatitis C virus-related cirrhosis admitted at the Hepatology and Intensive Care units of the Lyon University hospital. Fifty-three patients had an AD of cirrhosis and 23 patients with compensated cirrhosis and no history of AD served as pathological controls (PC). Circulating miR were profiled in plasma on a Nanostring platform, allowing to detect and quantify simultaneously 798 miR in 26 AD and 7 PC consecutive patients. Circulating

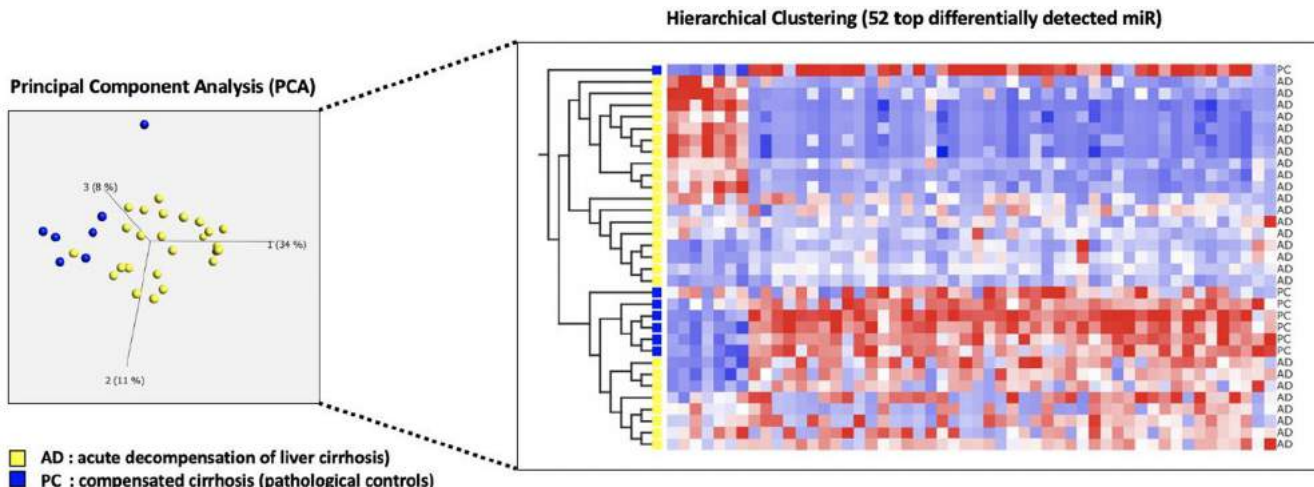


Figure: (abstract: PO-1549)

miR were profiled in plasma on a Nanostring platform, allowing to detect and quantify simultaneously 798 miR.

Results: Principal component analysis (PCA) of the circulating miRNAs profiles shows that AD patients are well separated from the PC group (Figure, left panel). We found a major dysregulation of circulating miR in the AD cirrhosis group, with 393 miR, being significantly differentially detected compared to the PC group. We defined a signature of 52 miR capable to separate AD and PC groups and to sub-classify AD patients in 2 groups (Figure, right panel). The majority of the differentially detected miR are down-regulated in AD cirrhotic patients with the exception of 7 miR with increased plasma levels in AD patients. Gene Set Enrichment Analysis (GSEA) shows a strong over-representation of differentially expressed miR in cancerogenesis pathways.

Conclusion: Circulating miR are strongly dysregulated in AD of cirrhosis as compared to compensated cirrhosis and might be useful to identify subgroups of patients with different clinical course and prognosis.

PO-1670

Use of rifaximin is not associated with infections by multi-drug resistant bacteria, but with occurrence of rifampicin-resistance in coagulase-negative staphylococci

Lina Schulte¹, Jacob Nattermann¹, Christian Strassburg¹, Philipp Lutz¹.
¹University Hospital Bonn, Department of Internal Medicine I, Bonn, Germany

Email: s4lischu@uni-bonn.de

Background and aims: Patients with cirrhosis are very likely to develop bacterial infections. However, data are still limited if use of rifaximin to prevent recurrent hepatic encephalopathy is associated with infections by multidrug-resistant bacteria or rifampicin resistance. Therefore, we analysed bacteria detected in hospitalized patients with liver cirrhosis with particular respect to intake of rifaximin.

Method: Patients with cirrhosis who were admitted to the hepatology ward of the department of Internal Medicine I were retrospectively analyzed for occurrence of bacterial infection and intake of rifaximin over a period of 12 months. Enterococci resistant to vancomycin (VRE), methicillin-resistant staphylococcus aureus (MRSA) and gram-negative bacteria resistant against at least 3 out of four antibiotic classes (carbapenems, fluoroquinolones, piperacillin/tazobactam or third-generation cephalosporins) were considered multi-drug resistant. Statistical analysis was performed with fisher's square test.

Results: 341 patients were included, who were admitted for a total of 501 hospital stays. Mean age was 60 years, 59% of patients were male and 55% had alcohol-associated cirrhosis. A total of 202 bacterial infections occurred, the top three being urinary tract infections (n = 73; 36%), spontaneous bacterial peritonitis (n = 35; 17%) and pneumonia (n = 30; 15%). Patients with infection were significantly more likely to die in hospital (24% versus 5%).

N = 23 of the isolated bacteria were multi-drug resistant (MDR): mostly VRE (n = 11) and gram-negative MDR (n = 9), but also MRSA (n = 3). MDR were detected in 9 cases of urinary tract infections, 5 cases of SBP, 3 cases of bacteremia, 3 skin infections, 2 cases of pneumonia and 1 bacterascites episode.

31% of patients were on rifaximin. Although a higher rate of bacterial infection occurred under rifaximin (39% vs 27%; p < 0.05), rate of infections by MDR bacteria were not significantly different (15% vs 9%). Coagulase-negative staphylococci displayed a higher rate of rifampicin resistance in patients taking rifaximin (13/19; 68%) compared to patients without rifaximin (3/28; 11%; p < 0.05), but were in general considered as contamination and not as cause of infection.

Conclusion: Our observations indicate that rifaximin intake may induce rifampicin resistance in colonizing coagulase-negative

staphylococci, but seems not to increase the rate of clinical significant infections by MDR.

PO-1701

Low incidence of SARS-CoV-2 infection in a prospective cohort of patients with liver cirrhosis and hepatocellular carcinoma treated at a German tertiary center during the 2020 pandemic

Thorben Fründt¹, Lilith Kuballa¹, Marc Luetgehetmann², Dominik Nörz², Canan Kurnaz¹, Thomas Theo Brehm^{1,3}, Karoline Rutter¹, Thomas Horvatis¹, Julian Schulze zur Wiesch^{1,3}, Samuel Huber¹, Ansgar W. Lohse¹, Henning Wege^{1,4}, Johannes Kluwe¹.

¹University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; ²University Medical Center Hamburg-Eppendorf, Institute of Microbiology and Virology, Hamburg, Germany; ³German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Hamburg; ⁴Klinikum Esslingen, Cancer Center Esslingen, Esslingen am Neckar
 Email: tfruentd@uke.de

Background and aims: Patients with liver cirrhosis (LC) are considered to be at increased risk for mortality when acquiring SARS-CoV-2 infection. During the COVID-19 pandemic, hospitals are regarded as sites with increased risk of infection, resulting in a limitation of in- and outpatient contacts to urgent indications, but data regarding infection rate in cirrhotic patients presenting as outpatients are limited. We conducted a prospective study to assess the incidence of SARS-CoV-2 infections in patients with LC with/without hepatocellular carcinoma (HCC) with physical presentation at our University Medical Center.

Method: Patients were enrolled between 1 April and 30 June 2020 at the University Medical Center Hamburg-Eppendorf, Germany, and were questioned for symptoms of upper airway infection at baseline. Presence of SARS-CoV-2 antibodies (IgG/IgM/IgA) was assessed at baseline and every follow-up using an Electro-chemiluminescence immunoassay (Roche Elecsys). Follow-up (FU) visits including liver function test, clinical assessment and questionnaire were conducted after 6–8 weeks (FU-1) and 6 months (FU-2).

Results: A total of 143 patients were enrolled at the outpatient department (n = 66) or as inpatients (n = 77): 108 with LC, 35 with LC and HCC (median age: 64 years, range: 19–86). 69% were male. Liver function according to Child Pugh Score (CPS) was: CPS A: 46% (n = 61); CPS B: 37% (n = 50); CPS C: 17% (n = 23). Clinical symptoms indicating upper airway infection were present in 77 patients: shortness of breath (n = 40) and coughing (n = 28) were the most frequent. After a median of 52 days, n = 110 patients completed FU-1, n = 72 were eligible for FU-2 between July 2020 and January 2021. Altogether, 284 visits to the outpatient department were registered and a cumulative number of 760 hospital days. SARS-CoV-2 antibodies were detected in one (0, 93%) asymptomatic patient at baseline and FU-1, an 80-year-old man with stable liver function (CPS A) and advanced HCC, receiving palliative treatment. All of the remaining patients were tested negative at baseline and every follow-up visit.

Conclusion: The risk of acquiring SARS-CoV-2 infection at our tertiary medical center during the pandemic was low in LC and HCC patients, when protective measures such as wearing face masks and keeping distance were followed. Of note, we found that SARS-CoV-2 infection in a patient with defined risk factors (older age, LC) was asymptomatic and did not lead to deterioration of liver function.

POSTER PRESENTATIONS

PO-1712

Baseline liver volume is a major prognostic factor in acute decompensation of alcohol-associated cirrhosis: results from the prospective multicentre PROLIV study

José Ursic-Bedoya¹, Claire Espérance¹, Ludovic Caillou², Magdalena Meszaros¹, Marie Pierre Ripault³, Safia Aouinti⁴, Laura Jaubert¹, Ardavan Prost², Lucy Meunier¹, Barbara Tassy¹, Stéphanie Faure¹, Cathy Soulayrac¹, Hélène Donnadiou-Rigole¹, Boris Guiu¹, Nicolas Molinari⁴, Georges-Philippe Pageaux¹. ¹Chu Montpellier St Eloi, Montpellier, France; ²University Hospital of Nîmes, Nîmes, France; ³Centre Hospitalier De Narbonne, Narbonne, France; ⁴Hospital Center University De Montpellier, Montpellier, France
Email: jose.ursic@yahoo.fr

Background and aims: Acute decompensation (AD) of alcohol-associated cirrhosis in nonabstinent subjects has a poor short-term prognosis. Abstinence allows an improvement of 2/3 of the patients after 3 months. For those who don't improve, the only treatment that can ameliorate the prognosis is liver transplantation (LT). Prognostic scores at the time of decompensation do not allow to distinguish between the patients who will improve from those who would need LT. So, it appears necessary to find new prognostic factors. We aimed to study prognostic factors in terms of transplant-free survival in the setting of AD of alcohol-associated cirrhosis.

Method: PROLIV (Clinical Trials #03508388) is a prospective, multicentre, observational study. We included patients with alcohol-associated cirrhosis, abstinent or not, hospitalized for AD. The main exclusion criteria were an HCC, an active viral B or C infection, the presence of a TIPS, an occlusive portal vein thrombosis. Patients were followed during 1 year with a visit every 3 months and cross-sectional imaging at inclusion, 6 and 12 months. Measurements included liver and spleen volume. They were semi-automated and made by a single operator blinded to the patient's outcome. The standardized liver volume was calculated per the usual formula based on the body weight. Alcohol consumption was assessed at each visit. The primary study end point was transplant-free survival.

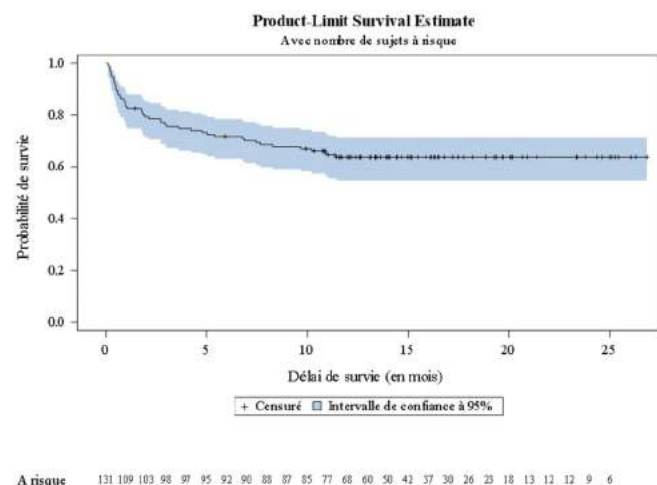


Figure:

Results: 156 patients were evaluated and 131 patients were included between April 2018 and September 2019. They were 75% male, median age was 58 years, 60.3% of patients were nonabstinent at the time of admission and 48.1% were admitted for a first episode of AD. Median Child-Pugh, Meld and AD-ACLF scores were 9.4, 18.3 and 53 respectively. The main etiologies of AD were alcohol-associated hepatitis (39.7%) and ascites (26.7%). At 12 months, 31 patients (23.7%) were dead and 16 (12.2%) were transplanted. Two patients were lost to follow-up. Among nonabstinent patients at the inclusion and alive without LT at 3 months, 52% of those who were abstinent during this period had an improvement in Meld score >2 points,

whereas they were only 38.5% of those who continued alcohol consumption in the interval. The mean measured/standardized liver volume ratio was 1.26 in our cohort. 27 variables were included in the survival analyses, 12 of which were significant in univariate analysis. In multivariate analysis, the variables significantly associated with transplant-free survival were hemoglobin (HR = 0.633; 95% CI [0.519; 0.771]), MELD score (HR = 1.111; 95% CI [1.036; 1.191]) and the measured/standardized liver volume ratio (HR = 0.322; IC95% [0.155; 0.666]).

Conclusion: Our study is the first to show that liver volume in a patient admitted for AD of alcohol-associated cirrhosis is a predictor of transplant-free survival. This measure could complement the classic cirrhosis scores.

PO-1730

Cirrhotic patients without prior antibiotic exposure may be eligible to lower first-line antibiotic strategies for nosocomial infections: results from a local antibiotic resistance study

Veyre Florian¹, Caroline Dellestable¹, Pierre Pradat¹, Nina Pronina¹, Fabien Zoulim^{1,2,3}, Patrick Miaillhes⁴, Fanny Lebossé^{1,2,3}. ¹Hospices Civils of Lyon, Hepatology department, Lyon, France; ²Lyon 1 university, Lyon, France; ³Cancerology Research Center of Lyon, Lyon, France; ⁴Hospices Civils of Lyon, Department of infectious diseases, Lyon, France
Email: fanny.lebosse@inserm.fr

Background and aims: Although adequacy of first line antibiotic (AB) strategies is crucial for the prognosis of cirrhotic patients with bacterial infections (BI), a rational use of AB is required to limit multidrug resistant bacteria (MRB) emergence. Our aims were to describe AB resistances in our center and to study the relevance of international guidelines for the treatment of BI in cirrhosis.

Method: We conducted an exhaustive retrospective study of BI occurring in cirrhotic patients admitted in Hepatology Unit of a tertiary center in 2018. We reported demographical, clinical and AB resistances data for each event. We defined prior antibiotic exposure (PAE) as prior AB treatment within last 6 months and/or norfloxacin prophylaxis regimen.

Results: We reported 135 BI in 72 cirrhotic patients, mostly suffering from alcoholic liver disease (n = 46). The median age was 68 years (IQR 59–73) and median MELD score 19 (IQR 14–24). Sixteen percent of patients had norfloxacin prophylaxis regimen and 67% had received previous AB therapy (mostly beta-lactamine) within last 6 months. The majority of BI was nosocomial (65%) whereas 32% were health care associated (HCA) and only 3% community acquired (CA) infections. Most common infections were urinary tract infection (38%) and spontaneous bacteremia (29%). MRB accounted for 44% of BI and were associated with PAE (54% in PAE group vs 18% in non-PAE group, p < 0.0001). MRB infections mostly developed in nosocomial infection (NI) group (83% vs 17% in HCA; p = 0.0004). In NI group, MRB infections were significantly associated to PAE (65% in PAE group vs 21% in non-PAE group; p = 0.0006) while no difference was found in HCA group. According to international guidelines for AB treatment of BI in cirrhosis, AB de-escalation was possible for 53% in NI group, 12% in HCA group whereas respectively none and 14% required increasing antibiotic strategy (p < 0.0001). In NI group, AB de-escalation opportunity was more frequent in non-PAE group (90%) compared to PAE one (44%; p = 0.0003).

Conclusion: Our results suggest that local knowledge of AB resistances could lead to local adjustment of international guidelines for the treatment of BI in cirrhosis. We could identify a subgroup of NI with reduced rate of MRB infections, which could be eligible to lower empiric first line antibiotic strategies. Further studies are required to confirm the extent of these findings.

PO-1766

High risk medication-related problems are associated with lower quality of life in decompensated cirrhosis

Kelly Hayward^{1,2}, Vikas Bansal¹, Patricia Valery^{1,3}, Preya Patel¹, Penny Wright², Caroline Tallis², Katherine Stuart², Katharine Irvine⁴, Neil Cottrell⁵, Jennifer Martin⁶, Elizabeth Powell^{1,2}. ¹The University of Queensland, Centre for Liver Disease Research, Woolloongabba, Australia; ²Princess Alexandra Hospital, Gastroenterology and Hepatology Department, Woolloongabba, Australia; ³QIMR Berghofer Medical Research Institute, Herston, Australia; ⁴The University of Queensland, Mater Research, Woolloongabba, Australia; ⁵The University of Queensland, Faculty of Health and Behavioural Sciences, St Lucia, Australia; ⁶University of Newcastle, School of Medicine and Public Health, Newcastle, Australia
Email: kelly.hayward@uq.edu.au

Background and aims: This study aimed to explore patient-related factors associated with 'high risk' medication-related problems (MRPs) to tailor delivery of a medication education intervention for people with decompensated cirrhosis.

Method: A post-hoc analysis was conducted in a cohort of out-patients with decompensated cirrhosis who were randomised to receive a patient-oriented medication education intervention during its implementation phase at a tertiary hepatology clinic. Patients received medication interviews with a clinical pharmacist on up to 4 occasions during a 6-month period. The pharmacist identified MRPs (including nonadherence, adverse drug reactions, interactions, indication, dosing, and monitoring issues) in real-time and a clinician panel classified each to be 'low', 'medium', or 'high' risk for patient harm using a severity * likelihood * duration risk matrix. Participants completed the Beliefs about Medicines Questionnaire, Brief Illness Perceptions Questionnaire and Chronic Liver Disease Questionnaire (quality of life) at recruitment and follow-up (6-months). Demographic and clinical variables were obtained from medical records. A generalised linear model with Poisson distribution was used to calculate incidence rate ratios (IRR) and 95% confidence intervals (CI). Number of interviews (range 1–4) was an offset in the model. The Wilcoxon signed ranks test was used to analyse paired data.

Results: Complete baseline data is available for 50 patients. Mean age was 58.4 ± 9.7 years, 68.0% were male, median Child-Pugh score was 8 (interquartile range 7–9) and patients took 9.9 ± 3.8 medications. Among 334 identified MRPs, 49.4% were classified as 'high risk' (mean 3.3 ± 2.3 per patient). Patients had more 'high risk' MRPs if they reported more *concerns* about their medicines (IRR = 1.08; 95%CI 1.02–1.14) and lower *coherence* of liver disease (IRR = 0.91; 95%CI 0.83–0.99). 'High risk' MRPs were also associated with greater perceived *consequences* of disease on daily life (IRR = 1.08; 95%CI 1.00–1.17) and lower *global quality of life* (IRR = 0.83; 95%CI 0.70–0.99), especially in terms of *systemic symptoms* (IRR = 0.83; 95%CI 0.70–0.98), *emotion* (IRR = 0.86; 95%CI 0.75–0.98) and *worry* (IRR = 0.87; 95%CI 0.78–0.98). 71.5% of 'high risk' MRPs were resolved with pharmacist intervention. This coincided with significant improvement in *global quality of life* (p = 0.049) and *coherence* (p = 0.030) scores at 6-months compared to baseline (follow-up data available for 36 patients; n = 6 deceased, n = 4 failed to attend, n = 1 withdrew, n = 3 'other').

Conclusion: Medicines intervention tailored to people with decompensated cirrhosis and with poor disease knowledge and negative beliefs about medicines may improve quality of life by aiding resolution of 'high risk' MRPs.

PO-1767

The prevalence of sarcopenia and myosteatosi s in cirrhotic patients: preliminary results from an italian multicenter study (EpatoSarco Group)

Simone Di Cola^{1,1}, Barbara Lattanzi¹, Alessio Aghemo², Carlo Alessandria³, Clara Balsano⁴, Paolo Caraceni⁵, Mariasole Fiumara¹, Pietro Lampertico⁶, Silvia Martini⁷, Saveria Lory Crocè⁸, Sergio Maimone⁹, Maria Grazia Rendina¹⁰, Loredana Simone¹¹, Gianluca Svegliati-Baroni¹², Lorenzo Surace¹³, Manuela Merli¹. ¹Policlinico Umberto I, Gastroenterologia, Rome, Italy; ²IRCCS Humanitas Research Hospital, Milano, Italy; ³Città della Salute e della Scienza di Torino, Torino, Italy; ⁴Ospedale de L'Aquila, Dipartimento di Medicina Clinica, L'Aquila, Italy; ⁵Sant'Orsola, Bologna, Italy; ⁶IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy; ⁷Città della Salute, Torino, Italy; ⁸Dipartimento Universitario di Scienze Mediche, Trieste, Italy; ⁹Policlinico "G. Martino", Messina, Italy; ¹⁰Policlinico consorziale universitario, Bari, Italy; ¹¹Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy; ¹²Ospedali Riuniti di Ancona, Ancona, Italy; ¹³Ospedale Giovanni Paolo II, Lamezia Terme, Italy
Email: simonedicola92@hotmail.it

Background and aims: Sarcopenia, myosteatosi s and sarcopenic obesity are important predictors of morbidity and mortality in patients with liver cirrhosis. Most of the studies have been retrospective, including non-European cohort and have mainly involved patients on the waiting list for liver transplantation which could represent a possible selection bias. We conducted a prospective multicenter Italian study aimed at evaluating the prevalence of sarcopenia, myosteatosi s and sarcopenic obesity in a large series of cirrhotic patients.

Method: A large series of patients with liver cirrhosis were enrolled from February 2019 in 19 Centers in Italy. Patients were included at the time of a CT-scan performed for any clinical reasons. Patients on the waiting list for liver transplantation, were purposely excluded. CT-scan has been utilized for the assessment of sarcopenia (with Skeletal Muscle Index-SMI) and myosteatosi s. Body weight and height were recorded to derive BMI. Clinical and laboratory data were also collected.

Results: 242 cirrhotic patients were enrolled in the study, 72% males (median age 59 ± 11). Median MELD was 13.7 ± 5, 31% were Child-Pugh class A, 49% class B and 20% class C. The median BMI adjusted-for-ascites was 25.9 ± 6 kg/m². Most of the patients were of alcoholic origin (39%), followed by viral etiology (19%) and NASH (13%). Twenty-three percent were obese at diagnosis (BMI>30). Ninety-two patients (38%) showed sarcopenia at enrolment, while 169 patients (70%) presented myosteatosi s. Sarcopenia and myosteatosi s were associated in 70 patients (29%). BMI was significantly lower in sarcopenic vs non sarcopenic patients (22.8 ± 4 vs 27.7 ± 8 p < 0.001). The severity of liver cirrhosis was similar in patients with and without sarcopenia (MELD 14.3 ± 6 vs. 13.3 ± 4.5 p 0.2). Patients with myosteatosi s were older (60 ± 9 vs 55 ± 7 p 0.002), presented lower BMI at enrollment (25.3 ± 6 vs. 27.8 ± 5 p < 0.001), higher value of MELD (12.3 ± 4.2 vs 14.2 ± 5 p 0.02) and higher prevalence of ascites (55% vs 34%, p 0.002).

Conclusion: this analysis confirms the high prevalence of sarcopenia in a large series of cirrhotic patients not on the waiting list for liver transplantation. Myosteatosi s was even more common and more frequent in patients with older age and low BMI. The prevalence of sarcopenia was not related to the degree of liver cirrhosis according to MELD score and Child Pugh Class.

POSTER PRESENTATIONS

PO-1930

Albumin dysfunction correlates with disease markers in patients with decompensated cirrhosis

Raquel Horrillo¹, Anna Mestre¹, Ana María Ortiz¹, Alba Pérez¹, Aida Raventós¹, Mireia Torres¹, Antonio Páez¹, Vicente Arroyo^{2,3}, Javier Fernández^{2,4}, Joan Clària⁴, Todd Willis⁵, Montserrat Costa¹.
¹Grifols, Bioscience Research Group, Barcelona, Spain; ²EF CLIF, EASL-CLIF Consortium, Barcelona, Spain; ³Grifols Chair, Barcelona, Spain; ⁴Hospital Clinic, IDIBAPS and CIBERehd, Barcelona, Spain; ⁵Grifols, Bioscience Research Group, Raleigh, United States
Email: raquel.horrillo@grifols.com

Background and aims: Non-oncotic functions of albumin may be related to beneficial effects of albumin administration in cirrhotic patients. These include its antioxidant capacity and the capacity to bind, transport and modulate biologically active molecules such as fatty acids, proinflammatory mediators and reactive oxygen species. In fact, the prevention of mortality by long-term albumin administration in decompensated cirrhotic patients with ascites is currently under investigation (PRECIOSA phase 3 trial, NCT03451292). In the present study, we analyzed the functional status of albumin from patients with decompensated cirrhosis compared to healthy controls (HC), and its correlation with disease markers.

Method: Plasma samples from patients with decompensated cirrhosis (n=21) and age-matched HC (n=24) were analyzed. Albumin binding capacity to Sudlow Binding Site II (BSII) was determined using a specific fluorescent marker and fatty acid binding capacity was measured by electronic paramagnetic resonance. Oxidation status of albumin on Cys34 thiol group was assessed by anion exchange chromatography. Albumin early glycation was determined using QuantiLab Glycated Albumin assay.

Results: In addition to hypoalbuminemia (Gastroenterology 2019; 157: 149–162), patients with decompensated cirrhosis presented functionally impaired albumin. Albumin from these patients showed a lower binding capacity to BSII and to fatty acids, higher irreversible oxidation, and higher levels of early glycation compared to HC. Interestingly, patients with lower albumin binding capacity to BSII presented worse hepatic (ALT [r = -0.78; p < 0.0001] and AST [r = -0.77; p < 0.0001]) and circulatory functions (PRA; r = -0.50; p < 0.05) and greater disease severity (Child-Pugh; r = 0.48; p < 0.05). Moreover, higher albumin oxidation was linked to greater impairment of hepatic (r = 0.45; p < 0.05) and circulatory functions (r = 0.40; p = 0.08). However, there was no relationship between disease markers and albumin fatty acid binding capacity or glycation.

Conclusion: Albumin from patients with decompensated cirrhosis had significant functional impairment. This dysfunctional albumin was correlated with poorer organ function (patients with more impaired albumin binding and more oxidized albumin presented worse hepatic and circulatory functions and greater disease severity). Further investigation is warranted to better understand the role of non-functional albumin in this pathology and the effects of albumin as a therapeutic agent in liver cirrhosis.

PO-1998

A study evaluating outcomes of cirrhotic patients managed virtually in a specialist liver cirrhosis service due to the COVID crisis

Alex Cole¹, Maria Bashyam¹, Rooshi Nathwani², David Kockerling², Sujit Mukherjee², Benjamin Mullish^{1,2}, Lucia Possamai^{1,2}, Heather Lewis^{1,2}, Maud Lemoine^{1,2}, Nowlan Selvapatt^{1,2}, Ameet Dhar^{1,2}. ¹Imperial College Healthcare NHS Trust; ²Imperial College London, United Kingdom
Email: mariabashyam@doctors.org.uk

Background and aims: Managing patients in a specialist cirrhosis clinic improves survival. The COVID-19 pandemic necessitated the urgent transition to virtual clinics (VC) in these patients. We aimed to evaluate the clinical impact of VC on survival, admission and decompensation rates in cirrhotic patients managed in a specialist

service, and to identify which patients can be managed safely in this setting.

Method: We retrospectively analysed cirrhotic patients who had a specialised VC from March to June 2020. Clinical parameters were collected at baseline and 6 months and compared with a cohort of patients reviewed face to face (F2F) in the same specialist cirrhosis clinics from March to June 2019. Patients with COVID-19 were excluded.

Results: 127 patients attended for VC, 101 for F2F review. Both groups were matched for age, sex, aetiology, and Child Pugh grade (CP). There was no difference at 6 months in survival, change in MELD/UKELD, decompensation, need for paracentesis (LVP) nor ambulatory review between VC and F2F groups in all cirrhosis grades combined or decompensated patients alone (CP BandC subgroup) (p=0.05) (Table 1). Less patients were admitted in the VC vs the F2F group (p = 0.05) but this was not validated in CP BandC subgroup (p > 0.05).

Table 1: Baseline Patient Demographics and 6 months outcome (*p > 0.05, **p = 0.05)

	VC (n = 127)	F2F (n = 101)
Age-yrs (range)	60 (30–85)	61 (32–84)
Gender-no (%)		
Male sex	87/127 (69%)	74/101 (73%)
Female sex	40/127 (31%)	27/101 (27%)
Main Aetiology-no (%)		
Alcoholic Liver Disease (ALD)	80/127 (63%)	61/101 (60%)
Baseline Disease Severity:		
CP A-no (%)	59/127 (46%)	49/101 (48%)
CP BandC-no (%)	68/127 (54%)	52/101 (52%)
MELD (median)	10	10
UKELD (median)	50	50
Outcomes at 6 months:		
Survival (all)-no (%)	124/127 (98%)	98/101 (97%)*
CP BandC	3/68 (2%)	3/52 (3%)*
MELD change (median)	0	0*
CP BandC	0	0*
UKELD change (median)	0	0*
CP BandC	0	0*
New decomp (all)-no (%)	37/127 (29%)	28/101 (28%)*
CP BandC	32/68 (47%)	23/52 (44%)*
LVP (all)-no (%)	9/127 (7%)	10/101 (10%)*
CP BandC	9/68 (13%)	10/52 (19%)*
Admissions (all)-no (%)	36/127 (28%)	41/101 (41%)**
CP BandC	29/68 (42%)	27/52 (51%)*
Ambulatory Review (all)-no (%)	18/127 (14%)	12/101 (11%)*
CP BandC	16/68 (24%)	12/56 (21%)*
Median Follow Up (all)- weeks	11	14
CP BandC	9	9

Conclusion: Compared to F2F clinics, VC have not resulted in poorer clinical outcomes, even in patients with decompensated cirrhosis. Access to ambulatory care was still required especially for CP BandC patients. Further studies need to confirm the long-term clinical impact, cost-effectiveness and acceptability of VC in management of cirrhotic patients within the setting of a specialist service.

PO-2194

Multidisciplinary assessment of neurocognitive impairment in a prospective cohort of patients with chronic liver disease: should we only think of hepatic encephalopathy?

Sultanik Philippe¹, Marika Rudler¹, Antoine Santiago², Lyes Kheloufi¹, Charlotte Bouzbib¹, Sarah Mouri¹, Aurélie Plessier³, Rodolphe Sobesky⁴, Audrey Coilly⁴, Damien Galanaud⁵, Vincent Navarro⁶, Nicolas Weiss⁷, Dominique Thabut¹. ¹Sorbonne Universités, Paris, France, Brain Liver Pitié-Salpêtrière (BLIPS) study group, Service d'Hépatogastroentérologie, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Assistance Publique-Hôpitaux de Paris, Paris, France, Paris, France; ²Département de Neuro-Psychologie, Centre Hospitalier Universitaire de Nîmes, Nîmes, Paris, France; ³Department of Hepatology, DHU Unity, Beaujon Hospital, AP-HP; ⁴AP-HP Hôpital Paul Brousse, Centre Hépatobiliaire, Inserm Unité 1193, Univ Paris-Sud, Université Paris-Saclay, FHU Hépatinov, Centre de Référence Maladies Inflammatoires des Voies Biliaires et Hépatites Auto-immunes, Villejuif, France; ⁵Sorbonne Universités, Paris, France, Brain Liver Pitié-Salpêtrière (BLIPS) study group, Service de Neuroradiologie, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Assistance Publique-Hôpitaux de Paris, Paris, France; ⁶Sorbonne Universités, Paris, France, Brain Liver Pitié-Salpêtrière (BLIPS) study group, Service de Neurologie, Unité Epilepsie, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Assistance Publique-Hôpitaux de Paris, Paris, France; ⁷France Email: psultanik@gmail.com

Background and aims: Minimal hepatic encephalopathy (MHE) remains difficult to diagnose. Even asymptomatic, patients (pts) with chronic liver disease (CLD) could display other causes of neurocognitive impairment (NI), like neurodegenerative disorders or sequelae of vascular brain diseases. Precisely exploring the causes of NI is needed in pts for whom liver transplantation is discussed, to fasten the transplant process in case of HE or rule out other neurological diagnosis. The aim of this prospective study was to phenotype pts with CLD referred for a suspicion of MHE, using an extensive work-up, and to assess the proportion of them finally diagnosed with MHE.

Method: Work-up was performed in our multidisciplinary outpatient clinics, and included clinical examination by a hepatologist, a neurologist, neuropsychological tests (including PHES and animal naming test) by a neuropsychologist, biochemical markers, electroencephalogram and multimodal brain MRI with spectroscopy. Factors

of brain dysfunction like active alcohol consumption, cardiovascular risk factors were collected. The diagnosis of MHE was made by an adjudication committee involving the aforementioned physicians.

Results: 111 pts were referred to our center from March 2018 to January 2021: 75% had cirrhosis (MASH/alcohol/virus/other in 58/57/19/7%), 23% had a liver vascular disease, and 2% other cause of CLD. 70% had a previous history of HE, including 96% with specific treatment. 72% displayed risk factors of NI outside HE, (obesity in 35%, diabetes in 40%, active alcohol consumption in 7%, psychoactive medication in 22%, previous traumatic brain injury (TBI) in 9%, previous ischemic stroke in 10%). 88% of pts reported one or more complains, i.e. altered sleep (75%), memory (67%) and attention impairment (54%). Overall, 63% of pts were diagnosed with MHE. Treatment was started in 17% and upgraded in 33% of those pts. Among pts diagnosed with MHE, 74% displayed another curable cause of NI (anxio-depressive disorders (40%), previous TBI/stroke (27%), altered sleep (21%), neurodegenerative disorders (4%)). 37% of pts were not diagnosed with MHE: 4% did not present any NI, vascular leukopathy was diagnosed in 51% of pts, anxio-depressive disorders in 29%, other psychiatric disorders in 10%, and others causes in 27%. Twenty percent displayed potential mixed causes of NI. In multivariate analysis, only obesity was independently associated with a no-HE diagnosis ($p=0.009$). A treatment was initiated in 73% of pts, including HE medications, medication withdrawal, psychological support or neurocognitive rehabilitation.

Conclusion: MHE was not the final neurological diagnosis in 37% of pts with CLD for MHE suspicion. Other diagnosis included curable disorders outside HE, but also non-reversible diagnosis like neurodegenerative disorders.

PO-2273

The impact of age in clinical outcomes in cirrhotic outpatients

Marta Tonon¹, Carmine Gabriele Gambino¹, Valeria Calvino¹, Alessandra Brocca¹, Simone Incicco¹, Marco Cola¹, Patrizia Pontisso¹, Salvatore Piano¹, Paolo Angeli¹. ¹University of Padova, Department of Medicine DIMED, Padova, Italy Email: martatonon11@gmail.com

Background and aims: The observation of differences in prognostic terms between compensated and decompensated cirrhosis led to the development of prognostic stages of cirrhosis based on the

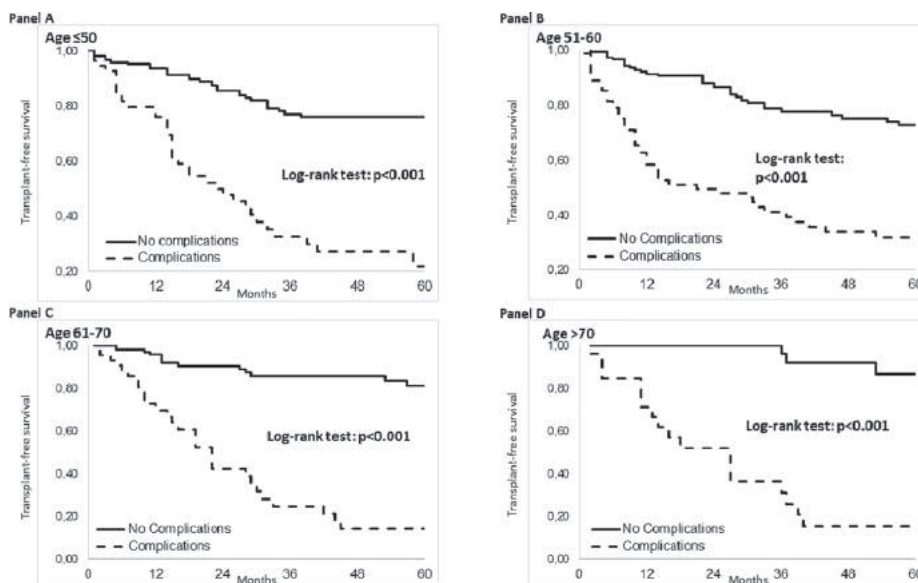


Figure 1: (abstract: PO-2273): 60-month transplant-free survival according to the development of complications in cirrhotic patients according to the class of age

POSTER PRESENTATIONS

development of complications. However, the role of age in determining survival and the development of complications in patients with cirrhosis has never been considered. The aim of the study was therefore to evaluate the role of age in clinical outcomes of cirrhotic outpatients.

Method: From March 2012 to March 2019 650 outpatients with cirrhosis were enrolled in the study and were followed until death, liver transplant or the end of follow-up. Patients were subdivided in 4 classes according to their age: 196 were younger than 50 years old at inclusion, 232 were 51–60 years old, 144 were 61–70 years old and 78 were older than 70 at inclusion.

Results: There was no significant difference in 12 and 60-month transplant-free survival in the comparison between the 4 groups. On the contrary, in every group transplant-free survival was significantly lower comparing patients who developed complications during follow-up and patients who didn't. Moreover, there was no difference in complications' development (SBP, HRS, ascites, refractory ascites, ACLF, hepatic encephalopathy, variceal bleeding) comparing the 4 groups. According Cox' regression, MELD score (HR 1.17, $p < 0.001$), mean arterial pressure (HR 0.98, $p < 0.001$) and the development of at least a complication (HR 3.30, $p < 0.001$) were found to be independent predictors of mortality at multivariate analysis.

Conclusion: Age doesn't seem to affect transplant-free survival and complications development in patients with cirrhosis. Thus, for patients at any age preventing and treating effectively any possible complication seems to be the key to reduce mortality.

PO-2524

Quality of life improvement is a top-rated but rarely assessed outcome in European and Australian patients with hepatic encephalopathy: Quality of life targeting and monitoring needs to be prioritised

Juha Halonen¹, Richard Hinde¹, Bharat Amlani¹. ¹Norgine Ltd, Harefield, United Kingdom
Email: jhalonen@norgine.com

Background and aims: Quality of life (QoL) is compromised in overt hepatic encephalopathy (HE). Adding rifaximin to lactulose improves QoL within 6 months versus lactulose alone [1]. We analysed how medical specialists value QoL improvement in HE versus other therapy objectives and whether QoL is monitored in patients with HE.

Method: This online survey in Sep-Dec 2019 in Belgium, Germany, Netherlands, Sweden, United Kingdom and Australia included hepatologists and gastroenterologists (with special interest in hepatology) who had personally seen and treated at least 5 patients for HE in the last 3 months and completed patient record forms (PRFs) based on their last 3 adult patients. Responses to "how important are each of the following therapy objectives to you for patients receiving HE primary or secondary prophylaxis therapy?" were collected on a Likert scale 1–7 where 1 was 'not at all important' and 7 was 'extremely important'. Mean scores were analysed with a 95% confidence interval (CI). PRF data were used to assess if quality of life was monitored in the last three patients, if they received a prophylaxis, and how many HE episodes patients had experienced. Statistical comparisons used the 2-sided t-test assuming equal variance.

Results: The 218 respondents shared 654 PRFs; 347 patients received rifaximin-alpha 550mg (RFX; mostly as a combination 84.1% [292/347]) while 307 were treated without rifaximin. Doctors rated "Improving a patient's quality of life" as the most important treatment objective with a mean score of 6.38 (6.27–6.49), greater than "Reducing the likelihood of further HE episodes" (6.19 (6.08–6.31); $p = 0.020$) or "Improving hepatic encephalopathy symptoms" (6.18 (6.06–6.31); $p = 0.021$) (Figure). Despite this high valuation of QoL improvement, the majority of PRFs lacked QoL data collection from the patient (71.7% [469/654] versus 28.3% [185/654]; $p < 0.001$). Whilst 84.5% [553/654] patients received prophylaxis and more patients on RFX versus other treatments were on prophylaxis (94.2%

[327/347] versus 73.6% [226/307]; $p < 0.001$), only 88.0% [227/258] received RFX as secondary prophylaxis. To qualify for RFX, patients had on average experienced more HE episodes (3.10 [2.78–3.42] versus 2.09 [1.86–2.32]; $p < 0.001$).

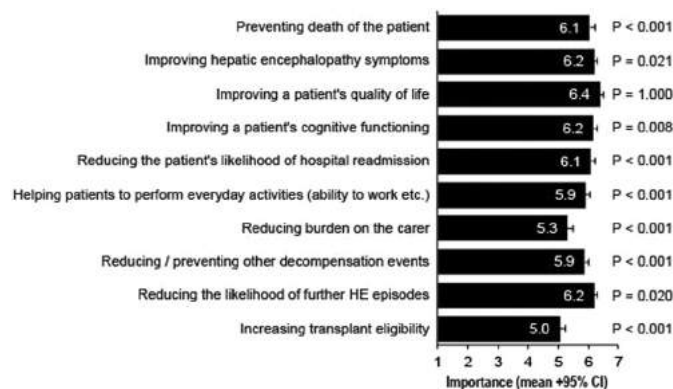


Figure:

Conclusion: QoL improvement was rated the main therapeutic objective in HE. Considering rifaximin-alpha 550mg as secondary prophylaxis could help align treatment choice with therapeutic targets.

References

Sanyal *et al.* APT. 2011; 34: 853–861.

PO-2608

Cost-Effectiveness of Rifaximin/alpha versus Lactulose in preventing recurrent episodes of overt hepatic encephalopathy: a systematic review and meta-analysis

Kashif Siddiqui¹, Sumeet Attri¹, Massimo Olando², Filippo Lelli², Valeria Maida³, Dominique Thabut⁴. ¹Parexel, Mohali, India; ²Corporate Market Access, Milan, Italy; ³Corporate Medical Affairs, Milan, Italy; ⁴Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France
Email: kashif.siddiqui@parexel.com

Background and aims: Several randomized controlled trials have reported rifaximin- α (alone or in addition to lactulose) to be more efficacious than lactulose alone in the treatment of hepatic encephalopathy (HE), with significant improvement in health-related quality of life. Many individual studies have been conducted to assess the cost-effectiveness of rifaximin- α .

Method: This systematic review (SR) and meta-analysis (MA) aimed to assess the cost-effectiveness (CE) of rifaximin- α versus lactulose. A systematic search of English-language studies was conducted in MEDLINE®, Embase®, MEDLINE® In-Process, and CENTRAL from database inception through November 2019. Relevant conference proceedings (2018–2020) were searched in Embase® or via the congress website. Studies were eligible if they assessed the cost-effectiveness of rifaximin- α in HE and reported incremental cost-effectiveness ratios. Incremental net benefits (INBs) were estimated for each study using $INB = \Delta E \times \lambda - \Delta C$ where ΔE is the difference in effectiveness, ΔC is the difference in costs, and λ is the threshold or gross domestic product per capita for each country. An MA based on the DerSimonian and Laird method was applied to pool INBs across studies [1]. When feasible, subgroup analyses were also performed based on treatment and time horizon of CE. All costs were standardized to the 2019 United States dollar. The heterogeneity of INB among studies was assessed using the Cochran Q test and the I-square statistic.

Results: Of the 15 studies identified in the SR, 11 studies contributed to the MA. The pooled INB was estimated at \$20, 156 (95% CI: \$13, 593–\$29, 887) for rifaximin- α with lactulose vs lactulose monotherapy irrespective of time horizons in the second-line (2L) setting

(Table). Significant heterogeneity was observed in the estimates (I-square = 100%). An MA assessing a combination strategy in the first-line (1L) setting and rifaximin- α salvage therapy was not feasible. The pooled INB for rifaximin- α monotherapy vs lactulose monotherapy in the 1L setting was \$3464 (95% CI: \$1601-\$14, 596) with no heterogeneity (I-square = 0%).

Conclusion: Rifaximin- α as an add-on treatment to lactulose in the 2L setting or as monotherapy in the 1L setting would be cost-effective.

Summary of MA results.

PO-2634

Real-world use of avatrombopag in patients with severe thrombocytopenia associated with chronic liver disease undergoing a procedure

Sanjaya Satapathy^{1,2}, Brian D. Jamieson³. ¹North Shore University Hospital, Northwell Health, Manhasset, United States; ²Methodist University Hospital, University of Tennessee Health Science Center, Memphis, United States; ³Dova Pharmaceuticals, a Sobi company, Inc., Durham, United States
Email: bjamieson@dova.com

Background and aims: Patients with severe thrombocytopenia due to chronic liver disease (CLD) have a greater risk of bleeding that complicates invasive procedures. The objective of this study (NCT03554759) was to describe the real-world effectiveness, safety and treatment patterns of the thrombopoietin receptor agonist

Study name (location)	Treatment (line)	Comparator	Time horizon	Pooled INB (95% CI), US dollars	Heterogeneity (I-square)
1. Kabeshova 2016 (France)[2]	Rifaximin- α + lactulose (2L)	Lactulose	2 years	4479.77 (390.38–51,407.43)	99.8%
2. Berni 2018 (UK)[3]					
1. Kabeshova 2016 (France)[2]	Rifaximin- α + lactulose (2L)	Lactulose	5 years	21,303.23 (14,864.67–30,530.60)	100.0%
2. Berni 2018 (UK) [3]					
3. Whitehouse 2015 (NL) [4]					
4. Poole 2015 (Sweden) [5]					
5. Berni 2015 (Belgium) [6]					
1. Jesudian 2020 (US) [7]	Rifaximin- α + lactulose (2L)	Lactulose	Lifetime	62,485.11 (23,691.15–164,803.69)	100.0%
2. Berni 2018 (UK) [3]					
1. Rivas 2010 (Mexico) [8]	Rifaximin- α (1L)	Lactulose	1. 14 days	3464.46 (3421.04–3508.44)	0.0%
2. Cardona 2012 (Mexico) [9]			2. 10 days		

Figure: (abstract: PO-2608)

POSTER PRESENTATIONS

avatrombopag (AVA) in patients with thrombocytopenia associated with CLD undergoing a procedure.

Method: Data were collected prospectively or retrospectively in the US. All treatment decisions were at the discretion of the treating physician per routine medical care. Effectiveness end points included change from baseline over time in platelet count (PC) and proportion of patients who received a platelet transfusion (PT) after baseline up to 7 days following a procedure. Subgroup analyses by baseline PC and Child-Turcotte-Pugh (CTP) grade were performed. Safety was evaluated, including serious adverse events (SAEs).

Results: Fifty patients were enrolled (48 unique; 2 patients enrolled twice for separate procedures). Mean age was 61.2 years; 82% were Caucasian. Most common aetiologies of liver disease were chronic viral hepatitis (n = 19), alcoholic liver disease (n = 13) and non-alcoholic steatohepatitis (n = 11). Of 40 patients with a reported CTP grade, 26 had grade A, 11 grade B, and 3 grade C. Common procedures were endoscopy (60%), colonoscopy (16%) and liver biopsy (8%). Patients received 40 mg (n = 27), 60 mg (n = 22) or 20 mg (n = 1) AVA per day, with 70% of patients dosed according to the prescribing information. Mean (standard deviation [SD]) PC was $46.9 \times 10^9/L$ ($24.52 \times 10^9/L$) at baseline (n = 50) and $85.1 \times 10^9/L$ ($41.63 \times 10^9/L$) (n = 38) on procedure day (day 8–15 after first dose). Mean (SD) change in PC from baseline to procedure was $41.1 \times 10^9/L$ ($33.29 \times 10^9/L$). No impact of baseline PC and CTP grade was shown on treatment effect. Forty-nine (98%) procedures did not require a PT. No thromboembolic events or clinically significant bleeding occurred. Most adverse events were mild or moderate and none related to AVA. SAEs occurred in 2 patients and included anaemia/pyrexia/abdominal pain and thrombocytopenia.

Conclusion: In the real-world setting, AVA at doses of 40 or 60 mg per day for 5 days was well tolerated, increased PC by procedure day and only one patient required PT. The safety and effectiveness of AVA observed in this study in patients with a PC $<50 \times 10^9/L$ was consistent with reported outcomes in pivotal studies.

PO-2683

Validation of a novel point-of-care test for gut leakage in cirrhosis based on dimeric to monomeric IgA ratio: a pilot cohort study

Jessica Howell^{1,2,3}, Huy Van⁴, Tim Spelman², Minh Pham², Mary Garcia⁴, Fan Li⁴, Rohit Sawhney⁵, John Lubel⁶, William Kemp⁶, Stephen Bloom⁵, Avik Majumdar⁷, Geoff McCaughan⁷, Joseph Doyle^{2,8}, Purnima Bhat⁹, Margaret Hellard^{2,8}, Kumar Visvanathan³, Alexander Thompson^{1,3}, David Anderson⁴.
¹St Vincent's Hospital Melbourne, Medicine, Fitzroy, Australia; ²Burnet Institute, Disease Elimination, Melbourne, Australia; ³University of Melbourne, Medicine, Fitzroy, Australia; ⁴Burnet Institute, Life Sciences, Melbourne, Australia; ⁵Eastern health, Gastroenterology, Box Hill, Australia; ⁶Alfred Hospital, Gastroenterology, Melbourne, Australia; ⁷Royal Prince Alfred Hospital, AW Morrow Gastroenterology and Liver Centre, Camperdown, Australia; ⁸Alfred Health, Infectious diseases, Melbourne, Australia; ⁹Australian National University, Medicine, Canberra, Australia
 Email: jessica.howell@svha.org.au

Background and aims: Diagnosis of liver cirrhosis is a critical step in chronic liver disease management, however access to transient elastography, liver biopsy and laboratory biomarker testing is limited in low resource/remote settings. Dimeric IgA to monomeric IgA ratio (dIgA ratio) is a potential biomarker of gut mucosal leakage, a key feature of cirrhosis. We evaluated the diagnostic performance of a novel point-of-care (POC) dIgA ratio test for cirrhosis.

Method: BioPoint® POC dIgA test is an antigen immunoassay-based lateral flow test which uses 15 µL of plasma or whole blood and provides a quantitative result <20 minutes using the Axxin hand-held lateral flow reader. Cirrhosis was defined by Fibroscan >12.5 kPa, clinical evidence of cirrhosis or liver biopsy.

Associations between dIgA ratio, cirrhosis and clinical parameters were determined by linear and logistic regression. ROC analysis was used to determine diagnostic accuracy. APRI score could be calculated in a subset of 680 individuals.

Results: 1478 plasma samples from 960 patients with chronic liver disease were included; 280 (29%) had cirrhosis. Median POC dIgA ratio was higher in Child-Pugh class B/C compared with A cirrhosis (1.4 B/C vs 0.6 A, $p < 0.001$) and correlated with bilirubin (Adj $R^2 = 0.22$, $p < 0.001$) and inversely with albumin (Adj $R^2 = -0.28$, $p < 0.001$). POC dIgA ratio test had good diagnostic accuracy for liver cirrhosis in the test cohort (AUROC 0.84) and moderate accuracy in the validation cohort (AUROC 0.74), similar to APRI score (Table 1). Restricting use of POC dIgA cutoff of 0.6 to those aged >30 years improved accuracy for cirrhosis.

Conclusion: POC dIgA ratio test had moderate accuracy for cirrhosis which was comparable to APRI. Further studies evaluating the clinical utility and cost-effectiveness of POC dIgA ratio test for liver cirrhosis screening compared with laboratory based APRI score calculation are warranted.

Table 1: (abstract: PO-2683): Performance of POC dimeric IgA ratio for cirrhosis

Ratio dIgA	No Cirrhosis	Cirrhosis	Sensitivity	Specificity	PPV	NPV	AUROC	95% CI	p value
Test cohort (n = 306; 40% cirrhosis, 5% healthy controls)									
≤0.6	152	20	84%	84%	78%	88%	0.84	0.80–0.88	<0.001
>0.6	30	104							
Validation cohort (n = 652, 1172 samples; 24% cirrhosis, 3% healthy controls)									
≤0.6	840	83	53%	84%	37%	91%	0.74	0.70–0.78	<0.001
>0.6	157	92							
Whole cohort aged >30 years (n = 897, 1389 samples)									
<0.6 + Age >30yrs	998	5	66%	85%	52%	90%	0.80	0.77–0.83	<0.001
>0.6 + Age >30 yrs	181	90							
APRI (n = 680) ≤ 1.0	591	5	55%	99%	90%	94%	0.77	0.72–0.82	<0.001
>1.0	38	46							

PO-2688

Safety and immunogenicity of Coronavirus disease 2019 vaccination in patients with chronic liver disease: a multicenter study

Jitao Wang^{1,2,3}, Zhiyun Hou³, Jianxin Liu⁴, Ye Gu⁵, Yunhong Wu⁶, Zhenhui Chen⁷, Jiansong Ji⁸, Shiqi Diao⁹, Yuanwang Qiu¹⁰, Shengqiang Zhou¹¹, Aiguo Zhang⁴, Nina Zhang¹², Fengxiang Wang⁴, Xue Li⁴, Yan Wang⁵, Xing Liu⁵, Cheng Lv⁵, Shubo Chen², Dengxiang Liu², Xiaolin Ji², Chao Liu⁶, Tao Ren⁶, Jingwei Sun⁷, Zhongwei Zhao⁸, Fazong Wu⁸, Fenxiang Li⁹, Ruixu Wang⁹, Yan Yan¹⁰, Shiliang Zhang¹⁰, Guohong Ge¹¹, Jianbo Shao¹¹, Shiyang Yang¹, Chuan Liu¹, Yifei Huang¹, Dan Xu¹, Xiaoguo Li¹, Jingwen Ai¹³, Ming-Hua Zheng¹⁴, Liting Zhang¹, Qing Xie¹⁵, Don Rockey¹⁶, Jonathan Fallowfield¹⁷, Wenhong Zhang¹³, Xiaolong Qi¹. ¹The First Hospital of Lanzhou University, CHESS Center, Institute of Portal Hypertension, Lanzhou, China; ²Xingtai People's Hospital, CHESS-COVID-19 Group, Xingtai, China; ³Jincheng People's Hospital, CHESS-COVID-19 Group, Jincheng, China; ⁴Jinzhou People's Hospital, CHESS-COVID-19 Group, Jinzhou, China; ⁵The Sixth People's Hospital of Shenyang City, CHESS Study Group, Shenyang, China; ⁶Hospital of Chengdu Office, People's Government of Tibet Autonomous Region, CHESS Study Group, Chengdu, China; ⁷Baoding People's Hospital, CHESS Study Group, Baoding, China; ⁸Lishui Central Hospital, CHESS Study Group, Lishui, China; ⁹The Third People's Hospital of Linfen City, CHESS Study Group, Linfen, China; ¹⁰Wuxi Fifth People's Hospital, CHESS Study Group, Wuxi, China; ¹¹The Third People's Hospital of Zhenjiang City, CHESS Study Group, Zhenjiang, China; ¹²Jincheng People's Hospital, CHESS Study Group, Jincheng, China; ¹³Huashan Hospital affiliated to Fudan University, Department of Infectious Disease, Shanghai, China; ¹⁴The First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ¹⁵Ruijin Hospital, Department of Infectious Disease, Shanghai, China; ¹⁶Medical University South Carolina, Digestive Disease Research Center, Charleston, United States; ¹⁷University of Edinburgh, Centre for Inflammation Research, Edinburgh, United Kingdom
Email: qixiaolong@vip.163.com

Background and aims: Concerns have been raised recently about SARS-CoV-2 vaccine responses in the large population of patients with chronic liver diseases (CLD), which may confer an immunocompromised state and is independently associated with high mortality from Coronavirus disease 2019 (COVID-19). The study aimed to explore the safety and immunogenicity of COVID-19 vaccination in patients with CLD in a large Chinese cohort.

Method: This multicenter study included CLD patients without a history of SARS-CoV-2 infection, from 11 designated centers in China between 4 October 2020 and 26 February 2021. The primary safety outcome was the incidence of adverse reactions within 7 days after each injection and the overall incidence of adverse reactions within 28 days, and the primary immunogenicity outcome was neutralizing antibody response at least 14 days after the whole-course vaccination.

Results: A total of 390 patients with pre-existing CLD were included in the analysis. The median age was 39.0 years (IQR, 33.0–48.3 years) and 185 (47.4%) were male. The median body-mass index was 26.0 kg/m² (IQR, 23.7–28.1 kg/m²). Of these, 357 (91.5%) patients were Han ethnicity, and 381 (97.7%) patients had non-alcoholic fatty liver disease. Comorbidities other than liver diseases were present in 54 (13.8%) patients, consisting of 44 (11.3%) hypertension, 15 (3.8%) diabetes, 4 (1.0%) arrhythmia and 1 (0.3%) asthma. The number of 7-days adverse reactions after each injection and adverse reactions within 28 days totaled 98 (25.1%) and 115 (29.5%) of patients, respectively. The most common adverse reactions were 71 (18.2%) injection site pain, followed by 23 (5.9%) muscle pain, 21 (5.4%) headache, and 18 (34.6%) fatigue. All adverse reactions were mild and self-limiting, and no grade 3 adverse reactions were recorded. Notably, neutralizing antibodies against SARS-CoV-2 were detected in 372 (95.4%) of patients with CLD. According to the locally weighted

scatterplot smoothing, the neutralizing antibody titers were maintained over the time since whole-course vaccination (Figure 1).

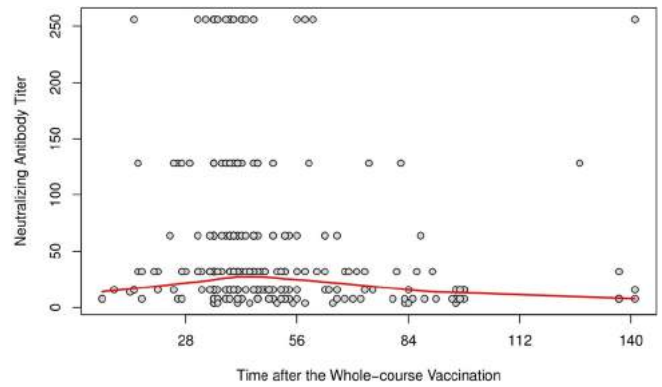


Figure: Correlation between the time since whole-course vaccination and the neutralizing antibody titer. General trend line is shown in red and was calculated using the locally weighted scatterplot smoothing algorithm.

Conclusion: The inactivated COVID-19 vaccine appears to be safe with good immunogenicity in patients with CLD.

PO-2753

Supplementation of branched-chain amino acids improves event-free survival in cirrhotic patients: systematic review and meta-analysis

Anne van Dijk^{1,2}, Alexandra Bruins Slot¹, Piero Portincasa³, Sebastiaan Siegerink¹, Najiba Charki⁴, Carina Verstraete¹, Joep de Bruijne¹, Frank Vleggaar¹, Karel J. van Erpecum¹. ¹University Medical Center Utrecht, Gastroenterology and Hepatology, Utrecht, Netherlands; ²University Medical Center Utrecht, Diabetics; ³University of Bari Aldo Moro, Biomedical Sciences and Human Oncology, Italy; ⁴University Medical Center Utrecht, Utrecht, Netherlands
Email: adjik20@umcutrecht.nl

Background and aims: Dietary supplementation with branched chain amino acids (BCAA) is often used in cirrhotic patients to improve nutritional state and prognosis. We aimed to explore evidence for BCAA supplementation.

Method: A systematic search was performed in MEDLINE and EMBASE using search terms “liver cirrhosis,” “hepatocellular carcinoma” (domain) and “BCAA” (determinant) and relevant synonyms. Interventional and observational studies with BCAA supplementation and a disease-control group (i.e. placebo or no intervention) were included. Available data on overall and event-free survival, (*de novo* or recurrent) hepatocellular carcinoma (HCC), liver function, nutritional status and quality of life were extracted. Risk of bias was assessed using ROBINS-I and RoB 2.0 tools. In case of meta-analysis risk ratio (RR) and 95% confidence interval (95%CI) was calculated with a random effects model.

Results: Of 4183 studies screened, 50 studies were included (31 randomized controlled trials, 4 prospective case control studies, 13 retrospective case-control studies: in total 2087 BCAA supplementation, 2649 disease-controls). Risk of bias was high/serious for all studies. In cirrhotics in general, long-term BCAA supplementation significantly improved event-free survival (figure; meta-analysis: $p = 0.01$; RR 0.73 95%CI 0.58–0.93), decreased risk of HCC occurrence (meta-analysis: $p = 0.02$; RR 0.71 95%CI 0.52–0.96) and tended to improve overall survival (meta-analysis: $p = 0.09$). No convincing beneficial effects of BCAA supplementation on liver function, nutritional status or quality of life were found. Available studies reported no beneficial effects or contradictory results of BCAA supplementation after specific therapeutic interventions (liver transplantation, large volume paracentesis and variceal ligation, for HCC the following: resection, radiofrequency ablation, transarterial chemoembolization, hepatic arterial infusion chemotherapy,

POSTER PRESENTATIONS

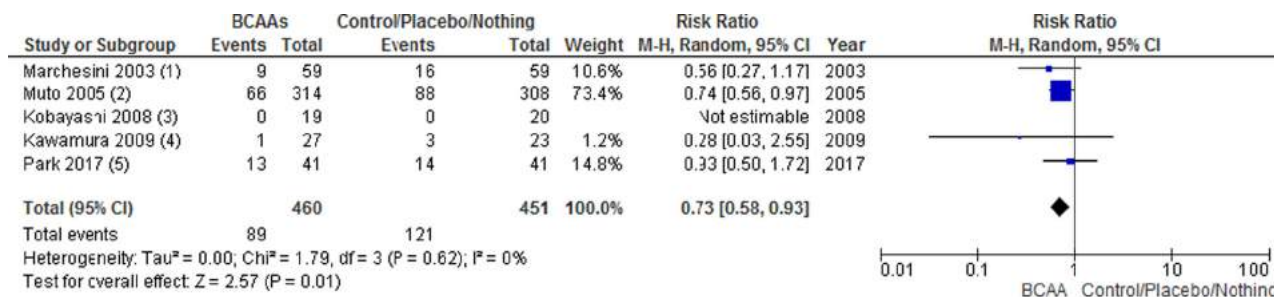


Figure: (abstract: PO-2753): Forest-plot: event-free survival in cirrhotic patients with or without BCAA supplementation

external radiotherapy, systemic therapy with Sorafenib). No study reported detrimental effects of BCAA.

Conclusion: Our data indicate that long-term (≥ 6 months) prophylactic BCAA supplementation could improve event-free survival, decrease risk of HCC occurrence and possibly also improve overall survival in cirrhotic patients. Further high-quality placebo-controlled studies are urgently needed.

PO-2832

High prevalence of hormonal changes and hepatic osteodystrophy in Frail patients with cirrhosis An observational study

Surender Singh¹, Sunil Taneja¹, Arka De¹, Nipun Verma¹, Madhumita Premkumar¹, Ajay Kumar Duseja¹, Radha Krishan Dhiman¹, Virendra Singh¹. ¹Postgraduate Institute of Medical Education and Research, Hepatology, Chandigarh, India
Email: drsuniltaneja@hotmail.com

Background and aims: Hormonal changes and hepatic osteodystrophy are less often studied complications of cirrhosis. This study describes the differences in hormone levels and hepatic osteodystrophy between Frail and Not frail patients with cirrhosis.

Method: 116 outpatients with cirrhosis were prospectively enrolled in this cross-sectional study. Frailty assessment was done using Liver Frailty Index (LFI). Socio-demographic assessment, anthropometry, nutritional assessment, hormone profile, and Dual-energy X-ray absorptiometry (DEXA) scan were done in all patients.

Results: 100 (86.2%) males and 16 (13.8%) females with a mean age of 50.16 years (95% CI, 48.43–51.89) were included. Malnutrition was more common in the Frail group as compared to the Not frail group. SGA class-B patients were significantly more in the Frail group (37 (74%) versus 3 (4.5%), $p = 0.001$). The prevalence of low PTH (14 (28%) vs 2 (3%)), testosterone (33 (66%) vs 15 (22.7%)), vitamin D3 (44 (88%) vs 39 (59.1%)) and cortisol (37 (74%) vs 37 (56.1) levels was higher in Frail group ($p < 0.05$). The number of patients diagnosed with hepatic osteodystrophy (34 (68%) vs 21 (31.8%), $p = 0.001$) was significantly higher in the Frail group. The marker of osteoclastic activity, beta cross laps was significantly higher in the Frail group both in males 736 (655–818) vs 380 (329–432), $p = 0.001$ and females 619 (479–758) vs 313 (83–543), $p = 0.02$). BMD at the lumbar spine and neck of the femur had a significant correlation with frailty, testosterone levels, Beta-cross laps, calcium, and cortisol levels.

Table: The difference in levels of parameters between Frail and Not frail patients

Parameters	Frail (n = 50) Mean (95% CI)	Not frail (n = 66) Mean (95% CI)	P value
Testosterone (nmol/l)			
Females	1.15 (0.79–1.52)	1.74 (0.39–3.9)	0.092
Males	4.28 (2.41–6.15)	19.26 (16.76–21.75)	0.001
Cortisol (nmol/l)	134.85 (109.4–160.29)	218.28 (192.53–244.04)	0.001
PTH (pg/ml)	28.38 (16.86–39.9)	38.59 (34.07–43.1)	0.001
Calcium (mg/dl)	8.26 (8.12–8.4)	8.84 (8.71–8.97)	0.001
Vitamin-D3 (ng/ml)	20.49 (17.76–23.21)	28.22 (24.79–31.64)	0.001
Beta cross laps (pg/ml)			
Females	619 (479–758)	313 (83–543)	0.026
Males	736 (655–818)	380 (329–432)	0.001

Abbreviations: CI, Confidence interval; PTH, Parathyroid hormone.

Conclusion: This is the first study that highlights the high prevalence of hormonal changes and hepatic osteodystrophy in Frail patients with cirrhosis and opens a new dimension for research in this field.

PO-2867

Hepatogenous diabetes in patients with cirrhosis and ascites: correlation with inflammatory activity, systemic hemodynamics, renal function, and outcome

Ilias Tsiakas¹, Georgios Kalambokis¹, Grigorios Despotis¹, Maria Christaki¹, Sempastien Fillipas-Ntekouan¹, Lampros Lakkas², Spyridon Tsiouris³, Xanthi Xourgia³, Christina Koustousi¹, Nikolaos Aggelis¹, Chalampos Milionis¹. ¹School of Medicine, University of Ioannina, 1st Department of Internal Medicine, Ioannina, Greece; ²School of Medicine, University of Ioannina, 2nd Department of Cardiology, Ioannina, Greece; ³School of Medicine, University of Ioannina, Laboratory of Nuclear Medicine, Ioannina, Greece
Email: gkalambo@uoi.gr

Background and aims: Hepatogenous diabetes (HD) complicates advanced cirrhosis. Its diagnosis often requires an oral glucose tolerant test (OGTT). We investigated the association of HD with inflammation markers, systemic hemodynamics, renal function, and outcome in patients with cirrhosis and ascites.

Method: 35 patients with known HD diagnosed by fasting plasma glucose (FPG)/glycosylated hemoglobin (HbA1c) results (Group-1) and 71 with normal FPG and HbA1c levels were evaluated. OGTT diagnosed HD in 34 of 71 patients who started antidiabetics (Group-2) and was normal in 37 (Group-3). Mean arterial pressure (MAP), cardiac output (CO) by cardiac ultrasound, systemic vascular resistance (SVR) calculated as MAP/CO ratio, plasma renin activity (PRA), plasma aldosterone, and serum noradrenalin by radioimmunoassays, glomerular filtration rate (GFR) and renal plasma flow using radionuclide scintigraphy, and renal blood flow (RBF) calculated as renal plasma flow/1-hematocrit were evaluated at baseline, and at 6 and 12 months. Plasma levels of lipopolysaccharide-binding protein (LBP) by ELISA, and tumor-necrosis factor-alpha (TNF-alpha) and

interleukin-6 by cytometric bead array were measured at baseline. Three-year survival was evaluated.

Results: Cirrhosis severity was similar in the 3 groups. LBP and TNF-alpha levels were significantly higher in Group-1 than in Group-2 ($p = 0.03$ and $p = 0.04$, respectively) and Group-3 ($p = 0.01$ and $p = 0.04$, respectively). Group-1 patients had significantly lower SVR and higher PRA compared to Group-2 ($p = 0.04$ and $p = 0.04$, respectively) and Group-3 ($p = 0.01$ and $p = 0.008$, respectively). GFR and RBF were also significantly lower in Group-1 compared to Group 2 ($p = 0.03$ and $p = 0.04$, respectively) and Group-3 ($p = 0.009$ and $p = 0.01$, respectively). After 12 months, a significant increase in SVR and a significant decrease in PRA were noted in Group-2 (1322 ± 44 vs. 1285 ± 56 dyn.sec.cm⁻⁵; $p = 0.008$ and 60.9 ± 18.7 vs. 74.6 ± 23.4 pg/ml; $p = 0.01$, respectively) together with significant increases in GFR and RBF (85 ± 5 vs. 77 ± 6 ml/min; $p = 0.009$ and 642 ± 32 vs. 614 ± 38 ml/min; $p = 0.03$, respectively). 3-year survival was significantly higher in Group-2 than in Group-1 (75.3% vs. 55.3%; $p = 0.01$) while it was similar in groups 2 and 3 (81.7%).

Conclusion: HD is associated with higher inflammatory activity. Systemic hemodynamics, renal function, and survival are adversely affected by HD but improve significantly with early diagnosis by OGTT and treatment.

PO-2951

An educational intervention that effectively reduces the inappropriate administration of proton pump inhibitors in patients with cirrhosis

Juvelyn Palomique¹, Walid Ayoub², Alexander Kuo², Mazen Nouredin², Vinay Sundaram², Mary-Lynn Brecht³, Ju Dong Yang². ¹Cedars Sinai Medical Center, Hepatology, Los Angeles, United States; ²cedars sinai medical center, Hepatology, Los Angeles, United States; ³University of California Los Angeles, School of Nursing Doctor of Nursing Practice, Los Angeles, United States
Email: juvelyn.palomique@cshs.org

Background and aims: Inappropriate use of proton pump inhibitors (PPI) is common in patients with cirrhosis. PPI's are associated with deleterious effects in cirrhosis including increased risk for hepatic encephalopathy, spontaneous bacterial peritonitis, and liver-related mortality. We aim to decrease the incidence of low-value, non-guideline supported prescription of PPI's in the inpatient setting, by implementing a PPI Clinician Update education.

Method: The study was implemented in a single inpatient transplant center. Key medical staff were identified to receive a PPI Clinician Update educational session, including Hospitalist, Gastroenterology

fellows, Hepatology, Liver transplant advanced practice provider (APP). The education session was 20 minutes in duration and utilized a two-page PPI Handout with a PPI deprescribing evidence-based algorithm for provider guidance. Knowledge level was measured using a one group pre-posttest design with a total of 10 questions. The primary outcome measure was the changes in the incidence of inappropriate PPI prescription. Incidence of inappropriate PPI was measured over one week duration four week prior and after the education session among cirrhosis patients admitted to hepatology inpatient service. Secondary outcome was percentage of correct response.

Results: A total of 26 providers completed the educational session and pre-posttest. Lack of knowledge regarding outpatient PPI indication were reported as the main barrier to verifying PPI prescription. There was a statistically significant increase in knowledge ($p = 0.0001$) one month after receiving the educational intervention (Figure 1A). There was a decrease in the incidence of inappropriate PPI use from 52% (23/44) to 25% (11/44) ($p = 0.009$) after receiving the educational intervention (Figure 1B). The most common reason for inappropriate PPI prescription was continuation of the patient's home medication without verifying the indication. The posttest survey showed that 46.2% of clinicians strongly agreed that their practice changed after the educational intervention and constructive feedback.

Conclusion: The most common reason for inappropriate PPI prescription was due to a continuation of a home medication without verifying the indication. An educational intervention is effective in increasing knowledge and decreasing the inappropriate PPI prescriptions in the inpatient setting.

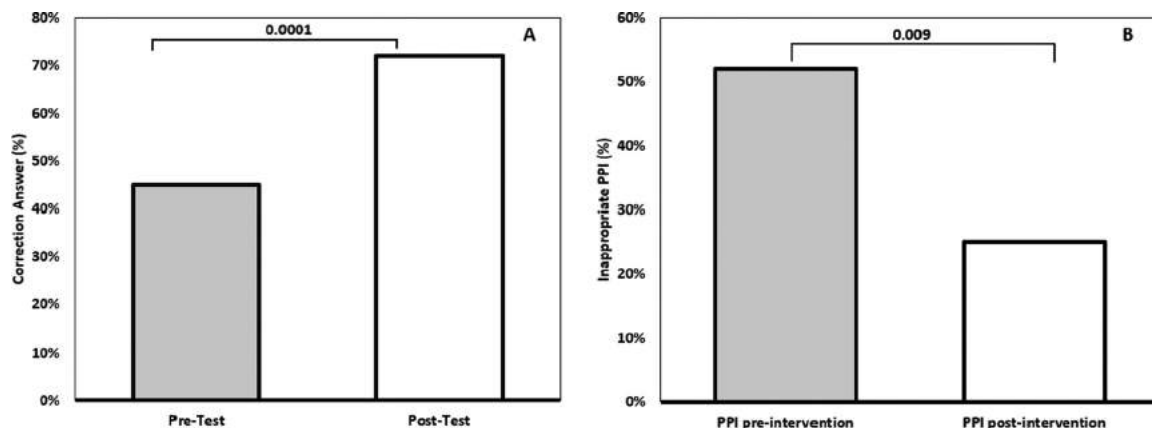


Figure: (abstract: PO-2951)

**Cirrhosis and its complications:
Portal Hypertension**

PO-309

Systemic inflammation promotes liver fibrogenesis and matrix turnover in patients with advanced chronic liver disease

Benedikt Simbrunner^{1,2,3}, Ida Villesen^{4,5}, Philipp Königshofer^{1,3}, David J.M. Bauer^{1,2}, Rafael Paternostro^{1,2}, Philipp Schwabl^{1,2,3}, Bernhard Scheiner^{1,2}, Katharina Wöran⁶, Gerald Timelthaler⁷, Albert Stättermayer¹, Rodrig Marculescu⁸, Matthias Pinter¹, Michael Trauner¹, Morten Karsdal⁴, Diana Leeming⁴, Thomas Reiberger^{1,2,3}, Mattias Mandorfer^{1,2,3}. ¹Medical University of Vienna, Dpt. of Internal Medicine III, Div. of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ³Medical University

of Vienna, Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Vienna, Austria; ⁴Nordic Bioscience, Herlev, Denmark; ⁵University of Copenhagen, Copenhagen, Denmark; ⁶Medical University of Vienna, Department of Pathology, Vienna, Austria; ⁷Medical University of Vienna, Dpt. of Medicine I, Institute of Cancer Research, Vienna, Austria; ⁸Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria

Email: mattias.mandorfer@meduniwien.ac.at

Background and aims: Preclinical studies indicate that bacterial translocation-induced systemic inflammation (SI) promotes liver fibrogenesis, however, evidence from studies in humans is limited. This prospective study investigated whether SI is linked to histological hepatic stellate cell (HSC) activation and blood biomarkers of liver fibrogenesis and matrix turnover in patients with advanced chronic liver disease (ACLD).

Method: Biomarkers of SI (CRP, IL-6, PCT), fibrogenesis (formation of type III [PRO-C3] and VI collagen [PRO-C6]), fibrolysis (degradation of type III collagen [C3M]), and matrix turnover (TIMP-1) were assessed

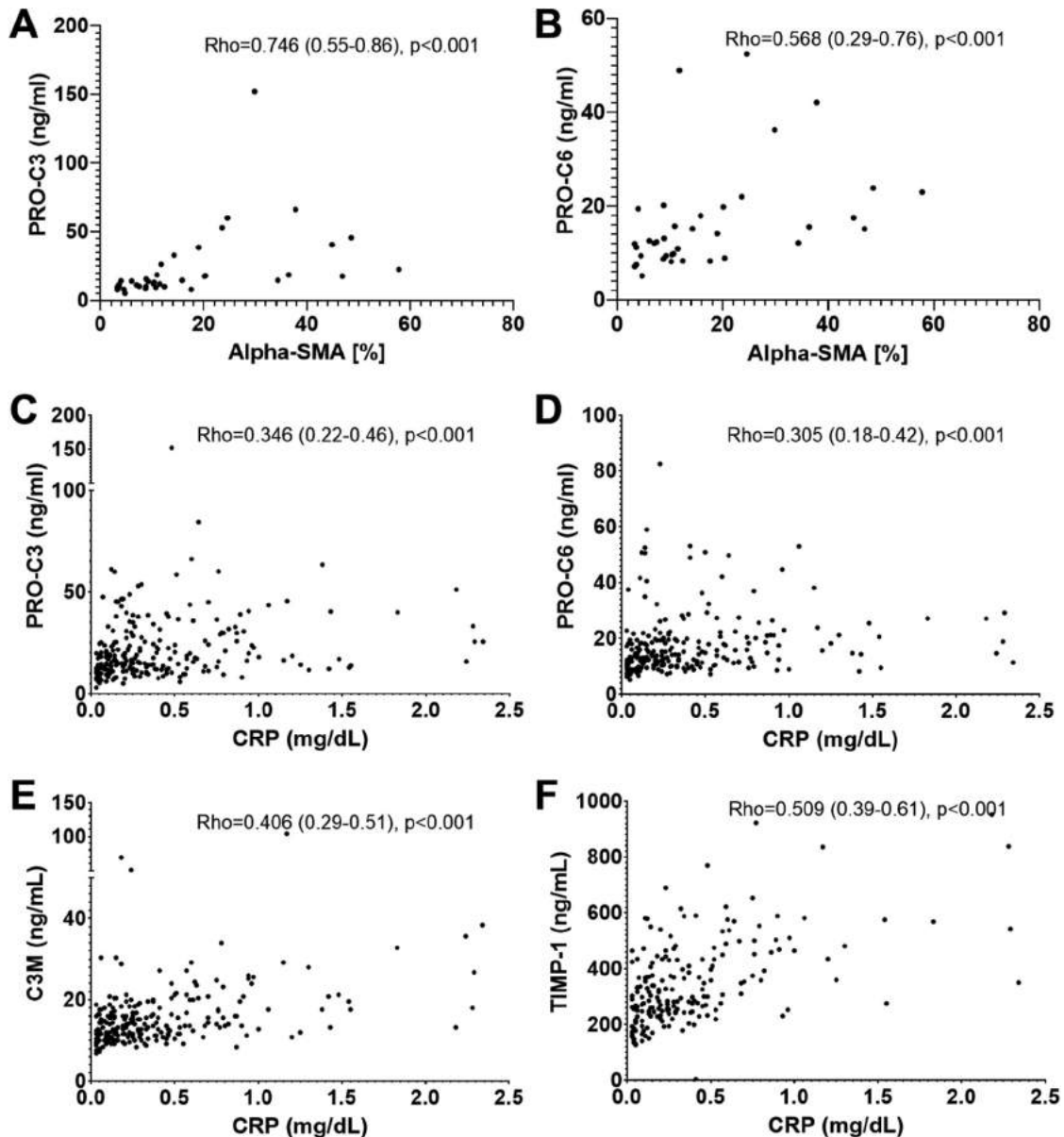


Figure: (abstract: PO-309)

in 234 patients with clinically stable ACLD (hepatic venous pressure gradient [HVPG] ≥ 6 mmHg; absence of bacterial infections or acute decompensation) undergoing HVPG-measurement. Alpha-smooth muscle actin proportionate area (alpha-SMA%) was analysed by slide scanner in a subset of patients (n = 38) with concomitant transjugular liver biopsy.

Results: Alpha-SMA% strongly correlated with markers of liver fibrogenesis (PRO C3:Spearman's $\rho = 0.746$, $p < 0.001$; PRO-C6: $\rho = 0.568$, $p < 0.001$), confirming that these biomarkers reflect HSC activation in ACLD (Figure). Furthermore, alpha-SMA% was directly associated with SI (CRP: $\rho = 0.517$, $p = 0.001$; IL-6: $\rho = 0.448$, $p = 0.005$; PCT: $\rho = 0.373$, $p = 0.021$).

Similarly, PRO-C3 (CRP: $\rho = 0.346$; IL-6: $\rho = 0.302$; PCT: $\rho = 0.389$; all $p < 0.001$) and PRO C6 (CRP: $\rho = 0.305$; IL-6: $\rho = 0.410$; PCT: $\rho = 0.331$; all $p < 0.001$) exhibited direct correlation with SI levels, as well as C3M (CRP: $\rho = 0.406$; IL-6: $\rho = 0.375$; all $p < 0.001$) and TIMP-1 (CRP: $\rho = 0.509$; IL-6: $\rho = 0.574$; PCT: $\rho = 0.421$; all $p < 0.001$; Figure).

Next, multiple linear regression analysis was performed to evaluate the impact of SI on fibrogenesis and matrix turnover while adjusting for HVPG to correct for the underlying severity of liver disease. The following SI biomarkers were independent determinants of fibrogenesis: CRP for PRO-C3 and IL-6 for PRO-C6. Moreover, matrix turnover was upregulated with increasing CRP and IL-6 levels for C3M as well as CRP and IL-6 for TIMP-1.

Conclusion: SI is associated with histological and blood biomarkers of liver fibrogenesis. Importantly, the association between SI and blood biomarkers was independent of, and thus, not confounded by the severity of underlying liver disease. These findings support the pathophysiological concept that bacterial translocation-induced SI promotes hepatic fibrogenesis and matrix turnover in patients who

have already progressed to ACLD, which in turn may be ameliorated by targeting the gut-liver axis/SI.

PO-310

Von Willebrand Factor (VWF) propeptide levels are similarly accurate for assessing portal hypertension as compared to VWF antigen

Ida Villesen^{1,2}, Benedikt Simbrunner^{3,4}, David J.M. Bauer^{3,4}, Rafael Paternostro^{3,4}, Philipp Schwabl^{3,4}, Bernhard Scheiner^{3,4}, Albert Stättermayer³, Matthias Pinter³, Michael Trauner³, Prof. Peter Quehenberger, MD⁵, Morten Karsdal¹, Thomas Reiberger^{3,4}, Diana Leeming¹, Mattias Mandorfer^{3,4}. ¹Nordic Bioscience, Herlev, Denmark; ²University of Copenhagen, Copenhagen, Denmark; ³Medical University of Vienna, Dpt. of Internal Medicine III, Div. of Gastroenterology and Hepatology, Vienna, Austria; ⁴Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ⁵Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria
Email: mattias.mandorfer@meduniwien.ac.at

Background and aims: Endothelial dysfunction is an important mechanism contributing to portal hypertension (PH) in advanced chronic liver disease (ACLD) and is reflected by increased von Willebrand factor antigen (VWF-Ag) levels. This prospective study aimed to elucidate VWF-release (by measuring its propeptide; VWF-N) and -cleavage (by measuring its ADAMTS13-processed form; VWF-A) as well as their association with PH severity in patients with ACLD.

Method: Levels of VWF-N/VWF-A (by ELISA) and VWF-Ag (by immunoturbidimetric assays) were assessed in 229 patients with

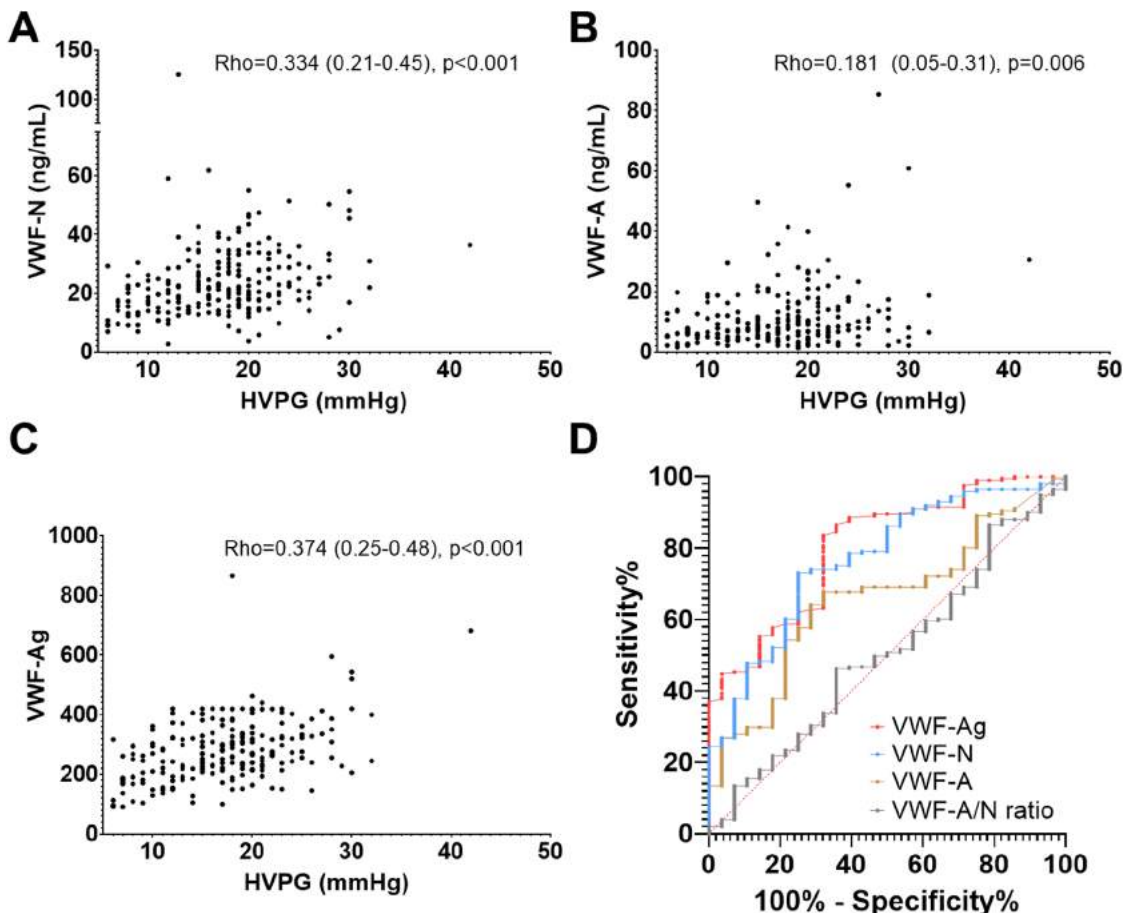


Figure: (abstract: PO-310)

POSTER PRESENTATIONS

clinically stable ACLD (hepatic venous pressure gradient [HVPG] \geq 6 mmHg; absence of bacterial infections or acute decompensation) undergoing HVPG measurement. Furthermore, ADAMTS13 (i.e., the main VWF-cleaving protease) activity was analysed in a subgroup (n = 166).

Results: VWF-N significantly correlated with VWF-Ag (Spearman's $\rho = 0.627$, $p < 0.001$) and HVPG ($\rho = 0.334$, $p < 0.001$; Figure). In contrast, its association with VWF-A levels was markedly weaker ($\rho = 0.263$, $p < 0.001$). Moreover, VWF-A exhibited only very weak correlations with VWF-Ag ($\rho = 0.207$, $p = 0.002$) and HVPG ($\rho = 0.181$, $p = 0.006$). Of note, the association between VWF-Ag and HVPG ($\rho = 0.374$, $p < 0.001$) attained a similar strength, as compared to VWF-N ($p = 0.225$ for comparison). VWF-Ag, VWF-A, and VWF-N continuously increased across PH severity strata (HVPG 6–9: n = 28 vs. 10–19: n = 121 vs. ≥ 20 mmHg: n = 80): Median VWF-Ag was 184/278/291 ($p < 0.001$), VWF-A 5.95/8.15/8.98 ($p = 0.013$), and VWF-N 14.8/21.5/24.1 ($p < 0.001$).

Finally, AUROC analyses identified VWF-Ag (0.80 [0.72–0.89], $p < 0.001$) and VWF-N (0.77 [0.68–0.86], $p < 0.001$) as non-invasive tests for clinically significant PH (HVPG ≥ 10 mmHg; CSPH; Figure). In contrast, the other parameters displayed limited accuracy (VWF-A: 0.66 [0.56–0.76], $p = 0.007$) or were not linked (VWF-A/-N ratio) to CSPH.

Interestingly, neither HVPG ($p = 0.94$), VWF-Ag ($p = 0.88$), VWF-N ($p = 0.49$), VWF-A ($p = 0.82$), nor VWF-A/-N ratio ($p = 0.39$) were linked to ADAMTS13 activity.

Conclusion: ADAMTS13 activity is unrelated to PH severity and not linked to VWF-related parameters in patients with clinically stable ACLD. In this patient group, levels of VWF-A are determined by increased VWF-release, rather than decreased ADAMTS13-mediated cleavage. VWF-Ag levels and its propeptide, VWF-N, are more suitable as surrogates of PH in patients with ACLD, as compared to VWF-A or ADAMTS13 activity.

PO-532

Clinical outcomes of cirrhotic patients with dysregulated hormones of vascular homeostasis

Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, Christopher Desbalmes^{1,2}, Dunja Schaufler^{1,2}, Benedikt Simbrunner^{1,2,3}, Rafael Paternostro^{1,2}, Philipp Schwabl^{1,2}, David J.M. Bauer^{1,2}, Georg Semmler^{1,2}, Bernhard Scheiner^{1,2}, Theresa Bucsecs^{1,2}, Ernst Eigenbauer⁴, Rodrig Marculescu⁵, Thomas Szekeres⁵, Markus Peck-Radosavljevic^{1,2,6}, Michael Trauner¹, Mattias Mandorfer^{1,2}, Thomas Reiberger^{1,2,3}. ¹Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ²Medical University of Vienna, Hepatic Hemodynamic Lab, Vienna, Austria; ³Medical University of Vienna, Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Vienna, Austria; ⁴Medical University of Vienna, IT-Systems and Communications, Vienna, Austria; ⁵Medical University of Vienna, Department of Laboratory Medicine, Vienna; ⁶Klinikum Klagenfurt am Wörthersee, Department of Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology and Nephrology, Central Emergency Medicine (ZAE), Klagenfurt, Austria
Email: thomas.reiberger@meduniwien.ac.at

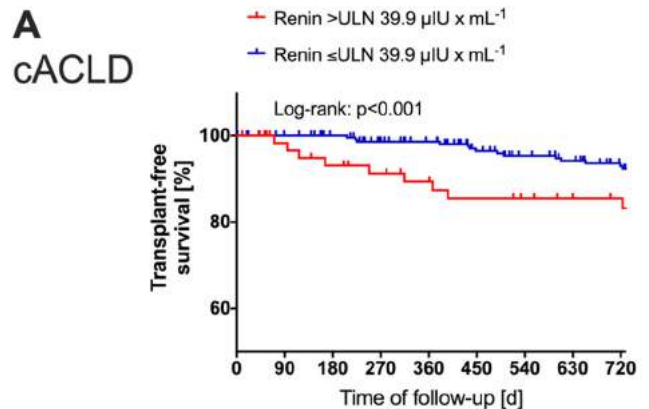
Background and aims: Renin, brain-type natriuretic peptide (BNP) and arginine-vasopressin (AVP) regulate circulatory homeostasis and these systems may be distorted in advanced chronic liver disease (ACLD).

Method: Plasma profiles of renin, proBNP and copeptin (an AVP biomarker) were assessed in portal hypertensive ACLD patients with compensated (cACLD) or decompensated (dACLD) at study inclusion. Patients with non-selective beta-blockers at the time of characterization were excluded from analysis. Decompensation/further decompensation and mortality were assessed by log-rank tests and Cox proportional hazard models. Multivariate models were adjusted for age, sex, MELD, HVPG, albumin and sodium.

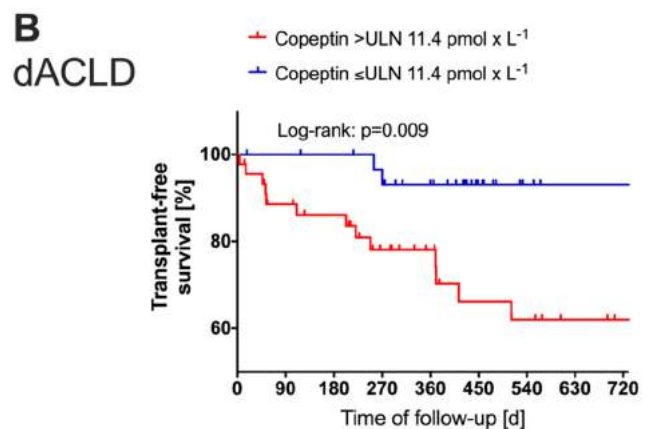
Results: Overall, 648 (cACLD: n = 302, dACLD: n = 346) patients were included. Median follow-up was 26.2 [IQR 40.4] months. 34.7% (n = 225) of patients had at least one decompensation event, 7.9% (n = 51) underwent liver transplantation and 24.8% (n = 161) died during follow-up including 82.6% (n = 133) liver-related deaths.

Time to first decompensation was shorter in cACLD patients with elevated renin (>39.9 $\mu\text{IU/ml}$; n = 64/294; $p = 0.096$) and copeptin (>11.4 pmol/L; n = 17/55; $p = 0.024$). Accordingly, plasma renin (aHR: 1.69; 95% CI: 1.07–2.68; $p = 0.025$) and in tendency copeptin (aHR: 2.69; 95% CI: 0.99–7.33; $p = 0.053$) independently predicted first decompensation. In dACLD, elevated proBNP (>125 pg/ml; n = 110/172; $p = 0.012$) and copeptin (n = 45/77; $p = 0.014$) were linked to further decompensation-but both did not independently predict further decompensation on multivariate analysis.

Transplant-free survival was shorter in ACLD patients with elevated renin (306/630; $p < 0.001$), proBNP (n = 139/277; $p = 0.004$) and copeptin (n = 62/132; $p = 0.006$), but only elevated copeptin was independently associated with decreased transplant-free survival (aHR: 3.29; 95% CI: 1.36–7.95; $p = 0.008$). In cACLD, increased renin (n = 64/294; $p < 0.001$) was an independent predictor of mortality (aHR: 3.21; 95% CI: 1.73–5.93; $p < 0.001$), whereas in dACLD mortality was independently associated with elevated copeptin (n = 45/80; $p = 0.009$; aHR: 5.77; 95% CI: 1.27–26.33; $p = 0.024$).



Patients at risk									
Follow-up [d]	0	90	180	270	360	450	540	630	720
No. of renin >ULN	64	58	54	52	48	45	43	40	39
No. of renin \leq ULN	230	222	215	202	194	178	168	162	151



Patients at risk									
Follow-up [d]	0	90	180	270	360	450	540	630	720
No. of copeptin >ULN	45	38	35	27	22	17	15	12	10
No. of copeptin \leq ULN	32	32	31	28	23	13	7	5	5

Figure:

Conclusion: Elevated levels of renin, proBNP and copeptin are linked to impaired outcomes in ACLD. In ACLD, increased renin might indicate systemic vasodilation preceding clinical decompensation, as it predicts first decompensation and mortality. Increased copeptin (indicative of circulatory stress/failure) is particularly relevant in dACLD, correlating with further decompensation and predicting mortality.

PO-560

Decreasing VWF levels upon NSBB therapy indicate a reduced risk of further decompensation, ACLF and death

Mathias Jachs^{1,2,3}, Lukas Hartl^{1,2,3}, Benedikt Simbrunner^{1,2,3}, David J.M. Bauer^{1,2,3}, Rafael Paternostro^{1,2}, Bernhard Scheiner^{1,2}, Philipp Schwabl^{1,2,3}, Albert Stättermayer¹, Matthias Pinter¹, Ernst Eigenbauer⁴, Prof. Peter Quehenberger, MD⁵, Michael Trauner¹, Thomas Reiberger^{1,2,3}, Mattias Mandorfer^{1,2,3}. ¹Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; ²Vienna Hepatic Hemodynamic Lab, Medical University of Vienna, Vienna, Austria; ³Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, Vienna, Austria; ⁴IT4Science, Medical University of Vienna, Vienna, Austria; ⁵Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria
Email: thomas.reiberger@meduniwien.ac.at

Background and aims: Bacterial translocation drives systemic inflammation (SI) as well as endothelial dysfunction, and thus, disease progression in cirrhosis. Non-selective beta-blockers (NSBBs) may exert beneficial effects beyond lowering portal pressure. We assessed (i) NSBB-related changes in von Willebrand factor levels (VWF) and (ii) their prognostic value for outcomes in decompensated cirrhosis.

Method: We assessed changes in VWF as a surrogate marker for endothelial dysfunction, as well as biomarkers of SI (C-reactive protein [CRP], procalcitonin [PCT]) and of hemodynamic derangement (mean arterial pressure [MAP]) in patients undergoing paired hepatic venous pressure gradient (HVPG) measurements before and under NSBB treatment. Patients were followed until last clinical contact, the occurrence of a significant risk-modifying event (antiviral therapy, alcohol abstinence, or hepatocellular carcinoma), liver transplantation, or death. Follow-up data was analyzed using competing risk regression stratifying patients according to presence ('VWF responders') or absence ('VWF non-responders') of VWF decrease upon NSBB treatment.

Results: 159 patients with a median Child-Pugh score of 8 (IQR: 6; 9) were included. Upon NSBB treatment, HVPG response was observed in 77 (48.4%) patients, while 113 (71.1%) patients were VWF responders (median relative decrease: -12.9 [IQR: -19.7; -7.4]%). The rates of HVPG response were comparable between VWF response groups (VWF responders: 47.8% vs. VWF non-responders: 50.0%; p = 0.938). However, VWF responders showed more pronounced relative reductions in SI, i.e. procalcitonin (-16.7 [IQR: -31.3; -2.5]% vs. VWF non-responders: 25.0 [IQR: 19.2; 44.6]%; p < 0.001) and CRP (-22.9 [IQR: -50.1; 10.0]% vs. VWF non-responders: -5.9 [IQR: -31.9; 20.4]%; p = 0.074). Notably, NSBB-induced relative decreases in MAP were less pronounced in VWF responders (-8.3 [IQR: -14.9; -1.2]%) than in VWF non-responders (-12.5 [IQR: -18.5; -5.4]%; p = 0.046). In adjusted competing risk regression models, VWF response was associated with decreased risks of further decompensation (adjusted subdistribution hazard ratio [aSHR]: 0.630 [95%CI: 0.399-0.993]; p = 0.047), acute-on-chronic liver failure (ACLF, aSHR: 0.407 [95%CI: 0.180-0.918]; p = 0.030), and liver-related death (aSHR: 0.434 [95%CI: 0.229-0.819]; p = 0.010).

Conclusion: NSBB-related reductions in VWF levels might reflect their anti-inflammatory activity. Decreases in VWF are accompanied by less pronounced adverse effects on systemic hemodynamics and are independently associated with a decreased risk of further decompensation, ACLF and death.

PO-1032

Impact of hyponatremia on morbidity, mortality and resource utilization in portal hypertensive ascites: a nationwide analysis

Joseph Alukal¹, Talan Zhang², Paul J. Thuluvath². ¹Institute of Digestive Health and Liver Disease, Mercy Medical Center, Baltimore, United States; ²Institute of Digestive Health and Liver Disease, Mercy Medical Center and University of Maryland School of Medicine, Baltimore, United States
Email: jjalukal@gmail.com

Background and aims: Ascites and hyponatremia are important milestones of worsening portal hypertension in those with cirrhosis. The objective of our study was to evaluate mortality and resource utilization of hospitalized cirrhotic patients with ascites with or without hyponatremia using a large national cohort.

Method: The National In-patient Sample (NIS) database was used to identify all adult hospitalized patients with a diagnosis of cirrhosis and ascites with or without hyponatremia from 2016 to 2017 using ICD-10 codes (cirrhosis K74.60, K70.30; ascites R18.8; hyponatremia E87.1).

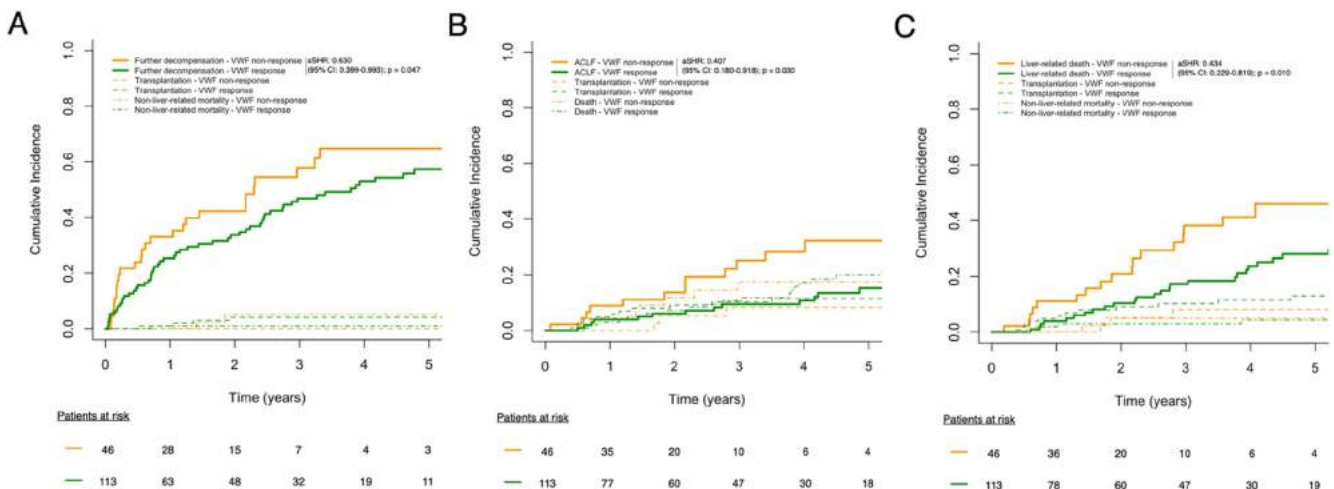


Figure: (abstract: PO-560)

POSTER PRESENTATIONS

Results: During the study period 10, 187 cirrhotic patients were hospitalized with ascites and hyponatremia, and 34, 555 cirrhotic patients were hospitalized with ascites without hyponatremia. Compared to those without hyponatremia, hyponatremic patients had a higher prevalence of acute kidney injury (AKI) (50.3% vs. 32.8%, $p < 0.001$), acute respiratory failure (12.8% vs. 10.4%, $p < 0.001$) and sepsis (16.8% vs. 11.8%, $p < 0.001$); they also had a higher prevalence of liver related complications such as coagulopathy (46.6% vs. 38.1%, $p < 0.001$), hepatic encephalopathy (29.4% vs. 24%, $p < 0.01$), HRS (12.2% vs. 5.7%, $p < 0.001$), SBP (10.3% vs. 6.6%, $p < 0.001$), HCC (10.1% vs. 7.1%, $p < 0.001$) and acute liver failure (ALF) (8.2% vs. 5.7%, $p < 0.001$). Hyponatremia patients underwent a higher number of procedures (mean 2.9 ± 3.3 vs. 2.3 ± 2.7 , $p < 0.001$) and paracentesis (53% vs. 44%, $p < 0.001$). Comorbidity score (20.9 ± 9.7 vs. 12.8 ± 11.4 , $p < 0.001$), length of stay (8.5 ± 9.2 vs. 6.5 ± 7.2 , $p < 0.001$), and total charges (\$97, 327 vs. \$72, 278, $p < 0.01$) were also significantly higher in hyponatremic patients (Table 1). In-patient mortality was 38% higher in hyponatremic patients (9.8% vs. 7.1%, $p < 0.001$). Multivariable analysis (OR and 95% Confidence Intervals) showed that age >60 years (1.28; 1.06–1.54, $p = 0.01$), variceal bleeding (2.0; 1.34–2.98, $p = 0.001$), ALF (2.16; 1.67–2.78, $p < 0.0001$), AKI (2.21, 1.82–2.70, $p = 0.001$), HCC (2.29; 1.79–2.94, $p < 0.0001$), sepsis (4.54; 3.77–5.47, $p < 0.0001$) and acute respiratory

failure (6.79; 5.61–8.22, $p < 0.0001$) were independent risk factors for mortality.

Conclusion: In hospitalized patients with portal hypertension related ascites, presence of hyponatremia was associated with 38% higher in-patient mortality and 35% higher costs compared to those without hyponatremia.

PO-1038

A scoring model to predict mortality in hospitalized patients with decompensated cirrhosis and hyponatremia

Joseph Alukal¹, Talan Zhang², Paul J. Thuluvath². ¹Institute of Digestive Health and Liver Disease, Mercy Medical Center, Baltimore, United States; ²Institute of Digestive Health and Liver Disease, Mercy Medical Center and University of Maryland School of Medicine, Baltimore, United States

Email: jjalukal@gmail.com

Background and aims: Patients with decompensated cirrhosis who develop hyponatremia have significant morbidity and mortality. The objective of our study was to develop a model to predict in-hospital mortality in such patients using easily available and verifiable clinical parameters.

Method: The National In-patient Sample (NIS) database was used to identify all adult hospitalized patients with a diagnosis of cirrhosis, ascites and hyponatremia from 2016 to 2017 using ICD-10 codes

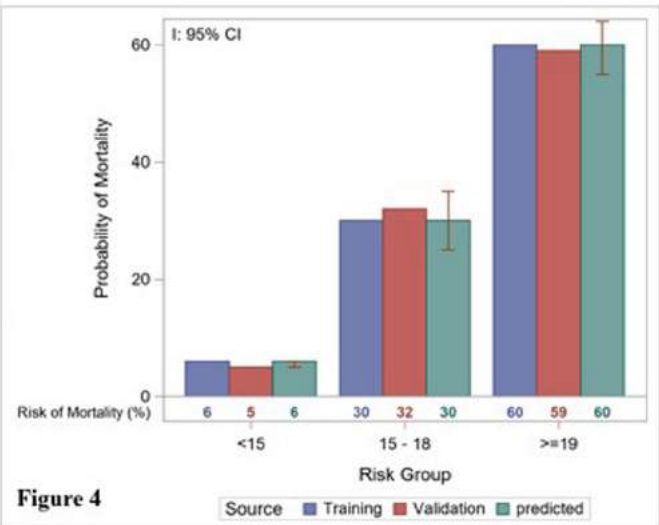
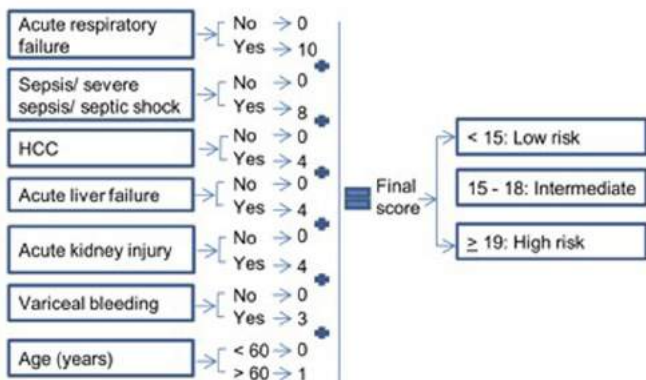
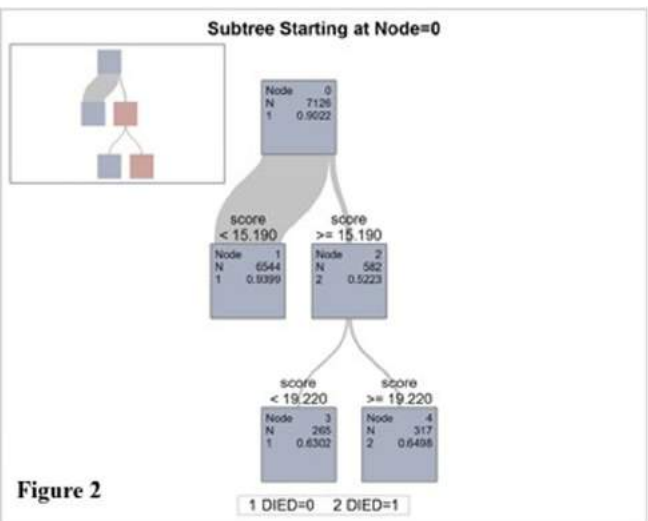
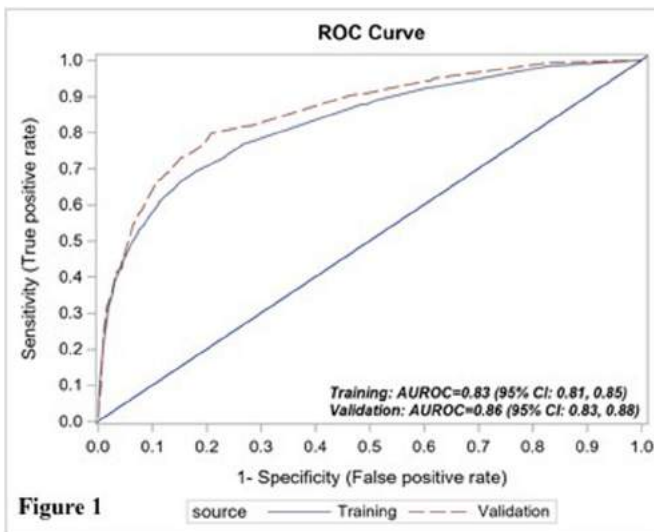


Figure: (abstract: PO-1038)

(cirrhosis K74, K74.60, K70.30; ascites R18.8; hyponatremia E87.1). After identifying independent risk factors for in-hospital mortality, we developed a prediction model using logistic regression analysis. The model was built and validated in a training and a validation dataset respectively. A clinical scoring model was created by first categorizing continuous predictors in the logistic regression models by using cutoff points selected by maximum Youden index and then refitting the logistic models using all predictors as categorical variables. To enhance the clinical utility of the score, we further classified patients into three mortality risk categories (low, intermediate, and high risk) using cutoff points selected by the Decision Tree model.

Results: During the study period we identified 10,187 hospitalized cirrhotic patients with ascites and hyponatremia with an overall mortality of 9.8%. Multivariate analysis showed that age, variceal bleeding, acute liver failure, acute kidney injury, hepatocellular cancer (HCC), sepsis and acute respiratory failure were independent risk factors for mortality. The mortality prediction model that incorporated these risk factors had an area under the receiver operating characteristic curve (AUROC) of 0.83 (0.81, 0.85) for the training data and 0.86 (0.83, 0.88) for the validation data (Fig. 1). We created an algorithm to stratify patients into low (score <15), intermediate (score 15–18) and high risk (score >19) categories. The cut-off points were determined based on Decision Tree model (Fig. 2–3). The probability of mortality of the training and validation cohorts as well as the predicted mortality (with 95% CI) based on this algorithm is shown in Figure 4. The predicted mortality in low, intermediate and high-risk groups were 6%, 30% and 60% respectively.

Conclusion: The prognostic model created using the NIS database was able to predict mortality in hospitalized patients with cirrhosis and hyponatremia with a very high accuracy.

PO-1040

The natural history of advanced chronic liver disease defined by transient elastography

Jessica Shearer^{1,2}, Rebecca L. Jones², Richard Parker², James Ferguson³, Ian Rowe^{1,2}. ¹University of Leeds, United Kingdom; ²St James's University Hospital, United Kingdom; ³Queen Elizabeth Hospital Birmingham, United Kingdom
Email: jshearer@doctors.org.uk

Background and aims: The clinical course of cirrhosis does not follow a predictable trajectory. Multistate models of disease progression have been adopted to assess its' natural history, mainly in cohorts with biopsy proven cirrhosis. Transient elastography (TE) is commonly used in clinical practice to diagnose liver fibrosis. The aim of this study was to assess survival and competing risk of liver and non-liver related events in a cohort of patients with advanced chronic liver disease (ACLD) defined by TE using electronic health record (EHR) data.

Method: TE data was collected from two large secondary care centres in the UK between 2008 and 2019. Patients with ACLD (defined by a liver stiffness measurement (LSM) of >10 kPa) were included. Disease and procedural codes extracted from the EHR were analysed. Validation of the coded information was done in a subset of patients using the full clinical record. Clinical events including decompensation (ascites, bleeding and non-bleeding varices, hepatic encephalopathy), hepatocellular carcinoma (HCC) and death were identified. Estimation of transition probabilities between clinical stages of cirrhosis was done using multistate models and flexible parametric survival models.

Results: 3029 patients were included, 1549 with LSM ≥ 15 kPa. Median follow-up was 3.3 years. During follow-up, 9% of patients died, 7.5% of patients developed varices, 2% had bleeding varices and 5.5% had a non-bleeding decompensation event. 2.4% were diagnosed with HCC. Baseline LSM was associated with the development of varices, the transition from compensated cirrhosis to decompensated cirrhosis, and the development of HCC. Disease aetiology was also associated with decompensation and the development of HCC. Example predicted disease trajectories derived from multistate modelling are shown in the **Figure**.

Conclusion: Transient elastography is strongly associated with outcomes in two large cohorts of patients with ACLD. EHR data can be used to define clinical progression and outcomes in large patient cohorts and estimates of disease progression in EHR cohorts are comparable to landmark studies of patients diagnosed using liver biopsy. Identification of ACLD using TE is a rational basis for registry-based analyses to facilitate quality improvement and clinical trials in patients with liver disease.

Estimated outcomes for 55 year old male patient with transient elastography value of 20kPa and the indicated liver disease

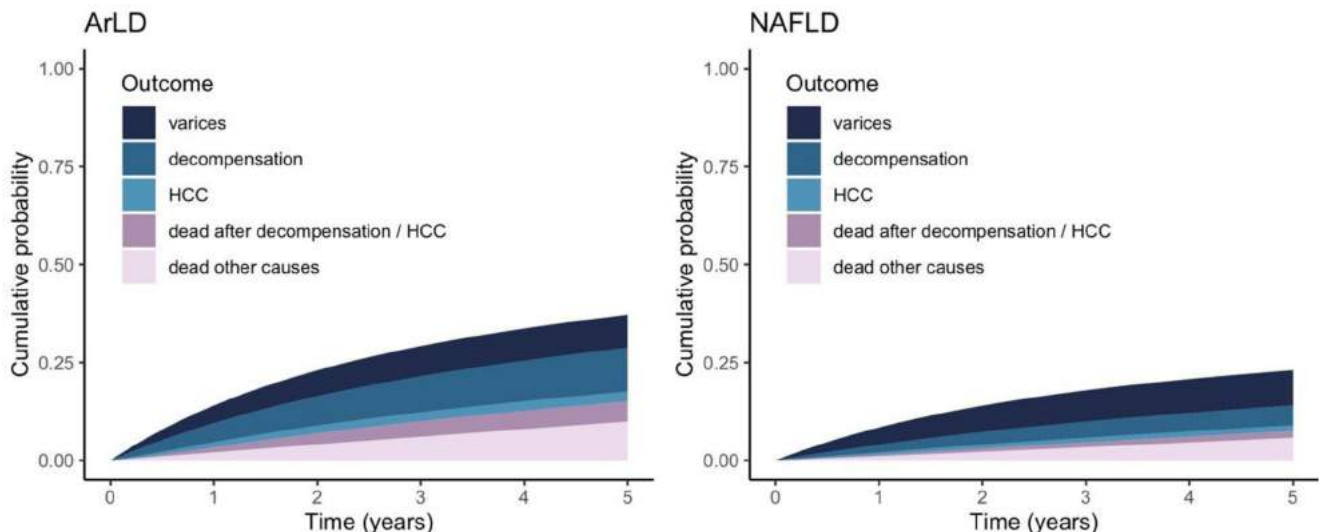


Figure: (abstract: PO-1040)

POSTER PRESENTATIONS

PO-1064

Emergency room care is essential in improving outcomes of decompensated cirrhosis patients: A Canadian experience

Jesse Stach¹, Edwin Enns², Kelly Burak¹, Mark G. Swain¹, Stephen Congly¹, Juan G. Abalde³, Carla Coffin¹, Abdel-Aziz Shaheen¹. ¹Cumming School of Medicine, University of Calgary, Gastroenterology and Hepatology Division, Department of Medicine, Calgary, Canada; ²Alberta Health Services, Calgary, Canada; ³University of Alberta, Edmonton, Canada
Email: azshaheen@me.com

Background and aims: Growing evidence highlights the importance of improved outpatient care. However, few studies have evaluated the role of emergency department (ED) care provided to cirrhosis patients and its impact on clinical outcomes. Therefore, we evaluated the implementation of standardized cirrhosis care practices in the ED and its impact on decompensated cirrhosis patient outcomes for those presenting with gastrointestinal bleeding (GIB).

Method: We used the electronic medical record system implemented in the four acute care hospitals serving the Calgary Health Zone (CHZ; 1.4 million people), to identify decompensated cirrhosis patients with evidence of GIB who presented to the ED via reviewing ED triages notes between 2017 and 2019. We evaluated implementation of standardized care measures for patients with decompensated cirrhosis such as antibiotic utilization, time to start antibiotics, administration of octreotide, proving endoscopy within 12 hours, consulting gastroenterology service, and performing a follow-up upper endoscopy for patients with banded varices. We then undertook a medical chart review to validate our findings in patients admitted in the last year of the study. Descriptive analysis methods were used.

Results: We identified 819 ED presentations for cirrhosis patients presenting with GIB over our study period. Among those identified, 88% were started on appropriate broad-spectrum antibiotics within a median time of 5.1 hours (IQR: 3.2–7.1) from ED presentation. Only 66% were started on octreotide infusion (median time from ED presentation 3.3 hours [IQR: 1.5–4.2]). Only 70% of this cohort were evaluated by the gastroenterology service (median time from ED presentation to consultation of 4.2 hours [IQR: 3.0–5.3]). Urgent upper endoscopy within 12 hours of ED presentation was provided to 58% of our cohort. Of 185 patients who had esophageal variceal banding during hospitalization, only 81 (44%) patients had a follow-up upper endoscopy within 3 months. For our patient cohort, the median length of stay for decompensated cirrhosis patients with variceal bleeding was 7.5 days (IQ: 6.2–8.5), 30-day readmission rate was 20.3% (IQR: 17.7–22.1), and in-hospital mortality was 15.3% (IQR: 12.1–17.5). In our validation study, 74% (139/187) of patients had a history of esophageal, gastric varices, or portal hypertensive gastropathy on endoscopy, while 26% had other etiologies for GIB such as Mallory-Weiss tear, peptic ulcer disease, or unknown etiology.

Conclusion: In our cohort, we identified high rates of poor clinical outcomes among decompensated cirrhosis patients presenting to the ED with suspected variceal bleeding. Implementation of various standard of care measures in the ED was suboptimal. Improved integration of high-quality ED management of cirrhosis patient care is essential to lower readmission and in-hospital mortality rates.

PO-1094

Timing of endoscopy for acute variceal bleeding in patients with cirrhosis (CHESS1905): a nationwide cohort study

Yifei Huang¹, Wenhui Zhang², Xiang Huiling³, Liyao Zhang⁴, Xiuping Zhang¹, Chuan Liu¹, Lili Yuan⁵, Lijun Peng⁶, Min Gao⁷, Dongli Xia⁸, Xing Wang⁹, Jia Li¹⁰, Ying Song¹¹, Xiqiao Zhou¹², Xingsi Qi¹³, Jing Zeng¹⁴, Xiaoyan Tan¹⁵, Mingming Deng¹⁶, Haiming Fang¹⁷, Shenglin Qi¹⁸, Song He¹⁹, Yongfeng He²⁰, Bin Ye²¹, Wei Wu²², Tang Dong²³, Jianbo Shao²⁴, Wei Wei²⁵, Jianping Hu²⁶, Xin Yong²⁷, Chaohui He²⁸, Jinlun Bao²⁹, Yuening Zhang³⁰, Guo Zhang³¹, Rui Ji³², Yang Bu³³, Shengjuan Hu³⁴, Wei Yan³⁵,

Hongjiang Li³⁶, Yanling Wang², Mengmeng Li², Jia Lian³, Chang'en Liu³, Yunhai Wu⁴, Ye Gu⁴, Yan Wang⁴, Ping Cao⁵, Lin Lu⁶, Shuni Tian⁶, Yanfei Fang⁷, Pan Jiang⁷, Zhenbei Liu⁸, Aimin Liu⁸, Bin Wu⁹, Lili Zhao¹⁰, Jinggui Qiao¹¹, Shuang Li¹⁰, Lihui Sun¹¹, Mengyu Li¹², Chengwen Fang¹², Hao Chen¹³, Zibin Tian¹³, Gaoyang Lin³⁷, Xuanhui Huang¹⁴, Ying Deng¹⁵, Jitao Chen¹⁵, Muhan Lv¹⁶, Jingyuan Liao¹⁶, Lijiu Zhang¹⁷, Junyu Lu¹⁹, Suhua Wu¹⁹, Xiaocui Yang²⁰, Wenwei Guo²⁰, Jianbo Wang²¹, Chao Chen²², Erjiong Huang²², Limei Ren²³, Hongduo Pan²³, Yuehua Yu²⁶, Yang Yang²⁸, Ming Yang²⁷, Shuangping Cheng²⁷, Xiaoli Wu²⁹, Limaocai Rang²⁹, Yunxiao Liang³¹, Ping Han³⁵, Yanmin Zhang³⁶, Fengmei Wang³, Wai-Kay Seto³⁸, Xiaolong Qi¹. ¹CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; ²CHESS Center, Diagnosis and Treatment Center, The Fifth Medical Center of PLA General Hospital, Beijing, China; ³Department of Hepatology and Gastroenterology, Tianjin Third Central Hospital, Tianjin, China; ⁴Department of Critical Care Medicine, Sixth People's Hospital of Shenyang, Shenyang, China; ⁵Department of gastroenterology, Shanxi Bethune hospital, Taiyuan, China; ⁶Department of Gastroenterology, Linyi People's Hospital, Linyi, China; ⁷Department of Gastroenterology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China; ⁸Department of Gastroenterology, Chongqing Fuling Central Hospital, Chongqing, China; ⁹Department of Gastroenterology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; ¹⁰Department of Gastroenterology and Hepatology, Tianjin Second People's Hospital, Tianjin, China; ¹¹Department of Gastroenterology, Xi'an GaoXin Hospital, Xi'an, China; ¹²Department of Gastroenterology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China; ¹³Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, China; ¹⁴Department of Emergency, Huizhou Third People's Hospital, Guangzhou Medical University, Huizhou, China; ¹⁵Department of Gastroenterology, Maoming People's Hospital, Maoming, China; ¹⁶Department of Gastroenterology, The Affiliated Hospital of Southwest Medical University, Luzhou, China; ¹⁷Department of Gastroenterology and Hepatology, the second hospital of Anhui Medical University, Hefei, China; ¹⁸Department of Hepatology, Dalian Sixth People's Hospital, Dalian, China; ¹⁹Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; ²⁰Department of Gastroenterology, Endoscopic center, Ankang Central Hospital, Ankang, China; ²¹Department of Gastroenterology, Lishui Hospital of Zhejiang University, the Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Central Hospital, Lishui, China; ²²Department of Gastroenterology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ²³Inner Mongolia Institute of Digestive Diseases, the Second Affiliated Hospital of Baotou Medical College. Inner Mongolia University of science and technology, Baotou, China; ²⁴Department of Liver Disease, The Third People's Hospital of Zhenjiang, Zhenjiang, China; ²⁵Gastroenterology Department, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China; ²⁶Department of Gastroenterology, First People's Hospital of Yinchuan City, Yinchuan, China; ²⁷Gastroenterology, General Hospital of Western Theater Command, Chengdu, China; ²⁸Department of Gastroenterology and Endoscopy, The fifth affiliated Zhuhai Hospital of Zunyi Medical University, Zhuhai, China; ²⁹Department of Gastroenterology, Shannan people's Hospital, Shannan, China; ³⁰Center of Hepatology and Gastroenterology, Beijing You'an Hospital, Capital Medical University, Beijing, China; ³¹The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; ³²Department of Gastroenterology, The First Hospital of Lanzhou University, Lanzhou, China; ³³Department of Hepatobiliary Surgery, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China; ³⁴Department of Gastroenterology, Endoscopic center, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China; ³⁵Department of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ³⁶Department of Hepatology, Baoding people's hospital, Baoding, China; ³⁷Department of cardiothoracic surgery, The Affiliated Hospital of Qingdao University, Qingdao, China;

³⁸Department of Medicine and State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong, China
Email: qixiaolong@vip.163.com

Background and aims: Endoscopy plays an important role in the management of acute variceal bleeding (AVB). This study aimed at determining the optimal timing of endoscopy for AVB in patients with cirrhosis.

Method: Cirrhotic patients with AVB who underwent endoscopy within 24 hours after admission were retrospectively enrolled between February 2013 and May 2020 across 34 university hospitals of 30 cities in China. Patients were divided into the urgent endoscopy group (<6 h) and the early endoscopy group (6–24 h). Outcomes included the incidence of 5-day rebleeding and in-hospital mortality after the endoscopy management. A 1:1 propensity score matching (PSM) analysis was performed.

Results: A total of 3,319 patients were enrolled in the urgent endoscopy group (n = 2,383) and the early endoscopy group (n = 936), respectively. The overall difference in the incidence of 5-day rebleeding between two groups was not statistically significant (p = 0.24), which remained unchanged after PSM analyses (p = 0.90)

(Figure). Among patients with Child-Pugh class B, the difference of the incidence of 5-day rebleeding was significant (before PSM, p = 0.02; after PSM, p = 0.03) (Figure). Additionally, the overall difference of in-hospital mortality between two groups was not significant after PSM analysis (1.93% vs. 1.18%, p = 0.26).

Conclusion: Timing of emergency endoscopy within 24 hours may not be associated with the incidence of rebleeding within 5 days and in-hospital mortality among cirrhotic patients with AVB. However, urgent endoscopy within 6 hours may not be recommended for Child-Pugh class B patients with cirrhosis.

PO-1103

In-hospital mortality after surgery in patients with liver cirrhosis: A nationwide study of 1,662,887 patients

Jeong-Ju Yoo¹, Sang Gyune Kim¹, Young Seok Kim¹. ¹SoonChunHyang University School of Medicine, Internal Medicine, Bucheon, Korea, Rep. of South

Email: puby17@naver.com

Background and aims: Patients with liver cirrhosis have an increased risk of in-hospital mortality after surgery. However, large-scale

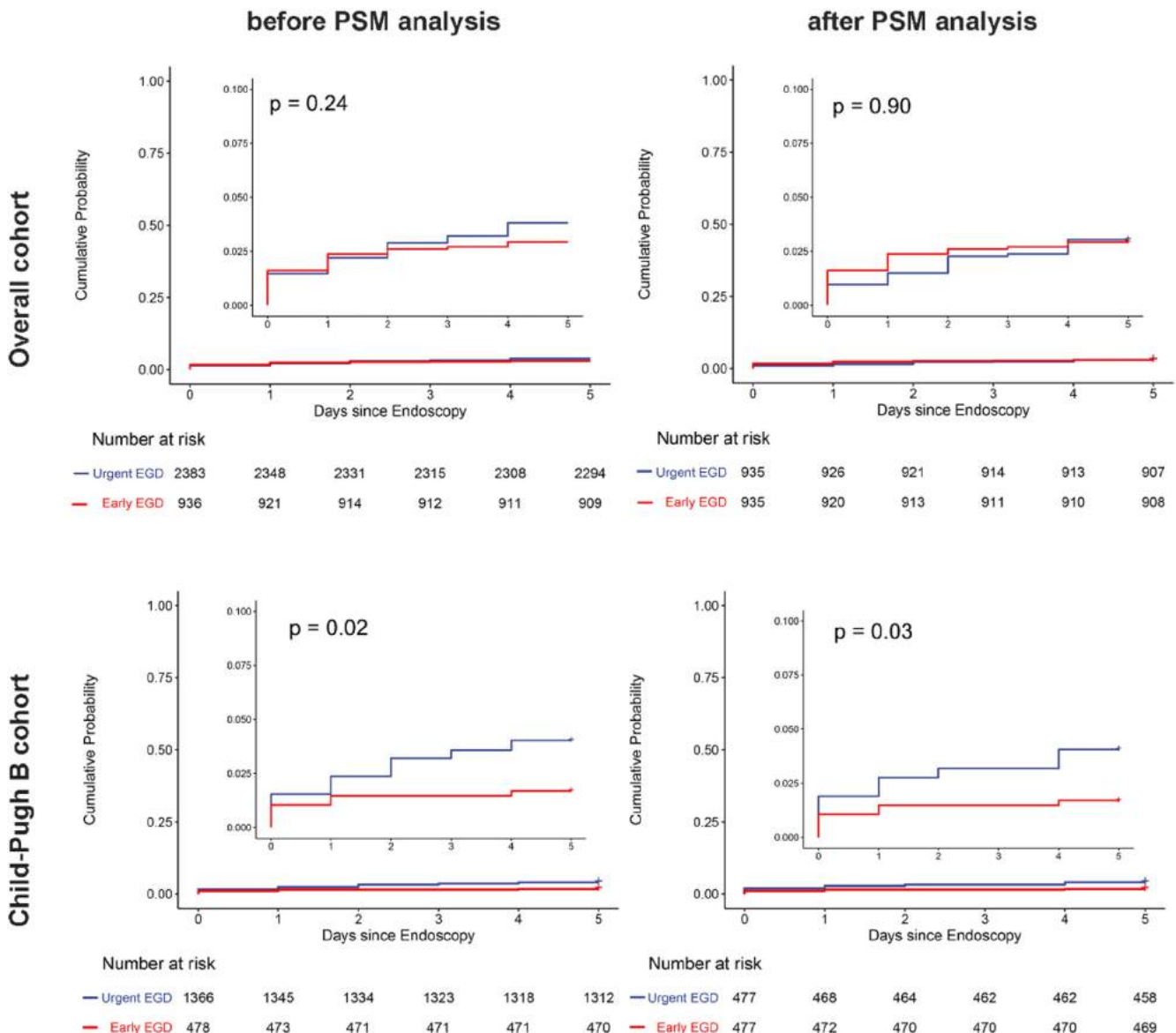


Figure: (abstract: PO-1094)

POSTER PRESENTATIONS

studies on the prognosis of these patients after surgery are lacking. The aim of the study was to investigate the in-hospital mortality of patients with liver cirrhosis after surgery over five years.

Method: We used the Health Insurance Review and Assessment Service-National Inpatient Samples (HIRA-NIS) between 2012 and 2016. In-hospital mortality and hospital stay were analyzed using the data. Mortality rates according to the surgical department were also analyzed.

Results: Of the 1, 662, 887 patients who underwent surgery, 16, 174 (1.0%) patients had cirrhosis. The in-hospital mortality was significantly higher in patients with cirrhosis than in those without cirrhosis (8.0% vs. 1.0%). Liver cirrhosis increased in-hospital mortality by about 5.3 times. In addition, the total hospitalization period and use of the intensive care unit were significantly higher in patients with liver cirrhosis. In the liver cirrhosis group, older age [odds ratio (OR) 1.03], male gender (OR 1.43), and low socioeconomic status (OR 1.34) were risk factors of in-hospital mortality. In-hospital mortality after surgery in patients with cirrhosis was the highest in patients who underwent otorhinolaryngology surgery (OR 2.21), followed by neurosurgery (OR 1.88), thoracic and cardiovascular surgery (OR 1.73), and plastic surgery (OR 1.37).

Conclusion: The in-hospital mortality of patients with cirrhosis is significantly high, despite advances in cirrhosis treatment. For precise surgical risk assessment of these patients, not only liver function, but also age, sex, and the type of surgery should be considered.

PO-1146

Metamizole intake is associated with acute kidney injury and a higher mortality in patients with decompensated liver cirrhosis

Tammo Lambert Tergast¹, Benjamin Schulte¹, Marie Schultalbers¹, Markus Cornberg¹, Heiner Wedemeyer¹, Dirk O. Stichtenoth², Benjamin Maasoumy². ¹Hanover, Department of Gastroenterology, Hepatology and Endocrinology, Hanover, Germany; ²Hanover, Department of Clinical Pharmacology, Hanover, Germany
Email: tergast.tammo@mh-hannover.de

Background and aims: Analgesia is a considerable challenge in patients with decompensated liver cirrhosis. Current guidelines advise against the use of non-steroidal anti-inflammatory drugs (NSAIDs) due to the nephrotoxic potential. Metamizole is not a typical NSAID and widely considered as a safe alternative treatment option. However, safety has not been systematically investigated for patients with decompensated cirrhosis so far. The aim of this study was to determine the impact of metamizole intake on the clinical course of these patients.

Method: Patients were recruited from the well-defined Hannover Ascites Cohort, including 667 patients with decompensated liver cirrhosis. Patients were carefully evaluated for metamizole intake. End points of this study were acute kidney injury (AKI) and death or liver transplantation (LTx) within 28 days. Kaplan-Meier curves were used to illustrate survival, p values were calculated with the log-rank test. To adjust for potential confounders like age, mean arterial pressure (MAP) <65 mmHg, leucocyte count, platelet count, sodium level and MELD score multivariate Cox-regression was performed.

Results: In total, 667 patients were included, 36% were female, mean age was 56 years, mean MELD score was 19. Metamizole was used by 22% of patients (n = 145/667) at a mean daily dose of 2 g (0.45g–5.00 g). Patients in the metamizole group were younger (p = 0.001), had higher CRP (p = 0.008), a numerically lower MAP and higher sodium levels (p = 0.068 and p = 0.098). Leucocyte counts and MELD scores were comparable between both groups (p = 0.416 and

Figure 2

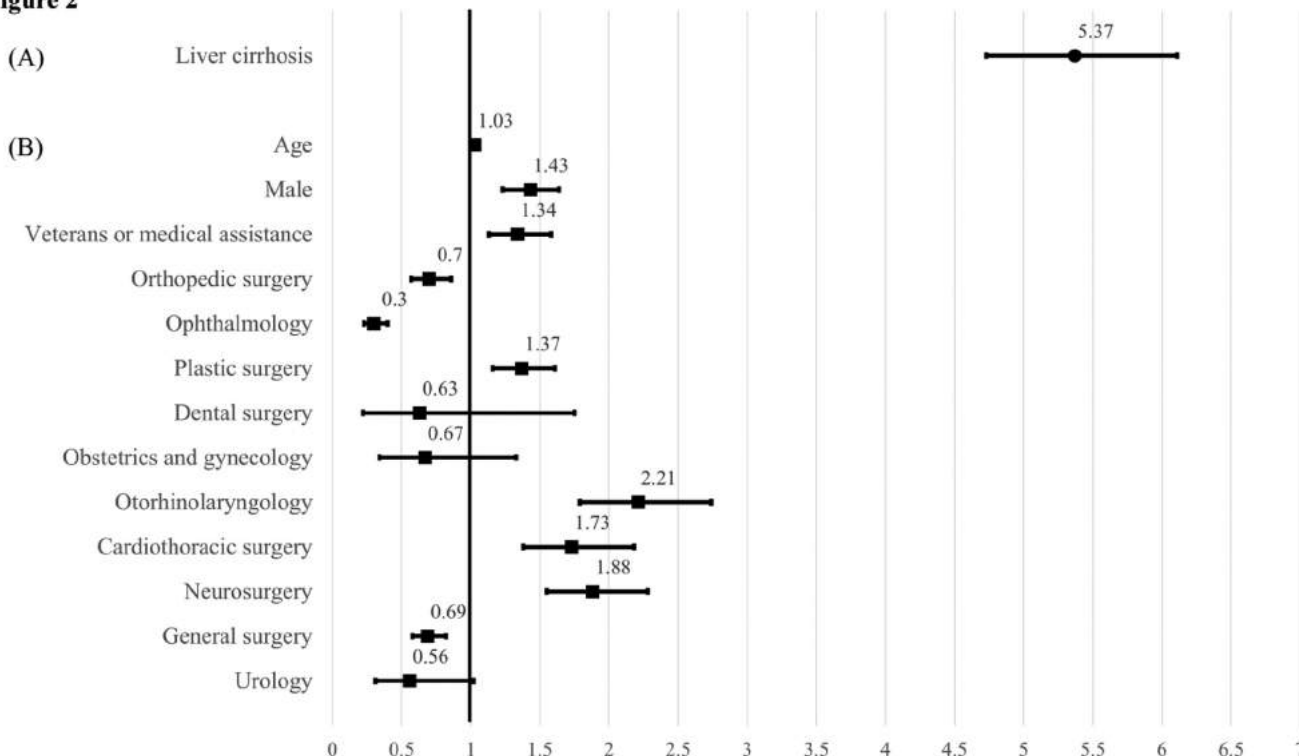


Figure: (abstract: PO-1103)

p = 0.210, respectively). Throughout the observation period 52% of patients (n = 346/667) developed AKI, 72% among those with (n = 105/145) and 46% without (n = 241/522) metamizole intake. Moreover, metamizole intake at baseline was associated with an increased risk of AKI (p < 0.001; Figure 1) and with a lower 28-day LTx-free survival (p = 0.001). Multivariate analysis revealed an independent association of metamizole intake with AKI after adjusting for several potential confounders (HR: 1.95, p < 0.001). Of note, metamizole intake was also independently associated with a higher risk of death or LTx (HR: 2.15, p = 0.001).

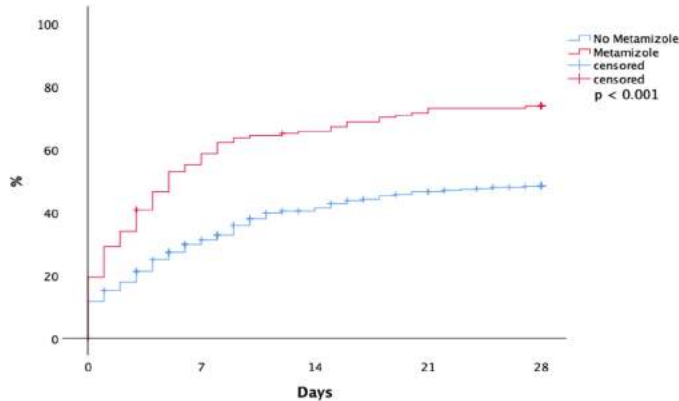


Figure 1: 28-day incidence of AKI

Conclusion: Metamizole intake is independently associated with AKI and mortality in patients with decompensated liver cirrhosis. Thus, metamizole should be used with caution in these patients.

PO-1151

Stratifying the risk of variceal bleeding by non-invasive tools in patients with compensated advanced chronic liver disease: A decision curve analysis

Sanchit Sharma¹, Samagra Agarwal¹, Ankur Jindal², Deepak Gunjan¹, Kanav Kaushal¹, Srikant Mohta¹, Sushrut Singh², Rakesh Kumar Jagdish², Shiv Kumar Sarin², Anoop Saraya¹. ¹AIIMS Hospital, Gastroenterology and Human Nutrition Unit, New Delhi, India; ²Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India
Email: ansaraya@yahoo.com

Background and aims: Non-invasive tools (NITs) reliably categorise patients with compensated advanced chronic liver disease (cACLD) into high and low risk group for harbouring varices needing treatment (VNTs). We aimed to assess the performance of this NITs based stratification at baseline to identify similar risk groups for variceal bleeding (VB) events on follow-up.

Method: In this retrospective multicentre analysis, patients with cACLD categorised at baseline into different risk groups by NITs (Baveno-VI, expanded Baveno-VI, platelet-albumin, platelet-MELD and ANTICIPATE study platelet criteria) and by endoscopy (high risk vs low risk/no varices) were assessed for VB events in different risk strata on follow-up. Decision Curve Analysis was used to estimate benefit of classifying patients using NITs over endoscopic classification for predicting VB. Decision thresholds for initiating prophylaxis

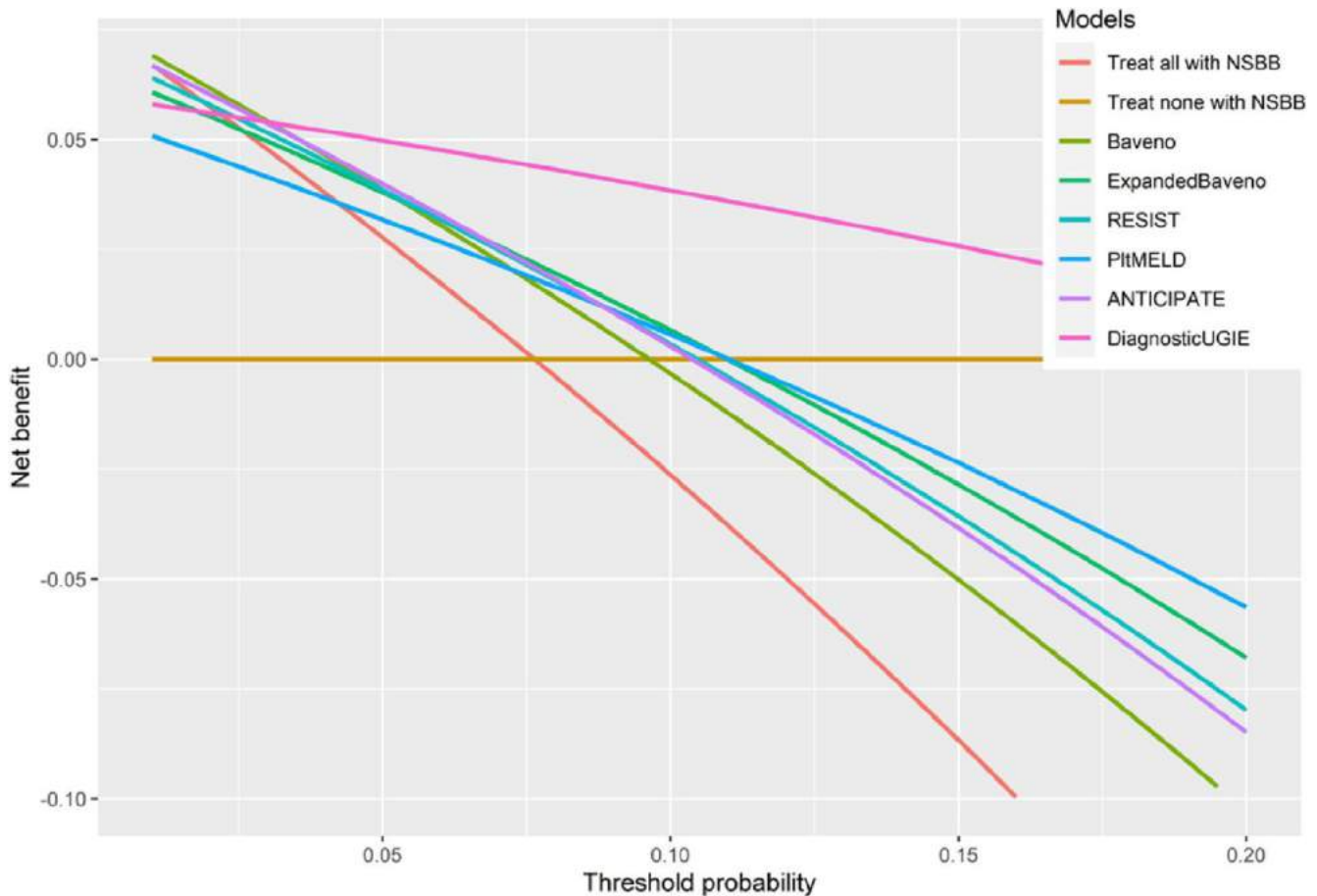


Figure: (abstract PO-1151): Decision curve plots demonstrating net benefit of basing the decision for prophylaxis for variceal bleeding using different NITs for cACLD across range of threshold probabilities against default strategies of giving prophylaxis based on endoscopic stratification (pink), for all (red) and no (brown)

POSTER PRESENTATIONS

were defined and number of additional patients needed to treat (NNT) for every additional VB identified by NITs over endoscopy was estimated.

Results: 1284 patients (mean age: 44.7 ± 13.5 years, 72.4% males) of hepatitis B (29.2%), non-alcoholic fatty liver disease (24.9%), hepatitis C (20.1%) and alcohol (17.5%) related cACLD were included with 323 (25.2%) patients having high risk varices on endoscopy at baseline. 98 (7.6%) patients developed VB over 20 (9–35) months of follow-up. The 1-year and 3-year rate of VB with all NITs was 5.7–7.4% and 13.2–16.4% among high-risk and 0–2.3% and 0–5% among low-risk subgroups respectively ($p < 0.001$, among different risk groups). At thresholds of $< 3\%$ event rate of VB, Baveno-VI (NNT: 176), Anticipate criteria (NNT-233) and platelet-albumin criteria (NNT-376) were superior to endoscopy while endoscopic classification was superior to NITs above this threshold for deciding the need for prophylaxis.

Table1: Rates of incident variceal bleeding on follow-up in high risk and low risk subgroups of endoscopy and NITs based stratification at baseline

NITs	N (%)	3-year bleeding rate n (%)	p value
Baveno-VI			< 0.001
• Low-risk	266 (20.7)	0	
• High-risk	1018 (79.3)	13.2 (10.5–15.8)	
Platelet-albumin criteria			< 0.001
• Low-risk	424 (34%)	3.1 (0.9–5.3)	< 0.001
• High-risk	860 (67%)	14.6 (11.5–17.6)	
ANTICIPATE (platelet criteria)			< 0.001
• Low-risk	378 (29.4%)	1.2 (0–2.5)	
• High-risk	906 (70.6%)	14.4 (11.4–17.2)	
Endoscopic classification			< 0.001
• Low-risk/No varices	961 (74.8%)	3.7 (1.9–5.5)	
• High-risk	323 (25.2%)	30 (23.6–35.9)	

Conclusion: Use of NITs at baseline can stratify risk of variceal bleeding with good accuracy comparable to endoscopic stratification.

PO-1152

Risk stratification based on liver stiffness and platelets for decompensation events in patients with compensated cirrhosis

Ning Kang¹, Ruiling He², Lili Zhao³, Zhongfang Yan⁴, Jing Gao³, Min Gao³, Li Zhou³, Ying Ma³, Chun Yan Wang³, Yifei Huang¹, Xiaoguo Li¹, Haijun Zhang¹, Dan Xu¹, Mingkai Liang¹, Fengmei Wang³, Xiaolong Qi¹, Jia Li³. ¹CHES Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; ²Department of Ultrasound, Donggang Branch the First Hospital of Lanzhou University, Lanzhou, China; ³CHES center, Department of Gastroenterology and Hepatology, Tianjin Second People's Hospital, Tianjin, China; ⁴Department of Nutriology, Tianjin Second People's Hospital, Tianjin, China

Email: qixiaolong@vip.163.com

Background and aims: Liver stiffness measurement (LSM) by transient elastography (TE) has been proved a good diagnostic performance for clinically significant portal hypertension (CSPH). LSM ≥ 25 kPa was chosen as the optimal cut-off for ruling in CSPH, and LSM ≤ 15 kPa and platelets (PLT) $\geq 150, 19L$ can be used to rule out CSPH. Our study aimed to do the risk stratification of decompensation events using LSM and PLT in patients with compensated cirrhosis.

Method: Patients with LSM and PLT were enrolled between December 1, 2015, and December 31, 2017, and then followed up for at least two years or until they experienced decompensation events (defined as ascites, upper gastrointestinal bleeding, and hepatic encephalopathy) or death. With LSM and PLT, patients were categorized as three groups: high risk group (LSM ≥ 25 kPa), low risk group (LSM ≤ 15 kPa and PLT $\geq 150, 19L$), and medium risk group (others).

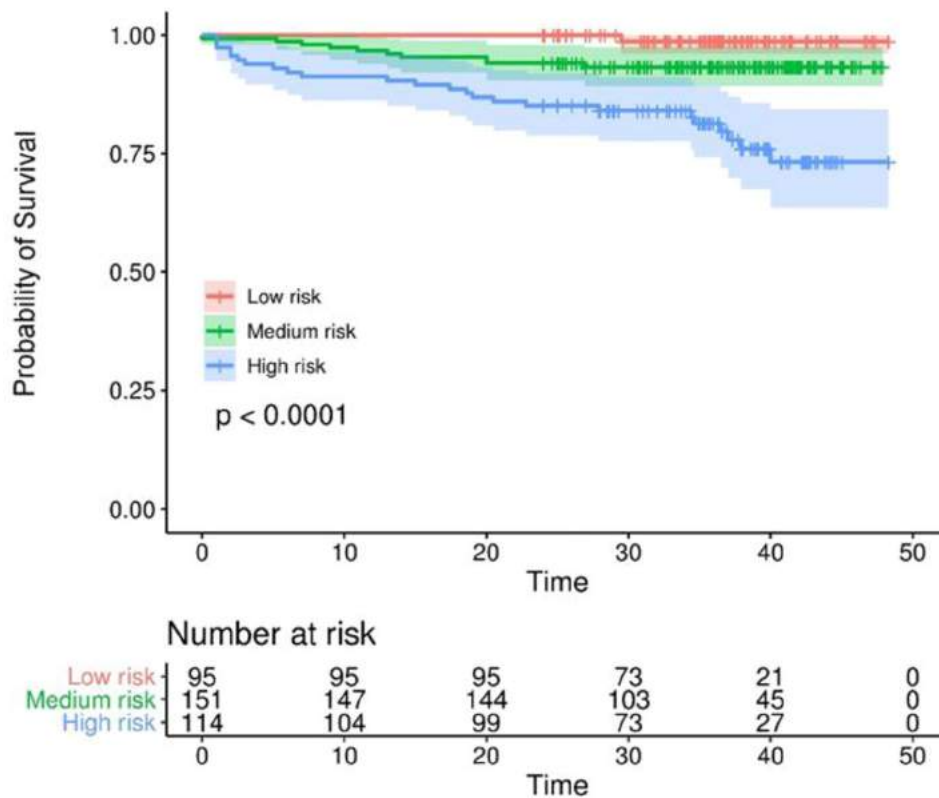


Figure: (abstract: PO-1152)

Results: A total of 360 patients with compensated cirrhosis were included in the analysis. Of them, 246 patients (68.33%) had chronic hepatitis B. The median follow-up time was 35.7 months. During the follow-up, 34 patients (9.44%) had decompensated events (including 27 cases of ascites, 5 cases of upper gastrointestinal bleeding and 2 case of hepatic encephalopathy) and 1 died. The results of univariate COX regression analysis showed that LSM combined with PLT have statistical significance in predicting the occurrence of decompensation events or death in patients with compensated cirrhosis. As the risk of group increased, the rate of decompensation events or death also increased ($p < 0.001$, hazard ratio = 3.828 [2.115–6.93]). Kaplan-Meier analysis showed that the higher risk of the group, the higher rate of decompensation events or death ($p < 0.001$). There was a trend of higher rate of decompensation events or death in the high risk group compared to that of low risk and medium risk groups ($p < 0.001$). In addition, compared with the low risk group, the medium risk group had a higher rate of decompensation events or death ($p = 0.038$) (Figure).

Conclusion: Risk stratification using LSM and PLT are with a satisfied predictive value for decompensation events or death in patients with compensated cirrhosis.

PO-1230

FIB-4 improves LSM-based prediction of clinical decompensation in overweight or obese patients with compensated advanced chronic liver disease

Yuly Paulin Mendoza¹, Mohamed Shengir², Jaime Bosch¹, Giada Sebastiani³, Annalisa Berzigotti¹. ¹Inselspital, University Hospital of Bern, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; ²McGill University, Division of Experimental Medicine, Department of Medicine, Montreal, Canada; ³McGill University, Division of Gastroenterology and Hepatology, Canada
Email: annalisa.berzigotti@insel.ch

Background and aims: Liver stiffness measurement (LSM) has an independent prognostic value in overweight/obese patients with compensated advanced chronic liver disease (cACLD). Whether the FIB-4 score predicts the first clinical complication and whether its use can improve the prognostic accuracy of LSM has not been well studied in this population.

Method: We analyzed the data of 233 overweight/obesity patients (55% with non-alcoholic steatohepatitis) with cACLD identified by LSM (LSM ≥ 10 kPa measured by XL probe), recruited from two academic centers and followed-up for a median of 17 months. We assessed the performance of FIB-4 and LSM for clinical complications using the area under the receiver operating characteristics (AUROC) and according to a pre-defined LSM cut-off (21 kPa) and to the optimized FIB-4 cut-off.

Results: Fourteen patients (6%) developed clinical complications during follow-up. FIB-4 score and LSM showed a good discriminative performance for clinical complications: AUROC FIB-4: 0.850 (95% confidence interval [CI] 0.766–0.933; $p < 0.001$); LSM: 0.767 (95% CI 0.652–0.883; $p = 0.001$; comparison: $p = 0.187$). A FIB-4 > 2.67 had a sensitivity $> 90\%$ for clinical complications. Accordingly, patients could be classified non-invasively in 4 different risk categories: LSM > 21 kPa + FIB4 > 2.67 : high-risk, LSM < 21 kPa + FIB-4 > 2.67 : intermediate-risk, LSM > 21 kPa + FIB4 ≤ 2.67 : intermediate-low Risk and LSM < 21 kPa + FIB-4 ≤ 2.67 : low risk; actuarial rates of remaining free of any complication were 25%, 73%, 96% and 100%, respectively (Log Rank $p < 0.001$) (Figure).

Conclusion: FIB-4 score helps refining the risk of developing clinical complications in overweight/obese patients diagnosed of cACLD based on LSM. Patients with FIB-4 ≤ 2.67 have an overall low risk of developing complications. Our data support the sequential use of LSM and FIB-4 score in this population.

PO-1236

Beta-blockers to prevent decompensation of cirrhosis: an emulation of the PREDESCI trial

Elliot Tapper¹, Zhe Zhao¹, James Henderson¹. ¹University of Michigan Hospital, Ann Arbor, United States
Email: etapper@med.umich.edu

Background and aims: The landmark PREDESCI trial showed that non-selective beta-blockers (NSBB) can prevent decompensation or death in patients with cirrhosis and portal hypertension but no conventional indications for NSBB. However, cirrhosis is plagued by a chasm between on-trial therapeutic efficacy and effectiveness, whereby positive trial results are sharply attenuated in real-world patients and adverse events are far more common than expected.

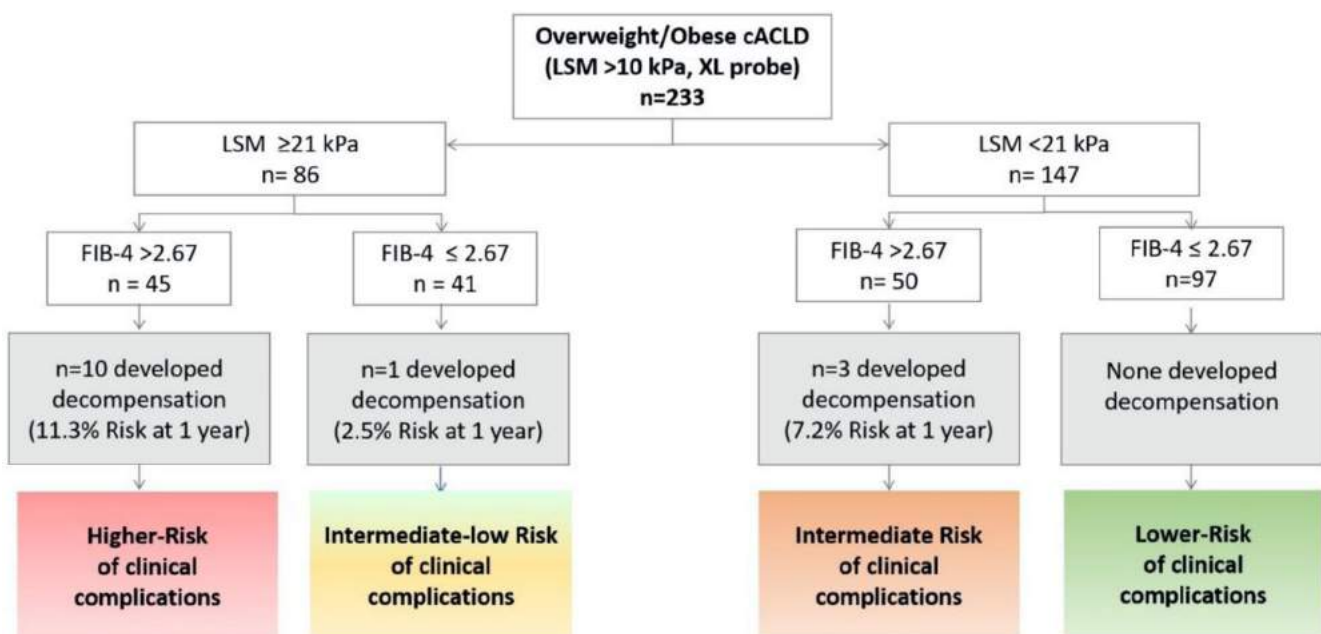


Figure: (abstract: PO-1230)

POSTER PRESENTATIONS

Method: We emulated the PREDESCI trial using observational data, recapitulating trial features by matching the inclusion/exclusion criteria, outcomes, and analytic approach to an analysis of US Medicare data. The primary outcome was time to variceal bleeding, ascites requiring paracentesis, and grade 3–4 hepatic encephalopathy (HE). We evaluated carvedilol, other NSBB (propranolol or nadolol), and, as a negative control, selective beta-blockers (SBB; metoprolol, atenolol, bisoprolol). We used a new-user, landmark design where allocation to treatment arm was defined by the first prescription within 90-days of cirrhosis diagnosis. All patients had ≥ 1 year of follow-up prior to cirrhosis diagnosis. Patients were matched 1:1 to balance baseline covariates using inverse-probability weighting.

Results: After applying PREDESCI inclusion/exclusion criteria we found 187 patients prescribed carvedilol, 713 prescribed other NSBB, 918 prescribed SBB, and 18,735 without BB prescriptions within 90-days of the index/diagnosis date. After matching there were no clinical or sociodemographic differences between treatment groups. Comorbidities were common (e.g. diabetes 17%, CHF 39%, COPD 46%) Carvedilol recipients were aged 74.1 ± 15.5 compared to 75.8 ± 1.41 among controls. Alcohol was the etiology for 31.6% vs 29.4%, NAFLD in 49.2% vs 49.2%. For carvedilol compared to control, there were no differences in the rate of incident HE (10.2% vs 8.2%), variceal bleeding (2.1% vs 4.8%), ascites (21% vs 17.6%), and mortality (21.4% vs 18.2%). Time-to-event and competing risk analysis was no different. Comparing other NSBB to control, there was a higher rate of HE, bleeding, ascites and mortality. There was no difference in outcomes for patients receiving SBB compared to control.

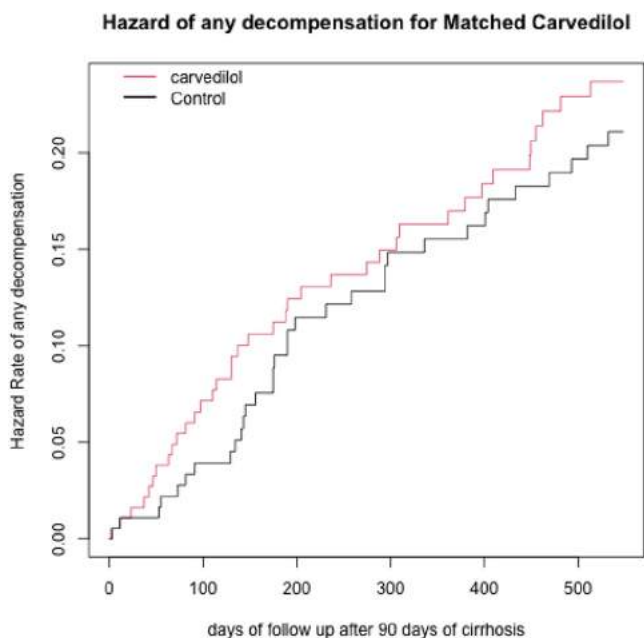


Figure:

Conclusion: PREDESCI trial data has the potential to revolutionize cirrhosis care. However, our data shows that careful patient selection is required. In our real-world trial emulation among older patients with comorbidities, NSBB do not prevent decompensation.

PO-1249

Safety of direct oral anticoagulants (DOACs) in patients with advanced liver disease

Georg Semmler^{1,2}, Katharina Pomej^{1,2}, David J.M. Bauer^{1,2}, Lorenz Balcar^{1,2}, Benedikt Simbrunner^{1,2,3}, Teresa Binter^{1,2}, Lukas Hartl^{1,2}, Jeanette Becker¹, Matthias Pinter^{1,2}, Prof. Peter Quehenberger, MD⁴, Michael Trauner¹, Mattias Mandorfer^{1,2}, Ton Lisman⁵, Thomas Reiberger^{1,2,3}, Bernhard Scheiner^{1,2}. ¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Vienna, Austria; ³Medical University of Vienna, Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Vienna, Austria; ⁴Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria; ⁵University of Groningen, Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Groningen, Netherlands
Email: thomas.reiberger@meduniwien.ac.at

Background and aims: While direct oral anticoagulants (DOACs) are increasingly used in patients with liver disease, safety data especially in advanced liver disease are limited. Therefore, the aim of this study was to evaluate (i) the safety of DOAC treatment in patients with advanced liver disease in general, (ii) the safety of DOAC treatment in liver patients undergoing procedures and (iii) to compare calibrated anti-Xa-assay levels and thrombomodulin-modified thrombin generation assays (TM-TGAs) between patients with different degrees of liver dysfunction.

Method: Liver disease patients receiving DOAC treatment between 01/2010–09/2020 were retrospectively included. Invasive procedures and bleeding events were recorded. Calibrated anti-Xa peak levels and TM-TGAs were measured in a subgroup.

Results: Among 86 patients, 43 patients (50.0%) had a history of hepatic decompensation while 76 patients (88.4%) had evidence for clinically significant portal hypertension. 44 patients (51.2%) had advanced liver dysfunction (Child-B/C) and 23 patients (26.7%) had hepatocellular carcinoma (HCC). 53 (61.6%) patients received edoxaban, 17 (19.8%) apixaban, 10 (11.6%) rivaroxaban, 2 dabigatran (2.3%) and 4 (4.6%) were sequentially treated with two drugs.

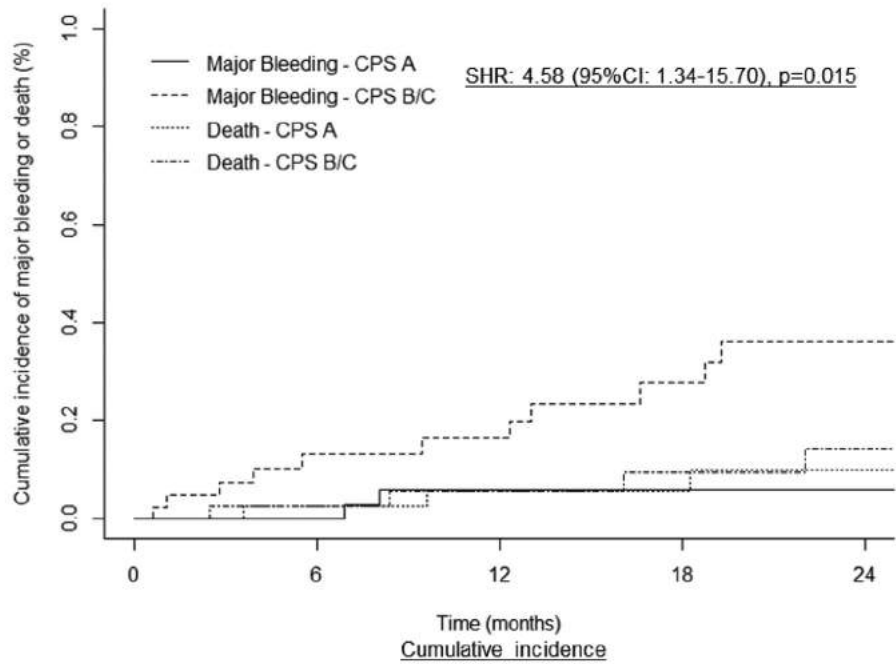
During DOAC treatment, 178 procedures (n=58 variceal band ligations; n=86 abdominal paracenteses) were performed in 42 patients and procedure-related bleedings occurred in 6 patients (3.4%). Additionally, 25 patients (29.1%) experienced spontaneous (11 minor, 14 major) bleedings. Bleedings at 6 months were more common in Child-B/C (24.6% vs. Child-A: 5.0%, subdistribution hazard ratio [SHR]: 3.97 [95%CI: 1.62–9.70], p=0.003) and HCC patients (37.0% vs. 6.8%, SHR: 2.96 [95%CI: 1.33–6.58], p=0.008). Similar results were obtained for major bleedings (Figure).

Spontaneous bleeding during DOAC treatment was associated with a worse survival (after 12 months: 76.2% with bleeding vs. 96.4% without bleeding; p=0.005). Child-Score (adjusted SHR: 1.41 [95%CI: 1.16–1.72], p<0.001) and HCC (aSHR: 3.12 [95%CI: 1.44–6.73], p=0.004) were independently associated with bleeding during DOAC treatment.

Calibrated edoxaban anti-Xa peak levels (n=35) were higher in patients with Child-B/C (345 [95%CI: 169–395] vs. Child-A: 137 [95%CI: 65–224] ng/ml, p=0.042), and were associated with lower endogenous thrombin potential (ETP) in TM-TGA (n=28; anti-Xa ≥ 100 ng/ml: ETP: 83 [95%CI: 34–605] vs. <100 ng/ml: ETP: 466 [95%CI: 281–941] nM, p=0.051).

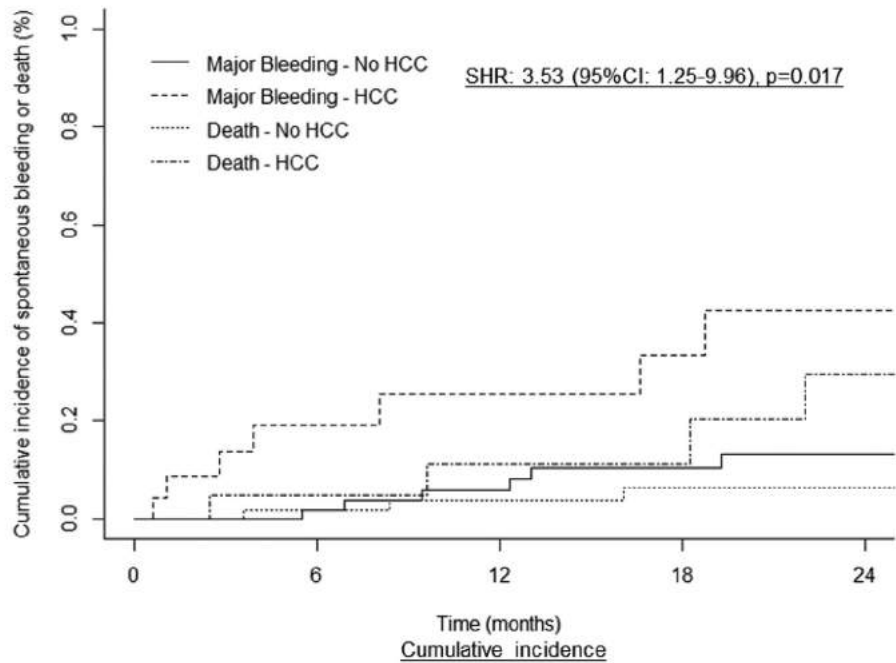
Conclusion: DOACs should be used with caution in patients with decompensated liver disease as well as patients with advanced HCC due to a significant rate of spontaneous bleeding events.

A



		0	6	12	18	24
Major Bleeding – CPS A:	0%	5.7%	5.7%	5.7%	5.7%	5.7%
Major Bleeding – CPS B/C:	13.2%	16.4%	27.7%	36.1%		
Death – CPS A:	2.6%	5.7%	5.7%	9.9%		
Death – CPS B/C:	2.6%	5.7%	9.4%	14.3%		

B



		0	6	12	18	24
Major Bleeding – No HCC:	1.9%	5.9%	10.3%	13.1%		
Major Bleeding – HCC:	19.2%	25.5%	33.5%	42.7%		
Death – No HCC:	1.8%	3.8%	6.4%	6.4%		
Death – HCC:	4.8%	11.1%	11.1%	29.6%		

Figure: (abstract: PO-1249): Competing risk analysis comparing the incidence of spontaneous major bleeding in patients with (A) CPS A vs. CPS B/C cirrhosis and (B) patients with and without hepatocellular carcinoma (HCC).

POSTER PRESENTATIONS

PO-1278

Does continuing anticoagulation increase the risk of bleeding during variceal band ligation in patients with portal hypertension? A meta-analysis and systematic review

Cheng Han Ng¹, Darren Tan¹, Jieling Xiao¹, Mark Muthiah^{1,2}. ¹Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; ²National University Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Singapore, Singapore
Email: mark_muthiah@nuhs.edu.sg

Background and aims: Anticoagulation use is often indicated in patients with portal hypertension, especially in cirrhotic patients, because of the elevated risk of developing portal vein thrombosis. However, the management of anticoagulation therapy in patients requiring variceal band ligation (VBL) for primary or secondary prevention of variceal bleeding remains unclear due to concerns regarding perioperative haemorrhagic complications and a paucity of data. Therefore, this meta-analysis and systematic review aims to evaluate the effects of continuing anticoagulation on the outcomes of VBL.

Method: Medline and Embase databases were screened for articles related to anticoagulant usage during VBL. A comparative meta-analysis was undertaken to compare outcomes associated with continuing versus stopping anticoagulation. Dichotomous outcomes were compared using odds ratio (OR) with the Mantel-Haenszel method, while continuous outcomes were evaluated using weighted mean difference (WMD). All analysis was conducted with random effects models.

Results: A total 361 patients were included for analysis, with 138 patients continuing anticoagulation during VBL. Continuation of anticoagulation was not associated with significantly increased risk of bleeding (OR: 0.84, 95%CI: 0.27–2.66, $p=0.77$) or postoperative mortality (OR: 1.16, 95%CI: 0.21–6.47, $p=0.87$) compared to patients that halted anticoagulation prior to banding sessions. There was also no significant difference in the rate of variceal recurrence or successful eradication of varices between the two groups. Additionally, the number of VBL sessions required for variceal eradication (WMD: -0.02 , 95%CI: -0.59 to -0.54 , $p=0.93$) and number of bands used per session (WMD: 0.16 , 95%CI: -0.27 to 0.60 , $p=0.46$) did not differ.

Conclusion: Results suggest that continuing anticoagulation during VBL is not associated with increased risk of adverse events, and similar rates of variceal eradication in patients with portal hypertension. Further studies are required to support these findings and confirm the safety profile of continuing anticoagulation continuation through VBL.

PO-1316

Factor VIII/protein C ratio independently predicts liver-related events but does not reflect the hypercoagulable state in patients with advanced chronic liver disease

Lorenz Balcar^{1,2}, Bernhard Scheiner^{1,2}, Rosa Johanna Nußbaumer¹, Johanna Weinzierl¹, Rafael Paternostro¹, Benedikt Simbrunner^{1,2}, Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, David J.M. Bauer^{1,2}, Albert Stättermayer^{1,2}, Georg Semmler^{1,2}, Matthias Pinter¹, Prof. Peter Quehenberger, MD³, Michael Trauner^{1,2}, Thomas Reiberger^{1,2}, Ton Lisman⁴, Mattias Mandorfer^{1,2}. ¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ³Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria; ⁴University of Groningen, Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Groningen, Netherlands
Email: mattias.mandorfer@meduniwien.ac.at

Background and aims: Thrombomodulin-modified thrombin generation assay (TM-TGA) results indicate a hypercoagulable state in patients with advanced chronic liver disease (ACLD) which may

contribute to disease progression. The ratio of procoagulant factor VIII and anticoagulant protein C (FVIII/PC) has been suggested as a simple marker that reflects the extent of hypercoagulability. Moreover, it predicted decompensation/death in a small study not accounting for HVPG.

We investigated (i) the prognostic value of FVIII/PC in a large cohort of ACLD patients and (ii) whether FVIII/PC reflects the hypercoagulable state (as assessed by TM-TGA).

Method: Patients undergoing HVPG-measurement at the Vienna Hepatic Hemodynamic Lab with evidence of ACLD and information on FVIII/PC were considered. Clinical stages (CS) were defined as follows: Probable compensated ACLD (cACLD): LSM ≥ 10 kPa and HVPG < 6 mmHg/0: cACLD and 6–9 mmHg/1: cACLD and HVPG ≥ 10 mmHg/2: bleeding/3: non-bleeding decompensation/4: ≥ 2 decompensations.

TM-TGA were assessed in a similar cohort of patients ($n=152$) from the prospective Vienna Cirrhosis Study (VICIS).

Results: (i) 518 patients were included in the prognostic sub-study; CS: probable cACLD: 36 (7%)/0:61 (12%)/1:154 (30%)/2:23 (4%)/3:130 (25%)/4:114 (22%), mean HVPG was 16 ± 7 mmHg, and mean MELD 13 ± 5 . FVIII/PC significantly increased across CS (probable cACLD: 2.1 [IQR: 1.5–2.8]/0:2.4 [1.9–3.5]/1:3.2 [2.6–4.7]/2:3.1 [2.7–3.8]/3:4.0 [3.1–5.8]/4:4.1 [3.2–6.3], $p < 0.001$) as well as HVPG ($p < 0.001$) and MELD ($p < 0.001$) strata. Additionally, FVIII/PC was predictive of outcomes (Figure) and independently associated with decompensation/liver-related mortality (e.g., aHR: 1.06 (95%CI: 1.02–1.12), $p=0.009$), even after adjusting for, e.g., CS, HVPG, hepatic dysfunction, and inflammation.

(ii) Although FVIII/PC showed a weak positive correlation with endogenous thrombin potential in TM-TGA (Spearman's $\rho=0.265$, $p=0.001$), this association completely disappeared after adjusting for severity of underlying liver disease.

Figure. Probability of remaining free of decompensation or liver-related death according to FVIII/PC quartiles.

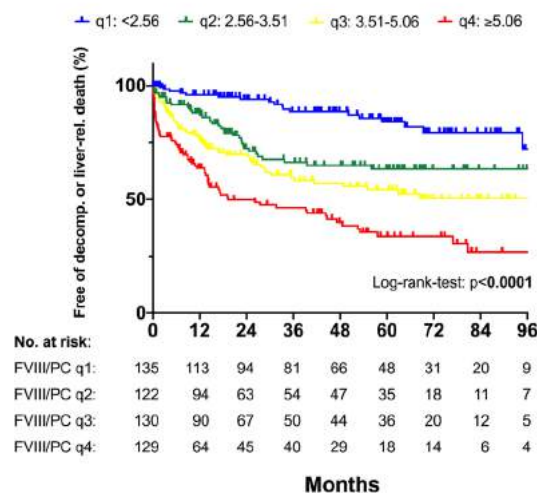


Figure:

Discussion: FVIII/PC is correlated with CS, HVPG, and liver dysfunction in ACLD. Even after extensive adjustment for potential confounding factors, it remained a robust prognostic indicator of liver-related events. Importantly, this should not be mistaken as evidence for the concept of procoagulant imbalance as a driver of disease progression, as the correlation between FVIII/PC and thrombin generation is confounded by liver disease severity, and thus, FVIII/PC does not reflect the haemostatic balance.

PO-1474

A new strategy to screen varices needing treatment via risk ranked from 0 to 100% by VARS and VANT tests

Paul Cales¹, Federico Ravaioli², Arthur Berger³, Oana Nicoara-Farcu⁴, Davide Festi², Horia Stefanescu⁴, Isabelle Cornu⁵, Pierre Nahon⁶, Christophe Bureau⁷, Nathalie Ganne-Carrié⁶, Annalisa Berzigotti⁸, Victor de Lédinghen³, Salvatore Petta⁹. ¹Angers University; ²Bologna University; ³Bordeaux University Hospital; ⁴Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca; ⁵Angers University Hospital; ⁶Paris Seine-Saint-Denis University Hospitals; ⁷Toulouse University Hospital; ⁸University of Bern; ⁹University of Palermo
Email: paul.cales@univ-angers.fr

Background and aims: The deficit in the screening of varices needing treatment (VNT) significantly impacts mortality in cirrhosis. So, improving this screening should improve the effectiveness of primary prevention of variceal bleeding. Therefore, we evaluated VNT risk factors in a population unrestricted for liver severity to improve the non-invasive screening of VNT.

Method: 2290 patients with chronic liver disease were included in a retro-prospective multicenter study. Their characteristics were: age: 59 ± 11 years; male sex: 63.5%; etiologies: virus: 50.0%, NAFLD: 29.5%, alcohol: 20.5%; BMI: 28.4 ± 5.8 kg/m²; MELD score: 9.5 ± 3.0; VNT prevalence: 14.9%. The main test descriptors were performance (spared endoscopy rate) and safety (missed VNT rate). VNT tests were evaluated either for patient diagnosis, with safety based on 95% negative predictive value, or population screening with safety based on 95% sensitivity.

Results: Independent VNT predictors were etiology, sex, platelets, prothrombin index, liver stiffness, albumin, ALT, and age or BMI through interactions. Most risk factors were then included in two new tests. First, the VANT test, designed for population screening, provided three patient categories: 1. missed VNT <5%, 2. VNT risk = 100% (new category), both resulting in spared endoscopy; 3. intermediate VNT risk: endoscopy is required. VANT outperformed (40.2%, p < 0.001) other safe tests: Baveno VI criteria (24.1%), Anticipate (24.7%), VariScreen (35.3%). VANT was secured with no missed VNT in MELD score >10. Second, the VARS score, used as score to predict VNT risk, was more discriminant for VNT (AUROC: 0.826) than published scores, e.g. Anticipate (0.771, p < 0.001). Sensitivity and specificity for VNT of VARS score reached 100%. For patient diagnosis, VARS was also used as a test to spare endoscopy by using a cut-off for 95% negative predictive value. The performance of VARS test was 62.0% vs 42.9% for the extended Baveno VI criteria (p < 0.001), also constructed for patient diagnosis, and up to 73% in NAFLD. With a 100% safety, the performance of VARS test was 12% (Figure).

Different clinical uses of tests as a function of safety criteria

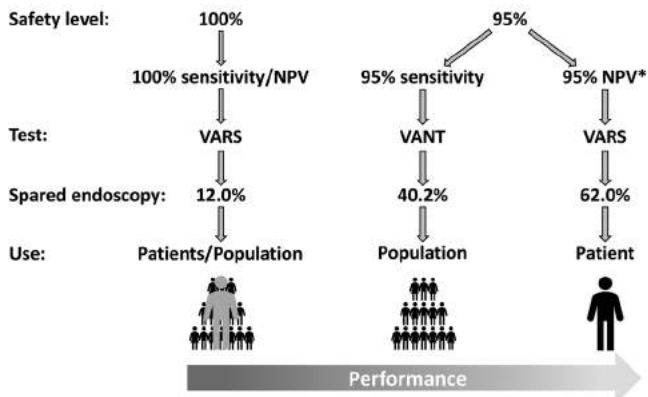


Figure:

Conclusion: VANT and VARS tests rule in or out VNT to spare endoscopies from 40% (population screening) to 62% (individual diagnosis) in main etiologies of chronic liver disease irrespective of liver severity. In addition, VARS score quantifies VNT risk from 0 to 100%. This precise prediction might improve poor compliance to VNT screening.

PO-1613

Clinical significance of substantially elevated von Willebrand factor antigen levels in patients with advanced chronic liver disease

Katharina Pomej^{1,2}, Bernhard Scheiner^{1,2}, Lorenz Balcar^{1,2}, Rosa Johanna Nußbaumer¹, Johanna Weinzierl¹, Rafael Paternostro¹, Benedikt Simbrunner^{1,2}, Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, David J.M. Bauer^{1,2}, Georg Semmler^{1,2}, Albert Stättermayer^{1,2}, Matthias Pinter¹, Michael Trauner^{1,2}, Prof. Peter Quehenberger, MD³, Thomas Reiberger^{1,2}, Mattias Mandorfer^{1,2}. ¹Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Laboratory, Vienna, Austria; ³Medical University of Vienna, Department of Laboratory Medicine, Vienna, Austria
Email: mattias.mandorfer@meduniwien.ac.at

Background and aims: VWF is increasingly used as a non-invasive marker for clinically significant portal hypertension (HVPG ≥ 10 mmHg) and also confers HVPG-independent prognostic information. While quantification of increased VWF levels is not relevant in the context of von Willebrand disease (i.e., the main indication for VWF testing), highly elevated VWF may be of clinical significance in ACLD. Thus, we have modified our analytical approach to quantify very high VWF levels (i.e., >420%) and investigated their prognostic value.

Method: Patients undergoing HVPG-measurement at the Vienna Hepatic Hemodynamic Lab with evidence of ACLD and information on VWF were considered. Clinical stages (CS) were defined as follows: Probable compensated ACLD (cACLD): LSM ≥ 10 kPa and HVPG < 6 mmHg; 0: cACLD and 6–9 mmHg; 1: cACLD and HVPG ≥ 10 mmHg; 2: bleeding; 3: non-bleeding decompensation; 4: ≥2 decompensations.

VWF was measured by an immuno-turbidimetric assay (STA LIATEST VWF:Ag) on a STA-R Evolution (both DIAGNOSTICA STAGO S.A.S., Asnières sur Seine, France) analyzer. In order to quantify values >420%, the respective samples were prediluted 1:20 with Owren-Koller buffer.

Results: 125 (16%) of 779 included patients had VWF > 420%. The proportion of VWF > 420% increased with disease severity (probable cACLD-0:5 (4%) vs. 1:22 (10%) vs. 2–4:98 (23%), p ≤ 0.001) as well as across HVPG (Figure) and MELD (<10:17 (6%) vs. 10–14:27 (10%) vs. ≥15:80 (35%), p ≤ 0.001) strata. Moreover, patients with VWF > 420% showed higher levels of CRP (0.9 (IQR: 0.4–1.5) vs. 0.2 (0.1–0.6) mg/dL, p ≤ 0.001) as a marker of systemic inflammation.

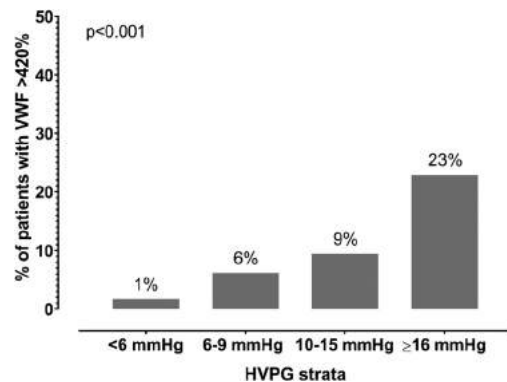


Figure:

POSTER PRESENTATIONS

Median VWF was 532% (IQR: 462–611) in the subgroup of patients with >420% and VWF was unrelated to HVPG (Spearman's $\rho = 0.140$, $p = 0.119$), but showed direct correlations of weak/moderate strength with MELD ($\rho = 0.337$, $p < 0.001$) and CRP ($\rho = 0.291$, $p = 0.001$). Among patients with VWF >420%, VWF was predictive of decompensation/liver-related mortality in univariate analysis (per 10%; HR: 1.02 (95%CI: 1.00–1.04), $p = 0.025$), however, this association did not attain statistical significance after adjusting for MELD.

Conclusion: The proportion of patients with substantially elevated VWF values (i.e., >420%) steadily increases with disease progression and is particularly high in patients who have profound portal hypertension. While VWF is not reflective of HVPG in these patients, it is correlated with hepatic dysfunction and systemic inflammation. Although the quantification of these high values provides prognostic information (i.e., there was no evidence of a ceiling effect), the lack of an association with clinical outcomes in MELD-adjusted analysis questions their relevance.

PO-1705

Application of a machine learning model to improve performance of endoscopic classification for prediction bleeding in patients with compensated cirrhosis with esophageal varices

Samagra Agarwal¹, Sanchit Sharma¹, Manoj Kumar², Shantan Venishetty², Ankit Bhardwaj², Kanav Kaushal¹, Srikanth Gopi¹, Srikant Mohta¹, Deepak Gunjan¹, Shiv Kumar Sarin², Anoop Saraya¹. ¹AIIMS Hospital, Gastroenterology and Human Nutrition Unit, New Delhi, India; ²Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India
Email: ansaraya@yahoo.com

Background and aims: Current endoscopic classification does not stratify and predicts variceal bleeding (VB) in all patients with compensated cirrhosis with esophageal varices (EVs). We aimed to supplement it with a novel machine learning (ML) model for prediction of VB

Method: In a retrospective analysis, data from patients of compensated cirrhosis with EVs, laboratory investigations and liver stiffness measurement (LSM) was used to generate an Extreme-gradient boosting (XGBoost) algorithm to predict the risk of VB. The performance characteristics of combination of ML and endoscopic classification were compared with the endoscopic classification alone and was assessed in internal and external validation cohorts

Results: Eight hundred and twenty eight patients of compensated cirrhosis with EVs, predominantly related to non-alcoholic fatty liver disease (28.6%), alcohol (23.7%) and hepatitis B (23.1%) were included, with 455 (55%) having the high-risk varices. Over a follow-up of 24 (12–43) months, 163 patients developed VB. Machine learning (ML) model had good performance characteristics to predict VB events with 85–99% accuracy in derivation (n = 497), internal validation (n = 149) and external validation (n = 182) cohorts. In combination with EGD based stratification, the model identified a “true high-risk” group with 1-year and 3-year bleed rates of 31–43% and 64–85%, respectively and a “true low-risk” group with 1-year and 3-year bleed rates of 0–1.6% and 0–3.4%. SHapley Additive exPlanations analysis showed endoscopic classification and LSM to be the major determinants of performance of the model.

Table: Comparison of performance characteristics of machine learning model applied to derivation and validation cohorts, and endoscopic classification applied to whole cohort

	Endoscopic classification alone (n = 828)	Machine Learning Model (XGboost)		
		Derivation Cohort (n = 497)	Internal Validation cohort (n = 149)	External Validation Cohort (n = 182)
Accuracy	0.589	0.987	0.939	0.857
95% CI	(0.555–0.623)	(0.974–0.995)	(0.888–0.972)	(0.821–0.905)
No	0.803	0.789	0.839	0.813
Information Rate (NIR)				
P value	1.0	<0.001	<0.001	0.043
[Accuracy >NIR]				
Kappa	0.225	0.963	0.736	0.441
Sensitivity	85.2%	94.3%	62.5%	41.2%
Specificity	52.4%	100.0%	100%	95.9%
Positive Predictive Value	30.5%	100.0%	100%	70.0%
Negative Predictive Value	93.6%	98.5%	93.2%	87.6%
Incidence of variceal bleed	19.7%	21.1%	16.1%	18.6%

Conclusion: Application of ML model in combination with EGD predicts VB more accurately than EGD alone in patients with compensated cirrhosis with esophageal varices

PO-1987

Carvedilol improves risk of decompensation and survival in compensated cirrhosis. A competing-risk meta-analysis of individual patient data

Candid Villanueva^{1,2}, Ferran Torres^{3,4}, Hasnain A. Shah⁵, Dhiraj Tripathi⁶, Shiv Kumar Sarin⁷, Anna Brujats¹, Susana G. Rodrigues⁸, Zahid Azam⁹, Peter Hayes¹⁰, Ankit Bhardwaj¹¹, Shahab Abid⁵, Ankur Jindal⁷, Edilmar Alvarado^{1,2}, Jaime Bosch^{2,8}. ¹Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIB Sant Pau). Universitat Autònoma de Barcelona, Barcelona, Spain; ²Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd). Instituto de Salud Carlos III; ³Medical Statistics Core Facility, IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain; ⁴BioStatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁵Section of Gastroenterology, Aga Khan University Hospital, Karachi, Pakistan; ⁶Liver Unit, NIHR Birmingham Biomedical Research Centre, Institute of Immunology and Immunotherapy. University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, United Kingdom; ⁷Hepatic Hemodynamic Laboratory, Departments of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India; ⁸Department of Biomedical Research, University of Bern and University Clinic for Visceral Surgery and Medicine, Inselspital, Bern University, Bern, Switzerland; ⁹National Institute of Liver and GI Diseases, Dow University of Health Sciences, Karachi, Pakistan; ¹⁰Department of Hepatology, The Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; ¹¹Clinical Research, Institute of Liver and Biliary Sciences, New Delhi, India
Email: cvillanueva@santpau.cat

Background and aims: Non-selective β -blockers can prevent decompensation of cirrhosis. However, a survival benefit has not been demonstrated. Carvedilol might be particularly adequate in early compensated cirrhosis. It has intrinsic vasodilator activity and may ameliorate hepatic vascular resistance, a relevant mechanism of

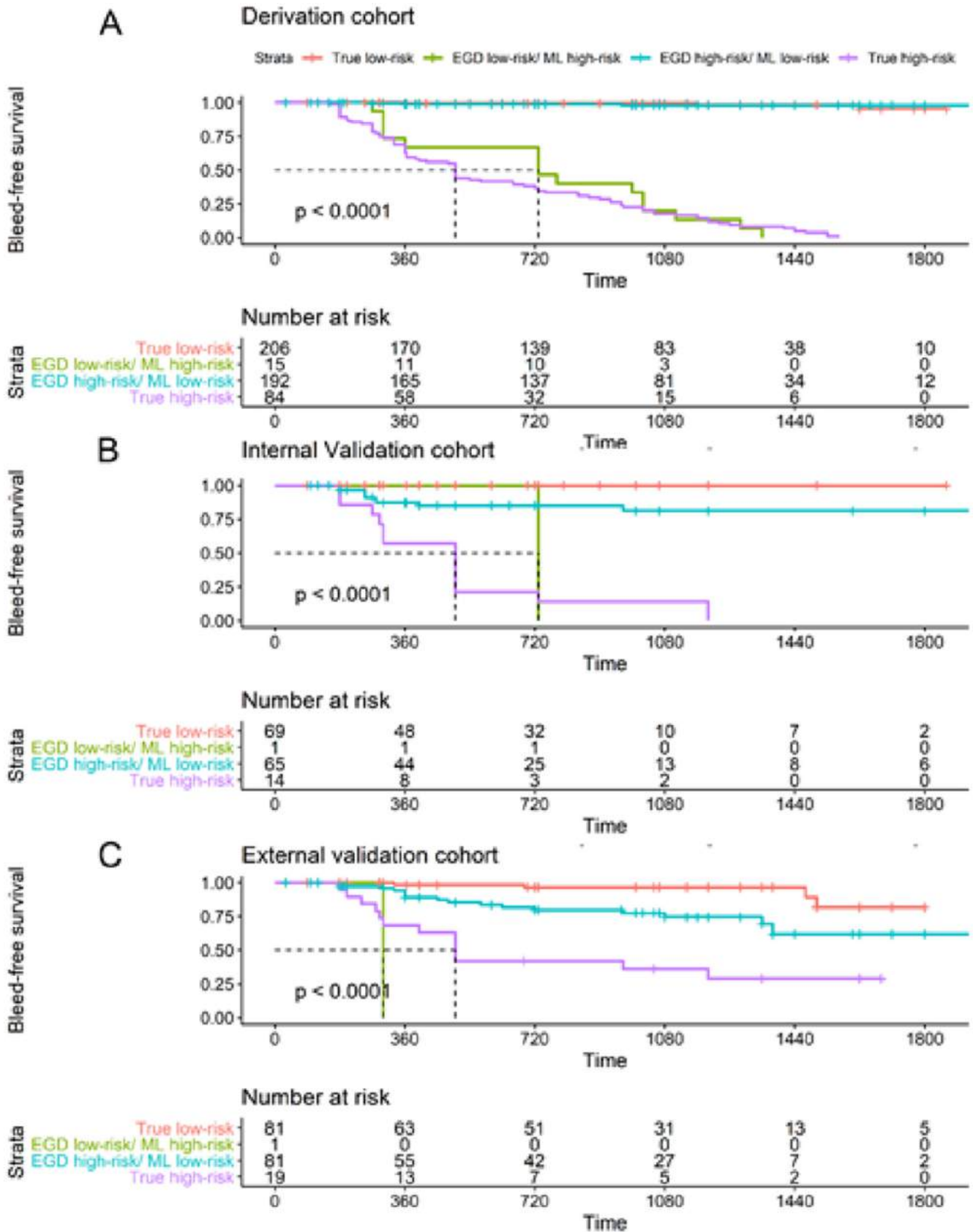


Figure: (abstract: PO-1705): Kaplan-Meier plots demonstrating bleed-free survival in patients stratified according to combination of endoscopic and machine learning (ML) classification in derivation (Figure-A) and internal/external validation cohorts (Figure-B and C).

POSTER PRESENTATIONS

portal hypertension (PH) in early cirrhosis. Carvedilol has greater HVPG-decreasing effect than traditional- β -blockers. Our aim was to assess whether carvedilol may prevent decompensation of cirrhosis and may improve survival in compensated cirrhosis with clinically significant PH (CSPH).

Method: By systematic review we identified RCTs comparing carvedilol vs control therapy (no-therapy, placebo or EVL) for primary or pre-primary prevention of bleeding in cirrhosis and CSPH. We performed a competing-risk time-to-event meta-analysis using individual patient data (IPD) obtained from principal investigators of RCTs. Only compensated patients were included. Primary outcomes were prevention of decompensation (competing-events: OLT and death) and death (OLT was competing-event). Adjusted models for risk evaluation were built using propensity score for baseline covariates using the Inverse Probability of the Treatment Weights (IPTW) approach.

Results: Among 125 full-text studies evaluated, 5 RCT were eligible for meta-analysis and 4 were finally included (no data was provided from 1). Overall, 352 patients with compensated cirrhosis were included, 181 treated with carvedilol and 171 controls (79 received EVL and 92 placebo). There were no major differences in baseline characteristics between groups and standardized differences were <10% by IPTW. The risk of developing decompensation was lower in patients treated with carvedilol than in controls (SHR = 0.506, 95% CI = 0.289–0.887, $P = 0.017$; $I^2 = 0.0\%$), with a significant reduction on the risk of ascites (SHR = 0.491, 95%CI = 0.247–0.974, $P = 0.042$; $I^2 = 0.0\%$). The risk of death was also lower with carvedilol than in controls (SHR = 0.417, 95%CI = 0.194–0.896, $P = 0.025$; $I^2 = 0.0\%$). The benefit of therapy with carvedilol was consistent across prespecified subgroups, reflecting etiology, liver dysfunction, presence of varices, age and control therapy.

Conclusion: In patients with compensated cirrhosis and CSPH, long-term therapy with carvedilol not only prevents decompensation of cirrhosis but improves survival. The study suggests a beneficial clinical effect from screening patients with compensated cirrhosis for CSPH to start carvedilol therapy.

PO-2136

Clinical decompensation and outcomes in patients with biopsy proven cirrhosis and a hepatic venous pressure gradient ≤ 10 mm Hg

Ankur Jindal¹, Manoj Kumar¹, Guresh Kumar¹, Shiv Kumar Sarin¹.

¹Institute of Liver and Biliary Sciences, New Delhi, India, India

Email: shivsarin@gmail.com

Background and aims: Clinically significant portal hypertension (CSPH), defined by hepatic venous pressure gradient (HVPG) >10 mmHg predicts clinical decompensation (CD) in compensated cirrhosis. A proportion of cirrhotics at presentation have HVPG ≤ 10 mmHg despite presence of varices and CD. Their natural history and clinical spectrum is largely unknown.

Method: Consecutive patients with HVPG ≤ 10 mmHg and biopsy proven cirrhosis ($n = 196$) or LSM > 15 kPa ($n = 65$) were included. Patients with non-cirrhotic portal hypertension were excluded. We analyzed the patterns and predictors of CD at presentation and follow-up, HVPG response to carvedilol and survival outcomes.

Results: Of 261 patients, 129 (49.4%) patients had CD at first presentation. The most common CDs were ascites ($n = 77$) and jaundice ($n = 65$). 78 patients had single CD and 51 patients had ≥ 2 CD. Each mmHg change in HVPG increased chances of CD by 72%. Baseline HVPG > 7.5 [OR: 1.7; $p = 0.002$], presence of esophageal varices [OR: 3.9; $p = 0.024$] and serum albumin < 3.2 [OR: 0.04; $p < 0.001$] were independently associated with CD. 14.4% patients developed new CD after a median duration of 23.1 months. Despite comparable baseline HVPG, higher follow-up HVPG was recorded in patients with new CD (15.3 ± 3.7 vs. 8 ± 2 mm Hg; $p < 0.001$). LSM > 26.6 kPa [OR: 1.1], presence of portosystemic shunt (s) [OR: 4.4] and serum albumin [OR: 0.27] at baseline predicted new CD. Overall

HVPG response ($>10\%$ reduction) ($n = 60$) was 23%, higher with HVPG $> 8-10$ mmHg (33.3% vs 15.2%; $p = 0.05$) but it did not influence survival. 5-year mortality was higher in patients with ≥ 2 CD [23.5%] compared to single and no CD [10.2% and 3% respectively; $p < 0.001$]. Neither HVPG nor LSM predicted higher mortality. Presence of ascites [HR: 2.75, $p = 0.05$], HE [HR: 8.76; $p < 0.001$] and new CD on follow-up [HR: 6.84; $p < 0.001$] were independent predictors of 5-y mortality.

Table: Comparison of patients based on HVPG groups

	HVPG 6–8 mmHg (n = 146)	HVPG > 8 to 10 mmHg (n = 115)	P value
Alcoholic cirrhosis	16 (11)	22 (19.1)	0.03
Viral cirrhosis	51 (34.9)	21 (18.3)	0.02
Esophageal varices	50 (34.2)	60 (52.2)	0.006
Platelet count ($\times 10^3/\text{cu. mm}$)	150 (93–195)	115 (82–160)	0.002
Serum albumin (g/dl)	3.4 + 0.67	3.09 + 0.54	<0.001
LSM (kPa)	25.26 + 14.68	30.2 + 16.78	0.012
Portosystemic shunt	17 (11.6)	13 (11.3)	NS
Ascites	26 (17.8)	46 (40)	<0.001
Jaundice	22 (15.1)	46 (40)	<0.001
HE	4 (2.7)	18 (15.7)	<0.001
Variceal bleed	7 (4.8)	11 (9.6)	NS
New CD on follow-up	27 (18.5)	24 (20.9)	NS

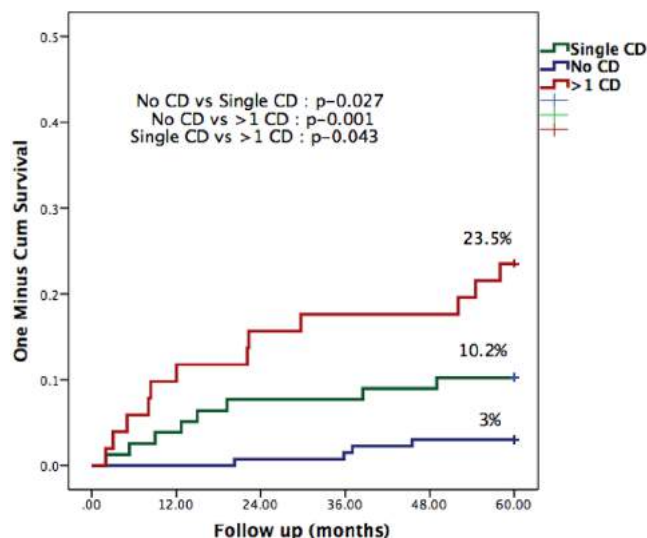


Figure: 5-year mortality in cirrhotics with HVPG ≤ 10 based on baseline clinical decompensation

Conclusion: Nearly one-half of cirrhotics with HVPG ≤ 10 mmHg had clinical decompensation and indicates need to reassess and reduce the level of defining CSPH. Early interventions to reduce portal pressure in patients with HVPG > 8 mmHg may improve long-term outcomes.

PO-2162

Value of Hitachi Shear Wave Elastography (SWE) to rule-in and rule-out the presence of esophageal varices in patients with compensated advanced liver disease

Simona Bota¹, Marcel Razpotnik¹, Christian Urak¹, Florian Hucke², Markus Peck-Radosavljevic¹. ¹Klinikum Klagenfurt am Wörthersee, Department of Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology and Nephrology and Emergency Medicine (ZAE) with Centralized Endoscopy Service, Klagenfurt, Austria; ²Department of Internal Medicine and Gastroenterology (IMuG), Hepatology, Endocrinology, Rheumatology and Nephrology and Emergency Medicine (ZAE) with Centralized

Endoscopy Service, Klagenfurt, Austria
 Email: bota_simona1982@yahoo.com

Background and aims: Liver stiffness (LS) assessed by Transient Elastography (TE) in combination with platelet count was introduced in the Baveno VI consensus to guide the need of screening gastroscopy for esophageal varices in patients with compensated advanced liver disease (cALD). According to the Baveno VI consensus, patients with an LS <20 kPa and platelet count >150,000 cells/mm³ have a very low risk for esophageal varices, and screening gastroscopy can be avoided safely. We aimed to assess the value of the Hitachi SWE to rule-in and rule-out the presence of esophageal varices in patients with cALD.

Method: LS was measured with Hitachi SWE (Arietta V70) and Transient Elastography (TE) (FibroScan®, Echosens, France). Reliable LS measurements with both methods were defined as the median value of ten valid measurements with an IQR/Med < 30% and expressed in kilopascals (kPa).

Recent gastroscopy (not older than six months) had been conducted in all patients.

Results: Our cohort included 195 patients with chronic liver diseases and different degrees of liver fibrosis, of which 107 were diagnosed as cALD (mean age 57.3 ± 12.4 years, 69.1% men). The most common etiology was alcohol use (50.4%). Esophageal varices were diagnosed in 43.9% of these patients.

The best predictive LS cut-off value by Hitachi SWE for the presence of F4 fibrosis was >8.7 kPa (Se 94.4%, Sp 92.5%, AUC = 0.965).

The rate of reliable measurements was 100% for Hitachi SWE and 94.3% for TE.

None of the patients with esophageal varices had LS assessed by TE <20 kPa and platelet count >150,000 cells/mm³, showing very good performance of the Baveno VI criteria.

LS assessed by Hitachi SWE was significantly higher in cALD cohort with esophageal varices than in those without varices: 14.1 ± 4.2 kPa vs. 11.2 ± 3.7 kPa, p = 0.0003. The best LS cut-off value assessed by Hitachi SWE for predicting the presence of esophageal varices was >11.7 kPa (Se 66%, Sp 70%, AUC = 0.742); while for a cut-off value >16.5 kPa more than 90% Sp was observed.

None of the patients with esophageal varices assessed by Hitachi SWE had LS < 11.7 kPa and platelet count >150,000 cells/mm³, demonstrating a very good performance to rule out the presence of esophageal varices.

Rule-in esophageal varices performance of LS assessed by Hitachi SWE and platelets count was significant lower. When both criteria (LS > 16.5 kPa, platelet count <150,000 cells/mm³) were fulfilled, a significantly higher positive predictive value (PPV = 76.9%, 10/13 patients) was calculated to rule-in esophageal varices compared to the presence of one criterion only (PPV = 57.3%, 47/82 patients)

Conclusion: LS assessed by Hitachi SWE combined with platelet count seems to be a reliable method to rule-out the presence of the esophageal varices in cALD patients, comparable to what can be achieved with LS through TE. To rule-in varices, the performance is significantly lower.

PO-2238

Influence of Shunt occlusion on Organ Functions in Hyperammonemic patients with Cirrhosis having Porto-systemic Shunt: a randomized controlled trial

Amar Mukund¹, Shakti Choudhury², Tara Prasad Tripathy¹, Venkatesh Hosur Ananthashayana¹, Vinod Arora², Vijayraghavan Rajan², Shiv Kumar Sarin². ¹*Institute of Liver and Biliary Sciences, Intervention Radiology, New Delhi, India;* ²*Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India*
 Email: dramarmukund@gmail.com

Background and aims: Cirrhosis patients with large spontaneous portosystemic shunts (SPSS) present with recurrent hepatic encephalopathy (HE) or gastric variceal bleeding. These shunts also deprive the liver of portal blood rich in nutrients and regenerative factors.

Plug-Assisted Retrograde Transvenous Obliteration (PARTO) of these shunts redirects the portal blood towards the liver. We evaluated the long-term effects of PARTO on change in the liver volume and functional status.

Method: Patients having SPSS with recurrent HE were randomized to receive standard medical treatment (SMT, control group) or shunt occlusion. SMT included, management of complications of decompensated cirrhosis, including HE, hyperammonemia and nutrition. Patients of both groups were evaluated for any change in the total liver volume (on CT volumetry). Clinical outcomes, MELD-Na, plasma ammonia levels and T scores in DEXA for bone density were analysed.

Results: Out of 40 patients in the study population, NASH (18, 45%) and alcohol associated (11, 27.5%) cirrhosis were commonest. The most common SPSS types were gastrosplenic shunts (n = 17, 42.5%) followed by splenoportal shunts (n = 11, 27.5%), paraumbilical vein (n = 6, 15%), gastrosplenoportal shunts (n = 3, 7.5%). The indications of PARTO were recurrent HE in 13 (65%) patients and large gastric varices with hyperammonemia in the rest. PARTO was successful in all the patients and all patients showed resolution of symptoms and clinical improvement within 7 days. The plasma ammonia levels improved post-PARTO shunt closure from 198 ± 99 to 107 ± 47 µ/dl (p = 0.001) whereas this remained unchanged in the SMT group [145 ± 70.5 to 157.8 ± 50.03 µ/dl, p = 0.139]. The mean serum albumin pre and post PARTO shunt closure [2.5 ± 0.6 and 2.8 ± 0.4 respectively] was significantly higher than control group [2.9 ± 0.4 and 2.6 ± 0.4 respectively] (p value <0.05). Post-PARTO shunt closure, there was a significant increase in liver volume (18 of 20 patients, p = 0.03), reduction in MELD-Na score (p = 0.03), plasma ammonia level (16 of 18 patients, p = 0.001) and improvement in DEXA-T scores (7 of 11 patients, p = 0.01). There was a 10.8% increase in the total liver volume from pre-procedure (mean volume = 1064 ± 368cc, median ± IQR = 968 ± 534) to post-procedure (mean volume = 1179 ± 375cc, median ± IQR = 1028 ± 510), providing an average 10.8% (difference of mean volume = 61cc) increase in mean liver volumes. On the other hand, there was a significant decrease in liver volume in SMT/control group on follow-up CT (14%, p = 0.003).

Conclusion: Large SPSS in cirrhotic patients diverts the mesenteric flow away from liver and can lead to a progressive reduction in the liver volume. The closure of such shunts by PARTO, besides reducing the incidence of HE and plasma ammonia levels, achieves about 10% increase in hepatic volume and synthetic functions.

PO-2294

Prognostic impact of Hepatic venous pressure gradient cut-off of 10 mm Hg to predict clinical decompensations in patients with compensated cirrhosis with liver stiffness above 25 kilopascals

Ankur Jindal¹, Sanchit Sharma², Samagra Agarwal², Manoj Kumar¹, Anoop Saraya², Shiv Kumar Sarin¹. ¹*Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India;* ²*AIIMS Hospital, Gastroenterology and Human Nutrition Unit, New Delhi, India*
 Email: shivsarinarin@gmail.com

Background and aims: Hepatic venous pressure gradient (HVPG) > 10 mmHg is an important predictor of clinical decompensations in patients with compensated cirrhosis. Liver stiffness measurement (LSM) is a non-invasive tool which correlates with HVPG upto 12 mmHg. We aimed to assess the predictive relevance of HVPG for clinical decompensations when stratified using LSM.

Method: Patients with compensated cirrhosis with valid measurement of baseline HVPG and LSM were retrospectively assessed for future clinical decompensations (ascites, variceal bleeding and hepatic encephalopathy). Optimal cut-offs for best diagnostic accuracy were identified and patients were stratified at cutpoints of 25 kilopascals (kPa) for LSM and 10 mm Hg for HVPG and incident clinical decompensation rates were compared

Results: 626 patients (mean age: 44.7 ± 13.5 years, 72.4% males) with compensated cirrhosis related to alcohol (30.3%), non-alcoholic steatohepatitis (26.4%), hepatitis C (16.6%), hepatitis B (10.2%) were

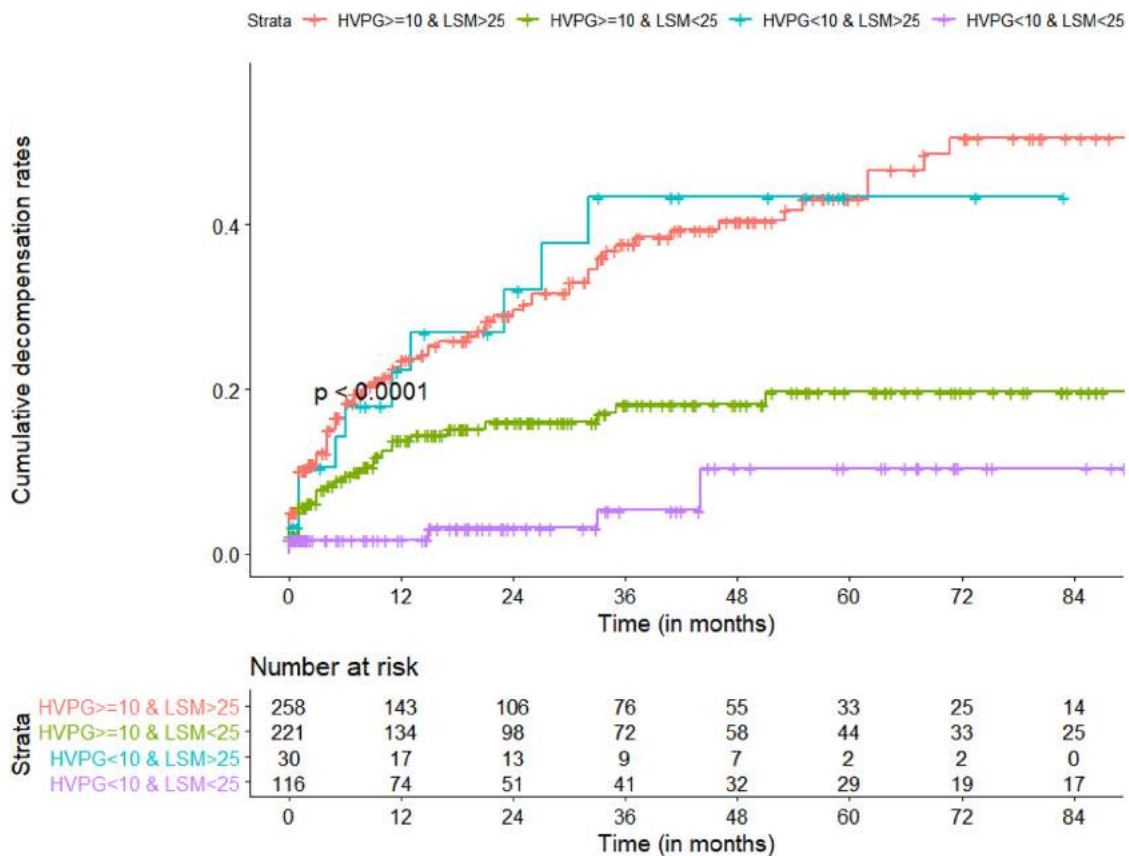


Figure: (abstract: PO-2294): Kaplan-Meier plots demonstrating clinical decompensation-free survival in patients stratified according to combination of liver stiffness measurement (LSM) of 25 kPa and hepatic venous pressure gradient (HVPG) of 10 mm Hg into different risk strata.

included. Patients were followed-up for a median duration of 26 (inter-quartile range 7–55) months over which 132 (21.0%) patients developed clinical decompensations. 1-, 3-, 5- and 7-year decompensation rates were significantly higher in patients with LSM > 25 and HVPG < 10 (22.3%, 43.4%, 43.4%, 43.4%) in comparison to those with LSM < 25 and HVPG > 10 (13.7%, 18.2%, 19.7%, 19.7%) (Log-rank test $p = 0.018$). Patients with LSM > 25 had similar decompensation rates irrespective of HVPG (Log-rank test $p = 0.99$). On univariate analysis, HVPG > 10 (Hazard Ratio 2.34 (1.79–3.05); $p = 0.001$), LSM > 25 (HR 3.16 (2.68–3.84); $p < 0.001$) and non-viral etiology (HR 1.65 (1.33–2.05); $p = 0.02$) were all significant for predicting future decompensations, however on multivariate Cox-proportional hazards model only LSM > 25 was significant (Multivariate HR 2.81 (2.30–3.43); $p < 0.001$).

Conclusion: Almost 40% patients with compensated cirrhosis and LSM > 25 kPa have follow-up clinical decompensations irrespective of HVPG, obviating the need for its measurement. However, for patients with LSM < 25 kPa, HVPG cut off of 10 mmHg is accurate to predict decompensations.

PO-2298

Prediction of cardiac outcomes post-transjugular intrahepatic portosystemic shunt placement using cirrhotic cardiomyopathy criteria

Claire Harrington¹, John Laurenzano², Nikhilesh Mazumder¹, Jing Gao¹, Anthony Borgmann², Deepakl Gupta², Lisa VanWagner³, Manhal Izzy², Justin Boike³. ¹McGaw Medical Center of Northwestern University, Chicago, United States; ²Vanderbilt University Medical Center, Nashville, United States; ³Northwestern Memorial Hospital, Chicago, United States
Email: justinboike@gmail.com

Background and aims: Transjugular intrahepatic portosystemic shunts (TIPS) have become a common treatment for the complications of portal hypertension, namely variceal bleeding, refractory ascites, and hepatic hydrothorax. Unfortunately, cardiac decompensation has been described as a serious complication after TIPS, occurring in up to 20% of patients. Despite the frequency of this complication, there is limited data available to help predict who will be at highest risk. Recently, the criteria for cirrhotic cardiomyopathy (CCM) were revised to include systolic dysfunction represented by ejection fraction (EF) < 50% (CCM-SD) and/or at least 2 diastolic dysfunction criteria (CCM-DD). The aim of this study is to evaluate the impact of CCM, per the new criteria, on cardiovascular (CV) outcomes post-TIPS.

Method: This is a retrospective cohort of 397 adult patients that underwent TIPS from two urban, tertiary hospitals between 01/2010 and 12/2015. Medical record review identified demographic, clinical, laboratory, and echocardiographic variables, when available, pre- and post-TIPS. Cardiovascular outcomes were defined as the incidence of myocardial infarction, coronary revascularization, atrial fibrillation/flutter or congestive heart failure (CHF).

Results: Among 397 patients undergoing TIPS (mean age 58.6, 62% male, 76% non-Hispanic), a total of 50 (12.6%) patients met criteria for CCM diagnosis prior to TIPS with 10 patients meeting criteria for CCM-SD and 40 for CCM-DD. Within 1 year after TIPS, 148 (37.3%) had a CV outcome. 43 patients (10.8%) developed post-TIPS CHF. The presence of CCM (OR 2.0, $p = 0.032$), increasing left atrial volume index (LAVI) (OR 1.25, $p = 0.034$ for every 10 ml/m² increase) and increasing severity of aortic stenosis (OR 2.27 for AV gradient > 20 mmHg, $p = 0.037$) were associated with CV outcomes. CCM was also associated post TIPS CHF admission (OR 2.29, $p = 0.025$).

Conclusion: The presence of Cirrhotic Cardiomyopathy, per the new criteria, in patients undergoing TIPS placement can increase the risk of both CV events and specifically CHF post-TIPS. Additional parameters, including elevated LAVI and the presence of aortic stenosis, may significantly increase the risk for post-TIPS CV events. Close follow-up post-TIPS in patients with these risk factors may be warranted.

PO-2305

Rifaximin for Prophylaxis of Post-TIPPS Hepatic Encephalopathy- A Meta Analysis

Aminah Abdul Razzack¹, Nabeel Hussain², Syed Adeel Hassan^{3,4}, Reem Gulzar⁵, Alvina Karam⁶, Priyanka Panday⁷, Prathima Guntipalli⁸, Ramya Pakala⁸, Sirisha Kumari Gara⁸. ¹Dr NTR University of Health Sciences, India; ²Saba University School of Medicine, Netherlands Antilles; ³University of Louisville, United States; ⁴University of Louisville, Department of Medicine, Louisville, United States; ⁵Fatima Jinnah Medical University for women, Pakistan; ⁶Khyber Medical College, Pakistan; ⁷Kathmandu Medical College, Nepal; ⁸Larkin Community Hospital, United States
Email: aminahrzzack1@gmail.com

Background and aims: The main drawback of transjugular intrahepatic portosystemic shunt (TIPSS) is development of hepatic encephalopathy. The effectiveness of rifaximin in preventing an episode of hepatic encephalopathy in patients who have underwent TIPSS is not well known.

To determine whether rifaximin is effective for prevention of Post-TIPSS hepatic encephalopathy when compared to placebo.

Method: Electronic databases (pubmed, Embase, Scopus, Cochrane) were searched from inception until 2nd February 2021. Unadjusted Risk ratios (rrs) were calculated from dichotomous data using Mantel Haenszel (M-H) random-effects with statistical significance to be considered if the confidence interval excludes 1 and p < 0.05. The primary outcome of interest was incidence of first episode of hepatic encephalopathy.

Results: A total of three studies with 535 participants (Rifaximin = 258; Placebo = 277) were included. Average follow-up period was 6 months. Mean age was 57.1 and 56.5 years in the rifaximin and placebo groups respectively. Patients receiving Rifaximin had lower odds of incidence of hepatic encephalopathy as compared to placebo (RR 0.69; 95%CI 0.52–0.92; p = 0.01, I² = 0). We had no publication bias in our results (Egger’s regression p > 0.05).

Conclusion: Rifaximin is superior to placebo for pharmacological prophylaxis of Post-TIPPS hepatic encephalopathy.

PO-2381

The modifications of adipose tissue and muscle mass are associated to the reduction of hepatic encephalopathy after TIPS

Stefania Gioia¹, Silvia Nardelli¹, Lorenzo Ridola¹, Ludovica Cristofaro¹, Oliviero Riggio¹. ¹Sapienza, Università di Roma, Department of translational and precision medicine
Email: stensgioia@hotmail.com

Background and aims: Sarcopenia and myosteatosis have been associated to a poor prognosis of cirrhosis and to a higher incidence of

hepatic encephalopathy (HE). Recently, aberrations in adipose tissue (high visceral adiposity and low subcutaneous adiposity) have attracted progressive substantial attention but their clinical implications and their co-incidence in cirrhotic patients are poorly investigated.

The aim of the study was to evaluate the modifications of visceral and subcutaneous adipose tissue after TIPS and to investigate their relationships with the modifications of muscle alterations and with the incidence of post-TIPS HE.

Method: 35 cirrhotic patients submitted to TIPS were studied. The modification of skeletal muscle index (SMI), muscle attenuation, subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI), assessed by CT-scan, and overt HE and plasma ammonia were evaluated before and after a mean follow-up of 19 ± 15 months after TIPS.

Results: During the follow-up, the mean SMI and muscle attenuation increased significantly; SATI significantly increased (p = 0.004) while VATI significantly decreased (p = 0.007), although not uniformly in all patients. MELD remained stable or worsened after TIPS and was not significantly different between the groups with or without improvement of the body composition. The number of episodes of overt HE during the follow-up was significantly reduced in the patients with improved SMI and in patients with improved SATI. Finally, inverse correlations were observed between delta ammonia and delta SMI (r = -0.61; p < 0.005), delta ammonia and delta SATI (r = -0.40; p < 0.05), delta ammonia and delta muscle attenuation (r = -0.40; p < 0.05).

Conclusion: Other than muscle, also adipose tissue modifies after TIPS. As confirmed for sarcopenia and myosteatosis, the improvement of subcutaneous adipose tissue was associated to the amelioration of cognitive impairment independently of liver function probably suggesting an active role of the adipose tissue in the inter-organ ammonia trafficking.

PO-2403

A single assessment of acute hemodynamic response to intravenous propranolol predicts hepatic decompensation in cirrhotic patients with portal hypertension

Benedikt S. Hofer^{1,2,3}, Benedikt Simbrunner^{1,2,3}, David J.M. Bauer^{1,2}, Rafael Paternostro^{1,2}, Philipp Schwabl^{1,2,3}, Bernhard Scheiner^{1,2}, Lukas Hartl^{1,2}, Mathias Jachs^{1,2}, Albert Stättermayer¹, Michael Trauner¹, Mattias Mandorfer^{1,2}, Thomas Reiberger^{1,2,3}.

¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Vienna, Austria; ³Medical University of Vienna, Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Vienna, Austria

Email: thomas.reiberger@meduniwien.ac.at

Background and aims: Non-selective beta-blockers (NSBB) are indicated for the prophylaxis of variceal bleeding. The acute hemodynamic response to intravenous propranolol (ivPROP-R), defined by a ≥10% decrease of hepatic venous pressure gradient (HVPG), has been shown to be associated with decreased rates of variceal bleeding and an increased probability of survival. We further



Figure: (abstract: PO-2305)

POSTER PRESENTATIONS

explored the prognostic value of ivPROP-R in patients with compensated (cACLD) and decompensated (dACLD) advanced chronic liver disease.

Method: We analyzed ACLD patients undergoing HVPG measurements with an intraprocedural assessment of ivPROP-R included in the prospective Vienna Cirrhosis Study (NCT03267615).

Results: 98 ACLD patients (mean age: 56.4 ± 11.5 years; 69.4% male; 88.8% varices; 72.4% dACLD) with a mean HVPG of 19.9 ± 4.4 mmHg were included in this study. Overall, ivPROP-R was achieved in 57 (58.2%) patients (51.9% in cACLD vs. 60.6% in dACLD; $p = 0.435$). With the exception of a lower proportion of male patients in the ivPROP-R group, there were no significant differences in baseline characteristics between ivPROP-R and non-responders (ivPROP-NR). 39/57 (68.4%) and 18/57 (31.6%) patients with ivPROP-R, as well as 25/41 (61.0%) and 16/41 (39.0%) patients with ivPROP-NR, were subsequently treated with carvedilol or propranolol, respectively. During a median follow-up of 9.6 (IQR: 6.5–18.2) months, patients with ivPROP-R demonstrated a significantly lower risk of variceal bleeding (at 12 months: 3.6% vs. 14.9%; log-rank $p = 0.038$). First/further hepatic decompensation occurred in 24.6% of patients with ivPROP-R versus 39.0% among ivPROP-NR (log-rank $p = 0.096$). Achieving ivPROP-R was independently linked to a reduced risk of first/further decompensation (adjusted HR: 0.30; 95%CI: 0.13–0.69; $p = 0.005$). Mean transplant-free survival tended to be longer in patients with ivPROP-R (34.2 (95%CI: 29.2–39.2) vs. 25.2 (95%CI: 19.8–30.6) months; $p = 0.191$). The trend towards a survival-benefit in patients with ivPROP-R seemed to be more pronounced in dACLD patients (at 12 months: 83.9% ivPROP-R vs. 66.9% ivPROP-NR; log-rank $p = 0.061$).

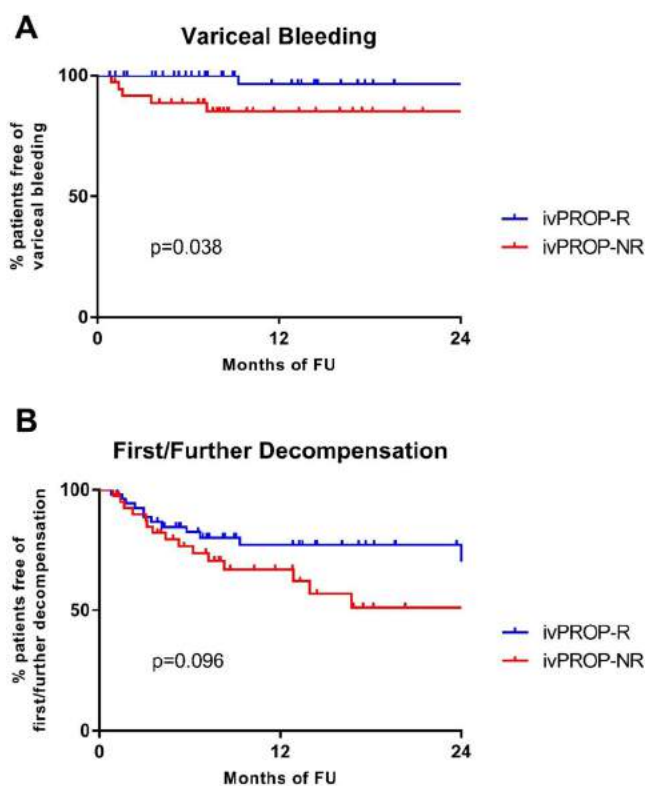


Figure:

Conclusion: A single assessment of ivPROP-R is a valuable prognostic marker in patients with ACLD, since achieving ivPROP-R was associated with a decreased risk of variceal bleeding and hepatic decompensation.

PO-2529

Effects and safety of atrial natriuretic peptide administered to cirrhosis patients with ascites: a systematic review and meta-analysis

Rasmus Hvidbjerg Gantzel¹, Mikkel Breinholt Kjær¹, Peter Jepsen¹, Niels Kristian Aagaard¹, Hugh Watson¹, Lise Lotte Gluud^{2,3}, Henning Grønbaek¹. ¹Aarhus University Hospital, Department of Hepatology and Gastroenterology, Århus N, Denmark; ²University of Copenhagen, Department of Clinical Medicine, Hvidovre, Denmark; ³Copenhagen University Hospital, Gastro Unit, Hvidovre, Denmark
Email: ragant@rm.dk

Background and aims: Atrial natriuretic peptide (ANP) is elevated in patients with cirrhosis and portal hypertension. Here, ANP undertake a physiological attempt to counterbalance anti-natriuretic factors and vasoconstriction. Since only small studies have investigated ANP in cirrhosis patients with ascites, we systematically reviewed the literature and meta-analysed results, with an aim to conclude on the effects and safety of ANP as treatment for cirrhotic ascites.

Method: We searched MEDLINE, Scopus, Web of Science, Embase, and Cochrane Library for all studies investigating an intravenous administration of ANP to cirrhosis patients with ascites. Inclusion was not limited by treatment duration or dose, nor by follow-up duration. Both RCTs and non-controlled studies were included. The primary outcome was change in renal sodium excretion. Secondary outcomes comprised change in renal water excretion, changes in plasma aldosterone concentration (PAC) and renin activity (PRA), and safety.

Results: 19 studies (215 patients) were included. Continuous ANP infusion increased sodium excretion from $5.6 \mu\text{mol}/\text{min}$ (95% CI: 3.7–7.4) at baseline to $27.0 \mu\text{mol}/\text{min}$ (95% CI: 41.5–103.5) at peak response. An infusion rate of $>30 \text{ ng}/\text{kg}/\text{min}$ induced a higher natriuretic response compared with $\leq 30 \text{ ng}/\text{kg}/\text{min}$ ($p < 0.01$). Natriuresis was more pronounced in study cohorts with mild/moderate ascites compared with moderate/severe and refractory ascites ($p < 0.01$). ANP induced an increase in water excretion, although with a less significant dose-response gradient ($p = 0.08$). Remarkably, PAC and PRA were lower in study cohorts that achieved a higher sodium balance compared with treatment non-responder study cohorts ($p < 0.01$). Finally, the most frequent complication was blood pressure falls. Infusion rates of $\leq 30 \text{ ng}/\text{kg}/\text{min}$ were in general well-tolerated, while higher infusion rates were prone to cause blood pressure falls with limited chance for recovery.

Conclusion: As the first to compile results on effects and safety of ANP in patients with cirrhotic ascites, we conclude that ANP infusions induce meaningful natriuresis, most pronounced with infusion rates of $>30 \text{ ng}/\text{kg}/\text{min}$ and in patients with mild/moderate ascites, though with higher tolerance at infusion rates of $\leq 30 \text{ ng}/\text{kg}/\text{min}$. Future pharmaceutical trials in this field are justified, and may benefit from including PAC and PRA to investigate their potential as predictors of responsiveness.

PO-2572

Achieving an effective pressure reduction after TIPS for cirrhotic patients with variceal bleeding

Xiaozhe Wang¹, Xuefeng Luo¹, Li Yang¹. ¹West China Hospital of Sichuan University, Department of Gastroenterology and Hepatology
Email: xiaozhe.wang@foxmail.com

Background and aims: The target portosystemic pressure gradient (PPG), is recommended to be less than 12 mm Hg after transjugular intrahepatic portosystemic shunt (TIPS) creation. However, there are few reports on the relevance between post-TIPS altered hemodynamics and clinical events during the follow-up since covered stents have been used. We would like to compare the outcomes of patients with portal pressure gradient (PPG) $>12 \text{ mmHg}$ and those with $\text{PPG} \leq 12 \text{ mmHg}$ after TIPS creation.

Method: Two hundred and sixteen cirrhotic patients who underwent de novo TIPS placement due to variceal bleeding between June 2015 and April 2019 in our department were retrospectively reviewed. TIPS

procedure was performed under local anaesthesia. The intrahepatic tract was dilated with an 8 × 60 mm angioplasty balloon, followed by the placement of an 8-mm Fluency ePTFE-covered stent (Bard, Murray Hill, USA). Persistent visualised collaterals on post-TIPS portography were embolised. Patients were evaluated at 1, 3, and 6 months after discharge and every 6 months until liver transplantation, death, or loss to follow-up. The primary end point was variceal rebleeding, which was defined as a single episode of clinically significant rebleeding from portal hypertensive sources.

Results: The haemodynamic success of TIPS (final PPG ≤ 12 mmHg) was not achieved in 37 patients (17.1%). In group 1 (PPG >12 mmHg), the median PPG was reduced from 27 mmHg (IQR, 25–30 mmHg) to 15 mmHg (IQR, 14–19 mmHg). In group 2 (PPG ≤ 12 mmHg), the median PPG was reduced from 20 mmHg (IQR, 17–23 mmHg) to 8 mmHg (IQR, 6–10 mmHg). The median percentage reduction of PPG was 44% (IQR, 31%–51.5%) in group 1 and 60% (IQR, 51.2%–68.5%) in group 2. There was no significant difference between group 1 and 2 in terms of 1-year probability of remaining free of variceal rebleeding (91.8% vs 90.1%), 1-year probability of hepatic encephalopathy (29.1% vs 29.5%), 1-year probability of shunt dysfunction (14.5% vs 17%) and 1-year probability of survival (91.9% vs 97.8%). In group 1, variceal rebleeding occurred in six patients. TIPS dysfunction was confirmed in each patient. Five patients received shunt revision, and one underwent endoscopic treatment. Still, three out of six patients died of variceal rebleeding after discharge. During follow-up, another three patients died due to liver failure 56, 112 and 480 days after TIPS placement, respectively.

Conclusion: In our cohort, the cumulative rates of variceal rebleeding, hepatic encephalopathy and mortality were similar between the two groups and were consistent with patients who had a final PPG ≤ 12 mmHg in previous reports. Further studies are required to assess the efficacy of a small diameter TIPS which may lead to a PPG > 12 mmHg, complemented by drugs, endoscopic or interventional procedures.

PO-2621

Fixed 8-mm diameter VCX stents do not provide clinical advantages compared to former underdilated VTS stents in cirrhotic patients treated with TIPS for refractory ascites

Sohaib Mansour¹, Arnaud Lemmers¹, Eric Trepo^{1,2}, Degré Delphine¹, Thierry Gustot^{1,2}, Christophe Moreno^{1,2}, Pierre Deltenre^{1,3}. ¹CUB Hopital Erasme, Université Libre de Bruxelles, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Anderlecht, Belgium; ²Université Libre de Bruxelles, Laboratory of Experimental Gastroenterology, Anderlecht, Belgium; ³Clinique Saint-Luc, Department of Gastroenterology and Hepatology, Bouge, Belgium
Email: sohaib.mansour@ulb.be

Background and aims: In patients with cirrhosis and refractory ascites (RA) treated with TIPS, new Viatorr controlled expansion (VCX) stents calibrated at 8 mm are designed to avoid passive expansion as opposed to conventional Viatorr TIPS Stent (VTS) for which the diameter may passively increase to 10 mm after TIPS insertion even if liver tract was underdilated at 8 mm, which may further increase portocaval shunting. We aimed to compare 1-year transplant-free survival, occurrence of hepatic encephalopathy (HE) and ascites persistence 1 year after TIPS insertion in patients with cirrhosis and RA treated either with fixed 8-mm diameter VCX stents or with VTS stents initially underdilated to 8 mm.

Method: Files of patients with cirrhosis who received TIPS for RA from 2010 to 2020 were retrospectively reviewed.

Results: 78 patients were included (32 treated with fixed 8-mm diameter VCX stents and 46 treated with underdilated VTS stents). Characteristics of patients were similar at baseline in both groups. 48 patients (62%) were male, median age was 62 years (95% CI: 57–64) and 59 patients (76%) had alcoholic-related cirrhosis. During follow-up, (median: 417 days [95% CI: 255–556]), 17 patients (5 treated with VCX stents and 12 with VTS stents) underwent stents dilatation, 42

died and 6 were transplanted. Compared to patients treated with underdilated VTS stents, patients treated with fixed 8-mm diameter VCX stents disclosed similar 1-year transplant-free survival (66%, [95% CI: 48–83%] vs. 69% [95% CI: 56–83%], p = 0.7), similar incidence of HE (50% [95% CI: 34–72] vs. 44% [95% CI: 31–63], p = 0.6), similar incidence of HE requiring hospitalization (37% [95% CI: 22–62] vs. 37% [95% CI: 24–57], p = 0.9) and similar incidence of ascites persistence (53% [95% CI: 30–75] vs. 64% [95% CI: 48–80], p = 0.7) 1 year after TIPS insertion. In multivariable analyses adjusted for age and MELD score, at 1 year, fixed 8-mm diameter stents were not associated with death or liver transplantation (HR: 1.35 [95% CI: 0.58–3.11], p = 0.5), HE (HR: 1.19 [95% CI: 0.59–2.40], p = 0.6), HE requiring hospitalization (HR: 1.04 [95% CI: 0.45–2.39], p = 0.9) or resolution of ascites (HR: 1.19 [95% CI: 0.52–2.72], p = 0.7). Exclusion of patients in whom stent was dilated during follow-up did not change the results.

Figure: Kaplan-Meier survival curves of patients with cirrhosis and refractory ascites treated with fixed 8-mm diameter VCX stents or former underdilated VTS stents

Conclusion: Fixed 8-mm diameter VCX stents were not associated with better survival or with lower rates of liver-related events than underdilated VTS stents in patients with cirrhosis and RA.

PO-2655

Splenic vein flow for non-invasive screening for esophageal varices in advanced liver disease patients

Sergii Kozlov^{1,2}, Elina Manzhali^{3,4}, Oleksandr Danylenko⁵, Oleksandr Kozlov^{5,6}, Andrii Dolot^{6,7}. ¹Bogomolets National Medical University, Surgery, Kyiv, Ukraine; ²Verum Expert Clinic, Radiology, Kyiv, Ukraine; ³Bogomolets National Medical University, Gastroenterology, Kyiv, Ukraine; ⁴Verum Expert Clinic, Gastroenterology, Kyiv, Ukraine; ⁵Bogomolets National Medical University, Kyiv, Ukraine; ⁶Verum Expert Clinic, Kyiv, Ukraine; ⁷Oberig Universal Clinic, Kyiv, Ukraine
Email: sergiinikol@gmail.com

Background and aims: Current work aimed to evaluate the prognostic value of splenic venous flow (SVF) as a possible non-invasive screening test of esophageal varices (EV) in patients with advanced liver disease (ALD). Despite esophagogastroduodenoscopy (EGD) is still the “gold standard” for revealing esophageal varices (EV) in patients with advanced liver disease (ALD), searching for an optimal diagnostic algorithm is actual. Many biochemical/elastography modalities were presented in modern literature to substitute this invasive and uncomfortable (for patients) examination. We tend to use the hemodynamic parameters of the portal system to solve the problem.

Method: Using Doppler sonography, we evaluated splenic vein flow in 377 patients; 87 of them (control group) had no varices, and 290 ALD patients had proved with endoscopy presence of EV. The mean, median and interquartile range (IQR) were calculated (we obtained abnormally distributed data), and Mann-Whitney U test was used for two groups comparisons. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUROC) were computed using EZR statistics software.

Results: Significant difference (p = 0.000, U test) of SVF was obtained in patients with ALD + EV versus control group: 1.06 l/min versus 0.32 l/min (mean), with median 0.88 l/min (IQR 0.58–1.27) versus 0.29 l/min (IQR 0.22–0.40). Area under the curve and cut-off values in the prediction model area were 0.93 and 0.55 l/min, respectively, with a sensitivity of 0.804 and specificity of 0.943 (Fig). According to literature data, the AUROCs for predicting varices using the shear method of wave elastography yielded around 0.80, which is less accurate than in the proposed model.

POSTER PRESENTATIONS

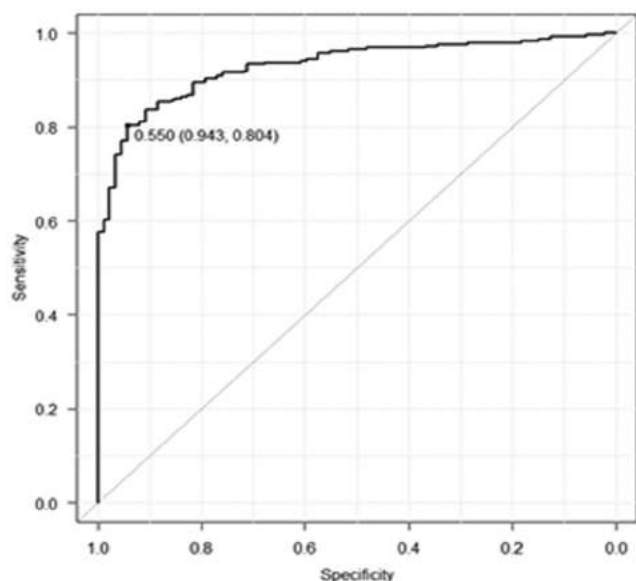


Figure: ROC of splenic vein flow in the prediction of varices revealing.

Conclusion: Splenic vein flow increases markedly in variceal patients with hepatic CSPH, and its measurement could be a helpful screening tool in selection patients who should be referred (if SVF exceeded 0.5 L/min) to endoscopy examination. Our model demonstrated more accuracy in varices prediction (AUROC = 0.93) than systems based on elastography. One more conclusion is that increased splenic vein flow plays a significant role in the pathogenesis of portal hypertension and esophageal varices formation, but further investigations are needed.

PO-2685

Using dimeric to monomeric IgA ratio to diagnose portal hypertension in liver disease: a pilot cohort study

Jessica Howell^{1,2,3}, Huy Van⁴, Tim Spelman², Minh Pham², Mary Garcia⁴, Fan Li⁴, Rohit Sawhney⁵, John Lubel⁶, William Kemp⁶, Stephen Bloom⁵, Avik Majumdar⁷, Joseph Doyle^{2,8}, Geoff McCaughan⁷, Purnima Bhat⁹, Margaret Hellard^{2,8}, Kumar Visvanathan³, Alexander Thompson^{1,3}, David Anderson⁴. ¹St Vincent's Hospital Melbourne, Gastroenterology, Fitzroy, Australia; ²Burnet Institute, Disease Elimination, Melbourne, Australia; ³University of Melbourne, Medicine, Fitzroy, Australia; ⁴Burnet Institute, Life Sciences, Melbourne, Australia; ⁵Eastern Health, Gastroenterology, Box Hill, Australia; ⁶Alfred Hospital, Gastroenterology, Melbourne, Australia; ⁷Royal Prince Alfred Hospital, AW Morrow Gastroenterology and Liver Centre, Sydney, Australia; ⁸Alfred Hospital, Infectious Diseases, Melbourne, Australia; ⁹Australian National University, Gastroenterology, Canberra, Australia
Email: jessica.howell@svha.org.au

Background and aims: Portal hypertension (PHT) diagnosis in liver cirrhosis is vital to prevent life-threatening variceal bleeding. Platelet count and transient elastography are used to triage PHT risk and endoscopy to confirm diagnosis of varices, however these tests are expensive and difficult to access in remote/low resource settings. Dimeric IgA to monomeric IgA ratio (dlgA ratio) is a potential biomarker of gut mucosal leakage present in portal hypertension. We evaluated the diagnostic performance of a novel point-of-care (POC) dIgA ratio test for PHT.

Method: BioPoint[®] POC dIgA test is an antigen immunoassay-based lateral flow test which uses 15 µL of plasma or whole blood and provides a quantitative result <20 minutes using the Axxin hand-held reader. PHT was defined as platelet count <150 and splenomegaly (liver ultrasound), or clinical evidence of portal hypertension on gastroscopy. Associations between dIgA ratio, PHT and clinical parameters were determined by linear and logistic regression. ROC analysis was used to determine diagnostic accuracy.

Results: 1407 plasma samples from 960 patients with chronic liver disease were included; 280 (29%) had cirrhosis, 121 (9%) had PHT and 21 (2%) had current varices. Median dIgA ratio was higher in patients with PHT (1.14 vs 0.4, $p < 0.001$), ascites (1.4 vs 0.7, $p < 0.001$) and hepatic encephalopathy (1.4 vs 0.82, $p < 0.001$). A POC dIgA ratio cutoff of 0.6 had good diagnostic accuracy and high NPV for PHT and varices in both the test (AUROC 0.84 and 0.83) and validation cohorts (AUROC 0.86, Table 1).

Conclusion: POC dIgA ratio test had good accuracy for the presence of PHT and varices. Given limited access to transient elastography and endoscopy in low resource settings, the high NPV of POC dIgA test for PHT in this study warrants further clinical utility and cost-effectiveness studies in low-resource settings.

PO-2788

Umbilical hernia repair in Cirrhosis: TIPS insertion improves one-year survival but not long-term outcomes

Abdullah Malik¹, Stuart Robinson¹, Gourab Sen¹, Mark Hudson¹, Derek Manas¹, Steven Masson¹, John Hammond¹. ¹Freeman Hospital, Liver Unit, High Heaton, United Kingdom
Email: abdullah.malik@nhs.net

Background and aims: Umbilical hernia occur in up to 20% patients with cirrhosis. Management is controversial with a paucity of studies. We aimed to determine outcomes and factors predicting mortality following repair of symptomatic umbilical hernia in patients with cirrhosis.

Method: Retrospective study of patients with cirrhosis undergoing repair of hernia in a single centre from 1998 to 2020. Survival following surgery was estimated using the Kaplan-Meier method, comparing use of TIPS perioperatively (TIPS vs. nTIPS). Cox proportional hazards model and logistic regression analysis were used to determine predictors of overall survival (OS) and 1-year mortality, respectively. Statistical significance was set at $p < 0.05$.

Table 1: (abstract: PO-2685) Performance of POC dimeric IgA ratio for portal hypertension (PHT)

Ratio dIgA	No PHT	PHT	Sensitivity	Specificity	PPV	NPV	AUROC	95% CI	p value
Test cohort (n = 306; 40% cirrhosis, 5% healthy controls)									
≤0.6	161	11	86%	71%	51%	94%	0.84	0.78–0.89	<0.001
>0.6	66	68							
Validation cohort (n = 652, 1097 samples; 24% cirrhosis, 3% healthy controls)									
≤0.6	875	8	80%	83%	15%	99%	0.86	0.80–0.92	<0.001
>0.6	182	32							
Presence of varices (validation cohort, 1097 samples)									
	No Varices	Varices							
≤0.6	877	6	71%	82%	7%	99%	0.83	0.73–0.93	<0.001
>0.6	199	15							

PPV, positive predictive value; NPV, negative predictive value.

Results: One-hundred and eleven patients with cirrhosis underwent hernia repair (emergency n = 81, 73%). Mortality at 30d and 1y was 4.5% and 16%, respectively. TIPS was performed in 29 patients (26%) preoperatively. Age, pre-operative bilirubin, sodium, creatinine, prothrombin time, albumin and UKELD were no different between groups ($p > 0.05$). Median overall survival was no different between TIPS and nTIPS (55 vs 64 months, respectively, $p > 0.05$). ITU admission (HR 2.7, $p = 0.002$) and pre-operative sodium < 130 (HR 3.0, $p = 0.011$) predicted long-term mortality. Predictors of mortality at one-year were age > 60 (HR 7.4 $p = 0.008$) and ITU admission (HR 8.7 $p = 0.002$). TIPS insertion (n = 29) was associated with survival at one year (OR 7.2, $p = 0.027$) but not with long-term survival ($p > 0.05$). Sixteen (14%) patients underwent transplantation.

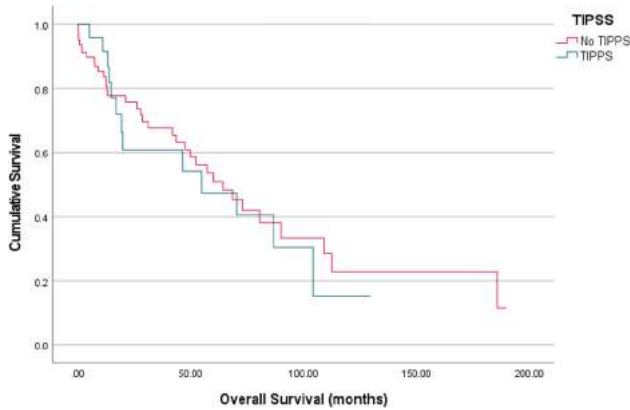


Figure:

Conclusion: Symptomatic umbilical hernias in patients with cirrhosis can be treated safely with acceptable long-term outcomes, however this remains a high risk intervention. Pre-operative sodium may identify high-risk patients, and allow appropriate counselling of such patients. TIPS may improve short-term outcomes but further prospective trials are warranted.

PO-2938

Application of surrogate end points in compensated cirrhotic patients with primary biliary cholangitis

Carla Fiorella Murillo Perez¹, Aliya Gulamhusein², Palak Trivedi³, Marilyn J. Mayo⁴, Ana Leo⁵, Pietro Invernizzi⁵, Marco Carbone⁵, Pier Maria Battezzati⁵, Tony Bruns⁶, Adriaan Van der Meer⁷, Willem J. Lammers⁷, Cyriel Ponsioen⁷, Harry Janssen², Frederik Nevens⁸, George Dalekos⁹, Nikolaos Gatselis⁹, Christophe Corpechot¹⁰, Nora Cazzagon⁵, Annarosa Floreani⁵, Albert Pares¹¹, Verhelst Xavier⁸, Andrew L. Mason¹², Douglas Thorburn³, Kris V. Kowdley⁴, Keith D. Lindor⁴, Gideon Hirschfield², Bettina Hansen². ¹Toronto general Hospital,

Toronto, Canada; ²Toronto, Canada; ³United Kingdom; ⁴United States; ⁵Italy; ⁶Germany; ⁷Netherlands; ⁸Belgium; ⁹Greece; ¹⁰France; ¹¹Spain; ¹²Edmonton, Canada
Email: bettina.hansen@utoronto.ca

Background and aims: The utility of common surrogate end points and associated thresholds used in primary biliary cholangitis (PBC) have not been assessed in cirrhotic patients, particularly those who are compensated.

Method: We included cirrhotic patients from the Global PBC Study Group Database that were diagnosed with PBC from 1990 to 2011 and treated with ursodeoxycholic acid (UDCA) for at least 1 year. Cirrhosis was established through biopsy or by clinical diagnosis. Liver biochemistry was considered baseline if within 6 months of start of follow-up. A compensated population was selected by excluding those with history of decompensation, biochemical criteria for Child Pugh-B/C (defined by 3 points in at least one or by 2 points in at least two of the following parameters: bilirubin, international normalized ratio [INR], albumin), and CP-score greater than 6, if known. Transplant-free survival was estimated with a Kaplan-Meier curve and compared between compensated and decompensated cirrhotic groups and within the compensated cirrhosis population with the log-rank test.

Results: We selected 573 patients with cirrhosis. A compensated population was selected (n = 419) after 154 patients were excluded (12 due to unknown decompensation status, 47 due to lab criteria for CP-B/C, and 95 due to prior decompensation). Their age at the start of follow-up after a cirrhosis diagnosis was 57.2 years (SD 11.4), as compared to 60.5 years (SD 11.1) in those excluded (decompensated). The 5-year transplant-free survival of those with compensated cirrhosis was 82% compared to 37% in those who were decompensated (Figure, $p < 0.001$). In patients who are compensated, those with abnormal bilirubin and ALP $> 1.67 \times$ ULN demonstrated worse transplant-free survival ($p < 0.001$ and $p = 0.01$), signaling they can also be extended to a compensated cirrhotic population.

Conclusion: The transplant-free survival of a compensated cirrhotic population is improved compared to those who are decompensated. The common surrogate end points and associated thresholds for ALP and bilirubin demonstrate utility for risk stratification in a compensated cirrhotic population.

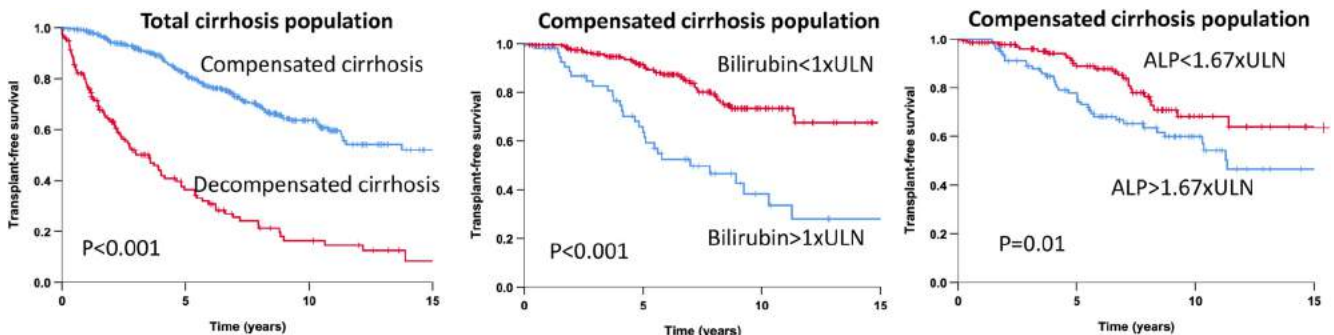


Figure: (abstract: PO-2938)

Fibrosis

PO-89

Survivin inhibition ameliorates liver fibrosis via inducing senescence in hepatic stellate cells

Sachin Sharma¹, Shaikh Maryam Ghufra¹, Sampa Ghose², Chhagan Bihari³, Subhrajit Biswas¹. ¹Amity University, ¹Amity Institute of Molecular Medicine and Stem Cell Research, Noida, Uttar Pradesh, India; ²All India Institute of Medical Sciences, Department of Medical Oncology, New Delhi, India; ³Institute of Liver and Biliary Sciences, Department of Pathology, New Delhi, India
Email: sachin.research@hotmail.com

Background and aims: Hepatic fibrosis is a wound healing response of liver during hepatic injury, characterized by activation of hepatic stellate cells (HSCs) and accumulation of extracellular matrix (ECM) proteins. The anti-apoptotic survivin is one of the regulatory factors that promotes cell division in proliferative activated HSCs. There was some clinical benefit shown in cancer by inhibiting survivin but unexplored in liver fibrosis. During fibrosis resolution, the activated HSCs converted to a less proliferative and deactivated senescence stage. In this study, we have targeted survivin protein to limit the fibrogenic activation of HSCs to ameliorate liver fibrosis.

Method: Here we targeted survivin expression through survivin inhibitor YM155 and siRNA-mediated knockdown in HSCs *in vitro*. Male Balb/c mice were treated with CCl₄ twice/week by *i.p.* injections for 6 weeks, followed by treatment with 10 mg/kg of survivin inhibitor YM155. We have analysed the ALT and AST level of mice serum to check liver injury. And sirius red, HandE and senescence-associated beta-galactosidase (SA-beta-gal) staining of liver section along with flow cytometry-based cell cycle assays were performed to

understand HSCs activation. Expression of survivin, αSMA, collagen, Ki67, p53 and p21 were examined through qPCR, western blots, immunohistochemistry and immunofluorescence.

Results: CCl₄ induced fibrotic liver shown increased survivin, collagen I and αSMA expression in peri-portal region. SA-beta-gal assay shown increased number of senescent cells in the peri-portal region. In contrast survivin inhibition in fibrotic liver not only reduced ALT, AST level in mice serum but also decreased αSMA, collagen and other extracellular matrix proteins. siRNA mediated knockdown of survivin in HSCs induced G2/M cell cycle arrest and became multinucleated. Immunohistochemistry and immunofluorescence results showed overexpression of p53 and p21 in HSCs after survivin inhibition. Lower expression of proliferative marker Ki67 and overexpression of SA-beta-gal in both activated HSCs and fibrotic peri-portal region with YM155 treatment confirmed senescence mediated deactivation of HSCs and regression of fibrosis *in vivo*.

Conclusion: Targeting the overexpressed survivin in activated HSCs decreased its fibrogenic activation and induced senescence that ameliorates liver fibrosis.

PO-223

Precision-cut liver slices as a dynamic tool to model liver fibrosis in vitro

Liza Dewyse¹, Vincent De Smet¹, Hendrik Reynaert², Leo A. van Grunsven¹. ¹Vrije Universiteit Brussel, Liver Cell Biology Research Group, Belgium; ²University Hospital Brussels (UZBrussel), Gastroenterology and Hepatology
Email: liza.dewyse@vub.be

Background and aims: Chronic liver disease, including liver fibrosis, accounts for two million deaths worldwide each year. Besides causal treatments, which can slow down fibrosis progression, no anti-fibrotic liver therapies are currently available, mainly due to the lack of robust and representative *in vitro* models. The most representative

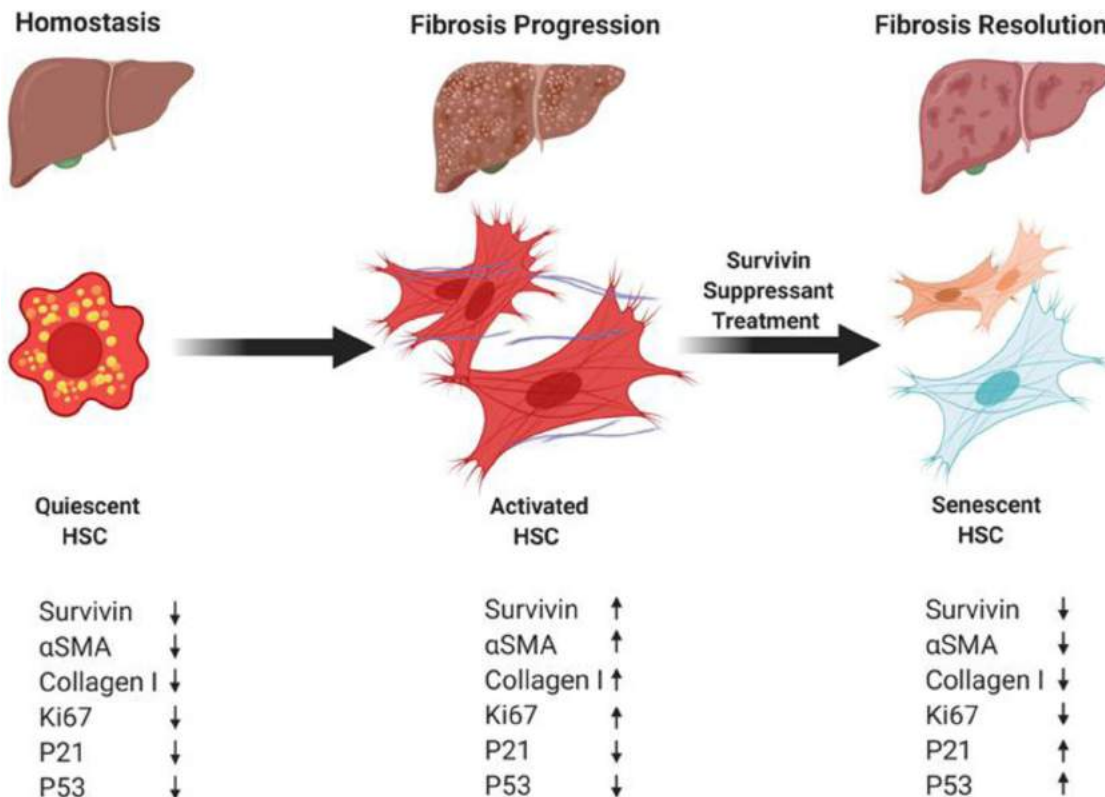


Figure: (abstract: PO-89)

in vitro model of human liver disease could be the use of precision-cut liver slices (PCLS), as these maintain the architecture and microenvironment as found in vivo. However, the major drawback of this model is that slice preparation results in cut surfaces, which eventually triggers the induction of spontaneous fibrosis progression in culture, as hepatic stellate cells (HSC) will activate within 96 hours upon slicing. The aim of this study was to establish stable PCLS cultures that allow direct and as well as hepatocyte-damage induced HSC activation in a reciprocal way (induction and inhibition).

Method: Human and mouse liver tissues were sliced with a Leica vibrating blade microtome VT1200S. Slices were eventually punched into 3 mm diameter discs (PCLS). PCLS were cultured during a period of 5 days in the presence or absence of valproic acid (VPA). RNAseq analysis was performed on PCLS cultured in the presence or absence of VPA over a time period of 5 days. In the presence of VPA, PCLS were exposed on day 3 for 48 hours to a direct trigger of 10 ng/ml TGFβ or an indirect trigger of 20 mM acetaminophen (APAP), a known hepatotoxic compound.

Results: In this study, we established stable mouse and human PCLS culture conditions demonstrating sustained viability, sustained albumin protein expression and low levels of culture-induced fibrosis for at least 5 days by the addition of VPA to the culture medium. More insight into the mechanisms by which VPA inhibits this PCLS culture-induced fibrosis will be obtained by the RNAseq analysis. Direct HSC activation could be induced by treatment with TGFβ, which could be blocked by simultaneous exposure to an Alk5 inhibitor. Hepatocyte-damage dependent HSC activation was established in mouse PCLS by the exposure of APAP. This HSC activation could be blocked by N-acetylcysteine, a compound used in the clinic to treat acetaminophen overdose or verteporfin, a YAP inhibitor. HSC activation and fibrosis induction by both compounds could be confirmed on both transcriptional and translational level.

Conclusion: The obtained results demonstrate the potential of both human and mouse PCLS as a reliable model to mimic inducible liver fibrosis. In the future, this model allows to perform mechanistic studies and offers the opportunity to model other chronic human liver diseases, such as non-alcoholic fatty liver disease or cholestasis.

PO-410

The inhibition of the YAP-1/CTGF pathway improves chronic biliary fibrosis in the Abcb4^{-/-} model by modulation of hepatic stellate cell physiology

Liangtao Ye^{1,2,3}, Andreas Ziesch^{2,3}, Andrea Ofner^{2,3}, Tobias Simon Schiergens⁴, Gerald Denk^{2,3}, Najib Ben Khaled^{2,3}, Simon Hohenester^{2,3}, Mayr Doris⁵, Ujjwal M. Mahajan^{2,3}, Ralf Wimmer^{2,3}, Alexander Gerbes^{2,3}, Julia Mayerle^{2,3}, Yulong He¹, Enrico de Toni^{2,3}, Changhua Zhang¹, Florian Paul Reiter^{2,3}. ¹Center for Digestive Diseases, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China; ²Department of Medicine II, University Hospital, LMU Munich, Germany; ³Liver Center, Department of Medicine II, University Hospital, LMU Munich, Germany; ⁴Department of General, Visceral and Transplantation Surgery, University Hospital, LMU Munich, Germany; ⁵Institute of Pathology, Faculty of Medicine, LMU Munich, Germany

Email: liangtao.ye@med.uni-muenchen.de

Background and aims: No effective medical treatment for primary sclerosing cholangitis (PSC) has yet been established. The yes-associated protein 1 (YAP-1) was shown to be a mediator of fibrosis in different models of liver fibrosis. However, the effect of YAP-1 inhibition as potential treatment of chronic biliary fibrosis has yet to be investigated. We addressed this issue by assessing: i. the expression of YAP-1 in human liver samples with non-biliary fibrosis vs. liver fibrosis in advanced PSC, ii. the function of YAP/connective tissue growth factor (CTGF) in promoting fibrogenesis in human hepatic stellate cell (HSC), and iii. the effects of YAP-1 inhibition in Abcb4^{-/-} mice.

Methods: Human liver sections were investigated by whole slide analysis after sirius red staining or immunohistochemistry for collagen 1alpha1 (col1alpha1) and alpha-smooth muscle actin (alpha-SMA). Abcb4^{-/-} mice were treated with different concentrations of Verteporfin (VP) and Metformin (MF), which were used as YAP-1 inhibitors. Primary human HSC (phHSC) and LX-2 cells were used for in vitro study. The biological effects of YAP-1/CTGF silencing by siRNA or of its inhibition by VP and MF were assessed by western blot and collagen contraction assay.

Results: Expression of YAP-1 and its downstream target CTGF were significantly higher in fibrotic liver tissues vs. non-fibrotic controls in liver samples from patients with biliary (all advanced PSC) and non-biliary fibrosis (p < 0.05; **A, B**). Treatment with VP and MF caused a significant reduction of liver fibrosis in Abcb4^{-/-} mice, as judged by quantitative analysis of sirius red, alpha-SMA and col1alpha1 staining (p < 0.05, **C-F**). This was accompanied by a reduced mRNA expression of YAP-1 (**G**) and CTGF (p < 0.05). The significantly lower alpha-SMA expression indicated a reduced activation of HSC. In phHSC, YAP-1 and CTGF increased upon spontaneous activation when seeded on uncovered plastic indicating its functional role for HSC activation. Silencing of YAP-1 and CTGF inhibited transforming growth factor beta (TGF-beta) induced alpha-SMA, platelet-derived growth factor beta (PDGF-beta) expression (**H**) and the contractility (**I, J**) of LX-2 cells.

Conclusion: We conclude that YAP-1 is a checkpoint of fibrogenesis in chronic cholestasis capable of modulating the activation of HSC, and provide evidence of VP and MF as inhibitors of biliary fibrosis. YAP-1 is therefore a potential target for treatment of chronic cholestatic liver diseases such as PSC.

PO-477

Hepatic LPI/GPR55 system regulates the development of non-alcoholic steatosis and steatohepatitis

Uxia Fernández¹, Marcos Fernandez Fondevila¹, María J. González Rellán¹, Natalia Da Silva Lima¹, Xabier Buque², Águeda González³, Teresa Cardoso Delgado⁴, Marta Varela-Rey⁴, Eva Novoa^{1,5}, Marta Tojo¹, Carlos Dieguez¹, Miguel Marcos⁶, María Luz Martínez-Chantar⁴, Marco Arrese⁷, Carmelo García-Monzón⁸, José M. Mato⁴, Patricia Aspichueta⁹, Ruben Nogueiras¹. ¹CIMUS, Physiology, Santiago de Compostela, Spain; ²Health Research Institute; ³Santa Cristina University Hospital; ⁴CICBiogune; ⁵Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain; ⁶University of Salamanca; ⁷Pontificia Universidad Católica de Chile; ⁸Instituto de Investigación Sanitaria Princesa; ⁹Biocruces Bizkaia Health Research Institute

Email: uxiafernandez.paz@usc.es

Background and aims: G protein-coupled receptor 55 (GPR55) is a putative cannabinoid receptor, and l-α-lysophosphatidylinositol (LPI) is its only known endogenous ligand. Although GPR55 has been linked to energy homeostasis in different organs, its specific role in lipid metabolism in the liver and its contribution to the pathophysiology of non-alcoholic fatty liver disease (NAFLD) remains unknown.

Method: We measured (1) GPR55 expression in the liver of patients with NAFLD compared with individuals without obesity and without liver disease, as well as animal models with steatosis and non-alcoholic steatohepatitis (NASH), and (2) the effects of LPI and genetic disruption of GPR55 in mice, human hepatocytes, and human hepatic stellate cells.

Results: Notably, we found that circulating LPI and liver expression of GPR55 were up-regulated in patients with NASH. LPI induced adenosine monophosphate-activated protein kinase activation of acetyl-coenzyme A carboxylase (ACC) and increased lipid content in human hepatocytes and in the liver of treated mice by inducing de novo lipogenesis and decreasing β-oxidation. The inhibition of GPR55 and ACCα blocked the effects of LPI, and the in vivo knockdown of GPR55 was enough to improve liver damage in mice fed a high-fat diet and in mice fed a methionine-choline-deficient diet. Finally, LPI

POSTER PRESENTATIONS

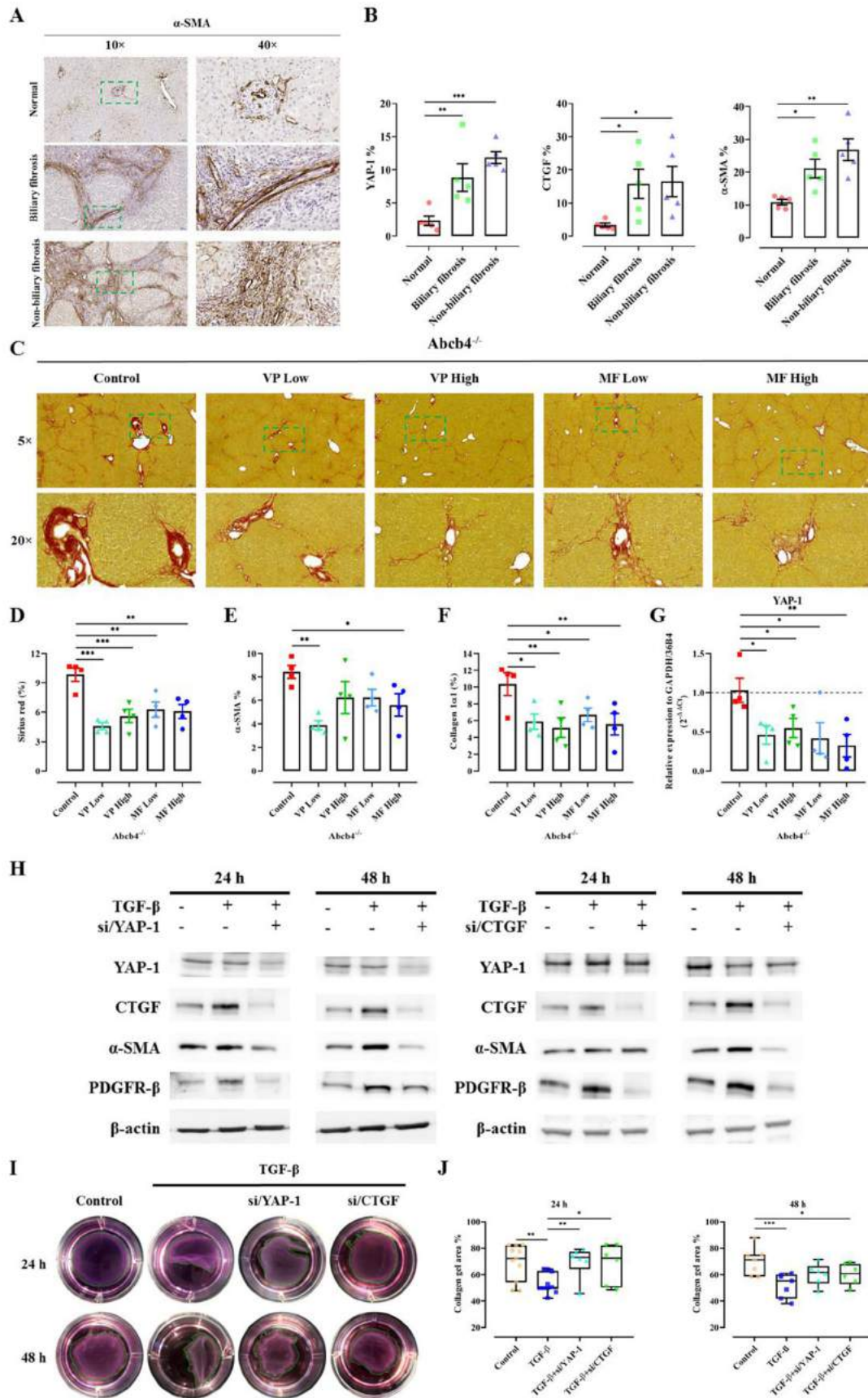


Figure: (abstract: PO-410)

promoted the initiation of hepatic stellate cell activation by stimulating GPR55 and activation of ACC.

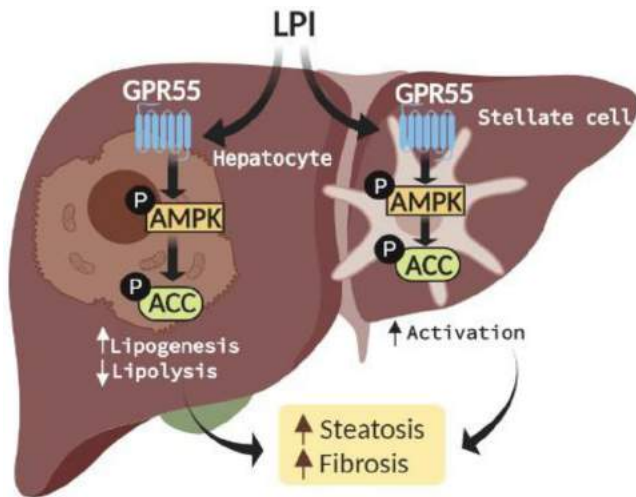


Figure:

Conclusion: The LPI/GPR55 system plays a role in the development of NAFLD and NASH by activating ACC.

PO-479

Inhibition of hepatic p63 reduces the fibrosis in NASH

Marcos Fernandez Fondevila¹, Eva Novoa¹, Uxia Fernandez¹, Maria J. Gonzalez-Rellán¹, Natalia Lima¹, Violeta Heras¹, Begoña Porteiro¹, Daniel Beiroa¹, Ana Senra¹, Susana Bravo², Juan Cuñarro¹, Sulay Tovar¹, Maria Luz Martinez-Chantar³, Miguel Fidalgo¹, Guadalupe Sabio⁴, Miguel Marcos⁴, Miguel Lopez¹, Carlos Dieguez¹, Rubén Nogueiras¹. ¹CiMUS, Department of Physiology, University of Santiago de Compostela, Spain; ²Proteomic Unit, Health Research Institute of Santiago de Compostela (IDIS), Spain; ³CIC BioGUNE, Spain; ⁴Spain
Email: ruben.nogueiras@usc.es

Background and aims: p53 family members control several metabolic and cellular functions. The p53 ortholog p63 controls lipid metabolism in hepatocytes and contributes to the development of liver steatosis. Here, we aimed to explore the potential role of p63 in NASH.

Method: We measured the levels of hepatic p63 in (1) patients NASH; (2) a variety of mice models of NASH with fibrosis; (3) human primary hepatic stellate cells (HSCs); (4) human HSCs LX-2. We manipulate the expression of p63 *in vivo* and *in vitro* with either genetic or virogenetic tools.

Results: P63 is upregulated in patients with NASH, correlating positively with fibrosis score and collagen 1a1 expression. P63 expression is also increased in different animal models of diet-induced NASH and chemically induced liver fibrosis. Mice with hepatic downregulation of p63 fed a high fat diet or choline deficient and high fat diet (CDHFD) for 52 weeks display reduced collagen deposition, hydroxyproline levels and expression of collagen markers. Similar results were found when these mice were challenged to methionine and choline deficient diet. Consistent with this, the hepatic overexpression of TAp63 α isoform accelerates the fibrosis induced by CDHFD.

Conclusion: Our findings indicate an unexpected role of p63 in the metabolic and profibrotic actions in liver disease.

PO-567

B-cell-mediated fibrogenesis in non-alcoholic steatohepatitis

Anja Moncsek¹, Cheuk Ting Wu¹, Joachim C. Mertens¹. ¹University Hospital Zürich, Gastroenterology and Hepatology, Zürich, Switzerland
Email: anja.moncsek@usz.ch

Background and aims: Non-alcoholic steatohepatitis (NASH) is characterized by steatosis, inflammation and hepatocellular injury with different degrees of fibrosis. The hepatic inflammatory response is the major driving force for disease progression, as it promotes liver fibrogenesis, which can ultimately lead to cirrhosis and hepatocellular carcinoma.

In NASH mice, the B cell response involves upregulation of B cell-activating factor (BAFF) in the liver, which drives B cell survival and maturation. In addition, BAFF inhibition and B cell depletion has been shown to ameliorate fibrosis in mice.

A pro-fibrogenic role of B cells has been suggested to involve the production of pro-inflammatory factors that stimulate hepatic stellate cells (liver resident fibroblasts) and liver macrophages but the molecular mechanism remains elusive. Therefore, we wanted to investigate the profibrotic role of B cells in NASH in detail.

Method: 10-week-old C57BL/6J mice were fed a fat-, fructose- and cholesterol-enriched (FFC) diet for up to 40 weeks. To explore intrahepatic immune cells, multiplex flow cytometry and immunofluorescence staining were performed. In addition, hepatic B cells were isolated via immunomagnetic separation and characterized in terms of expression and secretion of pro-fibrotic factors and chemoattractant using quantitative PCR and immune assays, respectively. Furthermore, co-culture studies were employed to analyze and modulate the potential of NASH-related B cells to activate fibroblasts *in vitro*.

Results: FACS analysis of intrahepatic immune cells and immunofluorescence staining of liver sections revealed that B cell abundance in NASH mice liver is not significantly increased. However, B cells locate in direct proximity to stromal cells allowing for direct cell-cell interaction.

As expected, mRNA analysis of liver tissue demonstrated and upregulation of BAFF in 40-week-old NASH mice compared to mice receiving standard chow.

Analysis of isolated hepatic B cells showed an increase in *Tgfb* and specifically *Pdgfb* mRNA in B cells from mice that received FFC diet for 40 weeks. In addition, analysis of chemoattractants revealed an increase of *Ccl4* mRNA in B cells from NASH mice. To confirm these results, ELISA verification is ongoing using cell culture supernatants of isolated B cells.

Preliminary *in vitro* co-culture experiments using 3T3 fibroblasts demonstrated the ability of isolated hepatic B cells to activate fibroblast as shown by increased *Acta2* mRNA expression.

Conclusion: B cells seem to be more activated in NASH mice, since FFC-fed mice exhibit enhanced BAFF expression in the liver. In addition, B cells contribute to fibrosis in NASH either directly by stimulating fibroblast activation through secretion of PDGF-B and indirectly by producing chemotactic factors such as CCL4 that recruit additional immune cells with profibrotic activity.

PO-663

Pharmacokinetics, safety, and tolerability of multiple-dose CC-90001, a c-Jun N-terminal kinase (JNK) inhibitor, in healthy Japanese and non-Japanese adults

Allison Gaudy¹, Barbara Burkhardt¹, Jian Chen¹, Leon Carayannopoulos¹, Maria Palmisano¹, Ying Ye¹. ¹Bristol Myers Squibb, United States
Email: allison.gaudy@bms.com

Background and aims: CC-90001 is a selective inhibitor of c-Jun N-terminal kinase (JNK), a stress-activated protein kinase implicated in the pathogenesis of non-alcoholic steatohepatitis (NASH) and other fibrotic diseases. This Phase 1 study compared the pharmacokinetics

POSTER PRESENTATIONS

Table: (abstract: PO-663)

CC-90001 Dose	Ratio (%) of Geometric Mean, JPN vs non-JPN (90% CI)			
	AUC _{tau}		C _{max}	
	Day 1	Day 7	Day 1	Day 7
100 mg	107.0 (87.6, 130.0)	88.9 (71.9, 110.0)	117.0 (96.5, 142.0)	102.0 (79.8, 130.0)
200 mg	108.0 (78.7, 147.0)	84.8 (68.6, 105.0)	107.0 (71.6, 159.0)	103.0 (87.8, 122.0)
400 mg ^a	119.0 (92.8, 152.0)	91.4 (72.7, 115.0)	129.0 (97.6, 170.0)	115.0 (95.2, 138.0)

^an = 9 non-JPN on Day 7; CI, confidence interval.

(PK), safety, and tolerability of CC-90001 in healthy Japanese (JPN) participants (ppts) and non-JPN ppts.

Method: This was a Phase 1, open-label, randomized, parallel-design study of CC-90001 (100, 200, or 400 mg) administered orally once daily (QD) for 7 days to age- and weight-matched cohorts of JPN and non-JPN adults (NCT03958864). JPN ppts were born in Japan, had not lived outside of Japan for >10 years, and had parents and grandparents of JPN origin. Non-JPN ppts were of European or Latin American descent.

Results: Sixty ppts were enrolled and received CC-90001 (10 JPN and 10 non-JPN ppts per dose). The majority of ppts were men (37/60; 62%) and the mean age of the study population was 38 years. On Day 1 and Day 7, similar CC-90001 plasma exposure (AUC_{tau}) and peak plasma concentration (C_{max}) were observed in JPN and non-JPN ppts at all doses (Table). Overall, 25/60 ppts (42%) reported ≥1 treatment-emergent adverse event (TEAE), and there were no apparent differences in TEAEs experienced by JPN vs non-JPN ppts. All TEAEs were mild (n = 23 ppts) or moderate (n = 2 ppts) in intensity; there were no serious TEAEs or deaths. One ppt (400 mg; non-JPN) discontinued the study on Day 6 due to TEAEs of chest discomfort, arthralgia, headache, dyspnea, and oral hypoesthesia which were all possibly related to CC-90001; all events resolved by the end of the study.

Conclusion: Oral administration of 100–400 mg CC-90001 QD for 7 days was generally well-tolerated; similar PK profiles were observed in JPN and non-JPN ppts after single and multiple doses. Phase 2 studies in patients with NASH and advanced fibrosis and idiopathic pulmonary fibrosis are ongoing.

PO-692

HBV-infection induces collagen VI expression by hepatocytes promoting stellate cell-activation and liver fibrosis

Alessia Virzi^{1,2}, Laura Heydmann^{1,2}, Sarah Durand^{1,2}, Emanuele Felli^{1,2,3}, Patrick Pessaux^{1,2,3}, Eloi Verrier^{1,2}, Catherine Schuster^{1,2}, Thomas Baumert^{1,2,3,4}, Joachim Lupberger^{1,2}.

¹Inserm U1110, Strasbourg, France; ²University of Strasbourg, Strasbourg, France; ³Institut Hospitalo-Universitaire, Pôle Hépatodigestif, Nouvel Hôpital Civil, Strasbourg; ⁴Institut Universitaire de France (IUF), Paris, France

Email: joachim.lupberger@unistra.fr

Background and aims: Chronic fibrotic liver disease is a major public health burden and represents the main risk factor for hepatocellular carcinoma (HCC) worldwide. Upon chronic liver injury, inflammation, and oxidative stress, stellate cells are activated causing an excessive deposition of collagens ultimately leading to a destruction of the normal liver architecture. The development of novel antifibrotic drug targets and therapies is thus urgently needed but hampered by a lack of understanding of the underlying molecular mechanism.

Method: Using hepatitis B virus (HBV) as a model, we analyzed the proteomic and phospho-proteomic changes caused in infected HepG2-NTCP cells using liquid chromatography-mass spectrometry (LC-MS) with tandem mass tag (TMT) labels¹. Disease-relevant proteomic dysregulation was studied using Gene Set Enrichment

Analysis (GSEA)² and validated in primary human hepatocytes (PHH) and by perturbation studies.

Results: We demonstrated that HBV infection of hepatocytes significantly modulates signaling pathways involved in the remodeling of extra-cellular matrix (ECM), which we validated on the transcriptomic level in HBV-infected PHHs. A leading-edge gene driving the enrichment was collagen VI being significantly upregulated upon HBV infection in hepatocytes, suggesting a relevance for HBV-associated liver fibrosis. HBV proteins notably induce Akt phosphorylation. By screening the impact of disease-relevant signaling pathways on collagen VI expression, we observed a correlation between a PI3K-Akt transcriptional signature and collagen VI expression in non-tumor liver tissue of HCC patients with HBV. Incubation of stellate cell line LX-2 with collagen VI strongly induced the expression of LX-2 activation markers compared to cells incubated with collagen I, suggesting a regulatory role of collagen VI for liver fibrosis.

Conclusion: Our proteomic and phospho-proteomic analysis of HBV infection highlights new mechanisms for HBV virology and virus-induced liver disease progression. HBV proteins induce Akt signaling and therefore highlight a role for Akt signaling and collagen VI in the dynamics of liver disease progression also potentially relevant for other disease etiologies stimulating PI3 K/Akt signaling. Collagen VI-relevant signaling pathways in hepatocytes may thus serve as potential antifibrotic drug targets in the liver.

References

- Mertins P, et al. *Nat Protoc.* 2018;13:1632–1661.
- Lupberger J, et al. *Gastroenterology.* 2019;157:537–551 e9.

PO-733

Pharmacokinetics, safety, and tolerability of CC-90001, a c-Jun N-terminal kinase (JNK) inhibitor, in participants with hepatic impairment

Kofi A Mensah¹, Allison Gaudy¹, Melissa Araujo¹, Liangang Liu¹, Francisco Ramirez-Valle¹, Maria Palmisano¹, Ying Ye¹. ¹Bristol Myers Squibb, United States

Email: Kofi.Mensah@bms.com

Background and aims: CC-90001 is a selective inhibitor of c-Jun N-terminal kinase (JNK), a stress-activated protein kinase implicated in the pathogenesis of non-alcoholic steatohepatitis (NASH) and other fibrotic diseases. This Phase 1 study compared the pharmacokinetics (PK), safety, and tolerability of CC-90001 in participants (ppts) with hepatic impairment (HI) with normal-matched adults.

Method: This was an open-label, multicenter, parallel-design study (NCT03742882). Ppts with HI were grouped into cohorts of 8 by Child-Pugh score (mild [5–6], moderate [7–9], or severe [10–13]). Two cohorts each of 8 ppts with normal hepatic function were sex-, age-, and weight-matched to ppts with moderate and severe HI. All ppts received 1 oral dose of 200 mg CC-90001 on Day 1. Blood samples were collected on Days 1–7 to assess PK end points, which were compared across arms by ANOVA. Safety was monitored throughout the study and was reviewed for ppts with mild and moderate HI prior to dosing ppts with severe HI.

Results: Forty ppts were enrolled and received CC-90001; 1 ppt with mild HI discontinued at Day 6 for personal reasons but was included in all analyses. Most ppts were men (26/40, 65%), mean age was 58 years, and mean BMI was 29.8 kg/m². Compared with normal-matched ppts, after a single dose of CC-90001, ratios of geometric mean exposure (AUC_{0-t}) were similar in ppts with mild or moderate HI, but higher in ppts with severe HI (Table). Ratios of geometric mean peak concentration (C_{max}) were similar to normal-matched ppts regardless of HI. Median T_{max} was delayed in ppts with moderate or severe HI relative to normal-matched ppts. Treatment-emergent adverse events (TEAEs) were reported by 6/40 ppts (15%) and were of mild (5/6 ppts) or moderate (1/6 ppts) intensity. There was no apparent relationship between TEAE incidence and HI. No ppts with severe HI had CC-90001-related TEAEs.

Degree of HI	Ratio (%) of Geometric Mean, HI vs Normal-Matched (90% CI)	
	AUC _{0-t}	C _{max}
Mild	71.90 (57.86, 89.35)	100.68 (77.06, 131.54)
Moderate	92.77 (74.81, 115.05)	88.42 (67.43, 115.93)
Severe	160.51 (115.16, 223.72)	117.77 (75.56, 183.56)

CI, confidence interval.

Conclusion: Mild to moderate HI had a minimal effect on CC-90001 AUC_{0-t} compared with normal-matched ppts. Severe HI modestly increased CC-90001 AUC_{0-t} but C_{max} was unchanged. CC-90001 was generally well tolerated. Phase 2 studies in patients with NASH and advanced fibrosis and in patients with idiopathic pulmonary fibrosis are ongoing.

PO-793

Endothelial GATA4 deficiency causes perisinusoidal liver fibrosis by impaired angiocrine signaling

Manuel Winkler¹, Theresa Staniczek¹, Sina Wietje Kürschner¹, Christian Schmid¹, Hiltrud Schönhaber¹, Julio Cordero², Linda Kessler², Arthur Mathes², Carsten Sticht³, Michelle Neßling⁴, Alexey Uvarovskii⁵, Simon Anders⁵, Xue-jun Zhang^{6,7}, Guido von Figura⁸, Daniel Hartmann⁶, Carolin Mogler⁹, Gergana Dobрева², Kai Schledzewski¹, Cyrill Géraud^{10,11}, Philipp-Sebastian Koch^{1,11}, Sergij Goerdt^{1,11}. ¹University Medical Center and Medical Faculty Mannheim, Heidelberg University, Department of Dermatology, Venereology and Allergology, Mannheim, Germany; ²Medical Faculty Mannheim, Heidelberg University, Department of Anatomy and Developmental Biology, European Center for Angioscience, Mannheim, Germany; ³Medical Faculty Mannheim, Heidelberg University, Core Facility Next Generation Sequencing, Mannheim, Germany; ⁴German Cancer Research Center (DKFZ), Central Unit Electron Microscopy, Heidelberg, Germany; ⁵Center for Molecular Biology (ZMBH), Heidelberg University, Heidelberg, Germany; ⁶School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Department of Surgery, Munich, Germany; ⁷Zhongda Hospital, School of Medicine, Southeast University, Department of Orthopedic Surgery, Nanjing, China; ⁸School of Medicine, Klinikum rechts der Isar, Technical University of Munich, II. Medical Clinic and Policlinic, Munich, Germany; ⁹School of Medicine, Technical University Munich, Institute of Pathology, Munich, Germany; ¹⁰University Medical Center and Medical Faculty Mannheim, Heidelberg University, Section of Clinical and Molecular Dermatology, Department of Dermatology, Venereology and Allergology, Mannheim, Germany; ¹¹Medical Faculty Mannheim, Heidelberg University, European Center for Angioscience, Mannheim, Germany
Email: manuel.winkler@medma.uni-heidelberg.de

Background and aims: Organ-specific microvascular endothelial cells (EC) actively regulate their tissue microenvironment through various paracrine acting signaling molecules, so called angiocrine factors. In the liver, the microvasculature is formed by discontinuous liver sinusoidal ECs (LSEC). LSEC are known to contribute to a variety of processes in liver development, health and disease. The transcription factor GATA4 acts as master regulator of LSEC specification during liver development. Herein, we studied the role of GATA4 in LSEC during adult liver homeostasis.

Method: We conditionally deleted GATA4 in LSEC using the EC subtype-specific Clec4g-iCre driver mouse with late-embryonic endothelial Cre-activity in LSEC. Murine livers were examined by histology, electron microscopy, immunohistochemistry/-fluorescence and in-situ hybridization. LSECs were isolated and supplied to gene expression profiling, CHIP- and ATAC-sequencing. Liver regeneration was investigated by partial hepatectomy and perisinusoidal liver fibrosis by choline-deficient l-amino acid-defined (CDAA) diet. Furthermore, we compared transcriptomic data from Gata4-deficient LSEC with single cell RNA-sequencing data of EC from healthy and cirrhotic human livers.

Results: LSEC-restricted deletion of Gata4 in mice caused transformation from discontinuous liver sinusoids into continuous capillaries including the formation of a continuous basement membrane. These mice developed a perisinusoidal liver fibrosis with collagen depositions in the space of Disse. In LSEC, increased chromatin accessibility and upregulation of several fibrosis-associated genes were detected including de novo expression of profibrotic angiocrine signaling molecules such as the hepatic stellate cell activating cytokine PDGFB. Transcription factor MYC was found to act in a counter-regulatory manner to GATA4. Moreover, impaired angiocrine Wnt signaling disturbed metabolic liver zonation. In CDAA diet-induced perisinusoidal liver fibrosis, LSEC showed repression of GATA4, activation of MYC and a similar profibrotic angiocrine switch. In human cirrhotic livers, GATA4-positive LSEC and endothelial GATA4 target genes were reduced, while non-LSEC endothelial cells and MYC target genes including PDGFB were enriched.

Conclusion: GATA4-deficiency in LSEC causes angiocrine-mediated liver fibrosis. Thus, primary LSEC dysfunction is a key driver and the GATA4/MYC/PDGFB axis is a potential target for prevention and treatment of liver fibrosis.

PO-938

Therapeutic targeting of integrin alpha v beta 1 in liver fibrosis

Emma Shepherd¹, Deepika Balakrishna², Ellie Northall³, Mark Sabat⁴, Daniel Carney⁴, Ron de Jong⁵, Hiroaki Yashiro⁶, Derek Erion⁶, Rohan Manohar⁶, Patricia Lalor³. ¹Centre for Liver and Gastroenterology Research, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom; ²Takeda Pharmaceuticals, Biological Sciences, Gastroenterology Drug Discovery Unit, San Diego, United States; ³Centre for Liver and Gastroenterology Research, Institute of Immunology and Immunotherapy, Birmingham; ⁴Takeda Pharmaceuticals, Medicinal Chemistry, Gastroenterology Drug Discovery Unit, San Diego, United States; ⁵Ron de Jong Consulting, LLC, San Diego, United States; ⁶Takeda Pharmaceuticals, Gastroenterology Drug Discovery Unit, Cambridge, United States
Email: e.l.shepherd@bham.ac.uk

Background and aims: Inhibition of TGF-b is a promising therapeutic approach to reduce organ fibrosis but is associated with safety liabilities. Arg-Glu-Asp (RGD) integrins are known to be the principal mediators of TGF-b activation in chronic fibrosis, and integrin inhibition allows for localized and therapeutically safe inhibition of TGF-b. Of the many integrin heterodimers, more than half contain either alphaV or beta1. Recent data suggest that the RGD integrin alphaVbeta1 plays a role in liver fibrosis but there remains limited data for alphaVbeta1 (aVb1) inhibition in human NASH tissue and preclinical NASH models. The aim of this study was to investigate the

ⁿn = 9 non-JPN on Day 7; CI, confidence interval.

POSTER PRESENTATIONS

effect of 2 aVb1 inhibitory small molecules in human NASH tissue and a diet induced preclinical NASH model.

Method: Expression of aVb1 heterodimers and phosphorylation of SMAD3 (pSMAD3) by Meso Scale Discovery (MSD) analysis. Adhesion to LAP was measured by xCELLigence impedance assay and adhesion assays. The effect of aVb1 inhibition *in vivo* was assessed in rats fed a Choline Deficient High Fat Diet (CDHFD) by MSD, qRT-PCR and histology. Effects of aVb1 inhibitors in perfused donor and cirrhotic human liver wedges was assessed by histology and qRT-PCR.

Results: We report that aVb1 integrin expression is up regulated in cirrhotic NASH tissue and was expressed on human hepatic stellate cells (HSCs) at higher levels than other primary liver cells. *In vitro* pharmacological inhibition of aVb1 resulted in decreased pSMAD3 in an overexpressing cell line, and abrogated human HSC binding to LAP but did not affect binding to other extracellular matrix ligands including fibronectin. Inhibition of aVb1 *in vivo* in CDHFD fed rats reduced pSMAD3, fibrogenic gene expression and histological liver fibrosis. Finally, perfusion of human liver wedges with an aVb1 inhibitor resulted in decreased integrin expression and gene expression associated with fibrosis (for e.g., LOX, Col1A1, TGF- β 1, PGDFRb, TIMP1 and CTGF).

Conclusion: In this study we have shown that 2 aVb1 inhibitors caused ligand-specific blockade of HSC function *in vitro* and reduced liver fibrosis *in vivo*. Importantly, our data demonstrate that these inhibitors can be delivered to cirrhotic human liver tissue *ex vivo* and still mediate phenotype regulation. Taken together, these data suggest that integrin inhibition in the context of chronic human fibrosis may be beneficial as a therapeutic strategy.

PO-1069

The AST/ALT ratio: a second line component of the hepatic fibrosis screening by FIB-4 calculated automatically in 131, 861 subjects

Denis Ouzan¹, Corneille Jeremie², Guillaume Penaranda³, Fino Antony⁴, Dubertrand Jean Marie⁴. ¹Institut Arnauld Tzanck, Hepatology, Saint-Laurent-du Var, France; ²Laboratoire Bioesterel Biogroup, Mougins; ³Laboratoire Alphabio Européen, Marseille, France; ⁴Laboratoire Bioesterel Biogroup, Mandelieu
Email: denis.ouzan@wanadoo.fr

Background and aims: Screening for hepatic fibrosis in the general population is a major public health issue. We have shown in a previous study (EASL 2020 FRI225) that Fib-4, a simple score combining age, measurement of ALAT/ASAT activity and platelet count made it possible to detect hepatic fibrosis in the general population and to find a possible cause of liver disease. In a study presented at the EASL 2020 (Yeoman A et al, EASL 2020, Abs. GS08) on 17, 700 patients with elevated ALAT, an AST/ALT ratio >1 was found in 12% of cases and showed severe fibrosis or cirrhosis on Fibrosan in 28 and 29% of cases, respectively.

Method: FIB-4 was calculated in an automated way since the 1 October 2020 in a group of 80 medical analysis laboratories of the French Alpes Maritimes area in all the subjects who benefited from a platelet and AST/ALT assay, i.e., in 131, 861 subjects during the last 3 months of 2020. The results of Fib 4, which express the risk of fibrosis are reported according to age: low risk if <1.30 (<65 years) and <2 (>65 years), intermediate risk if between 1.3 and 2.67 (<65 years), and if between 2 and 2.67 (>65 years), and high risk if >2.67 regardless of age. The AST/ALT ratio was calculated in all patients with high ALT.

Results: Among the 131 861 subjects, half were over 65 years of age, 56% were women and 44% men. ALT elevation was found in 12 472 of them (9.5%). The distribution of Fib-4 test according to age was as follows: low risk 107, 148 (81.3%), intermediate risk 16, 297 (12.4%), high risk 8, 416 (6.4%). The rate of high risk of fibrosis was higher in subjects >65 compared to subjects <65 years of age: 10.9% and 1.8%,

and higher in subjects whose prescribing physician was a gastroenterologist compared to general practitioners: 10.9% and 4.8%, $p < 0.0001$, respectively. An AST/ALT > 1 ratio was observed among 8.5% of the 12 472 subjects with elevated ALAT. Among subjects with elevated ALAT, the percentage of subjects with an AST/ALT ratio >1 was 67.3% for Fib-4 high risk, 25.1% for Fib-4 intermediate risk, and 7.6% for low-risk liver fibrosis by FIB-4 ($p < 0.001$). 20% of subjects at high risk of fibrosis (FIB4 > 2.67) had an elevated ALT with an AST/ALT > 1 ratio in 8.5% of them. FIB 4 score was >1.3 (<65)/2 (>65 years) in 32% of patients with elevated ALT.

Conclusion: The AST/ALT ratio that is part of the FIB4 calculation appears to be a second-line component that may, in subjects with elevated ALAT, reinforce the risk of fibrosis as defined by FIB4 automatically assessed during biological analysis under the condition that transaminases and platelets count analysis are prescribed. The high-risk of fibrosis in subjects with FIB4 > 2.67 is reinforced.

PO-1125

Using the Enhanced Liver Fibrosis test in Primary Care: A practical pathway to prioritise patients with fibrosis in Fatty Liver Disease

Alexander Hinkson¹, Jo Ann Wong¹, Timothy Canter¹, Elaine Ong¹, Ian Rowe¹, Paul Glynn², Rebecca L. Jones¹, Richard Parker¹. ¹St James's University Hospital, Leeds Liver Unit, Leeds, United Kingdom; ²Lingwell Croft Surgery, Leeds, United Kingdom
Email: alex.hinkson@doctors.org.uk

Background and aims: Non-alcoholic fatty liver disease (NAFLD) and Alcohol-related liver disease (ALD) are the most common causes of chronic liver disease in the UK. A minority of patients who have significant hepatic fibrosis will experience adverse health outcomes due to liver disease. There is a need to effectively triage patients with or without hepatic fibrosis to appropriate services. We assessed the use of the Enhanced Liver Fibrosis (ELF) score in primary care to stratify patients' risk of fibrosis to guide referrals to secondary care.

Method: Patients with suspected NAFLD or ALD in three primary care practices in Leeds underwent ELF testing to guide referral to a Community Hepatology Clinic (CHEP). Patients with ELF < 9.5 (based on analysis of local data) were deemed at low risk of significant fibrosis and not referred to secondary care. Patients with ELF > 9.5 were referred for transient elastography (TE) and a CHEP clinic review. Comparison was made with referrals from local primary care practices in Leeds, who did not have access to ELF testing. Cost analysis was performed by summing the costs of blood tests including ELF, TE, and clinic reviews for all patients with available data-478 patients on CHEP pathway and 292 patients referred directly.

Results: In total 882 patients were referred on the CHEP pathway, of which 838 had an ELF test. ELF was <9.5 in 464 (55.4%) of patients. Of the 269 patients with ELF > 9.5, 225 (51%) had a TE < 15 kPa and 44 (10%) patients had a TE > 15 kPa. Of the 169 patients with ELF < 9.5 and a subsequent TE, only three (0.7%) had stiffness > 15 kPa and one had fibrosis > F2. Per patient costs were lower in the CHEP pathway (Table).

Referral type	CHEP pathway	Standard referral
Diagnosis		
NAFLD	65.1%	57.1%
ALD	32.0%	28.6%
Other		
Liver stiffness by transient elastography (kPa)		
<9.5	73.8%	60.4%
8–15	26.0%	18.5%
≥15	11.8%	17.1%
Biopsy	7.3%	6.8%
Discharged after clinic	53.3%	9.6%
Cost per patient	£251.73	£354.76

Conclusion: Most patients assessed had ELF score <9.5 and were effectively screened out with low risk of fibrosis, preventing unnecessary referral to secondary care. In patients with raised ELF and low TE, further investigations consistently revealed low levels of fibrosis. The CHEP pathway enabled many more patients to be screened for significant liver disease in primary care, reducing referrals of low-risk patients and with a substantial cost saving per patient.

PO-1441

Characterization and study of hepatic stellate cells in a 3D bioengineered model of fibrosis

Sara Campinoti¹, Omolola Ajayi¹, Sveva Fagiolino^{1,2}, Lorenzo Cacioli¹, Lai Wei^{1,2}, Dipa Natarajan¹, Shilpa Chokshi^{1,2}, Luca Urbani^{1,2}. ¹Institute of Hepatology London; ²King's College London, Faculty of Life Sciences and Medicine
Email: sveva.fagiolino@kcl.ac.uk

Background and aims: Chronic liver disease (CLD) poses a significant health burden world-wide. Its progression is characterized by chronic injury, inflammation, and fibrosis brought by an excess accumulation of extracellular matrix (ECM) by activated hepatic stellate cells (HSCs). Several aspects of the molecular mechanisms underlying this chronic inflammation remain poorly understood, mainly due to the inability of conventional cell culture models to mimic the in vivo microenvironment.

Our project aims at using 3D bioreactor-based bioengineered systems as a tool to examine the crosstalk between hepatic cells and ECM in CLD.

Method: Human HSCs were isolated from total and partial hepatectomy. 3D-culture systems were generated by combining decellularized human liver ECM-scaffolds with seeded HSCs. 3D cultures were maintained using a custom-made confined-perfusion bioreactor (Figure).

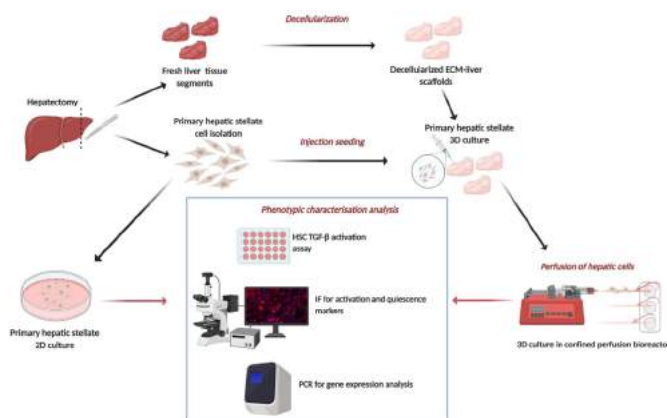


Figure:

Using immunostaining and gene expression analysis we provided a phenotypic analysis of the different cell subsets, quantified HSC activation and analysed ECM deposition.

Results: We successfully isolated human HSCs and provided an in-depth cell characterization in comparison with commercially available HSC lines. Primary HSC activation and ECM production was achieved in 2D and within the 3D constructs in confined perfusion bioreactors. However, we described consistent differences between HSC cell lines, highlighting that isolation and culture methods can have an impact in cell's phenotype and activation. Furthermore, culture of HSCs in 3D ECM-scaffolds with low stiffness reduced cell activation in comparison to standard 2D culture activation assays.

Conclusion: The confined perfusion bioreactor supported the culture of liver constructs populated with primary human stellate cells, generating a 3D model which reflects better liver pathogenesis than standard 2D cultures. Our 3D bioengineered model could host the co-culture of different liver cell types, representing a useful tool to investigate the liver microenvironment in CLD.

PO-1505

Fibrosis Biomarkers CA15-3 and Thrombospondin-2 are Associated with Higher Hepatic Collagen Content in Non-alcoholic Steatohepatitis (NASH)-related Fibrosis

Sean Felix^{1,2}, James M. Estep¹, Aybike Biredinc¹, Fanny Monge², Lakshmi Alaparthi², Maria Stepanova^{1,2}, Brian Lam^{1,2}, Bijal Rajput¹, Pegah Golabi^{1,2}, Thomas Jeffers^{1,2}, Samuel Hellings³, Elizabeth Brown³, Thomas Spires³, Melissa Yarde³, Yi Luo³, Anthony Sanfiz³, John Thompson³, Mary Ellen Cvjic³, Edgar Charles³, Lei Zhao³, David Gordon³, Azza Karrar¹, Albert Tan², Hala Abdelaal², Fatema Nader⁴, Zachary Goodman^{1,2}, Zobair Younossi^{1,2,5}. ¹Beatty Liver and Obesity Research Program, Inova Health System, Department of Medicine, Falls Church, United States; ²Centers for Liver Disease, Inova Fairfax Medical Campus, Department of Medicine, Falls Church, United States; ³Bristol Myers Squibb, Princeton, United States; ⁴Centers for Outcomes Research in Liver Diseases, Washington, DC, United States; ⁵Falls Church, United States
Email: abirerdi@gmail.com

Background and aims: Hepatic fibrosis in NASH is partially determined by dynamic equilibrium between fibrogenesis and fibrolysis; which can be measured, in part, by circulating biomarkers. Our aim is to investigate the changes in serum extracellular matrix (ECM) and fibrosis biomarkers in relation to hepatic collagen content in patients with NAFLD.

Method: Baseline serum and clinical data were available for patients with NAFLD. ECM proteins (C3M, C5M, C6M, PRO-C3, PRO-C5 and PRO-C6) were measured in serum using ELISA with another 50 fibrosis biomarkers measured by Luminex-based assays. Liver biopsies were read by a study pathologist and hepatic collagen was quantified using Computer Assisted Morphometry (CAM) following the acquisition of digitalized images of Sirius-Red stained slides using an Aperio Scanscope XT scanner. Aperio's positive pixel count algorithm was used to quantify % collagen. Values for % collagen were grouped into upper quartile (Q4 >4.0% n = 35) and below median quartile (Q1 ≤ 2.0%, n = 72). Multivariate analysis was used to identify changes in biomarkers concentrations that were independently associated with % collagen as quantified by CAM.

Results: We included 150 patients with NAFLD [100 NASH, 33% male, 71% white, 44% type 2 diabetes, 34% advanced fibrosis (≥F3)]. Univariate analysis revealed that subjects with the highest quartile (Q4) of collagen had significant differential concentrations in a number of important remodeling proteins (Figure) (p < 0.05). PRO-C3 positively correlated with collagen deposition (rho (p) = 0.2, p = 0.01). In multivariate model, higher levels of CA15-3 and Thrombospondin-2 were independently associated with higher % hepatic collagen (OR: 1.074 (CI: 1.001–1.15), p = 0.04], and OR: 1.14 (CI: 1.056–1.23), p < 0.0001, respectively).

POSTER PRESENTATIONS

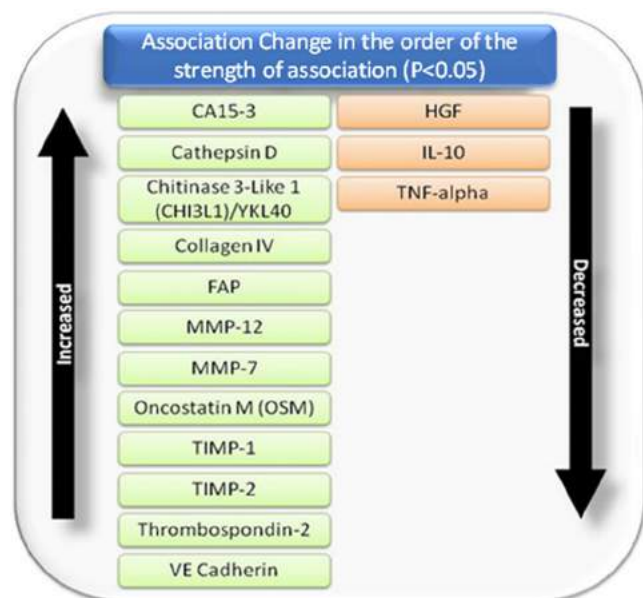


Figure:

Conclusion: CA15-3 (also known as MUC1 or epithelial membrane antigen), and Thrombospondin-2 are associated with higher hepatic collagen in patients with NAFLD. CA15-3 reflects extracellular matrix deposition and collagen remodeling while Thrombospondin-2 mediates cell-to-cell and cell-to-matrix interactions. Our findings highlight the potential role of CA15-3 and Thrombospondin-2 in quantifying ECM remodelling in NASH-related liver fibrosis.

PO-1579

Chinese traditional medicine Yiqi Huoxue recipe attenuates hepatic fibrosis via the YAP/TAZ signaling

Wen Zhao^{1,1}, Dandan Zhao¹, Lu Li¹, Yuemin Nan¹. ¹Third Hospital of Hebei Medical University, Traditional and Western Medical Hepatology, Shijiazhuang, China

Email: nanyuemin@163.com

Background and aims: Chinese traditional medicine Yiqi Huoxue (YQHX) has been shown to attenuate liver fibrosis in animal and human studies. Yet, the exact molecular mechanisms underlying its anti-fibrotic activity remain to be elucidated. Recently, the YES-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) signaling has been implicated in the pathogenesis of liver fibrogenesis. The aim of the present study was to investigate whether the YAP/TAZ signaling is involved in the therapeutic effect of YQHX on hepatic fibrosis in rats and patients with chronic hepatitis B (CHB)-associated liver fibrosis.

Method: Wistar rats were used to generate a model of carbon tetrachloride (CCl₄)-induced liver fibrosis. The experimental rats were randomly divided into three groups: normal control group, hepatic fibrosis model group, and YQHX treatment group. CHB patients with significant liver fibrosis were enrolled and assigned to receive nucleoside/nucleotide analogues (NAs) or NAs plus YQHX in combination. Histological analysis was performed in liver tissue sections of each group. Immunohistochemistry (IHC), real-time qRT-PCR, and Western blot (WB) were conducted to examine effects of YQHX treatment on liver fibrosis markers and key molecules in the TGF- β /Smad pathway, and YAP/TAZ signaling. The plasma YAP levels in CHB patients and healthy controls were measured by the enzyme-linked immunosorbent assay (ELISA).

Results: YQHX treatment markedly alleviated the morphological alterations in CCl₄-induced liver fibrosis in rats, and resulted in significant decreases in mRNA and protein levels of hepatic fibrosis markers, including Col I and α -SMA in the YQHX treatment group versus the model group. Furthermore, YQHX treatment significantly suppressed the CCl₄-mediated activation of the TGF- β /Smad pathway in rats. Notably, CCl₄ induced up-regulation of YAP, TAZ, and CTGF in the model group, which were significantly abrogated by YQHX in the YQHX treatment group in rats. In consistency with the major findings in rats, CHB patients treated with NAs and YQHX in combination achieved significantly higher percentage of improvement in liver fibrosis than those given NAs alone (71.1% vs. 28.6%; $p=0.057$). In addition, hepatic and plasma YAP levels were significantly decreased in response to YQHX treatment in CHB patients with liver fibrosis.

Conclusion: This study has demonstrated that YQHX treatment attenuates liver fibrosis in rats and CHB patients and that YQHX may exert its anti-fibrotic activity through inhibiting the YAP/TAZ signaling. As such, the findings may help better understanding the mechanisms for YQHX in the treatment of liver fibrosis.

PO-1580

Prospective screening of significant liver fibrosis in a large cohort of 131, 861 French subjects using, since October 2020, automatic calculation of FIB-4 in routine blood tests.

Denis Ouzan¹, Corneille Jeremie², Guillaume Penaranda³, Fino Antony⁴, Dubertrand Jean Marie⁵. ¹Institut Arnault Tzanck, Hepatology, Saint-Laurent-du-Var, France; ²Laboratoire Bioesterel; ³Laboratoire Alfabio Européen, Marseille, France; ⁴Laboratoire Bioesterel Mandelieu, Mandelieu, France; ⁵Laboratoire Bioesterel Mandelieu, Mandelieu

Email: denis.ouzan@wanadoo.fr

Background and aims: Screening for hepatic fibrosis in the general population is a major public health issue. We have shown in a previous study (EASL 2020, Abs FRI225) that FIB-4, a simple score combining age, measurement of ALT/AST activity and platelets count made it possible to detect hepatic fibrosis in the general population and to find a possible cause of liver disease.

Method: FIB-4 was calculated in an automated way since October 2020 in a group of 80 clinical laboratories of the French Alpes Maritimes area, in all the subjects who benefited from a platelets and AST/ALT assays. The results of FIB-4, which express the risk of fibrosis, are reported according to age: no risk if <1.30 (<65 years old) and <2 (>65 years old), low risk if between 1.3 and 2.67 (<65 years old) and if between 2 and 2.67 (>65 years old), and high risk if >2.67 regardless of age. ELF score was secondary calculated in a subgroup of 183 patients.

Results: During the 3 last months of year 2020, 131, 861 subjects were screened, half were over 65 years old, 56% were women and 44% men. ALT elevation was found in 12, 472 of them (9.5%). The distribution of FIB-4 according to age was as follows: low risk of fibrosis for 107, 148 (81.3%) subjects, intermediate risk of fibrosis for 16, 297 (12.4%) subjects, and high risk of fibrosis for 8, 416 (6.4%) subjects. The rate of high risk of fibrosis was higher in subjects >65 years old compared to subjects <65 years old: 10.9% and 1.8%, and higher in subjects whose prescribing physician was a gastroenterologist compared to general practitioners: 10.9% and 4.8%, $p < 0.0001$, respectively. Initial testing using FIB-4 was followed by assessment with the Enhanced Liver Fibrosis (ELF) test in 183 subjects with intermediate risk (132) or high risk (51) with FIB-4 for liver fibrosis. ELF score >9.8 that indicates advanced fibrosis has been observed in 71/132 (54%) subjects with indeterminate risk score and in 45/51 (88%) of those with FIB-4 high risk score of fibrosis. This comparison is ongoing in a larger series.

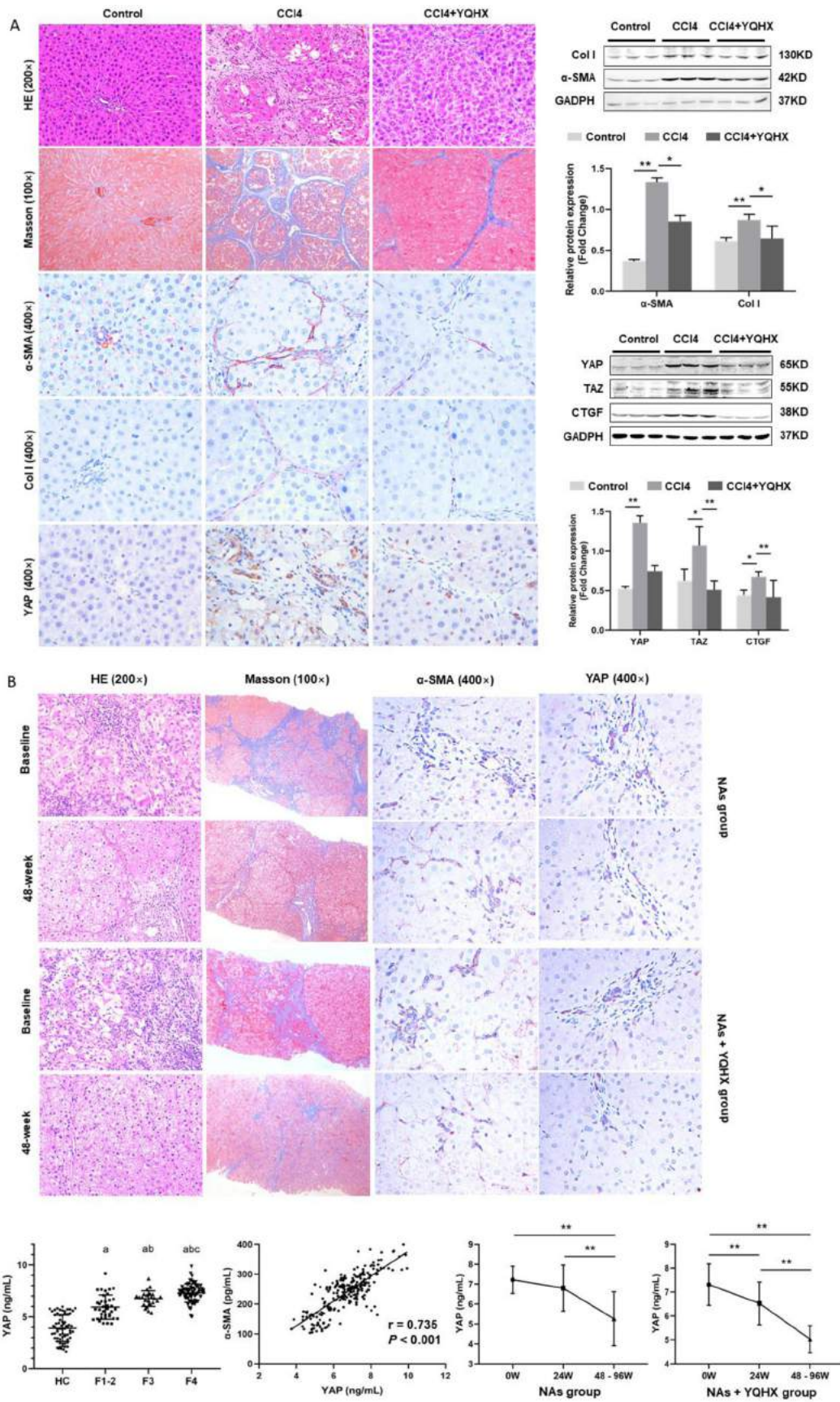


Figure: (abstract: PO-1579)

POSTER PRESENTATIONS

Conclusion: Our study strongly supports this easy-to-implement strategy using a simple FIB-4 measure resulting from the use of available routine test results. Liver fibrosis was suspected by FIB-4 score in of a large cohort of patients 18.8% (12.4% with intermediate and 6.4% with high risk of fibrosis). With the FIB-4 thresholds used as function of age, the still in progress work in a larger series at the time of writing this abstract, shows that 54% of subjects in the indeterminate zone with FIB-4 were confirmed to be at risk of advanced fibrosis with the ELF test.

PO-1582

Inter-system reproducibility of liver stiffness measurement with two different two-dimensional shear wave elastography techniques using transient elastography as the reference method

Victor Baldea¹, Felix Bende¹, Alexandru Popa¹, Radu Cotrau¹, Lupusoru Raluca¹, Alina Popescu¹, Roxana Sirli¹, Ioan Sporea¹. ¹Victor Babes University of Medicine and Pharmacy, Gastroenterology, Romania
Email: isporea@umft.ro

Background and aims: Several companies have developed different shear wave elastography (SWE) machines able to quantify liver stiffness (LS) as a marker of fibrosis. This study aimed to compare the technical success rate and reliability of measurements made using two-dimensional shear wave elastography (2D-SWE) with SuperSonic Imagine Aixplorer MACH 30 (2D-SWE.SSI) and General Electric LOGIQ P (2D-SWE.GE) ultrasound systems and to assess the inter-system reproducibility of the resultant liver stiffness measurements.

Method: We prospectively enrolled 228 patients with different chronic liver diseases (CLD) and 21 subjects without liver disease that were referred to our ultrasound department for liver fibrosis assessment. LS assessment was done using the same intercostal approach with all 3 systems. The technical success rates and measurement reliability of the two techniques were compared. LS values measured using the two SWE techniques and TE were compared using Spearman correlation coefficients and 95% Bland-Altman limits of agreement. Intra-class correlation coefficients (ICC) were used to analyze the inter-platform reproducibility of LS measurements.

Results: The two SWE techniques (2D-SWE.SSI, 2D-SWE.GE) and TE showed a similar technical success rate (96.4% vs 95.6% vs. 98.4%, $p = 0.186$) and similar reliability of LS measurements (98.8% vs. 99.6% vs. 99.2%, $p = 0.604$), with significant differences between mean LS measurements (7.5 kPa vs. 7.1 kPa vs. 7.2 kPa, $p = 0.0001$). A strong correlation (2D-SWE.SSI vs. 2D-SWE.GE, $r = 0.85$; 2D-SWE.SSI vs TE, $r = 0.82$ and 2D-SWE.GE vs. TE, $r = 0.76$) was observed across systems with various degrees of inter-system reproducibility (ICC, 0.43–0.90). The best agreement was observed between TE and 2D-SWE.SSI (ICC, 0.90) and the worst agreement between 2D-SWE.SSI and 2D-SWE.GE (ICC, 0.43). The Bland-Altman analysis revealed that the mean difference between 2D-SWE.SSI and 2D-SWE.GE values was 0.4 kPa (limits of agreement: -12.4 to 13.1).

Conclusion: No significant differences have been found between the feasibility of both systems when compared to TE. However, significant inter-system variability was observed in LS measurements made using both SWE techniques. Therefore, we advise caution when interpreting LS results from different SWE systems and cut-off values should not be used interchangeably.

PO-1589

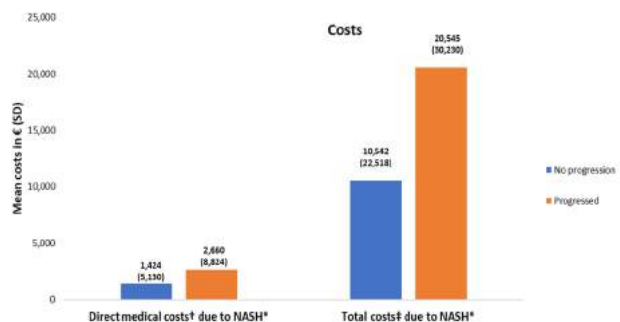
Non-alcoholic steatohepatitis-related costs changes in the context of fibrosis progression status in European patients

Jörn Schattnerberg¹, Manuel Romero Gomez², Anum Shaikh³, Leonardo Ruiz Casas³, Gabriel Pedra³, Margarida Augusto⁴, João Diogo da Rocha Fernandes⁵. ¹Metabolic Liver Research Programm, I. Department of Medicine, University Medical Center Mainz, Mainz, Germany; ²UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Sevilla, Spain; ³HCD Economics, Daresbury, United Kingdom; ⁴Novo Nordisk A/S, London, United Kingdom; ⁵Novo Nordisk A/S, Søborg, Denmark
Email: leo.ruiz@hcdeconomics.com

Background and aims: Little is known on the impact of liver fibrosis progression on the costs of non-alcoholic steatohepatitis (NASH). In this analysis the effect of fibrosis progression on NASH related costs in France, Germany, Italy, Spain and United Kingdom (EU5) populations of the GAIN study were assessed.

Method: GAIN is a retrospective study conducted in 2018–2019, in which a sample of secondary care physicians (including hepatologists, gastroenterologists, endocrinologists and diabetologists), recruited from public and private hospitals and practices, provided clinical and resource use information on patients suffering from NASH via an online survey. Participating patients completed a survey including information on direct non-medical and indirect (productivity-related) costs. Average annual direct medical and total costs (direct medical, direct non-medical and indirect costs) were estimated for all patients. An analysis of variance (ANOVA) was conducted comparing difference in mean costs by fibrosis progression status, together with an analysis testing the impact of progression on both medical and total costs after adjustment for confounders.

Results: Out of 2533 patients recruited in the EU5, 60% were male, average age was 56 (standard deviation [SD]: 12) and average body mass index was 30 (SD: 6). Average years since diagnosis was 2.5 (SD: 2.9). Direct medical costs and fibrosis progression status were collected for 2349 patients (93%), while total costs were collected for 644 (27%) patients. The ANOVA showed differences between progressed and non-progressed fibrosis status of €1236 and €10004 for direct medical and total costs, respectively ($p < 0.001$). The multivariable regression analysis found fibrosis progression was correlated with costs after adjusting for clinical and sociodemographic factors, such as age, gender, comorbidities, diagnosis information and treatment decisions (pharmacological, surgical and lifestyle changes). Medical and total costs of patients that progressed increased by 22% and 76%, respectively, vs patients that did not progress ($p < 0.05$), all others remaining constant.



* $p < 0.001$. **Definition of fibrosis status progression:** The physicians were asked in the survey what was the fibrosis stage (0–4) of their patients at two time points: at diagnosis and at the date of consultation. If a patient's fibrosis stage changed to a higher stage, it would be defined that their fibrosis condition progressed. However, if the fibrosis stage changed to a lower stage or remained the same, the patient's fibrosis status would have not progressed. **Abbreviations:** NASH, non-alcoholic steatohepatitis; SD, standard deviation. **Direct medical costs** include pharmacological treatments, consultations, tests and examinations, hospitalizations and surgical procedures. **Total costs** include direct medical costs, direct non-medical costs (sourcing, requirement for aids, transportation and transfer payments) and indirect costs (productivity-related costs, including short/long term absences and early retirement).

Figure: Annual costs due to NASH and fibrosis status progression (€)

Conclusion: The relationship of fibrosis progression and increase in NASH-related costs were retained after adjustment for relevant and potential confounders, which highlights the importance of tackling

fibrosis progression in NASH to reduce future costs not only from the health care systems perspective, but also from the societal perspective.

PO-1609

The impact of liver fibrosis progression on the Health-related quality of life of patients with non-alcoholic steatohepatitis in clinical practice in Europe

Manuel Romero Gomez¹, Jörn Schattenberg², Anum Shaikh³, Leonardo Ruiz Casas³, Gabriel Pedra³, Margarida Augusto⁴, João Diogo da Rocha Fernandes⁵. ¹UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Sevilla, Spain; ²Metabolic Liver Research Programm, I. Departament of Medicine, University Medical Center Mainz, Mainz, Germany; ³HCD Economics, Daresbury, United Kingdom; ⁴Novo Nordisk A/S, London, United Kingdom; ⁵Novo Nordisk A/S, Søborg, Denmark
Email: leo.ruiz@hcdeconomics.com

Background and aims: The disease burden of non-alcoholic steatohepatitis (NASH) has been previously studied, however little is known on the impact of liver fibrosis progression on health-related quality of life (HRQoL). In this analysis, the effect of fibrosis progression on HRQoL in the EU population of the GAIN study was assessed.

Method: GAIN is a retrospective study from 2018 to 2019 in which a sample of secondary care physicians (including hepatologists, gastroenterologists, endocrinologists and diabetologists), recruited from public and private hospitals and practices, provided clinical and resource use information on patients with a NASH diagnosis via an online survey. A subgroup of participating patients completed a survey including information on the HRQoL in the EU population. HRQoL was measured by the EQ-5D-5L and the Chronic Liver Disease Questionnaire for non-alcoholic steatohepatitis (CLDQ-NASH). An analysis of variance (ANOVA) comparing HRQoL scores by fibrosis progression status was performed. Further analyses to test the impact of progression on HRQoL after adjustment for confounders were conducted by a multivariable regression analysis.

Results: Out of 2533 patients recruited in France, Germany, Italy, Spain and United Kingdom, 60% were male, average age was 56 (standard deviation [SD]: 12), average body mass index was 30 (SD: 6) and average years since diagnosis was 2.5 (SD: 2.9). 629 (25%) patients responded to the EQ-5D-5L questionnaire and 607 (24%) responded to the CLDQ-NASH. The ANOVA showed differences between progressed and non-progressed fibrosis status of 0.16 and

0.62 points for the EQ-5D-5L and CLDQ-NASH outcomes, respectively ($p < 0.001$). These differences are higher than the established minimal clinically important differences for both EQ-5D-5L (0.07) and CLDQ-NASH (0.5). The multivariable regression analysis confirmed the impact of fibrosis progression on HRQoL after adjusting for potential confounders where clinical, sociodemographic and treatment decision factors were included. Patients that progressed had lower EQ-5D-5L and CLDQ-NASH scores of 0.12 and 0.34 points, respectively, vs patients that did not progress ($p < 0.05$).

Conclusion: This relationship of fibrosis progression and low HRQoL retained significance after adjustment for potential confounders. These results imply that halting or reversing fibrosis progression could impact HRQoL.

PO-1831

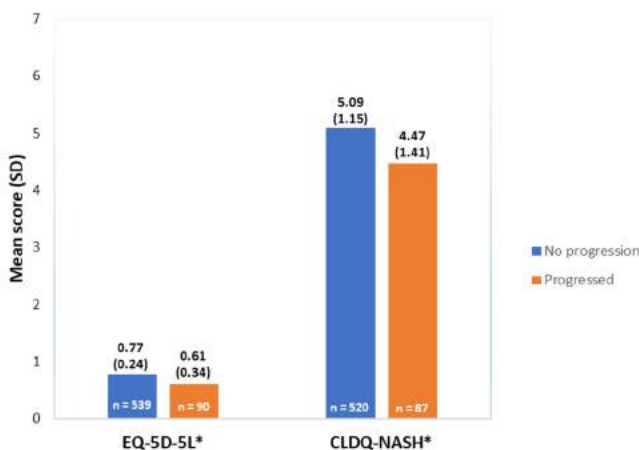
Combinations of an acetyl CoA carboxylase inhibitor, FXR agonist and GLP-1R agonist inhibits fibrosis progression in the rat choline-deficient, L-amino acid defined, high-fat diet model of advanced fibrosis

Archana Vijayakumar¹, Jenny Egecioglu Norlin², Pia Steen Petersen³, Sanne Veidal³, Michael Feigh³, James Trevasik¹, Markus Robert Latta². ¹Gilead Sciences; ²Novo Nordisk; ³Gubra ApS
Email: archana.vijayakumar@gilead.com

Background and aims: Semaglutide (SEMA; glucagon-like peptide-1 receptor agonist), firsocostat (FIR; acetyl CoA carboxylase inhibitor) and cilofexor (CILO; farnesoid X receptor agonist) are being investigated in patients with advanced fibrosis due to NASH. In the AMLN diet-induced murine NASH model, combinations of these agents lowered liver fat, expression of fibrogenesis markers, and NAFLD activity score (driven by improved steatosis and inflammation) more than monotherapies. Here we evaluated the effect of pairwise and triple combinations of SEMA, ACCi (FIR analog) and CILO on fibrosis progression in the rat choline-deficient, L-amino acid defined, high-fat diet (CDHFD) model of advanced fibrosis.

Method: Male Sprague-Dawley rats were fed CDHFD for 12 weeks and treated with SEMA (0.06 mg/kg, sc, qd), ACCi (10 mg/kg, po, qd) and CILO (30 mg/kg, po, qd) alone or in all pairwise and triple combinations from weeks 6–12 ($n = 15$ /group). Separate groups of rats were sacrificed before start of dosing (Baseline), dosed with Vehicle (Veh), or maintained on standard chow. Histopathological and biochemical analyses were performed on terminal liver and plasma biomarkers were measured by ELISA.

Results: SEMA-containing groups demonstrated 9–14% weight loss vs. Veh. Liver fibrosis assessed histologically (picosirius red (PSR) staining) or biochemically (hydroxyproline (HYP) content) was increased by CDHFD in Baseline (PSR: 4.6%, HYP: 0.1 µg/g) and Veh (PSR: 9.8%, HYP: 0.2 µg/g) vs. chow (PSR: 1.2%, HYP: 0.03 µg/g) ($p < 0.05$). All monotherapies partially inhibited fibrosis progression (PSR: 42–52%, HYP: 46–70%) (Figure). Fibrosis progression assessed by PSR was inhibited by 79%, 87%, 69%, and 87%, and HYP increase was inhibited by 93%, 82%, 76% and 99%, in the SEMA + CILO, SEMA + ACCi, ACCi + CILO and triple combination groups, respectively (all $p < 0.05$ vs. Veh) (Figure). Similar trends were observed in immunostaining for markers of fibrogenesis (Col1a1 and α -SMA), activated macrophages and Kupffer cells (Galectin-3) and macrophages (CD68), and plasma biomarkers (HA, PIIINP, TIMP-1, CK18-M30); numerically greater reductions were observed in triple vs. pairwise combinations.



* $p < 0.001$. **Definition of fibrosis status progression:** The physicians were asked in the survey what was the fibrosis stage (0–4) of their patients at two time points: at diagnosis and at the date of consultation. If a patient's fibrosis stage changed to a higher stage, it would be defined that their fibrosis condition progressed. However, if the fibrosis stage changed to a lower stage or remained the same, the patient's fibrosis status would have not progressed. **Abbreviations:** CLDQ-NASH, Chronic Liver Disease Questionnaire for non-alcoholic steatohepatitis; SD, standard deviation.

Figure: Health-related quality of life and fibrosis status progression

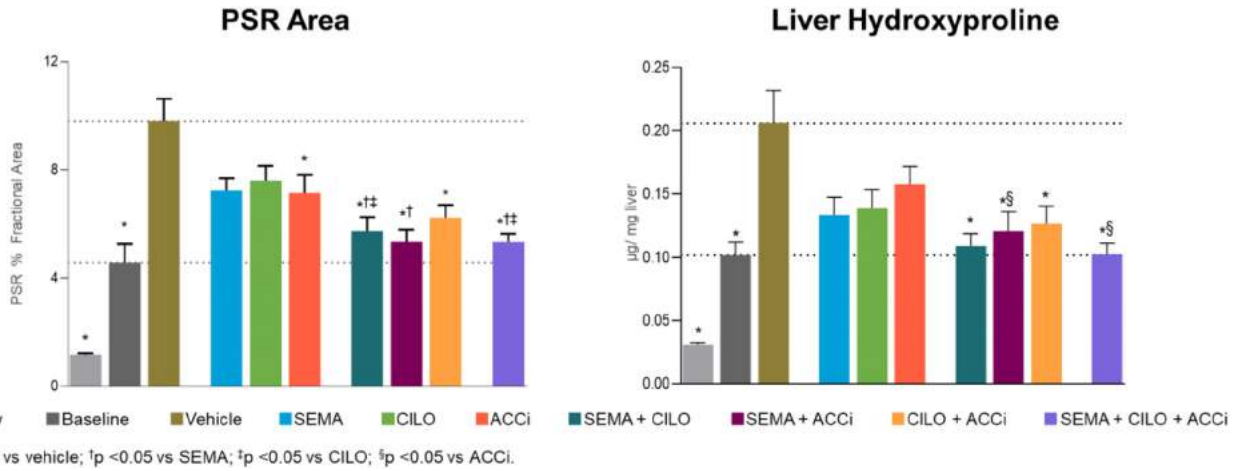


Figure: (abstract: PO-1831)

Conclusion: Pairwise and triple combinations of SEMA, ACCi and CILO almost completely inhibited fibrosis progression in the rat CDHFD model of advanced fibrosis. These data support evaluation of combinations of SEMA, FIR, and CILO to treat patients with advanced fibrosis due to NASH.

PO-1857

AI digital pathology using qFibrosis reveals heterogeneity of fibrosis regression in hepatitis B and C patients with SVR

Feng Liu¹, Yameng Sun², Dean Tai³, Yayun Ren³, Elaine Chng³, Aileen Wee⁴, Pierre Bedossa⁵, Rui Huang¹, Jian Wang¹, Lai Wei⁶, Hong You², Huiying Rao¹. ¹Peking University Hepatology Institute, Peking University People's Hospital Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing, China; ²Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ³Histoindex Pte. Ltd., Singapore; ⁴Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore, National University Hospital, Singapore; ⁵LiverPat SAS, France; ⁶Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, Beijing, China
Email: rao.huiying@163.com

Background and aims: Liver fibrosis is a dynamic process and complex fibrosis patterns comprising progressive and regressive features have been observed, particularly in post-intervention samples. Conventional staging systems are static assessments of fibrosis and lack granularity to examine the heterogeneity of fibrosis features in pre- and post-treatment biopsies, resulting in a less than adequate evaluation of fibrosis regression. The aim of this study is to understand the fibrosis dynamics and its relation to evaluating post-treated viral hepatitis cases by employing second harmonic generation/two-photon excitation fluorescence (SHG/TPEF)

microscopy which provides a reproducible and quantitative analysis for fibrosis features.

Method: 158 paired pre- and post-treatment liver biopsies from hepatitis B (n = 100) and C patients (n = 58) were examined. All hepatitis B patients achieved sustained virologic response (SVR) after 78 weeks of treatment. Hepatitis C cases achieved SVR after 24 weeks. Liver fibrosis was quantitatively assessed by qFibrosis employing SHG/TPEF microscopy and by collagen proportionate area (CPA), according to hepatic regions comprising portal tract (PT), periportal (PP), zone 2 (Z2), pericentral (PC), and central vein (CV).

Results: For biopsies staged F5/6 (Ishak system), all post-treatment cases contained significantly less CPA (11–70%) across all regions when compared to pre-treatment samples, suggesting significant fibrosis reduction, especially septal thinning. For the F3/4 cohort, a similar CPA trend was observed, except in the PC and CV regions where more CPA (9–14%) was observed in the post-treatment cases at 24 weeks. This suggested that the time frame was likely insufficient for resolution of some portal-central bridging. In the F0/1/2 cohort, less CPA (9–42%) was observed across all regions at 78 weeks of treatment while more CPA (30–42%) was observed at the PP and Z2 regions at 24 weeks treatment, suggesting fibrous expansion of residual portal areas.

Conclusion: Following successful antiviral treatment, the pre-and post-treatment liver biopsies provide quantitative evidence for the heterogeneity of fibrosis features even within the same fibrosis stage. Quantitative qFibrosis approach has the potential to provide new insights into the dynamics of fibrosis regression in viral hepatitis cases, as early as 24 weeks after SVR.

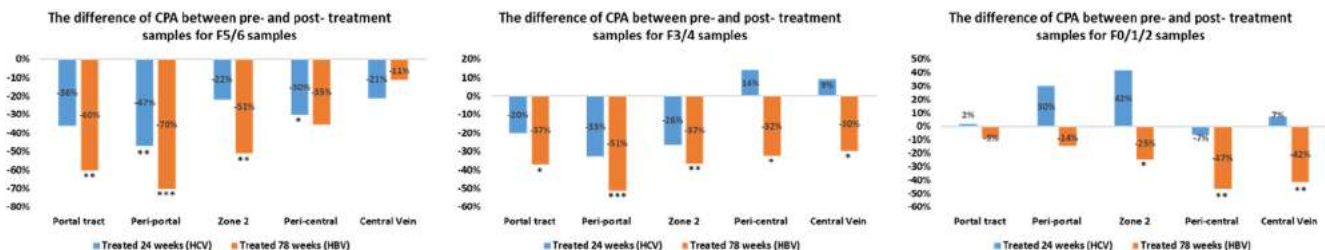


Figure: (abstract: PO-1857) Difference in CPA between pre- and post-treatment liver biopsies from hepatitis B and C patients with SVR

PO-1935

The hepatoprotective role of the antiretroviral drug Rilpivirine is associated with altered autophagy in in vitro and in vivo models of liver fibrosis

Federico Lucantoni^{1,2}, Aleksandra Gruevska^{1,2}, Ángela B. Moragrega^{1,2}, Alberto Martí-Rodrigo¹, Juan V. Esplugues^{1,2,3}, Ana Blas-García^{1,2,3,4}, Nadezda Apostolova^{1,2,3}.
¹Universidad de Valencia, Departamento de Farmacología, Valencia, Spain; ²FISABIO, Valencia, Spain; ³CIBERehd, Spain; ⁴Universidad de Valencia, Departamento de Fisiología, Valencia, Spain
 Email: lucantoni.federico@hotmail.it

Background and aims: Hepatic stellate cells (HSC) play a fundamental role in the liver response to injury, being at the core of liver fibrosis, a major component of virtually all chronic liver disease and a clinical phenomenon for which there are no specific treatments. Autophagy is considered crucial for the trans-differentiation of HSC from quiescent cells to myofibroblasts. Our group has recently described that the anti-HIV drug Rilpivirine (RPV) displays hepatoprotective effects in both animal models and in vitro, including STAT1-dependent induction of apoptosis in HSC. Given this, we studied if RPV affected autophagy in activated HSC.

Method: An *in vitro* approach consisted of HSC (the human cell line LX-2 and human HSC primary cells-hHSC), activated with TGF- β (10 ng/ml) and co-exposed to RPV (1–8 μ M) for 24 or 48 h. We also employed a mouse model of chronic liver disease induced with a high fat diet (HFD) for 12 weeks, in which animals were co-treated with RPV or vehicle.

Results: In LX2 cells co-treated with TGF- β and RPV, the analysis of several autophagic protein markers by WB (LC3, Atg5, Atg7, Beclin-1) revealed minor changes compared to cells exposed to TGF- β only. However, we observed increased formation of autophagolysosomes and lysosomes in both activated LX-2 and hHSC treated with RPV, through single-cell imaging of Lysotracker Red and Cyto-id fluorescent probes. By employing dual fluorescent eGFP-mCherry-p62 or -LC-3 indicators coupled to live cell imaging, we found that activated LX-2 treated with RPV accumulated increased levels of LC3 and p62 in autophagolysosomes. In the same line, livers of HFD mice exposed to RPV displayed decreased p62 and increased LC3-II protein levels, both markers of enhanced autophagy, compared to vehicle-treated HFD mice. The role of autophagy in the response of HSC to treatment with RPV was confirmed by silencing several primary mediators of autophagy-SQSTM1/p62, ATG5 or Beclin1- in activated LX-2 cells. We observed that cells lacking any of the aforementioned proteins and, subsequently, with altered/diminished autophagy, registered increased viability (assayed through an acid phosphatase assay) following RPV treatment.

Conclusion: RPV enhances the process of autophagy in TGF- β -induced HSC and in livers of HFD mouse model of chronic liver injury. These findings may be of relevance in the search of novel anti-fibrotic targets for the treatment of liver diseases.

PO-2113

Proteomic profiling of hepatic stellate cell differentiation from induced pluripotent stem cells: new tools to understand liver development and fibrosis

Raquel A. Martínez García de la Torre¹, Julia Vallverdú¹, Mikel Azkargorta², Félix Elortza², Juan José Lozano^{1,3}, Pau Sancho-Bru^{1,3}.
¹Insititut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) University of Barcelona, Barcelona, Spain; ²Proteomics Platform, CIC bioGUNE, Basque Research and Technology Alliance (BRTA), CIBERehd, ProteoRed-ISCI, Derio, Spain; ³Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain
 Email: rmartinezg@clinic.cat

Background and aims: Hepatic Stellate Cells (HSCs) are the main fibrogenic cell type in chronic liver disease. Understanding the embryonic development of HSCs and their activation is key to

develop new therapeutic strategies. By sequential addition of factors, we have generated functional human HSCs from Induced Pluripotent Stem Cells (iPSC-HSC). Here we performed a proteomic analysis to understand how the iPSC-HSC's differentiation mimics the embryonic development of HSCs and to uncover pathways involved in activation and liver fibrosis.

Method: Human iPSC-HSC were obtained following the protocol described in Coll et al. 2018; Vallverdú et al. 2021. Samples were collected and processed every two days for proteome analysis. Four independent differentiations were analysed and human primary HSCs were used as control. qPCR and FACS analysis were used for validation.

Results: The sequential proteomic profiling of the differentiation showed a reduction of pluripotent markers (RIF1, POU5F1, DPPA4) and an increase in HSC markers (LUM, DCN, PTN, COL1A1 and MMP2) along differentiation. A Pearson's correlation analysis indicated that differentiation occurred in three stages: undifferentiated phase (from day 0 to 4), intermediate foetal stage (from day 6 to 8) and final maturation stage (from day 10 to 12). Developmental markers of foetal HSC, such as VIM, ALCAM, FBLN1 and DCN were sequentially expressed at the foetal stage and were maintained during maturation phase, indicating recapitulation of the embryonic development *in vitro*. Comparison of iPSC-HSC with primary HSCs revealed that signalling pathways involved in HSC activation such as TGF β , PDGFR, VEGF signalling or autophagy were expressed early at the foetal stage, while most pathways involved in liver fibrosis were not expressed. Moreover, we identified a group of proteins that did not change across differentiation but were highly expressed in primary HSCs. DAVID bioinformatics predicted that RORA could be upstream them, thus regulating HSC differentiation. *In vitro* experiments with an agonist (SR1078) confirmed that RORA signalling regulates both HSCs differentiation and the quiescent phenotype.

Conclusion: The proteomic characterization of iPSC-HSC differentiation uncovered the recapitulation of embryonic development of HSCs and pathways involved in cell activation. This study indicates that iPSC-HSC differentiation is a good model to study HSCs biology and explore mechanisms of liver fibrosis.

PO-2415

An integrated approach on immune cell subtype characterization reveals common inflammatory pathways in non-alcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC)

Milessa Silva Afonso¹, Abhishek Aggarwal², David Lopez³, Adrien Guillot⁴, Swetha Pendem¹, Sangeetha Mahadevan², Frank Tacke⁴, Lauri Diehl², Ruchi Gupta¹.
¹Gilead Sciences, Fibrosis, San Mateo, United States; ²Gilead Sciences, NonClinical Safety and Pathobiology; ³Gilead Sciences, Biology Core Support; ⁴Charité University Medicine, Department of Hepatology and Gastroenterology
 Email: milessa.silvaafonso@gilead.com

Background and aims: Inflammation is a key driver for the progression of chronic liver diseases, however the similarities and differences in the immune contributors to liver diseases with different etiologies such as NASH and PSC is not fully understood. Therefore, we used novel technologies to map the immune landscape in the progression of NASH and PSC to provide the basis for therapeutically modulating immune responses.

Method: Transcriptomes of liver biopsies from 158 NASH and 77 PSC patients were analyzed using 200 inflammation signature genes established by the Broad Institute (MIT). To understand the alteration in immune profiling in non-lobular vs lobular areas in liver biopsies from healthy controls (n = 11), and patients with PSC (n = 11), F0-F1 (n = 21), and F4 NASH (n = 12), a 12-plex Ultimapper™ immunofluorescence assay (Ultivue Inc.) was performed. The spatial distribution of immune cell subsets was characterized by a novel sequential multiplex immunostaining method (Figure 1).

Results: RNAseq revealed that 64% and 47% of the inflammation signature genes were upregulated in livers from cirrhotic NASH and

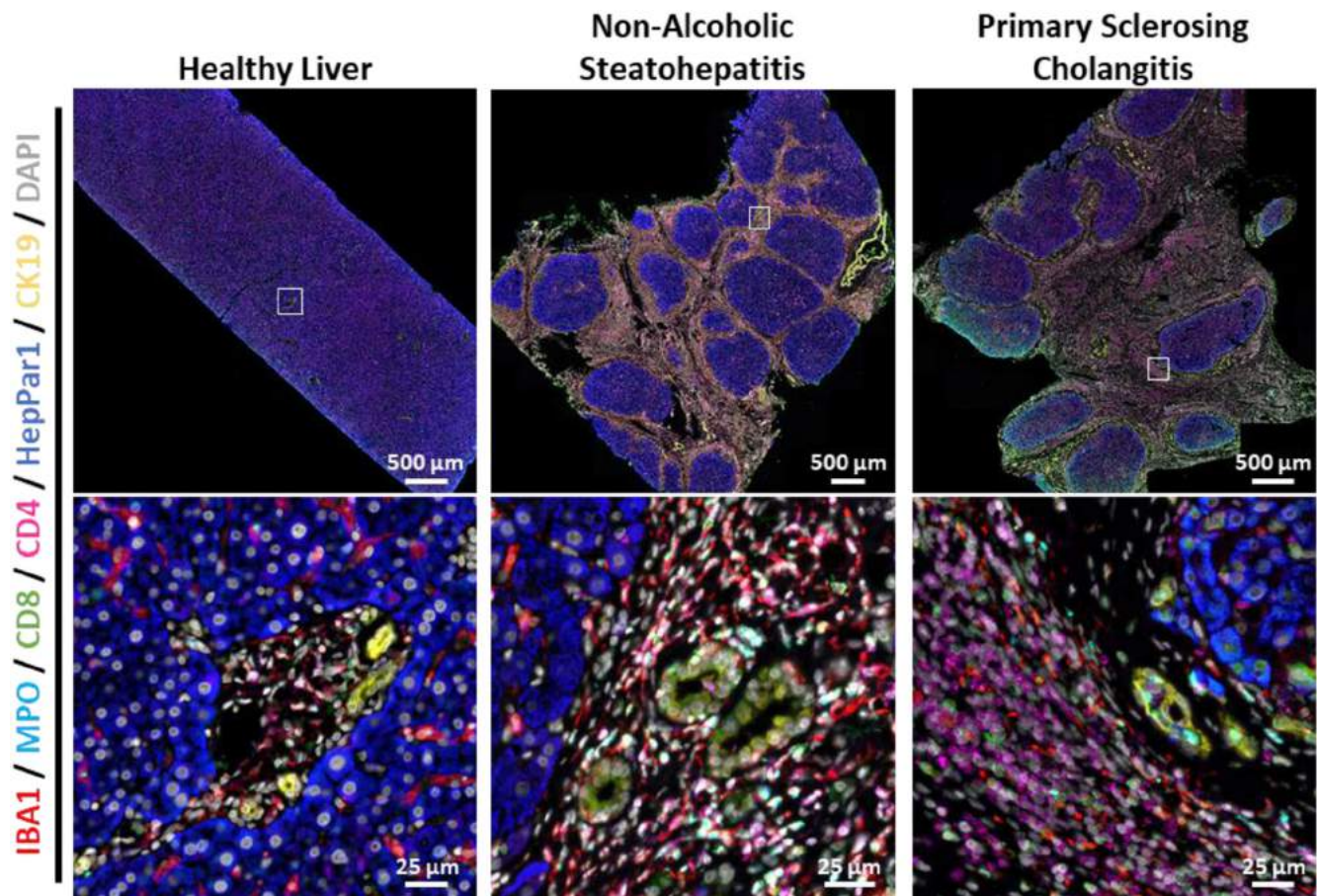


Figure: (abstract: PO-2415) Sequential multiplex immunostaining of biopsies from healthy, NASH and PSC livers

PSC Ishak 6 patients as compared to healthy livers. The highest upregulated genes in both diseases were *CCL20*, *CXCL6/8*, *LIF* and *SLAMF1*. The upregulation in inflammation signature genes was observed as disease progressed and it correlated with fibrosis markers (α SMA: $r = 0.88$, ELF: $r = 0.82$). This increase was accompanied by a 4.5- ($p < 0.05$) and 6.2-fold ($p < 0.01$) increase in CD8⁺ and CD4⁺ T cells, respectively, in non-lobular areas of NASH vs healthy livers. PSC liver samples also showed 11.9-fold {3.2% [0.2–6.2 CI] vs 0.2% [0.1–0.4 CI] healthy} elevation in CD8⁺ T cell infiltration, as well as an 18.5-fold ($p < 0.05$) increase in CD4⁺ T cells vs healthy. A 5.9-fold higher infiltration of FoxP3⁺ regulatory T cells in F4 NASH (0.13% [–0.004–0.26 CI] vs 0.02% [0.01–0.06 CI] F0/F1) and PSC (0.63% [–0.007–1.3 CI] vs 0.01% [0.003–0.02 CI] in Normal) was observed. In the innate immune component, CD163⁺ macrophages were 9-fold ($p < 0.05$) higher in the fibrotic NASH compared to F0/F1. PSC livers showed 11-fold increase in CD163⁺ macrophages {0.5% [0.16–0.82 CI] in Normal to 5.5% [1.4–9.6 CI] PSC}. Soluble CD163 was 1.4- ($p < 0.02$) and 2.5-fold ($p < 0.0001$) higher in NASH and PSC vs healthy, respectively. These data were further confirmed using sequential multiplex immunostaining and unbiased analysis on whole slide imaging from liver sections.

Conclusion: These results contribute to the understanding of the liver immune microenvironment and establish similarities in the inflammatory signature and its involvement in the progression of

NASH and PSC. Together, these approaches provide disease understanding and enable therapeutic discoveries to treat liver diseases.

PO-2695

FIB-4 based algorithm for screening significant fibrosis in diabetes with or without fatty liver in primary care setting

Eileen Yoon¹, Dae Won Jun¹, Su Hyun Park², Seong Ji Choi², Jai Hoon Yoon², Kang Nyeong Lee², Hang Lak Lee², Oh Young Lee², Byung Chul Yoon², Ho Soon Choi². ¹Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine; ²Hanyang University Hospital, Hanyang University College of Medicine
Email: noshin@hanyang.ac.kr

Background and aims: Apart from the NAFLD patients, the effectiveness of FIB-4 or NFS based screening in all diabetic patients regardless of fatty liver status is unknown. We investigated cost-effectiveness of screening algorithm in diabetes in primary care clinic. **Method:** A total of 1,288 who visited the health examination center and underwent the magnetic resonance elastography (MRE) were enrolled. The performance of FIB-4 and NFS was compared in diabetes patients. And diagnostic performance and cost-effectiveness according to screening algorithm were evaluated in three kinds of target population (diabetes, sonographic fatty liver, and elevated liver enzyme group). If FIB-4 value (≥ 1.3) falls into intermediate or

high-risk group, FIB-4 was followed by transient elastography. Lifestyle modification and monitoring prescribed to suspected significant hepatic fibrosis if hepatic fibrosis suspected in transient elastography.

Results: The prevalence of significant fibrosis ($\geq F2$) was 3.9% in total cohort, 5.9% in patients with sonographic NAFLD patients, and 14.2% in diabetes. Prevalence of significant fibrosis was considerable in patient with diabetes without fatty liver (6.7%). Area under the curve of the receiver operating characteristic (AUROC) of FIB-4 and NFS for significant fibrosis was similar in sonographic NAFLD subjects. But AUROC was of FIB-4 was slightly higher than NFS in diabetes without statistical significance (0.688 vs. 0.582, $P = 0.05$). Application of FIB-4 based algorithm for detecting significant fibrosis in diabetes showed comparable positive predictive value (31.4% vs. 7.6%) and sensitivity (22.0% vs. 18.0%) compared to sonographic NAFLD without decreasing NPV (96.9% vs. 96.5%). FIB-4 based algorithm in diabetic patients reduced unnecessary referral rate by 23.8% compared to NAFLD subjects. One-time FIB-4 based screening and lifestyle modification showed cost-effectiveness ratios (ICER) of 21, 849 \$USD per quality-adjusted life year.

Conclusion: FIB-4 based transient elastography screening algorithm for significant hepatic fibrosis in patients with diabetes was cost effective.

PO-2790

Liver fibrosis accumulation depends on underlying disease aetiology

Adam Watson¹, Rajarshi Banerjee², Jane D. Collier³, Jeremy Cobbold³, Stefan Neubauer^{4,5}, Eleanor Barnes^{3,5}, Lai Mun Wang⁶, Kenneth Fleming⁶, Michael Pavlides^{3,4,5}. ¹Medical Sciences Division, University of Oxford, Oxford, United Kingdom; ²Perspectum Ltd, Oxford, United Kingdom; ³Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; ⁴Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom; ⁵NIHR Biomedical Research Centre, University of Oxford, Oxford, United Kingdom; ⁶Department of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom

Email: adam.watson@hertford.ox.ac.uk

Background and aims: Traditional histological fibrosis assessment is categorical and describes progression from portal tract expansion, to bridging fibrosis to nodule formation. Morphometry by collagen proportionate area (CPA) estimation provides a quantitative evaluation of fibrosis. The aim of this study was to evaluate fibrosis progression using categorical scores and morphometry according to liver disease aetiology.

Method: Consecutive patients who had undergone liver biopsy for the assessment of diffuse liver disease were included. Liver histology slides stained with Sirius red were scanned to produce digital images which were then manually processed using ImageJ to calculate the CPA. Fibrosis was independently assessed using the Ishak staging system and categorised as mild (F0-2), moderate (F3-4) or severe (F5-6) fibrosis. All analyses were blinded. Aetiology was classified as either alcohol related liver disease (ARLD), non-alcoholic fatty liver disease (NAFLD), viral (chronic hepatitis B or C), or autoimmune (PBC, PSC or autoimmune hepatitis; AIH) liver disease. ANOVA was used to test for significance between groups.

Results: We included 137 patients (mean age 52 years, 39% female) for whom CPA strongly correlated with Ishak stage ($r_s = 0.76$, $p < 0.0001$). Mean CPA was 7.5% for mild fibrosis ($n = 28$), 9.3% for moderate fibrosis ($n = 56$) and 25.9% for severe fibrosis ($n = 53$). As fibrosis progressed through categorical classifications the mean CPA also increased in the ARLD ($n = 26$), NAFLD ($n = 57$) and viral ($n = 35$) groups ($p < 0.0001$); however, there was no significant increase in CPA for the autoimmune group ($n = 19$; $p = 0.11$). There was no variation in CPA across aetiological groups for mild ($p = 0.19$) and severe fibrosis ($p = 0.15$); however, there was a significant difference

between ARLD and autoimmune groups for moderate fibrosis ($p = 0.036$).

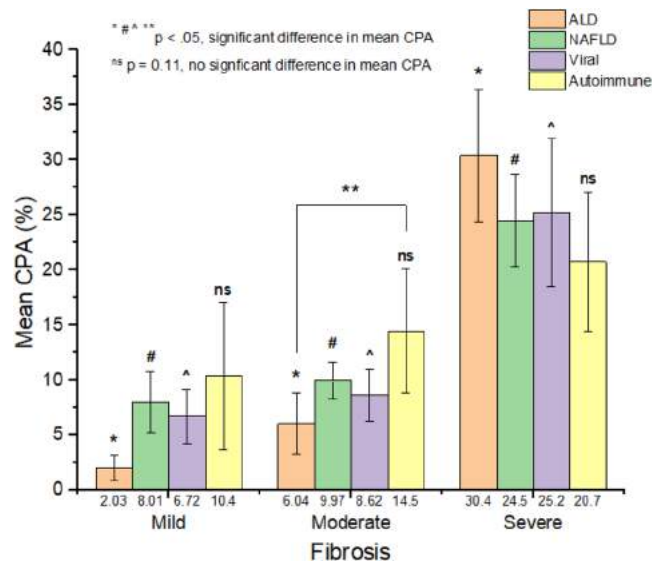


Figure: Mean CPA (%) for aetiological groups at each stage of fibrosis, with 95% confidence intervals shown.

Conclusion: Our data suggest that disease progression in patients with PBC, PSC and AIH is characterised primarily by architectural changes without significant changes in the amount of fibrosis, while in other aetiologies, fibrosis increases are commensurate with architectural changes. These findings may be confounded by the aetiological heterogeneity within the autoimmune group, therefore, confirmation of these findings in larger studies is warranted.

Gut microbiota and liver disease

PO-418

Rifaximin and Fecal Microbiota Transplant beneficially modulate gut metagenomic virulence factors in cirrhosis: Analysis of two trials

Jasmohan S. Bajaj¹, Amirhossein Shamsaddini², Andrew Fagan¹, Richard Sterling¹, Chathur Acharya¹, Hannah Lee¹, Edith Gavis¹, Masoumeh Sikaroodi², Patrick Gillevet². ¹Virginia Commonwealth University and Richmond VAMC, Richmond, United States; ²George Mason University
Email: jasmohan.bajaj@vcuhealth.org

Background and aims: Cirrhosis is linked with altered gut microbiota and higher pathobionts, which can carry several virulence factors (VFs). However, the role of therapies such as rifaximin or fecal microbiota transplant (FMT), in reducing this burden in cirrhosis is unclear.

Aim: Define change in metagenomic VF abundance with a trial of rifaximin in compensated cirrhosis and randomized trial of capsule FMT in decompensated cirrhosis.

Methods: Rifaximin trial: 20 cirrhotic outpts with compensated cirrhosis were given open-label 550 mg BID rifaximin for 8 weeks. Stool was collected pre/post rifaximin. Capsule FMT trial: 20 cirrhotic outpts with hepatic encephalopathy (HE) already on lactulose and rifaximin were randomized 1:1 into receiving 15 capsules of FMT enriched in beneficial Lachnospiraceae and Ruminococcaceae or placebo. Stool was collected at baseline and 4 weeks post-intervention. Changes were compared to metagenomics of the healthy donor. Microbial analysis: Metagenomics was performed

POSTER PRESENTATIONS

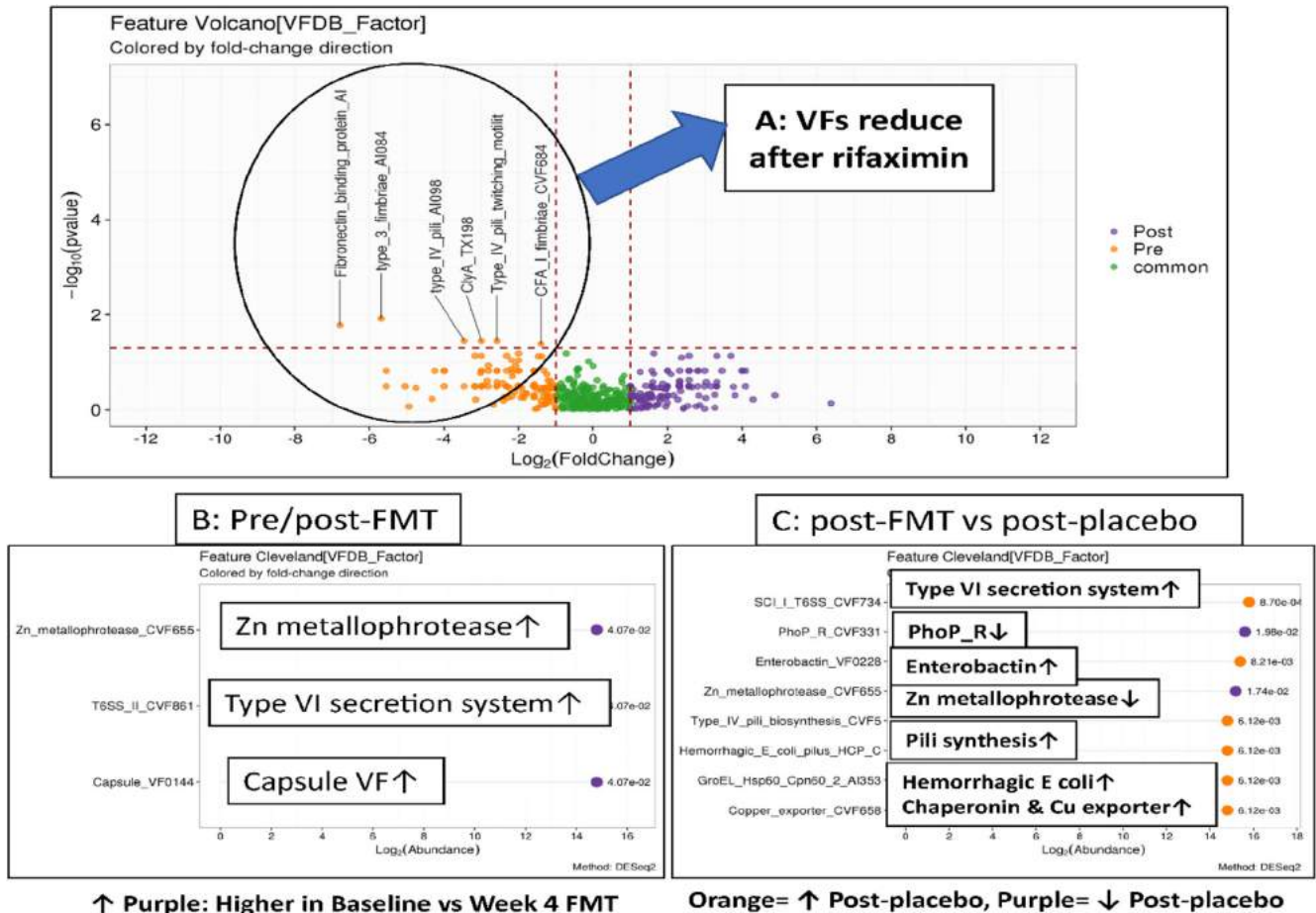


Figure: (abstract: PO-418) Changes in Virulence Factor Abundances after Rifaximin and Fecal Microbiota Transplant

for VFs using the virulence factor database. Comparisons pre vs post-rifaximin and pre vs post-FMT and post-FMT vs post-placebo were performed.

Results: Rifaximin trial: 20 pts (14 men, MELD 10, 60 yrs) were included and safely completed the trial. There was an increase in beneficial taxa belonging to *Butyrivimonas* and *Ruminococcus*. Fig A shows reduction in VFs that code for pili, fimbrial proteins and fibronectin that are related to Enterobacteriaceae spp after rifaximin compared to baseline. FMT trial: 10 randomized to FMT vs 10 placebo; groups were matched for demographics and cirrhosis severity (8 men/group, MELD 11 both, age 64 vs 63 yrs). MELD and disease remained stable at 4 weeks. Post-FMT showed a reduction in capsule encoding and secretion system vs pre-FMT (Fig B). Post-FMT there was a reduction in several VFs belonging to Enterobacteriaceae spp (pili, enterobactin, chaperonins) vs post-placebo (Fig C). There was an increase in 2 factors belonging to Mycobacteria (Zn metallophrotease and Phop/R) post-FMT, which were not transmitted by the donor.

Conclusion: Virulence factors that increase the pathogenicity of Enterobacteriaceae spp are reduced by rifaximin therapy in compensated cirrhosis and by capsule FMT in decompensated patients with cirrhosis. Precision therapies aimed at reducing the VFs in pathogens could potentially improve outcomes and may be mechanisms of action of rifaximin and FMT.

PO-799

Response failure to ursodeoxycholic acid treatment in primary biliary cholangitis is associated with a distinct stool and urine secondary bile acid profile

Laura Martinez-Gili¹, Alexandros Pechlivanis¹, Sofina Begum², George Mells³, Elaine Holmes², David Jones⁴. ¹Imperial College London, Division of Systems Medicine, Department of Metabolism, Digestion and Reproduction, London, United Kingdom; ²Imperial College London, Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, London, United Kingdom; ³Cambridge University Hospitals NHS Foundation Trust, Department of Hepatology; ⁴Newcastle University, Institute of Translational and Clinical Research, Newcastle-upon-Tyne, United Kingdom
Email: laura.martinez@imperial.ac.uk

Background and aims: Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease that can lead to progressive liver damage. The first-line treatment for PBC is ursodeoxycholic acid (UDCA); a hydrophilic bile acid which delays disease progression and improves biochemical markers of liver damage such as serum alkaline phosphatase (ALP). Patients who do not respond to UDCA have persistently altered serum biochemistry which is associated with higher risk of liver transplant and lower survival. Mechanisms underlying treatment failure remain unknown. We profiled patient bile acids (BA) to investigate whether differing treatment responses relate to changes in BA metabolism.

Method: Serum, urine and faeces of 454 patients in the UK-PBC cohort treated with UDCA for 1 year were collected and BA profiled with Ultra-Performance Liquid Chromatography coupled to Mass Spectrometry (UPLC-MS). Linear mixed effects models were fitted to each BA feature to assess differences across treatment responses, while adjusting for age, gender, body mass index, alcohol consumption, smoking, antibiotics and proton pump inhibitors as fixed effects, and sample collection site as random effect. Likelihood ratio test was used to assess significance, p values adjusted using the

Benjamini-Hochberg method and null hypothesis rejected with adjusted p value <0.1.

Results: We defined 3 response groups: responders with good prognosis (R_GP; n = 224), with a >40% reduction or normalised ALP levels after 1 year of treatment, responders with bad prognosis (R_BP; n = 16), with reduced ALP still higher than 1.67 times the upper limit of normal, and non-responders (NR; n = 214), who failed to reduce ALP. 12 stool and 8 urine BA were differently abundant, while there were no differences in serum. Stool BA displayed opposite trends in R_BP and R_GP with respect to non-responders (Figure); faecal UDCA increased in R_GP (95% CI [0.05, 0.23]) but not in R_BP (95% CI [-0.2, 0.25]). Urine BA decreased in R_GP, except for 12-Dehydrocholic acid (95% CI [0.06, 0.36]). In addition, the total pool of glycosylated BA in R_GP was higher in stool (95% CI [0.04, 0.17]), and lower in urine (95% CI [-0.19, -0.55]) compared to NR.

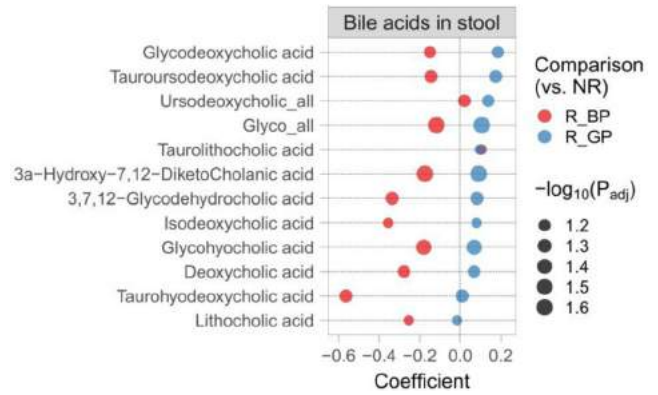


Figure:

Conclusion: Response to UDCA treatment is associated with a different bile acid signature in PBC, mainly involving microbial-derived secondary BA. These findings suggest a contribution of the intestinal microbiota to the response phenotype.

PO-1558

Hepatobiliary Phenotype of Individuals with Chronic Intestinal Disorders-The Gut-Liver Axis in UKBiobank

Jessica Voss¹, Carolin Victoria Schneider¹, Moritz Kleinjans¹, Tony Bruns¹, Christian Trautwein¹, Pavel Strnad¹. ¹Medical Clinic III, Gastroenterology, Metabolic diseases and Intensive Care, University Hospital RWTH Aachen, Medical Clinic III, Aachen, Germany
Email: pstrnad@ukaachen.de

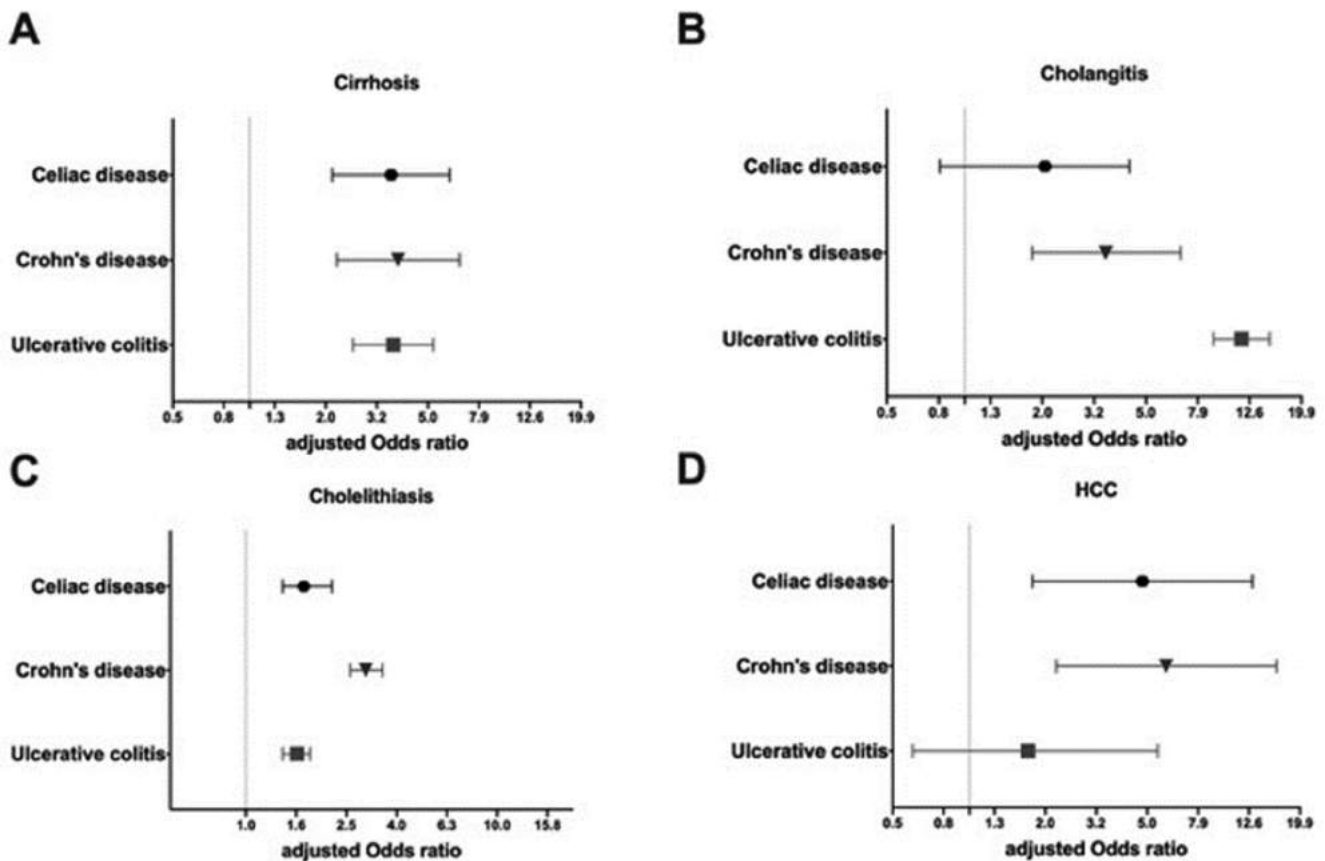


Figure: (abstract: PO-1558): Odds ratios to display selected ICD10 diagnoses in individuals with celiac disease, Crohn's disease, and ulcerative colitis compared to controls. Adjusted odds ratios (OR) with their corresponding 95% confidence intervals (CI) are shown. Odds ratios were adjusted for age, sex, BMI, alcohol consumption and diabetes mellitus. HCC, hepatocellular carcinoma.

POSTER PRESENTATIONS

Background and aims: While experimental data demonstrate a close relationship between the gut and the liver, the clinical consequences of this functional circuit remain poorly defined. Thus, we assessed the hepatobiliary phenotype of individuals with celiac disease (CeD), Crohn's disease (CD) and ulcerative colitis (UC) using the UK Biobank community sample.

Method: Baseline liver function tests and the frequency of hepatobiliary diseases were analyzed in 2377 CeD, 1738 CD, 3684 UC subjects, and 488941 controls prospectively recruited in 22 participating centers in the United Kingdom. Associations were adjusted for age, sex, BMI, diabetes, and alcohol consumption.

Results: Compared to controls, individuals with CeD, but not CD/UC displayed higher AST/ALT values. Subjects with CD/UC but not CeD had increased GGT levels. Elevated ALP and cholelithiasis were significantly more common in all intestinal disorders, but were most prominent in subjects with CD (aOR = 3.0 [2.6–3.5]). Non-alcoholic steatohepatitis and hepatocellular carcinoma (HCC) were enriched in CeD and CD (HCC: aOR = 4.8 [1.8–13.0] in CeD, aOR = 5.9 [2.2–16.1] in CD), while cholangitis was more common in CD/UC individuals. Chronic hepatitis, autoimmune hepatitis, and cirrhosis were more prevalent in all intestinal disorders. Non-alcoholic steatohepatitis was the most prevalent cause of cirrhosis in CD and CeD, while cholangitis was the most frequent one in UC. In UC/CD, a history of intestinal surgery was associated with elevated liver enzymes and increased occurrence of gallstones.

Conclusion: Our data demonstrate that different intestinal disorders predispose to distinct hepatobiliary phenotypes. An increased occurrence of liver cirrhosis and HCC in all analyzed disorders warrants a more thorough hepatologic surveillance, particularly in individuals with additional risk factors such as obesity or diabetes.

PO-1763

Rifaximin suppresses gut-derived systemic inflammation and promotes a gut microenvironment with reduced mucin degradation conducive to gut barrier repair in patients with cirrhosis and hepatic encephalopathy

Vishal C. Patel^{1,2,3}, Sunjae Lee⁴, Mark J. W. McPhail⁵, Ane Zamalloa¹, Elizabeth Witherden⁴, Sidsel Støy⁶, Godhev Manakkat Vijay⁵, Xiaohong Huang⁵, Selin Gencer⁷, Muireann Coen⁷, Thomas Tranah⁵, Julia Wendon⁵, Kenneth Bruce⁸, Dusko Ehrlich⁹, Lindsey A. Edwards⁵, Saeed Shoaie⁴, Debbie L. Shawcross⁵. ¹King's College Hospital NHS Foundation Trust, Institute of Liver Studies, United Kingdom; ²Institute of Hepatology, London, United Kingdom; ³King's College London, Institute of Liver Studies, Department of Inflammation Biology, School of Immunology and Microbial Sciences, FoLSM., London, United Kingdom; ⁴King's College London, Centre for Host-Microbiome Interactions, Dental Institute, London, United Kingdom; ⁵King's College London, Institute of Liver Studies, London, United Kingdom; ⁶Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; ⁷Imperial College London, Biomolecular Medicine, Division of Computational and Systems Medicine, Department of Surgery and Cancer, London, United Kingdom; ⁸King's College London, Institute of Pharmaceutical Science, London, United Kingdom; ⁹Institut National de la Recherche Agronomique, Metagenopolis, Paris, France
Email: debbie.shawcross@kcl.ac.uk

Background and aims: Rifaximin is efficacious in the prevention of recurrent hepatic encephalopathy (HE) but its mechanism of action remains unclear. We postulated that rifaximin reduces gut microbiota-derived endotoxemia and systemic inflammation, a known driver of HE.

Method: A randomised placebo-controlled double-blind study of rifaximin versus placebo [NCT02019784] was performed in 38 patients with cirrhosis and HE. Rifaximin- α 550 mg (TARGAXAN) twice daily (n = 19) or placebo (n = 19) was administered for 90-days. Primary outcome: 50% reduction in neutrophil oxidative burst (OB) at 30-days. Secondary outcomes: Psychometric Hepatic Encephalopathy Scale (PHES) testing, shotgun metagenomic

sequencing of saliva and faeces, plasma/faecal metabolome, blood bacterial DNA, neutrophil Toll-like Receptor-4 expression (TLR4) and plasma/faecal cytokine analysis.

Results: Patients were well-matched: baseline median MELD [11 rifaximin versus 10 placebo], ammonia and HE grade. Participants on rifaximin- α normalised their HE grade by day-30 [grade 1 to 0; p = 0.014]. Trail's A improved on rifaximin- α over 90-days; p = 0.012 and line tracing was significantly improved compared to placebo; p = 0.023. Neutrophil OB did not change but reduced neutrophil TLR-4 expression was observed in rifaximin-treated patients with a significant reduction in plasma tumour necrosis factor- α (TNF- α); p < 0.001. Rifaximin- α suppressed oralisation of the gut microbiome by reducing *Streptococcus spp*, *Veillonella parvula* and *Veillonella atypica*, mucin-degrading species rich in sialidase. Rifaximin- α promoted a gut microenvironment rich in TNF- α and IL-17E augmenting local host antimicrobial immunity and gut barrier repair. Those on rifaximin- α were less likely to develop an infection; odds ratio for developing an infection on rifaximin- α compared to placebo was 0.208 (0.045–0.959).

Conclusion: Rifaximin- α improved HE reducing oralisation of the gut with mucin-degrading species such as *Streptococcus spp*, *Veillonella parvula* and *Veillonella atypica* ameliorating bacterial translocation and systemic inflammation in association with improved clinical outcomes including reducing the likelihood of developing infection. These novel data for the first time link rifaximin- α as having a role in gut barrier repair as a mechanism by which it ameliorates bacterial translocation and systemic endotoxemia in cirrhosis.

PO-2010

Ethanol induced alterations in intestinal microbiota correlate with decreased intestinal nuclear receptor (PXR) pathway related proteins

Sudrishti Chaudhary¹, Adil Bhat¹, Anupama Kumari¹, Archana Rastogi¹, Guresh Kumar¹, Jaswinder Singh¹, Shiv Sarin¹, Shvetank Sharma¹. ¹Institute of Liver and Biliary Sciences, New Delhi, India
Email: shvetanks@gmail.com

Background and aims: Alcohol associated liver disease (ALD) leads to gut bacterial dysbiosis and intestinal dysfunction along with increased gut permeability. Pregnane X receptor (PXR), a ligand activated nuclear receptor has been implicated in transcriptional regulation of intestinal barrier integrity and inflammation. We investigated whether intestinal PXR expression plays a role in gut microbiota homeostasis affecting hepatic function in a mouse model of ALD.

Method: Male C57BL/6N type mice were fed with Lieber-DeCarli diets 0% to 25% (w/v) alcohol (gradual increase up to 12 weeks) whereas pair fed mice received an isocaloric liquid diet as control. Serum levels of ALT/AST and endotoxins were determined. Fecal microbiota was assessed using 16 s rRNA. Proteome linked to liver steatosis, injury and intestinal barrier integrity were evaluated by LC-MS.

Results: Chronic EtOH feeding increased serum ALT, lipopolysaccharide and liver injury in mice. These injurious effects in liver (both necrosis and fibrosis) were pronounced at 12 wks compared to 4 or 8 weeks. Alcohol exposure resulted in loss of normal villus structure of the ileum and downregulation of intestinal epithelial tight junction proteins *in vivo* and *in vitro*. Proteomic analysis of intestinal tissue revealed downregulation (>1.5-fold than control, p < 0.05) of several proteins involved in antimicrobial defence (Defa20, Reg3b and Reg3d) and anti-oxidative proteins (Sod1, GPX, GR, and Gsto1) whereas inflammation and injury related proteins linked with the RelA mediated NfKB pathway (Tgfb1, Il1rap, and Ccr6) showed upregulation (FC > 1.5, p < 0.05) in EtOH fed mice. Moreover, EtOH exposure in mice showed downregulation of proteins such as Cyp3a11 (FC < 1.5, p < 0.05) important for xenobiotic/bile acid detoxification linked to PXR. Further, gut microbiome alterations

revealed significant changes in EtOH versus control mice that may contribute to a higher inflammatory response. Short chain fatty acid producing bacteria such as *Chlorobaculum* and *Lachnospira* were altered prominently in EtOH and positively correlated ($r > 0.7$, $p < 0.05$) with the PXR proteins involved in tight junctions and PPAR signaling. *Coriobacterium* and *Galenea*, the secondary bile acid-producing bacteria correlated negatively with the downregulated protein Apo1 and Cyp1a2 involved in drug metabolism and AMPK signaling pathway ($r < 0.7$, $p < 0.05$).

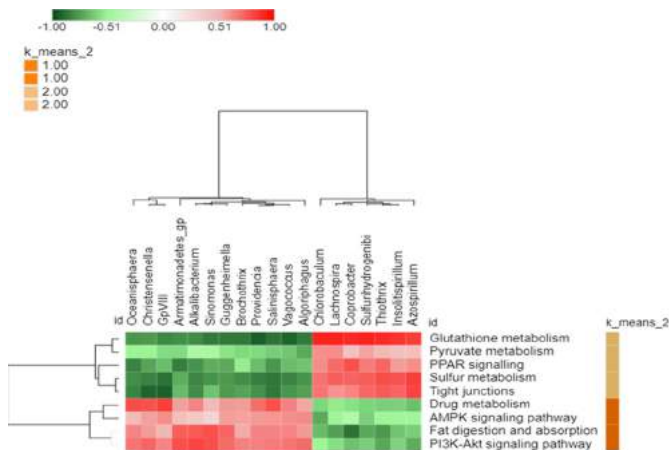


Figure: Functional annotation of change in intestinal PXR associated pathways and correlation with microbiota identified by KEGG analysis

Conclusion: Long term EtOH consumption promotes disruption in intestinal PXR expression. The identified bacterial families correlate with PXR linked proteins and pathways suggesting an important role of nuclear receptors in tissue injury which could be explored as therapeutic targets in advance stage of alcoholic liver disease to prevent dysbiosis.

PO-2363

Role of farnesoid-X receptor agonist in ameliorating NASH-disrupted intestinal permeability: Potential impact of autophagy on tight junctions

Rasha Tawfiq¹, Noha Nassar², Olfat Hammam³, Mohamed Elmazar¹, Dalaal Abdallah², Yasmeen Attia¹. ¹The British University in Egypt- Faculty of Pharmacy, Pharmacology and Biochemistry, Cairo, Egypt; ²Cairo University-Faculty of Pharmacy, Egypt; ³Theodor Bilharz Research Institute, Pathology Department, Egypt
Email: dalaal.abdallah@pharma.cu.edu.eg

Background and aims: Multiple lines of evidence point to the role of impaired intestinal permeability and bacterial translocation (BT) in promoting pro-inflammatory events in the liver mediated by Toll-like receptors (TLRs) leading to the progression of steatosis to non-alcoholic steatohepatitis (NASH). A relation between autophagy and intestinal integrity exists, however, the pivotal role of farnesoid-X-receptor (FXR) in maintaining intestinal homeostasis and autophagy is noticeable. The present study aimed at investigating the effect of the FXR agonist, obeticholic acid (OCA), on BT and autophagy to ameliorate NASH-related incidents and its mechanism of action.

Method: Eight-week male mice (n = 3–7) were fed an atherogenic high fat diet (AHFD) for 13 weeks. Mild intestinal inflammation was induced by 0.5% dextran sulfate sodium (DSS) in drinking water applied in cycles of 7 days followed by a 10-day interval of drinking water. OCA treatment started at week 10 (5 mg/kg/day, p.o. for 4 weeks). Intestinal permeability was evaluated using FITC-dextran, serum LPS, LBP levels by ELISA and tight junction (TJ) proteins, zonulin (ZO)-1, claudin-1 and occludin, by immunohistochemistry (IHC). Histopathological examination of liver, ileum and colon samples was performed along with IHC of ileal and hepatic TLR-4 and transforming growth factor (TGF)-beta1. Autophagy genes

expression, ULK1, BCLN-1, ATG5, were determined using qRT-PCR and LCII/I ratio was assessed by western blotting. Hepatic and ileal pAkt protein levels were assessed by ELISA. Statistical significance ($p < 0.05$) was determined using one-way ANOVA followed by Tukey-Kramer post hoc test.

Results: OCA preserved intestinal integrity through potentiating ZO-1, claudin-1 and occludin protein expression accompanied with histopathological amelioration of intestinal inflammation and NASH and normalization of serum FITC level with no change in LPS and LBP. This was accompanied by ileal autophagy activation where ATG5 gene was upregulated and ileal LC3II/I increased. Moreover, OCA immunomodulatory effect was obvious in reduction of hepatic and ileal TLR-4 and TGF- beta1, however, no noticeable change was shown in pAkt.

Conclusion: The FXR agonist, OCA, ameliorated bacterial translocation through affecting intestinal permeability, autophagy and immunity subsequently NASH-related events in a combined animal model of NASH and intestinal impairment through TLR4/TGF-beta1 suppression independently of PI3k/Akt.

PO-2914

Fecal microbiota transplantation (FMT) for corticosteroids (CS) non-responders and non-eligible (NoReNE) patients with severe alcoholic hepatitis (SAH)

Natalia Bystrianska¹. ¹FD Roosevelt University Hospital, HEGITO (Division of Hepatology, Gastroenterology and Liver Transplantation, Banská Bystrica, Slovakia
Email: naty2121@centrum.sk

Background and aims: Severe alcoholic hepatitis is one of the most serious forms of alcohol associated liver disease (ALD) with high mortality. The only recommended treatment option-corticosteroids (CS) show modest short-, and none long-term survival benefit. Unfortunately, the number of these patients (pts) is increasing and there is no alternative treatment. Recently, fecal microbiota transplantation (FMT) has gained attention as a potential therapeutic approach for ALD. We aimed to evaluate the impact of FMT on survival in NoReNE patients (pts) with SAH as determined by Lille-model.

Method: From 1/2018 to 12/2020, we performed FMT in 23 SAH patients. We recorded demographic, clinical and laboratory parameters before and after FMT. We used frozen faecal material from unrelated donors, delivered via upper GI tract in dose 100 ml over 5 days. Donors were selected according to general recommendations.

Results: We analyzed 23 patients (9 women and 14 men) with mean age, MELD-Na score, and Maddrey function of 46, 29, and 72, 5 respectively. In our cohort 18 pts were NoRe, and 5 pts were NE for full course CS. Sixteen pts had acute-on-chronic liver failure (ACLF) : ACLF 1:6 pts, ACLF 2: 6 pts, ACLF 3: 4 pts. Our data showed no statistically significant difference in MELD score, ACLF score, CRP and INR before and 7 days after FMT, except total bilirubin (p-value = 0.077). Observed 30-, and 90-day mortality was 26%, and 61%, respectively; in literature, these figures are 20–35% and 75% respectively.

POSTER PRESENTATIONS

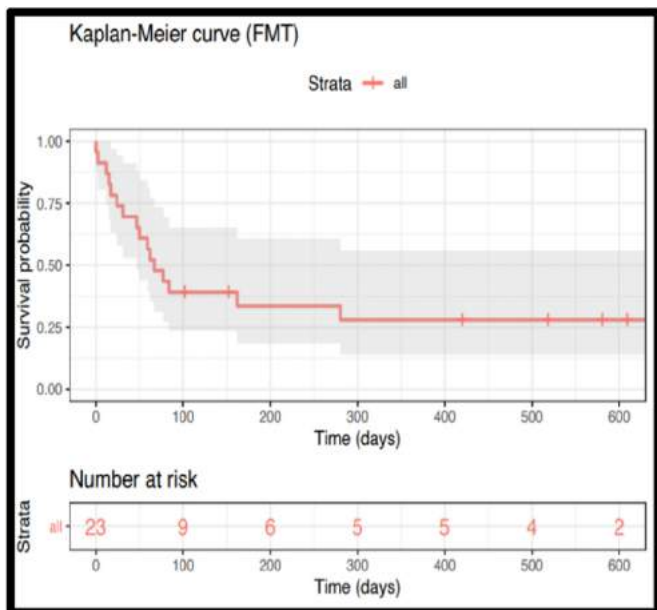


Figure:

Conclusion: SAH in CS non-responders/-eligibles is associated with high mortality, especially with ACLF. FMT offers alternative treatment option but we haven't documented clear survival benefit. We need larger, deeper and more granular analysis to determine, which patient's characteristics predict survival benefit.

Imaging and drug targeting

PO-301

Artificial Intelligence in medical imaging of the liver-a convolutional neural network solution for Computed Tomography exam phases recognition

João Martins Cortez Filho^{1,2}, Luis Gustavo Rocha Vianna³, Ana Ciconelle³, Bruno Aragão Rocha^{3,4}, Jean Michel Rocha Sampaio Leite⁵, Lucas Salume Lima Nogueira^{1,2}, Lenon Liberdade Alvares Guimarães³, Maurício Ricardo Moreira da Silva Filho⁴, Lorena Carneiro Ferreira⁴, Brunna Oliveira⁶, Wesley Borges de Paiva⁴, Ricardo di Lazzaro Filho^{3,7}, Suzane Kioko Ono^{1,2}. ¹Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil; ²Hospital das Clínicas da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil; ³MaChiron, São Paulo, Brazil; ⁴InRad-Instituto de Radiologia, São Paulo, Brazil; ⁵Faculty of Public Health, University of São Paulo, São Paulo, Brazil; ⁶USCS-Municipal University of São Caetano do Sul, São Caetano do Sul, Brazil; ⁷Instituto de Biociências-USP, São Paulo, Brazil
Email: joao.mcfilho@fm.usp.br

Background and aims: Contrast-enhanced Computed Tomography (CT) liver exams most commonly have four phases: unenhanced, arterial, portal and delayed, that are important to characterize different focal liver lesions, such as hepatocellular carcinoma. Those exams are usually in DICOM format, which contain exam-related information in tags that could identify each phase, but there is no standard in the annotation of those tags. i.e. there is large variation

between different CT machines and technologists. Hence, lack of standardized DICOM tags impairs the creation of automatic solutions using those labels. The aim of this project is to generate a fully automated solution to recognize each phase of the exam from the original DICOM data using only imaging data, which will facilitate the creation of CT exams databases and development of artificial intelligence (AI) systems for liver segmentation and lesions identification.

Method: A database with 121 CT scans of healthy liver donors and chronic hepatitis patients was built from the radiology archive of our institution. We developed an AI algorithm using convolutional neural networks (CNN) to assign a score to each input slice for all possible phases. The corresponding phase with the highest score is then chosen as the predicted label and compared to the true label of each volume to evaluate its accuracy, using a confusion matrix, as shown below. From the database, for training, validation and testing, about 70%, 15% and 15% of the patients were randomly selected, respectively, totalling 484 volumes and 67177 slices. All implementation was performed using Python with Keras and Tensorflow packages.

Results: The best CNN model predicted the correct phase in 85.4% of the images and in 94.4% of the volumes of the testing set, when combining each slice prediction into a single volume prediction. When analysing the volume prediction for each phase, the model predicted correctly 100% of the unenhanced, 94.4% of the arterial, 94.4% of the portal and 88.9% of the delayed volumes.

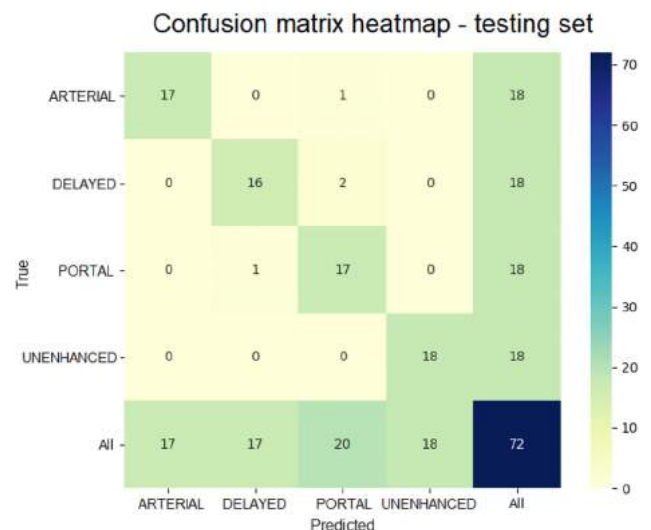


Figure:

Conclusion: We developed an algorithm to recognize the CT phases of exams in DICOM format, with good performance. This algorithm is important for the creation of CT liver exams databases and our study successfully demonstrated its deployment in practice. This fully automated AI solution can potentially be incorporated in other radiology-pipelines, improving the accuracy of algorithms for liver segmentation and identification of focal lesions.

PO-629

Multiparametric MRI as non-invasive tool to assess disease activity in autoimmune hepatitis

Johannes Hartl¹, Roman Zenouzi², Elizabeth Shumbayawonda³, Kelly Matt³, Andrea Dennis⁴, Ansgar Lohse², Rajarshi Banerjee⁵, Christoph Schramm^{6,7,8}. ¹University Hospital Hamburg-Eppendorf

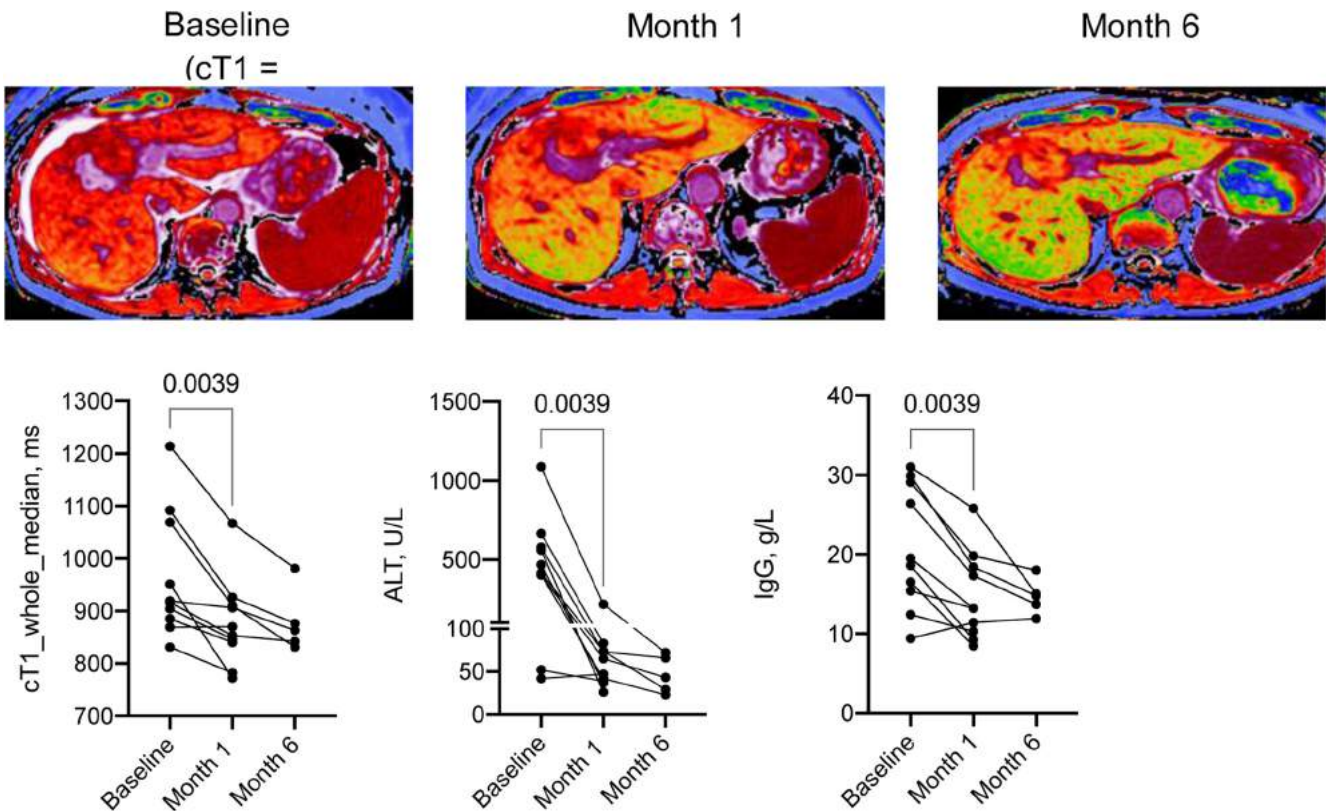


Figure (abstract: PO-629): Exemplary mpMRI imaging in a patients with AIH, whereby mpMRI was performed at diagnosis and after 1 and 6 months of immunosuppressive treatment (upper row). Changes of cT1 as well as of ALT and IgG upon immunosuppression of the total cohort (lower row). Data points represent individual patients. Data points corresponding to individual patients are connected via lines.

(UKE), 1st Medical Centre, Hamburg, Germany; ²University Hospital Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany; ³Perspectum Ltd, Oxford, Northern Ireland; ⁴Perspectum Ltd, Oxford, Northern Ireland; ⁵Perspectum Ltd; ⁶University Hospital Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany; ⁷University Hospital Hamburg-Eppendorf (UKE), Martin Zeitz Centre for Rare Diseases, Hamburg, Germany; ⁸University Hospital Hamburg-Eppendorf (UKE), Hamburg Center for Translational Immunology, Hamburg, Germany
 Email: j.hartl@uke.de

Background and aims: Up to 50% of patients with autoimmune hepatitis (AIH) show evidence of ongoing hepatic inflammation on histological assessment despite of biochemical markers within the range of normal. Hence, there is an unmet need for novel, non-invasive surrogate markers of disease activity in AIH. Therefore, we herein explored in a prospective proof-of-principle study the diagnostic performance of non-invasive imaging with multiparametric MRI (mpMRI) in assessing the degree of hepatic inflammation. **Method:** A total of 17 treatment-naïve patients who underwent liver biopsy to establish the diagnosis of AIH were prospectively enrolled into the study. MRI was carried out within 48 hours after liver biopsy, and after 1 and 6 months of treatment. mpMRI was performed using LiverMultiScan[®] software (Perspectum Ltd, UK). Median cT1 across

the whole liver, and mean cT1 of regions of interest of the right and the left liver lobe were measured.

Results: cT1 whole liver values strongly correlated with hepatic inflammation as assessed by modified hepatitis activity index score (mHAI) ($r = 0.58$, $p = 0.016$, $n = 17$), but not with liver fibrosis ($r = 0.23$, $p = 0.66$, $n = 17$). At baseline, cT1 readouts showed a strong positive correlation with serum ALT levels ($r = 0.62$, $p = 0.0096$, $n = 17$), while IgG did not correlate with neither cT1 ($r = 0.19$, $p = \text{ns}$, $n = 17$), mHAI, nor ALT. However, after one and six months of follow-up, the correlation of cT1 with IgG was excellent ($r = 0.75$, $n = 10$, $p = 0.026$, and $r = 1.0$, $p = 0.016$, $n = 5$). A decrease of ALT and IgG was paralleled by a significant decrease of cT1 within the first month of treatment ($p = 0.039$, respectively; Fig.) A large variability of cT1 values was noted in the six patients who had achieved complete biochemical remission (range: 927 ms to 772 ms), whereby mpMRI depicted high degrees of hepatic inflammation in some patients with biochemical markers within the upper range of normal. Hepatic inflammation showed a heterogenous distribution across liver slices (Fig. 1), with significant differences of cT1 in regions from the right and left liver lobe within patients ($p = 0.032$).

Conclusion: cT1 assessed by mpMRI might represent a valuable non-invasive surrogate marker for AIH activity that allows to monitor resolution of hepatic inflammation upon immunosuppression and identify patients with ongoing disease activity despite biochemical remission. Using mpMRI, which provides the opportunity to assess whole liver slices, confirmed the focal nature of AIH.

POSTER PRESENTATIONS

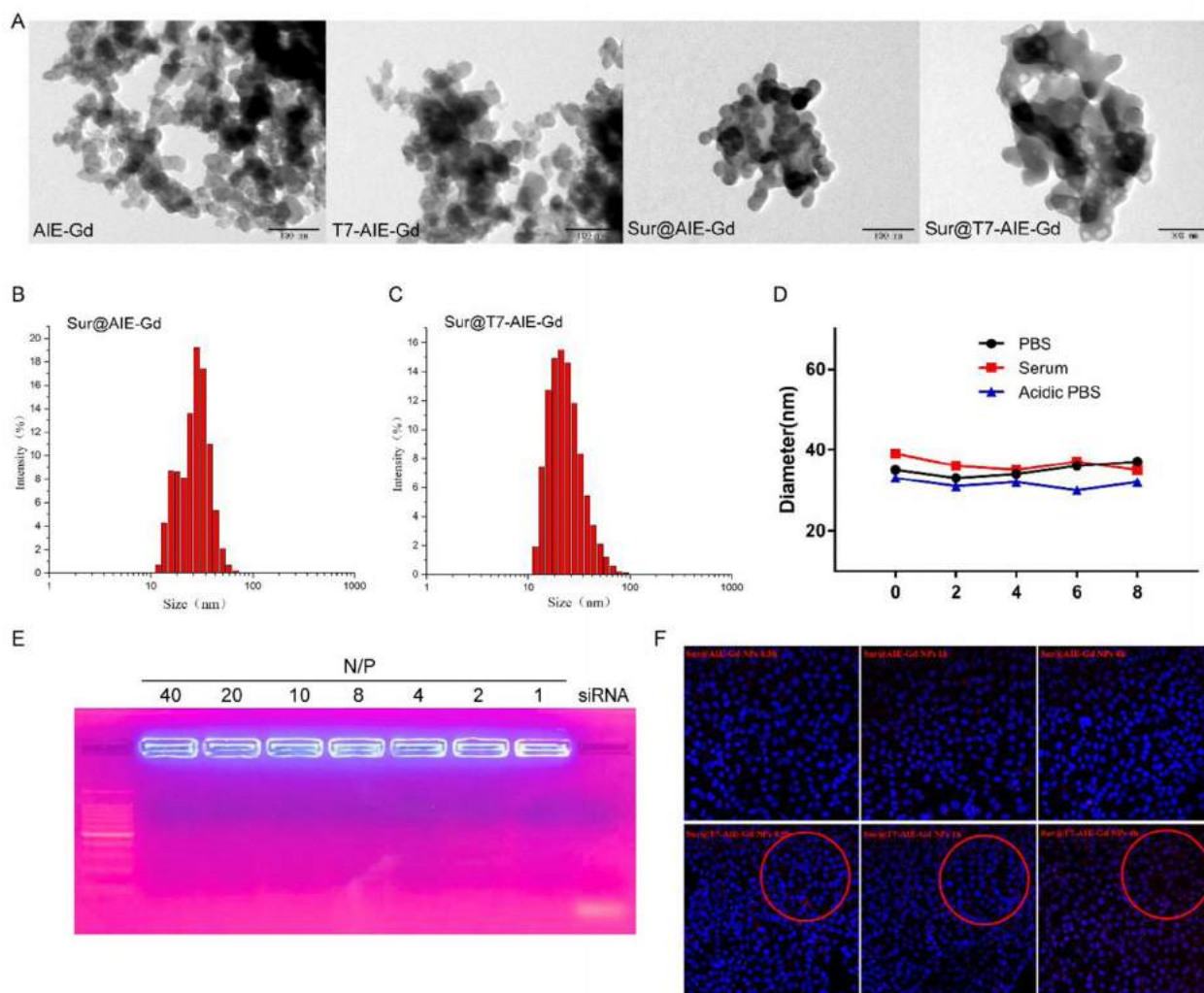


Figure 1: (abstract: PO-738)

PO-738

Theranostic nanodots with aggregation-induced emission and nuclear magnetic resonance imaging characteristics for targeted and image-guided siRNA therapy of hepatocellular carcinoma

Yuchen Hou¹, Hao Feng¹, Qiang Xia¹. ¹Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai
Email: hyczsyz@163.com

Background and aims: Genes, and lack of effective therapy has become a promising alternative for cancer treatment. RNA interference (RNAi), especially small interfering RNA (siRNA), with its good stability and gene silencing effect, brings a new opportunity for gene therapy. However, siRNA therapeutics still has the disadvantages of low targeting and effectiveness. Methods for quantitative analysis in vivo. To overcome the above disadvantages of siRNA therapy, we designed and synthesized a kind of siRNA transport vector with aggregation-induced emission and Nuclear magnetic resonance imaging characteristics targeted by hepatoma cells.

Method: Survivin siRNA was carried by PEI and interacted with T7-AIE/Gd NPs which were self-assembled of DSPE-PEG-PEI, DSPE-PEG-DTPA (Gd), DSPE-PEG-Mal and TPE. The in vitro physicochemical properties, MRI and AIE fluorescent imaging abilities, cytotoxicity and intracellular localization was evaluated. Then the subcutaneous xenograft model was established by subcutaneously injecting nude mice with LM3 cells. The in vivo antitumor, MRI and fluorescent

imaging, promotion of apoptosis and autophagy in tumor cells activities of the functionalized nanocarriers were estimated in this study.

Results: Survivin siRNA@T7-AIE/Gd NPs was synthesized and the characteristic of the nanodots was showed in figure 1. The siRNA@T7-AIE/Gd NPs have excellent MRI and AIE fluorescent imaging abilities in mice (figure 2). Survivin siRNA@T7-AIE/Gd NPs can effectively promote the autophagy and apoptosis of tumor cells (figure 3, 4). ATG7 and ATG12-ATG5-ATG16L1 was activated and the autophagy-dependent DNA damage was significantly increased in Survivin siRNA@T7-AIE/Gd NPs group (figure 4, 5).

Conclusion: a novel theranostic siRNA delivery system with dual-mode imaging characteristics of AIE/MRI was synthesized for targeted and image-guided gene therapy of HCC (Scheme).

PO-985

The liver fibroinflammatory marker α T1 is reduced with aldafermin therapy in a randomized, double-blind, placebo-controlled, multicenter study in patients with non-alcoholic steatohepatitis

Angelo Paredes¹, Lei Ling², Rajarshi Banerjee³, Cynthia Guy⁴, Juan Frias⁵, Ziad H. Younes⁶, James F. Trotter⁷, Nadege T. Gunn⁸, Anita Kohli⁹, Kristen Nelson², Mildred Gottwald², William Chang², Andrew Yan², Alex DePaoli², Hsiao Lieu², Stephen Harrison¹⁰. ¹Brooke

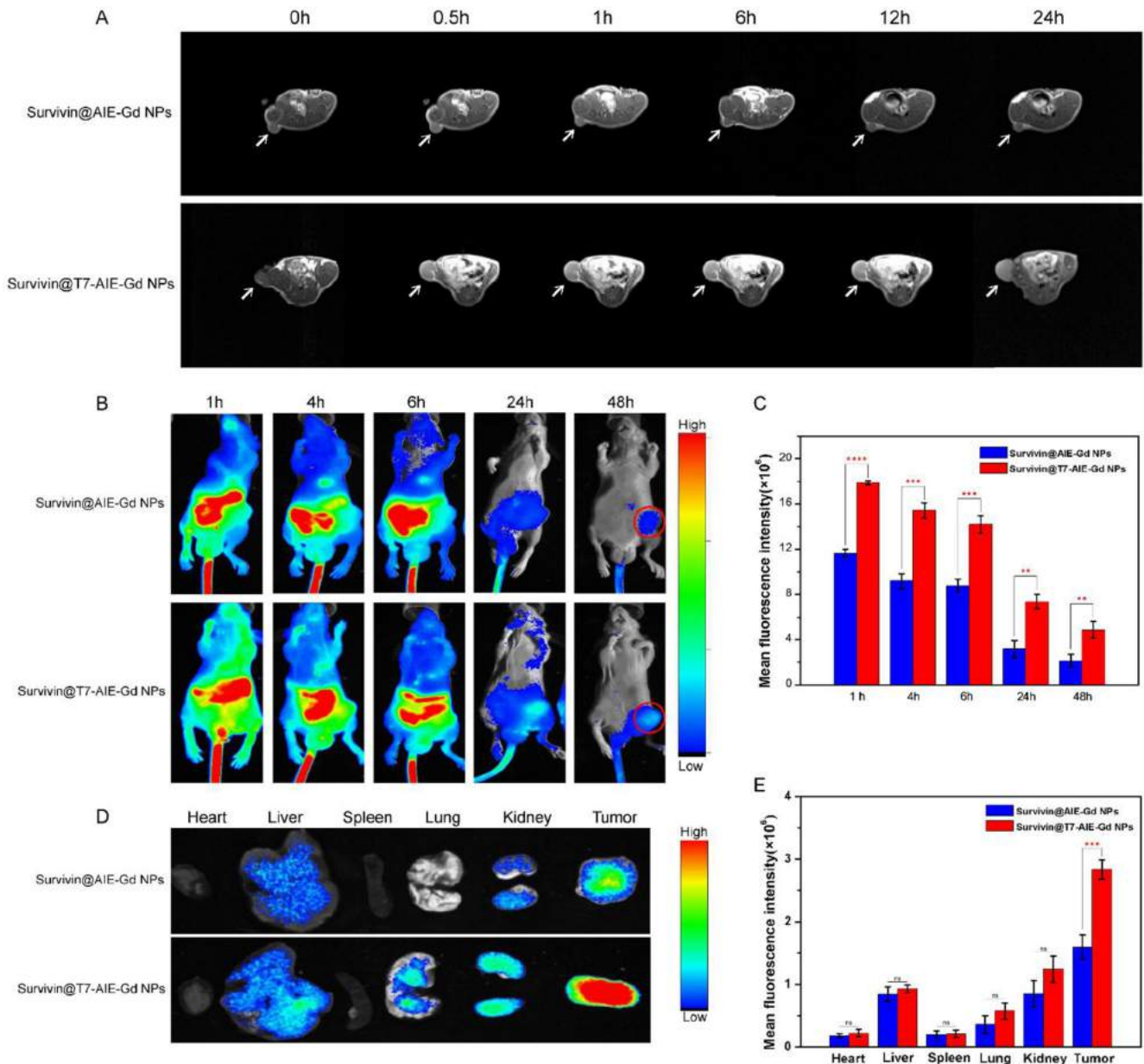


Figure 2: (abstract: PO-738)

Army Medical Center, San Antonio, United States; ²NGM Biopharmaceuticals, South San Francisco, United States; ³Perspectum Diagnostics, Oxford, United Kingdom; ⁴Duke University, Durham, United States; ⁵National Research Institute, Los Angeles, United States; ⁶Gastro One Research, Germantown, United States; ⁷Texas Digestive Disease Consultants, Dallas, United States; ⁸Pinnacle Clinical Research, Austin, United States; ⁹Arizona Liver Health, Chandler, United States; ¹⁰Pinnacle Clinical Research, San Antonio, United States
Email: lling94080@yahoo.com

Background and aims: The iron-corrected T1 relaxation time (cT1) is a novel imaging marker of intrahepatic fibro-inflammatory activity and is used in the UK Biobank population health study as the reference for liver fibroinflammatory disease. A threshold of cT1 >825 ms has been shown to predict clinical outcomes (ascites,

variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation, mortality; hazard ratio of 9.9, p=0.007; Jayaswal et al., Liver Int 2020). In contrast, liver fat content, as measured by MRI-PDFF, is not predictive of clinical outcomes. Aldafermin, an engineered FGF19 analog, produced fibrosis regression and NASH resolution in a 24-week, randomized, double-blind, placebo-controlled trial in patients with NASH. Here we report the effect of aldafermin on the novel imaging marker cT1 in this trial. **Method:** 78 subjects were randomized 1:2 to receive placebo (n = 25) or aldafermin 1 mg (n = 53) SC QD for 24 weeks at 9 US study sites. Key inclusion criteria included biopsy-proven NASH with NAS ≥ 4, F2 or F3 fibrosis and absolute liver fat content ≥8%. Patients underwent the LiverMultiScan™ acquisition protocol (Perspectum Diagnostics) at baseline and week 24. cT1 maps were obtained on multiparametric magnetic resonance imaging scanners standardized across field

POSTER PRESENTATIONS

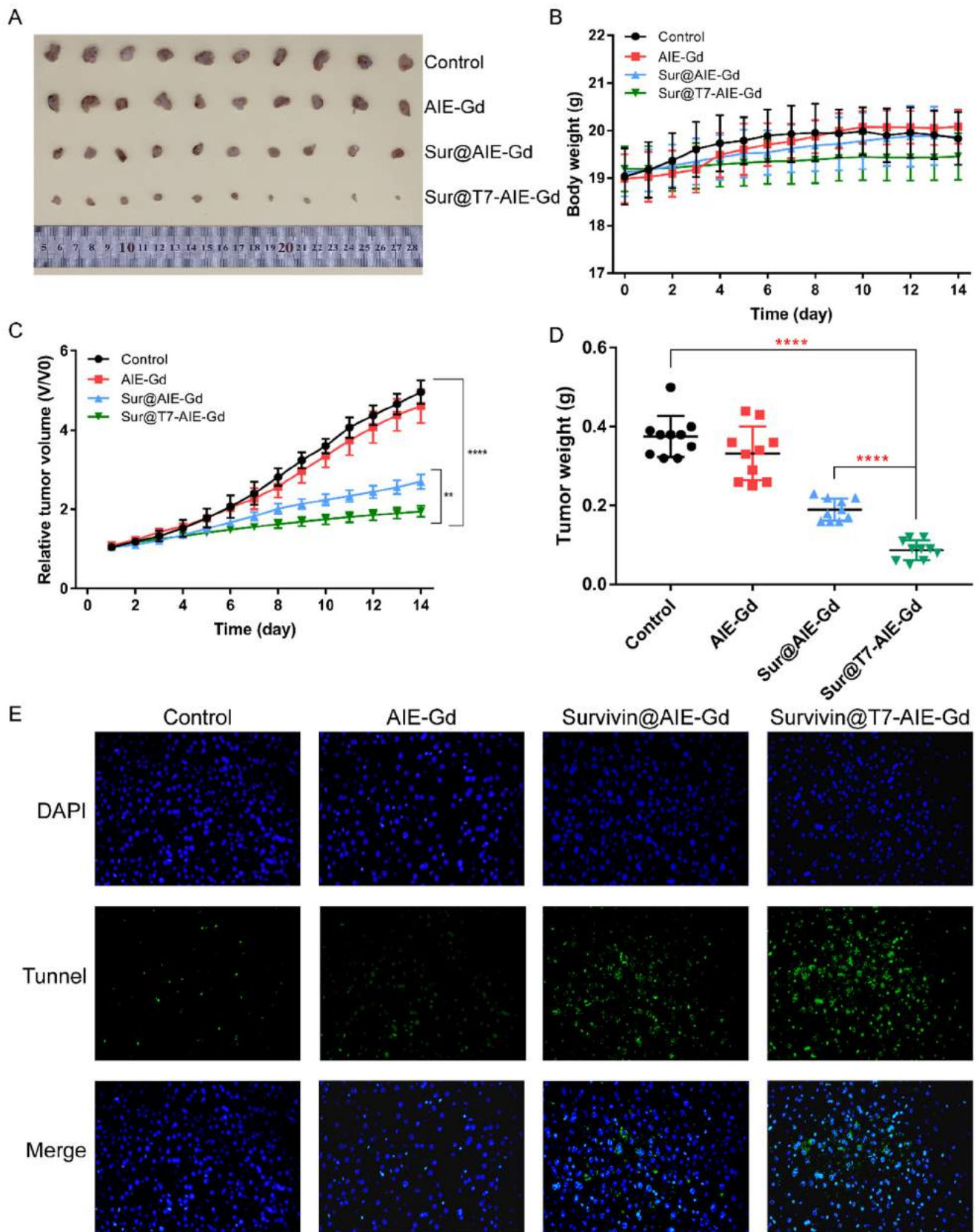


Figure 3: (abstract: PO-738)

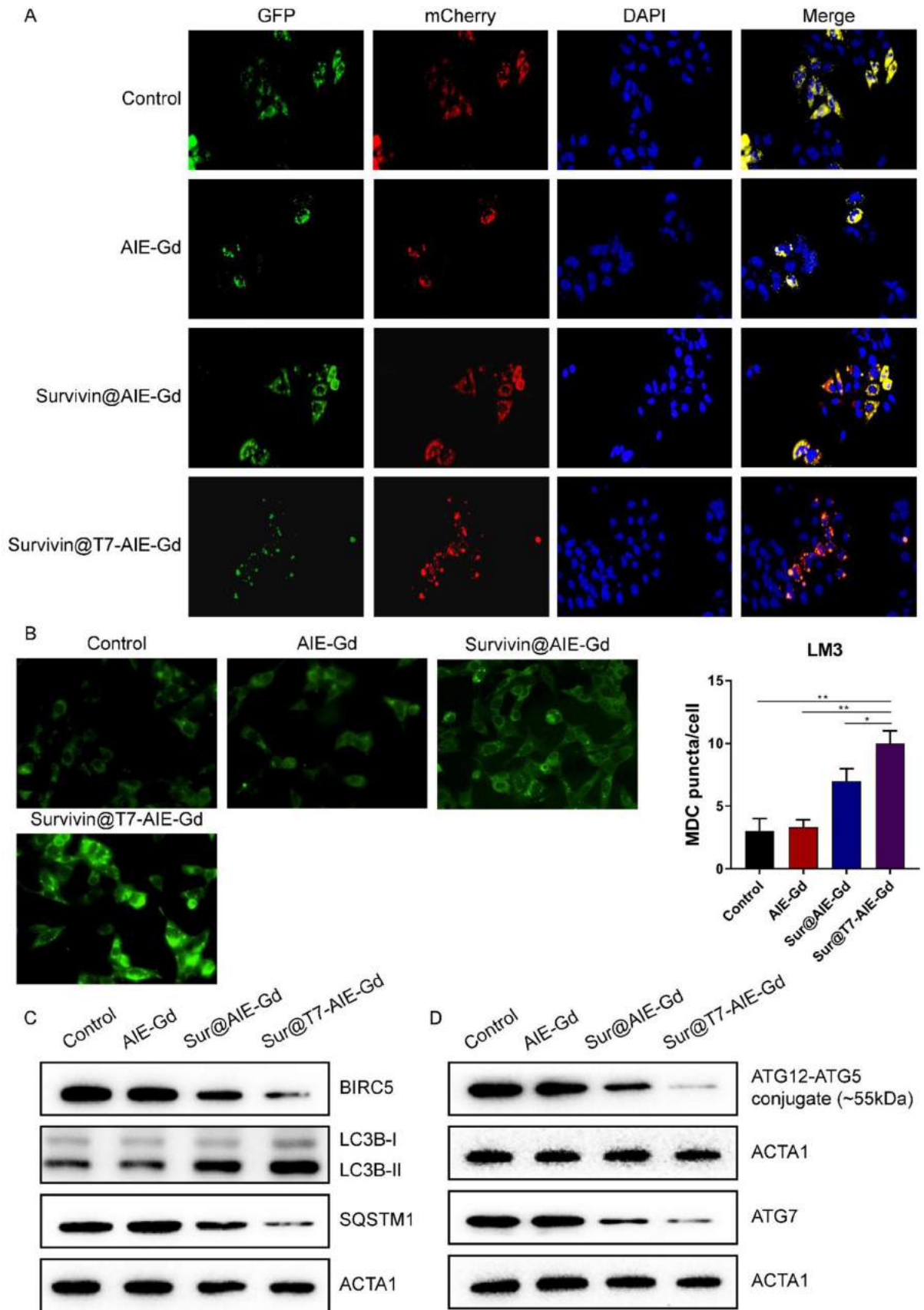


Figure 4: (abstract: PO-738)

POSTER PRESENTATIONS

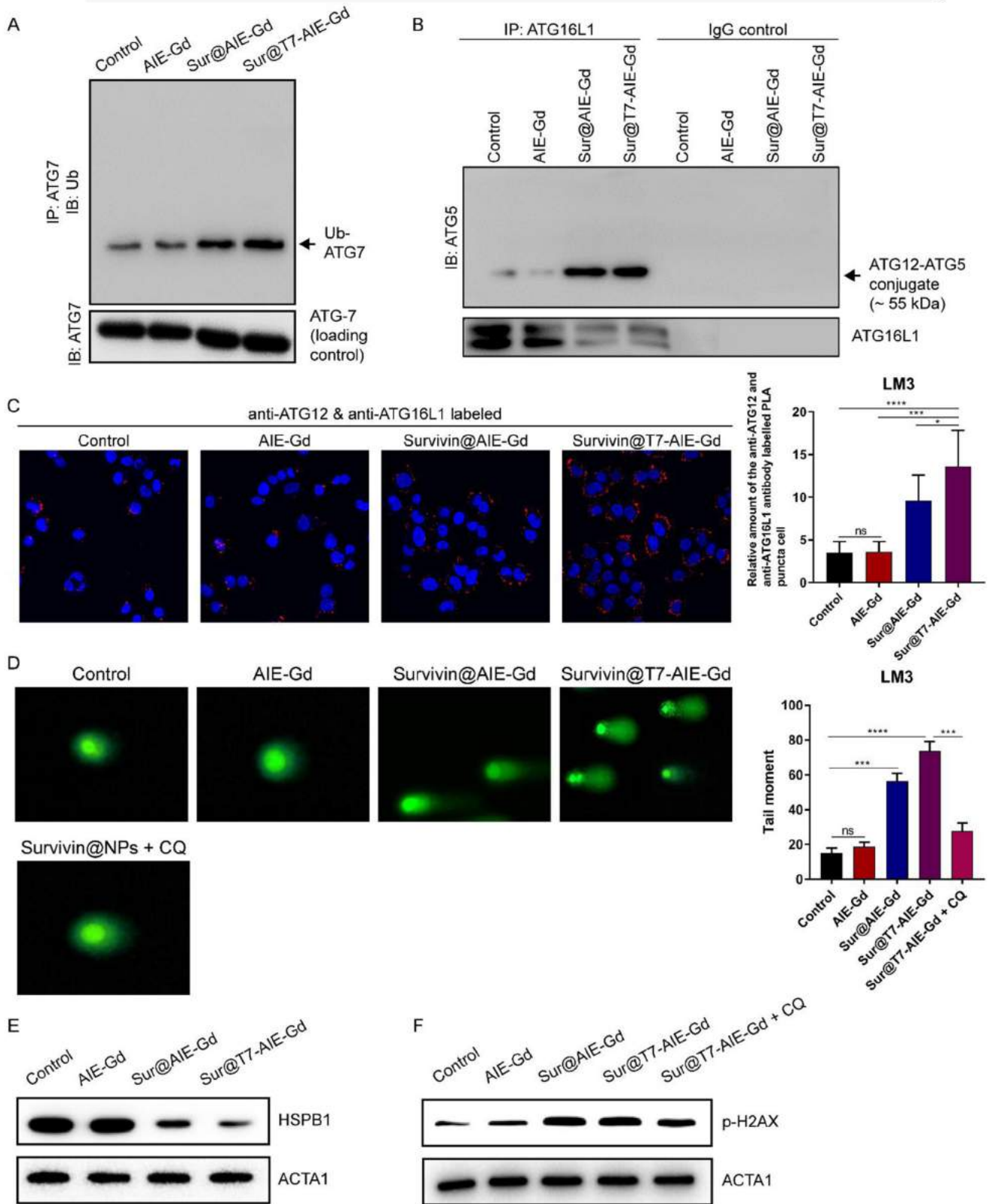
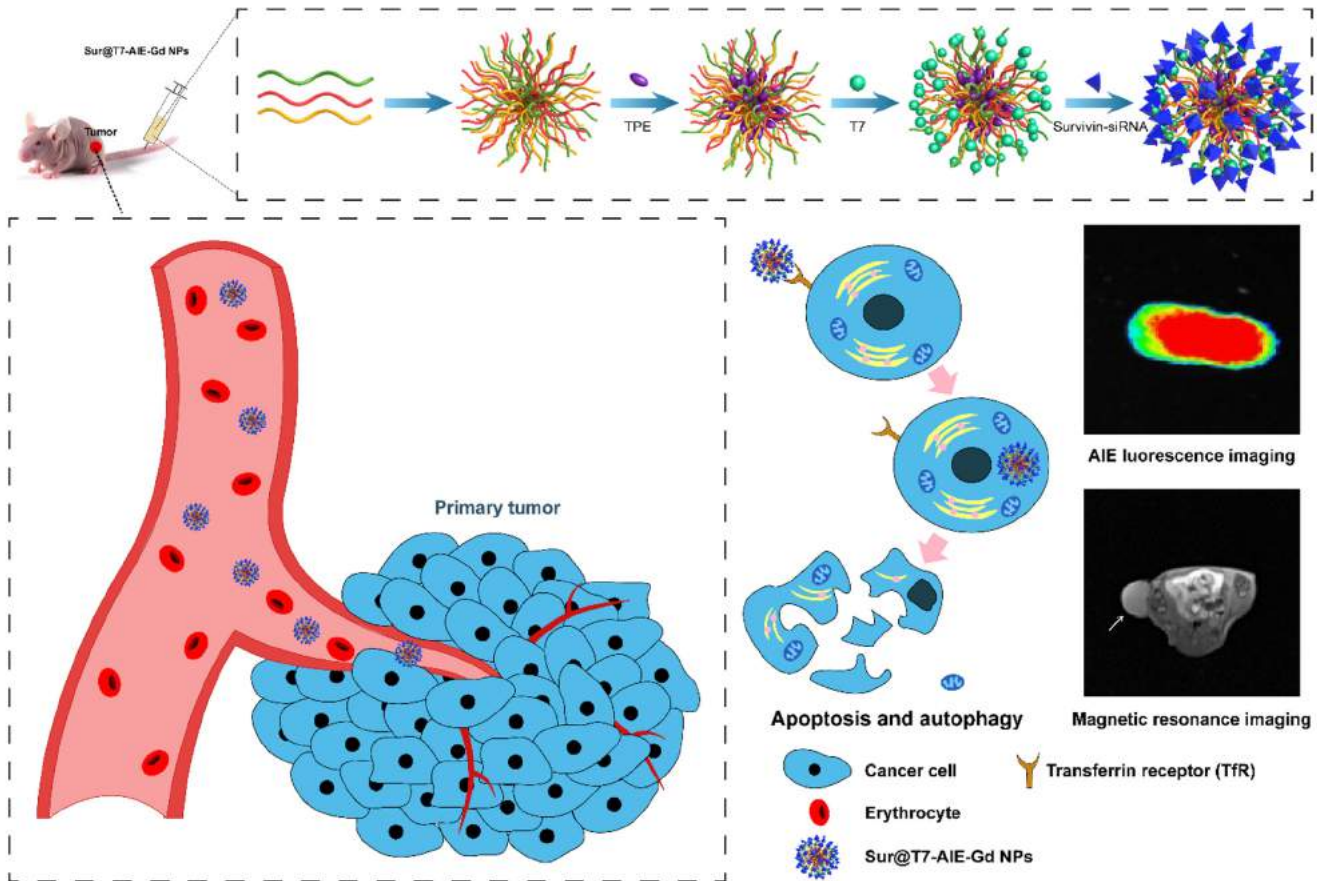


Figure 5: (abstract: PO-738)



Scheme: (abstract: PO-738)

strengths and vendors. Images were analyzed by trained central readers blinded to treatment assignment, clinical and histological information.

Results: At baseline, mean cT1 values were 906 ms and 902 ms in the aldafermin and placebo groups, respectively. At week 24, cT1 values declined significantly in aldafermin-treated subjects (−78 ms, $p < 0.001$ vs baseline). In contrast, a numeric increase in cT1 was observed in placebo-treated subjects (+9 ms, $p = 0.79$ vs baseline). Aldafermin reduced the proportion of subjects at risk (cT1 >825 ms) (67% at baseline vs 38% at week 24 in the aldafermin group; 89% at baseline vs 78% at week 24 in the placebo group). cT1 correlated with histological grade of ballooning ($\rho = 0.56$, $p < 0.001$), inflammation ($\rho = 0.42$, $p = 0.014$) and steatosis ($\rho = 0.70$, $p < 0.001$), as well as ALT ($\rho = 0.51$, $p = 0.002$), AST ($\rho = 0.53$, $p = 0.001$), ELF ($\rho = 0.48$, $p = 0.004$) and Pro-C3 ($\rho = 0.37$, $p = 0.027$) at week 24.

Conclusion: Compared to placebo, aldafermin demonstrated significant reductions in cT1 values, consistent with its anti-inflammatory and anti-fibrotic effect on the NASH liver. Given the prognostic value of cT1 on clinical outcomes, aldafermin treatment may provide benefits to the at-risk patient population defined as having cT1 >825 ms.

PO-1023

Intravital dynamic and correlative imaging reveals the mechanism of canalicular bile flux

Nachiket Vartak¹. ¹Leibniz Research Centre for Working Environment and Human Factors, Systems Toxicology, Dortmund, Germany
Email: vartak@bioimaging.tech

Background and aims: Small-molecule flux in tissue-microdomains is essential for organ function, but knowledge of this process is scant due to the lack of suitable methods.

Method: We developed two independent intravital imaging techniques, namely Fluorescence Loss After Photoactivation (FLAP) and Intravital Arbitrary Region Image Correlation Spectroscopy (IVARICS), that allow the quantification of advection (flow) and diffusion in individual bile canaliculi and in interlobular bile ducts of intact livers in living mice.

Results: Photoactivation of CMNB-caged fluorescein in entire lobules demonstrated the establishment of diffusive gradients in the bile canalicular network and the sink function of interlobular ducts. In contrast to the bile canalicular network, vectorial transport was detected and quantified in the mesh of interlobular bile ducts. These results were confirmed through the orthogonal IVARICS method. The results challenge the prevailing ‘mechano-osmotic’ theory of canalicular bile flow. After active transport across hepatocyte membranes bile acids are transported in the canaliculi primarily by diffusion. Only in the interlobular ducts, diffusion is augmented by regulatable advection.

Conclusion: In conclusion, the liver consists of a diffusion dominated canalicular domain, where hepatocytes secrete small molecules and generate a concentration gradient and a flow-augmented ductular domain, where regulated water influx creates unidirectional advection that augments the diffusive flux.

PO-2531

Fluid dynamics analyses of the portal vein flow changes after hepatectomy using 7T 3D PC-MRI

Yu Oshima¹, Satoshi Ogiso¹, Hirohiko Imai², Masanori Nakamura³, Kenta Makino¹, Satoshi Wakama¹, Katsuhiko Tomofuji¹, Takashi Ito¹, Ken Fukumitsu¹, Takamichi Ishii¹, Tetsuya Matsuda², Etsuro Hatano¹.
¹Graduate School of Medicine, Kyoto University, Division of Hepato-Biliary-Pancreatic surgery and Transplantation, Department of Surgery,

POSTER PRESENTATIONS

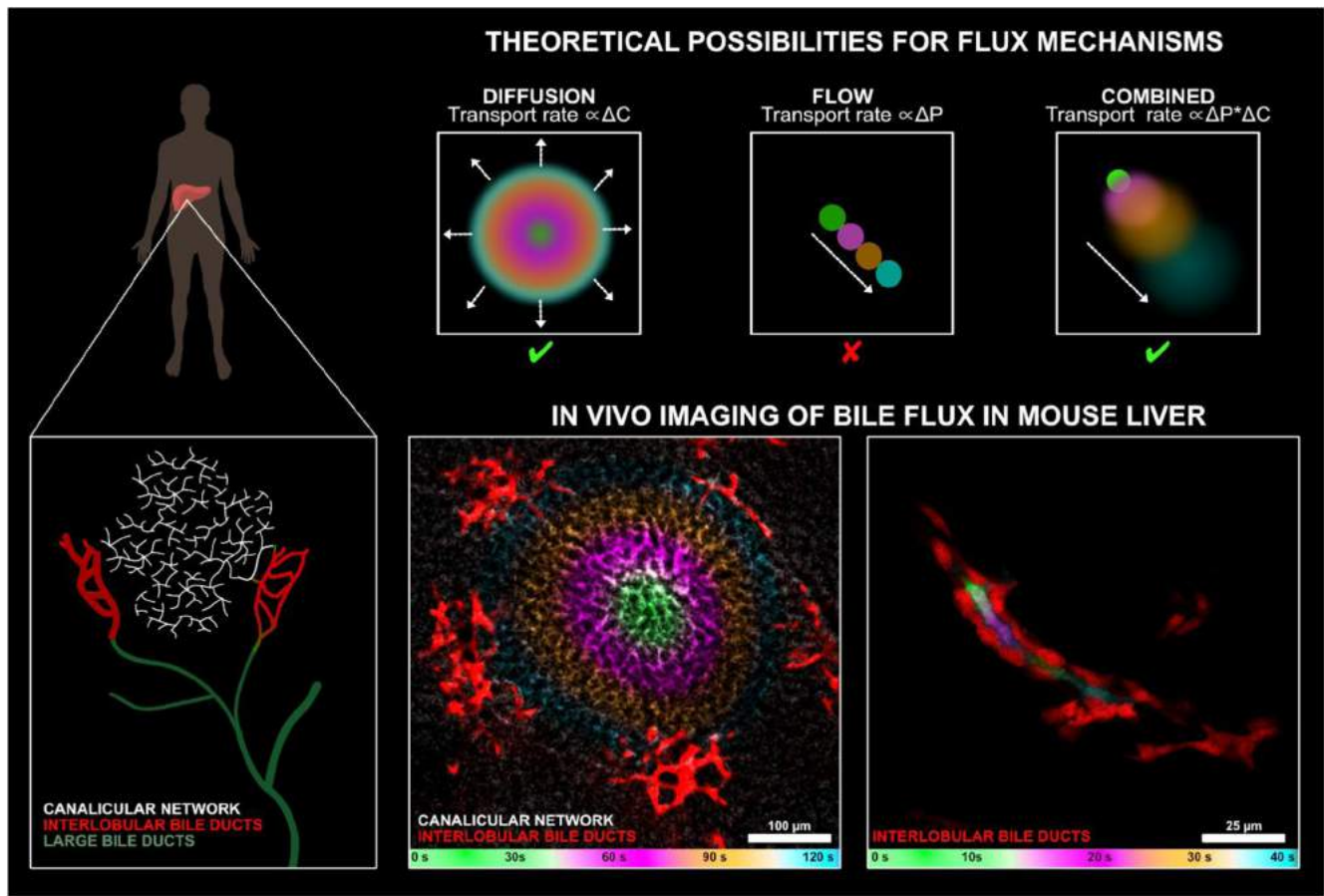


Figure: (abstract: PO-1023)



Figure: (abstract: PO-2531)

Kyoto, Japan; ²Graduate School of Informatics, Kyoto University, Department of Systems Science, Japan; ³Nagoya Institute of Technology, Department of Electrical and Mechanical Engineering, Japan
Email: yuoshima1118@gmail.com

Background and aims: Liver regeneration after hepatectomy is triggered by mechanical stimulus to vascular endothelial cells secondary to relative increase of portal vein flow in the remnant liver. This study aimed to analyse time-course changes in portal vein flow after hepatectomy and to evaluate its association with liver regeneration.

Method: A 70% hepatectomy, which preserves only the right and caudate lobes, was performed in five Lewis rats and the portal vein flow was measured just before hepatectomy, and 1, 24, 72, 168 hour after hepatectomy, using three-dimensional phase-contrast magnetic resonance imaging (3D PC-MRI). Flow parameters, such as flow volume rate, flow velocity, and wall shear stress (WSS), were assessed in the main portal vein (PV) and branches to the right and caudate lobes, and their associations with corresponding liver volume were evaluated.

Results: The whole liver volume at postoperative day 7 was 4.3 times as large as the preoperative volume of the right and caudate lobes and equivalent to 88.2% of the preoperative whole liver. The liver volume of the right and caudate lobes at d7 were 4.6 and 3.7 times as large as their preoperative volume, respectively. The flow volume rate of the main PV was 53.4% at 1 h, 56.3% at 1d, 75.6% at d3, and 102.9% at d7, compared with that before hepatectomy, whilst that in the branches of right lobe and caudate lobe at d7 was 4.3 and 13.2 times as much as that before hepatectomy, respectively. The flow volume rate per liver volume in the whole liver, right lobe, and caudate lobe was 2.2/2.8/1.5 before hepatectomy, 4.1/3.6/5.8 at 1 h, 3.0/2.4/3.6 at d1, and 2.6/2.4/3.6 ml/min/cm³ at d7, respectively. The WSS tended to remain constant over time. The range of WSS at each branch was 1.5–2.3 Pa in the main PV, 1.3–1.8 Pa in the right lobe branch, and 0.6–1.5 Pa in the caudate lobe branch.

Conclusion: Abovementioned flow parameters were successfully analyzed over time in the intrahepatic PV branches, as well as their corresponding liver volume. The flow volume rate per liver volume at d7 was similar with that before hepatectomy in each of the right and caudate lobe. The WSS was constant during the process of liver regeneration after 70% hepatectomy, suggesting WSS itself may not be requisite for liver regeneration after hepatectomy.

Immune-mediated and cholestatic – Experimental and pathophysiology

PO-855

Potential effect of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in preclinical model of cholestatic liver disease

Jung Kuk Kim¹, Jong Suk Lee¹, Yohan Kim¹, Jae Hyuk Choi¹, Hyunjoon Kwon¹, Eun Jin Park¹, Jong Soo Lee¹, Sung Min Bae¹, Sang Hyun Lee¹, In Young Choi¹. ¹Hanmi Pharm. Co., Ltd., Korea, Rep. of South
Email: iychoi@hanmi.co.kr

Background and aims: Cholestatic liver diseases such as PSC and PBC are characterized by destruction of intra- and/or extra-hepatic bile duct, leading to hepatic/biliary inflammation and fibrosis, and end-stage liver disease. To date, only limited therapy with suboptimal effect is available for this devastating disorder. Recently, we developed a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, and its therapeutic potential was observed across animal

models of NASH and fibrosis. The present study further explore whether HM15211 could also provide desired therapeutic effect on cholestatic liver diseases.

Method: To induce cholestasis-induced liver inflammation and fibrosis, the mice were subjected to common bile duct ligation (BDL mice). 2 days post surgery, BDL mice were administered either with HM15211 or obeticholic acid (OCA). After 2 weeks treatment, hepatic bile acid and hydroxyproline contents were measured. The liver tissue were subjected to HandE, Sirius red staining, and immunohistochemistry for CK-19 and myeloperoxidase (MPO), followed by histological grading. Hepatic expression level of relevant marker genes was evaluated by qPCR.

Results: In BDL mice, HM15211 treatment reduced hepatic hydroxyproline (–21.9, –43.7% vs. vehicle for OCA, HM15211), MPO positive cell (63.4, 73.5, 33.3 cells/field for vehicle, OCA, HM15211) and CK-19 positive area (3.9, 3.6, 2.8% for vehicle, OCA, HM15211) greater than OCA. Consistently, HM15211, but not OCA, treatment significantly reduced histological score for portal inflammation, bile duct hyperplasia (1.5, 1.3, 0.7 for vehicle, OCA, HM15211), parenchymal necrosis (2.1, 2.3, 1.0 for vehicle, OCA, HM15211), and fibrosis (1.7, 1.8, 1.0 for vehicle, OCA, HM15211). Similar results were also observed when determining hepatic expression of related marker genes such as TGF-beta and collagen, confirming anti-inflammatory and anti-fibrotic effects of HM15211 in BDL mice. To explore potential benefits of HM15211 on bile acid homeostasis, hepatic bile acid level was measured, and more reduction was observed for HM15211 treatment compared to OCA (–27.4, –76.7% vs. vehicle for OCA, HM15211). Together with reduced hepatic CYP7A1 expression, these results suggest additional favorable effect of HM15211 on hepatic bile acid homeostasis.

Conclusion: In BDL mice, the desired treatment effects of HM15211 are well-corroborated. These results warrant further evaluation for therapeutic potential of HM15211 in PSC and PBC.

PO-899

Deletion of Mecip1 in Mecip1fl/flAlbCre mice recapitulates the phenotype of human primary biliary cholangitis

Jerzy Kotlinowski¹, Tomasz Hutsch^{2,3}, Izabela Czyzowska-Cichon⁴, Marta Wadowska⁵, Natalia Pydyn¹, Agnieszka Jaształ⁴, Agnieszka Kij⁴, Ewelina Dobosz², Maciej Lech^{5,6}, Katarzyna Miekus¹, Ewelina Pośpiech⁷, Mingui Fu⁸, Jolanta Jura¹, Joanna Koziel⁵, Stefan Chlopicki^{4,9}. ¹Jagiellonian University, Faculty of Biochemistry, Biophysics and Biotechnology, Department of General Biochemistry, Krakow, Poland; ²Medical University of Warsaw, Laboratory of Centre for Preclinical Research, Department of Experimental Physiology and Pathophysiology, Warsaw, Poland; ³Veterinary Diagnostic Laboratory ALAB bioscience, Warsaw; ⁴Jagiellonian University, Jagiellonian Centre for Experimental Therapeutics, Krakow, Poland; ⁵Jagiellonian University, Faculty of Biochemistry, Biophysics and Biotechnology, Department of Microbiology, Krakow, Poland; ⁶LMU Hospital, Department of Medicine IV, Munich, Germany; ⁷Jagiellonian University, Malopolska Centre of Biotechnology, Krakow, Poland; ⁸University of Missouri-Kansas City, School of Medicine, Department of Biomedical Science and Shock/Trauma Research Center, Kansas City, United States; ⁹Jagiellonian University Medical College, Chair of Pharmacology, Krakow
Email: j.kotlinowski@uj.edu.pl

Background and aims: Primary biliary cholangitis (PBC) is an autoimmune disease characterized by progressive destruction of the intrahepatic bile ducts. The immunopathology of PBC involves excessive inflammation; therefore, negative regulators of inflammatory response, such as Monocyte Chemoattractant Protein-1-Induced Protein-1 (MCP1) may play important roles in the development of PBC. The aim of this work was to verify whether Mecip1 expression protects against development of PBC.

POSTER PRESENTATIONS

Method: Genetic deletion of *Zc3h12a* was used to characterize the role of *Mcip1* in the pathogenesis of PBC in 6-52-week-old mice.

Results: We found that *Mcip1* deficiency in the liver (*Mcip1*^{fl}/*flAlbCre*) recapitulates most of the features of human PBC, in contrast to mice with *Mcip1* deficiency in myeloid cells (*Mcip1*^{fl}/*flLysMCre* mice), which present with robust myeloid cell-driven systemic inflammation. In *Mcip1*^{fl}/*flAlbCre* livers, intrahepatic bile ducts displayed proliferative changes with inflammatory infiltration, bile duct destruction, and fibrosis leading to cholestasis. In plasma, increased concentrations of IgG, IgM, and AMA autoantibodies (anti-PDC-E2) were detected. Interestingly, the phenotype of *Mcip1*^{fl}/*flAlbCre* mice was robust in 6-week-old, but milder in 12–24-week-old mice, suggesting early postnatal origin of the phenotype. Hepatic transcriptome analysis of 6-week-old and 24-week-old *Mcip1*^{fl}/*flAlbCre* mice showed 812 and 8 differentially expressed genes, respectively, compared with age-matched control mice, and revealed a distinct set of genes compared to those previously associated with development of PBC.

Conclusion: *Mcip1*^{fl}/*flAlbCre* mice display early postnatal phenotype that recapitulates most of the features of human PBC.

Acknowledgment: This work was supported by research grants from National Science Centre, Poland no. 2015/19/D/NZ5/00254 and 2017/27/B/NZ5/01440 to JeKo, and 2018/29/B/NZ6/01622 to JeKo.

PO-903

Cholangiopathy-related necroptotic cell death recapitulated in human cholangiocyte organoids for screening novel drug targets

Shaojun Shi¹, Monique M.A. Versteegen¹, Jan Ijzermans¹, Luc J.W. van der Laan¹. ¹Erasmus MC-University Medical Center, Surgery, Rotterdam, Netherlands
Email: s.shi@erasmusmc.nl

Background and aims: Necroptosis is an emerging type of programmed cell death in liver diseases. However, detailed knowledge of necroptosis mechanisms in cholangiopathy is scarce due to the lack of appropriate in vitro models. We aimed to recapitulate necroptotic signalling in human intrahepatic cholangiocyte organoids (ICOs) for the study of cholangiopathy and application in preclinical drug screening.

Method: Immunostaining of receptor-interacting protein kinase (RIP)3 and cytokeratin 19 (KRT19) was performed on biopsies from patients with various chronic liver diseases and graft livers in liver transplantation (n = 16). ICOs were generated from the human graft livers (n = 6). Cell death was induced in ICOs by combinations of TNF- α (T)/Smac mimic (S) or T/S/Z-VAD-FMK (Z) and evaluated by ATP assay and transmission electron microscopy (TEM). Mediators of apoptosis, necroptosis, and nuclear factor kappa B (NF- κ B) signalling were assessed by immunostaining. Inflammatory genes were determined via RT-PCR. Ethanol metabolite- and bile-induced biliary damage were evoked in ICOs by palmitoleic acid in ethanol (POA/EtOH) and patient-derived bile.

Results: RIP3 was exclusively expressed in cholangiocytes in liver grafts and patients with chronic liver diseases. Apoptosis and necroptosis were evoked in ICOs by T/S or T/S/Z exposure without little inter-donor variation. Apoptosis- (T/S) and necroptosis (T/S/Z)-related morphologic features were seen and further confirmed by immunostaining of active caspase 3, cleaved caspase 8, and phospho-mixed lineage kinase domain-like protein (pMLKL). Exposure to POA/EtOH or bile induced cell death in ICOs. Apoptotic and necroptotic ICOs displayed divergent inflammatory gene transcription. Distinct NF- κ B signalling was activated in apoptotic (p100) and necroptotic (p65) ICOs. Of note, necroptosis but not apoptosis could be effectively prevented by established necroptosis inhibitors, including necrostatin-1, 7-Cl-O-Nec-1, GSK872, and necrosulfonamide. Emricasan, an FDA-approved caspase inhibitor, failed to attenuate apoptosis but switch it into necroptosis. Drug screening identified Dabrafenib as an inhibitor for both apoptosis and necroptosis, effectively preventing POA/EtOH- and bile-induced cell death.

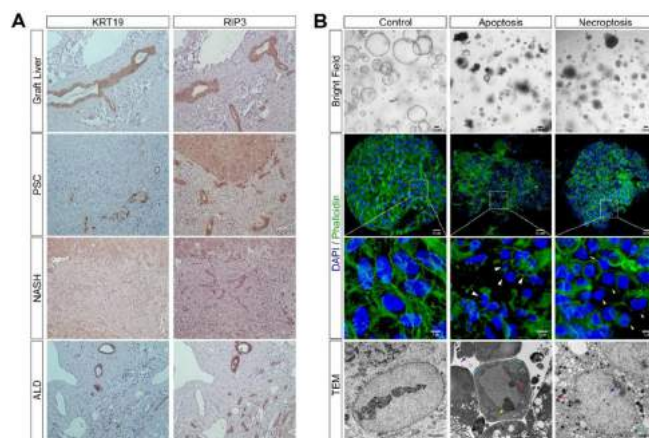


Figure:

Conclusion: RIP3 plays an exclusive role in biliary damage in liver diseases. ICOs recapitulate apoptosis and necroptosis, as well as concomitant inflammatory pathways, and are useful for drug screening. Dabrafenib is identified as a potent apoptosis and necroptosis inhibitor and represents a protective agent against biliary damage.

PO-1026

Serum nuclear magnetic resonance metabolomic signature can discriminate between immunoglobulin G4-related sclerosing cholangitis and primary sclerosing cholangitis

Emmanuel Selvaraj^{1,2,3}, Daniel E. Radford-Smith⁴, Rory Peters¹, Michael Orrell¹, Kate Lynch¹, Daniel C. Anthony⁴, Michael Pavlides^{1,2,3}, Alessandra Geremia¹, Adam Bailey^{1,3}, Emma Culver¹, Fay Probert⁵. ¹University of Oxford, Translational Gastroenterology Unit, Nuffield Department of Medicine, Oxford, United Kingdom; ²University of Oxford, Oxford Centre for Clinical Magnetic Resonance Research, Radcliffe Department of Medicine, Oxford, United Kingdom; ³NIHR Oxford Biomedical Research Centre, The Joint Research Office, Oxford, United Kingdom; ⁴University of Oxford, Department of Pharmacology, Oxford, United Kingdom; ⁵University of Oxford, Department of Chemistry, Oxford
Email: emmanuel.selvaraj@cardiov.ox.ac.uk

Background and aims: Global serum metabolomics can be used to identify biomarkers of disease. We performed serum metabolomic profiling in patients with immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) and primary sclerosing cholangitis (PSC) to assess for evidence of a distinctive signature that could discriminate between these conditions, predict response to therapy and provide a biomarker for disease relapse.

Method: Stored serum samples collected prospectively from patients with IgG4-related disease (IgG4-RD; n = 39 at diagnosis prior to therapy), PSC (n = 100; 81 large duct; 19 small duct) and healthy controls (HC; n = 16) were prepared for nuclear magnetic resonance (NMR) spectroscopy using a standardised protocol. Principal component analysis (PCA) and orthogonal partial-least squares discriminatory analysis (OPLS-DA) were used to identify discriminatory serum metabolites. Clinical data was obtained from review of electronic databases for correlation with metabolomics data and to adjust for confounders.

Results: Lactate, glucose, and glutamine were increased in IgG4-RD compared to PSC (p < 0.0001), whereas -CH₃ lipoprotein resonances were decreased (p < 0.001). OPLS-DA modelling with an optimised threshold diagnosed IgG4-RD-as opposed to PSC-with an accuracy of 86%, sensitivity 85% and specificity 90%, adjusted for age, gender, comorbidities, serum IgG4 level and medications. Both IgG4-RD and PSC were independently distinguishable from HC with an accuracy of 96% and 91%, respectively. When only IgG4-SC patients (n = 23) were included with large-duct PSC patients (n = 81), the accuracy was 88%.

When IBD was excluded as a comorbid condition (IgG4-SC n = 2, PSC n = 78), the diagnostic accuracy improved to 98%.

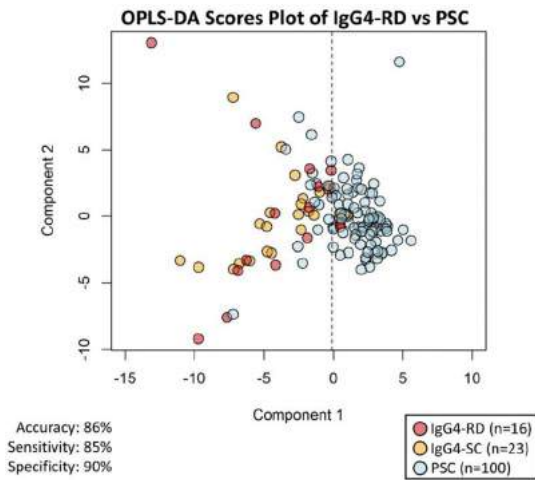


Figure:

Conclusion: The metabolomic signature determined by serum NMR in patients with IgG4-RD and more specifically IgG4-SC, is distinct from PSC and HC in our cohort. Metabolomic profiling has the potential to be incorporated as an additional criterion to improve the diagnosis of IgG4-RD and help distinguish IgG4-SC from PSC.

PO-1311

The peri-ductular CCL24 rich niche promotes bile duct fibrosis related liver damage in primary sclerosing cholangitis

Michal Segal¹, Neta Barashi¹, Adi Mor¹, Arnon Aharon², Douglas Thorburn³. ¹Chemomab Ltd, RandD, Tel-Aviv, Israel; ²Chemomab Ltd, Clinical, Tel-Aviv, Israel; ³UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom
Email: michal@chemomab.com

Background and aims: PSC is a chronic cholestatic liver disease characterized by peri-biliary inflammation and fibrosis. IL4 and IL13, representing a Th2 type inflammatory response were describe as part of PSC related inflammation. CCL24 is a chemokine that signals through the CCR3 chemokine receptor and was previously shown to be elevated in Th2 response and play a key role in pro-fibrotic processes. The aim of this study is to establish CCL24s pivotal role in PSC related pathophysiology and describe the CCL24 rich niche as main driver of fibrosis.

Method: Expression of CCL24 in primary human biliary epithelial cell (BEC) and M2 Macrophages was quantified using real time PCR and ELISA. Human primary hepatic stellate cells (pHSC) proliferation was assessed by CFSE staining and FACS. Serum samples from PSC patients, were analysed for CCL24 levels and ELF score. Multivariate linear regression analysis was used to test the dependence of CCL24 and ELF with respect to disease severity.

Results: Human BECs and monocytes derived macrophages were cultured with and without IL4, IL13 or both. Using Real time PCR and ELISA we demonstrated that in BEC CCL24 transcription and secretion was significantly increased. M2 macrophages polarized by IL4 resulted in robust increase of CCL24 expression and secretion. One of the hallmarks of biliary fibrosis is peri-ductular increase in number of fibroblasts. Incubation of pHSC with CCL24 promoted fibroblast proliferation while Inhibition of CCL24, by CM-101, a monoclonal antibody neutralizing CCL24, resulted in reduction of proliferation back to normal levels. Multi-variate analysis demonstrated that, in PSC patients sera, CCL24, ELF and Bilirubin are strong predictors of each other, the positive association increased with disease severity (r = 68%, p = 0.017 for patients with ALP >1.5 ULN).

Conclusion: We show that the immune response driving biliary fibrosis is characterized by creation of a CCL24 rich niche. Cholangiocytes (BEC) and M2 macrophages secrete CCL24 and drive the vicious circle in which fibroblast proliferation and activation, as well as inflammatory cells recruitment enhance CCL24 secretion and perpetuate bile duct fibrosis related damage. The key role of CCL24 in PSC pathophysiology is further supported by the bidirectional dependency of CCL24 and ELF, in PSC patient's sera, that is increased with disease progression. CM-101, a monoclonal antibody neutralizing CCL24, is currently studied in a phase 2 study as potential novel treatment for PSC.

PO-1364

Is it the scale (rather than the nature) of the inflammatory response in autoimmune hepatitis that determines treatment response?

Jessica Dyson^{1,2}, Ben Millar¹, Lin Lee Wong^{1,3}, Kile Green⁴, Anastasia Resteu⁴, Stuart Kendrick⁵, uk-aih consortium¹, David Jones^{1,2}. ¹Newcastle University, Translational and Clinical Research Institute, Newcastle-upon-Tyne, United Kingdom; ²Liver Unit, Freeman Hospital, Newcastle-upon-Tyne, United Kingdom; ³Royal Devon and Exeter Hospital, Gastroenterology, United Kingdom; ⁴Newcastle University, Faculty of Medical Sciences, Newcastle-upon-Tyne, United Kingdom; ⁵GlaxoSmithKline, Research and Development, United Kingdom

Email: jessica.dyson1@nhs.net

Background and aims: Autoimmune hepatitis (AIH) is traditionally considered to be highly treatable with immunosuppression. However, UK-AIH data show an incomplete response to therapy in 41% and significant treatment-related morbidity. Typically, standard induction with treatment tapering is used for all patients with no baseline risk stratification. This study used transcriptomics, on pre-treatment liver biopsies, to explore whether the inflammatory response in AIH prior to therapy is similar or divergent in high and low risk patients.

Method: RNA was isolated from formalin-fixed paraffin embedded (FFPE) biopsy curls using the AllPrep FFPE RNA extraction (Qiagen, UK). Transcriptomics were performed using Nanostring nCounter, analyzing 770 gene targets with statistics performed using R software. Pre-treatment, diagnostic biopsies were assessed for 29 patients with defined clinical outcomes and 16 liver transplant donor biopsies (control group). 'Low risk' was defined as ALL of normal ALT/IgG, no flares or progression to cirrhosis and on azathioprine (AZA) or mycophenolate mofetil (MMF) only. 'High' risk was defined as ANY of >5 mg prednisolone or >3 mg budesonide, raised ALT and/or IgG, immunosuppression other than AZA/MMF, history of flares or progression to cirrhosis. A threshold of log-fold increase or decrease in gene expression compared to controls with a corrected p value <0.05 was used for significance.

Results: 200 genes were significantly differentially expressed between AIH as a whole and controls (138 upregulated in AIH and 62 downregulated with highly significant gene clustering [p < 10⁻¹⁵]). There were 14 low risk and 15 high risk patients with minimal difference in the nature of the transcriptome (89% and 87% of the upregulated and downregulated genes, respectively, showed significance in both groups). However, there was a significant difference (p < 10⁻¹⁵) in the degree of gene upregulation (but not downregulation) in high risk compared to low risk patients (Figure).

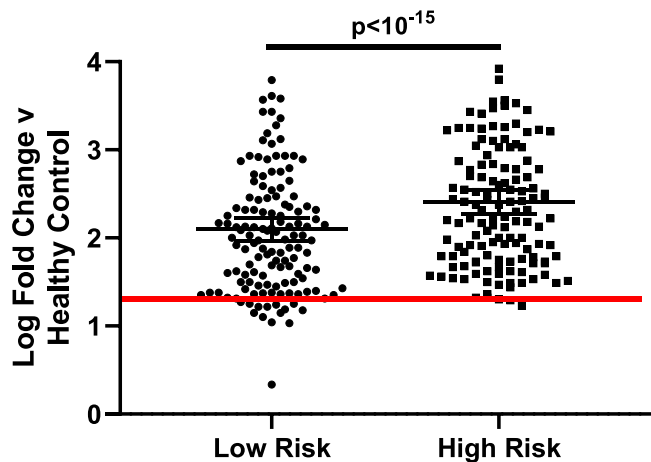


Figure:

Conclusion: The nature of the inflammatory transcriptome is very similar between high and low risk AIH patients suggesting a similar disease process in the two groups. There is, however, a marked amplitude difference with significantly high transcription of disease-linked genes in high risk patients. The augmented active response in high risk patients could be modified by treatment. Baseline biomarkers of the inflammatory response may allow us to titrate therapy more effectively.

PO-1578

Should normal liver blood tests be the treatment target in primary biliary cholangitis?

David Jones^{1,2}, Aaron Wetten^{1,2}, Ben Millar¹, Laura Ogle¹, George Mells³, Steven Flack³, Jonathan Badrock³, Richard N. Sandford³, John Kirby¹, Jeremy Palmer¹, Sophie Brotherston¹, Kowk Wong¹, Laura Jopson^{1,2}, John Brain¹, Graham Smith⁴, Steve Rushton⁵, Vinod Hegade⁶, Rebecca L. Jones⁶, Simon Rushbrook⁷, Douglas Thorburn⁸, Stephen Ryder⁹, Gideon Hirschfield¹⁰, UK-PBC Research Consortium¹¹, Jessica Dyson^{1,2}.
¹Newcastle University, Translational and Clinical Research Institute, United Kingdom; ²Newcastle Freeman Hospital, Liver unit, High Heaton, United Kingdom; ³Cambridge University, Dept. of Human Genetics, United Kingdom; ⁴Newcastle University, Bioinformatics Support Unit (BSU), Newcastle; ⁵Newcastle University, School of Natural and Environmental Science; ⁶St James's University Hospital, Liver unit, United Kingdom; ⁷Norfolk and Norwich University Hospital, Dept. of Gastroenterology, United Kingdom; ⁸Royal Free Hospital, Sheila Sherlock Liver Unit and UCL Institute of Liver and Digestive Health, London, United Kingdom; ⁹Queen's Medical Centre Nottingham, NIHR Nottingham Biomedical Research Centre, United Kingdom; ¹⁰University of Toronto-St. George Campus, 11-Toronto Centre for Liver Disease, Toronto, Canada; ¹¹UK-PBC Email: aaron.wetten@nhs.net

Background and aims: Second-line therapy for primary biliary cholangitis (PBC) has entered routine clinical practice for patients showing an incomplete response to first-line therapy with ursodeoxycholic acid (UDCA). Incomplete response is based on persistent elevation of liver biochemistry after 1 year of therapy. A number of biochemistry-based criteria have been described but it is unclear which is optimal and how they relate to the disease process. This study aimed to explore the relationship between UDCA response criteria and the underpinning disease mechanisms in PBC.

Method: O-link serum proteomics analysis of inflammatory markers was performed in 400 fully characterized PBC patients from the UK-PBC cohort treated for a minimum of 12 months with UDCA 13–15 mg/kg/day and for whom full biochemical response data were available. UDCA response was assessed using Paris 1 and 2, the POISE criteria and complete normalization of liver blood tests.

Results: Ongoing elevation of 19 protein markers (compared to healthy controls) was seen in UDCA-treated PBC patients and these formed the study panel. The study group included 182 (46%) PBC patients with normalised liver blood tests (160 of whom with bilirubin <0.6x upper limit of normal). Of the 218 patients with abnormal liver blood tests, 165 (76%) were Paris 1 responders, 107 (49%) were POISE responders and 92 (42%) were Paris 2 responders. For 17 (89%) of the protein markers there was significant variation across the study groups, with a significant increase according to the stringency of UDCA-response cut-offs (e.g. IL-4RA in Figure). Critically, significant elevation of protein markers was seen in UDCA-responders by all response criteria who had abnormal liver blood tests (88% of markers for Paris 1, 50% for POISE and 44% for Paris 2). However, none of the protein markers were significantly elevated in those with normal liver blood tests as compared to healthy controls.

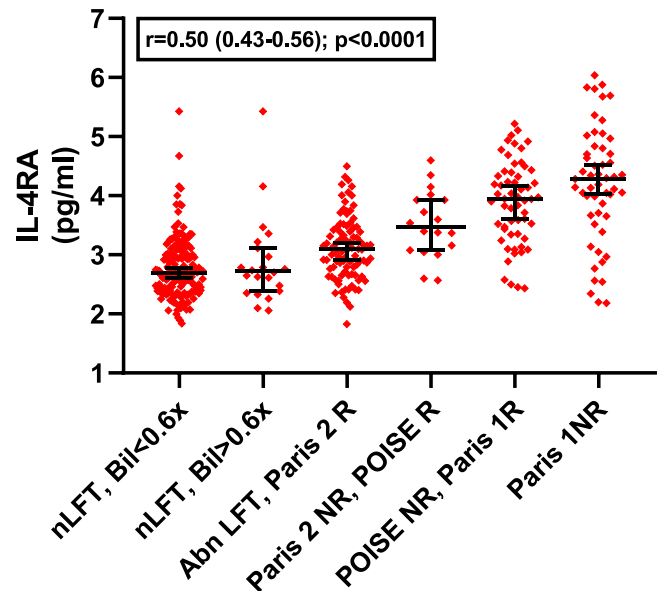


Figure:

Conclusion: This study demonstrates that proteomics are better markers of the biological processes in PBC than serum biochemistry. Ongoing disease activity is seen in patients with persistent abnormal liver blood tests even if they are classed as responders to UDCA therapy (irrespective of the response criteria used). This data shows that disease control in PBC requires normalization of liver blood tests and this should become the goal for both drug trials and clinical practice.

PO-1822

Cellular immune responses to human betaretrovirus in patients with primary biliary cholangitis

Hiatem Abofayed¹, Bruna Dutra¹, Hussain Syed¹, Mandana Rahbari¹, Andrew L. Mason¹. ¹University of Alberta, medicine, Edmonton, Canada Email: abofayed@ualberta.ca

Background and aims: We have characterized cellular immune responses to a human betaretrovirus (HBRV) infection in patients with primary biliary cholangitis (PBC) and reported that the intrahepatic proinflammatory cellular immune responses to HBRV greatly exceed the autoimmune response, suggesting that HBRV infection plays an important role in mediating PBC Hepatology, 2018;68 (Suppl)1101A. As part of the process, we identified 22 HBRV Gag and Env peptides (15-mer) that individually stimulated cellular immune responses in PBC patients by ELISpot. As serological diagnostics can only identify a small proportion of those with HBRV infection, our goal was to develop an interferon (IFN-gamma) release

assay in peripheral blood mononuclear cells (PBMC) and construct an "HBRV QuantiFERON" assay.

Method: Intrahepatic lymphocytes were isolated from transplant recipients' liver by flushing the portal vein (PBC n = 9, other hepatic disease n = 9) and PBMC were isolated from PBC patients (n = 32) and other liver diseases (n = 30). Following lymphocytes stimulation with 22 HBRV peptide pool, ELISpot was used to measure IFN-gamma spot forming colonies and Mesoscale V-Plex ELISA to quantify IFN-gamma production. To assess for inhibitory factors, 8µg anti-PD1 (nivolumab) was included with the stimulation assay.

Results: Following stimulation with 22 HBRV peptide pool, ELISpot analyses of intrahepatic lymphocytes from PBC patients showed a median of 111 spot forming colonies vs 9 in control subjects (Fig. 1A, $p < 0.001$). A higher proportion of PBC patients PBMC showed a greater than 10 pg of IFN-gamma production following HBRV pool peptide stimulation versus control subjects 50% vs. 8.7% ($p < 0.03$). Following addition of anti-PD-1, the response rate increased to 72% vs. 17% ($p = 0.0003$) in PBC vs. liver disease control (Fig. 1B).

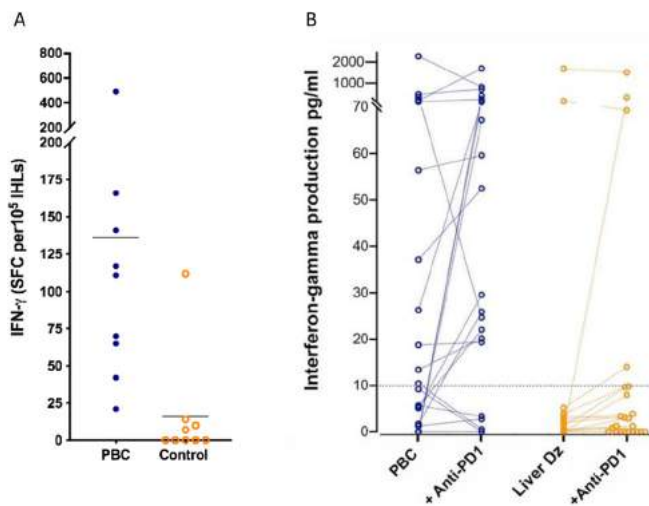


Figure 1:

Conclusion: Herein, we show that all PBC patients' intrahepatic lymphocytes and up to 75% of PBMC produce IFN-gamma following stimulation with the characterized peptide pool. The improved sensitivity of the QuantiFERON™ assay with the use of anti-PD1,

suggests that PBC patients' PBMC may express PD1 and have an exhausted phenotype in response to HBRV. This study provides further evidence of HBRV infection playing a role in the pathogenesis of PBC. The IFN-gamma release assay will be further refined as a diagnostic tool to determine the prevalence of HBRV in patients with liver disease and other disorders.

PO-2285

Vitamin B6 deficiency associates with liver transplantation-free survival in primary sclerosing cholangitis

Peder Rustøen Braadland¹, Annika M. Bergquist², Christian Rupp³, Robert Voitl³, Amandeep K. Dhillon¹, Trine Folseraas¹, Marius Trøseid⁴, Arve Ulvik⁵, Øyvind Middtun⁵, Per Ueland⁵, Tom Hemming Karlsen¹, Mette Vesterhus⁶, Martin Kummer¹, Johannes R. Hov¹. ¹Norwegian PSC Research Center, Oslo, Norway; ²Unit of Gastroenterology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; ³Dept. of Internal Medicine IV, Heidelberg University Hospital, Heidelberg, Germany; ⁴Section of Clinical Immunology and Infectious Diseases, Oslo, Norway; ⁵BEVITAL AS, Bergen, Norway; ⁶Haraldsplass Deaconess Hospital, Bergen, Norway
Email: pbraadland@gmail.com

Background and aims: We recently reported that patients with primary sclerosing cholangitis (PSC) have a reduced gut microbial potential to synthesize pyridoxal 5'-phosphate (PLP; the active form of vitamin B6, Kummer et al. 2020). PLP concentrations in plasma were also lowered, which associated with shortened survival. Here, we measured additional B6-related markers in this and several other cohorts aiming to define and validate the degree of B6 deficiency and the relationship with inflammation and prognosis.

Method: In total 530 PSC patients (71% male; median age 42 years; 72% IBD) and 100 healthy controls (HCs) were included; two cohorts from Norway (Oslo and Bergen, HC and PSC; plasma) and German and Swedish cohorts (both PSC only; serum). Targeted metabolomics was performed using LC-MS/MS (BEVITAL, Bergen, Norway). End point was defined as the earlier event of either liver transplantation (LTX) or death from all causes.

Results: In accordance with our derivation cohort, PLP concentrations were lower in PSC compared to HCs in an independent cohort. In a pooled Norwegian cohort, biochemical B6 deficiency (plasma PLP <20 nM) was prevalent in PSC (96/239 [40%] vs. 0/100 HCs). Plasma PLP may in part be degraded by alkaline phosphatase (ALP), which correlated inversely with PLP ($r = -0.36$). We also observed an elevated ratio of the PLP catabolite, 4-pyridoxic acid (PA), to the sum

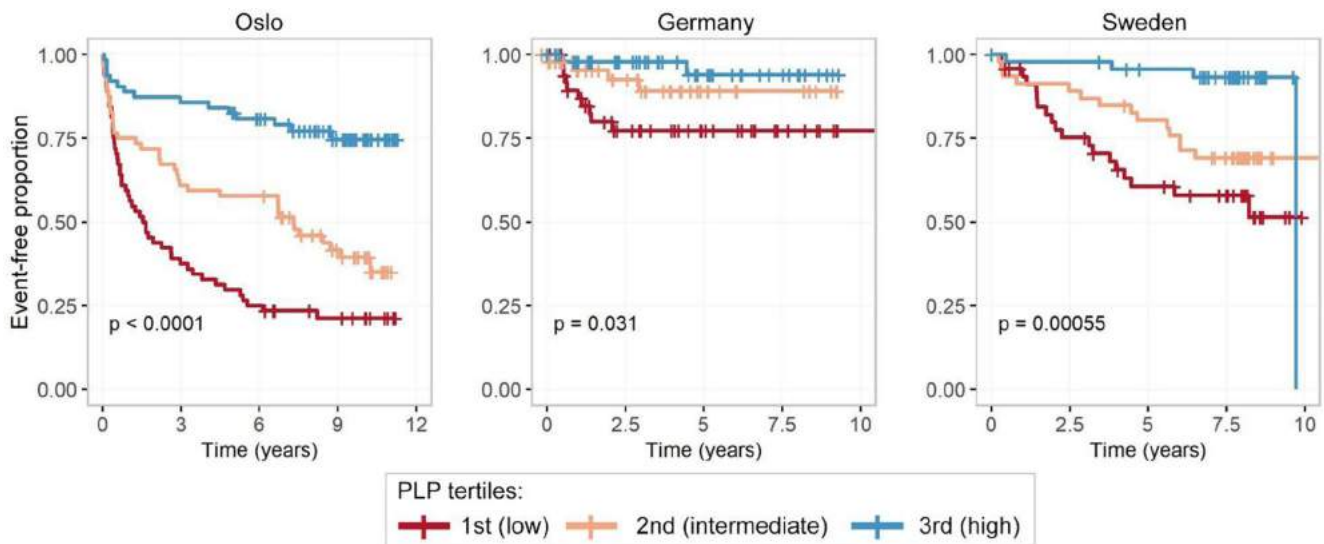


Figure: (abstract: PO-2285)

POSTER PRESENTATIONS

of PLP and pyridoxal (PL), which putatively implies inflammation-driven PLP catabolism. However, both PL and PA were also reduced, and the HK-ratio elevated, suggesting reduced activity in the PLP-dependent kynurenine pathway of tryptophan metabolism and hence functional B6 deficiency. PLP strongly predicted LTX-free survival in both the Norwegian, German (n = 150) and Swedish (n = 141) cohorts (figure). The association of PLP with outcome was independent of Mayo risk score (MRS) in the Norwegian cohort (adj. HR for log₁₀(PLP) = 0.12, p < 0.0001), but was at least partly explained by MRS in the validation cohorts (Germany: HR = 0.47, p = 0.25; Sweden: HR = 0.12, p = 0.013).

Conclusion: Low PLP was associated with PSC and predicted reduced survival. Both an altered gut microbiome, ALP, inflammation-driven B6 catabolism and intracellular, altered distribution of vitamin B6 may contribute to the lowered circulating PLP. However, functional deficits in PLP-dependent pathways suggest a commonality of real, intracellular B6 deficiency in PSC, which may have a clinical impact.

PO-2388

FXR Controls Effector Cytokine Production and Phenotype in Biliary Atresia

Alexander Miethke¹, Annika Yang vom Hofe¹, Astha Malik¹, Tiffany Shi², Brandee Wagner³. ¹Cincinnati Children's Hospital Medical Center, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati, United States; ²Cincinnati Children's Hospital Medical Center, Division of Immunobiology, Cincinnati; ³Metacrine, Inc., San Diego, United States

Email: alexander.miethke@cchmc.org

Background and aims: Biliary atresia (BA) is a progressive, inflammatory cholangiopathy of infancy that leads to fibrosis and obliteration of the extra and intrahepatic bile ducts. Farnesoid X receptor (FXR) is a bile acid activated nuclear receptor responsible for regulating de novo bile acid synthesis. We aimed to investigate the immunomodulatory functions of FXR in BA using both murine and human specimens.

Method: Newborn Balb/c mice were injected with type A rhesus rotavirus (RRV) within 24 hours of birth to induce experimental BA. Mice were dosed daily with FXR agonist, M044, at 10 mg/kg. Liver mononuclear cells (LMNCs) were isolated from RRV infected neonatal mice at 7 days after RRV infection. They were also separated from the explanted liver of an 8-month-old infant with BA. Cells were treated with M044 for 3 hours *in vitro*, cultured in presence of LPS for 16 hours, restimulated with PMA/Ionomycin, and subsequent subjected to intracellular flow cytometry.

Results: LMNCs isolated from RRV infected neonatal mice (Figure 1) or human explant specimen, when treated with M044 *in vitro* prior to LPS stimulation, showed a significant reduction of Ifng expression in macrophages (MP), CD4, CD8, and NKT cells were not responsive to the FXR agonist treatment. *In vivo* treatment of RRV infected mice with FXR agonist for 7 days resulted in a significant reduction of Ifng expression in hepatic immune cells (%Ifng+/MP: 0.8 ± 0.1% vs 1.6 ± 0.03%, %Ifng+/CD4: 11.2 ± 0.3% vs 17.9 ± 0.6%, %Ifng+/CD8: 2.1 ± 0.1% vs 9.8 ± 0.1% in M044 vs vehicle treated RRV infected mice; P < 0.002 for all subsets). 7-day-serum total bilirubin levels as biomarker for ductal obstruction were significantly reduced following administration of M044 (1.5 ± 0.7 vs 8.7 ± 1.2 mg/dL in M044 vs vehicle, P < 0.0001). M044 treatment improved survival by 2 days over RRV infected vehicle controls (n = 8 mice per group; P = 0.04).

	Macrophages	CD4	CD8	NKT
	14.3	19.7	19.4	45.6
UT	11.7	20.3	18.5	43
	11.8	15.9	21	49.4
	9	11.7	14.2	40.7
Treated	10.6	10	15.4	43
	8.55	10	14.9	39.4

Figure 1: Table showing %reduction in Ifng expression in subsets of hepatic immune cells isolated from RRV infected neonatal mice. Cells were either treated with LPS alone (UT) or with 1.0 μM FXR agonist.

Conclusion: Based on these preliminary findings— decrease in production of inflammatory cytokines, the improved biomarkers of liver injury, and increased survival—FXR agonists may provide a therapeutic strategy to block progression of liver disease in biliary atresia beyond their effects on bile acid homeostasis.

PO-2681

Altered DNA methylation characterizes autoimmune hepatitis

Pinelopi Arvaniti¹, Angeliki Lyberopoulou¹, Eirini Sevdali², Matthaios Speletas², Nikolaos Gatselis^{1,3}, Maria Ioannou⁴, Yves Renaudineau^{5,6}, George Dalekos^{1,3}, Kalliopi Zachou^{1,3}.

¹Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece; ²Department of Immunology and Histocompatibility, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece; ³Institute of Internal Medicine and Hepatology, Larissa, Greece; ⁴Department of Pathology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece; ⁵INSERM U1291, CNR U5051, University Toulouse III, Toulouse Institute for infectious and inflammatory diseases, Toulouse, France; ⁶Department of Immunology, Purpan University Hospital Toulouse, Toulouse, France

Email: zachoukalliopi@gmail.com

Background and aims: AIH is a chronic liver disease of unknown aetiology and favourable response to immunosuppression. Little is known about the impact of epigenetics on disease's pathogenesis. Our aim was to investigate the presence of DNA methylation modifications in AIH.

Method: CD19 (+) and CD4 (+) cells were isolated from 10 AIH patients at diagnosis (time-point 1; tp1), 9 primary biliary cholangitis (PBC) patients and 10 healthy controls (HC). 8/10 of AIH patients were also investigated on biochemical remission (time-point 2; tp2). Their global DNA methylation (5^{mC})/hydroxymethylation (5^{hmC}) state was assessed by ELISA. The mRNA of DNA methyl-transferases (DNMT1, DNMT3A, DNMT3B) and Ten-Eleven Translocation deoxygenases (TET1, TET2, TET3) was determined by quantitative RT-PCR. Epigenome wide association study (EWAS) in CD4 (+) cells was performed by Illumina HumanMethylation 850 K array in AIH and HC. Differences in total 5^{mC}/5^{hmC} state between AIH-tp1 and HC were also assessed by immunohistochemistry (IHC) on paraffin embedded liver sections.

Results: Global DNA 5^{mC}/5^{hmC} did not differ between groups. Reduced TET1 and increased DNMT3A mRNA levels were found in CD19 (+) and CD4 (+) lymphocytes from AIH-tp1 patients compared to HC and PBC, respectively. CD4 (+) DNMT3A mRNA levels of AIH-tp1 patients were negatively correlated with serum IgG levels (p = 0.03). Immunosuppression (AIH-tp2) decreased DNMT3A in both CD19 (+) and CD4 (+) cells (p = 0.02 and p = 0.03, respectively). EWAS in CD4 (+) cells from AIH-tp1 and AIH-tp2 patients revealed, altered methylation of genes implicated in immune responses, such as HLADP, TNF,

InRNAs and CD86. IHC showed no changes of total 5^{mC}/5^{hmC} level in hepatocytes, however, increased 5^{hmC} staining of periportal infiltrating lymphocytes in AIH-tp1 was detected.

Conclusion: Altered expression of TET1 and DNMT3A, characterizes peripheral immune cells in AIH. DNMT3A is associated with disease activity and decreased after complete biochemical response. Furthermore, DNA methylation modifications of specific genes implicated in immunologic pathways of peripheral CD4 (+) lymphocytes and dense 5^{hmC} staining of periportal lymphocytes support the notion that epigenetics may play an important role in AIH pathogenesis.

Immune-mediated and cholestatic disease: Clinical aspects

PO-60

Quantification of polyreactive immunoglobulin G facilitates diagnosis of autoimmune hepatitis

Bastian Engel¹, Richard Taubert¹, Jana Diestelhorst¹, Katharina Luise Hupa-Breier¹, Emily Saunders¹, Theresa Kirchner¹, Anna Baumann¹, Patrick Behrendt¹, Niklas T. Baerlecken¹, Kurt-Wolfram Sühs¹, Maciej K. Janik², Kalliopi Zachou³, Marcial Sebode⁴, Christoph Schramm⁴, Maria Carlota Londoño⁵, Sarah Habes⁶, Ye Htun Oo⁷, Claudine Lalanne⁸, Simon Pape⁹, Maren Schubert¹⁰, Michael Hust¹⁰, Stefan Dübel¹⁰, Mario Thevis¹¹, Danny Jonigk¹, Joost Ph Drenth⁹, Luigi Muratori⁸, David Adams⁷, Jessica Dyson¹², Amédée Renand¹³, Isabel Graupera⁵, Ansgar W. Lohse⁴, George Dalekos³, Piotr Milkiewicz², Martin Stangel¹, Benjamin Maasoumy¹, Torsten Witte¹, Heiner Wedemeyer¹, Michael P. Manns¹, Elmar Jaeckel¹. ¹Hannover Medical School, Hannover; ²Medical University of Warsaw; ³Institute of Internal Medicine and Hepatology, Larissa, Greece; ⁴University Medical Centre Hamburg-Eppendorf; ⁵Liver Unit, Hospital Clinic Barcelona; ⁶Hépto-Gastro-entérologie et Assistance Nutritionnelle, CHU Nantes; ⁷University Hospital Birmingham; ⁸Dept. of Medical and Surgical Sciences, University of Bologna; ⁹Dept. of Gastroenterology and Hepatology, Radboud University Medical Center Nijmegen; ¹⁰Technische Universität Braunschweig; ¹¹German Sport University Cologne; ¹²Liver Unit, Freeman Hospital, Newcastle upon Tyne Hospitals; ¹³INSERM Université de Nantes
Email: Engel.Bastian@mh-hannover.de

Background and aims: Detection of autoantibodies is a mainstay of diagnosing autoimmune hepatitis (AIH). However, conventional autoantibodies for workup of AIH lack either sensitivity or specificity leading to substantial diagnostic uncertainty. We aimed to identify more accurate serological markers of AIH with a protein macro-array and a solid phase ELISA.

Method: IgG antibodies with binding capacities to many human and foreign proteins were identified with a protein macro-array and confirmed with solid phase ELISAs in AIH patients. Subsequently, polyreactive IgG (pIgG) were exemplarily quantified by reactivity against human huntingtin-interacting protein 1-related protein in bovine serum albumin blocked ELISA (HIP1R/BSA). Diagnostic fidelity of HIP1R/BSA binding pIgG to diagnose AIH was assessed in a retrospective training, a retrospective multicenter validation and a prospective validation cohort, in cryo-conserved samples from 1568 adults from ten centers from eight countries.

Results: Sera from AIH patients exhibited IgG binding to various autoantigens on the protein macro-array. In subsequent ELISAs, AIH patients exhibited higher concentrations of IgG with broad reactivity against protein (human autoantigens and foreign antigens) and non-protein antigens than patients with non-AIH liver diseases and healthy controls. Polyreactivity of IgG was quantified by reactivity

against HIP1R/BSA. Reactivity against HIP1R/BSA had a 26–37% and 6–45% higher specificity to diagnose AIH than conventional anti-nuclear antibodies and anti-smooth muscle antibodies, respectively, and a significantly higher sensitivity to diagnose AIH than liver kidney microsomal antibodies and anti-soluble liver antigen/liver pancreas antigen. Importantly, HIP1R/BSA reactivity was present in up to 88% of patients with seronegative AIH and in up to 71% of AIH patients with normal IgG levels. Under therapy pIgG returns to background levels of non-AIH liver diseases.

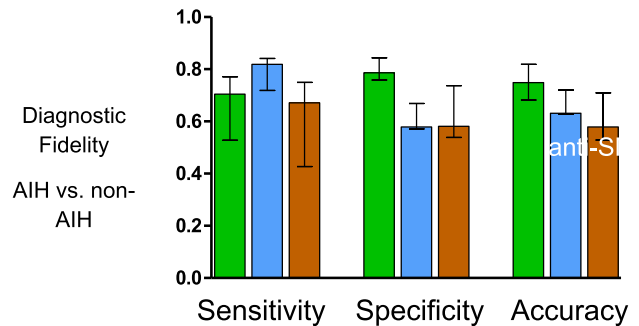


Figure:

Conclusion: pIgG could be used as a new promising marker to improve the diagnostic workup of liver diseases with a higher specificity for AIH compared to conventional antibodies and a utility in autoantibody negative AIH. Likewise, pIgG could be a major source of assay interference in untreated AIH.

PO-127

Quality of life is impaired in both physical and mental health domains, in patients with Autoimmune Hepatitis: A systematic review and meta-analysis

Selena Dixon¹, Jill Carlton², Marrisona Martyn-St James², Dermot Gleeson¹. ¹Sheffield Teaching Hospitals NHS Foundation Trust, Liver Unit, Sheffield, United Kingdom; ²University of Sheffield, School of Health and Related Research (SchARR), Sheffield, United Kingdom
Email: selenadixon@doctors.org.uk

Background and aims: Quality of life (QoL) has been measured using Patient-Reported Outcome Measures (PROMs) in patients with Autoimmune Hepatitis (AIH). We performed a meta-analysis of QoL in patients with AIH, compared to that in controls.

Methods: Medline, EMBASE and PsycINFO were searched from inception to September 2020. Study protocol was registered on PROSPERO (CRD 42020182668). Between-group QoL outcomes were pooled in a random-effects meta-analysis, as standardised mean differences (SMD) with 95% confidence intervals (CI). Study authors were contacted for missing data. Heterogeneity was assessed using I² statistic. Study quality was assessed by two review authors independently.

Results: Sixteen cross-sectional studies using fourteen different QoL PROMs (n = 2337 adults with AIH from nine countries) were included. Pooled effects of Short-Form (SF)-36 and SF-12 PROM summary scores from nine studies (n = 993) showed that Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were impaired in patients with AIH compared to controls. For PCS, SMD -0.59 (95% CI -0.87, -0.31), p < 0.00001 and for MCS, -0.43 (-0.57, -0.29), p < 0.00001. I² was 87% and 47%, respectively. Sensitivity analysis, excluding lower quality studies, reduced heterogeneity for MCS (I² = 0%) but not PCS (I² = 93%) outcomes. QoL was also reduced in all eight SF-36 subscales (SMD -0.25 to -1.11), with General Health (-1.11), Vitality (-0.82) and Role Physical (-0.70) domain scores most impaired.

Seven studies used mental health-specific PROMs. Control data was available in four (n = 1184). Pooled effects of PROM scores for depression (SMD 0.58 (95% CI 0.28, 0.89), I² = 85%, p = 0.00002) and

POSTER PRESENTATIONS

anxiety (0.44 (0.33, 0.56), $I^2 = 18\%$, $p < 0.00001$) were higher (worse) in patients with AIH versus controls.

Studies evaluating the relationship of QoL to remission status, presence of cirrhosis, co-morbidities or corticosteroid therapy were limited, or reported conflicting results. Study quality was variable.

Conclusions: Pooled evidence from cross-sectional studies indicates that patients with AIH have impaired QoL compared to controls, in both physical and mental health domains. However, statistical heterogeneity is evident for some outcomes and results should be interpreted with caution.

PO-210

A Dose-Finding, Positive Proof of Concept Study of HTD1801 in Patients with Primary Sclerosing Cholangitis

Kris Kowdley¹, Lisa Forman², Bertus Eksteen³, Nadege T. Gunn⁴, Vinay Sundaram⁵, Charles Landis⁶, Stephen Harrison⁷, Anita Kohli⁸, Cynthia Levy⁹, Adrian Di Bisceglie¹⁰, Gideon Hirschfield¹¹. ¹Liver Institute Northwest, Seattle, United States; ²University of Colorado School of Medicine, Aurora, United States; ³Aspen Woods Clinic, Calgary, Canada; ⁴Pinnacle Research; ⁵Cedars-Sinai Medical Records Office, Los Angeles, United States; ⁶University of Washington School of Medicine, United States; ⁷Pinnacle Clinical Research, San Antonio, United States; ⁸Arizona Liver Health, Chandler, United States; ⁹University of Miami, Coral Gables, United States; ¹⁰HighTide Therapeutics, Rockville, United States; ¹¹University of Toronto-St. George Campus, Toronto, Canada
Email: adibisceglie@hightidetx.com

Background and aims: Primary sclerosing cholangitis (PSC) is a progressive, inflammatory and cholestatic liver disease, without present effective medical therapy. HTD1801 is an ionic salt of berberine and ursodeoxycholic acid, with predicted enhanced anti-inflammatory, anti-cholestatic and anti-fibrotic effects. We report a proof of concept randomized, placebo controlled, two-part study of HTD1801 over 18 weeks in patients with PSC and elevated serum alkaline phosphatase (ALP).

Method: Subjects were initially randomized into one of three treatment groups: (1) placebo (2) HTD1801 500 mg BID or (3) HTD1801 1000 mg BID. Those who had been on UDCA were required to discontinue it at randomization. The primary end point for part 1 of the study was change in ALP at 6 weeks and differences in serum ALP and GGT among the three groups were compared using Mixed-Effect Model Repeated Measures. In part 2 of the study, HTD1801 was continued for an additional 6 or 12 weeks and safety and biochemical efficacy were evaluated.

Results: A total of 59 subjects were enrolled into the study and 55 received at least one dose of study drug. Their mean age was 43 years (range 21–75), 32 were male (58%) and 46 were white (84%); the cohort included 35 subjects with IBD (64%) and their mean serum ALP level was 375 (range 122–1048). A total of 16 subjects received placebo, 15 the lower dose of HTD1801 and 24 the higher dose of HTD1801 during part 1 of the study. At week 6, there was a statistically significant difference in ALP and GGT in both HTD1801 treatment groups compared to placebo (Fig. 1a). Among the 32 subjects not on UDCA at randomization, ALP reduction was dose

dependent (36% with high-dose HTD1801, 27% in low-dose vs 10% in PBO) (Fig. 1b). In part 2 of the study, ALP reduction was maintained through 18 weeks of treatment in both HTD1801-treated groups, while ALP and GGT recrudesced substantially among those who crossed over from HTD1801 to placebo. HTD1801 was generally well tolerated. Only 4 subjects experienced serious adverse events (motor accident, *C. difficile* colitis, colostomy hemorrhage, partial SBO respectively), none of which were attributed to study drug.

Conclusion: HTD1801 improved biochemical markers of cholestasis in a dose-dependent manner in patients with PSC and was safe and well-tolerated. Further study of HTD1801 is warranted for treatment of PSC.

PO-254

Effectiveness of obeticholic acid in patients with primary biliary cholangitis stratified by biochemical marker status in the real-world setting in the United States

Robert G. Gish¹, Darren Wheeler², Jay Lin³, Femi Adegunle², Melissa Lingohr-Smith³, Chiara Bassanelli², Amy Law². ¹Loma Linda University, Loma Linda, United States; ²Intercept Pharmaceuticals, Inc., New York, United States; ³Novosys Health, Green Brook, United States
Email: melissa.smith@novosyshealth.com

Background and aims: In the clinical trial setting, obeticholic acid (OCA) has been shown to improve biochemical markers of hepatic injury and cholestasis in patients with primary biliary cholangitis (PBC) intolerant or inadequately responsive to ursodeoxycholic acid. Limited data are available on OCA real-world effectiveness. Therefore, we examined the real-world treatment effectiveness of OCA in subgroups of PBC patients according to their baseline biochemical marker status.

Method: Adult patients diagnosed with PBC (ICD-10: K74.3) and newly treated with OCA (May 2016–September 2019) were selected from a US administrative claims and laboratory database. The date of the first OCA prescription claim was designated as the index date. Patients were required to have continuous medical/pharmacy insurance enrollment 6 months prior to index dates (baseline period). Patients were stratified by their alkaline phosphatase (ALP) level ($>$ or ≤ 180 IU/L) and separately by their total bilirubin (TBili) level ($>$ or ≤ 0.7 mg/dL) at baseline. Patient demographics, clinical characteristics, and lab test values were examined. Biochemical responses to treatment were determined according to Toronto criteria ($ALP \leq 1.67 \times ULN$) using the latest lab test values in the baseline and follow-up periods.

Results: Among 319 PBC patients initiated on OCA, 181 with ALP level at baseline (median age: 62 years; 92.3% female), 69.1% ($n = 125$) had $ALP > 180$ IU/L (median: 284.0 IU/L) and 30.9% ($n = 56$) had $ALP \leq 180$ IU/L (median: 147.5 IU/L); from baseline to follow-up, median ALP decreased to 232.0 IU/L (-18.3%) and 132.0 IU/L (-10.5%), respectively. Among 182 PBC patients with baseline TBili lab results (median age: 63 years; 91.8% female), 35.7% ($n = 65$) had $TBili > 0.7$ mg/dL (median: 1.40 mg/dL) and 64.3% ($n = 117$) had $TBili \leq 0.7$ mg/dL (median: 0.50 mg/dL); from baseline to follow-up, median TBili decreased to 1.00 mg/dL (-28.6%) and 0.40 mg/dL (-20.0%),

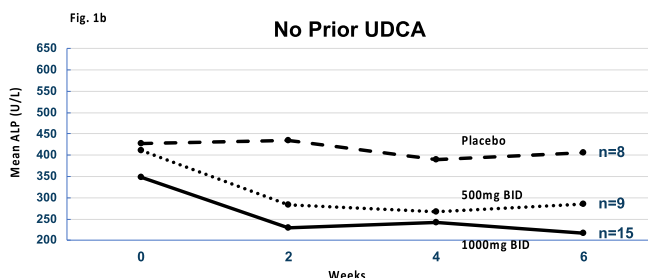
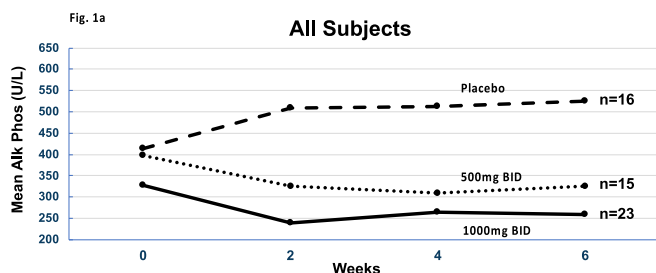


Figure: (abstract: PO-210)

respectively. Biochemical responses to OCA treatment according to Toronto criteria are shown in the figure.

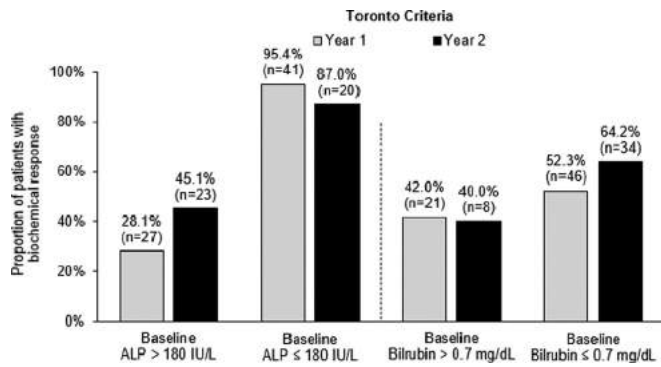


Figure:

Conclusion: In this real-world study of PBC patients in the US, OCA was effective in achieving biochemical responses after 1 and 2 years of treatment across patient subgroups with differing biochemical marker status. These real-world findings are generally consistent with that reported in the clinical trial setting.

PO-344

Immunohistochemical staining of cholangioscopy-directed biopsies of cholangiocarcinoma in Primary Sclerosing Cholangitis

Stephanie Yan¹, Sooraj Tejaswi², Kristin Olson³. ¹University of California, Davis, Gastroenterology and Hepatology, Sacramento, United States; ²University of California, Davis, Davis, United States; ³University of California, Davis, Pathology, Sacramento, United States
Email: soorajt@gmail.com

Background and aims: Primary sclerosing cholangitis (PSC) is associated with a high risk of cholangiocarcinoma (CCA).¹ Two pathways of carcinogenesis are known: the classic type with a yet-to-be identified precursor, and the more common intestinal metaplasia-dysplasia-carcinoma sequence.² Thus, intestinal metaplasia (IM) is a CCA precursor. Intestinal-type CCA demonstrates a distinct immunohistochemical (IHC) phenotype. We aimed to determine the feasibility of IHC staining of biliary biopsies obtained via cholangioscopy, identify IM in patients with CCA in PSC and compare the IHC profiles of CCA in PSC, CCA without PSC, and intraductal papillary neoplasm of the bile duct (IPNB).

Method: We performed IHC staining of cholangioscopic biopsies of 12 patients divided into 4 subgroups: 3 conventional CCA, 3 CCAs in PSC, 3 PSC with benign active inflammation, and 3 IPNB. An expert GI pathologist reviewed these.

Results: Adequate tissue for IHC staining was obtained by cholangioscopy-directed biopsies in 11/12 patients (91.6%). Intestinal phenotypes (MUC2, CK20, CDX2) were not detected in PSC with benign active inflammation or non-PSC CCA. In PSC cases with CCA, 2/3 markers were detected in 1/3 patients only. In the IPNB group, 2/3 cases stained positive for two intestinal markers. No similarities were noted between PSC-CCA and IPNB cases.

	MUC1	MUC2	MUC5AC	MUC6	CK7	CK20	CDX2
PSC active inflammation	1 +	-	+	+	+	-	-
	2 +	-	+	+	+	-	-
	3 +	-	+	+	+	-	-
PSC CCA	1 +	-	*	*	+	-	-
	2 +	+	*	*	-	*	+
	3 +	-	+	+	+	-	-
CCA without PSC	1 +	-	-	+	+	*	-
	2 +	-	*	-	+	-	-
	3 n/a	n/a	n/a	n/a	n/a	n/a	n/a
IPNB	1 +	+	+	+	+	-	+
	2 +	-	-	-	+	-	-
	3 +	*	-	-	-	+	+

*indicates cases with clear staining but involving ≤10% cells, thus classified as negative

Conclusion: Cholangioscopy-directed biopsies provided adequate tissue for IHC staining. Intestinal markers were only noted in 1 PSC-CCA case and 2 IPNB cases. Intestinal markers were absent in benign PSC and non-PSC CCA.

Larger longitudinal studies sampling different areas of the hilum and extrahepatic bile duct plus serial sampling over time may help identify patterns to risk stratify patients and evaluate the prognosis of premalignant changes such as intestinal metaplasia, to eventually help devise surveillance strategies for carcinogenesis in PSC.

Reference

Zen Y, Quaglia A, Heaton N, Rela M, Portmann B. Two distinct pathways of carcinogenesis in primary sclerosing cholangitis. *Histopathology*. 2011;59 (6):1100-1110. doi:10.1111/j.1365-2559.2011.04048.x
Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Precancerous bile duct pathology in end-stage primary sclerosing cholangitis, with and without cholangiocarcinoma. *Am J Surg Pathol*. 2010;34(1):27-34. doi:10.1097/PAS.0b013e3181bc96f9

PO-376

Cluster analysis reveals the prognostic role of serum albumin within the normal range in patients with primary biliary cholangitis

Alessio Gerussi¹, Damiano Verda², Davide Bernasconi³, Marco Carbone⁴, Atsumasa Komori⁵, Masanori Abe⁶, Mie Inao⁷, Tadashi Namisaki⁸, Satoshi Mochida⁷, Hitoshi Yoshiji⁸, Gideon Hirschfield⁹, Keith D. Lindor¹⁰, Albert Pares¹¹, Christophe Corpechot¹², Nora Cazzagon¹³, Annarosa Floreani¹³, Marco Marziani¹⁴, Domenico Alvaro¹⁵, Umberto Vespasiani Gentilucci¹⁶, Laura Cristofori^{3,4}, Maria Grazie Valsecchi³, Marco Muselli², Bettina Hansen⁹, Atsushi Tanaka¹⁷, Pietro Invernizzi⁴. ¹University of Milano-Bicocca,

POSTER PRESENTATIONS

Department of Medicine and Surgery, Monza, Italy; ²Rulex Inc., Newton, MA, United States; ³University of Milano-Bicocca, Bicocca Bioinformatics Biostatistics and Bioimaging Centre-B4, School of Medicine and Surgery, Monza, Italy; ⁴University of Milano-Bicocca, Division of Gastroenterology, Centre for Autoimmune Liver Diseases, Department of Medicine and Surgery, Monza, Italy; ⁵National Hospital Organization (NHO) Nagasaki Medical Center, Clinical Research Center, Japan; ⁶Ehime University Graduate School of Medicine, Department of Gastroenterology and Metabolism, Japan; ⁷Saitama Medical University, Department of Gastroenterology and Hepatology, Faculty of Medicine, Japan; ⁸Nara Medical University, Department of Gastroenterology, Japan; ⁹University Health Network, Toronto Centre for Liver Disease, Toronto Western and General Hospital, Toronto, Canada; ¹⁰Mayo Clinic, Division of Gastroenterology and Hepatology, Phoenix, United States; ¹¹University of Barcelona, Liver Unit, Hospital Clínic, CIBERehd, IDIBAPS, Barcelona, Spain; ¹²APHP-Sorbonne université, Centre de Référence des Maladies Inflammatoires des Voies Biliaires et des Hépatites auto-immunes, Hôpital Saint-, Antoine, Paris, France; ¹³University of Padua, Department of Surgery, Oncology and Gastroenterology, Italy; ¹⁴Ospedali Riuniti University Hospital, Division of Gastroenterology and Hepatology, Ancona, Italy; ¹⁵Sapienza University of Rome, Department of Translational and Precision Medicine, Rome, Italy; ¹⁶Campus Bio-Medico University of Rome, Clinical Medicine and Hepatology Unit, Rome, Italy; ¹⁷Teikyo University School of Medicine, Department of Medicine, Tokyo, Japan

Email: lessioigerussi@gmail.com

Background and aims: Machine learning (ML) is revolutionizing medicine, with clustering as one of the most promising ML approaches for prognostication. We explored whether clustering could support disease subphenotyping to enhance risk stratification in primary biliary cholangitis (PBC).

Method: ML was applied to the largest international dataset of PBC patients. The dataset was split into a derivation cohort (training set) and a validation cohort (validation set), and six key clinical features were analyzed: total serum bilirubin, alkaline phosphatase (ALP), albumin, sex, age at diagnosis and treatment with UDCA. The outcome was a composite of liver-related death or liver transplantation. Classification, clustering and standard survival analysis were performed.

Results: Training set was composed of 11, 819 subjects, while validation set was composed of 1, 069 subjects. Four clusters with different prognosis were generated in training set and later evaluated in validation set (Figure). Cluster 1 (n = 3, 566) included patients with excellent prognosis, whereas Cluster 2 (n = 3, 966) consisted of individuals at slightly worse prognosis differing from Cluster 1 only for lower median levels of albumin. Young patients with florid cholestasis represented the Cluster 3 (n = 2, 379), whereas patients in Cluster 4 (n = 1, 908) showed signs of advanced liver failure and had the worst prognosis. After restricting the analysis to patients with albumin values at baseline within the normal range, we found that patients with baseline albumin levels between 1.0 and 1.2 × LLN had worse 15-year survival compared to those with levels ≥1.2 × LLN (70.7% vs 84.6%, respectively, p < 0.001).

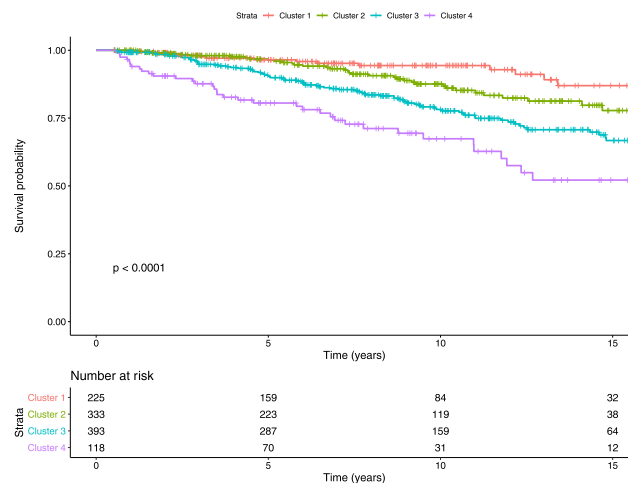


Figure:

Conclusion: Clustering identified four groups of PBC patients with different long-term prognosis. Reference ranges for serum albumin should be reappraised in this condition.

PO-770

Real-world evaluation of second line therapy in Primary Biliary Cholangitis: A multicentre nationwide study

Nadir Abbas^{1,2,3}, Emma Culver⁴, Douglas Thorburn⁵, Neil Halliday⁵, Hannah Crothers⁶, Jessica Dyson^{7,8}, Richard Aspinall⁹, Dr Yiannis Kallis¹⁰, Belinda Smith¹¹, Imran Patanwala¹²,

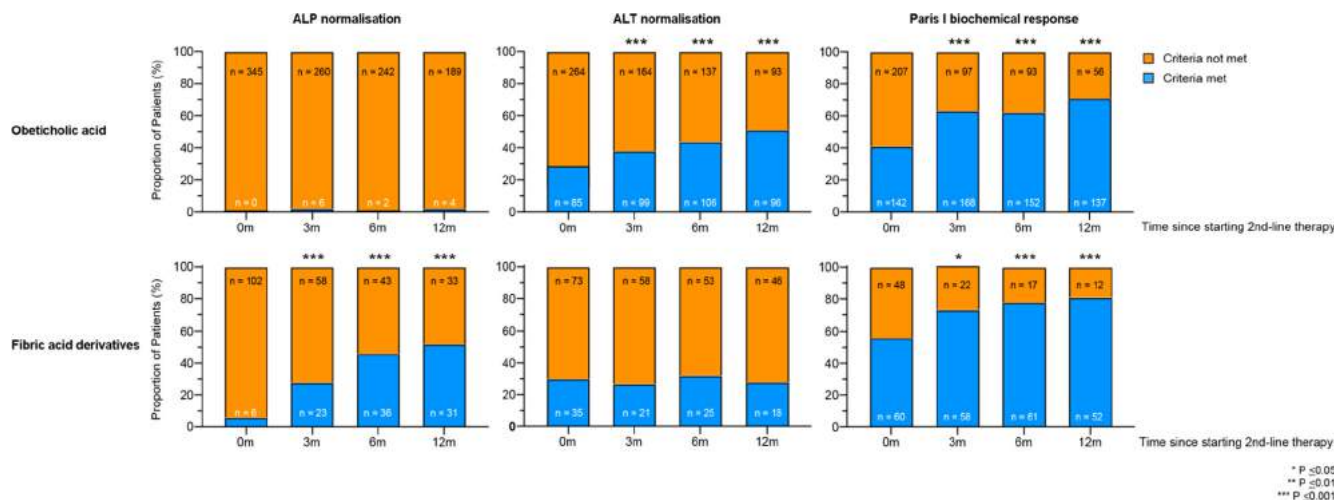


Figure: (abstract: PO-770)

Anne McCune¹³, Chenchu Chimakurthi¹⁴, Rebecca L. Jones¹⁴, Michael Orrell⁴, George Mells¹⁵, David Jones^{7,8}, Gideon Hirschfield¹⁶, Palak Trivedi^{1,2,3,17}. ¹NIHR Birmingham Biomedical Research Centre, Centre for Liver and Gastroenterology Research, University of Birmingham, Birmingham, United Kingdom; ²Liver Unit, University Hospitals Birmingham Queen Elizabeth, Birmingham, United Kingdom; ³Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; ⁴Oxford Liver Unit, John Radcliffe Hospital, Oxford, United Kingdom; ⁵Institute of Liver and Digestive Health, University College London, London, United Kingdom; ⁶Department of Informatics, University Hospitals Birmingham, Birmingham, United Kingdom; ⁷Department of Hepatology, Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle, United Kingdom; ⁸Institute of Cellular medicine, Newcastle University, Newcastle, United Kingdom; ⁹Department of Gastroenterology and Hepatology, Queen Alexandra Hospital, Portsmouth, United Kingdom; ¹⁰Department of Hepatology, Barts Health NHS trust and Blizard Institute, Queen Mary University of London, London, United Kingdom; ¹¹Department of Digestive Diseases, St Mary's Hospital, Imperial College London, London, United Kingdom; ¹²Department of Gastroenterology and Hepatology, Royal Liverpool and Boardgreen University Hospitals NHS trust, Liverpool, Liverpool, United Kingdom; ¹³Department of Liver Medicine, University Hospitals Bristol NHS foundation Trust, Bristol, United Kingdom; ¹⁴Department of Hepatology, Leeds Teaching hospital NHS trust, Leeds, United Kingdom; ¹⁵Academic Department of Medical Genetics, University of Cambridge, Cambridge, United Kingdom; ¹⁶Toronto Centre for Liver Diseases, University of Toronto and University Health Network, Toronto, Canada; ¹⁷Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom
Email: p.j.trivedi@bham.ac.uk

Background and aims: The aim of this study was to compare the effectiveness of second-line therapies in primary biliary cholangitis (PBC), with regards Obeticholic acid (OCA) and non-licensed therapy (fibric acid derivatives; FA) across a nationwide multicentre cohort of patients (pts).

Method: Efficacy and safety data was accrued from 12 centres across the UK. Biochemical parameters are presented relative to the upper limit of normal (ULN). Efficacy was determined according to the magnitude of reduction in liver biochemistry from baseline to 12 months (mo), and by pre-specified response criteria (Paris).

Results: Between August 2017-March 2020 we captured data from 457 PBC pts who initiated second-line therapy (n=349 OCA, 48 bezafibrate, 60 fenofibrate). At baseline, the OCA group appeared to be higher risk, as evidenced by greater ALP values than those initiating FA therapy (2.9 v 2.3 × ULN; p=0.001), and with a greater proportion being ursodeoxycholic acid non-responders (63.5% vs 45.4%; p=0.001), having cirrhosis (16.5% v 8.3%; p=0.03), or abnormal bilirubin values (22.1% v 12%; p=0.02). At 12mo, the magnitude of ALP reduction was 29.3% and 56.7% in the OCA and FA groups (p < 0.001 between groups), with 2% and 49% of pts attaining normal ALP values (Figure). By contrast, 50.8% and 28.1% attained a normal ALT at 12mo (p < 0.001 between groups; Figure). Moreover, 37.3% of the OCA group who had an abnormal bilirubin at baseline normalised values at 12mo (p < 0.05). 12mo composite biochemical response rates were 71.1% and 83.1% under OCA and FA therapy, respectively (p=0.141 between groups). In patients with cirrhosis under OCA treatment (n = 57), significant reductions in ALP, ALT and bilirubin were observed at 12 mo (p < 0.05 for all comparisons), with 61.5% attaining full biochemical response. The number of pts with an elevated bilirubin or cirrhosis in the FA group was too small to permit subgroup analysis therein. Escalation in anti-pruritus therapy was observed in 26.1% and 23.2% of pts (p=n.s.). Mild-moderate elevations in liver biochemistry (DILIN classification) were reported in 4.6% and 12.0% of pts under OCA and FA therapy, respectively (p < 0.05).

Conclusion: In this non-randomised study, the magnitude of ALP reduction was greater with FA derivatives, whereas rates of ALT and

bilirubin normalisation were more pronounced under OCA. The need for anti-pruritus treatment is similar between groups, although putative rates of drug-induced liver injury appear greater under FA therapy.

PO-860

Hepatolithiasis is a frequent and prognostic finding in patients with primary sclerosing cholangitis

Bellal Jubran¹, Marwa Ismail^{2,3}, Maya Stein⁴, Derek Little⁵, Bettina Hansen², Aliya Gulamhusein⁶, Gideon Hirschfield⁶.

¹University of Toronto, Gastroenterology and Hepatology, Toronto, Canada; ²University of Toronto; ³Institute of Health Policy Management and Evaluation; ⁴University of Toronto, Internal Medicine; ⁵University of Toronto, Gastroenterology and Hepatology; ⁶University of Toronto, Toronto Centre for the Study of the Liver
Email: bellal.jubran@mail.mcgill.ca

Background and aims: Intrahepatic biliary stones (hepatolithiasis) is not well characterised clinically in patients with primary sclerosing cholangitis (PSC).

Methods: Chart reviews were conducted in patients with a histologic or radiographic diagnosis of PSC, followed at the Toronto Centre for Liver Disease. Radiographic data were collected between the years 2008–2018. Depending on frequency of testing, magnetic resonance imaging (MRI) and ultrasound (US) data was reviewed every 3–5 years. We assessed factors associated with hepatolithiasis based on sex, race, age and phenotype of PSC and inflammatory bowel disease (IBD). Qualitative radiographic findings on image report review, episodes of cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) and occurrence of cholangiocarcinoma (CCA), death and transplant were documented. Data are reported with median and IQR and analyzed using chi-squared and Mann-Whitney U tests.

Results: 302 patients were reviewed. The median time to follow-up, defined as from date of diagnosis to last clinic visit or to transplantation date, was 98 months (IQR = 54.5–141.5). The mean age at diagnosis was 38 (SD = 15.1) years; 54% of patients were male. A total of 224 patients had IBD (74%). Of the 302 patients, 80 patients (26%) had evidence of hepatolithiasis on US or MRI. Patients with hepatolithiasis were more likely to be younger (37.4 vs 39.1, p = 0.025), male (65% vs. 50%, p = 0.021), and have large duct disease (99% vs. 88%, p = 0.004). Imaging report review revealed patients with hepatolithiasis were more likely to have intrahepatic biliary thickening (76% vs. 45%, p < 0.001), extrahepatic biliary thickening (69% vs. 50%, p = 0.003), focal biliary dilation (96% vs. 78%, p < 0.001) and disease characterised by more reported strictures on qualitative imaging report review (89% vs 69%, p < 0.001). Concomitant presence of cholelithiasis was greater in the hepatolithiasis vs. the non-hepatolithiasis group (45% vs. 19%, p < 0.001). Patients with hepatolithiasis were more likely to have experienced acute ascending cholangitis (50% vs. 20%, p < 0.001) and need for ERCP (50% vs. 35%, p = 0.020). CCA was numerically higher in the hepatolithiasis group (8.75% vs. 4%, p = 0.1). Patients with hepatolithiasis received transplant more frequently (26.3% vs 12.2%, p < 0.001) with no significant difference in mortality.

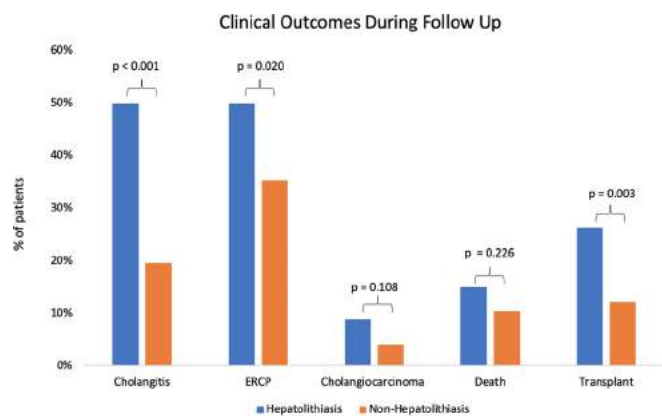


Figure 1: Comparison of clinical outcomes during follow-up

Figure:

Conclusion: Hepatolithiasis is common in PSC and associated with increased clinical and radiologic disease burden.

PO-872

Circulating B-cell activating factor of the tumour necrosis family (BAFF) and interleukin 21 levels predict treatment response in patients with autoimmune hepatitis

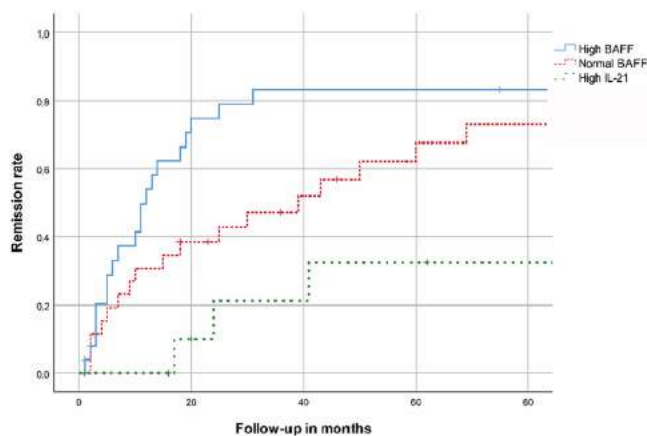
Maaïke Biewenga¹, Sebastiaan Heidt², Manon Vergunst², Camiel Marijnissen¹, Adriaan Van der Meer³, Robert De Man³, Annemiek Van der Eijk⁴, Leendert Trouw², Bart Van Hoek¹. ¹Leiden University Medical Center, Gastroenterology and Hepatology, Netherlands; ²Leiden University Medical Center, Immunology, Netherlands; ³Erasmus Medical Center, Gastroenterology and Hepatology, Netherlands; ⁴Erasmus Medical Center, Virology, Netherlands

Email: m.biewenga@lumc.nl

Background and aims: Increased serum IgG and autoantibodies suggest involvement of B-cell immunity in autoimmune hepatitis (AIH). The aim of this study was to assess levels of the important B-cell cytokines B-cell activating factor of the tumour necrosis family (BAFF), interleukin 21 (IL-21) and circulating B-cell populations in AIH and correlate these to presentation and treatment response.

Method: BAFF and IL-21 levels were determined in 10 healthy controls and 66 AIH patients before treatment. Treatment response was evaluated after 12 months. Flowcytometry was performed on isolated peripheral blood mononuclear cells of 10 AIH patients and 12 healthy controls.

Results: Based on the BAFF and IL-21 level, patients could be divided in 3 groups: 27 (41%) patients with normal BAFF and IL-21 (normal BAFF), 27 (41%) patients with elevated BAFF but normal IL-21 (high BAFF) and 12 (18%) patients with elevated IL-21 (high IL-21). Patients with high BAFF presented with higher bilirubin compared to patients with normal BAFF and high IL-21 (159 vs 26 vs 89 µmol/L; p = 0.001). After 12 months remission was reached in 54% of patients with high BAFF, 34% of patients with normal BAFF and none (0%) of patients with high IL-21 (p = 0.006). During follow-up 3 patients (25%) with high IL-21 developed primary sclerosing cholangitis (PSC) variant syndrome. Autoimmune associated B-cells were more prevalent in AIH patients compared to healthy controls (4.4% vs 1.4%; p = 0.003). Increase in BAFF was related to an increase in naïve B-cells (p = 0.01; r = 0.78) and to a decrease in class switched B-cells (p = 0.003; r = -0.85) and non-class switched B-cells (p = 0.005; r = -0.83).



Follow-up in months	0	20	40	60	80
Patients without remission					
High BAFF	26	6	4	4	3
Normal BAFF	27	15	10	6	5
High IL-21	12	8	7	6	5

Figure:

Conclusion: Using BAFF and IL-21 levels, different immunological phenotypes with a different presentation, treatment response and outcome were identified. Patients with high BAFF were often icteric at diagnosis but responded well to treatment. BAFF level was also related to shifts in circulating B-cell populations. Patients with high IL-21 had the poorest treatment response and are at risk to develop PSC variant syndrome.

PO-1017

Non-invasive scores of hepatic fibrosis in autoimmune hepatitis

Marco Ferronato¹, Luigi Muratori², Marco Lenzi². ¹University of Bologna, Internal Medicine, Bologna; ²University of Bologna, Internal Medicine, Bologna, Italy

Email: marco.ferronato@studio.unibo.it

Background and aims: Assessment of liver fibrosis stage is essential to determine prognosis and guide treatment strategies in autoimmune hepatitis (AIH). Several non-invasive markers have been proposed, but unlike studies in chronic viral hepatitis or NAFLD, they showed poor diagnostic accuracy in AIH patients. We aim to validate additional, low-cost and non-invasive tools to assess the hepatic fibrosis level among AIH patients. Moreover, we want to assess the reliability of these tests among different types of presentation of AIH.

Method: 122 consecutive AIH patients (88 female sex, mean age 46 ± 18 years) have been retrospectively studied. Among these, 52% had acute hepatitis at presentation (jaundice and/or transaminases >10× upper limit of normal), while the remaining 48% had non-acute onset (insidious or asymptomatic). We calculated the following non-invasive scores: fibrosis 4 score (FIB-4), AST to platelet count ratio (APRI), AST to ALT ratio (AAR), red blood cell width distribution to platelet count ratio (RDW/PC) and spleen diameter to platelet count ratio (SD/PC). All non-invasive scores were compared to the histological grading of liver fibrosis, evaluated according to Ishak. **Results:** The histological grading was 1 in 27, 2 in 41, 3 in 27, 4 in 17, 5 in 10. Advanced fibrosis (AF) (Ishak grading ≥4) was observed in 27 patients (22.1%). The distribution of the histological fibrosis was identical in acute versus non-acute onset and irrespective of age at onset. The non-invasive scores which best reflect the distribution of the histological grading were SD/PC (ANOVA p < 0.001), FIB-4 (ANOVA p = 0.002), and RDW/PC (ANOVA, p = 0.005). In addition, SD/PC, RDW/PC, AAR and FIB-4 are the best indicator of AF (p < 0.001 for all). The area under receiver operator curve (AUROC) for SD/PC, FIB-4, RDW/PC, APRI, AAR were respectively 0.814, 0.770, 0.768, 0.708, 0.694. The AUROC of SD/PC and FIB-4 in the non-acute subgroup were 0.902 and 0.834, while in patients with acute presentation they were 0.754 and 0.724; the comparison using DeLong's test didn't reach statistical

significance. There were no relevant differences for RDW/PC, APRI and AAR among the two types of presentation [Figure].

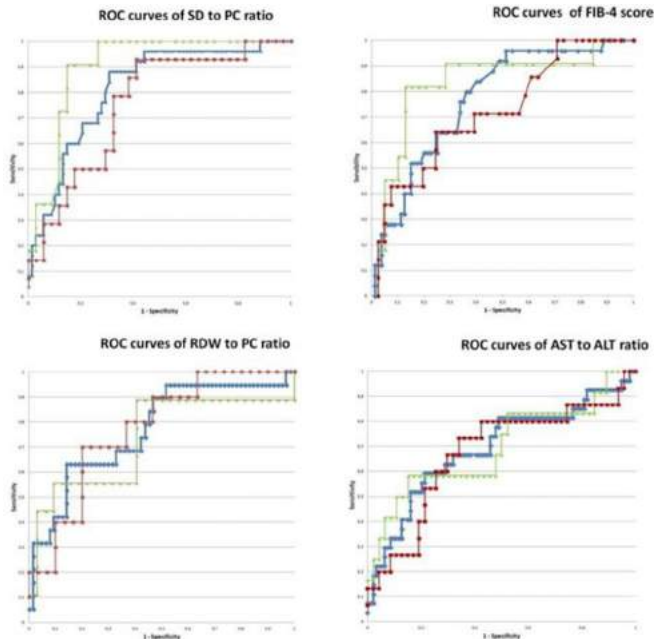


Figure: ROC curves of SD/PC, FIB-4, RDW/PC and AAR for the diagnosis of advanced fibrosis; blue line = all AIH patients, green line = non-acute AIH patients, red line = acute AIH patients.

Conclusion: Performance of FIB-4, SD/PC, and RDW/PC is good for the diagnosis of AF in AIH and it seems in line with what has been published in literature for other chronic liver diseases. We observed higher diagnostic accuracy of SD/PC and FIB-4 among patients with a non-acute presentation, that wasn't statistically significant probably due to limited sample size. Longitudinal application of these scores might be helpful to non-invasively monitor the progression of liver fibrosis alongside the complete biochemical response.

PO-1074

The FGF19 analogue aldafermin enriches the lactate-consuming, bile acid-sensitive commensal microbe *Veillonella* in patients with primary sclerosing cholangitis

Ulrich Beuers¹, Lei Ling², Duy Dinh³, Hsiao Lieu², Alex DePaoli², Rohit Loomba⁴, Gideon Hirschfield⁵. ¹Amsterdam UMC, Amsterdam, Netherlands; ²NGM Biopharmaceuticals, South San Francisco, United States; ³Diversigen, Houston, United States; ⁴University of California, San Diego, San Diego, United States; ⁵Toronto Centre for Liver Disease, UHN, Toronto, Canada
Email: lling94080@yahoo.com

Background and aims: Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic liver disease characterized by inflammation and fibrosis of intra- and extra-hepatic bile ducts. Emerging evidence suggests that alterations in bile acids and the microbiome are not simply a consequence but could be a potential cause of PSC. Aldafermin, a non-tumorigenic FGF19 analogue, suppressed bile acid synthesis and decreased hepatic inflammation and fibrosis markers in a randomized, double-blind, placebo-controlled phase 2 study in patients with PSC. Here we report results of aldafermin on the gut microbiota from this study.

Method: 62 subjects, with PSC by EASL criteria and an elevated ALP > 1.5 × ULN at baseline, were randomized to daily aldafermin 1 mg, 3 mg or placebo for 12 weeks. Stool samples were collected at baseline and week 12, extracted, and sequenced in the 16S rDNA V4 region on the MiSeq platform. Serum bile acids were measured by mass spectrometry method. We compared pre- and post-treatment

in alpha diversity, beta diversity and taxonomy. A principal coordinate analysis was used to show differences between groups. P values were calculated using Kruskal-Wallis or Mann Whitney tests with Benjamini-Hochberg false discovery rate correction.

Results: 81% of reads produced were mapped to the SILVA (v4) database. There were no differences in alpha diversity for each treatment group at baseline or week 12 (Figure 1). UniFrac-based principal coordinates analysis did not reveal any clustering in treatment groups by time. No changes were observed among phyla (*Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Fusobacteria*, *Actinobacteria*, *Tenericutes*, *Verrucomicrobia*, *Cyanobacteria*, *Euryarchaeota*, *Lentisphaerae*, *Deferribacteres* and *Synergistetes*) or the top 30 most abundant genera over time or between aldafermin and placebo. Subjects who received aldafermin, but not placebo, had a statistically significant increase from baseline in the relative abundance of a rare genus *Veillonella* at week 12 (1.7- and 5.8-fold increase in the 1 mg and 3 mg groups, respectively, vs no increase in the placebo group). *Veillonella* abundance was inversely correlated with deoxycholic acid ($\rho = -0.46$, $p = 0.001$).

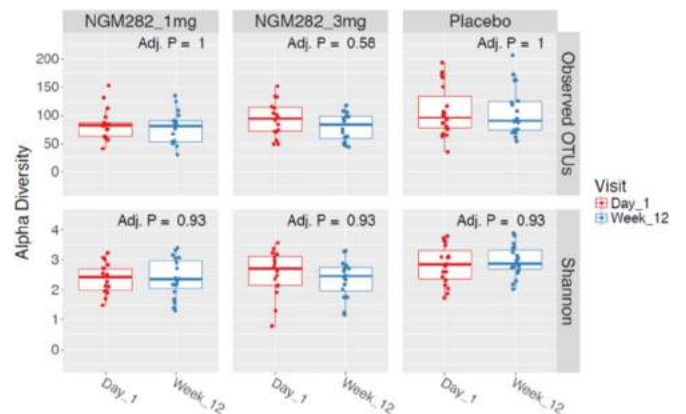


Figure 1. PSC patients treated with aldafermin had stable gut microbial composition and diversity over time.

Conclusion: PSC patients treated with aldafermin had stable gut microbial composition and diversity. No taxonomic differences were observed except for an increase in the rare genus *Veillonella*. These results echo our previous findings in non-alcoholic steatohepatitis, suggesting that *Veillonella* may serve as a microbiome-based marker for response to aldafermin irrespective of disease etiology.

PO-1294

Implementation of a national registry for patients with primary biliary cholangitis (PBC): The German PBC cohort

Johannes Wiegand¹, Kerstin Stein², Rainer Guenther³, Uwe Naumann⁴, Sebastian Zimny⁵, Philipp Reuken⁶, Tobias Böttler⁷, Heike Bantel⁸, Wolf Peter Hofmann⁹, Andreas E. Kremer¹⁰, Achim Kautz¹¹, Ulrich Beuers¹², Christian Trautwein¹³, Annegret Franke¹⁴, Katja Piotrowski¹⁴, Thomas Berg¹⁵. ¹University of Leipzig, Division of Hepatology, Leipzig, Germany; ²Hepatologisch-infektiologische Schwerpunktpraxis, Magdeburg; ³University of Kiel, Department of Internal Medicine I; ⁴UBN Private Practice, Berlin, Germany; ⁵LMU Munich, Department of Internal Medicine II; ⁶University of Jena, Department of Internal Medicine IV; ⁷University of Freiburg, Department of Internal Medicine II; ⁸Hannover Medical School, Department of Gastroenterology, Hepatology, and Endocrinology; ⁹Gastroenterologie am Bayerischen Platz, Berlin; ¹⁰University of Erlangen, Department of Internal Medicine I; ¹¹Deutsche Leberhilfe, Köln; ¹²University of Amsterdam, Academic Medical Center; ¹³University of Aachen, Department of Internal Medicine III; ¹⁴University of Leipzig, Clinical Trial Centre, Leipzig; ¹⁵University of Leipzig, Division of Hepatology, Leipzig
Email: johannes.wiegand@medizin.uni-leipzig.de

POSTER PRESENTATIONS

Background and aims: Primary biliary cholangitis (PBC) is characterized by inflammation and destruction of bile ducts, ultimately leading to biliary cirrhosis. Due to low prevalence and slow disease progression it is difficult to investigate the prognosis of subgroups or to evaluate the effectiveness of therapeutic interventions on clinical outcomes. National registry data for Germany do not exist so far. Thus, the German PBC Cohort was implemented as a non-interventional study (NIS).

Method: A confirmed PBC diagnosis according to EASL guidelines (at least two of three criteria positive: elevated alkaline phosphatase (AP), AMA-M2 positivity, PBC compatible liver biopsy) was requested and treatment with at least one licensed PBC medication. Subgroups were classified (Paris II criteria) according to their response to therapy with ursodeoxycholic acid (UDCA) as responders (R) or primary (P-IR) or secondary incomplete responders (S-IR). Newly diagnosed patients (ND) were diagnosed within the last six months prior to inclusion.

Results: As of January 10th 2021, there are 34 recruiting sites (n = 21 academic, n = 4 non-academic hospitals, n = 9 outpatient practices) participating in the PBC cohort of whom 29 sites recruited 320 patients (91% female, mean (SD) age 61.0 (11) years, mean BMI 27.5 (6) kg/m², 15% (n = 45/320) with cirrhosis).

PBC diagnosis was confirmed by elevated AP and AMA-M2 positivity in 235/320 (73%) cases, 95/320 (30%) underwent biopsy, 51/320 (16%) fulfilled all three diagnostic criteria.

Our PBC cohort consisted of responders (N = 188, 59%), or primary (N = 61, 19%) or secondary (N = 43, 13%) incomplete responders, respectively. Median disease duration was 278.5 [127.5; 483] vs. 397.5 [192; 604] vs. 485 [237; 729] weeks. 28 (9%) patients were newly diagnosed. Cirrhosis was present in 13% (R), 21% (P-IR), 12% (S-IR), and 21% (ND), respectively.

In patients with baseline data available n = 297 received UDCA. Mean UDCA daily dosage at initiation of therapy was 13.3 (R), 13.8 (P-IR), 12.5 (S-IR), and 11.0 (ND) mg/kg. 35 patients received obeticholic acid (OCA), 34 of them were incomplete responders. In 30, 12, and 10 individuals bezafibrate, prednisolone, or budesonide were prescribed, respectively.

All but one incomplete responder patients (of 98 with respective data) continued UDCA treatment. In 6/298 (2%) patients a discontinuation of PBC therapy was reported.

39/302 (13%) PBC patients complained on chronic fatigue, 70/295 (24%) reported on chronic pruritus with mild (56%), moderate (30%) or severe (14%) intensity.

Conclusion: The German PBC Cohort has been successfully established as prospective nationwide registry and reports important real-world data on therapy and clinical symptoms.

PO-1418

Risk of primary biliary cholangitis in first degree relatives: a prospective cohort study

Johannes Hartl^{1,2}, Claudia Kroll^{3,4}, Felix Stahl⁵, Ansgar Lohse^{1,2}, Christoph Schramm^{1,2,6}, Marcial Sebode^{2,7}. ¹University Medical Centre Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany; ²European Reference Network on Hepatological Diseases (ERN RARE-LIVER); ³University Medical Centre Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany; ⁴University Medical Centre Hamburg-Eppendorf (UKE), Martin Zeitz Centre for Rare Diseases; ⁵Institute of Clinical Chemistry and Laboratory Medicine, Hamburg, Germany; ⁶University Medical Centre Hamburg-Eppendorf (UKE), Martin Zeitz Centre for Rare Diseases, Hamburg, Germany; ⁷University Medical Centre Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany
Email: j.hartl@uke.de

Background and aims: In first degree relatives (FDR) of patients with primary biliary cholangitis (PBC), an increased risk of anti-mitochondrial antibodies (AMA) and PBC has been reported. However, studies on testing for PBC-specific anti-nuclear antibodies (ANA),

such as sp100 and gp210, in FDR and regular follow-ups of both FDR being tested positive or negative for PBC-specific antibodies are lacking. We herein prospectively analysed the prevalence and incidence of clinical, biochemical and serological features of PBC in FDR at a single tertiary centre.

Method: 231 FDR of 134 PBC patients and 93 age- and sex-matched healthy controls were prospectively screened for biochemical markers of cholestasis and for PBC-specific antibodies including AMA, MIT3, gp210 and sp100. All participants completed a comprehensive survey in order to assess environmental risk-factors for PBC such as urinary tract infection. FDR with biochemical or serological features of PBC were invited for further examination. All participants were invited for a follow-up after 2 and 4 years.

Results: In 23% (54/231) of FDR, screening results prompted further examination, which resulted in the diagnosis of PBC in 5/231 (2.2%) FDR. In 4 of the 5 identified cases, the affected family members were sisters, all were diagnosed at an early stage. In 16 (7%) additional cases, PBC-specific antibodies were detected, but these individuals showed no signs of cholestasis. In detail, the prevalence of disease specific antibodies at baseline was as follows: AMA-IFT: 5% (10/231), MIT3: 3% (8/231), SP100: 2% (4/231), and gp210: 0%. 188 and 75 FDR participated in the 2- and 4-year follow-up, respectively. Thereby, 48/188 (26%) and 22/75 (33%) individuals showed biochemical or serological features requiring further assessment. No further diagnoses of PBC were established, 7 additional cases with PBC-specific antibodies were identified. In total, 28/231 (12%) FDR showed at least at one time-point PBC-specific antibodies, 67% of those were female, and the highest prevalence was observed among sisters (23%). In contrast, only 1/93 healthy control (1%, p = 0.002) showed typical antibodies. None of the previously reported environmental risk factors could be confirmed in this cohort.

Conclusion: The prevalence of PBC and PBC-specific antibodies is considerably increased in FDR, and especially in sisters of PBC patients. Therefore, screening in this group enables early diagnosis and timely treatment in order to prevent disease progression. Short term development of clinical PBC in carriers of autoantibodies seems to be rare.

PO-1428

The measurement properties of the Dutch PBC-40: a validation study

Rozanne de Veer¹, Geraldine Da Silva¹, Maria van Hooff¹, Maren Harms¹, Herold Metselaar¹, José Willems², Elaine Utomo³, Adriaan Van der Meer¹. ¹Erasmus University Medical Center Rotterdam, Gastroenterology and Hepatology, Netherlands; ²Dutch Liver Patients Association, Hoogland, Netherlands; ³Independent Researcher, Berkel en Rodenrijs, Netherlands
Email: r.deveer@erasmusmc.nl

Background and aims: Patients with primary biliary cholangitis (PBC) have an impaired health-related quality of life (HRQoL). Practice guidelines recommend evaluating the HRQoL in all PBC patients. The aim of this study was to assess the reliability and validity of a Dutch translation of the PBC-40, a PBC-specific measure of the HRQoL.

Method: The PBC-40 was translated into Dutch following standardized forward-backward procedures. Participants received the Dutch PBC-40 and the RAND-36 (a validated Dutch version of the 36-Item Short Form Health Survey) through postal mail. Internal consistency between the items within the PBC-40 domains were assessed by Cronbach's alpha. Values between 0.70 and 0.95 were considered as adequate internal consistency. Content validity was subjectively assessed (face validity). In addition, score distributions were analyzed on floor and ceiling effects. Construct validity was assessed by hypotheses testing using Pearson's correlation between the PBC-40 domains and RAND-36 scales.

Results: In total, 177 patients with PBC were included. The mean (SD) age was 61.1 (9.9) years and the majority of patients was female (n = 164; 92.7%). From the total of 7080 PBC-40 items, 61 items (0.9%)

were missing and 342 items (4.8%) were answered with the 'does not apply' option. Each PBC-40 domain had a Cronbach's alpha >0.70, with the highest in the domain fatigue (0.95) (Table). Face validity was considered adequate. Floor effects were present in 2 domains (cognition 19.3% and itch 27.0%). No ceiling effects were observed. All domains were significantly correlated with the corresponding RAND-36 scale (s) ($p < 0.001$ for all). The strongest correlation was between the PBC-40 domain fatigue and the RAND-36 vitality scale ($r = -0.834$).

PBC-40 Domain	Median domain score (IQR)	Cronbach's alpha	Floor (%)	Ceiling (%)	Corresponding RAND-36 scales	Pearson's r*
Symptoms	2.4 (1.8-3.0)	0.81	1.7	0	Physical functioning Physical pain	-0.535 -0.620
Itch	1.7 (1.0-2.6)	0.83	27.0	0	Physical functioning	-0.322
Fatigue	3.1 (2.2-3.7)	0.95	1.7	0	Vitality	-0.834
Cognition	2.3 (1.4-3.0)	0.94	19.3	0.6	Mental health component summary	-0.579
Social	2.2 (1.6-3.2)	0.91	5.1	0.0	Social functioning	-0.779
Emotional	2.3 (1.3-3.0)	0.78	10.8	1.7	Mental health Role emotional	-0.708 -0.478

* $p < 0.001$ for all

Conclusion: These findings demonstrate the reliability and validity of the Dutch PBC-40 for the assessment of the HRQoL in patients with PBC. This PBC-specific measure can be used in Dutch-speaking patients with PBC for both research and clinical purposes.

PO-1484

Prevalence of immunological tolerance among type 1 autoimmune hepatitis patients on long-term remission

Laura Patricia Llovet¹, Lydia Sastre¹, Montserrat García-Retortillo², Mar Riveiro Barciela³, Mercé Roget⁴, Thais Leonel¹, Estibaliz Ruiz-Ortiz⁵, Odette Viñas⁵, Albert Parés^{1,6,7}, Alberto Sanchez-Fueyo⁸, Maria Carlota Londoño^{1,6,7}, ¹Hospital Clínic Barcelona, Liver Unit, Barcelona, Spain; ²Hospital del Mar, Department of Gastroenterology, Barcelona, Spain; ³Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain; ⁴Hospital Mútua Terrassa, Liver Unit, Terrassa, Spain; ⁵Hospital Clínic Barcelona, Immunology Department, Barcelona, Spain; ⁶CIBEREHD; ⁷IDIBAPS; ⁸King's College Hospital, Liver Unit, United Kingdom
Email: mlondono@clinic.cat

Background and aims: The incidence of relapse following an attempt at immunosuppression (IS) discontinuation in autoimmune hepatitis (AIH) is unknown given the retrospective nature of published studies and the lack of standardization in inclusion and exclusion criteria, and follow-up. To rigorously determine the proportion of AIH patients tolerating IS withdrawal, we conducted a prospective, multicentre, single arm trial (NCT03711669) in type 1 AIH patients meeting strict clinical, biological and histological criteria.

Method: Inclusion criteria: age >18 years, biochemical remission for at least 3 years, liver biopsy with a modified hepatitis activity index (mHAI) <3. Exclusion criteria: need of >7.5 mg/d of prednisone to maintain remission, cirrhosis, concomitant liver disease. Immunosuppression was gradually reduced (50% of previous dose) at 1 month-interval until complete withdrawal. In patients receiving combined therapy, azathioprine (AZA) was firstly reduced. The primary end point was disease remission 1 year after complete IS discontinuation.

Results: 53 (11%) of 501 patients with AIH met the clinical inclusion criteria, 12 declined to participate, 2 had cirrhosis in the screening biopsy, and 2 had high ALT levels in the screening visit. Finally, 37 patients initiated IS withdrawal: 21 (57%) patients reached the primary end point and 16 (43%) had a flare. In 6 (37%) patients the flare occurred during weaning and in 10 (63%) it happened a median

time of 9 months (3-24) after complete IS withdrawal. All flares were mild (median peak of ALT 96 U/L [51-704]) and resolved after the introduction of previous IS (only 4 patients needed steroids to control de flare). There was a trend towards higher ALT levels in patients who developed a flare (Table).

Table: Characteristics of patients at starting IS withdrawal

Variable	All (n = 37)	Flare (n = 16)	Remission (n = 21)	p
Age (years)	60 (22-80)	53 (42-75)	65 (22-80)	0.165
Female sex (n, %)	19 (51%)	8 (50%)	11 (52%)	0.886
ALT (U/L)	16 (5-40)	20 (10-34)	14 (6-23)	0.053
IgG (g/L)	10 (6-14)	10 (8-14)	10 (6-14)	0.403
Time on remission (years)	4 (3-11)	4 (3-10)	3.5 (3-11)	0.728
mHAI	1 (0-3)	1 (0-3)	1 (0-2)	0.423
Transient elastography (kPa)	4.8 (3.6-9.1)	4.9 (3.6-8.5)	4.6 (3.9-9.1)	0.773
Immunosuppression (n, %)				0.430
AZA	27 (74%)	12 (75%)	15 (72%)	
Steroids	5 (13%)	1 (6%)	4 (19%)	
AZA + Steroids	5 (13%)	3 (19%)	2 (9%)	

Median (range)

Conclusion: Patient selection using strict clinical and histological criteria allows for safe ISW in 57% of patients but shows a low applicability. No clinical, serological or histological features predict the development of flares. Liver biopsy might not be required before an attempt of IS discontinuation. New strategies are needed to increase the success of IS withdrawal.

PO-1486

Patient perspective on treatment and prognosis in Primary Biliary Cholangitis: a descriptive study

Maria van Hooff¹, Rozanne de Veer¹, Maren Harms¹, Geraldine Da Silva¹, José Willemse², Herold Metselaar¹, Elaine Utomo³, Adriaan Van der Meer¹, ¹Erasmus University Medical Center Rotterdam, Gastroenterology and Hepatology, Rotterdam, Netherlands; ²Dutch Liver Patients Association, Hoogland, Netherlands; ³Independent Researcher, Berkel en Rodenrijs, Netherlands
Email: m.vanhooff@erasmusmc.nl

Background and aims: Better understanding of patient expectations regarding their disease prognosis and management could improve patient care and counseling. In this study we evaluated the patient perspective on their treatment and prognosis in relation to objective disease parameters in primary biliary cholangitis (PBC).

Method: Patients with PBC registered at the Dutch Liver Patient Association or the Erasmus MC were sent a questionnaire in August 2020 to obtain self-reported data regarding treatment status, need for additional therapy, and expected survival ('impaired', equal' or 'superior') compared to their peers. In the Netherlands obeticholic acid (OCA) is not generally available. Bezafibrate (BZF) can be used off-label. Patients consented to medical chart review to collect objective disease parameters in order to assess their survival free of liver transplantation (based on the GLOBE score) and need for further treatment (defined by alkaline phosphatase (ALP) >1.67x upper limit of normal (ULN) and/or bilirubin >1.0x ULN).

Results: In total, 176 patients responded. The mean (SD) age was 61 (10) years, 163 (92.6%) were female and 168 (95.5%) reported the use of ursodeoxycholic acid (UDCA). The median UDCA dose was 13.9 (IQR 11.7-15.4) mg/kg/day, whereas 62 (36.9%) patients reporting a daily dose <13 mg/kg. Use of BZF and/or OCA was reported by 38 (21.6%) patients. A lifelong need for UDCA was expected by 161 (95.8%) patients. Only 4 (2.4%) patients reported to forget UDCA regularly (i.e. on a weekly basis). Among the 167 patients with available laboratory results, 52 (31.1%) had an ALP >.67x ULN and/or

POSTER PRESENTATIONS

a bilirubin $>1.0 \times \text{ULN}$, while 36 (69.2%) of the latter group did not consider themselves in need of additional therapy. The GLOBE score was available in 153 patients, predicted survival was lower compared to the matched general population in 29 (19.0%) patients, among whom 12 (41.4%) expected their survival to be similar to their peers. Of the 124 (81.0%) patients with a normal survival based on the GLOBE score, 42 (33.9%) expected to have impaired survival.

Conclusion: While UDCA compliance is high, and patients are generally aware of the need for lifelong therapy, the self-reported UDCA dosage is often lower than advised. With respect to prognosis and the need for additional therapy, discrepancies frequently exist between patients' perspectives and their objective disease parameters. This implies a need for better patient guidance in PBC care.

PO-1512

Multimarker analysis combining markers of fibrosis and inflammation in primary sclerosing cholangitis

Guri Fossdal^{1,2,3}, Lasse Melvær Giil², Trine Folseraas^{1,4}, Peder Rustøen Braadland^{1,4}, Morten Asser Karsdal⁵, Henning Grønbaek⁶, Eystein Husebye³, Tom Hemming Karlsen^{1,4}, Johannes Roksund Hov^{1,4}, Mette Vesterhus^{1,2,3}. ¹Norwegian PSC Research Center, Oslo University Hospital, Oslo, Norway; ²Haralds plass Deaconess Hospital, Bergen, Norway; ³Department of Clinical Science, University of Bergen, Bergen, Norway; ⁴Institute of Clinical Medicine, University of Oslo, Oslo, Norway; ⁵Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; ⁶Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
Email: guri.fossdal@outlook.com

Background and aims: There is a need to establish prognostic tools in primary sclerosing cholangitis (PSC). We have reported associations with clinical outcome for several biomarkers. In this head-to-head metaanalysis of a broad biomarker panel, we compare and combine markers of fibrosis, inflammation or metabolites from microbiota, aiming to detect improved prognostic value.

Method: We included 138 non-transplant Norwegian PSC patients (78% males; mean age 41 ± 22 years; 74% IBD) recruited 2008–2012, with biomarker data available from multiple previous studies. Revised Mayo risk score was calculated using the published algorithm. End point was defined as LTX or all-cause death. Combinations of biomarkers were explored by factor analysis.

Results: An end point was reached by 53% of patients. Univariate Cox-regression analysis using standardized variables demonstrated strong predictive ability with C-index in the similar range as Mayo score for several variables (Table). Factor analysis adjusted for sex, age and Mayo risk score identified two groups of biomarkers predicting clinical outcome, combining biomarkers reflecting fibrosis and inflammation. Group 1 (ELF test, Pro-C3, CD163, CD206, IL8, kynurenine/tryptophan ratio [KTR]) had HR 1.63, 95% CI (1.06, 2.49), $p=0.026$; group 2 (BGM, KTR, neopterin) had HR 1.51, 1.63, 95% CI (0.18, 1.93), $p=0.001$.

Conclusion: Our results indicate that a combination of biomarkers of fibrosis and inflammation may have stronger predictive ability than single markers in PSC. Validation in independent panels is warranted to identify the optimal biomarker combination.

	HR	95% CI	p value	Harrell's C
Mayo score ^b	1.80	1.41, 2.30	<0.001	0.69
Female ^a	1.08	0.63, 1.87	0.774	0.51
Age ^b	1.33	1.04, 1.70	0.025	0.60
Fibrosis, ECM, macrophage markers				
ELF test ^c	1.92	1.50, 2.47	<0.001	0.70
PRO-C3 ^c	1.80	1.43, 2.28	<0.001	0.68
CD163 ^c	1.65	1.33, 2.04	<0.001	0.67
C4M ^c	1.56	1.26, 1.93	<0.001	0.65
CD206 ^c	1.46	1.15, 1.86	0.002	0.63
PRO-C5 ^c	1.43	1.13, 1.80	0.003	0.61
C3M ^c	1.31	1.05, 1.64	0.015	0.61
BGM ^c	1.27	0.99, 1.61	0.053	0.61
Inflammation/microbiota-related markers				
PLP ^c	0.52	0.40, 0.67	<0.001	0.69
KTR ^c	2.05	1.60, 2.62	<0.001	0.67
Neopterin ^c	1.49	1.19, 1.86	<0.001	0.65
IL8 ^c	1.53	1.17, 1.99	0.002	0.61
Calprotectin ^c	1.22	0.95, 1.56	0.114	0.57
TMAO ^c	1.25	0.99, 1.57	0.055	0.57
Anti-GP2 ^a	1.09	0.82, 1.44	0.551	0.55

^aCategorical, binary variables

^bStandardized (z-scores) variables where 0 = mean and 1 = 1 SD

^cLog-transformed and then standardized variables where 0 = geometric mean and 1 = 1 SD.

PO-1574

MARC1 p.A165T polymorphism is associated with decreased liver injury and enhanced antioxidant activity in serum in patients with AIH

Maciej K. Janik^{1,2}, Wiktor Smyk^{1,2}, Beata Kruk³, Benedykt Szczepankiewicz⁴, Barbara Górnicka⁴, Magdalena Lebieźńska-Arciszewska⁵, Yaiza Potes⁵, Inês C.M. Simões⁵, Susanne N. Weber⁶, Frank Lammert^{2,6,7}, Mariusz Więckowski⁵, Piotr Milkiewicz^{1,2,8}, Marcin Krawczyk^{2,3,6}. ¹Medical University of Warsaw, Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Warsaw, Poland; ²European Reference Network on Hepatological Diseases (ERN RARE-LIVER); ³Medical University of Warsaw, Laboratory of Metabolic Liver Diseases, Department of General, Transplant and Liver Surgery, Laboratory of Metabolic Liver Diseases, Centre for Preclinical Research, Warsaw, Poland; ⁴Medical University of Warsaw, Department of Pathology, Warsaw, Poland; ⁵Nencki Institute of Experimental Biology, Laboratory of Mitochondrial Biology and Metabolism, Warsaw, Poland; ⁶Saarland University, Department of Medicine II Saarland University Medical Center, Homburg, Germany; ⁷Hannover Medical School, Hannover, Germany; ⁸Pomeranian Medical University, Translational Medicine Group, Szczecin, Poland
Email: mjanik24@gmail.com

Background and aims: The progression of autoimmune hepatitis (AIH) varies markedly between patients, which suggests the role of genetic modifiers. Recent analysis of individuals with fatty liver demonstrated that *MARC1* p.A165T polymorphism might have protective effects. Here, we analyse *MARC1*, as well as the *HSD17B13*, *PNPLA3*, *TM6SF2* and *MBOAT7* variants in patients with AIH.

Method: The study cohort was composed of 313 non-transplanted adults with AIH, in addition a group of 30 patients who underwent liver transplantation for AIH was included in the analyses. The *MARC1* (rs2642468), *HSD17B13* (rs72613567), *PNPLA3* (rs738409), *TM6SF2* (rs58542926) and *MBOAT7* (rs641738) polymorphisms were genotyped using TaqMan assays. Analysis of mitochondrial damage markers was conducted in relation to the *MARC1* variant.

Results: Presence of the *MARC1* minor allele was associated lower ALT ($p=0.04$) and AST ($p=0.02$). Among patients who were treated for AIH for at least 6 months, ones who carried the *MARC1* variant

had lower AST (p = 0.01), ALP and GGT (both P < 0.01), and lower APRI (p = 0.02). *MARC1* protective genotype correlated with higher catalase (p = 0.02) and higher total antioxidant activity (p = 0.003) in serum. On the other hand, the *PNPLA3* polymorphism correlated MELD (p = 0.02) whereas *MBOAT7* (rs641738) increased the odds of developing hepatocellular carcinoma (HCC) (OR = 3.71, 95% CI 1.22–11.28, P = 0.02) during follow-up. None of the tested variants increased the risk of liver transplantation or death.

Conclusion: Patients with AIH who carry the *MARC1* polymorphism have lower liver injury which is coupled with improved resistance to oxidative stress. Genotyping of the *MARC1*, *PNPLA3* and *MBOAT7* variants in patients with AIH might help to assess their risk of progressive liver disease.

PO-1644

A deep learning approach to analysis of MRCP images predicts clinical events and progression to cirrhosis in patients with primary sclerosing cholangitis

Aaditya Prakash¹, Hunter Elliott¹, Michael Montalto¹, Andrew Beck¹, Murray Resnick¹, Ilan Wapinski¹, Oscar Carrasco-Zevallos¹, Xiaomin Lu², Xiangyu Liu², Chuhan Chung², Robert Myers², Michael P. Manns³, Stephen Caldwell⁴, Raj Vuppalanchi⁵, Rajender Reddy⁶, Lisa Forman⁷, Mitchell Shiffman⁸, Aldo J. Montano-Loza⁹, Christopher Bowlus¹⁰, Cynthia Levy¹¹, Kris Kowdley¹², Michael Trauner¹³, Andrew Muir¹⁴, Clare Tempany-Afdhal¹⁵. ¹PathAI, Boston, MA, USA; ²Gilead Sciences,

Inc., Foster City, CA, USA; ³Hannover Medical School, Hanover, Germany; ⁴University of Virginia, Charlottesville, VA, USA; ⁵Indiana University School of Medicine, Indianapolis, IN, USA; ⁶University of Pennsylvania, Philadelphia, PA, USA; ⁷University of Colorado, Aurora, CO, USA; ⁸Bon Secours Mercy Health, Richmond, VA, USA; ⁹University of Alberta, Edmonton, AB, Canada; ¹⁰University of California Davis, Davis, CA, USA; ¹¹University of Miami, Miami, FL, USA; ¹²Liver Institute Northwest and Washington State University, Seattle, WA, USA; ¹³Medical University of Vienna, Vienna, Austria; ¹⁴Duke Clinical Research Institute, Durham, NC, USA; ¹⁵Brigham and Women's Hospital, Department of Radiology, Harvard Medical School, Boston, MA, USA
Email: chuhan.chung@gilead.com

Background and aims: Magnetic resonance cholangiopancreatography (MRCP) is the primary method of PSC diagnosis but its prognostic utility is unclear. We developed a machine learning (ML) algorithm using MRCP images and evaluated its ability to predict disease progression in patients with PSC.

Method: Baseline MRCP and liver biopsy images were available from 122 patients with compensated PSC enrolled in a 96-week, phase 2b clinical trial of simtuzumab (NCT01672853). Activation maps, obtained from feeding the MRCP slices to a convolutional neural network, were trained on a binary outcome of PSC-related clinical events (e.g., hepatic decompensation, ascending cholangitis, cholangiocarcinoma). Discrimination of the resultant ML MRCP score at baseline (range, 0 to 1) for clinical events and histologic progression to cirrhosis were determined and compared with other clinical parameters including a semi-quantitative MRCP risk score (Muir, AASLD 2017), Ishak fibrosis stage, collagen proportionate area (CPA), serum alkaline phosphatase (ALP) and ELF, Mayo risk score, the PReSTO algorithm, and ML-based histologic features (PathAI; Boston, MA [Travis, EASL 2020]).

Results: The median age was 45 years, 63% were male, 54% had bridging fibrosis or cirrhosis, 52% had ulcerative colitis, 52% were on

Parameter	PSC-Related Clinical Events		Progression to Cirrhosis	
	AUROC (95% CI)	p-value vs. ML MRCP score	AUROC (95% CI)	p-value vs. ML MRCP score
Cholangiography				
ML MRCP score	0.93 (0.86, 1.00)	--	0.77 (0.63, 0.90)	--
MRCP risk score*	0.69 (0.59, 0.80)	0.0004	0.71 (0.58, 0.83)	0.5374
Fibrosis				
Ishak fibrosis stage	0.67 (0.56, 0.79)	0.0003	0.71 (0.59, 0.84)	0.6122
CPA	0.53 (0.41, 0.65)	<0.0001	0.68 (0.55, 0.82)	0.4702
ML Ishak score (trichrome)	0.68 (0.55, 0.81)	0.0008	0.85 (0.74, 0.96)	0.2840
ML Ishak score (PSR)	0.66 (0.55, 0.77)	<0.0001	0.75 (0.63, 0.86)	0.8451
Clinical Parameters				
ALP	0.68 (0.57, 0.79)	<0.0001	0.75 (0.66, 0.85)	0.8958
ELF	0.69 (0.59, 0.80)	0.0002	0.78 (0.67, 0.90)	0.8438
Mayo risk score	0.69 (0.58, 0.80)	0.0004	0.69 (0.53, 0.84)	0.4759
PReSTo†	0.70 (0.58, 0.81)	0.0007	0.69 (0.53, 0.84)	0.5013

PSR, picrosirius red.

* MRCP risk score = 1 x hepatic dysmorphism + 1 x portal hypertension + 1 x peri-hepatic lymph nodes (Muir, AASLD 2017).

† PReSTo: ML model based on age, ALP, AST, bilirubin, albumin, sodium, hemoglobin, platelets, and PSC duration (Eaton, Hepatology 2020;71:214-24).

Figure: (abstract: PO-1644): Discrimination of the ML MRCP score and other parameters for disease progression in PSC

POSTER PRESENTATIONS

ursodeoxycholic acid, and the median ALP at baseline was 265 U/L (IQR, 126–455). Over a median follow-up of 23 months (range, 0.5–24.7), 25 patients (20%) had a PSC-related clinical event (ascending cholangitis [n = 14], cholangiocarcinoma [n = 1], ascites [n = 2], encephalopathy [n = 2], variceal hemorrhage [n = 2], jaundice [n = 4]) and 18/105 (17%) progressed to cirrhosis. The AUROC of the ML MRCP score for predicting PSC-related clinical events was 0.93 (95% CI 0.86, 1.00), significantly higher than that of the semi-quantitative MRCP risk score, fibrosis assessments, and other clinical parameters (Table). The AUROC of the ML MRCP score for histologic progression to cirrhosis was 0.77 (95% CI 0.63, 0.90), which was not significantly different from the other parameters (Table), but improved by addition of the ML fibrosis score based on trichrome-stained slides (AUROC 0.89; 95% CI 0.80, 0.97). The ML MRCP score was weakly correlated with the MRCP risk score ($\rho = -0.20$; $p = 0.025$), ELF ($\rho = -0.18$; $p = 0.042$), and PReSTo ($\rho = -0.19$; $p = 0.036$), but not the other parameters.

Conclusion: A deep learning approach to MRCP image analysis is able to predict disease progression in PSC and its prognostic utility exceeds that of other clinical and histologic assessments. Validation of these findings may provide a quantitative, ML-based assessment of PSC-related prognosis based on routinely collected MRCP images.

PO-1664

Incidence of hepatic outcomes in patients with cirrhosis due to primary biliary cholangitis: A population-based epidemiology study

Lina Titievsky¹, Erik Ness¹, Amy Law¹, Ellie Goldman¹, Darren Wheeler¹, Monica Bertoia², John D. Seeger², Mindie Nguyen³, Yuval Patel⁴, Femi Adekunle⁵, Chiara Bassanelli⁵. ¹Intercept Pharmaceuticals, Inc., New York, United States; ²Optum Life Sciences, United States; ³Stanford University, Redwood City, United States; ⁴Duke University, Durham, United States; ⁵Intercept Pharmaceuticals, Inc., London, United Kingdom
Email: lina.titievsky@interceptpharma.com

Background and aims: Primary biliary cholangitis (PBC) is a progressive cholestatic autoimmune disease characterized by inflammatory destruction of the intrahepatic bile ducts leading to cirrhosis and associated complications. Published data showing that PBC patients with advanced disease have worse prognosis compared to patients with early disease, though these were conducted in tertiary care setting, without explicitly focusing on cirrhosis. This study aimed to evaluate the incidence rates (IR) of hepatic related events in PBC patients with vs. without cirrhosis in a population-based setting.

Method: Patients with a diagnosis of PBC between October 2016 and September 2019 were identified from a US Electronic Health Records (EHR) Database using either an International Classification of Diseases, 10th revision (ICD-10) diagnosis code (K74.3, 'primary biliary cirrhosis') or an affirmation of Natural Language Processing term of 'biliary cirrhosis' on 2 or more dates within 6 months. The presence of cirrhosis was defined by ICD-10 codes for cirrhosis during baseline (one-year period prior to cohort entry). IRs for a priori specified hepatic outcomes and all-cause mortality were calculated as the number of incident outcomes within the follow-up period divided by the total person-time at risk per 100 Person-Years (PY) with corresponding 95% confidence intervals (CI).

Results: A total of 3,940 PBC patients with or without cirrhosis were included. Baseline characteristics showed PBC patients with cirrhosis as compared to those without cirrhosis were older (median age of 66 vs 63 years), less likely to be female (78% vs. 88%), demonstrate impairment in markers of liver function and have a lower platelet count (median of 167 vs. $237 \times 10^3/\text{ul}$). As compared to PBC patients without cirrhosis, IR (per 100 PY) of all-cause mortality was higher in PBC patients with cirrhosis: 8.3 vs. 2.8. For hepatic outcomes, IRs (per 100 PY) were several magnitudes greater among PBC with cirrhosis patients as compared to PBC without cirrhosis patients (liver

transplant: 3.1 vs 0.3; liver failure: 34.6 vs 4.7; and decompensating events: 12.0 vs 3.7).

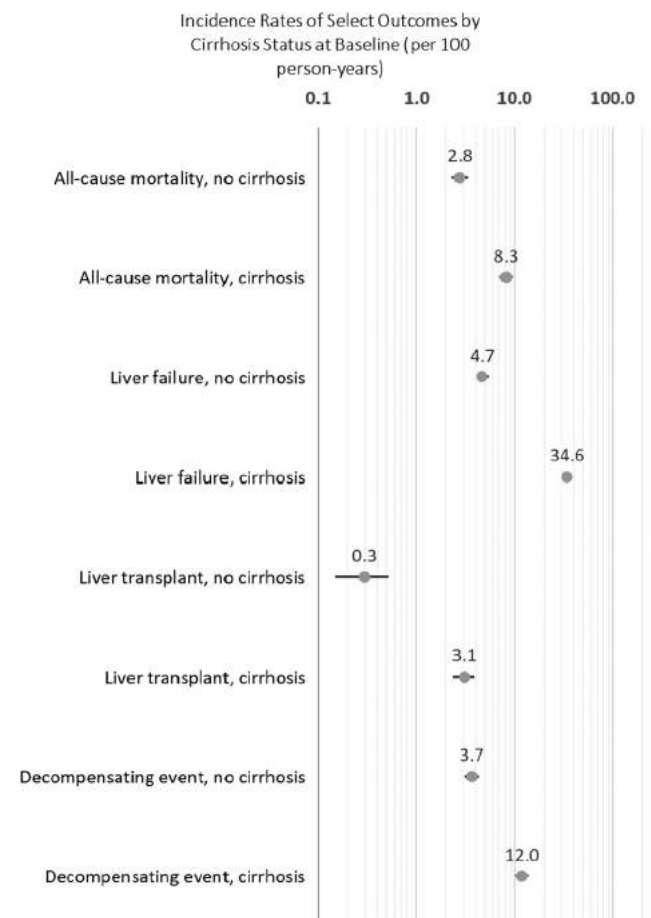


Figure:

Conclusion: To our knowledge, this is the first population-based longitudinal epidemiologic study in PBC patients, to evaluate the incidences of decompensating events, liver failure, liver transplant and death by cirrhosis status. We found IRs of key clinical outcomes to be significantly larger in those with cirrhosis.

PO-1748

Improvement in itch correlates with improved sleep in GLIMMER, a Phase 2b trial of linerixibat for the treatment of cholestatic pruritus in primary biliary cholangitis

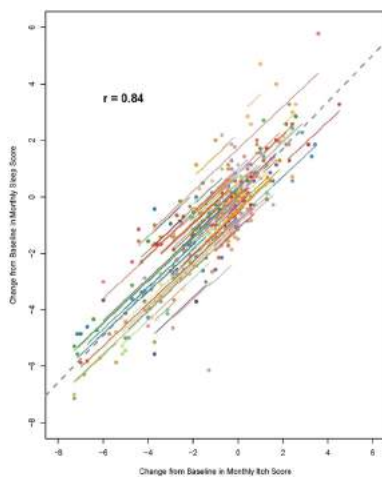
David Jones¹, Robyn von Maltzahn², Helen Smith², April Thompson³, M. Celeste Ferreira-Cornwell³, Megan McLaughlin³, Matthew Allinder³, Nazneen Haque², Marlyn J. Mayo⁴, Cynthia Levy⁵. ¹Newcastle University, United Kingdom; ²GSK, United Kingdom; ³GSK, United States; ⁴University of Texas Southwestern, United States; ⁵Miller School of Medicine, University of Miami, United States
Email: robyn.x.von-maltzahn@gsk.com

Background and aims: Pruritus is a common symptom in primary biliary cholangitis (PBC) and can affect sleep; this may impair quality of life, but objective data are limited. In the GLIMMER trial, the impact of linerixibat on itch in patients with PBC was evaluated. The present analysis explores the relationship between itch severity and sleep interference.

Method: Patients in the GLIMMER trial recorded itch (twice daily) and degree of sleep interference from itch (each morning) on a 0–10 numeric rating scale. Worst daily itch and sleep interference scores were averaged over 1 week to generate mean scores (weekly itch score [WIS] and weekly sleep score [WSS]). Monthly itch/sleep scores

were based on the most severe WIS and WSS scores in a given month (MIS and MSS, respectively), i.e. worst weekly score for that month. Analyses consisted of prespecified exploratory psychometric evaluations between WIS, WSS and other patient-reported outcome (PRO) measures used in the study; in particular, the 5-D itch measure, which was assessed at initial study period (Day 1), baseline (Day 28), Week 12 of treatment (Day 112) and final study period (Day 140). MIS and MSS calculations and analyses were post hoc as was the correlation of MIS versus MSS (Months 1–3) using Bland-Altman repeated measures analysis.

Results: The intent-to-treat (ITT) population comprised 147 patients. All analyses were conducted on the ITT population; however, psychometric analyses were conducted on a subset for whom all PRO data were available. Improvements in change in MIS and MSS from baseline were highly correlated ($r = 0.84$; $p < 0.0001$; Figure). Convergent validity analyses of WSS at baseline showed moderate correlations with the 5-D itch total ($r = 0.59$; $p < 0.0001$) and 5-D itch sleep item scores ($r = 0.58$; $p < 0.0001$).



Bland-Altman repeated measures correlation of change from baseline using Months 1, 2 and 3 MSS and MIS, across all treatment groups (ITT population). r , correlation coefficient

Figure: Bland-Altman repeated measures correlation of change from baseline using Months 1, 2 and 3 MSS and MIS, across all treatment groups (ITT population). r , correlation coefficient

Conclusion: Itch symptoms closely correlated with sleep interference, suggesting a possible close clinical relationship between itch and sleep; a significant correlation between 5-D itch total and WSS support this. In addition to improving the direct impact of the symptom of itch, an improvement in itch may have an impact on sleep. This is of importance, as sleep disturbance is a common complaint of patients with PBC that adds to disease burden.

Funding: GSK Study 201000.

PO-1755

Younger age is associated with lower self-reported quality of life among patients with autoimmune disease during Canada's response to the COVID-19 pandemic

Christina Plagiannakos^{1,2}, Surain Roberts^{1,2}, Monika Saini¹, Catherine Vincent³, Lawrence Worobetz⁴, Andrew L. Mason⁵, Jennifer Flemming⁶, Cynthia Tsien⁷, Karim Qumosani⁸, Gideon Hirschfield^{1,2}, Harry Janssen^{1,9}, Aliya Gulamhusein^{1,2}, Bettina Hansen^{1,2}. ¹University Health Network, Toronto Centre for Liver

Disease, Toronto Western and General Hospital, Toronto, Canada; ²University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada; ³University of Montreal, Department of Medicine, Montréal, Canada; ⁴University of Saskatchewan, Department of Medicine, Saskatoon, Canada; ⁵University of Alberta, Division of Gastroenterology and Liver, Edmonton, Canada; ⁶Queen's University, Department of Medicine, Kingston, Canada; ⁷University of Ottawa, Department of Medicine, Ottawa, Canada; ⁸Western University, Schulich School of Medicine and Dentistry, London, Canada; ⁹University of Toronto-St. George Campus, Department of Medicine, Toronto, Canada Email: christina.plagiannakos@uhn.ca

Background and aims: On March 11th 2020, COVID-19 was classified as a pandemic and a state of emergency (SoE) was declared across Canada. On September 23rd 2020, the government of Canada announced a second wave of COVID-19. We leverage our national multisite registry of patients with autoimmune liver disease to investigate changes in self-reported quality of life (QoL) in a combined cohort of patients with Autoimmune Hepatitis (AIH) and Primary Biliary Cholangitis (PBC) during the COVID-19 pandemic.

Method: We included patients with AIH or PBC who had completed at least 1 QoL survey between July 2019 and January 2021. Surveys completed prior to March 11th 2020 were classified as Pre-SoE, after March 11th as Wave 1, and surveys completed after September 23rd as Wave 2. QoL surveys included the Short-Form 36 (SF-36) and the Itch Numeric Rating Scale (iNRS), for PBC patients only. Mixed effects linear and negative binomial regressions estimated mean QoL scores across time stratified by age and adjusted for diagnosis and disease duration.

Results: There were 570 participants from 7 tertiary liver clinics across Canada included in the analysis, of whom 62.1% ($n = 354$) had PBC and 37.9% ($n = 216$) had AIH. Females represented 87.4% ($n = 498$), and 78.6% ($n = 448$) were Caucasian. A total of 40.9% ($n = 233$) were 55 years of age or younger. Median duration of disease was 7.7 years [2.96–13.8]. A total of 385 assessments were completed before the SoE, 267 during Wave 1, and 241 during Wave 2.

We observed a significant decreasing trend in estimated mean SF-36 Mental Component scores in younger patients ($p = 0.017$), while older patient QoL remained stable ($p = 0.123$, Figure 1a). Longer disease duration was associated with better scores, regardless of time ($p = 0.011$). For the SF-36 Physical Component, estimated mean scores were overall worse in younger PBC patients than older patients ($p = 0.034$). There was a non-significant weak decrease over time for all patients ($p = 0.191$, Figure 1b)

For PBC patients, estimated mean iNRS scores worsened over time ($p = 0.015$), and older age was associated with lower reported itch ($p = 0.007$, Figure 1c).

Conclusion: Younger patients reported worse mental and itch related QoL scores across time, suggesting that these patients are impacted differently than older patients during Canada's response to the pandemic. More attention into this problem is required.

PO-1790

National audit of diagnosis, management and surveillance in primary sclerosing cholangitis (PSC) in the United Kingdom.

Evangelia Fatourou¹, Sarah Hyde², Dominic King³, Martine Walmsley⁴, Graeme Alexander¹, Palak Trivedi^{3,5,6,7}, Simon Rushbrook², Douglas Thorburn¹. ¹Royal Free Hospital, Sheila Sherlock Liver Centre and UCL Institute for Liver and Digestive Health, London, United Kingdom; ²Department of Hepatology, Norwich Medical School, University of East Anglia; ³Liver Unit, University Hospitals Birmingham (UK), Birmingham, United Kingdom; ⁴PSC Support, Oxford, UK; ⁵NIHR Birmingham BRC Centre for Liver and Gastrointestinal Research, University of Birmingham, UK; ⁶Institute of Immunology and Immunotherapy, University of Birmingham (UK), Birmingham, United Kingdom; ⁷Institute of Applied Health, University of Birmingham (UK) Email: evangelia.fatourou@nhs.net

POSTER PRESENTATIONS

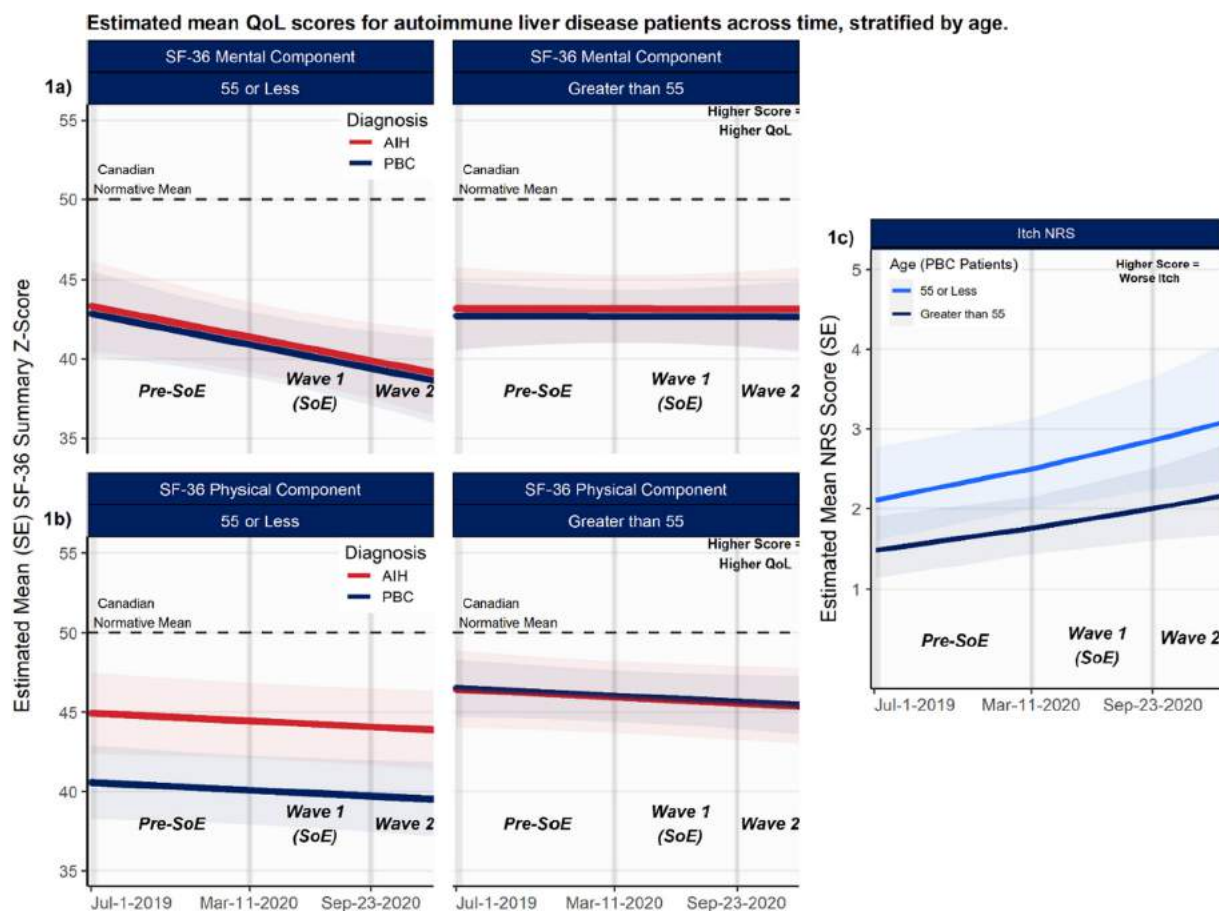


Figure: (abstract: PO-1755)

Background and aims: PSC is a rare disorder and as such clinical care can be heterogeneous. We audited PSC management across the UK against audit standards set by the British Society of Gastroenterology (BSG).

Method: All UK PSC investigators were invited to complete an electronic questionnaire encompassing demographics, diagnosis, bowel and biliary tract cancer surveillance, and risk stratification data (March 2019-Jan 2021).

Results: 1,795 patients across 30 centres (liver units $n = 1548$, general gastroenterology units $n = 247$) were included. Median age at diagnosis was 51 years and 62.2% were men. Magnetic resonance cholangiography (MRCP) was performed as a diagnostic investigation in 1616 patients (90.0%) and 777 (43.3%) had a liver biopsy. Most were monitored by a hepatologist ($n = 1610$, 89.7%). 931 patients (51.9%) received non-licensed therapy with Ursodeoxycholic acid.

Concurrent IBD was present in 1264 patients (70.4%) with 256 (20.3%) having had a colectomy. Where classified, pancolitis (Montreal classification E3) was the commonest disease distribution (673/939, 71.7%) with 1.6% ($n = 15$) having isolated ileal disease. In those without IBD, 140 (27.6%) patients had not had a colonoscopy and biopsies to exclude diagnosis.

785 patients (43.7%) had not undergone disease staging or risk stratification within the last 2 years; where performed, it was most commonly by transient elastography ($n = 645$, 78.7%). Surveillance for biliary tract cancer was not undertaken in 515 patients (28.7%); when performed, it was most commonly by ultrasound (US) ($n = 568$, 47.1%) or alternating MRCP/US ($n = 429$, $n = 35.6\%$). Ca 19-9 was utilised in 730 patients.

Among those with colitis, only 572 (77.8%) underwent annual colonoscopy surveillance. Of those patients who had any surveillance, 623 patients (49.2%) had protocol colonic biopsies and 417 patients (32.9%) had dye spray.

Conclusion: There is unwarranted variation in the care of patients with PSC in the UK. In particular relating to risk stratification, exclusion of colitis and surveillance for biliary tract and colonic cancer. The lack of uniformity in clinical practice highlights the need for better education of clinicians about PSC management and the potential role of clinical networks for rare liver diseases within the UK.

PO-1799

Among cancer patients, autoimmune hepatitis with cirrhosis increases mortality

Morten Daniel Jensen¹, Peter Jepsen^{1,2}, Hendrik Vilstrup¹, Lisbet Groenbaek^{1,3}. ¹Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; ²Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus, Denmark; ³Regional Hospital Horsens, Department of Medicine, Horsens, Denmark
Email: moje@clin.au.dk

Background and aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease associated with a high mortality. Patients with AIH have an increased risk of cancer, but the effect of AIH on cancer prognosis remains unclear. We examined mortality risks from the time of cancer diagnosis in a nationwide cohort of patients with AIH and compared with persons with cancer from the general population.

Method: This study was based on nationwide Danish healthcare registries. We identified all persons diagnosed with AIH between 1994 and 2018. We included 215 patients with AIH who developed cancer after AIH diagnosis and 2121 population controls matched by age, cancer type, and date of cancer diagnosis. For AIH patients and controls, we used the pseudo-value approach to estimate cumulative mortality risk and mortality risk ratio, adjusted for age, smoking, and alcohol consumption.

Results: The 10-year cumulative mortality after a cancer diagnosis was 61.1% (95% confidence interval [CI] 52.7–69.5) for AIH patients and 49.6% (95% CI 46.9–52.4) for population controls. The 10-year mortality risk was 1.3 (95% CI 1.1–1.5) times higher in AIH patients with cancer compared with controls with cancer. In AIH patients, those with cirrhosis had a higher 10-year mortality risk at 74.4% (95% CI 60.6–86.3) as compared with 53.0% (95% CI 42.8–63.9) in patients without cirrhosis. Comparing only AIH patients without cirrhosis with their matched controls yielded a 10-year mortality risk ratio of 1.1 (95% CI 0.9–1.4).

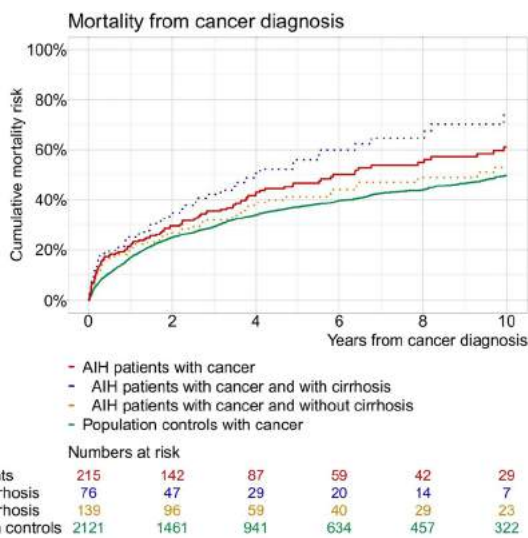


Figure:

Conclusion: Among patients with cancer, those with AIH had a 1.3-fold higher 10-year mortality than those without AIH. Importantly, this excess mortality was restricted to AIH patients with cirrhosis.

PO-2015

Immunological Background Pinpoints Patients at High Risk of Immune-related Hepatitis Recurrence during Check-points Inhibitors Rechallenge

Mar Riveiro Barciela^{1,2,3}, Ana Barreira^{1,3}, Ana Callejo-Pérez⁴, Eva Muñoz-Couselo⁴, Nely Díaz-Mejía⁴, Maria Teresa Salcedo⁵, Luisa Roade^{1,2,3}, Adriana Palom^{1,3}, Maria Buti^{1,2,3}. ¹Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; ²Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; ³Universitat Autònoma de Barcelona (UAB), Department of Medicine; ⁴Oncology Department, Instituto de Oncología Vall d'Hebron (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; ⁵Pathology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
Email: mar.riveiro@gmail.com

Background and aims: Immunotherapy has improved the survival of patients with many types of advanced tumours. However, its increasing widespread use has been associated with immune-related adverse events (irAEs) such as severe immune-related hepatitis, leading to permanent discontinuation of immunotherapy

according to the international guidelines. We report the outcome of a cohort of patients who presented severe immune-related hepatitis and were retreated with check-point inhibitors (CPI) after the resolution of the irAE.

Method: This is a prospective non-interventional study that included all consecutive patients with oncological disease who developed grade 3 or 4 immune-related hepatitis and were rechallenged with check-point inhibitors (CPI) in a university hospital in Barcelona (Spain).

Results: 21 patients who with severe immune-related hepatitis were included (52.4% female, median age of 62, 76.2% treated with anti-PD1 or anti-PD1/PD-L1). All of them discontinued CPI therapy temporary and were mainly retreated with the same CPI after a median time of 10 weeks (range, 1.5–53.5) from the severe immune-related hepatitis. Recurrence of the immune-related hepatitis was observed in six patients (28.6%), 4 of them grade-3 and 2 grade-4. There was a trend to a high rate of recurrence among those treated with concomitant chemotherapy (p=0.115). Five (83.3%) of 6 subjects with recurrence of the immune-related hepatitis had either an underlying autoimmune disease or significant antinuclear antibodies titers (p = 0.029).

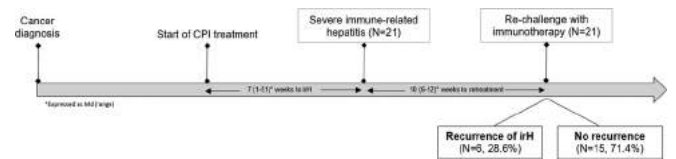


Figure: Flowchart of the study

Conclusion: Retreatment with check-point inhibitors is a feasible option after a severe immune-related hepatitis, even with the same check-point inhibitors, with a risk of recurrence of 29%. Given the higher risk of recurrence of the immune-related hepatitis in patients with underlying autoimmune diseases or positive antinuclear antibodies, the decision to rechallenge should be taken with caution in these patients.

PO-2230

Safety and efficacy of the JAK-inhibitor tofacitinib in patients with primary sclerosis cholangitis: a multicentre, retrospective study

Ida Schregel¹, Cynthia Levy², Stephanie Ioannou³, Emma Culver⁴, Martti Färkkilä⁵, Olivier Chazouillères⁶, Tobias Müller⁷, Jeremy Nayagam⁸, Deepak Joshi⁸, Ehud Zigmund⁹, Oren Shibolet⁹, Joost Ph Drenth¹⁰, Frank Hoentjen¹⁰, Anja Geerts¹¹, Tobias Weismüller¹², Taotao Zhou¹², Christoph Schramm¹. ¹University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ²University Miami Miller School of Medicine, Miami, United States; ³Jackson Memorial Hospital, Miami, United States; ⁴John Radcliffe Hospital, United Kingdom; ⁵Helsinki University Central Hospital, Helsinki, Finland; ⁶Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Faculté de Médecine Pierre et Marie Curie, Paris, France; ⁷Charité Campus Virchow Clinic, Berlin, Germany; ⁸King's College Hospital, United Kingdom; ⁹Tel-Aviv Sourasky Medical Center, and Sackler Faculty of Medicine, Tel Aviv, Israel; ¹⁰Radboud University Medical Center, Nijmegen, Netherlands; ¹¹Ghent University Hospital, Gent, Belgium; ¹²UKB University of Bonn, Bonn, Germany
Email: i.schregel@uke.de

Background and aims: Tofacitinib, mainly inhibiting JAK1/3, has been licensed for the treatment of ulcerative colitis. It is unknown whether tofacitinib can be safely and effectively used in patients with primary sclerosing cholangitis (PSC), an immune-mediated bile duct disease frequently associated with inflammatory bowel disease (IBD). We therefore retrospectively collected data on PSC patients treated with tofacitinib in order to assess safety and efficacy of tofacitinib on liver and bowel disease.

POSTER PRESENTATIONS

Method: Data was collected from 11 centres from Europe, North America and Western Asia participating in the international PSC study group (IPSCSG) and the European Reference Network on Hepatological Diseases (ERN RARE LIVER). Patients with PSC and associated colitis were included if they received past or ongoing treatment with tofacitinib. Data was collected prior to baseline, after 3-months follow-up, at last dose of tofacitinib given and at last follow-up.

Results: 28 patients with large duct PSC (71% male) were included in the analysis of whom 6/28 had evidence of cirrhosis. Median age at diagnosis was 37 (range 19–65) years. In 43% (12/28) treatment with tofacitinib was stopped, in 8/12 due to lack of efficacy, of which 5 patients received or were awaiting colectomy. The median treatment period before discontinuation of tofacitinib was 6 months (1–21).

In those patients where baseline and follow-up colonoscopy were reported (n = 17), colitis activity improved in the majority of patients (65%). Faecal calprotectin dropped from a median of 788 µg/g (124–2000) at baseline to 342 µg/g (15–2327, p = 0.09). At follow-up, one patient had developed high-grade dysplasia and one patient colorectal carcinoma.

ALP and total bilirubin levels did not show statistically significant differences between baseline and 3 month- and last follow-up under tofacitinib: 150 U/l (56–818) at baseline vs. 217 U/l (41–979) at 3 month-follow-up. For those still on treatment with tofacitinib, median ALP was 218 U/l (56–818) at baseline and 127 U/l (49–1132) at last follow-up (p = 0.87). Overall, there was no deterioration in liver biochemistry after commencing tofacitinib.

One patient developed bacterial cholangitis during treatment with tofacitinib. Two patients died, one of them due to metastatic colorectal carcinoma and the other due to unclear causes. No new cases of hepatobiliary malignancy occurred.

Conclusion: In a retrospective analysis of 28 patients with PSC and associated colitis, treatment appeared to be well tolerated and without significant worsening of liver enzymes over a median treatment period of 10 months (1–29). The majority of patients, most of them with several prior treatment regimens, demonstrated an improvement in their colitis activity. Further studies are needed to assess the impact of tofacitinib on the long-term course of PSC.

PO-2259

Intravenous ketamine and progressive cholangiopathy in covid-19 patients

Kilian Bock¹, Heiner Wedemeyer¹, Vincent Mallet². ¹Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²Université de Paris, AP-HP, Hôpital Cochin, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France

Email: bock.kilian@mh-hannover.de

Background and aims: Many institutions worldwide experienced or are experiencing shortages of vital anaesthetic drugs that are also commonly used in intensive care units (ICU) because of the coronavirus infectious disease 2019 (Covid-19) pandemic. Ketamine has been proposed as an off-label second-line agent for maintenance sedation of patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, including those with Covid-19. We report a series of five Covid-19 patients from five different centers with, dose-dependent, ketamine cholangiopathy.

Method: Five cases of cholangiopathy after covid-19 between march 20, 2020 and April 6, 2020 were retrospectively analysed.

Results: The median (range) age of patients was 59 (35–65) years, and three (60%) were males. All had undergone mechanical ventilation for a median (range) period of 40 (39–59) days, and had received intravenous ketamine at a dose of 0.6 (0.1–2.2) mg/kg/h for 16 (6–26) days. Jaundice under ketamine correlated with total ketamine exposure (R² = 0.95) and not with initial serum C-reactive protein level (R² = 0.14). All patients had recurrent episodes of cholangitis after a median (range) period of 6 (4–8) months after

ketamine withdrawal. The nadir of arterial oxygen saturation (SaO₂) was 81 (71–93) percent. All patients received norepinephrine for 10 (2–15) days with a maximum dose of 0.4 (0.1–0.6) µg/kg/min. Maximum arterial lactate level was 2.4 (1.5–4.9) mmol/L. All patients developed acute kidney injury, and three (60%) required renal replacement therapy. At the end of follow-up, one patient had died with sepsis and decompensated cirrhosis; one patient was on the waiting list for a liver transplant with jaundice, pruritus, portal hypertension, and a median (interquartile range) liver stiffness of 64.1 (4.5) kilopascal; one patient had overt sclerosing cholangitis; and two patients had recurrent episodes of biliary sepsis. The two most severe patients had received higher doses of ketamine: 2.2 mg/kg/d for 16 and 14 days, respectively. The patient with sclerosing cholangitis had received lower doses of ketamine (0.16 mg/kg/h) for 26 days, which corresponded to the longest exposition period in the series.

Conclusion: In conclusion, intravenous ketamine at the recommended doses for maintenance sedation of patients undergoing mechanical ventilation for ARDS, including Covid-19 patients, can be associated with biliary obstructions, cholestatic liver injury, biliary cirrhosis, and end stage liver disease. Covid-19 patients who underwent maintenance sedation with ketamine, especially those who developed jaundice in the intensive care unit, should be screened for long-term liver injury, including cholangiopathy.



Figure: ERCP showed contrast medium filling defects in the ductus hepatocholedochus and rarefaction of the intrahepatic biliary tract. Biliary Cast has been removed.

PO-2280

Identifying the early predictors of non-response to steroids in patients with flare of autoimmune hepatitis causing acute on chronic liver failure

Sanchit Sharma¹, Samagra Agarwal¹, Anoop Saraya¹, Ashok Choudhury², Sanjiv Saigal³, Arvinder Singh Soin⁴, Akash Shukla⁵, Manoj Sahoo⁶, Samir Shah⁷, Jinhua Hu Hu⁸, Soek-Siam Tan⁹, Dinesh Jothimani¹⁰, Mohd. Rela¹⁰, Virendra Singh¹¹, Ajay Kumar Duseja¹¹, Sunil Taneja¹¹, Saeed Sadiq Hamid¹², Wasim Jafri¹², Amna Subhan¹², Varun Mehta¹³, Guan Huei Lee¹⁴, Diana Payawal¹⁵, Mamun Al-Mahtab¹⁶, Laurentius A. Lesmana¹⁷, C.E. Eapen¹⁸, Ashish Goel¹⁸, Md. Fazal Karim¹⁹, Rino Alvani Gani²⁰, Zhongping Duan²¹, Shaojie Xin²², Qin Ning²³, Sombat Treeprasertsuk²⁴, Anand Kulkarni²⁵, Nagaraja Rao Padaki²⁵, AJIT Sood¹³, Vandana Midha¹³, Omesh Goyal¹³, S. Joyes²⁶, Dong Joon Kim²⁷, Shiv Kumar Sarin². ¹All India Institute of Medical

Sciences, Department of Gastroenterology and Human Nutrition Unit, New Delhi, India; ²Institute of Liver and Biliary Sciences, Department of Hepatology, New Delhi, India; ³Medanta -The Medicity, Department of Hepatology, Gurugram, India; ⁴Medanta -The Medicity, Department of Liver Transplantation and Regenerative Medicine, Gurugram, India; ⁵KEM Hospital and Seth GSMC, LTMMC, Department of Hepatology, Mumbai, India; ⁶Institute of Medical Sciences and SUM Hospital, Department of Hepatology, Bhubaneswar, India; ⁷Global Hospitals, Department of Hepatology, Mumbai, India; ⁸Military Hospital, Beijing, China; ⁹Selayang Hospital, Batu Caves, Malaysia; ¹⁰Dr. Rela Institute and Medical Centre-Multispecialty Hospital in Chennai, Chennai, India; ¹¹Post Graduate Institute of Medical Education and Research, Chandigarh, Department of Hepatology, Chandigarh, India; ¹²Aga Khan University Hospital, Karachi, Pakistan; ¹³Dayanand Medical College, Ludhiana, India; ¹⁴National University Health System, National University of Singapore, Singapore, Singapore; ¹⁵Fatima University Medical Center-Valenzuela, Valenzuela, Philippines; ¹⁶Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka, Bangladesh; ¹⁷Digestive Disease and Oncology Centers, Medistra Hospital, Jakarta, Indonesia; ¹⁸Christian Medical College, Department of Hepatology, Vellore, India; ¹⁹Sir Salimullah Medical College, Dhaka, Bangladesh; ²⁰Dr. Cipto Mangunkusumo National Central General Hospital, Indonesia; ²¹Hepatology Institute Capital Medical University, Beijing, China; ²²Medical School of Chinese PLA, China; ²³Tongji Hospital Tongji Medical College of HUST PET Center Tongji Hospital, Tongji Medical College/ Beijing Friendship Hospital, Capital University, Beijing, China; ²⁴Chulalongkorn University, Thailand; ²⁵Asian Institute of Gastroenterology, Department of Hepatology, Hyderabad, India; ²⁶Cardinal Santos Medical Center, San Juan, Philippines; ²⁷Chuncheon Sacred Heart Hospital, Chuncheon, Korea, Rep. of South
Email: shivsarini@gmail.com

Background: Early identification of non-response to corticosteroids is critical in patients with flare of autoimmune hepatitis (AIH) causing acute-on-chronic liver failure (ACLF). We aimed to identify this subgroup among patients with AIH-ACLF within the first week who merit early liver transplantation.

Methods: Patients with AIH-ACLF treated with steroids over 2012–2020 with no infection/overt hepatic encephalopathy at baseline were identified from APASL-ACLF database and were assessed for outcomes. Diagnosis of AIH-ACLF was based on simplified or probable IAIHG score and APASL ACLF definition. Clinical assessment and baseline laboratory parameters, MELD score and change in laboratory parameters at day 3 were assessed to predict non-response. Performance of a recently derived SURFASA score (for acute severe AIH) ($SURFASA = -6.80 + 1.92 * (DO-INR) + 1.94 * (\Delta\%3-INR) + 1.64 * (\Delta\%3-bilirubin)$) was also evaluated for AIH-ACLF patients.

Results: 57 of 165 patients (age- 38.2 ± 15.0 years, 68.4% females) of AIH-ACLF with median MELD 24 (IQR: 22–27) and median AARC score 7 (IQR: 6–9) were given prednisolone 40 mg per day. Liver biopsy was available in 45 out of 57 patients and showed interface hepatitis (80%), and underlying cirrhosis in (64%). Overall, 90-day survival was 51.7%. Twentyfive (43.8%) patients developed incident infections and had worse survival (28.0%; $p = 0.03$). Both SURFASA score and MELD predicted poor outcome (need for liver-transplant or death) with good accuracy within first 3 days of steroid administration (AUROC 0.795 (95% confidence interval:0.678–0.911) for SURFASA and 0.837 (0.733–0.94) for baseline MELD) which were significantly better than Δ MELD at 3 days (AUROC-0.541 (0.395, 0.687). At optimal cut point of -1.2 for SURFASA and 24 for MELD, need for transplant/death could be predicted with a sensitivity and specificity of 74.2% and 73.1% for SURFASA and 77.4% and 73.1% for MELD respectively.

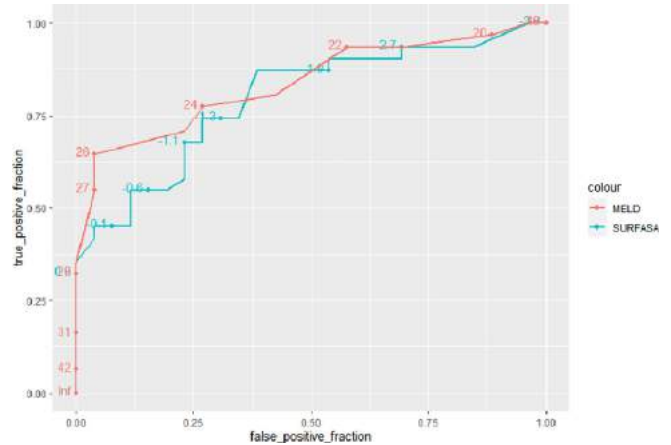


Figure: Receiver Operator Characteristics (ROC) curves for predictors of 90-day survival. Numbers on plot represent value of respective prognostic variable. Area under curve for MELD score and SURFASA score are 0.837 (95%CI: 0.733-0.94) and 0.795 (95% CI: 0.678-0.911) respectively

Conclusion: Both baseline MELD and SURFASA score can predict non-response to steroids within first 3 days of treatment initiation in AIH-ACLF.

PO-2327

Hepatic safety assessment of obeticholic acid (OCA) in primary biliary cholangitis (PBC): A post-hoc evaluation of a long term safety extension study with an external PBC cohort

Gideon Hirschfield¹, Bettina Hansen^{1,2}, Erik Ness³, Elizabeth Smoot Malecha³, Chiara Bassanelli³, Femi Adekunle³, Lina Titievsky³, Leigh MacConell³. ¹Toronto General Hospital, Toronto, Canada; ²University of Toronto, IHPME, Toronto, Canada; ³Intercept Pharmaceuticals, Inc., New York, United States
Email: gideon.hirschfield@uhn.ca

Background and aims: Ongoing safety evaluation is an important, but challenging, aspect of drug development. We sought to compare safety data from long-term trial use of obeticholic acid in patients with primary biliary cholangitis, with an externally derived real-world cohort of PBC patients with cirrhosis.

Method: An external cohort consisting of patients with a diagnosis of PBC (defined via ICD-10 codes) was identified from a large US Electronic Health Records Database during 2016–2019; a sub-cohort with baseline cirrhosis (defined via ICD-10 codes) was then analysed to provide event rates for cirrhotic patients with PBC over time. Obeticholic acid treated patients with PBC were identified from the POISE Long Term Safety Extension (LTSE) study. Presence of baseline cirrhosis in POISE was defined based on the following: PBC complete or incomplete cirrhosis in historical biopsy, baseline transient elastography ≥ 16.9 kPa or medical history of Hepatic Cirrhosis. An assessment of overall treatment-emergent hepatic disorders was conducted using the Standardized MedDRA Query of Hepatic Disorders. Exposure Adjusted Incidence Rates (EAIRs) in the POISE LTSE and Incidence Rates (IRs) in the external cohort for select hepatic adverse outcomes were calculated and expressed per 100 Person Years (PY) with 95% Confidence Intervals (CI).

Incidence Rates and 95% CIs, Cirrhosis at Baseline (per 100 person-years)

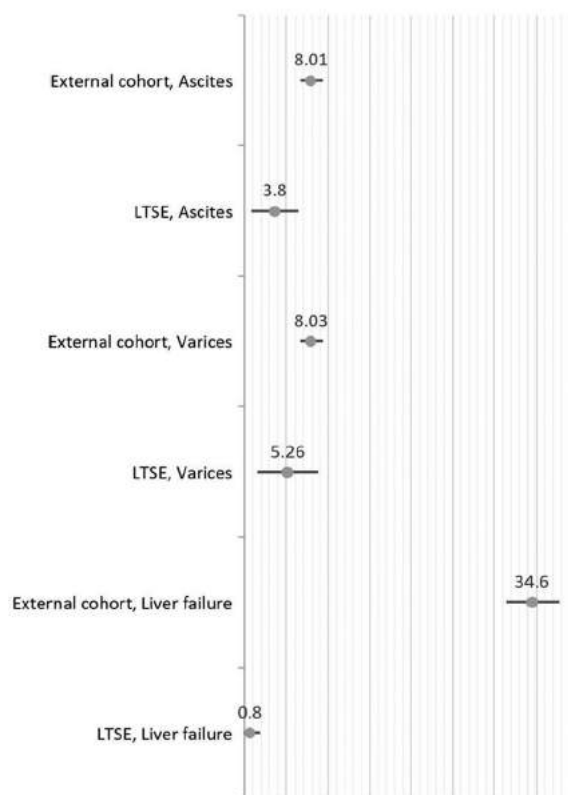


Figure:

Results: Of the 193 subjects in the POISE LTSE, 45 (23.3%) met the criteria for cirrhosis, most presumed Child-Pugh A. Patients with cirrhosis had a similar duration of disease at trial entry (median of 7.8 years) and were more likely to be ≥ 50 years at diagnosis (56% vs 36% respectively) compared to non-cirrhotic subjects. Overall, there was a trend towards higher EAIRs of hepatic AEs in cirrhotic subjects (9.78, 95% CI of 4.11 to 15.44) relative to non-cirrhotic subjects (6.04, 95% CI of 3.99 to 8.10) and this was primarily driven by differences in the EAIRs of esophageal varices and ascites. 1407 PBC patients with cirrhosis were identified in the external cohort and they showed higher IRs when compared to non-cirrhotic subject. In OCA treated patients with cirrhosis in POISE LTSE were appreciably lower than IRs in the external database [Figure].

Conclusion: The rate of hepatic AEs in PBC patients is associated with cirrhosis status at baseline. In the absence of a comparator arm, the US-population based external cohort suggests that the EAIRs of hepatic-related AEs with OCA treatment do not exceed the expected background rates in an OCA untreated real world PBC population.

PO-2657

Patient perspectives on pruritus in intrahepatic cholestasis of pregnancy: a multinational survey

Andrew McKibben¹, Jenny Chambers², Catherine Williamson³, George Saade⁴, Will Garner¹, Vyechi Low⁵, Elaine Chien¹. ¹Mirum Pharmaceuticals, Foster City, United States; ²ICP Support, Sutton Coldfield, United Kingdom; ³King's College London, Women's Health, London, United Kingdom; ⁴University of Texas Medical Branch at Galveston, Maternal-Fetal Medicine, Galveston, United States; ⁵Harvard University

Email: amckibben@mirumpharma.com

Background and aims: To provide information about the presentation and severity of intrahepatic cholestasis of pregnancy (ICP), its management, and its broader burden from the patient perspective.

Method: A multinational survey of women with current or previous ICP (funded by Mirum Pharmaceuticals). The 30-question web-based survey was distributed to participants via an ICP patient support group. Responses were collected between August 25 and September 10, 2020.

Results: Of 688 women who responded, 352 lived in the UK, 162 in the US, 54 in Australia, 19 in Canada, 10 in New Zealand, 8 in Ireland; 32 were from 19 other countries. Most (94%) had ICP in a previous pregnancy. The median worst itch reported was 9 on a numerical rating scale (NRS) (0 for 'no itch,' 10 for 'worst itch you can possibly imagine'), with 90% of women reporting a worst itch of ≥ 7 and 42% reporting a 10. Itch severity was associated with a higher degree of reported sleep disturbance and worsening fatigue. 59% reported that itch led to disruption of day-to-day responsibilities and routines, 44% of whom reported that the disruption lasted >30 days. 33% reported missing school or work. Itch severity was also associated with greater frequency of reported mood changes including but not limited to anxiety, irritability, and feelings of hopelessness.

58% of women reported taking ≥ 2 medications for itch and 29% took ≥ 3 , of which the most commonly used were ursodeoxycholic acid (UDCA; 76%), antihistamines (46%), topical creams or ointments (38%). These medications achieved only partial resolution (UDCA 45%; antihistamines 24%; creams/ointments 52%) or had no impact (UDCA 35%; antihistamines 61%; creams/ointments 40%).

Conclusion: This international survey underscores the burden of pruritus in ICP. A large proportion of participants had disruptions to sleep, worsening fatigue, adverse impacts on mood and other substantial impacts to quality of life. Most women reported either partial or no resolution of ICP-associated pruritus with existing therapies. These data highlight the high unmet need for development of safe and effective therapies for patients with ICP.

PO-2701

Artificial Intelligence and Digital Single-Operator Cholangioscopy: automatic identification of tumor vessels in patients with indeterminate biliary strictures.

Miguel Mascarenhas¹, Tiago Ribeiro², João Afonso², João Pedro Sousa Ferreira³, Filipe Vilas-Boas², Renato Natal Jorge³, Pedro Pereira², Guilherme Macedo². ¹Centro Hospitalar Universitário de São João, Gastroenterology, Porto; ²Centro Hospitalar Universitário de São João, Gastroenterology; ³Faculdade de Engenharia da Universidade do Porto, Engenharia Mecânica

Email: miguelmascarenhassaraiva@gmail.com

Background and aims: The diagnosis and characterization of biliary strictures is a significant clinical challenge. The introduction of digital single-operator cholangioscopy (D-SOC) allowing direct visual inspection of the bile ducts and guided tissue sampling significantly increased the diagnostic yield in patients with indeterminate biliary strictures. The identification of dilated, irregular and tortuous vessels, often described as tumor vessels, is a frequent element in biliary strictures with a high probability of malignancy. In recent years, the development of artificial intelligence (AI) algorithms for application to endoscopic practice has been intensely studied. This study aimed to develop and validate a convolutional neural network (CNN) for automatic detection of tumor vessels in D-SOC images.

Method: A deep learning algorithm was developed and trained for automatic recognition of tumor vessels in D-SOC images. A total of 6475 images from 85 patients who underwent D-SOC (Spyglass™, Boston Scientific, Marlborough, MA, USA). Each frame was classified by two endoscopists with experience in D-SOC regarding the presence or absence of tumor vessels. This pool of images was subsequently divided for constitution of two distinct datasets for training (80%) and validation (20%) of the CNN. The performance of the CNN was measured by calculating the area under the receiving

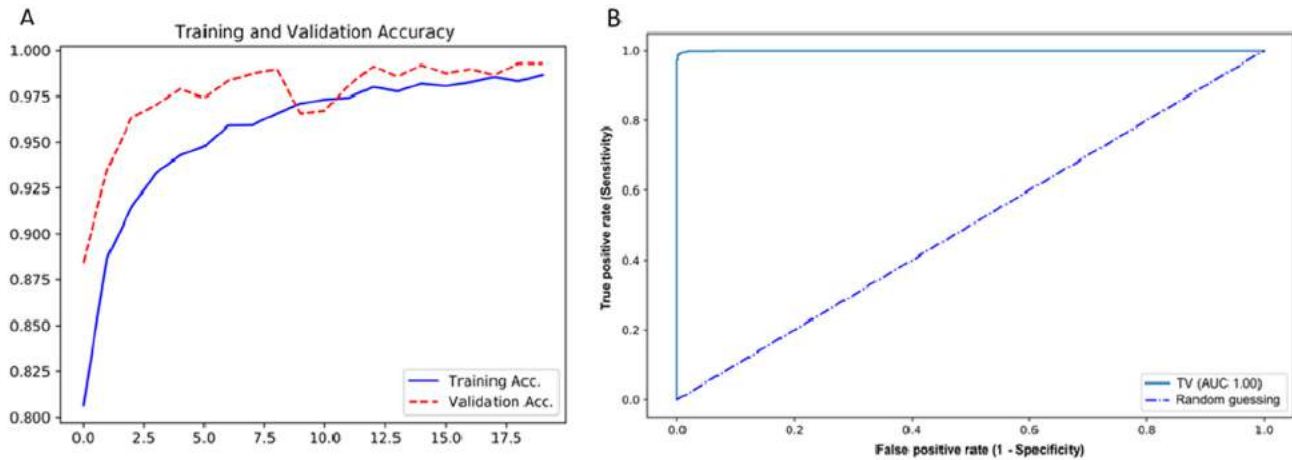


Figure: (abstract: PO-2701)

operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).

Results: Our CNN had an overall accuracy of 99.3% for detection of tumor vessels (Figure 1A). The sensitivity, specificity, PPV and NPV were 99.3%, 99.4%, 99.6% and 98.7%, respectively. The AUC was 1.00 (Figure 1B). The CNN had an image processing rate of 20 ms/frame.

Conclusion: Our CNN was able to detect tumor vessels with high sensitivity, specificity, and accuracy. The incorporation of AI tools to D-SOC systems may significantly enhance the detection of macroscopic characteristics associated with high probability of biliary malignancy, thus optimizing the diagnostic workup of patients with indeterminate biliary strictures.

PO-2719

Cholangiopathy associated with checkpoint inhibitors: a case series

Philip Berry¹, Sreelakshmi Kotha¹, Sophie Papa², Yoh Zen³, Deepak Joshi³, Michael Heneghan³. ¹Guy's and St Thomas' NHS Foundation Trust, Gastroenterology, Hepatology and Nutrition, London, United Kingdom; ²Guy's and St Thomas' NHS Foundation Trust, Medical Oncology, London, United Kingdom; ³Kings College Hospital NHS Foundation Trust, Institute of Liver Studies, London, United Kingdom
Email: philip.berry@gstt.nhs.uk

Background and aims: Cholestatic liver function profiles are common in immune-related hepatitis (irH) during treatment with checkpoint inhibitors (CPI) for malignancy. We investigated the

spectrum of bile duct injury and associated natural history in this cohort.

Method: Clinical data in patients with radiologic or histological evidence of bile duct injury from 2018 to 2020 was collected. Biopsies were reviewed by a single histopathologist (YZ).

Results: CPI were prescribed to 60 patients during the study period. 7 patients with bile duct disease were identified (Table 1). Pembrolizumab was the most commonly implicated CPI (5/7). Median CPI cycles prior to irH was 4. Median alanine aminotransferase and alkaline phosphatase were 500 U/L and 889 U/L respectively. There was no association with autoimmune or viral markers. Clinical jaundice and radiological evidence of bile duct pathology was seen in 5/7. Liver biopsy was performed in 5 patients and repeated in one. 3 patients had primary sclerosing cholangitis (PSC) like changes characterized by periductal concentric fibrosis and epithelial injury. In the case with sequential biopsies, the 1st showed severe small-duct cholangitis with significant inflammatory changes and minimal fibrosis, while the 2nd biopsy a year later exhibited less inflammatory, more fibrotic portal tract changes. One had features of obstructive large-duct cholangiopathy, one had cancer cells within a small blood vessel of the portal tract and 2 had mild hepatic changes. All patients were treated first-line with prednisolone, 3 with MMF and one with tacrolimus with clinical response in 3. 6 received ursodeoxycholic acid. 4 patients died after a mean follow-up of 7 weeks.

Table: (abstract: PO-2719)

Case	Demographics	Malignancy	CPI	Cycle	Bili, micmol/L	ALT, U/L	ALP, U/L	Radiology
1	79, M	Melanoma	Pembrolizumab	2	64	155	3380	Cholangiopathy
2	45, M	Melanoma	Ipilimumab, Nivolumab	4	64	800	790	Cholangiopathy
3	42, M	NSCLC	Atezolizumab	4	400	603	889	Biliary dilatation and liver metastases
4	71, F	Urothelial bladder	Pembrolizumab	4	11	500	1703	Normal
5	70, M	NSCLC/mucinous adenocarcinoma	Pembrolizumab	10	9	250	489	Normal
6	61, M	NSCLC	Pembrolizumab	6	391	600	400	Cholangiopathy
7	73, M	Epithelioid mesothelioma	Pembrolizumab	2	156	201	1910	Cholangiopathy

POSTER PRESENTATIONS

Conclusion: Within this heterogenous cohort we identified a PSC-like, potentially progressive phenotype that responded poorly to immunosuppression. Cholangiopathy should be suspected and actively diagnosed if the response to first-line treatment is poor.

PO-2724

Budesonide versus prednisolone in the treatment of autoimmune hepatitis: a cross-sectional patients' survey

Ceyhan Oztumer¹, Laith Al-Rubaiy². ¹Brighton and Sussex Medical School, Brighton, United Kingdom; ²St Mark's Hospital, London, United Kingdom

Email: c.oztumer1@uni.bsms.ac.uk

Background and aims: Autoimmune hepatitis (AIH) is a chronic liver disease that can lead to cirrhosis and liver failure. Prednisolone is the first-line treatment, though budesonide has recently been shown to be effective in inducing and maintaining remission in AIH patients while having a significantly lower incidence of side effects. We aimed to assess the real-life experiences of AIH patients in terms of their treatment and side effects.

Method: A cross-sectional study was conducted in partnership with a patient charity, AIH Support. Patients with a diagnosis of AIH completed an anonymous, self-reported questionnaire in 2016 assessing their treatment choices, prescribed medications, and side effects. An identical questionnaire was disseminated in 2020 to patients diagnosed with AIH after the previous survey closed in July 2016 to enable comparison between the two surveys. Survey responses were analysed using descriptive statistical analyses and chi-squared tests.

Results: There were 190 respondents (87% female) in 2016 and 170 respondents (88% female) in 2020. On diagnosis, significantly more patients were prescribed prednisolone than budesonide in both the 2016 survey (90% vs 10%) and 2020 survey (76% vs 22%). Of those patients prescribed either prednisolone or budesonide on diagnosis, only 3% (2016) and 5% (2020) recall being given a choice between the two medications, and only 67% (2016) and 62% (2020) recall potential side effects of steroids being discussed prior to commencing treatment. Patients receiving budesonide were significantly less likely to experience side effects including moon face, weight change, sleep disturbance, and mood swings ($p < 0.05$ for all). Overall, the proportion of patients experiencing more than one side effect was 92% for prednisolone and 54% for budesonide.

Conclusion: Despite the significantly higher incidence of side effects, prednisolone continues to be prescribed more frequently than budesonide on diagnosis of AIH. More emphasis on informing patients of potential side effects is needed to enable increased patient choice in their treatment. Additional randomised trials are required to assess the efficacy of budesonide before it can be implemented in national guidelines as a possible first-line treatment for AIH.

PO-2761

Ischemic cholangiopathy in biliary atresia: immunohistochemical and molecular evidence

Patricia Quelhas¹, Michele Breton¹, Rui Oliveira², Maria Augusta Cipriano², Pranavkumar Shivakumar^{3,4}, Jorge Bezerra³, Sandra Vieira⁵, Carlos Kieling⁵, Ignacio Verde⁶, Jorge Luiz dos Santos¹.

¹Avenida Infante Dom Henrique, Faculty of Health Sciences, Health Science Investigation Center (CIC-UBI), Hormones and Metabolism Group, Covilhã, Portugal; ²Praceta Carlos da Mota Pinto, Anatomopathology Service, Hospital Center of Coimbra University (SAP-CHUC, Coimbra, Portugal; ³3333 Burnet Ave, University of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, United States; ⁴Cincinnati Children's Hospital and the University of Cincinnati College of Medicine, Division of Gastroenterology, Hepatology and Nutrition and UC Department of Pediatrics, Cincinnati, United States; ⁵R. Ramiro Barcelos, 2350, Pediatric Gastroenterology and Hepatology Unit, Clinical Hospital of Porto Alegre (HCPA), Federal University of Rio Grande do Sul (UFRGS, Brazil); ⁶Avenida Infante Dom Henrique, Faculty of Health Sciences, Health Science Investigation Center (CIC-UBI), Covilhã, Portugal

Email: jlsantos@fcsaude.ubi.pt

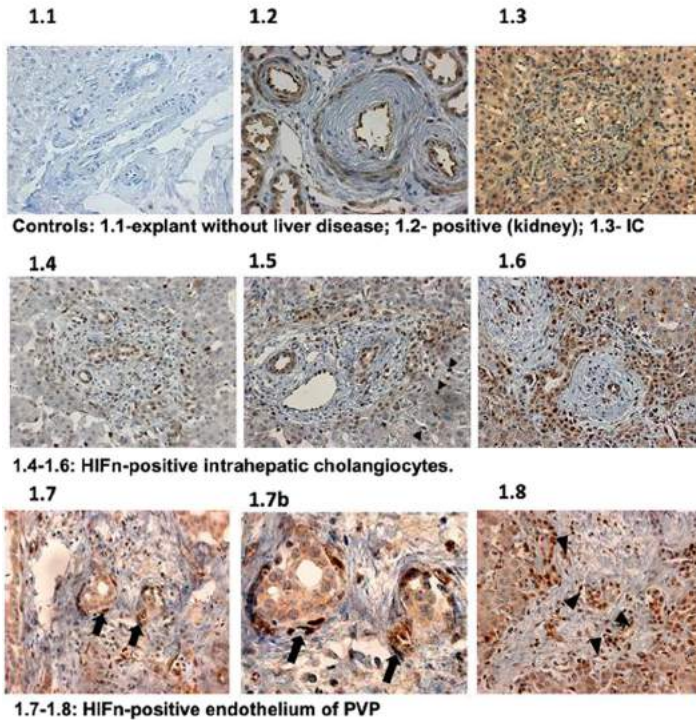
Background and aims: Biliary atresia (BA) is a severe cholangiopathy of infancy whose etiology remains undeciphered. The most frequent clinical form of BA is the isolated variant (iBA). We investigated the role of an ischemic cholangiopathy (IsChol) involving the peribiliary vascular plexus (PVP) as a pathogenic mechanism in BA.

Method: The cohorts comprised patients with iBA (N = 20) and intrahepatic cholestasis (IC; N = 5) serving as controls, at the time of exploratory laparotomies. Clinical and laboratory data on these patients were prospectively collected. Wedge liver biopsy (BA = 16; IC = 5) and porta hepatis (PH; BA only, N = 11) specimens were collected and paraffin-embedded. A segment of the liver specimen (BA = 11; IC = 4) was also collected in RNAholder and stored at -80°C . Immunohistochemical (IHC) analyses were performed on liver and PH specimens to confirm the presence of IsChol. IHC staining with anti-HIF1 α antibody to evaluate HIF nuclear positivity (HIFnP) was performed in paraffin-embedded sections. Frozen liver samples were used to determine gene expression of hypoxia-related molecules (HIF-1 α , VEGFA, VEGFR2, CK19, Caspase 3, VCAM1, Fibrocystin, GSS, GSR) by RT-PCR. IHC signals were correlated with gene expression and prognostic features using statistical approach.

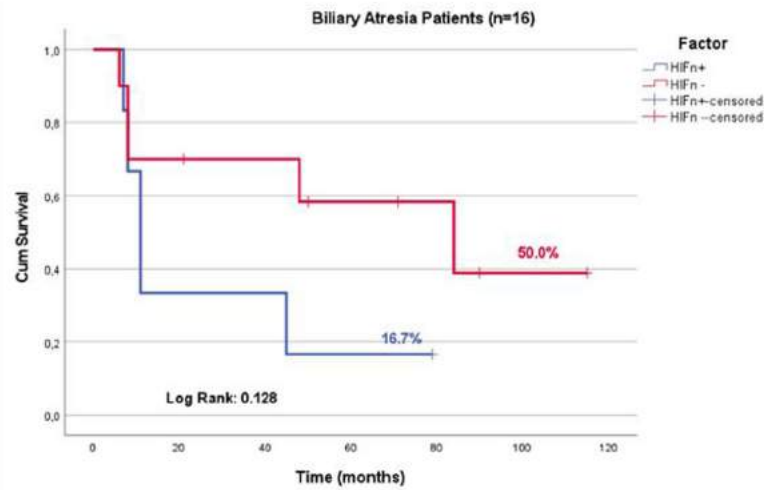
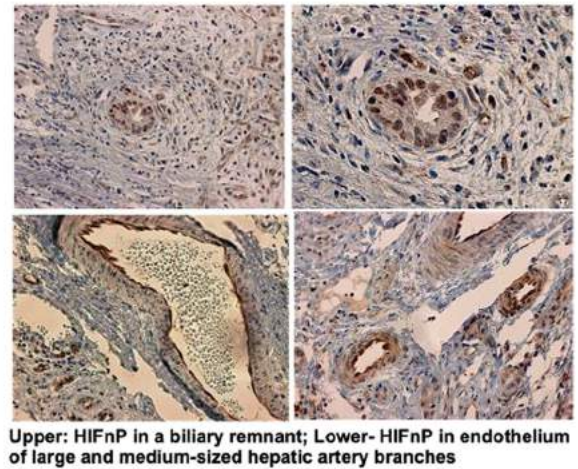
Results: IHC staining in liver and PH samples from iBA patients revealed the presence of HIFnP in cholangiocytes and endothelial cells of arteriolar vessels, including PVP, in 6/16 patients. Controls failed to show HIFnP. In cholangiocytes, HIFnP was localized to the interlobular bile ducts and areas of marginal ductular reaction (hepatic progenitor cell compartment, HPC). Importantly, a larger proportion of PH specimens (9/11) showed HIFnP in biliary remnants and the endothelium of hepatic artery branches. RT-PCR analysis showed overexpression of genes (GSS, GSR, CK19, VEGFA, VEGFR2) linked to REDOX status, ductular reaction, and angiogenesis in BA patients compared with IC controls. Comparing iBA cases with and without HIFnP showed a trend towards decreased GSR expression in the biliary HIFnP subset ($p < 0.07$).

Conclusion: Our work identified evidence of IsChol involving PVP in iBA patients affecting HPCs. Patients with HIFnP in intrahepatic cholangiocytes showed deregulated hepatic REDOX status. These results have potential prognostic and future therapeutic implications targeting the vascular pathologies in patients with BA.

LIVER Immunohistochemistry



PORTA HEPATIS Immunohistochemistry



Native liver survival HIFn-positive versus HIFn-negative iBA

Figure: (abstract: PO-2761): Ischol in iBA and native liver survival

PO-2801

Artificial Intelligence for automatic diagnosis of biliary strictures malignancy status in Single-Operator Cholangioscopy.

Miguel Mascarenhas¹, Tiago Ribeiro¹, João Afonso¹, João Pedro Sousa Ferreira², Filipe Vilas Boas¹, Ana Santos¹, Hélder Cardoso¹, Renato Natal Jorge², Pedro Pereira¹, Guilherme Macedo¹. ¹Centro Hospitalar Universitário de São João, Gastroenterology; ²Faculdade de Engenharia da Universidade do Porto, Engenharia Mecânica
Email: miguelmascarenhassaraiva@gmail.com

Background and aims: Diagnosis and characterization of biliary strictures is challenging. The introduction of digital single-operator cholangioscopy (D-SOC) allowing direct visual inspection of the lesion and targeted biopsies significantly improved the diagnostic

yield in patients with indeterminate biliary strictures. However, the diagnostic efficiency of D-SOC remains suboptimal. Convolutional neural networks (CNNs) have shown great potential for the interpretation of medical images. We aimed to develop a CNN-based system for automatic detection of malignant biliary strictures in D-SOC images.

Method: We developed, trained and validated a CNN based on D-SOC images. Each frame was labeled as normal/benign findings or as a malignant lesion if histopathological evidence of biliary malignancy was available. The entire dataset was split for 5-fold cross validation. Also, the image dataset was split for constitution of training and validation datasets. The classification provided by the CNN was compared with the labelling of the lesion (Figure 1). The performance of the CNN was measured by calculating the area under the receiving

POSTER PRESENTATIONS

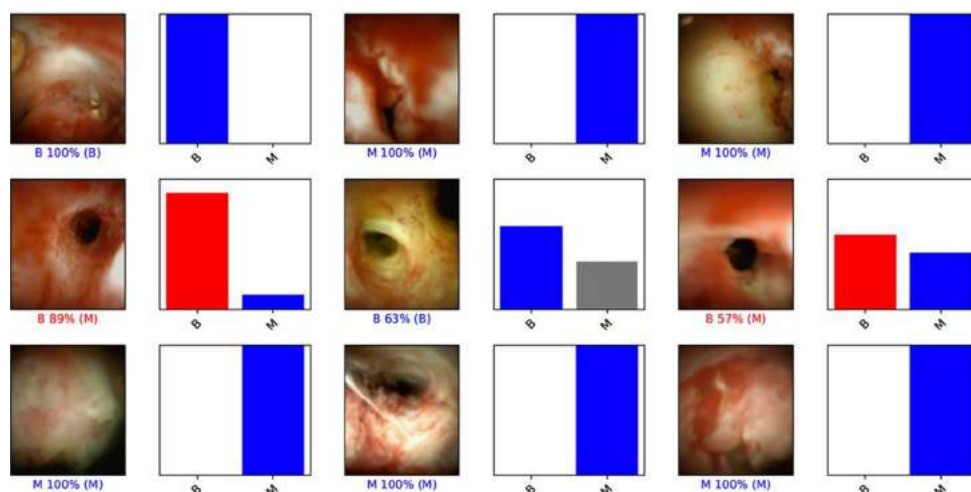


Figure 1: Output obtained during the training and development of the convolutional neural network. The bars represent the probability estimated by the network. The finding with the highest probability was outputted as the predicted classification. A blue bar represents a correct prediction. Red bars represent an incorrect prediction. B-benign biliary findings; M-malignant stricture.

Figure 1: (abstract: PO-2801)

operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).

Results: A total of 11855 images from 85 patients were included (9695 of malignant strictures and 2160 of benign findings). The model had an overall accuracy of 94.9%, a sensitivity of 94.7%, a specificity of 92.1% and an AUC of 0.988 in cross-validation analysis. The image processing speed of the CNN was 7 ms/frame.

Conclusion: The developed deep learning algorithm accurately detected and differentiated malignant strictures from benign biliary conditions. The introduction of artificial intelligence algorithms to D-SOC systems may significantly increase its diagnostic yield for malignant strictures.

PO-2830

A novel histological scoring system for primary sclerosing cholangitis: Impact on disease outcome

Nelli Sjöblom¹, Sonja Boyd¹, Hannu Kautiainen², Johanna Arola¹, Martti Färkkilä³. ¹Helsingin yliopisto, Pathology, Helsinki, Finland; ²Helsingin yliopisto, Department of General Practise and Primary Health Care, Helsinki, Finland; ³Helsingin yliopisto, Gastroenterology, Helsinki, Finland

Email: nelli.sjoblom@helsinki.fi

Background and aims: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease, which may lead to liver cirrhosis or cholangiocarcinoma. Liver histology and stage of fibrosis are predictive markers of disease progression. Histological cirrhosis is defined as a significant end point. PSC specific histological scoring method is lacking at present. We aimed to develop a tailored classification system for PSC, the PSC-histoscoring, that is based on histological features associated with disease progression.

Method: The cohort consisted of 300 PSC patients diagnosed between 1988–2018. Their data was collected from the PSC registry (Helsinki University Hospital) and liver specimens from the Biobank of Helsinki. Nine histological features included in the Nakanuma scoring system and four additional parameters typical for PSC histology were evaluated and compared with the clinical and laboratory data. A compound end point consisting of liver transplantation, development of cholangiocarcinoma or death served as outcome measurement.

Results: Parameters of stage (fibrosis, bile duct loss, ductulus proliferation, and chronic cholestasis) and grade (portal

inflammation, portal oedema, hepatitis activity, and cholangitis activity) were found to be independent predictive risk factors for the compound end point. ($p < 0.001$). High disease grade (2–3) and stage (2–4) correlated with clinical end points better when evaluated with the PSC-histoscoring system compared to Nakanuma classification. The risk for disease progression in sequential ERC examinations was elevated with high total PSC-histoscoring.

Conclusion: PSC-histoscoring is a novel potential histological classification system for PSC. Our findings support the applicability of liver histology as a marker for disease progression.

Figure: Correlations of histological grade and stage of disease with the compound end point according to the Nakanuma system and PSC-histoscoring.

PSC-histoscoring	End point reached		P value*
	No	Yes	
Total, median (IQR)**	4 (2, 9)	11 (8, 14)	<0.001
Grade, median (IQR)**	2 (1, 4)	5 (3, 8)	<0.001
Stage, median (IQR)	2 (1, 4)	6 (4, 7)	<0.001
Nakanuma Total score, median (IQR)	1 (0, 3)	5 (3, 6)	<0.001
Grade			<0.001
0	88 (33)	3 (8)	
1	53 (20)	3 (8)	
2	66 (25)	8 (22)	
3	30 (11)	9 (24)	
4	18 (7)	5 (14)	
5	7 (3)	9 (24)	
6	3 (1)	0 (0)	
Stage			<0.001
0	51 (19)	1 (3)	
1	82 (31)	11 (30)	
2	87 (33)	8 (22)	
3	43 (16)	15 (41)	
4	2 (1)	2 (5)	

*p for linearity
**pericholangitis was excluded

PO-2887

Artificial intelligence and digital single-operator cholangioscopy: automatic identification of neoplastic biliary nodules in patients with indeterminate biliary stenosis.

João Afonso¹, Miguel Mascarenhas¹, Tiago Ribeiro¹, João Pedro Sousa Ferreira², Filipe Vilas-Boas¹, Marco Parente², Renato Natal Jorge², Pedro Pereira¹, Guilherme Macedo¹. ¹Centro Hospitalar Universitário de S. João, Gastroenterology, Porto, Portugal; ²Faculdade de Engenharia da Universidade do Porto, Engenharia
Email: joaoafonso28@gmail.com

Background and aims: Digital single-operator cholangioscopy (D-SOC) provides direct visual exploration of the biliary tract. This tool has become essential for distinguishing benign from malignant biliary strictures. The visual aspect of these lesions is highly sensitive for the diagnosis of malignancy. Macroscopic characteristic such as tumor vessels, papillary projections, masses and nodules are common findings in patients with malignant biliary strictures. Recent endoscopic literature has demonstrated large interest in artificial intelligence (AI) systems for detection of endoscopic lesions. However, the application of these systems for automatic characterization of biliary lesions has not been explored. This study aimed to develop a convolutional neural network for automatic detection of biliary nodules in D-SOC images.

Method: A convolutional neural network (CNN) was designed for automatic identification of biliary nodules using D-SOC images. A total of 3010 frames were extracted from a pool of 85 cholangioscopies (Spyglass™ DS II system, Boston Scientific, Marlborough, MA, USA). Each frame was classified by two endoscopists with experience in D-SOC regarding the presence or absence of nodules. Two image datasets were built for training and validation of the CNN (80% and 20% of the full image dataset, respectively). The performance of the model was measured by calculating the area under the receiving operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).

Results: After the optimization of the architecture of the CNN for automatic detection of biliary nodules, our network showed a sensitivity of 100%, a specificity of 99.1%, a PPV of 97.2% and a NPV of 100%. The overall accuracy of the deep learning system was 99.3%. The AUC was 1.00. The image processing speed was of 16 ms/image.

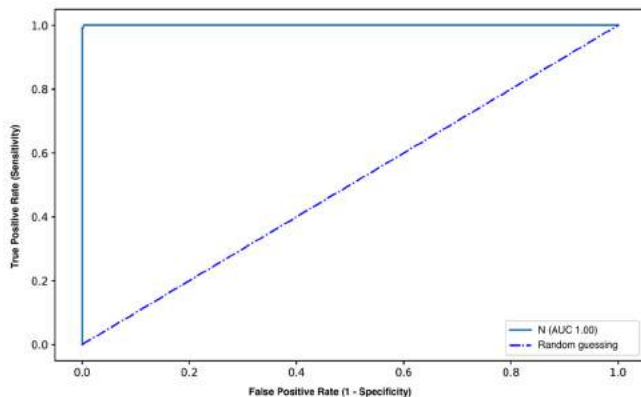


Figure 1: ROC analysis of the network's performance in the detection of biliary malignant nodules. ROC - receiver operating characteristic. N - nodules.

Conclusion: The integration of AI tools in D-SOC platforms may contribute to the optimization of the diagnosis of biliary malignancy, which may lead to a timelier treatment and better outcomes. Our deep learning algorithm has demonstrated high performance levels for the detection of malignant nodules of the biliary tract, with high sensitivity, specificity and overall accuracy.

PO-2898

Artificial intelligence and digital single-operator cholangioscopy: automatic identification of neoplastic masses in patients with indeterminate biliary strictures

Tiago Ribeiro^{1,2}, Miguel Mascarenhas^{1,2,3}, João Afonso^{1,2}, João Pedro Sousa Ferreira^{4,5}, Filipe Vilas-Boas^{1,2}, Marco Parente^{4,5}, Renato Natal Jorge^{4,5}, Pedro Pereira^{1,2,3}, Guilherme Macedo^{1,2,3}. ¹Centro Hospitalar Universitário de São João, Gastroenterology, Porto, Portugal; ²WGO Gastroenterology and Hepatology, Porto, Portugal; ³Faculty of medicine of the university of Porto, Porto, Portugal; ⁴Faculty of Engineering of the University of Porto, Department of mechanical engineering, Porto, Portugal; ⁵Institute of science and innovation in mechanical and industrial engineering, Porto, Portugal
Email: tiagofcribeiro@outlook.com

Background and aims: The characterization of indeterminate biliary strictures is a significant diagnostic challenge. Digital cholangioscopy allows direct visual inspection of the morphology of biliary strictures. The visual impression of these lesions is highly sensitive for the diagnosis of malignancy. Morphologic characteristics such as masses, tumor vessels or papillary projections are common findings in those with malignant biliary strictures. However, specificity and inter-observer variability remain significant limitations. Artificial intelligence (AI) tools have recently been applied with success to a wide spectrum of endoscopic modalities. The application of these systems for automatic cholangioscopic characterization of biliary lesions has not been explored. The aim of this study was to develop a neural network for automatic detection of biliary masses in D-SOC images.

Method: A convolutional neural network (CNN) was constructed for automatic identification of biliary masses in D-SOC images. A total of 3580 frames were extracted from a pool of 85 cholangioscopies (Spyglass™ DS II system, Boston Scientific, Marlborough, MA, USA). Each frame was classified by two endoscopists with experience in D-SOC regarding the presence or absence of masses. Two different image datasets were built for training and validation of the CNN (80% and 20% of the full image dataset, respectively). The performance of the model was measured by calculating the area under the receiving operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).

Results: The overall accuracy of the deep learning system was 99.9%. After the optimization of the architecture of the CNN for automatic detection of biliary masses, our network showed a sensitivity of 100%, a specificity of 99.8%, a PPV of 99.6% and a NPV of 100%. The AUC was 1.00. The image processing speed was of 17 ms/image.

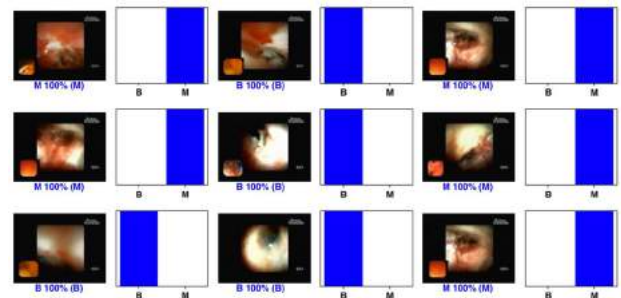


Figure 1: Output obtained during the training and development of the convolutional neural network. The bars represent the probability estimated by the network. The finding with the highest probability was outputted as the predicted classification. A blue bar represents a correct prediction. B - benign biliary findings; M - Masses.

Conclusion: Our neural network demonstrated high performance levels for the detection of biliary masses. The accurate automatic detection of this and other macroscopic characteristics associated with biliary malignancy may positively influence the diagnostic capacity of cholangioscopy, which may ultimately translate into prognostic gains.

Immunology

PO-147

Hepatitis B vaccine NON-RESPONDERS show higher frequencies of REGULATORY B CELLS, but lower levels of IL-10 expression compared to responders

Laureen Pohl¹, Nina Körber¹, Birgit Weinberger², Beatrix Grubeck-Loebenstein², Andrea Wawer³, Percy Knolle⁴, Hedwig Roggendorf⁴, Ulrike Protzer^{1,5,6}, Tanja Bauer^{1,6}. ¹Institute of Virology, Helmholtz Zentrum München, Munich, Germany; ²Institute for Biomedical Aging Research, University of Innsbruck, Innsbruck, Austria; ³Occupational Health Unit, Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany; ⁴Institute of Molecular Immunology and Experimental Oncology, Klinikum rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany; ⁵Institute of Virology, Technical University of Munich, School of Medicine, Munich, Germany; ⁶German Center for Infection Research (DZIF), partner site Munich, Munich, Germany
Email: laureen.pohl@gmx.de

Background and aims: The cellular mechanisms involved in the lack of protective antibody response after hepatitis B vaccination are still rather unclear. Regulatory B cells (Breg) known as modulators of B and T cell responses may contribute to poor vaccine responsiveness. The current study aimed to investigate the role of regulatory B cells (Breg) in hepatitis B vaccine non-responsiveness after immunization with second- (Twinrix[®]) or third-generation (Sci-B-VacTM) hepatitis B vaccines.

Method: We performed comparative phenotypic and frequency analysis of Breg subsets (CD24⁺CD27⁺ and CD24^{high}CD38^{high} Breg) in second-generation hepatitis B vaccine non-responders (2nd HBvac NR, n = 11) and responders (2nd HBvac R, n = 8) before (d0), on day 7 (d7), and 28 (d28) after Sci-B-VacTM or Twinrix[®] booster vaccination. Cryopreserved peripheral blood mononuclear cells were stimulated *ex vivo* with a combination of CpG, PMA, and Ionomycin (CpG+P/I) and analysed for numbers and IL-10 expression levels of Breg by flow cytometry-based analyses.

Results: Flow cytometry-based analyses revealed elevated frequencies of CD24⁺CD27⁺ Breg at all time points and significantly higher frequencies of CD24^{high}CD38^{high} Breg on day 0 (p = 0.004) and 28 (p = 0.012) in 2nd HBvac NR compared to 2nd HBvac R. In parallel, we observed significantly lower levels of CpG+P/I-induced IL-10 expression levels of CD24⁺CD27⁺ and CD24^{high}CD38^{high} Breg (d0: p < 0.0001; d7: p = 0.0004; d28: p = 0.0003 and d0: p = 0.016; d7: p = 0.016, respectively) in 2nd HBvac NR compared to 2nd HBvac R before and after booster immunization. Frequencies of CD24⁺CD27⁺ and CD24^{high}CD38^{high} Breg significantly decreased after third-generation hepatitis B booster vaccination (d7: p = 0.014; d28: 0.032 and d7: p = 0.045, respectively), whereas IL-10 expression levels of both Breg subsets remained stable. Sci-B-VacTM booster vaccination resulted in anti-HBs seroconversion (>10 anti-HBs IU/L) in 10/11 2nd HBvac NR subjects (90.9%). Anti-HBs levels on day 28 did not or correlated only moderate with pre-vaccination frequencies of CD24⁺CD27⁺IL-10⁺ (r_s = 0.083) or CD24^{high}CD38^{high}IL-10⁺ (r_s = 0.300) Breg.

Conclusion: Here we report significantly higher frequencies of CD24^{high}CD38^{high} Breg in parallel with significantly lower IL-10 expression levels of CD24⁺CD27⁺ and CD24^{high}CD38^{high} Breg in 2nd HBvac NR compared to 2nd HBvac R. Anti-HBs seroconversion accompanied by a decrease of Breg numbers after booster immunization with a third-generation hepatitis B vaccine could indicate a positive effect of third-generation hepatitis B vaccines on Breg mediated immunomodulation in hepatitis B vaccine non-responders.

PO-216

Liver resident Natural Killer cells are the dominant source of Fas ligand during chronic Hepatitis B virus mediated liver damage

Adrian Kuiper^{1,2}, Shirin Nkongolo¹, Deeqa Mahamed^{1,3}, Sam Kim⁴, Aman Mehrotra¹, Anjali Patel¹, Diana Chen⁴, Jordan Feld¹, Scott Fung¹, Jeffrey Wallin⁴, Anuj Gaggar⁴, Harry Janssen¹, Adam Gehring¹. ¹University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ²University of Toronto-St. George Campus, Immunology, Toronto, Canada; ³The Hospital for Sick Children, Centre for Advanced Single Cell Analysis, Toronto, Canada; ⁴Gilead Sciences, Inc., Foster City, United States
Email: adrian.kuiper@mail.utoronto.ca

Background and aims: Non-specific liver damage contributes significantly to disease progression during chronic Hepatitis B virus (HBV) infection. Soluble Fas ligand (FasL) is a secreted cytotoxic molecule that is associated with HBV-mediated liver inflammation in animal models and is elevated in the plasma during acute hepatitis B and in chronic hepatitis B (CHB) patients experiencing liver damage after stopping nucleoside analogue therapy. However, the intrahepatic cells responsible for FasL expression and its regulation are not well defined. The aim of our study was to identify the cells responsible for intrahepatic FasL expression to define which cell types may contribute to liver damage.

Method: Fifteen patients with chronic active hepatitis B were enrolled for this study. CHB patients started treatment with tenofovir alafenamide (TAF; 25 mg daily). Blood and liver fine-needle aspirates (FNAs) were collected at baseline, 12 weeks, and 24 weeks after starting therapy. Blood was analyzed for virological, chemical, and hematological parameters. Single-cell RNA sequencing (scRNAseq) was performed on cells collected from longitudinal liver FNAs from 5 patients to identify cells expressing FasL.

Results: Mean ALT at baseline was 6.4x the upper limit of normal (ULN) (range: 1.1–21.8 x ULN) and mean HBV-DNA was 2.5 x 10⁷ IU/ml (range: 1.9 x 10⁴–8 x 10⁷ IU/ml). After 24 weeks of TAF therapy, mean ALT was 0.8 x ULN (range: 0.4–1.3 x ULN) and mean HBV-DNA level was 77.65 IU/ml (range: 10.6–285 IU/ml). scRNAseq of liver FNAs revealed 32 cell populations. FasL transcriptional expression in all cells was highest at baseline. Intrahepatic expression of FasL decreased only 10% after 12 weeks of TAF therapy but declined by 54% at week 24, when ALT had normalized in almost all patients. At baseline, liver resident Natural Killer (NK) cells expressed the highest levels of FasL followed by liver resident CD8 T cells and granzyme K positive (GZMK+) CD8 T cells. In tissue resident NK cells, the expression of FasL was reduced by 41% by week 24, while FasL expression was reduced by 62.8% and 65.7% in tissue resident and GZMK+ CD8 T cells, respectively.

Conclusion: scRNAseq identified multiple populations that express FasL, with tissue-resident NK cells displaying the highest expression. Understanding the regulation of non-specific cytotoxic effectors, and the cell types responsible for their production, will provide greater insight into chronic hepatitis B pathogenesis.

PO-235

Combined PD-1 blockade plus IL-15 treatment restores HBV-specific CD8 T cell reactivity in short-term nucleos(t)ide analogue treated eAg chronic hepatitis B

Julia Peña Asensio^{1,2}, Henar Calvo^{2,3}, Joaquin Miquel^{2,3}, Eduardo Sanz de Villalobos^{2,3}, Alejandro González Praetorius^{2,4}, Miguel Torralba^{2,5,6}, Juan Ramón Larrubia^{2,3,6}. ¹University of Alcalá, Department of Biology of Systems, Alcala de Henares, Spain; ²Guadalajara University Hospital, Translational Hepatology Unit, Guadalajara, Spain; ³Guadalajara University Hospital, Section of Gastroenterology and Hepatology, Guadalajara, Spain; ⁴Guadalajara University Hospital, Section of Microbiology, Guadalajara, Spain; ⁵Guadalajara University Hospital, Service of Internal Medicine, Guadalajara, Spain; ⁶University of Alcalá, Department of Medicine and Medical Specialties, Alcala de Henares, Spain
Email: juan.larrubia@uah.es

Background and aims: Restoration of a reactive CD8 T cell response during eAg (-) chronic hepatitis B (eAg (-)CHB) treatment with nucleos(t)ide analogue (NUC) could lead to functional cure. Negative immunoregulatory checkpoint blocking could help in NUC mediated T cell restoration. PD-1 blockade could not be enough to restore exhausted T cells in short term (ST) treated cases due to the associated presence of mitochondrial impairment. IL-15 could reprogram mitochondrial fitness and favor exhaustion reversion.

Method: In HLA-A2+ NUC treated CHBeAg (-), (N = 46) and inactive carriers (IC), (N = 26) we checked for peripheral frequency and expansion ability of HBVcore18–27-specific CD8+ cells, according to NUC treatment duration (<78 months: ST; ≥78 months: long-term (LT)). We tested PGC1a, Glut1 and CPT1a after expansion in presence of either IL-2 or IL-15 in IC. In NUC treated CHBeAg (-) patients, we assessed the role of anti-PD-L1, IL-15 and both treatments together on T cell reactivity after Ag-specific in-vitro challenge. We visualized HBV-specific CD8T cells by flow-cytometric after staining with HLA-A2/peptide pentameric complexes.

Results: Ex-vivo frequency of HBVcore18–27 specific CD8 cells was higher in LT NUC treated cases than in IC and ST patients (p = 0.006). The expansion ability after Ag-specific in vitro challenge was preserved in all LT and in 75% IC but in only 50% of ST cases (p = 0.006). IL-15 increased PGC1a (p = 0.008) and CPT1a (p = 0.028) and decreased Glut1 (p < 0.05) expression on HBVcore18–27 specific CD8 T cells. The synergic effect of anti-PD-L1 plus IL-15 restored the T cell reactivity in all ST cases, while this effect was not observed with any of those treatments individually (p < 0.001).

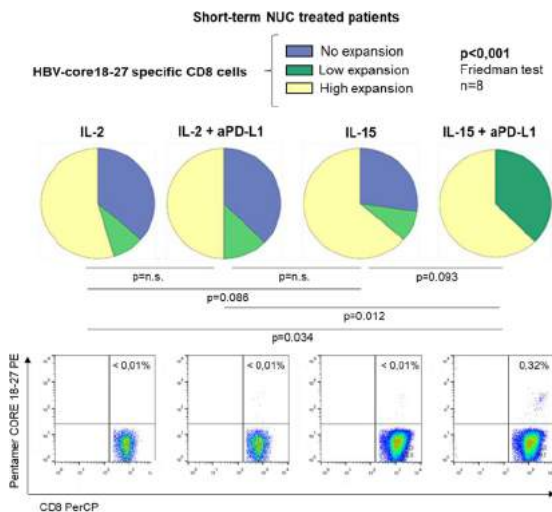


Figure: Pie charts describing the percentage of cases with peripheral HBV-core18-27 CD8+ T cells detectable after antigen encounter in short-term (<78months) nucleos(t)ide analogue treated patients according to in-vitro treatment with IL-2, IL-15, alone or combined with aPD-L1. Cytometry dot plots from a representative patient.

Figure:

Conclusion: LT treatment can restore the reactivity of HBV-specific CD8 T cell response. ST treatment does not reverse T cell exhaustion in 50% of cases. The blockade of the negative checkpoint PD1 in addition to the mitochondrial reprogramming by IL-15 is able to reestablish Ag-specific T cell reactivity in all ST. This combination could be considered as a potential strategy to achieve functional cure in NUC treated patients.

PO-240

Identification of a CD8 T cell population with a transcriptional profile consistent with non-specific hepatocyte killing in the inflamed human liver of chronic hepatitis B patients

Scott Fung¹, Diana Chen³, Anjali Patel¹, Anuj Gaggar³, Shirin Nkongolo¹, Sam Kim³, Aman Mehrotra¹, Jeffrey Wallin³, Harry Janssen¹, Jordan Feld¹, Deeqa Mahamed^{1,2}, Adam Gehring^{1,4}. ¹University Health Network, Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, Toronto, Canada; ²The Hospital for Sick Children, Centre for Advanced Single Cell Analysis, Toronto, Canada; ³Gilead Sciences, Foster City, United States; ⁴University of Toronto, Department of Immunology, Toronto, Canada
Email: Shirin.Nkongolo@uhnresearch.ca

Background and aims: While HBV-specific CD8 T cells contribute to viral clearance, non-specific CD8 T cell activation results in hepatocyte killing and tissue damage, driving disease progression to fibrosis and cirrhosis. It is not known if liver damage is driven by widespread CD8 T cell activation or whether damage is mediated by a specific sub-population of CD8 T cells. We analyzed longitudinal liver samples from chronic hepatitis B (CHB) patients using single-cell RNA sequencing (scRNAseq) with the aim of identifying the population of CD8 T cells responsible for non-specific hepatocyte killing.

Method: 15 CHB patients, who were not on antiviral treatment, with elevated alanine aminotransferase (ALT), were enrolled in this prospective study to receive tenofovir alafenamide (TAF) 25 mg daily. We collected blood and liver fine-needle aspiration (FNA) samples at baseline and after 12 and 24 weeks of TAF therapy. Blood was analyzed for virological markers, hematology, and clinical chemistry. Longitudinal liver FNAs from 5 patients were subjected to scRNAseq.

Results: Mean baseline ALT was 6.4×upper limit of normal (ULN) (range: 1.1–21.8) and mean HBV DNA at screening was 2.5 × 10⁷ IU/ml (range: 1.9 × 10⁴–8 × 10⁷). By week 24, ALT levels had decreased up to 21-fold and were normal or near-normal in all patients. HBV DNA had decreased up to 7 log₁₀-fold, with a maximum HBV DNA of 285 IU/ml. ScRNAseq analysis of liver FNAs at baseline revealed 32 clusters with 9 unique CD8 T cell populations. The largest CD8 T cell cluster displayed an activated immune signature (positive for CD27, CD38, HLA-DR, CD74, CD137, IL32, CD6) with a liver-resident phenotype. This population uniquely expressed high levels of IFN-gamma, known to drive antiviral immunity and mononuclear cell infiltration, and the cytotoxic effector Fas ligand. This population was enriched at baseline and showed the greatest change in differentially expressed genes as ALT levels normalized.

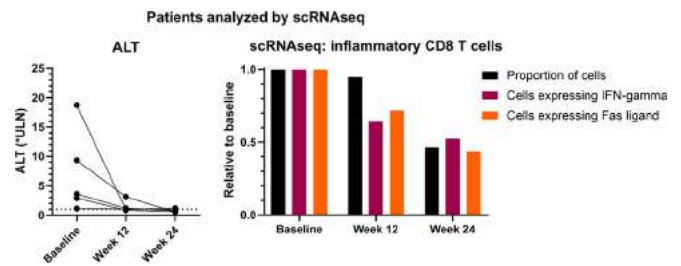


Figure:

Conclusion: Our data show that not all CD8 T cell populations are equally activated during chronic HBV-mediated liver inflammation. We identified an inflammatory CD8 T cell population that was

POSTER PRESENTATIONS

enriched at the time of liver damage, transcriptionally expresses mediators of inflammation and tissue damage, and whose activation profile declined as liver damage resolved under antiviral therapy—which may indicate that liver damage is driven by a polyclonal population of CD8 T cells resident within the liver.

PO-262

Blood-derived extracellular vesicles of patients with liver cirrhosis and acute-on-chronic liver failure display immunomodulatory functions

Mona-May Langer¹, Sabrina Guckenbiehl¹, Alina Bauschen¹, Christian M. Lange¹. ¹Gastroenterology and Hepatology, Essen, Germany
Email: mona-may.langer@uk-essen.de

Background and aims: Liver cirrhosis (LC) and acute-on-chronic liver failure (ACLF) lead to distinct changes regarding the cellular structure of the liver and the immune system. Cell-cell communication and interactions of different liver cell subtypes and immune cells play an important role during disease progression and complications (e.g. infections). Within the last years, the role of extracellular vesicles (EVs) as communicators between cells is raising more and more attention. We therefore aimed to characterize phenotype and function of EVs of LC patients with or without ACLF.

Method: A total of 84 patients with compensated or decompensated LC or ACLF were recruited from a monocentric, prospective cohort study. Blood of healthy donors was derived from discarded buffy coats. EVs were isolated from EDTA blood by precipitation and characterized regarding particle size and concentration by Nanoparticle Tracking Analysis (NTA). Surface markers were investigated using flow cytometry and protein as well as RNA content was analyzed using Western Blot, Mass Spectrometry and smallRNA Sequencing. For functional analysis, 20 µg blood-derived EVs were used to stimulate healthy donor peripheral blood mononuclear cells (PBMCs) which were then analyzed by flow cytometry or qPCR.

Results: EVs derived from LC and ACLF patients show lower expression of exosome-specific markers (e.g. CD9, CD81) and liver cell-specific markers (e.g. ASGPR1, CD163) compared to healthy donor EVs. Particle concentration in blood of patients decreased, whereas the average size increased with the severity of liver disease. In functional assays with PBMCs, blood-derived EVs of LC and to a stronger extend of ACLF patients lead to changes in the composition of immune cell populations, e.g. by downregulation of CD197 (lymph node-homing receptor) on T cells, increased amount of CD4⁺ TH2 cells or higher level of activated B cells (CD38⁺, HLA-DR⁺).

Conclusion: LC and ACLF patients have less differentiated EVs than healthy donors. The vesicles show immunomodulatory functions for example by leading to an increased amount of CD4⁺ and CD8⁺ effector memory T cells as well as changes in TH subpopulations.

PO-718

Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma: implications for immunotherapy

Sam Murray¹, Alejandro Forner^{2,3}, Takahiro Kaneko⁴, Petros Fessas⁵, Pierluigi Toniutto⁶, Beatriz Mínguez^{7,8}, Valentina Cacciato⁹, Claudio Avellini¹⁰, Alba Diaz¹¹, Rosemary J. Boyton¹², Daniel M. Altmann¹³, Robert D. Goldin¹⁴, Ayse U. Akarca¹⁵, Teresa Marafioti¹⁵, Francesco A. Mauri⁵, Edoardo Casagrande⁹, Federica Grillo¹⁶, Edoardo G. Giannini⁹, Sherrie Bhoori^{17,18}, Vincenzo Mazzaferro^{17,18}, David J. Pinato^{5,19}. ¹Imperial College London, Department of Infectious Disease, London, United Kingdom; ²Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; ³University of Barcelona, Hospital Clinic Barcelona, IDIBAPS, Barcelona, Spain; ⁴Tokyo Medical and Dental University, Tokyo, Japan; ⁵Imperial College London, Department of Surgery and Cancer, London, United Kingdom; ⁶University of Udine, Department of Medical Area (DAME), Udine, Italy; ⁷Universitat Autònoma de Barcelona, Liver Unit, Hospital

Universitari Vall d'Hebron, Barcelona, Spain; ⁸Liver Unit, Hospital Universitari Vall d'Hebron, CIBEREHD, Barcelona, Spain; ⁹University of Genoa, Department of Internal Medicine, Genoa, Italy; ¹⁰Azienda Ospedaliero-Universitaria "Santa Maria della Misericordia", Institute of Histopathology, Udine, Italy; ¹¹University of Barcelona, Pathology Department, Barcelona Clinic Liver Cancer (BCLC) Group, Barcelona, Spain; ¹²Imperial College London, Department of Infectious Disease, London, United Kingdom; ¹³Imperial College London, Department of Immunology and Inflammation, London, United Kingdom; ¹⁴Imperial College London, Centre for Pathology, London, United Kingdom; ¹⁵University College London Hospital, Department of Histopathology, London, United Kingdom; ¹⁶University of Genoa, Pathology Unit, Department of Surgical Sciences and Integrated Diagnostics, Genoa, Italy; ¹⁷University of Milan, Department of Oncology, Milan, Italy; ¹⁸Fondazione IRCCS Istituto Nazionale Tumori, Hepato-Pancreatic-Biliary Surgery and Liver Transplantation, Milan, Italy; ¹⁹Università degli Studi del Piemonte Orientale, Department of Translational Medicine, Italy
Email: sam.murray19@imperial.ac.uk

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 samples of patients who underwent surgery with (T+) or without (T-) prior-TACE treatment.

Method: We profiled intra-tumoural (IT), peri-tumoural (PT) and non-tumoural background tissue (NT) to evaluate regulatory CD4⁺/FOXP3⁺ (T-reg) and immune-exhausted CD8⁺/PD1⁺ T-cells across T⁺ (n = 58) and T⁻ (n = 61). We performed targeted transcriptomics and T-cell receptor sequencing in a restricted subset of samples (n = 24) evaluated 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.

Results: We analyzed samples from 119 patients resected (n = 25, 21%) or transplanted (n = 94, 79%) for Child Pugh A (n = 65, 55%) and TNM stage II (n = 73, 61%) HCC. T⁺ samples displayed lower IT CD4⁺/FOXP3⁺ (p = 0.006), CD8⁺ (p = 0.002) and CD8⁺/PD1⁺ (p < 0.001) and lower NT CD8⁺/PD1⁺ compared to T⁻. Lower IT (p = 0.005) and NT CD4⁺/FOXP3⁺ (p = 0.03) correlated with improved recurrence free survival (RFS), with IT CD4⁺/FOXP3⁺ density predicting for RFS benefit in multivariable analyses. In a subset of samples (12 T⁺, 12 T⁻), transcriptomic analysis revealed differential up-regulation of genes reflective of a pro-inflammatory response in T⁺. Compared to T⁻, T⁺ samples were significantly enriched for IRF2 expression (p = 0.01), an interferon-regulated transcription factor linked to immune-responsiveness in other malignancies. Expression PD-L1, IDO-1, CTLA-4, Lag-3, Tim-3 and CD163 was not different T⁺ versus T⁻. T-cell clonality by ImmunoSeq assay was not different in association with TACE pre-treatment.

Conclusion: Pre-treatment with TACE is associated by lower intra-tumoural density of immune exhausted effector and regulatory T-cells, with significant up-regulation of pro-inflammatory pathways. This highlights the pleiotropic effects of TACE in modulating the tumour microenvironment and strengthens the rationale for developing immunotherapy alongside TACE to improve outcomes of HCC patients.

PO-846

Chronic Hepatitis B inflammation gives rise to a novel macrophage population in the human liver

Juan Diego Sanchez^{1,2}, Shirin Nkongolo¹, Deeqa Mahamed^{1,3}, Sam Kim⁴, Aman Mehrotra¹, Anjali Patel¹, Diana Chen⁴, Jordan Feld¹, Scott Fung¹, Jeffrey Wallin⁴, Anuj Gaggar⁴, Harry Janssen¹, Adam Gehring^{1,2}. ¹University Health Network, Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, Toronto, Canada; ²University of Toronto, Department of Immunology, Toronto, Canada; ³The Hospital for Sick Children, Centre for Advanced Single Cell Analysis,

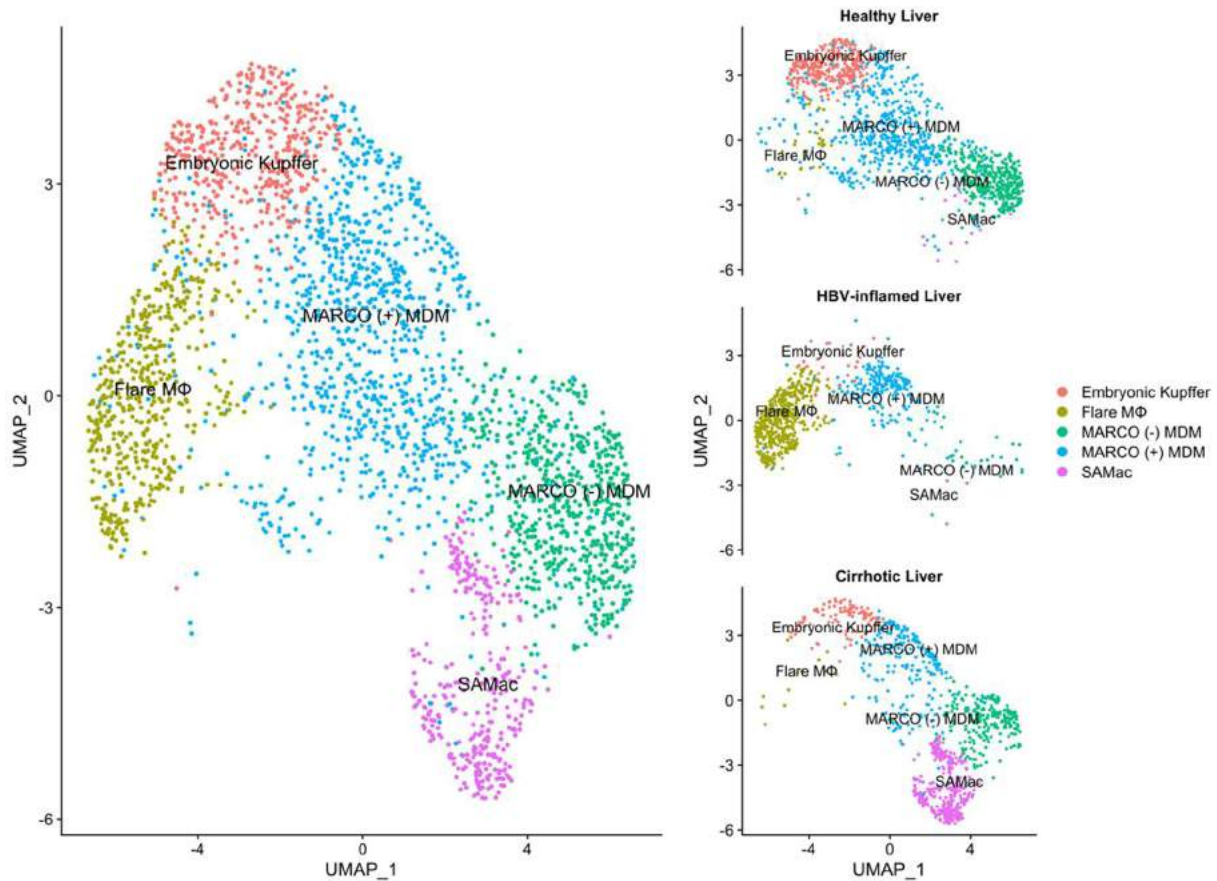


Figure: (abstract: PO-846)

Toronto, Canada; ⁴Gilead Sciences, Foster City, United States
 Email: jd.sanchezvasquez@mail.utoronto.ca

Background and aims: Kupffer cells are liver macrophages that maintain a tolerogenic environment. However, during inflammation, liver macrophage composition can change with the recruitment and differentiation of monocytes into inflammatory monocyte-derived macrophages. Preliminary data showed that markers of myeloid activation in the peripheral blood, such as CD163, Galectin-9 and IL-18, coincided with liver damage in chronic Hepatitis B (CHB) patients. The aim of our study was to determine if Hepatitis B virus (HBV)-mediated liver inflammation alters intrahepatic macrophage composition to propagate liver damage.

Method: In this study, 15 CHB patients with elevated alanine aminotransferase (ALT) and detectable viral load began treatment with tenofovir alafenamide (TAF). Liver fine-needle aspirates (FNAs) were collected prior to TAF therapy and weeks 12 and 24 of TAF treatment. Longitudinal FNAs from 5 patients were analyzed using scRNAseq of total liver FNA cells. Soluble plasma proteins were measured using the Luminex inflammatory panel. Liver macrophage subpopulations were identified in the HBV patient scRNAseq data and compared to macrophages from healthy and cirrhotic human livers.

Results: Luminex confirmed increased production of CD163, IL-18, and galectin-9 during peak of ALT levels which declined during TAF treatment. Macrophages were identified in the scRNAseq data by the expression of *CD68* and *C1QA*. A macrophage subpopulation was identified with markers of immune activation (*IL18*, *SPI1* and *MYD88*), interferon signaling (*IFIT3* and *IFI27*) and recent monocyte-to-macrophage differentiation (*MAFB* and *ZFP36L1*) which was confirmed by pseudotime trajectory analysis. Comparison of macrophage populations between the HBV infected liver to healthy and cirrhotic

human livers indicated that the inflammatory macrophage population was unique to the HBV infected liver. Inflammatory macrophages were distinguished from Kupffer cells by the expression of *LIPA*, *CTSL* and *TIMD4*.

Conclusion: Our results define a liver microenvironment during HBV-mediated inflammation that drives monocyte differentiation towards an inflammatory macrophage profile. The unique inflammatory macrophage population is distinct from Kupffer cells at the transcriptional level and has the potential to drive liver damage.

PO-896

Stimulation of Mucosal-associated invariant T (MAIT) cells by human serum derived from peripheral and portal blood

Martin Lett¹, Tina Jaeger¹, Maxime Jacquet¹, Christoph Zech², Magdalena Filipowicz Sinnreich^{1,3}. ¹University Hospital Basel, Department of Biomedicine, Basel, Switzerland; ²University Hospital Basel, Radiology and Nuclear Medicine, Basel, Switzerland; ³Basel University Medical Clinic, Liestal, Gastroenterology and Hepatology, Liestal, Switzerland
 Email: magdalena.filipowicz@unibas.ch

Background and aims: MAIT cells represent the most abundant T cells in human liver. They respond to bacterial metabolites derived from Riboflavin that are presented by MHC-like molecule MR1. The most potent stimulatory MAIT cell antigen (Ag) is the pyrimidine 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU). Recent mouse studies, showing that microbiota-derived Ag is necessary for intra-thymic development of MAIT cells, argue for 5-OP-RU absorption from the gut lumen. We investigated MAIT cell stimulatory Ags in human blood of healthy subjects and patients suffering from portal

POSTER PRESENTATIONS

hypertension to learn under which conditions Ags reach the circulation.

Method: We assessed MAIT cell stimulatory potential of serum derived from healthy subjects and 11 patients with a history of transjugular intrahepatic porto-systemic shunt stent (TIPSS). Portal and peripheral blood of six patients undergoing TIPSS was also analysed. Ag-presenting cells (K562 leukemia cells) overexpressing MR1 were exposed to serum and IFN- γ release by MAIT cells was measured by ELISA. MR1 blocking antibodies were used to assess MR1 dependence. To quantify amounts of Ag present in serum, control assays containing 0.006–25 pM 5-OP-RU were performed.

Results: We reproducibly measured MR1-dependent MAIT cell stimulation by sera obtained from all healthy subjects. When calculated as 5-OP-RU equivalents, serum concentration was in the range of 0.05–0.2 pM. Peripheral and portal sera of several TIPSS patients strongly stimulated IFN- γ production by MAIT cells (1–2 pM 5-OP-RU equivalent). In the remaining patients, portal serum was 1.7- to 3-fold more active than the peripheral counterpart. Patients with a history of TIPSS showed higher MAIT cell stimulatory potential than age- and sex-matched healthy control subjects.

Conclusion: We provide first evidence for the presence of MAIT cell stimulatory metabolites in human blood. Our results corroborate previous findings obtained in mice and provide rationale for the activated MAIT phenotype observed in human liver. Increased levels of gut-derived MAIT cell stimulatory ligands in portal and peripheral blood of TIPSS patients who suffer from portal hypertension, a condition associated with impaired intestinal barrier function, indicate that intrahepatic Ag-presentation may represent an important pathophysiological step in the development of liver disease.

PO-1333

Osteopontin expression identifies a subset of macrophages distinct from Kupffer Cells in the fatty liver

Anneleen Remmerie^{1,2}, Liesbet Martens^{1,2,3}, Tinne Thoné^{1,2,3}, Angela Castoldi⁴, Ruth Seurinck^{5,6}, Benjamin Pavie^{2,7}, Joris Roels^{5,6}, Bavo Vanneste^{1,2,3}, Sofie De Prijck^{1,2,3}, Mathias Vanhockerhout^{1,2,3}, Mushida Binte Abdul Latib^{1,2,3}, Lindsey Devisscher⁸, Anne Hoorens⁹, Johnny Bonnardel^{2,3}, Niels Vandamme^{5,6}, Anna Kremer^{2,7}, Peter Borghgraef^{2,7}, Hans Van Vlierberghe¹⁰, Saskia Lippens^{2,7}, Edward Pearce^{4,11}, Yvan Saeys^{5,6}, Charlotte L. Scott^{1,2}. ¹VIB-UGent Center for Inflammation Research, Laboratory of Myeloid Cell Biology in Tissue Damage and Inflammation; ²Ghent University, Department of Biomedical Molecular Biology; ³VIB-UGent Center for Inflammation Research, Laboratory of Myeloid Cell Biology in Tissue Homeostasis and Regeneration; ⁴Max Planck Institute of Immunobiology and Epigenetics; ⁵VIB-UGent Center for Inflammation Research, Data Mining and Modelling for Biomedicine; ⁶Ghent University, Department of Applied Mathematics; ⁷VIB-UGent Center for Inflammation Research, VIB BioImaging Core; ⁸Ghent University, Department of Basic and Applied Medical Sciences; ⁹Ghent University Hospital, Department of Pathology; ¹⁰Ghent University Hospital, Department of Gastroenterology and Hepatology; ¹¹University of Freiburg
Email: charlotte.scott@irc.vib-ugent.be

Background and aims: Metabolic-associated fatty liver disease (MAFLD) represents a spectrum of disease states ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Despite the high prevalence of MAFLD, we still do not understand the mechanisms driving the progression to NASH. Hepatic macrophages (MFs) are suggested to play important roles in driving this, however the exact roles they play and the specific contributions of resident Kupffer cells (KCs) vs other hepatic MFs remains unclear.

Method: Using CITE-seq analysis with the 10X genomics platform coupled with multi-parameter flow cytometry, confocal microscopy and lipidomics, we examined the hepatic MF populations during the

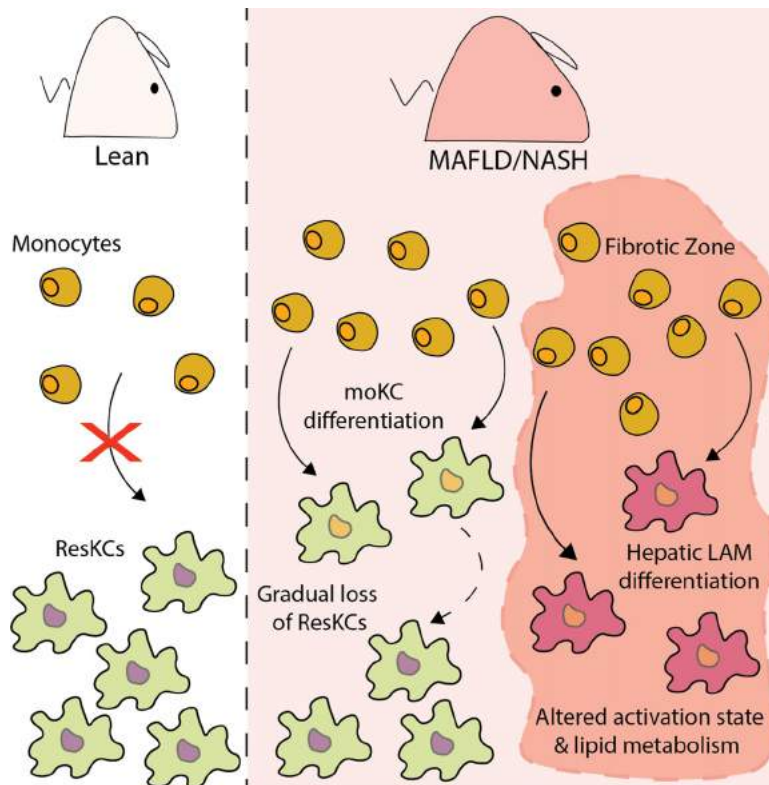


Figure: (abstract: PO-1333)

different stages of NAFLD, induced by feeding mice a Western diet (WD) or a Standard diet (SD) for 12, 24 or 36 weeks.

Results: Mice fed the WD for 24 and 36 weeks were found to harbor a reduced population of CLEC4F⁺TIM4⁺ resident KCs compared with controls. In addition, we also observed the significant recruitment of CLEC4F⁻ MFs and CLEC4F⁺TIM4⁻ KCs, which developed from bone marrow monocytes. While, contrary to the current hypothesis, resident KCs were not found to be activated in MAFLD and the CLEC4F⁺Tim4⁻ recruited KCs had a very similar profile to their resident counterparts, the CLEC4F⁻ MFs were found to have a very distinct activation and lipidomics profile. CLEC4F⁻ MFs expressed genes characteristic of lipid-associated MFs in obese adipose tissue and fibrotic MFs in the human liver. Moreover, they expressed the chemokine osteopontin, which has previously been associated with the progression to NASH. Notably, CLEC4F⁻ MFs were found to be localised in zones of established steatosis, which were largely devoid of KCs.

Conclusion: Taken together, our data highlight significant heterogeneity within the MF pool and suggest a need for more specific MF targeting strategies in MAFLD.

PO-1460

Harnessing liver-resident gamma delta T cells for immunotherapy of hepatocellular carcinoma

Nekisa Zakeri¹, Leo Swadling¹, Laura J. Pallett¹, Nathalie M. Schmidt¹, Mariana O. Diniz¹, Stephanie Kucykowicz¹, Oliver E. Amin¹, Amir Gander², Massimo Pinzani³, Brian R. Davidson², Mala K. Maini¹.
¹Division of Infection and Immunity, University College London, United Kingdom; ²Division of Surgery and Interventional Science, Royal Free London NHS Foundation Trust, United Kingdom; ³Institute for Liver and Digestive Health, Royal Free London NHS Foundation Trust, United Kingdom

Email: n.zakeri@ucl.ac.uk

Background and aims: Gamma delta ($\gamma\delta$) T cells are promising candidates for cancer immunotherapy, due to their potent cytotoxicity, tissue localisation, and MHC-unrestricted antigen recognition offering exciting potential for future pan-population immunotherapies. We characterised liver and tumour infiltrating $\gamma\delta$ T cells in hepatocellular carcinoma (HCC), and explored whether modulating features of $\gamma\delta$ T cell tissue-residency could provide a novel immunotherapeutic approach for HCC.

Method: Using multiparameter flow cytometry, we analysed lymphocytes isolated from paired peripheral blood, tumour-free liver tissue, and tumoural tissue resected from patients with HCC (n = 26), in comparison to colorectal cancer liver metastases (n = 28), and blood from healthy controls. Long-lived persistence of intrahepatic $\gamma\delta$ T cells was examined using donor and recipient HLA-mismatched liver allografts obtained 7–11 years post liver transplantation. Peripheral blood expanded V γ 9V δ 2T cells, intrahepatic lymphocytes, and tumour-infiltrating lymphocytes, were co-cultured with human hepatoma cell-lines (HepG2 and HuH7), pre-treated with the aminobisphosphonate Zoledronate to promote tumour cell phosphoantigen accumulation for V γ 9V δ 2T cell receptor activation.

Results: $\gamma\delta$ T cells were able to acquire a tissue-resident memory (T_{RM}) phenotype (CD69+CD49a+) in the liver, absent from blood, with a distinct functional profile (higher IFN γ , IL-2 expression). Examining donor and recipient HLA-mismatched liver allografts, $\gamma\delta$ T_{RM} cells demonstrated long-lived tissue-compartmentalised persistence in the liver and could be replenished from the circulation, an attractive profile to recapitulate with immunotherapy. A subset of $\gamma\delta$ T cells, V γ 9V δ 2T cells, were reduced in frequency in HCC livers (p < 0.001) and tumours (p < 0.01), but displayed the highest capacity to acquire an intra-tumoural $\gamma\delta$ T_{RM} phenotype. A *de novo* T_{RM} phenotype (CD69+CD49a+) with increased liver-homing chemokine receptor expression (CXCR6+ CXCR3+) could be recapitulated by expanding blood

V γ 9V δ 2T cells *in vitro* using clinically-approved Zoledronate and IL-2. Furthermore, direct priming of HCC cell-lines with Zoledronate increased the anti-tumour effector function (IFN γ , CD107a) of co-cultured expanded V γ 9V δ 2T cells, as well as V γ 9V δ 2 T_{RM} cells isolated from HCC livers and tumours, with increased tumour-cell lysis.

Conclusion: Intrahepatic $\gamma\delta$ T_{RM} cells demonstrate long-lived immunotherapeutic properties for HCC. We show that aminobisphosphonates such as Zoledronate can enhance the efficacy of $\gamma\delta$ T cell immunotherapy in HCC, via two mechanisms: direct delivery to the tumour increases V γ 9V δ 2 T_{RM} cells anti-tumour function, whilst *in vitro* expansion of blood V γ 9V δ 2T cells for adoptive cell transfer confers *de novo* liver-homing tissue-residency to achieve long-lived local tumour immunosurveillance.

PO-1472

CD4 T cell tolerance induced by nanoparticle-mediated autoantigen delivery to liver sinusoidal endothelial cells depends on interferon-gamma

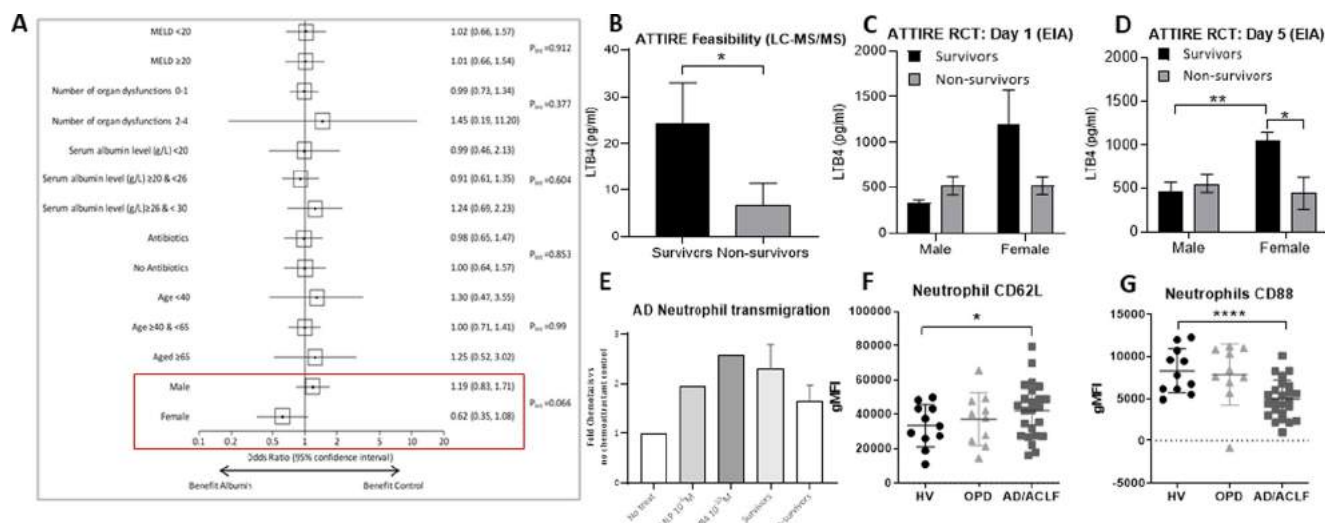
Daria Krzikalla¹, Disha Mungalpara², Reinaldo Digigow², Muharrem Selici², Dorothee Schwinge¹, Christoph Schramm¹, Ansgar Lohse¹, Antonella Carambia¹, Johannes Herkel¹.
¹Department of Medicine I, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ²Topas Therapeutics GmbH, Hamburg, Germany
 Email: d.krzikalla@uke.de

Background and aims: Targeted gene expression of myelin basic protein (MBP) in hepatocytes can induce MBP-specific CD4 T cell tolerance and prevent MBP-driven neuroinflammation in experimental autoimmune encephalomyelitis (EAE). The induction of tolerance depended on IFNG-CXCL9-CXCR3-mediated accumulation of autoreactive T cells in the liver and upregulation of CTLA-4 (EASL Abstract in: Journal of Hepatology 2020; Vol. 73, S82). Alternatively, MBP-specific CD4 T cell tolerance and suppression of EAE can be induced by delivery of MBP peptides to liver sinusoidal endothelial cells (LSECs) via nanoparticles (NP). Yet, it is unclear whether hepatic tolerance mechanisms as those activated by gene targeting to hepatocytes.

Method: B10.PL mice were immunised to MBP and injected with unloaded or MBP-loaded NP (MBP-NP). One day later, CD45.1- MBP-specific tg4 T cells were adoptively transferred into the CD45.1+ recipients. Additionally, mice received blocking IFNG antibody or isotype control. The transferred tg4 T cells were re-analysed *ex vivo* by flow cytometry on day seven after immunisation. Moreover, the clinical EAE course was monitored.

Results: Upon MBP peptide-delivery to LSECs via NP, the transferred tg4 T cells accumulated in livers of immunised mice, but not in livers of control mice. Analysis of hepatic tg4 T cells revealed an increased frequency of IFNG producers in MBP-NP-treated mice, suggesting that transmigration of tg4 T cells into the liver was dependent on the IFNG-CXCL9-CXCR3 axis. Indeed, hepatic *Cxcl9* and *Cxcr3* expression were induced in MBP-NP-treated mice. Moreover, hepatic tg4 T cells showed upregulation of CTLA-4 in MBP-NP-treated mice as compared to controls. *In vivo* inhibition of IFNG via blocking antibody prevented migration of tg4 T cells into the liver and decreased their expression of CTLA-4. Strikingly, *in vivo* blockade of IFNG completely abolished tolerance to MBP in MBP-NP-treated mice resulting in clinical EAE.

Conclusion: These results demonstrate that protection from autoimmune disease by autoantigen-delivery to LSECs is dependent on the induction of the IFNG-CXCL9-CXCR3 axis and upregulation of CTLA-4 on autoreactive T cells. Thus, these mechanisms are similar to those induced by hepatic autoantigen gene transfer, suggesting that LSEC-controlled transmigration of autoreactive lymphocytes into the liver parenchyma is essential for NP-mediated tolerance.



A) Statistics analysis of all re-randomised controlled trial (RCT) patients (828) in the ATTIRE trial. Data presented at British Association for the study of the liver Annual Meeting 2020 by A. O'Brien. B) Leukotriene B4 levels in human plasma from AD/ACLF patients in the ATTIRE Feasibility study at day 1 (n=5 per group) measured using LC-MS/MS. Results expressed as pg/mL, mean ± SEM. Leukotriene B4 levels in human plasma from AD/ACLF patients in the ATTIRE RCT on day 1 (C) and 5 (D) measured using ELISA according to gender (n=4-5 per group), with results expressed as pg/mL, mean ± SEM. Two-tailed unpaired Mann-Whitney test performed. E) Neutrophil Transmigration assay using Transwells® chambers with 50% v/v plasma of AD/ACLF patients from survivors (n=3) and non-survivors group (n=3). Results presented as fold change relative to no treated condition and conditions tested and shown as mean ± SEM. (F) and (G) Flow cytometry analysis of CD62L and CD88 expression, respectively, on blood derived neutrophils from HV (n=11), stable liver outpatients (n=10) and AD/ACLF (n=24) patients, mean ± SD. One-way ANOVA with Tukey multiple comparisons test performed. *p<0.05 and **p<0.01, ****p<0.0001.

Figure: (abstract: PO-1472)

PO-1598
Investigating the potential association of elevated plasma Leukotriene B4 and survival in females in the ATTIRE trial

Thais H. Tittanegro¹, Alexander Maini¹, Louise China¹, Natalia Becares¹, Nicholas Freemantle², Alastair O'Brien¹. ¹University College London, Institute for Liver and Digestive Health, London, United Kingdom; ²University College London, Comprehensive Clinical Trials Unit, London, United Kingdom
 Email: a.o'brien@ucl.ac.uk

Background and aims: Infection is a major cause for hospitalisation in patients with decompensated cirrhosis secondary to immune dysfunction. The ATTIRE trial (Albumin To prevent Infection in chronic liver failure) that used targeted albumin infusions to prevent infection, renal dysfunction and death had an overall null effect, however, post-hoc subgroup analyses suggest that there may be a differential effect according to gender, with perhaps some evidence of benefit in women. Leukotriene formation by androgens has been proposed as a molecular basis for gender differences in the immune response, with lower levels in men. We previously observed elevated Leukotriene B4 (LTB4) in acute decompensation/Acute-on-chronic Liver Failure (AD/ACLF) patients and investigated this neutrophil chemoattractant eicosanoid further.

Method: Using ATTIRE plasma samples from both the feasibility and randomized controlled trial (RCT), LTB4 was measured using *in vitro* Enzyme Immunoassay (EIA) kits and mass spectroscopy. Neutrophil transmigration profile was assessed with Transwell™ chambers using healthy neutrophils in the presence of LTB4 or ATTIRE patients' plasma. Flow Cytometric (FACs) analyses of neutrophils were performed using samples from a separate cohort of healthy

volunteers (HV), outpatients with ascites (OPD) and hospitalized AD/ACLF patients.

Results: Analyses revealed a significant association between elevated plasma LTB4 and improved outcome that was only observed in women. Moreover, we found that addition of LTB4 as a chemoattractant to healthy neutrophils increased neutrophil transmigration to a similar degree as addition of ATTIRE trial survivors' plasma, with less transmigration seen when non-survivors' plasma was used. FACS analyses identified a progressive increase in the neutrophil adhesion molecule, L-selectin (CD62L) according to liver disease severity (p < 0.05), coupled with a progressive reduction in CD88 expression compared to OPDs and HVs (p = 0.0002), suggesting that, although activated, AD/ACLF neutrophils have reduced phagocytosis.

Conclusion: We show an association between increased LTB4 in AD/ACLF females and improved survival in samples from two separate studies. Transmigration and FACs findings support the notion that this may be related to increased neutrophil transmigration to the site of infection in these patients. This association of elevated LTB4 with survival is in contrast to non-cirrhotic inflammatory conditions where increased LTB4 is implicated in increased susceptibility to sepsis. We hypothesise that elevated levels of LTB4 lead to increased neutrophil transmigration to infection sites that overcomes the cellular functional defect and effectively combats infection, underlying this association with improved outcome. Further studies are required to investigate this.

PO-1649

Acute liver injury results in temporal changes in hepatic macrophage pool

Anna Bujko¹, Liesbet Martens¹, Tinne Thoné¹, Djoere Gaublumme¹, Anneleen Remmerie¹, Johnny Bonnardel¹, Bavo Vanneste¹, Tineke Vanhalewyn¹, Mushida Binte Abdul Latib¹, Mathias Vanhockerhout¹, Sofie De Prijck¹, Dirk Elewaut¹, Charlotte L. Scott¹. ¹VIB-UGent Center for Inflammation Research, Ghent, Belgium
Email: anna.bujko@irc.vib-ugent.be

Background and aims: In recent years it has become clear that inflammation results in recruitment of monocytes to the liver which differentiate into short-lived macrophages (moMacs) distinct from Kupffer cells (KCs). However, we and others have also shown that under some circumstances these recruited monocytes also have the capacity to differentiate into long-lived monocyte-derived Kupffer cells (moKCs). However, the mechanisms dictating monocyte fate upon entry into the inflamed liver remain to be determined. One hypothesis recently put forward is that resident macrophages that have resided for prolonged periods of time in a homeostatic environment such as KCs would not be plastic enough to respond to injury. Thus one possibility is that the need for an activated KC population would drive moKC development. Here we set out to characterise and phenotype the distinct populations of macrophages present in the liver after paracetamol overdose-induced injury and determine the KC and monocyte responses to this insult.

Method: To study the different populations present in the liver during acute liver injury and repair and their activation status, we have performed CITE-Seq and spatial transcriptomics (Visium) analysis using the 10X genomics platform at various time points after paracetamol overdose. These transcriptomic analyses were further complemented with multi-parameter flow cytometry and confocal and intravital microscopy to identify and localize the distinct myeloid cell subsets present at various time points post paracetamol overdose.

Results: We identified two distinct subsets of macrophages CLEC4F⁺ KCs and CLEC4F⁻ macrophages. BM chimeras and lineage tracing studies revealed that CLEC4F⁻ macrophages were derived from the BM, were only transiently present in the liver and unlike in NAFLD, these did not further differentiate into moKCs. Attempts to localize these populations by confocal microscopy revealed additional heterogeneity within the KC pool, with phenotypically distinct KCs being located in healthy and damaged tissue, where they surrounded the recruited macrophages. We are currently investigating mechanisms behind the emergence of these populations and their functional consequences.

Conclusion: Monocytes infiltrating the liver after paracetamol overdose do not become moKCs. However, resident KCs are plastic enough to respond to the injury, with those closest to the damaged tissues being activated after paracetamol overdose-induced liver injury.

PO-1653

Sustained delivery of IL-10 using innovative cell-based platform for immune-mediated hepatitis

Sofia Brites Boss¹, Tiffany Vo¹, Jie Li¹, Janet Huang¹, Lauren Jansen¹, David Peritt¹, Hozefa Bandukwala¹. ¹Sigilon Therapeutics, Cambridge, United States
Email: sofia.bboss@sigilon.com

Background and aims: Autoimmune hepatitis (AIH) results from a breakdown in immune tolerance leading to production of pro-inflammatory cytokines by autoreactive T-cells and subsequent hepatocyte destruction. While AIH patients benefit from immunosuppressive agents, the life-long systemic administration often leads

to serious adverse effects and associated morbidities. Immunomodulatory cytokines, such as IL-10, are well established preclinically to treat autoimmune diseases including AIH. However, while these cytokines have high potency, they have an extremely short half-life, making it challenging to treat with the protein therapeutic. Thus, new approaches are essential for this treatment modality to be beneficial to patients. We hypothesized that the sustained low-dose treatment with immunomodulatory cytokines delivered using an innovative cell-based modular platform could restore immune homeostasis providing a functional cure for this disease. The platform consists of genetically modified allogeneic human cells engineered to produce the therapeutic protein of interest, encapsulated in a two-compartment hydrogel sphere. The use of implanted allogeneic cells, gene modified to express the cytokine transgene, has several potential safety advantages over other therapeutic modes. However, one of the major challenges of such therapies is protection from the host's immune system. While hydrogels can provide a physical barrier to allogeneic cells, they themselves can elicit an immune response which results in build-up of pericapsular fibrotic overgrowth (PFO), leading to cell death and inadequate therapy duration. Sigilon's two-compartment hydrogel sphere supports the function of cells (inner compartment) and shields the cells from the host's immune system and PFO (outer layer) (Barney ASGCT 2020, Bochenek Nat Biomed Eng 2018).

Results: First, we engineered allogeneic cells to produce active IL-10 in vitro. Second, the cells were efficiently encapsulated in the two-compartment hydrogel spheres and shown to produce functional IL-10. Next, the spheres were administered intraperitoneally (IP) in mice, and we observed sustained delivery of IL-10 which resulted in in vivo differentiation of peritoneal macrophages towards the immunomodulatory M2 phenotype marked by increased expression of CD206. Furthermore, we demonstrated that synthetic steroids can be co-encapsulated with IL-10 producing cells, enabling localized combination therapy approach. Finally, sustained IL-10 production alone or in combination with a synthetic steroid resulted in protection of mice from acute liver injury induced by Concanavalin A. **Conclusion:** Collectively our data demonstrate that localized and sustained IP administration of IL-10 with or without corticosteroids can provide a new, potentially safer, and more effective modality for the treatment of inflammatory liver diseases.

PO-1929

Discovery of conserved HDV-specific CD8+ T-cell epitopes in HDV/ HBV co-infection

Valerie Oberhardt^{1,2}, Maïke Hofmann¹, Robert Thimme¹, Christoph Neumann-Haefelin¹. ¹University Hospital Freiburg, Department of Internal Medicine II, Germany; ²University of Freiburg, Faculty of Biology, Germany
Email: christoph.neumann-haefelin@uniklinik-freiburg.de

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. The virus-specific CD8+ T-cell response is thought to have a major impact on the outcome of HDV infection. However, the HDV-specific T-cell epitope repertoire is only poorly characterized and mechanisms contributing to T-cell failure during chronic infection are not yet fully understood. Previously, we identified HDV-specific CD8+ T-cell epitopes in regions of the large hepatitis D antigen (L-HDAg) in which HDV tolerates mutations to escape immune recognition. In this study, we aimed to discover T-cell epitopes that are located in conserved regions, in order to characterize the influence of these T cells on infection outcome.

Method: PBMC from 19 chronic and 15 resolved HBV/HDV co-infected patients were stimulated with an overlapping peptide (OLP)

POSTER PRESENTATIONS

pool covering L-HDAg. After *in vitro* expansion virus-specific CD8+ T cells were detected by intracellular cytokine staining and responses were HLA-allele fine-mapped. Tetramers were generated for phenotypic characterization of HLA-B*08:01 restricted HDV-specific CD8+ T cell in six HLA-B*08+ patients.

Results: Interferon gamma (IFN γ) secretion of CD8+ T cells in response to peptide pool re-stimulation was detected in 52.6% of HDV RNA+ patient, whereas 66.6% of HDV RNA–patients responded to at least one peptide pool. OLP-specific CD8+ T cells predominantly co-secreted IFN γ and tumor necrosis factor (TNF). Interestingly, novel epitopes were exclusively restricted by rare HLA-B alleles. Of note, one HLA-B*08:01-restricted epitope was highly conserved in the L-HDAg of genotype 1. High-dimensional flow cytometry analyses revealed that HDV-specific CD8+ T cells restricted by this conserved epitope displayed phenotypical and functional features of T-cell exhaustion. Exhaustion traits were partially associated with HDV infection control.

Conclusion: In conclusion, we were able to further expand the HDV-specific-CD8+ T-cell epitope repertoire. The detection rate of HDV-specific CD8+ T cells was similar in chronic and resolved HBV/HDV co-infected patients. Analyses of HDV-specific CD8+ T cells restricted by an epitope not subjected to viral escape mutations indicate that T-cell exhaustion might play a key role in infection control.

PO-1983

HLA-B*27-restricted CD8+ T-cell response against hepatitis B virus: viral escape as central mechanism of T-cell failure

Elahe Salimi Alizei¹, Muthamia M. Kiraithe¹, Tatjana Schwarz², Emma Gostick³, John Sidney⁴, Matthias Marget⁵, Markus Cornberg⁶, Julia Lang¹, Phillipp Ehrenmann¹, Janine Kemming¹, Florian Emmerich⁷, Alessandro Sette⁴, David Price³, Tobias Böttler¹, Jörg Timm², Maike Hofmann¹, Robert Thimme¹, Christoph Neumann-Haefelin¹. ¹University Hospital Freiburg, Department of Medicine II, Freiburg, Germany; ²Heinrich-Heine-University, Institute for Virology, Düsseldorf, Germany; ³Cardiff University School of Medicine, Institute of Infection and Immunity, Cardiff, United Kingdom; ⁴La Jolla Institute for Allergy and Immunology, La Jolla, United States; ⁵University Hospital Hamburg-Eppendorf, Institute of Transfusion Medicine, Hamburg, Germany; ⁶Hannover Medical School, Department of Gastroenterology, Hepatology, and Endocrinology, Hannover, Germany; ⁷University Hospital Freiburg, Institute of Transfusion Medicine and Gene Therapy, Freiburg, Germany
Email: elahe.salimi.alizee@uniklinik-freiburg.de

Background and aims: Virus-specific CD8+ T cells play a major role in the control and clearance of HBV infections; however, the mechanisms of CD8+ T-cell failure in chronic hepatitis B (cHBV) infection have only been partially elucidated, especially the role of viral escape. Since viral escape has been demonstrated in HCV and HIV infection in the context of HLA-B*27, we speculated that HLA-B*27 may also have a dominant role in driving viral escape in HBV infection.

Method: Through HLA footprint analysis of 17 HLA-B*27 positive and 97 HLA-B*27 negative patients with cHBV genotype D infection and *in silico* epitope prediction, HLA-B*27-restricted HBV-specific CD8+ T-cell epitopes were identified. Candidate epitopes were validated by antigen-specific *in vitro* expansion. Sequence variations in epitopes found through footprint analysis were analyzed for viral escape in cHBV infected patients. Phenotypic analysis of CD8+ T cell was performed by *ex vivo* pMHC tetramer enrichment.

Results: 12 (5 by *in silico* prediction; 7 by footprint analysis) HLA-B*27-restricted HBV-specific CD8+ T-cell epitopes were identified. Epitopes identified by footprint analysis were preferentially targeted in cHBV, while epitopes identified by *in silico* prediction were targeted in both, acute-resolving and cHBV infection. Notably, we were able to detect viral escape mutations in 6 cHBV infected

patients. The *ex vivo* frequencies of HLA-B*27-restricted HBV-specific CD8+ T cells targeting conserved epitopes and epitopes with viral escape mutations were similar. The non-naïve CD8+ T-cell population targeting conserved and variant epitopes showed both a less differentiated memory-like phenotype characterized by co-expression of PD1 and CD127. The expression level of transcription factors TOX, TCF1 and Tbet were similar in HBV-specific CD8+ T cells targeting conserved epitopes and epitope with viral escape. Interestingly, Eomes and KLRG1 were expressed significantly higher in CD8+ T cells targeting conserved epitopes compared to CD8+ T cells targeting epitopes with escape mutations, indicating a more exhausted phenotype of CD8+ T cells targeting wildtype epitopes.

Conclusion: cHBV and acute-resolving HBV infected patients exhibited a different CD8+ T-cell repertoire, which may have further effects on HBV chronicity. Moreover, viral escape may play an important role in the failure of HBV-specific CD8+ T cell responses and may particularly affect CD8+ T-cell epitopes that are targeted during chronic infection only.

PO-2154

Characterization of in-vitro responses to different immune modulation of HBV core18-specific vs HBV pol455-specific CD8+ T cells

Elmira Aliabadi^{1,2,3}, Helena Lickei^{1,2,3}, Carola Mix^{1,2}, Heiner Wedemeyer^{1,2}, Anke Kraft^{1,2,3}, Markus Cornberg^{1,2,3,4}.

¹Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²German Centre for Infection Research (Deutsches Zentrum für Infektionsforschung DZIF), Partner Site Hannover-Braunschweig, Hannover, Germany; ³TWINCORE, Centre for Experimental and Clinical Infection Research, a Joint Venture between the Hannover Medical School (MHH) and the Helmholtz Centre for Infection Research (HZI), Hannover, Germany; ⁴Centre for Individualized Infection Medicine (CiM), c/o CRC, Hannover, Germany
Email: aliabadi.elmira@mh-hannover.de

Introduction and aim: Several new therapeutic strategies are being developed aiming at functional cure (HBsAg loss) of chronic HBV infection (CHB). Restoration of exhausted HBV-specific T cells is a potential option to modulate immune responses and achieve higher rates of HBsAg loss. Recently, it has been reported that T cells targeting different HBV epitopes (core₁₈ versus pol₄₅₅) can be phenotypically and functionally different. However, data are lacking on whether core- or pol-specific T cells respond differently to checkpoint inhibition or/and IL-12 and to what extent the HBsAg level influences this response.

Methods: Peripheral blood mononuclear cells from 35 HLA-A2+ CHB patients were isolated. Patients were categorized as HBsAg high (>10,000 IU/ml) or low (<100 IU/ml). Core₁₈- and pol₄₅₅-specific T cells were phenotypically characterized using pMHC I dextramer based enrichment. The function and the restoration capacity of epitope-specific T cells were measured after *in-vitro* culture of PBMCs with core₁₈ and pol₄₅₅ peptides with or without α -PDL-1 or/and IL-12. Intracellular cytokine assay was used as functional readout.

Results: Core₁₈- and pol₄₅₅-specific CD8+ T cells showed different phenotypes, with core₁₈-specific CD8+ T cells exhibiting higher functionality and a higher proportion of a memory-like phenotype. *In-vitro* treatment with anti-PDL-1 treatment showed a significant increase in IFN γ by pol₄₅₅-specific CD8+ T cells only in patients with HBsAg <100 IU/ml while there was no effect on core₁₈-specific CD8+ T cells. The effect of IL-12 alone or in combination with anti-PDL-1 was stronger compared with anti-PDL-1 alone. Importantly, IL-12 with or without anti-PDL-1 significantly increased core₁₈-specific IFN γ responses only in patients with HBsAg >10,000 IU/ml. The effect of IL-12 with or without anti-PDL-1 in enhancing the IFN γ expression of

pol₄₅₅-specific CD8⁺ T cells was significant in patients with low and high HBsAg levels but also more pronounced in patients with HBsAg >10, 000 IU/ml.

Conclusion: Our data confirmed previous studies that core₁₈- and pol₄₅₅-specific CD8⁺ T cells are phenotypically and functionally different. Furthermore, we showed that the response of HBV-specific T cells to different immune modulations varies depending on the targeted antigens and the HBsAg levels. These results have potential implications for developing immunotherapeutic approaches to achieve functional cure of CHB.

PO-2173

Treatment with GSK3228836 leads to HBsAg reduction and induction of interferon gamma related proteins and chemokines in a Phase 2a, randomized, double-blind, placebo-controlled study

Shihyun You¹, Jennifer Singh¹, Susan Smith¹, William Jordan¹, Katja Remingler², Shilpy Joshi¹, Megan Ermler¹, Jared Delahaye¹, Adam Taylor³, Suthirtha Chakraborty⁴, Dhyanesh Srivastava⁵, Melanie Paff¹, Dickens Theodore². ¹GlaxoSmithKline, Collegeville, PA, United States; ²GlaxoSmithKline, Research Triangle Park, NC, United States; ³GlaxoSmithKline, Stevenage, United Kingdom; ⁴GlaxoSmithKline, Bangalore, India; ⁵GlaxoSmithKline, Noida, India
Email: shihyun.k.you@gsk.com

Background and aims: GSK3228836 (GSK836) is a modified antisense oligonucleotide (ASO) targeting all HBV RNAs that has demonstrated rapid reductions in HBsAg and HBV DNA with four weeks of therapy in chronic hepatitis B (CHB) patients (Study: NCT02981602). The aim of this post-hoc analysis was to investigate the correlation of systemic biomarkers with antiviral responses of GSK836.

Method: The analysis is focused on treatment-naïve and nucleos (t) ide treated patients with CHB randomized (3:1) to receive GSK836 (150 mg or 300 mg) or placebo subcutaneously on Days 1, 4, 8, 11, 15, and 22. Treatment responses were monitored until Day 211. Longitudinal plasma samples collected at Days 0, 1, 2, 8, 15, 22, 23, 36, 57, 85, 113, and 211 were used to evaluate 251 soluble proteins in a multiplexed immunoassay (Myriad Discovery Map v3.3). For each protein, a generalized linear mixed effects model was fit to compare the changes from baseline between groups at each timepoint. Mean fold changes and p values generated from these analyses were used for pathway analyses and visualizations. We analyzed associations between GSK836 treatment, HBsAg decline, ALT elevation, and soluble proteins and then delineated potential cellular pathways associated with the responses.

Results: Within a day of GSK836 treatment, we observed a trending dose dependent change of plasma proteins related to tissue remodeling and immune responses such as collagen IV and IFNgamma. Of the 17 patients receiving 300 mg GSK836, 7 patients showed >2 log decline in HBsAg at day 29 and also demonstrated ALT elevation peaking around week 5. During the timecourse of HBsAg decline or elevation of ALT, inductions of various soluble immune mediators such as MCSF, MIP1b, IgM, IP10, and MIG were observed, suggestive of the activation of innate and adaptive T and B cell responses. Three patients showed <0.2 log decline in HBsAg and no ALT elevation. In these non-responders, the markers of tissue remodeling were changed within a day, but the markers associated with HBsAg

decline or ALT elevation were less in these patients compared to the responders.

Conclusion: Multiple immunological responses were triggered by GSK836 treatment and potential biomarkers associated with HBsAg response and ALT elevation were identified in responders. The IFNgamma pathway appears to be central to mediating immunological responses during HBsAg decline leading to ALT elevation in responders. **Funding:** GSK (Study 205695).

PO-2307

Ex vivo immune checkpoint blockade differentially regulates IFN-gamma and IL-2 responses in HBV-specific T cells across clinical HBV phases

Conan Chua¹, Aman Mehrotra¹, Anjali Patel¹, Shirin Nkongolo¹, Danie La¹, David Wong¹, Jordan Feld¹, Harry Janssen¹, Adam Gehring¹. ¹Toronto Centre for Liver Disease, Canada
Email: adam.gehring@uhnresearch.ca

Background and aims: HBV-specific T cells are the main mediators of viral clearance. However, in chronic infection, HBV-specific T cells exist at extremely low frequencies and exhibit varying degrees of functional exhaustion. Checkpoint blockade targeting the PD-1/PD-L1 axis can restore HBV-specific T cell functionality. The effects of PD-1 blocking have not been comprehensively tested across the different phases of chronic hepatitis B (CHB) and have only been demonstrated using in vitro expansion of HBV-specific T cells. The functional impact of ex vivo checkpoint blockade on HBV-specific T cells across the clinical phases of CHB remains to be investigated.

Method: We enrolled CHB patients with HBeAg+ immunotolerant, HBeAg+ active disease, HBeAg- active disease and HBeAg- inactive disease as well as patients virally suppressed on nucleoside analogue treatment and patients after functional cure (HBsAg loss; n = 10 each) to test the effects of ex vivo PD-1 blockade on HBV-specific T cell functionality. Patient PBMCs were pulsed with a panel of 313 overlapping peptides spanning the entire HBV genome ± PD-1 blockade. Ex vivo multifunctional T cell responses were measured using a 3-color FluoroSpot kit (C.T.L.) for IFN-gamma, IL-2 and Granzyme B secretion. Paired non-parametric t-tests were conducted for statistical analysis of checkpoint blockade.

Results: Preferential restoration of ex vivo IFN-gamma and IL-2 responses is observed among inactive disease patients, with average IFN-gamma spots increasing from 57 to 103 SFUs upon PD-1 blockade (n = 10; p = 0.0020); average IL-2 spots increased from 77 to 128 SFUs (n = 10; p = 0.0020). Immunotolerant patients also had significant increases in average IFN-gamma spots from 72 to 90 spots (n = 10, p = 0.0469). Calculation of signal:noise (S:N) ratios reveal significant restoration of IFN-gamma responses among immunotolerant (n = 10, p = 0.0137) and inactive disease patients (n = 10, p = 0.0059). IL-2 S:N ratios for inactive disease patients were not significant upon blockade (n = 10, p = 0.0527). Granzyme B responses remained unaffected across all clinical phases (n = 41).

Conclusion: Our data show that ex vivo PD-1 blockade significantly increases the functionality of HBV-specific T cells and that this can be measured using multi-analyte FluoroSpot assays. Functional restoration differed by clinical phase and increased T cell functionality was greater for IFN-gamma while changes in IL-2 production were minimal. These data suggest that ex vivo functional assays may identify patients with the greatest potential of responding to immune checkpoint blockade therapy.

POSTER PRESENTATIONS

PO-2339

Impact of hepatitis B core-related antigen (HBcrAg) level on HBV specific CD4+ and CD8+ T cell responses in HBeAg negative patients with chronic hepatitis B virus infection

Elmira Aliabadi^{1,2,3}, Benjamin Maasoumy^{1,2}, Birgit Bremer^{1,2,3}, Carola Mix^{1,2}, Helena Lickei^{1,2,3}, Heiner Wedemeyer^{1,2}, Anke Kraft^{1,2,3}, Markus Cornberg^{1,2,3,4}. ¹Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²German Centre for Infection Research (Deutsches Zentrum für Infektionsforschung DZIF), Partner Site Hannover-Braunschweig, Hannover, Germany; ³TWINCORE, Centre for Experimental and Clinical Infection Research, a Joint Venture between the Hannover Medical School (MHH) and the Helmholtz Centre for Infection Research (HZI), Hannover, Germany; ⁴Centre for Individualized Infection Medicine (CiiM), c/o CRC, Hannover, Germany
Email: aliabadi.elmira@mh-hannover.de

Background and aims: Loss of hepatitis B surface antigen (HBsAg) is considered as functional cure and new strategies are being developed for achieving this end point. For stratification in clinical trials, HBsAg level may be an important marker and could indicate the degree of immune dysfunction. However, the group of Bertolotti (Gastroenterology 2020) and we (ILC 2019) showed that age or duration of HBsAg exposure, rather than the amount of HBsAg, was associated with the level of anti-HBV T-cell responses in vitro. More recently, other HBV markers have become established and are used in clinical trials, such as HBcrAg. However, the correlation between HBcrAg levels and HBV-specific T-cell immune responses has not been investigated to date.

Method: 55 HBeAg negative patients were categorized into 3 groups based on their HBcrAg level (HBcrAg <3 logU/ml, HBcrAg 3–3.9 logU/ml, HBcrAg ≥4 logU/ml). Cytokine+ HBV-specific T cell responses were measured after in vitro culture with overlapping peptides covering polymerase (pol), surface and core of HBV genotype D in the presence or absence of anti-PD-L1 antibody. In 24 HLA-A2 positive patients we also analyzed HBV specific core₁₈- and pol₄₅₅-specific CD8+ T cells and the effect of anti-PD-L1 blockade.

Results: Stimulation of PBMCs with HBV-overlapping peptides induced core- and pol-specific T-cell responses. However, surface-specific T-cell responses were barely detectable. We found that HBV-specific CD4+ T-cell responses (core and pol) were significantly lower in patients with high HBcrAg (≥4 logU/ml). Blocking the PD-1/PD-L1 pathway during in vitro culture significantly increased both CD4+ and CD8+ T-cell responses (pol >core) in patients with low HBcrAg (<3 logU/ml) and CD8+ T-cell responses in the intermediate group (3–3.9 logU/ml). There was no effect of anti-PD-L1 blockade in patients with high HBcrAg. For single epitope-specific CD8+ T-cell responses, we observed only an effect of anti-PD-L1 blockade for pol₄₅₅ in the low HBcrAg group.

Conclusion: Our data suggest that HBcrAg level is associated with HBV-specific T-cell responses, particularly CD4+ T-cell responses. Moreover, patients with HBcrAg <4 logU/ml showed significantly stronger T-cell responses to in vitro HBV peptide stimulation after use of checkpoint inhibitors. Therefore, HBcrAg level may be more suitable than HBsAg level to stratify for patients to be treated with immunomodulatory therapies.

PO-2456

Transient Kupffer cell response to microbial components is critically regulated through expression of A20

Christian Zwicker¹, Anneleen Remmerie¹, Mathias Vanhockerhout^{1,2}, Tineke Vanhalewyn^{1,2}, Bavo Vanneste^{1,2}, Charlotte L. Scott¹.

¹Laboratory of Myeloid Cell Biology in Tissue Damage and Inflammation, VIB-UGent Center for Inflammation Research, Department of Biomedical Molecular Biology, Faculty of Science, Ghent University, Ghent, Belgium, Gent, Belgium; ²Laboratory of Myeloid Cell Biology in Tissue Homeostasis and Regeneration, VIB-UGent Center for Inflammation Research, Department of Biomedical Molecular Biology, Faculty of Science, Ghent University, Ghent, Belgium
Email:

Background and aims: Residing in the sinusoids, Kupffer cells (KCs), the tissue-resident macs of the liver are ideally positioned to recognize and clear microbes/their components and thus critically contribute to systemic immune surveillance. Upon inflammation/infection, monocytes are often recruited to the liver where they can differentiate into recruited macs (rMacs), which alongside KCs, participate in immune defense and tissue repair. Due to similar expression profiles and functions it has not been possible to unambiguously discriminate between resident KCs and rMacs in the past hampering our understanding of mac activation by microbes and microbial components. However, the identification of Clec4F as a KC-specific marker and the development of KC-specific mouse models now allows to unambiguously distinguish between resident and rMacs in the liver and to assess KC responses specifically.

Method: To mimic systemic infection, we treated mice with the microbial component lipopolysaccharide (LPS) and determined hepatic mac fate and activation profiles in response to microbial insult. To manipulate KC responses to LPS *in vivo* we used the Clec4f-CRE mice allowing us to remove genes in KCs selectively.

Results: We found that following LPS treatment resident KCs were reduced after challenge while rMac emerged in the liver. Transcriptionally, resident KCs strongly upregulated their expression of typical immune activation genes including *Tnf*, *Il6* or *Tnfaip3* (encoding A20) as early as 2 hours after LPS administration but expression of these genes rapidly returned to baseline (6 hours). As A20 functions as a negative regulator of NFκB, we sought to investigate the importance of this rapid shut down of the KC response. To this end, we manipulated KC activation by deleting A20 expression specifically from KCs. This dramatically altered the systemic immune response to LPS in Clec4f-CRE × A20^{fl/fl} mice evidenced by increased hypothermia and mortality of these animals. This phenotype was associated with increased systemic TNFα levels and global inhibition of TNFα signaling rescued Clec4f-CRE × A20^{fl/fl} mice after LPS challenge.

Conclusion: Our data demonstrate a critical function of A20 in KCs and suggest a role for KCs in limiting overt immune response to microbial components. Gaining a better understanding of these processes may allow to manipulate these responses and ultimately improve patient outcomes in systemic inflammatory conditions such as sepsis.

Liver development, physiology and regeneration

PO-279

Ablation of liver FXR results in an increased colonic mucus barrier in mice

Noortje IJssennagger¹, Kristel van Rooijen¹, Stefania Magnúsdóttir¹, José M. Ramos Pittol^{1,2}, Ellen C.L. Willemsen¹, Marcel R. de Zoete³, Matthijs J.D. Baars¹, Paul B. Stege³, Carolina Colliva⁴, Roberto Pellicciari⁴, Yvonne Vercoulen¹, Folkert Kuipers⁵, Saskia van Mil¹. ¹UMC Utrecht, Center for Molecular Medicine, Utrecht; ²University of Innsbruck, Institute of Biochemistry, Innsbruck, Austria; ³UMC Utrecht, Department of Medical Microbiology, Utrecht, Netherlands; ⁴TES Pharma S.r.l., Perugia, Italy; ⁵University of Groningen, University Medical Center Groningen, Departments of Pediatrics and Laboratory Medicine, Groningen, Netherlands
Email: s.w.c.vanmil@umcutrecht.nl

Background and aims: The inter-organ cross-talk between the liver and intestine has been focus of intense research. Key in this cross-talk are bile acids, which are secreted from the liver into the intestine, interact with the microbiome, and upon absorption reach back to the liver. The bile acid-activated Farnesoid X receptor (*Fxr*) mediates in the gut-to-liver axis. However, liver-to-gut communication and the roles of bile acids and *Fxr* herein remain elusive. Here, we aim to get a better understanding of *Fxr*-mediated liver-to-gut communication, particularly in colon functioning.

Method: *Fxr* floxed/floxed mice were crossed with cre-expressing mice to yield *Fxr* ablation in intestine (*Fxr-intKO*), liver (*Fxr-livKO*), or total body (*Fxr-totKO*). The effects on colonic gene expression (RNA sequencing), the microbiome (16S Sequencing) and mucus barrier function by *ex vivo* imaging, were analyzed.

Results: Despite relatively small changes in biliary bile acid concentration and composition, more genes were differentially expressed in colons of *Fxr-livKO* mice compared to *Fxr-intKO* and *Fxr-totKO* mice (3272, 731 and 1824, respectively). Colons of *Fxr-livKO* showed increased expression of anti-microbial genes, Toll-like receptors, inflammasome related genes and genes belonging to the 'Mucin-type O-glycan biosynthesis' pathway. *Fxr-livKO* mice have a microbiome profile favorable for the protective capacity of the mucus

barrier. The thickness of the inner sterile mucus layer was increased in *Fxr-livKO* compared to controls.

Conclusion: Targeting of *FXR* is at the forefront in the battle against metabolic diseases. We show that ablation of *Fxr* in the liver greatly impacts colonic gene expression and increased the colonic mucus barrier. Increasing the mucus barrier is of utmost importance to battle intestinal diseases like IBD and we show that this might be done by antagonizing *FXR* in the liver.

PO-1154

Influence of human fecal bacteria's secretome in the maturation and function of the liver

Joana Inês Almeida^{1,2,3}, Pedro Vicente^{2,3}, Paula M. Alves^{2,3}, Margarida Serra^{2,3}, Pedro Baptista^{1,4,5,6}. ¹IIS Aragón | Instituto de Investigación Sanitaria de Aragón, Zaragoza, Spain; ²iBET | Instituto de Biología Experimental e Tecnológica, Oeiras, Portugal; ³ITQB NOVA-Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Oeiras, Portugal; ⁴CIBERehd | Centro de Investigación Biomédica en Red en el Área Temática de Enfermedades Hepáticas, Madrid, Spain; ⁵ARAID | Fundación Agencia Aragonesa para la Investigación y el Desarrollo, Zaragoza, Spain; ⁶Universidad Carlos III de Madrid, Department of Biomedical and Aerospace Engineering, Getafe, Spain
Email: joana.almeida@ibet.pt

Background and aims: Liver maturation and functionality, that naturally occur during the early postnatal period, could be strongly associated with human intestinal microbiome. Lithocholic acid and vitamin K2, two common postbiotics, were shown to induce the expression of CYP450 enzymes in fetal hepatocytes and in hepatocytes derived from human pluripotent stem cells (hPSC-HLC). In line with these findings, studies on germ-free animals reported dissimilar xenobiotic enzyme profiles, impaired liver regeneration after partial hepatectomy and a higher predisposition to metabolic syndrome when compared to conventional counterparts. Surprisingly, these processes were reverted when germ-free mice were colonized with conventional mouse microbiota. Considering these evidences, we developed a nature-inspired protocol to investigate the role of gut microbiome in human primary hepatocytes (HPH) and in the generation of mature hiPSC-HLC.

Method: Herein, hiPSC were differentiated into HLC and matured with fecal bacteria's secretome in stirred tank bioreactors. Likewise, HPH were cultured in sandwich to assess its effect. Three different formulations of conditioned media (CM) based on microbial

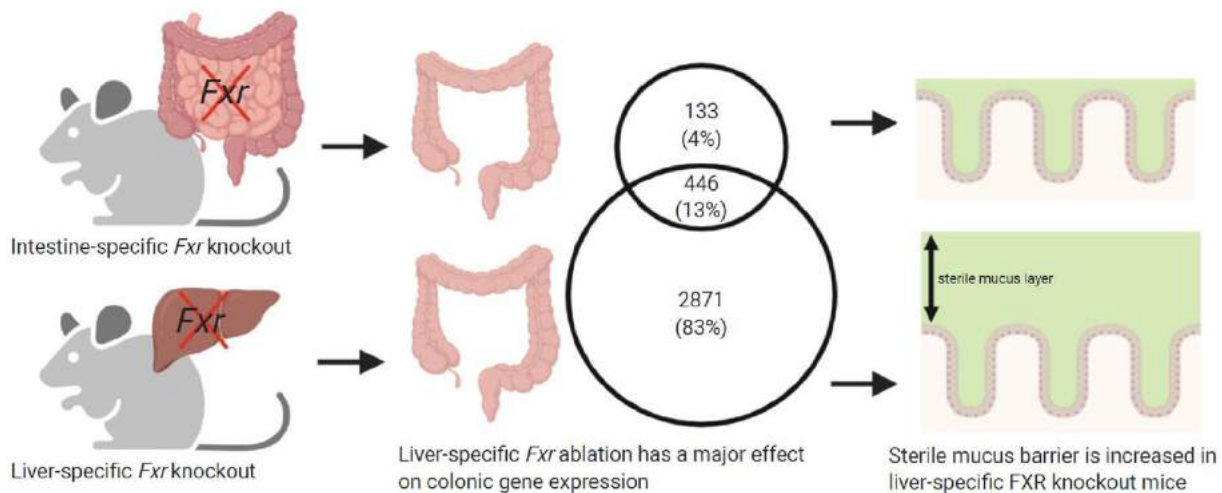


Figure: (abstract: PO-279)

POSTER PRESENTATIONS

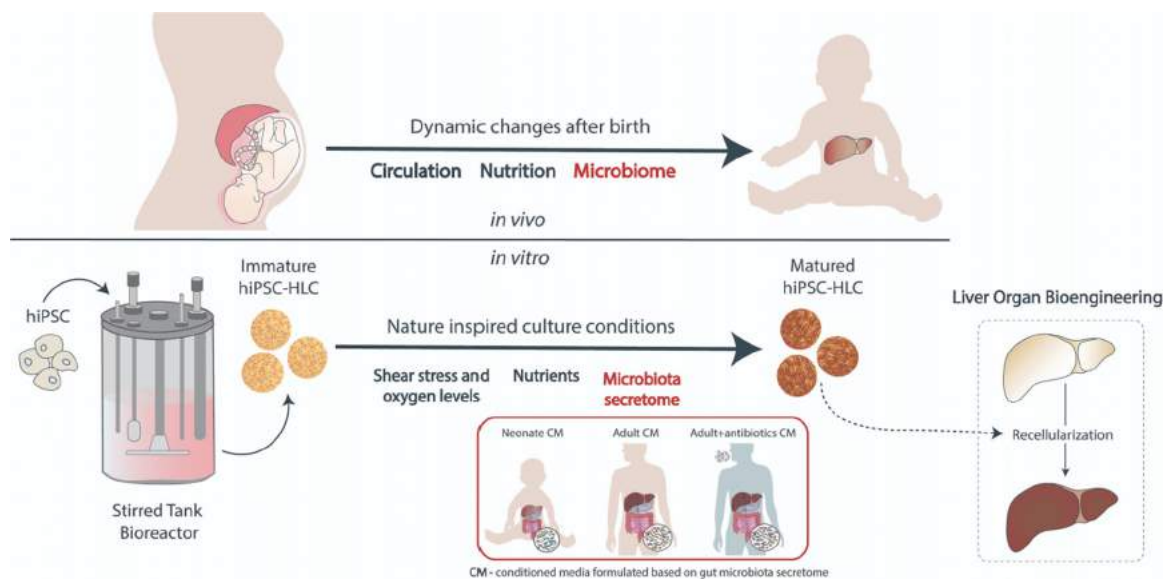


Figure: (abstract: PO-1154)

secretome (neonatal, adult and adult under antibiotics) were prepared and characterized. Lastly, the role of some bioactive peptides secreted by the intestinal bacteria, in hepatic cell maturation was also assessed.

Results: Quantitative gene-expression analysis throughout the differentiation process confirmed hiPSC commitment towards a HLC phenotype. HLC treated with neonatal and healthy adult CM showed up-regulation of the *CYP3A4*, *CYP2C9*, *HNF4a*, *FXR* and *PPARA* genes which was not verified in HLC supplemented with the CM obtained from an adult under antibiotic treatment. Characterization of all CMs revealed the presence of distinct bile acids, short-chain fatty acids and vitamins. Interestingly, HLC treated with 4 bacterial derived peptides expressed TLRs (-4, -2, -6) and some of their intracellular targets and mediators (TIRAP, Myd88, NF- κ B, TNF α), fact that has never been documented before and is absent in the early stages of hPSC differentiation into hepatic lineage. Finally, HPH exposed to CM or to bacterial peptides showed significant increased survival versus control at 3 weeks with upregulation of several hepatic genes (*CYP2B6*, *CYP3A4*, *ALB*, *TLR1-2*).

Conclusion: Our work provides, for the first time, novel insights into the interaction of fecal bacteria's secretome in the maturation of HLC and in the function/survival of HPH. Hence, the mechanisms revealed herein will not only bring stem cell technology closer to clinical practice but also open new paradigm shifts into hepatic function, an important unmet clinical need in many liver diseases.

PO-1356

Hypoxia-induced liver angiogenesis rescues survival upon small for size hepatectomy in mice

Maxime De Rudder¹, Alexandra Dili^{1,2}, Boris Pirlot¹, Caroline Bouzin¹, Isabelle Leclercq¹. ¹Institut of experimental and clinical research, Laboratory of Hepato-gastro-enterology, Woluwé-saint-Lambert, Belgium; ²CHU UCLouvain-Namur, Department of Surgery, Yvoir, Belgium

Email: isabelle.leclercq@uclouvain.be

Background and aims: After hepatectomy, hepatocytes (Hp) proliferate first, followed by sinusoidal endothelial cell (SEC) 2–3 days later. The larger the liver resection, the higher the portal hyperperfusion and the Hp proliferation rate. Hence at the onset of regeneration, proliferating Hp form transiently avascular clusters. After extended hepatectomy (eHx), large avascular, and thus non-functional, Hp islands are thought to cause liver failure (the “small-

for-size syndrome”-SFSS). Several groups proposed that the induction of hypoxia or the activation of hypoxia-driven pathways protects the liver during regeneration. In rats, we showed that induction of hypoxia in the liver after eHx rescues survival and prevents SFSS. Survival was associated with activation of hypoxia sensing pathways and increased expression of pro-angiogenic factors. To test whether hypoxia hasten angiogenesis in the regenerating liver, we analysed the remodelling of the liver sinusoidal network after SFSS-hepatectomy (eHx) with or without exposure to hypoxia.

Method: Mice underwent an 80% eHx (caudate and posterior right lobe left) and immediately after were housed in a hypoxic environment (11% FiO₂) (eHx-H) or kept in normoxia (ambient air; eHx-N). We detected proliferative SEC and Hp by double immunofluorescence (Ki67/CD31 or HNF4; pHH3/HNF4a) and counted mitosis on HandE staining. On CD31 immunostained liver sections, we measured the diameter of the liver sinusoids (Feret's diameter-24 h post eHx) and the sinusoidal area (semi-automatic morphometry-48 h post eHx).

Results: 7 days after surgery, mortality was 60% after eHx-N and exposure to hypoxia drastically reduced mortality to 20%. Expectedly, hepatocyte proliferation (Ki67/HNF4a, pHH3/HNF4a and mitosis) was observed 48 h post eHx with no difference between normoxia and hypoxia groups. By contrast, 72 h post eHx, Hp proliferation was significantly higher in mice exposed to normoxia compared to hypoxia and confirmed by higher liver mass in the former group. Conversely, SEC proliferation was already seen at 24 and 48 h post eHx-H but only at 72 h in eHx-N. Also, the mean diameter of sinusoids ($6.19 \pm 0.4 \mu\text{m}$ vs $4.94 \pm 0.2 \mu\text{m}$, $p = 0.001$) and the sinusoidal area ($54055 \pm 10850 \mu\text{m}^2$ vs $19864 \pm 9201 \mu\text{m}^2$, $p = 0.0007$) were significantly larger in eHx-H than in normoxic controls.

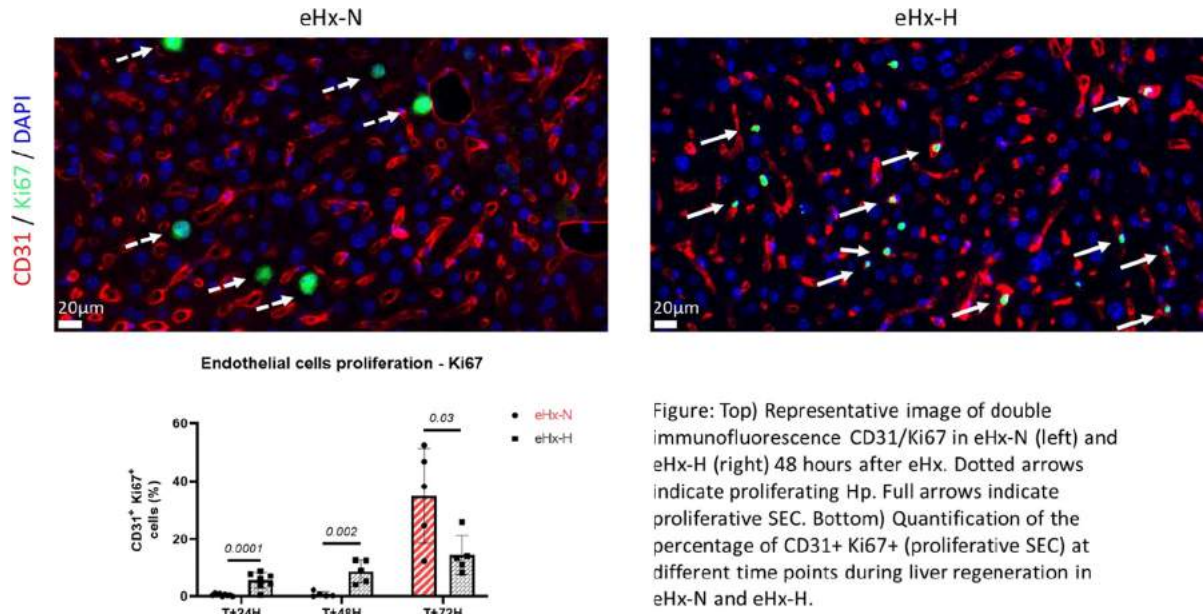


Figure: Top) Representative image of double immunofluorescence CD31/Ki67 in eHx-N (left) and eHx-H (right) 48 hours after eHx. Dotted arrows indicate proliferating Hp. Full arrows indicate proliferative SEC. Bottom) Quantification of the percentage of CD31+ Ki67+ (proliferative SEC) at different time points during liver regeneration in eHx-N and eHx-H.

Figure: (abstract: PO-1356)

Conclusion: Our results support that hypoxia triggers an angiogenic response after extended hepatectomy. We propose that this enable adequate blood supply to the regenerating hepatocytes, hence supporting hepatocellular function.

PO-2234
In vitro Transplantation of Biliary Organoids Support Hepatic Differentiation and proliferation in Chronic Liver Injury

Savneet Kaur¹, Impreet Kaur¹, Dinesh Mani Tripathi², Sumati Rohilla², Ashwini Vasudevan², Preety Rawal², Pinky Juneja¹, Iris Pla³,

Natalia Sanchez-Romero³, Pedro Baptista³, Shiv Sarin⁴. ¹Institute of Liver and Biliary Sciences, Molecular and Cellular Medicine, Delhi, India; ²Institute of Liver and Biliary Sciences, Molecular and Cellular Medicine, Delhi, India; ³Instituto de Investigacion Sanitaria de Aragon (IIS, Aragon), Zaragoza, Spain; ⁴Institute of Liver and Biliary Sciences, Department of Hepatology, Delhi, India
 Email: savykaur@gmail.com

Background and aims: The limited replicative potential of primary hepatocytes (PHep) is a major limitation of cell therapy in patients

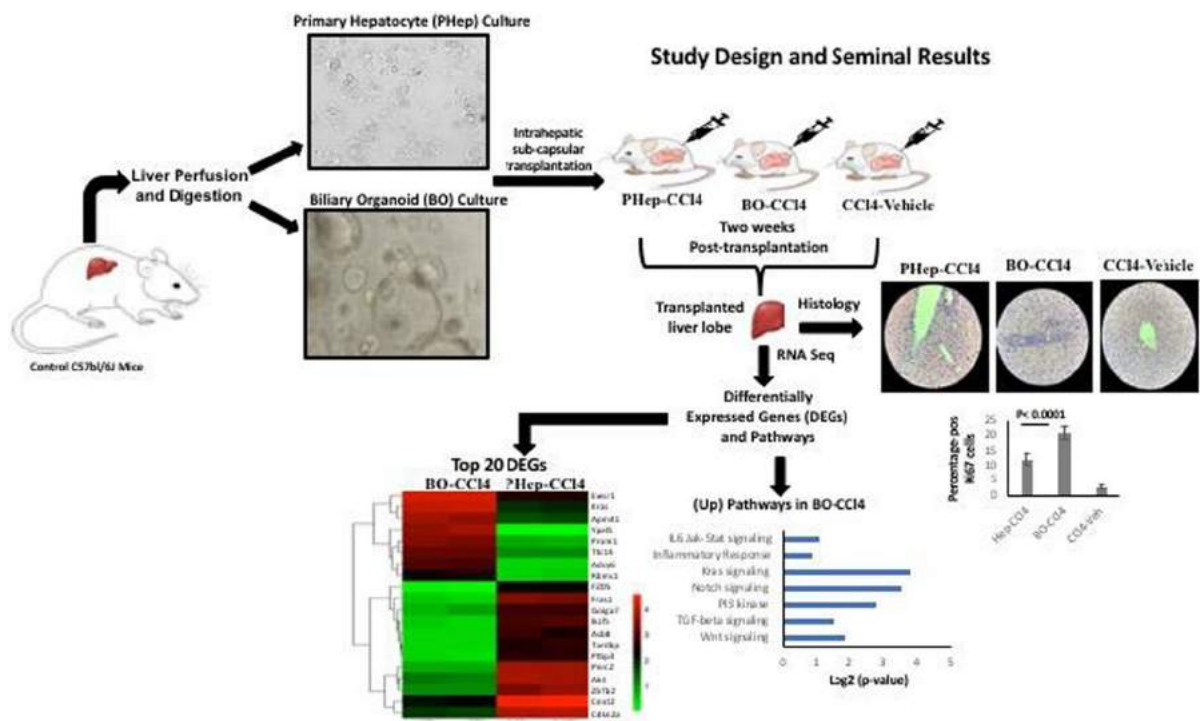


Figure: (abstract: PO-2234)

POSTER PRESENTATIONS

with liver failure. Biliary organoids (BO) derived from intrahepatic bile ducts have been reported to differentiate into both hepatocyte and cholangiocytes in vitro. Here, we studied the effects of intrahepatic transplantation of BO and PHep in chronic liver injury mice models and characterized the transcriptomes of the transplanted liver lobes by RNA sequencing.

Method: Cells isolated from intrahepatic mice bile ducts were cultured on matrigel to develop BO. Hep were isolated from mice livers by collagenase perfusion. Animal models of 3-week liver injury were prepared by CCl₄ injections. Well-characterized BO and PHep were injected into the subcapsular left lateral liver lobe of two groups of CCl₄ mice. CCl₄ mice transplanted with saline were the vehicle group. Two weeks post-transplantation, the transplanted liver lobes were collected from all the study groups and studied by histology and RNA-sequencing analysis on Illumina HiSeq 2500 with 2 × 150 paired-end chemistry.

Results: The cultured BO showed positivity for stem cell markers such as Lgr5 and ductal markers, Krt19. PHep were positive for Albumin (Alb) and Asgr1 in vitro. In vivo, post two weeks of transplantation, mice did not exhibit any tumors, mortality and morbidity in either vehicle, PHep- or BO-CCl₄ groups. Mice livers transplanted with BO had an increased Ki67-positive proliferative cells as compared to the PHep mice ($p < 0.0001$). Among the top 20 differentially expressed genes (DEGs) in the RNA seq data, an upregulation of genes including Ewsr1, Kras, Ypel5, Apm41 involved in cell cycle progression and hepatocyte differentiation was observed in transplanted liver lobes of BO-CCl₄ mice as compared to PHep-CCl₄ mice. BO mice had a significant upregulation of biliary marker genes, Prom1 (2-fold), Trop2 (2-fold), Krt7 (1.5 fold) and also some of the Hep-specific genes including HNF-4a (1.5-fold), ApoB (1.5-fold) and Krt18 (1.6-fold) as compared to the PHep mice. Among the signaling pathways, there was an upregulation of the KRAS and Notch signaling pathways in the BO as compared to the PHep mice.

Conclusion: The study demonstrates that transplantation of BO induces hepatic proliferation and differentiation in chronically-injured liver, indicating that they may serve as an efficient cell source and therapy for restoring hepatic insufficiency.

Liver transplantation and hepatobiliary surgery: Clinical aspects

PO-186

Real-world experience of mTOR inhibitors in liver transplant recipients in a region where living donation is predominant

Pil Soo Sung¹, Ji Won Han¹, Jeong Won Jang¹, Jong Young Choi¹, Seung Kew Yoon¹. ¹The Catholic University of Korea, Department of Internal Medicine, Seoul, Rep. of South Korea
Email: yoonsk@catholic.ac.kr

Background and aims: Mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, may be efficacious in preserving renal function in liver transplantation (LT) recipients while preventing hepatocellular carcinoma (HCC) recurrence. In this study, we retrospectively evaluated the safety, efficacy, and renoprotective effects of mTOR inhibitors in LT recipients.

Method: This retrospective observational study initially screened 500 patients who underwent LT at Seoul St. Mary's Hospital between November 2012 and October 2020. And 84 patients received everolimus or sirolimus as immunosuppressants. Median observational period was 1,016 days. Among these, 62 LT recipients had HCC before LT.

Results Among the 84 patients enrolled, mTOR inhibitor was commenced a mean of 269 days after LT. Regarding the type of mTOR inhibitor, everolimus was used in 71 patients and sirolimus in

13 patients. Concomitant tacrolimus was used in 63 patients (75.0%). A significant improvement in kidney function was observed in the eGFR <60 ml/min/1.73 m² group (n = 19) 12 months after initiation of mTOR inhibitors, for both patient groups with early + mid starters (n = 7, starting within 1 year after LT) and late starters (n = 12, starting over 1 year after LT). mTOR inhibitors were safely administered without serious adverse events that led to drug discontinuation. HCC recurred in only 4 patients (4/39, 10.3%) in patients with prophylactic mTOR inhibitor use, which was far less than in our previous report (19%).

Conclusion: Overall, this is the first real-world report of mTOR inhibitor application in Korea, where hepatitis B virus (HBV) infection is the principal cause of HCC and living donor LT is predominant. We demonstrated that patients with renal impairment showed significant improvement in renal function regardless of the timing of mTOR inhibitor start, suggesting that switch to mTOR inhibitors are required when renal function declines.

*This work was supported by the Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

PO-212

Early Renal Dysfunction Post Liver Transplant Predicts Long-term Adjudicated Cardiovascular Events

Ramzi Hassouneh¹, Steve Shen¹, Taseen Syed¹, Sean Flynn¹, Matthew Fasullo¹, Vaishali Patel¹, Chandra Bhati¹, Mohammad Shadab Siddiqui¹, Samarth Patel¹. ¹Virginia Commonwealth University Health, Richmond, United States
Email: ramzi.hassouneh@vcuhealth.org

Background and aims: Cardiovascular disease (CVD) is responsible for substantial long-term morbidity and mortality among liver transplant (LT) recipients, despite exclusion of patients with high-risk CVD prior to LT evaluation. The association between development of metabolic co-morbid conditions, such as diabetes or weight gain post-LT, is modest, thus, underscoring other potential pathways linking LT to CVD. We hypothesize that patients who develop CVD following LT are at higher risk at the time of LT, not captured via traditional CVD assessment at the time of LT. Renal impairment has been linked to CVD through multiple mechanistic pathways. Therefore, we evaluated the relationship between future risk of CVD and early renal function in LT recipients.

Method: We retrospectively analysed patients who had detailed pre-LT CVD assessment including coronary angiography, echocardiogram, electrocardiogram, and serum lipid profile between 2007 and 2019 (N = 651). Since glomerular filtration rate (GFR) can vary widely after LT, we used the highest GFR within 4 weeks after LT as the baseline surrogate of renal function. Patients were followed every 6 months post-LT. Major adverse cardiovascular events (MACE) included myocardial infarction, stroke, heart failure, and sudden cardiac death. MACE were adjudicated by study investigators according to the American Heart Association (AHA) definitions. Multivariate Cox regression models were used to evaluate the relationship between GFR and MACE.

Results: The mean age was 56 ± 10 years, 73% were male, and 72% were Caucasians. Coronary artery disease (CAD) was present in 178 (27%) of patients at the time of LT; however, this was mild in the majority of these patients (72%) and all patients with obstructive CAD had revascularization prior to LT. The mean GFR was 88 ± 28 ml/min/1.73m² at baseline and 58 ± 28 ml/min/1.73m² at 1-year post-LT. No association between GFR and baseline CAD or cardiac volumetric assessment on echocardiography was noted. The median follow-up in the study was 69 months (IQR 34 months, 101 months) and 116 (18%) patients had a MACE, with the most common event being myocardial infarction. In time to event analysis, GFR at 12 months was independently associated with future risk of MACE in unadjusted analysis. The relationship between MACE and GFR at 12 months persisted (HR 0.99, 95% CI 0.98, 0.99, $p = 0.02$ per unit increase in GFR)

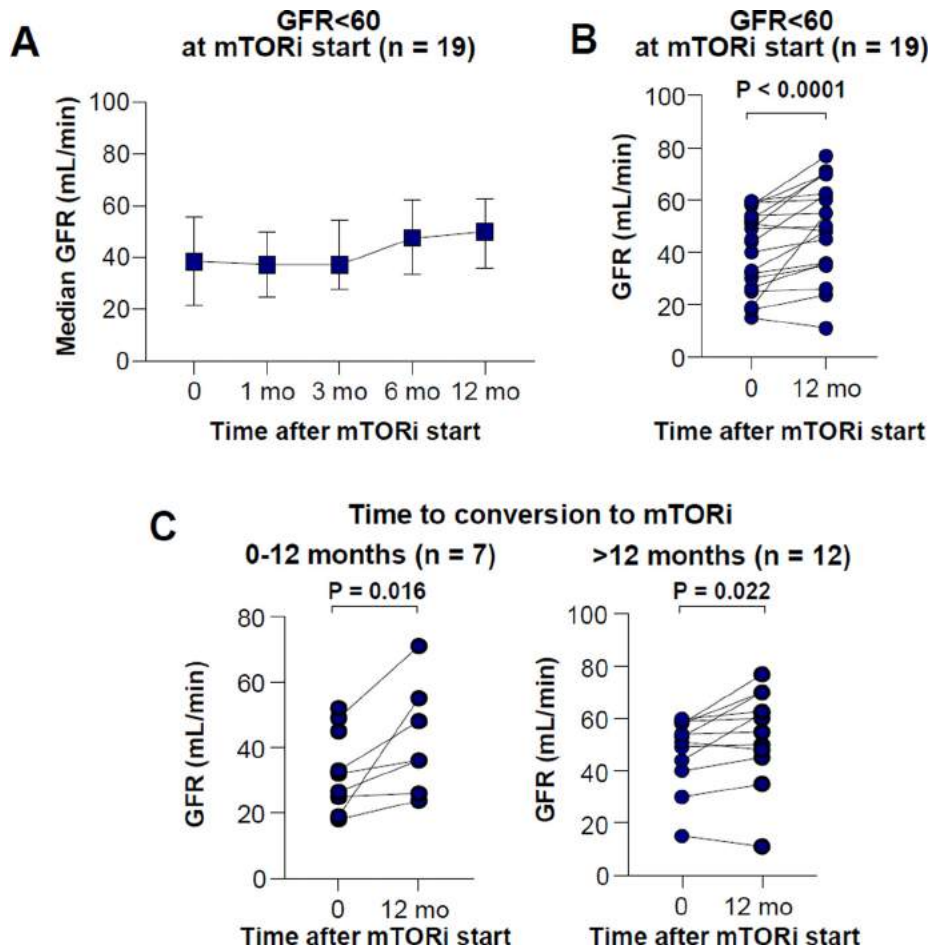


Figure: (abstract: PO-186)

after adjusting for gender, diabetes, CAD, dyslipidemia, hypertension, non-alcoholic steatohepatitis, and choice of immunosuppression.

Conclusion: Early changes in renal function are strongly associated with increased risk of MACE post-LT, which is independent of traditional cardio-metabolic risk factors. These findings suggest that GFR may potentially be used as a prognostic biomarker for more robust CVD risk assessment post-LT; however, this requires prospective validation.

PO-351

Liver transplantation for NAFLD cirrhosis : early overall patient survival is good

François Villeret¹, Sebastien Dharancy², Domitille Erard-Poinsot³, Armand Abergel⁴, Louise Barbier⁵, Camille Besch⁶, Olivier Boillot⁷, Karim Boudjema⁸, Audrey Coilly⁹, Filomena Conti¹⁰, Christophe Corpechot¹¹, Christophe Duvoux¹², François Faitot⁶, Stéphanie Faure¹³, Claire Francoz¹⁴, Emiliano Giostra¹⁵, Jean Gugenheim¹⁶, Jean Hardwigen¹⁷, Marie-Noëlle Hilleret¹⁸, HIRIART Jean-Baptiste¹⁹, Pauline Housset-Debry⁸, Nassim Kamar²⁰, Lassailly Guillaume², Marianne Latournerie²¹, Georges-Philippe Pageaux¹³, Didier Samuel⁹, Claire Vanlemmens²², Faouzi Saliba²³, Jérôme Dumortier²⁴. ¹Service d'hépatologie et de transplantation hépatique, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France; ²Service d'Hépatogastroentérologie, Centre Hospitalier Universitaire de Lille, Lille, France; ³Service d'hépatologie et de Transplantation hépatique, CHU de la Croix Rousse, Hospices Civils de Lyon, Lyon, France; ⁴Département de Médecine digestive, CHU Estaing, Clermont-Ferrand, France; ⁵Service de chirurgie digestive, oncologique et Transplantation hépatique, Hôpital Trousseau, Tours, France; ⁶Service

de chirurgie hépato-bilio-pancréatique et transplantation hépatique, CHRU Haute-pierre, Strasbourg, France; ⁷Fédération des Spécialités Digestives, Hospices civils de Lyon, Hôpital Edouard Herriot, Lyon, Lyon, France; ⁸Service d'Hépatologie et Transplantation hépatique, Hôpital Universitaire de Pontchaillou, Rennes, France; ⁹Centre Hépato-Biliaire, Hôpital Paul Brousse, AP-HP, Villejuif, Villejuif, France; ¹⁰Service de Chirurgie Digestive, Hépato-Biliaire et de Transplantation Hépatique, Hôpital Pitié Salpêtrière, Paris, France; ¹¹Service d'Hépatologie, Hôpital Saint-Antoine, CHU Saint-Antoine, Paris, France; ¹²Service d'hépatologie, Hôpital Henri Mondor, Créteil, France; ¹³Département d'hépatologie et transplantation hépatique, CHU Saint Eloi, Montpellier, France; ¹⁴Service d'Hépatologie et Transplantation Hépatique, Hôpital Beaujon, Clichy, France; ¹⁵Service de Gastroentérologie et Hépatologie, Hôpitaux Universitaires de Genève, Genève, Swaziland; ¹⁶Service de Chirurgie Digestive et de Transplantation Hépatique, CHU Archet II, Nice, France; ¹⁷Service chirurgie générale et transplantation hépatique, Hôpital La Timone, Marseille, France; ¹⁸Service d'hépatogastro-entérologie, CHU Michallon, Grenoble, France; ¹⁹Service de Chirurgie hépatobiliaire et de transplantation hépatique, CHU Haut Lévêque, Bordeaux, France; ²⁰Département de Néphrologie et Transplantation d'Organes, CHU Rangueil, Toulouse, France; ²¹Service d'hépatologie et de gastro-entérologie, CHU Dijon-Bourgogne, Dijon, France; ²²Service d'Hépatologie et Soins Intensifs Digestifs, Hôpital Jean Minjoz, Besançon, France; ²³Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, France; ²⁴Fédération des Spécialités Digestives, Hospices civils de Lyon, Hôpital Edouard Herriot, Lyon, France
Email: francois.villeret@gmail.com

Background and aims: NALFD is the most common liver disease worldwide. Liver transplantation (LT) is the only treatment for NAFLD

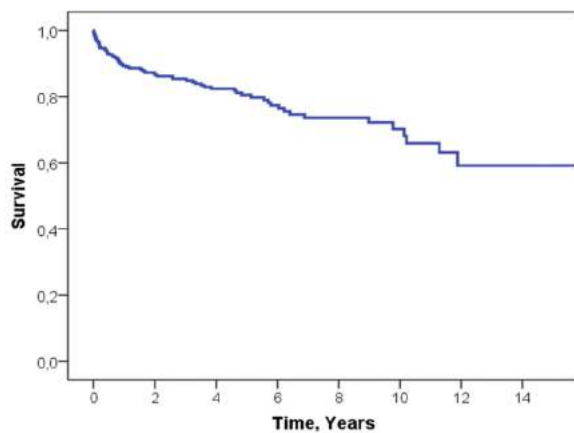
POSTER PRESENTATIONS

decompensated cirrhosis and/or hepatocellular carcinoma (HCC). Few data on long-term results are available, particularly in Europe where this indication represents a rapidly increasing number of patients. The aim of this study was to evaluate overall patient and graft survival and their predictive factors.

Method: This retrospective multicenter study included adult transplanted for 'pure' NAFLD cirrhosis between 2000 and 2019 in participating French-speaking centers. Cirrhosis of unknown or mixed origin were not included.

Results: A total of 361 patients (69.8% of male) were included in 19 centers. The median age at LT was 62.3 years (57.4–65.9) and the median MELD score was 13.9 (9.1–21.3). 51.8% of patients had HCC on liver explant but 149 patients were transplanted for HCC in 1st indication. Between 2004 and 2018, number of LT for NAFLD cirrhosis increased by 720%. A quarter of patients had a cardiovascular (CV) history before LT. Median follow-up after LT was 39.1 months (15.8–72.3).

Patient survival at 1, 5 and 10 years after LT was 89.3%, 79.8% and 68.1% respectively. During the 30 days after LT, 9 deaths occurred: 4 of which were of CV origin (44.4%). The mortality rate at 90 days after LT was 5.8%. Deaths occurring 12 months after LT were of infectious (59.5%) and CV (18.9%) origin. Deaths occurring after 12 months of LT were related to HCC recurrence (34.3%), CV disease (25.7%) or de novo malignancies (20.0%). Significant pejorative prognostic factors from multivariate analysis were: age of the recipient at LT time ≥ 62 years (OR: 2.3; $p = 0.012$), a history of coronary bypass or angioplasty before LT (OR: 2.7; $p = 0.043$), donor age ≥ 60 years (OR: 2.2; $p = 0.023$), occurrence of an early CV event (OR: 2.4; $p = 0.025$), HCC recurrence (OR: 2.4; $p = 0.026$) and dialysis immediately after LT (OR: 4.4; $p = 0.0001$). During the first year after LT, the only significant predictive factor of death was the age of the donor ≥ 60 years (OR: 3.0; $p = 0.035$). BMI before LT does not affect survival after LT.



Events	0	44	54	60	64	66	71	71
Number at risk	361	235	155	91	58	36	14	5

Figure:

Conclusion: Survival after LT for NAFLD cirrhosis was good at 5 years. Age at LT time, donor age, cardiovascular history and events and the recurrence of HCC are significant prognostic factors.

PO-353

Disease recurrence after liver transplantation for NAFLD cirrhosis : just wait!

François Villeret¹, Sebastien Dharancy², Domitille Erard-Poinsot¹, Armand Abergel³, Louise Barbier⁴, Camille Besch⁵, Olivier Boillot⁶, Karim Boudjema⁷, Audrey Coilly⁸, Filomena Conti⁹, Christophe Corpechot¹⁰, Christophe Duvoux¹¹, François Faitot⁵, Stéphanie Faure¹², Claire Francoz¹³, Emiliano Giostra¹⁴, Jean Gugenheim¹⁵, Jean Hardwigen¹⁶, Marie-Noëlle Hilleret¹⁷, HIRIART Jean-Baptiste¹⁸, Pauline Houssel-Debry⁷, Nassim Kamar¹⁹, Lassailly Guillaume², Marianne Latournerie²⁰,

Georges-Philippe Pageaux¹², Didier Samuel⁸, Claire Vanlemmens²¹, Faouzi Saliba⁸, Jérôme Dumortier⁶. ¹Service d'hépatologie et de transplantation hépatique, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France; ²Service d'hépatologie, Hôpital Claude Huriez, CHRU Lille, Lille, France; ³Département de Médecine digestive, CHU Estaing, Clermont-Ferrand, France; ⁴Service de chirurgie digestive, oncologique et Transplantation hépatique, Hôpital Trousseau, CHU Tours, Tours, France; ⁵Service de chirurgie hépato-bilio-pancréatique et transplantation hépatique, CHRU Hautepierre, Strasbourg, France; ⁶Fédération des Spécialités Digestives, Hospices civils de Lyon, Hôpital Edouard Herriot, Lyon, France; ⁷Service d'Hépatologie et Transplantation hépatique, Hôpital Universitaire de Pontchaillou, Rennes, France; ⁸Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, France; ⁹Service de Chirurgie Digestive, Hépato-Biliaire et de Transplantation Hépatique, Hôpital Pitié Salpêtrière, Paris, France; ¹⁰Service d'Hépatologie, Hôpital Saint-Antoine, CHU Saint-Antoine, Paris, France; ¹¹Service d'hépatologie, Hôpital Henri Mondor, Paris, France; ¹²Département d'hépatologie et Transplantation Hépatique, CHU Saint Eloi, Montpellier, France; ¹³Service d'Hépatologie et Transplantation Hépatique, Hôpital Beaujon, Paris, France; ¹⁴Service de Gastroentérologie et Hépatologie, Hôpitaux Universitaires de Genève, Genève, Switzerland; ¹⁵Service de Chirurgie Digestive et de Transplantation Hépatique, CHU Archet II, Nice, France; ¹⁶Service chirurgie générale et transplantation hépatique, Hôpital La Timone, Marseille, France; ¹⁷Service d'hépato-gastro-entérologie, CHU Michallon, Grenoble, France; ¹⁸Service de Chirurgie hépatobiliaire et de transplantation hépatique, CHU Haut Lévêque, Bordeaux, France; ¹⁹Département de Néphrologie et Transplantation d'Organes, CHU Rangueil, Toulouse, France; ²⁰Service d'hépatologie et de gastro-entérologie, CHU Dijon-Bourgogne, Dijon, France; ²¹Service d'Hépatologie et Soins Intensifs Digestifs, Hôpital Jean Minjot, Besançon, France

Email: francois.villeret@gmail.com

Background and aims: NAFLD is the most common liver disease worldwide. Liver transplantation (LT) is the only treatment for NAFLD decompensated cirrhosis and/or hepatocellular carcinoma (HCC). Few data on long-term results are available, particularly in Europe where this indication represents a rapidly increasing number of patients. The aim of this study was to evaluate the steatosis, fibrosis and NASH recurrence after LT and their predictive factors.

Method: This retrospective multicenter study included adult transplanted for 'pure' NAFLD cirrhosis between 2000 and 2019 in participating French-speaking centers. Cirrhosis of unknown or mixed origin were not included. Steatosis and fibrosis recurrence were determined on liver biopsies. The NASH diagnosis was performed according to the SAF or NAS scores, depending on the LT period.

Results: A total of 361 patients (69.8% of male) were included in 19 centers. The median age at LT was 62.3 years (57.4–65.9). 51.8% of patients had HCC on liver explant. At LT time, the median BMI was 30.9 kg/m² (26.8–34.1) with 57% obese and the median higher BMI before LT was 35.2 kg/m² (31.2–39.1). 77.3% of patients had type 2 diabetes, 83.4% hypertension and 56.8% metabolic syndrome. Ten patients underwent a bariatric surgery (BS) before LT with a median time to LT of 7 years. The median follow-up after LT was 39.1 months (15.8–72.3). The incidence of metabolic syndrome (MS) after LT was 73.5%, 86.2 and 92.5% at 1, 5 and 10 years respectively. After LT, incidence of overweight and obesity was 28% and 60% respectively (all grades).

From 291 patients who survived after 1 year, 150 patients (51.4%) had at least one liver biopsy during follow-up. Rate of steatosis recurrence was 62% and 80% at 1 and 5 years respectively: the only risk factor found was BMI ≥ 31 kg/m² at time of LT (OR: 2; $p = 0.035$). Rate of NASH recurrence was 8% at 1 year and 59% at 5 years. Risk factors for NASH recurrence were BMI ≥ 31 kg/m² at LT (OR: 3.6; $p = 0.039$), HDLc rate < 0.45 g/L after LT (OR: 5.5; $p = 0.001$) and the age of recipient at LT < 62 years (OR: 2.9; $p = 0.050$). The incidence of advanced fibrosis (F3-F4) was 44% at 5 years and no significant

predictive factors was found. No re-LT was performed for NAFLD cirrhosis recurrence.

Conclusion: Recurrence of steatosis and steatohepatitis on the graft is rapid and very frequent after LT for NAFLD cirrhosis. Treatment of MS is therefore a major goal in these patients.

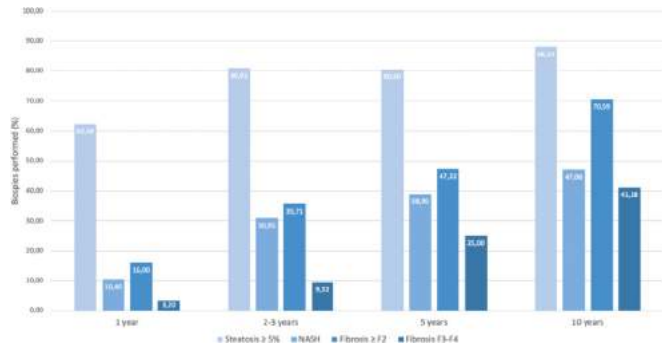


Figure:

PO-364
Waitlist outcomes for alcoholic hepatitis are more favorable than for other candidates with high Model for End-stage Liver Disease score in the current era

Therese Bittermann¹, Nadim Mahmud¹, Ethan Weinberg¹, Rajender Reddy¹. ¹University of Pennsylvania, Philadelphia, United States

Email: therese.bittermann@penmedicine.upenn.edu

Background and aims: In the appropriate candidate, liver transplantation (LT) is a viable treatment option for alcoholic hepatitis (AH). We compared the waitlisting trends and outcomes of AH patients in the context of others listed with high Model for End-stage Liver Disease (MELD) score in the United States.

Method: LT listings for AH between 1/1/2008–6/12/2020 were identified in the United Network for Organ Sharing database. Temporal trends in listings for AH were compared to those with

hepatitis C virus (HCV) and MELD 30+ and those with acute-on-chronic liver failure grade 3 (ACLF-3). Covariate-adjusted competing risks models evaluated waitlist mortality and LT rates among the three groups in the era of direct acting antivirals for HCV, using HCV MELD 30+ as the reference and stratified by listing period (2015–2017 and 2018–2020).

Results: Since 2014, listings for AH increased 0.2% per year, while those for HCV MELD 30+ decreased 0.4% per year and those of ACLF-3 increased marginally ($p < 0.001$ for all analyses). Waiting time between the 3 groups was comparably short: median 10 versus 8 versus 6 days, respectively ($p < 0.001$). Among 99 centers with ≥ 1 AH listing between 2018–2020, AH patients accounted for 0.2–18.2% of all alcohol-related listings. Overall listing volume was larger at these 99 centers than the 40 with no AH listings from 2008–2020 ($p < 0.001$). AH candidates in 2018–2020 experienced lower waitlist mortality (adjusted SHR 0.29, 95% CI: 0.18–0.49; $p < 0.001$; Figure Panel A) and higher transplant rates (adjusted SHR 1.23, 95% CI: 1.03–1.47; $p = 0.02$; Figure C) versus HCV MELD 30+, while outcomes in 2015–2017 were not different ($p = 0.1$ for both; Figure Panel B and D). By comparison, waitlist mortality and LT rates for ACLF-3 were not different from HCV MELD 30+ in 2018–2020: adjusted SHR 0.88 (95% CI: 0.65–1.19) and 0.96 (95% CI: 0.81–1.14), respectively.

Conclusion: AH has replaced the void on the waitlist left by decreasing numbers of high-MELD HCV candidates. Among high MELD patients, liver disease etiology increasingly influences waitlist outcomes, and those of AH candidates are most favorable.

PO-530
Chances of renal recovery in liver only transplant recipients who were eligible for simultaneous liver-kidney transplant

Jiawei Cui¹, Ashley Spann², Alexandra Shingina², Heidi Schaefer³, James Slaughter⁴, Sophoclis Alexopoulos⁵, Manhal Izzy². ¹Vanderbilt University Medical Center, Department of Medicine, Nashville, United States; ²Vanderbilt University Medical Center, Division of Gastroenterology, Hepatology, and Nutrition, Nashville, United States; ³Vanderbilt University Medical Center, Division of Nephrology, Nashville, United States; ⁴Vanderbilt University Medical Center, Department of

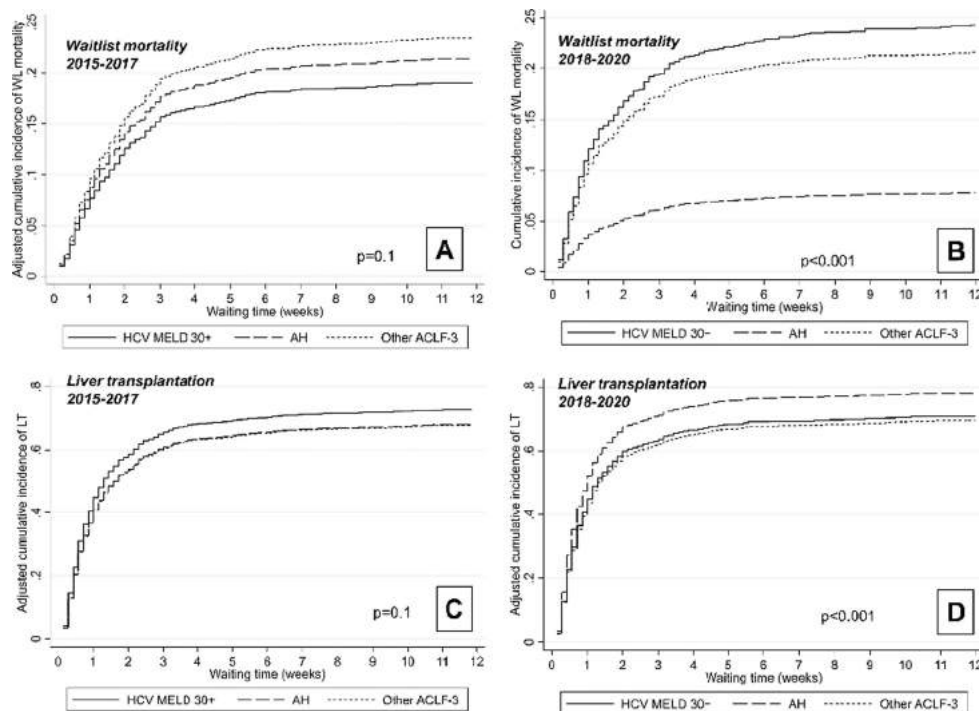


Figure: (abstract: PO-364)

POSTER PRESENTATIONS

Biostatistics, Nashville, United States; ⁵Vanderbilt University Medical Center, Division of Hepatobiliary Surgery and Liver Transplantation, Nashville, United States
Email: julie.cui@vumc.org

Background and aims: Progressive decline in renal function is common among patients with end-stage liver disease. Liver transplant (LT) candidates can often develop severely impaired renal function which prompts the consideration of simultaneous liver kidney transplantation (SLKT). In 2015, EASL guidelines suggested SLKT in patients with glomerular filtration rate (GFR) <30 ml/min and in 2017, the United Network for Organ Sharing (UNOS) recommended SLKT in patients with GFR <30 ml/min after being <60 ml/min for at least 90 days. This study aims to assess the post-LT renal recovery in patients who met EASL and UNOS criteria for SLKT, yet received liver alone.

Method: We performed a retrospective records review of adult patients who underwent LT between 1/1/2009 to 12/31/2018 at a North American Center. Liver only recipients whose last GFR before LT was <30 ml/min after being <60 ml/min for more than 90 days were included. Demographic, clinical, and laboratory data were collected. Partial recovery was defined as post-LT GFR increase to 30–60 ml/min and full recovery was defined as increase to >60 ml/min.

Results: Of 800 patients who underwent LT during the observation period, 123 patients had GFR <30 ml/min pre-LT and of them only 34 had GFR <60 ml/min preceding LT by 90 days or longer. Median age was 63 years. Females constituted 59% of the cohort. Following liver transplant, 20 patients (59%) had partial recovery and 10 patients (29%) had full recovery within a median of 6 and 61 days, respectively. Among baseline characteristics including comorbidities, abnormal radiologic appearance of the kidneys pre-LT, reflective of chronic disease, was the only predictor of lack of recovery ($p = 0.03$). All initial immunosuppressive regimens were tacrolimus-based. On last follow-up after a median of 4.8 years, 15 patients (44%) still had GFR >30 ml/min while 19 (56%) patients were on dialysis, awaiting kidney transplant, or received kidney transplant. Patients with pre-LT unrecovered AKI or HRS had the highest likelihood of recovery on last follow-up (OR 4.7, $p = 0.03$).

Conclusion: LT candidates who meet EASL and UNOS criteria for SLKT yet undergo LT only still have a remarkably high chance for post LT renal recovery, approaching 90% on short-term. Large proportion of patients can sustain recovery on long-term. Performing LT only in these patients and monitoring renal function post-LT to determine the need for kidney transplant may be the appropriate approach.

PO-594

Incidental Cholangiocarcinoma in Liver Transplantation

Nawaz Safdar^{1,2}, Rosemary Faulkes³, Fiona James¹, Lisa Mason⁴, Steve Masson⁵, James Powell⁴, Ian Rowe¹, Shishir Shetty³, Rebecca Jones¹, Richard Parker¹. ¹St James's University Hospital, Leeds Liver Unit, Leeds, United Kingdom; ²University of Leeds, School of Medicine, Leeds, United Kingdom; ³University Hospitals Birmingham, NHS Foundation Trust, Birmingham, United Kingdom; ⁴Royal Infirmary of Edinburgh, Liver Transplant Unit, Edinburgh, United Kingdom; ⁵Newcastle upon Tyne Hospitals, NHS Foundation Trust, Newcastle, United Kingdom
Email: n.safdar@nhs.net

Background and aims: Cholangiocarcinoma (CCA) is a contraindication to liver transplantation (LT) in the UK because of high recurrence rates and poor survival rates in previous series. However, some patients who undergo LT are found to have CCA that was not identified by pre-transplant investigations. We report on the outcomes of patients with incidental CCA from four UK liver transplant centres.

Method: Cases were identified retrospectively from pathology records. Biochemical and radiological data from before transplantation were collected as well as pathological data regarding tumour characteristics, and post-transplant survival. CCA were classified by TNM staging and anatomical location.

Results: 67 patients were identified. LT took place between 1988 and 2018. Follow-up after LT was up to 12.2 years with a median follow-up of 1.8 years. Most patients were male (72%) and the majority had PSC (55%). All patients had undergone cross-sectional imaging with at least one modality, usually MRI (97%) and often CT as well (62% MRI and CT). The median delay between last cross-sectional imaging and LT was 58 days. 4 patients were found to have distal CCA (dCCA), 31 patients had intrahepatic CCA (iCCA) and 28 had perihilar CCA (pCCA). Tumour classification by pTNM stage was classified as pT1 in 15 cases (22%), pT2a in 18 cases (27%), pT2b in 14 cases (21%), pT3 in 5 cases (7%) and pT4 in 9 cases (13%). A further 6 cases had no staging data. Overall median survival after LT was 4.95 years. Survival differed by tumour site: 1-year, 3-year and 5-year survival was 80.0%, 66.3% and 66.3%, respectively, in iCCA and 55.6%, 47.6% and 34.3% in pCCA, however this was not statistically significant {log rank (LR) $p = 0.054$ }. After grouping by stage of disease-'low risk' for pT1 and pT2a (49%), and 'high risk' for pT2b, pT3 and pT4 (42%), 1-year, 3-year and 5-year survival was 81.3%, 81.3% and 76.2%, respectively, in low risk, and 63.0%, 38.2% and 22.3%, respectively, in high risk {LR $p = 0.0056$ }, showing statistical significance.

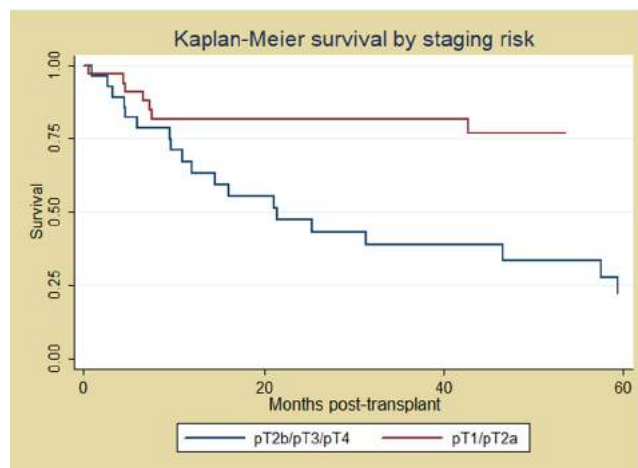


Figure:

Conclusion: Incidental CCA is uncommon. Overall survival is poor compared to usual outcomes for LT in the UK, however, intra-hepatic disease or disease at an earlier stage appeared to have favourable survival outcomes in this retrospective cohort.

PO-841

Elevated donor-derived cell-free DNA during subclinical T-cell mediated rejection after liver transplantation

Anna Katharina Baumann¹, Emily Saunders¹, Bastian Engel¹, Theresa Kirchner¹, Julia Beck², Björn Hartleben¹, Michael Oellerich³, Ekkehard Schuetz², Elmar Jaeckel¹, Richard Taubert¹. ¹Medizinische Hochschule Hannover, Hannover, Germany; ²Chronix Biomedical GmbH, Göttingen, Germany; ³Universitätsmedizin Göttingen, Göttingen, Germany
Email: baumann.anna@mh-hannover.de

Background and aims: Subclinical T-cell mediated rejection (subTCMR) is commonly found even late after liver transplantation (around 25%), associated with upregulation of rejection associated transcripts and can only be diagnosed through liver biopsies. Despite having a good prognosis even if left untreated, subTCMR should be excluded before immunosuppression minimization attempts are undertaken during individualized immunosuppression. Clinical TCMR (clinTCMR) after liver transplantation is associated with donor-derived cell-free DNA (dd-cfDNA) above a threshold of 10% of total cell free DNA. The aim of the current study was to evaluate dd-cfDNA as a non-invasive method to detect subclinical liver graft injury for the individualization of immunosuppression.

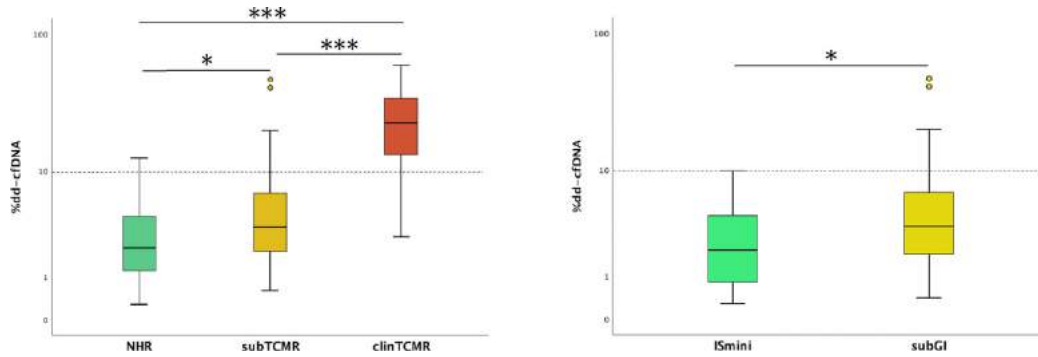


Figure:

Method: Samples with subclinical graft injury (liver enzymes ≤ 2 upper limit of normal) were taken from the prospective protocol biopsy program after liver transplantation at our centre. Liver biopsies were extensively reviewed for histological signs of graft injury including subTCMR (rejection activity index (RAI) $\geq 1 + 1 + 1$) and histological criteria for immunosuppression minimization (HCmini). Clinically relevant TCMR (clinTCMR; liver enzymes $> 2 \times$ ULN) was used as a comparator group. We used digital droplet PCR to measure dd-cfDNA in recipient plasma samples paired to liver biopsies. The t-test was used for statistical analysis.

Results: The mean dd-cfDNA was 3.4% in patients with no histological signs of rejection (NHR group (N = 26)), 6.5% in the subTCMR group (N = 45) and 25% in the clinTCMR group (N = 21). There was a significant difference between the mean dd-cfDNA of each group (NHR vs. subTCMR $p = 0.036$, NHR vs. clinTCMR $p < 0.001$, subTCMR vs. clinTCMR $p < 0.001$). Considering possible individualization of immunosuppression, we analysed 21 samples where HCmini were satisfied and 69 samples where they were not (subclinical graft injury (subGI)). The mean percentage of dd-cfDNA was 3.2% for the former and 5.2% for the latter ($p = 0.031$).

Conclusion: dd-cfDNA seems to be a promising marker for the non-invasive monitoring of subclinical liver graft injury in this study and thereby a potential clinical tool to facilitate individualized immunosuppression after liver transplantation without the need for protocol biopsies.

PO-922

A novel score to risk stratify and optimize use of liver graft among patients with grade 3 acute on chronic liver failure

Ashwani Singal¹, Yong-Fang Kuo², Robert Wong³, Vinay Sundaram⁴, Rajiv Jalan⁵. ¹University of South Dakota and Avera Transplant Institute, Medicine and Transplant Hepatology, Sioux Falls, United States; ²University of Texas Medical Branch, United States; ³Stanford University School of Medicine, United States; ⁴University of California Los Angeles, United States; ⁵University College London, United Kingdom
Email: ashwanisingal.com@gmail.com

Background and aims: Liver transplantation (LT) in select patients with ACLF provides survival benefit. However, post-transplant outcomes remains suboptimal even among select patients with ACLF-3 at LT. We performed this study to develop a risk score for use in selecting recipient and donor for LT among patients with ACLF-3.

Method: UNOS database (01/2002 to 06/2018) was queried on adult LT recipients (without HCC) using deceased donor graft, and stratify to ACLF using EASL-CLIF criteria. Study outcome was patient survival at one year after LT.

Results: 23, 947 LT recipients (mean age 54 years, 65% males, 60% Caucasians, median MELD 31) who were in ACLF (7166 ACLF-3) at LT were analysed. One yr. patient survival was 92.3%, 88.2%, 88.3%, and 83% for recipients without ACLF, and ACLF grades 1-3 respectively. Cox regression model performed using stepwise backward elimination process on derivation dataset (N = 3583) with ACLF-3 showed

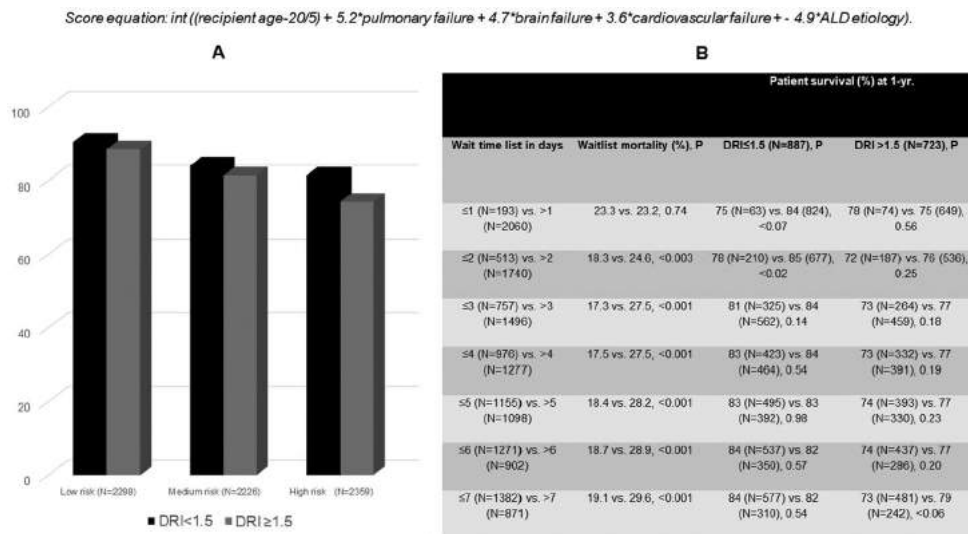


Figure: (abstract: PO-922): (A) patient survival rates at 1-year after liver transplantation (LT) among recipients with acute on chronic liver failure grade 3 at the time of transplant comparing good vs. poor quality donor graft (cut-off donor risk index or DRI at 1.50), (B) association of wait time in days on the liver transplant list and the quality of liver graft with the patient survival at one year after LT. The analyses are stratified for the three risk categories as stratified using the score equation shown above the figure.

POSTER PRESENTATIONS

recipient age, non-alcohol etiology, pulmonary failure, brain failure, and cardiovascular failure to be associated with 1-yr. patient survival. Risk score (median 9.7 and range -3.6 to 23.5) developed using significant variables from cox model on derivation dataset stratified 3583 recipients in validation cohort using cut-off score 7.55 and 11.57 to low (N = 1211), medium (N = 1168), and high risk (N = 1199), with 1-yr patient survival of 89%, 82%, and 80% respectively. The observed and expected post-transplant 1-yr. survival showed excellent correlation (R = 0.92). In the whole dataset with information on donor risk index (DRI), based on poor vs. good quality graft (DRI cut-off at 1.50), 1-yr. patient survival for low, medium, and high risk categories were 90 vs. 89%, P = 0.12, 84 vs. 81%, P < 0.07, and 81 vs. 74%, P < 0.001 respectively. Among 887 patients in high risk category and receiving good quality graft, the outcomes were better up to first 2 days from listing (85 vs. 78%, P = 0.02). Waiting beyond this time increased waitlist mortality (25 vs. 18%, P < 0.003) without further benefit on 1-year patient survival.

Conclusion: LT provides survival benefit to select patients with ACLF. In a cohort of ACLF-3 patients selected to receive LT, a novel score from recipient variables at transplant can be used to match recipients with donor quality, as basis to improve post-transplant outcomes and optimizing use of donor pool.

PO-935

Liver transplantation for severe alcoholic hepatitis: a multicentre Italian study

Giacomo Germani¹, Luca Saverio Belli², Giovanni Addolorato³, Manuela Merli⁴, Chiara Mazzarelli², Claudia Tarli³, Barbara Lattanzi⁴, Debora Angrisani², Adelaide Panariello⁵, Lucia Craxi⁶, Giovanni Forza⁷, Alessandra Feltrin⁸, Andrea Ronzan⁹, Paolo Feltracco¹⁰, Umberto Cillo¹¹, Patrizia Burra¹. ¹Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy; ²Hepatology and Gastroenterology, ASST GOM Niguarda, Milano, Italy; ³Alcohol Use Disorders Unit, Department of Internal Medicine, Institute of Internal Medicine, Gemelli Hospital, Catholic University of Rome, Rome, Italy; ⁴Gastroenterology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; ⁵Department of Mental Health and Addiction Services, ASST GOM Niguarda, Milan, Italy; ⁶Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), Institute of Pathology, University of Palermo, Palermo, Italy; ⁷Department of Legal and Occupational Medicine, Toxicology and Public Health, Padua University Hospital, Padua, Italy; ⁸Psychological Unit, Padua University Hospital, Padua, Italy; ⁹Psychiatry Unit, Padua University Hospital, Padua, Italy; ¹⁰Anesthesia and Intensive Care, Department of Medicine, Padua University Hospital, Padua, Italy; ¹¹Hepatobiliary Surgery and Liver Transplantation Unit, Padua University Hospital, Padua, Italy
Email: germani.giacomo@gmail.com

Background and aims: Acute alcoholic hepatitis (AAH) is a clinical syndrome characterized by high mortality rates. There is increasing evidence that early liver transplantation (LT), performed within strict and standardized protocols, can improve survival. The aim of this multicentre study was to assess outcomes after LT for severe AH in four Italian LT centres and to compare them with those of patients with severe AH non responding to medical therapy excluded from LT. **Method:** Patients admitted for severe AAH (2013–2019), according to NIAAA criteria, were included. Demographic, biochemical and clinic characteristics were evaluated. Patients not responding to medical therapy were placed on the waiting list for LT only if they were considered suitable candidates by a strict selection process. Explant histology was assessed in all liver transplanted patients and only patients with histologic features of AH with or without underlying chronic liver disease were considered for the purpose of this study. Post-transplant graft and patient survival as well as post-transplant alcohol relapse were evaluated.

Results: 93 patients with severe AAH were evaluated (65.6% male, median [IQR] age: 47 [42–56]). Forty-five/93 (48.4%) patients received corticosteroid therapy. 52/93 (55.9%) were classified as non responders to medical therapy and underwent the LT selection process. Amongst these, 20 (38.5%) patients were placed on the waiting list, whereas 32/52 (61.5%) patients were denied LT for the following reasons: psychosocial/psychiatric (n = 16, 50%), too sick for liver transplantation (n = 4, 12.5%), death (n = 6, 18.7%), clinical improvement during evaluation (n = 2, 6.3%), other reasons (n = 4, 12.5%). Median (IQR) interval time from admission to waiting list (WL) registration was 21 days (8.25–36 days). Sixteen patients underwent LT, median (IQR) MELD score at LT 32 (25–38), and median (IQR) time from WL registration to LT 6.5 days (2.25–20). Overall 6, 12 and 24-month survival rates were 100%, 100% and 100% significantly higher compared with patients with severe AH non responding to medical therapy who were denied LT (45%, 45% and 36% respectively; log-rank p < 0.001). Median (IQR) post-transplant hospital stay was 22.5 days (17–37.5). 2/16 (12.5%) patients resumed alcohol intake, one at 164 days and one at 184 days.

Conclusion: Early LT significantly improve survival in severe AAH non responding to medical therapy, when a strict selection process is applied. Further studies are needed to properly assess alcohol relapse rates with longer follow-up.

PO-1126

Patients with MELD exceptions have higher access to liver transplantation and lower waiting list mortality: the Swiss nationwide experience

Melisa Dirchwolf^{1,2}, Chiara Becchetti^{3,4}, Sarah G. Gschwend⁴, Christian Toso⁵, Philipp Dutkowski⁶, Julius Weiss⁷, Franz Immer⁷, Franziska Beyeler⁷, Simona Rossi⁸, Jonas Schropp^{3,9,10}, Zita Bischofberger⁴, Jean-François Dufour^{3,4}, Banz Vanessa⁴ and The Swiss Transplant Cohort Study (STCS)¹¹. ¹University of Bern, Novartis Fellowship in Hepatology, Department of Biomedical Research, Bern, Switzerland; ²Hospital Privado de Rosario, Liver Unit, Santa Fe, Argentina; ³University of Bern, Hepatology, Department of Biomedical Research, Bern, Switzerland; ⁴Inselhospital, University Hospital Bern, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; ⁵University Hospital of Geneva, Abdominal Surgery, Geneva, Switzerland; ⁶University Hospital of Zurich, Abdominal Transplant Surgery, Zurich; ⁷Swisstransplant, the Swiss National Foundation for Organ Donation and Transplantation, Bern, Switzerland; ⁸Swiss Transplant Cohort Study (STCS), Data Center, Basel, Switzerland; ⁹Open University of Cyprus, Department of Computer Science, Cyprus; ¹⁰University of Cyprus, Department of Psychology, Cyprus; ¹¹Swiss Transplant Cohort Study, Basel, Switzerland
Email: vanessa.banzwuethrich@insel.ch

Background and aims: MELD exceptions are used to balance mortality risk and access to liver transplantation for patients whose severity of the liver disease is not reflected by the calculated MELD score. We aimed to analyse the impact of MELD exception points on the liver transplant waiting list outcome in Switzerland.

Method: Nationwide cohort study including all adult patients registered on the Swiss liver transplant waiting list between 2012 and 2017. Outcome on the waiting list was analyzed according to MELD exception categories: patients receiving a standard exception due to HCC (SE-HCC); patients receiving another type of standard or non-standard exception (Other SE or NO-SE); patients receiving a MELD-Upgrade exception (MELDUP); patients did not receive any type of exception point and were allocated with their calculated MELD.

Results: Overall, 730 patients fitted the inclusion criteria. The proportion of patients with MELD exceptions increased from 2012 to 2017 (44% vs 88%). Concordantly, allocation MELD at the time of transplantation showed an annual increase (23 ± 8 points vs 32 ± 5 points, p < 0.001). Patients with any type of MELD exception were more likely to be transplanted when compared to patients without

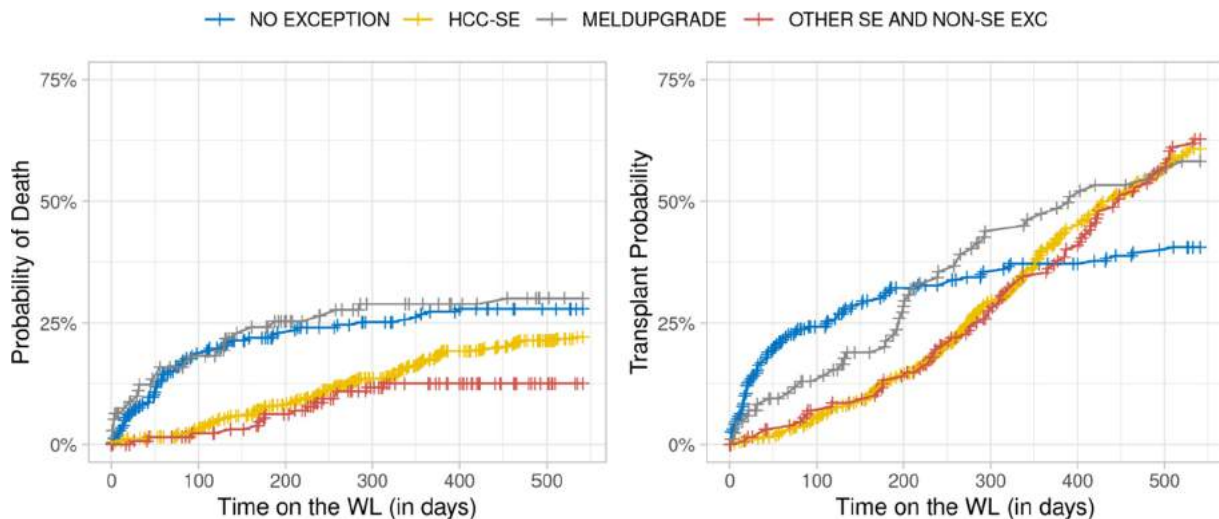


Figure: (abstract: PO-1126): Competing risk survival curves according to MELD exception categories divided by outcome: waiting list mortality and liver transplantation (Abbreviation: WL: waitlist, SE: standard exception)

MELD exceptions. Patients with MELDUP exceptions and those without MELD exceptions had the highest risk of dying while on the waiting list. For patients with HCC, the risk of dying increased over time, surpassing the risk of patients without MELD exceptions after 242 days on the waiting list.

Conclusion: A growing proportion of MELD exceptions were documented over time, resulting in MELD inflation. Candidates with MELD exceptions had an advantage regarding access to liver transplantation and a lower waiting list mortality. Regular analysis of waiting list and post-transplant outcome therefore remains paramount to maintain equity with regards to transplant accessibility and waiting list priority.

PO-1133

Post-transplant outcomes of previously refused liver grafts: a 10-years nationwide experience

Melisa Dirchwolf¹, Chiara Becchetti^{2,3}, Christian Toso⁴, Philipp Dutkowski⁵, Franz Immer⁶, Franziska Beyeler⁶, Daniel Candinas³, Jean-François Dufour^{2,3}, Banz Vanessa³, The Swiss Transplant Cohort Study (STCS)⁷. ¹University of Bern, Novartis Fellowship in Hepatology, Department of Biomedical Research, Bern, Switzerland; ²University of Bern, Hepatology, Department of Biomedical Research, Bern, Switzerland; ³Inselspital, University Hospital Bern, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; ⁴University Hospital of Geneva, Abdominal Surgery, Geneva, Switzerland; ⁵University Hospital of Zurich, Abdominal Transplant Surgery, Zurich, Switzerland; ⁶Swisstransplant, the Swiss National Foundation for Organ Donation and Transplantation, Bern, Switzerland; ⁷Swiss Transplant Cohort Study, Basel, Switzerland
Email: vanessa.banzwuethrich@insel.ch

Background and aims: Defining acceptable donor liver quality remains challenging with multiple variables influencing liver acceptance. We analysed the characteristics of donors with previously refused liver offers and the post-transplant outcome of recipients with and without previously refused liver offers.

Method: Nationwide cohort study including all deceased donors registered on the Swiss Organ Allocation System between 2008 and 2018. The rate of recipients re-listing and death were considered as composite outcomes at 1-week and 1-year after liver transplantation. Cox proportional hazards regression model was used considering donation after cardiac death, age, and split donation as covariates. Liver offer refusal was defined as refusals for at least the five top-listed recipients on the waiting list or livers refused for all recipients in at

least one center prior to being transplanted in a recipient in Switzerland.

Results: Overall, 1043 donors that effectively donated their liver were included and 193 (18.5%) fulfilled the definition of liver offer refusals. Donor age greater than 70 years (OR 2.22, CI 95% 1.4–3.5, p = 0.001), BMI > 30 (OR 2.7, CI 95% 1.61–452, p < 0.001) and donation after cardiac death (OR 37, CI 95% 20–68.5, p < 0.001) were independent predictors for liver offer refusals. For re-listing/death analysis, data of 1010 recipients were available. Recipients with liver offer refusals had a similar rate of re-listing or death during the first week and first year of follow-up after liver transplantation. Only donor age (OR 1.02, CI 95% 1.00–1.03, p = 0.003) significantly increased the risk of re-listing/mortality during the first year after transplantation.

Conclusion: In this 10-year analysis of liver donor selection criteria and related outcomes in Switzerland, donor age, obesity and donation after cardiac death were significantly associated with liver offer refusals. However, only donor age was found to result in an increased risk of graft loss at 1-year after transplantation.

PO-1168

Graft survival following retransplantation-a large single centre retrospective analysis

James Morgan¹, Sara Mahgoub¹, Dhiraj Tripathi^{1,2}, Tamara Perera¹. ¹Queen Elizabeth Hospital Birmingham, United Kingdom; ²University of Birmingham, United Kingdom
Email: james.morgan18@nhs.net

Background and aims: Liver transplantation is a life-saving modality for liver failure. Graft failure occurs in 5–22% of all liver transplant recipients. Liver re-transplantation has been considered controversial, with clinical, economic, and ethical considerations. A study from Birmingham in 2009, reported no survival benefit following second and third re-transplantation. However, recent international data has suggested that survival following re-transplantation is comparable with first re-transplantation. The data from one of the UK's largest liver transplant centres has been re-evaluated to provide contemporary knowledge to inform clinicians and assist with complex decision-making.

Method: A retrospective study from January 2009 to March 2020. All adult patients who underwent first, second or third re-transplantation during this study period at University Hospital Birmingham were included. Data collection included primary diagnosis requiring liver transplantation, aetiology of graft failure, donor and recipient factors and time interval between graft transplantation. Overall graft and patient survival rates were analysed with Kaplan-Meier curves.

POSTER PRESENTATIONS

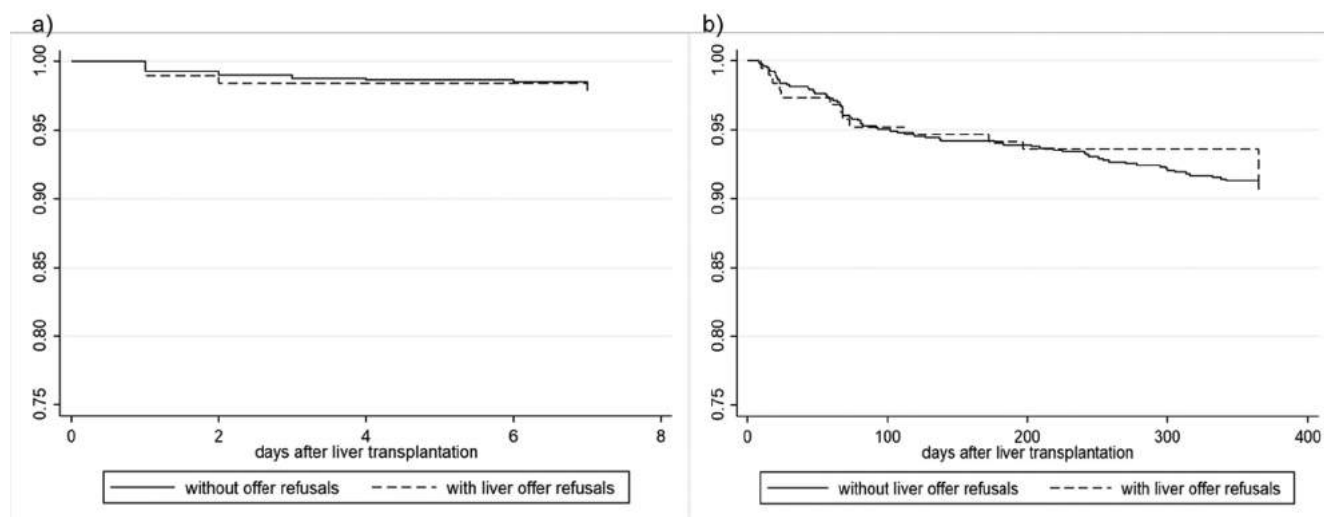


Figure: (abstract: PO-1133): (a) Kaplan-Meier curve for re-listing or mortality during 0–7 days after liver transplantation according to liver offer refusals; (b) Kaplan-Meier curve for re-listing or mortality during 8–365 days after liver transplantation according to liver offer refusals.

Results: There were 2454 adult and paediatric transplants during the study period. 6.6% (161) were re-transplanted, of which 15.5% (25) had a third retransplant and 1.2% (2) a fourth. The commonest indication for initial transplant in those who were subsequently re-transplanted were: PSC (25.5%), HCC (12.4%), Seronegative (9.3%) and PBC (9.3%). 12.8% of all grafts were DCD and 97.8% of these were used for initial transplant. Mean age at the time of first graft was 40 (range 0–68), second graft 44 (range 9–69) and third graft 33 (range 14–63). The most frequent reasons for re-transplantation were thrombotic and non-thrombotic graft infarction (28.7%), biliary complications (20.7%), early graft dysfunction (18.6%), graft rejection (17.5%) and recurrence of disease (14.9%). Mean MELD score prior to 1st graft was 13, 2nd graft 21 and 3rd graft 22. Machine perfusion was utilised for 13 re-transplants. Patient survival following 2nd graft at 12, 24 and 60 months was 96%, 86% and 80% respectively. Patient survival following 3rd graft at 12, 24 and 60 months was 96%, 96% and 84% respectively. Graft survival after 2nd graft was 90%, 82% and 79% at 12, 24 and 60 months, respectively. Graft survival after 3rd graft was 100% at 12, 24 and 60 months respectively.

factors influencing outcomes. Our findings support re-transplantation in carefully selected individuals.

PO-1169

Changes in the profile and outcomes of paediatric liver transplantation in the United States

Maria Stepanova^{1,2}, Khaled Kabbara^{2,3}, Elisabeth Eberly^{2,3}, Michael Herring^{2,3}, Saleh Alqahtani^{1,4}, Zobair Younossi^{3,5}. ¹Center for Outcomes Research in Liver Disease, Washington DC, United States; ²Inova Health System, Beatty Liver and Obesity Research Program, United States; ³Inova Health System, Medicine Service Line, Falls Church, United States; ⁴King Faisal Specialist Hospital, Riyadh, Saudi Arabia; ⁵Inova Health System, Department of Medicine, Center for Liver Diseases, United States

Email: zobair.younossi@inova.org

Background and aims: Indications for paediatric liver transplantation are different from those of adults. Our aim was to assess trends in indication and outcomes of paediatric patients waitlisted for liver transplantation in the U.S. over the last decade.

Method: We used Scientific Registry of Transplant Recipients (SRT) 2008–2020 to collect data for all patients <18 years of age listed for a liver transplant in the U.S. The study outcomes were receiving a transplant for candidates and time to post-transplant mortality for recipients. The cut-off date was December 2, 2020.

Results: There were 9488 paediatric liver transplant candidates in SRT between 2008 and 2020. Mean age was 5.4 years (SD 5.8), 49% were male, 50% white, 95% U.S. citizens, and 53% by Medicaid. Mean Paediatric End-stage Liver Disease (PELD) score was 13.5 (SD 14.5). The most common aetiology of liver disease was biliary atresia or biliary hypoplasia (33%), followed by metabolic liver disease (12%) and acute or drug-induced liver disease (12%). Over time, the most substantial change in the distribution of underlying aetiologies was a decrease in the rate of liver disease from external causes (total parenteral nutrition- or hyperalimentation-induced), which decreased more than two-fold (from 7.4% in 2008–2011 to 3.6% in 2017–2020). At the same time, the proportion of patients with biliary atresia or hypoplasia increased from 30% to 35% ($p < 0.01$). Of all waitlisted candidates, 76% eventually received a transplant after mean 142 (SD 260) days of waiting; that rate remained stable during the study years ($p > 0.05$). Independent predictors of a higher chance of receiving a transplant in paediatric patients were older age and a listing diagnosis of biliary atresia or hypoplasia (all $p < 0.01$). In addition, higher PELD score, having Medicaid, and a listing diagnosis

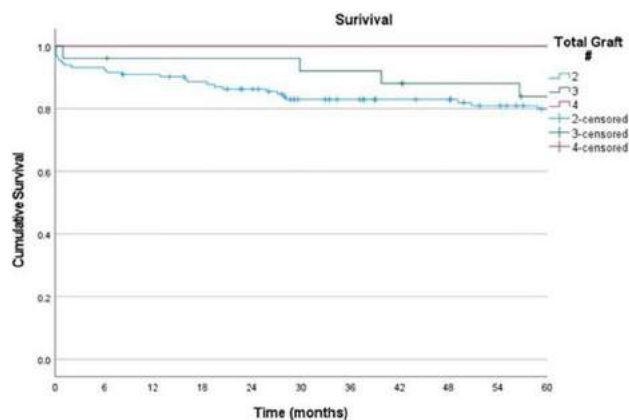


Figure 1: Kaplan Meier graph comparing patient survival following 2nd, 3rd and 4th graft.

Conclusion: Outcomes following re-transplantation have improved in the last 10 years despite increasing use of marginal donors. This could reflect careful patient selection, increased experience, and use of new technologies. Further study is suggested to identify specific

due to external causes were associated with a lower chance of receiving a transplant (all $p < 0.01$). In those who received a transplant, 5-year survival was 89%, which increased from 86% in the early years to 92% in those transplanted in 2014–2015 ($p < 0.0001$). Higher post-transplant mortality was found to be associated with earlier calendar year, higher PELD score, having Medicaid, and liver disease due to external causes (all $p < 0.01$).

Conclusion: Paediatric indications for liver transplantation are different from those seen in adults. There is a steady trend towards improvement of post-transplant outcomes in the paediatric population.

PO-1459

Recipient age influences the short- and long-term survival after liver transplant: results of the French national cohort 2007–2017

Lea Lerosey¹, Elea Ksiazek², Michal Abrahamowicz³, Corinne Antoine⁴, Sebastien Dharancy^{5,6}, Thomas Mouillot¹, Anne Minello Franza¹, Alexandre Doussot⁷, Vincent Di Martino⁸, Christine Binquet^{2,9}, Marianne Latournerie¹. ¹CHU François Mitterrand, Hepatogastroenterology, Dijon, France; ²CHU François Mitterrand, Centre d'Investigation Clinique, Dijon, France; ³McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montreal, Canada; ⁴Agence de Biomédecine, Direction Prélèvement Greffe Organes-Tissus, Saint-Denis La Plaine, France; ⁵CHRU de Lille, Service des maladies de l'appareil digestif, CHRU de Lille, France, Lille, France; ⁶Université Lille 2, Inserm U795, Lille, France; ⁷CHU Jean Minjot, Liver Transplantation, Besançon, France; ⁸CHU Jean Minjot, Hepatology, Besançon, France; ⁹INSERM, CIC1432, Module Epidémiologie Clinique, Dijon, France
Email: marianne.latournerie@chu-dijon.fr

Background and aims: Advances in liver transplant (LT) procedures, along with epidemiology changes, led to increase the number of liver recipients aged over 65 years despite the lack of donors. In this context, we aimed to investigate the impact of recipient's age on the five- and ten-years post-transplantation mortality.

Method: All patients aged over 18 years who received a first LT between 2007 and 2017, registered in the nationwide database of the French Biomedicine Agency, were included. The association between age and observed mortality was estimated using a conventional Cox proportional hazards (PH) model. Flexible models were used, allowing to estimate time dependent and/or non-log-linear effects and to account for the expected mortality of each patient given their sex and age.

Results: Overall, 7610 patients were included (mean age at LT = 55.0 ± 10.5 years). Older recipients were less likely to have an alcoholic cirrhosis and had more frequently hepato-cellular carcinoma. Older were the recipients, better was their liver function and lower was the risk of being hospitalized or under mechanical ventilation. Cox proportional hazard modeling showed that recipients' age was significantly associated with an increased risk of death within the 5 years following LT (mean increase over the 5 years post-LT for 10 additional years of age = 15%; 99%-CI = 13%-16%). The flexible extension of the Cox model showed that this risk excess was especially marked in the 1st year post-LT and then decreased over time. The net survival analysis, accounting for the expected age- and sex-related-mortality for each recipient, showed a remaining absolute difference of 8% in 10-years-net survival between recipients aged 28 and 71 years.

Conclusion: Despite the selection process for older LT recipients, age at transplant was associated with an increased risk of death, particularly in the first year after LT. This effect decreased thereafter, but was still present at five and ten years, even after accounting for age-and-sex-related expected mortality in the French population. These results suggest that the selection of older recipients has to be reinforced.

PO-1496

Impact of bacterial infections prior liver transplantation on post-transplant outcomes in patients with cirrhosis

Salvatore Piano¹, Simone Incicco¹, Marta Tonon¹, Carmine Gabriele Gambino¹, Valeria Calvino¹, Alessandra Brocca¹, Patrizia Burra², Umberto Cillo³, Paolo Angeli¹. ¹University of Padova, Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine-DIMED, Padova, Italy; ²University of Padova, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padova, Italy; ³University of Padova, Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Oncology and Gastroenterology, Padova, Italy
Email: salvatorepiano@gmail.com

Background and aims: Bacterial infections (BI) are frequent in cirrhosis, and increase the risk of decompensation, death and drop-out from the liver transplant (LT) waiting list. LT in patients with BI is frequently delayed due to the fear of poor LT outcomes. However, there is a paucity of data on the impact of BI prior LT on post-LT outcomes. We evaluated the impact of pre-transplant BI on post-LT complications and survival.

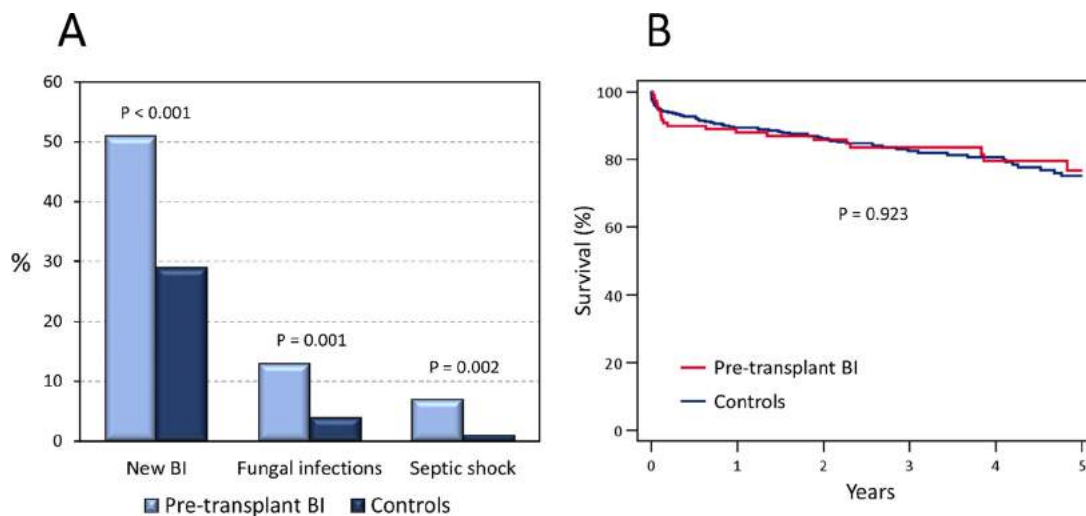


Figure: (abstract: PO-1496): (A) Occurrence of bacterial infections (BI), fungal infections and septic shock after LT in patients with pre-transplant BI and controls; (B) Probability of survival after liver transplant in patients with pre-transplant BI and controls.

POSTER PRESENTATIONS

Method: From 2012 to 2018 we identified 109 LT candidates surviving an episode of BI within 3 months prior LT, and 359 patients without BI before LT (control group). Demographic, clinical and laboratory data were collected at the time of LT; for patients with infection, the clinical laboratory and microbiological characteristics of infections were collected. After LT data on complications occurred, length of stay and survival were collected.

Results: Patients with pre-transplant BI had a worse liver function and a higher MELD-Na score at transplant than those without. Donor characteristics, cold ischemia time and time of surgery were not significantly different between the 2 groups. Patients with pre-transplant BI had a more complex postoperative course, with longer stays in intensive care unit (9 vs 6 days, $p = 0.010$) and in-hospital (29 vs 21 days, $p = 0.002$), and higher incidence of new BI after LT (51% vs 29%, $p < 0.001$), fungal infections (13 vs 4%; $p = 0.001$) and septic shock (7 vs 1%; $p = 0.002$; Figure A). Nevertheless, no difference was found in 1- and 5-year survival between patients with or without pre-transplant BI (88 vs 89% and 77 vs 75%, respectively, $p = \text{N.S.}$; Figure B). In patients with pre-transplant BI no association was found between the time elapsed from the diagnosis of BI to LT and post LT outcomes.

Conclusion: Patients with BI prior LT have a more complex clinical course after LT and higher risk of new BI, fungal infections and septic shock. However, post LT survival is excellent. Therefore, as soon as BI is resolving, it is safe to proceed with the LT, but patients with pre-transplant BI require an active surveillance for infections after LT.

PO-1523

Significantly higher mortality post liver transplantation in patients with psychosocial risk factors

Preya Patel¹, Jeevan Barn¹, Lianne Downey¹, Aaron Wetten¹, Louise MacDougall¹, Mark Hudson¹. ¹The Newcastle upon Tyne Hospitals NHS Foundation Trust, Liver Unit, Newcastle upon Tyne, United Kingdom
Email: jeevanbarn@gmail.com

Background and aims: Organ allocation for liver transplantation (OLT) presents an ethical dilemma. Psychosocial factors may influence post-transplantation outcomes however assessment of these risk factors is not standardised across UK centres. We used a

psychosocial risk profile tool (PSRPT) to quantify these risk factors and assessed their impact on post OLT outcomes.

Method: We retrospectively applied the PSRPT to all patients undergoing elective OLT assessment from January 2010 to December 2014. Data was collected on assessment outcomes, transplantation, late onset medical/psychiatric complications and mortality.

Results: 273 patients were included; their median age was 57 years and 62.3% were male. 168 patients were listed for transplant and 126 underwent OLT. The main indications for transplant were synthetic dysfunction (35.9), refractory ascites (31.9%) and hepatic encephalopathy (32.6%). Sixty-five percent of patients assessed were classed as medium/high psychosocial risk (MPSR). MPSR patients were more likely to have underlying alcohol related liver disease ($p = 0.005$), were less likely to undergo transplantation ($p < 0.001$) and were more likely to return to alcohol misuse ($p < 0.001$) when compared to low-risk patients (LPSR). MPSR patients had a significantly higher all-cause mortality than LPSR patients ($p = 0.005$). Factors independently associated with mortality were undergoing transplantation (OR 0.10 (95% CI 0.06–0.20)) and concerns regarding financial support (OR 4.85 (95% CI 1.16–20.32)). Figure 1 illustrates the survival difference between those classed as MPSR vs LPSR. In those transplanted, MPSR patients had significantly higher mortality ($p = 0.037$). 35 (27.7%) patients who underwent transplant died during the follow-up period. Factors significantly associated with mortality post transplantation were recidivism ($p = 0.026$) and concerns regarding social ($p = 0.002$) and financial support ($p = 0.050$). Lack of social support was independently associated with increased mortality in those who underwent OLT (OR 7.18 (95% CI 1.68–30.73)).

Conclusion: MPSR patients had a higher all-cause mortality and increased risk of recidivism. This suggests that utilizing the PSRPT may highlight at-risk patients, thus enabling implementation of enhanced support to prevent poor outcomes.

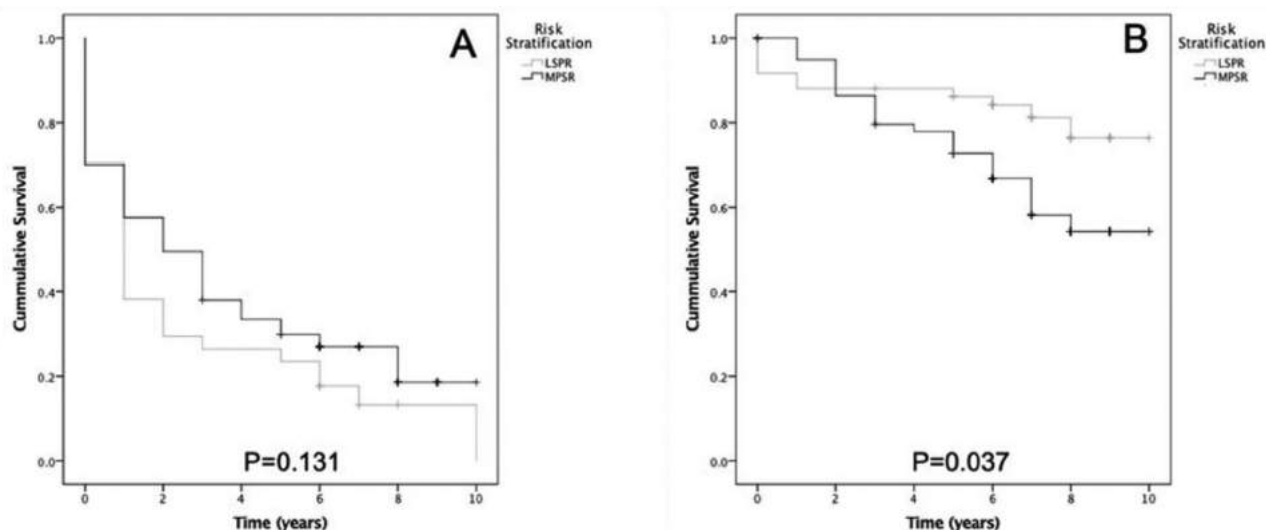


Figure 1: (abstract: PO-1523): Kaplan-Meier survival curves comparing risk stratification groups in (a) patients who did not undergo transplantation and (b) patients who were transplanted.

PO-1773

Clinical value of surveillance biopsies in pediatric liver transplantation: A single center experience with >800 biopsies

Brittany Rocque¹, Aaron Zaldana¹, Carly Weaver², Julia Huang¹, Arianna Barbeta¹, Victoria Shakhin², Cameron Goldbeck¹, George Yanni², Rohit Kohli², Yuri Genyk^{1,2}, Juliet Emamaullee^{1,2}.
¹University of Southern California, Surgery, Los Angeles, United States;
²Children's Hospital Los Angeles, Pediatrics, Los Angeles, United States
 Email: Brittany.Rocque@med.usc.edu

Background and aims: While pediatric liver transplantation (LT) results in excellent long-term outcomes, a high incidence of early acute cellular rejection (ACR) and late graft fibrosis persists. Routine liver function tests may not reliably detect rejection episodes or identify patients who are candidates for reduced/modified immunosuppression (IS). Surveillance biopsies (SB) can provide valuable information in this regard, but their role in pediatric LT continues to be controversial.

Method: A retrospective cohort of 232 pediatric LT recipients who underwent biopsy between 2003–2019 was studied to characterize the potential risks and benefits of SB vs 'for cause' biopsies. At our center, SB was performed >5 years post-LT with stable graft function or 1-year post biopsy-proven ACR.

Results: Among 816 biopsies obtained from 232 patients, 150 (18%) were SB. Only 6 (0.7%) of patients in the entire cohort had a biopsy-related complication, and none were observed in the SB subset. Liver function tests did not predict rejection severity on biopsy (ALT AUROC 0.65 (very poor prediction), Bilirubin AUROC 0.58 (no prediction), GGT AUROC 0.56 (no prediction)). SB identified a subclinical rejection episode in 18.6% of biopsies. When obtained within 24 months of LT, 7.7% of SB led to changes in IS, when obtained >24 months post-LT 18.7% prompted IS change including reduction. SB obtained <10-years post-LT trended toward higher incidence of ACR (Figure 1A), with reversal at >10 years, although this was not significant (p=0.24). Graft survival and patient survival did not differ between SB and 'for cause' groups (Figure 1B and C). 63% of SB had some evidence of fibrosis.

Conclusion: In our experience, SB in pediatric LT have a good safety profile and provide valuable information about subclinical rejection episodes, leading to changes in management of IS. Further multi-center studies are needed to examine the role for SB on long-term outcomes in pediatric LT.

PO-1971

Factors associated with unplanned intensive care unit readmission following liver transplantation

Marcus Robertson^{1,2,3}, Andy Lim³, Ben Johnstone¹, Elise Cannan¹, Andrew Tsoi¹, Paul Gow^{1,2}, Peter Angus^{1,2}, Daryl Jones^{4,5}.
¹Austin Hospital, Liver Transplant Unit, Heidelberg, Australia; ²University of Melbourne, Department of Medicine, Heidelberg, Australia; ³Monash University, Department of Medicine, Clayton, Australia; ⁴Austin Hospital, Intensive Care Department, Heidelberg, Australia; ⁵Monash University, Department of Medicine, Heidelberg, Australia
 Email: robbo10@hotmail.com

Background and aims: Patients undergoing liver transplantation (LT) have a high-risk of postoperative clinical deterioration (CD). Previous studies indicate that 6–19% LT recipients require unplanned intensive care unit (ICU) readmission, which most commonly occurs following Rapid Response Team (RRT) activation and is associated with morbidity and mortality. There is a paucity of data on predictors of unplanned ICU admission following RRT activation post-LT. We aimed to determine the incidence and factors predicting unplanned ICU admission post-LT.

Method: We conducted a cohort study of consecutive LT recipients (≥18 years) of the Victorian Liver Transplant Unit who experienced a CD event and RRT activation from 2011–2017. The primary outcome was unplanned ICU admission. Secondary outcomes were hospital length of stay (LOS) and inpatient mortality. Multivariable logistic regression with cluster specific robust standard errors was used to predict the primary outcome, while accounting for baseline variables, RRT triggers, biochemistry and vital signs. Models were compared with information criteria. Model discrimination was assessed by the area under the receiver operating curve (AUROC) and calibration examined by a calibration plot.

Results: 381 patients were included. Median age was 56 (IQR 48–61), 65% were male and mean MELD score was 19 (SD 9.6). Post-LT CD occurred in 88 (23%) patients with a total of 160 RRT activations at a median of 11-days (IQR 5–23) post-LT. Unplanned ICU readmission occurred in 16.9% (27 of 160) of RRT activations, or 6.0% (23 of 381) transplant recipients. Variables independently associated with unplanned ICU admission in the regression model are listed in Table 1, which predicted the primary end point with an AUROC of 0.82. Compared to patients without ICU readmission, patients with unplanned ICU admission had longer post-LT LOS (median, 23 days vs 13 days, p < 0.001), ICU LOS (median, 189 hours vs 72 hours, p < 0.001) and a non-significant trend towards higher mortality (13.0% vs. 3.6%, p = 0.06). No difference in mean MELD at time of LT was noted between groups (21 vs. 19, p > 0.05).

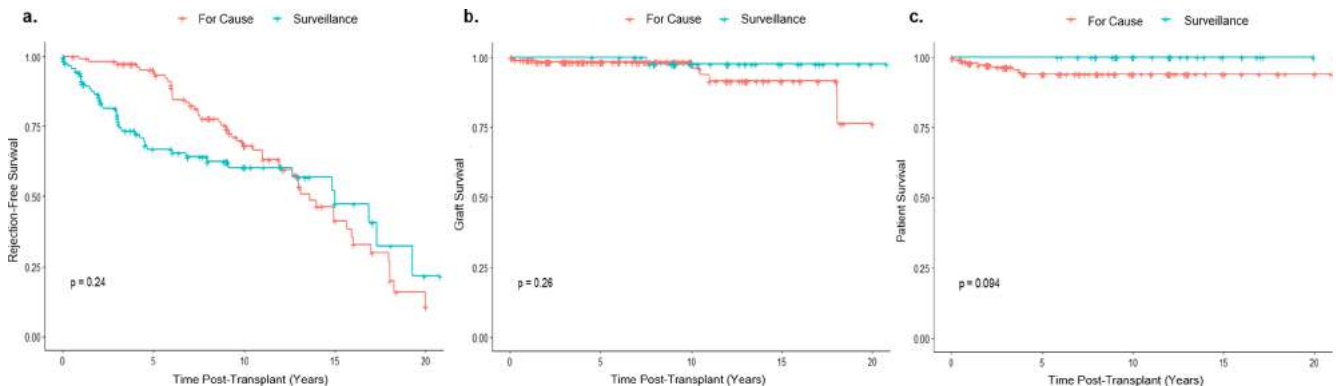


Figure 1: Pediatric LT recipient outcomes based on having biopsy 'For Cause' or for 'Surveillance'

Figure: (abstract: PO-1773)

POSTER PRESENTATIONS

Figure: Factors associated with ICU readmission post-LT in multivariate logistic regression

	OR (95% C.I.)	P value
RRT activation delay >1 hour	6.0 (1.6–23.1)	0.002
Glasgow Coma Scale \leq 13	6.6 (2.1–20.5)	<0.001
Mean arterial blood pressure <70 mmHg	4.9 (1.6–14.7)	0.007
Serum creatinine, per 1 μ mol/L	3.6 (1.6–8.3)	0.003
Serum sodium <133 mmol/L	3.1 (1.1–9.2)	0.028

Conclusion: LT patients with CD requiring unplanned ICU readmission are a high-risk group with increased morbidity, ICU and hospital LOS. We identified a model that predicted ICU readmission with an AUROC of 0.82, however further validation is required. Early identification and correction of these factors may lead to improved outcomes and a reduction in health-care costs.

PO-2001

Covid-19 in Liver Transplant Recipients: A National Cohort

Gökhan Kabaçam¹, Ilker Turan², Murat Kiyici³, Zeynep Melekoğlu Ellik⁴, Süleyman Dolu⁵, Murat Dayangac⁶, Derya Ari⁷, Dilara Turan Gökçe⁷, Abdullah Emre Yildirim⁸, Genco Gencdal⁹, Murat Harputluoglu¹⁰, Aysun Kartal¹¹, Emine Kübra Dindar Demiray¹², Feyza Gündüz¹³, İlkay Ergenç¹³, Cumali Efe¹⁴, Hale Gokcan Sumer⁴, Meral Akdogan Kayhan⁷, Murat Taner Gulsen⁸, Murat Akyildiz⁹, Cigdem Arıkan¹⁵, Sedat Karademir¹⁶, Deniz Balci¹⁷, Ziya Dünder¹⁸, Mesut Akarsu⁵, Fulya Günsar², Zeki Karasu², Ramazan İdilman⁴. ¹Güven Hospital, Dept of Gastroenterology and Liver Transplantation, Ankara, Turkey; ²Ege University School of Medicine, Dept of Gastroenterology, Izmir, Turkey; ³Uludağ University School of Medicine, Dept of Gastroenterology, Bursa, Turkey; ⁴Ankara University School of Medicine, Dept of Gastroenterology, Ankara, Turkey; ⁵Dokuz Eylül University School of Medicine, Dept of Gastroenterology, İzmir, Turkey; ⁶Medipol University School of Medicine, Dept of Liver Transplantation, Istanbul, Turkey; ⁷Ankara City Hospital, Dept of Gastroenterology, Ankara, Turkey; ⁸Gaziantep University School of Medicine, Dept of Gastroenterology, Gaziantep, Turkey; ⁹Koç University School of Medicine, Dept of Gastroenterology, Istanbul, Turkey; ¹⁰İnönü University School of Medicine, Dept of Gastroenterology, Malatya, Turkey; ¹¹Kütahya Education and Research Hospital, Dept of Gastroenterology, Kütahya, Turkey; ¹²Bitlis State Hospital, Dept of Infectious Diseases, Bitlis, Turkey; ¹³Marmara University School of Medicine, Dept of Gastroenterology, Istanbul, Turkey; ¹⁴Harran University School of Medicine, Dept of Gastroenterology, Şanlıurfa, Turkey; ¹⁵Koç University School of Medicine, Dept of Pediatric Gastroenterology, Istanbul, Turkey; ¹⁶Güven Hospital, Dept of Liver Transplantation, Ankara, Turkey; ¹⁷Ankara University School of Medicine, Dept of Liver Transplantation, Ankara, Turkey; ¹⁸Uludağ University School of Medicine, Dept of General Surgery, Bursa, Turkey
Email: gokhankabacam@yahoo.com

Background and aims: The effect of coronavirus disease 2019 (COVID-19) on outcomes of liver transplant recipients is not known very well. The aim of the present study was to describe the early outcomes of liver transplant recipients with COVID-19.

Method: Liver transplant recipients with concomitant confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from 14 tertiary liver transplant centers of Turkey were enrolled into the study. The diagnosis of SARS-CoV-2 infection was made according to the World Health Organization guidelines and based on the presence of clinical features, laboratory and radiological findings. The immunosuppressive protocol mainly consisted of calcineurin inhibitors (CNIs) plus mycophenolate mofetil (MMF) and a steroid.

Results: A total of 129 liver transplant recipient had diagnosed with COVID-19. Median age was 56 years. The recipients were predominantly male (69%). The median interval between liver transplantation (LT) and COVID-19 diagnosis was 48 months: 18 recipients had been transplanted less than one year, while 49 recipients had been transplanted more than 5 years. The most common etiology of LT was hepatitis B virus related liver disease (45.7%). Immunosuppressive protocol comprised of single agent in 42% of the patients, double agents in 48%, triple agents in 7%.

At the time of COVID-19 diagnosis, most recipients (54%) had at least one co-morbidity including diabetes mellitus (31.8%), hypertension (36.4%). Main presenting symptoms were fatigue (78%), fever (51%), cough (47%), dyspnea (26%), and diarrhea (10%). Pneumonic infiltration was observed in 64% of the recipients, 22.5% had relevant increase in liver enzymes.

After the diagnosis, 47% of the recipients were treated in the ward, and 12% was taken to the ICU. Among whole cases 14.7% of them needed nasal oxygen therapy, and 10.2% required intubation and invasive mechanical ventilation.

Overall, 12 recipients (9.4%) died due to COVID-19 related respiratory or multisystem failure. With multivariate analysis, c-reactive protein (CRP), procalcitonin levels and mechanical ventilation requirement were the risk factors that are significantly associated with mortality ($p < 0.001$, $p = 0.004$, $p < 0.001$).

Conclusion: COVID-19 significantly affects the outcome of LT recipients. Increased CRP and procalcitonin levels in admission and mechanical ventilation requirement are the most important risk factors for mortality.

PO-2121

The impact of COVID-19 on liver transplant (LT) centers across the world during the first wave: a Multisociety Survey (EASL-ESOT/ELITA-ILTS)

Francesco Paolo Russo¹, Manhal Izzy², Ashwin Rammohan³, Varvara Kirchner⁴, Luca Saverio Belli⁵, Thomas Berg⁶, Marina Berenguer Haym⁷, Wojciech Polak⁸. ¹University Hospital Padua, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; ²Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, Nashville, United States; ³The Institute of Liver Disease and Transplantation, Dr. Rela Institute and Medical Centre, Chennai, India; ⁴Department of Surgery, University of Minnesota, Minneapolis, United States; ⁵Department of Hepatology and Gastroenterology, Niguarda Hospital, Milan, Italy; ⁶Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; ⁷Hepatology and Liver Transplantation Unit, IIS La Fe, Hospital Universitario y Politécnico La Fe, Valencia, Spain; ⁸Department of Surgery, Erasmus MC, University Medical Center, Rotterdam, Netherlands
Email: francescopaolo.russo@unipd.it

Background and aims: The global impact of SARS-CoV-2 on LT practice across the world is unknown. The aim of this survey was to collect and analyse data during the first COVID-19 wave.

Method: A prospective web-based survey (available online September 2020–December 31 2020) was proposed to EASL-ESOT/ELITA-ILTS active members in Europe (C1), Africa, Australia, Asia (C2), and the Americas (C3). The survey was made up of 4 parts, concerning transplant processes, therapy, living donor and organ procurement.

Results: Of >470 transplant centers reached, 128 answered each part of the survey, 50%, 27%, and 23% from regions C1, 2, and 3, respectively. When we compared the practice during the first 6 months of the pandemic in 2020 with that during the same period but a year earlier in 2019, statistically significant differences in the number of patients added to the wait-list (WL) in C2, and in the number of transplantations in C1 and in C2 were observed. No difference in WL mortality was seen. Of note, in Europe, waitlisting, WL mortality and LT rates changed significantly in countries heavily hit by the pandemic whereas no significant changes occurred in

those less impacted. While 30–50% of the centers transplanted recipients with previous COVID-19, only 12–17% used organs from previously SARS-CoV-2 infected donor. 18–36% of recipients turned positive after the transplant. Only 8–14% of centers routinely stopped CNI in post-transplant SARS-CoV-2 infection.

Conclusion: The SARS-CoV-2 pandemic significantly impacted transplant activities, particularly in heavily hit countries. Individualized modifications of immunosuppression were applied in infected recipients.

PO-2211

Long-term survival after living donor liver transplantation in primary sclerosing cholangitis

Timur Liwinski¹, Melina Heinemann¹, René Adam², Marina Berenguer Haym³, Darius F. Mirza⁴, Seyed Ali Malek-Hosseini⁵, Michael Heneghan⁶, Peter Lodge⁷, Johann Pratschke⁸, Karim Boudjema⁹, Andreas Paul¹⁰, Krzysztof Zieniewicz¹¹, Jiri Fronck¹², Arianeb Mehrabi¹³, Koray Acarli¹⁴, Yaman Tokat¹⁵, Ahmet Coker¹⁶, Sezai Yilmaz¹⁷, Vincent Karam², Christophe Duvoux¹⁸, Ansgar W. Lohse¹, Christoph Schramm¹. ¹University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; ²Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ³Hospital Universitario y Politécnico de La Fe, València, Spain; ⁴Queen Elizabeth Hospital, United Kingdom; ⁵Shiraz University of Medical Sciences, Avicenna Center for Medicine and Organ Transplant, Shiraz, Iran; ⁶King's College Hospital NHS Foundation Trust, King's Liver Transplant Unit, United Kingdom; ⁷Leeds General Infirmary, United Kingdom; ⁸Charité-Universitätsmedizin Berlin, Campus Charité Mitte (CCM), Department of Surgery, Berlin, Germany; ⁹Pontchaillou University Hospital Center, Department of Hepatobiliary and Digestive Surgery, Rennes, France; ¹⁰Department of Visceral and Transplant Surgery; ¹¹Medical University of Warsaw, Department of General, Transplant and Liver Surgery, Warszawa, Poland; ¹²Institute of Clinical and Experimental Medicine, Department of Transplant Surgery, Czech Republic; ¹³University Hospital Heidelberg, Department of Internal Medicine IV, Heidelberg, Germany; ¹⁴Memorial Hospital, Organ Transplantation Center, Turkey; ¹⁵GAYRETTEPE FLORENCE NIGHTINGALE HOSPITAL, Liver Transplantation Center, Turkey; ¹⁶Ege Üniversitesi, Department of General Surgery, Turkey; ¹⁷Department of Surgery and Liver Transplant Institute, Malatya, Turkey; ¹⁸Hôpital Henri-Mondor Ap-Hp, Department of Hepatology and Gastroenterology, Créteil, France Email: c.schramm@uke.de

Background and aims: Living donor liver transplantation (LDLT) is an option to ameliorate the global donor-organ shortage. However, knowledge on LDLT in autoimmune liver diseases (AILDs) is scarce.

Method: The present study analyzed long-term patient survival in LDLT recipients with autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) registered in the European Liver Transplant Registry (ELTR). The non-autoimmune disorder alcohol-related cirrhosis (ALC) served as a control. Outcomes after LDLT were compared with donation after brain death (DBD) for each diagnosis.

Results: Between 1998 and 2017 a total of 28899 individuals were registered in the ELTR database, including 1003 with LDLT. For AILDs, patient survival from >90 days after LDLT was 86.3%, 76.5%, and 63.6% after 5, 10, and 15 years. PSC patients receiving LDLT compared to DBD had an increased risk of death (hazard ratio [HR] = 2.07, p < 0.001). This was not observed for patients with AIH, PBC or ALC. Risk factors for deaths in PSC patients receiving LDLT were recipient age ≥47 years (HR = 3.65, p < 0.001), donor age ≥50 years (HR = 3.93, p < 0.001), and a male donor (HR = 3.71, p < 0.001). PSC patients receiving LDLT were at increased risk of death from disease recurrence (subHR = 5.66, p < 0.001) and biliary complications (subHR = 4.78, p = 0.005) compared to DBD.

Conclusion: Long-term survival after LDLT for AILD is favorable. Nevertheless, PSC patients receiving LDLT have an increased mortality compared to DBD.

PO-2425

Complete response after biological downstaging in patients with hepatocellular carcinoma: XXL-like prioritization for liver transplantation or "wait and see" strategy?

Alessandro Vitale¹, Paolo Angeli², Patrizia Burra³, Umberto Cillo¹. ¹University of Padua, Department of Surgical, Oncological, and Gastroenterological Sciences, Hepatobiliary Surgery and Liver Transplantation Unit, Padua University Hospital, Italy, Italy; ²University of Padua, Unit of Internal Medicine and Hepatology, Padua University Hospital, Italy, Italy; ³University of Padua, Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Italy, Italy Email: alessandro.vitale@unipd.it

Background and aims: Although some methodological and ethical issues, the recently published XXL trial represents the first prospective validation of "biological downstaging" in liver transplantation for hepatocellular carcinoma (i.e. selecting tumors with a good biology irrespective of morphological criteria). The aim of this study is to compare our downstaging protocol with the XXL protocol in terms of downstaging failure rates and patient outcome.

Method: A total of 191 patients undergoing surgical downstaging and potentially eligible for transplantation from 2012 to 2018 at our Center, were selected according to the XXL trial enrolment criteria. Differently from the XXL trial we used an aggressive surgical downstaging protocol, and patients with a complete response to downstaging did not receive any prioritization to transplant. Downstaging failure was defined as progressive disease or post treatment mortality. The statistical method "matching-adjusted indirect comparison" was used to match the study group to the XXL population and to compare the proportion of downstaging failures. The software Engauge digitizer was used to allow a statistical comparison between Kaplan Meier survival curves.

Results: Downstaging failure rate was significantly lower in our cohort than in the XXL trial (12% vs. 39%). Patients with partial response to downstaging had a much greater probability of being included in the waiting list than patients with a complete response (OR 20.4, 95% CI 6.9–69.9, p = 0.0001). Although patients with complete response were not prioritized to transplant, the survival curves of our cohort overlapped with that of the XXL protocol (p > 0.05). Survival curves of non-transplant candidates with a complete response to downstaging were similar to that of transplanted patients (p > 0.05).

Conclusion: Our study represents a validation of the current Italian policy of denying any prioritization to patients with complete response to downstaging. Such a policy seems to spare organs without worsening patient outcome.

PO-2821

SARS-CoV-2-specific cellular and humoral immunity in COVID-19 convalescence after liver transplantation

Theresa Kirchner¹, Hagen Sauer¹, Agnes Bonifacius², Ruhl Louisa³, Isabell Pink⁴, Bastian Engel¹, Emily Saunders¹, Joerg Martens³, Marius M. Hoeper⁴, Rainer Blasczyk², Heiner Wedemeyer¹, Elmar Jaeckel¹, Christine Falk³, Britta Eiz-Vesper², Richard Taubert¹. ¹Hanover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²Hanover Medical School, Institute of Transfusion Medicine and Transplant Engineering, Hannover, Germany; ³Hanover Medical School, Institute of Transplant Immunology, Hannover, Germany; ⁴Hanover Medical School, Department of Pneumology, Hannover, Germany Email: kirchner.theresa@mh-hannover.de

Background and aims: Mortality due to Coronavirus Disease-2019 (COVID-19) is not increased in immunosuppressed individuals after orthotopic liver transplantation (OLT) compared to individuals without immunosuppression. Data on protective immunity against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in immunosuppressed convalescents, especially after mild COVID-19,

POSTER PRESENTATIONS

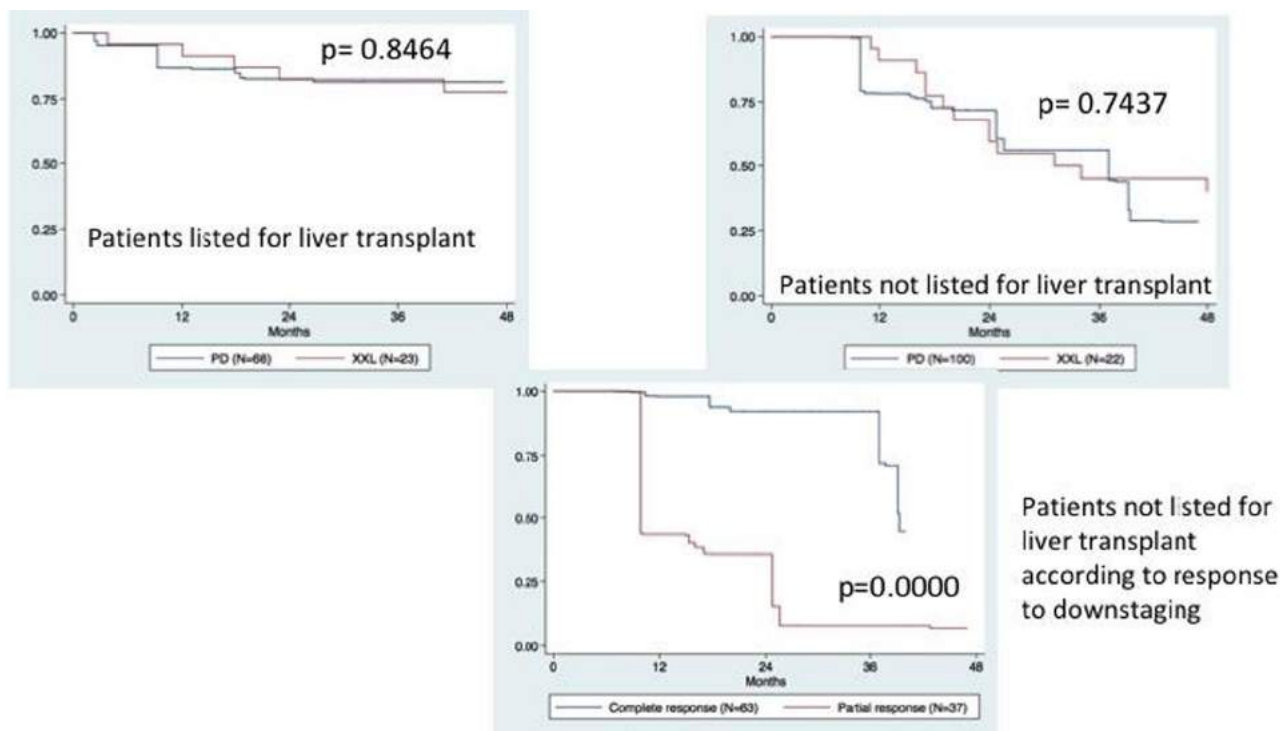


Figure: (abstract: PO-2425)

are limited. The aim of the current study was to assess the immune response in COVID-19 OLT convalescents with ongoing immunosuppressive therapy.

Method: Immune responses against SARS-CoV-2 were measured prospectively in 16 OLT convalescents at the first outpatient visit after COVID-19, in comparison to matched non-immunosuppressed convalescents (non-IS-Con, n = 24 for cellular and n = 11 for humoral immunity). SARS-CoV-2-specific T cell reactivity was detected by IFN- γ ELISPOT assay with 5 different SARS-CoV-2 antigen pools. SARS-CoV-2-specific antibodies (IgG, IgA, IgM) were detected against four different SARS-CoV-2 antigens (S1/2, RBD, nucleocapsid).

Results: The majority of OLT patients (15/16) had a mild or moderate COVID-19 and were managed as outpatients (12/16). At the first outpatient visit liver function tests and liver stiffness measurements were not suggestive for increased alloreactivity.

Anti-SARS-CoV-2 IgA and IgG antibodies were detectable in 62–100%, IgM in 31–100% of OLT convalescents. Anti-SARS-CoV-2 IgG antibodies of OLT convalescents were not reduced, neither in frequency nor in concentration, compared to non-IS-Con. None of these OLT recipients with available cryo-conserved samples before appearance of SARS-CoV-2 (n = 12) had preexisting anti-SARS-CoV-2 IgG, but some had preexisting IgA with cross-reactivity against RBD, nucleocapsid, S1 and S2. OLT convalescents had no reduced IFN- γ production, normalized to numbers of PBMCs and T cells against SARS-CoV-2 compared to non-IS-Con. No relevant T cell reactivity could be detected in pre-corona samples.

Conclusion: The study complements the data sets on cellular and humoral immunity of immunosuppressed COVID-19 convalescents by showing a robust and indistinguishable cellular and humoral immunity against SARS-CoV-2 also after mild/moderate infections without hints for a decline of cellular immunity during the first months after COVID-19. The development of a robust immunity without COVID-19-triggered rejection justifies the continuation of immunosuppressive therapy during mild to moderate COVID-19.

PO-2842

Periods of high or low intensity transplant activity are not associated with changes in liver transplant outcomes

Neil Halliday¹, Lewis Downward², Joerg-Matthias Pollok³, Rhiannon Taylor², Douglas Thorburn⁴. ¹University College London, Institute for Liver and Digestive Health, London, United Kingdom; ²NHS Blood and Transplant, Statistics and Clinical Studies, Bristol, United Kingdom; ³Royal Free Hospital NHS Foundation Trust, Hepatopancreatobiliary Surgery and Liver Transplantation, London, United Kingdom; ⁴Royal Free Hospital NHS Foundation Trust, Sheila Sherlock Liver Centre, London, United Kingdom
Email: neilhalliday@doctors.org.uk

Background and aims: The unpredictable availability of donor organs and the fact that liver transplants (LTs) are performed based on clinical need rather than scheduled capacity results in fluctuating activity within each centre. Coupled with increasing overall LT activity this results in periods of high and low LT activity. As low volume LT activity has been associated worse outcomes we hypothesised that fluctuations in work-load intensity may be associated with variation in LT outcomes and tested whether there was a threshold associated with worse LT outcomes.

Method: 11,280 liver only, deceased donor, adult LT operations (01/01/00-31/12/17) were identified from the UK Transplant registry. 32 LTs were excluded due to missing data. Cox proportional hazards models were built to estimate graft and transplant failure at 30 days, 90 days, one and three years post-LT. Unit workload was assessed as the number of LT operations performed over 1, 3, 7 and 28 days before each LT, grouped as low, medium and high ($\leq 24^{\text{th}}$, $25^{\text{th}}-74^{\text{th}}$ and $\geq 75^{\text{th}}$ percentile) compared to the unit's average activity for that year (to account for changes in LT activity over time). We tested whether unit workload was associated time and hazard of graft and transplant failure.

Results: We observed small differences in recipient characteristics with a greater proportion of LT during low activity periods for acute liver failure (17%, 15% and 15% for low, medium and high activity, p = 0.01). No differences were observed in transplant survival between

low medium and high preceding 28 day activity, stratified by individual unit activity levels (see figure). Similar findings were observed for 1, 3 and 7 day activity.

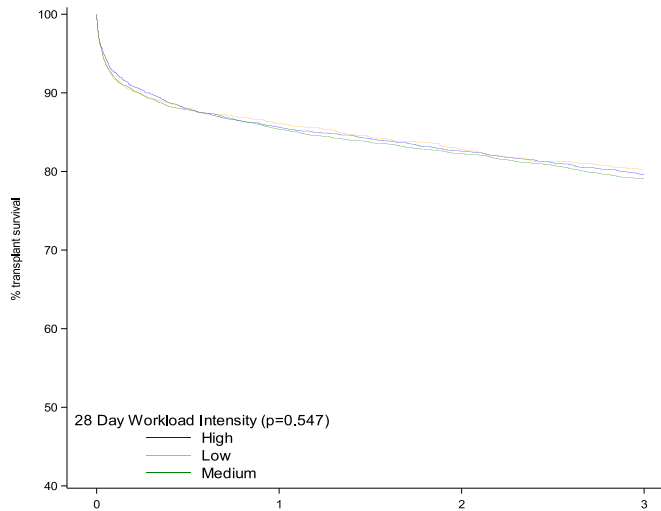


Figure: Cox-proportionate hazard models demonstrated that there were no consistent differences in graft or patient survival at 30 days, 90 days, 1 year and 3 years post LT depending on 1, 3, 7 and 28 day unit workload intensity. Further testing, assessing preceding unit LT activity as a continuous variable, did not demonstrate robust evidence of a threshold for absolute numbers of LT influencing adverse outcomes.

Conclusion: Fluctuations in unit workload did not influence LT graft or patient survival in the UK. In this large cohort we were unable to demonstrate that periods of low or high intensity LT activity, relative to the unit's own baseline activity, influenced outcomes. The model of LT delivery in the UK can absorb the necessary variations in workload without adverse impact on graft outcomes.

PO-2890
A new tool for predicting survival in liver transplantation for hepatocellular carcinoma combining molecular and clinical variables

Joana Cardoso¹, Hugo Pinto Marques², Marta Mesquita³, Andre Manso¹, Sara Carapeta¹, Mafalda Sobral², Silvia Silva², Clara Rodrigues⁴, Ana Carvalho⁴, Adelaide Milheiro⁴, Rui Perdigoto², Eduardo Barroso Garcia Da Silva², Jose Pereira-Leal¹. ¹Ophiomics-Precision Medicine, Lisboa, Portugal; ²Hospital Curry Cabral, Hepato-Biliary-Pancreatic and Transplantation Centre, Lisboa, Portugal; ³Instituto Gulbenkian de Ciência (IGC), Oeiras, Portugal; ⁴Hospital Curry Cabral, Anatomia Patológica, Lisboa, Portugal
 Email: jvaz@ophiomics.com

Background and aims: Liver cancer is one of the most frequent cancers in the world, and one of the most frequent causes of cancer-related mortality. Liver Transplantation is the best treatment for

cirrhotic patients with hepatocellular carcinoma. Clinical criteria are currently used to ascertain eligibility of patients for transplant. We developed a decision algorithm where biomarkers measured in a tumour biopsy, together with clinical variables, predicts overall survival after transplantation.

Method: A systematic review of the literature was performed to single out candidate biomarkers. RNA levels of these candidates was assessed by quantitative reverse transcriptase PCR in formalin-fixed, paraffin-embedded tumor tissue, resulting in a five gene signature. These were then considered together with clinical variables to develop a decision algorithm using machine learning approaches. Development and validation of this algorithm was based on a retrospective cohort with more than 5 years follow-up.

Results: A three step algorithm can identify a significant number of patients outside of Milan criteria that remain disease free at five year, as well as stratifying within-Milan criteria patients for overall survival. Step 1 achieves highest predictive power and accounting for over 60% of the predictions; a second step with higher recall but lower precision retrieves an additional 20% of the successful transplants, and a third, final step, reverts to Milan Criteria insuring retrieving an additional 15% of the successful transplants, but with a lowering of accuracy. The overall number of patients selected for transplant is not different from those predicted by Milan criteria, but the performance of the predictor is better.

Conclusion: The multigene and clinical variable method proposed (HepatoPrediic) outperforms conventional clinicopathologic risk factors both in Milan and San Francisco criteria, providing superior prognostic information. We show that for the same number of transplantations, including biomarkers with clinical variables in patient selection can increase the number of lives saved.

PO-2910
Liver and/or kidney transplantation after SARS-CoV-2 infection: Prevalence, short-term outcome and kinetics of serum IgG antibodies

Jef Verbeek¹, Casper Vrij¹, Pieter Vermeersch¹, Sofie Vets¹, Katrien Lagrou¹, Ina Jochmans¹, Diethard Monbaliu¹, Jacques Pirenne¹, Dirk Kuypers¹, Frederik Nevens¹. ¹University Hospital KU Leuven, Leuven, Belgium
 Email: jef.verbeek@uzleuven.be

Background and aims: Uncertainty remains on whether and when it is safe to perform transplantation (Tx) in patients with previous SARS-CoV-2 infection. We assessed: (1) the prevalence of pre-Tx SARS-CoV-2 infection in pts who underwent a liver and/or kidney Tx, (2) their short-term post-Tx outcome and (3) their longitudinal IgG antibody seroprevalence.

Method: All pts receiving a liver and/or kidney Tx at UZ Leuven between May 1st, 2020 to March 18th 2021 were included. SARS-CoV-2 PCR via nasopharyngeal swabbing (all negative) and serum SARS-CoV-2 anti-nucleocapsid (N) IgG antibodies were assessed within 24 h before Tx. Pre-Tx infection was defined as prior positive PCR and/or presence of anti-N IgG. In all pts with pre-Tx infection, serial assessment of anti-N and anti-spike (S) IgG were performed after Tx.

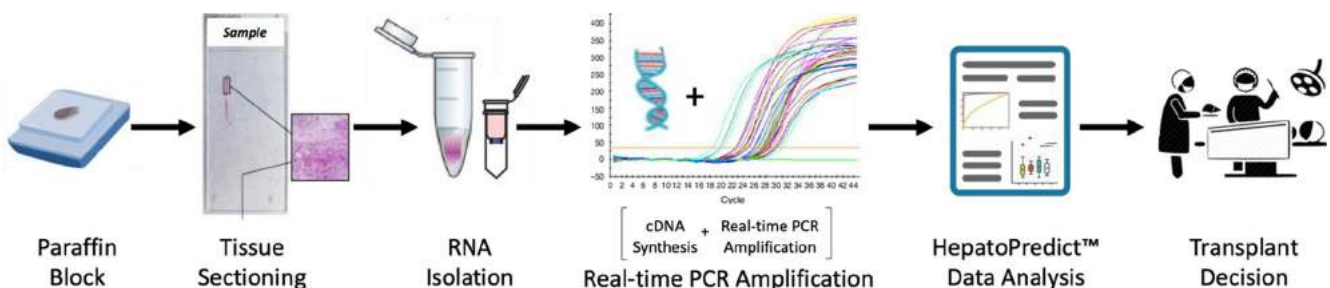


Figure: (abstract: PO-2890)

POSTER PRESENTATIONS

Results: 168 liver and/or kidney Tx procedures were performed, including 62 single liver Tx, 101 single kidney Tx and 5 combined liver-kidney Tx. 11/186 (6.54%) pts had a previous SARS-CoV-2 infection (Table 1) of which 5/62 (8.06%) single liver recipients, 3/101 (2.97%) single kidney recipients and 3/5 combined liver-kidney recipients. Median interval between infection (day PCR positivity) and Tx was 4.5 m (range 0.9–11). Median follow-up after Tx was 4.9 m (range 0.3–8.9). At last post-Tx follow-up, 10/11 pts were alive. No clinical signs of active/recurrent SARS-CoV-2 infection were detected. One pt (⁷; frail and oxygen dependent with cholangiopathy and renal failure at the moment of Tx due to previous critical COVID-19) died from septic shock 5 wks after combined liver-kidney Tx. Absolute anti-N and anti-S IgG levels were positively correlated ($r = 0.58, p \leq 0.001$) and both declined in all pts. The median duration of IgG seropositivity was 168 d (range 47–397) for anti-N and 196 d (range 71–397) for anti-S IgG after positive PCR. In 3 pts, anti-N IgG disappeared after a median of 243 d (range 71–326) after initial positive PCR, but all pts remained anti-S IgG positive until last follow-up. In 2/11 pts with pre-Tx infection, anti-N and anti-S IgG were negative at the day of Tx and remained negative after Tx.

Pt	Tx Organ (L)/Kidney (K)	Age (yr)/Gender	Tx indication	COVID-19 Severity	Interval PCR+ and Tx (d)	Follow-up after Tx (d)
1	L	67/M	ICU cholangiopathy	Critical	167	226
2	L	68/M	NASH	Asymptomatic	169	148
3	L	50/F	AIH	Critical	195	156
4	L	57/F	ALD	Mild	26	95
5	L	52/F	ALD	Mild	60	65
6	L + K	72/F	ADPKD and ESKD	Asymptomatic	56	233
7	L + K	69/M	ICU Cholangiopathy and kidney failure	Critical	148	38
8	L + K	63/M	NASH and HRS	Asymptomatic	47	30
9	K	69/M	Dent's disease	Severe	246	151
10	K	62/M	Nephroangiosclerosis	Asymptomatic	49	270
11	K	61/M	Hypertensive nephropathy	Severe	339	10

Figure:

Conclusion: With the largest case series to date, we provide real-world data supporting the recommendation that liver and/or kidney Tx can safely be performed in patients with complete symptom resolution and a negative SARS-CoV-2 PCR at the moment of Tx.

Liver transplantation and hepatobiliary surgery: Experimental

PO-246

CD44v6+gp38+ large extracellular vesicles in gall bladder survival prognosis-a pilot study

Marcin Krawczyk^{1,2}, Bingduo Wang³, Joanna Ligocka², Krzysztof Zieniewicz², Waldemar Patkowski², Sabine K. Urban³, Arnulf G. Willms⁴, Tudor Mocan⁵, Piotr Milkiewicz^{2,6}, Veronika Lukacs-Kornek⁷, Christian P. Strassburg³, Mirosław Kornek³.
¹Saarland University Hospital, Department of Medicine II, Homburg, Germany; ²Medical University of Warsaw, Department of General, Transplant and Liver Surgery, Warszawa, Poland; ³Universitätsklinikum Bonn, Medizinische Klinik und Poliklinik I, Bonn, Germany; ⁴German Armed Forces Central Hospital, Department of General, Visceral and Thoracic Surgery, Koblenz, Germany; ⁵Iuliu Hatieganu University of Medicine and Pharmacy, Octavian Fodor Institute for Gastroenterology and Hepatology, Cluj-Napoca, Romania; ⁶Pomeranian Medical University, Translational Medicine Group, Szczecin, Poland;

⁷Universitätsklinikum Bonn, Institut für Experimentelle Immunologie, Bonn, Germany
 Email: miroslawkornek@web.de.

Background and aims: Biliary cancer, comprising cholangio- and gallbladder carcinomas (CCA and GbCA), is associated with high mortality due to asymptomatic disease onset and resulting late diagnosis. Currently, no robust prognostic biomarker is clinically available in GbCA. Here, we present combinations of antigens being simultaneously present on the same large extracellular vesicle in order to predict the outcome in GbCA. Additionally, we are discriminating closely related HCC from GbCA.

Method: The presence of CD44v6⁺, gp38⁺ (podoplanin) and double positive cells was confirmed in wild type C57Bl/6j mice *in vivo* by FACS. Large EVs from patients' sera were isolated by sequential centrifugation at 2, 000 and 20, 000 × g. NTA was performed to verify the size of isolated EVs. To identify large EVs FACS was applied with AnnexinV (AnnV) serving as a general EV marker. Small EVs were used as negative control to establish large EV FACS methodology. In total, 23 GbCA, 31 HCC, 15 non-small cell lung carcinoma (NSCLC), 19 colorectal cancer (CRC) patients and 30 healthy subjects were enrolled in the study. Blood sampling took place prior to palliative or curative treatment.

Results: (i) gp38 and CD44v6⁺ were differentially expressed in wild type mice indicating a likely parental cell population for EVs. (ii) AnnV⁺CD44v6⁺ EVs alone allowed a significant discrimination of biliary cancer from HCC, NSCLC, CRC and healthy subjects. AUC values for biliary cancer vs. HCC reached 0.81 for AnnV⁺CD44v6⁺. AnnV⁺gp38⁺ and AnnV⁺CD44v6⁺gp38⁺ EVs were inferior regarding their diagnostic properties. (iii) AnnV⁺CD44v6⁺gp38⁺ EVs predicted the outcome regarding survival time, indicating a possible cut-off value that can be associated with a shorter survival time of gallbladder patients who underwent typically a cholecystectomy, in some cases with a liver resection and lymphadenectomy of hepatoduodenal ligament or endoscopic retrograde cholangiopancreatography (ERCP). Survival log-rank test for difference gave a p value of 0.008. Kaplan Meier curve analysis revealed that the probability of survival is approximately 77.77% at week 20, if AnnV⁺CD44v6⁺gp38⁺ EVs were below 13.72/1000 AnnV⁺ EVs in GbCA. Survival cut-off was defined as the median of all GbCA AnnV⁺CD44v6⁺gp38⁺EVs/1000 AnnV⁺ EVs values. The median survival was given as 8 weeks if EVs were above 13.72 AnnV⁺CD44v6⁺gp38⁺ EVs/1000 AnnV⁺ EVs and only 18.8% at week 20. In sum, survival probability at week 20 was 4.3 times bigger if AnnV⁺CD44v6⁺gp38⁺ EVs were below 13.72/1000 AnnV⁺ EVs in GbCA.

Conclusion: Our results show that AnnV⁺CD44v6⁺gp38⁺ EVs serve as a clinically relevant overall survival biomarker for gallbladder cancer. Thus, EVs represent an early, minimal-invasive screening option for this fatal cancer entity that currently lacks the existence of other clinically reliable serum markers.

PO-982

Development of a novel rat bioreactor to facilitate manufacture of human hepatocyte cell therapies for the treatment of patients with severe liver diseases

Raymond Hickey¹, Elizabeth Wilson¹, Rafal Witek¹, Tin Mao¹, Kristen Darrell¹, Michael Wong¹, Glen Mikesell¹, Gabriel Peixoto¹, Alan Mendoza¹, Prativa Sharma¹, Craig Wise¹, Peter Lee¹, Tiffany Tse¹, Douglas Matje¹, Charity Juang¹, Janice Kim¹, Carol Alvarez¹, Gaetano Faleo¹, Jason Hulse¹, Abeba Demelash¹, Chy-Anh Tran¹, Kenneth Dorko¹, Glenn Pierce¹, FEI Yi¹, Stanley Hollenbach¹, Michael Holmes¹.
¹Ambys Medicines, South San Francisco, United States
 Email: rhipkey@ambys.com.

Background and aims: Hepatocyte transplantation is a potential therapy for acute and chronic liver diseases, but this approach has been limited by the availability of high-quality donor livers and well-characterized, functional hepatocytes. Given no methods exist to expand transplantable hepatocytes *ex vivo*, we hypothesized that an

in vivo rat bioreactor could be used for the large-scale expansion of functional primary human hepatocytes for clinical use.

Method: An immune-deficient rat model of hereditary tyrosinemia type 1 (*Fah*^{-/-}, *Rag1*^{-/-}, *Il2rg*^{-/-} [FRG] rats) was generated. Phenotypic, histological, and molecular characterization was performed on and off the protective drug NTBC. Transplantation of rodent and human hepatocytes were performed to determine in vivo repopulation kinetics and therapeutic efficacy.

Results: FRG rats exhibited normal health while administered NTBC in the drinking water. FRG rats off NTBC displayed a failure-to-thrive phenotype resulting in liver and kidney damage that was associated with hypertyrosinemia and elevated succinylacetone. Transplantation of FAH+ rat hepatocytes, combined with NTBC cycling, provided selective pressure for FAH+ cells to expand and rescue the lethal phenotype. Next, immunodeficiency of FRG rats, needed for xenograft maintenance, was confirmed by flow cytometry which demonstrated severely reduced T, B, and NK cells in peripheral blood. Repopulation of FRG rat livers was achieved with multiple human hepatocyte donors based on human albumin ELISA (>5 mg/ml) and FAH immunohistochemistry (>50%). Purified expanded human hepatocytes exhibited typical hepatocyte transcription profiles based on multiple analyses, including scRNA-Seq. Expanded cells retained their synthetic (e.g. albumin expression), metabolic (e.g. cytochrome P450 activity), and detoxification (e.g. ammonia clearance) functions. Finally, FRG rat-derived human cells demonstrated robust engraftment and expansion in a mouse model of hereditary tyrosinemia. Transplanted human hepatocytes normalized tyrosine and succinylacetone levels, preventing onset of liver failure, and demonstrating therapeutic efficacy of bioreactor-expanded human cells.

Conclusion: Development of the FRG rat bioreactor for large-scale expansion of primary human hepatocytes may provide the quantity of high-quality cells necessary for clinical testing of hepatocyte transplantation as an alternative to organ transplantation for severe liver diseases.

PO-1119

Anti-apoptotic effect of mycophenolate mofetil in human hepatocytes cultures

Razvan Iacob^{1,2}, Mihaela Uta¹, Andrei Chiosa¹, Ioana Manea¹, Luminita Stoica¹, Codruta Popa¹, Susanne Beckebaum³, Vito Cicinnati³, Cristian Gheorghe^{1,2}, Simona Dima¹, Irinel Popescu¹, Liliana Simona Gheorghe^{1,2}, Speranta Iacob^{1,2}. ¹Fundeni Clinical Institute, Center for Digestive Diseases and Liver Transplantation; ²Carol Davila University of Medicine and Pharmacy, Department of Gastroenterology; ³Universitätsklinikum Münster-UKM
Email: raziacob@gmail.com.

Background and aims: Liver transplant (LT) recipients have higher hepatic apoptotic markers in comparison to non-transplanted subjects. This is due to the immunosuppression agents used after LT with cytotoxic and proapoptotic effects, promoting liver apoptosis and contributing to inflammation, allograft injury and subsequent fibrosis. Studies regarding the effects of tacrolimus or cyclosporine on apoptosis are contradictory. Also, the cytotoxic action of mycophenolate mofetil on hepatocytes remains ill-defined. The aim of our study was to assess the apoptotic effects of immunosuppressive agents in human hepatocytes cultures isolated from cirrhotic livers.

Method: Human cirrhotic hepatocytes have been isolated from liver explant fragments by the collagenase perfusion technique described by Seglen et al. In contrast to normal hepatocytes cirrhotic hepatocytes generate rapidly proliferative cultures, that can be propagated and represent a valuable in vitro study model for personalized medicine. Cirrhotic hepatocytes have been cultured in low glucose DMEM culture medium and have been treated for 24 hours with 1 µM tacrolimus (TAC), sirolimus (SIR), mycophenolate mofetil (MMF), or combinations (TAC + SIR, MMF + TAC). At 24 hours apoptosis and necrosis was assessed using Tali™ Apoptosis Kit-

Annexin V Alexa Fluor™ 488 and Propidium Iodide (Thermo Scientific). Gene expression has been assessed by qRT-PCR using a microarray of 19 genes significant for apoptosis.

Results: Cytometry analysis has indicated the lowest apoptotic cells percentage in human cirrhotic hepatocytes cultures treated with MMF (5%) and TAC+MMF (2%) whereas the highest apoptosis percentage was registered for the TAC alone (11%). The highest toxicity indicated by apoptosis and necrosis was registered for the association of TAC + SIR (17%). Gene expression analysis has suggested a marked antiapoptotic effect of MMF in human cirrhotic hepatocytes cultures, mediated by a significant decrease in the gene expression of membrane receptors mediating apoptosis (TNFRSF1A and 10A, CD40 and FAS), the down regulation of genes mediating mitochondrial apoptosis (BAK1, BAX, RIPK1, ASK1, SMAC, HTRA2), of apoptosis specific effector proteins, especially DFFB-CAD, parallel by a significant decrease in the expression of the transcription factor NFkB1. The gene expression results are concordant to cytometry study results, indicating the lowest apoptotic effect for MMF and MMF+TAC immunosuppressive regimens.

Conclusion: MMF based immunosuppressive regimens have a favourable anti-apoptotic profile in vitro, in human cirrhotic hepatocytes cultures, as suggested by cytometry and gene expression studies, supporting its use in case of liver transplants recipients at high risk for liver graft fibrosis.

PO-1207

Selective hypoxia-inducible-factor stabilisation alleviates hepatocellular steatosis and ballooning in a rodent model of 70% liver resection

Samuele Iesari^{1,2}, Isabelle Leclercq³, Nicolas Joudiou⁴, Mina Komuta⁵, Aurelie Daumerie⁶, Jérôme Ambroise⁷, Alexandra Dili³, Caroline Bouzin⁶, Bernard Gallez⁴, Francesco Pisani², Eliano Bonaccorsi Riani¹, Pierre Gianello¹. ¹Université catholique de Louvain, Pôle de Chirurgie Expérimentale et Transplantation, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium; ²University of L'Aquila, Department of Biotechnological and Applied Clinical Sciences, L'Aquila, Italy; ³Université catholique de Louvain, Laboratory of Hepato-Gastroenterology, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium; ⁴Université catholique de Louvain, Nuclear and Electron Spin Technologies, Louvain Drug Research Institute, Brussels, Belgium; ⁵Keio University, Department of Pathology, Tokyo, Japan; ⁶Université catholique de Louvain, IREC Imaging Platform, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium; ⁷Université catholique de Louvain, Centre for Applied Molecular Technologies, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium
Email: samuele.iesari@gmail.com.

Background and aims: Small-for-size syndrome looms over patients needing liver resection or living-donor transplantation. Hypoxia has been shown to be crucial for the success of liver resection in the very early postoperative phase. While poorly acceptable as such in real-world clinical practice, hypoxia responses can still be simulated by pharmacologically raising levels of its transducers, the hypoxia-inducible factors (HIF).

We aimed to assess the potential role of a selective inhibitor of HIF degradation in 70% hepatectomy (70%Hx).

Method: We tested the required dose of roxadustat to stabilize liver HIF1alpha in a pilot study. We then performed 70% hepatectomy in male 8-week-old Lewis rats and administered 25 mg/kg of roxadustat (RXD25) at the end of the procedure. We assessed regeneration: ki67 and EdU immunofluorescent labelling, and histological parameters. We assessed also liver function via a blood panel and functional gadoxetate-enhanced magnetic resonance imaging, up to 47 hours after the procedure. Metabolic results were analysed by means of RNA sequencing.

Results: Roxadustat effectively increased early HIF1alpha transactivity: 1-hour nuclear-to-cytoplasm ratio in the study group: median 1.42 (interquartile range = 1.26–1.75) vs. 0.88 (0.83–1.07) in the

POSTER PRESENTATIONS

control group, $p = 0.022$. Roxadustat did not improve liver function or regeneration but, on postoperative day 1, treated livers showed mitigation in hepatocellular steatosis and ballooning, hallmarks of cellular stress after liver resection. RNA sequencing confirmed that roxadustat unexpectedly upregulated gene pathways associated with lipid breakdown and cellular respiration.

Figure: Table 1: Day 1 histology report

	70%Hx- RXD25 n (%)	70%Hx- placebo n (%)	Sham-placebo n (%)	P
Mitoses	0/13 (0.00)	0/8 (0.00)	0/8 (0.00)	-
Inflammation	0/13 (0.00)	0/8 (0.00)	0/8 (0.00)	-
Endothelial denudation	0/13 (0.00)	0/8 (0.00)	0/8 (0.00)	-
Microvascular thrombosis	0/13 (0.00)	0/8 (0.00)	0/8 (0.00)	-
Parenchymal haemorrhage	0/13 (0.00)	0/8 (0.00)	0/8 (0.00)	-
Necrosis	0/11 (0.00)	0/8 (0.00)	0/7 (0.00)	-
Hepatocellular ballooning	2/13 (15.38)	7/8 (87.50)	1/8 (12.50)	0.001 ^a
Steatosis ($\geq 5\%$)	5/13 (38.46)	7/8 (87.50)	1/8 (12.50)	0.005 ^a
Degree of steatosis Undetectable (steatosis 0%)	3/13 (23.08)	1/8 (12.50)		0.028 ^b
Healthy hepatocytes (steatosis <5%)	5/13 (38.46)	0/8 (0.00)		
Mild (steatosis 5–33%)	5/13 (38.46)	4/8 (50.00)		
Moderate (steatosis 33–66%)	0/13 (0.00)	3/8 (37.50)		
Severe (steatosis >66%)	0/13 (0.00)	0/8 (0.00)		

^bMaximum likelihood chi square test.

^dMantel-Haenszel test of trend.

Conclusion: Selective HIF stabilisation did not result in an increase in liver function after standard liver resection. Yet roxadustat alleviated markers of hepatocellular suffering after standard liver resection and induced intriguing metabolic changes that are worth studying in extended liver resection and fatty liver diseases.

PO-1346

Double negative T cells mediate CD39-dependent protection in hepatic ischemia and reperfusion injury

Hua Jin¹, Mingyang Li¹, Chunpan Zhang¹, Guangyong Sun¹, Dong Zhang¹. ¹Beijing Key Laboratory of Tolerance Induction and Organ Protection in Transplantation, Beijing Friendship Hospital, Capital Medical University, Beijing, China
Email: zhangd@ccmu.edu.cn.

Background and aims: Hepatic ischemia and reperfusion injury (HIRI) is a significant cause of morbidity and mortality following liver transplantation and major hepatic resections. Double negative T cells (DNT) are unique regulatory T cells which are discovered in recent decades. We have demonstrated that DNT significantly inhibit allo- or auto-immune responses mainly through perforin/granzyme B pathway. However, whether other mechanisms are involved in the immune regulation of DNT and the potential application of DNT in HIRI are still unknown. The aim of the research is to investigate the mechanisms involved in the immune regulation of DNT and the potential application of DNT in hepatic ischemia and reperfusion injury.

Method: WT or CD39 deficient DNT were adoptively transferred before surgery, and then the mouse model of partial (70%) warm HIRI was established. In vitro, WT or CD39 deficient DNT were cocultured with neutrophils with or without ATP stimulation. Transcriptome sequencing of ATP treated WT or CD39 deficient DNT were analyzed.

Results: In this study, we found DNT highly expressed CD39, a cell surface enzyme hydrolyzing extracellular ATP. Adoptively transferring with wild type (WT) but not CD39 deficient DNT significantly inhibited TNF- α and IL-1 β secretion of liver infiltrated neutrophils, decreased neutrophil extracellular traps (NETs) generation and increased neutrophil apoptosis in warm HIRI in both C57BL/6 and T cell deficient B6.Rag2/IL2rg KO mice.

Mechanistically, compared with WT DNT, CD39 deficient DNT were unable to hydrolyze extracellular cytotoxic ATP and became apoptotic under ATP stimulation. Transcriptome sequencing analysis suggested that ATP treated CD39 KO DNT had reduced expression of cell activation, survival, proliferation, chemotaxis and MAPK signaling pathway related genes than WT DNT. However, no differences of Prf1 or Gzmb gene expression were observed between groups. Furthermore, the level of extracellular immunosuppressive molecule, adenosine, was significantly higher in the culture of ATP treated WT DNT compared with that of CD39 deficient DNT. ATP-treated WT DNT but not CD39 deficient DNT significantly increased neutrophil apoptosis and inhibited inflammatory mediators secreted by neutrophils in vitro, suggesting that CD39 expressed by DNT might drive a shift from an ATP driven proinflammatory environment to an anti-inflammatory milieu induced by adenosine.

Conclusion: Our study reveals a new intrinsic mechanism that CD39 is crucial for DNT homeostasis and immunosuppressive function. These data support the concept and the feasibility of potentially utilizing this novel cell therapy for the prevention of HIRI during liver transplantation or hepatic surgery.

PO-1422

Longitudinal monitoring of bioengineered whole liver constructs using a novel perfusion bioreactor

Omolola Ajayi¹, Lisa Sassi¹, Sara Campinoti¹, Claire McQuitty^{1,2}, Dipa Natarajan¹, Riccardo Rayan Siena¹, Sara Mantero³, Alessandro Pellegata^{3,4}, Paolo De Coppi^{4,5}, Shilpa Chokshi^{1,2}, Luca Urbani^{1,2}. ¹Institute of Hepatology London; ²King's College London, Faculty of Life Sciences and Medicine; ³Politecnico di Milan, Department of Chemistry, Materials and Chemical Engineering "Giulio Natta"; ⁴University College of London, Stem Cells and Regenerative Medicine, Great Ormond Street Institute of Child Health, United Kingdom; ⁵Great Ormond Street Hospital, London, Specialist Neonatal and Pediatric Surgery

Background and aims: Whole liver constructs from decellularized scaffolds hold significant promise for in vitro disease modelling and regenerative medicine as a valuable alternative for organ transplantation. Nevertheless, there are still constraints to the use of whole organ constructs, with one of the biggest issues being the inadequacy of whole organ specific bioreactors to support multi-cellular seeding, long term cell viability and monitoring in culture.

Here, we have designed and validated a novel custom-made bioreactor for long-term 3D hepatocyte culture within a whole liver construct.

Method: We designed and produced a custom-made bioreactor using materials with high chemical resistance, not susceptible to corrosion or release of cytotoxic products, specifically for long-term culture experiments. The chamber is compatible with the use of bioluminescence imaging for longitudinal monitor of cells at different time points and to allow changing of culture media and addition of chemical/toxic compound during culture.

Rat whole liver scaffolds were obtained using perfusion decellularization. Luc+HepG2 cells and primary human hepatocytes (PHH) were perfusion-seeded into whole liver decellularized scaffolds and cultured for up to 30 days in the perfusion bioreactor or in static culture conditions as control. Dynamic perfusion was obtained using a programmable syringe pump, providing unidirectional flow within the bioreactor. Seeded cells were longitudinally monitored non-invasively using bioluminescence and periodic sampling, assessing cell viability, distribution and function.

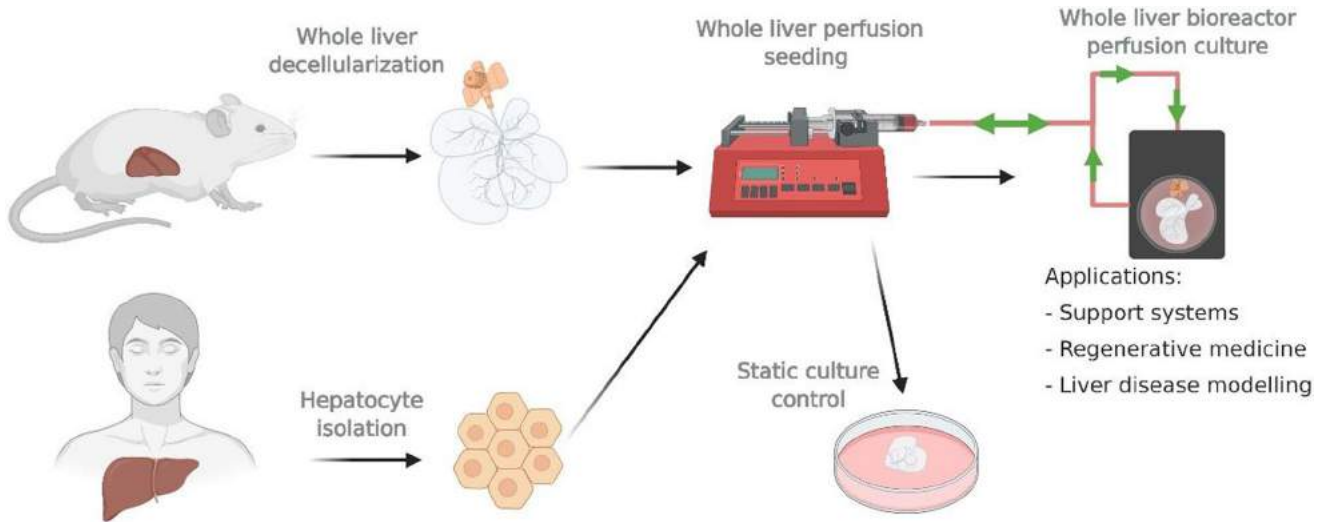


Figure: (abstract: PO-1422)

Results: We demonstrate the advantages of perfusion culture compared to static conditions, for both HepG2 cells and PHH, shown by significantly higher cell viability and uniform cell distribution verified by bioluminescence and histology. Perfusion culture facilitated enhanced cellular function in respect to static conditions, confirmed by increased albumin and urea production and expression of CYP enzymes, HNF4 α and FOXA2.

Conclusion: The perfusion bioreactor has proven suitable for supporting engineered liver constructs, successfully maintaining hepatocyte culture long-term preserving viability, distribution and functionality with the potential to culture multiple cell types for regenerative medicine and disease modelling.

respectively. The nomogram showed good calibration, and decision curve analysis demonstrated the nomogram is of clinical value.

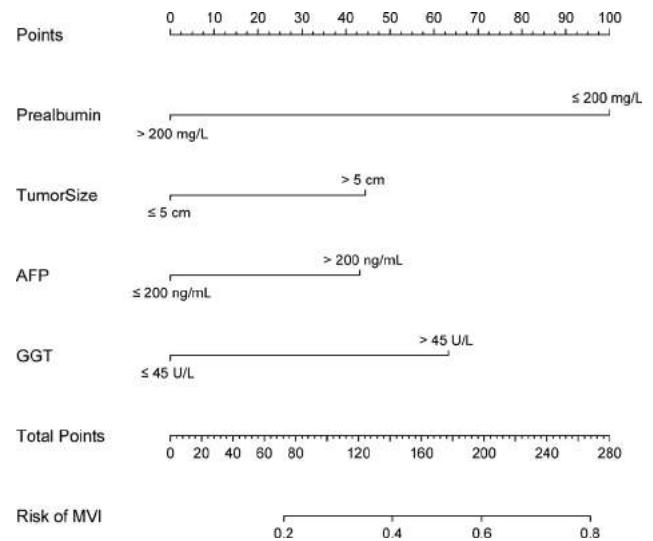


Figure:

Conclusion: We developed a new nomogram that uses basic clinical and laboratory variables to predict the probability of MVI before surgery for HCC patients. This nomogram can help clinicians choose appropriate treatment procedures.

Liver tumours: Clinical aspects except therapy

PO-250

Prognostic value of a nomogram predicting microvascular invasion for patients with hepatocellular carcinoma

Liying Ren¹, Dongbo Chen², Wentao Xu¹, Pu Chen², Tingfeng Xu¹, Hongsong Chen², Weijia Liao¹. ¹Medical University Affiliated Hospital, Laboratory of Hepatobiliary and Pancreatic Surgery, Guilin, China; ²Peking University People's Hospital, Institute of Hepatology, Beijing, China

Email: liaoweijia288@163.com.

Background and aims: For patients with hepatocellular carcinoma (HCC), preoperative diagnosis of microvascular invasion (MVI) is a difficult task. This study aimed to develop and validate a nomogram to predict the risk of MVI before surgery.

Method: A total of 424 HCC patients undergoing curative resection were entered into the study. Independent risk factors were identified by univariate/multivariate analyses and were built into a nomogram to estimate the risk of MVI. The receiver operating characteristic curve (ROC), concordance index (c-index), calibration curve and decision curve analysis were used to evaluate predictive performance.

Results: Prealbumin, gamma-glutamyl transpeptidase (GGT), alpha-fetoprotein (AFP) level, and tumor size were independent risk factors of MVI and formed the basis of the nomogram. The area under the ROC of nomogram was 0.775 (C-indexes of 0.781) in training and 0.787 (C-indexes of 0.785) in validation cohort for predicting MVI,

PO-409

Cause of Death and Cause-Specific Mortality in Primary Liver Cancer: Temporal Trends in a Hepatitis B Virus Endemic Area

Bo Hyun Kim^{1,2}, Dahhay Lee², Kyu-Won Jung³, Young-Joo Won^{2,3}, Hyunsoo Cho^{2,3}. ¹National Cancer Center, Center for Liver and Pancreatobiliary Cancer, Goyang-si, Korea, Rep. of South; ²National Cancer Center, Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, Goyang-si, Korea, Rep. of South; ³National Cancer Center, Division of Cancer Registration and Surveillance, National Cancer Control Institute, Goyang-si, Korea, Rep. of South

Background and aims: Causes of death in liver cancer patients have not been studied in detail. We aimed to investigate the causes of

POSTER PRESENTATIONS

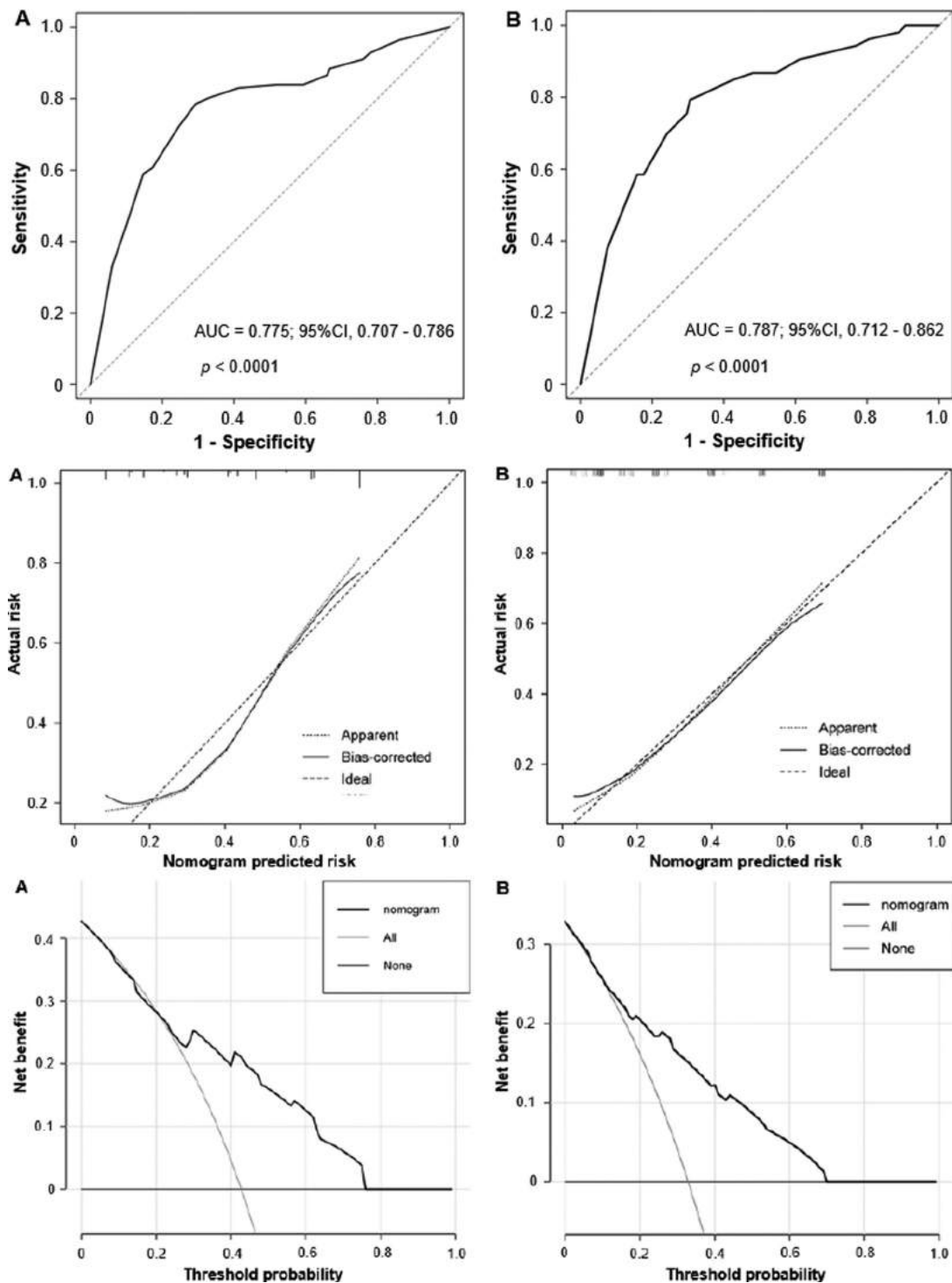


Figure: (abstract: PO-250)

death and cause-specific mortality trends in primary liver cancer patients.

Method: Causes of death and proportionate mortalities in liver cancer patients diagnosed from 2000–2016 were investigated using a retrospective cohort from nationwide cancer registry data ($n = 231,338$). Risks of non-cancer deaths relative to the general population were compared by standardized mortality ratios (SMR). The 5-year probabilities of death were estimated under the competing risks.

Results: Of the total, 179,921 patients died. Among the deaths, 92.4%, 1.7%, and 6.0% died of primary liver cancer, cancer from other sites, and non-cancer illnesses. Proportionate mortality from liver cancer persisted high. The five-year probability of death attributed to liver cancer varied by tumor stage from 42% to 94% and remained high after ten years post-diagnosis. Mortality from other causes has continuously increased from 3.3% in 2002 to 11.7% in 2016. The most common causes of non-cancer death were liver disease (34.5%) and viral hepatitis (10.7%). Relative to the Korean general population,

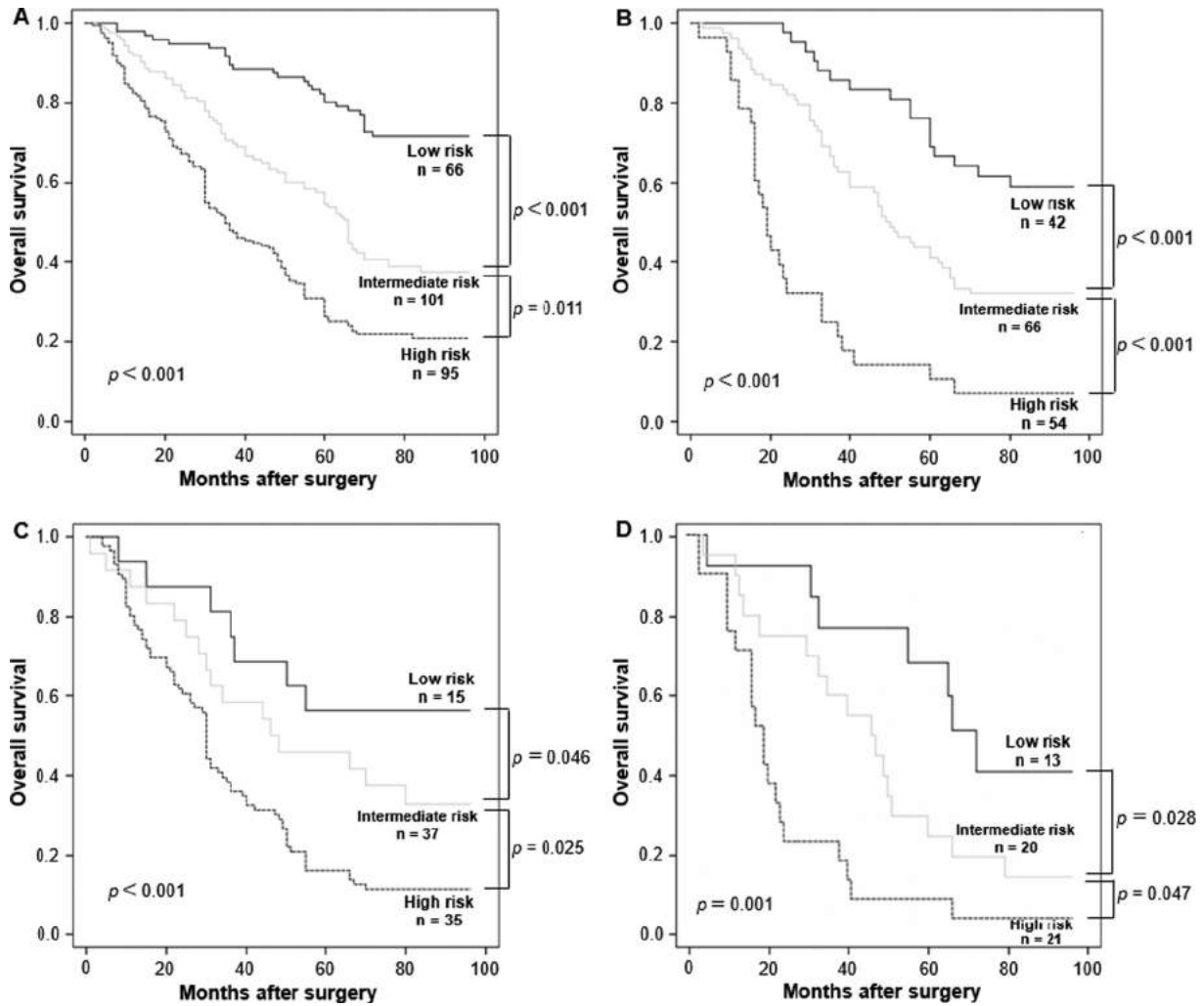


Figure: (abstract: PO-250)

mortality risks due to liver disease (SMR = 15.6, 95%CI: 15.1, 16.1) and viral hepatitis (SMR = 46.5, 95%CI: 43.9, 49.2) were higher in liver cancer patients. Meanwhile, mortality risks due to suicide were also higher (SMR = 2.6, 95%CI: 2.4, 2.8), suggesting an additional need for psychological support for these patients.

Conclusion: Patients with liver cancer are most likely to die from liver cancer even ten years after the diagnosis. These findings highlight a need for specialized long-term follow-up care for patients with liver cancer.

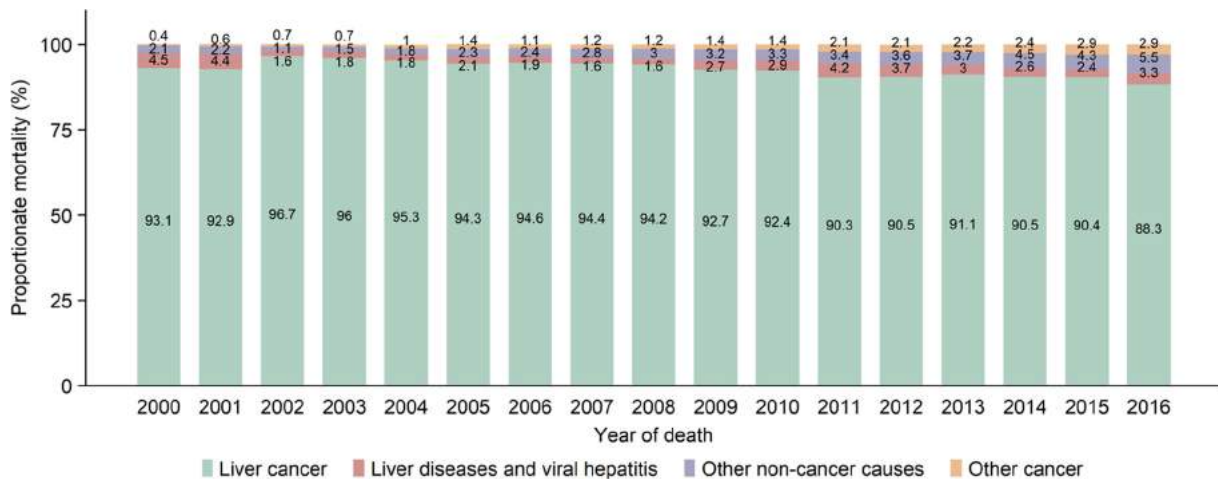


Figure: (abstract: PO-409)

POSTER PRESENTATIONS

PO-707

Thyroid disease and hepatocellular carcinoma survival. A Danish nationwide cohort study

Linda Skibsted Kornerup¹, Frederik Kraglund¹, Ulla Feldt-Rasmussen², Peter Jepsen^{1,3}, Hendrik Vilstrup¹. ¹Aarhus University Hospital, Hepatology and Gastroenterology, Aarhus, Denmark; ²Rigshospitalet, Endocrinology, København, Denmark; ³Aarhus University Hospital, Clinical Epidemiology, Aarhus, Denmark
Email: lindajen@rm.dk.

Background and aims: Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer mortality worldwide. Recent animal studies suggest that thyroid hormone treatment improves HCC prognosis. The aim of this study was to describe the association between thyroid disease and HCC prognosis in humans.

Method: We performed a nationwide cohort study including all persons with an HCC diagnosis from 2000–2018. Patients' age, sex, HCC treatment, and diagnoses of thyrotoxicosis, nontoxic goitre, and myxoedema, were obtained from Danish national healthcare registries. We used regression models to examine the association between thyroid disease and mortality hazard and restricted mean survival time after HCC diagnosis, adjusting for confounding by sex and age.

Results: We included 4,812 patients with HCC and 107 patients with thyroid disease. Median follow-up time was 5 months (total 5,985 person-years). The adjusted mortality hazard ratio was 0.68 (95% CI 0.47–0.96) for thyrotoxicosis and 0.60 (95% CI 0.41–0.88) for nontoxic goitre. The restricted mean survival time during the five years following HCC diagnosis was 6.8 months (95% CI 1.1–12.6) longer for HCC patients with thyrotoxicosis than for patients without thyroid disease, and it was 6.9 months (95% CI 0.9–12.9) longer for HCC patients with nontoxic goitre than for patients without thyroid disease.

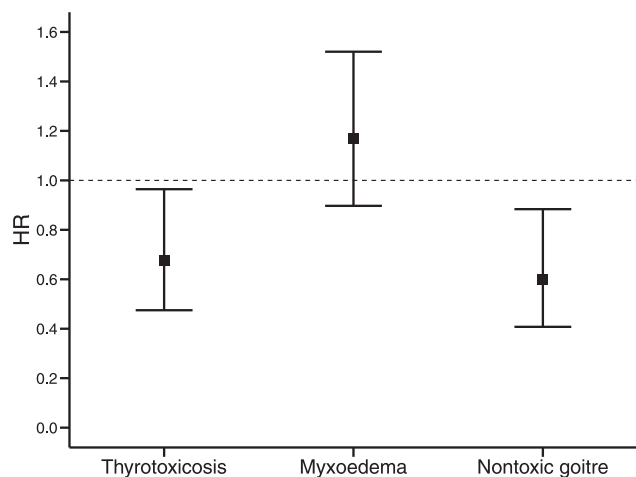


Figure:

Conclusion: In this large nationwide cohort study, thyrotoxicosis and nontoxic goitre were associated with prolonged HCC survival. Our results are concordant with recently published animal studies.

PO-750

Two trans-arterial chemo-embolizations during liver transplantation waiting list and absence of complete radiological response: time for a systemic strategy?

Edoardo Poli¹, Marc Antoine Allard², Ilias Kounis¹, Alina Pascale¹, Cyrille Feray¹, Catherine Guettier³, Maite Lewin⁴, Jean-Charles Duclos-Vallée¹, Audrey Coilly¹, Eric Vibert², René Adam², Antonio Sa Cunha², Didier Samuel¹, Daniel Cherqui², Olivier Rosmorduc¹. ¹Centre Hépatobiliaire, Paul Brousse Hospital,

Hepatology, Villejuif, France; ²Centre Hépatobiliaire, Paul Brousse Hospital, Hepatobiliary Surgery, Villejuif, France; ³Kremlin-Bicêtre Hospital, Pathology, Le Kremlin Bicêtre, France; ⁴Centre Hépatobiliaire, Paul Brousse Hospital, Radiology, Villejuif, France
Email: edoardo.poli88@gmail.com.

Background and aims: Hepatic trans-arterial chemoembolization (TACE) is a widely used treatment to prevent hepatocellular carcinoma (HCC) progression in patients enlisted for liver transplantation (LT). Several sessions can be performed but the clinical benefit of repeated TACE remains uncertain. Several therapeutic alternatives are currently becoming available. Our study aimed to assess the impact of TACE number and efficacy on the risk of pre-LT tumor-related delisting and/or post-LT HCC recurrence.

Method: All patients enlisted for LT who prospectively received at least one TACE for HCC within the LT criteria (French AFP score ≤ 2) in a single institution, from 2013 to 2018, were included. Treatment strategy failure was defined as pre-LT tumor-related delisting or post-LT HCC recurrence. TACE response was evaluated using the mRECIST criteria to identify the absence of a complete radiological response (CRR).

Results: A total of 172 patients were included in the study. At last follow-up, 127 (73.8%) patients were transplanted, 37 (21.5%) were delisted because of HCC progression and 14 presented post-LT HCC recurrence (11% of transplant recipients). At univariate analysis, factors associated with treatment failure were: higher pre- and post-TACE serum AFP, absence of CRR in post-TACE, number of TACE sessions before LT > 2 (Table 1). The risk of treatment failure was 38% in patients who received > 2 TACE vs. 20% in patients who received 1 or 2 TACE ($p = 0.02$). At multivariate analysis, being treated with > 2 TACE was highly predictive of treatment failure [RR 3.3 (1.52–7.31), $p = 0.003$] after adjusting for serum AFP, Child-Pugh score, maximum HCC size and number of HCC. Moreover, the overall survival was significantly decreased in patients without a CRR compared to those with a CRR after 1 (if unique) or 2 TACE (67% vs 88% at 2 years from the date of enlisting; $p = 0.003$; Figure 1).

Table:

	Univariate analysis		
	Delisting of post-LT HCC recurrence		p
	NO N = 127	YES N = 45	
Age, years	62.0 [33.0;74.0]	60.0 [42.0;70.0]	0.358
Male gender, n (%)	109 (85.8%)	39 (86.7%)	1.000
Cirrhosis aetiology:			
–Virus	51 (40.2%)	16 (35.6%)	0.520
–Alcohol	46 (36.2%)	22 (48.9%)	
–NASH	18 (14.2%)	4 (8.89%)	
–other	12 (9.45%)	3 (6.67%)	
MELD score	8 [6–20]	9 [6–18]	0.441
AFP pre-TACE (ng/ml)	7.40 [2.00–700]	17.0 [3.00–780]	0.002
AFP post-TACE (ng/ml)	6.00 [1.60–519]	41.0 [1.40–25979]	< 0.001
Number of HCC	2 [1–6]	2 [1–9]	0.708
Maximum HCC size, mm	23 [7–60]	24 [12–50]	0.651
Absence of CRR	67 (52.8%)	43 (95.6%)	< 0.001
Number of TACE sessions	2 [1–5]	2 [1–6]	0.068
> 2 sessions of TACE, n (%)	36 (28.3%)	22 (48.9%)	0.020

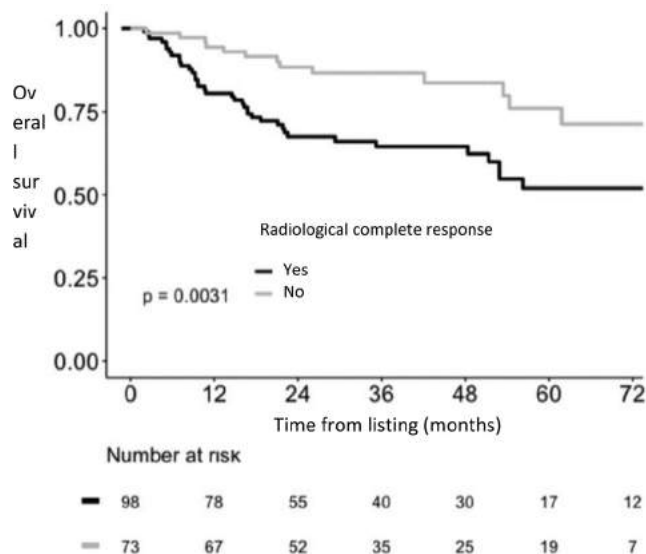


Figure:

Conclusion: Enlisted patients who receive more than 2 TACE without complete response have a poorer outcome with a higher risk of pre-LT tumor-related delisting or of post-LT HCC recurrence. An alternative strategy should be considered in these cases.

PO-1090

The impacts of gender differences in muscle mass and adipose tissue on the outcomes of hepatocellular carcinoma after surgical resection

Pei-Chang Lee^{1,2,3}, Tsung-Yi Cheng¹, Kuo-Wei Huang¹, Gar-Yang Chau⁴, Yi-Hsiang Huang^{1,3,5}, Ming-Chih Hou^{1,3}, Chien-Wei Su^{1,3}. ¹Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; ²National Yang-Ming University School of Medicine, Institute of Pharmacology, Taiwan; ³National Yang-Ming University School of Medicine, Faculty of Medicine, Taiwan; ⁴Taipei Veterans General Hospital, Division of General Surgery, Department of Surgery, Taiwan; ⁵National Yang-Ming University School of Medicine, Institute of Clinical Medicine, Taiwan

Email: cwsu2@vghtpe.gov.tw

Background and aims: Body composition assessments are objective surrogates reflecting nutrition status and severity of liver diseases. Sarcopenia has been reported to predict mortality in patients with hepatocellular carcinoma (HCC). However, the roles of muscle mass and adipose tissue in HCC after resection are still uncertain and diverse. In this study, we aimed to assess and investigate the impacts of muscle and adipose tissues on outcomes of HCC after surgical resection distinguished by genders.

Method: From January 2013 to December 2016, 304 consecutive patients who received surgical resection of HCC in Taipei Veterans General Hospital were retrospectively reviewed. All patients had received computed tomography (CT) for diagnosis and post-operative follow-up. Cross areas of adipose tissue and muscle mass were measured from CT scan by SliceOmatic software at L3 vertebra level; and body composition indices (cm²/m²), including psoas muscle index (PMI), skeletal muscle index (SMI), intramuscular adipose tissue index (IMATI), visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI) were calculated. Optimal cut-off values were defined by area under receiver operating characteristic curve (AUROC), and survival analyses were performed.

Results: No significant change of body composition was observed from the images before and after surgical resection of HCC (median PMI: 8.58 vs 8.59 cm²/m², p = 0.99, SMI: 50.17 vs 49.66 cm²/m², p = 0.427, IMATI: 3.49 vs 3.38 cm²/m², p = 0.385, VATI: 40.61 vs 36.3 cm²/m², p = 0.142, SATI: 45.88 vs 44.83 cm²/m², p = 0.504). Male patients with post-surgery body composition indices including SMI less than 46.6 cm²/m² (OR: 2.029; 95% C.I. 1.096–3.758, p = 0.024), IMATI higher than 2.9 cm²/m², (OR: 2.671; 95% C.I. 1.389–5.134, p = 0.003) and SATI lower than 44.8 cm²/m² (OR: 2.299; 95% C.I. 1.200–4.403, p = 0.012) were independent predictors to survival after surgery. Female patients with post-surgery IMATI higher than 5.0 cm²/m² (OR: 5.453; 95% C.I. 1.571–18.927, p = 0.008) had significant worse survival after surgery.

Conclusion: In conclusion, body composition after surgery, including muscle mass, muscle steatosis and subcutaneous fat mass could predict survival in male HCC patients; only muscle steatosis could predict survival in female HCC patients, especially in those with better liver reserves.

PO-1147

Global burden of major gastrointestinal cancers and its association with socioeconomic development status, 1990–2019

Xuan Dong¹, Jing-Mao Li², Dan-Yi Zeng¹, Qing-Qing Xing¹, Yan-Dan Ren³, Wei-Ming Chen⁴, Yan-Yan Cai⁵, Kuangnan Fang², Mei-Zhu Hong⁶, Jin-Shui Pan¹. ¹First Affiliated Hospital of Fujian Medical University, Hepatology, Fuzhou, China; ²Xiamen University, Department of Statistics, Xiamen, China; ³Zhongshan Hospital Xiamen University, Department of Gastroenterology, Xiamen, China; ⁴Xiamen University, School of Medicine, Xiamen, China; ⁵Fujian Medical University, School of Clinical Medicine, Fuzhou, China; ⁶Mengchao Hepatobiliary Hospital of Fujian Medical University, Traditional Chinese Medicine, Fuzhou, China

Email: 363111396@qq.com

Background and aims: Among the top seven causes of cancer-related death, common gastrointestinal tract cancers are major contributors including colon and rectum cancer, stomach cancer, liver cancer, pancreatic cancer, and esophageal cancer. Data on global and country-specific levels and trends of common cancers of the gastrointestinal tract are essential to understand the impact of these diseases and to help policymakers to allocate resources.

Method: Cancer mortality, and incidence were obtained from GBD 2019, which were stratified by country and territory, sex, and level of Socio-demographic Index (SDI). The association between burden of cancers and socioeconomic development status, represented in SDI, was also described.

Results: In 2019, there was an age-standardized incidence rate of 61.9 (95% CI 56.1–67.6) per 100 000 person-years in terms of five major cancers of the gastrointestinal tract. There was a decrease in age-standardized death rates due to the five common tumors from 1990 to 2019 (–22.7% [–31.1 to –13.5]). Globally, Mongolia, and several regions or countries located in East Asia exhibited the highest age-standardized incidence rates in 2019. Stratified using SDI, the high SDI, and high-middle SDI locations recorded the highest incidence rate and death rate of colon and rectum cancer and pancreatic cancer, whereas the low-middle SDI, and low SDI locations possessed the highest-burden of stomach cancer and esophageal cancer.

Conclusion: There is a pronounced association between socioeconomic development status and burden of common cancers of the gastrointestinal tract. Data of GBD 2019 are valuable for policymakers to implement cost-effective interventions for gastrointestinal tract cancers.

POSTER PRESENTATIONS

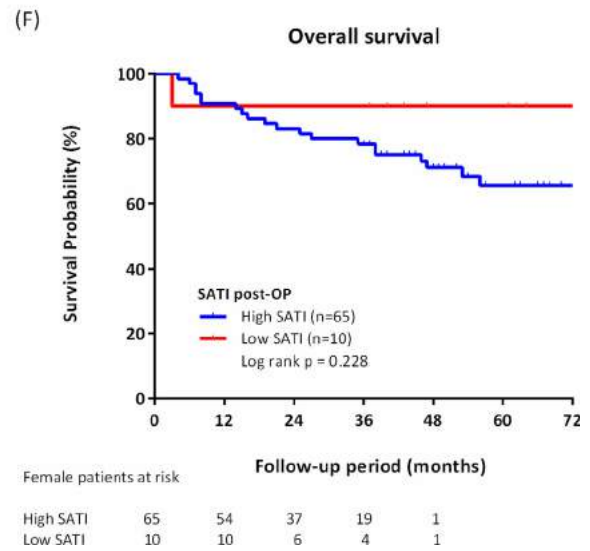
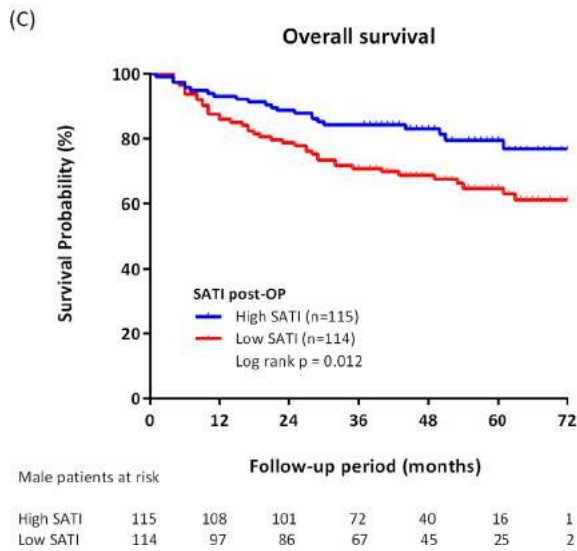
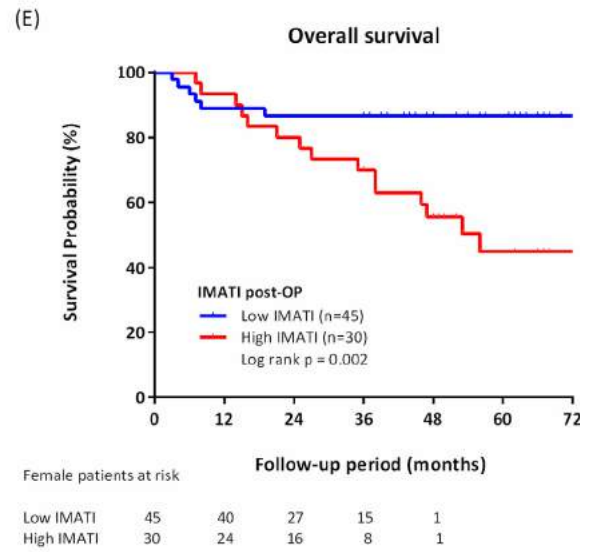
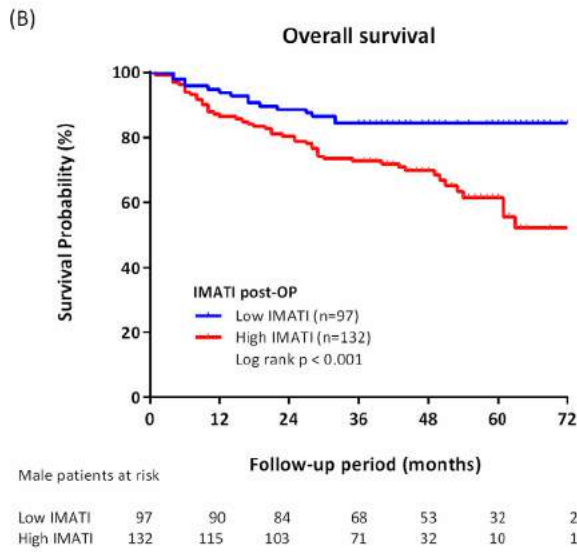
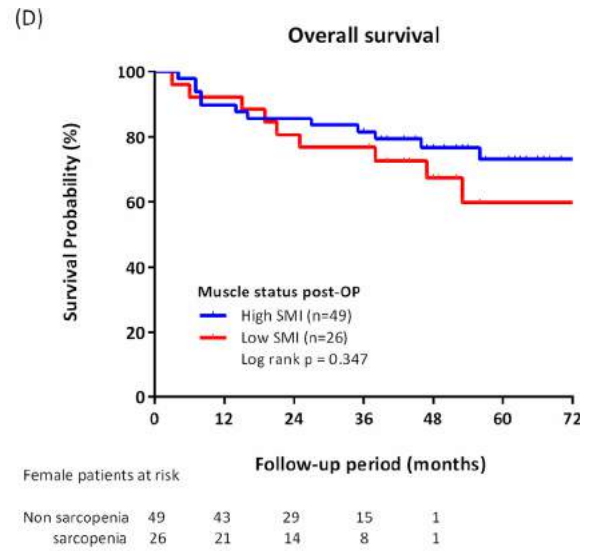
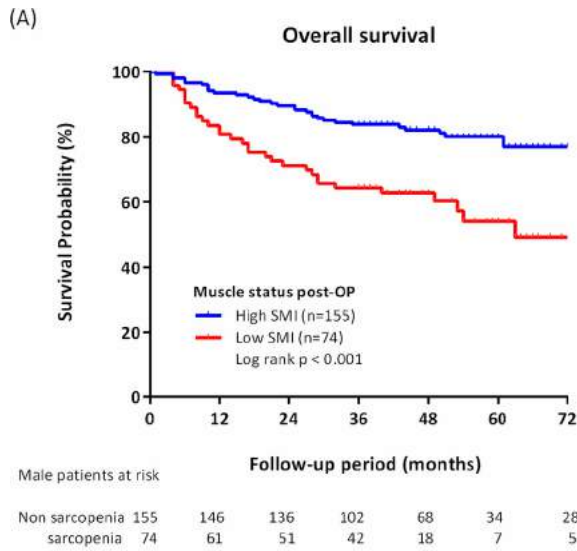


Figure: (abstract: PO-1090)

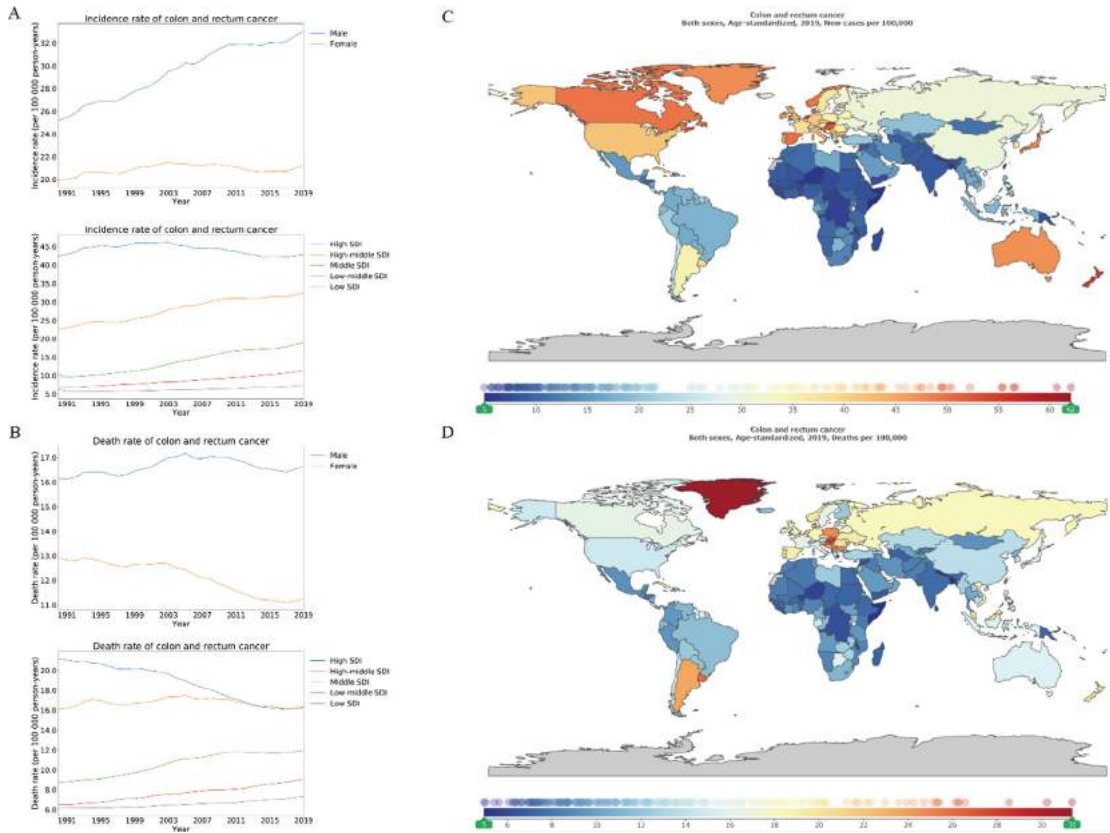


Figure 1: (abstract: PO-1147): Burden of colorectal cancer for 204 countries and territories.

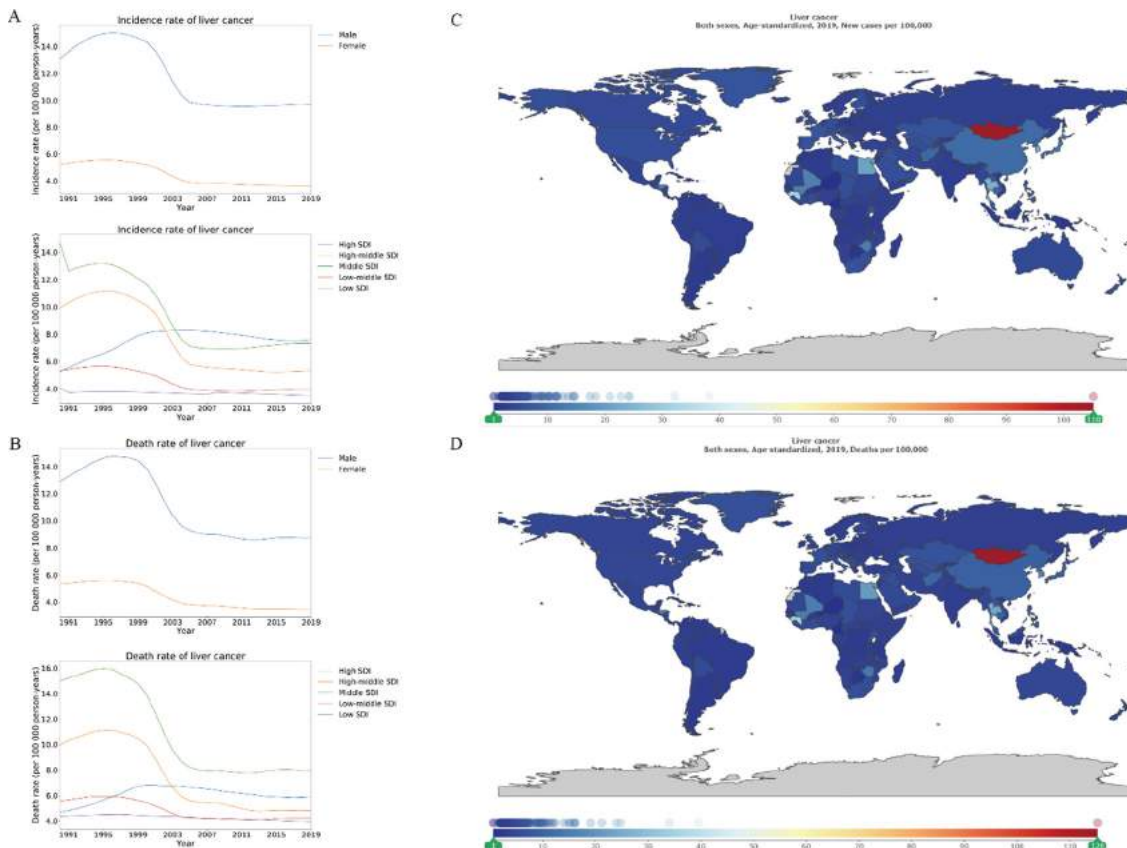


Figure 2: (abstract: PO-1147): Burden of liver cancer for 204 countries and territories.

POSTER PRESENTATIONS

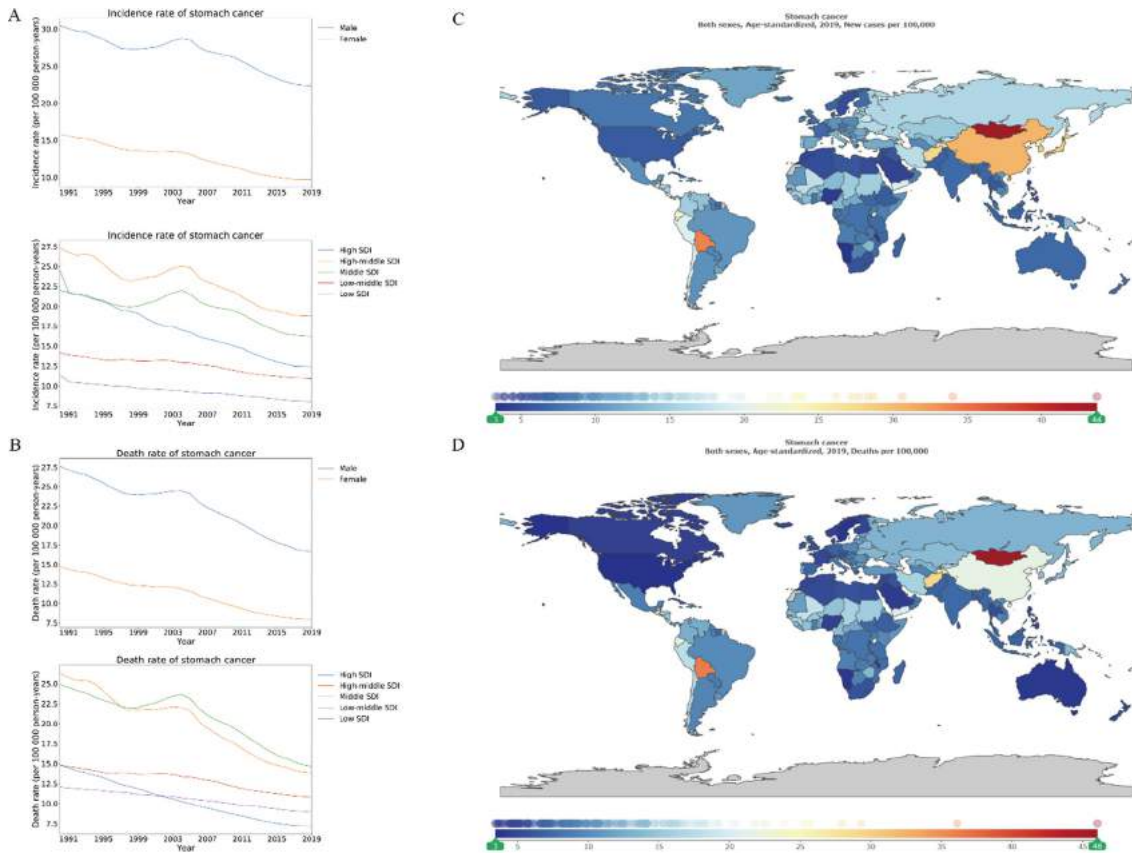


Figure 3: (abstract: PO-1147): Burden of stomach cancer for 204 countries and territories.

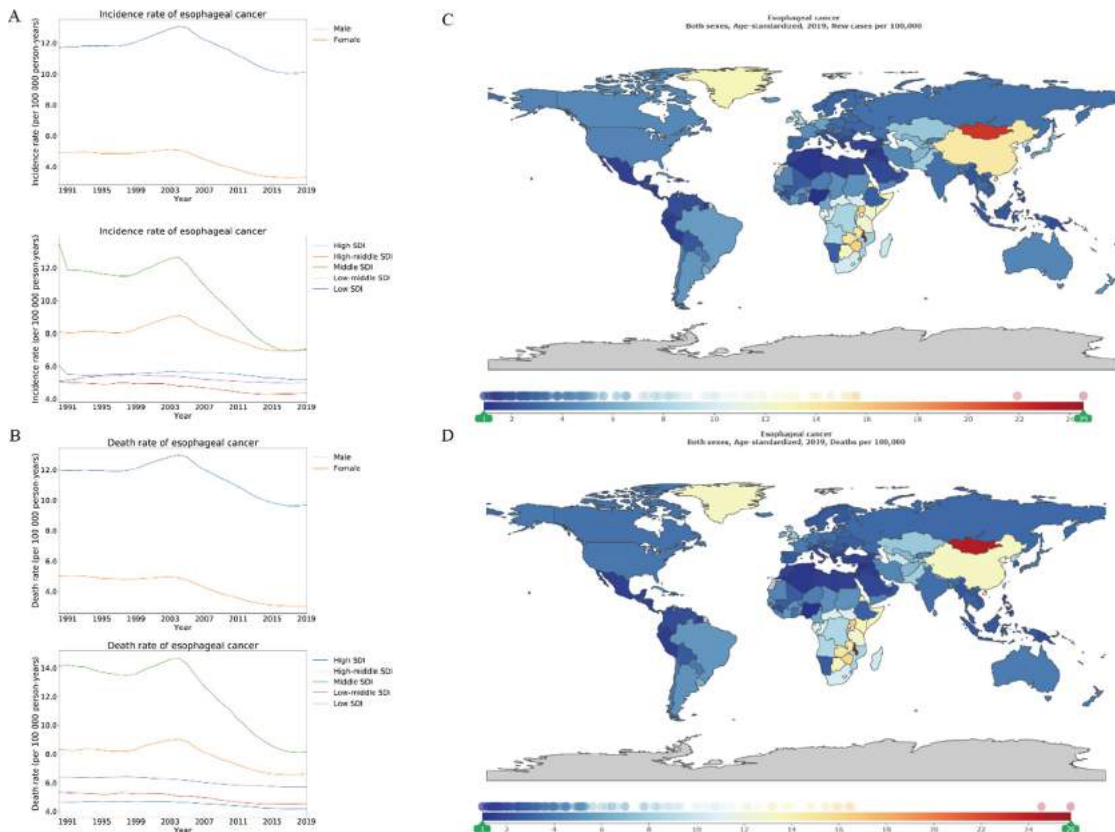


Figure 4: (abstract: PO-1147): Burden of esophageal cancer for 204 countries and territories.

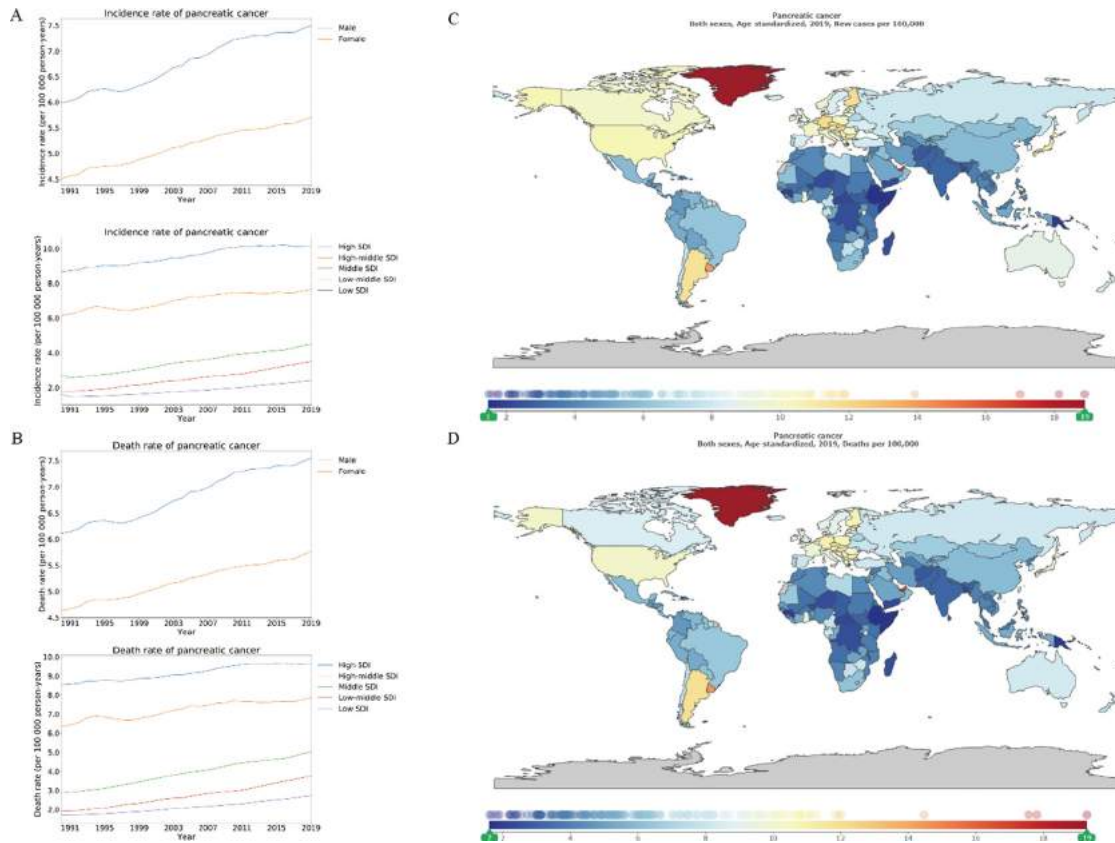


Figure 5: (abstract: PO-1147): Burden of pancreatic cancer for 204 countries and territories.

PO-1153

Weight variations and level of estrogen exposure predict the evolution of hepatocellular adenomas

Alix Demory¹, Jean Marie Peron², Maxime Ronot³, Julien Calderaro⁴, Fatima Zohra Mokrane⁵, Selves Janick⁶, Charlotte Maulat⁷, Thomas Eche⁵, Giuliana Amaddeo⁸, Valérie Paradis⁹, Marianne Ziolo¹⁰, Olivier Sutter¹¹, Lorraine Blaise¹, Nathalie Ganne¹, Jessica Zucman-Rossi¹², Jean Charles Nault¹. ¹Avicenne Hospital, Liver Unit, Bobigny, France; ²Rangueil Hospital, Liver Unit, Toulouse, France; ³Beaujon Hospital, Radiology, Clichy, France; ⁴Mondor Hospital, Pathology, Créteil, France; ⁵Rangueil Hospital, Radiology, Toulouse, France; ⁶Rangueil Hospital, Pathology, Toulouse, France; ⁷Rangueil Hospital, Digestive Surgery, Toulouse, France; ⁸Mondor Hospital, Liver Unit, Créteil, France; ⁹Beaujon Hospital, Pathology, Clichy, France; ¹⁰Avicenne Hospital, Pathology, Bobigny, France; ¹¹Avicenne Hospital, Radiology, Bobigny, France; ¹²Cordeliers Research Center, Inserm U1138, Paris, France
 Email: alix.demory@gmail.com

Background and aims: The natural history of hepatocellular adenomas (HCA) remains to be better described especially in non-resected patients. We aim to identify the predictive factors of HCA evolution after estrogen withdrawal.

Method: We retrospectively included patients with a histological diagnosis of HCA on a biopsy or a surgical resection between 2000 and 2019 in 3 centers. Clinical, radiological and pathological data were collected in order to identify predictive factors of radiological evolution of HCA in number and in size (using RECIST criteria) and of bleeding and malignant transformation. HCA were classified as *HNF1A* inactivated, inflammatory and *CTNNB1* mutated HCA. We built a score based on variables modulating estrogen levels: body

mass index, duration of estrogen-based contraception and alcohol intake. An external cohort from a 4th center was used to validate this score.

Results: 184 patients were included with 161 women (87.6%), 88.6% with an estrogen-based contraception during a median of 12 years, all have estrogen withdrawal after the diagnosis. 49.8% of patients had at least one inflammatory HCA, 31.1% at least one *HNF1A* inactivated HCA and 8% at least one *CTNNB1* mutated HCA. 21 symptomatic bleedings (11.4%) and 12 transformation in HCC (6.5%, half in men) were identified. HCA >5 cm at imaging was associated with symptomatic bleeding (p=0.003). Male (p=0.0005) and *CTNNB1* mutated HCA (p=0.0001) were associated with malignant transformation. An age <37 years old (median age of the population) was associated with bleeding (p=0.004) whereas those of >37 years old were at risk of HCC occurrence (p=0.024). 119 patients with residual HCA were followed-up for a median of 4.5 years. Radiological regression was observed in 31%, stabilization in 47% and progression in 22% of the cases. Weight loss was associated with regression (p=0.0004) and weight gain with progression (p=0.0021). A high estrogen exposure score predicted radiological regression (OR 2.45; CI95% [1.347-5.553]; p=0.009) with a linear relation between the rate of estrogen exposure and the probability of regression. This result was confirmed in an external cohort of 72 female patients (p=0.0032).

Conclusion: Weight variation is strongly associated with evolution of HCA in size and number. Moreover, a score of estrogen exposure predicts regression of HCA during follow-up. This score is easily assessable in clinical practice in order to guide therapeutic decision.

POSTER PRESENTATIONS

PO-1164

External validation of the Toronto hepatocellular carcinoma risk index in a Swedish population

Hanne Åström¹, Nelson Ndegwa², Hannes Hagström^{1,3,4}. ¹Karolinska Institutet, Department of Medicine, Huddinge, Sweden; ²Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden; ³Karolinska University Hospital, Division of Hepatology, Department of Upper GI, Stockholm, Sweden; ⁴Karolinska Institutet, Clinical Epidemiology Unit, Department of Medicine, Solna, Stockholm, Sweden
Email: hannes.hagstrom@ki.se

Background and aims: The Toronto hepatocellular carcinoma (HCC) risk index (THRI) stratifies patients with cirrhosis into three HCC risk groups based on weighted values for age, gender, etiology of cirrhosis, and platelet count. The THRI has previously been reported to identify patients at low risk for HCC that do not benefit from biannual HCC surveillance. In this study, we aimed to independently externally validate the THRI in a Swedish setting to investigate if it could identify patients that do not require surveillance.

Method: We included 2491 patients with cirrhosis seen at the Karolinska University Hospital, Stockholm, between 2004 and 2017. Patients were stratified into low-, intermediate- and high risk of HCC based on their respective THRI values at baseline. The performance of the THRI was evaluated using model discrimination and model calibration. Harrell's C-index was calculated to assess the discriminative ability of the THRI. Calibration-in-the-large, calibration slope and goodness of fit estimates were calculated to evaluate model calibration. Cox proportional hazards regression was used to determine the risk of HCC. Annual and cumulative HCC incidence was calculated at 5- and 10 years.

Results: Most patients were male (1638, 66%). The etiology of cirrhosis was most frequently alcohol-related liver disease and non-alcoholic related fatty liver disease (1182, 48%), or viral hepatitis (987, 40%). In total, 317 (13%) patients developed HCC during follow-up. We identified 131 patients (5.3%) as low risk according to the THRI. The Harrell's C-index of the THRI was 0.69. Calculations for the calibration-in-the large (0.11), calibration slope (1.24, not different from 1, $p=0.66$) and goodness of fit showed at good model calibration. The risk of HCC development was increased in both the high-risk group (hazard ratio = 6.8, 95% CI = 2.8–16.6) and the intermediate risk group (hazard ratio = 2.8, 95% CI = 1.1–6.8) compared to the low-risk group. 10-year annual HCC incidence in the low-, intermediate-, and high-risk group was 0.7%, 1.7% and 4.3% respectively.

Conclusion: In a Swedish setting, the THRI could differentiate between low and high risk of HCC development. However, the low-risk group was relatively small (5.3%) in this external validation which limited the clinical applicability in this cohort.

PO-1238

Natural history and clinical impact of non-neoplastic portal vein thrombosis in cirrhotics with hepatocellular carcinoma

Sarah Shalaby¹, Marco Grasso¹, Alessandro Vitale², Enrico Pizzirani³, Alberto Zanetto¹, Paolo Feltracco⁴, Patrizia Burra¹, Umberto Cillo², Marco Senzolo¹. ¹Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy; ²Hepatobiliary Surgery and Liver Transplantation Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy; ³Institute of Radiology, Department of Medicine-DIMED, Padua, Italy; ⁴Section of Anesthesiology and Intensive Care, Department of Medicine-DIMED, Padua, Italy
Email: sarahshalaby18@gmail.com

Background and aims: Portal vein thrombosis (PVT) is a common thrombotic complication in cirrhosis; however, data on its

epidemiology and prognostic role in patients with hepatocellular carcinoma (HCC) are still scarce.

Method: Cirrhotic patients with HCC undergoing laparoscopic microwave ablation and non-neoplastic PVT were consecutively enrolled over a period of 4 years. Non-neoplastic PVT extension for each portal branch and HCC total tumour volume (TTV) were calculated by a single-radiologist blinded to report in every patient, at baseline and for each follow-up interval. Characteristics of patients and HCC were correlated with presence of PVT and to its evolution. The role of PVT on survival was evaluated by Uni and multivariate Cox analyses.

Results: Among 900 consecutive patients 122 were excluded because of previous hepatic resection, 3 for previous portosystemic shunt creation and 25 due to neoplastic PVT. Seven hundreds-fifty patients were finally included, 88 with PVT. Fifty patients showed isolated PVT (18% complete); 33 showed portal and mesenteric vein involvement (22% complete); 5 had porto-spleno-mesenteric thrombosis (0% complete). At multivariate analysis, median pre-treatment TTV (OR 1.10, 95%CI 1.05–1.15, $p < 0.0001$) and presence of clinically significant portal hypertension (OR 2.90, 95%CI 1.37–6.59, $p = 0.0046$) were the only independent variables associated with PVT. Fifty six patients with PVT were followed-up for >3 months (median follow-up 9 months) and 14 were treated with anticoagulation. PVT improved in 43% of anticoagulated patients vs only 9.5% of untreated patients ($p = 0.002$). Anticoagulant therapy was independently associated with PVT improvement, together with HCC response to ablative treatment, while lack of HCC response to ablative treatment predicted PVT progression. Median survival in patients with complete or progressive PVT was 10.9 vs 47.2 months in other patients ($p < 0.001$). The prognostic negative impact on survival of complete/progressive PVT persisted at multivariable analysis (HR 2.1, 95%CI 1.2–3.4, $p = 0.007$), along with Child-Pugh score and TTV.

Conclusion: HCC TTV and recurrence after treatment are independent predictors of non-neoplastic PVT development and progression. Complete/progressive PVT is an independent factor associated with mortality, therefore thromboprophylaxis in patients with large HCC should be evaluated in future studies.

PO-1275

Significance of TERT genetic alterations and telomere length in hepatocellular carcinoma

Jin Seoub Kim¹, Hye Seon Kim¹, Soon Kyu Lee², Hee Chul Nam², Pil Soo Sung², Chang Min Kim³, Jin Young Park³, Si Hyun Bae², Jong Young Choi², Seung Kew Yoon², Jeong Won Jang². ¹St. Mary's, Biomedicine and Health Sciences, Seoul, Korea, Rep. of South; ²St. Mary's, Internal Medicine, Seoul, Korea, Rep. of South; ³CBSBioscience, Daejeon, Korea, Rep. of South
Email: garden@catholic.ac.kr

Background and aims: Telomerase reverse transcriptase (TERT) mutations are reportedly the most frequent somatic genetic alterations in hepatocellular carcinoma (HCC). An integrative analysis of TERT-telomere signal during hepatocarcinogenesis is lacking. This study aimed to investigate the clinicopathological association and prognostic value of TERT gene alterations and telomere length in HCC patients undergoing hepatectomy as well as transarterial chemotherapy (TACE).

Method: TERT promoter mutation, expression and telomere length were analyzed in 305 tissue samples by Sanger sequencing and real-time PCR, respectively. Protein-protein interaction (PPI) networks were examined to identify a set of genes interacting with TERT.

Results: The PPI networks identified eight key TERT-interacting gene sets, such as CCT5, TUBA1B, mTOR, RPS6KB1, AKT1, WHAZ, YWHAQ, and TERT. Among these, TERT was the strongest differentially expressed gene. TERT promoter mutations were more frequent, TERT expression was significantly higher, and telomere length was longer in tumors

versus non-tumors. *TERT* promoter mutations were most frequent in HCV-related HCCs and less frequent in HBV-related HCCs. *TERT* promoter mutations were associated with higher *TERT* levels and longer telomere length and were an independent predictor of worse overall survival after hepatectomy. *TERT* expression was positively correlated with tumor differentiation and stage progression, and independently predicted worse progression-free survival after TACE. Telomere length was marginally associated with survival in TACE-treated patients, but not in those undergoing hepatectomy.

Conclusion: The *TERT*-telomere network has a crucial role in the development and progression of HCC. *TERT*-telomere abnormalities might serve as useful biomarkers for HCC, but the prognostic values may differ with tumor characteristics and treatment.

PO-1289

Cirrhosis regression based on both Enhanced Liver Fibrosis (ELF) and Fibrotest after direct-acting hepatitis C therapeutics corresponded to a lower incidence rate of hepatocellular carcinoma (HCC) below the cost-effective threshold for surveillance

Winston Dunn¹, Devin Koestler², Liyun Ni³, Kathryn Kersey³, Kyle Hammond³, Anand Chokkalingam³, Diana Brainard³, Steven Weinman¹. ¹University of Kansas Medical Center, Internal Medicine, Kansas City, United States; ²University of Kansas Medical Center, Biostatistics, Kansas City, United States; ³Gilead Sciences, Inc., Foster City, United States
Email: winstondunmd@gmail.com

Background and aims: Direct-acting antivirals effectively clear hepatitis C virus even in the setting of cirrhosis. After sustained virological response (SVR), the incidence of hepatocellular carcinoma (HCC) decreases but is still higher than in patients without cirrhosis (~0.24% per year). Surveillance is generally recommended if HCC risk >1.5% per year. Within a year of SVR, approximately 25% of patients have regression of cirrhosis. We thus sought to assess HCC risk in post-SVR cirrhosis patients who experienced cirrhosis regression based on Enhanced Liver Fibrosis (ELF) and FibroTest.

Method: We included patients from the Gilead Cirrhosis Registry study that enrolled patients with compensated or decompensated cirrhosis who had achieved SVR in clinical trials of sofosbuvir-based treatment. Patients underwent follow-up every 6 months and were monitored for evidence of cirrhosis regression based on either ELF <9.5, FibroTest <0.58, or both and for HCC by ultrasound. Time to HCC was analyzed using extended-Cox model with cirrhosis regression as a time dependent covariate. Multivariable analysis adjusted for age, gender, race, ethnicity and BMI.

regression. In this group there were 10 cases of HCC for an incidence rate of 0.88% per year. 463 patients met either ELF or FibroTest criteria but not both. This group had 21 cases of HCC for a rate of 1.61% per year. 535 patients met neither criterion for cirrhosis regression. This group had 74 cases of HCC for a rate of 5.00% per year. The hazard ratio for development of HCC was 0.28 (95% CI 0.13–0.58, p = 0.0006) for meeting both criteria and 0.50 (95% CI 0.30–0.83, p = 0.0078) for meeting one criterion of cirrhosis regression compared to no cirrhosis regression.

Conclusion: Patients with cirrhosis regression after SVR based on both ELF and FibroTest criteria have reduced incidence of HCC compared to patients who did not have cirrhosis regression. While the incidence rate at 0.88% per year is still above the published data on patients who had SVR without cirrhosis, it is below the incidence threshold of 1.5% per year that is considered cost-effective for HCC surveillance.

PO-1729

Risk based HCC surveillance has the potential to minimise patient harm

Chris Curran¹, Adrian Stanley², Ewan Forrest², Matthew Priest¹, Shouren Datta¹, Stephen T. Barclay². ¹Queen Elizabeth University Hospital, Gastroenterology, Glasgow, United Kingdom; ²Glasgow Royal Infirmary, Gastroenterology, Glasgow, United Kingdom
Email: chriscurran152@gmail.com

Background and aims: International guidelines recommend screening for hepatocellular carcinoma (HCC) with ultrasound (US) and AFP levels biannually. However, patients may experience harm from unnecessary investigations, triggered by false positive tests. Utilising a cohort of patients with cirrhosis of mixed aetiology, we sought to calculate numbers needed to benefit (NNB) and harm (NNH) from screening, along with the positive and negative predictive values (PPV/NPV) of screening. In addition, we aimed to analyse these by risk strata from previously validated HCC risk scores.

Method: Data was collected on 482 patients with cirrhosis attending at least one clinic between Jan13–Dec14. Patients were followed until 31/12/2019. Risk scores (aMAP, Toronto risk index, ADDRESS-HCC/HCC risk score) were derived from index clinic results. NNB was defined as total screening US per screening diagnosed (US or AFP) early (stage 0/ A) HCC. NNH was defined as total US performed per false positive (positive screening/negative HCC investigation). False negatives were HCCs diagnosed within 6 months of negative screening. Compliance was defined as total ultrasounds/expected ultrasounds (1 per 6 months).

Results: 98% (473/482) of patients attended for 3137 screening ultrasounds (mean 6.6 (±4.2)/patient). Compliance was 68%. 22 (4.6%) patients developed HCC, 77% (17/22) screening diagnosed, of which 13/17 (76%) were early stage. There were 88 false positives, and no false negatives. NNB and NNH were 241 and 36, respectively. Results according to HCC risk score strata are shown below.

Conclusion: The PPV of abnormal screening tests increases across risk score strata. Low risk strata demonstrated no screen benefit (AMAP, THRI), or had a high NNB of >300/900 (ADDRESS-HCC/HCC risk score), with low NNH (24–38); Risk based screening has the potential to reduce patient harm and increase likelihood of benefit from HCC surveillance.

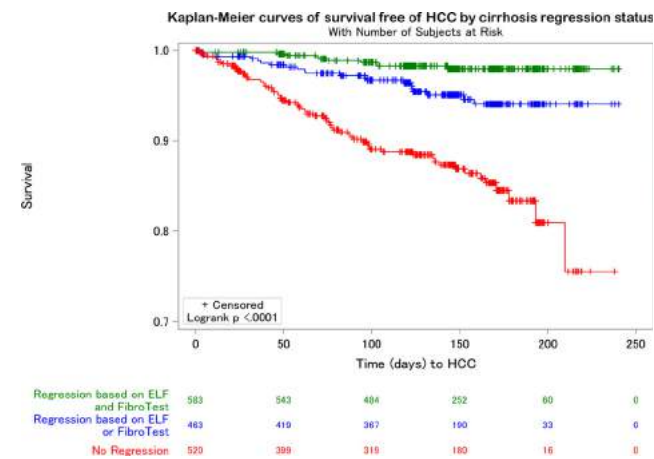


Figure:

Results: Analysis included 1581 subjects with median follow-up of 144 wks. 583 patients met both ELF and FibroTest criteria for cirrhosis

POSTER PRESENTATIONS

Figure:

Score	Risk Strata	No of pts. (%)	Total HCC	Early/ Total screen detected	NNB	NNH	PPV (%)
AMAP	Low	36 (7.6)	0	0/0	-	24.4	0
	Medium	136 (28.8)	1	0/0	-	45.5	0
	High	301 (63.6)	21	13/17	154.1	33.9	22.3
THRI	Low	44 (9.3)	1	0/0	-	30.9	0
	Medium	243 (51.4)	5	2/3	154.5	32.8	5.8
	High	186 (39.3)	16	11/14	111.0	42.1	32.6
HCC risk score	Low	149 (38.0)	3	1/1	963	38.5	3.8
	Medium	185 (47.2)	12	10/11	121.4	35.7	23.9
	High	58 (14.8)	5	0/3	-	46.8	27.3
ADDRESS-HCC	Low	46 (9.7)	3	3/3	323.7	31.6	9.4
	Medium	269 (56.9)	16	9/12	206.7	35.8	18.8
	High	158 (33.4)	3	1/2	306.0	43.7	22.2

PO-2070

Discriminatory changes in circulating lipid and small molecule metabolites in patients with MAFLD associated hepatocellular cancer

Rohini Sharma¹, Haonan Lu¹, Jacob George², Mohammed Eslam², Augusto Villanueva³, Caroline Ward¹, Helen L. Reeves⁴, Misti McCain⁴, Edward Chambers¹, Caroline Sands¹, Lynn Maslen¹, Matthew Lewis¹, Ramya Ramaswami¹. ¹Imperial College London; ²Storr Liver Centre; ³Icahn School of Medicine at Mount Sinai; ⁴University of Newcastle
Email: r.sharma@imperial.ac.uk

Background and aims: The burden of metabolic (dysfunction) associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD) is rapidly rising, the sequelae including an increase in hepatocellular cancer (HCC). There is an

acute need for screening programs for the early detection of MAFLD associated HCC, the majority of whom present with late stage disease. MAFLD and its sequelae are characterised by perturbations in lipid handling, inflammation and mitochondrial damage. The profile of circulating lipid and small molecule metabolites with the development of HCC is poorly characterized in MAFLD and could be used in future studies as a marker for the detection of HCC.

Method: We assessed the profile of 273 lipid and small molecule metabolites by ultra-performance liquid chromatography coupled to high-resolution mass spectrometry (UPLC-MS) in serum from patients with MAFLD (n = 113) and patients with MAFLD-associated HCC (n = 144) from six different centres. Regression models were used to identify a predictive model of HCC using minimal circulating features.

Results: Asymmetric dimethylarginine and twenty lipid species were found to successfully predict the presence of cancer on a background of MAFLD with high accuracy (AUC 0.94). In particular, the presence of these metabolites was associated with cirrhosis in the MAFLD subgroup (p < 0.001). When considering the HCC cohort alone, the metabolic signature was an independent predictor of overall survival (HR 1.42, 95%CI: 1.09–1.83, p < 0.01).

Conclusion: Taken together, these exploratory findings reveal a diagnostic metabolic signature in serum which is capable of accurately detecting the presence of HCC on a background of MAFLD. This unique serum signature will be taken forward for further investigation of diagnostic performance.

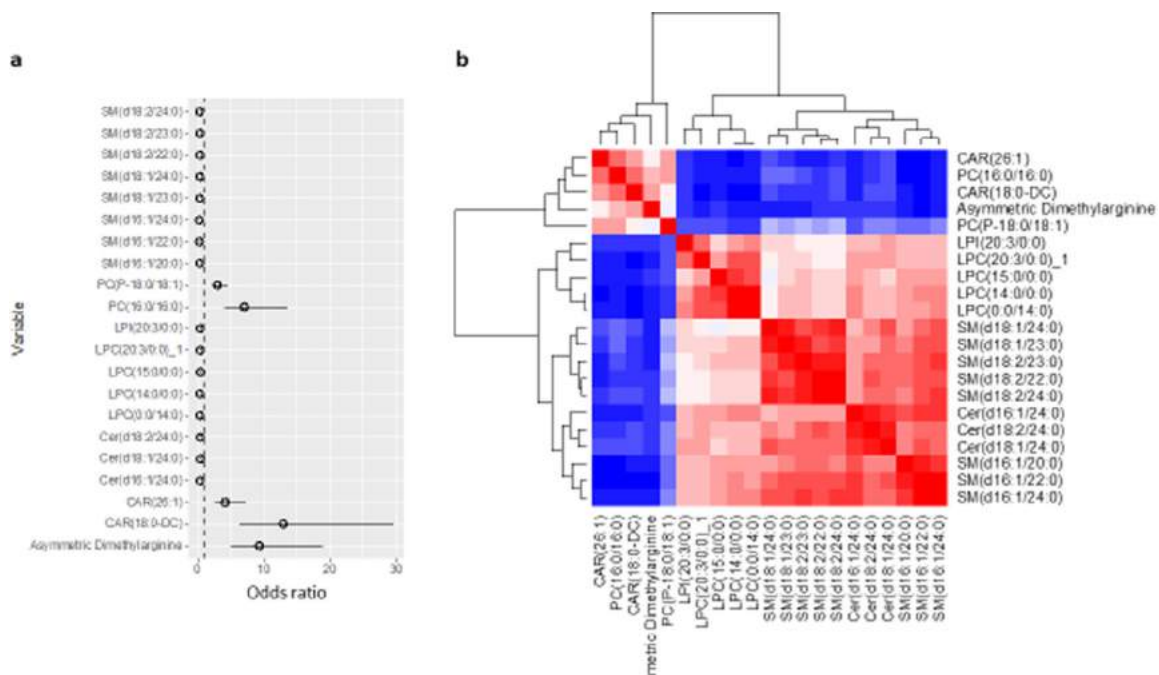


Figure: (abstract: PO-2070): **Inter-correlations among lipid species.** a) Forest plot analysis illustrating the association between the 21 metabolites and HCC. b) Heat-map demonstrating the inter-metabolite correlations within the entire cohort. Red colour indicates high similarity between the two species whereas blue indicates low similarity.

PO-2181

Abdominal ultrasound and alpha-foetoprotein for the diagnosis of hepatocellular carcinoma. A diagnostic test accuracy Cochrane review

Agostino Colli¹, Tin Nadarevic², Damir Miletic³, Vanja Giljaca⁴, Fraquelli Mirella⁵, Davor Stimac⁶, Giovanni Casazza⁷. ¹Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Department of Transfusion Medicine and Haematology; ²Clinical Hospital Center, Department of Radiology, Rijeka, Croatia; ³University of Rijeka, Clinical Department of Radiology; ⁴University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ⁵Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Milano, Italy; ⁶University Hospital Rijeka, Division of Gastroenterology, Department of Internal Medicine, Rijek, Croatia; ⁷Universita' degli Studi di Milano, Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Milano, Italy Email: mfraquelli@yahoo.it

Background and aims: Hepatocellular carcinoma (HCC) ranks fifth in terms of global instances of cancer and second in terms of cancer deaths for men. Current guidelines recommend ultrasound (US) with or without alpha-foetoprotein (AFP) as surveillance programme in high risk population even if there is no clear evidence of benefit in terms of overall-survival. Assessing the diagnostic accuracy of US and AFP may clarify whether the absence of benefit might be related to under-diagnosis.

Method: We searched (June 2020): Cochrane Hepato-Biliary Group DTA Studies Register, MEDLINE, Embase, Web-of-Science. We assessed the risk of bias with QUADAS-2 checklist. We used a hierarchical meta-analysis model and presented uncertainty of estimates using 95% confidence intervals (CIs).

Results: Overall, 374 studies, with 168816 participants, were included. Only one study was judged at low risk of bias. As the primary studies with AFP used different cut-offs, we performed two meta-analyses including studies reporting cut-off around 20 or 200 ng/ml (the most used values).

The results' heterogeneity remains mostly unexplained, in part referable to different cut-offs or settings.

A direct comparison of six studies showed a higher sensitivity of AFP₂₀+US with similar specificity compared to US alone.

Figure:

Index test (cut off)	Studies (n.)	Sensitivity (95% CIs)	Specificity (95% CIs)
AFP ₂₀ (20 ng/ml)	147	60 (58–62)	84 (82–86)
AFP ₂₀₀ (200 ng/ml)	56	36 (31–41)	99 (89–99)
US	39	72 (63–79)	94 (91–96)
AFP ₂₀ (20 ng/ml) + US	6	96 (88–93)	85 (73–93)

Conclusion: Using AFP₂₀, around 40% of HCC would be missed; with US alone more than a quarter. AFP₂₀+US shows the highest sensitivity and less than 5% of HCC would be missed with around 15% of false-positive results. The uncertainty resulting from the poor study quality and the heterogeneity of results limit our ability to confidently draw conclusions

PO-2223

Proposal and validation of a novel scoring system for hepatocellular carcinomas beyond curability borders: Unresectable hepatocellular carcinoma prognostic index

Coskun Ozer Demirtas¹, Gabriele Ricco^{2,3}, Osman Cavit Ozdogan¹, Feyyaz Baltacioglu⁴, Tunc Ones⁵, Perran Fulden Yumuk⁶, Ender Dulundu⁷, Sinan Uzun⁸, Piero Colombatto², Filippo Oliveri², Maurizia Brunetto^{2,3,9}, Feyza Gunduz¹. ¹Marmara University, School of

Medicine, Department of Gastroenterology, Istanbul, Turkey; ²Pisa University Hospital, Hepatology Unit, Pisa, Italy; ³Pisa University, Department of Clinical and Experimental Medicine, Pisa, Italy; ⁴Marmara University, School of Medicine, Department of Radiology, Istanbul, Turkey; ⁵Marmara University, School of Medicine, Department of Nuclear Medicine, Istanbul, Turkey; ⁶Marmara University, School of Medicine, Department of Medical Oncology, Istanbul, Turkey; ⁷Marmara University, School of Medicine, Department of General Surgery, Istanbul, Turkey; ⁸Marmara University, School of Medicine, Department of Medical Biostatistics, Istanbul, Turkey; ⁹Biostructure and Bio-imaging Institute of National Research Council of Italy, Naples, Italy Email: coskun_demirtas10@hotmail.com

Background and aims: The optimal system to refine the stratification of prognosis in patients with unresectable hepatocellular carcinoma (HCC) is currently uncertain. We aimed to develop and externally validate an easy-to-use tool particularly for this population, and named it the "Unresectable Hepatocellular Carcinoma Prognostic Index" (UHPI).

Method: We evaluated the data of treatment-naïve unresectable HCC patients diagnosed in the training center from 2010 to 2019 (n = 209). A simple prognostic model was developed by assigning points for each co-variate in proportion to the beta-coefficients in the Cox-multivariable model. An independent European validation cohort (n = 147) was studied to reveal its performance and distinction ability, and UHPI was also compared with 11 other available models.

Results: A simple scoring system was derived, assigning 0.5/1/2 scores for six independent co-variables including, the Child-Pugh score, Eastern Cooperative Oncology Group performance status, maximum tumor size, extrahepatic vascular invasion or metastasis, lymph node involvement, and alpha-fetoprotein. UHPI score, ranging from 0 to 6, showed superior performance in predicting prognosis and outperformed 11 other staging or prognostic models giving the highest homogeneity (c-index [0.803] and area under the receiver operator characteristics curves for 6-month [0.829] and 1-year [0.845]), lowest Akaike information criterion, and -2 log-likelihood ratio values. UHPI score well-allocated the risk of unresectable HCC patients for mortality within the first year, using two cut-off values (Low-risk:<1, intermediate-risk:1–3 and high-risk:>3).

Table: Unresectable HCC Prognostic Index

Variable	Point
Child-Pugh Class	
–A	0
–B	1
–C	2
–ECOG performance status	
–0–1	0
–2–4	1
–Maximum tumor size	
–≤8 cm	0
–>8 cm	1
Vascular invasion or metastasis	1
Lymph node involvement	0.5
–Alpha-fetoprotein	
–<500 ng/ml	0
–≥500 ng/ml	0.5
• UHPI-stage 1 (<1): 100% 6-month, >85% 1-year survival probability	
• UHPI-stage 2 (1–3): 70–85% 6-month, 45–55% 1-year survival probability	
• UHPI-stage 3 (>3): 20–50% 6-month, <5% 1-year survival probability	

ECOG: Eastern Cooperative Oncology Group, HCC: Hepatocellular carcinoma, UHPI: Unresectable HCC prognostic index.

Conclusion: UHPI score can predict prognosis better than other systems in unresectable HCC subjects and can be used in clinical practice or trials to estimate the 6-month and 1-year survival probabilities for this group.

POSTER PRESENTATIONS

PO-2242

Incidence of Hepatocellular carcinoma in patients with Non-Alcoholic Fatty Liver Disease. A systematic Review, Meta-Analysis and Metaregression

Marco Sanduzzi Zamparelli¹, Lorenzo A. Orci^{2,3}, Berta Caballo⁴, Víctor Sapena⁵, Nicola Colucci^{2,6}, Ferran Torres^{7,8}, Jordi Bruix⁵, Christian Toso^{2,3}, María Reig⁵. ¹BCLC Group, Liver Unit, Hospital Clinic Barcelona, Fundacio Spain.; ²Abdominal and Transplantation Surgery, Department of Surgery, Geneva University Hospitals and Faculty of Medicine, Swaziland; ³Hepato-pancreato-biliary Center, Geneva University Hospitals and Faculty of Medicine, Swaziland; ⁴BCLC Group, Liver Unit, ICMDiM. Hospital Clinic Barcelona, Spain., Spain; ⁵BCLC Group, Liver Unit, ICMDiM. Hospital Clinic Barcelona, CIBERehd. Spain.; ⁶University of Pavia, Pavia, Italy, Italy; ⁷Medical Statistics core facility, IDIBAPS, Hospital Clinic Barcelona, Spain., Spain; ⁸Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

Email: mreigt@clinic.cat

Background and aims: Non-alcoholic fatty liver disease (NAFLD) may be identified as a risk factor for hepatocellular carcinoma (HCC), but the extent of this association still needs to be properly addressed. The aim of the present study is to estimate by a meta-analysis the pooled-incidence rates of HCC across the disease spectrum of NAFLD.

Method: In this systematic review, we searched Web of Science, Embase, Pubmed, and the Cochrane library from January 1st, 1950 through July 30th, 2020. We included studies reporting on HCC incidence in patients with NAFLD. The main outcomes were pooled HCC incidences in patients with NAFLD at distinct severity stages. Sensitivity analyses and meta-regression analyses were carried out to address heterogeneity. The protocol for this review was registered in Prospero (CRD42018092861).

Results: We identified 10, 263 studies and 18 of those involving 470, 404 patients were finally included. Heterogeneity in cirrhotic patients was of 81% and of 98% in non-cirrhotic. In patients with NAFLD without established cirrhosis, HCC incidence was 0.03 per 100 person-years (PYs) (95% confidence interval 0.01–0.07, $I^2 = 98\%$). When considering studies that only included patients with cirrhosis the rate was of 3.78 per 100PYs (2.47–5.78, $I^2 = 81\%$). Among the latter patients, those undergoing regular HCC screening displayed an incidence of 4.62 per 100PYs (2.77–7.72, $I^2 = 77\%$). Sensitivity analyses and meta-regression analyses did not significantly improve heterogeneity.

Conclusion: The high heterogeneity of the studies hampers robust conclusions. However, patients with NAFLD-related cirrhosis have a risk of developing HCC similar to that reported for patients with cirrhosis from other aetiologies. Data documenting the risk in patients with NASH or steatosis are limited, but HCC incidence in these populations may lie below thresholds used to recommend HCC screening. Considering the high heterogeneity and the absence of informative screening programs in non-cirrhotic patients, well-designed prospective studies are needed in such subgroup of patients to properly assess the risk.

PO-2364

The added value of PIVKA-II levels over AFP in patients with hepatocellular carcinoma undergoing locoregional treatment

Massimo Iavarone¹, Alessandro Rimondi¹, Floriana Facchetti¹, Mariangela Bruccoleri¹, Anna Maria Ierardi¹, Riccardo Perbellini¹, Sara Colonia Uceda Renteria¹, Ferruccio Ceriotti¹, Alberto Peregò², Corinna Orsini², Angelo Sangiovanni¹, Gianpaolo Carrafiello¹, Pietro Lampertico¹. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy; ²Fujirebio Italia, Pomezia, Italy

Email: massimo.iavarone@policlinico.mi.it

Background and aims: The potential usefulness of Prothrombin Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) has been suggested in surveillance of hepatocellular carcinoma (HCC), but its

role in HCC diagnosis and prognosis according to staging and treatment lacks evaluation.

Methods: In this single-center study, we tested 135 consecutive patients with first diagnosis of HCC for PIVKA-II and alpha-fetoprotein (AFP) (Fujirebio, Japan) on samples collected the day of ablation or chemoembolization (TACE). Primary aim was identification of reference range of PIVKA-II levels for diagnosis of HCC and according to stage of HCC (size of largest tumor, number of nodules, BCLC), secondary aim was evaluation of predictive role of PIVKA-II for fast-progression (tumor progression at first CT-scan after treatment) and early recurrence (less than 12 month after complete response-CR).

Results: 127 patients were finally evaluated (8 excluded due to anticoagulant interference with PIVKA-II measurement): age 66 (IQR: 58–75) years, 83% males, 61% HCV-Ab positive, HCC size 22 mm (IQR: 17–30), 64% single nodule. 40 patients were treated with ablation and 87 with TACE. PIVKA-II and AFP levels were 149 mAU/ml (IQR: 58–489) and 6.6 ng/ml (IQR: 3.6–21.7), respectively. In a linear regression model at univariate and multivariate analysis, high levels of PIVKA-II independently predicted the number of nodules ($p = 0.002$) and the diameter of the largest nodule ($p < 0.001$), whereas AFP has no correlation with both ($p = 0.42$ and $p = 0.21$, respectively). At multivariate analysis a strong correlation between PIVKA-II and AFP was found ($p < 0.001$). As for the secondary end points: 1) PIVKA-II was 479 mAU/ml (IQR: 131–3004) in 19 patients fast-progressors of HCC after treatment vs 121 mAU/ml (IQR: 56–396) in the other 108 patients ($p = 0.045$), while AFP was 14 mAU/ml (IQR: 7–65) vs 6 mAU/ml (IQR: 3.4–18), $p = 0.86$; 2) PIVKA-II was 279 mAU/ml (IQR: 66–499) in 18 patients with early recurrence after CR vs 223 mAU/ml (IQR: 57–447) in the other 50 patients ($p = 0.10$), while AFP was 11 ng/ml (IQR: 4–19) vs 6 ng/ml (IQR: 3–13), $p = 0.60$. At multivariate analysis, only diameter and number of nodules were baseline independent predictors of fast-progression (OR: 1.046, 95%CI 1.003–1.091, $p = 0.03$; OR 1.459, 95%CI 1.001–2.151, $p = 0.04$).

Conclusion: High PIVKA-II levels predict HCC stage more accurately than AFP but failed to predict fast progression after treatment and early progression after CR.

PO-2594

Free Androgen Index Levels May Influence the Transarterial Chemoembolization with Doxorubicin-Eluting Beads Response in Hepatocellular Carcinoma Patients: Preliminary Results.

Silvia Acosta-López¹, Dácil Díaz Bethencourt¹, Teresa Concepcion-Masip², Julian Portero-Navarro³, María Cecilia Martín-Fernández de Basoa², Antonio González Rodríguez¹, Francisco Andrés Pérez Hernández¹, Julio Plata-Bello⁴. ¹Hospital Universitario Nuestra Señora de Candelaria, Liver Unit, Santa Cruz de Tenerife, Spain; ²Hospital Universitario Nuestra Señora de Candelaria, Hormone Section of the Biochemical Laboratory, Santa Cruz de Tenerife, Spain; ³Hospital Universitario Nuestra Señora de Candelaria, Interventional Radiology, Santa Cruz de Tenerife, Spain; ⁴Hospital Universitario de Canarias, Department of Neuroscience, San Cristóbal de La Laguna, Spain

Email: sacostalopez9@gmail.com

Background and aims: Hepatocellular carcinoma (HCC) shows a male predominance. It has been demonstrated that testosterone avoid apoptosis and senescence in cells treated with doxorubicin. Bearing this mind, it can be hypothesized that testosterone can be related with a worse response to Trans-arterial Chemoembolization with Doxorubicin-Eluting Beads (DEB-TACE) in HCC.

The aim of the present study is to analyze the effect of total testosterone levels and free androgenic index (FAI) in the DEB-TACE response in HCC patients.

Method: Patients with HCC with any indication of DEB-TACE performance were included. Total testosterone was measured by radio-immune assay and FAI was calculated by using the formula reported by Vermeulen et al (1999). These determinations were

performed the same day of the DEB-TACE. All chemoembolization were performed by a single radiologist and using the same kind of doxorubicin particles. Treatment response was measured after one month with a multiphase contrast-enhanced computed tomography (CT). Modified RECIST (mRECIST) criteria were used to evaluate the response to DEB-TACE in each patient. Parametric statistical tests were performed, using a threshold of $p=0.05$ for statistical significance.

Results: Forty-one DEB-TACE performed in 22 patients (3 women; mean age: 70.4 [SD = 9.6]) were included in this analysis. A mean of 2 DEB-TACEs were performed per patient (rank: 1–5). The mean level of total testosterone prior to DEB-TACE was 4.7 ng/ml (SD = 2.6) and the mean level of FAI was 26.2 (SD = 13.8). Total response was achieved in 12 DEB-TACEs (29.3%) and partial response in 13 (31.7%). Stable disease was considered after 13 procedures (31.7%) and progression was found in 3 cases (7.3%). No significant differences were identified in total testosterone levels between the response groups (ANOVA; $p=0.542$). However, higher levels of FAI were identified in the progression group compared to the others (ANOVA; $p=0.029$). Bonferroni post-hoc test showed that the main difference was between progression and stable disease groups (45.6 vs. 20.6; $p=0.025$). Additionally, despite the few number of cases, a binary-logistic regression analysis showed that higher FAI levels were associated with a slight increase in the risk of progression after a DEB-TACE (OR = 1.142; 95% C.I. [1.008–1.293]; $p=0.037$).

Conclusion: Patients with higher levels of FAI prior to a DEB-TACE performance may be associated with a higher risk of progression at 1 month after the procedure.

PO-2612

Prior or current hepatocellular carcinoma does not adversely affect the evolution of LI-RADS 4 lesions.

Louise Hanly¹, William Shanahan¹, Michele Bourke¹, Niamh Mehigan¹, Cathal Clifford¹, Bilal Shoukat¹, Mohamed Osman¹, Diarmaid Houlihan¹, Ross MacNicholas¹. ¹St. Vincent's University Hospital, Dublin, Ireland
Email: louisehanly_100@hotmail.com

Background and aims: The Liver Imaging and Reporting Data System (LI-RADS) criteria are used to non-invasively diagnose hepatocellular carcinoma (HCC) in cirrhosis/chronic hepatitis B at the de facto national HCC service in Ireland. LI-RADS 5 lesions are classified as definite HCCs and can be treated as such. Not all lesions can be definitively characterised however. LI-RADS 4 lesions are described as probable HCCs, the management of which is recommended to be decided at multidisciplinary team (MDT) meetings. Many of these lesions are followed up with interval multiphase CT/MR imaging at our institution. We questioned whether the evolution of these lesions may vary depending on the cancer context at recognition; current/past HCC (HxHCC) or without definite HCC (NoHCC). We aimed to compare the evolution of these lesions between these two patient groups.

Method: We reviewed the MDT records at our institution over a 3 year period (2017–2019). We identified all patients with LI-RADS 4 lesions and sub-categorized them into the two groups (HxHCC and NoHCC). For those who underwent interval imaging we collected data on the time to progression to LI-RADS 5 of these lesions. Time to progression between cohorts was compared using Kaplan-Meier analysis. Significance was determined using log rank test.

Results: We identified 85 patients with LI-RADS 4 lesions. Of those, 63 underwent interval imaging. The remainder underwent targeted therapy or biopsy and were excluded. The mean follow-up time was 14.4 months. 35 patients were included in the HxHCC cohort, and 28 were included in the NoHCC cohort. Of these, 17 (48%) patients in the HxHCC cohort and 16 (57%) patients in the NoHCC cohort progressed to LI-RADS 5 during the follow-up period. There was no difference in the time to progression to LI-RADS 5 between either group, $p=0.877$.

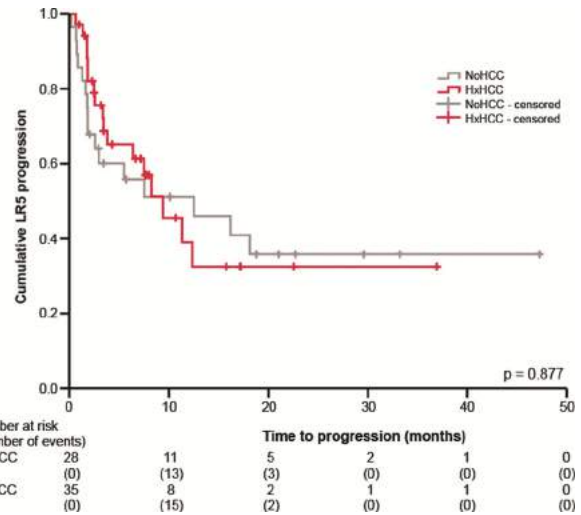


Figure:

Conclusion: The cancer context does not appear to influence the progression of probable HCCs to definite HCCs using the LI-RADS criteria.

PO-2687

SARS-CoV-2 one year on-the worrying impact on early detection of primary liver cancers

Daniel Geh¹, Robyn Watson¹, Stuart Mcpherson², Steven Masson², Jessica Dyson², Louise MacDougall², Mhairi Donnelly², Preya Patel², Lucy Walker², John Hammond^{3,4}, Jeremy French^{3,4}, Steven White^{3,4}, Stuart Robinson^{3,4}, Gourab Sen^{3,4}, Paul Turner^{4,5}, John Scott^{4,5}, Michael McNeil⁵, Misti McCain¹, Syed Asghar⁶, Nick Wadd⁷, Lavanya Mariappan^{4,8}, Jane Margetts^{4,8}, Peter Littler^{4,5}, Derek Manas^{3,4}, Helen Louise Reeves^{4,9,10}. ¹Newcastle University Translational and Clinical Research, Newcastle University; ²Department of Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust; ³Department of Surgery, Newcastle upon Tyne Hospitals NHS Foundation Trust; ⁴Hepatopancreatobiliary Multidisciplinary Team, Newcastle upon Tyne Hospitals NHS Foundation Trust; ⁵Department of Radiology, Newcastle upon Tyne Hospitals NHS Foundation Trust; ⁶Department of Oncology, Cumberland Infirmary, North Cumbria Integrated Care NHS Foundation Trust; ⁷Department of Oncology, South Tees Hospital NHS Foundation Trust; ⁸Department of Oncology, Newcastle upon Tyne Hospitals NHS Foundation Trust; ⁹Newcastle University Translational and Clinical Research, Newcastle University, United Kingdom; ¹⁰Department of Medicine, Newcastle-upon-Tyne NHS foundation Trust
Email: h.l.reeves@ncl.ac.uk

Background and aims: In Northern England new patients with primary liver cancer (PLC) have increased by 10–15% year on year. The rising prevalence of NAFLD and/or alcohol excess underpins this. We evaluated the impact of the SARS-CoV-2 pandemic.

Method: In this retrospective, observational, regional study we evaluated 455 consecutive new patients with PLC referred to the Newcastle-upon-Tyne NHS Foundation Trust, comparing the 12 months directly preceding the pandemic (YR1) to the first 12 months of it (March 2020–Feb 2021; YR2). Variables included mode of presentation, etiology, stage, 1st line treatment and SARS-CoV-2 infection.

Results: New referrals with hepatocellular carcinoma (HCC) fell for the 1st time in 15 years in YR2 (35%; 125 in YR2 from 190 in YR1; Fig1A), with fewer detected by surveillance or routine care-monitoring for HCC in the presence of cirrhosis, or incidentally as part ongoing care for other conditions. This was striking for NAFLD patients (surveillance/incidental/symptomatic 32.5/54.4/13.2% in YR1 compared to 28.3/39.6/32.1% in YR2, $p=0.04$, Fig1B). Tumour size was greater in YR2 (med 42.5 vs 35.5 mm; $p=0.036$, Fig1C), most

POSTER PRESENTATIONS

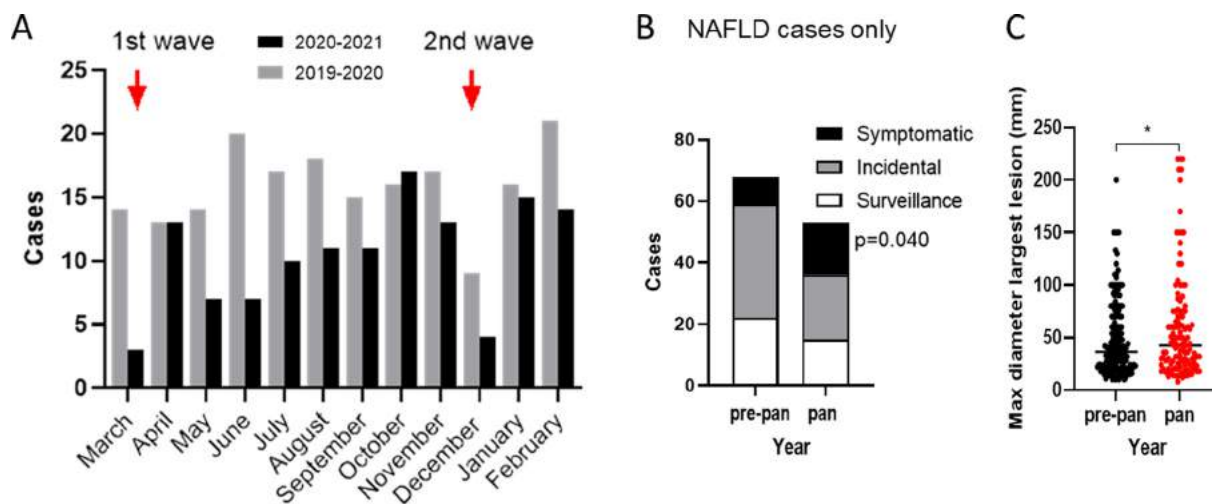


Figure: (abstract: PO-2687)

notable in months 11–12 (Jan-Feb 2020: mean 48.1 ± 5.1 n = 36, vs Jan-Feb 2021: 81.6 ± 11.9 n = 29; $p = 0.007$), with 6 patients experiencing life threatening hemorrhage at diagnosis/awaiting treatment in 2021. Despite challenges in YR2, patients received treatments-transplant, resection, locoregional and medical therapies (including atezo/bev) appropriate for stage, in accordance with NHS waiting times, although numbers receiving active treatment was reduced by 41% compared to YR1. 11/125 (9%) acquired SARS-CoV-2. In 5 it followed their HCC diagnosis-3 have died of advanced HCC, 1 continues atezo/bev and 1 supportive care. In 6 the diagnosis of advanced HCC was after/synchronous; 2 recovered to have active treatment with 4 receiving supportive care. Cases presenting with intrahepatic cholangiocarcinoma were also reduced in YR2, but less so (64 vs 76), with the commonest mode of presentation unchanged (symptomatic ~75%).

Conclusion: SARS-CoV-2 has placed an unprecedented burden on healthcare resources, with many routine activities such as chronic disease management and cancer surveillance postponed, compounded by patients fearful of leaving their homes. The tragic consequences are already evident for patients with NAFLD in our region-whose cancers are often detected at advanced stages incidentally, but are now presenting symptomatically. In our series, 9% of patients contracted SARS-CoV-2. These have died or been unfit to treat because of their advanced cancer stage, rather than SARS-CoV-2. At least 35% of our anticipated patients with HCC are 'missing'. If routine activities, including HCC surveillance, are not re-instituted and patients encouraged to attend, it is likely that they too will present with symptomatic advanced HCC.

PO-2755

A lesson from COVID19: the persevering benefits of hepatocellular carcinoma surveillance

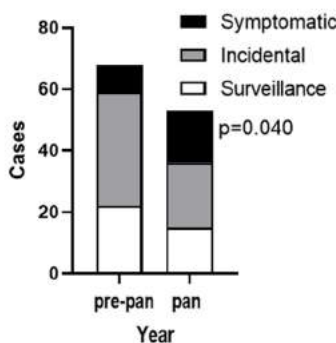
William Cunliffe¹, Tom Pembroke^{1,2}. ¹Cardiff University, School of Medicine, Cardiff, United Kingdom; ²Cardiff and Vale University Health Board, Department of Gastroenterology and Hepatology, Cardiff, United Kingdom

Email: pembroket@cardiff.ac.uk

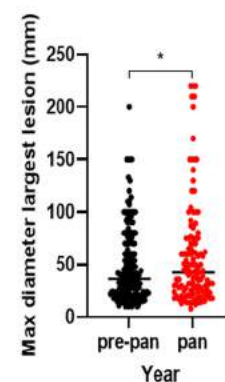
Background and aims: The incidence of hepatocellular carcinoma (HCC) in Wales is rising. We aimed to evaluate the impact of the COVID-19 pandemic on the South Wales HCC multi-disciplinary meeting (MDM) referrals and patient management.

Method: Baseline patient characteristics at MDM and treatment information was collated for index HCC discussion from the electronic health record. The year of the COVID period (CP) 01/03/

B NAFLD cases only



C



2020–28/2/2021, was compared to the pre-pandemic period (PP) 01/03/2018–29/02/2020.

Results: There was a 3-fold increase in index HCC diagnoses in South Wales MDM between 2002 and 2018. 803 patients were discussed from March 2018–21; follow-up (372) and non-HCC (90) cases were excluded. There were 245 PP and 96 CP index HCC diagnoses; a 22% reduction in annual index HCC diagnoses in the COVID period. The absolute number of HCCs detected by surveillance remained consistent at 33 per annum in PP and CP periods (27% v 34% respectively).

During CP the proportion of patients offered best supportive care and undergoing further investigation increased (47 to 56% and 1.2 to 13.5% respectively) whilst all anti-cancer interventions fell (figure 1): ablation/surgery (22 to 15.6%), chemo-embolisation (21.2 to 11.5%) and systemic anti-cancer therapies (8.2 to 3.1%, $p < 0.0001$). However, during CP a greater proportion of those on HCC surveillance received curative therapies compared to HCC detected outside of screening in individuals (27.3 vs. 8.5%, $p = 0.03$).

Median time from point of suspicion of HCC to MDM and MDM to first definitive treatment reduced slightly during the CP (43 v 40.5 days and 56 v 55 days respectively).

Conclusion: The COVID-19 pandemic had a significant impact on referrals to the HCC MDT, yet HCC surveillance identified the same number of hepatomas. HCC identified by surveillance in the pandemic were more amenable to radical therapies. The fall in the proportion of patients receiving both curative and palliative therapies reflects the fall in incidental treatable HCC during the COVID period. A relatively high proportion of patients received best supportive care in all three years; reflecting an older population with high burden of comorbidities in South Wales linked to socio-economic deprivation. Median waiting times are in excess of the Welsh Government's target of 62 days, suggesting that the current diagnosis and referral process requires revision and resources to expedite therapies.

PO-2786

Insulin like growth factor-1 as a prognostic tool for overall survival in chronic hepatitis C cirrhotic Egyptian patients with hepatocellular carcinoma

Elsayed Ghoneem¹, Sawzan Moniem Mohamed¹, Wafa Elemshaty², Ahmed Kaseb³, Ahmed Sultan^{1,4}. ¹Faculty of Medicine, Mansoura University, Gastroenterology and Hepatology Unit, Internal Medicine Department, Mansoura, Egypt; ²Faculty of Medicine, Mansoura University, Clinical Pathology, Mansoura, Egypt; ³The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ⁴Department of Gastrointestinal Medical Oncology, Houston, United States; ⁴Cleveland

Treatment outcomes for HCC MDM discussion in South Wales in the pre-pandemic and COVID periods

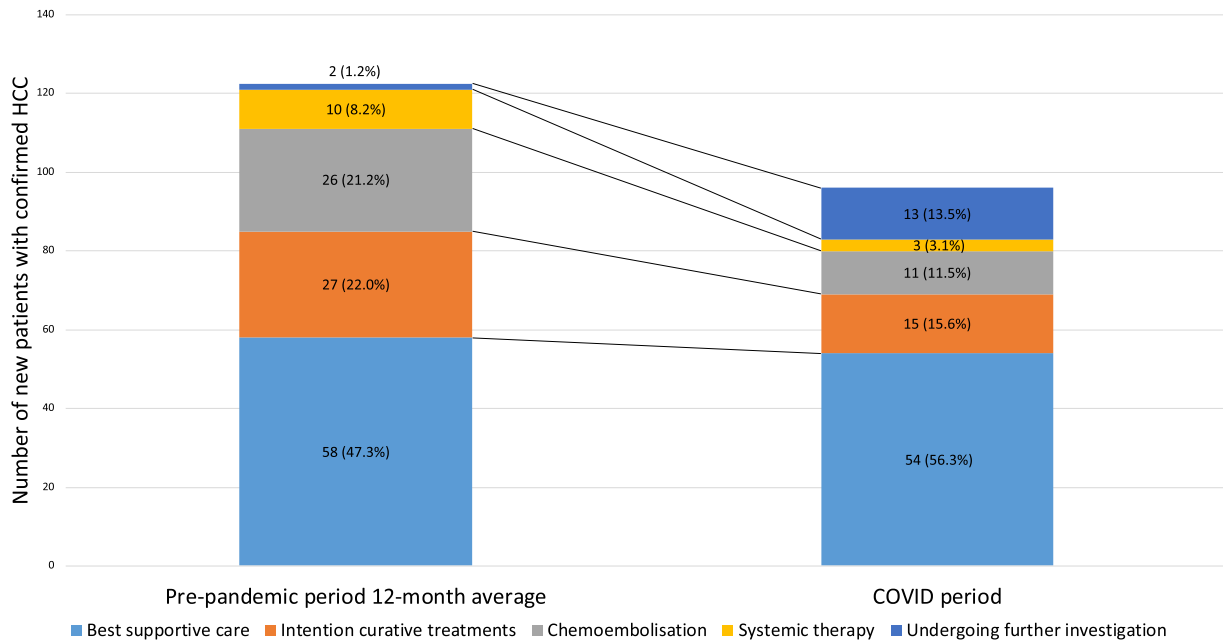


Figure: (abstract: PO-2755)

Clinic Abu Dhabi, Digestive Disease Institute, Abu Dhabi, United Arab Emirates
 Email: dr.ahmed.sultan@gmail.com

Background and aims: Hepatitis C virus “HCV” infection is a common cause of end stage liver disease “ESLD” and hepatocellular carcinoma “HCC.” Because of its high prevalence among Egyptian, HCV infection is the commonest cause of HCC in Egypt. Child Pugh score “CPS” is the standard score to stage the liver status and estimate an overall prognosis. Yet, the prognosis of HCV induced HCC remains poor due to the aggressive nature of the tumor and cirrhosis complications. Insulin like growth factor-1 “IGF-1” is known to reflect the overall hepatic reserve and are inversely correlated with the severity of liver disease. Moreover, a decline in serum IGF-1 level is associated with the development of HCC regardless the grade of hepatic dysfunction. This study aimed to evaluate the predictive value of serum IGF-1 levels alone or in combination with CPS on the overall survival (OS) of Egyptian patients with HCV induced HCC.

Method: The study group was formed of 125 patients with treatment naïve HCC secondary to chronic HCV infection. Patients who had non-HCV chronic liver disease, end stage organ failure rather than liver and diabetes mellitus on insulin therapy were excluded. All patients were subjected to complete physical examination, abdominal ultrasonography and triphasic CT abdomen. Fasting blood samples were collected for assessment of liver function, liver enzymes, creatinine, fasting blood sugar, complete blood count, serum alpha-fetoprotein, and IGF-1. OS time was calculated from the date of sampling to the date of death or the date of the last follow-up. Patients alive were censored.

Results: The serum IGF-1 level was inversely correlated with OS. The higher IGF-1, the lower risk of death (HR = 0.98, p = 0.008) with the worst prognosis with IGF-1 <26 ng/ml. Almost one third of patients who were staged CPS-A and B were down staged to IGF-CPS-B and C respectively and consequently had a less OS.

Conclusion: In Egyptian patients with HCV induced HCC, serum IGF-1 alone or in combination with CPS “IGF-CPS” showed better correlation with OS compared with standard CPS alone.

Figure: Table 1: Univariate Cox model to evaluate the association of IGF with OS

	HR (95% CI)	P value
IGF (as continuous variable)	0.98 (0.97, 0.99)	0.0082
IGF (<26 vs. >26)	2.89 (1.67, 5.03)	0.0002
IGF		
26–50 vs. >50	0.9 (0.41, 1.97)	0.7925
<26 vs. >50	2.73 (1.34, 5.54)	0.0056
≤26 vs. 26–50	3.03 (1.59, 5.77)	0.0008

PO-2799

Early SARS-CoV-2-related mortality of liver cancer patients: Cancer stage matters

Sergio Munoz-Martínez^{1,2,3}, Víctor Sapena^{1,2,4}, Alejandro Forner^{1,2}, Jordi Bruix^{1,2,4,5}, Marco Sanduzzi Zamparelli^{1,2,3,5}, Mohamed Bouattour⁶, Cassia Regina Guedes Leal⁷, Carmem Ferguson Theodoro⁸, Mohammed El-Kassas⁹, Jean Charles Nault¹⁰, Lorraine Blaise¹⁰, Tudor Mocan¹¹, Leonardo Gomes da Fonseca¹², Helen L. Reeves¹³, Rogério Alves¹⁴, Ignacio Garcia Juarez¹⁵, Maria Varela¹⁶, David J. Pinato¹⁷, Andrea Casadei Gardini¹⁸, Mario Reis Álvares-da-Silva¹⁹, Jesús González Santiago²⁰, María del Mar Lozano²¹, Juan Carlos Bandi²², Lorenza Rimassa^{23,24}, Margarita Sala^{5,25}, Saleh Alqahtani²⁶, Maria Margarita Anders²⁷, Federico Pinero²⁸, Anja Lachenmayer²⁹, Frank Tacke³⁰, Christoph Roderburg³⁰, Manuel Romero Gomez^{5,31}, Markus Peck-Radosavljevic³², Giuseppe Cabibbo³³, Alessandra Elvevi³⁴, Maria Guarino³⁵, Alex Vianey Callado França³⁶, Rosanna Villani³⁷, Mercedes Vergara Gómez^{5,38,39}, Juan Acevedo⁴⁰, Carlos Rodriguez de Lope⁴¹, Vivianne Mello⁴², Christie Perelló⁴³, Sonia Pascual^{5,44}, Chiara Braconi⁴⁵, Massimo Iavarone⁴⁶, María Reig^{1,2,4,5}. ¹Hospital Clínic de Barcelona, BCLC group, Liver Unit,

POSTER PRESENTATIONS

Barcelona, Spain; ²IDIBAPS, Spain; ³Fundació Clínic per la Recerca Biomèdica (FCRB), Spain; ⁴University of Barcelona, Barcelona, Spain; ⁵CIBERehd, Barcelona, Spain; ⁶Hospital Beaujon AP-HP, Digestive Oncology, Clichy, France; ⁷Hospital Federal dos Servidores do Estado, Gastroenterology, Rio de Janeiro, Brazil; ⁸Hospital Universitário Antônio Pedro, Brazil; ⁹Faculty of Medicine-Helwan University, Endemic Medicine, Cairo, Egypt; ¹⁰Hôpital Avicenne, Service d'hépatologie, Bobigny, France; ¹¹Institutul Regional de Gastroenterologie și Hepatologie Prof. Dr. Octavian Fodor, 3rd Medical Department, Cluj-Napoca, Romania; ¹²Instituto do Câncer do Estado de São Paulo, Clinical Oncology, Brazil; ¹³N H S Foundation Trust, Liver Unit, United Kingdom; ¹⁴Hospital do Servidor Público Estadual, Gastroenterology, Sao Paulo, Brazil; ¹⁵Salvador Zubirán National Institute of Health Sciences and Nutrition, Gastroenterology, Ciudad de México, Mexico; ¹⁶Hospital Universitario Central de Asturias, Department of Gastroenterology and Hepatology, Oviedo, Spain; ¹⁷Imperial College London, Department of Surgery and Cancer, London, United Kingdom; ¹⁸University of Modena and Reggio Emilia, Medical Oncology, Modena, Italy; ¹⁹Hospital de Clínicas de Porto Alegre, GI/Liver Unit, Porto Alegre, Brazil; ²⁰University of Salamanca Hospital, Salamanca, Spain; ²¹Hospital Universitario Infanta Leonor, Aparato Digestivo, Madrid, Spain; ²²Hospital Italiano, Hepatology, Buenos Aires, Argentina; ²³Humanitas University, Department of Biomedical Sciences, Italy; ²⁴Humanitas Research Hospital, Medical Oncology and Hematology Unit, Cascina Perseghetto, Italy; ²⁵Hospital Universitari de Girona Doctor Josep Trueta, Gastroenterology, Hepatology Unit, Girona, Spain; ²⁶King Faisal Specialist Hospital and Research Centre, Liver Transplant, Riyadh, Saudi Arabia; ²⁷Hospital Alemán, Hepatologia, Argentina; ²⁸Hospital Universitario Austral, Liver Unit, Pilar Centro, Argentina; ²⁹Inselspital, Bern University Hospital, Department of Visceral Surgery and, Bern, Switzerland; ³⁰Charité-Universitätsmedizin Berlin, Department of Hepatology and Gastroenterology, Berlin, Germany; ³¹Virgen del Rocío University Hospital, SeLiver group. UGC de Enfermedades Digestivas, Sevilla, Spain; ³²Klinikum Klagenfurt am Woerthersee, Innere Medizin and Gastroenterologie, Klagenfurt am Wörthersee, Austria; ³³PROMISE, University of Palermo, Section of Gastroenterology and Hepatology, Palermo, Italy; ³⁴University of Milan, Division Gastroenterology and Center for Autoimmune Liver Diseases, Milano, Italy; ³⁵University of Naples Federico II, Dpt of Clinical Medicine and Surgery, Napoli, Italy; ³⁶Federal University of Sergipe, Medicine, Aracaju, Brazil; ³⁷University of Foggia, Liver Unit, Department of Surgical and Medical Sciences, Foggia, Italy; ³⁸Hospital Parc Taulí de Sabadell, Unitat d'Hepatologia. Servei d'Aparell Digestiu, Sabadell, Spain; ³⁹Universitat Autònoma de Barcelona, Bellaterra, Spain; ⁴⁰Plymouth Nhs Trust, South West Liver Unit, Plymouth, United Kingdom; ⁴¹Marqués de Valdecilla University Hospital, Servicio de Aparato Digestivo, Santander, Spain; ⁴²AMO, Oncology, Salvador, Brazil; ⁴³Puerta de Hierro Majadahonda University Hospital, Gastroenterology and Hepatology, Majadahonda, Spain; ⁴⁴Hospital General Universitario de Alicante, Liver Unit, Alacant, Spain; ⁴⁵Beatson West of Scotland Cancer Centre, Medical Oncology, United Kingdom; ⁴⁶Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milano, Italy
Email: mreig1@clinic.cat

Background and aims: The SARS-CoV-2 infection in cirrhotic patients has been associated with liver function deterioration and the 30 day-COVID-19-associated-mortality rate of 25% (Iavarone et al JHEP, 2021). However, there are no data about mortality in a large cohort of liver cancer patients with SARS-CoV-2 infection. To evaluate the 30 day-mortality of liver cancer patients with SARS-CoV-2 infection.

Method: CERO-19 is a retrospective, observational, multicenter and international project, evaluating clinical outcomes of SARS-CoV-2 in liver cancer. Variables related to type of liver cancer, BCLC or TNM-8th stage at SARS-CoV-2 diagnosis and others related to patient outcome were registered. The 30-day SARS-CoV-2-related mortality rates and hazard ratios (SHR) were estimated considering non-related- SARS-CoV-2 deaths as competing events. Hazard ratios were calculated considering non-related- SARS-CoV-2 deaths as competing risks.

Results: This analysis evaluated 242 patients infected with SARS-CoV-2 from 38 centers (Europe, America, Asia, and Africa) from February to December 2020. From the 213 hepatocellular carcinoma (HCC), 54 were de-novo diagnosis and 159 patients had prior history of HCC. The median age was 60 [IQR: 54.6–67] years and 29% received systemic treatment. Among the 29 intrahepatic cholangiocarcinoma (iCCA) only 6 were de-novo. Sixty-seven (27.7%) patients died: 42 deaths were SARS-CoV-2-related (71.4% were cirrhotic) and 25 non-SARS-CoV-2-related (92% were cirrhotic).

The 30-day mortality rate of the whole cohort, and SARS-CoV-2-related death were 21.2% (95%CI: 15.7–26.7), and 17.4% (95%CI: 12.7–22.8), respectively. The 30-day mortality rate in patients with history of liver cancer were: 23.2% (95%CI: 16.2–30.2) with HCC and 42.9% (95%CI: 21.4–64.4) with iCCA. Figure 1 describes the 30-day mortality due to SARS-CoV-2 infection according to BCLC-0/A, B, C and D stage. From the 60 de-novo liver cancer diagnosis, 60% of the HCC were BCLC ≥B stages and 5 out of 6 iCCA were stage IV. The 30-day mortality rate in de-novo HCC was 8.3% (95% CI: 0.5–16.1).

Conclusion: The 30-day SARS-CoV-2-related mortality in HCC seems similar to the mortality reported in cirrhotic patients without HCC. However, the 30-day SARS-CoV-2-related mortality rate varies according to the BCLC stage, even when BCLC D patients are excluded. The small sample size of iCCA limited the interpretation of the 30-day SARS-CoV-2-related mortality in this population.

PO-2812

Trend and correlates of increased serum alpha-fetoprotein in hepatocellular carcinoma: US National Cancer Database analysis

Aarshi Vipani¹, Marie Lauzon¹, Michael Luu¹, Mazen Nouredin¹, Alexander Kuo¹, Walid Ayoub¹, Vinay Sundaram¹, Irene Kim¹, Tsuyoshi Todo¹, Andrew Hendifar¹, Jun Gong¹, Nicole Rich², Kambiz Kosari¹, Nicholas Nissen¹, Lewis Roberts³, Amit Singal², Ju Dong Yang¹. ¹Cedars-Sinai Medical Center; ²UT Southwestern; ³Mayo Clinic

Email: aarshi.vipani@cshs.org

Background and aims: Serum alpha-fetoprotein (AFP) is a biomarker for hepatocellular carcinoma (HCC). Large-scale data analysis of 1) temporal trend of AFP level at diagnosis and 2) demographic,

Figure 1. Thirty-day mortality according to BCLC stage in HCC patients

BCLC stage at SARS-CoV-2 diagnosis	Events (30-day SARS-CoV-2-related death)	Competing Events (30-day non-SARS-CoV-2-related death)	Patients at risk	Mortality rate at 30-day due SARS-CoV-2, % (95% CI)	p-value (Gray's Test)	p-value excluding BCLC-D (Greys's Test)	HR (95%CI)	p-value
0 or A	4	1	77	6.1 (1.9 - 13.7)	0.007	0.048	ref.	
B	7	1	51	14.6 (6.3 - 26.1)			2.59 (0.76 - 8.81)	0.13
C	11	0	57	21.2 (11.2 - 33.3)			3.86 (1.25 - 11.93)	0.02
D	8	5	28	33.1 (15.2 - 52.3)			-	
Total	30	7	213					

Figure: (abstract: PO-2799)

socioeconomic and clinical factors associated with increased serum AFP levels independent of tumor stage has not been investigated in HCC.

Method: We identified HCC patients diagnosed between 2010 and 2017 in the US National Cancer Database. Multivariable logistic regression modeling was performed to determine factors associated with elevated serum AFP levels, which was defined as greater than or equal to 20 ng/ml.

Results: Out of 133, 542 patients, AFP level was reported in 108, 353 patients (81%) and baseline characteristics were comparable between patients with and without AFP results. AFP level was increased in 62.6% of patients. Since 2011, the median range of AFP at HCC diagnosis has trended down from 70 to 79 ng/ml in 2011 to 30–39 ng/ml in 2017 ($p < 0.001$). Additionally, the percentage of HCC tumors with elevated AFP has been declining, most significantly in TNM stage 1 and 2 (Figure 1). There was an inverse association between the year of HCC diagnosis and elevated AFP (adjusted odds ratio (AOR) per year: 0.93, 95% CI: 0.93–0.94) after adjusting for covariates including TNM tumor stage. Additionally, female sex (AOR: 1.11, 95% confidence interval (CI): 1.08–1.15) and younger age (AOR per 10 years: 0.96, 95% CI: 0.95–0.98) were more likely to have elevated AFP. Black (AOR: 1.59, 95% CI: 1.53–1.66), Asian (AOR: 1.30, 95% CI 1.24–1.36), Hispanic (AOR: 1.11, 95% CI 1.06–1.16) vs. White was associated with elevated AFP. Community cancer programs vs. academic cancer programs (AOR: 1.74, 95% CI: 1.62–1.86) and South vs. Northeast regions (AOR: 1.07, 95% CI: 1.03–1.11) were associated with elevated AFP levels while private insurance (AOR: 0.81, 95% CI 0.76–0.87), Medicaid/Medicare (AOR: 0.81, 95% CI: 0.76–0.86) vs. no insurance was inversely associated with elevated AFP. Among clinical factors, patients with at least 3 Charlson/Deyo Comorbidity Score were inversely associated with elevated AFP (AOR: 0.85, 95% CI: 0.82–0.88) while higher MELD scores (AOR per 10 units: 1.09, 95% CI: 1.07–1.10) were associated with elevated AFP.

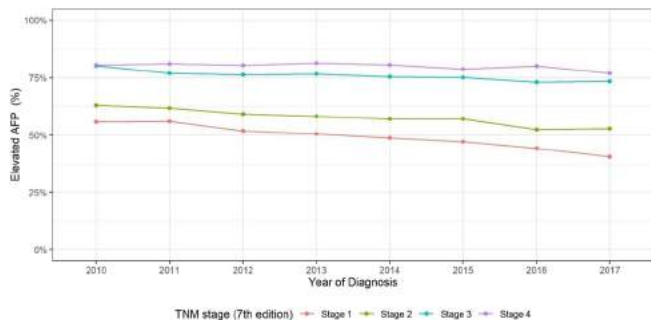


Figure 1: Temporal trend of HCC with elevated AFP based on TNM tumor stage.

Conclusion: Our study revealed that serum AFP level at diagnosis has been trending down in the US, especially in TNM tumor stages 1 and 2, likely due to shifting etiologies of HCC. Certain demographic groups (younger age, female, Black and Asian race) as well as those without medical insurance or receiving care at community cancer centers showed a strong association with increased AFP independent of tumor stage.

PO-2893

Micro ribonucleic acid- 26a as a diagnostic biomarker for hepatitis C induced hepatocellular carcinoma in Egyptian patients.

Elsayed Ghoneem¹, Ahmed Kaseb², Wafa Elemshaty³, Sawsan Moniem Mohamed¹, Ahmed Sultan^{1,4}. ¹Faculty of Medicine, Mansoura University, Gastroenterology and Hepatology Unit, Internal Medicine Department, Mansoura, Egypt; ²University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Medical Oncology Unit, Houston, United States; ³Faculty of Medicine, Mansoura

University, Clinical Pathology department, Mansoura, Egypt; ⁴Cleveland Clinic Abu Dhabi, Digestive disease Institute, Abu Dhabi, United Arab Emirates

Email: dr.ahmed.sultan@gmail.com

Background and aims: The incidence of hepatocellular carcinoma (HCC) is rapidly growing in Egyptian patients secondary to chronic hepatitis C virus (HCV) infection. Early diagnosis of HCC is associated with wider range of treatment modalities and consequently better outcome compared to late diagnosis. However, the early HCC diagnosis is still challenging due to lack of sensitive/specific markers. This study aimed of to evaluate the role of plasma level of Micro ribonucleic acid- 26a (miRNA-26a) as an early diagnostic biomarker of HCV induced HCC in Egyptian patients.

Method: In this case-controlled study, 75 Egyptian patients with HCV infection were divided into 3 equal groups (25 patients each); HCV induced HCC, HCV induced cirrhosis and HCV induced fibrosis. The 4th group, the control group, was formed of 25 healthy individuals. Patients with non-HCV chronic liver disease were excluded. All cases were subjected to clinical history, examination and following investigations: abdominal ultrasound, basic laboratory investigations, alfa fetoprotein (AFP) and miRNA-26a assay in plasma. The liver states were assessed using different scoring systems including: Child Pugh score (CPS), FIB4, APRI, AAR and API. Triphasic CT abdomen and AFP were used to diagnose HCC patients. Liver fibroscan was used to assess stage of liver fibrosis.

Results: The plasma level of miRNA-26a was comparable among all HCV groups (p value >0.05). Whereas AFP level was higher in patients with HCC relative to those in the cirrhosis and fibrosis groups (p value <0.05). Regarding the other scores (FIB4, APRI, AAR and API), the difference between HCC and fibrosis groups was significance (p value <0.05) but the difference between HCC and cirrhotic groups was not (p value >0.05). In both HCC and cirrhotic groups, patients with CPS-B had a lower miRNA-26a level relative to those with CPS-A (p value <0.05), but the AFP level was comparable.

Conclusion: miRNA-26a could not differentiate between HCV induced HCC and HCV induced liver cirrhosis or fibrosis.

Liver tumours: Experimental and pathophysiology

PO-133

Repression of fatty acid oxidation in steatohepatic-HCC is mediated by E2F1 and E2F2 transcription factors

Francisco Gonzalez-Romero¹, Daniela Mestre Congregado^{1,2}, Igor Aurrekoetxea^{1,2}, Colm O. Rourke³, Jesper Andersen³, Ashwin Woodhoo^{4,5}, Miguel Tamayo-Caro⁴, Marta Varela-Rey⁶, Marta Palomo-Irigoyen⁴, Beatriz Gómez Santos¹, Diego Saenz de Urturi¹, Maitane Núñez¹, Juan Luis García Rodríguez¹, Larraitz Fernández-Ares^{1,2}, Xabier Buque^{1,2}, Ainhoa Iglesias⁷, Irantzu Bernales⁸, Virginia Gutiérrez de Juan⁶, Teresa Cardoso Delgado⁶, Naroa Goikoetxea⁶, Igotz Delgado¹, María Jesús Perugorria^{9,10}, Gaizka Errazti Olartekoetxea², Lorena Mosteiro González², Sonia Gaztambide^{2,11}, Idoia Martínez de la Piscina², Paula Iruzubieta¹², Javier Crespo¹², Jesus Maria Banales^{5,9}, María Luz Martínez-Chantar⁶, Luis A. Castaño González^{2,11}, Ana Zubiaga⁷, Patricia Aspichueta^{1,2}. ¹Department of Physiology, Faculty of Medicine and Nursing, University of Basque Country UPV/EHU, Leioa, Spain; ²BioCruces Bizkaia Health Research Institute, Cruces University Hospital, Barakaldo, Spain; ³Biotech Research and Innovation Centre, Department of Health and Medical Sciences, University of Copenhagen, Denmark; ⁴Center for Cooperative Research in Bioscience (CIC bioGUNE), Derio, Spain;

POSTER PRESENTATIONS

⁵Ikerbasque, Basque Foundation for Science, Bilbao, Spain; ⁶Liver Disease Laboratory, Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), CIBERehd Derio, Spain; ⁷Department of Genetic, Physical Anthropology and Animal Physiology, Faculty of Science and Technology, University of Basque Country UPV/EHU, Leioa, Spain; ⁸SGIKER, University of Basque Country UPV/EHU, Leioa, Spain; ⁹Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute, Donostia University Hospital, University of the Basque Country UPV/EHU, CIBERehd, San Sebastian, Spain; ¹⁰Department of Medicine, Faculty of Medicine and Nursing, University of the Basque Country UPV/EHU, Leioa, Spain; ¹¹Faculty of Medicine and Nursing, University of Basque Country UPV/EHU, CIBERDEM, CIBERER; ¹²Gastroenterology and Hepatology Department, Marqués de Valdecilla University Hospital, Santander, Spain
Email: frangonzalez2909@gmail.com

Background and aims: Modulation of fatty acid oxidation (FAO) plays an important role in the metabolic rearrangements of liver cancer cells to survive and proliferate. Decreased FAO through downregulation of CPT2 contributes to carcinogenesis in steatohepatic-HCC. E2F1 and E2F2, well-known cell cycle regulators, are upregulated in human HCC but it is unknown whether they can regulate hepatic FAO in non-alcoholic fatty liver disease (NAFLD)-related HCC. Thus, here the contribution of E2F1 and E2F2 transcription factors in the metabolic rewiring of NAFLD-related HCC and their role in modulation of FAO were investigated.

Method: *E2f1*^{-/-}, *E2f2*^{-/-}, *E2f1/E2f2* double knockout (DKO) and wild-type mice (WT) were used. Liver disease was induced in mice by administration of diethylnitrosamine (DEN) (25 mg/kg) at 14 day-old plus high-fat diet (HFD) until sacrificed at 9 month-old. Adeno-associated viruses-serotype 8 (AAV8) were used to specifically upregulate E2F2 in mouse livers *in vivo* and adenoviruses were used to overexpress E2F2 in hepatocytes *in vitro*. Metabolic fluxes, transcriptome, ChIP and gene expression analyses were performed. Data from the TCGA-LIHC cohort were also used.

Results: Our data showed that *E2F1* and *E2F2* positively correlates in human HCC livers within the TCGA-LIHC cohort. Accordingly, *E2f1* and *E2f2* levels were increased in mouse livers with NAFLD-related HCC and both *E2f1*^{-/-} and *E2f2*^{-/-} mice were protected against liver disease. The analysis of the transcriptome that underlies the resistance to develop HCC in DEN-HFD treated *E2f1*^{-/-} or *E2f2*^{-/-} mice showed that the most significantly common changed pathways between the two genotypes within the upregulated genes were those related to fatty acid metabolism and oxidation. The validation of these results revealed that the expression of genes involved in FAO and oxidative phosphorylation, including *Cpt2*, were upregulated in both DEN-HFD *E2f1*^{-/-} and *E2f2*^{-/-} mice together with the FAO rate compared to DEN-HFD WT mice. Of relevance, the levels of *Cpt2* expression in *E2f1/E2f2* DKO mice were practically the sum of those found in single knockout mice. Both *E2F1* and *E2F2* were negatively correlated with *CPT2* in human HCC (TCGA-LIHC cohort). Specific overexpression of E2F2 in mice liver led to downregulation of *Cpt2* and repression of FAO. Even more, *in vitro* assays showed that upregulation of E2F2 in hepatocytes also induced downregulation of *Cpt2*. The ChIP analyses and *in vitro* assays with *Rb* siRNA showed that E2F2 directly binds in the corresponding *Cpt2* promoter binding site and that pRB is not involved in the E2F2-mediated *Cpt2* repression.

Conclusion: E2F1 and E2F2 transcription factors, required for NAFLD-HCC development, directly repress *Cpt2* expression in liver preventing FAO from activation, which promotes lipid accumulation and NAFLD progression to HCC.

PO-196

Chronic liver damage favours induction of CD44v6 epithelial cells and subsequent liver carcinoma formation

Akshaya Srikanth¹, Umesh Tharehalli Mattada¹, Reinhold Schirmbeck¹, André Lechel¹. ¹Ulm University, Internal Medicine I, Ulm, Germany
Email: akshaya-1.srikanth@uni-ulm.de

Background and aims: Liver carcinoma is the third leading cause of cancer-related death worldwide. Tumor heterogeneity and limited therapeutic options are primarily responsible for the high mortality of liver cancer patients. Most liver cancers originate from liver epithelial cells within a chronic inflammatory microenvironment. The hyaluronic acid receptor variant CD44v6 is a marker for tumor stem cells, and its expression dramatically increases in liver epithelial cells upon carcinogen exposure. In this study, we aim to understand the role of the microenvironment on the induction of CD44v6 positive epithelial cells in the premalignant liver in the background of chronic liver damage and Trp53 deletion.

Method: For this study, we used transgenic liver-specific mouse models of Trp53 loss in combination with chronic liver damage: (1) HBV-S tg mice associated with continuous ER stress, (2) HCV-tg mice developing liver steatosis, (3) IKK2/NF- κ B tg mice, mimicking chronic inflammation and (4) CCl4-treated mice developing liver cirrhosis. The induction and location of CD44v6 expressing epithelial cells and the immune-microenvironment in the premalignant liver were investigated.

Results: Chronic liver damage resulted in the induction of CD44v6 positive epithelial cells in all four mouse models, which was not observed in wildtype mice. We observed clusters of hepatocyte-like cells with CD44v6 expression in the HBV-S tg and the CCl4 model which are characterized by the presence of diffuse inflammation. Interestingly, CD44v6 positive epithelial cells in the HCV-tg and the IKK2/NF- κ B cohorts were associated with the occurrence of ectopic lymphoid structures (ELS) and were located within the ELS and resulted in increased formation of intrahepatic cholangiocarcinoma.

Conclusion: The inflamed microenvironment is important for the induction of CD44v6 positive epithelial cells, indicating a role in tumor differentiation.

PO-336

Differential requirement of RAS-dependent signaling pathways in tumor development and differentiation in murine liver cancer

Carina Rupp¹, Thomas Rösner¹, Christian Lechler¹, Saumya Manmadhan¹, Kohnke-Ertel Birgit¹, Julia Schwenke¹, Pooya Shokoohi¹, Katja Steiger^{2,3}, Carolin Mogler^{2,3}, Diana Becker⁴, Jens Marquardt⁵, Thomas Engleitner^{6,7}, Roland Rad^{1,6,7}, Roland M. Schmid¹, Ursula Ehmer¹. ¹Klinikum rechts der Isar, TU Munich, Internal Medicine II, Munich, Germany; ²TU Munich, Institute of Pathology, Munich, Germany; ³TU Munich, Comparative Experimental Pathology, Munich, Germany; ⁴University Mainz, Department of Medicine, Lichtenberg Research Group, Mainz, Germany; ⁵University Hospital Schleswig-Holstein, Department of Medicine I, Lübeck, Germany; ⁶TU Munich, Institute of Molecular Oncology and Functional Genomics, Munich, Germany; ⁷TU Munich, Center for Translational Cancer Research (TranslaTUM), Munich, Germany
Email: ursula.ehmer@tum.de

Background and aims: RAS mutations are found in cholangiocarcinoma as well as in some hepatocellular carcinoma (HCC). However, the relevance of different RAS-dependent signaling pathways in liver tumorigenesis is not well understood. In a genetic mouse model of RAS-activated liver cancer with early development of intrahepatic cholangiocarcinoma (ICC), tumors showed activation of PI3 K/AKT and MEK/ERK signaling. To gain insight into the relevance of different RAS-dependent signaling pathways, animals with activation of oncogenic *Kras* and genetic inactivation of either PI3K-activated AKT (*Pdk1*^{lox/lox}) or MEK/ERK signaling (*Map2k1*^{lox/lox}; *Map2k2*^{-/-}) were generated.

Method: Cre was activated in hepatocytes of adult *Rb^{lox/lox};p53^{lox/lox};Kras^{LSL-G12D/+}* (RPK) mice, in RPK animals deficient for MEK proteins (*RPK;Map2k1^{lox/lox};Map2k2^{-/-}*) or deficient for PI3K-activated AKT signaling (*RPK;Pdk1^{lox/lox}*) via an Albumin-driven CreER by intraperitoneal injection of tamoxifen. Liver samples were analyzed for cell proliferation, tumor development as well as for mRNA and protein expression.

Results: RPK tumors showed activation of PI3 K/AKT and MEK/ERK signaling by immunohistochemistry and western blot. While RPK livers showed hepatocyte proliferation 4 weeks after tamoxifen induction, reduced proliferation was detected in *RPK;AlbCre^{ER};Pdk1^{lox/lox}* and also *RPK;AlbCre^{ER};Map2k1^{lox/lox};Map2k2^{-/-}* knock-out models. In line with reduced proliferation at early time points, *Mek1/2*- as well as *Pdk1*-deleted RPK mice show significantly prolonged survival and delayed tumor formation in comparison to RPK control mice. Strikingly, deficiency of RAS downstream signaling was associated with differential changes in tumor appearance by histopathology. While PDK1-deficient RPK tumors were more well differentiated than tumors in RPK control mice, MEK-deficient RPK animals showed a differentiation shift towards HCC and mixed HCC/ICC.

Conclusion: In our model of RAS-dependent liver cancer, both PI3 K/AKT signaling and MEK/ERK-signaling are relevant downstream pathway that drive cell proliferation and tumor development. The differential impact of RAS-downstream signaling pathways on tumor differentiation and grading offers novel insight into liver tumorigenesis. Further investigation will be needed to investigate the impact of the observed differentiation shift on tumor targeted therapies and a potential impact of combined targeting of AKT and MEK/ERK signaling.

PO-541

Molecular characterization of HCC in Mongolia delineates unique genomic features

Laura Torrens^{1,2}, Marc Puigvehí^{1,3}, Miguel Torres-Martín^{1,2}, Huan Wang⁴, Miho Maeda¹, Philipp Haber¹, Thais Leonel⁵, Mireia García-López⁵, Wei Qiang Leow^{1,6}, Carla Montironi^{1,2}, Sara Torrecilla², Ajay Ramakrishnan Varadarajan⁴, Patricia Taik⁴, Genís Campreciós¹, Chinbold Enkhbold⁷, Erdenebileg Taivanbaatar⁸, Amankyeldi Yerbolat⁸, Augusto Villanueva¹, Sofía Pérez-del-Pulgar⁵, Swan N. Thung¹, Jigjidsuren Chimburen⁸, Eric Letouzé⁹, Jessica Zucman-Rossi⁹, Andrew Uzilov^{4,10}, Jaclyn Neely¹¹, Xavier Forns⁵, Sasan Roayaie¹², Daniela Sia¹, Josep M. Llovet^{1,2,13}.

¹Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States;

²Translational research in Hepatic Oncology, Liver Unit, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Barcelona, Spain;

³Hepatology Section, Gastroenterology Department, Parc de Salut Mar, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain;

⁴Sema4, Stamford, United States;

⁵Liver Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBEREHD, University of Barcelona, Barcelona, Spain;

⁶Department of Anatomical Pathology, Singapore General Hospital, Singapore, Singapore;

⁷Hepato-Pancreatico-Biliary Surgery Department, National Cancer Center, Ulaanbaatar, Mongolia;

⁸National Cancer Center, Ulaanbaatar, Mongolia;

⁹Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université de Paris, Université Paris 13, Functional Genomics of Solid Tumors laboratory, F-75006, Paris, France;

¹⁰Department of Genetics and Genomic Sciences and Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, United States;

¹¹Bristol Myers Squibb, Princeton, United States;

¹²Department of Surgery, White Plains Hospital, White Plains, United States;

¹³Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Email: josep.llovet@mssm.edu

Background and aims: Mongolia has the world's highest incidence of hepatocellular carcinoma (HCC), with ~100 cases/10⁵ inhabitants/

year. Here, we aimed at performing a molecular characterization of HCC in Mongolia and compare it with Western HCC.

Method: 192 paired fresh-frozen HCC/non-tumoral samples from patients undergoing resection were collected at the National Cancer Center in Ulaanbaatar, Mongolia. Whole exome sequencing (WES) and RNAseq were performed in 151 and 106 samples, respectively. WES, RNAseq and clinical data from an in-house Western cohort were used for comparison (n=187). Mutation calling and mutational signature analysis were evaluated. HBV viral genotype was assessed by direct sequencing.

Results: Mongolian patients, compared to Western, were younger (61 vs 66 years old), with lower male predominance (54% vs 80%), less advanced hepatic fibrosis (F3-4, 38% vs 79%), higher rate of HBV-HDV co-infection (84% vs 7% of HBV infected), and predominance of HBV genotype D (90% vs 43% of HBV infected) (all p < 0.001). Mongolian HCC presented unique molecular features including: a) Higher number of protein-coding mutations (121 vs 70 mut/tumor, p < 0.001), as well as higher mutational rate in known (e.g. *TP53* [46% vs 32%], *APOB* [15% vs 5%], *KMT2* family [34% vs 17%]) and putative HCC drivers in Mongolian tumors (*TSC2*, 9% vs 1%) (all p < 0.05). b) Presence of a new mutational signature (SBS Mongolia, 25% vs 4.5%, p < 0.05) not matching any previous substitution profile in liver cancer. SBS Mongolia was characterized by T>G substitutions and enrichment for dimethyl sulfide genotoxic signature, related to coal combustion. c) A distinct transcriptomic profile consisting in three molecular clusters (Figure). MGL1 class (44%) was associated with HCV infection (32% vs 7%/3%) in older patients (62 vs 56 years old) (p < 0.05) and resembled Western HCCs. MGL2 (26%) and MGL3 classes (30%) were specific for Mongolian tumors and were enriched in HBV-HDV infection (93%/97% vs 60%, p < 0.001). MGL2 class showed a female/male ratio of 2:1, and clinical and molecular features of aggressiveness (e.g. higher AFP >400, proliferation classes). MGL3 was enriched in inflammatory signaling.

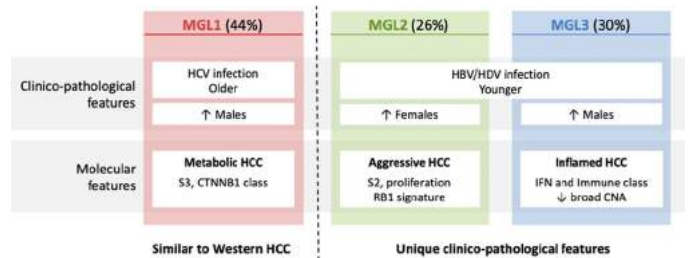


Figure:

Conclusion: HCC in Mongolia presents specific molecular traits characterized by a high mutational burden, a newly described mutational signature and two novel molecular classes. Further studies exploring environmental factors associated with these alterations are required.

PO-677

New mouse model of cholangiocarcinoma arising in the setting of progressive biliary injury and fibrosis

Pinzhu Huang¹, Guangyan Wei², Shuangshuang Zhao², Disha Badlani¹, Li Chen³, Mathieu Petitjean⁴, Xin Chen⁵, Gregory Gores⁶, Yury Popov². ¹Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology and Hepatology, Boston, United States; ²Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology and Hepatology, Boston, United States; ³PharmaNest, Inc, United States; ⁴PharmaNest, Inc, Princeton, United States; ⁵University of California, San Francisco, United States; ⁶Mayo Clinic

Email: ypopov@bidmc.harvard.edu

Background and aims: Cholangiocarcinoma (CCA) is a dreaded complication of primary sclerosing cholangitis (PSC), difficult to diagnose and associated with high mortality. Currently, lack of animal

POSTER PRESENTATIONS

models of CCA recapitulating the hepatic microenvironment of progressive sclerosing cholangitis precludes tumor treatment. Thus, we sought to develop a PSC associated CCA animal model and test the therapeutic value of TGF β signalling via targeting ALK5.

Method: Ten weeks old Mdr2 $^{-/-}$ mice with congenital PSC-like progressive biliary disease, and healthy wild-type littermates (WT) mice were subjected to either modified retrograde biliary instillation (Yamada, et al. *Hepatology* 2015, without concomitant IL-33 or bile duct ligation) or hydrodynamic tail vein injection (Zhang, et al. *J Hepatol* 2017) of sleeping beauty transposon-transposase plasmid system with activated forms of AKT (myr-AKT) and Yap (YapS127A) protooncogenes (SB AKT/YAP1). ALK5 inhibitor (SB-525334, 300 mg/kg in diet) or placebo diet was administered into tumor-bearing mice in early (1–4 weeks post injection) or delayed (3–6 weeks post oncogene transduction) to interrogate functional role of TGF β signalling in our model. Tumor phenotype and burden were analyzed using histological methods. Desmoplastic stroma of the tumors was quantified using automated FibroNest platform (PharmaNest Inc) from Sirius Red (SR) staining.

Results: While SB AKT/YAP1 plasmids via retrograde biliary injection caused tumors in all Mdr2 $^{-/-}$ but not in healthy wildtype mice (n = 10), only 26.67% (4/15) of these tumors were CCA and this approach was deemed unsuccessful.

Alternative, hydrodynamic tail vein injection of SB AKT/YAP1 resulted in robust tumorigenesis in fibrotic Mdr2 $^{-/-}$ mice (n = 10), with 100% incidence and high CCA burden after 6 weeks. In contrast, only 6 out of 9 healthy wildtype mice (66.67% incidence) developed tumors. Higher CCA numbers (52.60 \pm 6.81 vs. 1.11 \pm 0.51, p < 0.01) with profound desmoplastic reaction and significantly shortened survival were observed in Mdr2 $^{-/-}$ mice compared to non-fibrotic controls. Early, but not delayed, pharmacological TGF β inhibition via Alk5 reduced tumor burden by 2.4 fold (11.00 \pm 1.41 vs. 24.80 \pm 5.75, n = 5, p = 0.0481) and desmoplastic stroma of the tumors by 2 fold (tumor collagen area %, 7.36 \pm 0.57 vs. 13.96 \pm 1.92, n = 5, p = 0.01), respectively, compared to placebo.

Conclusion: We established a new high-fidelity cholangiocarcinoma model in mouse, termed SB CCA.Mdr2 $^{-/-}$. It recapitulates the increased susceptibility to CCA in the setting of progressive biliary injury and fibrosis observed in PSC, and enables mechanistic research and formal testing of new therapies for this devastating disease. Furthermore, pharmacological targeting of Alk5 in our model suggests that TGF β signalling functionally drives CCA tumorigenesis and promotes desmoplastic reaction in a complex, stage-specific manner.

PO-920

Immuno-responsive classification of hepatocellular carcinomas as a potential surrogate for precision immuno-oncology

Jihyun An¹, Ji-Hye Oh², Wonkyung Kim², Bora Oh², Yoo-Jin Oh², Chang Ohk Sung², Ju Hyun Shim². ¹Hanyang University, Korea, Rep. of South; ²Asan Medical Center, Seoul, Korea, Rep. of South
Email: s5854@amc.seoul.kr

Background and aims: Programmed cell death ligand-1 (PD-L1) expression has not served as a predictive marker for immunotherapy targeting the checkpoint in patients with hepatocellular carcinoma (HCC). The cross-talk among various intrinsic or extrinsic immune-related composites within the tumor microenvironment could play a role in the PD-L1 regulation. Here, we explored the dynamic interplay between PD-L1 expression and other predefined predictors of response to checkpoint inhibitors in HCC, and classified the tumors based on potential responsiveness to the therapy.

Method: This study included the Asan genomic cohort of 206 HCC patients receiving primary hepatectomy who had both whole exome sequencing and RNA sequencing datasets. PD-L1 expression was evaluated by immunohistochemical assay using the 22C3 antibody with a Combined Positive Score (CPS) cut-off of 1%. Tumor mutational

burden (TMB), neoantigen load, and T-cell inflamed phenotype were measured using genomic data.

Results: PD-L1 positivity was observed in 29 (14.1%) of the 206 patients. Genesets related to immune system and proliferation were highly enriched in the PD-L1-positive group with no difference in clinical and pathological data. PD-L1 expression was significantly correlated with T cell-inflamed phenotype, as was not with neoantigen or TMB. We next constructed a novel Immuno-responsive classification of HCC by PD-L1 and TMB that were mutually exclusive: C1, +/+; C2, \pm ; C3, -/+; and C4, -/-, respectively for PD-L1 and TMB. Most immune cell types were highly infiltrated in the C1 and C2 groups with the relative abundance of Immune-checkpoint genes. Survival outcomes were also better in the two subclasses.

Conclusion: Our immunogenomic analysis uncovered potential immuno-responsive HCC subtypes with distinct patterns of targetable immune biology. Tailored studies of patients treated with immunomodulators are needed for future clinical use of the classification.

PO-1118

Metabolic reprogramming in a c-Myc/h-Ras transgenic mouse model of hepatocellular carcinoma

Marina Serra¹, Mario di Matteo², Amedeo Columbano¹, Massimiliano Mazzone². ¹Università degli Studi di Cagliari, Biomedical Sciences, Monserrato (CA), Italy; ²VIB-Center for Cancer Biology, Oncology, Leuven, Belgium
Email: mari_serra93@hotmail.it

Background and aims: Hepatocellular carcinoma (HCC), as well as many other solid tumors, develops through a multi-step process whereby abnormally proliferating cancer cells undergo a large metabolic reprogramming. Mounting evidence suggests that the different metabolic alterations taking place in hepatocarcinogenesis are dependent on the activation of specific oncogenes, thus partially explaining the HCC heterogeneity. The aim of the present study was to investigate the metabolic reprogramming occurring in liver tumors induced by the concomitant expression of c-Myc and h-Ras, two of the most frequently upregulated oncogenes in human HCCs.

Method: C57BL/6J mice were hydrodynamically co-transfected with PB_h-Ras^{G12V} and PB_c-Myc, in conjunction with a plasmid encoding a hyperactive PB transposase (hyPBBase). The liver-specific promoter minimal transthyretin (TTRmin) was used to drive oncogene expression exclusively in hepatocytes. Tumor bearing mice were sacrificed 14 weeks after hydrodynamic injection. QRT-PCR, immunohistochemistry and histochemistry were performed to assess the mRNA levels and protein levels, as well as enzymatic activity.

Results: The present work revealed that c-Myc/h-Ras^{G12V} driven tumors display a striking glycolytic metabolism suggestive of a switch to a Warburg phenotype, and an enhanced activity of pentose phosphate pathway (PPP). Differently from HCCs generated by the overexpression of c-Myc alone, glutamine seems to be mostly utilized to sustain glutathione synthesis instead of Tricarboxylic acid cycle (TCA), in order to protect cancer cells from oxidative damages. All these changes were associated to an impairment of oxidative phosphorylation (OXPHOS), as determined by a reduction of succinate dehydrogenase activity.

Conclusion: Our results obtained in an engineered mouse model of hepatocarcinogenesis demonstrate a metabolic switch from OXPHOS to glycolysis caused by the concomitant overexpression of c-Myc and h-Ras, two of the most frequently altered oncogenes in HCC. This finding further supports the notion that targeting metabolism may represent a critical strategy for HCC therapy. Our study will be further extended to a set of clinically relevant oncogenic cooperation to quickly unravel oncogene-specific metabolic vulnerabilities in HCC.

PO-1304

Targeting tumor-initiating cells and compensatory YAP pathway activation to overcome sorafenib-induced resistance in hepatocellular carcinoma

Darko Castven^{1,2}, Carolin Czauderna^{1,2}, Diana Becker², Sharon Pereira², Kai Breuhahn³, Jennifer Schmitt³, Marcus-Alexander Wörns², Jovana Hajduk^{1,2}, Snorri Thorgeirsson⁴, Peter Galle², Jens Marquardt^{1,2}. ¹University Hospital Schleswig-Holstein, Department of Medicine I, Lübeck, Germany; ²University Hospital Mainz, Department of Medicine I, Mainz, Germany; ³University Hospital Heidelberg, Institute of Pathology, Heidelberg; ⁴National Cancer Institute, NIH, Laboratory of Human Carcinogenesis, Bethesda, United States
Email: castvendarko@gmail.com

Background and aims: Induction of chemoresistance upon systemic therapy is frequently observed in the majority of HCC patients. Accumulating evidence suggests that tumor-initiating cells (TICs) may contribute to the acquisition of resistance in many solid tumors, but their exact role for HCC remains to be defined. Here, we evaluate the importance of TICs in the development of resistance and relapse formation after exposure to sorafenib in HCC and define concomitant adaptive molecular targets.

Method: Four HCC cell lines and two primary HCC isolates were exposed to sorafenib for a total of 14 days. The treatment effects on TICs were estimated by sphere forming capacity *in vitro* and tumor-initiating potential *in vivo*, as well as the side-population (SP) approach. Expression of key CSC marker EpCAM was assessed by flow cytometry. Furthermore, whole transcriptome analyses were performed across the cell lines and identified potential targets, which were further validated by immunohistochemistry, western blot and administration of specific inhibitors.

Results: Treatment with sorafenib effectively reduced oncogenic properties in all investigated HCC cells. However, sustained anti-proliferative effect after treatment was observed in half of the cell lines, while initial treatment effect in other lines was followed by rapid re-growth thereby resembling the responses observed in patients. Anti-oncogenic effects in sensitive cell lines were associated with significant reduction in sphere-forming and tumor-initiating capacity, CSC marker EpCAM as well as SP cells, while resistant cell lines showed transient induction in TIC properties. Acquired resistance uniformly developed in cell lines suggesting that common molecular mechanisms might be operative. These adaptive molecular changes involved signaling pathways known to be associated to cell survival, proliferation and cell cycle regulation (RAS, IL6, MYC, E2F3). Furthermore, the resistant cell lines showed compensatory upregulation of key oncogenic molecules such as EGFR, as well as YAP. Validation on authentic HCC samples confirmed enrichment of YAP signaling in the patients with worst response to sorafenib treatment. Conclusively, combined treatment including sorafenib and specific YAP inhibitor showed beneficial effects in resistant cell lines which resulted in complete response to the therapy.

Conclusion: Our model recapitulates features of drug resistance observed in human HCC patients. Resistance to anti-angiogenic therapy might be fueled by transient expansion of TICs. Therefore, specific targeting of TICs as well as pro-oncogenic compensatory signaling pathways might be an effective therapeutic strategy to overcome resistance in HCC.

PO-1352

Study on the mechanism of chemokine CCL21 mediating IRBIT in the malignant biological behavior of liver cancer

Jingyu Xu¹, Jianhong Ding¹, Biguang Tuo¹, Rui Xie¹. ¹Affiliated Hospital of Zunyi Medical University, Department of Gastroenterology, Zunyi, China
Email: xujingyu_gzzy@126.com

Background and aims: Liver cancer is highly malignant and has a high incidence. It is currently believed that the migration and

invasion of liver cancer are the significant factors leading to the poor prognosis of patients with liver cancer, but the specific mechanism is still unclear. Studies have shown that the chemokine CCL21 play a crucial role in the malignant biological behavior of tumors. Our research shows that the CCL21 causes the increase of intracellular calcium ($[Ca^{2+}]_i$) and promotes the migration and invasion of liver cancer, indicating that the relevant ion channels involved in the regulation of $[Ca^{2+}]_i$ activation. IRBIT is a binding protein for the IP3 receptor and the dissociated IRBIT can activate a variety of ion channels. Moreover, our research shows that CCL21 can induce the up-regulation of IRBIT expression. Therefore, this study aims to explore the potential mechanism of CCL21-mediated IRBIT in liver cancer, in order to seek new drug targets for the treatment of liver cancer.

Method: Western blotting and immunohistochemistry were used to detect the expression of IRBIT in liver cancer. CCK8 assays, Transwell assays with matrigel, wound healing assay, and western-bolt to detect the proliferation and migration ability of liver cancer cells after silencing IRBIT. The migration and invasion ability of liver cancer cells and the expression of IRBIT was detected after CCL21 stimulation. Cell calcium imaging detected the $[Ca^{2+}]_i$ of liver cancer cells caused by CCL21, and using different calcium blockers to screen calcium channels that were affected by CCL21 in liver cancer cells.

Results: 1.The expression of IRBIT in liver cancer tissues and cells is significantly increased. 2.After IRBIT silenced in Huh7 cells, the proliferation, migration and invasion abilities were significantly reduced compared to control cells, and the expression of E-cadherin and ZO-1 increased, and the expression of N-cadherin and Vimentin decreased. 3.CCL21 culture increased the migration and invasion ability and IRBIT expression of the Huh7 cells. 4.20 uM CCL21 can induce the concentration of $[Ca^{2+}]_i$ increase in Huh7 cells. 5.Inhibitor KB-R7943 can inhibit the increase of $[Ca^{2+}]_i$ and decrease the expression of NCX1 induced by CCL21, and can inhibit the migration and invasion of liver cancer cells.

Conclusion: CCL21/IRBIT may acts a promoting role in the development of liver cancer, providing a new theoretical basis for the treatment or prevention of recurrence and metastasis of liver cancer.

PO-1629

Influence on cancer cell energy metabolism by pharmacological inhibition of the histone modifying lysine-specific demethylase 1

Jie Wang¹, Marcel Schmiel¹, Yefeng Shen¹, Priya Dalvi¹, Xiaojie Yu¹, Yue Zhao², Reinhard Büttner¹, Lingyu Wang¹, Margarete Odenthal¹. ¹University Hospital of Cologne, Institute for Pathology, Cologne, Germany; ²University Hospital of Cologne, Department of General, Visceral and Tumor Surgery, Cologne, Germany
Email:

Background and aims: Epigenetic alterations are important features in the process of carcinogenesis. The lysine-specific histone demethylase-1 (LSD1) affects cell growth and is overexpressed in a wide variety of cancer types. Interestingly, recent work has shown that LSD1 also influences mitochondrial function in adipocytes, but its role in mitochondrial activity in cancer has not yet been addressed. Therefore, in the present study, we investigated mitochondrial gene expression and function upon LSD1 inhibition in hepatocellular carcinoma (HCC).

Method: LSD1 was inhibited in different hepatoma cell lines by means of RNA interferences or application of a specific LSD1 inhibitor HCI-2509. Global transcriptomics was carried out by RNA ultra-deep sequencing and protein expression profiles were analyzed by MS-spectrometry. Divergent expression in response to LSD1 inhibition was validated by quantitative PCR. LSD1 influence on promoter interaction was performed by ChIP. Changes of the mitochondrial membrane potential were investigated by confocal microscopy and flow cytometry. Metabolic and respiratory changes were further determined by the Seahorse platform. Besides, TCGA data (National

POSTER PRESENTATIONS

Cancer Institute) from HCC patients were evaluated in malignant versus healthy liver samples.

Results: Gene expression profiling followed by pathway analysis of hepatoma cell types revealed a prominent dysregulation of genes involved in the cell cycle control and mitochondrial function after LSD1 inhibition. Especially, genes encoding subunits of the mitochondrial respiratory complex I were repressed. Accordingly, we proved a decrease of the mitochondrial membrane potential, lower ATP production and lower maximal respiration upon LSD1 inhibition in cancer cells. Furthermore, TCGA data from HCC patients pointed to a distinct difference in the expression of LSD1 targeted metabolic genes in tumor samples compared to non-transformed tissues.

Assesment of the respiration upon LSD1 inhibition

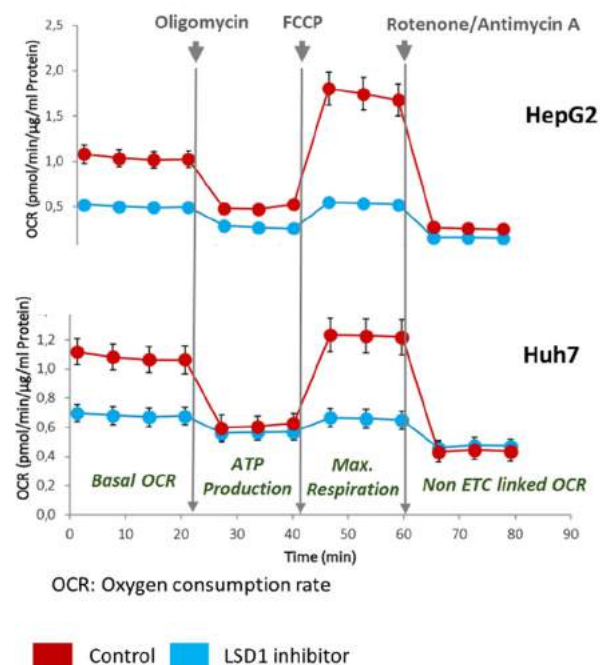


Figure:

Conclusion: Our data emphasize the value of LSD1 inhibition in new strategies of cancer therapy, revealing the impact of LSD1 inhibition not only on cell cycle arrest but also by energy depletion due to mitochondrial dysfunction.

PO-1752

Human antigen R (HuR) SUMOylation fine-tunes hepatocellular carcinoma (HCC) progression by modulating the expression of mitochondrial mRNAs

Sofia Lachiondo-Ortega¹, Jorge Simón Espinosa¹, Fernando Lopitz Otsoa², Teresa Cardoso Delgado¹, Naroa Goikoetxea¹, Marina Serrano-Macia¹, María Mercado-Gómez¹, Irene González-Recio¹, Rubén Rodríguez Agudo¹, David Fernández Ramos², Ruba Abdulla³, Alejandro Velázquez-Cruz⁴, Mikel Azkargorta⁵, Joris Guyon⁶, Thomas Daubon⁶, Leire Egia-Mendikute⁷, Asís Palazón⁷, Cesar Augusto Martín⁸, Juan Diego Riveros Zalamea⁹, Nicola G. A. Abrescia⁹, Felix Elortza⁵, Ana María Aransay¹⁰, Myriam Gorospe¹¹, Amaia Lujambio¹², Luis Alfonso Martínez-Cruz¹, Antonio Diaz-Quintana⁴, Irene Diaz-Moreno⁴, Manuel S. Rodríguez¹³, María Luz Martínez-Chantar¹. ¹Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Liver Disease Lab, Derio, Spain; ²Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Precision Medicine and Metabolism Lab, Derio, Spain; ³Biomedical Research Institute of Salamanca (IBSAL), Laboratory of

Experimental Hepatology and Drug Targeting (HEVEFARM), Salamanca, Spain; ⁴Universidad de Sevilla, Instituto de Investigaciones Químicas (IIQ)-Centro de Investigaciones Científicas Isla de la Cartuja (cicCartuja), Sevilla, Spain; ⁵Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Proteomics Platform, Derio, Spain; ⁶Institut national de la santé et de la recherche médicale (Inserm), Angiogenesis and Cancer Lab, Pessac, France; ⁷Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Cancer Immunology and Immunotherapy Lab, Derio, Spain; ⁸Centro Superior de Investigaciones Científicas (CSIC) and University of the Basque Country, Biofisika Institute, Leioa, Spain; ⁹Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Molecular Recognition and Host-Pathogen Interactions Programme, Derio, Spain; ¹⁰Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Genome Analysis Platform, Derio, Spain; ¹¹National Institute on Aging Intramural Research Program, National Institutes of Health (NIH), Laboratory of Genetics and Genomics, Baltimore, United States; ¹²Icahn School of Medicine at Mount Sinai, Department of Oncological Sciences, New York, United States; ¹³UbiCARE, Advanced Technology Institute in Life Sciences (ITAV)-CNRS-IPBS, Toulouse, France
Email: mlmartinez@cicbiogune.es

Background and aims: As we await the results from ongoing phase III clinical trials, we sought to identify additional approaches for the management of hepatocellular carcinoma (HCC). Considering the numerous and complex molecular mechanisms underlying the malignant transformation of a healthy liver into HCC, drugs against more than one signaling route would need to be developed in order to stop the progression of the disease. In this context, the posttranslational modification (PTM) of proteins, which controls the specificity, timing, duration and amplitude of virtually all cellular processes, has emerged as a robust and multidimensional therapeutic strategy in cancer. Interestingly, PTMs are key mechanisms that regulate the function of the RNA-binding protein Human antigen R (HuR), which is known to be involved in HCC transformation, in addition to playing a role in liver physiology. Moreover, a Gene Set Enrichment Analysis (GSEA) based on The Cancer Genome Atlas (TCGA) mRNA expression repository associated HuR expression with the ubiquitin-like PTM SUMOylation in HCC. Given that SUMOylation has never been described for HuR, the main aim of the present work is to elucidate the pathophysiological role of this PTM in liver cancer.

Method: A novel protein pull-down technology based on GST-tagged SUMO Binding Entities (SUBEs) was used to capture the native SUMO-interacting proteome from human and mouse liver tissue and cell line extracts, in combination with Western Blotting and Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) for protein identification purposes. Additionally, human HCC HuH-7 cell lines that stably express the wild-type and the SUMOylation mutant versions of HuR were developed in-house and their phenotypes studied.

Results: HuR is SUMOylated in the tumor sections of HCC patients in contrast to the surrounding tissue, as well as in the *MYC-luc;sg-p53* genetically engineered mosaic mouse model of liver cancer, and in human hepatoma cell lines. SUMOylation of HuR promotes major cancer hallmarks, namely proliferation and invasion, in the HuH-7 cell line. Conversely, the absence of HuR SUMOylation results in a senescence-like phenotype with damaged mitochondrial structure and function. Regarding the mechanism of action, we propose that HuR SUMOylation might drive HCC progression by modulating mitochondrial structural integrity and functionality through the regulation of the stability and translation of mRNAs encoding key mitochondrial proteins.

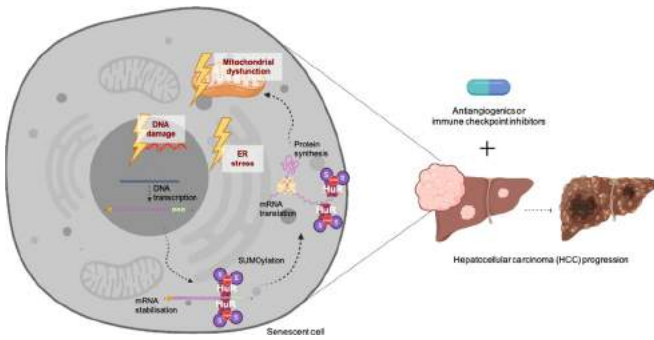


Figure:

Conclusion: SUMOylation constitutes a novel mechanism of HuR regulation that could be potentially exploited as an aptamer-based therapeutic strategy for liver cancer, thus highlighting the importance of PTMs as disease targets. Furthermore, understanding the effects of HuR SUMOylation in hepatocarcinogenesis will provide new functional insights into the relatively unknown role of SUMOylation in cancer.

PO-1771

The expressions of CCNB1, CDC20 and CENPF is both peripheral blood and liver is associated with anti-tumour immunity in HCC
 Zhenlin Huang^{1,2}, Tengfei Si², Yun Ma², Nigel Heaton³, Wael Jassem³, Shirin Elizabeth Khorsandi³. ¹Shanghai University of Traditional Chinese Medicine, The MOE Key Laboratory for Standardization of Chinese Medicine; ²King's College Hospital, Institute of Liver Studies; ³King's College Hospital, Transplant Service
 Email: yun.ma@kcl.ac.uk

Background and aims: Hepatocellular carcinoma (HCC) is one of the most common malignant tumours in the liver, accounting for 90% of primary liver cancer. It has been reported that CCNB1, CDC20 and CENPF may play important roles in the development of various

cancers, including HCC. However, the impact of these three genes on host immunity in patients with HCC remains unknown.

Method: Peripheral blood mononuclear cells (PBMCs) were isolated using density gradient centrifugation from 50 HCC patients at the King's College Hospital from February 2020 to November 2020. Sixteen paired tumour tissue and adjacent liver tissue, and 12 normal liver tissues from patients with hemangioma or focal nodular hyperplasia (FNH) were collected. Real-time PCR was used to measure the mRNA expression levels of CCNB1, CDC20, CENPF, TNF- α , IFN- γ and IL-17 using commercially available kits (RNAqueous, Maxima™ H Minus cDNA Synthesis Master Mix, and SYBR Select Master Mix, Thermo Fisher Scientific, USA). The phenotypic analysis of PBMCs was conducted by a 5-laser BD LSR Fortessa™ Flow Cytometer.

Results: CCNB1, CDC20 and CENPF mRNA in tumour tissue were up-regulated compared to adjacent tumour tissue and normal liver tissue, while in PBMCs the expression of three genes in untreated HCC was significantly down-regulated compared to normal liver tissues, the expression of three genes in untreated HCC was significantly down-regulated while along with treatment, the expression levels were gradually increased. In PBMCs, mRNA expressions of TNF- α , IFN- γ and IL-17 in treated HCC patients without active tumour were significantly higher than untreated HCC patients, being similar to that in normal liver or treated HCC patients with active tumour. Moreover, in PBMCs of untreated HCC patients the proportion of both CD8+ T cells and double negative (CD8-CD4-) T cells were lower, while the percentage of CD4+ T cells was higher than in healthy controls. The expression level of CENPF was positively correlated with the counts of CD8+ T cells and negatively with CD4+ T cells. mRNA expression of CCNB1, CDC20 and CENPF showed positive correlation with mRNA expression levels of anti-tumour cytokines in PBMCs.

Conclusion: CCNB1, CDC20 and CENPF showed strong association with anti-tumour immunity in both peripheral blood and liver of HCC patients. To quantify the expression of these genes in association with anti-tumour cytokine genes in both PBMCs and tumour tissue may help in assessing the treatment efficacy in HCC patients.

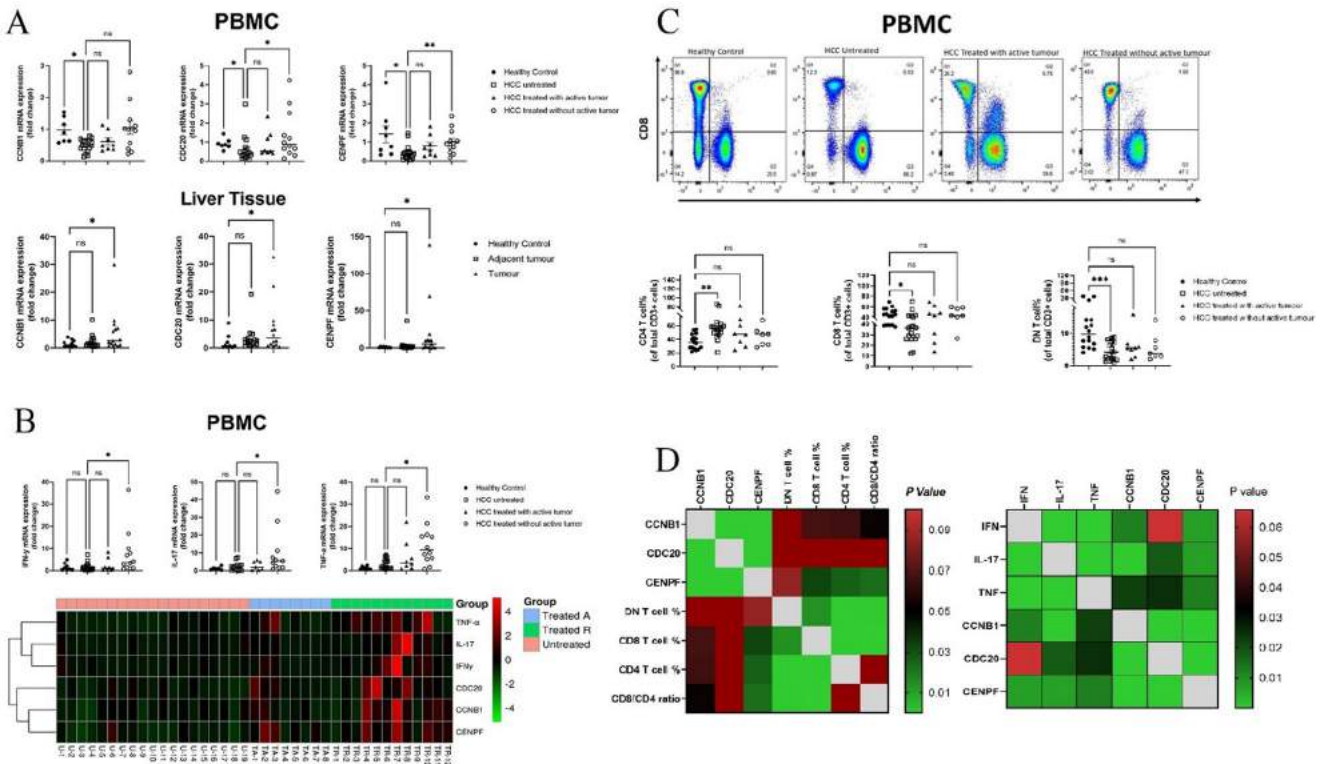


Figure: (abstract: PO-1771)

POSTER PRESENTATIONS

PO-1825

Programmed Death-Ligand 1 protein is preferentially expressed in tumor-associated macrophages in peritumoral regions of hepatocellular carcinoma

Pil Soo Sung¹, Dong Jun Park¹, Jeong Won Jang¹, Si Hyun Bae¹, Jong Young Choi¹, Seung Kew Yoon¹. ¹The Catholic University of Korea, Internal Medicine, Seoul, Korea, Rep. of South
Email: pssung@catholic.ac.kr

Background and aims: Biomarker for predicting immune-based treatments in advanced hepatocellular carcinoma (HCC) has not been clearly demonstrated. In this study, we focused on the infiltration and programmed death ligand 1 (PD-L1) expression of T cells and tumor-associated macrophages (TAMs) in HCC.

Method: Peripheral blood mononuclear cells (PBMCs) were obtained from eight patients with unresectable HCC before and 4 weeks after nivolumab treatment. Immunohistochemical staining and multicolor flow cytometry were performed on liver tissues and PBMCs of patients with HCC. For *in vitro* experiments, anti-PD-L1-treated M2 macrophages were co-cultured with activated T cells to evaluate the role of PD-L1-expressing TAMs in anti-PD-1/PD-L1 treatment. For *in vivo* experiments, an immunogenic syngeneic HCC mouse model was established to determine the frequency and role of tumor-infiltrating T cells and TAMs.

Results: Three of the eight enrolled patients responded to anti-PD-1 treatment. Increased frequency of Ki-67-positive CD4+ and CD8+ T cells was noted in nivolumab-responder PBMCs obtained after 4 weeks of treatment. Immunohistochemical staining for PD-L1 as well as for the CD 3 and CD68 demonstrated that T cells and PD-L1-expressing TAMs were infiltrated in both intratumoral and peritumoral tissue of patients with HCC. The number of peritumoral TAMs positively correlated with PD-L1 expressing cells and PD-L1 protein co-localized with CD68, suggesting that PD-L1 was mainly expressed in TAMs rather than T cells or tumor cells in HCC ($p < 0.05$). *In vitro* experiments confirmed that T-cell functionality (INF- γ and TNF- α production) significantly increased when M2 macrophages were treated with anti-PD-L1. In syngeneic Hepa1-6 mouse model, TAMs expressed very high levels of PD-L1. In this model, tumors with anti-PD-L1 or lenvatinib treatment showed significantly smaller diameter that those with IgG treatment. In these experiments, after anti-PD-L1 treatment, intra-tumoral CD8+ T cells showed higher expression of activation markers and the frequency of TAMs was significantly reduced, suggesting that the decreased size of the tumors after anti-PD-L1 treatment resulted from the reinvigoration of CD8+ T cells.

*This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) and funded by the Ministry of Education (NRF-2019R111A1A01059642).

PO-1949

Role of hypoxia-inducible factors 1alpha and 2alpha in prognosis and sorafenib chemoresistance in hepatocarcinoma

Carolina Méndez-Blanco¹, Flavia Fondevila¹, Paula Fernández-Palanca¹, Jos van Pelt², Chris Verslype², Javier González-Gállego¹, José Luís Mauriz¹. ¹Institute of Biomedicine (IBIOMED), University of León, León, Spain and Centro de investigación biomédica en red de enfermedades hepáticas y digestivas (CIBERehd), Instituto de salud Carlos III, Madrid, Spain; ²Laboratory of Clinical Digestive Oncology, Department of Oncology, KU Leuven and University Hospitals Leuven and Leuven Cancer Institute (LKI), Leuven, Belgium
Email: jl.mauriz@unileon.es

Background and aims: Hepatocarcinoma (HCC) is a recurrent tumor and is closely related to hypoxia. Hypoxic response is mediated by hypoxia-inducible factors (HIFs), which contribute to tumor progression and chemoresistance. We evaluated the prognostic role of HIF-1alpha and HIF-2alpha in HCC patients and its implication in sorafenib resistance development in an *in vitro* HCC model.

Method: We systematically searched Embase, Cochrane, PubMed, Scopus and WOS for studies testing HIF-1alpha and/or HIF-2alpha expression in HCC until June 1, 2020. Selected articles assess HIFs by immunohistochemistry in patients after surgical resection and its relationship with prognosis. We metaanalyzed the data extracted or estimated according to Parmar method using STATA. We evaluated the overall Hazard Ratio with 95% Confidence Interval, heterogeneity with I² statistic and Q test, subgroup analysis and publication bias by Egger's test. Likewise, we used HepG2 cells and sorafenib resistant derived lines (HepG2S1 and HepG2S3), CoCl₂ to mimic hypoxia, and cycloheximide and MG132 to repress protein synthesis and proteasome degradation. Proliferation was analyzed by ki67 assessment; gene expression by array or qRT-PCR, protein expression by Western blot and immunofluorescence; subG1 population by flow cytometry; viability by MTT; and gene silencing by siRNA transfection.

Results: 32 articles were included in the quantitative analysis, showing that HIF-1alpha overexpression correlated with overall survival (OS) and disease-free survival (DFS)/recurrence-free survival (RFS) in HCC patients. Initially only DFS/RFS was associated with HIF-2alpha overexpression, but subgroup analysis related it to OS. Publication bias was denoted in HIF-1alpha OS. Experimentally, resistant cells showed higher proliferative rate and increased HIFs

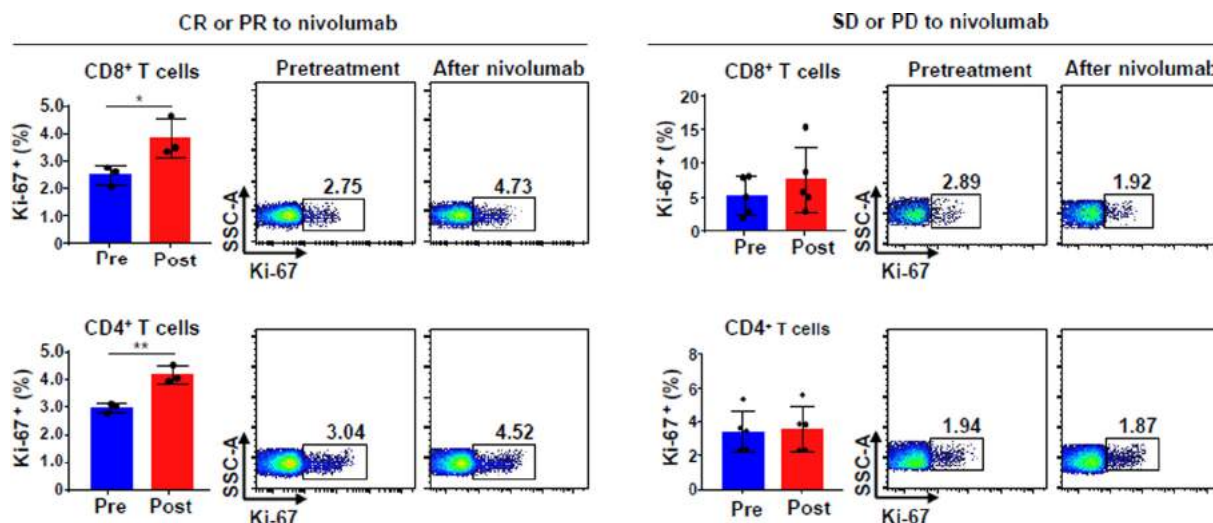


Figure: (abstract: PO-1825)

protein levels and nuclear translocation. HIFs overexpression was observed even under normoxia due to a deregulation of its proteasomal degradation. Levels of proapoptotic proteins and subG1 cells declined significantly in resistant lines, suggesting evasion of sorafenib-mediated apoptosis. HIFs silencing reduced resistant cells viability, relating HIFs overexpression with its pro-survival ability.

Conclusion: HIFs overexpression is related to recurrence and poor survival in HCC patients after resection and it seems to be a hallmark of sorafenib resistance acquisition. Hence, both HIFs could be useful HCC biomarkers as well as potential therapeutic targets.

PO-1957

Resistance to sorafenib in hepatocarcinoma: role of BCL2 interacting protein 3 promoter hypermethylation

Paula Fernández-Palanca¹, Carolina Méndez-Blanco¹, Flavia Fondevila¹, Jos van Pelt², Chris Verslype², Javier González-Gállego¹, José Luis Mauriz¹. ¹Institute of Biomedicine (BIOMED), University of León, León, Spain and Centro de investigación biomédica en red de enfermedades hepáticas y digestivas (CIBERehd), Instituto de salud Carlos III, Madrid, Spain; ²Laboratory of Clinical Digestive Oncology, Department of Oncology, KU Leuven and University Hospitals Leuven and Leuven Cancer Institute (LKI), Leuven, Belgium
Email: jl.mauriz@unileon.es

Background and aims: The antiangiogenic activity of sorafenib, first-line drug against advanced hepatocarcinoma (HCC), ends with the establishment of hypoxia that is closely related to chemoresistance. BCL2 interacting protein 3 (BNIP3) is a mitochondrial protein expressed in hypoxic tumor areas whose silencing has been associated to poor prognosis and chemoresistance in cancer. We aimed to assess the implication of BNIP3 in the development of hypoxia-related resistance to sorafenib in an in vitro model of human HCC with acquired sorafenib resistance.

Method: HepG2 cell line and sorafenib resistant derived lines (HepG2S1 and HepG2S3) were employed. We used CoCl₂ to mimic hypoxia, trichostatin-A (TSA) as histone deacetylases (HDACs) inhibitor and decitabine (5-Aza) as DNA methyltransferases (DNMTs) inhibitor. Gene expression was analyzed by RT-PCR, qRT-PCR, and protein expression by Western blot and immunofluorescence. Promoter methylation was assessed by methylation-specific PCR (MSP) and cell viability by MTT. Finally, gene silencing was performed via transfection of a pool of BNIP3-specific siRNA. Statistical analysis was performed using GraphPad Prism 6, considering significant differences when $p < 0.05$.

Results: Resistant cells HepG2S1 and HepG2S3 showed a significant decrease in BNIP3 protein levels in comparison to the parental line under both normoxia and hypoxia. Accordingly, higher BNIP3 levels were found in HepG2 cells, which reduced after sorafenib treatment. Moreover, we also observed lower BNIP3 mRNA levels in both resistant lines under hypoxia compared to HepG2. Epigenetic study revealed that HDACs were not involved in BNIP3 silencing, since BNIP3 protein levels were not detected in resistant cells after TSA administration. However, an increase in the methylation status of BNIP3 promoter was observed in both HepG2S1 and HepG2S3 lines under hypoxia. This was reversed by DNMTs inhibition, leading to an increase in the expression of BNIP3 similar to the levels registered in the parental line. Lastly, BNIP3 silencing achieved to decrease BNIP3 protein expression previously induced by 5-Aza and to significantly rise resistant cell viability initially inhibited by 5-Aza treatment.

Conclusion: BNIP3 silencing by promoter hypermethylation seems to constitute a key mechanism in the development of sorafenib

resistance. Hence, BNIP3 expression recovery could be a promising approach in the therapeutic landscape of advanced HCC.

PO-1969

Abnormal glycosphingolipid patterns in human cholangiocarcinoma stem-like subset

Antonella Mannini¹, Chiara Raggi¹, Margherita Correnti², Elisabetta Rovida¹, Massimo Aureli², Emma Carsana², Benedetta Piombanti¹, Mirella Pastore¹, Jesper B. Andersen³, Cedric Coulouarn⁴, Fabio Marra⁵. ¹University of Florence; ²University of Milan; ³University of Copenhagen; ⁴University of Rennes; ⁵University of Florence, Italy
Email: fabio.marra@unifi.it

Background and aims: Cancer stem cells (CSC) are a crucial therapeutic target in cancer. Several studies in different types of cancer (e.g. Burkitt's lymphoma, pancreatic carcinoma, other epithelial cancers) indicate that glycosphingolipids (GSL), a class of plasma membrane lipids, are prevalently expressed in CSC, and could be considered as markers of cancer stemness. Gangliosides (GS), sialic acid-containing GSL, have been investigated for their role in the malignant phenotype of several cancers (breast, melanoma, glioblastoma, ovary), and in tumor-stem like cells. However, no data are available on GSL composition in cholangiocarcinoma (CCA) and on their possible significance. Aim of this study is to provide a GSL and GS profiling of both stem-like subsets (SPH) and their parental cells in human CCA.

Method: Stem-like subset was enriched by sphere culture (SPH) in established human intrahepatic CCA cells (HUCCT1, CCLP1). CCA GS patterns were determined by chromatographic analytical procedures. Identification of GSL and GS molecular species and assessment of GS turnover were evaluated by feeding cells with 3H-sphingosine. GS role in the modulation of stem features was investigated using D-threo-1-phenyl-2-palmitoylamino-3-N-morpholine-1-propanol (PPMP), a glucosylceramide synthase inhibitor. FACS-sorted SPH expressing the GD2 synthase were examined for stem-like gene expression in comparison to compared to GD2- SPH.

Results: In both CCA lines, SPH showed drastic changes in the amount of specific sphingolipids (ceramide, Gb3, sphingomyelin) compared to parental cells grown in monolayer conditions (MON). In both CCA lines, amount of total GS was markedly different between MON and their SPH. Specifically, CCA-SPH showed an increase content of GM3, and reduction of GM2. Among complex GS, GD1a was strongly increased in SPH, and GD2 expression was present. This was corroborated by high expression levels of GM3 synthase as well as GD3- and GM2/GD2 synthases in CCA-SPH. GS biosynthesis enzymes, such as GlcCer-, LacCer-, and GM3 synthases, resulted strongly expressed in CCA-SPH compared to MON. Notably, sphere forming ability and expression of CSC-related genes were affected by PPMP. Likewise, GD2+ SPH cells were enriched with CSC-markers (CD133, EpCAM, CD44) at the protein and gene level in addition to several genes involved in pluripotency, self-renewal and epithelial-mesenchymal transition compared to GD2- SPH. Notably, expression of GM2/GD2 synthases was significantly expressed in tumor samples compared to paired non-tumoral liver tissue of CCA patients (n = 104) and strongly correlated with presence of satellite nodules, lymph node invasion and recurrence.

Conclusion: CCA stem-like properties are associated with GSL synthetic pathways and patterns. GSL synthases could represent potential markers for CCA.

POSTER PRESENTATIONS

PO-2227

Diagnostic and prognostic value of miR-16, miR-146a and miR-192 in exosomes of hepatocellular and liver cirrhosis patients

Thorben Fründt¹, Linda Krause², Bettina Steinbach³, Daniel Köhler⁴, Johann von Felden¹, Kornelius Schulze¹, Ansgar W. Lohse¹, Henning Wege^{1,5}, Heidi Schwarzenbach³. ¹University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Germany, Germany; ²University Medical Center Hamburg-Eppendorf, Institute for Medical Biometry and Epidemiology, Hamburg, Germany; ³University Medical Center Hamburg-Eppendorf, Department of Tumor Biology, Hamburg, Germany; ⁴University Medical Center Hamburg-Eppendorf, Department of Diagnostic and Interventional Radiology and Nuclear Medicine, Hamburg; ⁵Klinikum Esslingen, Cancer Center Esslingen, Esslingen am Neckar, Germany
Email: tfruentd@uke.de

Background and aims: Exosomes are extracellular vesicles and are indicative mediators of both cell communication and cancer progression, via transferring proteins and nucleic acids, such as microRNAs (miRNAs). We aimed to identify a specific miRNA pattern to determine the diagnostic and prognostic value in plasma exosomes of hepatocellular carcinoma (HCC) patients.

Method: A two-stage study was carried out: exosomal miRNAs were quantified in plasma of 24 HCC patients, including patients at stage A, B and C of the Barcelona Clinic Liver Cancer (BCLC) Classification, 37 liver cirrhosis (LC) patients and 20 healthy individuals (HI) by PCR-based microarray cards containing 47 different miRNAs (training cohort). Then, four deregulated miRNAs (miR-16, miR-146a, miR-192 and miR-221) were selected and quantified in the validation analysis using exosomes derived from 85 HCC patients, 50 LC patients and 20 HI. Expression levels of miRNAs, tumor characteristics, alpha fetoprotein (AFP) and clinical parameters including Child Pugh Score (CPS) to assess liver function were correlated with overall survival (OS).

Results: Exosomal miR-16 was downregulated in both HCC patients and liver cirrhosis patients ($p = 0.0001$), whereas miR-146a ($p = 0.0001$), miR-192 ($p = 0.002$) and miR-221 ($p = 0.032$) were upregulated in HCC patients, but not in cirrhosis patients. Repeated 10-fold cross validation showed that miR-146a was superior to miR-16, miR-192 and miR-221 to distinguish HCC from liver cirrhosis patients with AUC 0.80 ± 0.14 (sensitivity: $81 \pm 13\%$, specificity: $58 \pm 22\%$) in a logistic regression model. High miR-192 expression was associated with poor overall survival (OS) in all HCC patients ($p = 0.027$) and the subgroup of patients with stage BCLC A and B ($p = 0.017$). In uni- and multivariate Cox regression models, levels of miR-192 (HR: 3.44, 95% CI: 1.32–8.91; $p = 0.01$), CPS (HR: 3.08; 95% CI: 1.65–5.72, $p < 0.001$) and AFP (HR: 2.1; 95% CI: 1.52–2.92, $p < 0.001$) were independent predictors of OS in HCC patients. Decreased expression of miR-16 correlated with OS in liver cirrhosis patients ($p = 0.034$).

Conclusion: Exosomes secreted into the plasma carry differentially expressed miRNAs of which in particular, miR-192 was found as a promising prognostic maker for HCC patients while miR-146 demonstrated promising diagnostic potential to identify HCC patients in a high-risk cohort. Furthermore, expression level of miR-16 has a prognostic impact in liver cirrhosis patients.

PO-2375

Dynamics of endothelial progenitor cells in patients with advanced hepatocellular carcinoma

Claudia Campani¹, Manuela Capone¹, Francesco Liotta¹, Umberto Arena¹, Chiara Di Bonaventura¹, Stefano Colagrande¹, Francesco Annunziato¹, Fabio Marra¹. ¹University of Florence
Email: fabio.marra@unifi.it

Background and aims: Angiogenesis inhibitors are widely used for the treatment of advanced hepatocellular carcinoma. Previous studies have highlighted the importance of circulating endothelial progenitor cells (EPC) as predictors of tumor vascularization and

disease progression. However, only limited information is available on the levels of EPC in HCC, and their dynamics upon treatment.

Method: We prospectively analyzed the levels of different populations of circulating EPC (total CD34+, CD34+ /CD133+, CD34+ /KDR+, CD34+ /133+/KDR+, CD34+ /133-/KDR-) in patients with advanced HCC candidate to therapy with sorafenib. Patients were studied before the start of therapy (T0) and after two (T2) and eight weeks (T8), using high-performance flow-cytometry. Tumor response was evaluated at T8 according to mRECIST criteria. Patients were divided in progressive disease (PD) and clinical benefit (CB, all other responses).

Results: Sixteen patients (15 men, mean age 71 years) were enrolled. The median alpha-fetoprotein at T0 was 129 ng/ml. Eight patients were intolerant to sorafenib and stopped the treatment before T8. At T8 five patients had CB and three had PD. The median OS was 132 days. At baseline, in the whole population, frequencies of CD34+ KDR+ and CD34+ CD133+ KDR+ were strongly correlated with platelet count ($r = 0.788$ and $r = 0.734$, respectively, $p = 0.001$). In the CB group platelets were positively correlated with CD34+ KDR+ at T0 ($r = 0.929$, $p = 0.023$), total CD34 and CD34+ CD133+ at T2 ($r = 0.944$ $p = 0.016$ and $r = 0.924$ $p = 0.025$) and total CD34 ($r = 0.990$ $p = 0.001$), CD34+ CD133+ ($r = 0.968$ $p = 0.007$), CD34+ KDR- CD133- ($r = 0.976$ $p = 0.04$) at T8. Conversely in the PD group a negative correlation between total CD34 at T2 and platelets was found ($r = -0.999$ $p = 0.025$). At baseline, a borderline correlation between CD34+ CD133+ KDR+ cells and BMI was also found ($r = 0.45$, $p = 0.08$). No correlation with other clinical features at baseline were found. Frequencies of all EPCs subpopulation declined at T8 compared with T0. Remarkably, levels of CD34+ /CD133+ were higher at T0 in patients with CB compared to patients with PD ($p = 0.05$). Moreover, mean frequency of CD34+ cells significantly declined in patients with CB comparing T0/T2 and T0/T8, but not in patients with PD.

Conclusion: In patients with advanced HCC treated with sorafenib EPC levels are directly correlated with platelet count, suggesting a common activation of selected bone marrow pathways. Levels of a subset of EPC are higher at baseline in patients responding to this angiogenesis inhibitor.

PO-2601

TIGIT + TIM-3 + NK cells are correlated with NK cell exhaustion and disease progression in patients with hepatitis B virus-related hepatocellular carcinoma

Lihua Yu¹, Xiaoli Liu¹, Xinhui Wang¹, Fengna Yan¹, Peng Wang¹, Yuyong Jiang¹, Juan Du¹, ZhiYun Yang¹. ¹Center of Integrative Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, China
Email: yangzhiyun2016@163.com

Background and aims: The prognosis of hepatocellular carcinoma is extremely poor, of which hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) accounts for the majority in China. NK cells play a vital role as the first line of defense against tumors. Immune checkpoint inhibitors have become an effective immunotherapy method for the treatment of HCC, but they are mainly used for T cells. Therefore, we explored the characteristic expression pattern of immune checkpoints on NK cells of HBV-HCC patients.

Method: We included 133 patients with HBV-HCC, 25 patients with hepatitis B virus-related liver cirrhosis (HBV-LC), 23 patients with chronic hepatitis B (CHB), and 32 healthy donors (HDs). Flow cytometry was used to detect the co-expression of TIGIT and TIM-3 in peripheral blood NK cells of the above population. Moreover, we analyzed the correlation between the co-expression of TIGIT and TIM-3 and the clinical progress of patients with HBV-HCC.

Results: The co-expression of TIGIT and TIM-3 on NK cells is elevated in patients with HBV-HCC. The high level of co-expression of TIGIT and TIM-3 is associated with the clinical progress of patients with HBV-HCC. TIGIT⁺TIM-3⁺NK cells showed exhausted phenotypic characteristics and displayed dysfunction manifested as weakened

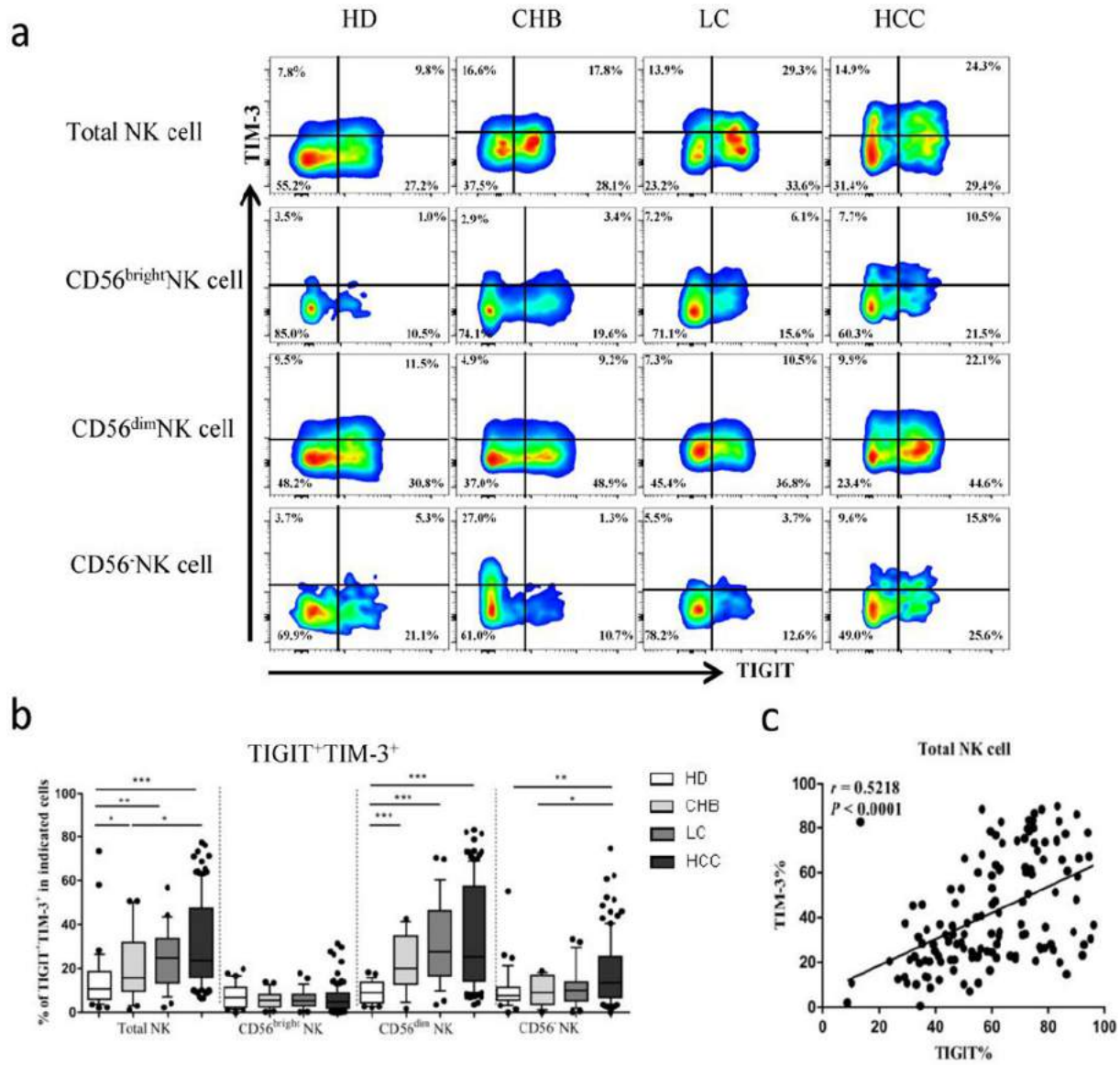


Figure: (abstract: PO-2601)

killing function, reduced cytokine production, and proliferation function.

Conclusion: TIGIT⁺TIM-3⁺NK cells participate in NK cells function exhaustion and are closely related to the disease progression of patients with HBV-HCC, suggesting a new target for future immunotherapy.

PO-2694

lncRNA HOTAIR regulates cancer glucose metabolism in hepatocellular carcinoma via the miR-122/PKM2 pathway

Jijia Zhou¹, Di Cheng¹, Junge Deng¹, Leyi Huang¹, Jie Zhang¹, Xiaogeng Deng¹. ¹Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China
Email: jijiazh2004@126.com

Background and aims: Reprogrammed glucose metabolism of enhanced aerobic glycolysis (or the Warburg effect) is known as a hallmark of cancers, including hepatocellular carcinoma (HCC). The roles of long noncoding RNAs (lncRNAs) in regulating cancer metabolism remains largely elusive. This study aimed to investigate whether lncRNA HOTAIR could regulate glucose metabolism in HCC.

Method: The expression level of HOTAIR in HCC tissues and cell lines was detected. pHOTAIR or shHOTAIR were employed to ectopically increase or decrease HOTAIR expression in HCC cells. Then cell proliferation, colony formation, migration, glucose consumption, and lactate production, as well as expression of PKM2, HK2, GLUT1 and miR-122 were analyzed. Luciferase reporter assay was used to test the predicted miR-122 target sites on PKM2.

Results: Here we showed that lncRNA HOTAIR was highly expressed in HCC tissues and cell lines. Knockdown of HOTAIR markedly repressed the proliferation, colony formation, migration, and aerobic glycolysis of HCC cells, whereas ectopic expression of HOTAIR dramatically promoted the aerobic glycolysis. Furthermore, HOTAIR upregulated a cluster of glycolytic genes including PKM2, HK2, GLUT1, in which PKM2 was found to be among the most significant one. Mechanically, HOTAIR inhibited liver-specific miR-122 expression via EZH2, leading to upregulation of PKM2 expression and maintenance of enhanced aerobic glycolysis. Moreover, Treatment with miR-122 mimics abolished the effect of HOTAIR on the process of aerobic glycolysis, as well as the expression of PKM2. In addition,

POSTER PRESENTATIONS

Luciferase reporter assay showed that miR-122 regulated PKM2 expression by binding to the 3'-untranslated region of PKM2.

Conclusion: Collectively, our findings suggest that lncRNA HOTAIR contributes to HCC development by reprogramming cancer glucose metabolism via the miR-122/PKM2 pathway. Targeting HOTAIR/miR-122/PKM2 axis would provide a novel therapeutic strategy for HCC.

PO-2742

Preoperative artemin as predictive biomarker for survival in curatively resected hepatocellular carcinoma

Ulf Zeuge¹, Luna Zhan¹, Roxana Bucur¹, Kristen Sauerzopf¹, Reenika Aggarwal², Sophie Feng¹, Hao-Wen Sim³, Dangxiao Cheng¹, Wen-Jiang Zhang¹, Carol-Anne Moulton¹, Ian Mcgilvray¹, Sean Cleary⁴, Steven Gallinger¹, Gonzalo Sapisochin¹, Jennifer Knox¹, Alice Wei⁵, Geoffrey Liu¹, Eric Chen¹. ¹University Health Network, Toronto, Canada; ²Temerty Faculty of Medicine, University of Toronto, Toronto, Canada; ³NHMRC Clinical Trials Centre at the University of Sydney, Australia; ⁴Mayo Clinic, Rochester, United States; ⁵Memorial Sloan Kettering Cancer Center, New York, United States
Email: geoffrey.liu@uhn.ca

Background and aims: Tumor-induced generation of splenic erythroblast-like cells (Ter-cells) has been shown to promote tumor progression. These Ter-cells produce artemin (ARTN), a glial-line derived neurotrophic factor. We investigated the association of pre-operative serum ARTN with overall (OS) and disease-free survival (DFS) in an ethnically diverse North American HCC cohort undergoing curative resection for HCC.

Method: From samples taken within 12 months prior to surgery, serum ARTN concentration was measured using an enzyme-linked immunosorbent assay (ELISA). Clinicopathologic variables were abstracted via retrospective chart review. Serum ARTN was dichotomized at the median into high vs. low groups. Log-rank tests, Kaplan-Meier curves, and a log-transformed ARTN as a continuous variable in Cox proportional hazard models evaluated ARTN's association with OS/DFS.

Results: Preoperative blood samples were available for 56 patients (pts); Median age, 66 years; 73%, male. Etiology of liver disease included hepatitis B (45%), hepatitis C (23%), alcohol (9%) and NAFLD (9%). In 36% of pts, HCCs did not arise on the background of pre-existing cirrhosis; 58% had a maximum diameter of ≥ 5 cm with 17% having macrovascular invasion. Barcelona clinic liver cancer (BCLC) staging was A in 74% pts with the baseline alpha-fetoprotein (AFP) being >40 ug/l in 50% pts. Median follow-up was 60 months.

In our cohort, median OS was not reached; median DFS was 22.2 months. Using high vs. low ARTN, the median DFS was 14.7 vs 30.9 months (log-rank $p = 0.64$) respectively.

Univariate analysis using ARTN as continuous variable found that each log-unit increase in concentration was associated with a worse OS: hazard ratio (HR), 1.69 (95% CI: 1.10–2.6, $p = 0.016$); for DFS, HR 1.16 (95% CI: 0.96–1.39, $p = 0.128$). OS HRs for ARTN remained between 1.60 and 1.81 after separately controlling for various variables including age, gender, ethnicity, cirrhosis, alpha-Fetoprotein, vascular invasion, pathology stage, solitary tumor, tumor size and HBV-infection.

Conclusion: In our population a high pre-operative serum ARTN is associated with shorter OS but not DFS in HCC pts undergoing curative resection. Serum ARTN is a biologically supported biomarker for HCC; results from this study should be validated prospectively.

PO-2787

Identifying effective subtype-specific treatment responses in hepatocellular carcinoma in genetically engineered mouse models

Miryam Müller¹, Stephanie May¹, Lynn McGarry², Tim Kendall³, William Clark¹, Matthew Neilson¹, Robin Shaw¹, Thomas Jamieson¹, Colin Nixon¹, Karen Blyth^{1,2}, Daniel Murphy^{1,2}, Crispin Miller^{1,2}, Carlin Leo^{1,2}, Owen Sansom^{1,2}, Thomas G. Bird^{1,2,3}. ¹CRUK Beatson

Institute, Glasgow, United Kingdom; ²Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom; ³MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

Email: m.mueller@beatson.gla.ac.uk

Background and aims: Systemic treatment options for advanced hepatocellular carcinoma (HCC) have increased over the last decade but typically have modest efficacy and are generally applied as a one-size-fits-all approach. Refining stratified therapies is hindered by a lack of suitable in-vivo models of HCC subtypes. Our aim was to develop a suite of genetically engineered mouse models (GEMMs) representing human subtypes of HCC and to use these to identify and test new therapies.

Method: We generated the GEMMs combining loxP technology with hepatocyte-specific AAV8-TBG-Cre mediated recombination resulting in clonal HCC outgrowth driven by oncogenes/tumor suppressors identified in human HCC. Over 20 genetic models were disease positioned against human HCC using transcriptomics and histopathological characteristics and cross referenced to classical HCC models. Current standard-of-care therapies were tested for effect on overall survival. Tumoroids were generated from GEMMs and FDA-approved oncology drugs were analyzed for effect on tumoroid growth. Drugs were validated in vitro and survival studies were performed in the respective mouse models.

Results: Targeted hepatocytes expanded from a clonal source to form nodules and ultimately HCC within 3–4 months. The resulting tumors reproduce key features of human disease, including histological patterns, tumor hemorrhage and metastasis. Established tumors respond to first-line tyrosine kinase inhibitors (TKIs; Sorafenib or Lenvatinib) leading to modest but significant survival benefits. We demonstrate lack of efficacy of anti-PD-1 treatment (alone and with TKI) in β -catenin driven tumors, similar to reports in human HCC. Utilizing high-throughput drug screens we identify licensed anticancer drugs, novel in HCC therapy, that markedly increase survival in vivo, including in combination with TKIs.

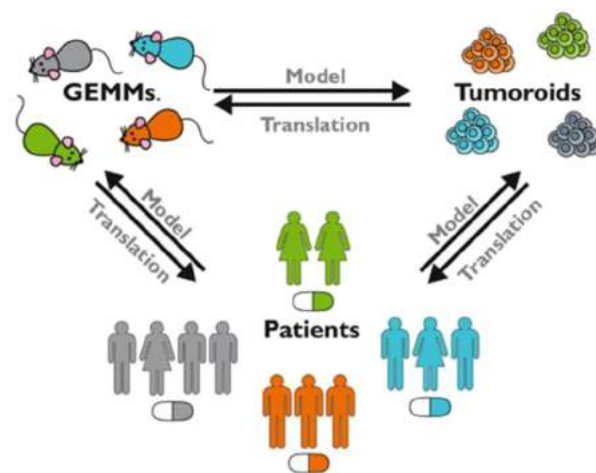


Figure:

Conclusion: These models provide a platform for both detailed interrogation of the biological mechanisms driving HCC and improved translational research using a subtype-specific approach to pre-clinical therapeutic identification and testing. We have developed a bank of tumoroids across the range of GEMMs and a pipeline for using these for high-throughput in vitro drug screening, followed by subsequent in vivo validation. This allows us to rapidly link in vitro and in vivo efficacy both identifying and testing novel therapies in immunocompetent mice with the ultimate aim of guiding precision medicine trials in human HCC patients.

PO-2798

Phosphoinositide 3-kinase dependent carcinogenesis in the liver

Dayana Tsoлова^{1,2}, Angelika Ulrich¹, Dieter Saur^{1,3}. ¹University Hospital rechts der Isar, Technical University of Munich, Department of Medicine II, Munich, Germany; ²Central Institute for Translational Cancer Research (TranlaTUM), Technical University of Munich, Munich; ³Central Institute for Translational Cancer Research (TranlaTUM), Technical University of Munich, Munich, Germany
Email: dayana_tsoлова1992@abv.bg

Background and aims: Hepatocellular carcinoma and intrahepatic cholangiocarcinoma—the most and the second most common primary liver cancer respectively, are devastating diseases with low chances of cure and poor survival outcome. The exact pathomechanism driving the tumour development is still poorly understood. In this study we investigate the role of oncogenic Phosphoinositide 3-kinase signalling in inducing liver damage and metabolic changes, as well as in the formation and progression of both types of liver cancer. Therefore, we compare two genetically modified murine models—Alb-Cre, PIK3CA^{H1074R/+} and Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff}. Both models harbour the mutant PIK3CA^{H1074R/+} encoding for the oncogene Phosphoinositide 3-kinase catalytic unit p110α^{H1074R}, which lead to constitutive Phosphoinositide 3-kinase pathway activation in the liver. The double transgenic mice (Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff}) harbour, in addition to the PIK3CA^{H1074R/+} mutation, a liver specific Pdk1 Knockout. The aim of this study is to analyse the pathomechanisms of carcinogenesis in both models and to investigate if the Pdk1 deletion can prevent the liver damage and tumour formation induced by the oncogenic Phosphoinositide 3-kinase signalling.

Method: Polymerase chain reaction; western blot; real time polymerase chain reaction; hematoxylin and eosin, immunohistochemical and oil red o staining; bloodserum and blood sugar analysis.

Results: Whereas Alb-Cre, PIK3CA^{H1074R/+} mice developed diffuse steatosis and hepatomegaly, observed from the first month of life, followed by formation of benign and malign liver lesions, Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff} mice showed macroscopically normal liver morphology up to an age of 3 months comparable to controls. The development of liver tumours occurred later and in rather non-diffuse steatosis liver environment compared with the mice from the Alb-Cre, PIK3CA^{H1074R/+} genotype. The Alb-Cre, PIK3CA^{H1074R/+} mice presented recurrent episodes of apathy, decreased mobility, sleepiness and lethargy up to sudden death. They showed elevated aspartate transaminase, alkaline phosphatase and cholesterol parameters throughout the whole longitudinal surveillance, as well as significantly decreased blood sugar levels in 4 hours fast test at the age of 3 months compared to control animals. The Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff} mice, on the other hand, showed normal liver and cholesterol parameters up to an age of 8–12 months and an increase afterwards. Furthermore, the Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff} mice showed more than 3 times longer median survival than the Alb-Cre, PIK3CA^{H1074R/+} mice.

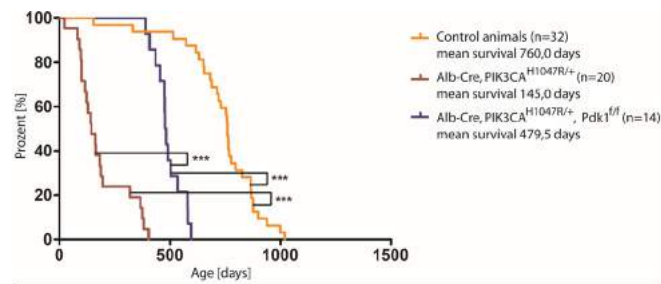


Figure: Kaplan Meier curve comparison between Alb-Cre, PIK3CA^{H1074R/+}; Alb-Cre, PIK3CA^{H1074R/+}, Pdk1^{ff} mice and control animals (***)p<0.0001, log-rank test)

Figure:

Conclusion: The Pdk1 deletion manages to delay the oncogenic and metabolic effects of the constitutive Phosphoinositide 3-kinase pathway activation in the liver.

PO-2828

Characterization of disease progression and pharmacological intervention in a diet-induced obese mouse model of NASH with advanced fibrosis and hepatocellular carcinoma

Michael Feigh¹, Mathias Møllerhøj¹, Sanne Veidal¹, Martin Rønn Madsen¹, Henrik B. Hansen¹. ¹Gubra, Hørsholm, Denmark
Email: mfe@gubra.dk

Background and aims: Obesity-associated non-alcoholic steatohepatitis (NASH) predisposes to the development of severe fibrosis and hepatocellular carcinoma (HCC), thus pharmacological interventions targeting metabolic NASH and fibrosis might also affect HCC. The present study aimed to characterize disease progression and evaluate treatment response for the late-stage clinical candidate elafibranor (peroxisome proliferator-activated receptor α/δ agonist) in the extended GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH.

Method: Male C57Bl/6J mice were fed the GAN diet (40 kcal-% fat, 22% fructose, 10% sucrose, 2% cholesterol) for up to 88 weeks (n = 12–15/group). Disease progression in DIO-NASH mice was evaluated by liver histopathological NAFLD Activity Score (NAS) and Fibrosis Stage, histomorphometry, macroscopic tumor evaluation and liver transcriptome analysis. DIO-NASH mice with extended GAN diet-induction (60 weeks) and biopsy-confirmed steatosis (score ≥2), advanced fibrosis (stage F3) and HCC (DIO-NASH-HCC) received treatment (PO, QD) with vehicle (n = 16), elafibranor (30 mg/kg, n = 14) for 12 weeks. Age-matched lean control animals (n = 10) received vehicle.

Results: DIO-NASH animals demonstrated progressive NASH with consistent development of liver fibrosis from 28 weeks on diet. Advanced bridging fibrosis (stage F3) and tumour development including HCC was consistently observed from ≥58 weeks on diet. Hepatic transcriptome signatures were consistent with severe disease progression in DIO-NASH mice. In DIO-NASH-HCC mice, elafibranor treatment demonstrated ≥2-point significant improvement in NAFLD Activity Score and promoted a 1-stage significant improvement in Fibrosis Stage, compared to vehicle group. Therapeutic effects of elafibranor were supported by quantitative histological markers of steatosis (lipids, hepatocytes with lipid droplets), inflammation (number of inflammatory cells/foci, galectin-3), fibrogenesis (α-SMA) and fibrosis (PSR, collagen 1a1). Elafibranor had no effect on macroscopically evaluated tumor numbers and size, although improved HCC-associated transcriptomic signatures including lowered expression of hepatic genes involved in apoptosis, inflammation, cell cycle and proliferation.

Conclusion: DIO-NASH mice show progressive advanced fibrosis and high HCC incidence. Elafibranor treatment improved hepatic steatosis, inflammation, and fibrosis in DIO-NASH-HCC mice with advanced fibrosis but had no effect on HCC burden. The extended GAN DIO-NASH-HCC mouse model is suitable for profiling novel drug therapies for advanced fibrosing NASH and HCC.

PO-2839

Tumor progression in intrahepatic cholangiocarcinoma

Mickael Di-Luoffo¹, Sophie Pirenne^{1,2}, Thoueiba Saandi¹, Axelle Loriot¹, Claude Gérard¹, Nicolas Dauguet^{1,3}, Fatima Manzano-Nunez¹, Natalia Alves Souza Carvalhais⁴, Florence Lamoline¹, Sabine Cordi¹, Katarzyna Konobrocka¹, Vitaline De Greef¹, Mina Komuta⁵, Georg Halder⁴, Patrick Jacquemin¹, Frédéric Lemaigre¹. ¹de Duve Institute, Université Catholique de Louvain, Brussels, Belgium; ²Department of Pathology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ³CYTF platform, Université Catholique de Louvain, Brussels, Belgium; ⁴VIB Center for Cancer Biology and KU Leuven, Department of Oncology, University of Leuven, Leuven, Belgium; ⁵Department of Pathology, Keio University School of Medicine, Tokyo, Japan
Email: sophie.pirenne@uclouvain.be

Background and aims: Intrahepatic cholangiocarcinoma (iCCA) is an aggressive cancer presenting a dismal prognosis. Early diagnosis of

POSTER PRESENTATIONS

iCCA is necessary to improve prognosis. However, there is still limited information available about the initiation of this rare cancer and its progression from precursor lesions. The aim of the work is to identify mechanisms driving formation of precancerous lesions of iCCA and their progression towards invasive tumor using experimental models that faithfully recapitulate human tumorigenesis.

Method: We generated a new mouse model which combines cholangiocyte-specific expression of KrasG12D with 3, 5-diethoxy-carbonyl-1, 4-dihydrocollidine diet-induced inflammation to mimic iCCA development in patients with cholangitis. Histological and transcriptomic analyses of the mouse precancerous lesions and iCCA were performed and compared with human analyses.

Results: Mice expressing KrasG12D in cholangiocytes and affected with cholangitis developed intraductal papillary neoplasms of bile ducts (IPNBs) and eventually iCCAs comparable to the human large duct type iCCA. Our RNA sequencing analysis showed that the transcriptomes of IPNB and iCCA were closely related. We noticed the presence of transitional lesions between IPNB and iCCA. These data support that iCCA originate from IPNB. We provide evidence that Tensin-4 (TNS4) is upregulated in iCCA and increases cell proliferation and migration *in vitro* and tumor growth *in vivo*. Further *in vitro* experiments allowed to consider a gene cascade involved in tumor progression.

Conclusion: We developed a novel mouse model of iCCA that faithfully recapitulates human iCCA tumorigenesis and identified a gene cascade, involving TNS4, promoting tumor progression.

PO-2865

Proteomic profiling of hepatocellular adenomas paves the way to new diagnostic and prognostic approaches

Cyril Dourthe¹, Céline Julien², Sylvaine Di-Tommaso¹, Jean-William Dupuy³, Nathalie Dugot-Senant⁴, Alexandre Brochard⁵, Brigitte Le Bail⁶, Jean-Frédéric Blanc⁷, Laurence Chiche², Charles Balabaud⁸, Paulette Bioulac-Sage⁸, Frederic Saltel¹, Anne-Aurélien Raymond⁹. ¹Univ. Bordeaux, INSERM, BaRITOn, U1053; ²Oncoprot Platform, TBM-Core US 005, Bordeaux, France; ³Bordeaux University Hospital, Department of Digestive Surgery, Bordeaux, France; ⁴Univ. Bordeaux, Proteome Platform, Bordeaux, France; ⁵TBM-Core US 005, Histopathology Platform, Bordeaux; ⁶Neurocentre Magendie, INSERM U1215, Bordeaux, France; ⁷Bordeaux University Hospital, Department of Pathology, Bordeaux, France; ⁸Bordeaux University Hospital, Department of Hepatology and Oncology, Bordeaux, France; ⁹Univ. Bordeaux, INSERM, BaRITOn, U1053, Bordeaux, France; ⁹Univ. Bordeaux, INSERM, BaRITOn, U1053; ⁹Oncoprot Platform, TBM-Core US 005, Bordeaux, France
Email: anne-aurelie.raymond@inserm.fr

Background and aims: Through an exploratory proteomic approach based on typical hepatocellular adenomas (HCA), we previously identified a new diagnostic biomarker for a distinctive subtype of HCA with high risk of bleeding, already validated on a multicenter cohort. We hypothesized that the whole protein expression deregulation profile could deliver much more informative data for tumors characterization. Therefore, we pursued our analysis with the characterization of HCAs proteomic profiles, evaluating their correspondence with the established genotype/phenotype classification and assessing whether they could provide added diagnosis and prognosis values.

Methods: From a collection of 260 cases, we selected 52 typical cases of all different subgroups on which we built the first HCA proteomics database. Combining laser microdissection and mass spectrometry based proteomic analysis, we compared the relative protein abundances between tumoral (T) and non-tumoral (NT) liver tissues from each patient and we defined specific proteomic profile of each HCA sub-groups. Next, we built a matching algorithm comparing proteomic profile extracted from a patient with our reference HCA database.

Results: Proteomic profiles allowed HCA classification and made diagnosis possible, even for complexes cases with immunohistological or genomic analysis that did not lead to a formal conclusion. Despite a well-established pathomolecular classification, clinical practices have not substantially changed and HCA management link to the assessment of the malignant transformation risk remains delicate for many surgeons. That's why we also identified and validated a proteomic profile that directly evaluate malignant transformation risk regardless of HCA subtype.

Conclusion: This pioneering work proposes a proteomic-based machine learning tool, operational on fixed biopsies, that can improve diagnosis and prognosis and therefore patient management for HCA.

PO-2919

Transcriptomic analysis reveals circWHSC1 and circCPSF6 serves as the oncogene to promote hepatocellular carcinoma progression

Fei Lu², Jing Gao¹, Yang Luo³, Wei-lin Jin⁴, Chuan-xing Li¹, Xun Li⁴. ¹Karolinska Institutet, Department of Medicine and Center for Molecular Medicine, Stockholm, Sweden; ²Lanzhou University, The First Clinical Medical College of Lanzhou University, Lanzhou, China; ³The First Hospital of Lanzhou University, Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou, China; ⁴The First Hospital of Lanzhou University, Department of General Surgery, Lanzhou, China
Email: lxd21@126.com

Background and aims: Circular RNAs (circRNAs) have been recently proposed for important contributions to hepatocarcinogenesis. We aim to investigate crucial circRNAs in the pathogenesis of hepatocellular carcinoma (HCC) by comprehensive transcriptomic profiling of circRNA, and further validate therapeutic targets by downstream functional experiments.

Method: CircRNA microarray was performed to detect the transcriptomic-wise circRNA expression in HCC and corresponding normal adjacent samples. The differentially expressed candidates were further validated by Real-time PCR in both HCC cell lines and a larger HCC tissue cohort, and identified the differentially expressed circWHSC1, circCPSF6, circRREB1, and circWHSC1-006. Examine the potential role of critical circRNA in tumor cell growth by using a lentivirus-mediated RNA interference (RNAi) system in the HCC cell lines *in vitro*. Using lentivirus to construct four knockdown targets and one overexpression target of circWHSC1 and circCPSF6 conducting function experiments at the cell level. CCK-8 assay was used to assess cell proliferation.

Results: CircRNA microarray reveals 83 up- and 20 down-expressed circRNA in HCC, then the prioritized four candidates (circWHSC1, circCPSF6, circRREB1, and circWHSC1-006) were validated by PCR in HCC cell lines (Hep3B, SK-HEP-1, HCCLM3, and Huh7) and human tissue samples, respectively. The expression of circWHSC1 and circCPSF6 were higher in HCC tissue compared to these in normal adjacent samples (each, n = 37, Figure, a-b) and in HCC cell lines Hep3B and SK-HEP-1, respectively. CircWHSC1 knockdown or overexpression significantly inhibited or promoted HCC cell lines proliferation *in vitro*, respectively (Figure, c-e). Knockdown of circCPSF6 increased the proportions of HCC cells in G0/G1 phase and promoted cell apoptosis *in vitro*.

Conclusion: CircWHSC1 and circCPSF6 played the tumor-promoting roles in HCC, suggesting the two circRNA might be the novel therapeutic target in HCC.

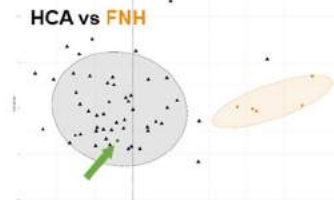
Prescriber :
 Date of receipt :
 File number :

Bordeaux, 2020/09/01

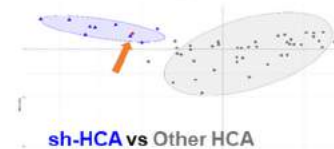
Results

Comparison of the proteomic patterns with the reference profiles of the molecular subtypes of HCA and FNH (classification database updated on 2020/08/03):

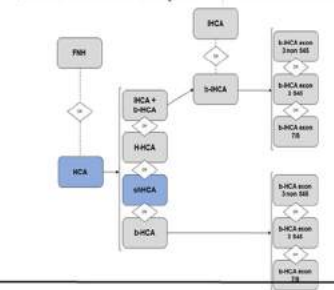
Case	Random Forest	χ^2 Score (highest score)	Euclidean distance (lowest score)
Case 280	HCA	HCA = 20.08 FNH = 10.39	HCA = 13.33 FNH = 17.02



Case	Random Forest	χ^2 Score (highest score)	Euclidean distance (lowest score)
Case 280	sh-HCA	sh-HCA = 109.37 Other HCA = 16.47	sh-HCA = 21.68 Other HCA = 24.87

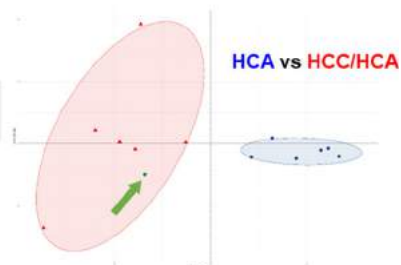


Tests results :
 Concordance of the three tests in favour of a sh-HCA



Comparison with the malignancy profile (database updated on 2020/08/03):

Case	Random Forest	Euclidean distance (lowest score)
Case 280	HCC/HCA	HCA = 4.99 HCC/HCA = 4.27



Tests results :
 Concordance of the two tests in favour of a HCC developed on HCA.

Figure: (abstract: PO-2865)

PO-2920
Exploring molecular signatures (circulating tumour cells, microRNAs, proteomics) as possible biomarkers of early hepatocellular carcinoma

Athanasios Armakolas¹, Vassiliki Dimopoulou¹, Andrianos Nezos¹, Georgios Stamatakis², Martina Samiotaki², Georgios Panagiotou², Maria Tampaki³, P. Spyridon Dourakis³, John Koskinas³. ¹National and Kapodestrian University of Athens, Greece, Physiology Laboratory, Medical School, Athens, Greece; ²Biomedical Sciences Research Center Alexander Fleming, Vari, Greece; ³Hippokratieo General Hospital,

Internal Medicine Department, Athens, Greece
 Email: aarmakol@med.uoa.gr

Background and aims: The molecular signature of hepatocellular carcinoma (HCC) is associated with prognosis and plays a significant role in the response/resistance to systemic therapy. The aim of this study was to determine molecular signatures based on the proteome analysis, microRNAs (miRNAs) and circulating tumour cells (CTCs) that will define and predict the development of HCC at very early stages in patients with cirrhosis.

Method: Blood of 89 patients with HCC (56 patients with advanced and 33 patients with early HCC), 28 age-matched cirrhotic patients

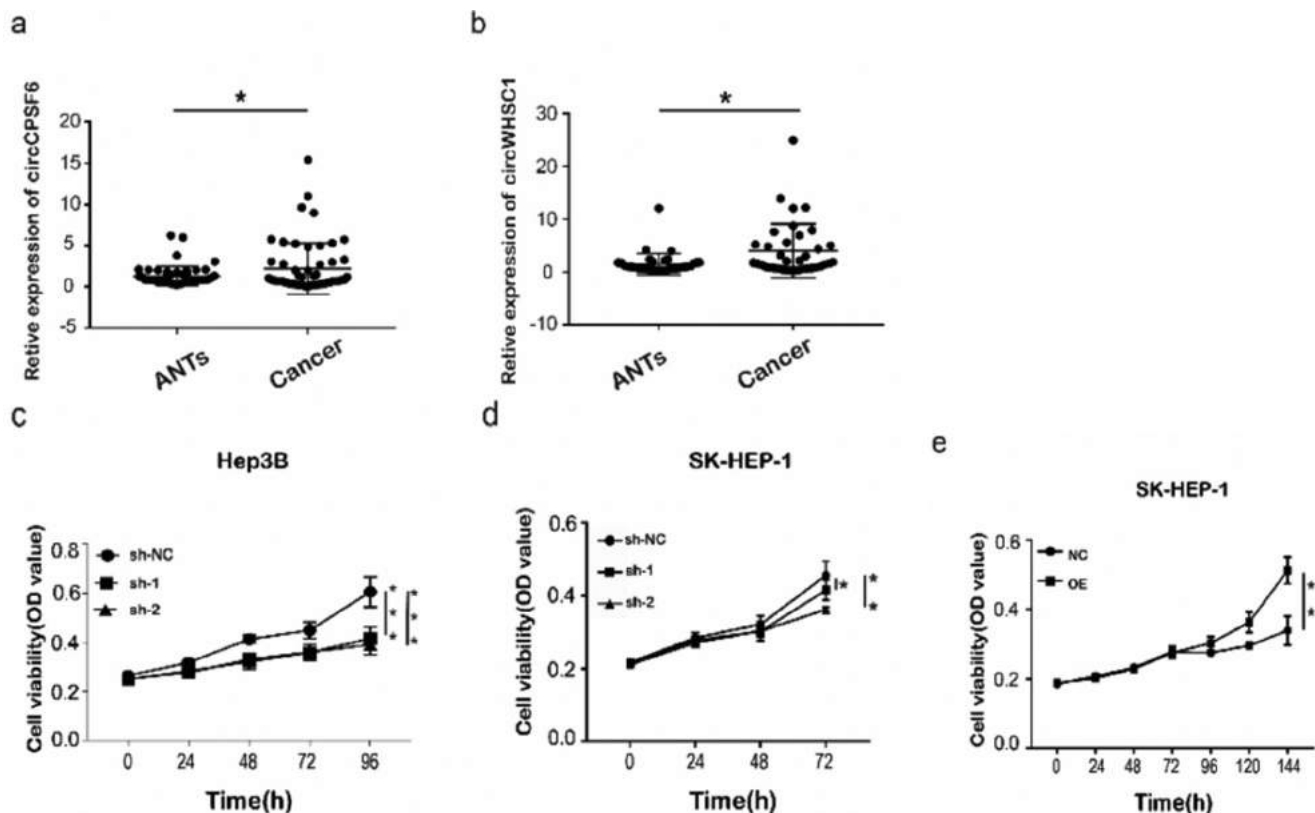


Figure: (abstract: PO-2919): Relative expression of target genes in HCC tissue and function experiments. a-b: HCC tissues displayed elevated circCPSF6 and circWHSC1 expression; c-d: circWHSC1 knockdown inhibited HCC cell lines proliferation in vitro; d: circWHSC1 overexpress promoted HCC cell lines proliferation in vitro. ANTs: adjacent normal tissue; sh-NC: RNAi negative control; NC: negative control; OE: overexpression. * p value <0.05.

with no evidence of HCC and 5 healthy controls were examined for CTCs by Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) using the markers Epithelial cell adhesion molecule (EPCAM), Vimentin, alpha-fetoprotein (α FP) and surface major Vault protein (sMAVP). Patients' serum was also examined for the presence of a set of miRNAs that are involved in HCC (miR122, miR221, miR222, miR200a and miR200b) and for protein signatures by whole proteome analysis (LC/MS).

Results: Blood examination showed that 27/56 (48%) patients with advanced HCC had detectable CTCs. Among them, 10/27 (37%) presented evidence of mesenchymal or intermediate stage cells (vimentin and/or sMAVP positive). Moreover, 4/33 (12%) patients with early HCC and 4/28 (14%) cirrhotic patients had detectable CTCs. Patients with HCC exhibited a significant increase of miR-200b ($p = 0.007$) and a significant decrease in miR-122 ($p = 0.023$) when compared to cirrhotic patients. Finally, the proteome analysis using stringent criteria indicated a significant increase in APOA2, CLU, HRG and APOD proteins in patients with early HCC when compared with the cirrhotics. All non-HCC cirrhotic patients with CTCs had increased levels of proteins that characterize early HCC.

Conclusion: CTCs were found in a significant number of patients with advanced HCC. Proteome analysis revealed that patients with early HCC had a unique increase of certain proteins in comparison with non-HCC cirrhotic patients that could be used as possible biomarkers.

Liver tumours: Therapy

PO-75

Irreversible electroporation vs radiofrequency ablation for hepatocellular carcinoma: A single centre propensity matched comparison

Elliot Freeman¹, Wa Cheung², Sapphire Ferdousi¹, Helen Kavnoudias², Majeed Ammar^{1,3}, William Kemp^{1,3}, Stuart K. Roberts^{1,3}. ¹Alfred Hospital, Department of Gastroenterology, Melbourne, Australia; ²Alfred Hospital, Department of Radiology, Melbourne, Australia; ³Monash University, Department of Medicine, Central Clinical School, Melbourne, Australia

Email: elliotfreeman@hotmail.com

Background and aims: Irreversible electroporation (IRE) is a relatively new non-thermal ablation technique for unresectable hepatocellular carcinoma (HCC) not amenable to standard thermal therapies. The efficacy of this technique, compared to radiofrequency ablation (RFA), has not been reported. The aim of this study, therefore, was to compare the efficacy of IRE vs RFA in the treatment of unresectable HCC.

Method: We identified all patients at our institution who underwent IRE or RFA for HCC. Demographic and clinical data up until 1st March, 2020 were analysed. Local recurrence-free survival (LRFS) was compared between groups after propensity score matching for age, gender, BCLC stage, Child-Pugh grade, lesion size and alpha-fetoprotein (AFP) level.

Results: A total of 190 HCC ablations (31 IRE, 159 RFA) were identified. After propensity score matching, we compared 25 IRE procedures

(76% males, median age 62.4 years, median tumour size 20 mm) to 96 RFA procedures (84.4% males, median age 64.3 years, median tumour size 18.5 mm). LRFS did not differ between groups, with a 1-, 2- and 5-year LRFS of 80.4% (95% CI 55.8–92.2), 69.1% (95% CI 43.3–84.9) and 44.9% (95% CI 18.9–68.1%) respectively for IRE and 84.8% (95% CI 75.2–90.9), 71.3% (95% CI 58.3–81.0) and 52.1% (95% CI 35.4–66.4%) respectively for RFA ($p=0.63$). There were no major procedure-related complications or deaths in either group.

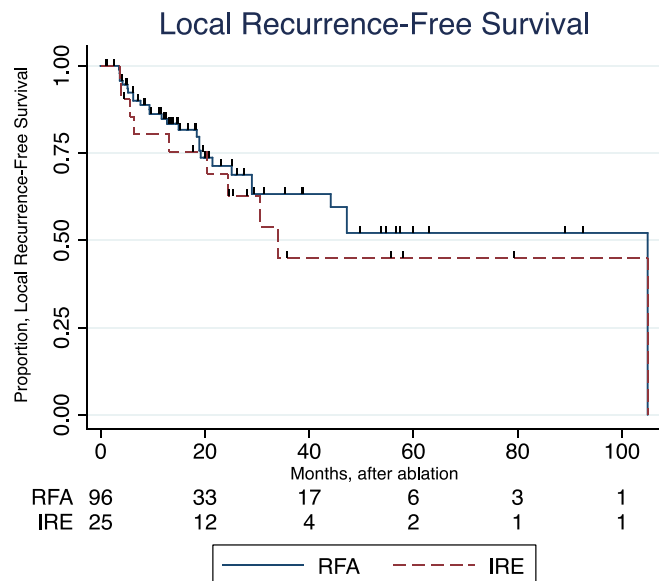


Figure: Kaplan-Meier estimated LRFS curve of the propensity matched IRE and MWA groups

Conclusion: Whilst IRE remains a relatively novel therapy for HCC cases where standard thermal ablation is contraindicated, the LRFS in our centre is comparable to that of RFA. IRE should therefore be considered as a treatment option in such cases when available before stage-migration to non-curative therapies such as transarterial chemoembolization (TACE).

PO-573

TIAM1, a potential synthetic lethal gene and candidate therapeutic target for hepatocellular carcinoma

Chalermsein Permtersin¹, Sirinitra Nakjang², Schwalbe Ed³, Helen L. Reeves⁴, Gordon Strathdee¹, Ruchi Shukla¹. ¹Biosciences Institute, Newcastle Upon Tyne, Northern Ireland; ²Bioinformatics Support Unit, Newcastle University, Newcastle Upon Tyne, United Kingdom; ³Faculty of Health and Life Sciences, Northumbria University, Newcastle Upon Tyne, United Kingdom; ⁴Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, United Kingdom

Email: c.permtersin2@newcastle.ac.uk

Background and aims: Available therapies for hepatocellular carcinoma (HCC) patients often have low efficacy and significant toxicities, with deaths continuing to rise. We developed a novel bioinformatics pipeline to identify genes required for survival of cancer cells, but not normal cells. Targeting these genes may induce ‘synthetic lethality’; specifically killing cancer cells, with no impact on healthy ones. The aims of this study are; (1) to utilise the new bioinformatics approach to identify candidate synthetic lethal genes for specific subgroups of HCC patients; (2), to functionally assess the identified candidate genes in cell lines to validate their synthetic lethality.

Method: Genome-wide DNA methylation data from 224 HCC patient samples was utilised for methylation subgrouping using non-negative matrix factorization (NMF). Synthetic lethal (SL) gene identification was performed using an in-house developed pipeline, integrating

methylation and matched genome-wide expression data. Expression/siRNA manipulation of candidates was explored *in vitro* in HCC cell lines, with MTT cell viability assay, Caspase-Glo[®] 3/7 apoptosis assay and CellTox™ green cytotoxicity assays.

Results: NMF clustering identified five potential HCC molecular subtypes. Subtype-2 exhibited the most unique methylation profile and was utilised for SL gene analysis. This identified two candidate SL genes, *LDHB* and *TIAM1*. *TIAM1* is a member of family of guanine nucleotide exchange factors (GEFs) with known roles in cancer cell growth, adhesion and invasion, that is known to activate Rac1 signalling. We investigated *TIAM1* siRNA silencing and small molecule inhibition of *TIAM1*/Rac1 signalling (NSC23766, a specific Rac1 inhibitor) in *TIAM1* positive (PLC/PRF-5, and SNU182) and negative (HepG2, Huh-7) HCC cell lines and immortalised hepatocytes (HHL5, *TIAM1* positive) *TIAM1* knockdown inhibited proliferation in the *TIAM1*-positive PLC/PRF-5 (30%, $p<0.05$) and SNU182 (36%, $p<0.05$) with no impact in negative cells. Similarly, cell proliferation was suppressed at significantly lower NSC23766 concentrations in PLC/PRF-5 and SNU182 cells (IC₅₀, 25 and 29 micromolar, respectively) than in *TIAM1* negative lines. Induction of apoptosis by NSC23766 was specific to SNU182.

Conclusion: We report a novel pipeline for the identification of SL genes in HCC. Targeting *TIAM1* signalling in *TIAM1*-positive HCC cells may have therapeutic benefit, with little impact on healthy or *TIAM1* negative cells.

PO-574

Pre-transplant AFP >25.5 is associated with a higher risk of HCC recurrence after liver transplantation for patients meeting Milano criteria

Bianca Magro¹, Domenico Pinelli², Massimo De Giorgio¹, Maria Grazia Lucà¹, Arianna Ghirardi³, Giuseppe Baronio², Luca Del Prete², Andrea Gianatti⁴, Michele Colledan², Stefano Fagioli¹. ¹Bergamo, Gastroenterology, Hepatology and Liver Transplantation, Department of Medicine-Papa Giovanni, XXIII Hospital, Bergamo, Italy, Bergamo, Italy; ²Unit of Hepato-biliary Surgery and Liver Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy; ³FROM Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy; ⁴Pathology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy. Email: bianca_magro@hotmail.it

Background and aims: Hepatocellular carcinoma (HCC) recurrence rates after liver transplantation (LT) range between 8 and 20%. Elevated alpha-fetoprotein (AFP) levels at transplant can predict post-transplant HCC recurrence, however a clear cut-off value is needed in order to identify patients at higher risk, aiming at improving surveillance program after LT. We retrospectively analyzed a cohort of patients meeting Milano criteria (MC) underwent LT to evaluate rate of HCC recurrence and possible predictors.

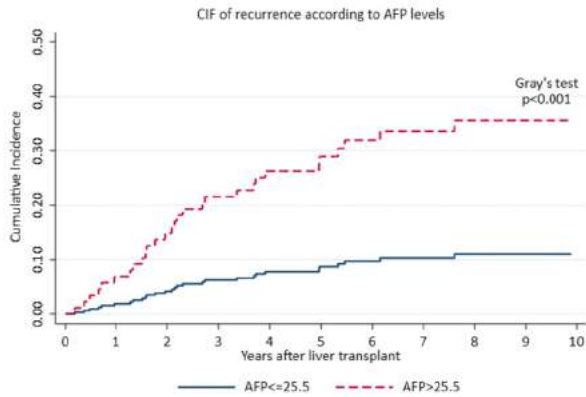
Method: We retrospectively analysed 236 consecutive patients waitlisted for HCC, all meeting Milan criteria, from January 2001 to December 2017 at our liver transplant centre. Twenty-nine patients dropped out while waitlisted, and 207 patients were included in the final analysis. All survival analyses included the competing-risk model.

Results: Mean age was 56.8 ± 6.8 years. Fourteen percent were female (n = 29/207). Median MELD at LT was 12 (9–16). Median time on waitlist was 92 (41–170) days.

HCC recurrence rate was 16, 4% (n = 34/208). Mean time to recurrence was 3.3 ± 2.8 years. Median AFP levels at transplant were higher in patients with HCC recurrence ($p<0.001$). At multivariate analysis AFP value at transplant greater than 25.5 ng/ml (AUC 0.69) was a strong predictor of HCC recurrence after LT [sHR 3.3 (1.6–6.81); $p=0.001$]. HCC cumulative incidence function (CIF) of recurrence at 10 years from LT was significantly higher in patient with AFP >25.5 ng/ml [34.3% vs. 11.5% ($p=0.001$)]. Moreover, an increase in AFP >20.8%, is significantly associated with HCC recurrence ($p=0.034$).

POSTER PRESENTATIONS

Figure 1. 10-year Cumulative Incidence Function (CIF) of recurrence according to AFP level



*death was considered as competing event

Figure:

Conclusion: In conclusion, in our retrospective study, AFP level at transplant >25.5 ng/ml and its increase (greater than 20.8% on waitlist) are strong predictors of HCC recurrence after LT in a cohort of patients waitlisted within Milan criteria. However further studies are needed to validate these data.

PO-591

Higher number of transarterial treatments might have detrimental effects on the overall survival of patients eventually receiving systemic treatments

Vito Sansone^{1,2}, Francesco Tovoli^{1,2}, Andrea Casadei Gardini^{3,4,5,6}, Giovan Giuseppe Di Costanzo⁷, Giulia Magini⁸, Rodolfo Sacco^{9,10}, Tiziana Pressiani¹¹, Franco Trevisani^{1,12}, Margherita Rimini¹³, Raffaella Tortora⁷, Luca Ielasi^{1,2}, Sara Marinelli^{1,2}, Fabio Piscaglia^{1,2}, Alessandro Granito^{1,2}. ¹Division of Internal Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italia; ²Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italia; ³Department of Medical Oncology, Università Vita-Salute, San Raffaele Hospital IRCCS, Milan, Italy; ⁴Dipartimento di Oncologia, IRCCS Ospedale San Raffaele, Milan, Italy; ⁵School of Medicine, Vita-Salute San Raffaele University, Milan, Italy; ⁶Unit of Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁷Liver Unit, Department of Transplantation, Cardarelli Hospital, Naples, Italy; ⁸Department of Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, Bergamo, Italy;

⁹Gastroenterology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; ¹⁰Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy; ¹¹Medical Oncology and Hematology Unit, Humanitas Clinical and Research Center, Rozzano (Milan), Italy; ¹²Semeiotica Medica, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italia; ¹³Division of Oncology, Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy
Email: vito.sansone@studio.unibo.it

Background and aims: Transarterial chemoembolisation (TACE) is commonly used for the treatment of intermediate-stage hepatocellular carcinoma (HCC). While effective in controlling HCC, TACE can negatively impact on liver function. In the age of sequential systemic treatments for HCC, this detrimental effect could theoretically lead to an impaired overall survival in patients who become unresponsive or unsuitable for further locoregional treatments. We investigated the prognostic role of the number of previously received TACE in patients who received sorafenib as a frontline systemic treatment.

Method: We analyzed a large retrospective-prospective database gathering the clinical data of 668 patients from 7 Italian centres, who were prescribed with sorafenib between 2008 and 2017. We explored the prognostic role of previously received TACE (dichotomised as 0-1 vs >1 treatment) in the overall population and in the subgroup of sorafenib-responders (i.e., patients achieving a disease control at the first imaging follow-up).

Results: A total of 451 (67.5%) patients had received less than 2 TACE (no TACE = 322, 1 TACE = 129), while 217 (32.5%) received 2 TACE (n = 102) or more (n = 115). In the whole study population, the number of TACE was not related to the OS (which was instead predicted by ECOG-PS, AFP > 400 ng/ml, macrovascular invasion, extrahepatic spread, and dermatological adverse events). Instead, a higher number of TACE was independently associated with an impaired survival [15.6 vs 19.3 months, HR 1.46 (95% CI 1.04-2.06), p = 0.028] amongst the 282 sorafenib-responders patients (42.2% of the whole population).

Conclusion: The effects of the number of previous TACE are negligible in the whole population receiving sorafenib, where the OS largely depends on the response to the treatment (and therefore any potential prognostic correlate is masked by early deaths due to tumour progression). However, the negative prognostic effects of repeated TACE are evident in the subgroup of responders, which are more likely to have a prolonged survival. The identification of the correct timing to switch from transarterial to systemic treatments becomes of pivotal importance in a setting of sequential systemic treatments.

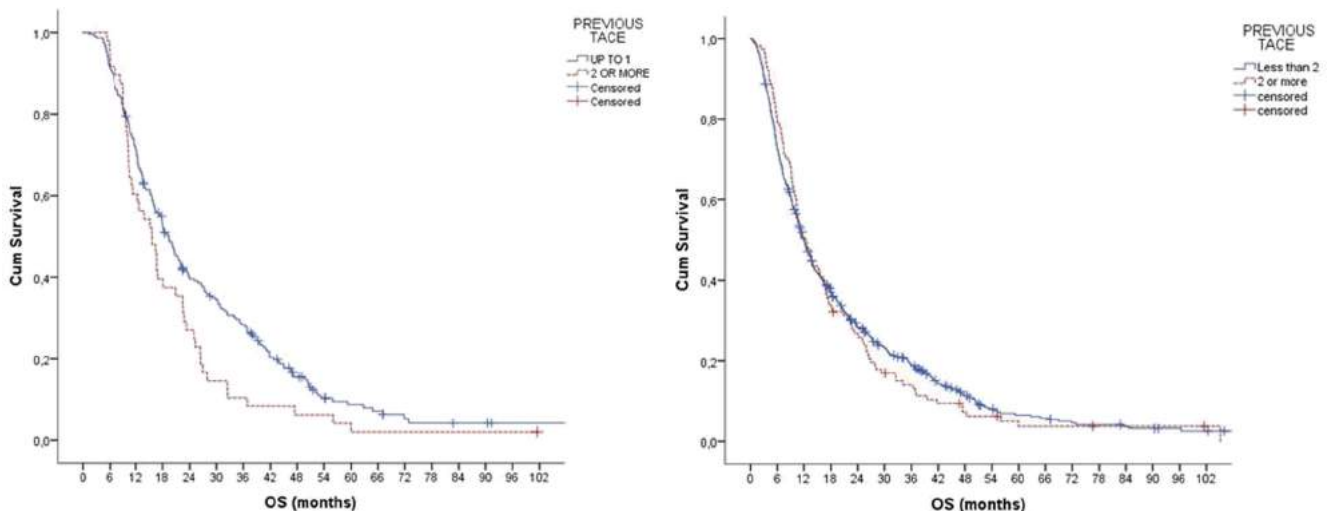


Figure: (abstract: PO-591)

PO-767

comparison of hbv-related hcc incidence between entecavir and tenofovir treated cohorts: a population-based study

Sichan He¹, Maryam Alavi¹, Behzad Hajarizadeh¹, Jason Grebely¹, Matthew Law¹, Janaki Amin^{1,2}, Jacob George³, Mark Danta^{4,5}, Gregory Dore^{1,5}. ¹The Kirby Institute, UNSW Sydney; ²Macquarie University, Sydney, Department of Health Systems and Populations; ³Westmead Institute for Medical Research, University of Sydney and Westmead Hospital, Storr Liver Centre; ⁴St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney; ⁵St Vincent's Hospital, Sydney Email: she@kirby.unsw.edu.au

Background and aims: Chronic hepatitis B (CHB) infection is the leading cause of hepatocellular carcinoma (HCC) globally. Current HBV practice guidelines recommends entecavir (ETV) or tenofovir disoproxil fumarate (or tenofovir, TDF) as the first-line antiviral treatment. There has been controversy regarding a differential impact of ETV and TDF in mitigating HBV-related HCC.

Method: HBV notifications (1993–2017) were linked to hospitalisations, cancer registry, Pharmaceutical Benefits Scheme (PBS), and mortality databases in New South Wales, Australia to evaluate the HBV cohort characteristics and HCC incidence among ETV and TDF treated subpopulations (2010–2018).

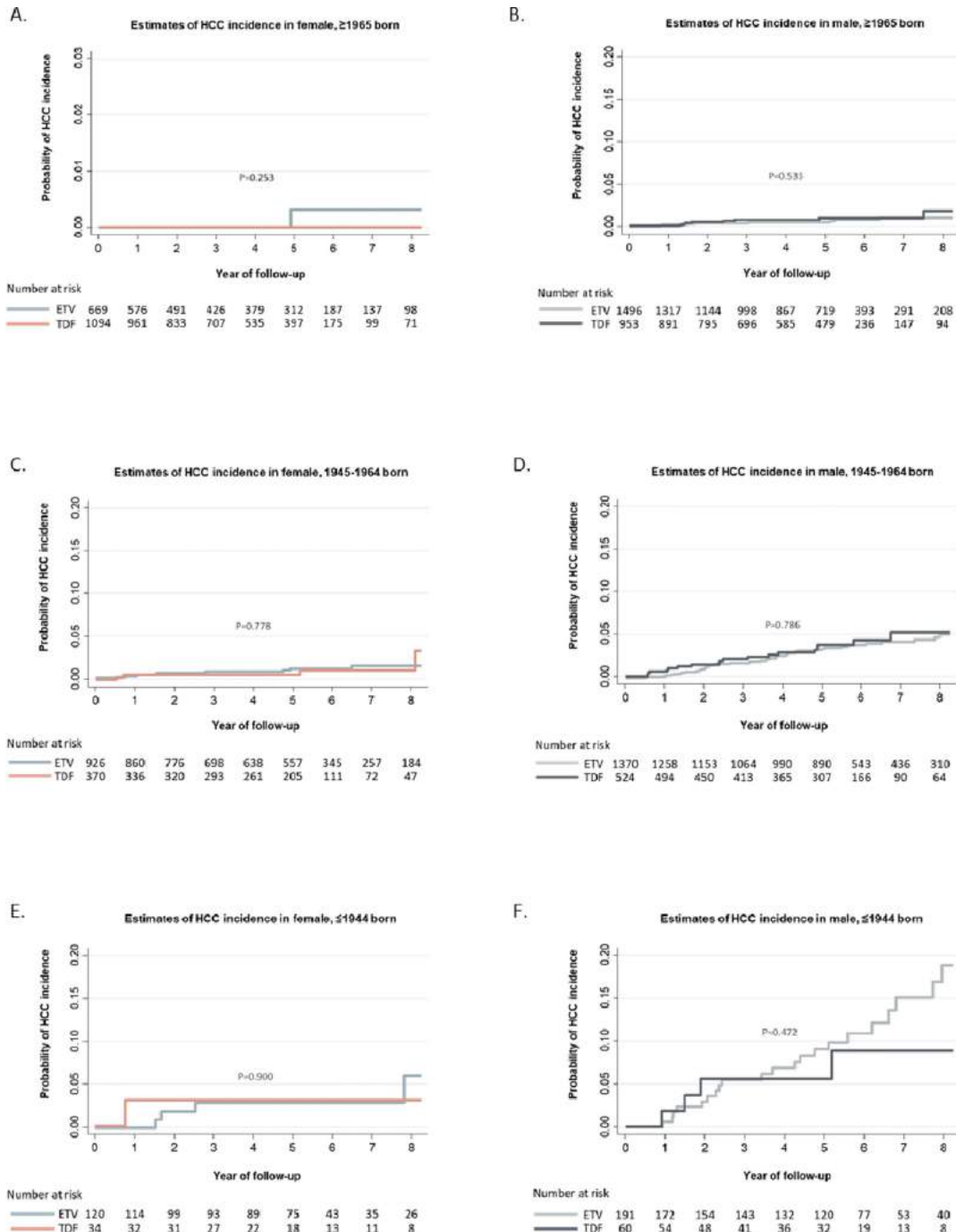


Figure: (abstract: PO-767): Comparison of cumulative HCC incidence between patients who received Entecavir and Tenofovir treatment, by gender and birth cohort

POSTER PRESENTATIONS

Results: In 53,350 people with an HBV notification, 4,785 individuals received ETV, and 3,055 received TDF. HCC occurred in 89 individuals in the ETV group (incidence: 3.87/1000 person-years, 95% CI: 3.14–4.77) and 35 individuals in the TDF group (incidence: 2.58/1000 person-years, 95% CI: 1.85–3.60). In adjusted Cox regression analysis, no significant difference was found in HCC risk between ETV and TDF groups (adjusted HR [aHR] = 1.01, 95% CI 0.67–1.53, $P < 0.958$), while older age (born 1945–1964 vs. ≥ 1965 , aHR = 3.85, 2.20–6.72, $P < 0.001$; and born ≤ 1944 vs. ≥ 1965 , aHR = 10.05, 5.30–19.07, $P < 0.001$), male gender (aHR = 3.61, 2.15–6.08, $P < 0.001$) and decompensated cirrhosis (aHR = 6.59, 3.79–11.45, $P < 0.001$) were associated with greater risk of HCC. In stratified analyses, no significant difference was observed in cumulative HCC incidence between ETV group and TDF group across different genders and age groups (Figure).

Conclusion: There was no differential effect on HCC risk between ETV and TDF in this population-based study. Older age, male, and decompensated cirrhosis were associated with higher risk of HCC.

PO-857

Kinetics of the neutrophil-lymphocyte ratio during PD-1 inhibition as a prognostic factor in advanced hepatocellular carcinoma

Won-Mook Choi¹, Ji Yoon Kim¹, Kang Mo Kim¹. ¹University of Ulsan College of Medicine, Rep. of South Korea
Email: kimkm70@amc.seoul.kr

Background and aims: Programmed death-1 (PD-1) inhibitors such as nivolumab have improved survival outcomes and produced durable responses in advanced hepatocellular carcinoma (HCC). However, predictive biomarkers to identify suitable patients for these treatments are still lacking. Here, we evaluated the relationship between the baseline and kinetics of the neutrophil-lymphocyte ratio (NLR) and clinical outcomes in nivolumab-treated HCC patients.

Method: All consecutive HCC patients treated with nivolumab between July 2017 and June 2020 were screened for the eligibility. The NLRs were calculated before and at 2, 4, and 6 weeks after treatment. Survival outcomes were compared based on the baseline and kinetics of NLR. We additionally analyzed the association

between the baseline and dynamic changes in the NLR with hyperprogression (HPD).

Results: Among the 194 included cases, most patients were male (82.0%) and had a Child-Pugh class A disease (70.6%). Patients with a baseline NLR ≥ 3 (hazard ratio [HR] 2.46; 95% CI 1.63–3.71) had a poorer overall survival compared to patients with baseline NLR < 3 . During the treatment, the NLR increased rapidly in the patients developing HPD and only a Δ NLR at 4 weeks was predictive of HPD. Indeed, the risk of HPD increased by 20% for every 20% increase in the Δ NLR at 4 weeks, and a Δ NLR $> 75\%$ at this timepoint had an 86.1% accuracy for predicting HPD. Accordingly, an NLR increase at 4 weeks (HR 1.79; 95% CI 1.19–2.68) was associated with an increased risk of death, especially among patients with a baseline NLR ≥ 3 .

Conclusion: The baseline and on-treatment kinetics for the NLR are effective prognostic indicators in nivolumab-treated patients with HCC. This may help to guide patient selection and on-treatment strategies for immunotherapies in advanced HCC.

PO-1010

Evaluation of cardiovascular events in patients with hepatocellular carcinoma treated with sorafenib in the clinical practice: CARDIO-SOR study.

Lorena Carballo Folgoso¹, Miriam Celada Sendino¹, Pablo Florez Díez¹, Andrés Castano-García¹, Javier Cuevas Pérez², Rut Álvarez-Velasco², Rebeca Lorca^{2,3}, Carmen Álvarez-Navascués¹, Valle Cadahía-Rodrigo¹, María Luisa Gonzalez Dieguez¹, Manuel Rodríguez^{1,3,4}, María Varela^{1,3,4,5}. ¹Hospital Universitario Central de Asturias, Liver Unit, Oviedo, Spain; ²Hospital Universitario Central de Asturias, Department of Cardiology, Oviedo, Spain; ³ISPA, OVIEDO, Spain; ⁴Universidad de Oviedo, Medicine, Oviedo, Spain; ⁵IUOPA, Oviedo, Spain
Email: lorenacarballo93@gmail.com

Background and aims: The effectiveness of systemic treatment in hepatocellular carcinoma (HCC) depends on the selection of suitable patients, carefully management of cirrhosis complications and expertise to treat adverse events. The aim of this study is to assess the cardiovascular (CV) events in a cohort of HCC patients treated with sorafenib (SOR).

Figure. The NLR kinetics at week 4 are predictive of survival outcomes in advanced HCC patients receiving nivolumab (n = 194). Kaplan-Meier survival plots for OS are shown according to the NLR kinetics at week 4 in (a) patients with a baseline NLR < 3 and (b) patients with baseline NLR ≥ 3 .

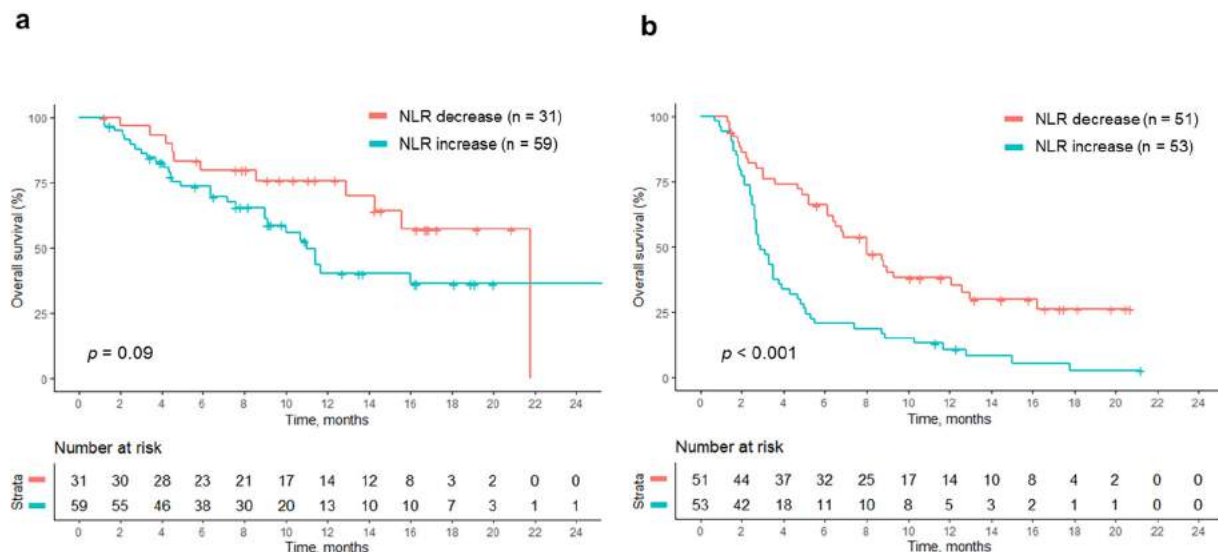
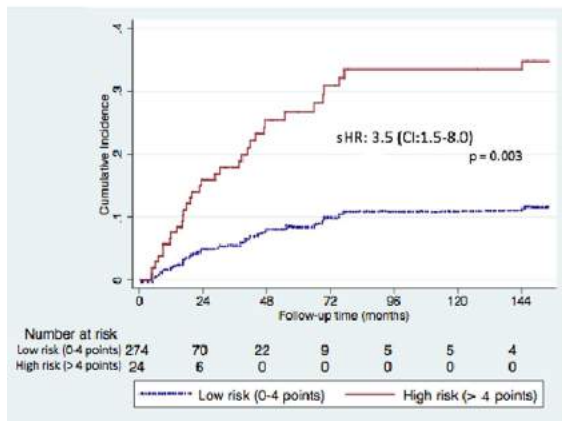


Figure: (abstract: PO-857)

1A. Competing-risks regression to predict major cardiovascular events by CARDIOSOR scale



1B. Kaplan Meier graph estimation to predict major cardiovascular events by CARDIOSOR scale

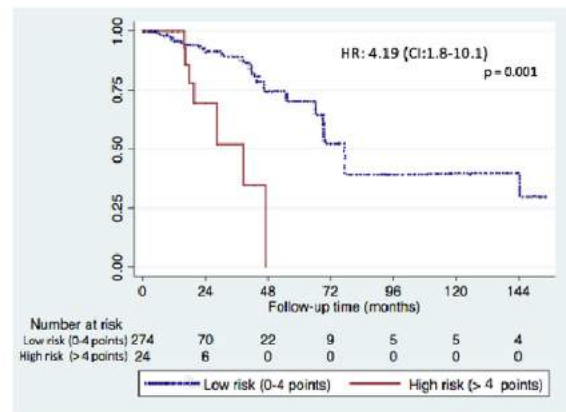


Figure: (abstract: PO-1010)

Method: Observational retrospective study including all HCC patients treated with SOR from 2007 to 2019 in a western tertiary hospital, except those included in clinical trials or treated after liver transplantation. In order to classify CV risk pre-sorafenib, we designed the CARDIOSOR scale with baseline age plus hypertension, diabetes, dyslipidaemia, smoking, chronic kidney disease and prior CV history, giving each one a point. Blood pressure measurement, EKG, adverse events, dosing and outcome data were collected during a standardized follow-up.

Results: 299 HCC patients, median age 66 years, Child A 85%, BCLC-C 73%, ECOG-PS 0 67%, cirrhosis 90% (mostly alcohol, 43%), diabetes 32%, hypertension 42%, dyslipidaemia 25%, obese 28%, smokers 53%. Median overall survival was 11.1 months (IQR 5.6–20.5); ECOG-PS 0 vs PS 1–2 (16.0 vs 5.3, $p < 0.001$). Median treatment duration was 7.4 months (IQR 3.3–14.7). Over the 13.6 months' median follow-up (IQR 5.9–24.2), 33 patients (11%) had a major CV event: heart failure ($n = 11$), acute coronary syndrome ($n = 11$), cerebrovascular accident ($n = 12$) and peripheral vascular ischemia ($n = 8$), with median time from SOR-start 12.7 months (IQR 4.5–28.0). Ninety-nine of all patients (33%) had a minor CV event: increase arterial hypertension ($n = 81$), long QT ($n = 20$) and new atrial fibrillation ($n = 11$). Multivariate cox regression analysis found age as the only independent factor associated to CV event (HR 1.07; 95% CI 1.03–1.12; $p = 0.002$). The CARDIOSOR scale allowed us to identify the group of patients (>4 points) with higher cardiovascular risk compared to those with 0–4 points (sHR 3.5; 95% CI 1.5–8; $p = 0.003$). The main reason for SOR cessation was CV event in 19 patients (6.3%). Only 2 died due to CV event: 1 acute coronary syndrome; 1 cerebrovascular accident.

Conclusion: The incidence of CV events in HCC patients treated with SOR in clinical practice is high, appears late, and independently associated with age. To manage these patients with high risk of CV toxicity, clinical tools like CARDIOSOR scale could be helpful. The awareness of CV risk may allow a successful sequential therapy for tumor progression.

PO-1046

Serum levels of CXCL13 are an independent predictor of survival following resection of biliary tract cancer

Sven H. Loosen¹, Tom Florian Ulmer², Christoph Roderburg¹, Ulf Neumann², Tom Luedde¹. ¹University Hospital Duesseldorf, Clinic for Gastroenterology, Hepatology and Infectious Diseases, Duesseldorf, Germany; ²University Hospital RWTH Aachen, Department of General, Visceral and Transplant Surgery, Aachen, Germany
Email: Sven.Loosen@med.uni-duesseldorf.de

Background and aims: The prognosis of biliary tract cancer (BTC) has remained poor. Although tumor resection represents a potentially curative therapy for selected patients, disease recurrence is common and 5-year survival rates remain below 50%. As stratification algorithms comprising parameters of the individual tumor biology are missing, the identification of the ideal patients for extensive liver surgery is often challenging. The CXC chemokine family exerts decisive functions in cell-cell interactions and has only recently been associated with cancer. However, only very little is known on their role in BTC. Here, we aim at evaluating a potential role of circulating CXCL1, CXCL10 and CXCL13 in patients with resectable BTC.

Method: Serum levels of CXCL1, CXCL10 and CXCL13 were measured by multiplex immunoassay in a cohort of 119 BTC undergoing tumor resection as well as 50 healthy control samples.

Results: Circulating levels CXCL1, CXCL10 and CXCL13 were all significantly elevated in BTC patients compared to healthy controls and increased the diagnostic power of established tumor markers when used in combination. Importantly, elevated levels of CXCL13 both before and after tumor resection identified a subgroup of patients with a significantly impaired outcome following tumor resection. As such, BTC patients with initial CXCL13 levels above the ideal prognostic cut-off value (25.01 pg/ml) had a median OS of 290 days compared to 969 days for patients with low initial CXCL13 levels. The prognostic value of circulating CXCL13 was further confirmed by uni- and multivariate Cox-regression analyses. Finally, the individual kinetic of CXCL13 before and after tumor resection was also indicative for patients' outcome.

Conclusion: Our data suggest a fundamental role of the CXC chemokine family in BTC and identified circulating levels of CXCL13 as a previously unrecognized parameter for the prediction of outcome following resection of BTC.

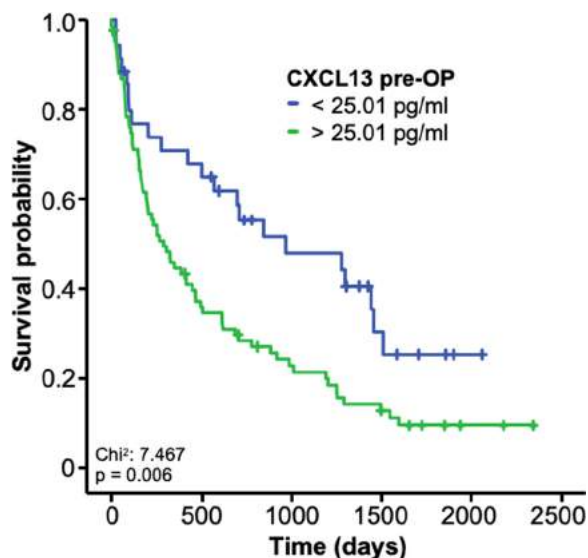


Figure 1. At the optimal cut-off values, preoperative CXCL13 identify BTC patients with a significantly impaired postoperative overall survival.

PO-1124

Hepatocellular carcinoma recurrence after direct-acting antiviral therapy for hepatitis C virus. A systematic review and meta-analysis.

Leonardo Frazzoni^{1,2}, Usama Sikandar¹, Flavio Metelli¹, Sinan Sadalla¹, Giuseppe Mazzella¹, Franco Bazzoli^{1,2}, Lorenzo Fuccio^{1,2}, Francesco Azzaroli^{1,2}. ¹University of Bologna, Department of Medical and Surgical Sciences, Italy; ²IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
Email: leonardo.frazzoni@gmail.com

Background and aims: The risk of hepatocellular carcinoma (HCC) recurrence after direct-acting antivirals (DAA) therapy has not been fully elucidated yet. Aim was to assess the risk of HCC recurrence after DAA therapy for HCV, also in comparison with IFN treatment and no intervention.

Method: Systematic review across PubMed, Scopus and Scholar up to November 2020, including full-text studies which assessed the pattern of HCC recurrence after DAA therapy for HCV. Random-effect meta-analysis and univariable meta-regression was applied to obtain pooled estimates for proportions, relative risk (RR) and influential variables on the outcome, respectively.

Results: Thirty-one studies with 2, 957 patients were included. Overall, 30% (CI 26–34%) of patients with a history of HCC experienced HCC recurrence after DAA therapy, at a mean time interval ranging from 4 to 21 months. This result was increasing ranging from European studies (23%, CI 17–28%) to US studies (34%, CI 30–38%) to Egypt studies (37%, CI 27–47%) to Asian studies (33%, CI 27–40%). Sixty-eight percent (CI 45–91%) of recurrent HCCs developed within 6 months of follow-up since DAA treatment, among 8 studies providing stratified data. Among studies providing head-to-head comparisons, the HCC recurrence risk was significantly lower after DAA therapy than IFN (RR 0.64, CI 0.51–0.81) and after DAA therapy than no intervention (RR 0.68, CI 0.49–0.94).

Conclusion: The recurrence of HCC after DAA is not negligible, being higher soon after the end of treatment and among non-European countries. DAA therapy significantly reduces the risk of HCC recurrence as compared to IFN regimen and no intervention.

PO-1142

Duration of response and outcomes in advanced hepatocellular carcinoma patients with objective response to sorafenib: role of subsequent treatment.

Kuo-Wei Huang^{1,2}, Pei-Chang Lee^{1,3}, Yi-Tzen Chen⁴, Yee Chao⁵, Chien-Wei Su^{1,3}, Ming-Chih Hou^{1,3}, Yi-Hsiang Huang^{1,3}. ¹Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei City, Taiwan; ²Taipei City Hospital Yangming Branch, Department of Medicine, Taipei City, Taiwan; ³National Yang-Ming University, Faculty of Medicine, Taipei City, Taiwan; ⁴Taipei Veterans General Hospital, Department of nursing, Taipei City, Taiwan; ⁵Taipei Veterans General Hospital, Department of oncology, Taipei City, Taiwan
Email: yhhuang@vghtpe.gov.tw

Background and aims: Sorafenib is the standard of care for advanced hepatocellular carcinoma (HCC) since 2008, but the objective response rates were only 2% to 10% in previous clinical trials and real-world data. Little is known for the duration of response and long-term outcome in HCC patients with objective response to sorafenib. There are emerging second-line therapies for patients who failed for sorafenib in recent years. In this study, we aimed to delineate the duration of response and the role of subsequent treatment after responding to sorafenib.

Method: From August 2012 to December 2019, 992 patients received sorafenib treatment for advanced HCC in Taipei Veterans General Hospital were retrospectively reviewed. Of them, 21 (2.1%) achieved complete responses (CR) and 55 (5.5%) had partial responses (PR) based on mRECIST criteria. The impacts of sequential therapy after sorafenib on overall outcomes were analyzed.

Results: The median duration of response was 17.3 months (range 2.3–44.5 months) for patients achieving CR, and 10.0 months (range 1.9–71.3 months) in PR patients. The median overall survival (mOS) was 44.9 months (95% confidence interval [CI]: 32.8–57.0 months) for the 76 patients, including not reached for CR, and 26.6 months (95% CI: 20.6–32.6 months) in PR patients. Patients experienced treatment-related adverse events (TRAE) had better mOS than those without (47.8 vs 19.2 months, p=0.044). Afterward, 65 patients (85.5%) discontinued sorafenib due to progressive disease or adverse events. Of them, 28 patients received subsequent systemic treatment, including nivolumab (n = 8), regorafenib (n = 12), and chemotherapy (n = 8). Patients with subsequent systemic therapy had a longer post-sorafenib survival (PSS) than those with best supportive care (BSC) only (median PSS: 29.5 vs. 11.5 months, p=0.029). Sorafenib-nivolumab sequential therapy had the longest mOS than sorafenib-regorafenib, sorafenib-chemotherapy, or sorafenib-BSC in these patients (55.8, 36.3, 25.5 and 27.4 months, respectively; p=0.020, 0.048, and 0.044 for sorafenib-nivolumab vs. sorafenib-regorafenib, sorafenib-chemotherapy, and sorafenib-BSC).

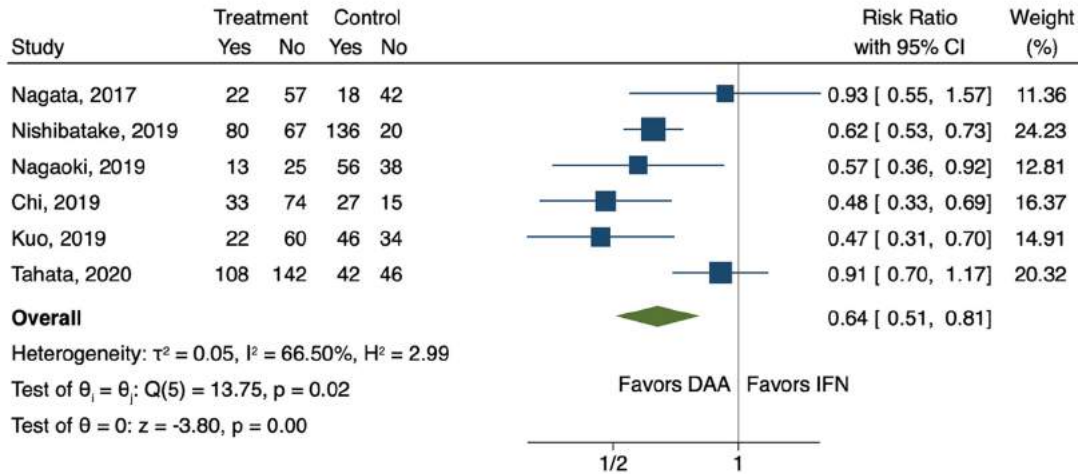
Conclusion: For advanced HCC patients with response to sorafenib, the duration of response can last for one year, and subsequent immunotherapy provided the best survival.

PO-1209

Multibipolar radiofrequency ablation versus liver resection for the treatment of hepatocellular carcinoma within Milan criteria developed on advanced fibrosis/cirrhosis: a multicentric study on 1060 patients

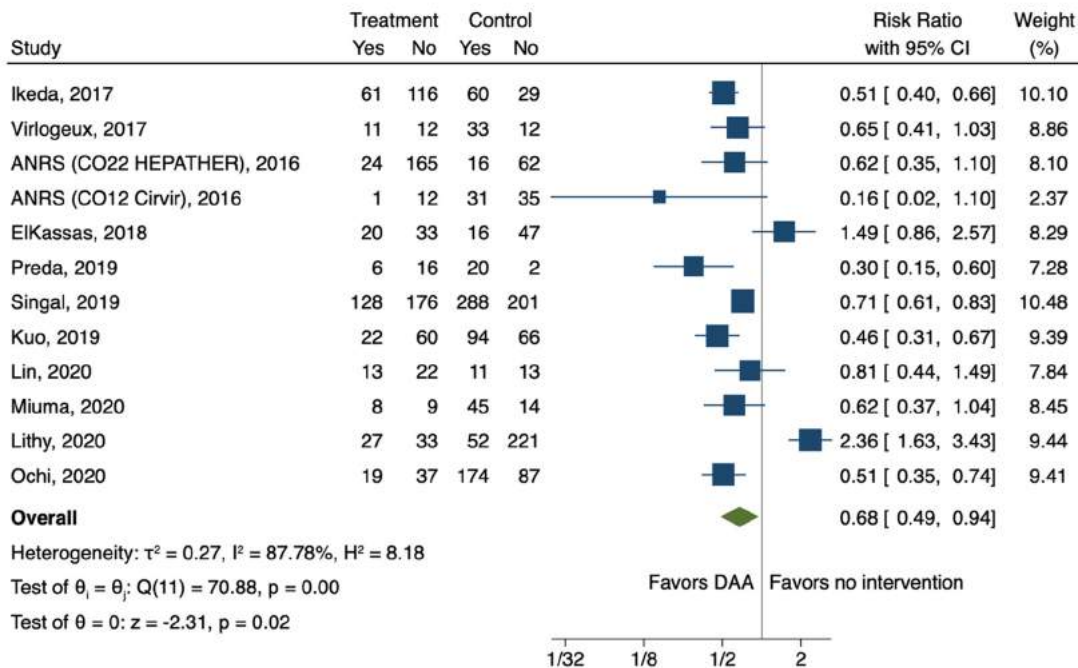
Francois Cauchy^{1,2}, Agnès Rode³, Alexis Laurent⁴, Louise Barbier⁵, Olivier Scatton⁶, Hervé Trillaud⁷, Christophe Aubé⁸, Lilian Schwarz⁹, Alain Luciani¹⁰, Suzanne Gay⁹, Anne-Frederique Manichon³, Ephrem Salamé⁵, Chetana Lim⁶, Nathalie Ganne¹¹, Lorraine Blaise¹¹, Olivier Soubrane¹², Olivier Seror¹³, Eric Vicaut¹⁴, Jean Charles Nault¹¹. ¹APHP, Hepatobiliary Department; ²Beaujon Hospital; ³Radiology Department, Hopitaux Civil de Lyon; ⁴APHP, Hepatobiliary Department, CHU Mondor; ⁵Hepatobiliary Surgery Department, Chu Tours; ⁶Hepatobiliary Surgery Department, CHU Pitié salpêtrière, APHP;

A) HCC recurrence after DAA vs. IFN



Random-effects REML model

B) HCC recurrence after DAA vs. no intervention



Random-effects REML model

Figure: (abstract: PO-1124): Relative risk of developing recurrent hepatocellular carcinoma according to strategy. (A) Direct-acting antivirals vs. interferon; (B) Direct-acting antivirals vs. no intervention.

⁷Radiology Department, CHU Bordeaux; ⁸Radiology Department, CHU Tours; ⁹Hepatobiliary Surgery Department, CHU de Rouen; ¹⁰Radiology Department, CHU Mondor, APHP; ¹¹Liver Unit, CHU Avicenne, APHP, Centre de Recherche Des Cordeliers; ¹²APHP, Hepatobiliary department, CHU Beaujon; ¹³Department of Radiology, CHU Avicenne, APHP; ¹⁴Unité de Recherche Clinique, Hôpital Lariboisière, APHP
 Email: naultjc@gmail.com

Background and aims: Multibipolar radiofrequency ablation (RFA) increase the ability to ablate hepatocellular carcinoma (HCC) up to 5 cm. We aim to compare multibipolar RFA to liver resection (LR) in patients with HCC within Milan criteria developed on advanced

fibrosis or cirrhosis in order to identify the best candidate for each treatment.

Method: We included retrospectively patients treated either by multibipolar percutaneous RFA or LR for a first diagnosis of HCC within Milan criteria developed on advanced fibrosis (F3) or cirrhosis (F4) in 9 centers between 2008 and 2018. Overall survival (OS), overall tumor recurrence and adverse events were compared according to the type of treatments (RFA, laparoscopic or open LR) using a propensity score (double robust method).

Results: 1060 patients were included (median age 64 years old, 82.7% of men) with 620 (58.5%) treated by RFA and 440 (41, 5%) by LR (laparoscopic n = 271; open n = 169). HCC was uninodular in 83.8% of

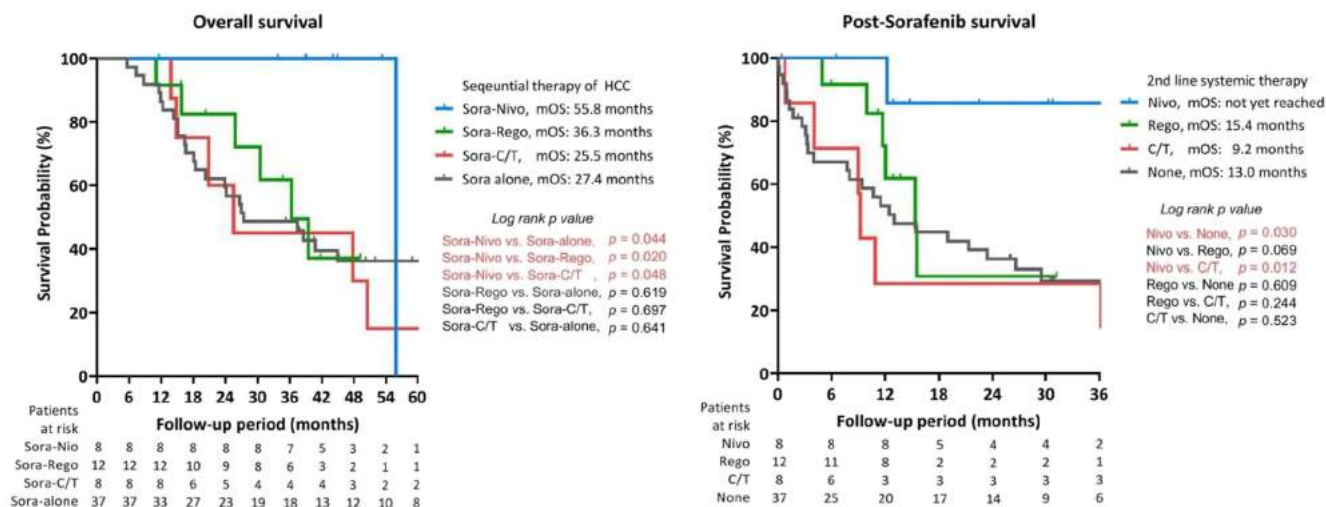


Figure: (abstract: PO-1142):

the cases, of less than 3 cm in 40% of the case and developed on cirrhosis in 89% of the cases. Before adjustment, patients treated by RFA were significantly older with more liver failure and portal hypertension and have more multinodular tumors of smaller size compared to patients treated by LR. After adjustment, OS was not different between RFA and LR (OR: 1, 05; CI95%: 0, 98-1, 13; $p = 0, 173$) whereas overall recurrence was higher after RFA (OR: 1, 13; CI95%: 1, 03-1, 23, $p = 0, 007$). Morbidity (OR: 0.86; CI95%: 0, 80-0, 93; $p < 0, 001$) and treatment-related mortality (OR: 0.96; CI95%: 0, 93-0, 99; $p = 0, 031$) were lower after RFA. For unique HCC, OS was identical between treatments ($p = 0, 0539$) with more overall recurrence after RFA ($p = 0, 0014$). In patients with a least one HCC > 3 cm OS was lower after RFA ($p = 0, 003$) with more tumor recurrence ($p = 0, 034$). For multinodular HCC, OS ($p = 0, 401$) and overall recurrence ($p = 0.359$) was similar between RFA and LR with less morbidity after RFA ($p < 0, 001$). Laparoscopic LR was associated with a longer OS ($p = 0, 021$) and less overall recurrence ($p = 0.0003$). In contrast, OS ($p = 0, 172$) and overall recurrence ($p = 0.118$) were identical between RFA and open LR with less morbidity after RFA ($p = 0, 016$).

Conclusion: Multipolar RFA and LR are two efficient treatments of early HCC developed on advanced fibrosis/cirrhosis. The treatment could be tailored according tumor size, tumor number, presence of portal hypertension/liver failure and the ability to perform laparoscopic resection.

PO-1263

Impact of metabolic syndrome and non-alcoholic fatty liver disease in outcomes and tolerance after percutaneous multipolar radiofrequency ablation for early hepatocellular carcinoma

Thi Thu Nga Nguyen¹, Agnès Rode², Hervé Trillaud³, Christophe Aubé⁴, Anne-Frederique Manichon², Anita Paisant⁴, Thong Dao¹, Pierre Nahon⁵, Nathalie Ganne-Carrié⁵, Lorraine Blaize⁵, Francois Cauchy⁶, Olivier Sutter⁷, Olivier Seror⁷, Jean Charles Nalet⁵.

¹Caen University Hospital, Hepatogastroenterology, Caen, France; ²Hospices Civils de Lyon, Radiology, Lyon, France; ³Bordeaux University Hospital, Radiology, Bordeaux; ⁴Angers University Hospital, Radiology, Angers, France; ⁵Avicenne Hospital, APHP, Hepatology, Bobigny, France; ⁶Beaujon Hospital, APHP, Hepatobiliary and Digestive Surgery, Clichy, France; ⁷Avicenne Hospital, APHP, Interventional Radiology Unit, Bobigny, France
Email: nguyen.nga@live.com

Background and aims: Long-term outcomes after percutaneous radiofrequency ablation (RFA) in patients with non-alcoholic fatty

liver disease (NAFLD) have been poorly studied. We aim to describe the outcomes after multipolar RFA in these patients and the prognostic impact of metabolic syndrome among other etiologies.

Method: Patients who underwent multipolar RFA as first treatment for HCC within Milan criteria in 4 tertiary centers (2008–2018) were enrolled in a retrospective study. Patients with pure NAFLD-HCC were compared to those with alcoholic liver disease (ALD), hepatitis B (HBV) and hepatitis C virus (HCV). The association between pure NAFLD or between metabolic syndrome in other etiologies and adverse events and survival were assessed using Kaplan-Meier method, the log-rank test and uni/multivariate analysis using the Cox model.

Results: 520 patients were enrolled including 82% of male with a median age of 66 years. 494 patients (95%) had cirrhosis, 81% had a unique nodule with a median size of 25 mm. 75% of patients had at least one component of metabolic syndrome including obesity in 155 patients. Sixty-two patients (12.6%) had pure NAFLD, 225 (45.5%) had ALD, 36 (7.3%) had HBV and 171 (34.6%) had HCV. Patients with pure NAFLD were significantly older (median age 72.6 years, $p < 0.0001$), more often obese (median BMI 30.3 kg/m², $p < 0.0001$), have more components of metabolic syndrome, had more ischemic heart disease (17.7%, $p = 0.017$) and more esophageal varices (39, 3%, $p = 0.004$) than patients with other etiologies. In the whole series, median overall survival (OS) was 66.5 months with a 1-, 3- and 5-years OS of 94%, 74% and 56%, respectively. In pure NAFLD patients, median, 1-, 3- and 5-years OS were 79 months, 90%, 71% et 59%, respectively. There were no differences in morbidity, tumor recurrence and overall survival in patients with pure NAFLD versus other etiologies. In patients with HBV, HCV or ALD, there was no prognostic impact of the components of the metabolic syndrome on treatment-related adverse events, the number of sessions to achieve complete ablation and oncological outcomes of RFA for HCC.

Conclusion: Patients with pure NAFLD or with both viral infection or alcoholic liver disease and metabolic syndrome have a prolonged overall survival after multipolar RFA without increased morbidity or tumor recurrence compared to patients without metabolic syndrome suggesting that percutaneous ablation is an efficient treatment in this population.

PO-1312

The impact of betablocker treatment on cancer prognosis in patients with advanced hepatocellular carcinoma receiving sorafenib treatment

Lorenz Balcar^{1,2}, Katharina Pomej^{1,2}, Mattias Mandorfer¹, Tobias Meischl^{1,2}, Christian Müller^{1,2}, Michael Trauner¹, Thomas Reiberger¹, Matthias Pinter^{1,2}, Bernhard Scheiner^{1,2}. ¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Liver Cancer (HCC) Study Group Vienna, Vienna, Austria
Email: bernhard.scheiner@meduniwien.ac.at

Background and aims: Non-selective betablocker (NSBB) treatment is indicated in most patients with cirrhosis. Patients with hepatocellular carcinoma (HCC) may additionally benefit from BB treatment due to various effects on cancer biology as shown for other cancer types. However, most studies evaluated the impact of cardio-selective (CSBB) and NSBBs on HCC development as well as in patients with early-stage HCC. The impact of BB-treatment on cancer prognosis in HCC patients receiving systemic treatment is unclear. We investigated the impact of BB treatment on time-to-progression (TTP), progression-free (PFS) and overall survival (OS) in patients with advanced HCC receiving systemic treatment with sorafenib.

Method: Patients treated with sorafenib between 05/2006 and 03/2020 at the Medical University of Vienna were retrospectively included.

Results: The majority of patients were male (213/250 patients, mean age 66 ± 9 years) and 117 patients received BB treatment (n = 35 CSBB and n = 82 NSBB). Clinically significant portal hypertension (CSPH) was present in more than half of patients (n = 137, 55%) and most patients (58%) had BCLC C.

At sorafenib start, patients receiving BB treatment had a more advanced tumor stage (BCLC D: 25% vs. 10%, P = 0.008), more advanced liver dysfunction (Child-Pugh stage B/C, 66% vs. 45%, P = 0.001), and were more often diagnosed with CSPH (70% vs 41%, P < 0.001) when compared to patients not receiving BB therapy.

TTP (evaluable in 173 patients with at least one follow-up imaging) was significantly shorter in patients with BB treatment at baseline (4.2 [95% CI: 3.0–5.3] vs. 5.9 [95% CI: 4.4–7.3] months, P = 0.021). BB treatment remained an independent risk factor for TTP (HR 1.52 [95% CI: 1.07–2.18], P = 0.021) after multivariable adjustment for Child-Pugh stage, ECOG performance status and extrahepatic metastases. However, this did not translate into a worse median OS (BB vs. no BB, 8.5 [95% CI: 6.6–10.3] months vs. 10.4 [95% CI: 8.3–12.5] months, P = 0.247) or PFS (BB vs. no BB, 3.9 [95% CI: 3.2–4.6] months vs. 4.6 [95% CI: 3.5–5.8] months, P = 0.152).

Conclusion: In contrast to results from other cancer types, we did not find improved outcomes for BB treatment in HCC patients receiving systemic treatment with sorafenib. Instead, concomitant NSBB or CSBB use was independently associated with shorter TTP.

PO-1351

Preliminary experience on safety of cabozantinib in recurrent hepatocellular carcinoma after liver transplantation. A case series

Federica Invernizzi¹, Massimo Iavarone¹, Francesco Tovoli², Irene Bergna¹, Caterina Vivaldi³, Martina Gambato⁴, Federico Pinero⁵, Matthias Pinter⁶, Carolin Czuderna^{7,8}, Fabio Piscaglia^{2,9}, Gianluca Masi³, Marcus Alexander Worns⁷, Pietro Lampertico^{1,10}. ¹Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Department of Gastroenterology and Hepatology, Milan, Italy; ²IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Internal Medicine, Bologna, Italy; ³University of Pisa, Department of Translational Research and New Technologies in Medicine and Surgery, Pisa, Italy; ⁴Padua University Hospital, Multivisceral Transplant Unit and Gastroenterology, Department of Surgery, Padua, Italy; ⁵Hospital Universitario Austral, School of Medicine, Latin American Liver Research Educational and Awareness Network (LALREAN), Argentina; ⁶Medical

University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ⁷University Medical Centre of the Johannes Gutenberg-University, Department of Internal Medicine I, Mainz, Germany; ⁸University Medical Center Schleswig-Holstein-Campus Lubeck, Department of Medicine I, Lubeck, Germany; ⁹University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; ¹⁰University of Milan, CRC “A. M. and A. Migliavacca” Center for Liver Disease, Department of Pathophysiology and Transplantation, Milan, Italy
Email: federica.invernizzi@policlinico.mi.it

Background and aims: Cabozantinib (CABO) is a second/third line treatment option for hepatocellular carcinoma (HCC), improving overall survival (OS) of sorafenib-treated patients who develop progression or are intolerant to. We aimed to evaluate safety and outcomes of CABO as second/third-line treatment for HCC-recurrence after liver transplantation (LT).

Method: This is a retrospective, multicentre, international study including CABO-treated LT-patients, with analysis of baseline characteristics and evolutionary-events during treatment.

Results: Sixteen LT patients were included: 60 years, 12 men, ECOG-performance status (PS) 1 in 8, ECOG-PS 0 in 6 and ECOG-PS 2 in 2; HCC both intra- and extra-hepatic sites in 10 patients, extrahepatic sites in 5 and in one case HCC was limited to the liver. Median time from LT to CABO initiation was 4.2 (1.2–14) years; 10 patients received CABO as second line treatment (after sorafenib discontinuation for tumor progression 9/10), while 6 received CABO as third line (first line sorafenib discontinued for tumor progression, second line regorafenib discontinued for tumor progression in 4 and intolerance in 2). Overall, median time on sorafenib was 8.7 (0.3–76.9) months and 3.4 (0.2–17.6) months on regorafenib. During 3.6 (1.4–14.6) months of CABO treatment, the most common adverse events (AEs) were diarrhoea (n = 11; G2 = 4, G3 = 1), fatigue (n = 9; G2 = 4, G3 = 1) and dermatological reaction (n = 7, G2 = 2). Severe AEs were proteinuria (n = 3, G2 = 1, G3 = 2), hyperthyroidism (G3 = 1), and neutropenia (n = 2, G4 = 1). No liver rejection was observed, and no drug-to-drug interactions with immunosuppressive drugs were reported. Nine patients developed progression, 8 discontinued CABO (for tumor progression in 4) and 4 patients died. The median OS from CABO initiation was 15.6 (95% CI: 10.1–21.0), and 37.6 months (95% CI: 21.6–53.6) from sorafenib initiation for the 10 patients in whom CABO was used as second line drug.

Conclusion: This is the first study showing the safety profile of cabozantinib after LT, thus providing the rationale of considering cabozantinib in the management of patients with HCC-recurrence after LT with progression/intolerance to first/second line treatment.

PO-1420

Molecular markers of response to anti-pd1 therapy in advanced hepatocellular carcinoma

Philipp Haber¹, Miguel Torres-Martín², Carmen Andreu-Oller¹, Marc Puigvehí^{1,3}, Miho Maeda¹, Florian Castet², Pompilia Radu⁴, Jean-François Dufour^{4,5}, Chris Verslype⁶, Carolin Czuderna^{7,8}, Jens U. Marquardt^{7,8}, Peter Galle⁷, Arndt Vogel⁹, Melanie Bathon⁹, Tim Meyer¹⁰, Ismail Labgaa¹¹, Antonia Digkilia¹², Lewis Roberts¹³, Mohamed A. Mohamed Ali¹³, Beatriz Minguez¹⁴, Davide Citterio¹⁵, Vincenzo Mazzaferro¹⁵, Fabian Finkelmeier¹⁶, Jörg Trojan¹⁶, Burcin Oezdirik¹⁷, Tobias Müller¹⁷, Moritz Schmelzle¹⁸, Anthony Bejjani¹⁹, Richard Finn¹⁹, Swan N. Thung²⁰, Augusto Villanueva^{1,21}, Daniela Sia¹, Josep M. Llovet^{1,22}. ¹Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States; ²Translational Research in Hepatic Oncology, Liver Unit, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain; ³Hospital del Mar Medical Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁴University Clinic for Visceral Surgery and Medicine, University of Bern, Inselspital, Bern, Switzerland; ⁵Hepatology,

POSTER PRESENTATIONS

Department of Clinical Research, University of Bern, Bern, Switzerland;

⁶Department of Gastroenterology and Hepatology, KU Leuven, Leuven, Belgium;

⁷Department of Medicine I, University Medical Center of the Johannes-Gutenberg University Mainz, Mainz, Germany;

⁸Department of Medicine I, University of Lübeck, UKSH-Campus Lübeck, Lübeck, Germany;

⁹Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;

¹⁰Department Oncology, University College London Cancer Institute, London, United Kingdom;

¹¹Department of Visceral Surgery, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;

¹²Department of Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;

¹³Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, United States;

¹⁴Liver Unit, Hospital Universitari Vall d'Hebron, Liver Diseases Research Group, Vall d'Hebron Institute of Research (VHIR), Vall d'Hebron Barcelona Hospital Campus, CIBERehd, Universitat Autònoma de Barcelona, Barcelona, Spain;

¹⁵Gastrointestinal Surgery and Liver Transplantation Unit, National Cancer Institute, Milan, Italy;

¹⁶Department of Gastroenterology, University Liver and Cancer Centre, Frankfurt, Germany;

¹⁷Department of Hepatology and Gastroenterology, Campus Virchow Klinikum and Campus Charité Mitte, Charité University Medicine, Berlin, Germany;

¹⁸Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité-, Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany;

¹⁹Division of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, United States;

²⁰Liver Cancer Program, Divisions of Liver Diseases, Pathology Department and RM Transplant Institute, Tisch Cancer Institute, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, United States;

²¹Division of Hematology and Medical Oncology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, United States;

²²Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain

Email: jmllovet@clinic.cat

Background and aims: Anti-PD1 checkpoint inhibitors convey clinical benefits in 20% of patients with advanced hepatocellular carcinoma (aHCC), although markers predicting response are unknown. We develop biomarkers of response/primary resistance to checkpoint inhibitors in aHCC through dissecting molecular traits prior to systemic therapy.

Method: Overall, 111 HCC tissue samples obtained prior any systemic therapy from patients with aHCC treated with single agent nivolumab or pembrolizumab were collected through an international consortium of 13 centers. We performed molecular studies including gene expression microarrays, a CTNNB1 exon 3 mutational analysis and histological evaluation and correlated with clinical outcomes.

Results: Among 83 patients included in the transcriptomic analysis, 28 were treated in first-line (objective response rate [ORR]: 42.9%), whereas 55 patients were treated after tyrosine kinase inhibitors (TKI, sorafenib/lenvatinib) either in 2nd line (41 patients, ORR 29.3%) or 3rd line (14 patients, ORR 7.1%). Responders treated in frontline showed a significant upregulation in Interferon- γ signaling (IFN γ) and MHCII-related antigen presentation ($p < 0.001$ vs non-responders). We generated a 11-gene signature-involving IFN and antigen presentation genes-capable of predicting ORR (AUC 0.93), and progression-free survival (PFS; median 28.8 vs 5.0 months, $p = 0.037$) in aHCC patients that was validated in melanoma and NSCLC patient cohorts. This signature predicted both ORR and PFS in patients with these solid tumors. In HCC, cases with a positive gene signature showed increased M1 macrophages ($p = 0.003$), CD4 memory T cell ($p < 0.001$) and CD4 naïve T cell-infiltration ($p = 0.026$), whereas an increase in T-regs was seen in tumors with low expression of the gene signature ($p = 0.001$). Neither the immune infiltrate nor CTNNB1 exon 3 mutations predicted response or primary resistance. Of note, the same signature was unable to predict response in patients treated after first-line TKIs, suggesting

changes in the microenvironment rendering a previously inflamed phenotype no longer responsive to immunotherapy.

Conclusion: We identified an 11-gene signature of response to anti-PD1 therapy in first line advanced HCC, which was validated in other solid tumors. This signature did not identify responders after TKI treatment, thus calling for the need of biopsies prior to anti-PD1 therapy to enable biomarker-based precision oncology.

PO-1745

Equal overall survival in elderly patients with hepatocellular carcinoma receiving palliative treatment

Thorben Fründt¹, Christian Casar², Johann von Felden¹, Jenny Krause¹, Ines Gil-Ibanez¹, Ulrike Schöler¹, Maximilian Priebe¹, Jenny Kraczik¹, Gerhard Adam³, Ansgar W. Lohse¹, Henning Wege^{1,4}, Kornelius Schulze¹.

¹University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany;

²University Medical Center Hamburg-Eppendorf, Bioinformatics Facility, Hamburg, Germany;

³University Medical Center Hamburg-Eppendorf, Department of Diagnostic and Interventional Radiology and Nuclear Medicine, Hamburg, Germany;

⁴Klinikum Esslingen, Cancer Center Esslingen, Esslingen am Neckar

Email: tfruentd@uke.de

Background and aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer with an increasing incidence worldwide, especially in elderly patients. Diagnosis is often made in an advanced stage, rendering curative treatment impossible. Although therapeutic options for patients in a palliative setting have improved in recent years, treatment of elderly patients is often complicated by challenging comorbidities and frailty. Since data about the outcome and overall survival (OS) in elderly HCC patients receiving palliative therapy is limited, we conducted a retrospective study at a tertiary referral center.

Method: Data from 987 patients with HCC, who were treated at the University Medical Center Hamburg-Eppendorf between January 2007 and October 2017, were analyzed. Tumor stage and liver function were rated according to the Barcelona Clinic Liver Cancer (BCLC) classification and Child-Pugh-Turcotte score (CPS), and therapy related adverse events (AE) were assessed via CTCAE 5.0. Patients were grouped according to their age as young (<60 years; YP), intermediate (60–70 years; IP) or elderly (>70 years; EP). Administration of tyrosine kinase inhibitor (TKI) and transarterial chemoembolization (TACE) was defined as palliative treatment. Patients receiving curative intended treatment (e.g. liver transplantation, resection or microwave ablation following TACE) were excluded from this analysis.

Results: Out of 987 patients, $n = 330$ were considered for curative treatment and excluded, $n = 657$ received palliative treatment; YP $n = 194$; IP $n = 241$; EP $n = 222$. 82.5% ($n = 542$) were male, median age was 67 (range 23–87) years. All patients had underlying liver cirrhosis with a larger proportion of impaired liver function in the YP cohort (CPS A/B/C [%]: YP 53/28/18 vs. IP 61/26/12 vs. EP 66/28/6; $p = 0.01$). Patients performance status according to Eastern Cooperative Oncology Group (ECOG) was comparable between YP, IP, and EP (ECOG 0/1/2/3 [%]: 40/37/16/4 vs. 36/40/14/6 vs. 33/41/17/6; $p = 0.85$). OS in patients receiving TACE, including CPS A and B patients, was 16 vs. 16 vs. 20 months for YP, IP, and EP, respectively; $p = 0.38$. In TKI-treated patients, OS was 13 vs. 15 vs. 13 months; $p = 0.73$. The rate of AE in TKI-patients was comparable with 47 vs. 43 vs. 49%, and the most prevalent AE in all three groups was diarrhea.

Conclusion: In this study, OS was equal in elderly patients with liver cirrhosis receiving palliative treatment for HCC with TACE or TKI. Furthermore, the rate of AE was comparable in younger and elderly patients. Therefore, we propose regular palliative treatment stratification in spite of high age of patients.

PO-1801

Evolutionary learning derived clinical-radiomic models for predicting early recurrence of hepatocellular carcinoma after surgical resection

I-Cheng Lee¹, Jo-Yu Huang², Ting-Chun Chen², Gar-Yang Chau³, Rheun-Chuan Lee³, Shinn-Ying Ho², Yi-Hsiang Huang¹. ¹Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Taipei, Taiwan; ²National Yang Ming Chiao Tung University, Taiwan; ³Taipei Veterans General Hospital, Taipei, Taiwan
Email: iclee@vghtpe.gov.tw

Background and aims: Current prediction models for early recurrence of hepatocellular carcinoma (HCC) after surgical resection remain unsatisfactory. The aim of this study is to develop accurate prediction models with interpretability using both clinical and radiomic features to predict early recurrence of HCC after surgical resection.

Method: 517 consecutive HCC patients receiving resection with contrast-enhanced computed tomography (CECT) images before resection were retrospectively enrolled. Tumor segmentation of all CECT images including non-contrast phase, arterial phase and portal venous phase were manually performed for radiomic feature extraction. A novel evolutionary learning derived method called GARSL (Genetic Algorithm for predicting Recurrence after Surgery of Liver cancer) was proposed to design prediction models for early recurrence of HCC within 2 years after surgery.

Results: A total of 143 features, including 26 pre-operative clinical features, 5 post-operative pathological features and 112 radiomic features, were finally adopted to develop GARSL pre-operative and post-operative models. GARSL pre-operative and post-operative models achieved the test performance 0.739 and 0.741 of areas under the receiver operating characteristic curves (AUCs), respectively, for early recurrence of HCC within 2 years. The accuracy of GARSL models derived from evolutionary learning method was significantly better than models derived from other well-known machine learning methods or the ERASL models using clinical features only.

Conclusion: The GARSL models using both clinical and radiomic features significantly improved the accuracy to predict early recurrence of HCC after surgical resection, which were significantly better than other well-known machine learning derived models and currently available clinical models.

PO-1856

Anti-tumor activity of TRN-000546, a liver-distributed monophosphate prodrug of FdUMP, in orthotopic liver tumor models

Martijn Fenaux¹, Kevin Klucher¹, Christopher Jones¹, Anne Bonneville¹, Weidong Zhong¹. ¹Terns Pharma, Research, Foster City, United States
Email: kklucher@ternspharma.com

Background and aims: TRN-000546 is a monophosphate prodrug of FdUMP, the potent anti-tumor metabolite of 5-FU. The TRN-000546 prodrug was designed to protect FdUMP from enzymatic deactivation and improve its delivery into the liver. Here, we report the tissue distribution of FdUMP in hamsters dosed with TRN-000546. Additionally, TRN-000546 was tested in rodent orthotopic liver cancer models mimicking hepatocellular carcinoma (HCC), metastatic gastric cancer (GC), and metastatic colon cancer (CC).

Method: The in vitro potency of TRN-000546 was determined against the tumor cell lines Huh7, MKN45, and HT-29. To measure tissue distribution, TRN-000546 was administered as a single IP dose (30 mg/kg) to hamsters and tissues were collected for FdUMP quantification at 4 hours after dosing. In vivo anti-tumor efficacy was determined in mouse orthotopic liver cancer models of HCC, GC, and CC using tumor-derived bioluminescent cell lines Huh7-luc, MKN45-luc, and HT-29-luc, respectively. Cell lines were suspended in DMEM/Matrigel mixtures (1:1) and surgically implanted under the

liver capsule prior to treatment with TRN-000546 (20 or 30 mg/kg IP BID for 17 days [HCC] or 20 mg/kg IP BID for 21 days [GC and CC]). Standard of care (SOC) treatment groups included sorafenib (30 mg/kg PO QD for 17 days, HCC) and capecitabine (400 mg/kg PO QD for 21 days, GC and CC). At the end of treatment, mice were sacrificed and tumors (primary and 2nd metastatic) weights were compared to vehicle treated controls.

Results: TRN-000546 was 561-, 80- and 988-fold more potent than 5-FU against Huh7, MKN45, and HT-29 tumor cell lines, respectively. The highest concentration of FdUMP was detected in the liver after a single IP dose of TRN-000546 (30 mg/kg), while FdUMP was undetectable in bone marrow and skin, the tissues known to be associated with 5-FU toxicity. In the mouse orthotopic tumor models, TRN-000546 treatment reduced mean HCC tumor weights by 84% ($p < 0.05$) relative to the vehicle control, while SOC treatment (sorafenib) decreased HCC tumor weights by only 41%. TRN-000546 treatment reduced mean metastatic GC and CC tumor weights by 45% ($p < 0.05$) and 53% ($p < 0.05$), respectively, while capecitabine reduced GC tumor weights by 57% ($p < 0.05$) and CC tumor weights by 3.5%.

Conclusion: TRN-000546, a monophosphate prodrug of FdUMP, showed increased in vitro potency against tumor cell lines and improved liver tissue distribution relative to the parent drug 5-FU. Furthermore, treatment with TRN-000546 demonstrated comparable or better efficacy in the mouse orthotopic models of HCC and liver metastases relative to SOC treatments, supporting its continued development as a potential therapy for liver cancers.

PO-1883

A Novel Prognostic Calculator to Optimize Individualized Treatment for Patients with HCC within the Milan the Milan Criteria.

Ningning Zhang^{1,2,3}, Jian Zheng⁴, Ying Wu⁵, Yamin Zhang⁶, Wentao Jiang⁷, Tianqiang Song¹, Jiayu Lv⁸, Tian Liu⁶, Wei Zhang⁶, Jie Gu¹, Zeyu Wang¹, Shuwen Zhang¹, Yuhong Suo¹, Shuai Wang¹, Wang Li¹, Li Zhang⁷, Yan Xie⁷, Yonghe Zhou⁷, Jianyong Liu⁷, Yibo Qiu⁸, Wei Lu^{1,2,3}. ¹Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Clinical Research Center for Cancer, Hepatobiliary Oncology Department, Tianjin, China; ²Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Clinical Research Center for Cancer, Liver Cancer Center; ³Nankai University, Post-doctoral Research Center, Tianjin, China; ⁴University of Pittsburgh Medical Center, Surgical Oncology, Tianjin, China; ⁵Nankai University, Key Laboratory for Medical Data Analysis and Statistical Research of Tianjin, Tianjin 300071, China ⁵Department of Hepatobiliary Surgery, Tianjin First Central Hospital, Tianjin Key Laboratory for Organ Transplantation, School of Statistics and Data Science, Tianjin, China; ⁶Tianjin First Central Hospital, Tianjin Key Laboratory for Organ Transplantation, Department of Hepatobiliary Surgery, Tianjin, China; ⁷Tianjin First Center Hospital, NHC Key Laboratory for Critical Care Medicine, Key Laboratory of Transplantation, Chinese Academy of Medical Sciences, Department of Liver Transplantation, Tianjin, China; ⁸The First Central Clinical College of Tianjin Medical University, Tianjin, China
Email: luwei1966@126.com

Background and aims: Liver transplantation (LT), liver resection (LR) and local ablation (LA) are curative-intent treatments for patients with early hepatocellular carcinoma (HCC). However, the best management warrants an individualized multidisciplinary discussion. The aim of present study was to develop a prognostic calculator to compare long term outcomes following each of these therapies, which will help guide a personalized discussion of treatment plans with the patients.

Method: 976 patients with HCC within the Milan criteria (MC) undergoing LT, LR and LA with curative intent were recruited from 4

POSTER PRESENTATIONS

different centres. Multistate competing risks prediction models for recurrence free survival (RFS), recurrence within the Milan criteria (RWM), HCC-specific survival (HSS) were derived in the Chinese training cohort. The models were then internally validated in Chinese validation cohort and externally validated in American validation cohort to develop a prognostic calculator.

Results: In the multivariable analysis, in addition to tumour size and interaction effects between treatment allocation and tumor number, clinicopathologic data including patient's age, gender, AFP, albumin-bilirubin grade, and portal hypertension were significantly associated with recurrence and HCC-specific survival. Prediction models of RFS, RWM and HSS with 3 risk strata were constructed and validated with satisfactory discrimination abilities and calibration curves in both Chinese internal and American external validation cohorts. A web-based prognostic calculator was then successfully developed.

Conclusion: While liver transplantation offers the best recurrence and survival outcomes, liver resection and local ablation also offer comparable long-term outcomes for patients with early HCC who are limited by organ availability. Our present prognostic calculator can be used to compare these long-term outcomes in different tumor subgroups and optimize the individualized care for patients with HCC.

Lay summary: Our current study developed the multistate competing risks models to exhibit an accurate continuous range of HCC-specific prognosis probability algorithm of recurrence free survival, recurrence within the Milan criteria and HCC-specific survival for early-stage HCC with composite multi-parametric evaluations, including different curative treatment allocation for different tumour status and liver function. A web-based prognosis calculator based on the prognosis algorithm was developed for convenient assessment of the curative treatment allocation for HCC patients within the Milan criteria.

PO-2075

Aspirin and the risk of hepatocellular carcinoma in chronic liver disease: A systematic review and meta-analysis

Jin Lin Tan¹, Sandeep Sidhu-Brar¹, Richard Woodman², Asif Chinnaratha^{1,3}. ¹Lyell McEwin Hospital, Department of Gastroenterology and Hepatology, Elizabeth Vale, South Australia, Australia; ²Flinders University, College of Medicine and Public Health, Bedford Park, South Australia, Australia; ³The University of Adelaide, Faculty of Health and Medical Sciences, Adelaide, South Australia, Australia

Email: tanjinlin@gmail.com

Background and aims: Hepatocellular carcinoma (HCC) represents >80% of primary liver cancers and it is the fourth most common cause of cancer related death globally. There is conflicting evidence on the impact of Aspirin on the incidence of HCC in those with chronic liver disease. This meta-analysis of observational studies was undertaken to evaluate the association of Aspirin use on the incidence of HCC in patients with chronic liver disease.

Method: Electronic reference databases (PubMed Medline, EMBASE Ovid, and the Cochrane Central) were searched from inception to 30th April 2020 for studies involving adult patients with chronic liver disease. The primary outcome assessment was the development of HCC in those exposed to regular Aspirin therapy compared to those who were not exposed or used Aspirin intermittently (comparator). The secondary outcome was the occurrence of major gastro-intestinal (GI) bleeding events. We estimated the unadjusted and propensity score (PS) adjusted pooled Hazard Ratio (HR) (95% CI) of HCC among regular Aspirin use versus non-use using a random-effects model.

Results: Six observational studies with 71,211 subjects were included in this meta-analysis. Median duration of follow-up of the included studies ranged from 2.7–7.9 years. Four studies had viral hepatitis as the underlying aetiology while one had alcohol and the other had mixed aetiology. Patients in five out of the six studies used Aspirin 100 mg/day while those in the other study used either 75 or 160 mg.

All six studies reported the unadjusted HR and there was a 54% reduction in HCC development in those exposed to Aspirin [HR (95% CI): 0.46 (0.31–0.67), $p < 0.001$] (Figure). Four studies reported on the PS adjusted HR and this showed a 46% reduced incidence of HCC in those using Aspirin [HR (95% CI): 0.54 (0.38–0.79), $p < 0.001$]. Four studies reported on the incidence of major GI bleeds and there was no significant difference between the two groups [HR (95% CI): 1.00 (0.69–1.45), $p = 0.9$]. All the outcome analysis had significant inter-study heterogeneity ($I^2 > 50\%$ and $P < 0.05$).

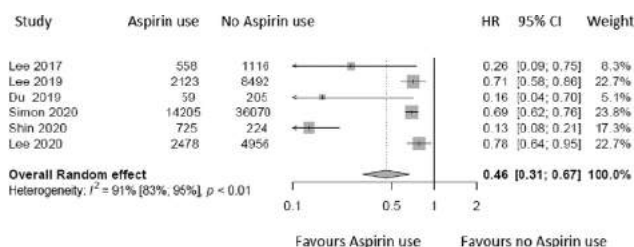


Figure:

Conclusion: Regular Aspirin use in patients with chronic liver disease is associated with a reduced risk of HCC without a significant increased risk of GI bleeding.

PO-2401

Tailoring the management of HCC during the COVID-19 pandemic: a single center comparative analysis of 4 periods during 2020 versus 2019

Massimo Iavarone¹, Barbara Antonelli¹, Anna Maria Ierardi¹, Angelo Sangiovanni¹, Ferruccio Ceriotti¹, Giorgio Rossi¹, Gianpaolo Carrafiello¹, Pietro Lampertico¹. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
Email: massimo.iavarone@policlinico.mi.it

Background and aims: During the first COVID-19 pandemic, we learned the unpredictable fluctuation of hospital resources and the risk of the nosocomial spread of SARS-CoV-2, directly impacting on hepatocellular carcinoma (HCC) management. To protect patients and healthcare workers, while guaranteeing the continuity of HCC treatment, we redesigned our management paradigms. The aim of this study is to evaluate the impact of these measures on the management of HCC patients during the pandemic.

Methods: Since April 2020 COVID-19 testing was performed every other week to all healthcare workers involved in the management of HCC patients, since May 2020 a dedicated room has been elected for HCC patients who were tested approximately 48 hours before admission. The multidisciplinary team (MDT) evaluated the risk of potential exposure versus presumed benefit of treatment for each patient, also considering the minimum time of exposure to the hospital environment and the effective availability of specialists. As measure of effectiveness for HCC management, we compared the number of visits, cases discussed in MDT, surgical treatments, percutaneous ablations and endovascular procedures performed in 2020 to those performed in 2019, considering 4 periods: pre-pandemic (January-February), first pandemic (March-May), summertime (June-September) and second pandemic (October-December).

Results: The number of swabs tested positive for SARS-CoV-2 before admission was 3.7% and these patients were postponed until negative. No patients turned symptomatic for COVID-19 after discharge. Table 1 shows the differences between 2019 and 2020 according to the predefined periods. The total number of surgical procedures performed in 2019 was 30 compared to 17 in 2020, while the number of liver transplants for HCC was 28/53 in 2019 vs 19/40 in 2020.

	Out-patients' visits	MDT cases	Ablation	TACE/TARE
Jan-Feb 2019	261	82	2	36
Jan-Feb 2020	301 (+15%)	108 (+32%)	5 (+150%)	33 (-8%)
March-May 2019	413	160	3	46
March-May 2020	213 (-48%)	101 (-37%)	16 (+433%)	19 (-59%)
Jun-Sept 2019	437	187	8	69
Jun-Sept 2020	475 (+9%)	193 (+3%)	16 (+100%)	52 (-24%)
Oct-Dec 2019	444	168	9	39
Oct-Dec 2020	427 (+4%)	214 (+27%)	11 (+22%)	43 (+10%)

Conclusion: During the pandemic, particularly after the implementation of measures to guarantee safety of patients, we were able to maintain an adequate number of treatments for HCC, favouring ablative treatments to ensure greater efficacy and a reduced exposure to the hospital environment with available resources.

PO-2408

The Number of Small Hepatocellular Carcinoma Nodules in Patients within the Alpha-Fetoprotein Score before Liver Transplantation Is a Prognostic Risk Factor

Alina Pascale¹, Alessandro Mazzotta², L. Cano³, Marc Antoine Allard², Audrey Coilly¹, Antonio Sa Cunha², Rene Adam², Daniel Cherqui², Didier Samuel¹, Olivier Rosmorduc¹, Eric Vibert², Nicolas Golse². ¹Paul Brousse Hospital, Hepatology, Villejuif, France; ²Paul Brousse Hospital, Hepato-Biliary Surgery, Villejuif, France; ³Rennes University, INSERM-UMR 1241, Rennes, France
Email: alina_pascale@yahoo.com

Background and aims: In France, the criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC) require an alpha-fetoprotein (AFP) score ≤ 2 . According to this score, patients with >3 HCC nodules are eligible for LT, as long as they are small (≤ 3 cm) and the AFP level is ≤ 100 ng/ml. This study shows that the number of small HCC nodules in patients within the AFP score before LT has a prognostic value.

Method: We included 143 patients consecutively transplanted for HCC in our center, between 2013 and 2017, with an AFP score ≤ 2 . The number and size of HCC nodules, and the AFP level were assessed at listing and at the last evaluation before LT. HCC histological features on native liver were assessed. We compared the overall survival (OS) and disease-free survival (DFS) post-LT of patients with ≤ 3 versus >3 HCC nodules (current criteria) and, respectively, <5 versus ≥ 5 HCC nodules. The Mann-Whitney U test for continuous variables and Pearson's chi-square test were used, or Fisher's exact test for categorical variables. Survival rates were calculated using the Kaplan-Meier method, and groups were compared with the log-rank test.

Results: Among 196 patients listed for HCC, 36 (18.4%) were not transplanted due to drop-out. The median age of the 143 transplanted patients was 63.3 years. The two main causes of the underlying liver disease were alcohol (41.3%) and HCV infection (27.9%). The number of patients with more than 3 HCC nodules at listing and at the last imaging before LT was of 16 (11%) and 17 (12%), respectively. 128 (89.5%) patients had at least one bridging treatment: transarterial chemoembolization n = 83, radiofrequency n = 16, surgical resection n = 22, other treatment n = 22, without any difference among the subgroups (≤ 3 versus >3 HCC nodules). The median follow-up of the whole cohort was of 44 months. The 3-years OS of patients with ≤ 3 versus >3 HCC nodules at listing were of 90.3% and 67.3%, respectively ($p = 0.04$). At last imaging before LT, 8 patients presented ≥ 5 HCC nodules, while still within the AFP score; they had a significantly lower OS than those with <5 nodules: 5-years OS of 24.4% versus 78.1%, $p = 0.01$), as showed in Figure 1.

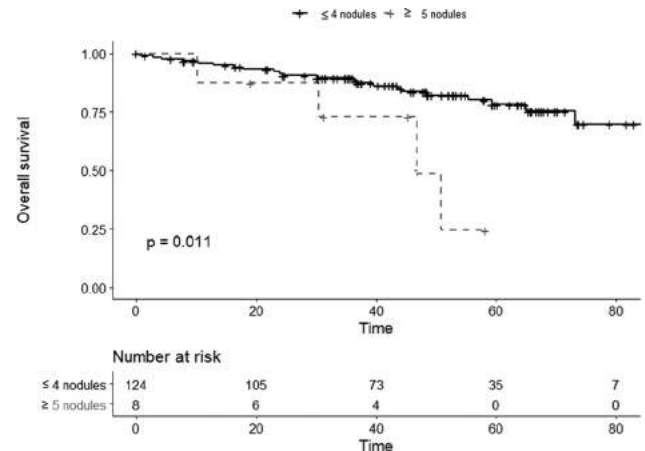


Figure: Overall survival for patients with ≤ 4 HCC nodules (bold line) versus ≥ 5 HCC nodules (dashed line) at last imaging before LT.

Conclusion: Although the current AFP score provides satisfactory outcomes post-LT for HCC, we highlight here the poorer outcomes when more than five HCC nodules persist despite bridging therapy. A modification of the AFP score, by adding an upper threshold of five HCC nodules could be considered, to exclude progressive HCC after listing, as they show shorter survival rates.

PO-2666

Primary non-response affects the prognosis of hepatitis B virus-related Hepatocellular Carcinoma after antiviral therapy

Peng Wang¹, Xinhui Wang^{1,2}, Xiaoli Liu¹, Fengna Yan¹, Huiwen Yan³, Dongdong Zhou¹, Lihua Yu¹, Xian-bo Wang¹, ZhiYun Yang¹. ¹Capital Medical University Affiliated Beijing Ditan Hospital, Center of Integrative Medicine, Beijing, China; ²Beijing, China; ³Beijing University of Chinese Medicine, First Clinical Medical College, Beijing, China
Email: yangzhiyun2016@163.com

Background and aims: Despite antiviral treatment has been revealed to affect the recurrence and long-term survival of hepatocellular carcinoma (HCC) in patients with high viral load, but the effect of different response on clinical outcomes after antiviral therapy remains unclear. This study aims to assess the effect of primary non-response on survival or prognosis of hepatocellular carcinoma patients with high-level hepatitis B virus (HBV) DNA.

Method: A total of 493 patients with HBV-HCC admitted to the Beijing Ditan Hospital of Capital Medical University were enrolled in this study. Patients were divided into primary response group and primary non-response group. This bar graphs were used to compare the changes in virus levels between different groups. Risk factors, serum viral load, and other clinical variables were analyzed. The Kaplan-Meier curve were used to express the survival rate of the two groups of patients. Scoring chart was used to distinguish patients with different risk levels.

Results: The cohort consisted of 392 patients in primary response group and 101 in primary non-response group. The median survival time of PR group and no PR group was 39.6 months and 15 months. The average level of HBV DNA in primary response was higher than non-response group after 3 months of antiviral treatment. Then we divided the PR patients into higher level group (HBV DNA ≥ 5 log) and relatively lower level group (HBV DNA < 5 log) based on baseline virus levels. As a result, there were no statistical differences between the two subgroups of PR patients. The Kaplan-Meier curve showed that primary non-response had a lower overall survival in different categories of HBV DNA and hepatitis B e antigen. Primary non-response had lower overall survival and progress free survival in patients with alanine aminotransferase (ALT) < 50 IU/L and cirrhosis. A multivariate Cox regression analysis indicated that primary non-response was an independent risk factor for 1-year survival (HR = 1.883, 95% CI 1.289–2.751, $P = 0.001$). All patients were divided into

POSTER PRESENTATIONS

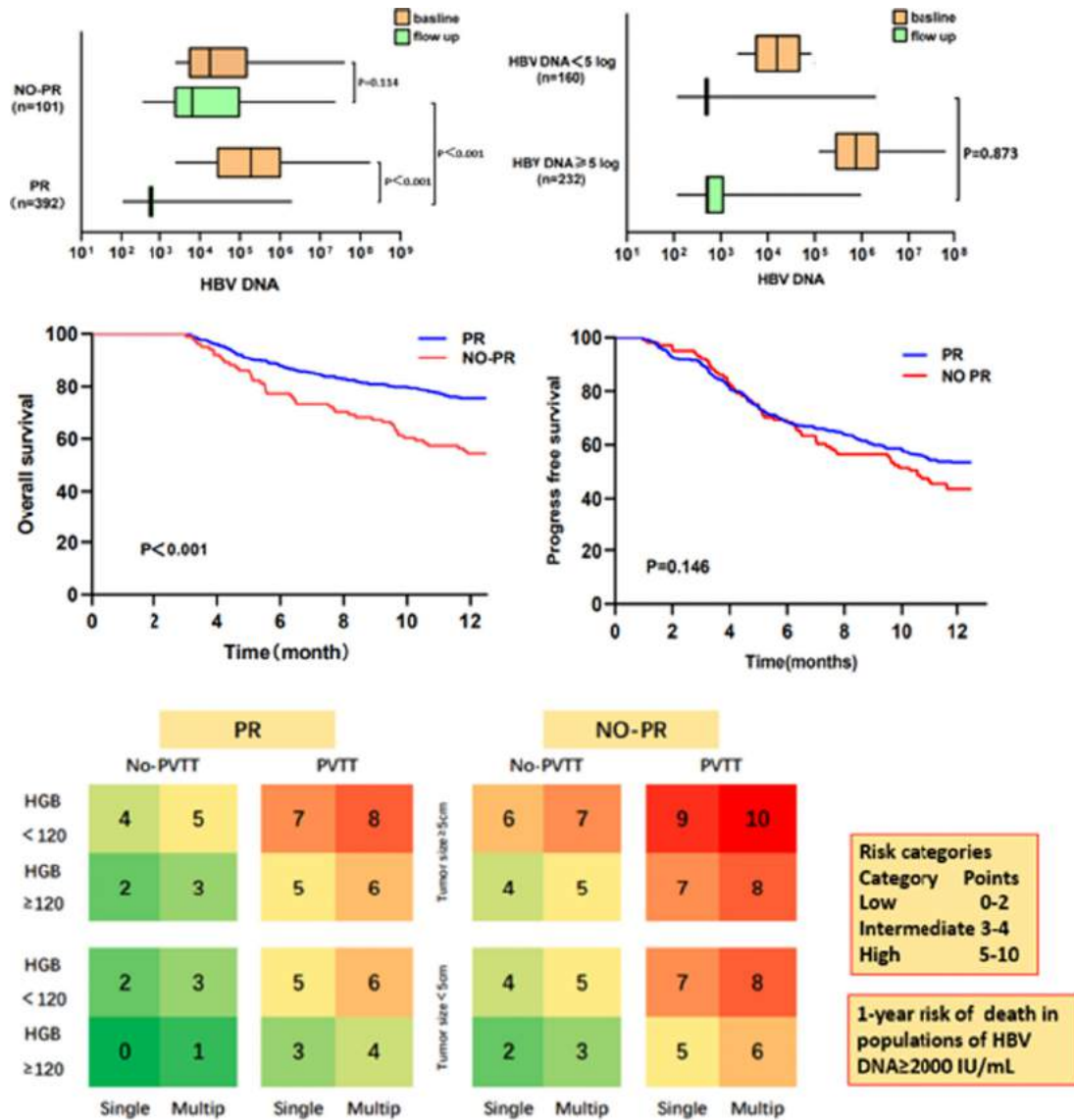


Figure: (abstract: PO-2666)

high (61.7%)-, medium (30.5%)-, and low (14.1%)-risk groups according to the score chart.

Conclusion: The level of viral decline at 3 months can predict the overall survival, and primary non-response probably shorten the median survival time among patients of HCC with high HBV DNA levels. Therefore, it should be considered to adjust antiviral programs for HBV-HCC patients with a decline of less than 1 log within 3-months.

PO-2712

Real-world experience of atezolizumab/bevacizumab in hepatocellular carcinoma

Yeonjung Ha¹, Jaekyung Cheon², Seong Gyu Hwang¹, Hong Jae Chon².
¹CHA Bundang Medical Center, CHA University, Gastroenterology, Seongnam-si, Rep. of South Korea; ²CHA Bundang Medical Center, CHA University, Oncology, Seongnam-si, Rep. of South Korea
 Email: hongjaechon@gmail.com

Background and aims: Atezolizumab/bevacizumab became the standard of care for advanced hepatocellular carcinoma (HCC)

patients; however, data on efficacy and safety are limited in a real-world clinical setting.

Method: We retrospectively reviewed consecutive advanced HCC patients who received atezolizumab/bevacizumab between Jun 2020 and Jan 2021 at CHA Bundang Medical Center. Baseline variables, treatment patterns, response rates, toxicities, and clinical outcomes including overall survival (OS) and progression-free survival (PFS) were described. Predictive factors for the outcomes were determined by Cox proportional hazards models.

Results: A total of 50 patients were analyzed. The mean age was 63 years and 42 (84.0%) patients were male. Thirty-five (70.0%) patients received various anti-cancer therapies before atezolizumab/bevacizumab. Atezolizumab/bevacizumab was used as the first-line systemic therapy for 47 (94.0%) patients. In the Child-Pugh A group (n = 45), 28 (62.2%) patients showed non-progression as of Feb 2021. The mean OS and PFS were 7.4 (95% confidence interval [CI], 6.7–8.2) and 5.6 (95% CI, 4.5–6.6) months, respectively. The average OS and PFS were 4.9 (2.9–7.0) and 7.7 (95% CI, 1.5–13.9) months in 5 patients with Child-Pugh B liver function. Grade 3 treatment-related hypertension occurred in 5 (10.0%) patients and 2 (4.0%) patients experienced duodenal perforation. Patients with high neutrophil-to-

lymphocyte ratio (NLR), low lymphocyte-to-monocyte ratio, high platelet counts, high aspartate aminotransferase (AST) levels, and high Child-Pugh score showed shorter OS (hazard ratio [HR], 1.52; 95% CI, 1.24–1.86; $P < 0.001$ for NLR and HR, 0.20; 95% CI, 0.07–0.58; $P = 0.003$ for LMR). Similarly, NLR (HR, 1.29; 95% CI, 1.08–1.54; $P = 0.005$), platelet counts, and AST levels were associated with PFS.

Conclusion: Atezolizumab/bevacizumab was well tolerated and effective in heavily treated advanced HCC patients in real-world clinical practice. Pretreatment NLR predicted OS and PFS.

Molecular and cellular biology

PO-375

A profibrotic role for the orphan G-protein coupled receptor 176 during hepatic stellate cell activation

Vincent De Smet¹, Stefaan Verhulst¹, Liza Dewyse¹, Mina Kazemzadeh Dastjerdi¹, Hendrik Reynaert², Georg Halder³, Inge Mannaerts¹, Leo A. van Grunsven¹. ¹Vrije Universiteit Brussel, Liver Cell Biology Research Group, Jette, Belgium; ²UZ Brussel, Gastroenterology, Jette, Belgium; ³VIB-Center for Cancer Biology, Leuven, Belgium

Email: vincent.de.smet@vub.be.

Background and aims: Hepatic stellate cells (HSC) are the major scar forming cells in liver fibrosis. During liver fibrosis, quiescent, vitamin-A-storing, HSCs (qHSC) transdifferentiate to an activated myofibroblast-like phenotype (aHSC) and exert fibrotic characteristics. Despite great advances in our understanding of these cells at different stages of disease, HSC-targeting drugs are still not used in the clinic, leaving an unmet need. In this study we set out to characterize transcriptional dysregulation in mouse HSCs during experimental induction and reversal of liver fibrosis. From said dysregulated program, we aimed to identify candidate targets for HSC-based anti-fibrotic treatment.

Method: Experimental fibrosis was induced in Balb/c mice through 4 weeks of semi-weekly carbon tetrachloride (CCl₄) injections. Reversal was accomplished by an additional 2-week recovery. HSCs were isolated from healthy, 4 weeks CCl₄-treated and 2-week recovery livers by FACS-based sorting for UV positivity and processed for RNA sequencing analysis. For 2D in vitro culture, mouse HSCs were isolated using Nycodenz density gradient. Gpr176 knockdown on cultured mouse HSCs was carried out using Gpr176 specific siRNAs on days 1 and 5 using scramble siRNAs as control. Mouse precision cut liver slice (mPCLS) cultures were performed by slicing liver tissue with a vibratome followed by punching into 3 mm discs. At the start of the cultures, mPCLSs were transfected with Gpr176 specific siRNAs using scramble siRNAs as control.

Results: RNA sequencing data show reversion of HSCs to a quiescent like phenotype after 2 weeks of recovery marked by upregulation of qHSC markers Gfap and Ngfr and downregulation of HSC activation markers Acta2 and Col1a1 when compared to 4 weeks CCl₄. To define the transcriptional dysregulation in aHSCs, we generated a gene set including genes that are downregulated during recovery. By excluding genes that remain upregulated during recovery, we pinpointed the dysregulated transcriptional program that, at least, has to be targeted in any future therapeutic experiment. From this gene set, we identified the orphan G protein coupled receptor (GPCR) 176 (Gpr176) as a marker of HSC activation and show that it is conserved in both human HSCs and mouse HSCs from different models of experimental liver disease. Additionally, we noted reduced expression of HSC activation markers Acta2, Col1a1 and Lox when performing RNA interference for Gpr176 mRNA in 2D in vitro model of mouse HSC activation as well as in mPCLS cultures.

Conclusion: We provide new insight in an orphan GPCR for which, currently, only limited information exists and place it in a context of chronic liver disease. Gpr176 could potentially exert pro-fibrotic characteristics which marks it as a potential novel target for liver fibrosis. In vivo experiments using Gpr176 knock-out mice are currently ongoing to confirm this hypothesis.

PO-608

Multicellular primary mouse liver spheroids for DILI, NAFLD, NASH and fibrosis studies

Elise Anne van Os¹, Laura Cools¹, Nathalie Eysackers¹, Ayla Smout¹, Stefaan Verhulst¹, Hendrik Reynaert¹, Inge Mannaerts¹, Leo van Grunsven¹. ¹Vrije Universiteit Brussel, BMW-E-LIVR, Brussel, Belgium

Email: elise.anne.van.os@vub.ac.be.

Background and aims: Drug induced liver injury (DILI), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), fibrosis and subsequently cirrhosis are a great health burden and a major cause of death worldwide, for which currently no therapies are available. During chronic liver disease hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs) respond to liver injury and play a crucial role in fibrosis development. Currently, no robust multicellular mouse in vitro culture models are available that can recapitulate the complex fibrotic response upon hepatocyte damage or NAFLD/NASH, therefore animal studies remain necessary. Our aim was to develop a multicellular spheroid in vitro model with primary isolated mouse HSCs, KCs, LSECs and hepatocytes that can be used to model DILI, fibrosis, NAFLD and NASH and for research into its mechanism of action and the development of new anti-fibrotic/NASH therapies.

Methods: Multicellular liver spheroids (MCLSs) were generated by the 3D co-culture of freshly isolated primary mouse hepatocytes, isolated by Percoll gradient, and LSECs, HSCs and KCs isolated by FACS. **Results:** MCLSs can be cultured for at least 14 days without significant change in cellular composition or induction of HSC activation. HSCs can be directly activated by exposure to TGFβ as shown by upregulation on mRNA levels of Acta2 and Col1a1 and on collagen protein levels in the culture media determined by ELISA. DILI was induced by an acute (24 h) or chronic (72 h) exposure to APAP. Chronic exposure of APAP generated a fibrotic response with an upregulation of Acta2 and Collagen genes as well as more collagen deposition in the spheroids and release into the culture media. Exposure of MCLSs to free fatty acids (oleic and palmitic acid for 9 days) resulted in NASH induction evidenced by an intracellular lipid accumulation and change in both pro-fibrotic (Acta2, Col1a1, Col3a1, Col5a2) and inflammatory genes (Il-1 and Il-6). Accumulation of lipids and fibrosis could be inhibited by treatment with Pioglitazone, Elafibranor and Lanifibranor.

Conclusion: We established a robust multicellular in vitro spheroid culture model from primary mouse liver cells that can display a fibrotic response upon chronic exposure to APAP and under NASH conditions.

PO-778

The FXR-RXR interaction inhibits FXR isoform-specific gene activation in liver cells

Jose Miguel Ramos Pittol^{1,2}, Suzanne van der Veen², Jelmer Dijkstra³, Ellen Willemsen², Michiel Vermeulen³, Saskia van Mil². ¹University of Innsbruck, Institute of Biochemistry, Innsbruck, Austria; ²Center for Molecular Medicine, University Medical Center Utrecht, University Utrecht, Utrecht, Netherlands; ³Department of Molecular Biology, Faculty of Science, Radboud Institute for Molecular Life Sciences, Oncode Institute, Radboud University Nijmegen, Nijmegen, Netherlands

Email: s.w.c.vanmil@umcutrecht.nl.

Background and aims: The Farnesoid-X-receptor (FXR) is a nuclear receptor activated by bile acids, and a promising therapeutic target for diverse metabolic diseases. FXR is expressed as four isoforms

POSTER PRESENTATIONS

(alpha1-4), which heterodimerize with the Retinoid-X-Receptor (RXR) and activate transcription from a DNA motif (IR-1, inverted repeat-1). We recently showed that FXR isoforms alpha 2/4 bind to an additional DNA motif (ER-2, everted repeat-2), representing 90% of FXR binding events and regulating numerous genes of therapeutic interest. Here we investigated regulators of FXR activation from the IR-1 and ER-2 DNA binding motifs.

Method: Differential interactors of the ER-2 and IR-1 motifs were identified by DNA pull down followed by mass-spectrometry. The effect of candidate proteins on FXR-driven transactivation was tested on luciferase reporter assays. DNA binding was assessed by EMSA and ChIP in HepG2 cells. A novel mutation in the LBD of FXR was generated to abrogate its binding to RXR and further validate the role of this interaction in FXR target selectivity.

Results: RXR, the classical heterodimerization partner of FXR, is not required for FXR binding to ER-2 sites. Instead, RXR inhibits FXR-driven transactivation from these sites in reporter constructs and cell lines. Concomitantly, pharmacological and mutational abrogation of the FXR-RXR interaction selectively negates activation from IR-1 sites while retaining ER-2 activation capacities. Interestingly, transactivation by FXR α 2 from overlapping IR-1/ER-2 motifs is not affected by RXR availability.

Conclusion: Our results reveal a novel mechanism behind FXR alpha 2/4 target gene selectivity, and demonstrate the FXR-RXR interaction as a negative regulator of transcription from ER-2 sites upon FXR agonism. As the FXR alpha 2/4 selective binding to ER-2 sites induces a transcriptional profile predictive of enhanced handling of nutrient stress, promoting this FXR feature will likely increase therapeutic efficacy for metabolic disorders such as NAFLD/NASH.

PO-895

cell cycle-regulatory genetic aberrations and their prognostic implications in early-stage hepatocellular carcinomas

Jihyun An¹, Ji-hye Oh², Wonkyung Kim², Bora Oh², Yoo-Jin Oh², Chang Ohk Sung², Ju Hyun Shim². ¹Hanyang University, Korea, Rep. of South; ²Asan Medical Center, Korea, Rep. of South
Email: s5854@amc.seoul.kr.

Background and aims: Uncontrolled proliferation induced by cell cycle deregulation is a hallmark of cancer cells. This study aimed to explore fusional and non-fusional aberrations related to the cell cycle, and investigate their prognostic relevance in a surgical series of hepatocellular carcinomas (HCCs).

Method: Based on high-resolution transcriptomic data for 206 early-stage HCC samples obtained after curative hepatectomy at Asan Medical Center, South Korea, we fully characterized distinct patterns of fusion events using STAR-Fusion. The presence of the fusion transcripts was subsequently confirmed by Sanger sequencing. We also identified non-fusional genetic aberrations deregulating the cell cycle in the same cohort. Prognostic effects of genomic events were evaluated by competing risks regression analyses.

Results: We identified a total of 89 gene fusion events in 49 samples, including 77 novel and 7 recurrent fusion transcripts. The cell cycle-related gene fusions, *ERRF1-CCNE1*, *UPF3A-CDC16*, and *ITM2B-RB1*, were observed in different tumors (n = 4). Notably, the *UPF3A-CDC16* fusions recurrently detected in two samples harbored biallelic loss of function of *CDC16*, together with abnormally high levels of *cyclin B1* and *Ki-67*. We additionally found that a sub-category of 17 cell cycle gene aberrations other than gene fusions were present in 61 (29.6%) of the 206 patients. These fusional and non-fusional subgroups were enriched for gene sets related to cell proliferation, and were associated with poorer outcomes for cancer-specific death, when compared to non-affected individuals (adjusted hazard ratios [95% confidence intervals], 16.86 [5.37–52.88] and 2.58 [1.30–5.09], respectively).

Conclusion: We have provided a comprehensive overview of fused and mutated cell-cycle genes that confer a negative effect on tumor

behavior in early HCCs. Our clinical and biological insights may serve as the basis for better-tailored cares for patients with the disease.

PO-1027

A low carbohydrate diet partially prevents the hepatic histological damage of hepatocyte OGT-deficient mice.

Lucia Parlati¹, Paula Ortega Prieto¹, Fadila Benhamed¹, Melanie Montabond¹, Tarik Issad¹, Catherine Postic¹. ¹Institut Cochin, U1016 INSERM, Université de Paris, PARIS 14E ARRONDISSEMENT, France
Email: lucia.parlati85@gmail.com.

Background and aims: O-GlcNAcylation (O-GlcNAc) is a post-translational modification, controlled by two enzymes, OGT (O-GlcNAc transferase), which adds N-Acetylglucosamine on the serine or threonine residues and OGA (O-GlcNAcase) which eliminates it. O-GlcNAc is one of the main effectors of metabolism and contributes to gluco-lipototoxicity in the liver. A recent study reports that hepatocytes from liver OGT-deficient mice undergo massive necroptosis, elevated transaminases, inflammation and fibrosis (1). Our hypothesis is that since OGT is a glucose sensor, lowering glucose intake may protect OGT-deficient mice from liver damage.

Method: We analysed the hepatic phenotype and the clinical-biological parameters, the variation in the expression of the genes involved in proliferation, inflammation, fibrogenesis and metabolic pathways of control mice (OGT^F) and mice with a selective deletion of hepatic *ogt* (OGT^A) after weaning with a standard diet (SD: 72.4% of carbohydrates, 8.4% of fat, 19.3% of protein) and a low carbohydrate diet compensated by lipid enhancement (LCLE: 35% of carbohydrates, 45% of fat, 20% of protein). We used male and female mice.

Results: The OGT^A mice did not exhibit any major disturbance in metabolic homeostasis, regardless of the diet used. We measured key genes involved in gluconeogenesis and lipogenesis and did not observe any significant difference in OGT^A mice compared to controls, regardless of the diet used. The hepatic phenotype of OGT^A mice, compared to OGT^F mice, was characterized by: an increase in hepatocellular proliferation and inflammatory infiltrate, fibrosis and a tendency to increased hepatic triglycerides concentrations, regardless of the diet. Interestingly, OGT^A mice under LCLE showed a decreased in serum alkaline phosphatase suggesting a less severe phenotype. Indeed, this was associated with a decreased in the expression of specific inflammatory, ER stress and DNA damage markers (TNF α , MCP1, CHOP, NQO1, pH2AX).

Conclusion: The loss of hepatic OGT leads to a severe hepatic phenotype with inflammation and fibrosis. While the LCLE regimen did not prevent the hepatic histological alterations of OGT^A mice it partially reverted some aspects of the phenotype. Our data suggest that lowering glucose intake may prevent the deleterious effect of OGT silencing in liver.

Reference

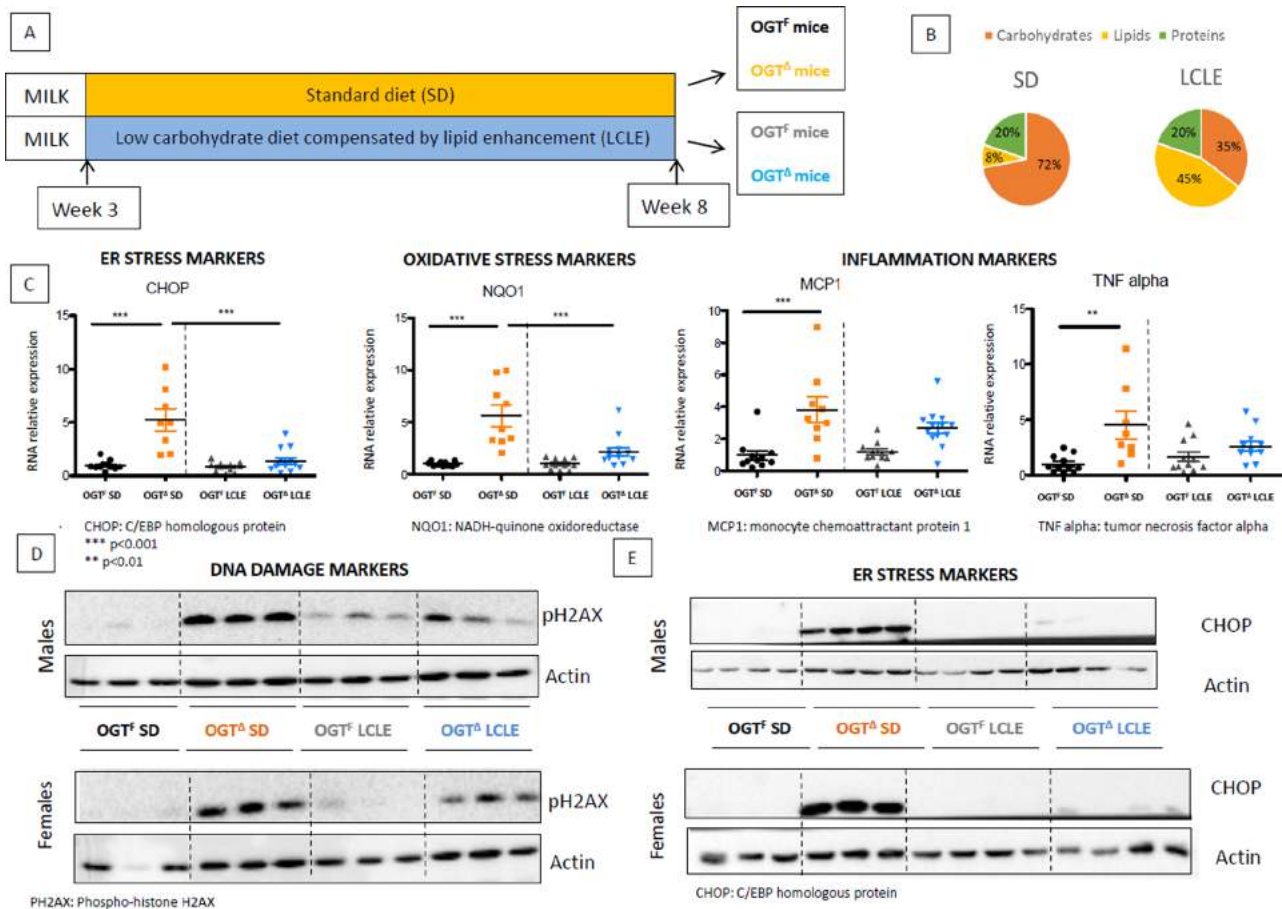
Zhang B, Li MD, Yin R, Liu Y, Yang Y, Mitchell-Richards KA, et al. O-GlcNAc transferase suppresses necroptosis and liver fibrosis. *JCI Insight*. 2019 Nov 1; 4(21): e127709.

PO-1357

Role of ASCT2 and KGA for ammonia-induced astrocyte senescence

Olivia Knappe¹, Alina Schrimpf¹, Ayse Karababa¹, Linda Czeszewski¹, Hans Jürgen Bidmon², Tom Luedde¹, Dieter Häussinger¹, Boris Görg¹. ¹Clinic for Gastroenterology, Hepatology and Infectiology, Heinrich Heine University, Düsseldorf, Germany; ²C. and O. Vogt Institute for Brain Research, Heinrich Heine University, Düsseldorf, Germany
Email: boris.goerg@uni-duesseldorf.de.

Background and aims: Recent studies suggested a role of astrocyte senescence for permanent cognitive impairment in patients with liver cirrhosis and hepatic encephalopathy (HE) (Görg et al. 2019, *J Hepatol* 71: 930–941). In the present study, we examined a potential relevance of the mitochondrial glutamine importer ASCT2 and



A) Weaning and group composition, B) Diets' characteristics, C) RNA relative expression of ER stress (CHOP), oxidative stress (NQO1), and inflammation markers (MCP1 and TNFalpha), D) Western Blot of pH2AX (DNA damage markers), E) Western Blot of CHOP (ER stress markers)

Figure: (abstract: PO-1027)

kidney-type glutaminase (KGA) for the ammonia-induced and glutamine and glucosamine synthesis-dependent astrocyte senescence.

Method: KGA and ASCT2 protein and/or mRNA levels were investigated in ammonia-exposed rat astrocytes *in vitro* and in brain samples from ammonia acetate-treated rats and in *post mortem* samples from patients with liver cirrhosis with or without HE. mRNA levels were quantified by qPCR and protein levels were analysed by Western blot and immunofluorescence and confocal laserscanning and super-resolution microscopy. Senescence-associated beta-galactosidase (SA-beta-Gal) activity was measured using the SA-beta-Gal substrate C12FDG and fluorescence microscopy.

Results: Immunofluorescence analyses revealed that KGA and ASCT2 are both present in astrocytes *in vitro* and in rat brain *in situ*. KGA and ASCT2 were both localized in mitochondria and KGA mRNA and ASCT2 mRNA and protein levels were upregulated by NH₄Cl (5 mM, 72 h) in astrocytes *in vitro*. Glutamine synthetase inhibition by methionine-sulfoximine (3 mM) or phosphinothricin (100 μM) prevented the NH₄Cl-induced upregulation of KGA. siRNA-mediated knockdown of KGA or ASCT2 or ASCT2 inhibition by O-benzyl-L-serine (10 mM) inhibited the NH₄Cl-induced upregulation of heme oxygenase 1, glucose regulated protein 78 and growth arrest and DNA damage inducible 45alpha. KGA knockdown also prevented the NH₄Cl-induced upregulation of SA-beta-Gal activity and proliferation inhibition in astrocytes *in vitro*. KGA and ASCT2 protein levels were also elevated in cerebral cortex of ammonia acetate-treated rats

(4.5 mmol/kg, 24 h) and ASCT2 mRNA levels were increased in *post mortem* brain samples from patients with liver cirrhosis and HE.

Conclusion: Our findings suggest that ammonia triggers oxidative and ER stress and senescence in astrocytes by ASCT2-dependent mitochondrial glutamine import and subsequent KGA-mediated glutaminolysis. These findings may have important implications for senescence-induced persistent cognitive impairment in patients with liver cirrhosis and HE.

Supported by German Research Foundation (DFG) through Collaborative Research Centre (CRC) 974.

PO-1606

FXR agonists increase liver-derived serum alkaline phosphatase by species-specific pharmacologic mechanisms independent of cholestasis

Justin Schumacher¹, Ting Su¹, Anthony Azzara¹, Vasanthi Bhaskaran¹, Gary Cao¹, Milinda Ziegler¹, Lisa Burns¹, Bo Kong², Grace Guo², Kristina Chadwick³, John Krupinski¹, Evan Janovitz¹. ¹Bristol Myers Squibb, Nonclinical Research and Development; ²Rutgers University, Department of Pharmacology and Toxicology; ³Bristol Myers Squibb, Global Regulatory Strategy and Policy
Email: justin.schumacher@bms.com.

Background and aims: Serum alkaline phosphatase (ALP) activity is a commonly used biomarker to detect biliary injury. Targeting the farnesoid X receptor (FXR), a nuclear hormone receptor, has shown therapeutic potential in non-alcoholic steatohepatitis (NASH). Non-bile-acid based FXR agonists increase serum ALP without

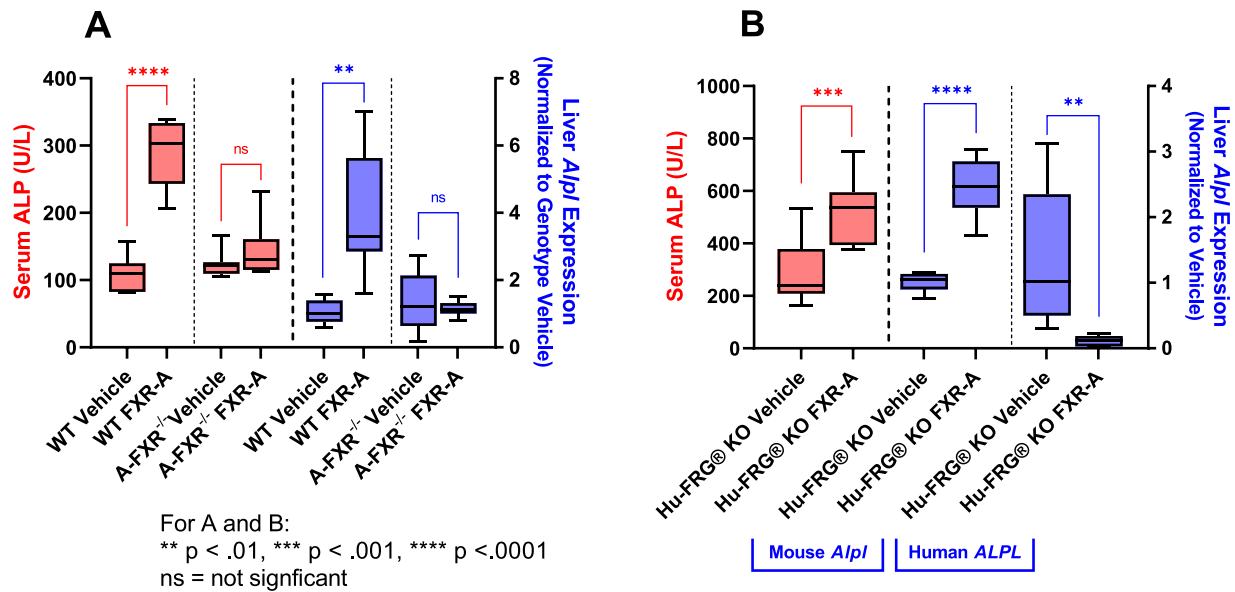


Figure: (abstract: PO-1606)

exacerbating underlying liver diseases. Increased serum ALP has been observed in mice, rats and monkeys treated with FXR agonists and it is hypothesized that the increase is based on de novo synthesis of ALP via transcriptional upregulation of genes encoding ALP.

Method: Wild-type mice (WT), hepatocyte specific FXR knockout mice (A-FXR^{-/-}), human hepatocyte chimeric mice (Hu-FRG® KO), Sprague-Dawley (SD) rats and monkeys were treated orally with either of two structurally similar, non-bile acid derived FXR agonists (FXR-A or FXR-B). Serum ALP activity and expression of genes encoding ALP isoforms in the liver (*Alpl*) and ileum (*Alpi*) were determined. Putative FXR response elements in *Alpl* regulatory regions were identified using bioinformatics and confirmed to be functional using a luciferase assay.

Results: FXR-A and/or FXR-B increased serum ALP in WT mice, Hu-FRG® KO mice, SD rats and monkeys, but not in A-FXR^{-/-} mice. These increases correlated with increased expression of liver *Alpl*, and were independent of bilirubinemia, cholestasis or biliary tract pathology. In the livers of A-FXR^{-/-} mice, *Alpl* was unchanged by FXR-A (Figure A). In the ileum of both WT and A-FXR^{-/-} mice, *Alpi* was unchanged by FXR-A. In the livers of Hu-FRG® KO mice, expression of murine *Alpl*, but not human, *ALPL* increased with FXR-A (Figure B). Correspondingly, functional FXR response elements in the rodent, but not human, regulatory regions of the *ALPL/Alpl* gene were identified. Response elements diverged between different species of non-human primates.

Conclusion: These studies indicate that FXR agonists increase serum ALP activity by FXR-dependent induction of hepatic *Alpl/ALPL* in mice, rats and monkeys, but suggest a different mechanism in humans.

PO-1615

Role of cytosolic phospholipase A2 and 5-lipoxygenase for ammonia-induced astrocyte senescence

Philipp Heimers¹, Tom Luedde¹, Dieter Häussinger¹, Boris Görg¹.
¹Heinrich Heine University Düsseldorf, Clinic for Gastroenterology, Hepatology and Infectiology, Düsseldorf, Germany
 Email: Philipp.Heimers@uni-duesseldorf.de.

Background and aims: 5-lipoxygenase (5-LO) and cytosolic phospholipase A2 (cPLA2) have been suggested to play an important role for cerebral senescence during aging. Whether 5-LO and cPLA2 also contribute to astrocyte senescence and hepatic encephalopathy (HE) is currently unknown and was investigated in the present study.

Method: Effects of ammonia on protein levels and nuclear accumulation of cPLA2, 5-LO, coactosin-like protein 1 (COTL1), P53, P21 and growth arrest and DNA damage inducible protein 45alpha (GADD45alpha) were analyzed by immunofluorescence analyses and fluorescence microscopy in rat astrocytes *in vitro*. mRNA levels of surrogate markers for oxidative (heme oxygenase 1, HO1) and endoplasmic reticulum stress (78 kDa glucose-regulated protein, GRP78) and senescence (P21, GADD45alpha) were quantified by qPCR. The activity of the senescence-associated beta-galactosidase (SA-beta-gal) was measured using the fluorogenic SA-beta-gal substrate C12FDG and fluorescence microscopy.

Results: NH4Cl (5 mM) strongly increased cytosolic and nuclear cPLA2, nuclear P-Ser505-cPLA2, 5-LO and COTL1 immunoreactivities after 24 and 72 h in rat astrocytes *in vitro*. Nuclear levels of P-Ser392-P53 and mRNA levels of HO1, GRP78, P21 and GADD45alpha were increased in NH4Cl (5 mM)-exposed astrocytes. Inhibition of cPLA2 using CAY10650 (1 uM) and inhibition of 5-LO with Zileuton (10 uM) prevented the upregulation of HO1, GRP78, P21 and GADD45alpha mRNA at 24 h but not at 72 h after NH4Cl (5 mM)-exposure. Zileuton also prevented the NH4Cl (5 mM, 72 h)-induced nuclear accumulation of P21 and GADD45alpha and increase in C12FDG fluorescence. mRNA levels of 5-LO, 5-LO activating protein (FLAP) and COTL1 were upregulated in human *post mortem* brain tissue from patients with liver cirrhosis with HE but not in those without HE.

Conclusion: The findings of the present study suggest a role of cPLA2 activation and upregulation of 5-LO for ammonia-induced oxidative and ER stress and senescence in rat astrocytes *in vitro*. mRNA levels of 5-LO, FLAP and COTL1 were also elevated in *post mortem* brain samples from patients with liver cirrhosis with but not in those without HE. The data suggest that 5-LO dependent leukotriene synthesis may play a role for senescence in ammonia-exposed rat astrocytes and in the brain in HE. Supported by German Research Foundation (DFG) through Collaborative Research Center (CRC) 974.

PO-1887

Signal regulatory protein alpha promotes immune escape of hepatocellular carcinoma through mediating T-cells apoptosis

Dongbo Chen¹, Pu Chen¹, Kangjian Deng², Liying Ren², Xingwang Xie¹, Weijia Liao², Hongsong Chen¹. ¹*Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for liver Disease, Beijing, China;* ²*Laboratory of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Guilin Medical University, Guilin, China*
Email: chen hongsong@pkuph.edu.cn.

Background and aims: Activation-induced cell death (AICD) in T lymphocytes helps maintain T cell homeostasis and peripheral immune tolerance. While tumor-mediated AICD of tumor-infiltrating T lymphocytes is more likely to be involved in tumor immune escape, detailed understanding of the mechanism is limited. In our study, we aimed to perform a genome-wide CRISPR/Cas9 knockout (GeCKO) library screening to identify key genes that, when lost, play an important role in tumor-mediated AICD of tumor-specific T cells.

Method: Firstly, the human leukemic T cell line Jurkat E6-1 cells were infected with the GeCKO lentiviral library in low multiplicity of infection (MOI), which consists 123, 411 single-guide RNAs (sgRNAs) targeting 19, 840 human genes. Then, the Jurkat E6-1-GeCKO library cells were stimulated with ConA, PMA + PHA and PMA + Ionomycin, respectively, which could lead to AICD in T-cells. Subsequently, the viable cells after culture and amplification were subjected to PCR and high-throughput sequencing to determine the corresponding genes of enriched sgRNAs that promote AICD. The candidate genes were verified in Jurkat cells with the corresponding sgRNAs, and the protein expression of these genes was detected in human HCC tissues using a novel multi-labelling immunohistochemical technique. Finally, the correlation between candidate genes and the frequency of tumor-infiltrated immune cells was determined by analyzing RNA-seq data of TCGA liver hepatocellular carcinoma (LIHC) dataset.

Results: By using GeCKO library screening, we identified 519 sgRNAs were enriched in ConA group, while 151 sgRNAs in PMA + PHA group and 449 sgRNAs in PMA + Ionomycin group. Interestingly, 121 sgRNAs were enriched in three groups. The gene ontology (GO) analysis showed that signal regulatory protein alpha (SIRPa) was involved in T cell-mediated cytotoxicity and other biological processes, suggesting that SIRPa might play an important role in promoting AICD in T-cells. In addition, we identified that the apoptosis level of Jurkat cells with SIRPa overexpression was significantly higher than that of the control group, while SIRPa depletion could significantly inhibit apoptosis. Importantly, compared to the adjacent normal tissues, SIRPa was overexpressed in tumor-infiltrating T lymphocytes of HCC tissues. Finally, the analysis of RNA-seq data of TCGA LIHC dataset revealed that the mRNA expression level of SIRPa in patients with advanced HCC was significantly higher than that in patients with early HCC, and was positively correlated with the frequency of tumor-infiltrated T cells, which suggested that SIRPa might mediate the immune escape of HCC through promoting AICD in tumor-infiltrated T cells.

Conclusion: SIRPa plays an important role in promoting AICD in T-cells and it may be as a potential therapeutic target in preventing tumor immune escape.

PO-2627

Hepatocytes Caspase6 inhibition exacerbated inflammation and fibrosis in 3D liver spheroids, stellate cells, and the GAN mouse model of NASH

Hani Jouihan¹, Sheng-Ping Wang¹, George Ho¹, Stephen Beck¹, Lifeng Wang¹, Wensheng Lang¹, Stephanie Rivera¹, Carlos Rodriguez¹, Krishna Yekkala¹, Dozie Amuzie¹, Fritz Kramer¹, Andrea Nawrocki¹, Alessandro Pocaï¹. ¹*Janssen Research and Development Spring House, Spring House, United States*
Email: hjouihan@its.jnj.com.

Background and aims: Non-alcoholic steatohepatitis (NASH) is a chronic liver disease that can result in cirrhosis and hepatocellular carcinoma (HCC). Cell death, including apoptosis is increased in human NASH and correlates with disease severity. Apoptosis is driven by the caspase cascade, which involves a series of protein cleavage and activation steps. Recent findings demonstrated that liver caspase 6 (Casp6) is increased in NASH patients and is a critical driver of hepatic cell death, however, the precise mechanism and cell type in which Casp6 is exerting its effects remains unclear.

Method: Here, we investigated the role of Casp6 across hepatic cellular populations. We leveraged siRNA to inhibit Casp6 in human 3D liver spheroids, primary human hepatic stellate cells (HSC) and the GAN diet-induced obese mouse model of NASH.

Results: Despite marked downregulation of Casp6 expression in primary HSC and 3D spheroids (-96% and -70%, respectively), no significant differences were observed in inflammatory (*IL1b*, *CCL2*, *CXCL1*) or fibrotic (*COL1a1*, *COL4a1*, *TIMP1*, *MMP-2*, -9) genes. We next utilized GalNAc-siRNA to specifically knockdown Casp6 in hepatocytes in the GAN mice. Hepatocyte Casp6 inhibition in GAN mice resulted in reduced Casp6 protein and mRNA (77% and 82% respectively) and a trend toward reduction of whole liver apoptosis (-20%, p < NS). Although no significant changes were observed in plasma ALT and AST levels, Casp6 KD resulted in reductions in liver fat mass (-12%, p < 0.01), and plasma cholesterol (-13%, p < 0.05) while expression of proinflammatory and pro-fibrotic genes such as *Tnfa*, *IL-6*, *Nlrp3*, *Col1a1*, and *Timp1* were increased. Consistent with these data, histological assessment of livers obtained from Casp6 KD mice exhibited significant increases in markers of inflammation (CD11b, +112%), fibrosis (*Col1a1* and *aSMA* +83% and +113%), newly synthesized collagen (+122%), plasma TIMP1 (+27%), and worsening of parenchymal Fibrosis Score (+88%).

Conclusion: Our data suggest that hepatocyte casp6 does not play a major role in whole liver apoptosis and its inhibition in hepatocytes exacerbated inflammation and fibrosis, thereby increasing NASH severity in the GAN mouse model of NASH.

PO-2793

Disrupted glucose-6-phosphate-ChREBP signalling aggravates hepatomegaly and accelerates liver disease progression in a mouse model for Glycogen Storage Disease type 1a

Martijn Rutten¹, Yu Lei², Joanne Hoogerland¹, Trijnie Bos¹, Aycha Bleeker¹, Rachel Thomas³, Gilles Mithieux⁴, Fabienne Rajas⁴, Alain de Bruin³, Bart van de Sluis², Maaïke Oosterveer¹. ¹*University Medical Center Groningen, Department of Pediatrics;* ²*University Medical Center Groningen, Department of Pediatrics, Netherlands;* ³*University of Utrecht, Dutch Molecular Pathology Center, Faculty of Veterinary Medicine, Netherlands;* ⁴*INSERM U1213, Université de Lyon, Université Lyon 1, France*
Email: m.h.oosterveer@umcg.nl.

Background and aims: Glycogen storage disease type 1a (GSD 1a) is an inborn error of metabolism caused by a defect in glucose-6-phosphatase (G6PC1) activity that is associated with hepatomegaly and hepatocellular tumour formation. Sustained intracellular glucose-6-phosphate (G6P) accumulation in GSD 1a results in constitutive activation of Carbohydrate Response Element Binding Protein (ChREBP), a glucose-sensitive transcription factor that has been proposed as a proliferative molecular switch. Here we assessed the consequence of disrupted G6P-ChREBP signalling on liver disease progression in a mouse model for GSD 1a.

Method: Male hepatocyte-specific *G6pc* knockout (L-*G6pc1*^{-/-}) mice were treated with AAV-shChREBP to normalize hepatic ChREBP activity to levels observed in wildtype (L-*G6pc1*^{+/+}) mice receiving AAV-shScramble. Animals were sacrificed three weeks after combined *G6pc1* knockout/ChREBP knockdown for organ and blood collection.

Results: Hepatic ChREBP knockdown severely aggravated hepatomegaly and hepatocyte size in L-*G6pc1*^{-/-} mice. The livers of these

POSTER PRESENTATIONS

animals showed increased nuclear expression and transcriptional activity of the oncogenic transcription factor Yes Associated Protein (YAP). This was paralleled by higher gamma-H2AX expression, mitotic induction, enhanced BrdU incorporation, and an enrichment of chromosomal instability, cGAS-STING cytosolic DNA sensing and hepatocyte dedifferentiation gene signatures.

Conclusion: Hepatic G6P-ChREBP signaling protects against liver disease progression in GSD Ia. These findings contribute to a better understanding of glucose imbalance-induced liver tumor development.

NAFLD: Clinical aspects except therapy

PO-19

Modeling Disease Burden of Non-alcoholic Fatty Liver Disease (NAFLD) in Japan

Junko Tanaka¹, Chris Estes², Aya Sugiyama¹, Akemi Kurisu¹, Anvarjon Rakhimov¹, Ko Ko¹, Tomoyuki Akita¹, Homie Razavi².
¹Hiroshima University, Department of epidemiology, Infectious Disease Control and Prevention, Hiroshima, Japan; ²Centers for Disease Analysis Foundation, California, United States
Email: jun-tanaka@hiroshima-u.ac.jp

Background and aims: NAFLD and resulting non-alcoholic steatohepatitis (NASH) is increasingly recognized as a growing cause of hepatocellular carcinoma (HCC) and indicator for liver transplantation globally. In Japan, a growing prevalence of obesity and metabolic syndrome, in combination with an aging population, will result in increasing rates of NAFLD-related liver disease.

Method: A dynamic disease progression model was used to track NAFLD incidence, prevalence, and related morbidity and mortality, by age- and gender-defined cohorts. New NAFLD cases were based upon trends for the increase in adult obesity (BMI ≥ 25 kg/m²) in Japan. The prevalence of NASH was based on the population-weighted distribution of NAFLD cases by fibrosis stage. Model assumptions were based on published literature and unpublished data. Changes in prevalence, advanced liver disease, and related mortality were examined.

Results: In 2020, there were an estimated 22.39 M NAFLD cases in Japan and 60% occurred among males (16.23 M cases). During 2020–2040, total NAFLD cases in Japan were estimated to decrease 7% to 20.90 M, due to decreasing total population. However, age-adjusted NAFLD prevalence (all ages) increased from 20.9% to 22.3% by 2040. The median age of the modeled NAFLD population increased from 57.6 years (2020) to 60.0 years (2040). \geq F2 NAFLD cases accounted for 7.2% of total cases, increasing to 8.9% of total cases in 2040, while the portion of \geq F3 NAFLD cases increased from 2.9% to 4.0% of total. Prevalent NASH cases were estimated to increase 2%, from 6.26 M

(2020), to 6.40 M (2040). Prevalent cases of advanced disease (cirrhosis, HCC, and liver transplant) increased by 30%, from 203,000 to 298,000 cases during 2020–2040. Incident HCC cases were projected at 1,600 cases in 2040, an increase of 20% from 2020 (1,200 cases). In 2020, there were an estimated 311,000 total deaths among the NAFLD population; 55% were among males (166,000 deaths) and 98% were classified as background mortality (306,000 deaths). Mortality attributable to NAFLD increased from 5,300 deaths in 2020 to 8,100 deaths in 2040 (35% increase).

Conclusion: The results demonstrate that growing prevalence of NAFLD will increasingly contribute to liver-related morbidity and mortality in Japan. Increasing case numbers of advanced liver disease will account for a growing portion of total liver transplants. Strategies to curb the growth of the NAFLD population, including interventions to prevent obesity and metabolic syndrome, are necessary to mitigate disease burden.

PO-33

Association between sarcopenic obesity and non-alcoholic fatty liver disease and fibrosis detected by fibroscan

Karn Wijarnpreecha¹, Elizabeth Aby², Aijaz Ahmed³, Donghee Kim³.
¹Mayo Clinic, Gastroenterology and Hepatology, Jacksonville, United States; ²University of Minnesota; ³Stanford University, United States
Email: dr.karn.wi@gmail.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) and sarcopenic obesity share several pathophysiologic backgrounds. No prior studies have determined a plausible association between sarcopenic obesity and NAFLD and NAFLD-associated fibrosis. We aim to investigate the association between sarcopenic obesity and NAFLD, and NAFLD-associated fibrosis detected by transient elastography.

Method: In a cross-sectional study from the 2017–2018 National Health and Nutrition Examination Survey, 1,925 participants were identified. NAFLD was defined by controlled attenuation parameter (CAP) scores and fibrosis/cirrhosis by liver stiffness measurements on transient elastography. Sarcopenic obesity was defined by appendicular lean mass and body fat.

Results: Individuals with sarcopenic obesity have a significantly higher odds of having NAFLD (CAP score ≥ 263 dB/m, odds ratio [OR]: 2.88, 95% confidence interval [CI] 1.82–4.57, and CAP score ≥ 285 , OR 3.71, 95% CI: 2.24–6.14) after adjusting for age, gender, and race/ethnicity. The association remains statistically significant after adjustment for socioeconomic status, lifestyle and behavioral risk factors, and metabolic conditions (CAP score ≥ 263 , OR 2.61, 95% CI: 1.51–4.50, and CAP score ≥ 285 , OR 3.31, 95% CI: 1.85–5.96). Sarcopenic obesity is also associated with higher odds of having NAFLD-associated fibrosis (OR 2.22, 95% CI 1.03–4.80) in the multivariate model.

Conclusion: Sarcopenic obesity is independently associated with an increased risk of NAFLD and NAFLD-associated fibrosis independent of well-defined risk factors. Targeted interventions to improve

Table:(abstract: PO-33): Univariate and Multivariate Odds Ratio of Risk Factors for NAFLD, NAFLD-associated Fibrosis and Cirrhosis based on the Prevalence of Sarcopenic Obesity

	Sarcopenic Obesity OR (95% CI)	P value	Sarcopenic Obesity OR (95% CI)	P value
	NAFLD (CAP ≥ 263 dB/m)		NAFLD (CAP ≥ 285 dB/m)	
Age, sex, ethnicity-adjusted	2.88 (1.82–4.57)	<0.001	3.71 (2.24–6.14)	<0.001
Multivariate model 1	2.69 (1.57–4.60)	0.001	3.37 (1.88–6.01)	<0.001
Multivariate model 2	2.61 (1.51–4.50)	0.002	3.31 (1.85–5.96)	0.001
	Significant fibrosis		Cirrhosis	
Age, gender, ethnicity-adjusted	2.60 (1.24–5.46)	<0.001	3.15 (0.56–17.75)	0.178
Multivariate model 1	2.28 (1.09–4.75)	0.030	3.31 (0.63–17.28)	0.144
Multivariate model 2	2.22 (1.03–4.80)	0.043	3.89 (0.69–21.94)	0.115

The multivariate model 1 included age, gender, race/ethnicity, education status, marital status, diabetes, smoking status, hypertension, and total cholesterol. The multivariate model 2 includes physical activity, total calorie intake, and alcohol consumption in addition to the variables in model 1.

sarcopenic obesity may reduce the risk of NAFLD and NAFLD-associated fibrosis.

PO-381

Relevance of psychosocial biomarkers on therapeutic adherence in patients with non-alcoholic fatty liver disease

Jesús Funuyet-Salas¹, María Ángeles Pérez-san-Gregorio¹, Agustín Martín-Rodríguez¹, Manuel Romero Gomez². ¹Faculty of Psychology, Department of Personality, Assessment, and psychological treatments, University of Seville, Seville, Spain; ²Digestive Diseases Unit, Virgen del Rocío University Hospital, SeLiver group at Institute of Biomedicine of Seville (IBIS), University of Seville, Seville, Spain
Email: jfunuyet1@us.es

Background and aims: The influence of psychosocial biomarkers on therapeutic adherence in patients with non-alcoholic fatty liver disease (NAFLD) is unknown. Therefore, we propose: (1) To find out whether depressive symptomatology mediates the relationship between social support and adherence to diet, as well as the relationship between physical quality of life (QoL) and adherence to physical activity, and (2) Test in both cases whether self-efficacy exerts a moderating effect on these relationships.

Method: Four hundred and thirteen biopsy-proven NAFLD patients (252 men and 161 women, mean age 55.51 ± 11.64) were evaluated using the SF-12, MSPSS, HADS, GSE, IPAQ and MEDAS instruments. For the first objective, Model 4 mediation was performed using the SPSS PROCESS v3.5 macro, while for the second objective, Model 7 for moderated mediation was used. In both models, 5000 bootstrap samples were employed to test the indirect effects estimated, which were considered significant when the confidence interval (CI) at 95% did not include 0.

Results: Depressive symptomatology mediated the association between social support and adherence to diet (effect = 0.148, CI = 0.035–0.275), as well as the relationship between physical QoL and adherence to physical activity (effect = 6.248, CI = 1.917–10.727). Self-efficacy moderated the effects that social support (beta = 0.026, p < 0.001) and physical QoL (beta = 0.004, p < 0.001) exerted through depressive symptomatology, on the adherence to diet and physical activity, respectively. In both cases, the higher self-efficacy was, the more the indirect conditional effects decreased: low self-efficacy (diet, effect = 0.095, CI = 0.025–0.181; physical activity, effect = 5.232, CI = 1.593–9.309), moderate (diet, effect = 0.050, CI = 0.011–0.103; physical activity, effect = 2.342, CI = 0.671–4.385) and high (diet, effect = 0.005, CI = -0.029–0.041; physical activity, effect = -0.549, CI = -2.557–0.817).

Conclusion: These results showed self-efficacy as a protective factor for therapeutic adherence in NAFLD patients with a psychosocial risk profile. The higher self-efficacy the lower the negative impact on the NAFLD patient's mental health. The probability of success of lifestyle intervention could be improved by self-efficacy, which could prevent a negative impact of low social support and poor physical QoL on adherence. Self-efficacy should be a psychological target in future multidisciplinary approaches for NAFLD.

PO-441

Low alcohol consumption is associated with a decreased frequency of cirrhosis and hepatocellular carcinoma in a cohort of NAFLD outpatients

Silvia Ferri¹, Bernardo Stefanini¹, Luca Muratori¹, Lorenzo Mulazzani¹, Margherita Alvisi¹, Simona Leoni¹, Francesco Tovoli¹, Fabio Piscaglia¹. ¹Division of Internal Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
Email: silvia.ferri@aosp.bo.it

Background and aims: The role of moderate degrees of alcohol use in the evolution of Non-alcoholic Fatty Liver Disease (NAFLD) is still debated, as most studies evaluated ongoing drinking habits but did not consider lifetime drinking histories. The aim of this study is to evaluate the impact on natural history of liver disease of both current and lifelong alcohol consumption in a

cohort of outpatients with NAFLD. We created a new tool, called LACU (lifetime alcohol consuming unit) to estimate the amount of alcohol consumed in lifetime: 1 LACU was defined as 7 alcohol units per week for 1 drinking year.

Method: From 1 March 2015 to 01 February 2020, we enrolled 276 consecutive patients fulfilling criteria of NAFLD: fatty liver at ultrasound, HSI (hepatic steatosis index) >30 and exclusion of other well-known causes of fatty liver. A Physician performed an interview at baseline and after 2 years regarding alcohol consumption including questions about current and lifetime alcohol consumption.

According to their current alcohol intake per week, 276 patients were divided in: abstainers, current low consumers (C1, 1–70 g per week) and moderate consumers (C2, 71–140 g per week for women and 71–210 g for men). In a different analysis patients were divided according to lifetime exposure to alcohol in abstainers and consumers. The latter were furtherly divided into quartiles: Q1 (0.1–4.29 LACU), Q2 (4.30–12.85 LACU), Q3 (12.86–40.00 LACU), and Q4 (>40.01 LACU).

Results: Age, diabetes, hypertension and alcohol consumption were independent predictors of cirrhosis and hepatocellular carcinoma (HCC) in the multivariable models. Stratification according to alcohol intake showed that a lower current alcohol consumption (C1) was associated with a decreased risk of cirrhosis and HCC compared to abstinence (p < 0.001 and p = 0.009, respectively) and to moderate alcohol consumption (C2) (p < 0.009 and p = 0.001, respectively). Similarly, low alcohol consumers attested by LACU, specifically subgroup composed by patients in Q1, Q2 and Q3, had a decreased risk of cirrhosis and HCC compared to abstainers (p = 0.005 and p = 0.001, respectively) and moderate consumers (Q4) (p = 0.002 for cirrhosis and p < 0.001 for HCC).

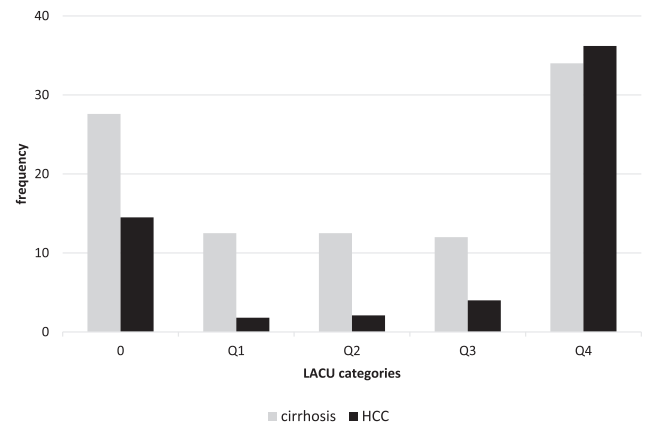


Figure:

Conclusion: Low alcohol consumption, both evaluated as current and lifelong exposure, is associated with a decreased frequency of cirrhosis and HCC compared to both abstainers and moderate alcohol consumers in patients with NAFLD.

PO-445

association of maflD with mortality in patients with covid-19 in México

Martín Uriel Vázquez Medina¹, Cesar Montejo Velazquez², Cruz Vargas-de León¹, Arcelia Carolina Barrón Campos², José Antonio Almeyda-Farfán², Alejandro Gutierrez Atemis², Julián-Gonzalo Gándara², Claudia Pantaleón Martínez², Nerina De Carmen Fernández-Martínez², Maria Del Rosario Herrero Maceda², EIRACERDA Reyes². ¹ESM-Escuela Superior de Medicina-IPN, Ciudad de México, Mexico; ²Hospital Central Militar Mexico, Gastroenterology, Ciudad de México, Mexico
Email: arkiiman@hotmail.com

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

POSTER PRESENTATIONS

It will be uploaded to the conference website once the embargo has lifted.

PO-534

Pharmacokinetics of tropifexor, a potent farnesoid X receptor agonist, are similar in subjects with mild, moderate, and severe hepatic impairment: results from a multi-centre, open-label, single-dose study

Rowan Stringer¹, Jin Chen², Jessie Gu³, Melissa Hackling², Bharti Shah², Prasanna Kumar Nidamarthy⁴, William Prince³, Ralph Woessner¹. ¹Novartis Institutes for BioMedical Research, Basel, Switzerland; ²Novartis Pharmaceutical Corporation, East Hanover, New Jersey, United States; ³Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States; ⁴Novartis Healthcare Pvt. Ltd., Hyderabad, India
Email: rowan.stringer@novartis.com

Background and aims: Tropifexor is a potent farnesoid X receptor (FXR) agonist that is currently under development for the treatment of non-alcoholic steatohepatitis. As a non-bile acid FXR agonist, tropifexor has no obvious enterohepatic circulation and shows dose-proportional pharmacokinetics. This study evaluated safety and the effect of hepatic impairment (HI) on the systemic exposure of

tropifexor, to support treatment and dosing decisions for patients with varying degrees of HI.

Method: This open-label, single-dose, parallel-group study enrolled 42 subjects: 8 each with mild, moderate, and severe HI (Child-Pugh classification) and 18 matched healthy controls. Tropifexor 200 mcg was administered as a single oral dose under fasting conditions. Dosing in the severe HI group began after half of subjects in the mild and moderate HI groups completed the study. Serial blood samples for pharmacokinetic (PK) assessments (maximum drug concentration [C_{max}], area under the concentration-time curve from time zero to (i) the time of last quantifiable concentration [AUClast], and (ii) infinite time [AUCinf]) were collected up to 168 h post-dose. Safety assessments included vital signs, electrocardiogram (ECG), and adverse event (AE) monitoring up until and including 30 days post-dose.

Results: Geometric mean treatment ratio and 90% confidence interval for tropifexor PK parameters are summarized below (Table). Exposure to total tropifexor was similar in the mild and severe HI and control groups. A geometric mean C_{max} decrease of 10% in the mild HI group and of 36% in the severe HI group was noted, while AUClast and AUCinf were similar versus controls. In patients with moderate HI, AUClast and AUCinf increased by 28%. Plasma protein binding of tropifexor was ~99.8% in all groups. Exposure to unbound (u) tropifexor was similar in the mild HI and control groups. C_{max, u} increased on average by 30% in the moderate HI group but was similar in the severe HI and control groups. AUClast, u and AUCinf, u increased on average by 64% in the moderate HI group and by 61% in the severe HI group versus controls. No drug-related AEs, serious AEs or deaths were reported. None of the vital signs or ECG abnormalities were reported as an AE for any subject.

Conclusion: A single oral dose of tropifexor 200 mcg was well tolerated in all subjects, with exposure of total tropifexor similar across groups. Although increased exposure to unbound tropifexor was seen in the moderate and severe HI groups, it was within the well-tolerated limit seen previously in healthy subjects. The safety and efficacy profile for doses planned in future studies will determine if dose adjustments in patients with moderate and/or severe HI will be warranted based on the observed increase in tropifexor unbound AUC.

Pharmacokinetic parameter	Comparison	Group comparison (total tropifexor)		Group comparison (unbound tropifexor)	
		Geo-mean ratio	90% CI	Geo-mean ratio	90% CI
C _{max} (ng*h/mL)	Mild (n = 8) versus control (n = 6)	0.90	0.52, 1.55	0.95	0.52, 1.75
	Moderate (n = 8) versus control (n = 9)	1.03	0.74, 1.44	1.30	0.96, 1.76
	Severe (n = 8) versus control (n = 5)	0.64	0.38, 1.07	1.02	0.60, 1.72
AUC _{last} (ng*h/mL)	Mild (n = 8) versus control (n = 6)	1.04	0.71, 1.53	1.11	0.70, 1.74
	Moderate (n = 8) versus control (n = 8)	1.28	1.02, 1.59	1.64	1.26, 2.15
	Severe (n = 8) versus control (n = 5)	1.01	0.66, 1.54	1.61	1.04, 2.50
AUC _{inf} (ng*h/mL)	Mild (n = 8) versus control (n = 6)	1.05	0.71, 1.54	1.11	0.71, 1.75
	Moderate (n = 8) versus control (n = 8)	1.28	1.03, 1.58	1.64	1.25, 2.16
	Severe (n = 8) versus control (n = 5)	1.01	0.66, 1.54	1.61	1.04, 2.49

AUC_{inf}, area under the concentration-time curve from time zero to infinite time; AUC_{last}, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; geo, geometric; PK, pharmacokinetic

A separate linear mixed effects model, with group as a fixed effect and matched pair as random effect, was fitted to compare each hepatic impairment group with its matching control group for each log-transformed PK parameter. Results were back transformed to obtain geo-mean ratio and 90% CI on the original scale.

Figure: (abstract: PO-534): Pharmacokinetic parameters of total and unbound tropifexor

PO-566

Association between hepatic fat and subclinical vascular disease burden in the general population

Xinting Cai^{1,2,3}, Susanne Rospleszcz^{1,4,5}, Birger Mensel⁶, Ulf Schminke⁷, Jens-Peter Kühn⁸, Ali Alexander Aghdassi⁹, Corinna Storz¹⁰, Roberto Lorbeer¹¹, Christopher Schlett¹², Wolfgang Rathmann^{13,14}, Michael Roden^{14,15,16}, Simon Hohenester¹⁷, Robin Buelow¹⁸, Fabian Bamberg¹², Annette Peters^{1,2,5,14}, Barbara Thorand^{1,14}, Henry Völzke^{19,20}, Jana Nano^{1,14}. ¹German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany; ²Ludwig-Maximilians University of Munich, Institute for Medical Information Processing, Biometry, and Epidemiology-IBE, Munich, Germany; ³Pettenkofer School of Public Health, Munich, Germany; ⁴Ludwig-Maximilians University of Munich, Institute of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology-IBE, Munich, Germany; ⁵German Center for Cardiovascular Disease Research (DZHK), Munich, Germany; ⁶University Hospital Jena, Institute of Diagnostic and Interventional Radiology, Jena, Germany; ⁷University Medicine Greifswald, Department of Neurology, Greifswald, Germany; ⁸University Hospital Carl-Gustav-Carus, Dresden University of Technology, Institute and Polyclinic for Diagnostic and Interventional Radiology, Dresden, Germany; ⁹University Medicine Greifswald, Department of Internal Medicine A, Greifswald, Germany;

¹⁰Medical Center-University of Freiburg, Faculty of Medicine, Department of Neuroradiology, Freiburg, Germany; ¹¹University Hospital, Ludwig-Maximilian-University Munich, Department of Radiology, Munich, Germany; ¹²Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Department of Diagnostic and Interventional Radiology, Freiburg, Germany; ¹³German Diabetes Center at Heinrich-Heine University, Institute for Biometrics and Epidemiology, Düsseldorf, Germany; ¹⁴German Center for Diabetes Research (DZD), partner site Munich-Neuherberg, Neuherberg, Germany; ¹⁵Medical Faculty, Heinrich-Heine University, Division of Endocrinology and Diabetology, Düsseldorf, Germany; ¹⁶German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich-Heine University, Institute for Clinical Diabetology, Düsseldorf, Germany; ¹⁷University Hospital, Ludwig-Maximilian-University Munich, Department of Medicine II, Munich, Germany; ¹⁸University Medicine Greifswald, Institute of Diagnostic Radiology and Neuroradiology, Greifswald, Germany; ¹⁹SHIP/Clinical-Epidemiological Research, University Medicine Greifswald, Institute for Community Medicine, Greifswald, Germany; ²⁰German Center for Cardiovascular Disease Research (DZHK), partner site Greifswald, Greifswald, Germany Email: xinting.cai@helmholtz-muenchen.de

Background and aims: It is still controversial if increased hepatic fat independently contributes to cardiovascular risk. Although magnetic resonance imaging (MRI) has demonstrated its overall best

POSTER PRESENTATIONS

performance in detecting subclinical changes in different organs, there is a paucity of studies utilizing MRI to examine the association between hepatic fat content and parameters of subclinical vascular disease. We aimed to assess the association between hepatic fat quantified by MRI and various subclinical vascular disease parameters.

Method: We included two cross-sectional investigations imbedded in two independent population-based studies (SHIP: n = 1341; KORA: n = 386). The participants underwent a whole-body MRI examination. Hepatic fat content was quantified by proton-density fat fraction (PDFF). Aortic diameters in both studies and carotid plaque-related parameters in KORA were measured with MRI. In SHIP, carotid intima-media thickness (cIMT) and plaque were assessed by ultrasound. We used (ordered) logistic or linear regression to assess associations between hepatic fat and subclinical vascular disease.

Results: The prevalence of fatty liver disease (FLD) (PDFF > 5.6%) was 35% in SHIP and 43% in KORA. In SHIP, hepatic fat was positively associated with ascending (beta, 95% confidence interval [CI]: 0.06 [0.04, 0.08]), descending (0.05 [0.04, 0.07]) and infrarenal (0.02 [0.01, 0.03]) aortic diameters, as well as with higher odds of plaque presence (odds ratio [OR], 95% CI: 1.22 [1.05, 1.42]) and greater cIMT (beta, 95% CI: 0.01 [0.004, 0.02]) in the age- and sex-adjusted model. However, further adjustment for additional cardiometabolic risk factors, particularly body mass index, attenuated these associations. In KORA, no significant associations were found.

Conclusion: The association between hepatic fat and subclinical vascular disease was not independent, but explained by overall adiposity. Given the close relation of FLD with cardiometabolic risk factors, in accordance with guidelines, people with FLD should still be prioritised for cardiovascular disease screening.

PO-614

Additive Effects of Diabetes and NAFLD on Liver Disease Severity and Clinical Outcomes in the General Population (NASH-CO Study)

Oumarou Nabi¹, Nathanaël Lapidus², Jerome Boursier^{3,4}, Victor de Lédinghen⁵, Philippe Mathurin^{6,7}, Marcel Goldberg⁸, Marie Zins^{8,9}, Karine Lacombe^{10,11}, Lawrence Serfaty¹². ¹Institute Pierre Louis Epidemiology And Public Health, Sorbonne Université, Paris, France; ²Institute Pierre Louis Epidemiology and Public Health, Sorbonne Université, Paris, France; ³Centre Hospitalier Universitaire d'Angers, Angers, France; ⁴UPRES EA3859, Angers, France; ⁵Hospital Center University De Bordeaux, Medecine, Bordeaux, France; ⁶Chu De Lille, Lille, France; ⁷Inserm U995, Lille, France; ⁸Inserm UMS 11, Villejuif, France; ⁹Hôpital Paul-Brousse Ap-Hp, Villejuif, France; ¹⁰Hospital Saint-Antoine Ap-Hp, Paris, France; ¹¹Institute Pierre Louis Epidemiology And Public Health, Medecine, Paris, France; ¹²Arlin Alsace Hospitals Academics De Strasbourg, Strasbourg, France
Email: lawrence.serfaty@chru.strasbourg.fr

Background and aims: Relationships between diabetes and NAFLD have been mainly investigated at the hospital setting, with the risk of an overestimation of the true burden of liver disease. From a general population-based cohort, this study aimed to assess the severity of NAFLD and clinical outcomes among type 2 diabetic subjects in a community setting.

Method: The study population consisted of 199, 341 participants from the nationwide CONSTANCES cohort. After exclusion of subjects with excessive alcohol consumption, viral hepatitis or other causes of liver diseases, 164, 285 were analyzed. Among them, 8386 (5.3%) had type 2 diabetes. Non-invasive diagnosis of NAFLD and advanced fibrosis was performed using the combination of Fatty Liver Index and Forns Index. Outcomes analyzed were liver-related events, cardiovascular disease, extrahepatic cancer, chronic kidney disease, liver transplantation and overall mortality. Median follow-up was 2.5 years.

Results: The prevalence of NAFLD and NAFLD with advanced fibrosis among diabetic versus non-diabetic subjects was 61.1% (95% CI 60–62.2) vs 15.2% (95% CI 15–15.3) ($p < 0.0001$) and 4.8% (95% CI 4.2–5.4)

vs 1.2% (95% CI 1–3) ($p < 0.0001$), respectively. Rate of advanced fibrosis raised to 10% (95% CI 8–12) in case of additional metabolic disorders and to 13.9% (95% CI 7.2–20.6) in diabetic requiring insulin therapy. When adjusted for other risk factors, diabetes, diabetes remained associated with both NAFLD and advanced fibrosis (OR = 1.36, 95% CI 1.24–1.51 and OR = 1.95, 95% CI 1.36–2.8, respectively). When adjustment for usual risk factors, presence of diabetes in NAFLD subjects was associated with increased risk of liver-related events (aHR = 4.26, 95% CI 2.46–7.38), while presence of NAFLD in diabetic subjects was associated with increased risk of cardiovascular-related events or extra-hepatic malignancy (aHR = 1.99, 95% CI 1.16–4.22, and aHR = 4.63, 95% CI 1.18–15.1, respectively). Risk of death was significantly increased by both the presence of diabetes among NAFLD subjects (aHR = 1.32, 95% CI 1.02–2.31) and the presence of NAFLD among diabetic subjects (aHR = 1.25, 95% CI 1.03–2.51).

Conclusion: From a large community-based cohort with no excessive alcohol consumption, this study confirms the additive effect of diabetes and NAFLD on liver disease progression, diabetes-related complications and overall mortality, regardless of usual risk factors. Advanced fibrosis, which was less frequent in this unselected population than previously reported, should be screened in subjects with additional metabolic disorders or advanced diabetes.

PO-630

Undiagnosed obstructive sleep apnoea is a major component in NAFLD quality of life impairment

Wenhao Li¹, Benjamin Karl Kadler¹, James Hallimond Brindley¹, Victoria Berryman¹, Johanna Preston¹, Melanie Patrick¹, Caroline Sutcliffe¹, Gillian Hood¹, Wing-kin Syn², William Alazawi¹. ¹Barts Liver Centre, Blizard Institute, Queen Mary University of London, London, United Kingdom; ²Division of Gastroenterology and Hepatology, Department of Medicine, Medical University of South Carolina, Charleston, United States
Email:

Background and aims: Quality of life (QOL) is lower in people with NAFLD compared to the general population. This particularly affects physical health-related domains and is associated with co-morbid obesity and type 2 diabetes (T2DM). Obstructive sleep apnoea (OSA) is a breathing disorder that can affect people with obesity and is also associated with reduced QOL. However the role of undiagnosed OSA on QOL in NAFLD is unclear. Epworth Sleepiness Scale (ESS) is a validated screening questionnaire that identifies individuals with symptoms of OSA. However, ESS is not routinely utilised in QOL assessments in NAFLD patients. We aim to assess whether ESS-determined symptoms of OSA are independently associated with reduced QOL in NAFLD patients.

Method: In a prospective study, we conducted QOL assessments in 192 individuals with NAFLD using Short Form-36 (SF-36) version 2 questionnaire and ESS questionnaire. SF-36 consists of 36 questions related to physical and mental wellbeing, resulting in physical component score (PCS) and mental component score (MCS). QOL data were analysed with using multivariate linear regression to identify factors independently affecting QOL scales.

Results: Individuals with NAFLD reported lower SF-36 scores compared to published data for the general UK population. Physical health in particular was significantly reduced (PCS: 35.33 vs 50.02, $p < 0.0001$). 1 in 8 NAFLD patients had known OSA at enrolment, but a significantly higher proportion (1 in 4) recorded ESS score >10. Compared to NAFLD individuals with ESS score ≤ 10 , those with ESS score >10 were more obese (36.7 kg/m² vs 31.3 kg/m², $p < 0.0001$), with higher prevalence of T2DM (58.9% vs 42.7%, $p = 0.044$), and had lower PCS (26.9 vs 38.2, $p < 0.0001$) and MCS (39.3 vs 51.5, $p < 0.0001$). No differences in age or gender were observed. In multivariate linear regression, ESS score >10 was the most significant independent predictor of reduced PCS. Age, BMI and transient elastography score were also significantly associated (Table).

Predictors of physical health-related QOL	Multivariate analysis (whole cohort, n = 192)				Multivariate analysis (excluding pre-existing OSA, n = 166)			
	B Coefficient	(95% CI)		P value	B Coefficient	(95% CI)		P value
Age	-0.254	-0.401	-0.106	0.001	-0.229	-0.378	-0.080	0.003
Diabetes diagnosis	-1.364	-5.413	2.684	0.507	-1.531	-5.821	2.760	0.482
BMI	-0.510	-0.817	-0.203	0.001	-0.565	-0.888	-0.243	0.001
Transient elastography score	-0.318	-0.579	-0.057	0.017	-0.302	-0.586	-0.018	0.037
ESS score > 10	-8.478	-12.907	-4.049	<0.001	-7.498	-12.445	-2.551	0.003

(Only variables with p < 0.05 in univariate analysis were included for multivariate analysis)

Table: (abstract: PO-630)

Sensitivity analysis showed that after excluding those with diagnosed OSA, ESS score >10 remained the strongest predictor of reduced PCS. **Conclusion:** Elevated ESS score >10, which is likely to represent undiagnosed OSA, is an independent predictor of reduced QOL in patients with NAFLD. Risk of OSA, as determined by elevated ESS scores, should be considered in clinical practice and when evaluating patient-related outcomes in clinical trials.

PO-685
The benefits of the novel nomenclature of metabolic fatty liver disease

Álvaro Santos-Laso¹, Paula Iruzubieta^{1,2}, María Teresa Arias Loste^{1,2}, Tatiana Fernandez¹, Lorena Cayon¹, Agustín García¹, Laura Rasines¹, Ana Álvarez-Cancelo¹, José Luis Calleja Panero^{2,3}, Javier Crespo^{1,2}.
¹Marqués de Valdecilla University Hospital, Clinical and Translational Research in Digestive Diseases, IDIVAL, Santander, Spain; ²Centro De Investigación Biomédica En Red De Enfermedades Hepáticas y Digestivas (CIBEREHD), Spain; ³Hospital Universitario Puerta de Hierro, IDIPHISA, Gastroenterology and Hepatology, Madrid, Spain
 Email: javier.crespo@scsalud.es

Background and aims: A consensus of international experts has recently proposed a new nomenclature and diagnostic criteria for fatty liver disease associated with metabolic dysfunction, opening a great debate. The impact of this new classification in clinical practice is not yet known. We aim to determine the prevalence of metabolic-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD) in general population and to evaluate the clinical-related differences between both criteria.

Method: Observational, cross-sectional, population-based study from the ETHON Cantabrian cohort (n = 5, 989). This population cohort includes clinical data, laboratory test, transient elastography (TE) and controlled attenuation parameter (CAP) obtained the same day. Fatty liver was defined by CAP ≥ 248 dB/m or fatty liver index (FLI) ≥ 60, and significant fibrosis by TE ≥ 7.2 kPa.

Results: We excluded 48 subjects for lacking CAP and FLI. A total of 3, 167 subjects had fatty liver and, consequently, were amenable to meet the NAFLD and/or MAFLD diagnostic criteria. NAFLD and MAFLD were diagnosed in 2, 883 (48.5%) and 2, 809 (47.3%) subjects of general population, respectively. Compared with NAFLD, MAFLD patients were significant more likely to be male, older and with higher body mass index. Moreover, MAFLD patients showed higher levels of triglycerides, liver enzymes, FLI and CAP, as well as higher rate of significant fibrosis (8.8% vs 7.2%, p = 0.03), in comparison to NAFLD patients. Importantly, when we excluded MAFLD patients with other causes of liver injury (i.e., alcohol, viral hepatitis or cholestatic disorders) (n = 264), no significant difference was found in significant fibrosis between purely metabolic MAFLD and NAFLD patients (7.9% vs 7.2%, p = 0.3). In fact, in MAFLD patients, the presence of other concomitant factor of liver injury was identified as an independent risk factor for fibrosis (OR 2.583; 95% CI 1.374–4.855; p = 0.003). Diabetes was also associated with a risk for significant fibrosis in MAFLD patients (OR 6.029; 95% CI 3.519–10.328; p < 0.001).

Conclusion: The presence of MAFLD led to increased risk of significant fibrosis, being incremented when other causes of liver injury were identified.

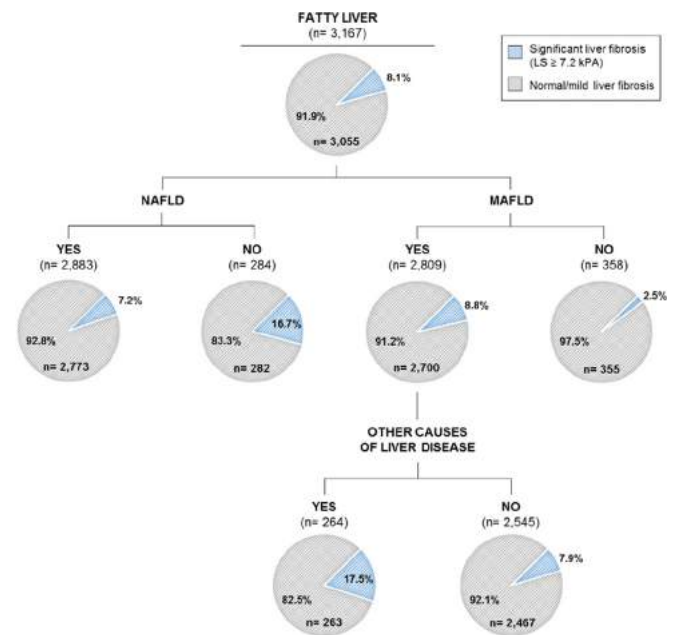


Figure:

PO-711
Binge Eating Disorder is associated with an unfavourable body mass composition in patients with Non-Alcoholic fatty liver disease

Roberta Forlano¹, Chris Harlow¹, Benjamin H. Mullish¹, Mark Thursz¹, Pinelopi Manousou¹, Michael Yee². ¹Imperial College London, Department of Metabolism, Digestion and Reproduction, London, Northern Ireland; ²Imperial college NHS Trust, Department of Endocrinology, London, Northern Ireland
 Email: r.forlano@imperial.ac.uk

Background: The impact of eating disorder on NAFLD remains unexplored, especially with regards to eating disorders such as Binge Eating Disorder (BED). The aim of this study was to assess the risk factors for the presence of BED among patients with Non-Alcoholic Fatty liver disease and the impact of BED on body mass composition.

Methods: all consecutive referrals of NAFLD were prospectively assessed in a tertiary hepatology centre in London. Patients were asked to fill a BED screener-7 (BEDS-7), while clinical parameters, body mass composition on bioelectrical impedance analysis (BIA) and Fibroscan measurements were recorded at baseline and at 6 months follow-up.

Results: 81 patients were included, 23 (28.4%) of whom screened positive for BED. BED positive patients were younger (52 vs 59 years, p = 0.03), more frequently not committed in a stable relationship (61.5% vs 20.8%, p = 0.013) compared to BED negative (n = 58). On

POSTER PRESENTATIONS

multivariate analysis, a previous diagnosis of depression (OR 3.8, $p = 0.025$) and marital status (OR 6.08, $p = 0.018$) were associated with a positive BEDS-7. Furthermore, BED positive patients were heavier (BMI 33.8 vs 29.6 kg/m², $p = 0.01$), presented with larger waist ($p = 0.03$) and hip ($p = 0.01$) circumferences, with further increase of waist circumference during follow-up (+0.04 vs -0.23 cm/month, $p = 0.02$). Finally, those with BED presented with greater fat mass (37.1% vs 31.4%, $p = 0.002$) and lower muscle mass (56.7% vs 65.1%, $p = 0.001$) on BIA, when compared to the non-BED (Figure 1). There was no difference in terms of disease stage as assessed by liver stiffness, although CAP score was higher among those positive for BED (331 vs 299 dB/m, $p = 0.041$).

Figure 1: Fat and muscle mass as percentage of total body weight in BED and non-BED patients on bioelectrical impedance analysis.

Blue: BED positive. Yellow: BED negative

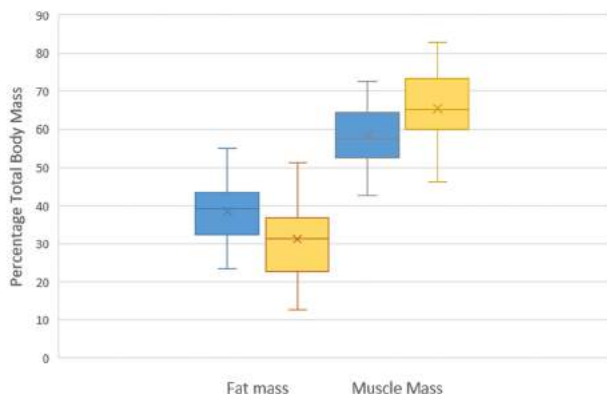


Figure:

Conclusion: BED is highly frequent and associated with an unfavourable body mass composition in patients with NAFLD. Tackling obesity and metabolic diseases requires a holistic approach.

PO-719

Carriage of CYP2E1rs2070673:A is associated with higher prevalence of non-alcoholic steatohepatitis in patients with biopsy-proven non-alcoholic fatty liver disease

Hong-Lei Ma¹, Sui-Dan Chen², Kenneth I. Zheng¹, Yue Yu³, Xin-Xin Wang³, Liangjie Tang³, Gang Li³, Rafael Rios³, Ou-Yang Huang³, Xiao-Yong Zheng³, Ren-Ai Xu³, Giovanni Targher⁴, Chris Byrne⁵, Xiaodong Wang¹, Yong-Ping Chen¹, Ming-Hua Zheng¹.
¹the First Affiliated Hospital of Wenzhou Medical University, Department of Hepatology, wenzhou, China; ²the First Affiliated Hospital of Wenzhou Medical University, Department of Pathology; ³the First Affiliated Hospital of Wenzhou Medical University; ⁴University and Azienda Ospedaliera Universitaria Integrata of Verona; ⁵Southampton General Hospital
 Email: zhengmh@wmu.edu.cn

Background and aims: Cytochrome P450 2E1 (CYP2E1) plays a role in lipid metabolism, and by increasing hepatic oxidative stress and inflammation, up-regulation of CYP2E1 may be involved in development of non-alcoholic steatohepatitis (NASH). We aimed to explore the relationship of CYP2E1 genetic variants and histological severity of non-alcoholic fatty liver disease (NAFLD).

Method: We studied a cohort of 438 consecutive patients with biopsy-proven NAFLD. NASH was defined as NAFLD Activity Score ≥ 5 with existence of steatosis, ballooning and lobular inflammation. SNP rs2070672 and rs2070673 encoding CYP2E1 were genotyped by MALDI-TOF mass spectrometry. Serum cytokines related to inflammation were measured by the Bio-plex 200 system to investigate possible mediating factors involved in the process.

Results: Carriage of rs2070673:A in CYP2E1 was associated with a higher prevalence of severe lobular inflammation (26.1% vs. 13.3%, $P < 0.01$) and NASH (52.9% vs. 40.5%, $P = 0.01$). Multivariable regression modelling showed that this genetic variant was associated with severe lobular inflammation (adjusted-odds ratio: 2.79, 95% CI 1.57–4.93, $P < 0.01$) or NASH (adjusted-odds ratio, 95% CI: 1.74, 1.13–2.67, $P = 0.01$), independently of age, sex and common metabolic risk factors. Compared with no-NASH, patients with NASH had significantly higher levels of serum interleukin-1 receptor antagonist, interleukin-18 and interferon-inducible protein-10 (IP-10), whereas only IP-10 was increased with rs2070673:A ($p < 0.01$). Mediation analysis showed that IP-10 was responsible for 66% of the association between the CYP2E1 rs2070673 variant and NASH.

Conclusion: rs2070673:A in the CYP2E1 gene is strongly associated with NASH and this effect is largely mediated by serum IP-10 levels.

SNP	rs2070673		P-value	
	Genotype	AA+TA		TT
N		280	158	
Clinical characteristics				
Age (years)		41 ± 13	42 ± 13	0.18
Male sex (%)		205 (73.2%)	110 (69.6%)	0.42
Total bilirubin (mmol/L)		14 ± 6	14 ± 7	0.72
Albumin (g/L)		46.0 ± 4.2	46.3 ± 3.7	0.82
ALT (U/L)		57.0 (35.8-99.2)	52.5 (28.0-87.0)	0.03
ALP (U/L)		84 ± 24	83 ± 22	0.57
GGT (U/L)		55.0 (35.0-86.2)	47.5 (30.2-78.8)	0.07
Fasting glucose (mmol/L)		5.8 ± 1.7	5.7 ± 1.4	0.70
Creatinine (mmol/L)		67 ± 14	68 ± 16	0.70
Uric acid (mmol/L)		398 ± 103	396 ± 117	0.51
Total cholesterol (mmol/L)		5.11 ± 1.16	5.12 ± 1.16	0.89
Triglycerides (mmol/L)		1.98 (1.44-2.92)	1.88 (1.37-2.59)	0.23
HDL-cholesterol (mmol/L)		1.00 ± 0.22	0.99 ± 0.21	0.98
LDL-cholesterol (mmol/L)		3.05 ± 0.94	3.08 ± 0.90	0.75
HOMA-IR score		3.45 (2.60-5.10)	3.90 (2.40-5.30)	0.76
BMI (kg/m ²)		27 ± 3	27 ± 4	0.80
Comorbidity				
Hypertension (%)		88 (31.4%)	54 (34.2%)	0.56
Type 2 diabetes (%)		92 (32.9%)	52 (32.9%)	0.99
Dyslipidemia (%)		254 (91.4%)	143 (91.1%)	0.92
Central obesity (%)		205 (75.1%)	112 (73.7%)	0.75
Liver histology features				
Moderate/severe steatosis		181 (64.6%)	88 (55.7%)	0.07
Presence of ballooning		243 (86.8%)	136 (86.1%)	0.83
Moderate/severe lobular inflammation		73 (26.1%)	21 (13.3%)	<0.01
Definite NASH		148 (52.9%)	64 (40.5%)	0.01
Presence of fibrosis		217 (77.5%)	119 (75.3%)	0.60

Categorical values are shown as n (%). Continuous variables are shown as mean ± SD. Significant p values were marked in bold italics.

Abbreviations: BMI, body mass index; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ -glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.

Figure:

PO-819

Real-world assessment of NAFLD stages using FibroScan in the US population and diabetes subpopulation based on data from NHANES 2017–2018

Mazen Nouredin¹, Fady Tanios², Birol Emir², Deepa Malhotra², Euan McLeod³, Katherine Hoover², Naim Alkhouri⁴.
¹Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, United States; ²Pfizer Inc, New York, United States; ³Pfizer Ltd, Tadworth, Surrey, United Kingdom; ⁴Arizona Liver Health, Chandler, United States
 Email: mazen.nouredin@cshs.org

Background and aims: Non-alcoholic steatohepatitis (NASH) is a progressive subset of non-alcoholic fatty liver disease (NAFLD), and

can lead to hepatic fibrosis, cirrhosis and cardiovascular disease. This analysis aimed to determine the prevalence of NAFLD with fibrosis, as assessed by transient elastography (FibroScan®), in the National Health and Nutrition Examination Survey (NHANES) database (2017–2018), including a cohort with type 2 diabetes mellitus (T2DM).

Methods: Adult subjects with valid FibroScan® measurements were included (N = 4, 471) in this analysis. The age-adjusted prevalence of NAFLD was calculated for the overall population and a subpopulation with T2DM. Clinical characteristics, NAFLD, fibrosis stage and comorbidities were compared between groups. Controlled attenuation parameter cut-off of 302 dB/m determined NAFLD; liver stiffness cutoffs were ≤8.2, ≤9.7, ≤13.6 and >13.6 kPa for F0–F1, F2, F3 and F4, respectively.

Results: Dataset included 3, 831 eligible subjects (excluding subjects with heavy alcohol use, viral hepatitis and HIV), 821 (21.4%) of whom had T2DM. Of eligible subjects, 1, 226 (32.0%)/468 (57.0%) had NAFLD in the overall/T2DM cohorts. For the NAFLD cohorts (overall/T2DM), most subjects had F0–F1 fibrosis (71.4/66.2%), followed by F2 (6.4/8.5%), F3 (6.9/9.0%) and F4 (4.6/8.1%). Rates and means of clinical characteristics and comorbidities are in the Table.

Table: Age-adjusted characteristics and comorbidities of subjects

	Overall NAFLD/non- NAFLD	NAFLD F2– F3/F0–F1	T2DM NAFLD/non- NAFLD
% of subjects	31/69	12/75*	66/34
Characteristics			
Age, years, mean	48/47	48/48	49/50
Male, %	57/44	66/57	45/39
BMI ≥ 30 kg/m ² , %	74/29	94/73	82/48
Alanine aminotransferase, U/L, mean	29/20	37/29	33/25
Aspartate aminotransferase, U/L, mean	24/20	27/22	25/21
Comorbidities, %			
Hypertension	45/24	43/44	51/47
Diabetes	30/8	44/24	100/100
Hypercholesterolaemia	43/33	50/43	53/45
Ischaemic heart disease	7/4	11/6	11/8

*Remainder NASH F4 (5%), cryptogenic cirrhosis (2%), fibrosis and moderate steatosis (6%)

Conclusion: Results estimate NAFLD prevalence in the US population and in a subpopulation with T2DM. Results may inform disease diagnosis rates, health regulators and access to treatment as they provide real-world size estimates of the NAFLD population that needs therapeutic intervention. Results also highlight the clinical characteristics and higher prevalence of NAFLD with fibrosis in patients with T2DM.

PO-825

Use of machine learning to develop a NAFLD screening tool using demographic, clinical and FibroScan data from the NHANES 2017–2018 database

Birol Emir¹, Mazen Nouredin², Naim Alkhoury³, Deepa Malhotra¹, Euan McLeod⁴, Katherine Hoover¹, Darren Jeng⁵, Gordon Siu¹, Fady Tanios¹. ¹Pfizer Inc, New York, United States; ²Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, United States; ³Arizona Liver Health, Chandler, United States; ⁴Pfizer Ltd, Tadworth, Surrey, United Kingdom; ⁵Pfizer Inc, Groton, United States
Email: birol.emir@pfizer.com

Background and aims: Several scores have been developed to predict NAFLD based on liver ultrasound. However, liver ultrasound has known sensitivity and specificity limitations and may be difficult

to apply for screening in large health system populations. Machine learning (ML) techniques have been used clinically to predict outcomes based on subject-level data. The objective of this analysis was to explore a new screening tool to predict NAFLD, identified by the controlled attenuation parameter (CAP; FibroScan®) using demographic and clinical data from a large US cohort in the National Health and Nutrition Examination Survey (NHANES) database (2017–2018).

Methods: Adult subjects (>20 years of age) with valid FibroScan® measurements were included, and heavy drinkers were excluded. Overall, 3, 381 subjects were analysed. The population was split into training (N = 2, 874) and test/validation (N = 957) sets. NAFLD was defined as CAP > 302 dB/m; other causes of liver disease were excluded. Covariates for which less than 10% of data were missing were imputed using a random forest approach. Over 100 features were inputted to the models. Six different ML methods were fit to the training data: an elastic net (lasso), logistic regression, conditional single classification tree, random forest, support vector machine and neural network.

Results: The test/validation performances of the ML methods were very similar with respect to predictive ability (area under the receiver-operating characteristics curve [ROC] ranged between 0.79–0.84, sensitivity between 0.66–0.71 and specificity between 0.75–0.86) (Figure). The following variables were statistically significant predictors of NAFLD (p value <0.01): age, body mass index, waist, HbA1c, aspartate aminotransferase, alkaline phosphatase, diastolic blood pressure, high-density lipoprotein, triglycerides and gender. Logistic regression was selected as the most appropriate model due to its simplicity, ease of interpretation and similar performance, compared with the other models, to develop a new ML-based screening tool to predict NAFLD in the general population.

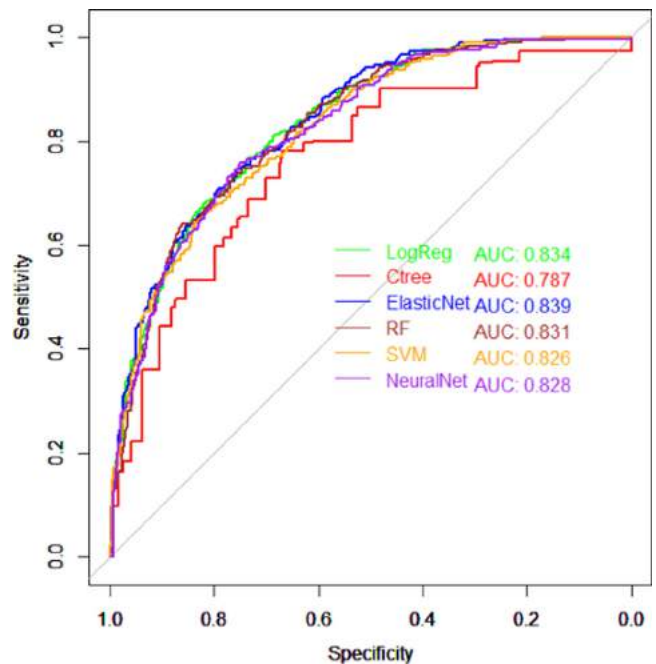


Figure: Validation/test performances of area under the ROC for the six different ML methods.

Conclusion: The newly developed ML models may be used to screen patients with NAFLD using standard demographic and clinical data and to potentially replace more costly, less accurate or invasive diagnostic tools.

POSTER PRESENTATIONS

PO-831

Liver related and extrahepatic events in patients with non-alcoholic fatty liver disease: a competing risk analysis

Grazia Pennisi¹, Marco Enea², Manuel Romero Gomez³, Mauro Viganò⁴, Elisabetta Bugianesi⁴, Vincent Wai-Sun Wong⁵, Anna Ludovica Fracanzani⁶, Giada Sebastiani⁷, Jerome Boursier⁸, Annalisa Berzigotti⁹, Mohammed Eslam¹⁰, Javier Ampuero³, Amine Benmassaoud⁷, Yuly Paulin Mendoza⁹, Jacob George¹⁰, Antonio Craxi¹, Calogero Camma¹, Salvatore Petta¹. ¹University of Palermo, Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), Palermo, Italy; ²University of Palermo, Dipartimento di Scienze Economiche, Aziendali e Statistiche, Palermo, Italy; ³Institute of Biomedicine of Seville de Biomedicina de Sevilla, University of Seville, Digestive Diseases Unit, Hospital Universitario Virgen del Rocío, Biomedical Research Networking Center in Hepatic and Digestive Diseases (CIBEREHD), Sevilla, Spain; ⁴University of Torino, Division of Gastroenterology, Department of Medical Sciences, Torino, Italy; ⁵The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China; ⁶Policlinico Hospital, University of Milan, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Milano, Italy; ⁷McGill University Health Centre, Montreal, Division of Gastroenterology and Hepatology, Montreal, Canada; ⁸Centre Hospitalier Universitaire d'Angers, Angers, Service d'Hépatogastroentérologie et Oncologie Digestive, Angers, France; ⁹University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Department for Biomedical Research, Berna, Switzerland; ¹⁰Westmead Hospital, University of Sydney, Storr Liver Centre, Westmead Institute for Medical Research, Sydney, Australia
Email: graziapennisi901@gmail.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is associated with a high risk of liver-related events (LRE) and also extrahepatic events (EHE). We evaluated the competitive risk occurrence of LRE and EHE in a large cohort of biopsy-proven NAFLD stratified according to baseline severity of fibrosis.

Method: Patients with a histological diagnosis of NAFLD were enrolled. During follow-up, LRE and EHE were recorded. Observed cumulative incidence functions (CIFs) were used to evaluate the risk of LRE and EHE occurrence; cause-specific Cox, subdistribution hazard models and predicted CIFs were fitted to identify predictors of LRE and EHE. Models were validated in a replication cohort of NAFLD with non-invasive assessment of liver fibrosis by liver stiffness.

Results: 2135 patients (F0–F1 = 1136; F2 = 362; F3–F4 = 637) with biopsy-proven NAFLD were enrolled. According to the observed CIFs the 60 month probability of LRE and EHE was 0.2% and 3% in F0–F1, 2% and 3.8% in F2, and 9.7% and 6.4% in F3–F4 patients, respectively. In the cause-specific Cox model, in F0–F1 and F2 patients, age >50 years (HR2.7, beta0.99, p = 0.001) was the only one predictor of LRE, while age >50 years (HR2.96, beta1.08, p < 0.001), previous cardiovascular events (CVE, HR2.07, beta0.73, p = 0.03) and previous extra hepatic cancer (EHC, HR2.36, beta0.86, p = 0.003) were independent risk factors for EHE. In F3–F4 patients, age >55 years (HR1.73, beta0.55, p = 0.03), obesity (HR1.52, beta0.42, p = 0.03), PLT < 150,000/mm³ (HR3.66, beta1.30, p < 0.001) and GGT (HR1.77, beta0.57, p < 0.001) were associated with LRE, while age >55 years (HR1.74, beta0.55, p = 0.006) and previous CVE (HR2.51, beta0.92, p < 0.001) were independent predictors of EHE. Predicted CIFs for HE and EHE in F0–F1, F2 and F3–F4 patients well stratified the risk of events. The results were confirmed with the FineandGray model, and externally validated.

Conclusion: In NAFLD patients, by using competing risks models, the likelihood of EHE is relevant and raises according to the severity of liver fibrosis, while the risk of LRE is negligible in F0–F1, low but clinically relevant in F2 and high in F3–F4 patients. These data could help to personalize follow-up in NAFLD.

PO-950

A serum metabolic fingerprint may predict advanced fibrosis due to NAFLD in a cohort of diabetic patients

Roberta Forlano¹, Benjamin H. Mullish¹, Jesus Miguens Blanco¹, Nathan Danckert¹, Mark Thursz¹, Pinelopi Manousou¹. ¹Imperial college London, Department of Metabolism, Digestion and Reproduction, London, United Kingdom
Email: r.forlano@imperial.ac.uk

Background and aims: Several serum metabolites have been previously-associated with the onset and progression of non-alcoholic fatty liver disease (NAFLD) and type-2 diabetes mellitus (T2DM). However, only a relatively limited number of such metabolites are currently recognised, and study to design to date has made it difficult to delineate whether such metabolites represent NAFLD *per se* or if they are proxies of T2DM. The aim of this study was to identify serum metabolomic profiles in T2DM patients with and without NAFLD and with different disease stage.

Method: Fasting serum samples obtained from patients with T2DM who were screened for liver disease by blood tests, ultrasound (US), fasting liver stiffness measurement (LSM) and CAP score. Samples were analysed using a non-targeted approach with Proton-Nuclear Magnetic Resonance (H¹-NMR)-based metabolomics. Results were explored by performing multivariate statistical analysis using SIMCA[®].

Results: Of 300 patients enrolled, serum samples were collected from 254 subjects. Overall, 167 (65%) had NAFLD, 20 (7%) other causes of liver disease (BAFLD and HBV) and 67 (26%) no liver disease. Among those with NAFLD, 46 (18%) showed evidence of significant fibrosis (LSM > 8.1 kPa).

A range of serum metabolites-including amino acids, lipoproteins and other small molecules-were identified and quantified in all samples. A valid model separated the serum metabolite profile of NAFLD vs non-NAFLD patients, with NAFLD patients demonstrating higher serum glutamate and lower glycine and glutamine compared to those without NAFLD (cross-validated residuals (CV) ANOVA, p = 0.02) (Figure 1). Similarly, patients with NAFLD and increased LSM demonstrated higher serum glutamate and lower glycine and glutamine compared to those with NAFLD and normal LSM (CV-ANOVA, p = 6.5 × 10⁻⁶) and compared to those without NAFLD (CV-ANOVA, p = 1.1 × 10⁻⁵; R2X: 0.137; R2Y: 0.535; Q2: 0.228).

On linear regression, glycine correlated inversely with CAP score (R² = -0.18, p = 0.003) and with LSM (R² = -0.15, p = 0.014). Conversely, the glutamate to glutamine ratio (glutamate/glutamine) correlated positively with CAP score (R² = 0.26, p < 0.0001) and with LSM (R² = 0.41, p < 0.0001). Furthermore, the glutamate/glutamine ratio predicted the presence of significant fibrosis (LSM > 8.1 kPa) with AUROC 0.74 (p = 0.0001, 95% CI: 0.65–0.83) and advanced fibrosis (LSM > 12.1 kPa) with AUROC 0.809 (p = 0.001, 95% CI: 0.71–0.9) (Figure 1).

Conclusion: In T2DM patients, the glutamate to glutamine ratio may predict NAFLD with fibrosis accurately. Metabolomics in combination with clinical parameters holds promise for improving the non-invasive detection of NAFLD. New insights from metabolomics may also allow for discovering novel drug targets and precision treatment of patients with NAFLD.

PO-969

Successful implementation of a weight loss intervention pathway for non-alcoholic fatty liver disease patients by advanced practice hepatology providers with obesity training

Vicki Shah¹, Sarah Repking¹, Colleen Folkers¹, Sujit Janardhan¹, Lelani Fetrow¹, Nancy S. Reau¹. ¹Rush University Medical Center, Chicago, United States
Email: vickishah2@gmail.com

Background and aims: American Association for the Study of Liver Diseases (AASLD) practice guidelines state that 5–10% weight loss with lifestyle changes or bariatric surgery in obese patients are treatments of choice to prevent NAFLD progression. Weight loss

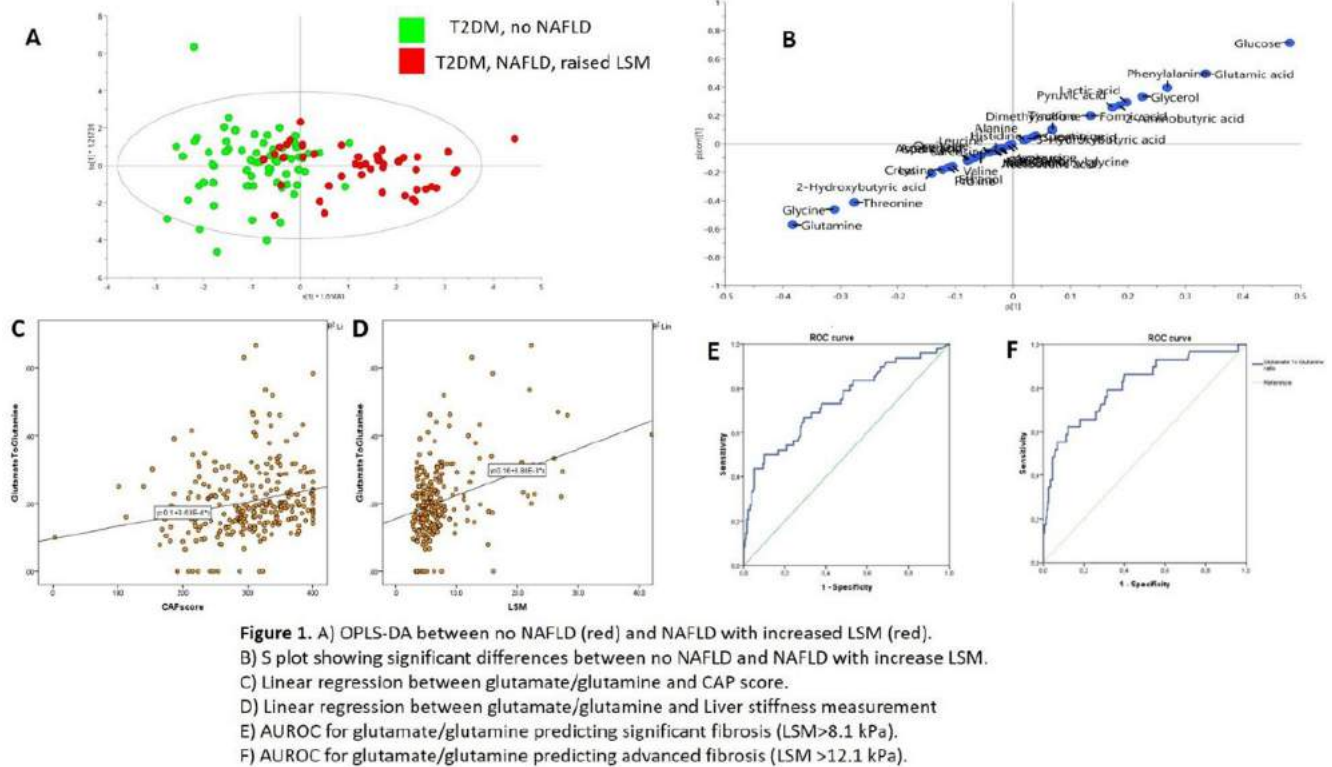


Figure 1: (abstract: PO-950)

interventions may include dietary changes, behavioral modifications, physical activity, and pharmacologic treatment. While clinical trials for weight loss in NASH have shown to achieve >5% total body weight loss (TBWL) in 30% of patients and >10% TBWL in 10% of patients, it is unclear if this can be recreated in the real-world clinical setting.

Method: In 2018, our department started an embedded Weight Loss Intervention in Liver Disease (WILD) pathway led by a hepatologist and advanced practice providers (APPs) all trained in obesity medicine. WILD provided intensive lifestyle strategies for those with liver disease and BMI > 25. Patients are followed monthly after initial consultation. A retrospective review was completed for retention rate and percent weight change for patients who attended at least one WILD appointment.

Results: Between November 2018 to December 2020, 77 patients attended at least one WILD appointment. Fifteen failed to return after the first visit with mean TBWL of 0.6%. Sixty-two patients attended >1 WILD visit indicating 80.6% retention rate. 45 (73%) achieved TBWL of 5.47%, 14 (22%) had weight gain of 1.22%, and three (5%) had no change. Of the 45 patients with TBWL, 15 patients achieved >5% weight loss and 7 achieved >10% weight loss.

Conclusion: Our study demonstrates that an APP run weight intervention was successful in achieving weight loss in engaged patients comparable to those achieved in clinical trials for weight loss in NASH patients. 73% WILD patients achieved weight loss and 33% of patients that remained in the pathway lost at least 5% of TBW which has been associated with improvement in NAFLD.

PO-1030

Different associations of variants in hydroxysteroid 17-beta dehydrogenase 13 with liver histology in ethnic Chinese

Wen-yue Liu¹, Mohammed Eslam², Kenneth I. Zheng³, Hong-Lei Ma³, Rafael Rios³, Min-Zhi Lv⁴, Gang Li³, Liangjie Tang³, Pei-Wu Zhu⁵, Xiao-Dong Wang³, Chris Byrne⁶, Giovanni Targher⁷, Jacob George², Ming-Hua Zheng^{3,8,9}. ¹Department of Endocrinology, the First Affiliated

Hospital of Wenzhou Medical University, Wenzhou, China; ²Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia; ³MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ⁴Department of Biostatistics, Zhongshan Hospital, Fudan University, Shanghai, China; ⁵Department of Laboratory Medicine, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ⁶Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, UK; ⁷Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; ⁸Institute of Hepatology, Wenzhou Medical University, Wenzhou, China; ⁹Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China
Email: zhengmh@wmu.edu.cn

Background and aims: In Europeans, variants in the hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) gene impact the liver histology of metabolic associated fatty liver disease (MAFLD). The impact of these variants in ethnic Chinese is unknown. The aim of this study was to investigate the potential associations in Chinese patients

Method: 427 Han Chinese with biopsy-confirmed MAFLD were enrolled. Two single nucleotide polymorphisms in HSD17B13 were genotyped-rs72613567 and rs6531975. Logistic regression was used to test the association between the SNPs and liver histology.

Results: As shown in Table, the minor allele TA of the rs72613567 variant was related to an increased risk of fibrosis [OR = 2.93 (1.20–7.17), p = 0.019 for the additive model; OR = 3.32 (1.39–7.91), p = 0.007 for the recessive model], an inverse association as compared to the results from European cohorts. In contrast, we observed a protective effect on fibrosis for the minor A allele carriers of the HSD17B13

POSTER PRESENTATIONS

Table. Association between *HSD17B13* variants and liver histology features in Chinese MAFLD patients

SNPs	Severe steatosis		Severe ballooning		Severe Inflammation		Presence of fibrosis		
	OR	P	OR	P	OR	P	OR	P	
rs72613567*									
Additive model									
T/T	ref.	---	ref.	---	ref.	---	ref.	---	
T/TA	1.24	0.368	0.93	0.737	1.24	0.437	0.77	0.252	
TA/TA	1.62	0.203	1.37	0.368	1.99	0.092	2.93	0.019	
Dominant model									
T/T	ref.	---	ref.	---	ref.	---	ref.	---	
T/TA + TA/TA	1.30	0.234	1.01	0.973	1.38	0.216	0.96	0.867	
Recessive model									
T/T + T/TA	ref.	---	ref.	---	ref.	---	ref.	---	
TA/TA	1.46	0.292	1.42	0.295	1.8	0.127	3.32	0.007	
rs6531975**									
Additive model									
G/G	ref.	---	ref.	---	ref.	---	ref.	---	
G/A	0.69	0.104	0.95	0.802	0.94	0.83	0.65	0.063	
A/A	0.91	0.809	0.59	0.164	0.84	0.69	0.48	0.043	
Dominant model									
G/G	ref.	---	ref.	---	ref.	---	ref.	---	
G/A + A/A	0.73	0.138	0.87	0.496	0.92	0.751	0.62	0.025	
Recessive model									
G/G + G/A	ref.	---	ref.	---	ref.	---	ref.	---	
A/A	1.08	0.833	0.60	0.17	0.86	0.726	0.59	0.123	

*OR and 95% CI obtained by binary logistic regression analysis adjusted for age, sex, BMI, presence of diabetes, fasting glucose, triglycerides and HDL-cholesterol.

**OR and 95% CI obtained by binary logistic regression analysis adjusted for age, sex, BMI, presence of diabetes.

Abbreviations: BMI, body mass index; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; ref., reference.

Table 1: (abstract: PO-1030)

rs6531975 variant [OR = 0.48 (0.24–0.98), $p = 0.043$ for the additive model; OR = 0.62 (0.40–0.94), $p = 0.025$ for the dominant model]. HSD17B13 variants were only associated with fibrosis but not other histological features. Furthermore, HSD17B13 rs6531975 modulated the effect of PNPLA3 rs738409 on hepatic steatosis.

Conclusion: The HSD17B13 rs72613567 variant is a risk variant for fibrosis in a Han Chinese MAFLD population but with a different direction for allelic association to that seen in Europeans. This data exemplifies the need for studying diverse populations in genetic studies in order to fine map GWAS signals.

PO-1205

Prevalence of lean NAFLD vs lean MAFLD indicates a distinct risk of mortality

Georg Semmler^{1,2}, Sarah Wernly¹, Sebastian Bachmayer¹, Isabella Leitner¹, Matthias Egger¹, Lorenz Balcar^{1,2}, Marie Semmler¹, David Niederseer³, Elmar Aigner⁴, Christian Datz¹. ¹General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Department of Internal Medicine, Oberndorf, Austria; ²Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ³University Hospital

Zurich, Department of Cardiology, Zurich, Switzerland; ⁴Paracelsus Medical University Salzburg, First Department of Medicine, Salzburg, Austria
Email: c.datz@kh-oberndorf.at

Background and aims: Recently, the novel “metabolic associated fatty liver disease” (MAFLD) definition has been introduced. However, lean patients with (non-alcoholic-) fatty liver disease (NAFLD) not meeting MAFLD-criteria are left without diagnosis, and management of these patients is unclear.

Method: 5372 patients without chronic liver disease other than NAFLD/MAFLD or significant alcohol consumption participating in a colorectal screening program were grouped according to their BMI and the presence or absence of NAFLD/MAFLD. Mortality was compared among these groups by performing a systematic read-out of the national health insurance system using Kaplan-Meier analyses with log-rank-test.

Results: Overall, 1574 (29.3%) subjects were lean and did not have NAFLD/MAFLD, 119 (2.2%) were lean and had NAFLD, but did not fulfil criteria for MAFLD, and 237 (4.4%) subjects were lean and fulfilled criteria for MAFLD. Additionally, 1093 (20.3%) and 976 (18.2%) were

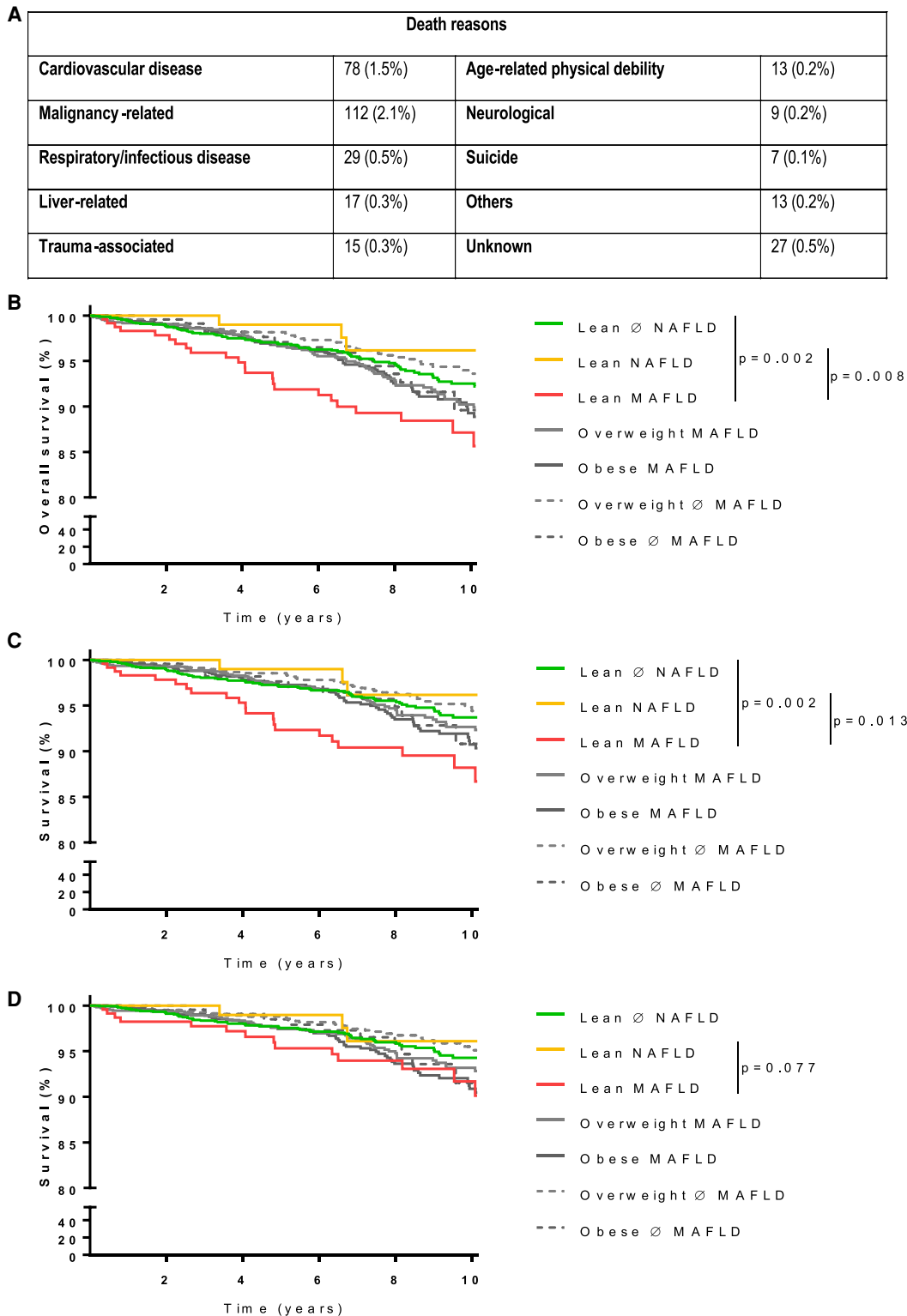


Figure: (abstract: PO-1205): (A) Reasons for death, (B) overall survival among all patients, (C) excluding traumatic deaths, suicide, and unknown deaths, and (D) also excluding patients with newly diagnosed colorectal cancer and active malignancy at baseline.

overweight (BMI 25–30 kg/m²) and obese (BMI ≥ 30 kg/m²) and had MAFLD while 1134 (21.1%) and 239 (4.4%) were overweight and obese without MAFLD. During a median follow-up was 7.5 (IQR: 5.7) years, 320 deaths (6.0%) occurred. Of these, 112 (2.1%) were malignancy-associated and 78 (1.5%) were cardiovascular, among others (Figure 1A). Overall survival

(Figure 1B) was different among patient strata, attaining statistical significance for lean patients without NAFLD, lean NAFLD and lean MAFLD (after 5 years: 96.9% vs. 99.0% vs. 91.9%, $p = 0.002$; lean NAFLD vs. lean MAFLD: $p = 0.008$). Results were similar after excluding patients with trauma-associated death, suicide, and unknown reasons (Figure 1C) being significantly different for lean subjects (p

POSTER PRESENTATIONS

=0.002) and lean NAFLD vs. lean MAFLD (after 5 years: 99.0% vs. 92.3%, $p=0.013$). However, results did not attain statistical significance when also excluding patients with newly diagnosed colorectal cancer at baseline and active malignancy (lean NAFLD vs. lean MAFLD: 99.0% vs. 95.3%, $p=0.077$; Figure 1D).

Conclusion: Survival is different among lean patients according to the presence/absence of NAFLD and MAFLD. Specifically, lean NAFLD seems to follow a benign course.

PO-1227

Poor Awareness of Non-alcoholic Fatty Liver Disease (NAFLD) Among Adults in the United States

James Paik^{1,2}, Rakish Biswas³, Tamooore Arshad³, Saleh Alqahtani^{1,4}, Alita Mishra^{1,2,5}, Zobair Younossi^{1,2,5}. ¹Inova Health System, Department of Medicine, Center for Liver Diseases, Falls Church, United States; ²Inova Health System, Beatty Liver and Obesity Research Program, Falls Church, United States; ³Center for Outcomes Research in Liver Disease, Washington DC, United States; ⁴King Faisal Specialist Hospital, Riyadh, Saudi Arabia; ⁵Inova Health System, Medicine Service Line, Falls Church, United States

Email: zobair.younossi@inova.org

Background and aims: Despite being the most common cause of liver disease, there is substantial lack of disease awareness about NAFLD. We aimed to estimate disease awareness about NAFLD in the US general population.

Method: We used data for adults (≥ 18 years) collected as a part of National Health and Nutrition Examination Survey (NHANES) from 2007 to 2016. The U.S. Fatty Liver Index for the (US-FLI) was used to establish the diagnosis of NAFLD in the absence of secondary causes of liver disease. Advanced fibrosis was defined by Fibrosis-4 score of >2.67 . Awareness was defined as a positive response to the question "Have you ever told by a doctor or health professional that you had any kind of liver condition?"

Results: Among 11,700 eligible participants [mean age 47.4 years; 48.8% male; 67.6% white, 10.2% black and 8.7% Mexican American], 34.19% (95% confidence interval [CI], 32.77%–35.62%) had NAFLD. This prevalence rate remained stable over time: 32.6% (2007–2008) to 36.6% (2015–2016) (trend $P=0.286$). Awareness of having liver disease among NAFLD subjects increased from 4.27% (2.92%–5.63%) in 2007–2008 to 6.31% (4.76%–7.86%) in 2015–2016. When stratified by age, awareness of having liver disease among NAFLD subjects improved during the same period (from 1.18% to 3.68% for aged 30–44, from 5.45% to 8.28% for aged 45–64 and from 6.09% to 7.67% for aged ≥ 65), while the awareness decreased from 2.65% to 0% for aged 18 to 29. Awareness was higher in female subjects (8.23% vs. 4.83%). In multivariable analysis, presence of diabetes (adjusted odds ratio [aOR] = 2.44, 95% CI, 1.53–3.88), having advanced fibrosis (aOR = 2.17, 1.14–4.41) and higher numbers of health care visits (aOR = 1.31, 1.13–1.50) were independently associated with better awareness of having liver disease among subjects with NAFLD. In contrast, non-Hispanic Black race/ethnicity (aOR = 0.37, 0.18–0.77) was associated with lower awareness of having liver disease.

Conclusion: Nearly 95% of adults with NAFLD in the U.S. were unaware that they had liver disease. These data suggest that substantial efforts are needed to improve awareness of NAFLD among the general population, particularly among the young adults and the non-Hispanic Black Americans.

PO-1296

Pruritus, anxiety, and depression in patients with non-alcoholic fatty liver disease

Albrecht Boehlig¹, Florian Gerhardt¹, David Petroff^{2,3}, Florian van Bömmel¹, Thomas Berg², Valentin Blank^{3,4}, Thomas Karlas⁴, Johannes Wiegand¹. ¹Division of Hepatology, Department of Medicine II, Leipzig University Medical Center; ²Clinical Trial Center Leipzig, University of Leipzig, Leipzig, Germany; ³Integrated Research and Treatment Center AdiposityDiseases Leipzig, Faculty of

Medicine, University of Leipzig, Leipzig, Germany; ⁴Division of Gastroenterology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany

Email: Albrecht.Boehlig@medizin.uni-leipzig.de

Background and aims: Patient reported outcomes are gaining attention in non-alcoholic fatty liver disease (NAFLD). Interventional trials show increased prevalence of depression in NAFLD patients compared to the general population. Pruritus is of special interest for evolving therapies with farnesoid X receptor (FXR) agonists. Thus, we aimed to analyse the prevalence of pruritus, anxiety, and depression and possible associations.

Method: We offered a screening for patient reported outcomes to outpatients with NAFLD. Pruritus was assessed using a visual-analogue- (VAS) and 5-D itch-scale (5-D) and classified (VAS/5-D) as absent (0/5–8), mild (1–3/9–11), moderate (4–6/12–17), severe (7–8/18–21), or very severe (9–10/22–25). Anxiety and depression were evaluated by Beck's-Depression-Inventory (BDI, relevant score ≥ 18) and the Hospital Anxiety and Depression Scale (HADS-A and HADS-D, relevant score ≥ 11). Fibrosis and steatosis were assessed with vibration controlled transient elastography including liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). An optimal logistic regression model was found with a step-wise procedure to investigate variables associated with pruritus. Contingency tables were analysed with Fisher's Exact Test.

Results: 123 NAFLD patients were prospectively recruited (mean age 56 years, 53% women, 12% cirrhosis, mean BMI 29.8 ± 5.1 kg/m²; 33% diabetes mellitus). Mean VAS was 1.7 ± 2.2 and was 8.3 ± 4.0 for 5-D with a strong correlation between the two (Spearman 0.89). Moderate or severe pruritus was observed in 19% (VAS) and 21% (5-D) of patients. Clinically relevant anxiety was found in 12% of patients and depression in 4% (HADS-D) and 12% (BDI). There was a significant association between VAS and BDI ($p=0.019$). The final multivariate model for VAS included CAP with odds ratios (OR) for moderate/severe itching per 10 dB/m of 1.06 (95% CI 0.97–1.17; $p=0.17$) and relevant HADS-A (OR 2.78, 95% CI 0.75–9.53; $p=0.12$). For 5-D, the model included diabetes mellitus (OR 4.51; 95% CI 1.43–15.3; $p=0.01$), relevant BDI (OR 5.98; 95% CI 1.27–28.8; $p=0.024$) and relevant HADS-A (OR 7.75; 95% CI 1.62–40.1; $p=0.011$).

Conclusion: One fifth of NAFLD patients report moderate or severe pruritus. 5-D and VAS were highly correlated, however, only 5-D but not VAS was significantly associated with diabetes mellitus, depression (BDI) and anxiety. These findings should be tested in larger populations to further clarify comorbidities associated with pruritus and consider them in candidates for treatment with FXR agonists.

PO-1334

Mild alcohol consumption and risk for cardiovascular disease in patients with non-alcoholic steatohepatitis: data from a multicenter observational study

Savvoula Savvidou¹, Margarita Papatheodoridi², Konstantinos Zisimopoulos³, Kanellos Koustenis⁴, Demetrios N. Samonakis⁵, Theodoros Voulgaris², Spilios Manolakopoulos⁴, Christos Triantos³, Christos Tsoulas⁶, George Papatheodoridis², Ioannis Goulis¹. ¹Hippocraton University Hospital of Thessaloniki, Medical School of Aristotle University, Thessaloniki, 4th Department of Internal Medicine, Thessaloniki, Greece; ²General Hospital of Athens "Laiko", Medical School of National and Kapodistrian University of Athens, Department of Gastroenterology, Athens, Greece; ³Department of Internal Medicine, University Hospital of Patras, Medical School of Patras, Division of Gastroenterology, Patras, Greece; ⁴Hippocraton University Hospital of Athens, Medical School of National and Kapodistrian University of Athens, Gastroenterology and Endoscopy Unit, 2nd Department of Internal Medicine, Athens, Greece; ⁵University Hospital of Heraklion, Crete, Gastroenterology and Hepatology Department, Heraklion Crete, Greece; ⁶Gilead Sciences Hellas, Medical Department, Athens, Greece

Email: ssavidou@med.auth.gr

Background and aims: The beneficial effects of light alcohol drinking on the cardiovascular system have never been investigated in patients with non-alcoholic fatty liver disease (NAFLD). Aim of this multicenter study was to investigate possible associations of mild/occasional alcohol consumption with the risk for cardiovascular disease (CVD) in patients with advanced NAFLD, namely non-alcoholic steatohepatitis (NASH).

Method: Consecutive NASH pts from five tertiary liver centers were assessed with the QRISK2 formula (incl. age, gender, ethnicity, smoking, diabetes, antihypertensive drugs, cholesterol to HDL ratio and BMI) that estimates the % risk of experiencing a major CVD incidence in the forthcoming decade. Mild/occasional drinking was defined as self-reported consumption of less than 1 standard drink per day, for less than 3 days per week, in the preceding 6-month period. Current or past use of alcohol exceeding this limit was within exclusion criteria.

Results: 804 NASH pts were included, of which 106 with NASH-related compensated cirrhosis: 428 (53.2%) males, mean age 58.3 ± 14.5 years, all of white Caucasian origin, mean BMI 30.3 ± 4.7 kg/m², diabetes 239 (29.7%), dyslipidemia 404 (50.2%), hypertension 211 (26.2%), current smokers 38.6%-former 16.3%. Distribution of hepatic fibrosis to F0–F4 stages: 13.1%–28.8%–21.2%–15.3%–21.6%. Liver biochemistry: median ALT 66 IU/L (IQR 49–96), AST 42 IU/L (IQR 31–58), γGT 63 IU/L (IQR 38–117). About 1/3 of pts (n = 256, 31.8%) reported mild/occasional alcohol consumption compared to none. QRISK2 was calculated in 776 (96.5%) NASH pts without previous history of CVD (median 5.2%, IQR 1.8–12.7%, 26.2% high-risk pts with QRISK2 ≥ 10%). Mild alcohol was associated with male gender (p <

0.001), younger age (p < 0.001), smoking (p < 0.001), absence of diabetes (p = 0.042) and higher cholesterol/HDL ratio (p = 0.017). QRISK2 ranged to lower values in pts consuming mild/occasional alcohol (3.8%, IQR 1.15–10.9 vs. 5.9%, IQR 2.15–13.55, Mann-Whitney test, p = 0.005), irrespective of age, gender, BMI or fibrosis stage. (GRAPH). Comparisons between groups revealed that mild alcohol was associated with statistically significant lower CVD risk independently in pts with normal BMI (p = 0.03) or with F2 fibrosis stage (p = 0.011).

Conclusion: The results of this study suggest that mild/occasional alcohol consumption compared to absolute abstinence may lower risk for CVD in NASH. Prospective studies are needed to confirm this effect.

PO-1429

Clinical and prognostic differences between non-alcoholic fatty liver disease and mixed fatty liver disease

Nicolau Vallejo-Senra¹, Maria-Violeta Mauriz-Barreiro¹, Esther Molina^{1,2}. ¹Hospital Clínico Universitario de Santiago de Compostela, Gastroenterology and Hepatology, Santiago de Compostela, Spain; ²Hospital Clínico Universitario de Santiago de Compostela, Liver Transplantation Unit, Spain
Email: nicolau.vallejo@hotmail.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most frequent liver disease in developed countries. Alcohol itself can cause liver steatosis and cell damage. However, there is little data about the differences between patients with low-risk alcohol intake

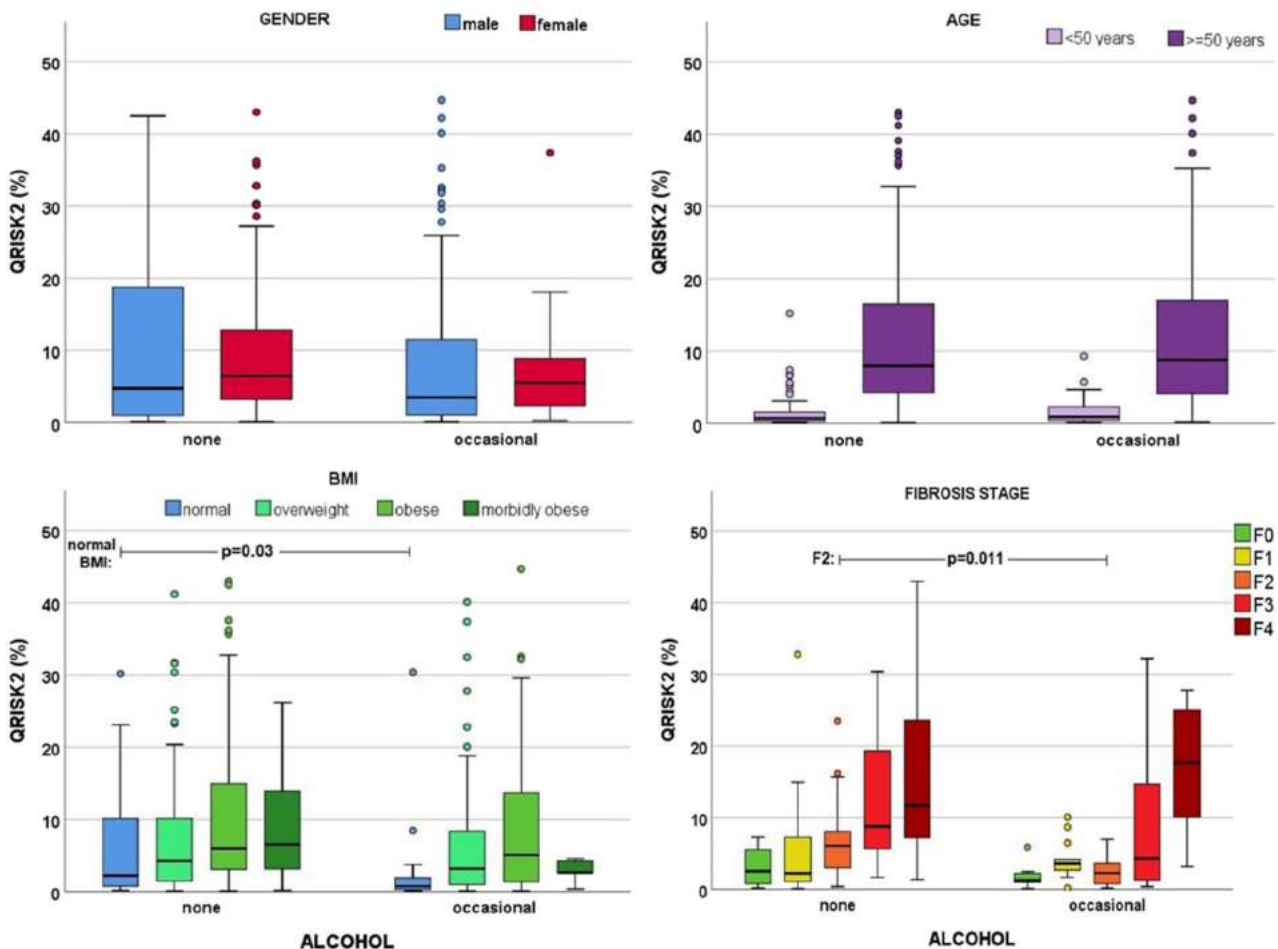


Figure: (abstract: PO-1334)

POSTER PRESENTATIONS

and liver steatosis (mixed fatty liver disease [MiFLD]) and non-alcohol intake with liver steatosis ("pure" non-alcoholic fatty liver disease [NAFLD]). The aim of this study is to assess the characteristics of these 2 types of non-predominant-alcoholic liver steatosis diseases.

Method: A retrospective study of all patients visited at our unit during the year 2019 with the diagnosis of NAFLD was performed. Sex, age, date of diagnosis, obesity, arterial hypertension, diabetes, dyslipidemia were evaluated. Patients with high-risk alcohol intake (≥ 4 units/day for men and ≥ 3 units/day for women) were excluded, as well as patients with other liver diseases. Patients with low-risk alcohol intake (1–3 units/day for men and 1–2 units/day for women) were defined as MiFLD. Patients without any intake of alcohol were defined as NAFLD. The diagnosis of F3 and cirrhosis was based on a combination of radiological studies, histology, transient elastography (considering $F3 > 10$ kPa and $F4 > 15$ kPa in two occasions, when histology was not available) and analysis parameters (platelets, liver function test). Results are shown as means and percentages and analyzed by chi-square test and Student-t test. P value < 0.05 was considered significant.

Results: 495 patients were included (60.4% male), with median age of 58 years (range 19–86). 63.4% were considered NAFLD, and 36.6% were MiFLD. The global prevalence of obesity, diabetes, dyslipidemia and arterial hypertension were 57.7%, 33.3%, 60.6% and 54.5%, respectively. The prevalence of $\geq F3$ was 23.6%, with cirrhosis in 15.7%. There were significant differences between NAFLD and MiFLD in age (57 vs 61, $p = 0.001$), male sex (43.3% vs 90%, $p < 0.001$), arterial hypertension (46.2% vs 69.1%, $p < 0.001$), $\geq F3$ (18.1% vs 33.1%, $p < 0.001$) and cirrhosis (11.4% vs 23.2%, $p = 0.001$). However, no significant differences in diabetes ($p = 0.919$), obesity ($p = 0.306$) and dyslipidemia ($p = 0.083$) were found.

Conclusion: Patients with MiFLD have a higher risk of advanced fibrosis and cirrhosis than NAFLD, without more prevalence of metabolic factors except hypertension. This data supports that any amount of alcohol intake should be avoided in fatty liver disease.

PO-1436

Ultra-processed food is associated with features of the metabolic syndrome and nafl related liver damage

Dana Ivancovsky Wajcman¹, Naomi Fliss Isakov², Revital Kariv^{2,3}, Muriel Webb^{2,3}, Oren Shibolet^{2,3}, Shira Zelber-Sagi^{1,2}. ¹University of Haifa, School of Public Health, Haifa, Israel; ²Tel Aviv Medical Clinic, Gastroenterology, Tel Aviv-Yafo, Israel; ³Tel Aviv University, Sackler Faculty of Medicine, Tel Aviv-Yafo, Israel
Email: danaivanc@gmail.com

Background and aims: Ultra processed foods (UPF) comprise up to 50% of the calories in a western diet and are characterized by low nutritional quality, high energy, sugar and fat density and additives. High consumption of UPF was recently found to be associated with all-cause mortality, cancer, cardiovascular disease, type-2 diabetes and metabolic syndrome, but has not been studied in relation to non-alcoholic fatty liver disease (NAFLD) or fibrosis. Therefore, we aimed to test the association of UPF consumption with the metabolic syndrome and its components and with NAFLD.

Methods: A cross-sectional study among subjects who underwent anthropometrics, blood pressure measurements and fasting blood tests including FibroMax for non-invasive assessment of NASH and borderline significant fibrosis (F1–F2 and above). Fatty liver was diagnosed by abdominal ultrasound (US). The metabolic syndrome was diagnosed according the acceptable criteria. Food-frequency questionnaire was used to evaluate UPF consumption using the NOVA classification. UPF Kcal/total Kcal intake above the sample median (corresponding to $>28\%$) was considered as high consumption. Smoking habits were evaluated by self-reported questionnaires.

Results: A total of 789 subjects were included in the total sample (mean age 58.83 ± 6.58 years, 52.60% men), reliable FibroMax test was obtained from 714 subjects, 305 subjects were diagnosed with NAFLD by US. In multivariate analysis adjusting for age, gender, body mass index and other nutritional habits, high consumption of UPF was significantly associated with higher odds for metabolic syndrome (OR = 1.88, 95% CI 1.31–2.71, $P = 0.001$) and its components hypertension, high triglycerides and low HDL (OR = 1.53, 95% CI 1.07–2.19; $P = 0.020$; OR = 1.55, 1.05–2.29, $P = 0.028$; OR = 1.51, 1.08–2.11, $P = 0.017$, respectively) among the entire sample and with higher

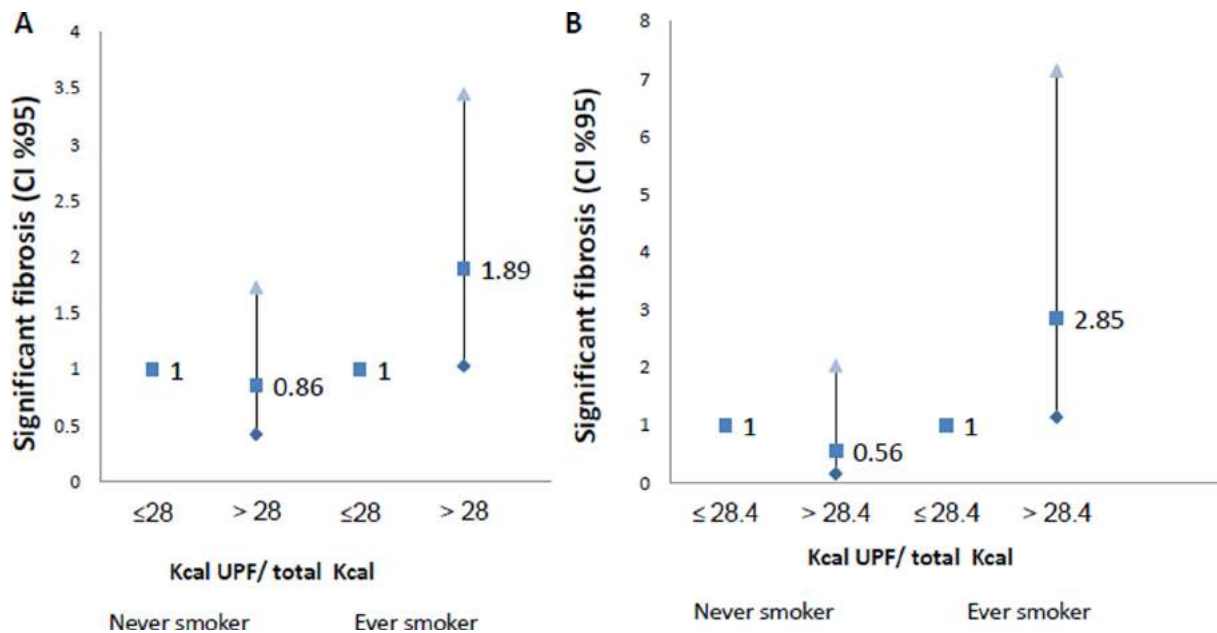


Figure: (abstract: PO-1436): Multivariate association between UPF consumption (by medians) and significant fibrosis stratified by smoking status among the entire sample (A) or subjects with NAFLD (B). The multivariate model is adjusted for: age, gender, BMI, saturated fat and protein intake (% of total Kcal), fibers intake (gr/d), physical activity (hours/week) and coffee (cups/d).

odds for NASH and hypertension (OR = 1.89, 95% CI 1.07–3.38, P = 0.030; OR = 2.26, 1.20–4.26, P = 0.012, respectively) among subjects with NAFLD. Stratification by smoking status (ever vs. never smokers) revealed an association between high UPF consumption and significant fibrosis among ever smokers in the entire sample and in a sub sample of subjects with NAFLD (OR = 1.89, 95% CI 1.03–3.45, P = 0.039; OR = 2.85, 1.14–7.14, P = 0.026, respectively).

Conclusions: High UPF consumption is associated with the metabolic syndrome and NASH marker. Among smokers, high UPF consumption is associated with significant fibrosis, suggesting a synergistic effect.

PO-1526

The natural history of pediatric Non-alcoholic Fatty Liver Disease: interim analysis of a long term follow-up study

Laura Draijer¹, Maaïke Voorhoeve¹, Marian Troelstra², Meeïke Kusters³, Eric de Groot^{4,5}, Aart Nederveen², Marc Benninga¹, Bart Koot¹. ¹Amsterdam UMC, location AMC, Pediatric Gastroenterology, Hepatology and Nutrition, Amsterdam, Netherlands; ²Amsterdam UMC, location AMC, Radiology and Nuclear Medicine, Amsterdam, Netherlands; ³Amsterdam UMC, location VUmc, Pediatrics, Amsterdam, Netherlands; ⁴Imagelabonline and Cardiovascular, Erichem, Netherlands; ⁵Amsterdam UMC, location AMC, Gastroenterology, Amsterdam, Netherlands
Email: l.g.draijer@amsterdamumc.nl

Background and aims: The long term hepatic outcome of pediatric Non-alcoholic fatty liver disease (NAFLD) remains unclear due to the lack of robust longitudinal data. Between 2008–2012, an unselected cohort of 104 children with severe obesity was screened for NAFLD. Steatosis was detected in 50% of the children based on Proton Magnetic Resonance Spectroscopy (¹H-MRS). None of them had significant fibrosis based on the Enhanced Liver Fibrosis Test (ELF test). Cardiovascular risk was assessed by measuring the carotid intima-media thickness (c-IMT) using ultrasound. The aim of this follow-up study is to determine the 10 year natural history of pediatric onset NAFLD.

Method: A prospective follow-up study was carried out in all 104 subjects that participated in the previous study of 2008–2012. All subjects underwent ¹H-MRS, ELF test and Liver Stiffness Measurement (LSM) by FibroScan® to detect fibrosis and all subjects underwent c-IMT. Significant fibrosis was defined as LSM > 8.2 kPa. The main study objectives were to evaluate the change in proportion of subjects with steatosis measured by ¹H-MRS; evaluate the change in proportion of subjects with fibrosis measured by ELF test and FibroScan®; determine risk factors for progression of NAFLD; evaluate the association between vascular changes (c-IMT) and progression of NAFLD.

Results: An interim analysis included 29 patients (7 males, 22 females) with a median age of 24 years, mean BMI of 41.1 kg/m², median ALT of 24 IU/L (IQR 15–31) and median HOMA-IR of 2, 13 (IQR 1, 14–3, 21). Seven out of 22 subjects that underwent ¹H-MRS had steatosis at 10 years follow-up (32%), as compared to four subjects (18%) at baseline. Three out of seven subjects with steatosis at follow-up already had steatosis had baseline. Five out of 24 patients that underwent FibroScan® (21%) had developed significant fibrosis and had significantly higher HOMA-IR, BMI and waist circumference. Results of the ELF test and c-IMT will be available and analyzed in March 2021.

Conclusion: These preliminary results indicate that a substantial proportion of young adults who had childhood obesity develop steatosis or fibrosis in young adulthood. The severity of obesity and higher HOMA-IR at follow-up was associated with progression of NAFLD. This suggests that adequate follow-up in children and adolescents with NAFLD is necessary in order to monitor disease progression. However, a larger number of subjects is needed to validate this hypothesis.

PO-1667

Elevated serum bile acids in NASH patients with fibrosis in the context of their cholestatic genetic predisposition

Monika Rau¹, Theresa Schmitt¹, Marcin Krawczyk², Lütjohann Dieter³, Jose Marin⁴, Andreas Geier¹. ¹University Hospital Würzburg, Department of Internal Medicine II, Würzburg, Germany; ²Saarland University Medical Center, Saarland University, Department of Medicine II; ³University Hospital Bonn, Institute of Clinical Chemistry and Clinical Pharmacology; ⁴University of Salamanca, Laboratory of Experimental Hepatology and Drug Targeting (HEVEPHARM), CIBERehd, IBSAL
Email: rau_m@ukw.de

Background and aims: Current drug development in NAFLD patients show promising results for FXR agonists, a bile acid (BA) receptor, which appears to be protective against NAFLD progression, but BA retention could also promote liver injury. Genetic variant p.V444A (c.1331T>C) of the bile-salt export pump (ABCB11) as the most frequent pro-cholestatic polymorphism represents a predisposition factor for bile salt retention under pathologic conditions and may render carriers more susceptible to cholestatic insults. To analyze whether the relationship between serum BAs and NAFLD patients depends on the p.V444A variant.

Method: In total, 70 NAFL, 124 NASH patients, and 165 clinically diagnosed NAFLD patients (Fibroscan, CAP) were included in this study. The c.1331T>C variant was genotyped using TaqMan assays. Serum BAs were analyzed by mass-spectrometry in 33 NAFL, 58 NASH, and 146 clinically diagnosed NAFLD patients.

Results: The pattern of serum biochemical markers in NAFLD patients was cholestatic with (ALT/ALTULN)/(AP/APULN) <2 in 69% of cases (26% of patients with mixed and 5% with cytolytic pattern). Total serum BAs were significantly higher in NASH patients compared to NAFL (2.64 ± 2.24 vs. 1.77 ± 1.63 μM, p = 0.02). Serum BA profiles showed higher levels of deoxycholic acid in NASH patients compared to NAFL. No significant association between overall BAs and histological signs of steatosis, inflammation, or ballooning was found. Histology proved NAFLD patients with advanced disease (F3/F4) had the highest BAs, and F1/F2 patients still had higher BAs compared to F0 (p = 0.02 F3/4 vs. F0–2). All NAFLD patients with cholestasis (BAs >10 μM) had significantly higher liver stiffness compared to non-cholestatic NAFLD patients (41.1 ± 28.6 vs. 8.4 ± 9.1 kPa, p < 0.001). A trend towards less steatosis was observed in cholestatic NAFLD patients measured by CAP. No significant elevation in serum BAs was observed in TT carriers compared to CT+CC (1.90 ± 1.02 vs. 2.36 ± 2.01). A significant correlation between liver stiffness and serum BA was observed for CT+CC patients (R = 0.261, p < 0.05), but not for TT patients (R = 0.104, p > 0.05).

Conclusion: Cholestatic serum biomarkers are frequently present in NAFLD patients. NASH patients are characterized by higher serum BAs, and BAs are associated with advanced fibrotic disease. The ABCB11 c.1331T>C variant might be a co-factor for cholestasis in NAFLD patients, but a significant impact was not found in the present study cohort. Whether the genetic susceptibility affects systemic and intrahepatic obeticholic acid levels under therapy-particularly in those with advanced fibrosis-remains to be determined.

PO-1693

Frailty in non-alcoholic fatty liver cirrhosis in comparison to alcoholic cirrhosis, risk patterns and impact on prognosis

Lubomir Skladany¹, Janka Vnencakova¹, Pavol Molcan¹, Petra Vrbova², Lukas Laffers³, Tomáš Koller². ¹FD Roosevelt Faculty Hospital, Department of Hepatology, Gastroenterology and Transplantation (HEGITO), 2nd Department of Medicine, Slovak Medical University, Banska Bystrica, Slovakia; ²Comenius University Faculty of Medicine, 5th Department of Internal Medicine, Subdiv. Gastroenterology and Hepatology, Bratislava, Slovakia; ³Faculty of Natural Sciences Matej Bel University, Department of Mathematics, Banska Bystrica, Slovakia
Email: koller.tomas@gmail.com

POSTER PRESENTATIONS

Background and aims: Physical frailty increases the susceptibility to stressors and predicts a wide range of adverse outcomes in cirrhosis. Data on its impact on the disease course in NAFLD cirrhosis are scarce. We aimed to explore the differences in the prevalence of frailty, its associated factors and the impact on prognosis between alcoholic and non-alcoholic cirrhosis.

Method: Cirrhosis registry RH7 operates since 2014 and includes patients requiring hospitalization for decompensated cirrhosis, liver transplant evaluation, or curable hepatocellular carcinoma (HCC) from 2 centers. From the registry, we identified all ALD and NAFLD patients having complete data, nutritional (BMI, arm circumference (MAC), skinfold) and functional parameters (handgrip strength, chair stands, equilibrium, liver frailty index (LFI)) and at least 6 months of follow-up.

Results: 280 ALD and 105 NAFLD patients were included. NAFLD patients were significantly older (62 vs. 57 y), with a higher proportion of females (47 vs. 30.4%), higher BMI (28.6 vs. 26) and MAC (29 vs. 26 cm), lower MELD (15 vs. 19), CRP (11 vs. 16.2 mg/l), and a lower proportion of refractory ascites (22.3 vs. 33.1%, all $p < 0.05$). NAFLD patients had a higher proportion of HCC (17.1 vs. 6.8%, $p = 0.002$). Frailty (LFI > 4.5) did not differ between the groups (47.6 vs. 47.9%). Age, sex, albumin and CRP were independent predictors of frailty in both groups. In NAFLD, frailty was also driven by higher BMI and lower MAC, in ALD only by the MELD score. A transplant-free survival model adjusted for age, sex, MELD, CRP, HCC and LFI, showed that NAFLD patients had a higher risk of death or LT (HR = 1.9, 95% CI 1.32–2.67, $p < 0.001$, Figure). The HR for NAFLD was more sensitive to 1 unit increase in LFI compared with ALD (HR = 1.51, 1.05–2.2).

Adjusted Cox model for the probability of survival in NAFLD cirrhosis (dotted line) and ALD cirrhosis (solid line), NAFLD HR=1.9 (95% CI 1.31-2.7)

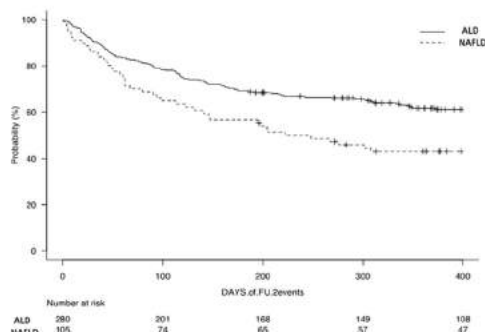


Figure:

Conclusion: Hospitalized patients with NAFLD compared with ALD cirrhosis had a lower liver disease burden and higher prevalence of HCC. However, all-cause mortality was higher in NAFLD and it was associated with an increased sensitivity to frailty which likely reflected a higher all-disease burden.

PO-1747

Spleen size does not correlate with stage of liver disease in people with non-alcoholic fatty liver disease

Tessa Cacciottolo^{1,2,3}, Anupa Kumar¹, Susan E. Davies⁴, Michael Allison^{1,3}. ¹Liver Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge NIHR Biomedical Research Centre, Cambridge, United Kingdom; ²Department of Medicine, University of Cambridge, Cambridge, United Kingdom; ³Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, United Kingdom; ⁴Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Email: tc463@medschl.cam.ac.uk

Background and aims: Splenomegaly in the context of liver disease is classically driven by portal hypertension, and is a sign of advanced

liver disease. However, through clinical experience, we observed that this was often not the case in people with non-alcoholic fatty liver disease (NAFLD), and others have reported an increased incidence of splenomegaly in NAFLD compared to other disease groups. We hypothesised that specifically in NAFLD, splenomegaly is not representative of the degree of underlying liver fibrosis. In this study, we sought to test the correlation between histological stage of liver disease and longitudinal spleen size in a large group of subjects with biopsy-proven NAFLD.

Method: We undertook a retrospective analysis of all patients who had a liver biopsy for staging NAFLD between 2015 and 2018, and sonographic measurement of longitudinal spleen size within one year. Liver biopsies were scored using the SAF (Steatosis, Activity and Fibrosis) scoring system by an experienced pathologist. Body height and weight were measured during clinical review, and fasting blood tests were measured using standard methods. Data was analysed using simple linear regression or Fisher's exact test, using GraphPad Prism v8.

Results: We identified 226 patients who had both a liver biopsy and recorded spleen size at our centre between 2015 and 2018 (59% males, mean body mass index (BMI) = 35.2 ± 6.1 kg/m², mean Age = 55.7 ± 10.8 years). There was good representation of the various stages of fibrosis (3.1% = F0, 26.1% = F1, 19.9% = F2, 39.8% = F3, 11.1% = F4). We found no correlation between spleen size and histological stage of hepatic steatosis ($p = 0.39$), inflammation ($p = 0.07$) or fibrosis ($p = 0.68$). Spleen size was positively correlated with age ($R^2 = 0.05$), height ($R^2 = 0.05$), body mass index ($R^2 = 0.05$) and the triglyceride to HLD-cholesterol ratio, a surrogate marker of insulin resistance ($R^2 = 0.05$).

Conclusion: In this study, we found no correlation between splenomegaly and the degree of underlying liver disease in a large population of people with biopsy proven NAFLD. We found a strong correlation between spleen size, BMI and markers of insulin resistance, which may represent increased visceral deposition of adipose deposition in the spleen. This work indicates that splenomegaly is not a good indicator of advanced liver disease in people with NAFLD, and other methods for monitoring disease progression are required.

PO-1772

Metabolic-associated fatty liver disease is associated with length of stay but not worse survival post COVID-19

Konstantinos-Cédric Perdakis¹, Alexandre Balaphas², Kyriaki Gkoufa³, Nicolas Colucci^{2,4}, Sebastian Carballo¹, Christophe Gaudet-Blavignac^{5,6}, Christian Lovis^{5,6}, Francesco Negro^{7,8}, Christian Toso², Nicolas Goossens^{6,7,9}. ¹Hôpitaux Universitaires de Genève (HUG), Internal Medicine, Genève, Switzerland; ²Hôpitaux Universitaires de Genève (HUG), Digestive Surgery, Genève, Switzerland; ³Hôpitaux Universitaires de Genève (HUG), Endocrinology, Diabetology, Nutrition and Patients Education, Genève, Switzerland; ⁴The University of Pavia, Department of Clinical-Surgery, Diagnostic and Pediatric Sciences, Pavia, Italy; ⁵Hôpitaux Universitaires de Genève (HUG), Medical Information Sciences, Genève, Switzerland; ⁶Faculty of Medicine, Genève, Switzerland; ⁷Hôpitaux Universitaires de Genève (HUG), Gastroenterology and Hepatology, Genève, Switzerland; ⁸Hôpitaux Universitaires de Genève (HUG), Clinical Pathology, Genève, Switzerland; ⁹Hôpitaux Universitaires de Genève (HUG), Transplantation, Genève, Switzerland
Email: nicolas.goossens@hcuge.ch

Background and aims: The prognostic role of advanced liver disease and metabolic-associated fatty liver disease (MAFLD) in patients with coronavirus disease 2019 (COVID-19) remains unclear. Previous studies have suggested that advanced liver disease and MAFLD are associated with increased severity of COVID-19. However, most studies relied on samples of convenience or case reports with non-systematic clinical characterization. We aimed to investigate the implication of advanced liver disease and MAFLD on the prognosis of

COVID-19 in a mono-centric cohort of consecutive hospitalized subjects.

Method: We collected data of all >16-year-old COVID-19 patients hospitalized at the Geneva University Hospital during the first wave of the COVID-19 pandemic (i.e. between February and June 2020). MAFLD was diagnosed in line with recent position statements with the presence of steatosis (imaging, biomarker or biopsy) and evidence of metabolic dysregulation. Advanced liver fibrosis was diagnosed based on biopsy, imaging (signs of portal hypertension) or a high FIB4 score in the 12 months before COVID-19 diagnosis. Outcomes were assessed over 90 days after adjusting for confounders.

Results: Among 1026 patients consecutively hospitalized with COVID-19, 73 (7.1%) had advanced fibrosis from any aetiology of liver disease, and 117 (11.4%) had MAFLD. Subjects with advanced liver fibrosis were older (79.7 vs 68.7 y, $p < 0.001$) and, more often male (60.3 vs 53.9%, $p = 0.330$) than those without advanced liver fibrosis. MAFLD subjects had similar age (72.8 vs 69.2 y, $p = 0.594$) and proportions of male sex (60.3 vs 53.9%, $p = 0.33$) than non-MAFLD subjects but higher proportions of T2D (42 vs 18%, $p < 0.001$) and obesity (35 vs 4.0%, $p < 0.001$). The presence of advanced liver fibrosis was associated with increased 90-day death (adjusted OR 2.8 [1.2–6.2], $p = 0.010$) but lower admission to the ICU (adjusted OR 0.39 [0.13–0.94], $p = 0.058$), whereas length of hospital stay was similar. MAFLD was associated with similar 90-day death (adjusted OR 0.9 [0.5–1.6], $p = 0.761$) and ICU admissions (adjusted OR 1.1 [0.6–1.9], $p = 0.702$) than non-MAFLD but increased length of hospital stay (adjusted beta 37.1 [1.9–753], $p = 0.019$).

Conclusion: In a consecutive monocentric cohort of more than 1000 patients hospitalized with COVID-19, we found that patients with advanced liver fibrosis, but not MAFLD, had increased 90-day mortality but decreased ICU admission possibly in part related to the triage of these patients and less access to ICU. MAFLD patients had increased length of hospital stay.

PO-1823

Body weight variability and the risk of cardiovascular outcomes in patients with non-alcoholic fatty liver disease: a nationwide cohort study

Mi Na Kim¹, Kyungdo Han², Juhwan Yoo³, Yeonjung Ha¹, Young Eun Chon¹, Ju Ho Lee¹, Seong Gyu Hwang¹. ¹CHA University School of Medicine, Division of Gastroenterology, Department of Internal Medicine, Rep. of South, Seongnam, Korea; ²Soongsil University, Department of Statistics and Actuarial Science; ³the Catholic University of Korea, Department of Biomedicine and Health Science
Email: mina2015@cha.ac.kr

Background and aims: Body weight variability is often hypothesized to be an indicator of poor health outcome, including cardiovascular diseases (CVDs) and mortality. In consideration of substantial non-alcoholic fatty liver disease (NAFLD) patients who try weight loss experiencing weight regain, the investigation of the influence of body weight variability on NAFLD outcome is crucial to prevent the deleterious consequences of NAFLD. We aimed to investigate the association between body weight variability and risk of CVD and mortality in patients with NAFLD using large-scale, nationwide cohort data.

Method: We included 726, 736 individuals with NAFLD who underwent health examinations provided by the Korean National Health Insurance System between 2009 and 2010 until the end of 2017. Body weight variability was assessed using four indices, including variability independent of the mean (VIM). A multivariate-adjusted Cox proportional hazards regression analysis was performed. NAFLD was defined as a fatty liver index ≥ 60 , after excluding excess alcohol intake and viral hepatitis.

Results: During the follow-up, 11, 358, 14, 714, and 22, 164 cases of myocardial infarction (MI), stroke, and all-cause mortality, respectively, were recorded. Body weight variability was associated with increased risks of major cardiovascular outcomes after adjusting for confounding variables. Compared with the hazard ratios (HRs) of the lowest quartile group, the HRs (95% CIs) of the highest quartile group of VIM for body weight were 1.15 (1.10–1.20), 1.22 (1.18–1.26), and 1.56 (1.53–1.62) for MI, stroke, and all-cause mortality, respectively.

Conclusion: Body weight variability was associated with increased risks of MI, stroke, and all-cause mortality in NAFLD patients and may be a predictor of cardiovascular outcomes in such patients. Appropriate interventions to maintain stable weight could positively influence health outcomes in NAFLD patients.

PO-1865

Association between non-alcoholic fatty liver disease and extrahepatic malignancy

Mesut Gumussoy¹, Ramazan Idilman¹, Hale Gokcan¹, Dilara Turan Gokce², Bahar Beliz Ulas², Ozge Koc², Gokturk Karatas², Emin Bodakci¹, Mubin Ozercan¹, Fatih Karakaya¹, Ramazan Erdem Er¹, Zeynep Ellik Melekoglu¹, Serkan Duman¹. ¹Ankara Üniversitesi Tıp Fakültesi, Gastroenterology, Ankara, Turkey; ²Ankara Üniversitesi Tıp Fakültesi, Internal Medicine, Turkey
Email: mesutgumussoy1987@hotmail.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is strongly associated with metabolic disorders and is associated with extrahepatic complications. The aim of the present study was to determine the development of extrahepatic malignancy in patients with NAFLD over a long-term period of follow-up.

Method: This was a single-center, retrospective cohort study. Between January 2001 and January 2020, a total of 1099 patients had been diagnosed with NAFLD, who were followed for at least six months were included into the study. The diagnosis of NAFLD was made based on biochemical, radiological and histological when available. The median follow-up period was 62.3 months (interquartile range: 23.3–128.0 months).

Results: The mean age was 51.1 ± 11.0 years. Female gender was predominant (57%). Of 1099 patients, 40.7% were obese, 19.7% had diabetes mellitus, 29.5% had hypertension. Ninety and three patients (8.5%) had cirrhosis. Extrahepatic malignancy was developed in 54 NAFLD patients during the follow-up period, whereas hepatocellular carcinoma developed in 10 patients. Of 54 patients, 48 patients had solid organ malignancies and 9 had hematological malignancies. Of note, two different malignancies were developed in three patients. Female breast cancer was more commonly developed (28%, 16/57), followed by thyroid cancer (19%), lymphoma (12%) and lung cancer (11%). Extrahepatic malignancy was more commonly developed in older patients (54.4 ± 8.4 years vs. 50.9 ± 11.1 years, $p = 0.038$), in female patients ($n = 40$ 6.4% vs $n = 14$, 2.9%, $p = 0.01$), in patients with baseline high GGT level (72.1 ± 68.0 U/L vs. 60.7 ± 80.2 U/L), $p = 0.038$). There was no significant association in term of development of extrahepatic malignancy between obese and non-obese NAFLD patients ($p = 0.71$). Obesity was not associated with female breast cancer ($p = 1.0$). The severity of NAFLD did not effect on the development of extrahepatic malignancies. There was no association in term of development of extrahepatic malignancy between patients with a high FIB-4 score (≥ 1.45) and patients with a low FIB-4 score (< 1.45) ($p = 0.97$). With logistic regression analysis, the development of extrahepatic malignancy was significantly associated with female gender (adjusted odds ratio (OR): 1.92, $p = 0.05$).

Conclusion: NAFLD was associated with development of extrahepatic malignancies, especially breast cancer in female patients.

PO-1880

Association between Non-alcoholic Fatty Liver Disease and the Risk of Dementia: A Nationwide Cohort Study

Gi-Ae Kim¹, Chi Hyuk Oh¹, Jung Wook Kim¹, Su Jin Jung², In-Hwan Oh², Jin San Lee³, Key-Chung Park³, Jae-Jun Shim¹. ¹Kyung Hee University School of Medicine, Department of Internal Medicine, Rep. of South, Seoul, Korea; ²Kyung Hee University School of Medicine, Department of Preventive Medicine, Rep. of South, Seoul, Korea; ³Kyung Hee University School of Medicine, Department of Neurology, Rep. of South, Seoul, Korea
Email: joyshim@khu.ac.kr

Background and aims: Little is known about the association between non-alcoholic fatty liver disease (NAFLD) and dementia. Given that hepatic steatosis is one of the abnormal fat metabolisms in the body and fat dysregulation in the brain is related to dementia, this study aimed to investigate whether NAFLD is associated with the risk of dementia.

Method: We conducted a nationwide population cohort study involving 4, 031, 948 subjects aged 40 to 69 years who had health checkups twice or more under the National Health Insurance Service in Korea between January 2004 and December 2007. Based on the hepatic steatosis index (HSI), the subjects were categorized into non-NAFLD (HSI < 30 at all health checkups) and NAFLD (HSI > 36 once or more). The development of dementia was assessed using the International Classification of Diseases Codes and the prescription of any anti-dementia drug until December 2017. Cox proportional hazards regression models analyzed the dementia risk of each group.

Results: During follow-up of 38, 302, 553 person-years, 414, 851 subjects developed dementia. Compared with the non-NAFLD group, the NAFLD group was associated with a higher risk of dementia on multivariable-adjusted analysis (HR, 1.05; p < 0.001), competing risk analysis (HR, 1.08; p < 0.001) and propensity-score matched analysis (HR, 1.09; p < 0.001). The association between NAFLD and dementia risk was more prominent among females (HR, 1.16; p < 0.001) than males (HR, 1.02; p = 0.001). The association between NAFLD and the risk of dementia was stronger among non-obese NAFLD (BMI < 25 kg/m²; HR, 1.09; p < 0.001).

Conclusion: This nationwide study found that NAFLD was associated with the increased risk of dementia. The association between NAFLD and dementia risk was stronger among females and non-obese NAFLD.

PO-1904

Low skeletal muscle mass is a potential risk factor for lean non-alcoholic fatty liver disease in patients with non-alcoholic fatty liver disease

Min Kyu Kang¹, Jung Gil Park¹. ¹Yeungnam University, College of Medicine, Internal Medicine, Rep. of South, Daegu, Korea
Email: kmggood111@naver.com

Background and aims: Recently, low skeletal muscle mass (LSMM) has emerged as a potential risk factor for NAFLD. However, the association between LSMM and lean NAFLD are not well-known. We investigated the association between LSMM and lean NAFLD in patients with NAFLD.

Method: Lean-NAFLD was defined as a body mass Index (BMI) ≤ 23 kg/m² with NAFLD. Fatty liver was defined using ultrasound and appendicular skeletal muscle mass (ASM) was adjusted by the height² using bioelectrical impedance analysis. LSMM was based on 1SD below the sex-specific mean for Korean adults (cut-off values of 6.74 for men and 4.93 for women).

Results: Of 10, 711 NAFLD patients, 4300 (40.1%) were diagnosed with lean NAFLD. Lean NAFLD group were younger (45.0 vs 49.0 years, p < 0.001), more likely to be women (66.3 vs. 34.3%, p < 0.001), had a lower waist circumference (74.0 vs 85.0 cm, p < 0.001), had lower prevalence of diabetes (3.2 vs. 7.8%, p < 0.001), hypertension (4.4 vs. 16.5%, p < 0.001), metabolic syndrome (3.9 vs. 18.3%, p <

0.001), and higher proportion of low skeletal muscle mass (4.5% vs. 0.3%, p < 0.001) than non-lean NAFLD group.

The presence of LSMM was associated with lean NAFLD in patients with NAFLD (odd ratio [OR] = 11.34, p < 0.001) using stepwise adjusted models for age, sex, diabetes, hypertension, waist circumference, fasting glucose, triglyceride, and high sensitivity C-reactive protein (Table).

Table 1: Adjusted odds ratio of low skeletal muscle mass for lean non-alcoholic fatty liver disease in patients with non-alcoholic fatty liver disease

	Low skeletal muscle mass	
	OR (95% CI)	P value
Total NAFLD population (n = 10, 711), OR for lean NAFLD		
Unadjusted	14.45 (9.43–23.39)	<0.001
Multivariate model 1	33.93 (21.79–55.59)	<0.001
Multivariate model 2	11.42 (5.93–23.24)	<0.001
Multivariate model 3	11.34 (5.90–23.03)	<0.001

OR, odds ratio; CI, confidential interval; NAFLD, non-alcoholic fatty liver disease

Low skeletal muscle mass was defined as the appendicular skeletal muscle mass divided by the square of the height (mm²/m²) using bioelectrical impedance analysis, with sex-specific cut-off values of <6.74 mm²/m² for men and <4.93 mm²/m² for women.

Model 1 was adjusted for age and sex.

Model 2 was adjusted diabetes, hypertension, and waist circumference inclusive of model 1.

Model 3 was adjusted for serum fasting glucose, triglyceride, and C-reactive protein inclusive of model 2.

Conclusion: LSMM may be a potential risk factor for lean NAFLD patients compared with non-lean NAFLD patients independently of classic metabolic factors.

PO-1951

Novel MAFLD criteria identifies additional individual at risk for FIBROSIS: in depth comparison of MAFLD and NAFLD criteria in the Rotterdam Study

Laurens van Kleef¹, Ibrahim Ayada¹, Qiuwei Pan¹, Robert De Knegt¹. ¹Erasmus MC, University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands
Email: laurensvkleef@gmail.com

Background and aims: Recently a transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction associated fatty liver disease (MAFLD) has been proposed to shift the focus to metabolic health, one of the main drivers of fatty liver disease (FLD). We investigated the application of the MAFLD criteria compared to the conventional NAFLD criteria.

Method: We performed a cross-sectional study within The Rotterdam Study, a large ongoing prospective population-based cohort study. All participants between the years 2008 and 2013 who attended the abdominal ultrasound and FibroScan program were eligible for inclusion. Viral hepatitis and alcohol abuse were exclusion criteria. In addition, participants with insufficient metabolic or alcohol data were excluded for the MAFLD or NAFLD analysis, respectively. Both NAFLD and MAFLD criteria were applied and participants were subsequently allocated in overlap FLD, NAFLD only, MAFLD only and no FLD for further analysis. Multivariate analyses were adjusted for age, gender, alcohol, smoking and education level.

Results: Of the participants in both analysis (n = 5513), 34.2% had MAFLD and 29.7% had NAFLD. Exclusion criteria for NAFLD were present in 14.1% and among them 39.4% met the MAFLD criteria. Overall, this resulted in 306 (5.4%) participants with MAFLD only and 58 participants (1.1%) with NAFLD only (Figure). MAFLD only was strongly associated with fibrosis (aOR 4.02, p = 0.001) compared to no FLD. This is in contrast to NAFLD only, where no cases of fibrosis were identified. Moreover, NAFLD only was not associated with changes in

liver stiffness measurement (kPa) compared to no FLD (Beta = -0.15, p = 0.57). Furthermore, among participants with MAFLD, there was a significant association with fibrosis for meeting all MAFLD inclusion criteria (aOR 3.55, p < 0.001) or having the metabolic syndrome (aOR 1.87, p = 0.006).

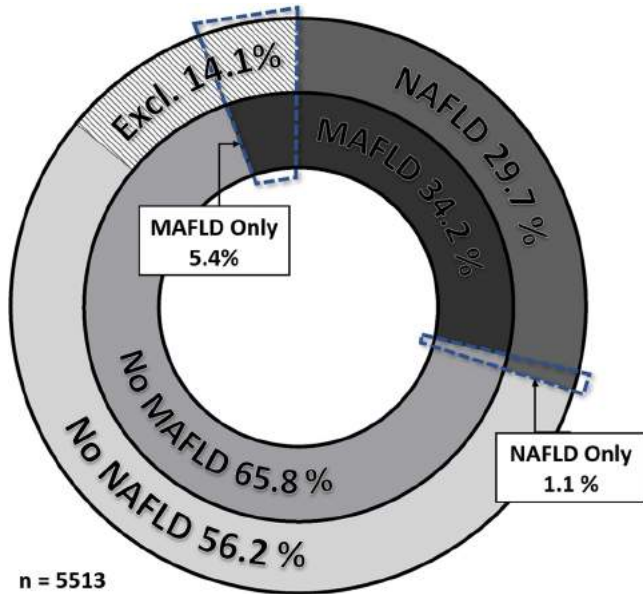


Figure: NAFLD and MAFLD distribution in participants that were eligible for both analyses (n = 5513). The inner circle represents MAFLD and outer circle NAFLD diagnosis.

Conclusion: Applying the novel criteria, NAFLD only was uncommon (1.1%) and not associated with increased liver stiffness, whereas MAFLD only was present in 5.4% of the study population and was associated with fibrosis. Moreover, among participants with MAFLD, the presence of all MAFLD inclusion criteria or the presence of the metabolic syndrome was associated with fibrosis, underlining the importance of metabolic health. To identify the MAFLD only group and provide them with appropriate multidisciplinary treatment, we recommend to consider using the novel MAFLD criteria in addition to the conventional NAFLD criteria.

PO-2002

MAFLD-related cirrhosis is the main contributor to admissions for decompensated cirrhosis in intensive care unit. A single-center, 18-month experience

Marika Rudler¹, Charlotte Bouzbib¹, Christiane Stern¹, Raluca Pais¹, Filomena Conti¹, Philippe Sultanik¹, Sarah Mouri¹, Vlad Ratziu¹, Dominique Thabut¹. ¹GH Pitié-Salpêtrière Charles Foix, Hepatology, Paris, France
Email: marika_rudler@yahoo.fr

Background and aims: The burden of NASH among patients (pts) hospitalized for decompensated cirrhosis, either alone or in combination with alcohol, is unknown. The concept of metabolic-associated fatty liver disease (MAFLD) allows to identify pts exposed to metabolic risk factors (MRF) either alone or in combination with alcohol. We estimated the prevalence, severity and prognosis of MAFLD and dual MAFLD-alcoholic cirrhosis in pts with cirrhotic decompensation.

Method: All consecutive cirrhotic pts hospitalized in intensive care were prospectively included between February 2019 and July 2020. MAFLD was diagnosed based on long-term exposure to diabetes or obesity/overweight, or the association of 2 other MRF (hypertension,

dyslipidemia). We analyzed 3 groups of pts: MAFLD alone (alcohol <30 g/d), mixed MAFLD (MAFLD + alcohol ≥40 g/d), and alcoholic cirrhosis alone. Six-month survival, readmission, and liver transplantation were compared.

Results: 231 pts were included (73% males, mean age 58 yrs, obesity 35%, diabetes 28%, alcohol ≥40 g/d 71%, MELD score 21, Child-Pugh class A/B/C 10/31/59%, previous episode of decompensation 68%). Causes of cirrhosis were: 14% MAFLD alone, 36% mixed MAFLD, 35% alcohol alone, 15% other. Overall, 39% of pts were admitted for gastrointestinal bleeding, 9% for neurological disorder, 7% for suspected acute alcoholic hepatitis, 22% for sepsis, 10% for renal failure, 11% for TIPS placement, and 2% for other causes. At admission, pts with MAFLD alone were significantly older (64 ± 1.9 vs 58 ± 1 and 55 ± 1 yrs, p = 0.001), had a lower Child-Pugh score (8.8 ± 0.4 vs 10.1 ± 0.3 and 10.4 ± 0.3, p = 0.02), and MELD score (18 ± 1.4 vs 21 ± 0.9 and 23 ± 0.9, p = 0.02) than pts of the 2 other groups. In-hospital mortality rates were 9.4%, 17.8% and 18.5%, respectively (p = 0.47). Readmission rate was higher in MAFLD alone (56.2% vs 34.5% vs 31.2%, p = 0.03). Six-month survival was 55% and 6-month transplant-free survival was 48%, similar between the 3 groups. Independent factors associated with 6-month transplant-free survival were: lower MELD score (HR = 1.06, CI 95%:10.4–1.09, p < 0.001), absence of HE at admission (HR = 2.3, CI 95%: 1.5–3.5, p < 0.001), and alcohol abstinence post discharge (HR = 1.7; CI: 1.1–2.7, p = 0.02).

Conclusion: In pts with decompensated cirrhosis MRF are second only to alcohol as an etiology of liver disease, with the dual MAFLD-alcohol currently a leading cause. Morbidity and mortality are as severe as those seen with other causes of cirrhosis.

PO-2074

Systematic review with meta-analysis: Non-Alcoholic Fatty Liver Disease (NAFLD) in Pregnancy

Hydar ElJamaly^{1,2}, Martin Weltman^{1,2}, GUY Eslick³. ¹Nepean Hospital, Department of Gastroenterology and Hepatology, Kingswood, Australia; ²The University of Sydney, Nepean Clinical School, Kingswood, Australia; ³The University of Sydney, The Whiteley-Martin Research Centre, PENRITH, Australia
Email: h.eljamaly@gmail.com

Background and aims: Maternal and fetal outcomes in pregnant patients with NAFLD has been largely unexplored. To determine the level of evidence associated with both maternal and fetal outcomes in pregnant women with NAFLD.

Method: We conducted a comprehensive literature search. The studies included pregnant patients with a previous, current or subsequent diagnosis of NAFLD. We used a random-effects model using odds ratios (OR) with 95% confidence intervals (CI).

Results: Twenty-one studies, with 13, 461 NAFLD patients. NAFLD patients had a statistically significant increased likelihood of Baseline DM (OR = 5.79, 95% CI: 1.23–27.36, p = 0.027; I² = 84.85, p = 0.01), Baseline HTN (OR = 5.78, 95% CI: 5.38–6.21, p < 0.001; I² = 0.00, p = 0.41), GDM (OR = 3.06, 95% CI: 1.74–5.39, p < 0.001; I² = 83.50, p = 0.002), GHTN (OR = 1.83, 95% CI: 1.03–3.26, p = 0.041; I² = 43.81, p = 0.18), and Pre-eclampsia (OR = 2.43, 95% CI: 1.46–4.04; P = 0.001; I² = 0.00, p = 0.94). Analysis revealed that pregnant NAFLD patients were more likely to have a premature birth (OR = 1.87, 95% CI: 1.50–2.33; P < 0.001; I² = 21.03, p = 0.28) or large for gestational age (LGA) birth (OR = 2.06, 95% CI: 1.83–2.31; P < 0.001, I² = 0.00, p = 1.00). Egger's regression revealed no evidence of publication bias (p > 0.05).

Conclusion: This meta-analysis provides pooled evidence that NAFLD is associated with a substantial increase in maternal diabetic and hypertensive complications and that mothers with NAFLD are more likely to have premature births and a LGA birth compared to normal controls. This data is important for clinicians managing these patients before, during and after pregnancy.

POSTER PRESENTATIONS

PO-2326

Assessment of how modifiable and non-modifiable factors can impact fibrosis outcomes in non-alcoholic steatohepatitis patients: a 12-country real-world assessment

Kate Hallsworth^{1,2}, James Pike³, James Carroll³, Jessica Jackson³, Victoria Higgins³. ¹The Newcastle upon Tyne Hospitals NHS Foundation Trust, United Kingdom; ²Newcastle University, Newcastle upon Tyne, United Kingdom; ³Adelphi Real World, Bollington, United Kingdom
Email: victoria.higgins@adelphigroup.com

Background and aims: It is well recognised that the rising prevalence of obesity and non-alcoholic steatohepatitis (NASH) are closely associated, with NASH estimated to increase 63% by 2030. Guidelines recommend weight loss as a key strategy for NASH management. This analysis examines how modifiable (diet, exercise levels, weight concerns, patient knowledge/engagement with NASH management) and non-modifiable (age, comorbidities including type 2 diabetes (T2DM), socio-economic status (SES) factors impact patient outcomes as measured by a change in fibrosis stage.

Method: Data were derived from the 2018/19 Adelphi NASH Disease Specific Programme, a real-world, point-in-time chart review across 12 countries across Europe, North America, Middle East and Australasia. Physicians completed questionnaires describing up to 8 NASH patients capturing fibrosis score, age and comorbidities, including T2DM status. Patients completed a voluntary questionnaire measuring diet, exercise, weight concerns, SES and degree of knowledge/engagement with NASH management. Generalized structural equation modelling was used to explore associated relationships of modifiable/non-modifiable factors and their impact on outcomes as measured by a change in fibrosis stage and patient-reported overall health.

Results: 654 physicians (29% Hepatologist, 48% Gastroenterologist, 21% Diabetologist, 2% PCP) provided data on 3434 patients. Of these, 1880 NASH patients qualified for the analysis. Of non-modifiable factors, high SES correlated with good knowledge/engagement with NASH management, and overall improved fibrosis score but does not influence diet, exercise or weight concern levels; T2DM presence was negatively associated with diet, exercise and weight concern levels, but not associated with NASH knowledge/engagement level. Of modifiable factors, higher diet, exercise and weight concern levels are likely to be present in younger patients with fewer comorbidities, patients who are more informed/engaged about NASH management, and patients that present with an improvement to fibrosis score/overall health. High patient NASH knowledge/engagement is negatively associated with improved fibrosis stage/overall health.

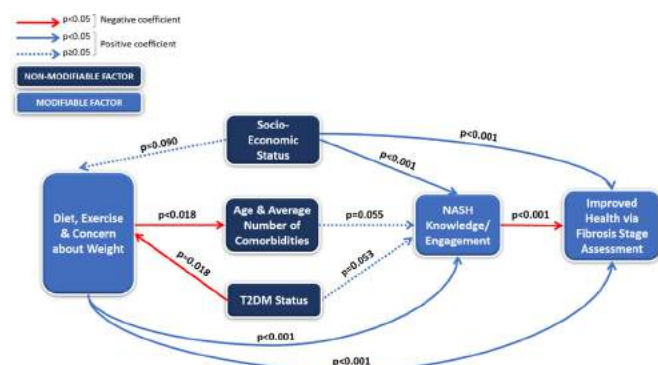


Figure:

Conclusion: Non-modifiable factors such as age, SES and T2DM status present as potential barriers to achieving fibrosis improvement. This analysis suggests, however, that fibrosis outcomes could be improved if modifiable factors, such as patient awareness of importance of diet, exercise and weight status, are targeted.

PO-2328

NAFLD and colorectal adenoma-rather an association than causality

Lorenz Balcar^{1,2}, Georg Semmler^{1,2}, Sarah Wernly¹, Sebastian Bachmayer¹, Matthias Egger¹, Marie Semmler¹, David Niederseer³, Elmar Aigner⁴, Christian Datz¹. ¹General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Department of Internal Medicine, Oberndorf, Austria; ²Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ³University Heart Center Zurich, University Hospital Zurich, Department of Cardiology, Zurich, Switzerland; ⁴Paracelsus Medical University Salzburg, First Department of Medicine, Salzburg, Austria
Email: c.datz@kh-oberndorf.at

Background and aims: Since NAFLD and hepatic fibrosis have been associated with an increased risk for colorectal adenoma and/or colorectal cancer (CRC) in selected cohorts, we tested this hypotheses in asymptomatic subjects participating in a program for colorectal cancer screening (SAKKOPI).

Method: 5311 subjects were included if none of the exclusion criteria were fulfilled: (I) significant alcohol consumption ($\varnothing \geq 20$ g/d, $\sigma \geq 30$ g/d), (II) established autoimmune, cholestatic, viral or hereditary liver disease, (III) missing data on the prevalence and severity of NAFLD, and (IV) insufficient colonoscopy. Diagnosis of NAFLD was established using ultrasound (Cohort I, n = 3945) and liver stiffness measurement (LSM) using transient elastography with controlled attenuation parameter (CAP; Cohort II, n = 1366). Colorectal neoplasia were classified macroscopically and histologically as hyperplastic polyps (HP), adenomas, advanced adenomas (AA) and CRC.

Results: Cohort I: Mean age 58.7 ± 10.0 years, mean BMI 26.6 ± 4.7 kg/m². Prevalence was 29.9% for adenoma, 7.2% for AA, 46.2% for NAFLD and 3.1% for advanced fibrosis (Fib-4 > 2.67). Adenoma were more prevalent in patients with NAFLD (38.9% vs. 33.3%, $p = 0.033$), severe NAFLD (41.1% vs. 33.6%, $p = 0.005$) and advanced fibrosis (45.5% vs. 35.9%, $p = 0.072$) with no differences for HP or AA. HP (30.8% vs. 24.4%, $p < 0.001$), adenoma (34.9% vs. 25.6%, $p < 0.001$) and AA (8.7% vs. 6.0%, $p = 0.001$) were more prevalent in subjects with NAFLD, adenoma (43.5% vs. 26.4%, $p < 0.001$) and CRC (3.2% vs. 0.7%, $p = 0.015$) were more prevalent in subjects with Fib-4 > 2.67 vs. < 1.45. After correcting for age and gender, NAFLD was associated with adenoma (aHR: 1.253 [95% CI: 1.084–1.447], $p = 0.002$) and HP, but not AA. Although Fib-4 strata (<1.45 vs. 1.45–2.67 vs. 2.67) were associated with adenoma and AA, these associations were driven by age.

Cohort II: Mean age 58.9 ± 8.8 years, mean BMI 26.8 ± 4.6 kg/m². Prevalence was 36.5% for adenoma and 7.3% for AA. Mean CAP was 262 ± 62 dB/m with 57.8% having NAFLD (≥ 248 dB/m) and 39.4% having severe steatosis (≥ 280 dB/m), mean LSM was 5.0 ± 2.9 kPa with 6.4% suspected advanced fibrosis (≥ 8 kPa). Adenoma were more prevalent in patients with NAFLD (38.9% vs. 33.3%, $p = 0.033$), severe NAFLD (41.1% vs. 33.6%, $p = 0.005$) and advanced fibrosis (45.5% vs. 35.9%, $p = 0.072$) with no differences for HP or AA. While LSM was not associated with adenoma after correcting for age and gender, CAP (aHR per 10 points: 1.025 [95% CI: 1.001–1.049], $p = 0.038$) and severe NAFLD (aHR: 1.339 [95% CI: 1.021–1.756], $p = 0.035$) were associated only if stringent quality criteria were applied.

Associations of NAFLD and adenoma were attenuated when correcting for BMI or metabolic syndrome in both cohorts.

Conclusion: NAFLD indicates a metabolic situation promoting colorectal adenoma while advanced fibrosis assessed non-invasively is not associated with colorectal lesions.

PO-2343

Does fibrosis severity or diabetes status influence patient-reported lifestyle changes and degree of success among non-alcoholic steatohepatitis patients?

Victoria Higgins¹, James Carroll¹, Jessica Jackson¹, Liane Gillespie-Akar¹. ¹Adelphi Real World
 Email: victoria.higgins@adelphigroup.com

Background and aims: Non-alcoholic steatohepatitis (NASH) often presents asymptotically and is highly associated with metabolic comorbidities such as type 2 diabetes mellitus (T2DM). While EASL-EASD-EASO clinical guidelines advocate first addressing diet and lifestyle factors in T2DM and NASH, evidence suggests patients struggle to change their lifestyle, especially those with milder disease. This analysis aimed to evaluate if the degree of patient

weight and lifestyle change adopted is associated with fibrosis stage and/or T2DM status.

Method: Data were derived from the 2018/19 Adelphi NASH Disease Specific Programme, a real-world, cross-sectional chart review in Europe, North America, Middle East and Australasia. Physician-completed forms described up to 8 consecutive NASH patients including assessment of T2DM status, clinical test values and weight assessment. Patients completed a voluntary form measuring weight concerns and lifestyle changes. Retrospective assessment of fibrosis staging applied a hierarchical approach from most recent liver biopsy (EF F0–2; AF F3–4); vibration-controlled transient elastography (EF < 6.5 kPa; AF ≥ 12.1 kPa) or FIB-4 results (EF < 1.30; AF ≥ 2.67). Patients were categorized into 4 sub-groups, EF-T2DM, EF+T2DM, AF-T2DM, AF+T2DM. All results p > 0.05 unless stated.

	EF-T2DM (n=264)	EF+T2DM (n=399)	AF-T2DM (n=209)	AF+T2DM (n=440)
Managing Physician, n (%)				
Gastroenterologist	157 (59.5)	177 (44.4)	125 (59.8)	211 (48.0)
Hepatologist	80 (30.3)	119 (29.8)	62 (29.7)	119 (27.0)
Diabetologist/Endocrinologist	19 (7.2)	92 (23.1)	16 (7.7)	95 (21.6)
PCP	8 (3.0)	11 (2.8)	6 (2.9)	15 (3.4)
Demographics				
Mean age, n (SD)	49.7 (12.4)	54.8 (11.4)	56.2 (13.9)	60.2 (11.2)
Gender: male, n (%)*	150 (56.8)	210 (52.8)	130 (62.2)	249 (56.6)
Body Mass Index, n (SD)	30.1 (5.1)	33.2 (5.8)	31.8 (7.3)	33.3 (6.3)
Socio-economic status: low, n (%)	98 (37.1)	193 (48.4)	85 (40.7)	230 (52.3)
Physician-reported Weight Concerns				
Advised patient to lose weight: yes, n (%)	204 (77.3)	386 (91.7)	170 (81.3)	407 (92.5)
Satisfaction with current weight, n (%)				
Yes	20 (9.1)	12 (3.2)	7 (3.9)	12 (2.8)
No, but best patient can achieve	60 (27.4)	95 (25.1)	71 (38.4)	187 (44.3)
No, believe patient can achieve lower weight	139 (63.5)	271 (71.1)	102 (56.7)	223 (52.8)
Concern about weight, mean (SD) 1-5 scale; 1=not at all 7=very concerned				
How concerned physician thinks patient is about weight?	3.9 (1.4)	4.3 (1.4)	4.1 (1.7)	4.5 (1.5)
Physician concern about patient's weight?	4.6 (1.6)	5.3 (1.3)	5.0 (1.6)	5.5 (1.2)
Patient-reported Weight Concerns & Lifestyle Changes				
Satisfaction with current weight, n (%)				
Yes	67 (28.4)	46 (11.9)	38 (18.9)	61 (14.2)
No, but best patient can achieve	57 (22.4)	132 (34.0)	51 (25.4)	180 (42.0)
No, patient believes can achieve lower weight	130 (51.2)	210 (54.1)	112 (55.7)	188 (43.8)
Lifestyle changes: recommended, n (%)				
Change in diet	213 (85.9)	356 (92.0)	155 (79.9)	354 (85.9)
Change to Mediterranean diet*	87 (35.1)	125 (32.3)	55 (28.4)	141 (34.2)
Reduce foods high in sugar*	143 (57.7)	242 (62.5)	110 (60.7)	266 (62.1)
Reduce fizzy carbonated drinks	110 (44.4)	173 (44.7)	82 (42.3)	225 (54.6)
Increase fluid intake	74 (29.8)	129 (33.3)	79 (40.7)	187 (45.4)
Stop/cut down smoking	39 (15.7)	72 (18.6)	38 (19.6)	106 (25.7)
Maintain healthy weight	142 (57.3)	276 (71.3)	116 (60.8)	284 (68.9)
Visit a dietician/health coach	84 (33.9)	155 (40.1)	64 (33.0)	187 (45.4)
Increase daily exercise	135 (54.4)	281 (67.4)	111 (57.2)	285 (69.2)
Of lifestyle changes recommended: changed a lot [score of 4 or 5], n (%) 1-5 scale; 1=not changed at all 5=changed a lot				
Change in diet	85 (41.5)	129 (37.3)	44 (29.7)	128 (37.3)
Change to Mediterranean diet	39 (48.8)	50 (41.0)	13 (24.1)	46 (33.8)
Reduce foods high in sugar*	56 (41.8)	110 (47.4)	40 (39.2)	120 (48.2)
Reduce fizzy carbonated drinks*	47 (46.5)	83 (49.7)	35 (48.7)	118 (55.1)
Increase fluid intake*	33 (50.8)	58 (47.5)	24 (32.0)	78 (43.8)
Stop/cut down smoking*	13 (41.9)	23 (35.4)	12 (37.5)	37 (37.8)
Maintain healthy weight	29 (22.0)	64 (24.7)	14 (12.6)	50 (18.4)
Visit a dietician/health coach*	28 (36.8)	66 (44.3)	21 (35.0)	74 (41.3)
Increase daily exercise*	27 (21.8)	47 (18.7)	25 (23.6)	47 (17.0)
How lifestyle changes have helped with health, n (%)				
Controlled blood sugar	25 (10.4)	134 (34.7)	29 (15.4)	130 (31.4)
Helped you lose weight	73 (30.3)	142 (38.8)	40 (21.3)	102 (24.6)
All results p>0.05 except where stated *				

Figure: (abstract: PO-2343)

POSTER PRESENTATIONS

Results: 654 physicians recruited 4656 patients of which 1312 qualified for the analysis; 56% male, mean age 56 years. T2DM presence increases BMI, low socio-economic status and physician-recommended weight loss, regardless of NASH fibrosis. Physician weight loss concern increases as fibrosis worsens and with T2DM presence. Physicians report high dissatisfaction on weight-loss achievements with opportunity for improvement, which becomes increasingly difficult by AF+T2DM status; patients in contrast report greater satisfaction and acceptance with current weight loss status. Patient-reported physician-recommended lifestyle changes are more likely among AF+T2DM patients. Though success varies across the 4 patient groups, AF-T2DM patients are least likely to succeed. Patients report controlling blood sugar and losing weight as key lifestyle changes helping with health.

Conclusion: Fibrosis severity and T2DM status seem to influence patients to implement lifestyle changes. NASH+T2DM patients, irrespective of fibrosis stage, appear to understand the importance of weight loss to help manage their condition vs. non-diabetic patients. This highlights the need to make patients more aware of how implementing preventative lifestyle changes in early disease whilst still asymptomatic is important.

PO-2583

Indirect healthcare costs in biopsy-proven NAFLD is higher than in matched controls and independent of comorbidities

Lina Gruneau¹, Linnea Widman², Martin Henriksson¹, Hannes Hagström². ¹Linköping University, Sweden; ²Karolinska Institutet, Sweden
Email: lina.gruneau@liu.se

Background and aims: Patients with NAFLD have high direct healthcare costs, but studies analysing the costs outside the healthcare sector are limited. The aim of this study was to investigate non-healthcare costs of NAFLD.

Method: We analysed data from a cohort of 646 biopsy-proven Swedish NAFLD patients diagnosed between 1974 through 2009. Reference individuals from the general population were matched on age, sex, and municipality. The number of days with sickness leave covered by sickness benefits from the Swedish Social Insurance Agency and the incidence of permanent long-term benefit due to the inability to ever work again (long-term sickness benefit) were quantified using data from national register data and compared between NAFLD-patients and reference individuals. Linear and Cox regression was used to investigate the association between NAFLD and these outcomes. Confounders in the models included age, sex, several somatic and psychiatric comorbidities, and socio-economic parameters such as income levels and education.

Results: Full data was available from 400 patients. Patients with NAFLD had a mean annual number of sick-leave benefit days of 23.9 (95% CI: 21.7–26.0), the corresponding figure for controls was 11.5 (95% CI: 11.1–12.0). The mean annual number of sick-leave benefit days was higher for NAFLD patients with fibrosis stage 3–4 (40.0, 95% CI = 28.5–51.5) compared to patients with stage 0–2 (22.7, 95% CI = 20.0–25.3). Patients with NAFLD also had a higher rate of permanent long-term benefit (aHR 1.68, 95% CI = 1.40–2.03). Results were stable across a range of sensitivity analyses.

Conclusion: Patients with biopsy-proven NAFLD have a higher risk for needing long-term sickness benefit, and higher annual days of sickness leave, independent of several confounders. The highest risk was found in patients with advanced fibrosis. These data suggests that the indirect costs due to NAFLD will further contribute to a high total cost on society.

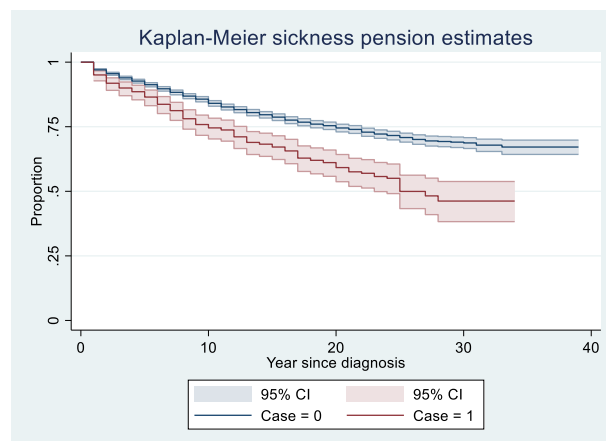


Figure: Kaplan-Meier risk estimate of sickness pension requirement in patients with NAFLD and matched reference individuals.

PO-2673

Colonic permeability is increased in non-cirrhotic non-alcoholic fatty liver disease

Toon De Munck¹, Pauline Verhaegh¹, Corinne Spooen¹, Tobias Wienhold¹, Zlatan Mujagic¹, Daisy Jonkers¹, Ad Masclee¹, Ger Koek¹, Jef Verbeek². ¹Academic Hospital Maastricht, Maastricht, Netherlands; ²University Hospital KU Leuven, Gastroenterology and Hepatology, Leuven, Belgium
Email: jef.verbeek@uzleuven.be

Background and aims: Increased intestinal permeability (IP) plays an important role in the pathophysiology of non-alcoholic fatty liver disease (NAFLD). However, colonic permeability has not been assessed in human non-cirrhotic NAFLD to date. We assessed site-specific (gastroduodenum, small intestine, colon and whole gut) IP in NAFLD patients and healthy controls (HC) and its association with the degree of hepatic steatosis, hepatic fibrosis and dietary composition in NAFLD patients.

Method: *In vivo* site-specific IP was analysed with a validated multi-sugar test in non-cirrhotic NAFLD patients and HC. Furthermore, in NAFLD patients, hepatic steatosis (chemical shift MRI), hepatic fibrosis (transient elastography) and dietary composition (253-item food frequency questionnaire on food intake in prior year) were assessed. Clinically significant fibrosis was defined as liver stiffness ≥ 7 kPa (F2–3).

Results: Fifty-two NAFLD patients (median age 54 (IQR 47–61), 25 (48%) female, median BMI 33 (IQR 29–39)) and forty-six non-obese HC (23 (50%) female; $p = 1.000$) were included in this study. Small intestinal ($p < 0.001$), colonic ($p = 0.004$) and whole gut ($p < 0.001$) permeability were increased in NAFLD patients compared to HC (Figure). Furthermore, colonic ($p = 0.024$) and whole gut ($p = 0.042$) permeability were significantly higher in NAFLD patients with clinically significant fibrosis ($n = 16$) compared to those without ($n = 32$). Colonic permeability, but not whole gut permeability, remained positively associated with the presence of clinically significant fibrosis ($p = 0.047$) after adjustment for age, sex and BMI in a multivariable linear regression analysis. Furthermore, no association between IP and the degree of hepatic steatosis or dietary composition was observed.

Conclusion: Colonic, small intestinal and whole gut permeability are increased in at least a subset of non-cirrhotic NAFLD patients compared to HC. Colonic permeability is independently associated with clinically significant NAFLD fibrosis.

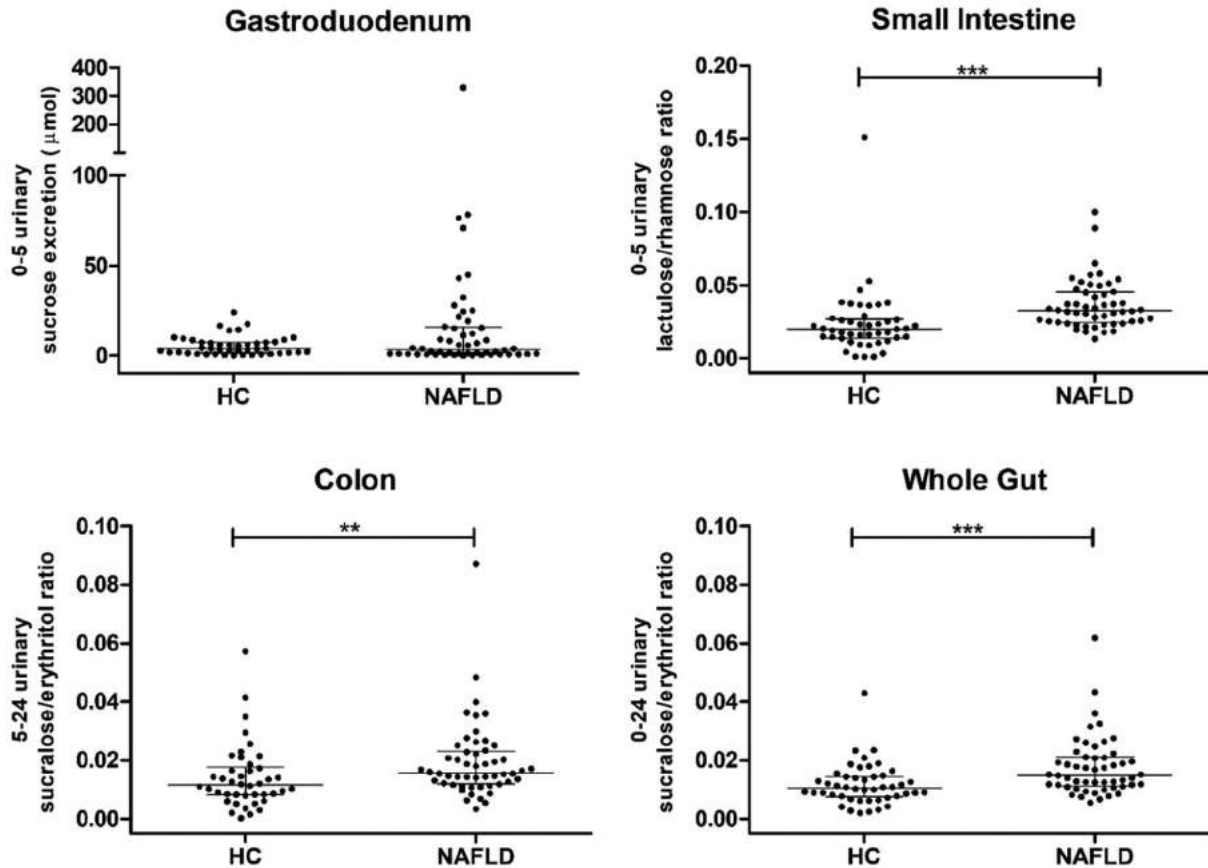


Figure: (abstract: PO-2673)

PO-2692

High rate of biopsy-proven advanced fibrosis/cirrhosis among type 2 diabetes patients screened for NAFLD in diabetology clinics (the QUID-NASH project)

Laurent Castera¹, Tiphaine Vidal-Trecan², Anais Vallet Pichard³, Gault Nathalie⁴, Valérie Paradis⁵, Sebastien Czernichow⁶, Benoit Terris⁷, Pauline Manchon⁴, Christian Boitard⁸, Dominique Roulot⁹, Helene Bihan¹⁰, Thierry Poynard¹¹, Angelique Brustowsky¹², Etienne Larger⁸, Stanislas Pol³, Pierre Bedossa¹³, Cedric Laouenan⁴, Jean-François Gautier², Dominique Valla¹. ¹Hôpital Beaujon, University of Paris-7, Hepatology, Clichy, France; ²Hôpital Lariboisière, Diabetology, Paris, France; ³Hôpital Cochin, Hepatology, France; ⁴Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Epidemiologie, Biostatistiques et Recherche Clinique, Paris, France; ⁵Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Pathology, Clichy, France; ⁶Hôpital Européen Georges Pompidou, Nutrition, Paris, France; ⁷Hôpital Cochin, Pathology, Paris, France; ⁸Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Diabetology, Paris, France; ⁹Hôpital Avicenne, Internal Medicine, Bobigny, France; ¹⁰Hopital Avicenne, Diabetology, Bobigny, France; ¹¹Biopredictive, Paris, France; ¹²Inserm, Paris, France; ¹³Liverpath, Paris, France
Email: laurent.d.castera@gmail.com

Background and aims: According to a recent meta-analysis (Younossi et al. J Hepatol 2020), type 2 diabetes (T2D) is frequently associated with NASH (37.3%) and advanced fibrosis (F3F4, 17.0%). Marked heterogeneity among studies (n=7) and small number of patients (n < 500 for fibrosis assessment) limit extrapolation of the data. The objectives of the present study were: (1) to assess the prevalence of NASH and F3F4 in a large group of T2D patients

in the QUID-NASH program*; (2) to determine the features associated with NASH, F3F4, and cirrhosis (F4), including T2D complications.

Method: Between October 2018 and March 2021, 1159 T2D patients from 4 diabetes clinics were referred to liver clinic after systematic screening for NAFLD during their annual routine workup. A liver biopsy (LB) was proposed to patients with persistently elevated ALT (>20 IU/L in females or >30 IU/L in males) and no other causes for liver disease. LBs were scored according to NASH CRN by a single pathologist (PB) blinded to patient characteristics. Multivariate analyses were performed.

Results: 360 patients underwent a LB, which was adequate in 330 (males 63%; medians: age 59 yrs; BMI 32 kg/m²; waist circumference (WC) 109 cm; HbA1c 7.5%; AST 35 IU/L; ALT 49 IU/L; normal AST (according to lab ULN) 66%; CAP 340 dB/m; liver stiffness measurement (LSM) 8.3 kPa). NASH was present in 58% of patients and was independently associated with increased CAP, AST and triglycerides and low albumin and creatinine (AUROC = 0.82 (0.77–0.87)). Fibrosis staging was: F0 23%; F1 23%; F2 17%; F3 28%; F4 10%. F3F4 was independently associated with increased LSM and FIB-4 and low HDL cholesterol (AUROC = 0.83 (0.78–0.87) whereas F4 was associated with increased LSM, ischemic heart disease (IHD) and low HDL cholesterol (AUROC = 0.87 (0.81–0.94)).

Conclusion: In this population of T2D patients, the prevalence of NASH (58%) and advanced fibrosis (38%) is 2-fold higher than expected from previous data. Ischemic heart disease and low HDL cholesterol are independently associated with cirrhosis. Screening for NAFLD and fibrosis should be part of routine workup in DT2 patients attending diabetology clinics.

*a French program for developing a virtual liver biopsy in T2D patients, funded by ANR, and implemented by Inserm, Université de Paris, CNRS, CEA, Laboratoires Servier, Biopredictive, and AP-HP

PO-2791

Liver test-derived R factor is associated with portal hypertension in patients with non-alcoholic fatty liver disease

Dor Shirin¹, Ana Tobar², Ahinoam Glusman Bendersky¹, Rabab Naamneh², Amir Shlomai^{3,4}. ¹Beilinson, Internal ward D, Petah Tikva, Israel; ²Beilinson, Pathology, Petah Tikva, Israel; ³Beilinson, Internal Medicine D, Petah Tikva, Israel; ⁴Beilinson, Liver institute, Petah Tikva, Israel
Email: dorshirin@yahoo.com

Background and aims: Early development of portal hypertension (PHT) is a well described phenomenon in some patients with non-alcoholic fatty liver disease (NAFLD), but the underlying mechanism is still elusive. Several studies suggest that isolated elevated alkaline phosphatase (ALP), or alternatively, a “cholestatic pattern” of liver enzymes, reflected by R factor (calculated as alanine transaminase (ALT)/upper limit of normal (ULN) divided by alkaline phosphatase (ALP)/ULN at presentation) <2, are associated with a more progressive form of NAFLD. Compared to patients with liver tests abnormalities of hepatocellular pattern. We therefore hypothesized that patients with established NAFLD and a “cholestatic” pattern of liver injury are more likely to develop PHT compared to non-cholestatic NAFLD patients.

Method: We collected data of 80 constitutive patients with a diagnosis of NAFLD, who underwent trans jugular liver biopsy and hepatic venous pressure gradient (HVPG) measurement in our institute during the years 2008–2020. Patients were divided into cholestatic (R < 2) vs. non-cholestatic (R ≥ 2) liver injury groups, and further divided into advanced (F3–4) vs. non-advanced (F0–2) liver fibrosis, based on liver histology results.

Results: Patients with R < 2 were significantly older, had a lower platelet count and a significantly higher HVPG (12.68 ± 6.09 vs. 7.60 ± 4.13, p = 0.001), although the percentage of patients with advanced fibrosis was not significantly different between the groups. We next focused only on patients with no significant fibrosis (F0–F2). Interestingly, in contrast to the R ≥ 2 group who had a normal mean HVPG, the R < 2 group had an abnormally high mean HVPG (5.00 ± 2.86 vs. 10.61 ± 5.92, p < 0.001). We next incorporated the R factor in a multivariate analysis, including age, sex, platelet count and METAVIR score, known predictors for advanced liver disease. Both, higher METAVIR score (beta = 0.319, p = 0.004) and a lower R factor (beta = -0.298, p = 0.007) were significantly associated with HVPG.

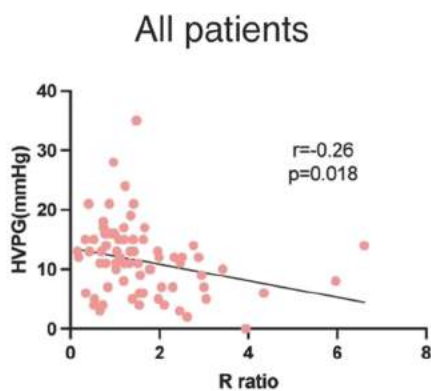


Fig 1

Figure: XY Graphs with the HVPG values as a function of the R factor values at the time of trans jugular HVPG measurement and liver biopsy in all patients with NAFLD.

Conclusion: Among patients with NAFLD, those with the lower R factor are at increased risk for PHT.

NAFLD: Diagnostics and non-invasive assessment

PO-167

Derivation and validation of the NAFLD cirrhosis score (NCS) to distinguish bridging fibrosis from cirrhosis and to predict liver-related outcomes

Christian Labenz¹, Gerrit Toenges², Peter Galle¹, Ming-Hua Zheng³, Dora Ding⁴, Robert Myers⁵, Angelo Armandi⁶, Javier Ampuero⁷, Manuel Romero Gomez⁷, Elisabetta Bugianesi⁶, Jörn M. Schattenberg¹. ¹University Medical Center of the Johannes Gutenberg-University Mainz, Department of Internal Medicine I, Mainz, Germany; ²University Medical Centre of the Johannes Gutenberg-University, Institute of Medical Biostatistics, Epidemiology and Informatics, Mainz, Germany; ³First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ⁴Gilead Sciences, Foster City, United States; ⁵Gilead Sciences, Foster City, United States; ⁶AOU Citta della Salute e della Scienza, University of Torino, Department of Medical Sciences, Division of Gastroenterology, Turin, Italy; ⁷Digestive Disease Department, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain

Email: christian.labenz@unimedizin-mainz.de

Background and aims: The distinction of bridging fibrosis from cirrhosis in non-alcoholic fatty liver disease (NAFLD) is critical to guide the clinical management. It was the aim of this study to develop an easy-to-perform score predicting the presence of cirrhosis in the subgroup of patients with advanced fibrosis.

Method: A derivation cohort comprising 251 NAFLD patients from Germany, Italy and Spain with biopsy-proven bridging fibrosis (F3) or cirrhosis (F4) was used to develop the NAFLD cirrhosis score (NCS). The NCS was externally validated in two cohorts consisting of 1,666 patients recruited in the STELLAR trials and 47 patients from China. Patients of the STELLAR trials were also followed-up for the progression to cirrhosis (in the F3 cohort) or time to first hepatic decompensation/qualification for transplantation (MELD ≥ 15)/all-cause mortality/liver transplantation.

Results: A model including INR, gGT, ALT, platelets and age discriminated between patients with bridging fibrosis and cirrhosis with an area under the curve (AUC) of 0.733 (95% CI 0.671–0.795). Diagnostic performance of the NCS was similar in the large external validation cohort from the STELLAR studies (AUC 0.700; 95% CI 0.680–0.730) and the smaller cohort from China (AUC 0.727; 95% CI 0.533–0.921). We derived two NCS cut-off values (<64.5 points and >79.17 points) to classify patients at low, intermediate, or high risk for the presence of cirrhosis. Using the above-mentioned cutoffs and considering that patients in the intermediate-risk group subsequently receive additional diagnostic workup, the sensitivity, specificity, PPV and NPV of the resulting diagnosis algorithm were high and are displayed in Table 1. By using NCS, further diagnostic workup could be avoided by ruling in or ruling out cirrhosis in approximately one half of the patients. Furthermore, NCS identified patients at risk for progression to cirrhosis in the F3 cohort and liver-related clinical events in the F4 cohort.

Table 1: Diagnostic performance of the NAFLD cirrhosis score (NCS)

	Derivation cohort.	Validation cohort. (STELLAR)	Validation cohort. (China)
Sensitivity	91% (83–96)	88% (86–90)	70% (35–92)
Specificity	90% (84–94)	92% (90–94)	97% (84–100)
PPV	85% (76–92)	93% (90–94)	88% (47–99)
NPV	94% (89–97)	88% (85–90)	92% (78–98)
LR+	5.80 (3.61–9.32)	12.34 (9.70–15.69)	7.00 (1.10–44.61)
LR–	0.06 (0.03–0.12)	0.14 (0.12–0.17)	0.08 (0.03–0.25)
Intermediate-risk group	50.4%	61.6%	34.0%

Diagnostic performance of the NAFLD cirrhosis score for the detection of liver cirrhosis in the derivation and validation cohorts considering cutoff values of <64.5 and >79.17 points with subsequent specialized testing in the intermediate group.

Conclusion: The NCS is a simple tool able to identify patients with compensated cirrhosis in the larger group of advanced disease stage. In addition, NCS is prognostic for liver-related outcomes.

PO-313

The prognosis is impaired in NAFLD patients with diabetes despite negative FIB4 <1.30

Jerome Boursier¹, Mattias Ekstedt², Manuel Romero Gomez³, Clemence Moreau⁴, Martin Bonacci⁵, Sandrine Cure⁵, Aldo Trylesinski⁵, Hannes Hagström⁶. ¹Angers University Hospital, Angers, France; ²Linköping University, Linköping, Sweden; ³University of Seville, Seville, Spain; ⁴Angers University, Angers, France; ⁵Intercept, London, Northern Ireland; ⁶Karolinska Institutet, Stockholm, Sweden
Email: jeboursier@chu-angers.fr

Background and aims: Non-invasive liver fibrosis tests play a key role in identifying NAFLD patients at greatest risk of developing liver-related events (LRE). Diabetes (T2D) is strongly associated with NAFLD severity and progression. We evaluated the ability of the blood test FIB4 and vibration controlled transient elastography (VCTE) by FibroScan to correctly identify NAFLD patients with impaired prognosis, with comparison between T2D and non-T2D patients.

Method: NAFLD patients with data on FIB4 and/or VCTE from 4 European academic centers were included. The main study outcome was LRE, a composite end point combining cirrhosis complication or hepatocellular carcinoma. Incident LRE were ascertained by chart review. T2D was defined as the use of antidiabetic treatment. FIB4 and VCTE results were stratified in 3 groups according to published cut-offs (FIB4: 1.30 and 3.25, VCTE: 8.0 and 15.7 kPa). Multivariate Cox regression models were performed including each time one fibrosis test together with age, sex, antidiabetic treatment, anti-hypertensive treatment, and lipid-lowering treatment.

Results: Data were available at baseline in 984 patients for FIB4 (35% T2D) and 835 patients for VCTE (38% T2D). Baseline characteristics were similar across these 2 groups. After a median follow-up of 3.8 and 2.9 years, respectively, LRE occurred in 53 (5.3%) and 51 (6.1%) patients from FIB4 and VCTE groups. Multivariate Cox models identified T2D and the fibrosis test evaluated (FIB4 or VCTE) as independent predictors of LRE. Of note, in patients with baseline FIB4 < 1.30, Kaplan-Meier curves showed a significantly impaired prognosis in T2D compared to non-T2D patients (p < 0.001). Ten patients from the FIB4 group had LRE during their follow-up despite baseline FIB4 < 1.30, 7 of them having T2D. These patients could be identified by following the evolution of FIB4 which became >1.30 several years before LRE occurrence, or by using VCTE (available in 7 patients and always >8.0 kPa before FIB4 > 1.30). Liver biopsy was available at baseline in respectively 557 and 428 patients from the FIB4 and VCTE groups. Among patients with baseline FIB4 < 1.30, advanced fibrosis F3-4 was present in 37% of T2D versus 8% in non-T2D patients (p <

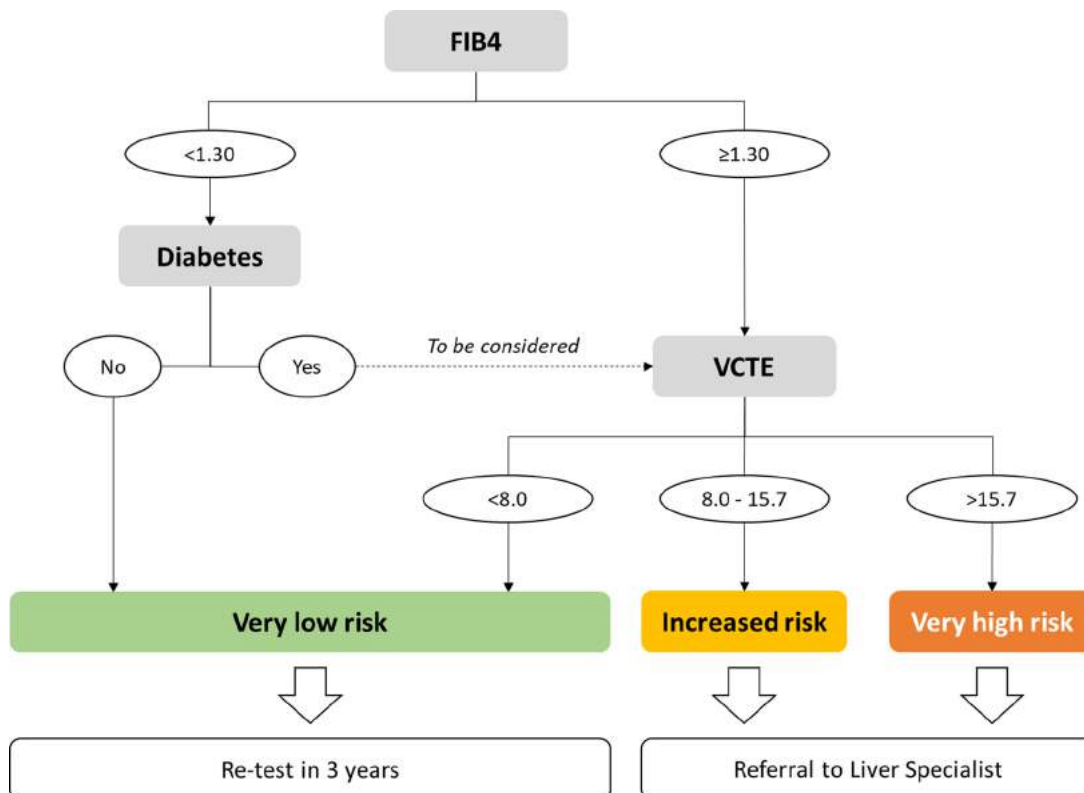


Figure: (abstract: PO-313)

POSTER PRESENTATIONS

0.001). VCTE result was >8.0 kPa in 83% of the T2D patients having false negative result with FIB4 (advanced fibrosis despite FIB4 < 1.30). Based on these results and our previous report (increased LRE risk from FIB4 ≥ 1.30 with VCTE ≥ 8.0 kPa; AASLD Liver Meeting 2020), an adapted FIB4-VCTE algorithm is proposed by considering VCTE examination in T2D patients despite FIB4 < 1.30 (Figure).

Conclusion: Diabetes is associated with an impaired prognosis in NAFLD, and an increased advanced fibrosis rate despite FIB4 < 1.30. To decide referral to the liver specialist, NAFLD patients with diabetes and FIB4 < 1.30 should undergo a close follow-up or be considered for VCTE.

PO-454

The use of age-specific cutoffs for FIB4 and NAFLD Fibrosis Score in a primary care setting finds over one-third of older diabetic patients are at high risk for NAFLD with advanced fibrosis

Kendall Islam¹, Danielle Brandman¹, Janet Chu¹, Rena Fox¹. ¹University of California, San Francisco, San Francisco, United States
Email: rena.fox@ucsf.edu

Background and aims: There is a need for tools to assist primary care (PC) in identifying and risk stratifying patients with NAFLD. The FIB4 and NAFLD Fibrosis Score (NFS) accurately characterize the risk of advanced fibrosis, but since specificity decreases with advancing age, age-specific score cutoffs have been proposed. No studies have examined age-specific cutoffs in PC. We aimed to examine a cohort of older PC patients with diabetes mellitus (DM) categorized by FIB4 and NFS with age specific cutoffs.

Method: We created a cohort of all adult DM patients from a large academic PC practice using the electronic medical record (EMR). Patients with HBV, HCV or alcohol disorder were excluded. For the study period 2015–2020, we computed a FIB4 and NFS per patient per year. Those ≥65 yo were categorized as low- (FIB4 < 2.0, NFS < 0.12), indeterminate- (FIB4 2.0–2.67, NFS 0.12–0.676), and high-risk (FIB4 > 2.67, NFS > 0.676).

Results: From a total clinic population of 26, 602, 3, 040 patients met criteria for the cohort and 1, 821 were ≥65 yo. Mean age was 77 (SD 7.6) and 74% (n = 1, 354) had data in the EMR to calculate at least one FIB4 or NFS. Of these, 498 (37%) were low risk, 346 (25%) indeterminate risk, and 510 (38%) high risk. Characteristics of the risk groups are shown in Table 1. In univariate analyses, age, gender, BMI, AST, ALT, platelet and albumin were significantly associated with high-risk classification, though average laboratory values were all in the normal range.

Conclusion: Using age-specific cutoffs for FIB4 and NFS, we found that over 1/3 of DM patients ≥65 yo met criteria for high risk of advanced fibrosis but only 13% were already diagnosed with NAFLD. Since ¾ had available data, these scores could be a practical first step for DM patients in PC.

PO-565

A prospective cohort study for the prevalence and screening policy of NAFLD in patients with T2DM in primary care

Roberta Forlano¹, Benjamin H. Mullish¹, Michael Yee², Robert D. Goldin³, Mark Thursz¹, Pinelopi Manousou¹. ¹Imperial College London, Department of Metabolism, Digestion and Reproduction, Northern Ireland; ²Imperial college NHS Trust, Department of Endocrinology, London; ³Imperial College London, Department of Cellular Pathology, London, Northern Ireland
Email: r.forlano@imperial.ac.uk

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is associated with Type-2 diabetes mellitus (T2DM), with diabetics being at higher risk for adverse outcomes. The aim of this study was to establish prevalence and develop a screening pathway for NAFLD referral/management.

Method: Consecutive patients with T2DM, between 18 and 69 years, were enrolled from North-West London Community Care. Patients were screened for liver disease by bloods (including NAFLD fibrosis score and FIB-4), ultrasound (US) and fasting liver stiffness measurement (LSM) and CAP.

Results: Of 300 patients enrolled, 287 were included; 13 withdrew. Overall, 184 (73%) had NAFLD, 28 (10%) other causes of liver disease (BAFLD and HBV) and 75 (26%) no liver disease. Those with NAFLD had larger waist (p = 0.0001) and hip (p = 0.0001) circumferences and higher BMI (p = 0.0001) compared to those without NAFLD. They also had higher ALT (p = 0.0001), AST (p = 0.0001), GGT (p = 0.0001) and HbA1c (p = 0.0001).

Among those with NAFLD, 50/183 (28%) and 50/287 (17%) of total had increased LSM (>8.1 kPa). Those with increased LSM had larger waist (p = 0.0001) and hip (p = 0.0001) circumferences and higher BMI (p = 0.0001) compared to those with normal LSM (n = 134). Those with increased LSM also presented higher ALT (p = 0.001), AST (p = 0.0001), GGT (p = 0.0001) and HbA1c (p = 0.0001). Multivariately, waist circumference (OR 1.089, p = 0.006), BMI (OR 1.24, p = 0.005) and AST (OR 1.092, p = 0.0001) were independent predictors of increased LSM. A variable was derived by logistic regression: 0.086*

Table 1: (abstract: PO-454): Characteristics of primary care diabetes patients by risk of advanced fibrosis

	Low risk n = 498	Intermediate risk n = 346	High risk n = 510	p value
Age [mean (SD)]	75 (6.3)	75 (7.9)	79 (8)	<0.001
Gender (% female)	60.4%	52.9%	48.2%	<0.001
Race/Ethnicity				0.83
White or Caucasian	136 (28.0%)	98 (29.1%)	139 (27.5%)	
Black or African American	54 (11.1%)	44 (13.1%)	60 (11.9%)	
Hispanic or Latino	67 (13.8%)	40 (11.9%)	59 (11.7%)	
Asian	184 (37.9%)	126 (37.4%)	211 (41.7%)	
BMI categories				0.046
Normal	100 (20.1%)	60 (17.3%)	106 (20.8%)	
Overweight	132 (26.5%)	84 (24.3%)	151 (29.6%)	
Obese	261 (52.4%)	192 (55.5%)	249 (48.8%)	
HbA1C % [mean (SD)]	7.11 (1.3)	7.13 (1.5)	7.0 (1.3)	0.50
NASH/NAFLD ICD coding	53 (10.6%)	41 (11.8%)	67 (13.1%)	0.47
AST U/L [mean (SD)]	22 (6)	24 (7)	28 (10)	<0.001
ALT U/L [mean (SD)]	22 (7)	23 (8)	27 (10)	<0.001
Platelet x10 ⁹ /L [mean (SD)]	278 (61)	227 (44)	185 (44)	<0.001
Albumin g/dL [mean (SD)]	4.02 (0.3)	3.95 (0.4)	3.87 (0.3)	<0.001
Liver biopsy (ever)	1 (0.2%)	2 (0.6%)	5 (1.0%)	0.27
FIB-4 [mean (SD)]	1.37 (0.3)	1.86 (0.4)	3.25 (2.0)	<0.001
NFS [mean (SD)]	-0.47 (0.9)	0.62 (0.8)	1.68 (0.8)	<0.001

(Waist circumference, cm) + 0,08* (BMI, kg/m²) + 0,025* (AST, IU/L) - 14,607.

In the whole population, the derived variable predicted the presence of increased LSM with an AUROC of 0.868 (p = 0.0001, cut-off 0.19, PPV 90%, NPV 96%). AUROCs for predicting the presence of increased LSM were 0.81 (p = 0.0001, cut-off 0.057, PPV 79%, NPV 97%) for US plus LFTs (AST, ALT plus GGT), 0.75 (p = 0.0001, cut-off 1.07, PPV 56%, NPV 98%) for LFTs alone, 0.73 (p = 0.0001, cut-off 1, PPV 45%, NPV 90%) for US alone, 0.72 (p = 0.0001, cut-off -1.4, PPV 46%, NPV 85%) for NFS and 0.61 (p = 0.013, cut-off 1.00, NPV 32%, PPV 84%) for FIB-4 (Figure 1).

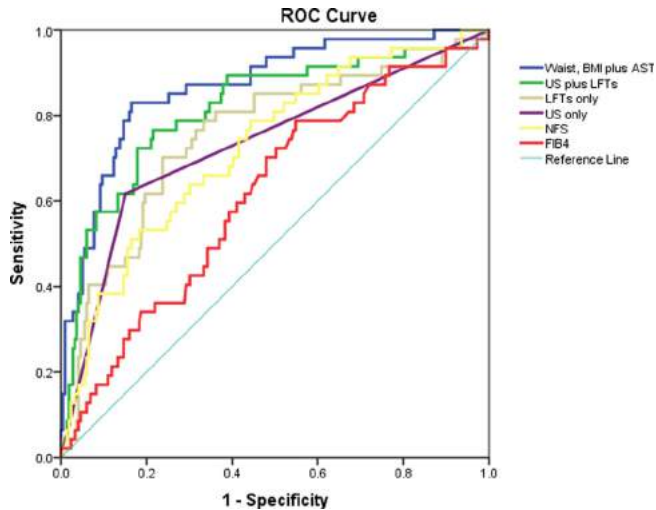


Figure:

Conclusion: In patients with diabetes in the community, 73% had NAFLD and 17% significant fibrosis. BMI, AST and waist circumference combined, could identify those at higher risk for significant fibrosis better than current non-invasive markers. This model may be used to shape a referral management pathway in this population.

PO-569

Long term prognosis of patients with alcoholic disease or nafld according to metabolic syndrome or alcohol use

Marie Decraecker¹, Dan Dutartre², HIRIART Jean-Baptiste¹, Marie Irlès-Depe¹, Marraud Des Grottes¹, Faiza Chermak¹, Juliette Foucher¹, Adele Delamarre³, Victor de Lédighen^{1,4}. ¹Chu Haut Leveque, Pessac, France; ²University of Bordeaux-Talence Campus, Talence, France; ³Avenue du Haut Lévêque, Pessac, France; ⁴CHU Bordeaux, Service d'Hépatologie, Bordeaux, France
Email: marie.decraecker@gmail.com

Background and aims: The boundary between non-alcoholic (NAFLD) and alcoholic fatty liver disease (AFLD) is based on alcohol consumption. However, metabolic syndrome and alcohol use frequently co-exist. The aim of this study was to determine prognostic factors of long-term mortality and morbidity in patients with chronic alcoholic and/or metabolic fatty liver disease.

Method: From 2003 to 2016, all consecutive NAFLD or AFLD patients with valid liver stiffness measurement (FibroScan®) were prospectively included in a cohort study and followed until December 2017. We evaluated overall survival, specific cause of mortality (hepatic, cardiovascular or neoplastic) and occurrence of any complication (hepatic, cardiovascular or cancer). The occurrence of mortality was analysed by the Kaplan-Meier method. The risk of morbidity was estimated by logistic regression. Factors independently associated with mortality and morbidity were identified by a multivariate Cox model. The prognostic performance of liver stiffness for mortality prediction was evaluated by Harrell's C-index; and morbidity prediction by AUC.

Results: A total of 3,365 patients (1,667 AFLD and 1,698 NAFLD) were included: median age 56 years, men 63%, BMI 28 kg/m², metabolic syndrome 43%, abdominal obesity 61%, type II diabetes 30%, HBP 45%. Median follow-up was 54 months [30 – 86] and 563 subjects died.

In overall population, overall and cause-specific mortality were higher in patients with AFLD (p < 0.0001) and with weekly alcohol consumption >7 units (p < 0.0001). Liver stiffness was an independent predictor of morbimortality (global and specific, p < 0.001). A model combining liver stiffness and clinical parameters had the best performance in predicting overall mortality (C-index 0.81).

In NAFLD group, weekly alcohol consumption >1 unit was associated with higher overall (p = 0.025) and cardiovascular (p = 0.028) mortality and weekly alcohol consumption >7 units was associated with higher overall (p < 0.001) and cardiovascular (p = 0.021) morbidity.

In AFLD group, the presence of metabolic syndrome was associated with higher overall (p = 0.029), liver (p < 0.001) and cardiovascular (p = 0.033) mortality and overall (p < 0.001), hepatic (p = 0.031), cardiovascular (p = 0.028) morbidity.

Conclusion: In NAFLD, light alcohol consumption is associated with mortality and morbidity and abstinence should be recommended. In AFLD, metabolic syndrome is associated with mortality and morbidity and should be managed.

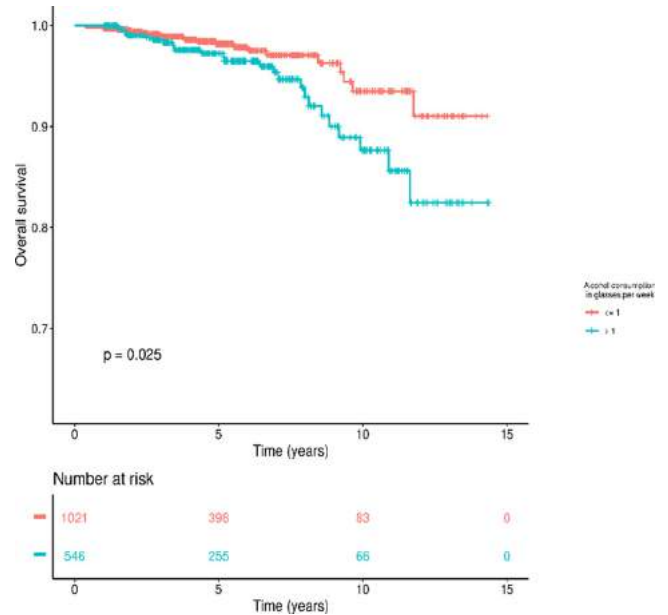


Figure: Mortality in non-alcoholic fatty liver disease patients according to alcohol use.

Overall survival with a threshold of 1 unit/week.

PO-580

Modeling regional variation in the return on investment of VCTE for fatty liver disease (FLD) in the U.S.

Mazen Nouredin¹, Andrew Mackenzie², Elaine Zhao², Scott Howell³, Michael Tunkelrott⁴, Ian Duncan². ¹Cedars-Sinai Medical Center, Fatty Liver Program, Los Angeles; ²Santa Barbara Actuaries, Santa Barbara; ³AIDS Healthcare Foundation, Los Angeles; ⁴Echosens North America, Waltham, United States
Email: mazen.nouredin@cshs.org

Background and aims: FLD is the most common cause of chronic liver disease. Despite high prevalence, FLD remains underdiagnosed, with complex and wasteful diagnostic pathways. This study explores U.S. regional variations for potential cost savings of deploying VCTE in a general population.

POSTER PRESENTATIONS

Method: Our model leveraged administrative claims data of 5 million commercial members in 2015–2017 from IBM's MarketScan dataset and 3 million Medicare members in CMS' Limited Data Set from 2012 to 2016, informing baseline statistics on disease prevalence, healthcare cost and utilization associated with each stage of liver disease (i.e., simple fatty liver, steatohepatitis, fibrosis, cirrhosis, end stage liver disease and liver cancer). All statistics and calculations were performed by U.S. census regions. A multi-state model was developed to represent disease transition probabilities. With limited U.S. deployment of VCTE by 2016, we consulted expert clinical opinion and literature to inform other assumptions. Longitudinal results were modelled for up to 5 years.

Results: In one scenario, a Medicare payer with 100,000 members deploying VCTE devices to primary care may expect 4-year discounted cumulative net savings (subtracting device rental at \$2,800/month) as follows: \$11.8 million in the Midwest; \$10.2 million in the South; \$7.5 million in the West; and \$7.4 million in the Northeast region. These correspond to a Return on Investment (ROI) ranging from 2.0:1 to 3.2:1 over 4 years. Repeating in a commercial population resulted in the following: \$9.3 million in the South; \$7.2 million in the Midwest; \$6.6 million in the West region; and \$4.0 million in the Northeast. These correspond to ROIs ranging from 1.1:1 to 2.6:1 over 4 years.

Savings are created in two ways: (1) VCTE tests result in early identification of patients with FLD (as majority are currently undiagnosed) allowing for proactive intervention and behavior change to slow disease progression. (2) VCTE tests can reduce the aggregate volume of some current diagnosis methods such as liver biopsy or advanced imaging.

Conclusion: Scenario testing demonstrated net savings within 2 years across most scenarios and regions. We conclude that broad deployment of VCTE devices is a financially advantageous solution to address the FLD epidemic, with the South and Midwest regions standing to benefit the most, likely due to a combination of the higher prevalence rates of FLD and relevant comorbidities as well as medical utilization and costs.

PO-632

Prevalence of hepatic steatosis and advanced fibrosis in patients living with HIV in Germany

Maurice Michel¹, Alica Wahl¹, Malena Andres¹, Peter Galle¹, Marcus-Alexander Wörns¹, Martin Sprinzl¹, Jörn M. Schattenberg¹.

¹Metabolic Liver Disease Research Programm, I. Department of Medicine, University Medical Centre Mainz, Mainz, Germany

Email: schatten@uni-mainz.de

Background and aims: The prevalence of advanced liver disease and hepatic steatosis in patients living with HIV is poorly defined. An independent risk of HIV infection or antiretroviral therapy (ART) has been proposed. The current analysis explored hepatic steatosis and fibrosis stages defined by transient elastography in patients living with HIV.

Method: In this cross-sectional study, 280 patients with an HIV mono-infection were prospectively enrolled and liver steatosis as well as liver fibrosis were measured with transient elastography (TE). Based on controlled attenuation parameter (CAP; db/m) and liver stiffness measurement (LSM; kPa), patients were analyzed according to the presence of steatosis (>280 db/m) or relevant fibrosis (>8.2 kPa). Independent predictors of liver steatosis and fibrosis were identified using linear regression models. To identify patients with NASH and at least F2 fibrosis, the FAST-score was calculated.

Results: In this cohort of 280 patients with HIV mono-infection on ART, the prevalence of liver steatosis was 34.3% (n = 96) and the prevalence of relevant liver fibrosis was 7.1% (n = 20). Among these patients, 28 (10%) exhibited severe steatosis (CAP > 337 db/m) and 13 (4.6%) had advanced fibrosis (E > 9.7 kPa). The FAST-score (cutoff > 0.35) identified 32 (12, 4%) patients. Multivariable regression analysis revealed ALT and waist-circumference (cm) as independent risk

factors for higher degree steatosis and fibrosis, respectively. In general, factors associated with the metabolic syndrome were more common in patients with relevant steatosis and fibrosis. Patients with liver fibrosis showed a longer disease duration in comparison to those with no fibrosis (22 years vs 10 years, p < 0.05).

Conclusion: Hepatic steatosis is highly prevalent among patients living with HIV and compared to epidemiological studies patients with steatosis and relevant fibrosis were younger. This study identified modifiable and preventable risk factors. Addressing these factors by education may support metabolic health in patients living with HIV.

Funding: This analysis was in parts supported by a research grant from Gilead Sciences.

PO-751

M comes first: Impact of initial probe choice on diagnostic performance of vibration controlled transient elastography

Valentin Blank^{1,2}, David Petroff^{2,3}, Johannes Wiegand⁴,

Thomas Karlas¹. ¹Leipzig University Medical Center, Division of Gastroenterology, Department of Medicine II, Leipzig, Germany;

²University of Leipzig, Integrated Research and Treatment Center AdiposityDiseases Leipzig, Faculty of Medicine, Leipzig, Germany;

³University of Leipzig, Clinical Trial Centre Leipzig, Leipzig, Germany;

⁴Leipzig University Medical Center, Division of Hepatology, Department of Medicine II, Leipzig, Germany

Email: thomas.karlas@medizin.uni-leipzig.de

Background and aims: Non-invasive assessment of fibrosis and steatosis is used to rule in/out advanced liver disease. Vibration controlled transient elastography (VCTE) with liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) has become a reference standard. A VCTE-based score (FAST-score) was recently introduced to identify patients with non-alcoholic fatty liver disease (NAFLD) at risk for steatohepatitis (NASH). VCTE probe choice (M or XL) can be made either by the user's own measure of skin-to-liver-capsule distance (SCD) or based on an automated probe selection tool (auto-PS). Consider three scenarios: (i) The "M-first clinic" always uses the auto-PS from the M probe to choose either to retain the M probe or switch to the XL probe. (ii) The "XL-first clinic" always uses auto-PS from the XL probe. (iii) A "reference clinic" uses SCD for probe selection. This study aimed to compare the results from these three scenarios.

Method: VCTE (FibroScan 530) was performed prospectively in patients with chronic liver disease with the M and XL probes. The SCD at the measurement site was determined using a linear ultrasound probe. SCD ≥ 25 mm defined the need for the XL probe. Auto-PS from the M and XL probes was compared with Fleiss' kappa and discrepancies in LSM and CAP (>5% difference to the reference) using McNemar's test. FAST-score categories in NAFLD patients were compared between the three clinics.

Results: 200 patients with NAFLD (42%) and other liver diseases were included (58% female, 56 years old, BMI 28.1 kg/m²). Fleiss' kappa for agreement in auto-PS between the M and XL probes was 0.11 (95% CI -0.09 to 0.31), but accuracy was 0.855 (95% CI 0.800 to 0.897) for the M probe and 0.825 (95% CI 0.766 to 0.871) for the XL probe. Probe failure occurred for 16 (M-first clinic), 4 (XL-first clinic) and 3 patients (reference clinic). Use of XL probe in case of M probe failure improved performance of the M-first approach. The odds ratio for a discrepancy in the XL-first vs the M-first clinic is 2.4 (95% CI 1.2 to 5.2, p = 0.012) for LSM and 4.8 (95% CI 1.8 to 16.1, p < 0.001) for CAP. FAST-score was misclassified in one (1%) NAFLD patient in the M-first clinic and there were seven probe failures (8%) compared to four (5%) misclassifications in the XL-first clinic with no probe failures.

Conclusion: Agreement in automated probe selection between the M and XL probes is poor although each has fairly good accuracy. The M-first approach leads to fewer discrepancies than the XL-first strategy. Initial probe choice is crucial to obtain reliable and comparable VCTE results using auto-PS although it had little impact on FAST-score

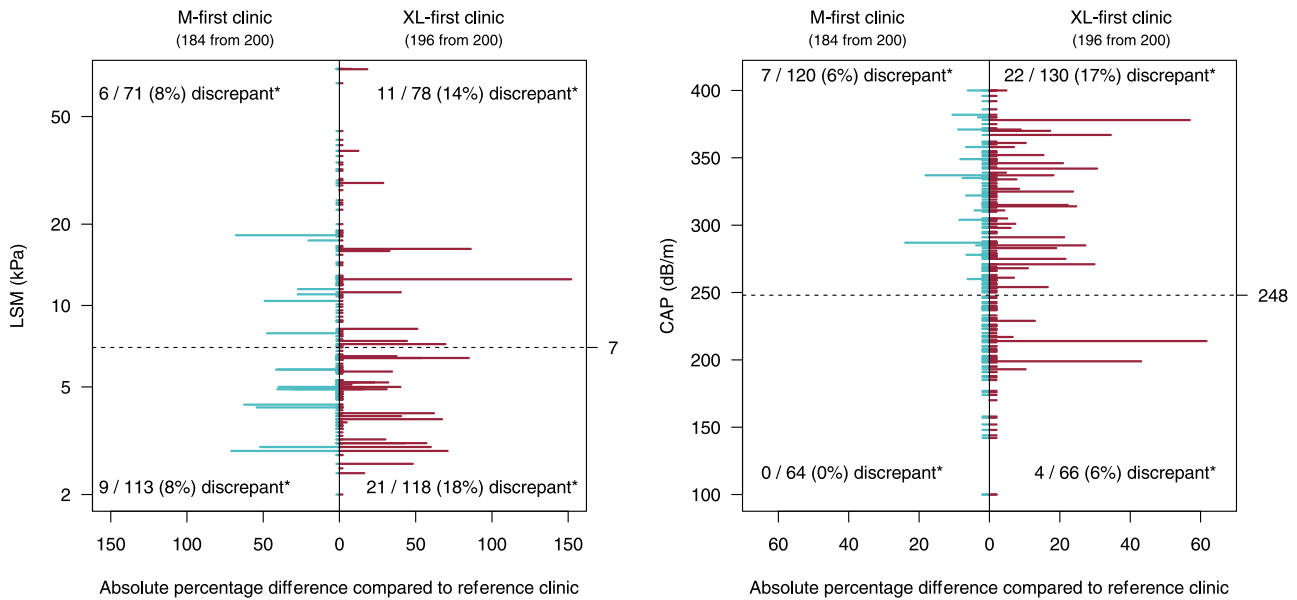


Figure: (abstract: PO-751): Discrepancies for CAP and LSM according to probe choice strategy. Dashed line indicates upper limit of normal values.

categories in our data. The M-first approach should be adopted as standard, especially for multicenter studies where data comparability is an important prerequisite.

PO-756

Combination treatments including semaglutide, cilofexor, and/or firsocostat lead to greater improvements in the FibroScan-AST (FAST) score compared to semaglutide alone in patients with non-alcoholic steatohepatitis

Naim Alkhour¹, Robert Herring, Jr.², Zeid Kayali³, Tarek Hassanein⁴, Anita Kohli¹, Lars Damgaard⁵, Kristine Buchholtz⁵, Mette Kjaer⁵, Clare Balendran⁵, Yanni Zhu⁶, Andrew Billin⁶, Ryan Huss⁶, Robert Myers⁶, Rohit Loomba⁷, Mazen Noureddin⁸. ¹Arizona Liver Health, Chandler, AZ, United States; ²Quality Medical Research, Nashville, TN, United States; ³Jubilee Clinical Research, Las Vegas, NV, United States; ⁴Southern California Research Center, Coronado, CA, United States; ⁵Novo Nordisk A/S, Bagsvaerd, Denmark; ⁶Gilead Sciences, Inc., Foster City, CA, United States; ⁷University of California at San Diego, La Jolla, CA, United States; ⁸Cedars-Sinai Medical Center, Los Angeles, CA, United States
Email: ryan.huss@gilead.com

Background and aims: The FAST score is a non-invasive tool that includes liver stiffness (LS) and controlled attenuation parameter (CAP) by transient elastography (TE; FibroScan) and serum AST. FAST can identify non-alcoholic steatohepatitis (NASH) patients at risk of progressive disease, and changes in FAST are associated with histologic response. Our aims were to evaluate the effects of the glucagon-like peptide-1 receptor agonist semaglutide (sema), alone or in combination with the farnesoid X receptor agonist cilofexor (CILO) and/or the acetyl-CoA carboxylase inhibitor firsocostat (FIR) on FAST, and to evaluate associations between changes in FAST with other parameters.

Method: NASH patients (n = 108) with mild to moderate fibrosis (F2-F3 on biopsy, or MRI-PDFF ≥ 10% and LS by TE ≥ 7 kPa) were randomized to sema (n = 21), sema+CILO 30 mg (n = 22), sema+CILO 100 mg (n = 22), sema+FIR 20 mg (n = 22), or sema+CILO 30 mg+FIR 20 mg (n = 21) for 24 weeks (W24). Semaglutide was dose escalated to 2.4 mg weekly in all groups. Exploratory end points included changes in liver biochemistry, LS by TE and MRE, and hepatic steatosis by CAP and MRI-PDFF, and Enhanced Liver Fibrosis score (ELF). Patients were categorized according to FAST at baseline (BL) and W24 (rule-out zone: ≤0.35; grey zone: >0.35- <0.67; rule-in zone: ≥0.67).

In patients with BL and W24 FAST, changes in FAST were compared between groups (analysis of covariance, Wilcoxon rank sum and Fisher's exact tests) and Spearman correlations with other parameters were calculated.

Results: At BL, median (Q1, Q3) LS by TE, CAP and AST were 9.25 kPa (7.70, 12.00), 344 dB/m (319, 375), and 40 U/L (26, 57), respectively. Median BL FAST was 0.56 (0.40, 0.70) and similar across groups; 31% and 45% of patients were in the rule-in and grey zones, respectively. Compared to sema alone (LSmean change in FAST from BL to W24: -0.19), treatment with sema+CILO 30 mg (-0.32), sema+FIR (-0.37) and sema+CILO+FIR (-0.39) led to significant improvements in FAST (all p < 0.05). At W24, the proportion of patients with ≥1-zone improvement in FAST was greater with combinations (90-100%) vs sema alone (58%). Treatment with sema+CILO+FIR led to the highest proportion of subjects in the rule-out zone at W24 (94% vs 42% with sema; Figure). Across groups, changes from BL to W24 in FAST were correlated with changes in alanine aminotransferase (ρ = 0.67), gamma-glutamyl transpeptidase (ρ = 0.33), ELF (ρ = 0.30), CK18-M30 (ρ = 0.44), and glucose (ρ = 0.24; all p < 0.05), but not body weight, MRI-PDFF, LS by MRE, HbA1c, insulin, or HOMA-IR.



*Patients with Baseline and Week 24 FAST included in analysis. BL, baseline; CILO, cilofexor; FAST, FibroScan-aspartate aminotransferase; FIR, firsocostat; SEMA, semaglutide; W24, week 24.

Figure: FAST by Zone at Baseline and Week 24

Conclusion: In patients with mild to moderate fibrosis due to NASH, treatment with CILO and/or FIR in addition to sema, leads to greater improvements in FAST score. Changes in FAST are correlated with

POSTER PRESENTATIONS

changes in other biomarkers, suggesting potential utility as an end point in NASH clinical trials.

PO-769

A novel radiomics signature based on T2WI accurately predicts hepatic inflammation in individuals with biopsy-proven NAFLD: a derivation and independent validation study

Zhongwei Chen¹, Huanming Xiao², Xinjian Ye³, Kun Liu³, Rafael Rios⁴, Kenneth I. Zheng⁴, Yi Jin⁵, Giovanni Targher⁶, Chris Byrne⁷, Zhihan Yan³, Xiaoling Chi², Ming-Hua Zheng^{4,8,9}. ¹the First Affiliated Hospital of Wenzhou Medical University, Department of Radiology, Wenzhou, China; ²Guangdong Provincial Hospital of Chinese Medicine, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Department of Hepatology, Guangzhou, China; ³the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Department of Radiology, Wenzhou, China; ⁴the First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ⁵the First Affiliated Hospital of Wenzhou Medical University, Department of Pathology, Wenzhou, China; ⁶University and Azienda Ospedaliera Universitaria Integrata of Verona, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Verona, Italy; ⁷Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, United Kingdom; ⁸Wenzhou Medical University, Institute of Hepatology, Wenzhou, China; ⁹Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China

Email: zhengmh@wmu.edu.cn

Background and aims: Currently, there is no effective method for assessing hepatic inflammation without resorting to histological examination of liver tissue obtained by biopsy. T2 weighted images (T2WI) are routinely obtained from liver magnetic resonance imaging (MRI) scan sequences. We aimed at establishing a radiomics signature based on T2WI for assessment of hepatic inflammation in people with non-alcoholic fatty liver disease (NAFLD).

Method: A total of 203 individuals with biopsy-confirmed NAFLD from two independent Chinese cohorts with liver MRI examination were enrolled in this study. The hepatic inflammatory activity score was calculated by the unweighted sum of the histologic scores for lobular inflammation and ballooning. 1032 radiomics features were extracted from the localized region of interest on the right liver lobe of T2WI and, subsequently, selected by minimum redundancy maximum relevance and least absolute shrinkage and selection operator (LASSO) methods. The T2-radiomics signature (T2-RS) was calculated by summing the selected features weighted by their coefficients.

Results: 18 radiomics features from Laplacian of Gaussian, wavelet, and original images were selected for establishing T2-RS. The T2-RS value differed significantly between groups with increasing degrees of hepatic inflammation ($p < 0.01$). The T2-RS yielded an area under the ROC curve (AUROC) of 0.80 (95% confidence intervals 0.71–0.89) for predicting hepatic inflammation in the training cohort with excellent calibration. The AUROCs of T2-RS in the internal cohort and external validation cohorts were 0.77 (0.61–0.93) and 0.75 (0.63–0.84), respectively (Table 1).

Table 1: Operating characteristics of T2-RS for discriminating hepatic inflammatory activity in NAFLD

	Training Set (n = 91)	Internal Validation Set (n = 38)	External Validation Set (n = 74)
AUC (95% CI)	0.80 (0.71–0.89)	0.77 (0.61–0.93)	0.75 (0.63–0.84)
Sensitivity, % (n/N)	76.19 (32/42)	70.59 (12/17)	71.43 (40/56)
Specificity, % (n/N)	73.47 (36/49)	76.19 (16/21)	72.22 (13/18)
Accuracy, % (n/N)	74.73 (68/91)	73.68 (28/38)	71.62 (53/74)
PPV, % (n/N)	71.11 (32/45)	70.59 (12/17)	88.89 (40/45)
NPV, % (n/N)	78.26 (36/46)	76.19 (16/21)	44.83 (13/29)
LR+	2.87	2.96	2.57
LR-	0.32	0.38	0.40
Diagnostic odds ratio	8.97	7.79	6.43

Note: T2-RS, radiomics signature based on T2WI.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predict value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Conclusion: T2-RS derived from radiomics analysis of T2WI shows promising utility for predicting hepatic inflammation in people with NAFLD.

PO-775

The effectiveness of a community based two-tier risk stratification pathway for non-alcoholic fatty liver disease

Rebecca Harris^{1,2}, David Harman³, Timothy Card^{1,4}, Guruprasad Aithal^{1,2}, Neil Guha^{1,2}, Joanne Morling^{1,4}. ¹NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom; ²Nottingham Digestive Diseases centre, School of Medicine, University of Nottingham, Nottingham, United Kingdom; ³Royal Berkshire NHS Foundation Trust, Reading, United Kingdom; ⁴Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

Email: rebecca.harris@nottingham.ac.uk

Background and aims: Developing community-based strategies which identify patients at risk of cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD) is imperative to reduce associated complications. Yet, this poses a significant challenge due to the large number of people exposed to the risk within the general population. A two-tier risk stratification pathway using inexpensive clinical algorithms initially, could be a valuable strategy to reduce the referral rate for more specialist tests of liver fibrosis. We aimed to determine the effectiveness of this strategy.

Method: A two-tier risk stratification pathway was applied to a prospective community cohort who had risk factors for NAFLD and stratified using transient elastography (TE) and the Enhanced liver fibrosis test (ELF). Validated cut offs from the literature, specific to TE and ELF, were used to define patients with significant liver fibrosis. Five clinical algorithms including Fibrosis-4 (Fib4), BARD score (BARD), NAFLD fibrosis score (NFS), AST:ALT ratio and AST to platelet ratio index (APRI) were applied as first line tests to evaluate the reduction in referral rate along with the misclassification rate.

Results: Of the 887 patients within the cohort, 21.2% had a reliable TE reading ≥ 8 kPa and 45.7% had an ELF score ≥ 9.5 , consistent with a classification of significant liver fibrosis. Application of the simple non-invasive tests would have resulted in a decrease in referrals (Fib4: 57.0–58.6%; BARD: 11.1–12.4%; NFS: 23.9–26.4%; AST:ALT ratio: 27.9–28.1%; APRI: 98.6–98.7%). However, a large proportion of patients with significant fibrosis would have been misclassified (Fib4: 42.1–51.8%; BARD: 7.2–9.2%; NFS: 13.9–15.0%; AST:ALT ratio: 22.2–34.7%; APRI: 95.7–97.3%). Increasing the sensitivity of these

clinical algorithms reduced the misclassification rate but resulted in the majority still requiring a second test.

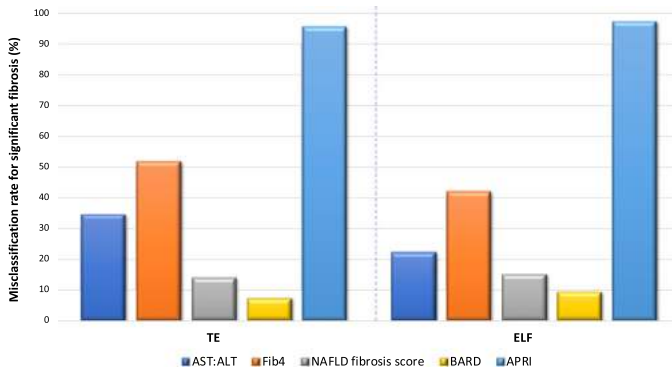


Figure:

Conclusion: A two-tier risk stratification pathway utilising widely accessible clinical algorithms in the first instance would reduce the referral rate, but leads to a large proportion of patients with significant liver fibrosis being missed and inappropriately reassured.

PO-836

Patients with elevated Fibrosis-4 Index or NAFLD Fibrosis Score have higher rates of cardiovascular events: a post-hoc analysis from two large, randomised statin clinical trials in 18 814 patients

Frank Tacke¹, Naim Alkhouiri², Mazen Nouredin³, David DeMicco⁴, Rana Fayyad⁴, Fady Taniou⁴. ¹Charité University Medicine Berlin, Department of Hepatology and Gastroenterology, Berlin, Germany; ²Arizona Liver Health, Chandler, United States; ³Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, United States; ⁴Pfizer Inc, New York, United States
Email: fady.ntaniou@pfizer.com

Background and aims: Patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are at increased risk for cardiovascular (CV) diseases. Non-invasive scoring tools, Fibrosis-4 Index (FIB-4) and NAFLD Fibrosis Score (NFS), correlate with an elevated risk of NASH with fibrosis. This post-hoc analysis aimed to identify correlations between CV events and elevated FIB-4 or NFS.

Method: Baseline data were pooled from two large, prospective Phase 4 trials comparing high-dose with usual-dose statins for secondary prevention of CV events (IDEAL, NCT00159835 and TNT, NCT00327691). Patients with established coronary heart disease were enrolled. FIB-4 and NFS were calculated from baseline assessments. Associations between baseline FIB-4 and NFS were modelled using a Cox proportional hazards model with adjustments.

Results: Patient characteristics are shown in the Table. Those in FIB-4 high and intermediate score categories experienced more CV and mortality events vs the low score category for all events except any coronary event (Table). Results from NFS categories were consistent with those for FIB-4. Age increased with FIB-4 score and was a significant predictor of incidence of any major coronary, CV, myocardial infarction, and stroke event and death ($p < 0.02$ for all).

Table: Characteristics and CV event risk by FIB-4 score category in pooled IDEAL and TNT population

	FIB-4 score		
	LOW <1.30 n = 11659	INTERMEDIATE 1.30–2.67 n = 6800	HIGH >2.67 n = 355
Baseline characteristics ^a			
Age (years), mean (SD)	58.2 (9)	66.3 (7)	69.1 (7)
Diabetes	1589 (14)	921 (14)	47 (13)
Hypertension	3009 (26)	2290 (34)	108 (30)
AST (IU/L), mean (SD)	18.3 (7)	21.3 (8)	31.2 (22)
ALT (IU/L), mean (SD)	24.2 (14)	21.2 (13)	23.4 (17)
CV event ^{a,b}			
Any CV event	3309 (28)	2154 (32)*	131 (37) [†]
Hazard ratio (95% confidence limit)	-	1.16 (1.10, 1.23)	1.40 (1.18, 1.67)
Any coronary event	2643 (23)	1606 (24) [‡]	92 (26)
Major coronary event	934 (8)	641 (9)*	39 (11) [‡]
Myocardial infarction	701 (6)	425 (6) [‡]	31 (9) [‡]
Stroke	314 (3)	260 (4)*	19 (5) [‡]
All-cause mortality	630 (5)	624 (9)*	43 (12)*

* $p < 0.0001$; [†] $p < 0.001$; [‡] $p < 0.01$; [§] $p < 0.05$

^an (%) unless otherwise noted; ^bReference group is FIB-4 < 1.30
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; FIB-4, Fibrosis-4 index; SD, standard deviation

Conclusion: Baseline high and intermediate score groups (defined by FIB-4 and NFS) had higher CV event rates vs the low score group. However, this association was not independent of the association with age.

PO-866

Comparing traditional machine learning and deep learning models to Fibrosis-4 index in the prediction of non-alcoholic fatty liver disease-associated liver fibrosis

Devon Y. Chang^{1,2}, Naim Alkhouiri³, Mazen Nouredin². ¹Arnold O. Beckman High School, Irvine, United States; ²Cedars Sinai Medical Center, Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Los Angeles, United States; ³Arizona Liver Health, Chandler, United States
Email: devonychang@gmail.com

Background and aims: Patients with non-alcoholic fatty liver disease (NAFLD) who develop liver fibrosis (LF) are at increased risk of liver-related complications and death. Identifying NAFLD patients with LF to allow early intervention is crucial. Even though machine learning (ML) has touched many aspects of human life, its application in diagnostic prediction of NAFLD is only in its infancy. We demonstrate that ML can be used as an effective tool to help predict clinically significant NAFLD-associated LF.

Method: We trained and tested ML models, including logistic regression (LR), random forests (RF), and artificial neural networks (ANN), to predict NAFLD-associated LF using data from the 2017–2018 National Health and Nutrition Examination Survey. A cohort of 2099 subjects without significant alcohol intake and with CAP (controlled attenuation parameter) scores ≥ 274 dB/m on Fibroscan[®] were selected. Clinically significant LF ($\geq F2$) was defined as LSM (liver stiffness measurement) ≥ 8.2 kPa on Fibroscan. Ten variables with the highest absolute Pearson correlation coefficients to LSM were chosen to train the models. 80% of the cohort was used to train the models, and 20% was used for testing. The sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), accuracy (Ac), and area under receiving operator characteristic curve (AUC) of the ML models for predicting LF in our cohort were compared to those of Fibrosis-4 index (FIB-4) using a threshold of ≥ 1.45 ($\geq F2$).

Results: The performances of the models are shown in Table 1. LR and ANN had higher Sn than RF ($p < 0.5$). Sp and Ac of RF were higher than

POSTER PRESENTATIONS

LR and ANN ($p < 0.5$). All ML models had higher Sn and AUC than FIB-4 ($p < 0.5$). FIB-4 had higher Sp than all ML models ($p < 0.5$).

Table 1:

	Sn (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	Ac (95% CI)	AUC (95% CI)
LR	0.61 (0.57–0.66)	0.70 (0.69–0.71)	0.28 (0.26–0.30)	0.90 (0.88–0.92)	0.69 (0.66–0.72)	0.69 (0.67–0.72)
RF	0.29 (0.25–0.33)	0.90 (0.89–0.91)	0.35 (0.30–0.40)	0.87 (0.85–0.89)	0.80 (0.78–0.82)	0.67 (0.64–0.69)
ANN	0.60 (0.51–0.69)	0.67 (0.64–0.70)	0.26 (0.23–0.29)	0.90 (0.87–0.93)	0.66 (0.64–0.68)	0.68 (0.66–0.71)
FIB-4	0.15	0.93	0.31	0.85	0.81	0.54

Conclusion: All ML models performed better than FIB-4 at predicting LF in our cohort. Among the ML models, LR and ANN were better than RF at identifying patients with LF. If trained on a larger cohort with more balanced datasets, ML could serve as an effective screening tool to help identify NAFLD patients with LF for population health management.

PO-916

Non-alcoholic fatty liver disease cardiovascular risk by metabolic subtype

Ibon Martínez-Arranz¹, Chiara Bruzzone², Rubén Gil-Redondo², Enara Arretxe¹, Marta Iruarrizaga-Lejarreta¹, Maider Bizkarguenaga², Itziar Mincholé¹, David Fernández Ramos², Fernando Lopitz Otsoa², Rebeca Mayo¹, Nieves Embade², Elizabeth Newberry³, Martine C. Morrison⁴, Robert Kleemann⁴, Libor Vitek⁵, Radan Bruha⁵, Rocío Aller⁶, Javier Crespo⁷, Manuel Romero Gomez⁸, Jesus Maria Banales^{9,10}, Marco Arrese¹¹, Kenneth Cusi¹², Elisabetta Bugianesi¹³, Samuel Klein³, Mazen Noureddin¹⁴, Shelly C. Lu¹⁴, Quentin Anstee¹⁵, Oscar Millet², Nicholas O Davidson³, Cristina Alonso¹, José M. Mato². ¹OWL Metabolomics, Derio, Spain; ²CIC bioGUNE-BRTA-CIBERhd, Precision Medicine and Metabolism, Derio, Spain; ³Washington University School of Medicine, Department of Medicine and Department of Developmental Biology, St. Louis, United States; ⁴Netherlands Organisation for Applied Scientific Research (TNO), Department of Metabolic Health Research, Leiden, Netherlands; ⁵Charles University in Prague, Faculty General Hospital and the First Faculty of Medicine, Prague, Czech Republic; ⁶Clinic University Hospital, University of Valladolid, Department of Digestive Disease, Valladolid, Spain; ⁷Marqués de Valdecilla University Hospital, Cantabria University, Research Institute Marqués de Valdecilla (IDIVAL), Department of Digestive Disease, Santander, Spain; ⁸Valme University Hospital-CIBERhd, Unit for the Clinical Management of Digestive Diseases, Seville, Spain; ⁹Biodonostia Research Institute, Donostia University Hospital, Department of Liver and Gastrointestinal Diseases, Donostia, Spain; ¹⁰Donostia University Hospital, University of the Basque Country (UPV-EHU), CIBERhd, IKERBASQUE, Donostia, Spain; ¹¹Pontificia Universidad Católica de Chile, Department of Gastroenterology, Escuela de Medicina, Santiago de Chile, Chile; ¹²University of Florida, Division of Endocrinology, Diabetes and Metabolism, Gainesville, United States; ¹³University of Turin, Gastroenterology Department, Turin, Italy; ¹⁴Cedars-Sinai Medical Center, Division of Gastroenterology and Hepatology, Los Angeles, United States; ¹⁵Institute of Cellular Medicine, The Medical School, Newcastle University, Liver Research Group, Newcastle-upon-Tyne, United Kingdom
Email: director@cicbiogune.es

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a complex heterogeneous disease with impaired hepatic lipid metabolism reflecting nutritional and environmental factors acting on a susceptible genetic background. Here we examine CVD risk in an international cohort of 1099 individuals with biopsy-proven NAFLD. **Method:** We used LC-MS serum metabolomic subtyping and NMR lipoprotein profiling in 5 mouse models of NASH and fibrosis: (1) germline methionine adenosyltransferase 1a knockout (Mat1a-KO);

(2) C57BL/6 mice fed 0.1% methionine and choline deficient (0.1MCD) diet; (3) liver-specific microsomal triglyceride transfer protein KO (Mttp-LKO); (4) liver-specific transmembrane 6 superfamily member 2 KO (Tm6sf2-LKO); and (5) germline Ldlr-deficient (Ldlr-/-Leiden) KO mice fed high fat diet (HFD). Murine serum metabolomes were compared to serum metabolomes of 1099 patients with biopsy-proven NAFLD. Lipoprotein profiles were determined in a subgroup of 233 NAFLD patients. VLDL-triglyceride (TG) secretion rate (SR) was measured in 20 obese individuals with high intrahepatic TG (IHTG), and in 10 lean subjects with normal IHTG and VLDL-TG SR.

Results: NAFLD patients were classified into three major subtypes (A, B, and C). Subtype A phenocopies the serum metabolome of four mice with impaired VLDL-TG secretion (Mat1a-KO, 0.1MCD, Mttp-LKO, Tm6sf2-LKO), while subtype C phenocopies the metabolome of Ldlr-/-Leiden/HFD mice. VLDL-TG secretion rate was lower in obese individuals with high IHTG and subtype A vs subjects with increased IHTG and subtypes B and C. Grades of steatosis/NASH or fibrosis were comparable among subtypes. The frequency of NAFLD subtypes was 44%, 25%, and 31% for A, B, and C, respectively. Serum VLDL-TG was independent of steatosis grade (S1-3) in subtype A, whereas subtypes B and C showed a curvilinear relationship in VLDL-TG and steatosis with a peak at grade S2. The same pattern was observed for each of the VLDL subclasses (VLDL₁₋₅). Hepatic biosynthetic capacity (serum albumin) was similar for all three subtypes. Total serum TG, VLDL, small dense LDL_{5,6} and remnant lipoprotein cholesterol, were lower among subtype A vs subtypes B and C, while the typical LDL-cholesterol-to-HDL-cholesterol ratio was similar.

Conclusion: Metabolomic signatures identify 3 NAFLD subgroups, independent of histological disease severity. These signatures align with known CVD risk factors that may account for the variation in hepatic vs cardiovascular outcomes and, if validated, offers novel, clinically relevant, risk stratification.

PO-919

Comparative diagnostic accuracy of blood-based biomarkers for diagnosing NASH: phase 1 results of the LITMUS project

Yasaman Vali¹, Jenny Lee¹, Jörn Schattenberg², Manuel Romero Gomez³, Dina Tiniakos⁴, Pierre Bedossa⁴, M. Julia Brosnan⁵, Kevin Duffin⁶, Richard Torstenson⁷, Clifford Brass⁸, Mike Allison⁹, Helena Cortez-Pinto¹⁰, Jean-Francois Dufour¹¹, Mattias Ekstedt¹², Sven Franqu¹³, Andreas Geier¹⁴, Stephen Harrison¹⁵, Morten Karsdal¹⁶, Diana Leeming¹⁶, George Papatheodoridis¹⁷, Michael Pavlides¹⁵, Jerome Boursier¹⁸, Salvatore Petta¹⁹, Elisabetta Bugianesi²⁰, Vlad Ratziu²¹, Quentin Anstee⁴, Patrick Bossuyt¹. ¹Amsterdam UMC, Department of Epidemiology and Data Science, Amsterdam, Netherlands; ²University Hospital Mainz, Department of Medicine, Mainz, Germany; ³Virgen del Rocío University Hospital, University of Seville, Sevilla, Spain; ⁴Newcastle University, Translational and Clinical Research Institute, Newcastle upon Tyne, United Kingdom; ⁵Pfizer, Internal Medicine Research Unit, Cambridge, United States; ⁶Eli Lilly and Company Ltd (LLY), Lilly Research Laboratories, Indianapolis, United States; ⁷AstraZenica; ⁸Novartis Pharmaceuticals Corporation, New Jersey; ⁹Cambridge University NHS Foundation Trust, Liver Unit, Department of Medicine, Cambridge NIHR Biomedical Research Centre, Cambridge, United Kingdom; ¹⁰Lisbon University, Portugal; ¹¹University of Bern, Department of Biomedical Research, Bern, Switzerland; ¹²Linköping University, Department of Health, Medicine and Caring Sciences, Sweden; ¹³Antwerp University, Belgium; ¹⁴Wurzburg University Hospital, Division of Hepatology, Department Medicine II, Wurzburg, Germany; ¹⁵Oxford University, Oxford, United Kingdom; ¹⁶Nordic Bioscience Clinical Studies A/S, Herlev, Denmark; ¹⁷National and Kapodistrian University of Athens, University Club Reading Room, Athina, Greece; ¹⁸Angers University Hospital, Hepatology Department, Angers, France; ¹⁹Università di Palermo,

Sezione di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, Palermo, Italy; ²⁰University of Turin, Department of Medical Sciences, Division of Gastro-Hepatology, A.O. Città della Salute e della Scienza di Torino, Torino, Italy; ²¹Sorbonne University, ICAN (Institute of Cardiometabolism and Nutrition), hôpital Pitié Salpêtrière, Paris, France
Email: y.vali@amc.uva.nl

Background and aims: The presence of active steatohepatitis (NASH) is a regulatory requirement for NAFLD trial recruitment and an important severity indicator in clinical care. There is a pressing need for robust, non-invasive tests (NITs) to discriminate simple steatosis from NASH, but most evaluations have been non-comparative and performed in small groups. The LITMUS project independently assessed NITs that, singly or in combination, would enable detection of NASH.

Method: Thirteen NITs, including single markers and combination panels, were evaluated against histology to identify NASH (NAS \geq 4 with \geq 1 point in each component). The area under the receiver operating curve (AUC) \pm 95% confidence interval (95% CI) were calculated for each NIT. Due to the absence of any existing validated NIT for NASH and the high collinearity between NASH and fibrosis stage, performance of FIB-4, a widely used simple fibrosis test, was adopted as a comparator in the same subgroup of patients for whom biomarker results were available to aid interpretation.

Results: Data from 686 participants from nine European centers were included. Mean age 50 years; 57% male; 36% type2 diabetics; mean BMI 35. Histological evidence of NASH was present in 54%. AUCs ranged from 0.51 to 0.76, with some marker combinations showing higher AUCs than single markers (Table 1). The SomaScan™ algorithm showed the highest AUC (0.76) followed by MACK-3 (0.69).

Table 1: Diagnostic accuracy of markers in detecting active NASH vs. FIB-4

NIT	n	AUC (95% CI)	
		NIT	FIB-4
CK-18 (M30)	588	0.67 (0.62–0.71)	0.64 (0.59–0.68)
CK-18 (M65)	608	0.65 (0.60–0.69)	0.63 (0.59–0.68)
PRO-C3	431	0.64 (0.59–0.69)	0.64 (0.59–0.69)
P4NP7S	229	0.63 (0.56–0.70)	0.63 (0.55–0.70)
ADAPT	417	0.68 (0.63–0.73)	0.63 (0.58–0.69)
FIBC3	413	0.64 (0.59–0.69)	0.63 (0.58–0.69)
ABC3D	413	0.64 (0.58–0.69)	0.63 (0.58–0.69)
DIAFIR	242	0.67 (0.60–0.74)	0.63 (0.56–0.70)
MACK-3	391	0.69 (0.63–0.74)	0.61 (0.56–0.67)
GLP (fibrosis)	324	0.51 (0.45–0.57)	0.63 (0.57–0.69)
SomaScan	278	0.76 (0.71–0.82)	0.62 (0.55–0.69)
ELF	673	0.62 (0.58–0.66)	0.61 (0.57–0.66)
NFS	668	0.60 (0.56–0.64)	0.62 (0.58–0.66)

Conclusion: Fibrosis targeted biomarkers and single biomarkers (eg CK18) showed limited performance in detecting NASH. However, novel combinations produced more promising results. Among these, panels specifically developed to detect NASH, such as the SomaScan algorithm and MACK-3, significantly outperformed FIB-4 (P value <0.05). Validation in an expanded cohort is underway.

PO-941

Independent validation of Agile 4: novel FibroScan based score for the diagnosis of cirrhosis in patients with non-alcoholic fatty liver disease

Jerome Boursier^{1,2}, Marine Roux², Charlotte Costentin³, Adele Delamarre⁴, Clémence M. Canivet^{1,2}, Nathalie Sturm⁵, Victor de Lédinghen⁴. ¹Angers University Hospital, Hepato-gastroenterology and Digestive Oncology Department, Angers, France; ²Angers University, HIFIH UPRES EA3859 Laboratory, Angers, France; ³Grenoble Alpes University Hospital, Hepatology, Gastroenterology and Digestive Oncology, Grenoble, France; ⁴Haut Leveque Hospital,

Hepatology, Gastroenterology and Digestive Oncology, Pessac, France; ⁵Grenoble Alpes University Hospital, Pathology Department, Grenoble, France
Email: jeboursier@chu-angers.fr

Background and aims: Currently available non-invasive tests, including FIB-4 and liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE-FibroScan), are highly effective in excluding cirrhosis yet their ability to rule in cirrhosis is moderate. Recently, Agile 4, a score combining LSM with routine clinical parameters (AST/ALT ratio, platelets count, age, sex, diabetes status) was proposed to identify cirrhosis in NAFLD patients with the aim to optimize positive predictive value (PPV) and reduce the number of cases with indeterminate results (1). The objective of the present work was to independently validate this score.

Method: This retrospective study included adults with NAFLD from three French tertiary care centers who underwent liver biopsy, LSM by VCTE, and blood sampling as part of routine clinical practice. Calibration was assessed with goodness of fit (calibration plot), and discrimination with the area under the receiver operating characteristic curve (AUROC) with comparison to LSM alone and FIB-4. Cut-off values for high sensitivity (Se) and high specificity (Sp) previously determined (1) were applied to this cohort in order to define rule-out, indeterminate and rule-in zones.

Results: The cohort comprised 1042 patients of which 13% had cirrhosis. Calibration plot for Agile 4 was close to the ideal calibration, which conveyed a satisfactory goodness of fit. The AUROC of Agile 4 was 0.89 and significantly different from that of FIB-4 (Table). 88% of the patients without cirrhosis had Agile 4 result below the rule out cut-off, which was higher compared to LSM and FIB-4 (respectively 54% and 79%). Using the high cut-off, Agile 4 provided better PPV (68%) compared to FIB4 and LSM (respectively 55% and 62%). Finally, using Agile 4, the number of patients in the indeterminate zone was respectively 4 and almost 2 times lower than with FIB-4 and LSM (Table).

	FIB-4	LSM	Agile 4
AUROC [95% CI]	0.81 [0.77;0.85]	0.88 [0.85;0.91]	0.89 [0.86;0.92]
Delong test p (vs Agile)	<0.0001	0.2363	NA
Rule out cut-off (\geq 85% Se)	<1.39	<12.1	<0.251
% patients	49%	72%	81%
Se/Sp	0.85/0.54	0.76/0.79	0.71/0.88
NPV	0.96	0.96	0.96
Indeterminate zone			
% patients	43%	19%	11%
Rule in cut-off (\geq 95% Sp)	\geq 3.25	\geq 23.2	\geq 0.565
% patients	8%	9%	8%
Se/Sp	0.35/0.96	0.44/0.96	0.44/0.97
PPV	0.55	0.62	0.68

Conclusion: This study externally and independently validates Agile 4 confirming previous results (1). It indeed improves the identification of cirrhotic patients and may reduce the need for liver biopsy for this diagnostic target. It also demonstrates its interest in the identification of patients to start hepatocellular carcinoma and esophageal varices screening.

Reference

1. YounossiZM *et al.* AASLD 2020 LP12.

POSTER PRESENTATIONS

PO-944

Prognostic value of FibroScan based Agile 3+ and Agile 4 scores in patients with non-alcoholic fatty liver disease

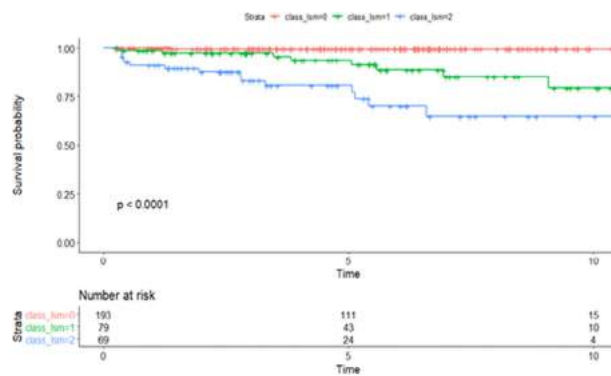
Jerome Boursier^{1,2}, Clémence M. Canivet^{1,2}, Marine Roux², Lannes Adrien^{1,2}, Isabelle Fouchar^{1,2}, Frédéric Oberti^{1,2}. ¹Angers University Hospital, Hepato-gastroenterology and Digestive Oncology Department, Angers, France; ²Angers University, HIFIH UPRES EA3859 Laboratory, Angers, France
Email: jeboursier@chu-angers.fr

Background and aims: Recently, Agile 4 and Agile 3+, two scores combining liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) with routine clinical parameters were proposed to diagnose cirrhosis and advanced fibrosis in NAFLD patients, respectively (1). The objective of the present work was to assess the prognostic accuracy of Agile 4 and Agile 3+ for the prediction of liver-related events (LRE) and to compare them to LSM alone.

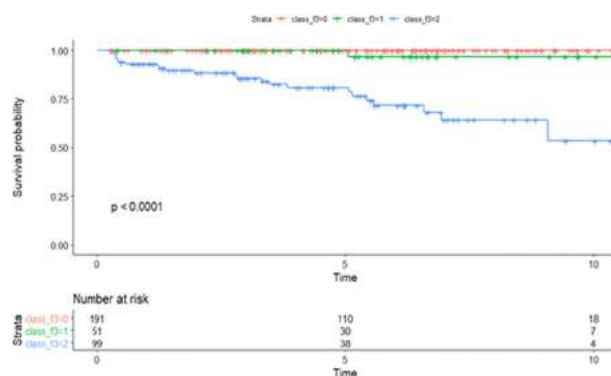
Method: This retrospective study included adults with NAFLD from a French tertiary care center who underwent LSM and blood sampling as part of routine clinical practice. The main study outcome was LRE, a composite end point combining cirrhosis complication or hepatocellular carcinoma. LRE were ascertained by chart review. Cut-off values of Agile 4 and Agile 3+ previously determined (1) and Baveno cut-off values for LSM (10 kPa–15 kPa) were used to define the rule-out, indeterminate and rule-in zones at baseline. Kaplan-Meier curves were compared using the Log-rank test.

Results: 341 NAFLD patients were included in the study (median age: 58 years, male sex: 65%, diabetes: 36%). LRE occurred in 27 (7.9%) patients after a median follow-up of 5.2 years (1st and 3rd quartiles: 2.9–7.2). The rate of patients included in the rule-out/indeterminate/rule-in zones of the Agile 3+ and Agile 4 were respectively 56%/15%/29% and 83%/9%/8%. Kaplan-Meier curves (Figure) for Agile 4 and Agile 3+ showed significant differences between the rule-out and the rule-in zones ($p < 0.001$ for both) and between indeterminate and rule-in zones ($p \leq 0.002$ for both), while the difference between indeterminate and rule-out zones was not significant. By comparison, the rates of patients included in the rule-out/indeterminate/rule-in zones with LSM were 57%/23%/20%. Using LSM, patients experiencing a LRE were initially either in the indeterminate or the rule-in zones and consequently, a significant difference ($p < 0.001$) between the rule-out and the indeterminate zone was observed while the difference between the indeterminate and rule-in was less significant ($p = 0.03$).

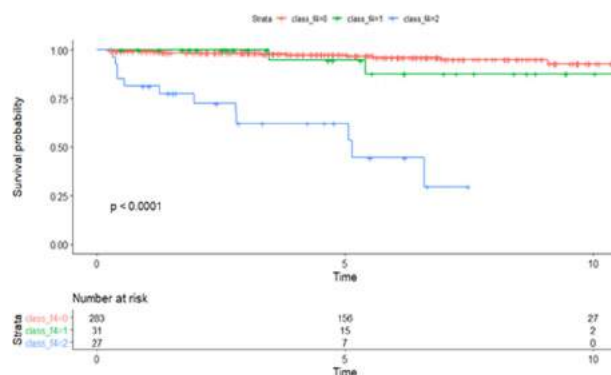
Conclusion: Agile 4 and Agile 3+ well predict the occurrence of liver-related events in patients with NAFLD. Particularly, rule-in cut-offs of both scores better identify at-risk patients than LSM alone. These results demonstrate the interest of those scores in the identification of patients requiring hepatocellular carcinoma and esophageal varices screening. 1. Younossi, ZM et al. AASLD 2020 LP12.



a. Kaplan-Meier curves for LSM



b. Kaplan-Meier curves for Agile 3+



c. Kaplan-Meier curves for Agile 4

Figure:

PO-980

Incidence rates of hepatobiliary outcomes among patients with non-alcoholic steatohepatitis based on fibrosis-4 score severity at baseline

Lina Titievsky¹, Aziza Jamal-Allial², Kerrin Gallagher², Thomas Capozza¹, Stephen Dodge¹, Simo Du², Amy Law¹, Macky Natha¹, Erik Ness¹, Mindie Nguyen³, Yuval Patel⁴, Amarita Randhawa¹, Daina Esposito^{2,5,6}. ¹Intercept Pharmaceuticals, Inc., New York, United States; ²HealthCore, Inc., Watertown, United States; ³Stanford University, Redwood City, United States; ⁴Duke University, Durham, United States; ⁵Boston University School of Public Health, Boston, United States; ⁶Ciconia, Inc., United States
Email: lina.titievsky@interceptpharma.com

Background and aims: Non-alcoholic steatohepatitis (NASH) is a chronic inflammatory condition that can generate fibrosis over time, resulting in liver dysfunction and poor outcomes. The fibrosis-4 (FIB-4) index score is a simple, accessible non-invasive test of liver fibrosis

based on laboratory data that is used as an alternative to biopsy to categorize degree of fibrosis and associated risk. This study estimated incidence rates of hepatobiliary outcomes among NASH patients stratified by FIB-4 defined fibrosis severity.

Method: The HealthCore Integrated Research Database was used to identify NASH patients from October 01, 2015, to March 31, 2020. The NASH algorithm required either (1) NASH as the principal discharge diagnosis on an inpatient claim, (2) liver biopsy followed by NASH diagnosis, or (3) liver imaging followed by NASH diagnosis, liver function procedure, and ≥ 1 risk factor (obesity, type 2 diabetes, pre-diabetes, or dyslipidemia). Patients with concurrent liver disease or a history of liver transplant were excluded. All patients had ≥ 12 months of baseline continuous health plan enrolment. All patients with sufficient lab data to determine the FIB-4 score were categorized as no/early fibrosis (NF), indeterminate (INF), or advanced fibrosis (AF), using published thresholds. Incidence rates (IR) and 95% confidence intervals were calculated as the number of outcomes of interest in the follow-up period divided by the total person-time at risk and expressed per 1,000 Person Years (PY).

Results: Baseline FIB-4 was estimated for a total of 7,937 NASH patients (~40% of the final NASH cohort): 55.6% NF, 28.2% INF, and 16.2% AF. The presence of hepatic comorbidities at baseline was greatest among AF, followed by INF and NF (e.g., baseline cirrhosis was 63.1%, 17.1%, and 4.6%, respectively). AF patients were older (28% ≥ 65 years vs. 18% and 8%) and more likely to have type 2 diabetes (69% vs. 54% and 38%) and hypertension (89% vs. 82% and 67%) than INF and NF, respectively. The IR (Figure) of new events followed an expected pattern with increasing fibrosis severity where the lowest rates were seen among the NF followed by INF and AF (e.g., the cholelithiasis IR increased from 9.4 to 13.0 and 45.8).

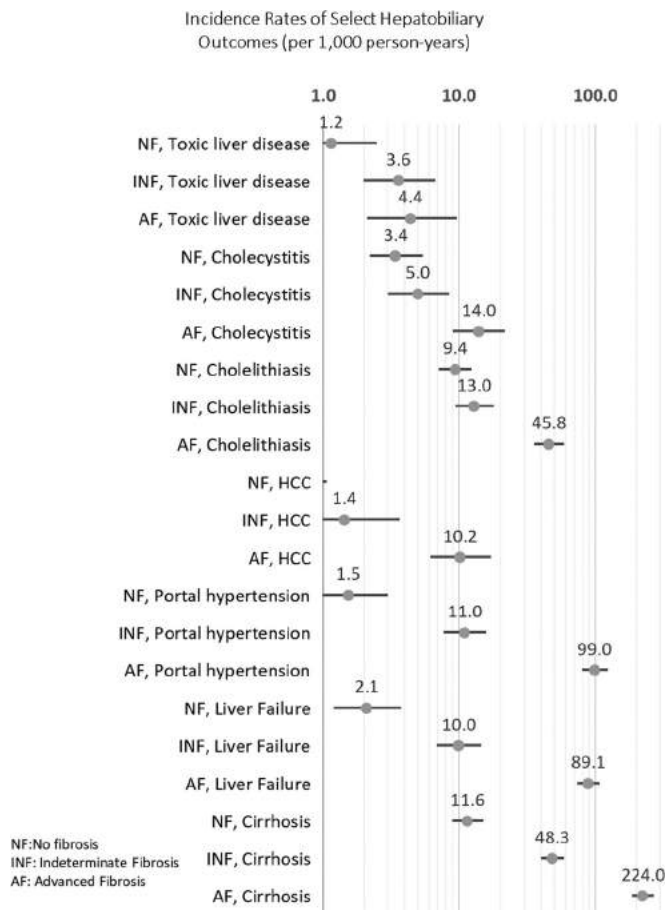


Figure:

Conclusion: AF per FIB-4 assessment corresponds to a higher burden of hepatic comorbidities at baseline and a higher IR of new outcomes during the follow-up period. These findings further support to the utility of FIB-4 as a prognostic indicator in NASH patients.

PO-1001

External Validation of the FAST Score as a Predictor of Fibrotic NASH in a Large Cohort of U.S. Adults with Biopsy-Proven NAFLD

Prido Polanco^{1,2}, Phuc Le³, Rashmee Patil⁴, Mario Dgyves¹, Nikhil Kahlon¹, Pranay Garg¹, Sahil Choudhri¹, Shrika Kantala¹, Vinyas Bhat¹, Yash Chatha¹, Anita Kohli¹, Mazen Noureddin⁵, Naim Alkhouri¹. ¹Arizona Liver Health; ²Arizona Liver Health, Chandler, United States; ³Cleveland Clinic, Department of Internal Medicine; ⁴South Texas Research Institute, Edinburg, TX; ⁵Cedars-Sinai Medical Center, Department of Gastroenterology and Hepatology, Los Angeles, California Email: naim.alkhouri@gmail.com

Background and aims: The FAST score was recently developed to predict the presence of fibrotic NASH defined as having NAFLD activity score (NAS) ≥ 4 and Fibrosis ≥ 2 using the following variables: liver stiffness measurement (LSM) by transient elastography (TE) for fibrosis, controlled attenuated parameter (CAP) for steatosis, and AST for inflammation. The FAST score was initially developed in a UK cohort and externally validated in several other international cohorts but limited data exist on multiethnic U.S. patients who tend to have higher BMI. We aimed to evaluate the performance of the FAST score in a large U.S. cohort using liver histology as the gold standard.

Method: Consecutive patients seen at 4 tertiary care centers were included. NAFLD was diagnosed based on society guideline recommendations. NASH, NAS, and fibrosis stage were assessed using the Kleiner's histology score. M and XL probes were chosen based on the automated machine recommendation. Liver biopsy was done within 6 months from VCTE and patients were excluded if they had $>5\%$ change in body weight. C statistics were used to assess FAST accuracy and sensitivity, specificity, NPV, and PPV were calculated.

Results: 733 patients were included with mean age of 56.5 years (± 3.7), 246 (33.6%) were from Hispanic ethnicity, 39.7% had type 2 diabetes, and a mean BMI of 36.4 (± 4.1) kg/m². The prevalence of fibrotic NASH was 24% and that of significant fibrosis (F2-F4) was 31.7%. The FAST score had good overall accuracy in predicting fibrotic NASH with AUC of 0.76 (95% CI: 0.72–0.79). At the low cutoff value (<0.35) that corresponds to 90% sensitivity (rule out zone), the FAST had an excellent NPV of 91.1%. However, at the high cutoff value (>0.67) that corresponds to 90% specificity (rule in zone), the FAST score had low PPV of 46.2%. 350 patients were in the rule out zone, 186 were in the rule in zone, and 197 were classified as indeterminate.

Conclusion: The FAST score is an accurate score in ruling out the presence of fibrotic NASH in U.S. adults. However, the score has low PPV indicating lower accuracy in making a definitive diagnosis of fibrotic NASH.

PO-1020

Individualized polygenic risk score identifies NASH in the eastern Asia region: a derivation and validation study

Feng Gao¹, Kenneth I. Zheng², Sui-Dan Chen³, Donghyeon Lee⁴, Xi-Xi Wu¹, Xiao-Dong Wang², Giovanni Targher⁵, Chris Byrne⁶, Yong-Ping Chen^{2,7,8}, Won Kim⁴, Ming-Hua Zheng^{2,7,8}. ¹the First Affiliated Hospital of Wenzhou Medical University, Department of Gastroenterology, Wenzhou, China; ²the First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ³the First Affiliated Hospital of Wenzhou Medical University, Department of Pathology, Wenzhou, China; ⁴Seoul Metropolitan Government Boramae Medical Center, Division of Gastroenterology and Hepatology, Seoul, Rep. of South Korea; ⁵University and Azienda Ospedaliera Universitaria Integrata of Verona, Section of Endocrinology, Diabetes and Metabolism, Verona, Italy; ⁶University

POSTER PRESENTATIONS

Hospital Southampton, Southampton National Institute for Health Research Biomedical Research Centre, Southampton, United Kingdom;
⁷Wenzhou Medical University, Institute of Hepatology, Wenzhou, China;
⁸Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China
 Email: zhengmh@wmu.edu.cn

Background and aims: The correct identification of patients at increased risk of non-alcoholic steatohepatitis (NASH) is a critical step in the assessment of non-alcoholic fatty liver disease (NAFLD). Genome-wide association studies have showed that some genetic variants play an important role in the development and progression of NAFLD. On this background of evidence, the aim of our study was to develop and validate a polygenic risk score for identifying NASH in a large multi-national cohort of Asian patients with biopsy-proven NAFLD.

Method: The primary cohort comprised 538 patients with biopsy-proven NAFLD at a tertiary hospital in China. Another independent validation cohort of 532 patients with NAFLD from a tertiary medical centre in South Korea was also included. NASH was diagnosed based on an overall pattern of histological hepatic injury consisting of steatosis, inflammation, and hepatocellular ballooning.

Results: In the primary Chinese cohort, patients were randomly assembled into a "training set" (n = 402) and a "validation set" (n = 136). Patients had a median age of 42 years in the training set, and a median age of 43 in the validation set. The prevalence of NASH was 42.5% in the training set and 36.8% in the validation set, respectively. In the external validation cohort (South Korean), the median age was 54 years and the prevalence of NASH was 33.5%. An individualized risk score was developed based on the multivariable regression coefficients. The formula for the score was as follows: $0.548 \times \text{sex}$ (female = 1; male = 0) + $0.467 \times \text{MetS}$ (yes = 1; no = 0) + $1.909 \times$

elevated AST levels (AST $\geq 40 = 1$; AST < 40 U/L = 0) + $1.074 \times$ insulin resistance (HOMA-IR > 2.5 = 1; HOMA-IR $\leq 2.5 = 0$) + $0.581 \times$ PNPLA3 (rs738409) genotype (GC = 1; CC or GG = 0) + $1.228 \times$ PNPLA3 (rs738409) genotype (GG = 1; CC or GC = 0) + $0.607 \times$ HSD17B13 (rs72613567) genotype (AA or -/A = 1; -/- = 0). As shown in Figure, the score had a good discriminatory capacity (assessed by the area under the receiver operating characteristic curve [AUROC]) and calibration (assessed by the calibration curve and the Hosmer-Lemeshow goodness of fit test) in both the training and validation cohorts.

Conclusion: We have developed and validated a novel score incorporating both genetic and clinical risk factors that accurately identifies NASH in a large cohort of Asian patients with biopsy-proven NAFLD. These results may translate into clinical practice to guide the risk stratification of NAFLD and also stimulate further research into the pathogenic role of our risk score in NASH.

PO-1056

Biomarker screening strategies to identify fibrosing steatohepatitis cases for clinical trial recruitment in NAFLD

Yasaman Vali¹, Jenny Lee¹, Jörn M. Schattenberg², Manuel Romero Gomez³, Dina Tiniakos⁴, Pierre Bedossa⁴, M. Julia Brosnan⁵, Kevin Duffin⁶, Richard Torstenson⁷, Clifford Brass⁸, Mike Allison⁹, Helena Cortez-Pinto¹⁰, Jean-Francois Dufour¹¹, Mattias Ekstedt¹², Sven Franque¹³, Andreas Geier¹⁴, Stephen Harrison¹⁵, Morten Karsdal¹⁶, Diana Leeming¹⁶, George Papatheodoridis¹⁷, Michael Pavlides¹⁵, Jerome Boursier¹⁸, Salvatore Petta¹⁹, Elisabetta Bugianesi²⁰, Vlad Ratziu²¹, Quentin Anstee⁴, Patrick Bossuyt¹. ¹Amsterdam UMC, locatie AMC,

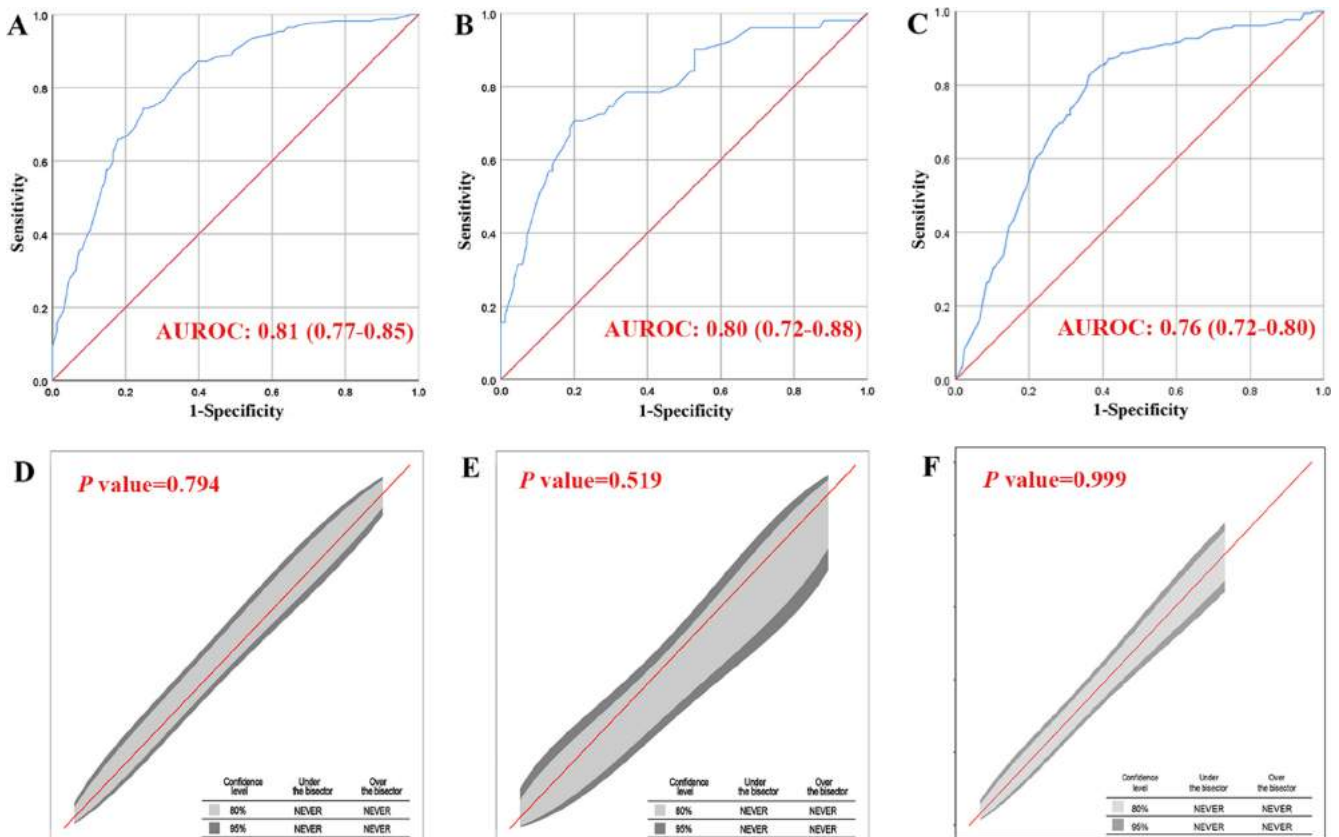


Figure: (abstract: PO-1020)

Amsterdam, Netherlands; ² University Mainz, Department of Medicine, Mainz, Germany; ³Institute of Biomedicine of Seville, Digestive Disease Department Virgen del Rocío University Hospital, Seville, Spain; ⁴Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; ⁵Pfizer, Internal Medicine Research Unit, Cambridge, United States; ⁶Lilly Research Laboratories, Eli Lilly and Company Ltd (LLY), Indianapolis, United States; ⁷AstraZeneca, Gaithersburg, United States; ⁸Novartis Pharmaceuticals Corp., East Hanover, United States; ⁹NIHR Cambridge Biomedical Research Centre, Cambridge University NHS Foundation Trust Liver Unit, Department of Medicine, United Kingdom; ¹⁰University of Lisbon, Lisboa, Portugal; ¹¹University of Bern, Hepatology, Department of Biomedical Research, Bern, Switzerland; ¹²Department of Health, Medicine and Caring Sciences, Linköping University, Sweden; ¹³University of Antwerp, Antwerpen, Belgium; ¹⁴Division of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany; ¹⁵University of Oxford, United Kingdom; ¹⁶Nordic Bioscience Clinical Studies A/S, Herlev, Denmark; ¹⁷Gastroenterology Department, National and Kapodistrian University of Athens, General Hospital of Athens "Laiko," Athina, Greece; ¹⁸Hepatology Department, Angers University Hospital, Angers, France; ¹⁹Sezione di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo, Palermo, Italy; ²⁰Department of Medical Sciences, Division of Gastro-Hepatology, A.O. Città della Salute e della Scienza di Torino, University of Turin, Torino, Italy; ²¹Assistance Publique-Hôpitaux de Paris, hôpital Pitié Salpêtrière, Sorbonne University, ICAN (Institute of Cardiometabolism and Nutrition), Paris, France
Email: y.vali@amc.uva.nl

Background and aims: A widely adopted recruitment target for NAFLD clinical trials is "fibrotic NASH," identified through liver biopsy (NAS ≥ 4 with ≥ 1 point in each component, plus fibrosis $\geq F2$). The ability to accurately pre-select cases for biopsy using non-invasive tests (NITs) could increase the efficiency of recruitment and accelerate drug development. In this respect, blood-based NITs are particularly tractable as no specialist equipment is required at recruitment sites. The LITMUS consortium evaluated blood-based NITs as tools to reduce histological screen failure rates in future trials.

Method: Following a survey among clinicians and leading drug developers, we determined that a screen failure rate of 37% was acceptable for efficient trial enrolment. For 10 NITs, we then identified thresholds that yield the corresponding failure rate and selected the threshold with the highest sensitivity.

Results: Data from 686 participants from nine centers were included. Table 1 shows the biomarker thresholds that achieved a screen failure rate $<37\%$ when biopsy is selectively performed in participants with a positive biomarker result, as well as the number of eligible patients found among those undergoing liver biopsy. We identified several NITs that would substantially reduce histological screen failure rates when biopsy was reserved for only biomarker positive patients.

Conclusion: Non-invasive pre-screening strategies for potential trial participants based on MACK-3, CK-18 M65 or the SomaScan proteomic algorithm could lead to substantial efficiencies in recruitment of trials targeting fibrotic NASH: reducing the number of cases biopsied to identify each eligible patient. Given the high screen failure rate in current trials, such preselection could facilitate trial recruitment and accelerate drug development. These results also have implications to guide risk-stratification in routine clinical practice.

Table 1: NIT to increase the efficiency in identifying patients with fibrotic NASH for trial recruitment

Biomarker	N	Threshold	Number of patients undergoing biopsy (per 100)	Screen failure rate	Number of eligible patients found (per 100)	Number needed to test
No screening	686	-	100	59%	41	-
MACK-3	391	0.30	60	37%	38	3
SomaScan	278	0.03	50	36%	32	3
CK-18 M65	608	296.1	38	37%	24	4
Diafir-Model S	242	2.18	39	38%	24	4
PRO-C3	431	17.6	36	36%	23	4
CK-18 M30	588	450.3	31	39%	19	5
ELF	673	9.98	25	36%	16	6
FIB-4	668	2.16	14	36%	9	11
GLP-Fibrosis score	324	0.23	4	25%	3	36
GLP-Cirrhosis score	324	0.22	3	33%	2	52

PO-1106

Screening for compensated advanced chronic liver disease using refined Baveno VI elastography cutoffs in Asian patients with NAFLD

Yu-Jie Zhou^{1,2}, Feng Gao³, Wen-Yue Liu⁴, Grace Lai-Hung Wong^{5,6}, Sanjiv Mahadeva⁷, Nik Raihan Nik Mustapha⁸, Xiao-Dong Wang^{1,9,10}, Wah-Kheong Chan⁷, Vincent Wai-Sun Wong^{5,6}, Ming-Hua Zheng^{1,9,10}. ¹the First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, Wenzhou, China; ²Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Division of Gastroenterology and Hepatology, Shanghai, China; ³the First Affiliated Hospital of Wenzhou Medical University, Department of Gastroenterology, Wenzhou, China; ⁴the First Affiliated Hospital of Wenzhou Medical University, Department of Endocrinology, Wenzhou, China; ⁵The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China; ⁶The Chinese University of Hong Kong, State Key Laboratory of Digestive Disease, Hong Kong, China; ⁷Faculty of Medicine, University of Malaya, Department of Medicine, Gastroenterology and Hepatology Unit, Kuala Lumpur, Malaysia; ⁸Hospital Sultanah Bahiyah, Department of Pathology, Alor Setar, Malaysia; ⁹Wenzhou Medical University, Institute of Hepatology, Wenzhou, China; ¹⁰Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China

Email: zhengmh@wmu.edu.cn

Background and aims: Recently, Papatheodoridi *et al.* proposed refined Baveno VI elastography dual cutoffs (8 and 12 kPa) for detecting compensated advanced chronic liver disease (cACLD) in patients with liver diseases of various etiologies including non-alcoholic fatty liver disease (NAFLD). They also proposed an algorithm for unclassified patients whose liver stiffness (LS) were between 8 and 12 kPa. We aimed to validate the performance of this 'two-step' method in three Asian NAFLD cohorts.

Method: We included 830 biopsy-proven NAFLD from three Asian cohorts. Clinical and pathological information, and LS measured by FibroScan were documented.

Results: The prevalence of cACLD was 6.9%, 35.6%, and 20.7% in the three cohorts. Compared with the original Baveno VI elastography criteria (10 and 15 kPa), the new cutoffs showed a comparable specificity (about 90%) and a higher sensitivity for identifying cACLD (Figure A). In this study, 44, 87, and 94 patients in Wenzhou, Hong Kong, and Malaysia fell in the grey zone. However, the risk model for unclassified patients proposed by Papatheodoridi *et al.* was not better

POSTER PRESENTATIONS

than LS value alone identified by ROC curves in the Asian population (all $p > 0.1$). Thus, we attempted to construct a simplified risk model for Asian patients with intermediate results. We merged unclassified patients within two Chinese cohorts with available laboratory data ($n=101$ in total) as the training set. Based on the adjusted multivariate logistic regression with bootstrap resampling, we proposed a simplified risk model: Risk of cACLD = $e^a / (1 + e^a)$, with $a = -5.421 + 0.868 \times \text{age (per quintile)} + 0.469 \times \text{LS} - 0.526 \times \text{platelet count (10}^9/\text{mm}^3 \text{ per quintile)}$. The simplified risk model outperformed the LS alone in two Chinese cohorts ($p = 0.001$), and was further validated in 94 Malaysia NAFLD patients with intermediate results by LS alone ($p = 0.04$; Figure B). Overall, the 'two-step' screening of cACLD improved correct classification rates from 73.5% by original dual cutoffs to 86.7% in the whole cohort; both refined screening approach by Papatheodoridi *et al.* and our simplified risk model yielded a classification rate of about 85%. Notably, the simplified risk model missed less cACLD cases in all three cohorts.

Conclusion: The dual cutoffs of 8 and 12 kPa are more reasonable to identify cACLD in patients with NAFLD. For Asian patients with intermediate results, a simplified risk model for cACLD prediction in unclassified patients can be used.

PO-1195

PNPLA3 and SERPINA1 are associated with liver disease severity in an unselected fatty liver disease cohort

Lorenz Balcar^{1,2}, Georg Semmler^{1,2}, Hannes Oberkofler², Stephan Zandanel², Michael Strasser², David Niederseer³, Alexandra Feldman², Felix Sticker⁴, Pavel Strnad⁵, Christian Datz⁶, Bernhard Paulweber², Elmar Aigner². ¹Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Wien, Austria; ²Paracelsus Medical University, First Department of Medicine, Salzburg, Austria; ³University Hospital Zurich, Department of Cardiology, Zürich, Switzerland; ⁴University Hospital Zurich, Department of Gastroenterology and Hepatology, Zürich, Switzerland; ⁵Universitätsklinikum Aachen, Medical Clinic III, Aachen, Germany; ⁶General Hospital Oberndorf, Internal Medicine, Oberndorf, Austria

Email: e.aigner@salk.at

Background and aims: Single nucleotide polymorphisms (SNPs) including PNPLA3 (rs738409 G-allele) and Serpin Family A Member 1 (SERPINA1 rs17580, Pi**MZ*, Pi**Z*, Pi**ZZ*) have been identified as risk modifiers of progression in alcoholic (ALD) and non-alcoholic fatty liver disease (NAFLD). While PNPLA3 has been studied in various settings, the value of both SNPs has so far not been addressed in a

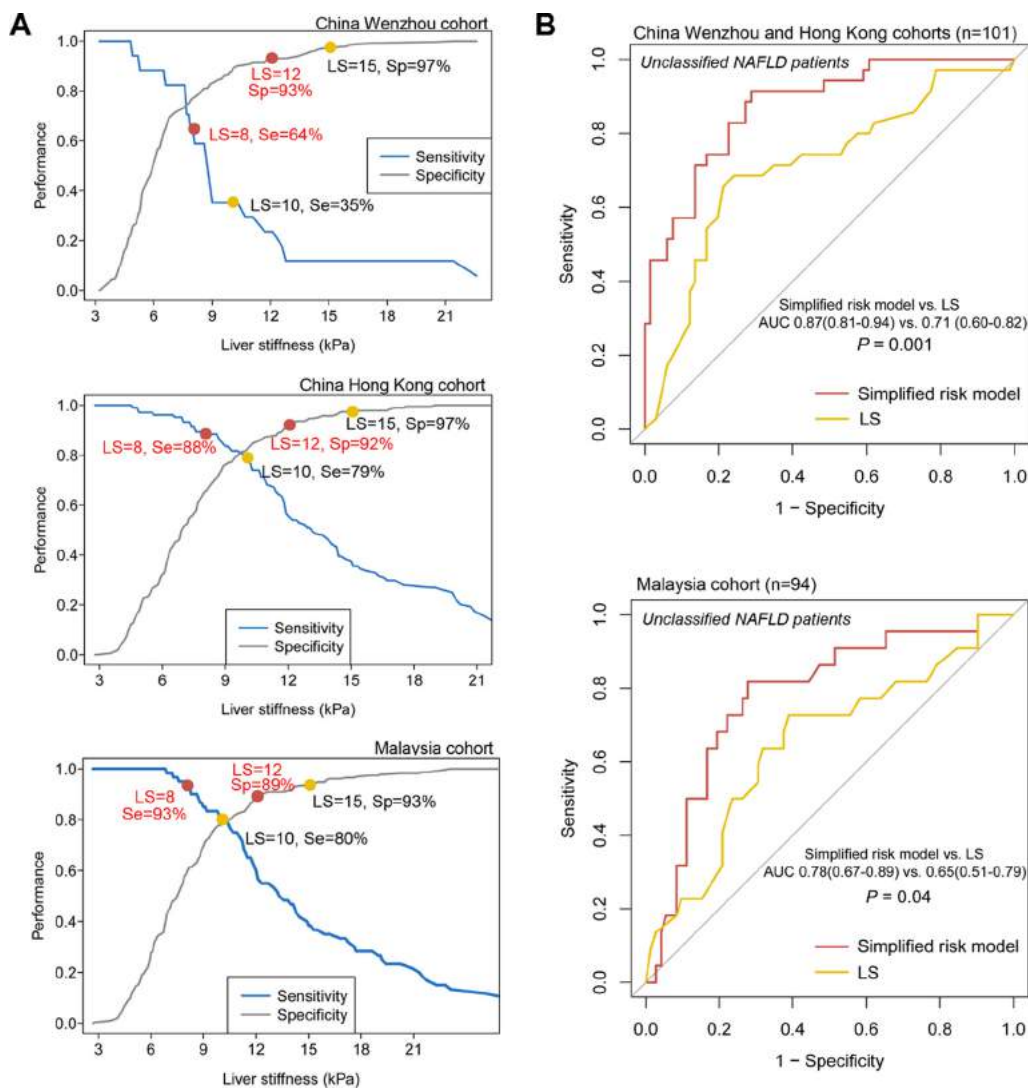


Figure: (abstract: PO-1106)

real-world cohort of subjects referred for diagnostic work-up of liver disease.

Method: Liver disease severity was assessed by liver stiffness measurement (LSM) and clinical manifestations of advanced chronic liver disease (ACLD) in 1257 consecutive patients with suspected fatty liver disease (ALD and NAFLD) at the time of first referral to a tertiary center. ACLD and clinically significant portal hypertension (CSPH) were defined as LSM \geq 20/10 kPa or unequivocal clinical signs of cirrhosis. The associations of risk variants with disease severity were calculated.

Results: The majority of patients were male (n = 759, 60%) with a mean age of 53 \pm 15 years. 1048 (83%) were diagnosed with NAFLD and 209 (17%) with ALD. ACLD was present in 309 (25%) and CSPH in 185 (15%) patients. The PNPLA3 G-allele was independently associated with higher LSM (adjusted B: 2.707 [1.435–3.979], P < 0.001), higher odds of ACLD (aOR: 1.971 [1.448–2.681], P < 0.001) and CSPH (aOR: 1.685 [1.180–2.406], P = 0.004) and there was a numeric trend towards more frequent hepatocellular carcinomas (HCC, GC/GG: 2.1% vs. CC: 0.8%, P = 0.063). While SERPINA1 Z-allele was not associated with higher LSM (adjusted B: 2.581 [-0.244–5.406], P = 0.073) or the presence of ACLD (aOR: 1.748 [0.925–3.307], P = 0.086), it was independently associated with higher odds of CSPH (aOR: 2.122 [1.067–4.218], P = 0.032). Associations of PNPLA3 G-allele and SERPINA1 Z-allele with CSPH were maintained independently of each other and results of the overall cohort were similar in patients with either NAFLD or ALD. The presence of both risk variants further increased the likelihood of ACLD (aOR: 3.892 [1.561–9.706], P = 0.004) and CSPH (aOR: 4.282 [1.667–10.996], P = 0.003).

Conclusion: PNPLA3 G-allele is independently associated with liver disease severity in an unselected patient cohort while SERPINA1 was only associated with end-stage liver disease, suggesting a dominant influence of PNPLA3 over SERPINA1 as a genetic risk modifier in fatty liver disease on a population level.

PO-1202

Curriculum-based education in NAFLD/NASH improves knowledge, competence, and confidence among gastroenterologists

Shari Dermer^{1,1}, Susan Smith¹, Briana Betz¹, John Maeglin¹. ¹*Medscape Education, Education, New York, United States*
Email: SDERMER@MEDSCAPE.NET

Background and aims: Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are the most common causes of chronic liver disease worldwide, affecting an estimated 25% of the world's population. The aim of this study was to assess the educational impact of a series of continuing medical education (CME) activities on the knowledge, competence, and confidence of gastroenterologists on the diagnosis and management of NAFLD/NASH.

Method: The educational series consisted of 6 online, CME-certified activities in multiple delivery formats, including a baseline practice assessment. For each activity, educational effect was assessed with a repeated pairs pre-/post-assessment study including a 3-item, multiple choice, knowledge/competence questionnaire and one confidence assessment question, with each participant serving as his/her own control. To assess changes in knowledge, competence, and confidence data from all clinicians who completed both pre- and post-questions were aggregated across activities and stratified by learning theme. McNemar's test or paired samples t-test (p < 0.05) assessed educational effect. The first activity launched August 2019 and the last launched October 2020; data were collected until December 2020.

Results: Overall gastroenterologists had significant improvements in knowledge (N = 733, p < 0.001) and competence (N = 831, p < 0.001) after education. Improvement in knowledge and competence measured as relative % change in correct responses pre/post education across the learning themes are reported:
Diagnostic Tools: 24% increase, 66% pre/82% post (n = 312; p < 0.001)
Risk Stratification: 38% increase, 32%pre/44% post (n = 614; p < 0.001)
Current Management of NAFLD/NASH: 69% increase, 42% pre/71% post (n = 312; p < 0.001)
New and Emerging Therapies: 21% increase, 57% pre/69% post (n = 733; p < 0.001)

	LSM	ACLD	CSPH
Age, yr	0.113 (0.070-0.156) <i>P</i> <0.001	1.055 (1.042-1.067) <i>P</i> <0.001	1.042 (1.028-1.056) <i>P</i> <0.001
BMI, kg/m²	0.332 (0.205-0.459) <i>P</i> <0.001	1.125 (1.090-1.161) <i>P</i> <0.001	1.054 (1.018-1.092) <i>P</i> =0.003
Alcohol consumption, y/n	13.302 (11.658-14.947) <i>P</i> <0.001	7.896 (5.573-11.188) <i>P</i> <0.001	7.553 (5.252-10.862) <i>P</i> <0.001
PNPLA3 (G=1)	2.715 (1.444-3.986) <i>P</i> <0.001	1.989 (1.461-2.709) <i>P</i> <0.001	1.707 (1.194-2.441) <i>P</i> =0.003
SERPINA1 (Z=1)	2.624 (-0.182-5.430) <i>P</i> =0.067	1.832 (0.963-3.483) <i>P</i> =0.065	2.196 (1.103-4.371) <i>P</i> =0.025

Linear and logistic regression analyses investigating the association of individual risk alleles with liver stiffness measurement (LSM), presence of advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH) in a combined regression model for both PNPLA3 and SERPINA1. Covariables were: Age (yr), BMI (kg/m²), active or past alcohol abuse (women \geq 2 drinks per day, men \geq 3 drinks per day).

Figure: (abstract: PO-1195)

POSTER PRESENTATIONS

Across the educational activities, 27% (n = 1045; p < 0.001) of learners had a measurable increase in confidence following education. Comparison of baseline knowledge from the Clinical Practice Assessment with pre-/post-education assessment is shown in Figure 1.



Figure:

Conclusion: This series of online, CME-certified educational activities delivered in multiple formats resulted in significant improvements in knowledge, competence, and confidence regarding the diagnosis and management of patients with NAFLD/NASH. These results demonstrate the effectiveness of curriculum-based education for gastroenterologists designed to address specific gaps in care.

PO-1217

Hepatocellular carcinoma in patients with NASH is associated with a specific pattern of muscle fat infiltration: a first-order radiomics study based on MRI-PDFF

Maxime Nachit^{1,2}, Marco Dioguardi Burgio^{3,4}, Anton Abyzov³, Philippe Garteiser³, Valérie Paradis^{5,6}, Valerie Vilgrain^{3,4}, Isabelle Leclercq¹, Bernard E. Van Beers^{3,4}. ¹UCLouvain, Laboratory of Hepato-Gastroenterology, Institut de Recherche Expérimentale et Clinique, Belgium; ²KULeuven, Department of Imaging and Pathology, Belgium; ³Université de Paris, Laboratory of Imaging Biomarkers, Center of Research on Inflammation, UMR 1149, Inserm, France; ⁴AP-HP Beaujon University Hospital Paris Nord, Department of Radiology, France; ⁵Université de Paris, Center of Research on Inflammation, UMR 1149, Inserm, F-75018, France; ⁶AP-HP Beaujon University Hospital Paris Nord, Department of Pathology, France
Email: maxime.nachit@gmail.com

Background and aims: The prevalence of NAFLD-associated hepatocellular carcinoma (HCC) is alarmingly increasing. Tools evaluating the risk of HCC development are needed to optimize surveillance in the still growing NAFLD population. Muscle fat infiltration has been associated with increased HCC incidence in patients with chronic liver disease. The aim of this study was to evaluate the association between muscle fat infiltration and HCC in patients with NAFLD.

Method: In a cohort of 72 histologically-proven NAFLD patients in which a subset had histological-diagnosed HCC, we used proton density fat fraction (PDFF) at MRI to evaluate fat infiltration in muscles (mean fat concentration and 1st order radiomic-based pattern) at the third lumbar level (L3): erector spinae, quadratus lumborum, psoas, oblique and rectus muscles.

Results: In patients with NASH and HCC, mean muscle PDFF was twice as high compared to patients with NASH but without HCC (quadratus lumborum: $5.7 \pm 3.9\%$ versus $3.2 \pm 2.4\%$, erector spinae $11.0 \pm 5.0\%$ versus $5.4 \pm 3.1\%$ and oblique: $12.6 \pm 6.9\%$ versus $8.1 \pm 4.9\%$, all p < 0.05) (Fig. 1a). HCC presence was a significant predictor of the mean PDFF of erector spinae (ES_{PDFF}) in patients with NAFLD even when multiple confounding factors (age, sex, activity and fibrosis score, visceral fat area) were taken into account (p = 0.014). Further, ES_{PDFF} was an independent and significant predictor of HCC presence in patients with NASH when adjusted for similar confounders (associated AUROC = 0.79–0.94, all p < 0.05). Energy [a radiomics feature for homogeneity] in erector spinae (ES_{Energy}) was a strong and independent predictor of HCC in patients with NASH (AUROC 0.87, 95% CI 0.73–1.00, p < 0.001) (Fig. 1b).

Conclusion: In patients with NASH, the presence of HCC is associated with a heterogenous increase of fat infiltration in skeletal muscles. Whether the pattern and magnitude of fat infiltration in skeletal muscles could be an indirect sign of and/or a risk factor for HCC development in patients with NASH needs to be investigated.

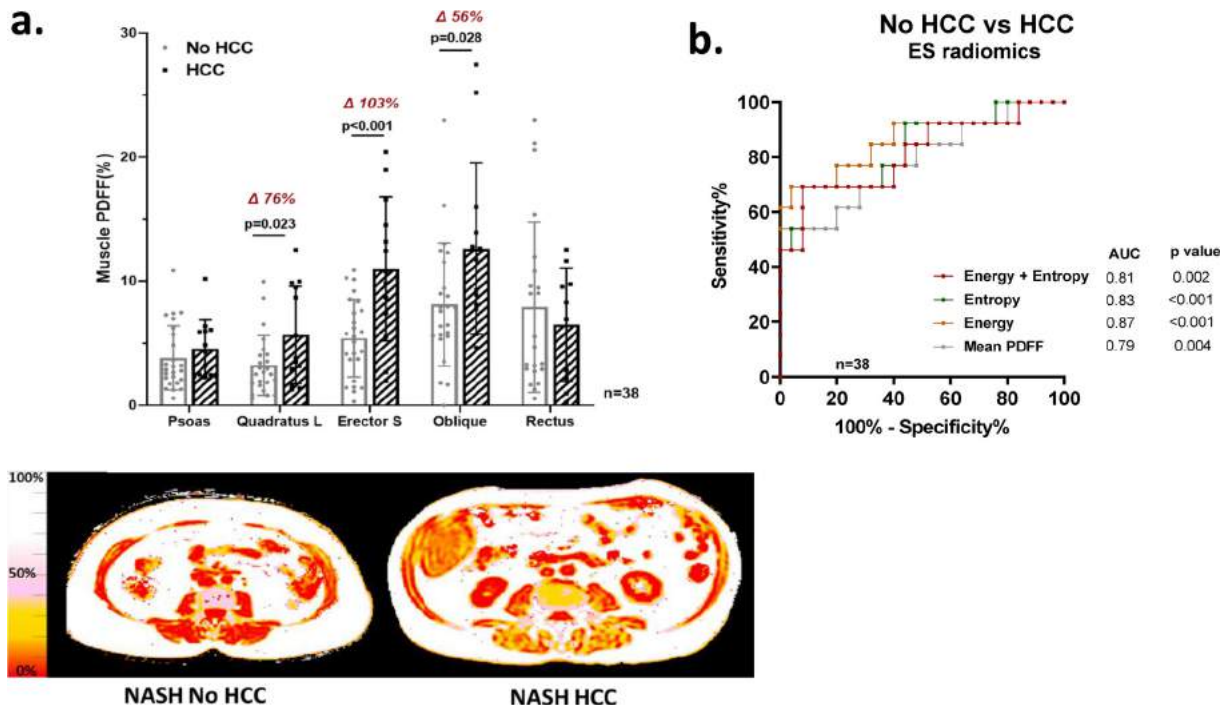


Figure: (abstract: PO-1217)

PO-1220

PNPLA3 and TM6SF2 are neither associated with decreased cardiovascular nor increased liver-related mortality in the general population

Lorenz Balcar^{1,2}, Georg Semmler^{1,2}, Sarah Wernly¹, Sebastian Bachmayer¹, Matthias Egger¹, Marie Semmler¹, Elmar Aigner³, David Niederseer⁴, Christian Datz¹. ¹General Hospital Oberndorf, Department of Internal Medicine, Oberndorf, Austria; ²Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ³Paracelsus Medical University Salzburg, First Department of Medicine, Salzburg, Austria; ⁴University Hospital Zurich, Department of Cardiology, Zürich, Switzerland
Email: c.datz@kh-oberndorf.at

Background and aims: Single nucleotide polymorphisms in PNPLA3 and TM6SF2 genes have been associated with increased risk and severity of liver disease. At the same time, they have been discussed as being potentially protective from cardiovascular diseases due to their implications on serum lipid levels. Thus, the aim of this study was to evaluate whether PNPLA3 and/or TM6SF2 are associated with cardiovascular or liver-related mortality in a cohort of asymptomatic patients.

Method: The study cohort comprised 1762 Caucasians undergoing routine screening colonoscopy at a single center in Austria between 2010 and 2014 with information on PNPLA3 and TM6SF2 genotype variants. All patients with established liver diseases, colorectal cancers and significant alcohol consumption were excluded. Survival analyses were performed using Kaplan Meier analyses.

Results: Half of included patients were male (n = 903 [51%], mean age 60 ± 10 years) with a mean BMI of 27 ± 5 kg/m². Among cardiovascular comorbidities, arterial hypertension and hypercholesterolemia were most frequent (n = 1008 [57%] and n = 1383 [79%]). Overall, hepatic steatosis was present in 792 patients (45%). NAFLD (PNPLA3-G: 41% vs. 38%, p = 0.055, TM6SF2-K: 51% vs. 37%, p < 0.001) and MAFLD (PNPLA3-G: 40% vs. 37%, p = 0.054, TM6SF2-K: 49% vs. 36%, p < 0.001) were more frequently diagnosed in patients carrying PNPLA3-G or TM6SF2-K alleles. Framingham risk score was lower for PNPLA3-G alleles (median 8 vs. 10, p = 0.011). Atrial fibrillation (n = 72 [4%]), coronary heart disease (n = 130 [7%]) and history of strokes (n = 53 [3%]) were equally distributed in each group.

During a median follow-up of 7.5 years, 132 patients died (7.5%), mainly due to cardiovascular- (n = 42) or tumor-related deaths (n = 40). PNPLA3 G-allele was neither associated with overall mortality (Log-rank-test: p = 0.100), nor with cardiovascular (Log-rank-test: p = 0.720) or liver-related mortality (Log-rank-test: p = 0.325). Similarly, TM6SF2 risk allele was also not associated with overall mortality (Log-rank-test: p = 0.539), cardiovascular (Log-rank-test: p = 0.993) or liver-related mortality (Log-rank-test: p = 0.179). Combining those two risk alleles did not increase granularity.

Conclusion: Whereas genotyping for symptomatic patients with liver disease seems useful, it does not provide prognostic information in asymptomatic patients. Therefore, genotyping for PNPLA3 and TM6SF2 should not be routinely performed in the absence of risk behavior.

PO-1336

The liver fibrosis marker PRO-C3 increases with fibrosis stage and is neither elevated in diabetics without liver disease nor in healthy obese subjects

Elisabeth Erhardt¹, Daniel Guldager Kring Rasmussen¹, Tina Manon-Jensen¹, Peder Frederiksen¹, Diana Leeming¹, Diane Shevell², Morten Karsdal¹, Guruprasad Aithal³, Jörn Schattenberg⁴. ¹Nordic Bioscience A/S, Fibrosis Biology, Herlev,

Denmark; ²Bristol-Meyers Squibb, Clinical Biomarkers, New Jersey, United States; ³University of Nottingham, Faculty of Medicine and Health Sciences, Nottingham, United Kingdom; ⁴Medical Centre of the Johannes Gutenberg-University, Mainz, Germany
Email: dgr@nordicbio.com

Background and aims: Progressive fibrosis has been identified as predictor of mortality in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Biomarkers are currently being evaluated for their ability to substitute the liver biopsy as the reference standard for staging the disease. Recent clinical studies in NAFLD/NASH patients support the utility of PRO-C3 as a marker for the degree of fibrosis, and effect of treatment. NAFLD patients suffer from several comorbidities, such as type 2 diabetes (T2D) and obesity. Even in type 1 diabetes, progressive liver injury can occur. It is therefore critical that biomarkers for determination of fibrosis in non-alcoholic liver injury are not influenced by comorbidities. In this study we define levels of PRO-C3 in type 1 and type 2 diabetics, non-diabetic obese, and non-obese otherwise healthy subjects. These are compared to PRO-C3 levels measured in NAFLD/NASH patients.

Method: We analyzed samples from 326 healthy subjects with no signs of liver disease obtained from Discovery Life Science. 97 patients were obese and 54 were nonobese type 1 and type 2 diabetics (subjects with abnormal levels of ALT, AST, ALP, or bilirubin were excluded from the study). PRO-C3 levels were compared across gender, age, ethnicity, BMI, and diabetes and reference ranges were estimated. Levels of PRO-C3 was measured in 222 NAFLD/NASH patients diagnosed and staged based on histology of a liver biopsy.

Results: In the 326 healthy subjects assessed PRO-C3 median levels were not influenced by gender, age, ethnicity, BMI, or diabetes (all p > 0.05). Median levels in all healthy groups were below the median levels measured in patients diagnosed with NAFLD/NASH. As expected for a biomarker reflecting fibrosis, PRO-C3 levels in the NAFLD/NASH population gradually increased with fibrosis stage (Table 1). Levels of PRO-C3 were able to identify patients with both significant (AUC = 0.83, sensitivity 63.0%, specificity 91.2%, p < 0.0001) and advanced fibrosis (AUC = 0.79, sensitivity 73.6%, specificity 75.0%, p < 0.0001).

	N	Lower limit (ng/ml) [90% CI]	Upper limit (ng/ml) [90% CI]	Median [90% CI]
All (healthy + Diabetes +obese)	326	6.1 [6.1–6.1]	16.3 [15.0–17.7]	8.9 [8.6–9.2]
Healthy	175	6.1 [6.1–6.1]	16.2 [14.4–18.2]	8.8 [8.5–9.4]
Diabetes	54	6.1 [6.1–6.1]	18.0 [14.9–21.8]	8.8 [8.0–9.6]
Obese (BMI > 30)	97	6.1 [6.1–6.1]	16.1 [14.0–19.0]	9.0 [8.4–9.4]
Total NAFLD/ NASH Patients	222			
Stage F0/F1	57	6.1 [6.1–6.3]	15.5 [14.1–17.0]	9.5 [8.6–10.2]
Stage F2	59	6.1 [6.1–6.5]	25.4 [21.2–29.5]	11.5 [10.7–13.1]
Stage F3	66	6.5 [6.1–7.7]	34.2 [29.1–40.2]	14.8 [13.7–16.6]
Stage F4	40	6.1 [6.1–7.3]	54.2 [39.1–69.8]	16.3 [15.0–20.5]

Conclusion: We show PRO-C3 to be a robust marker that is not affected by age, gender, ethnicity, obesity, or diabetes and that it increased with fibrosis stage in patients with NAFLD/NASH.

POSTER PRESENTATIONS

PO-1453

Screening for non-alcoholic fatty liver disease (NAFLD)-related advanced fibrosis, real life data and comparison of two endocrinology-hepatology referral strategies

Cyrielle Caussy^{1,2,3}, Charlène Telliam¹, Bader Alnuaimi¹, Massimo Levrero^{2,4,5}, Marie Louyot^{4,5}, Marianne Maynard^{4,5}, Jérôme Dumortier^{2,6}, Fabien Zoulim^{2,4,5}, Emmanuel Disse^{1,2,3}, Cyrille Colin^{2,7}, Philippe Moulin^{2,3,8}. ¹Hospices Civils de Lyon, Endocrinologie, Diabète et Nutrition, Hôpital Lyon Sud, Pierre Bénite, France; ²Université de Lyon, Université Claude Bernard Lyon 1, Lyon, France; ³INSERM, CarMen Laboratory, Unité 1060, LYON, France; ⁴Hospices Civils de Lyon, Service d'Hépatologie, Hôpital Croix-Rousse, Lyon, France; ⁵INSERM, Centre de Recherche sur le Cancer de Lyon, Unité 1052, Lyon, France; ⁶Hospices Civils de Lyon, Fédération des Spécialités Digestives, Hôpital Edouard Herriot, Lyon; ⁷Hospices Civils de Lyon, Service d'Evaluation Economique en Santé, Pôle de Santé Publique, Lyon; ⁸Hospices Civils de Lyon, Département Endocrinologie, Diabète et Nutrition, Hôpital Cardiologique, Bron
Email: cyrielle.caussy@chu-lyon.fr

Background and aims: Patients with type 2 diabetes (T2D) or obesity are at high risk of non-alcoholic fatty liver disease (NAFLD)-related advanced fibrosis (AF). Strategies for endocrinology-hepatology referral are needed to improve the clinical care of these patients but real-life data remain scarce. We compared the capacity of two different referral strategies for the screening of AF in patients with T2D or obesity and NAFLD.

Method: This is a retrospective comparative study from two endocrinology clinics at the Lyon University Hospital with distinct screening strategies for NAFLD-related AF. Data from adult patients included in the referral pathways from November 2018 to December 2019 were extracted from electronic charts. Other causes of chronic liver diseases were excluded. The proportion of patients with histological or high suspicion of AF (F3-F4), as defined by transient elastography (TE) ≥ 9.7 kPa, among the patients referred to hepatologists were compared.

Results: Center 1 included 285 patients requiring a hepatology assessment based upon a standardized and systematic screening using the EASL-EASD-EASO algorithm. The mean (SD) age was 53.9

(13.6) years, BMI: 39.1 (8.0) kg/m² and 62.8% had T2D. Only 44.2% (n = 126) had a hepatology consultation due to the saturation of the referral pathway and a minority 3.2% (n=4) had a liver biopsy including 2 with AF (Figure 1A). Center 2 included 225 patients with a suspicion of AF based upon a non-standardized screening strategy using NAFLD fibrosis score, abnormal liver enzymes and TE assessment. The mean (SD) age was 57.1 (10.8) years, BMI: 33.5 (6.0) kg/m² and 84.4% had T2D. Of them 27.9% (n = 63) were referred in hepatology and a minority 6.3% (n = 4) had a liver biopsy, including none with AF (Figure 1B). The proportion of patients with a strong suspicion of AF among those referred in hepatology was significantly higher in Center 2 compared to Center 1: 66.1% (n = 41) versus 17.4% (n = 22), OR: 9.5, 95% CI [4.6–19.6], p < 0, 0001. However, 18.4% (n = 30) patients from Center 2 had TE ≥ 9.7 kPa and were not referred in hepatology.

Conclusion: A referral strategy using TE in the endocrinology clinic significantly improves the screening capacity for NAFLD-related AF and reduces the risk of over-referral. However, a lack of standardized referral criteria may lead to an under-referral of AF patients. Collaboration between endocrinologists and hepatologists is key to optimize the referral strategy for patients with T2D or obesity.

PO-1518

Serum metabolomics-based steatohepatitis score for the non-invasive identification of patients with non-alcoholic steatohepatitis (NASH) in multiethnic, including type 2 diabetes mellitus population

Pablo Ortiz¹, Itziar Mincholé², Rebeca Mayo², Ibon Martínez-Arranz², Jesus María Banales³, Marco Arrese⁴, Javier Crespo⁵, Paula Iruzubieta⁵, Libor Vitek⁶, Radan Bruha⁶, Manuel Romero Gomez⁷, Cristina Alonso⁸, Kenneth Cusi⁹, Mazen Noureddin¹⁰, José M. Mato¹¹, Arun Sanyal¹². ¹OWL Metabolomics, Derio, Spain; ²OWL metabolomics, Derio, Spain; ³Biodonostia Research Institute, Donostia University Hospital, University of the Basque Country (UPV-EHU), CIBERehd, IKERBASQUE, Donostia, Spain; ⁴Pontificia Universidad Católica de Chile, Santiago de Chile, Chile; ⁵Marqués de Valdecilla University Hospital, Cantabria University, IDIVAL, Santander, Spain; ⁶Faculty General Hospital and the First Faculty

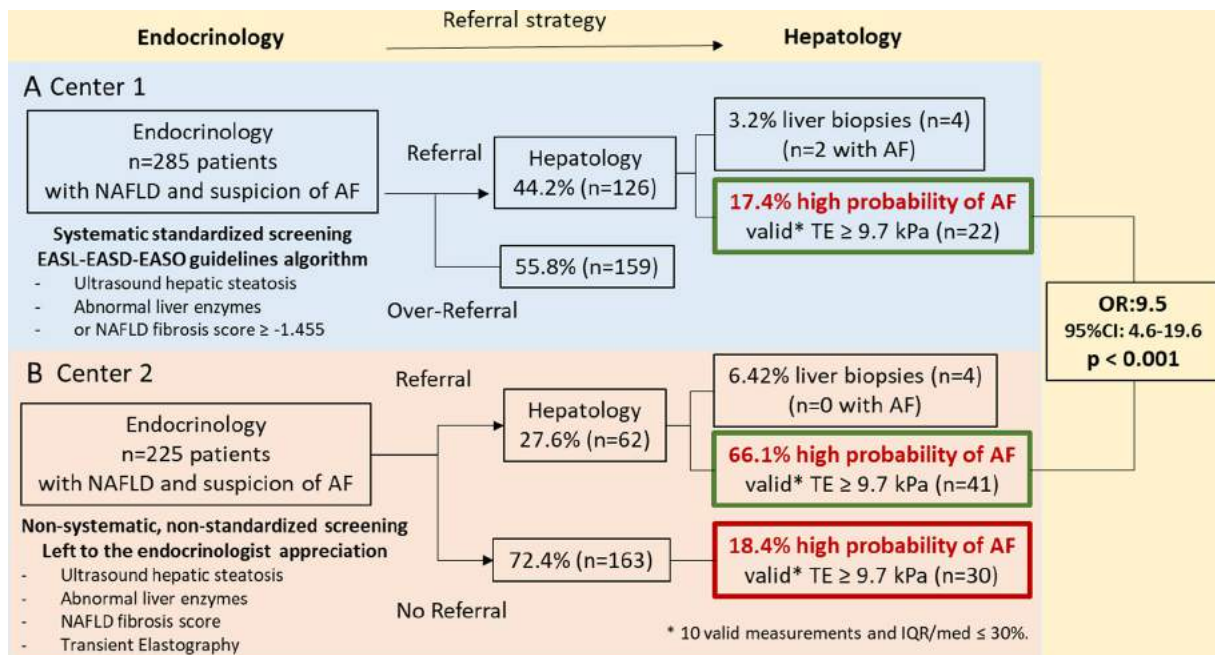


Figure: (abstract: PO-1453)

of Medicine, Charles University, Prague, Czech Republic; ⁷UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Sevilla, Spain; ⁸OWL Metabolomics, Spain; ⁹University of Florida, Gainesville, FL, United States; ¹⁰Cedars-Sinai Medical Center, Los Angeles, CA, United States; ¹¹CIC bioGUNE, Derio, Spain; ¹²Virginia Commonwealth University Medical Center, Richmond, VA, United States
 Email: iminchole@owlmetabolomics.com

Background and aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) is high in the western world and it is often comorbid with type 2 diabetes mellitus (T2DM). We aimed to develop an accurate, serum-based, easy to use test independent of glycated hemoglobin (HbA1c) for the diagnosis of non-alcoholic steatohepatitis (NASH) regardless of the presence of T2DM.

Method: Serum metabolomic testing was performed in an original cohort of 682 patients that was subsequently blind validated in two separate international cohorts of 202 patients (100 from Chile and 102 from USA). The derivation cohort was a cross-sectional, multi-center study of patients aged 18 years or older, who underwent liver biopsy for suspicion of NAFLD. To classify those patients with NASH, a NAFLD Activity Score (NAS) ≥ 3 (with at least one point on each of steatosis, lobular inflammation and ballooning) was considered. The best fitting multivariable logistic regression model was identified and internally validated using a K-fold Cross-Validation process. Score calibration and discrimination performance were determined in both the derivation and validation datasets.

Results: We performed serum metabolomic testing in a multiethnic, multicenter derivation cohort of 682 subjects with biopsy proven NAFLD (312 Steatosis, 370 NASH). The characteristics of this cohort were 51% Male, BMI 35.5 ± 7.3 ; alanine aminotransferase, ALT 51.4 ± 37.6 ; aspartate aminotransferase, AST 37.2 ± 24.3 and HbA1c 6.5 ± 1.2 . The final score (OWLiverDM2) includes 16 lipids, BMI, AST and ALT. Using logistic regression analysis, we could discriminate between patients with NASH and steatosis. The diagnostic performance of the OWLiverDM2 showed an area under the receiver operating characteristic curve (AUC) of 0.80 ± 0.03 , while a model generated with only clinical variables, could only reach to an AUC of 0.71 ± 0.04 , this difference being statistically significant (DeLong Test z-score = 5.239, p value = 1.62×10^{-7}). Sensitivity, specificity, PPV and NPV of both models were 0.74, 0.73, 0.71 and 0.77 for OWLiverDM2 and 0.61, 0.69, 0.60 and 0.70 for the clinical variables algorithm.

Furthermore, the new test maintained a better performance and the statistical significance versus the clinical algorithm in a subgroup of 406 subjects with T2DM or HbA1c ≥ 6 , AUC = 0.78 versus AUC = 0.71 (DeLong test, z-score = 3.064, p value = 0.00218).

Finally, we validated OWLiverDM2 performance in an independent cohort of 202 patients of similar characteristics with the following values of AUC, sensitivity, specificity, PPV and NPV: 0.81 ± 0.02 , 0.78, 0.76, 0.66 and 0.85, respectively.

Conclusion: The new serum-based OWLiverDM2 score accurately discriminates between steatosis and NASH in a more general, multiethnic, including controlled and non-controlled T2DM population without using HbA1c.

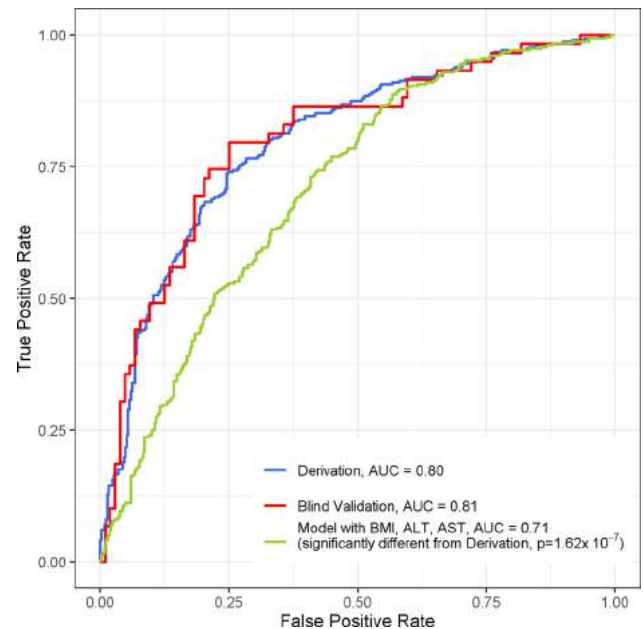


Figure:

PO-1568

Longitudinal variability of non-invasive tests of fibrosis: Implications for treatment response monitoring in patients with NASH

Quentin Anstee^{1,2}, Eric Lawitz³, Naim Alkhoury⁴, Vincent Wai-Sun Wong⁵, Manuel Romero-Gomez⁶, Takeshi Okanoue⁷, Michael Trauner⁸, Andrew Billin⁹, Lulu Wang¹⁰, Yevgeniy Gindin¹⁰, Ryan Huss¹⁰, Chuhan Chung¹⁰, Robert Myers¹⁰, Zobair Younossi¹¹, Stephen Harrison¹². ^{1,2}Translational and Clinical Research Institute, Faculty of Medical Science, Newcastle-upon-Tyne, United Kingdom; ³University of Texas Health San Antonio, Texas Liver Institute, San Antonio, United States; ⁴Arizona Liver Health, Chandler, United States; ⁵The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong; ⁶University of Seville, Hospital Universitario Virgen del Rocio, Sevilla, Spain; ⁷Saiseikai Suita Hospital, Osaka, Japan; ⁸Medical University of Vienna, Division of Gastroenterology and Hepatology, Vienna, Austria; ⁹Gilead Sciences, Biomarker Science, Foster City, United States; ¹⁰Gilead Sciences, Foster City, United States; ¹¹Inova Fairfax Hospital, Falls Church, United States; ¹²Pinnacle Clinical Research, San Antonio, United States
 Email: andrew.billin@gilead.com

Background and aims: Non-invasive tests of fibrosis (NITs), including the ELF score, FIB-4, and liver stiffness by transient elastography (LS by TE), have utility as diagnostic/prognostic biomarkers, and are increasingly used to monitor treatment response. We evaluated longitudinal variation of these NITs using the placebo groups from the STELLAR trials in NASH patients with stable, advanced fibrosis.

Method: Patients with advanced fibrosis due to NASH (NAS ≥ 3 , NASH CRN F3-F4) were enrolled in two randomized, placebo-controlled trials of selonsertib (STELLAR-3/-4). FIB-4 and ELF (Siemens) were collected at baseline (BL) and weeks 12 (W12), 24 (W24), and 48 (W48), and LS by TE (FibroScan; Echosens) was measured by trained operators at BL, W24, and W48. Intra- and inter-subject variability of these NITs was assessed in placebo-treated patients between BL and W48 by within- and between-subject coefficients of variation (CVs) using mixed-effect models with visit as a fixed effect and subject as a random effect. The impact of BL covariates and on-treatment weight loss (<vs $\geq 5\%$) on these CVs was assessed using linear models.

Results: 251 placebo-treated patients with stable fibrosis were included in this analysis. 57% had cirrhosis and median LS by TE

POSTER PRESENTATIONS

Figure: (abstract: PO-1568): CVs of NITs According to Baseline Covariates and On-Treatment Weight Loss

	FIB-4		LS by TE		ELF	
	Intra-individual CV (%)	Inter-individual CV (%)	Intra-individual CV (%)	Inter-individual CV (%)	Intra-individual CV (%)	Inter-individual CV (%)
Overall	20.1	46.9	33.0	55.6	3.8	7.8
Age (years)						
<65	20.9	48.4	35.4	54.2	3.8	7.9
≥65	18.1	39.9	25.3	60.0	3.8	7.1
Sex						
Female	18.8	46.3	30.5	53.9	3.6	7.5
Male	21.9	48.1	34.9	56.6	4.0	8.1
Diabetes						
Yes	20.8	49.0	30.6	56.1	3.8	7.8
No	17.7	38.7	43.0	42.6	3.6	7.7
BMI						
<25.0	15.8	35.9	25.0	47.4	3.0	8.4
25.0–29.9	18.7	41.5	28.9	54.8	3.8	6.9
≥30	21.1	50.5	34.0	55.0	3.9	8.0
Weight loss*						
Yes	31.6	37.1	34.2	27.2	4.5	7.0
No	19.4	41.8	29.1	46.2	4.0	8.0
ALT†						
Normal	17.3	48.5	33.2	69.0	3.8	7.7
Elevated	20.5	46.8	33.0	51.5	3.8	7.7
Fibrosis stage						
F3	21.3	42.8	30.2	42.8	4.1	7.8
F4	19.1	48.1	32.3	48.1	3.6	6.8

*≥5% reduction between BL and W48.

†≤33 U/L for males and ≤25 U/L for females..

was 16.2 kPa (IQR 11.8, 24.7). Over 48 weeks, intra- and inter-individual CVs of FIB-4 and LS by TE were 20.1% and 46.9%, and 33.0% and 55.6%, respectively. ELF had the lowest variability (intra- and inter-individual CVs of 3.8% and 7.8%). Only BL BMI and weight loss were associated with variability of FIB-4; greater within-subject CVs were observed in patients with BL BMI ≥ 30 (21.1% vs 15.8% with BMI < 25; $p = 0.02$) and those with ≥5% weight loss (31.6% vs. 19.4% with <5%; $p = 0.001$) (Figure).

Conclusion: In NASH patients with advanced fibrosis, FIB-4 and LS by TE have high variability compared to ELF, suggesting that ELF may have greater precision for disease monitoring in NASH.

PO-1575

Fibrosis response assessed by enhanced liver fibrosis and FibroScan liver stiffness measurement in patients with non-alcoholic steatohepatitis treated with subcutaneous semaglutide

Quentin Anstee^{1,2}, Jacob George³, Mette Kjaer⁴, Steen Ladelund⁴, Louise Nitze⁴, Vlad Ratziu⁵, Adriana Rendon⁴,

Vincent Wai-Sun Wong⁶, Anja Geerts⁷, Philip N. Newsome⁸.

¹Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom;

²Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom;

³Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia; ⁴Novo Nordisk A/S, Søborg, Denmark; ⁵Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France; ⁶The Chinese University of Hong Kong, Hong Kong, China; ⁷Hepatology Research Unit, Ghent University, Ghent, Belgium; ⁸University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

Email: quentin.anstee@newcastle.ac.uk

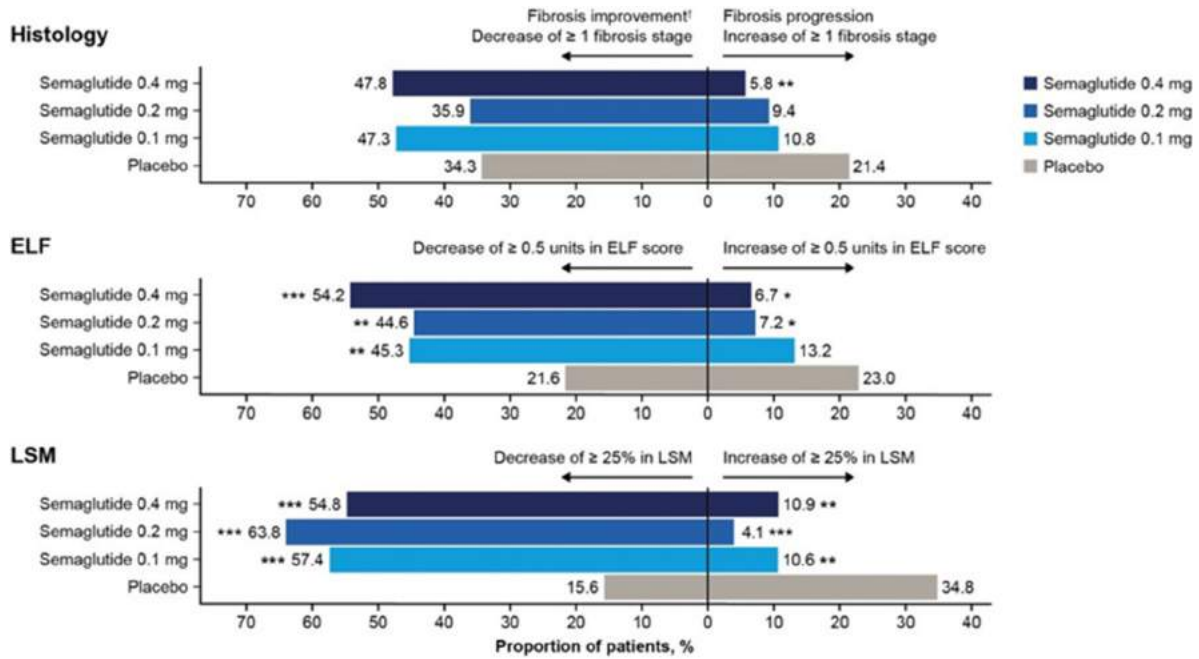
Background and aims: Assessment of liver fibrosis in clinical trials relies primarily on histology, and there is a need for non-invasive methods. Fibrosis response in patients with non-alcoholic steatohepatitis (NASH) treated with subcutaneous semaglutide was compared

using enhanced liver fibrosis (ELF) score, FibroScan® liver stiffness measurement (LSM) and histology assessment.

Method: This was a post-hoc analysis of the 72-week phase 2 trial (NCT02970942) of once-daily subcutaneous semaglutide (0.1, 0.2 or 0.4 mg) vs placebo on NASH resolution in 320 patients with NASH and fibrosis stage F1-F3, which showed significant NASH resolution and a non-significant trend for fibrosis improvement with semaglutide 0.4 mg vs placebo. Fibrosis improvement or progression was categorised using ELF (decrease or increase of ≥0.5 units), LSM (decrease or increase of ≥25%) and liver histology (decrease or increase of ≥1 stage) at baseline and at week 72. For ELF and LSM response, the proportion of subjects were compared using a logistic regression model.

Results: Baseline median (min-max) ELF score was 10.3 (0.8–54.7) and LSM was 9.7 (7.4–12.8). At baseline, a weak correlation was found between ELF and LSM (r [95% confidence interval] = 0.22 [0.13–0.31]), and fibrosis stage assessed by histology was associated with ELF ($p < 0.001$) and LSM ($p = 0.016$). At week 72, mean change from baseline in ELF score with semaglutide 0.4 mg was –0.7 (vs 0 with placebo) and mean ratio to baseline in LSM was 0.79 with semaglutide 0.4 mg (vs 1.66 with placebo). Although the percentage of patients with histological improvement in fibrosis was not significantly different between groups, the proportion of ELF and LSM responders was higher with semaglutide vs placebo (Figure). At week 72, fewer patients in the semaglutide 0.4 mg arm had fibrosis progression, as assessed by histology (5.8% vs 21.4%; $p = 0.009$), ELF (6.7% vs 23.0%; $p = 0.01$) and LSM (10.9% vs 34.8%; $p = 0.002$). For both the placebo and semaglutide 0.4 mg treatment groups, change from baseline to week 72 in ELF and LSM correlated with biomarkers of NASH activity (aspartate aminotransferase, alanine aminotransferase, cytokeratin 18 M65 and M30), fibrosis (Fibrosis-4, AST to platelet ratio index, Forns index) and body weight.

Conclusion: Treatment with semaglutide for 72 weeks reduced fibrosis progression measured by histology as well as ELF and LSM. The changes were suggestive of fibrosis response related to semaglutide treatment.



Data are from all randomized patients during the on-treatment period. *p < 0.05; **p < 0.01; ***p < 0.001 vs placebo; †Fibrosis improvement was defined as decrease of ≥ 1 fibrosis stage without worsening of NASH (increase of ≥ 1 point in either the lobular inflammation score or the hepatocyte ballooning score, according to the NASH Clinical Research Network criteria). ELF, enhanced liver fibrosis; LSM, liver stiffness measurement; NASH, non-alcoholic steatohepatitis.

Figure: (abstract: PO-1575)

PO-1588
Comorbidity and healthcare utilization burden of patients diagnosed with non-alcoholic steatohepatitis based on fibrosis-4 score severity

Lina Titievsky¹, Aziza Jamal-Allial², Kerrin Gallagher², Thomas Capozza¹, Stephen Dodge¹, Simo Du², Amy Law¹, Macky Natha¹, Erik Ness¹, Mindie Nguyen³, Yuval Patel⁴, Amarita Randhawa¹, Dr. Daina Esposito^{2,5,6}. ¹Intercept Pharmaceuticals, Inc., New York, United States; ²HealthCore, Inc., Watertown, United States; ³Stanford University, Redwood City, United States; ⁴Duke University, Durham, United States; ⁵Boston University School of Public Health, Boston, United States; ⁶Ciconia, Inc., United States
 Email: lina.titievsky@interceptpharma.com

Background and aims: Non-alcoholic steatohepatitis (NASH) is a chronic, progressive condition that can lead to cirrhosis. The fibrosis-4 (FIB-4) score is a non-invasive test of liver fibrosis based on laboratory data. This study characterized the comorbidity burden and healthcare resource utilization (HCRU) among NASH patients stratified by FIB-4 defined fibrosis severity.

Method: An algorithm to identify NASH patients was applied to a large US administrative claims database (01 October 2015 and 31 March 2020). The algorithm required either (1) NASH as the principal discharge diagnosis from an inpatient claim, (2) liver biopsy followed by NASH diagnosis, or (3) liver imaging followed by NASH diagnosis, procedure codes for liver function testing, and ≥1 risk factor (obesity, type 2 diabetes, pre-diabetes, or dyslipidemia). Patients with concurrent liver diseases or history of liver transplantation were excluded. Continuous health plan enrolment was required for ≥12 months prior to index date (i.e., baseline period). All patients with sufficient lab data to determine their FIB-4 scores were categorized as no/early fibrosis (NF), indeterminate (INF), and advanced fibrosis (AF) using published thresholds. Descriptive statistics were used to summarize baseline patient characteristics and HCRU.

Results: Of 20,198 qualifying NASH patients, baseline FIB-4 were available for 7,937 (39%): 4,415 (56%) had NF, 2,239 (28%) INF, and 1,283 (16%) AF. AF patients were older, with higher rates of type 2 diabetes (69% vs. 54% and 38%) and hypertension (83% vs 77% and 61%) than patients with INF or NF, respectively. Similar proportions of patients had liver biopsies (13% for AF vs. 13% INF and 11% NF). A larger proportion of patients with INF had undergone liver elastography than NF or AF (13% vs. 10% and 8%), and a greater proportion of patients with AF was seen by a gastroenterologist (GI) than patients with INF or NF (49% vs. 38% and 33%). Inpatient stays were also more common for those with AF (mean ± SD: 0.85 ± 1.55) than those with INF or NF (0.42 ± 1.12 and 0.35 ± 1.07).

Conclusion: Patients across all FIB-4 levels of fibrosis severity have appreciable burden of metabolic comorbidities. However, diagnosis by GI specialty, comorbidity burden and HCRU, including inpatient stays, increased with worsening FIB-4. FIB-4 offers a simple, accessible, non-invasive tool that has the ability to risk stratify NASH patients for liver-related morbidity and mortality.

PO-1648
Clinical utility of 30% relative decline in MRI-PDFF in predicting fibrosis regression in non-alcoholic fatty liver disease

Nobuharu Tamaki¹, Nagambika Munaganuru¹, Jinho Jung¹, Aed Qas Yonan¹, Rohan Loomba^{1,2}, Ricki Bettencourt¹, Veeral Ajmera¹, Mark Valasek³, Cynthia Behling⁴, Claude Sirlin⁵, Rohit Loomba^{1,6}. ¹University of California San Diego, NAFLD Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, La Jolla, United States; ²Cathedral Catholic High School; ³University of California San Diego, Department of Pathology, La Jolla, United States; ⁴University of California San Diego, Sharp Medical Group, Department of Pathology, La Jolla, United States; ⁵University of California San Diego, Liver Imaging Group, Department of Radiology, La Jolla, United States; ⁶University of California San Diego, Division of Epidemiology, Department of Family Medicine and Public Health, La Jolla, United States
 Email: roloomba@health.ucsd.edu

POSTER PRESENTATIONS

Background and aims: Liver fibrosis is most important factor associated with the prognosis and liver-related complications in non-alcoholic fatty liver disease (NAFLD) and improvement in liver fibrosis is an important end point in non-alcoholic steatohepatitis (NASH) clinical trials. Emerging data suggest that $\geq 30\%$ relative decline in magnetic resonance imaging-proton density fat fraction (MRI-PDFF) is correlated with NAFLD Activity Score response (≥ 2 points improvement, with no worsening in fibrosis), but the association between decline in MRI-PDFF and fibrosis regression is still unclear. Therefore, we investigated the association between $\geq 30\%$ relative decline in MRI-PDFF and fibrosis regression in NAFLD.

Method: This is a prospective study including 100 well-characterized NAFLD patients who received paired biopsy with contemporaneous MRI-PDFF assessment. The primary outcome was ≥ 1 stage fibrosis regression using the NASH CRN Histologic Scoring System. MRI-PDFF response was defined as $\geq 30\%$ relative decline in MRI-PDFF.

Results: The median (interquartile range) age was 54 (43–62) years, and body mass index was 31.9 (29–36) kg/m². Twenty patients had fibrosis regression at the follow-up biopsy, and 25 patients had MRI-PDFF response. In univariable analysis, gamma-glutamyl transferase (GGT) level at baseline, MRI-PDFF response, and an increase in platelet count were significantly associated with fibrosis regression. In multivariable-adjusted logistic regression analysis (adjusted for age, gender, diabetes status, race/ethnicity, GGT, and change in platelet counts), MRI-PDFF response was an independent predictor of fibrosis regression with adjusted-odds ratio (OR) of 5.16 (95% confidence interval [CI]: 1.1–24.9, $p = 0.04$). The proportion of patients with MRI-PDFF response with fibrosis regression, fibrosis no change, and fibrosis progression were 40.0%, 24.6%, and 13.0%, respectively, and the proportion of patients with MRI-PDFF response increased with fibrosis regression ($p = 0.03$). In sensitivity analysis for histological outcome, MRI-PDFF response was associated with an interval decrease in steatosis grade (OR: 3.78, 95% CI: 1.5–9.8), NAS response (OR: 4.75, 95% CI: 1.8–12), and fibrosis regression (OR: 3.75, 95% CI: 1.2–12).

Conclusion: MRI-PDFF response defined as a $\geq 30\%$ relative decline in MRI-PDFF is associated with fibrosis regression and may be used as a potential surrogate marker for evaluating therapeutic effect in a NASH trial.

PO-1689

Combination treatment with cilofexor and firsocostat leads to improvements in the FibroScan-AST (FAST) score which are associated with treatment response in patients with advanced fibrosis due to NASH

Rohit Loomba¹, Mazen Nouredin², Kris Kowdley³, Anita Kohli⁴, Aasim Sheikh⁵, Guy Neff⁶, Bal Raj Bhandari⁷, Nadege T. Gunn⁸, Stephen Caldwell⁹, Zachary Goodman¹⁰, Ling Han¹¹, Catherine Jia¹¹, Jay Chuang¹¹, Ryan Huss¹¹, Chuhan Chung¹¹, Robert Myers¹¹, Keyur Patel¹², Brian Borg¹³, Reem Ghalib¹⁴, John Poulos¹⁵, Ziad H. Younes¹⁶, Magdy Elkhatab¹⁷, Tarek Hassanein¹⁸, Rajalakshmi Iyer¹⁹, Peter Ruane²⁰, Mitchell Shiffman²¹, Simone Strasser²², Vincent Wai-Sun Wong²³, Naim Alkhouri⁴. ¹NAFLD Research Center, University of California at San Diego, La Jolla, CA, United States; ²Fatty Liver Program, Cedars-Sinai Medical Center, Los Angeles, CA, United States; ³Liver Institute Northwest and Washington State University, Seattle, WA, United States; ⁴Arizona Liver Health, Chandler, AZ, United States; ⁵GI Specialists of Georgia, Marietta, GA, United States; ⁶Covenant Research, LLC, Sarasota, FL, United States; ⁷Delta Research Partners, Bastrop, LA, United States; ⁸Pinnacle Clinical Research, San Antonio, TX, United States; ⁹University of Virginia, Charlottesville, VA, United States; ¹⁰Inova Fairfax Hospital, Falls Church, VA, United States; ¹¹Gilead Sciences, Inc., Foster City, CA, United States; ¹²University of Toronto, Toronto, ON, Canada; ¹³Southern Therapy and Advanced Research, Jackson, MS, United States; ¹⁴Texas Clinical Research Institute, Arlington, TX, United States; ¹⁵Cumberland Research Associates, Fayetteville, NC, United States; ¹⁶Gastro One, Germantown, TN, United States; ¹⁷Toronto Liver Centre, Toronto, ON, Canada; ¹⁸Southern

California Research Center, Coronado, CA, United States; ¹⁹Iowa Digestive Disease Center, Clive, IA, United States; ²⁰Ruane Medical and Liver Health Institute, Los Angeles, CA, United States; ²¹Bon Secours Mercy Health, Richmond, VA, United States; ²²Royal Prince Alfred Hospital and The University of Sydney, New South Wales, Australia; ²³Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong
Email: ryan.huss@gilead.com

Background and aims: The FAST score is a non-invasive tool that includes liver stiffness (LS) and controlled attenuation parameter (CAP) by transient elastography (TE; FibroScan) and AST, for the identification of patients at risk of progressive NASH. Our aims were to evaluate the effects of cilofexor (CILO) and firsocostat (FIR) on FAST and to explore associations between treatment-induced changes in FAST with histologic and non-invasive test (NIT) responses.

Method: NASH patients with histologically-confirmed, advanced fibrosis (NASH CRN F3–F4) in the phase 2b ATLAS trial were treated with regimens including CILO 30 mg ($n = 40$), FIR 20 mg ($n = 40$), CILO +FIR ($n = 78$), or placebo ($n = 39$), once daily for 48 weeks (W48). Liver histology was evaluated by a central reader and a machine learning (ML) approach (PathAI; Boston, MA). End points included a ≥ 1 -stage improvement in fibrosis without worsening of NASH (primary end point [PE]), ≥ 2 -pt reduction in NAFLD Activity Score (NAS response [NAS-R]), and ELF response (ELF-R), defined as a ≥ 0.5 -unit reduction from baseline to W48. Patients were categorized according to FAST at baseline (BL) and W48 (rule-out zone: < 0.35 ; grey zone: 0.35 to < 0.67 ; rule-in zone: ≥ 0.67) and changes in FAST were evaluated using ANCOVA and Wilcoxon rank sum and Fisher's exact tests.

Results: At BL, 56% of patients had cirrhosis (F4). Median BL FAST was 0.69 (IQR 0.51, 0.81); 53% and 33% of patients were in the rule-in and grey zones, respectively. FAST was similar between cirrhotic and non-cirrhotic patients (0.71 vs 0.67; $p = 0.081$). Compared with placebo (LSmean change in FAST from BL to W48: -0.04), treatment with CILO (-0.18), FIR (-0.22), and CILO+FIR (-0.22) led to significant improvements in FAST (all $p < 0.05$). Improvements in FAST category were observed in 16% of placebo-treated patients compared with 53% to 65% treated with CILO, FIR, or CILO+FIR (all $p < 0.05$; Figure). Across study groups, changes in FAST were correlated with changes in ELF score ($\rho = 0.28$), LS by TE ($\rho = 0.61$), ALT ($\rho = 0.57$), CK18-M30 ($\rho = 0.45$), CK18-M65 ($\rho = 0.49$), ML NASH CRN fibrosis score ($\rho = 0.28$), and proportionate areas by ML of steatosis ($\rho = 0.40$) and hepatocellular ballooning ($\rho = 0.22$; all $p < 0.05$), but not portal or lobular inflammation. Greater reductions in FAST were observed in responders vs non-responders for all W48 end points: PE (-0.27 vs -0.10 , $p = 0.0013$), NAS-R (-0.24 vs -0.10 , $p = 0.0069$), and ELF-R (-0.25 vs -0.09 ; $p < 0.001$).

Conclusion: In patients with advanced fibrosis due to NASH, treatment with CILO and/or FIR leads to significant improvements in FAST score. Changes in FAST are greatest in histologic and ELF responders, suggesting that FAST is a useful marker of treatment response in NASH patients with advanced fibrosis.

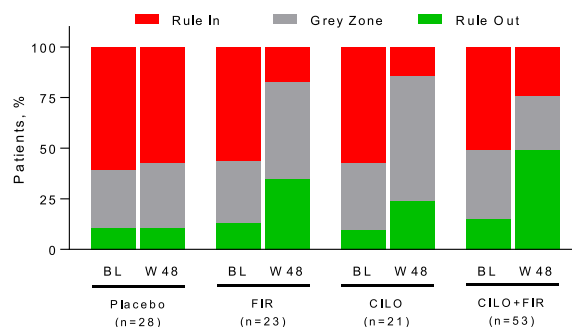


Figure includes only subjects with baseline and week 48 FAST data.

PO-1714

Liver stiffness by vibration-controlled transient elastography predicts disease progression in patients with advanced fibrosis due to NASH

Rohit Loomba¹, Arun Sanyal², Quentin Anstee³, Michael Trauner⁴, Eric Lawitz⁵, Dora Ding⁶, Catherine Jia⁶, Ryan Huss⁶, Chuhan Chung⁶, Robert Myers⁶, Zachary Goodman⁷, Vincent Wai-Sun Wong⁸, Takeshi Okanoue⁹, Manuel Romero Gomez¹⁰, Andrew Muir¹¹, Nezam Afdhal¹², Jaime Bosch¹³, Stephen Harrison¹⁴, Zobair Younossi⁷.
¹NAFLD Research Center, University of California at San Diego, La Jolla, CA, USA, La Jolla, United States; ²Virginia Commonwealth University, Richmond, VA, United States; ³Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; ⁴Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; ⁵Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, United States; ⁶Gilead Sciences, Inc., Foster City, CA, United States; ⁷Inova Fairfax Hospital, Falls Church, VA, United States; ⁸Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong; ⁹Saiseikai Suita Hospital, Suita City, Osaka, Japan; ¹⁰Digestive Diseases Unit, Hospital Universitario Virgen del Rocío, Institute of Biomedicine of Seville, University of Seville, Sevilla, Spain; ¹¹Duke University, Durham, NC, United States; ¹²Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, United States; ¹³Hospital Clinic, University of Barcelona, Spain and Bern University, Bern, Switzerland, Barcelona, Spain; ¹⁴Pinnacle Clinical Research, San Antonio, TX, United States
 Email: rob.myers@gilead.com

Background and aims: Liver stiffness (LS) measured by vibration-controlled transient elastography (VCTE) is associated with fibrosis stage and risk of decompensation in patients with NAFLD. However, prospective data describing associations between LS and disease progression in well-characterized NASH cohorts with biopsy-confirmed advanced fibrosis are limited. The aim of this study was to establish thresholds of LS by VCTE that predict clinical outcomes in patients with bridging fibrosis and cirrhosis due to NASH.

Method: Patients with advanced fibrosis (NASH CRN F3-F4) due to NASH were enrolled in four placebo-controlled trials of simtuzumab and selonsertib. The trials were discontinued due to lack of efficacy; hence treatment groups were combined for this analysis. Liver fibrosis (baseline [BL] and W48) was staged centrally according to the NASH CRN classification, and LS was measured by VCTE (FibroScan; Echoscans, Paris, France) by trained operators. Cox regression determined associations between LS at BL with disease progression (i.e. progression to cirrhosis in patients with bridging fibrosis and adjudicated clinical events [e.g. decompensation, transplantation, death] in those with cirrhosis), and discrimination was assessed using c-statistics. Optimal LS thresholds were determined based on Youden's index.

Results: 1, 398 patients with bridging fibrosis (n = 664) or cirrhosis (n = 734) were included in this analysis (median age 59 years, 60% female, 73% with diabetes). Median (IQR) LS at BL was 12.7 kPa (9.7, 17.3) in those with bridging fibrosis and 21.1 kPa (14.2, 29.3) in those with cirrhosis. During a median follow-up (FU) of 17 mos (range 1, 40), 16% of patients with bridging fibrosis (96/103 with post-baseline biopsies) progressed to cirrhosis. The risk of histological progression was greater with higher LS at BL (hazard ratio [HR] per 3-kPa: 1.16; 95% CI 1.12, 1.20). The c-statistic of BL LS to predict progression to cirrhosis was 0.72 (95% CI 0.66, 0.77) and the optimal threshold was 16.6 kPa (sensitivity 58%, specificity 76%, PPV 31%, NPV 91%). During a median FU of 16 mos (range 0, 39), 27 cirrhotic patients (4%) had liver-related events. The risk of events was greater with higher BL LS (HR per 5-kPa: 1.29; 95% CI 1.18, 1.41). The c-statistic of BL LS to predict clinical events was 0.77 (95% CI 0.67, 0.87) and the optimal threshold was 30.7 kPa (sensitivity 70%, specificity 79%, PPV 11%, NPV 99%).

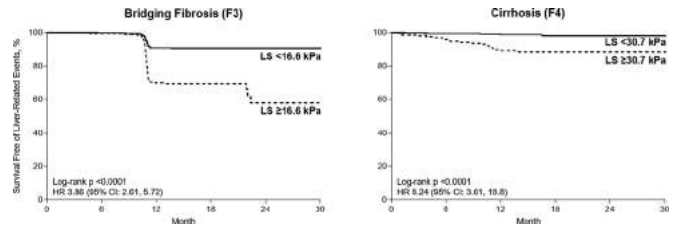


Figure: Clinical Disease Progression According to LS by VCTE at BL

Conclusion: Clinical disease progression in patients with advanced fibrosis due to NASH is associated with higher LS by VCTE. The LS thresholds identified in this study may be useful for risk stratification of NASH patients in clinical trials and clinical practice.

PO-1777

The Metabolomics of Non-Alcoholic Fatty Liver Disease: Of Networks and Biomarkers

Aidan McGlinchey¹, Dawei Geng², Olivier Govaere³, Vlad Ratziu⁴, Elisabetta Bugianesi⁵, Jörn M. Schattenberg⁶, Ann Daley⁷, Tuulia Hyötyläinen⁸, Quentin Anstee⁹, Matej Orešič⁸.
¹Örebro University, School of Medical Sciences, Örebro, Sweden; ²Örebro University, Man-Technology-Environment Research Centre, Örebro, Sweden; ³Newcastle University, Institute of Cellular Medicine, Newcastle, United Kingdom; ⁴Sorbonne Université, France; ⁵University of Torino, Department of Medicine, Sorino, Italy; ⁶Johannes Gutenberg-Universität Mainz, Mainz, Germany; ⁷Newcastle University, United Kingdom; ⁸Örebro University, Örebro, Sweden; ⁹Newcastle University, Newcastle-Upon-Tyne, United Kingdom
 Email: aidan.mcglinchey@oru.se

Background and aims: Non-alcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease, affects 25%+ of people worldwide. Detailed understanding of the metabolomics of NAFLD, and non-invasive diagnostic techniques for the stages of NAFLD are unavailable. We identify specific serum molecular lipid signatures to these ends.

First, we leverage lipidomic and polar metabolomic data (n = 643) subjects, to produce a clear, meaningful interaction map, linking lipids, metabolites, clinical factors and disease outcomes. We find non-spurious associations therein, as features of interest, and for downstream analysis.

Third, NAFLD fibrosis biomarker identification was performed using machine learning, with our candidate lipids/metabolites to be forwarded to a successor project; the LITMUS project, towards clinically-applicable, non-invasive, sensitive and specific classification of NAFLD patients.

Method: Serum lipids and polar metabolites were measured by mass spectrometry in the EPoS cohort of patients (n = 176 lipids and n = 36 polar metabolites), combined with clinical data from (n = 643 subjects), followed by model-based clustering, giving 10 lipid clusters (LCs).

Correlations were calculated pairwise between (1) all LCs, (2) "input" clinical data (height, weight, BMI, blood platelet count) and (3) outcomes (fibrosis, steatosis, NAS score, etc.). Non-rejection rates (NRRs) were calculated for relationships, remove spurious associations (NRR > 0.4). We project the remaining associations as a network; a novel metabolomic overview NAFLD.

ANOVA and Tukey's Honest Significant Differences (Tukey HSDs) revealed detailed metabolic signatures across NAFLD, fibrosis and steatosis stages.

Random forest machine learning was used to classify NAFLD patients: LOW (0-1 fibrosis grade) or HIGH (2-4 fibrosis grade), using individual lipids and metabolites, identifying putative biomarkers.

Results: In line with our previous findings, many lipids associate with steatosis and fibrosis in NAFLD. Our novel overview network reveals associations between specific LCs and clinical variables, such as TGs (LC3), and a subgroup of TGs of lowest and highest carbon numbers

POSTER PRESENTATIONS

(LC9) along with PC (O)s (LC7) positively associating with NAFLD score and fibrosis. Conversely, LPCs (LC4), particularly sphingomyelins (SMs, LC6), negatively associated with these variables. Many other metabolites changing across NAFLD stages beg further discussion.

Conclusion: In addition to generation of a novel metabolomic network of NAFLD, we demonstrate feasibility of lipidomic and

metabolomic data to classify NAFLD patients' fibrosis grades (median AUC: 0.765), competitive with gold-standard clinical variables (age, BMI, sex, diabetes, liver AST/ALT, platelet count) (median AUC: 0.778). These biomarkers are being taken forward (LITMUS project) to develop clinical testing.

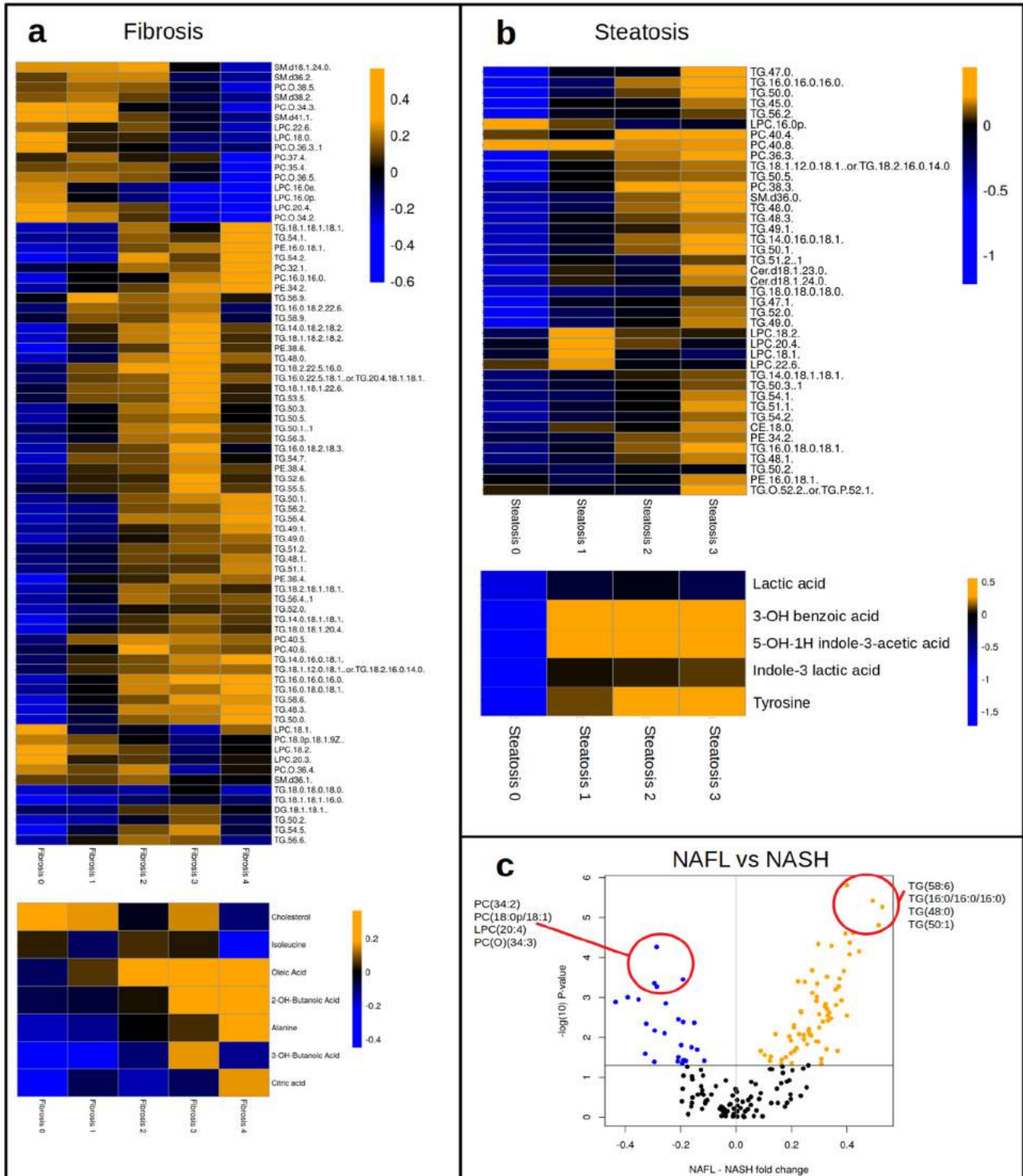


Figure: (abstract: PO-1777)

PO-1808

Clinical care pathways for non-alcoholic fatty liver disease (NAFLD) in U.S. Veterans will improve resource utilization and linkage to specialty care

Puneet Puri^{1,2}, Joseph Spataro², April Morris¹, Shuchi Jain³, Michael Fuchs^{1,2}. ¹Central Virginia VA Healthcare System, Department of Medicine, Richmond, United States; ²Virginia Commonwealth University, Department of Medicine, Richmond, United States; ³Virginia Commonwealth University, Department of Statistical Sciences and Operations Research, Richmond, United States
Email: laura1fuchs@icloud.com

Background and aims: The Veterans Health Administration is the largest single healthcare system in the U.S. providing care for 6 Million Veterans. Accurate disease assessment and staging of NAFLD still heavily relies on liver biopsies because non-invasive tests (NITs) such as FIB-4 and transient elastography (TE) have suboptimal discrimination for early (F0-2) vs. advanced (F3-4) liver fibrosis. We aimed to develop clinical care pathways to better discriminate F0-2 vs. F3-4 and address the resource limitations of a single healthcare system operating throughout the entire U.S.

Method: A prospective cohort of Veterans referred for NAFLD evaluation and undergoing a liver biopsy was studied. Fibrosis staging was based on NASH Clinical Research Network criteria. Machine learning with decision tree analysis (DTA) incorporating comorbidities, medications, demographics, biochemical, ultrasound (US) and TE parameters was performed.

Results: Of 201 Veterans, 154 (72%) were stage F0-2 and 56 (28%) had advanced fibrosis (F3-4). DTA generated good discrimination for F0-2 vs. F3-4. Clinical Care Pathway-A (without using TE and US): Using DTA, providers can avoid specialist referral in 93/201 (46%) patients as it correctly predicted stage F0-2 in 94% (87/93). The model generated first split at FIB-4 < 1.34, then absence of gastroesophageal reflux disease (GERD) to diagnose F0-2 with 97% probability. In patients with FIB-4 < 1.34 and GERD (+), gamma-glutamyl transferase of <70 U/L had 88% probability of F0-2. When FIB-4 was ≥1.34, after excluding diabetes patients with obesity, neutrophil lymphocyte ratio of <1.5 had 94% probability of F0-2. Clinical Care Pathway-B: When TE was used with variables in CCP-A, specialist referral can be avoided in 96/201 (48%) patients with stage F0-2 correctly predicted in 90% (89/96). The model generated first split at liver stiffness (kPa) <9.7 to diagnose F0-2 with 91% probability. When kPa ≥9.7, a FIB-4 < 1.53 and absence of GERD had 96% probability of diagnosing F0-2. Clinical Care Pathway-C: Use of US and TE with all other variables in CCP-A can decrease referral to specialists in 85/201 (42%) patients correctly predicting stage F0-2 in 94%. The model generated first split with spleen size <12.5, then AST < 27 to diagnose F0-2 with 95.5% probability. When AST was ≥27, then kPa <12.4 on TE and patients not on aspirin had 91% probability of F0-2.

Conclusion: Using machine learning decision tree analysis models we demonstrate that nearly 50% of U.S. Veterans with NAFLD can be managed by primary care with a small risk (<10%) of missing patients with advanced fibrosis. This resource based diagnostic heuristic for NAFLD merits further evaluation and validation in larger cohorts. If confirmed, this approach may be a major step forward towards identification of U.S. Veterans with NAFLD and advanced liver fibrosis and their linkage to specialty care.

PO-1826

Agreement in non-invasive fibrosis risk assessments in a primary care NAFLD cohort

Andrew Schreiner¹, Sherry Livingston², Justin Marsden¹, Jingwen Zhang¹. ¹Medical University of South Carolina, Medicine, Charleston, United States; ²Medical University of South Carolina, Biostatistics
Email: schrein@muscc.edu

Background and aims: Using natural language processing (NLP) to create a primary care non-alcoholic fatty liver disease (NAFLD)

cohort, we assessed advanced fibrosis risk with the Fibrosis-4 Index (FIB-4) and NAFLD Fibrosis Score (NFS) and evaluated risk score agreement.

Method: In this retrospective cohort study of adults with radiographic evidence of hepatic steatosis, we calculated patient-level FIB-4 and NFS scores and categorized them by fibrosis risk. Risk category and risk score agreement was analyzed using weighted kappa, Pearson correlation, and Bland-Altman analyses. A multinomial logistic regression model evaluated the associations between clinical variables and discrepant FIB-4 and NFS results.

Results: Of the 767-patient cohort, 71% had either a FIB-4 or NFS score in the indeterminate or high-risk category for fibrosis. Risk categories disagreed in 43% and FIB-4 and NFS scores would have resulted in different clinical decisions in 30% of the sample. The weighted kappa statistic for FIB-4 and NFS category agreement was 0.41 (95% CI: 0.36–0.46) and the Pearson correlation coefficient for log FIB-4 and NFS was 0.66 (95% CI: 0.62, 0.70). The multinomial logistic regression analysis identified Black race (OR 2.64, 95% CI 1.84–3.78) and A1c (OR 1.37, 95% CI 1.23–1.52) with higher odds of having a higher NFS risk category than FIB-4.

Conclusion: In a primary care NAFLD cohort, many patients had high FIB-4 and NFS risk scores and these risk categories were often in disagreement. The choice between FIB-4 and NFS for fibrosis risk assessment can impact clinical decision making and may contribute to gaps in quality of care.

Figure: Patient FIB-4 and NFS scores, categorized by advanced fibrosis risk.

		NAFLD Fibrosis Score			Total (%)
		Low NFS ≤ -1.455	Indeterminate -1.455 < NFS ≤ 0.676	High NFS > 0.676	
Fibrosis-4 Index					
Low	FIB-4 ≤ 1.3	222	177	20	419 (55%)
Indeterminate	1.3 < FIB-4 ≤ 2.67	30	152	65	247 (32%)
High	FIB-4 > 2.67	4	37	60	101 (13%)
Total (%)		256 (33%)	366 (48%)	145 (19%)	767

PO-1895

Evaluation of the Fibrosis-4 score for referral from primary care patients for NAFLD in Belgium

Leen Heyens^{1,2,3}, Dana Busschots^{1,4}, Judith Wellens⁵, Marlies Devos⁶, Luc Present⁷, Birgitte Schoenmakers⁸, Kitty De Munck⁹, Eva Rubens⁹, Katrien Joris¹⁰, Roy Remmen¹¹, Anouk Bongaerts¹², Karen Breure¹², Frederik Vanstraelen¹², Valerie Vos¹², Tom Bijmens¹², Inge Houben¹³, Sanne Bertels¹³, Lisa Vanbrabant¹³, Yoni Groenendaels¹³, Liesbeth Vernijns¹², Anneleen Robaey¹³, Thomas De Somer¹⁴, Ger Koek^{2,15}, Sven Francque^{16,17}, Christophe Van Steenkiste^{14,16}, Geert Robaey^{1,3,18}. ¹Hasselt University, Faculty of Life Sciences and Medicine, Hasselt, Belgium; ²Maastricht University, Faculty of Health, Medicine and Life Sciences, Maastricht, Netherlands; ³Ziekenhuis Oost-Limburg, Gastro-enterology, Genk, Belgium; ⁴Ziekenhuis Oost-Limburg, Gastro-enterology and Hepatology, Genk, Belgium; ⁵K.U. Leuven, Translational Research in Gastrointestinal Disorders, Leuven, Belgium; ⁶K.U. Leuven, Maatschappelijke Gezondheidszorg en Eerstelijnszorg, Leuven, Belgium; ⁷Huisartsenpraktijk Rendekens, Destelbergen, Belgium; ⁸K.U. Leuven, Academisch Centrum voor Huisartsgeneeskunde, Leuven, Belgium; ⁹University of Antwerp, Faculty of Medicine, Antwerpen, Belgium; ¹⁰University of Antwerp, Faculty of Medicine, Wilrijk, Belgium; ¹¹University of Antwerp, Maatschappelijke

POSTER PRESENTATIONS

Gezondheidszorg en Eerstelijnszorg, Wilrijk, Belgium; ¹²Huisartsenbox, Genk, Belgium; ¹³Huisartsenpraktijk Termolen, Zonhoven, Belgium; ¹⁴AZ Maria Middelaers, Gastro-enterology and Hepatology, Gent, Belgium; ¹⁵Mumc+, Gastro-enterology, Maastricht, Netherlands; ¹⁶University of Antwerp, Gastro-enterology and Hepatology, Antwerpen, Belgium; ¹⁷Antwerp University Hospital, Gastro-enterology and Hepatology, Edegem, Belgium; ¹⁸University Hospitals KU Leuven, Gastro-enterology, Leuven, Belgium
Email: leen.heyens@uhasselt.be

Background and aims: Non-alcoholic fatty liver disease (NAFLD) has become the most frequent cause of chronic liver disease. Moreover, fibrosis stage has been identified as the most important predictor of prognosis. The majority of fibrotic NAFLD patients are currently undetected. The general practitioner's (GP) outpatient clinic is usually their first contact in the health care system. The Fibrosis-4 (FIB-4) is a non-invasive score to predict fibrosis based on routine blood parameters and is therefore easy to use in primary care. We aimed to determine whether the FIB-4 is a valuable tool for identifying NAFLD patients with fibrosis for referral to secondary or tertiary care.

Method: In a prospective pilot study in the Belgian regions of Limburg, East-Flanders, and Antwerp, patients were invited for screening in five GP practices. The fibrosis stage was determined using Vibration Controlled Transient Elastography (VCTE) by FibroScan[®] (Echosens, France) as a reference method. Based on the most recent laboratory data from the electronic patient file, the FIB-4 was calculated. Cut-off values stated in the guidelines of the Belgian Association for the Study of the Liver were used to grade the FibroScan[®] measurements. To determine the intermediate and high risk of significant liver fibrosis with the FIB-4 score, a cut-off value of 1.3 was used for patients younger than 65 years and 2.0 for patients older than 65 years.

Results: Of the 292 patients who signed up for the screening, 151 (51.7%) were male, mean age was 65 ± 12 years, BMI was 28.9 ± 5.6 kg/m², and waist circumference was 107.8 ± 84.5 cm. For 248 (84.9%) patients, both the FIB-4 and VCTE were available. FIB-4 values ≥ 1.3 or 2.0 were present in 64 (26.8%) patients. Of these, 11 (16.4%) had a fibrosis grade F4, four (6.0%) were staged F2-F3 and 52 (77.6%) F0-F1. FIB-4 values ≤ 1.3 or 2.0 were present in 181 (72.9%) patients. Of these, 19 (10.5%) patients had F4, 14 (7.7%) had F2-3 and 148 (81.8%) had a fibrosis grade of F0-F1. This results in a positive predictive value of 22.4%, a negative predictive value of 81.8%, and an overall accuracy of 65.7% for screening of ≥ F2 fibrosis in primary care. Of the 48 ≥ F2 patients diagnosed according to VCTE, only 15 (31.3%) were correctly identified as having fibrosis.

Conclusion: The parameters for calculating the FIB-4 score were available in more than 80% of patients in primary care in Belgium. However, the use of the FIB-4 score has only moderate accuracy to correctly identify patients with significant fibrosis for referral: missing 69% of cases, and the false-positive rate is high. Therefore, we suggest evaluating other test strategies in primary care for referral of fibrotic NAFLD patients to secondary and tertiary care centres.

PO-1927

In vivo SPECT imaging of steatohepatitis in NAFLD preclinical models using VCAM-1 nanobody: a proof-of-concept study

Maxime Nachit^{1,2}, Christopher Montemagno³, Romain Clerc³, Mitra Ahmadi³, François Briand⁴, Nick Devoogdt⁵, Yvon Julé⁶, Thierry Sulpice⁴, Catherine Ghezzi³, Alexis Broisat³, Isabelle A. Leclercq¹, Pascale Perret³. ¹UCLouvain, Laboratory of Hepato-Gastroenterology, Institut de Recherche Expérimentale et Clinique, Belgium; ²KU Leuven, Department of Imaging and Pathology, Belgium; ³CHU Grenoble Alpes, LRB U1039, Laboratory of Bioclinical Radiopharmaceuticals, INSERM, France; ⁴Physiogenex, France; ⁵Vrije Universiteit Brussel, Laboratory of in vivo Cellular and Molecular Imaging, ICMI-BEFY, Belgium; ⁶Biocellvia, France
Email: maxime.nachit@gmail.com

Background and aims: We lack non-invasive tools to detect the presence of liver inflammation (i.e. steatohepatitis) in patients with non-alcoholic fatty liver disease (NAFLD). Vascular cell adhesion molecule-1 (VCAM-1) is a vascular protein that contributes to *in situ* recruitment of inflammatory cells. Here, we evaluated the hepatic expression of VCAM-1 in relation to liver inflammation severity in preclinical NAFLD models. Next, we performed *in vivo* imaging of VCAM-1 as to detect liver inflammation using ^{99m}Tc-cAbVCAM1-5.

Method: C57BL6/J mice fed a choline deficient (MCD) or a normal diet (ND) were injected either with ^{99m}Tc-cAbVCAM1-5 (V-MCD) or an irrelevant control (C-MCD) to evaluate the specificity of VCAM-1 imaging in a fast model of liver inflammation. Wild-type (WT) and FOZ mice fed a high fat diet (WT HF and FOZ HF) or control WT mice fed a normal diet (WT ND), and C57BL6/J fed a choline- deficient (CDH) or supplemented (CSH) fat rich diet, were employed as murine models of NAFLD. Liver histology was evaluated with NAS score and digital automated analysis. We measured liver VCAM-1 and proinflammatory markers expression using RT-qPCR and VCAM-1 protein content with ELISA. Liver inflammation was monitored by single-photon emission computed tomography (SPECT) following mice injection of a ^{99m}Tc-cAbVCAM1-5. ^{99m}Tc-cAbVCAM1-5 liver uptake was measured *in vivo* and expressed either as a concentration (SUV: standard uptake value) or as a total uptake (%ID Liver_{in-vivo}: % of injected dose).

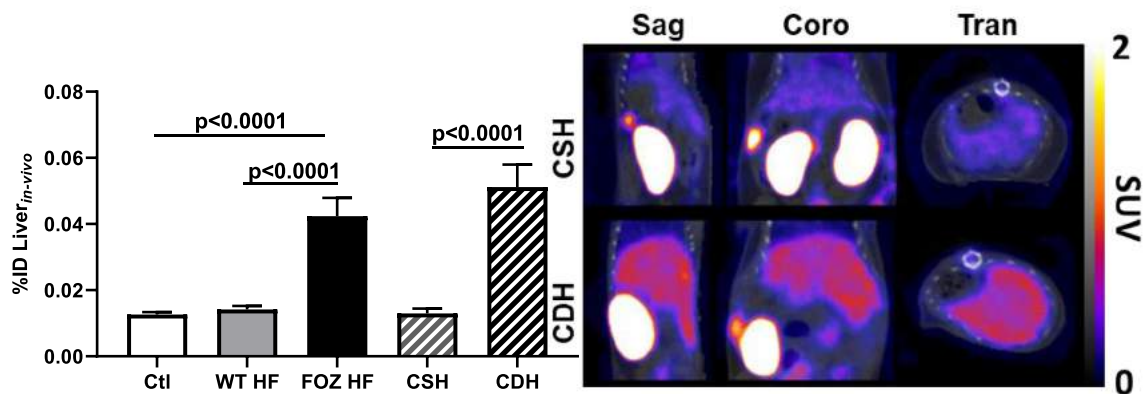


Figure: (abstract: PO-1927)

Results: Proinflammatory marker MCP1 was markedly elevated in V-MCD and C-MCD when compared to Ctl (up to 15-fold, $p < 0.0001$). V-MCD, but not C-MCD, had up to 2-fold increase of SUV Liver when compared to Ctl (0.48 ± 0.11 vs 0.28 ± 0.04 and 0.26 ± 0.03 , respectively, $p < 0.001$) thus confirming the high specificity of ^{99m}Tc -cAbVCAM1-5. NAFLD was found in WT HF, FOZ HF, CDH and CSH (steatosis score: 1.2 ± 0.7 , 3.0 ± 0.0 , 3.0 ± 0.0 and 0.8 ± 0.4 , respectively) with severe or mild steatohepatitis in FOZ HF and CDH or in WT HF and CSH, respectively (inflammation score: 2.7 ± 0.5 and 3.0 ± 0.0 vs 1.0 ± 0.6 and 0.7 ± 0.5). VCAM-1 expression was higher in mice with NAFLD when compared to Ctl (FOZ HF: 7.61 ± 2.28 , CDH: 8.29 ± 4.52 , WT HF: 1.40 ± 0.70 and CSH: 2.74 ± 0.38 fold) and was highly correlated with the expression of proinflammatory marker F4/80 and MCP1 ($r = 0.97$ and $r = 0.77$, respectively, $n = 30$, $p < 0.0001$). The % ID Liver_{in-vivo} of VCAM-1 was respectively 6-fold and 3-fold higher in FOZ HF and CDH liver than in controls and was strongly correlated with histological inflammatory score ($r = 0.86$, $p < 0.0001$, $n = 31$) (Fig. 1). %ID Liver_{in-vivo} of VCAM-1 robustly distinguishes steatohepatitis from simple steatosis in mice with NAFLD (AUROC = 0.89, 95% CI 0.72–1.00, $p = 0.035$).

Conclusion: ^{99m}Tc -cAbVCAM1-5 is suitable to detect liver inflammation and distinguish steatohepatitis from steatosis *in vivo* in NAFLD preclinical models.

PO-1981

Non-invasive LIVERFAST transition rate to liver fibrosis is similar to that estimated with liver biopsy in NAFLD patients

Victor de Lédighen¹, Adèle Delamarre^{2,3}, Brigitte Le Bail^{4,5}, Marraud des Grottes², Marie Irlès-Depe², Marie Decraecker², Juliette Foucher^{2,6}, HIRIART Jean-Baptiste², Mona Munteanu^{7,8}, Ronald Quiambao⁷, Imtiaz Alam^{9,10}. ¹Hospital Center University De Bordeaux, Liver Fibrosis Investigation Center, Bordeaux, France; ²Hospital Center University De Bordeaux, Bordeaux, France; ³Hospital Center University De Bordeaux, Hepatology, Bordeaux, France; ⁴Hôpital Pellegrin Bordeaux, Pathology, Bordeaux, France; ⁵INSERM UMR1053, Bordeaux, France; ⁶Hôpital Du Haut-Lévêque, Hepatology, Bordeaux, France; ⁷Fibronostics, Medical Affairs Division, United States; ⁸University Paris-Descartes, Paris, France; ⁹Dell Medical School, Austin, Texas, United States; ¹⁰Austin Hepatitis Center, Hepato-Gastroenterology, TEXAS, United States
Email: mona_munteanu@hotmail.com

Background and aims: Due to the high prevalence of NAFLD and the drawbacks of liver biopsy (LB) including the poor acceptance, its routine use is limited. There is an urgent need for reliable non-invasive tools (NITs) of differentiating NAFL from NASH and disease staging. Moreover, screening non-invasively for NASH fibrosis in Type 2 diabetes (T2D) patients (pts) is mandatory, as liver enzymes are often normal despite advanced fibrosis. LIVERFAST (LF) is a serum NIT with CPT code for assessing liver fibrosis (LF-Fib) along with activity and steatosis and with prognostic value to predict mortality and morbidity (overall and liver-related). (submitted). The aim was to demonstrate that LF-Fib is an alternative to LB for the estimation of the transition rate to fibrosis [transition to stage F1 or more (TRF)] in T2D and noT2D, comparatively to other NITs [FIB-4, liver stiffness measurement (LSM) by Fibroscan].

Method: TRF was evaluated using Cox-Mantel Hazard Ratio [HR (95% CI) and logrank comparison, p value $< 0, 05$] with a modeling of hazard from birth to age of LB or NIT in a prospectively collected NAFLD population evaluated for fibrosis with LB, and 3 concomitant NITs (LF-Fib, LSM, FIB4). NITs cut-offs with highest sensitivity for minimal fibrosis were used (0.28, 1.45 and 5.6 kPa, respectively).

Results: N = 583 pts were included, 52% T2D, 56% males, median (range) age 59.5 (18–85), HbA1c 6.6% (4.7–12), BMI 31.5 (20–54) kg/m² (obesity 59%), mean (SE) time lapse between LB and NITs 1.7 (0.4) months. The estimation of TRF [HR (95% CI)] using LF-Fib was similar to that using LB in both T2D [0.67 (0.56–0.80) vs. 0.65 (0.54–0.79)], and noT2D [1.50 (1.26–1.78) vs. 1.54 (1.27–1.86)], respectively, with earlier TRF in noT2D compared to T2D (logrank $p < 0.0001$). The TRF of TE and FIB4 were also similar to LB however, less fit in both T2D and noT2D groups for both TE [0.75 (0.63–0.89) vs 1.34 (1.12–1.60), $p < 0.001$] and FIB4 [0.79 (0.63–0.99) vs 1.26 (1.01–1.59), $p < 0.05$], respectively. In pts having ALT > 30 IU compared to those with ALT ≤ 30 IU, the TRF was faster in noT2D [2.13 (1.55–2.95) vs 0.47 (0.34–0.65), logrank $p < 0.001$] and not significantly different in T2D [1.28 (0.93–1.75) vs 0.78 (0.57–1.07), $p = \text{ns}$]. In multivariate analysis, including NITs, arterial hypertension (AHT), HbA1c and BMI, only AHT, BMI ≥ 35, male gender, FIB-4 and LF (Ste, Act and Fib) were significantly associated to TRF in T2D (all $p < 0.001$) and the same with the exception of BMI and FIB-4 in noT2D ($p < 0.0001$ for AHT and LF, $p < 0.05$ for male gender).

Hazard Rate Plot HR (95%CI, logrank) for the transition to fibrosis according to:

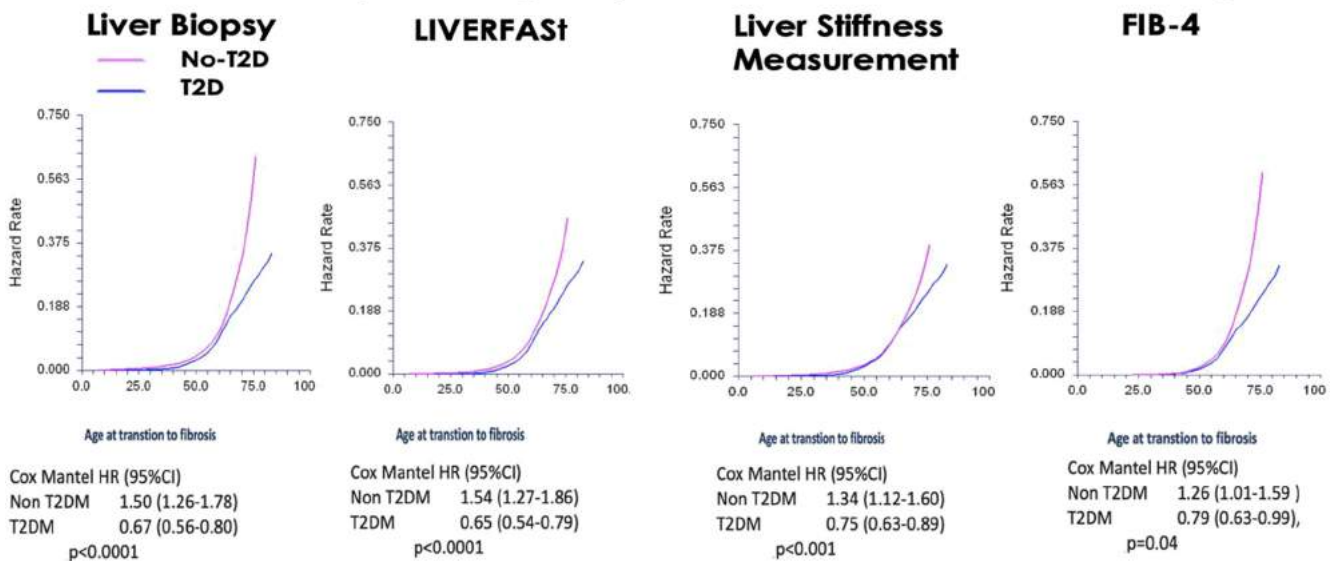


Figure: (abstract: PO-1981)

POSTER PRESENTATIONS

Conclusion: Validated biomarkers such as LIVERFAST should allow a powerful analysis of fibrosis progression in NAFLD, similar to LB and better screening strategies for stratifying patients.

PO-2030

Screening of advanced liver fibrosis in patients with coronary arterial disease, the CORONASH Study

Thierry Thévenot¹, Sophie Vendeville¹, Linda Akkouche², Delphine Weil-Verhoeven¹, Claire Vanlemmens¹, Carine Richou¹, Jean Paul Cervoni¹, Marie-France Seronde², Jerome Boursier³, Vincent Di Martino¹. ¹CHU Besançon, Hepatology, Besançon, France; ²CHU Besançon, Cardiology, Besançon, France; ³CHU Angers, Hepatology, Angers, France
Email: tthevenot@chu-besancon.fr

Background and aims: It has been previously suggested an association between coronary arterial disease (CAD) and advanced liver fibrosis (ALFib) in patients with non-alcoholic fatty liver disease (NAFLD) selected by liver biopsy. However, the “real-life” prevalence of ALFib and the results of non-invasive fibrosis tests (NITs) in patients with CAD have never been evaluated so far. This study reports a systematic screening of ALFib in patients with proved CAD.

Method: Consecutive patients aged ≤ 70 yrs with significant stenosis at coronarography were prospectively included. ALFib was suspected on biochemical NIT using the following cutoffs: APRI ≥ 1.5 , Forns ≥ 6.9 , NAFLD fibrosis score (NFS) ≥ 0.676 , Fib4 ≥ 2.67 and eLIFT ≥ 8 . All patients underwent Fibroscan examination (FS), and liver biopsy was proposed in case of suspected ALFib (FS ≥ 8 kPa). Results were given in intent-to-screen FS ≥ 8 kPa.

Results: 199 patients (males 81%; age 60 ± 7 yrs; BMI 28 ± 4 kg/m²; metabolic syndrome 57%; diabetes 30%; normal serum ALT 92%) were included in the study. Liver stiffness was ≥ 8 kPa in 10 patients (5%) and 5 of them underwent liver biopsy (F3/F4: n = 3; no fibrosis: n = 2). According to NITs, ALFib was suspected in 32% of the patients using eLIFT (specificity for FS ≥ 8 kPa, Sp 69%), 14% with Forns (Sp 19%), 6% with NFS (Sp 62%), 3% with Fib4 (Sp 75%), and 1% with APRI (Sp 91%). In selected “high-risk NAFLD subgroup” (111 patients with ≥ 1 of the following conditions: elevated ALT, diabetes, hypertriglyceridemia or BMI ≥ 30 kg/m²), the proportion of patients with ALFib using the combined intermediate and high-risk zones of NITs ranged between 14% (APRI) to 86% (Forns). In this “high-risk subgroup,” the best strategy to minimize the number of patients referred for FS examination because of positive NIT (Sp) and to maximize sensitivity (Se) was to use eLIFT (Se 63%, Sp 67%) or NFS (Se 63%, Sp 67%). Using eLIFT, 39 “high-risk” patients (20% of the study population) were considered at risk of ALFib, 5 of them had FS ≥ 8 kPa among whom 3 were biopsied and were F3/F4. Using NFS, 58 “high-risk” patients had ALFib, 5 of them had FS ≥ 8 kPa among whom 2 were biopsied and were F3/F4.

Conclusion: Screening of ALFib in CAD patients could be implemented by cardiologists using a simple two-step procedure: the first step identifies “high-risk NAFLD patients” using common risk factors, and the second step calculates the user-friendly eLIFT to determine which patients need to be referred for a Fibroscan.

PO-2369

Current non-invasive tests have suboptimal performance for the identification of candidates for pharmacological therapy for pre-cirrhotic non-alcoholic steatohepatitis.

Jesús Rivera¹, Jose Luis Calleja², Rocio Aller³, Hugo Gonzalo-Benito³, María Teresa Arias Loste⁴, Paula Ireuzubieta⁴, Javier Ampuero⁵, Ana Lucena⁵, Yolanda Sanchez⁵, Manuel Romero-Gomez⁵, Salvador Augustin¹, Javier Crespo⁴. ¹Vall d'Hebron Hospital

Universitari, Liver Unit, Department of Internal Medicine; ²Hospital Universitario Puerta de Hierro, Majadahonda, Department of Gastroenterology and Hepatology; ³Clinic University Hospital, Department of Gastroenterology; ⁴Marqués de Valdecilla University Hospital, Department of Gastroenterology and Hepatology; ⁵University Hospital Virgen del Rocío, Unit of Digestive Diseases and Ciberehd
Email: jesusriveraest@gmail.com

Background and aims: The clinical burden of non-alcoholic steatohepatitis (NASH) is growing rapidly, but still there are no approved therapies. Under the current regulatory framework, upcoming therapies are being targeted to patients with biopsy-proven NASH with fibrosis stage 2–3 and NAFLD Activity Score (NAS) ≥ 4 . Non-invasive identification of these pre-cirrhotic pharmacological-therapy candidate patients (PTCP) is challenging. The aim of this study was to evaluate different diagnostic strategies based on non-invasive tests (NITs) to identify pre-cirrhotic PTCP.

Method: This was an observational, multi-centric, retrospective, cross-sectional study in 501 consecutive patients with biopsy-proven NASH with paired clinical and elastography data from 5 tertiary centers in Spain between 2015–2020. Patients with liver stiffness (LS) < 7 kPa were excluded, under the assumption that in practice these patients will not be followed-up in specialized clinics. We also excluded patients with LS > 25 kPa due to the low prevalence of PTCP above that value ($< 15\%$), in line with usual clinical practice. In the targeted LS 7–25 kPa NASH population, diagnostic accuracy for PCTP histological criteria was analyzed for the most commonly recommended NITs in NASH (FIB4, NFS, LS, FAST), using the usual cutoffs for maximizing sensitivity (Se) or specificity (Sp) for each NIT.

Results: Among the 501 patients, 77 (15%) had LS < 7 kPa and 39 (8%) had LS > 25 kPa and were excluded for analysis. Among the remaining 385 patients with LS 7–25 kPa, 109 (28%) fulfilled histological PCTP criteria. Diagnostic accuracy for ruling in/out PCTP criteria was poor for the usual cutoffs for FIB-4 and NFS (negative predictive values, NPV, $< 80\%$ and positive predictive values, PPV, $< 35\%$). In this population, the strategy of performing a biopsy only in all patients with LS > 10 kPa did not increase the detection yield (PPV 29%). Of all NITs tested, only FAST had a potentially useful diagnostic accuracy: Se and NPV for 0.35 cutoff were 0.92 and 90%, respectively, and Sp and PPV for 0.67 cutoff 0.74 and 49%, respectively. Only 32% of patients had FAST > 0.67 . Thus, among the LS 7–25 population, only 16% [$(0.32 \times 0.49) \times 100$] fulfilled PCTP criteria.

Conclusion: Pre-cirrhotic PTCP represent a small proportion of all the patients currently seen in specialized NASH clinics. Use of some NITs (such as the FAST score) improve the ability to identify these patients as compared to use of TE alone, but still half of the patients selected for biopsy with FAST will not fulfill PCTP histological criteria. Better NIT-based strategies are urgently needed to identify candidates for inclusion in trials and for implementation of effective therapies.

Figure:

	Cutoff	Sn (%)	Sp (%)	PPV (%)	NPV (%)
FIB-4	1.30	70.6	45.2	34.8	78.8
	2.67	15.5	87.4	34.0	71.4
NFS	-1.45	70.3	29.8	29.3	70.9
	0.67	13.8	85.8	28.8	70.6
LS	10 kPa	64.2	37.2	29.5	71.7
FAST	0.35	91.6	30.8	36.2	89.6
	0.67	55.2	75.5	49.0	79.8

PO-2485

Assessment of imaging modalities against liver biopsy in non-alcoholic fatty liver disease: the Amsterdam NAFL-NASH cohort

Julia Witjes¹, Marian Troelstra², Anne-Marieke van Dijk¹, Anne Linde Mak¹, Oliver J. Gurney-Champion², Jurgen Runge², Diona Zwirs¹, Daniela Stols-Gonçalves¹, Aeilko Zwinderman³, Marije ten Wolde⁴, Houshang Monajemi⁵, Dewkoemar Ramsoekh⁶, Ralph Sinkus⁷, Otto van Delden², Ulrich Beuers⁸, Joanne Verheij⁹, Max Nieuwdorp¹, Aart Nederveen², Adriaan G. Holleboom¹.
¹Amsterdam UMC, locatie AMC, Department of Vascular Medicine, Amsterdam, Netherlands; ²Amsterdam UMC, locatie AMC, Department of Radiology and Nuclear Medicine, Amsterdam, Netherlands; ³Amsterdam UMC, locatie AMC, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam, Netherlands; ⁴FlevoHospital Almere, Department of Internal Medicine, Almere, Netherlands; ⁵Rijnstate, Department of Internal Medicine, Arnhem, Netherlands; ⁶Amsterdam UMC, locatie VUmc, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands; ⁷King's College Hospital, Biomedical Engineering, Imaging Sciences and Biomedical Engineering Division, United Kingdom; ⁸Amsterdam UMC, locatie AMC, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands; ⁹Amsterdam UMC, locatie AMC, Department of Pathology, Amsterdam, Netherlands
 Email: j.j.witjes@amsterdamumc.nl

Background and aims: Multiparametric MRI is a promising technique to assess hepatic steatosis as well as inflammation and fibrosis, potentially enabling non-invasive identification of individuals with active and advanced stages of NAFLD. We aimed to examine the diagnostic performance of multiparametric MRI for assessment of disease severity along the NAFLD disease spectrum compared to histology.

Method: Histological steatosis grades were compared to proton density fat fraction measured by MR spectroscopy (PDFF_{MRS}), magnitude-based MRI (PDFF_{MRI-M}) and 3-point-Dixon (PDFF_{Dixon}), as well as FibroScan[®] controlled attenuation parameter (CAP). Fibrosis and disease activity were compared to intravoxel incoherent motion (IVIM) MRI and MR elastography (MRE). FibroScan[®] liver stiffness measurements (LSM) were compared to fibrosis levels. Diagnostic performance of all imaging parameters was determined for distinction between simple steatosis and NASH.

Results: 37 patients with NAFLD were included. Histological steatosis grade correlated significantly with PDFF_{MRS} ($r_s = 0.66$, $p < 0.001$), PDFF_{MRI-M} ($r_s = 0.68$, $p < 0.001$) and PDFF_{Dixon} ($r_s = 0.67$, $p < 0.001$), whereas no correlation was found with CAP. MRE and IVIM diffusion and perfusion significantly correlated with both disease activity ($r_s = 0.55$, $p < 0.001$; $r_s = -0.40$, $p = 0.016$; $r_s = -0.37$, $p = 0.027$ resp.) and fibrosis ($r_s = 0.55$, $p < 0.001$; $r_s = -0.46$, $p = 0.0051$; $r_s = -0.53$, $p < 0.001$ resp.). Of the MRI parameters, MRE and IVIM diffusion had the highest area-under-the-curve for distinction between simple steatosis and NASH (0.79 and 0.73 resp.). Specificity was highest for MRE (86.7%) and sensitivity for IVIM diffusion (85.7%).

Figure:

	AUROC	CUT-OFF VALUES	SENSITIVITY (%)	SPECIFICITY (%)
MRE	0.79	2.27 kPa	70	86.7
FIBROSCAN [®]	0.73	9.9 kPa	63.6	86.7
LSM				
IVIM D	0.73	0.0012 mm ² /s	85.7	53.3
IVIM F	0.68	22.90%	81	53.3
FIBROSCAN [®]	0.65	336 m/s	77.3	53.3
CAP				
IVIM D*	0.58	0.10 mm ² /s	47.6	80
PDFF _{MRI-M}	0.57	23.72%	40.9	86.7
PDFF _{MRS}	0.56	21.19%	45.5	73.3
PDFF _{DIXON}	0.52	21.84%	33.3	86.7

Conclusion: Multiparametric MRI is a promising method for non-invasive, accurate and sensitive distinction between simple hepatic steatosis and NASH, as well as for the assessment of steatosis and fibrosis severity.

PO-2710

Gamma-Glutamyl Transpeptidase Dynamics as a Biomarker for Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

Yeonjung Ha¹, Joo Ho Lee¹, Seong Gyu Hwang¹. ¹CHA Bundang Medical Center, CHA University, Gastroenterology, Seongnam-si, Korea, Rep. of South Korea
 Email: yeonjung.ha@gmail.com

Background and aims: Abnormal lipid profiles and liver biochemistry are common in non-alcoholic fatty liver disease (NAFLD). However, it is unclear whether changes in blood tests are associated with advanced fibrosis.

Method: Patients diagnosed with NAFLD between 2009 and 2017 at a health check-up were included. The changes in blood tests were calculated using the following formula: [(value at 6-month-value at baseline)/value at baseline] × 100. The end point was advanced fibrosis determined by the NAFLD fibrosis score, calculated every year from the index date until 2019. Cox proportional hazards models were used to identify factors predicting advanced fibrosis.

Results: After a median follow-up of 31.7 (19.4–50.8) months, advanced fibrosis occurred in 64 (6.3%) of 1021 patients. The advanced fibrosis group was older and had a higher prevalence of obesity, hypertension, or diabetes ($P_s < 0.05$). Gamma-glutamyl transpeptidase (GGT) levels (72.9 vs. 51.1 IU/L; $P = 0.23$) and Δ GGT (+6.0% vs. -6.9%; $P = 0.06$) were higher in the advanced fibrosis group. After multivariate adjustment, Δ GGT (hazard ratio [HR] 1.03; $P < 0.001$), age, and platelet counts were significantly associated with advanced fibrosis. The positive Δ GGT group showed a higher incidence of advanced fibrosis than the negative group ($p = 0.01$). The 1-standard deviation increment in Δ GGT showed a significant association with advanced fibrosis both in statin users (HR, 1.35) and in non-users (HR, 1.31; $P_s < 0.001$). The restricted cubic spline model identified a positive correlation between Δ GGT and the NAFLD fibrosis scores ($p < 0.001$). The sensitivity analysis showed consistent results.

Conclusion: Δ GGT calculated at 6 months following NAFLD diagnosis is associated with advanced fibrosis.

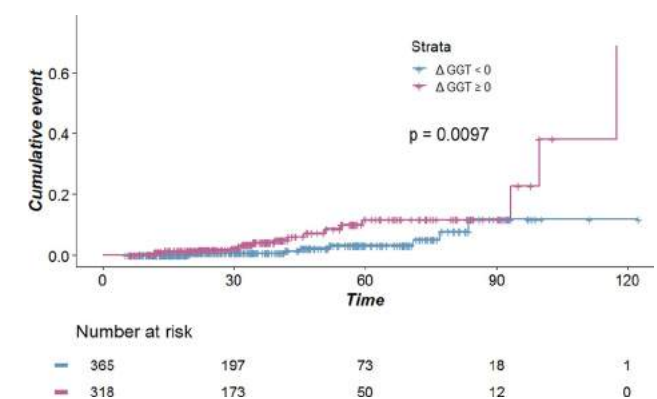


Figure:

POSTER PRESENTATIONS

PO-2739

In type-2 diabetic patients, the identification of at-risk NASH is impacted by age: a comparison of serum-based NITs including NIS4

Vlad Ratziu¹, Jeremy Magnanensi², Sylvie Deledicque², Elodie Delecroix², Yacine Hajji², Christian Rosenquist², Suneil Hosmane², Arun Sanyal³. ¹Sorbonne Université, Institute for Cardiometabolism and Nutrition, Hôpital Pitié-Salpêtrière, Paris, France; ²Genfit, Loos, France; ³VCU School of Medicine, Department of Internal Medicine, Richmond, United States
Email: arun.sanyal@vcuhealth.org

Background and aims: At-risk NASH, defined as NASH with a NAFLD Activity Score ≥ 4 and fibrosis stage ≥ 2 , is associated with high risk of disease progression. The risk is substantially modulated by age and type-2 diabetes (T2D). EASL guidelines recommend screening patients (pts) with T2D for at-risk NASH using a NIT-based algorithm, which implies robust NIT performance across all pts ages. This work investigated the effect of age on NITs performance for the identification of at-risk NASH, particularly among pts with T2D.

Method: 1129 pts with T2D screened for a phase 3 NASH trial (NCT02704403) with available data for NIS4TM, FIB-4, NFS, and ELF were analysed. Pts were stratified by age into 4 groups (≤ 45 yo, N = 146; 46–55 yo, N = 306; 56–64 yo, N = 394; ≥ 65 yo, N = 283). Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and percentage of pts in the moderate risk zone were computed for each NIT within the specified age group, using either published low (Lc) and high (Hc) cut-offs and new optimized ones. Area under the curve (AUC) was used for comparison within each age group, independent of cut-offs values.

Results: Prevalence of at-risk NASH, defined histologically, ranged from 60 to 66% across age groups. In both not-at-risk and at-risk NASH pts, NIS4TM, FIB-4, NFS and ELF mean values increased with age. Published cut-offs were not optimal across age groups for any NIT (FIB-4: 3–24% Se at Hc, NFS: 6–25% Se at Hc, ELF: 0–7% Sp at Lc, NIS4TM: 30–44% Sp at Lc). We computed new Lc and Hc to respectively achieve 80% Se and 90% Sp in each age group. Even with optimized cut-offs, NFS had the lowest performance (18–31% Sp at Lc, 8–18% Se at Hc, 0.5–0.63 AUC) and the largest proportion of pts in the moderate risk zone (61–71%). FIB-4 and ELF achieved reasonable performance for 46–55 and ≤ 45 yo age groups, respectively (0.74 AUC). NIS4TM

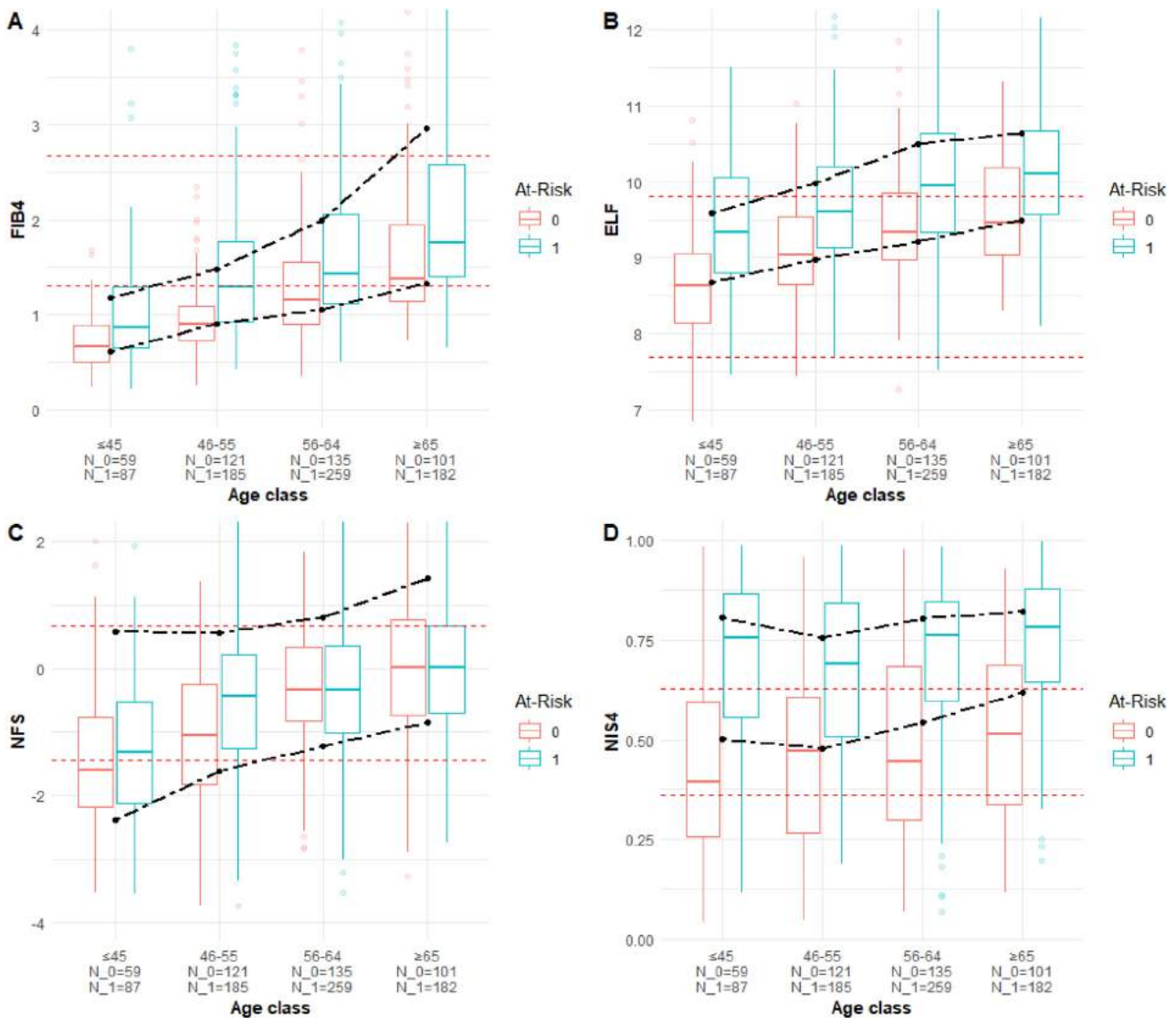


Figure: (abstract: PO-2739): Red dashed lines stand for published cut-offs, black two-dashed lines for “optimized” cut-offs.

globally outperformed all other NITs: 51–63% Sp at Lc, 37–43% Se at Hc, 62–69% NPV, 85–89% PPV, AUC of 0.76–0.79 and a proportion of pts in the moderate risk zone of only 33–41%.

Conclusion: Age significantly impacts the performance of NITs for the diagnosis of at-risk NASH and therefore age-adapted cut-offs should be factored in the interpretation of the results. NFS is not performant for the identification of at-risk NASH in pts with T2D. NIS4™ was the most robust NIT across all age groups. It outperformed all other NITs in diagnosing at-risk NASH among pts with T2D, in particular in those aged ≥55 yo which are at highest risk of disease progression.

NAFLD: Experimental and pathophysiology

PO-195

Role of Mcpip1 in obesity-induced hepatic steatosis as determined by myeloid and liver-specific conditional knockouts

Natalia Pydyn¹, Dariusz Zurawek¹, Joanna Koziel², Edyta Kus³, Kamila Wojnar-Lason³, Agnieszka Jaształ³, Mingui Fu⁴, Jolanta Jura¹, Jerzy Kotlinowski¹. ¹Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Department of General Biochemistry, Kraków, Poland; ²Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Department of Microbiology, Kraków, Poland; ³Jagiellonian Centre for Experimental Therapeutics, Jagiellonian University, Kraków, Poland; ⁴School of Medicine, University of Missouri, Department of Biomedical Science and Shock/Trauma Research Center, Kansas City, United States
Email: j.kotlinowski@uj.edu.pl

Background and aims: Monocyte chemoattractant protein-induced protein 1 (MCP1P1) is a negative regulator of inflammation, acting through cleavage of transcripts coding for proinflammatory cytokines and by inhibition of NFκB activity. Moreover, it was demonstrated, that MCP1P1 regulates lipid metabolism both in adipose tissue and hepatocytes. In this study, we investigated the effects of tissue-specific Mcpip1 deletion on the regulation of hepatic metabolism and development of non-alcoholic fatty liver disease (NAFLD).

Method: We used control Mcpip1^{fl/fl} mice and animals with deletion of Mcpip1 in myeloid leukocytes (Mcpip1^{fl/fl}LysM^{Cre}) and in liver cells (Mcpip1^{fl/fl}Alb^{Cre}), which were fed chow or a high-fat diet (HFD) for 12 weeks.

Results: Mcpip1^{fl/fl}LysM^{Cre} mice fed a chow diet were characterized by reduced hepatic expression of genes regulating lipid and glucose metabolism, which resulted in decreased glucose concentration and dyslipidemia. These animals displayed also systemic inflammation manifested by increased serum levels of Il-6, Il-12, Il-16, Tnf-alpha, Mcp-2, Mip-1 alpha and hepatic leukocyte infiltration. Although we detected a reduced hepatic expression of genes regulating glucose metabolism and β-oxidation in the Mcpip1^{fl/fl}Alb^{Cre} mice, they did not develop any abnormalities related to lipid metabolism. Despite feeding with HFD for 12 weeks, Mcpip1^{fl/fl}LysM^{Cre} mice did not develop obesity, glucose intolerance, nor hepatic steatosis. Mcpip1^{fl/fl}Alb^{Cre} animals, following a HFD, became hypercholesterolemic, but accumulated lipids in the liver at the same level as Mcpip1^{fl/fl} mice.

Conclusion: In conclusion, we demonstrated that Mcpip1 protein plays an important role in the liver homeostasis. Depletion of Mcpip1 in myeloid leukocytes, followed by systemic inflammation, has a more pronounced effect on controlling liver metabolism and homeostasis than its deletion in liver cells.

Acknowledgments: This study was supported by National Science Centre, grant number 2015/19/D/NZ5/00254.

PO-283

Transcriptomics identifies longitudinal biomarker gene signatures of NASH fibrosis regressors

Christina Ebert¹, Narayanan Raghupathy¹, Elizabeth Brown¹, Alice Walsh¹, Edgar Charles¹, Yi Luo¹, Peter Schafer¹, Leon Carayannopoulos¹, Lei Zhao¹, Francisco Ramirez-Valle¹, David Gordon¹, Raymond Chung², Kathleen Corey². ¹Bristol Myers Squibb, Lawrence Township, United States; ²Massachusetts General Hospital/Harvard Medical School, Boston, United States
Email: kathleen.corey@mgh.harvard.edu

Background and aims: Non-alcoholic steatohepatitis (NASH) prevalence is estimated at 1.5–6.5% globally and can progress to cirrhosis, liver failure and hepatocellular cancer. NASH, a complex and heterogeneous disease associated with both environmental and genetic risk factors, has no effective treatment other than lifestyle intervention. Developing an understanding of NASH at the molecular level could lead to potential prognostic and patient stratification biomarkers, and novel therapeutic hypotheses. In this study, we used longitudinal RNA-seq data to identify hepatic genes/gene signatures associated with NASH fibrosis regression to understand NASH pathophysiology, which may provide a basis for exploration of non-invasive biomarkers of disease regression.

Method: High quality RNA from FFPE liver tissues from 47 biopsy-proven NASH patients, collected at Massachusetts General Hospital Fatty Liver Clinic at baseline (METAVIR F0-F3) and follow-up (METAVIR F0-F4) within 8 years, were sequenced by Illumina RNA-seq. To perform longitudinal analysis, individuals were grouped based on change in disease stage from baseline to follow-up. NASH fibrosis regressors (13 out of 47 patients) were defined as individuals whose fibrosis stage improved by ≥1 stage from baseline to follow-up. Principal Component (PC) analysis was used after adjusting for covariates such as age and RNA quality to identify genes/gene signatures associated with biological signals in regressors.

Results: Transcriptomic analysis of regressors identified over 490 genes highly correlated with the first PC that captured the effect of time points under stringent 0.9 Spearman rank correlation. Analysis of these genes revealed significant gene signatures reflecting several mechanistic pathways associated with NASH including ECM remodeling, immune response, lipid metabolism, and cell death. These genes include some previously identified, such as C7 and CD24, and novel biomarkers of steatosis, fibrosis and NASH.

Conclusion: We have identified gene signature changes associated with a favorable prognostic outcome in NASH patients who are likely to regress in fibrosis stage. These findings provide a framework for the development of potential prognostic models of fibrosis regression using composite panels of biomarkers, which enable patient stratification.

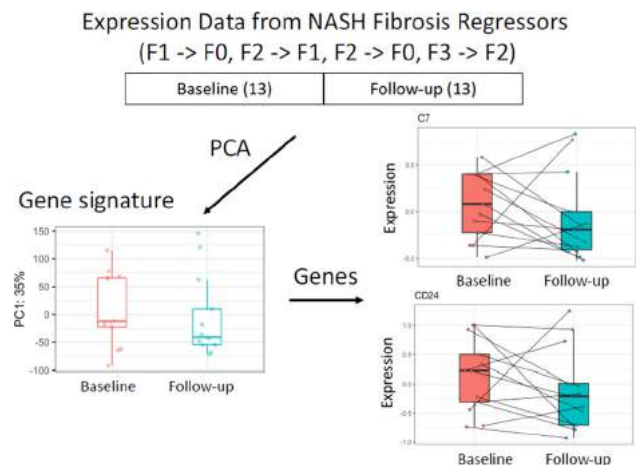


Figure:

POSTER PRESENTATIONS

PO-470

Restoration of altered bile acid pool inhibits the development of non-alcoholic steatohepatitis

Justine Gillard¹, Anne Tailleux², Laure-Alix Clerbaux³, Christine Sempoux⁴, Bart Staels², Laure Bindels⁵, Isabelle Leclercq¹.

¹UCLouvain, Laboratory of Hepato-Gastroenterology, Institute of Experimental and Clinical Research, Brussels, Belgium; ²University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-EGID, Lille, France; ³University of Zurich, Institute of Molecular Cancer Research, Department of Molecular Pathology, Zurich, Switzerland; ⁴Lausanne University Hospital CHUV, Institute of Pathology, Lausanne, Switzerland; ⁵UCLouvain, Metabolism and Nutrition Research Group, Louvain Drug Research Institut, Brussels, Belgium
Email: justine.gillard@uclouvain.be

Background and aims: We previously reported that *foz/foz* mice with NASH (NAFLD Activity Score (NAS) ≥ 7) have a markedly altered bile acid pool with low concentration in secondary deoxycholic acid (DCA) in bile and portal blood compared to WT mice (NAS ≤ 1). Perturbed bile acid pool results in reduced activation of the Takeda G-protein coupled receptor 5 (TGR5), a receptor mainly activated by secondary bile acids and that regulates lipid and glucose homeostasis, energy expenditure, inflammation and fibrosis. Low TGR5 agonism and resulting low TGR5 signaling could thereby contribute to NASH pathogenesis in this experimental model. We thus sought whether a modulation of the bile acid pool could prevent NASH.

Method: *Foz/foz* mice received a high fat diet (HFD) enriched or not with 0.03% or 0.1% of DCA for 12 weeks. They were compared to 12 weeks HFD-fed WT mice (n = 7 per group). Portal blood and tissues were sampled after 12 hours of fasting and 4 hours of refeeding. Bile acid profile was established by LC-MS/MS. We used a cell reporter assay, HEK293T cells overexpressing TGR5 and a CRE luciferase reporter, to quantify TGR5 ligand activity.

Results: A HFD supplemented with 0.1% DCA, but not 0.03%, increased total bile acids as well as cholic and deoxycholic acids concentrations in portal blood of *foz/foz* mice, to values seen in WT mice. While very low in HFD-fed *foz/foz* mice, the activation of TGR5 as measured in a reporter assay was higher when mice were supplemented by DCA 0.1%. While 0.03% DCA did not improve metabolic features in HFD-fed *foz/foz* mice, 0.1% DCA significantly reduced body weight gain and fat mass, despite an increased food intake. Glucose intolerance, fasting glycemia and insulinemia were also lowered by 0.1% DCA. As shown in the figure, 0.03% DCA did not

significantly change liver weight, hepatic steatosis or inflammation and slightly decreased the histological NAS compared to HFD-fed *foz/foz* mice. By contrast, 0.1% DCA reduced liver weight, hepatic steatosis and ballooning. Although inflammation continued, 0.1% DCA treatment significantly decreased NAS such as six out of the seven *foz/foz* mice treated with 0.1% DCA did not have NASH.

Conclusion: Supplementation of the HFD with a secondary bile acid restored bile acid pool and TGR5 agonism and in consequence, prevented the development of NASH and associated metabolic features in this mouse model.

PO-475

Inactivation of ACSL5, an interacting protein of TM6SF2, results in decreased plasma TG and cholesterol without affecting hepatic lipids

Fei Luo^{1,2,3}, Eriks Smagris², Jonathan Cohen⁴, Helen Hobbs^{2,4,5}. ¹The Second Xiangya Hospital of Central South University, Department of Cardiovascular Medicine, Changsha, China; ²University of Texas Southwestern Medical Center at Dallas, Molecular Genetics; ³The Second Xiangya Hospital of Central South University, Department of Cardiovascular Medicine; ⁴University of Texas Southwestern Medical Center at Dallas, Internal Medicine; ⁵Howard Hughes Medical Institute
Email: Helen.Hobbs@utsouthwestern.edu

Background and aims: Transmembrane 6 Superfamily Member 2 (TM6SF2) is a polytopic protein that is expressed predominantly in liver and small intestines. A missense variant in *TM6SF2* (E167K) is strongly associated with alcoholic and non-alcoholic fatty liver disease (FLD) as well as hypocholesterolemia. Mice expressing no *TM6SF2* (*Tm6sf2*^{-/-}) also have FLD and reduced plasma lipid levels. *TM6SF2* is required for normal lipidation of ApoB-containing apolipoprotein; *Tm6sf2*^{-/-} have a reduced rate of secretion of VLDL-TG but not of ApoB secretion. To glean possible insights into how *TM6SF2* promotes lipidation of VLDL, we identified proteins that interact physically with *TM6SF2*.

Method: Proteins that co-immunoprecipitated (Co-IP) with *TM6SF2* were identified using mass spectrometry. Mouse embryonic stem cells with an inactivated *Acs15* allele were used for generation of *Acs15*^{-/-} mice. The animals were fed a chow diet and fasted for 4 hours before sacrifice.

Results: We identified Apolipoproteins B (APOB) and Long chain Fatty Acid-CoA Ligase 5 (ACSL5) as interacting partners of *TM6SF2*. To determine if *TM6SF2* is required for *ACSL5* action in the ER, we

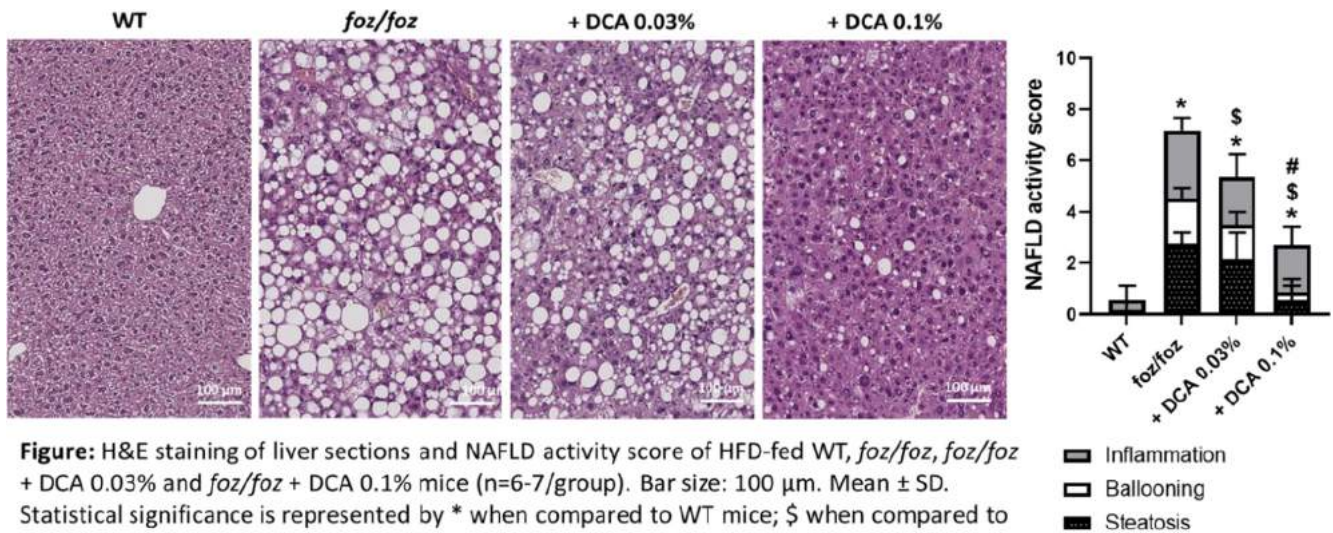


Figure: H&E staining of liver sections and NAFLD activity score of HFD-fed WT, *foz/foz*, *foz/foz* + DCA 0.03% and *foz/foz* + DCA 0.1% mice (n=6-7/group). Bar size: 100 μ m. Mean \pm SD. Statistical significance is represented by * when compared to WT mice; \$ when compared to *foz/foz* and # when compared to *foz/foz* + DCA 0.03%.

Figure: (abstract: PO-470)

generated *Acs15*^{-/-} mouse. The body weight of the male *Acs15*^{-/-} mice and wild-type (WT) littermate controls did not differ significantly but the knockout (KO) mice had reduced fat mass and increased lean body mass when compared to the WT animals. The mean levels of plasma triglycerides (122.2 mg/dl vs 85.0 mg/dl, *p* < 0.05) and cholesterol (111.0 mg/dl vs 72.1 mg/dl, *p* < 0.01) were lower in the *Acs15*^{-/-} mice. Although the rate of secretion of VLDL-TG was decreased in the male KO mice, these mice did not have any increase in hepatic triglyceride or cholesterol content. The levels of alanine transaminase (ALT) and aspartate transaminase (AST) were both higher in the KO mice.

Conclusion: TM6SF2 interacts with ApoB and ACSL5. Inactivation of *Acs15* results in a reduction in plasma TG and cholesterol and secretion of VLDL-TG without any increase in hepatic TG or cholesterol.

PO-550

serpina3c deficiency promotes high-fat diet-induced steatohepatitis through mediating necroptosis via β-catenin-foxo1 axis

Linglin Qian¹, Jingjing Ji², Jiaqi Guo², Yu Jiang², Ya Wu², Yuyu Yao².
¹Zhongda Hospital, School of Medicine, Southeast University, Cardiology, Nanjing, China; ²Zhongda Hospital, School of Medicine, Southeast University, Cardiology, Nanjing, China
 Email: qianlinglin0703@163.com

Background and aims: Non-alcoholic steatohepatitis (NASH) is a severe form of non-alcoholic fatty liver disease characterized by fat accumulation and inflammation in liver. However, the underlying molecular basis remains elusive. Serpina3c is a serine protease inhibitor (serpin) that plays a key role in metabolic diseases in previous studies. This study aimed to investigate the role of serpin3c in NAFLD and regulation of hepatocyte necroptosis and possible mechanisms.

Method: Male *Apoe*^{-/-}/*serpina3c*^{-/-}-double-knockout (DKO) and *Apoe*^{-/-} mice were fed with a high-fat diet (HFD) for 12 weeks to induce non-alcoholic steatohepatitis. Several markers of steatosis, inflammation and fibrosis were evaluated. Activation of necroptosis in alpha mouse liver 12 (AML-12) cells by palmitic acid (PA) were evaluated by Western Blot after overexpression and knockdown serpin3c.

Results: In vivo, serpin3c deficiency in DKO mice evidently increase the levels of alanine transaminase (ALT), aspartate transaminase (AST) in plasma. DKO mice exhibited significantly aggravated hepatic steatosis, liver damage, hepatic triglyceride content, fibrosis as well as increase hepatic cell death, liver inflammatory cell infiltration and gene expression of inflammatory factors, compared to *Apoe*^{-/-} mice. In vitro saturated palmitic acid (PA) treatment aggravated hepatic cell death, lipid droplet formation, the expression of inflammatory factors, however, these phenomena were reversed by overexpression serpin3c. The results also indicated that both lipotoxicity with HFD in vivo and saturated PA treatment in vitro were able to increase markers of necrosis, liver receptor-interacting protein 1/3 (RIP1/3) and phosphorylated mixed lineage kinase domain-like (MLKL). Mechanistically, downregulation serpin3c promoted beta-catenin signaling resulting in beta-catenin nuclear transfer. Meanwhile, downregulation serpin3c increased expression of the transcription factor FOXO1 and decrease phosphorylated FOXO1, and FOXO1 and beta -catenin colocalized in the nucleus, whereby the Foxo1 interaction with beta -catenin under lipotoxicity conditions, and consequent upregulation of and toll-like receptor 4 (TLR4), a death receptor at the plasma membrane. Additionally, disruption of the FOXO1- beta -catenin axis by Foxo1 inhibitor ameliorated hepatic cell death, lipid droplet formation, and decreased expression of TLR4, leading to decrease of necrosis markers, RIP3 and phosphorylation of MLKL.

Conclusion: Serpina3c plays an important role in protection of HFD-induced steatohepatitis through regulation necroptosis via beta-catenin-FOXO1 axis inhibiting TLR4 expression.

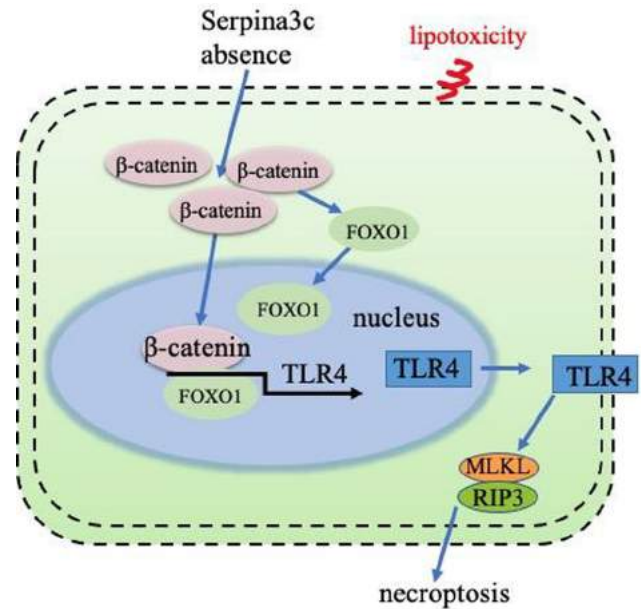


Figure:

PO-716

Distinctive alterations of the hepatic unfolded protein response in models of diabetes and non-alcoholic fatty liver disease

Bedair Dewidar^{1,2,3}, Lucia Mastrototaro^{1,2}, Cornelia Englisch^{1,2}, Michelle Reina Do Fundo^{1,2}, Fariba Zivehe^{1,2}, Dominik Pesta^{1,2}, Claudia Röss⁴, Irene Esposito⁵, Michael Roden^{1,2,6}. ¹German Diabetes Center, Institute of Clinical Diabetology, Düsseldorf, Germany; ²German Center for Diabetes Research, München-Neuherberg, Germany; ³Faculty of Pharmacy, Tanta University, Department of Pharmacology and Toxicology, Tanta, Egypt; ⁴Medical University Innsbruck, Department of Internal Medicine I, Innsbruck, Austria; ⁵Medical Faculty, Heinrich-Heine University Düsseldorf, Institute of Pathology, Düsseldorf, Germany; ⁶Medical Faculty, Heinrich-Heine University, Division of Endocrinology and Diabetology, Düsseldorf, Germany
 Email: michael.roden@ddz.de

Background and aims: Diabetes mellitus (DM) worsens prognosis of non-alcoholic fatty liver disease (NAFLD) likely by accelerating its progression to steatohepatitis (NASH) and fibrosis. For both diseases, endoplasmic reticulum (ER) stress-mediated cellular dysfunction has been described. As adaptive response to ER stress, unfolded protein response (UPR) activates three signaling branches i.e. PKR-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor (ATF) 6, which cooperatively interact to restore ER homeostasis. Here, we examined these pathways in experimental models of DM, obesity, and NASH.

Method: Two-days old male C57BL/6j mice received streptozotocin (STZ) or vehicle (placebo, PLC). From week 4 on, they were kept either on high-fat diet (HFD) or continued standard chow diet (SCD), thus yielding 4 groups (n = 8 each) as models of obesity [PLC+HFD], DM [STZ+SCD], NASH [STZ+HFD] and control [PLC+SCD]. NASH development was confirmed by histology, immunohistochemistry, and ELISA, whereas alterations in UPR were assessed using immunoblotting and qPCR. Body composition analysis was performed using nuclear magnetic resonance.

Results: Fasting blood glucose was about 180% higher in NASH and DM than in controls (both *p* < 0.0001). Obesity and NASH models had 3.9fold (*p* < 0.0001) and 1.8fold (*p* = 0.014) greater relative fat mass than the controls. In NASH, hepatic steatosis and fibrosis were 23.5-

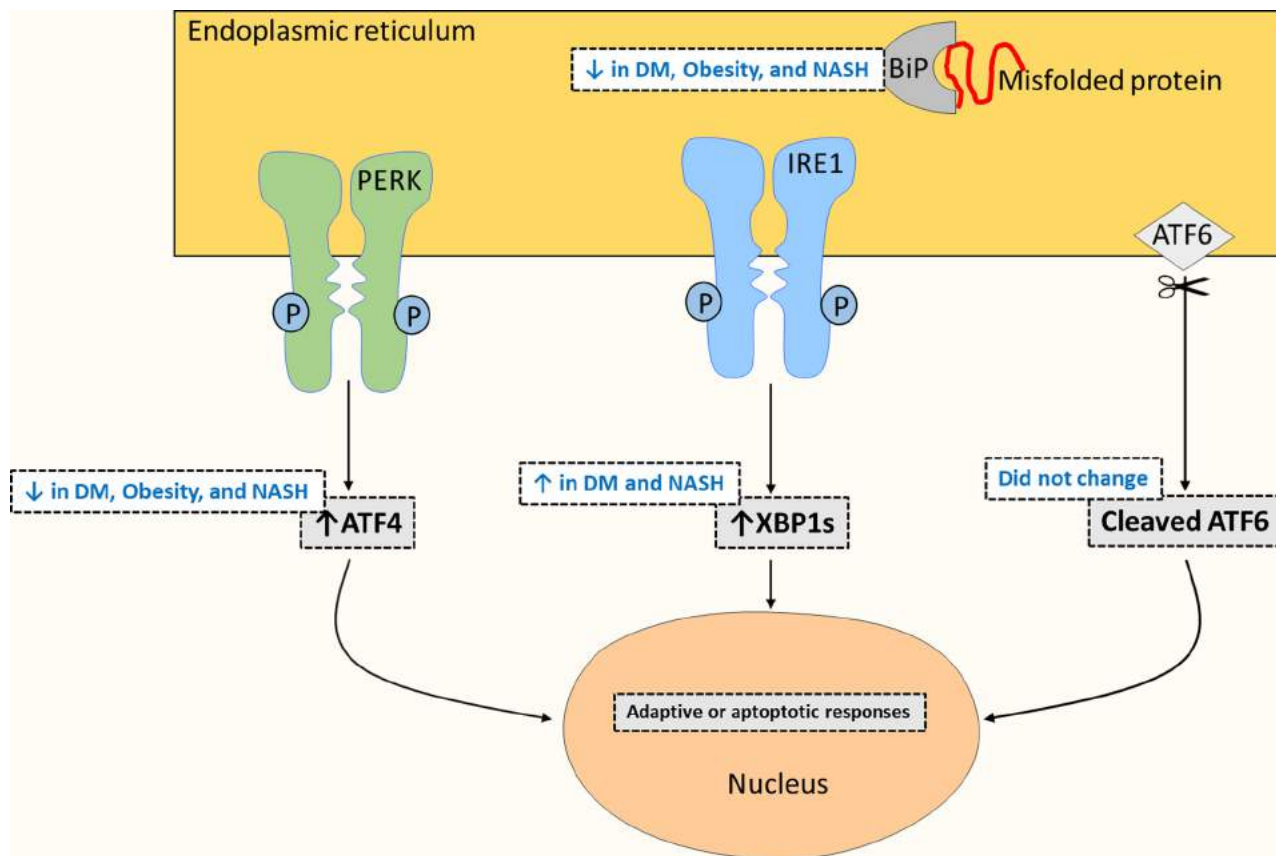


Figure: (abstract: PO-716)

and 2.9-fold increased, respectively ($p < 0.0001$ and $p = 0.013$ vs control). Elevation of hepatic MCP-1 in DM and NASH ($p = 0.02$ and $p < 0.0001$) and TNF- α in DM, obesity and NASH ($p = 0.013$, $p = 0.002$, and $p < 0.0001$ all vs control) indicated inflammation. The downstream target of the PERK branch, ATF4, was markedly decreased by 53%, 70%, and 73% in DM, obesity, and NASH ($p = 0.012$, $p = 0.0007$, $p = 0.0004$ vs control) and negatively correlated with liver TNF- α expression in NASH (Pearson $r = -0.72$, $p = 0.046$). Spliced X box binding protein 1 (XBPs) was increased by 58% and 50% in DM and NASH, suggesting activation of IRE1 axis ($p = 0.0001$, $p = 0.0009$ vs control). Cleaved ATF6 was not different between all groups. Interestingly, ER resident chaperone, BiP, was decreased by 43–73% in all groups as compared to control (obesity $p = 0.044$, DM $p = 0.014$, and NASH $p = 0.0003$).

Conclusion: This study shows differential changes in the UPR signaling axes in metabolically driven liver diseases and suggests that they may independently associate with NAFLD progression (Figure).

PO-725

Effects of empagliflozin and L-ornithine L-aspartate on behaviour, cognitive function, and physical performance in mice with non-alcoholic steatohepatitis

Veronika Prikhodko¹, Yuriy Sysoev^{1,2}, Sergey Okovityi¹. ¹Saint Petersburg state chemical pharmaceutical university, Department of pharmacology and clinical pharmacology, Saint Petersburg, Russian Federation; ²Saint Petersburg state university, Institute of translational biomedicine, Saint Petersburg, Russian Federation
Email: veronika.prihodko@pharminnotech.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) has a number of extrahepatic complications, which include cerebrovascular disease, cognitive and behavioural alterations, and accelerated

brain aging. Patients with NAFLD are at a 4 times higher risk to develop cognitive impairment, and tend to have decreased physical performance. As current treatment options for these complications are often insufficient, our aim was to evaluate the effects of empagliflozin (EMPA) and L-ornithine L-aspartate (LOLA) in a mouse model of non-alcoholic steatohepatitis (NASH).

Method: A total of 52 male C57BL/6 mice were randomized into four groups: Intact (0.9% NaCl; $n = 10$), Control (NASH + 0.9% NaCl; $n = 14$), EMPA (NASH + 2 mg/kg b.w. EMPA; $n = 14$), and LOLA (NASH + 1.5 g/kg b.w. LOLA; $n = 14$). To model NASH, the mice were fed a high-fat, high-calorie “western” diet for 6 months, given 42 g/L fructose solution to drink, and injected with carbon tetrachloride (0.32 mg/kg) once a week. Intact mice were offered standard chow and tap water. All drugs were administered orally once a day as freshly prepared solutions. Behaviour and cognitive function were assessed in the open field, elevated plus maze (EPM), light/dark box (LDB), and Barnes maze (BM) tests. Physical performance was assessed using the weight-loaded (7.5% of b.w.) forced swim (FS) and triple weight-loaded exhaustive swim (TES) tests.

Results: In all NASH groups, the mortality rate equalled about 40% and was not affected by either of the drugs. Movement speed was decreased ($p < 0.01$), while total freezing time ($p < 0.01$) and the number of head dips ($p < 0.05$) and rearing episodes ($p < 0.05$) were increased in the Control group. Control mice had higher error rate ($p < 0.05$) and latency to reach the target hole ($p < 0.05$) when tested for long-time memory in the BM, and exhibited poorer physical performance ($p < 0.05$) in both swimming tests. EMPA increased the number of grooming bouts ($p < 0.01$) and time spent in the light chamber of the LDB ($p < 0.05$), and LOLA increased the time spent in the open arms of the EPM ($p < 0.05$). LOLA also restored maximal swimming time in FS ($p < 0.05$) and swimming time in the third trial of TES ($p < 0.01$) to intact levels.

Conclusion: Experimentally induced NASH causes anxiety-like behaviour, impairs long-time memory, and reduces physical performance in C57BL/6 mice. Chronic administration of EMPA or LOLA ameliorates NAFLD-related cognitive deficit, while LOLA also improves physical performance and post-exercise recovery.

PO-1037 inhibition of atg3 ameliorates liver steatosis by increasing sirt1 in an autophagic-independent action

Eva Novoa^{1,2}, Natália da Silva Lima³, Marcos Fernández Fondevila^{1,4}, Xabier Buque⁵, María Jesús González¹, Uxía Fernández⁶, María García², María Del Pilar Chantada², Susana Bravo², Patricia Marañón⁷, Adriana Escudero⁶, Magdalena Leiva⁸, Diana Guallar⁶, Miguel Fidalgo⁶, Pedro Gomes⁹, Marc Claret^{10,11}, Guadalupe Sabio⁸, Marta Varela¹², Teresa Delgado¹², Miguel López^{4,6}, Carlos Diéguez^{4,6}, María Martínez^{7,12}, Carmelo García⁷, Agueda González⁷, Patricia Aspichueta^{5,13}, Rubén Nogueiras^{4,6}.
¹CiMUS-Centro Singular de Investigación en Medicina Molecular y Enfermedades Crónicas, Department of Physiology, Santiago de Compostela, Spain; ²Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain; ³University of Santiago de Compostela, Department of Physiology, CIMUS, Santiago de Compostela, Spain; ⁴CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Spain; ⁵Campus De Bizkaia-Campus of Biscay, Lejona, Spain; ⁶CiMUS-Centro Singular de Investigación en Medicina Molecular y Enfermedades Crónicas, Santiago de Compostela, Spain; ⁷Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas; ⁸Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; ⁹Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto; ¹⁰Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ¹¹CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM); ¹²CIC bioGUNE-Centro de Investigación Cooperativa en Biociencias, Derio, Spain; ¹³Biocruces Bizkaia Health Research Institute, Barakaldo, Spain
 Email: evam.novoa@usc.es

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a major health threat in both developed and developing countries and is a precursor of the more advanced liver diseases including non-alcoholic steatohepatitis (NASH), liver cirrhosis and liver cancer. One of the numerous molecules participating in the development of liver steatosis is p63. Although p63 is mainly known for its roles as a tumor suppressor and cell maintenance and renewal, we have recently reported that it is also relevant in the control of lipid metabolism. More specifically, TAp63 α isoform is elevated in the liver of animal models of NAFLD as well as in liver biopsies from obese NAFLD patients. Furthermore, downregulation of p63 α in the liver attenuates liver steatosis in diet-induced obese (DIO) mice. Autophagy is a critical intracellular pathway that targets cytoplasmic components

to the lysosome for degradation. A specialized form of autophagy that degrades lipid droplets, is known to be a major pathway of lipid mobilization in hepatocytes. Its impairment has been associated with the development of fatty liver and insulin resistance. Thus, it is established that autophagy acts as a protective mechanism in the pathogenesis of NAFLD. Autophagy-related gene 3 (ATG3) is an enzyme mainly known for its actions in the LC3 lipidation process, which is essential for autophagy. Despite it is implicated in different biological functions, its role in lipid metabolism and its contribution to NAFLD remains unknown.

Method: We performed proteomics in the liver of mice with genetic knockdown or overexpression of TAp63 α to get insights into novel proteins modulating lipid metabolism in a global and unbiased manner. Since ATG3 was increased in NAFLD and NASH preclinical models, we next evaluated its expression in liver biopsies of patients. HEPG2 cells treated with oleic acid (OA), and TAp63 α and ATG3 were up and downregulated with plasmids and siRNAs. *In vivo*, hepatic ATG3 and SIRT1 were specifically downregulated in the liver of mice through the tail vein injection of lentivirus encoding shRNA for ATG3. Over-expression of hepatic p63 was achieved by tail vein injection of the adenoviral vector encoding p63.

Results: We found that autophagy-related gene 3 (ATG3) was modified by TAp63 α activation and downregulated after p63 α inhibition. Further *in vitro* and *in vivo* experiments demonstrated that ATG3 is elevated in several animal models of NAFLD and in the liver of patients with NAFLD, who also show a positive correlation between ATG3 and steatosis grade and NAS score. Genetic over-expression of ATG3 increased the lipid load in hepatocytes, while its repression alleviated TAp63 α - and diet-induced steatosis. Unexpectedly, ATG3 exerted its role in lipid metabolism by regulating SIRT1 independent of an autophagic action.

Conclusion: Our findings indicate that ATG3 is a novel gene implicated in the development of NAFLD.

PO-1150 The hepatic IKK-NFkB axis induces liver steatosis by increasing de novo lipogenesis and cholesterol synthesis

Andries Heida¹, Nanda Gruben¹, Leen Catrysse², Martijn Koehorst³, Mirjam Koster¹, Niels Kloosterhuis¹, Rick Havinga¹, Vincent Bloks¹, Theo van Dijk³, Geert van Loo², Alain de Bruin⁴, Folkert Kuipers^{1,3}, Debby Koonen¹, Bart van de Sluis¹. ¹UMCG, Pediatrics, Groningen, Netherlands; ²Vib, Inflammation Research Center, Ghent, Belgium; ³UMCG, Laboratory Medicine, Groningen, Netherlands; ⁴Utrecht University, Department of Biomolecular Health Sciences, Utrecht, Netherlands
 Email: a.j.a.van.de.sluis@umcg.nl

Background and aims: Obesity-related chronic inflammation plays an important role in the development of Metabolic Associated Fatty

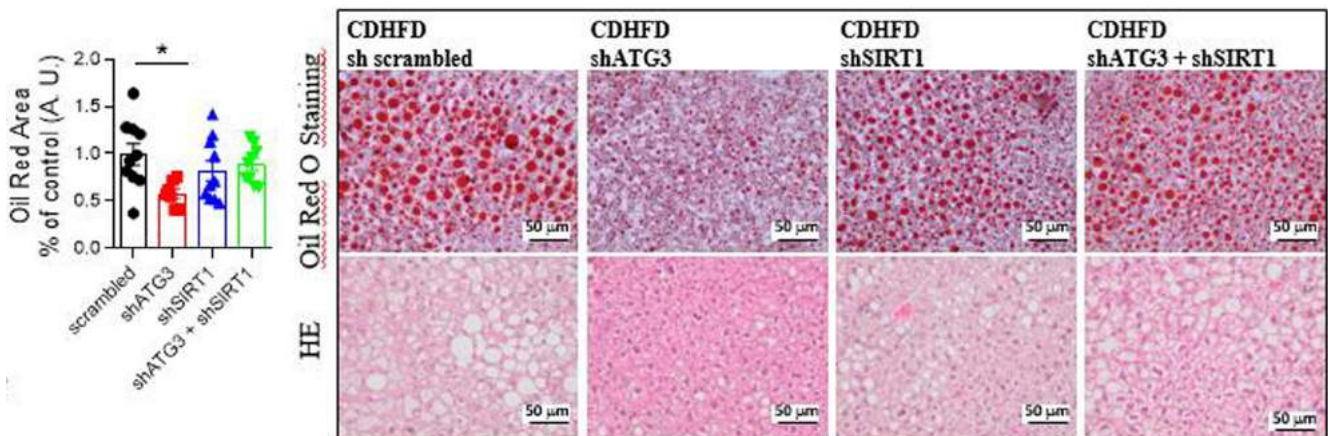


Figure: (abstract: PO-1037)

POSTER PRESENTATIONS

Liver disease (MAFLD). Although the contribution of the pro-inflammatory NF κ B signaling pathway to the progression from simple steatosis to non-alcoholic steatohepatitis (NASH) is well established, its role as a driver of steatosis remains unclear.

Method: To study the impact of hepatic NF κ B activation on MAFLD development we used a hepatocyte-specific constitutively active IKK β mouse model (Ik κ bc α ^{Hep}) and Ik κ bc α ^{Hep} mice in a hepatocyte A20-deficient background (Ik κ bc α ^{Hep}A20KO). Both models were fed on a carbohydrate-rich diet. These mice were histologically characterized and metabolic fluxes were determined using C¹³-labelled acetate water. Gene and protein expression were determined using qPCR analysis and RNA-sequencing, and immunoblotting, respectively.

Results: Hepatic NF κ B activation by a constitutively active form of *Ikk2* resulted in steatosis but not liver inflammation in mice (Hep-IKK β α). The upstream inhibitor of the IKK-NF κ B axis, *A20*, was highly upregulated in Hep-IKK β α livers. Ablation of hepatocyte *A20* in Hep-IKK β α mice (IKK β α ;A20^{LKO}) did not lead to liver inflammation but exacerbated steatosis, characterized by hepatic accumulation of triglycerides and cholesterol, accompanied by high plasma cholesterol levels. *De novo* lipogenesis (DNL) and cholesterol synthesis were both elevated in IKK β α ;A20^{LKO} mice. Phosphorylation of AMPK-a central regulator in lipogenesis and cholesterol synthesis-was decreased in IKK β α ;A20^{LKO} mice. This was paralleled by elevated protein levels of hydroxymethylglutaryl-CoA synthase (HMGCS1) and reduced phosphorylation of HMG-CoA reductase (HMGCR), both key enzymes in the cholesterol synthesis pathway. Whereas inflammation was not observed in young IKK β α ;A20^{LKO} mice, sustained hepatic NF κ B activation resulted in liver inflammation, together with elevated hepatic and plasma cholesterol levels in middle-aged mice.

Conclusion: Our data reveals a hepatocyte-specific role for the NF κ B signaling pathway in MAFLD, which is distinct from its central role in inflammation. The IKK-NF κ B axis controls DNL and cholesterol synthesis by regulating the phosphorylation levels of AMPK and HMGCR and the protein levels of HMGCS1 and, thereby, acts as a driver of steatosis and may also contribute to cardiovascular disease risk in MAFL patients.

PO-1235

Proteomics Signature of Advanced Fibrosis in Non-alcoholic Steatohepatitis (NASH) using Data-independent Acquisition (DIA) Mass Spectrometry

Thomas Jeffers^{1,2}, Aybike Bireddinc², Sean Felix^{1,2}, James M. Estep^{1,2}, Brian Lam^{1,2}, Bijal Rajout^{1,2}, Pegah Golabi^{1,2}, Arathi Krishnakumar³, Elizabeth Brown³, Qing Xiao³, Samuel Hellings³, Ashok Dongre³, John Thompson³, Yi Luo³, Edgar Charles³, Lei Zhao³, David Gordon³, Azza Karrar^{1,2}, Fatema Nader⁴, Zachary Goodman^{1,2}, Maria Stepanova⁴, Zobair Younossi^{1,5}. ¹Inova Health System, Department of Medicine, Center for Liver Diseases, Falls Church, United States; ²Inova Health System, Beatty Liver and Obesity Research Program, Falls Church, United States; ³Bristol Myers Squibb, Princeton, United States; ⁴Center for Outcomes Research in Liver Disease, Washington DC, United States; ⁵Inova Health System, Medicine Service Line, Falls Church, United States

Email: zobair.younossi@inova.org

Background and aims: NASH is the most common liver disease with potential for progression. Histologic stage of fibrosis is the most important predictor of liver-related mortality. Our aim is to use Data-independent Acquisition (DIA) Mass Spectrometry to evaluate the serum proteome signature associated with advanced fibrosis in NASH.

Method: Sera samples were obtained from patients with biopsy-proven NASH and non-NASH NAFLD who are enrolled in our center. All liver biopsies were read by a single hepatopathologist. Proteomics analysis was performed using high-performance LCMS, peptides missing in >50% samples were filtered out, leaving 372 proteins

assessed. Proteome signatures associated with NASH and advanced fibrosis were determined using Limma regression modeling after adjusting for age, sex, and type 2 diabetes (T2DM), applying Benjamini-Hochberg correction for multiple testing. Multivariate analysis adopting a stricter cut off ($p < 0.01$) and a lasso selection algorithm were performed to detect peptides independently associated with NASH and advanced fibrosis.

Results: We included 150 patients with NAFLD [100 with histologic NASH, 33% male, 71% white, 44% T2DM 34% advanced fibrosis ($\geq F3$)]. Patients with advanced fibrosis had higher levels of AST, ALT, and lower platelet count and had higher rate of T2DM than patients with early fibrosis or non-NASH NAFLD (all $p < 0.02$). Limma modeling revealed that a signature of 22 proteins was differentially expressed between NASH and non-NASH patients (adjusted $p \leq 0.05$) (Figure 1a). Furthermore, 29 proteins were differentially expressed between advanced fibrosis and non-advanced fibrosis (Figure 1b). Multivariate modeling revealed that Insulin-like growth factor binding protein, and acid labile subunit (IGFALS), were independently associated with lower risk of advanced fibrosis (OR = 0.963 (CI: 0.989–0.996), $p < 0.0001$) while C7 was associated with higher risk of advanced fibrosis (OR = 1.009 (CI: 1.006–1.012), $p < .0001$).

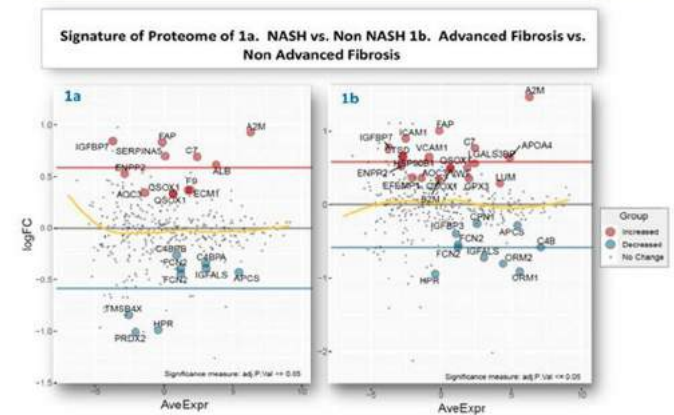


Figure:

Conclusion: This serum proteome signature suggests that NASH-related advanced fibrosis is associated with protein profile involved in insulin-like growth factor pathway, including IGFALS, IGFBP7 and IGFBP3, which regulate, metabolic and liver regenerative functions and C7 which has immune activation functions.

PO-1369

Non-alcoholic fatty liver disease in a rodent model of bariatric surgery with different bypass lengths

Paula Richwien¹, Magdalena Eilenberg¹, Jakob Eichelter¹, Carolin Lackner², Sarocchi Francesca², Gerhard Prager¹, Katharina Stauer³. ¹Department of General Surgery, Medical University of Vienna, Vienna, Austria; ²Institute of Pathology, Medical University Graz; ³Department of Visceral Surgery and Medicine, Inselspital, University Hospital Bern

Email: paula.richwien@meduniwien.ac.at

Background and aims: Non-alcoholic fatty liver disease (NAFLD) usually improves after bariatric-metabolic surgery. However, in some cases clinical and histological liver deterioration was described. We established a rodent model to investigate if one-anastomosis gastric bypasses (OAGB) with extended limb lengths, are more likely to lead to a histological worsening compared to moderate bypass lengths.

Method: Thirty-two male Sprague-Dawley rats received high-fat high-fructose diet (HFHFD) for a total of 16 weeks. Glucose tolerance, and body weight were assessed. After the first 8 weeks, either moderate OAGB (35 cm bypass length, n = 9), extended OAGB (55 cm bypass length, n = 9), or sham surgery (n = 7) was performed. Liver

tissue was gained during surgery, as well as 8 weeks thereafter, and was analyzed according to the clinical research network's scoring system.

Results: Body weight increased after 8 weeks of HFHFD (median: 561.5 g, Q1;Q3: 535.3;612.8, $p < 0.001$). At week 16 median weight was 719.0 g in sham, 644.5 g in moderate and 532.0 g in extended bypass, and significantly reduced after OAGB in comparison to sham operated animals (sham vs. moderate bypass: $p = 0.042$, sham vs. extended bypass: $p < 0.001$). Glucose tolerance was impaired after 8 weeks of HFHFD compared to baseline ($p < 0.001$). Surgery induced a significant improvement of glucose tolerance after moderate ($p = 0.021$) and extended bypass ($p = 0.038$) in contrast to sham operated animals ($p = 0.859$). Eight weeks of HFHFD led to liver fibrosis, inflammation and macrosteatosis in 15.6%, 84.4% and 56% respectively. After 16 weeks of HFHFD, liver fibrosis was present in 42.9%, 33.3%, and 11.1% in sham, moderate and extended OAGB, respectively, but advanced fibrosis (F3) was substantially more frequent after OAGB than in sham operated animals (0% vs. 16.7%, $n = 3/18$, $p = 0.074$). Inflammation was present in 100%, 66.7%, and 55.6%, respectively (sham vs moderate $p = 0.003$; sham vs extended $p = 0.001$). Macrosteatosis was present in 71.4%, 55.6%, and 44.4%, with no significant differences over the course of time nor in between the groups.

Conclusion: OAGB animals showed a significant improvement in body weight, allover presence of liver fibrosis, inflammation and steatosis. However, advanced fibrosis was substantially more frequent after OAGB. There was no significant difference in body weight, glucose tolerance or liver pathology between moderate and extended OAGB.

PO-1407

No impact of non-alcoholic fatty liver disease severity on hepatic and adipose tissue mitochondrial respiration but hepatic respiration increases after bariatric surgery

Julie Steen Pedersen¹, Marte Opseth Rygg¹, Karoline Chrøis², Elahu Gosny Sustarsic³, Zach Gerhart-Hines³, Nicolai J. Wever Albrechtsen⁴, Reza Serisawa⁵, Viggo Bjerregaard Kristiansen⁶, Astrid Elisabeth Bruun Boilesen⁶, Beth Hærstedt Olsen⁷, Torben Hansen³, Lise Lotte Gluud¹, Sten Madsbad⁸, Steen Larsen², Flemming Bendtsen¹, Flemming Dela².
¹Copenhagen University Hospital Hvidovre, Gastro Unit, Medical Division, Hvidovre, Denmark; ²University of Copenhagen, Department of Biomedical Sciences, Center for Healthy Ageing, Copenhagen N, Denmark; ³University of Copenhagen, NNF Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, Copenhagen N, Denmark; ⁴University of Copenhagen, NNF Center for Protein Research, Faculty of Health and Medical Sciences, Copenhagen N, Denmark; ⁵Copenhagen University Hospital Hvidovre, Department of Pathology, Hvidovre, Denmark; ⁶Copenhagen University Hospital Hvidovre, Gastro Unit, Surgical Division, Hvidovre, Denmark; ⁷Copenhagen University Hospital Hvidovre, Department of Nuclear Medicine and Functional Imaging, Ultrasound Section, Hvidovre, Denmark; ⁸Copenhagen University Hospital Hvidovre, Department of Endocrinology, Hvidovre, Denmark
 Email: julie.steen.pedersen@regionh.dk

Background and aims: Impaired mitochondrial oxidative phosphorylation (OXPHOS) in liver tissue has been hypothesized to contribute to the development of non-alcoholic steatohepatitis (NASH) in patients with non-alcoholic fatty liver disease (NAFLD). It is unknown whether OXPHOS capacities in human visceral (VAT) and subcutaneous adipose tissue (SAT) associate with NAFLD severity and how hepatic OXPHOS responds to improvement in NAFLD. We predicted that hepatic, VAT and SAT OXPHOS would mirror NAFLD severity and be lowest in those with NASH and that 12 months post bariatric surgery hepatic OXPHOS capacity would increase.

Method: We prospectively enrolled 62 bariatric candidates with obesity (OBE) and a median (IQR) BMI of 42.7 kg/m² (35.7–46.7) and

nine non-obese control subjects (CON) undergoing cholecystectomy. Liver, VAT and SAT biopsies were sampled perioperatively. Fresh tissue underwent high-resolution respirometry (HRR) analyses and mitochondrialDNA/nuclearDNA (mtDNA/nDNA) content and citrate synthase activity were estimated. Histological evaluation of NAFLD severity was used to stratify OBE into three groups at baseline: OBE without liver steatosis (NAFL-, $n = 31$), OBE with liver steatosis (NAFL+, $n = 16$) and OBE with NASH (NASH, $n = 15$). Twelve months after bariatric surgery 21 OBE with different NAFLD status at baseline underwent repeat liver biopsy with histological assessment and HRR. **Results:** At baseline hepatic OXPHOS was numerically increased in both NAFL-, NAFL+ and NASH when compared to CON. Mitochondrial content did not differ significantly between groups ($p = 0.355$). VAT and SAT OXPHOS were significantly but similarly reduced in all NAFLD groups compared to CON, and even after correction for mtDNA/nDNA content the significant decrease remained for SAT. Twelve months after surgery median NAFLD activity score was 1 (0.5–2) ($p < 0.001$), BMI decreased to 32.5 kg/m² (27.3–37.5) ($p < 0.001$), and hepatic electron transport chain system capacity (FCCP) ($p < 0.01$) (Figure 1), complex II ($p < 0.05$) and complex IV ($p < 0.05$) OXPHOS markedly increased.

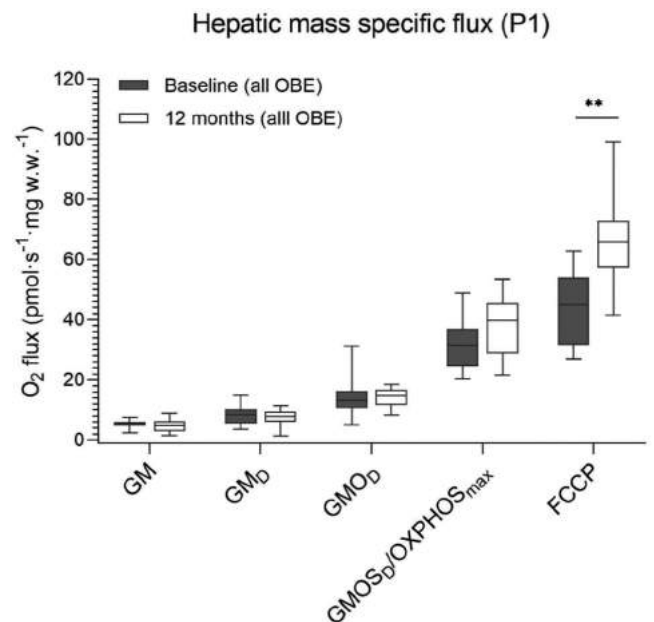


Figure:

Conclusion: Obesity appears to have an opposing effect on mitochondrial respiration in adipose- and liver tissue but with no additive effect of NAFLD severity and no evidence of affected hepatic respiration in those with NASH. Yet, weight loss and amelioration of NAFLD have major impact on hepatic OXPHOS which increases 12 months after bariatric surgery.

PO-1504

An independent blinded review of suspected drug-induced liver injury (DILI) in non-alcoholic steatohepatitis (NASH) patients by a panel of pathologists and hepatologists: lessons learned from the seladelpar hepatotoxicity review committee (SHRC)

Paul Watkins¹, David E. Kleiner², Pierre Bedossa³, Zack Goodman⁴, Neil Kaplowitz⁵, Willis Maddrey⁶, John M. Vierling⁷, Michael Charlton⁸, Cynthia Guy⁹, Elizabeth Brunt¹⁰, Stephen Harrison¹¹, Sujal Shah¹², Klara Dickinson¹², Charles McWhorter¹².
¹UNC, School of Pharmacy Institute for Drug Safety Sciences, Research Triangle Park, United States; ²National Cancer Institute, Bethesda, United States; ³University Paris-Diderot, Paris, France; ⁴Inova Healthcare Services; ⁵University of Southern California,

POSTER PRESENTATIONS

1A. Incidence of Findings in ET Bx Not Typically Reported in NASH					
Treatment	Any Interface Hepatitis*	Any Bile Duct Injury †	Any Vascular Lesion‡	Other	
Placebo (n = 25)	1 (4.0%)	3 (12.0%)	1 (4.0%)	1 (4.0%)	
Seladelpar 10 mg (n = 39)	3 (7.7%)	4 (10.3%)	2 (5.1%)	1 (2.6%)	
Seladelpar 20 mg (n = 42)	8 (19.0%)	5 (11.9%)	1 (2.4%)	1 (2.4%)	
Seladelpar 50 mg (n = 46)	11 (23.9%)	8 (17.4%)	4 (8.7%)	2 (4.3%)	
Total (N = 152)	23 (15.1%)	20 (13.2%)	7 (5.2%)	5 (3.3%)	
Notes	* Often with numerous plasma cells	† 3 granulomas were noted (1 florid granulomatous duct lesion; 2 in placebo)	‡ Primarily portal vein extrusion		

1B. Causality Assessment for Evidence of New or Progressive Pathology					
Treatment	Not Related 0-10% Causality	Unlikely < 25% Causality	Possible 25 to 49% Causality	Highly Likely 50 to 74% Causality	Probable 75 to 100% Causality
Placebo (n = 25)	0	2	0	0	0
Seladelpar 10 mg (n = 39)	1	2	0	0	0
Seladelpar 20 mg (n = 42)	1	2†	0	0	0
Seladelpar 50 mg (n = 46)	1	3*	1‡	0	0

*One 50 mg case was a split decision: 3 votes Unlikely and 3 votes Not Related; † One 20 mg case was a split decision: 5 votes Unlikely and 1 vote Possible; ‡ Subject with long standing lupus and diverticulitis prior to biopsy*One 50 mg case was a split decision: 3 votes Unlikely and 3 votes Not Related; † One 20 mg case was a split decision: 5 votes Unlikely and 1 vote Possible; ‡ Subject with long standing lupus and diverticulitis prior to biopsy

Figure: (abstract: PO-1504)

Los Angeles, United States; ⁶University of Texas Southwestern, Dallas, United States; ⁷Baylor College of Medicine, Houston, United States; ⁸University of Chicago, Chicago, United States; ⁹Duke University, Durham, United States; ¹⁰Washington University School of Medicine in St. Louis, St. Louis, United States; ¹¹Pinnacle Clinical Research, San Antonio, United States; ¹²CymaBay Therapeutics, Newark, United States Email: cmcwherter@cymabay.com

Background and aims: Surveillance for hepatotoxicity relies on clinical status and liver tests as signs and symptoms suggestive of DILI. Liver biopsy (Bx) is reserved for confirmation or exclusion of indefinite cases. This approach is useful for acute toxicity, but drugs (e.g., methotrexate, amiodarone) can cause chronic toxicity leading to cirrhosis without clinical or laboratory signs. NASH trials with baseline (BL) and end-of-treatment (ET) Bxs might detect such cases. In a seladelpar NASH study, a study pathologist (SP) read BL Bx for study eligibility. ET Bxs were read by 2 SPs without rescored BL Bxs. Atypical histology for NASH was noted in 42/152 ET Bxs (**1A**): Portal inflammation (PI) and Interface Hepatitis (IH) with plasma cells, bile duct injury/cholangitis (BDI), vascular changes (VC), and other misc. findings. We describe the adjudication of suspected chronic hepatotoxicity of seladelpar identified in ET Bxs.

Method: The SHRC comprised of 3 pathologists and 5 hepatologists experienced in DILI and NASH reviewed clinical, biochemical and histological data for all patients with paired Bxs. Two blinded randomized Bx reviews were conducted: 1) 302 BL and ET Bxs using the Ishak Histologic Activity Index and, 2) 151 BL and ET paired comparisons classified as "Better, Same or Worse." Reviews scored BL and ET Bxs for IH, PI, BDI, and VC. The SHRC reviewed the 42 cases for BL characteristics, NASH diagnosis, medical history, medications, labs, adverse events, immune biomarkers and BL and ET Bx histology.

Cases were assessed for evidence of DILI using clinical and laboratory results and for new or progressive unexpected liver pathology. The SHRC was unblinded to the treatment groups only after adjudication of cases.

Results: BL Bxs commonly showed IH (61–73%), PI (88–92%) and BDI (22%) with various grades. SHRC adjudication identified no cases of DILI. New or progressing unexpected histology (**1B**) was noted in 13 cases, but none were scored as "probable" or "highly likely" related to drug.

Conclusion: The SHRC determined that the ET Bx features identified by the 2 SPs were confirmed and were qualitatively similar in both BL and ET Bxs. They found no clinical, biochemical or histologic evidence that seladelpar was hepatotoxic. These results suggest the necessity of concurrent review of both BL and ET Bxs in NASH studies. The association of NASH with uncommonly reported histological features of IH and PI with plasma cells and BDI should be further investigated.

PO-1547

Steatosis, inflammasome upregulation and fibrosis are attenuated in microRNA-155 deficient mice in a diet-induced model of NASH

Mrigya Babuta¹, Shashi Bala¹, Michal Ganz², Yuan Zhuang¹, Timea Csak², Charles D. Calenda¹, Gyongyi Szabo¹. ¹Beth Israel Deaconess Medical Center (BIDMC), Department of Medicine, Boston, United States; ²University of Massachusetts Medical School, Department of Medicine, Worcester, United States Email: gszabo1@bidmc.harvard.edu

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease globally. miRNAs (miRs) regulate various cellular events that lead to NAFLD. In this

study we tested the hypothesis that miR-155 is an important regulator of steatohepatitis and fibrosis pathways in diet induced NASH.

Method: C57BL/6 wild type (WT) and miR-155 deficient (KO) mice received a high fat-high cholesterol-high sugar-diet (HF-HC-HS) for 34 weeks. Human liver samples were from controls and patients with NASH. Samples were analyzed by western blotting and qPCR.

Results: In patients with NASH and in the mouse model of HF-HC-HS diet we found increased miR-155 levels in the liver compared to normal livers. Upon HF-HC-HS diet feeding for 34 weeks, miR-155 KO mice displayed less liver injury, decreased steatosis, and attenuation of fibrosis compared to WT mice. Furthermore, we observed a decrease in the ALT levels, triglyceride levels in miR-155 KO mice suggesting a decrease in liver injury. In HF-HC-HS diet-fed WT mice, we found increased expression of genes involved in fatty acid metabolic pathway (Cpt1 α , FAB4, ACC2, FAS) mice which were attenuated in miR-155 KO mice. HF-HC-HS diet induced a significant increase in the expression of NLRP3 inflammasome components (NLRP3, ASC, Caspase-1) in the livers of WT mice compared to chow fed diet. Compared to WT mice, miR-155 KO showed attenuated induction in the NLRP3, ASC and caspase1 inflammasome expression on HF-HC-HS diet. Fibrosis markers such as collagen content and deposition, α SMA and Zeb2, were all increased in WT mice while miR-155 KO mice showed attenuated fibrosis marker expression.

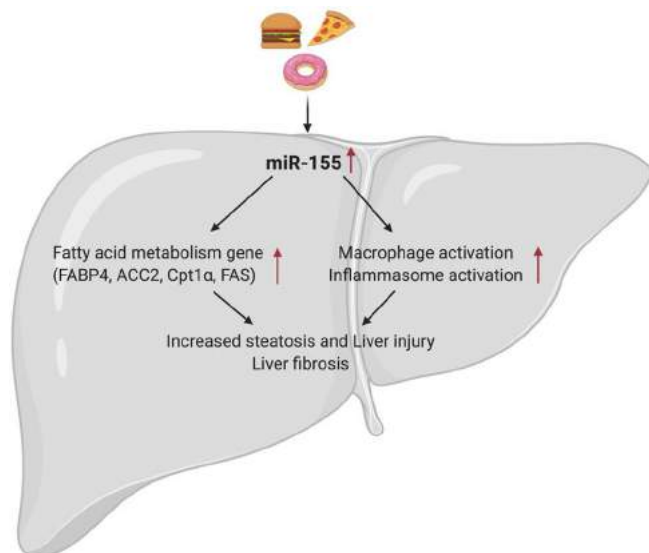


Figure:

Conclusion: Our study indicates that miR-155 KO mice display attenuated liver damage, steatosis, NLRP3 inflammasome complex upregulation and fibrosis compared to WT mice after 34 weeks of HF-HC-HSD feeding suggesting that miR-155 plays a role in steatosis, inflammation and fibrosis in NASH.

PO-1626

Rilpivirine-induced anti-inflammatory effects in non-alcoholic fatty liver disease involve the inhibition of CCL2/CCR2 axis

Ángela B. Moragrega^{1,2}, Aleksandra Gruevska^{1,2}, Isabel Fuster-Martínez^{1,2}, Ana Benedicto^{1,2}, Federico Lucantoni^{1,2}, Juan V. Esplugues^{1,2,3}, Nadezda Apostolova^{1,2,3}, Ana Blas-García^{2,3,4}.
¹Universitat de València, Farmacologia, Valencia, Spain; ²FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana), Valencia, Spain; ³CIBERehd (Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas), Valencia, Spain; ⁴Universitat de València, Fisiología, Valencia, Spain
 Email: angela.moragrega@uv.es

Background and aims: Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease worldwide. Both liver resident macrophages and monocyte-derived macrophages (MDMs) are key regulators of inflammation and hepatic injury. Recruitment of monocytes into the liver is mainly regulated by the chemokine receptor CCR2 and its ligand CCL2, which is synthesized and released by Kupffer cells (KC), hepatic stellate cells (HSC), liver sinusoidal endothelial cells (LSEC) and hepatocytes. In addition, evidence supports a central role of NLRP3-mediated pathways in the development of hepatic inflammation and fibrosis. As our group has previously described that treatment with RPV induces clear anti-inflammatory and anti-fibrotic effects in murine models of chronic liver diseases, the aim of this study is to determine the molecular mechanisms by which RPV exerts its anti-inflammatory properties.

Method: *In vivo*, a nutritional model of NAFLD in C57BL/6 mice (12 weeks) was used; RPV was daily administered at clinical doses. *In vitro*, MDMs obtained from human peripheral blood mononuclear cells isolated from healthy donors, LX-2 (as HSC model) and human umbilical vein endothelial cells (HUVEC) were treated with RPV for 48 h. The molecular routes involved were studied using transcriptomic analysis, immunohistochemistry and standard molecular biology techniques (RT-PCR, Western Blot and ELISA).

Results: Transcriptomic analysis performed with liver samples from NAFLD mice showed RPV down-regulated biological processes associated with the inflammatory response and leukocyte chemotaxis and migration. In-depth study of these functions revealed a decrease in *Adgre1* and *Ccr2* expression and in the number of CCR2+ cells in the periportal areas of RPV-treated NAFLD mice. This RPV-induced effect on the CCL2/CCR2 axis was confirmed *in vitro* by a decrease of CCL2 expression in HUVEC, and a significant reduction of the synthesis and release of CCL2 by MDMs and LX-2. In addition, RPV inhibited the NLRP3 inflammasome pathway *in vivo* and *in vitro* (MDMs and LX-2), decreasing NLRP3 protein expression, Caspase-1 activation and *IL-1 β* gene expression.

Conclusion: Beyond its well-described role in antiretroviral therapy, RPV has a clear anti-inflammatory effect which involves the inhibition of CCL2/CCR2 axis. Although further studies are needed to clarify the mechanisms involved, this effect could be of great relevance in the treatment of chronic liver diseases.

PO-1727

Combination therapy of lanifibranor and firsocostat further improves steatohepatitis and fibrosis compared to monotherapy in a diet-induced murine model of NASH

Guillaume Wettstein¹, Francois Briand², Thierry Sulpice², Jean-Louis Junien¹, Pierre Broqua¹. ¹Inventiva, Daix, France; ²Physiogenex, Escalquens, France
 Email: guillaume.wettstein@inventivapharma.com

Background and aims: lanifibranor, a panPPAR agonist with moderate and well-balanced activity on the three PPAR isoforms (α , δ and γ) showed clinical efficacy on both resolution of NASH and fibrosis improvement in NASH patients. Firsocostat, an ACC1/2 inhibitor, reduced liver fat and markers of fibrosis in patients with advanced fibrosis due to NASH. ACC inhibitors inhibit de novo lipogenesis and reactivate beta oxidation, whilst PPARs stimulate lipid catabolism and redirect hepatic lipids to adipocytes. The potential complementary mode of action of both compounds provides a rationale to investigate whether their combination has additive effects in a nonclinical model of NASH and fibrosis.

Method: Mice were fed a 60% high fat/1.25% cholesterol/0.5% cholic acid diet with 2% 2-hydroxypropyl beta-cyclodextrin in drinking water for 3 weeks. After 1 week of diet, mice were randomized according to their ALT, AST plasma levels and body weight and were orally treated (QD) for 2 weeks either with vehicle, lanifibranor (10 mg/kg), firsocostat (15 mg/kg) or the combination lanifibranor

POSTER PRESENTATIONS

Table: (abstract: PO-1727)

	Vehicle Mean (SD)	Lanifibranor 10 mg/kg		Firsocostat 15 mg/kg		Combination lanifibranor/ firsocostat
		Mean (SD)	Stats	Mean (SD)	Stats	Mean (SD)
FA (nmol/mg liver)	41.6 (7.7)	45.4 (12.3)	andandandand	35.1 (6.3)	and	22.5 (5.1)
TG (µg/mg liver)	80.9 (12.7)	74.8 (12.0)	andandandand	69.4 (13.7)	andandandand	41.9 (5.7)
TC (µg/mg liver)	62.0 (12.0)	51.0 (5.7)	andand	56.5 (2.9)	andandandand	35.5 (5.5)
total score (steatosis + inflammation + fibrosis)	6.9 (0.3)	4.7 (0.7)	andandandand	5.1 (0.3)	andandandand	2.9 (0.7)

and vs combination lanifibranor/firsocostat (and $p < 0.05$; andand $p < 0.01$; andandand $p < 0.001$; andandandand $p < 0.0001$).

and firsocostat. Biochemistry, liver histology and gene expression were analyzed.

Results: Combination treatment of a suboptimal dose of lanifibranor with firsocostat showed a stronger decrease in hepatic free fatty acid (FA), total cholesterol (TC) and triglycerides (TG) and further improved histological parameters such as Steatosis, inflammation and fibrosis as well as the global NASH/fibrosis scores compared to each single treatments (Table 1).

Conclusion: Lanifibranor and firsocostat combination reach greater efficacy than monotherapy at the selected doses for each parameters evaluated. These data emphasize the complementary effect of these two compounds on lipids metabolic leading to further improvement of NASH and fibrosis. These data support the clinical investigation of a combination of lanifibranor and firsocostat in NASH patients.

PO-1753

Implication of the Patatin-like phospholipase domain-containing 3 I148M mutation on hepatic stellate cells mitochondrial dysfunction and profibrogenic potential

Elisabetta Caon¹, Maria Martins¹, Ana Levi¹, Dong Xia², Leo Ghemtio³, Kessarar Thanapirom¹, Walid Al-Akkad Abu Zeina¹, Jan-Willem Taanman⁴, Michele Vacca^{5,6}, Giuseppe Mazza¹, Massimo Pinzani¹, Krista Rombouts¹. ¹University College of London, Royal Free Campus, Regenerative Medicine and Fibrosis Group, Institute for Liver and Digestive Health, London, United Kingdom; ²University College of London, Royal veterinary College, Comparative Biomedical Sciences, London, United Kingdom; ³University of Helsinki, Faculty of Pharmacy, Division of Pharmaceutical Biosciences, Drug Research Program, Helsinki, Finland; ⁴University College of London, Queen Square Institute of Neurology, Department of Clinical and Movement Neurosciences, London, United Kingdom; ⁵University of Cambridge, Metabolic Research Laboratories, Institute of Metabolic Science, Cambridge, United Kingdom; ⁶University of Bari "Aldo Moro", Clinica Medica "Frugoni", Interdisciplinary Department of Medicine, Bari, Italy Email: elisabetta.caon@gmail.com

Background and aims: The I148M variant of the Patatin-like phospholipase domain-containing 3 (PNPLA3) protein is a well validated risk locus for the hHSC-driven fibrogenic progression of chronic liver diseases, particularly in NAFLD. Mitochondrial dysfunction has also been associated with NAFLD development. In this study we investigated the impact of PNPLA3 I148M mutation on mitochondrial dysfunction in hHSCs in 2D and 3D culture models.

Method: Primary hHSC were isolated (n = 23 donors) and cultured in 2D, then genotyped for PNPLA3 (I148M) variants CG/GG. RNAseq data was analysed on 3 donors/genotype with Ingenuity pathway analysis (IPA). Cell behaviour of PNPLA3 (WT) hHSC and PNPLA3 (I148M) hHSC was evaluated in 3D decellularized scaffolds from human

healthy and cirrhotic liver. Cells were cultured for 13 days and stimulated 3×48 h with TGFβ1. QRT-PCR, western blot and cytochrome-c-oxidase activity assay was performed.

Results: IPA associated the PNPLA3 (I148M) hHSC variant to the "NRF2 mediated oxidative stress response" and "Oxidative phosphorylation" signalling pathways. A possible derangement of intracellular anti-oxidant response was also suggested by qPCR on 3D cultured hHSC, with a significant decreased expression in VARS2, a mitochondrial enzyme, and GSTT1, a Glutathione-S-Transferase in PNPLA3 (I148M) hHSC compared to PNPLA3 (WT) hHSC with/without TGFβ1 treatment ($p < 0.05$). This was further confirmed by protein expression of VARS2 and cytochrome-c-oxidase subunit MTCO1, which was significantly downregulated in PNPLA3 (I148M) hHSC compared to PNPLA3 (WT) hHSC ($p < 0.05$) and in PNPLA3 (WT/I148M) hHSC when cultured in healthy scaffolds compared to cirrhotic scaffolds ($p < 0.05$). The lower expression of MTCO1 protein also determined a significant reduction in enzymatic activity of the cytochrome-c-oxidase in PNPLA3 (I148M) hHSC compared to PNPLA3 (WT) hHSC when measured in 2D and healthy scaffolds ($p < 0.005$ and $p < 0.05$).

Conclusion: In this study, following IPA analysis on the genetic background of hHSC carrying different variants of the PNPLA3 I148M mutation, mitochondrial function of hHSC was investigated in a 3D model recapitulating the ECM microenvironment of normal and cirrhotic human liver. Results indicate that the PNPLA3 (I148M) variant is linked to a disrupted expression and activity of different mitochondrial proteins, including a key enzyme of the respiratory chain. This leads to a dysfunctional hHSC mitochondrial phenotype which is worsened by the fibrotic ECM.

PO-1797

Effect of seladelpar and CB-0406 combination therapy on obesity, liver fibrosis and steatosis in a diet-induced obese (DIO) mouse model of biopsy-confirmed non-alcoholic steatohepatitis (NASH) with fibrosis

Yun-Jung Choi¹, Jeffrey Stebbins¹, Ed Cable¹, Jianga Song¹, Jeff Johnson¹, Charles McWherter¹. ¹CymaBay Therapeutics, Newark, United States Email: ychoi@cymabay.com

Background and aims: The rising prevalence of NASH, for which there are no approved therapies, has fueled a search for combinations of drugs to address its multifactorial nature. Seladelpar, a potent transcription factor PPAR delta agonist, regulates pathways involved in metabolism, inflammation, and fibrosis. Our aim is to evaluate the combination of seladelpar with CB-0406, a non-agonist ligand of PPAR gamma with anti-inflammatory activity, in a DIO mouse model of NASH.

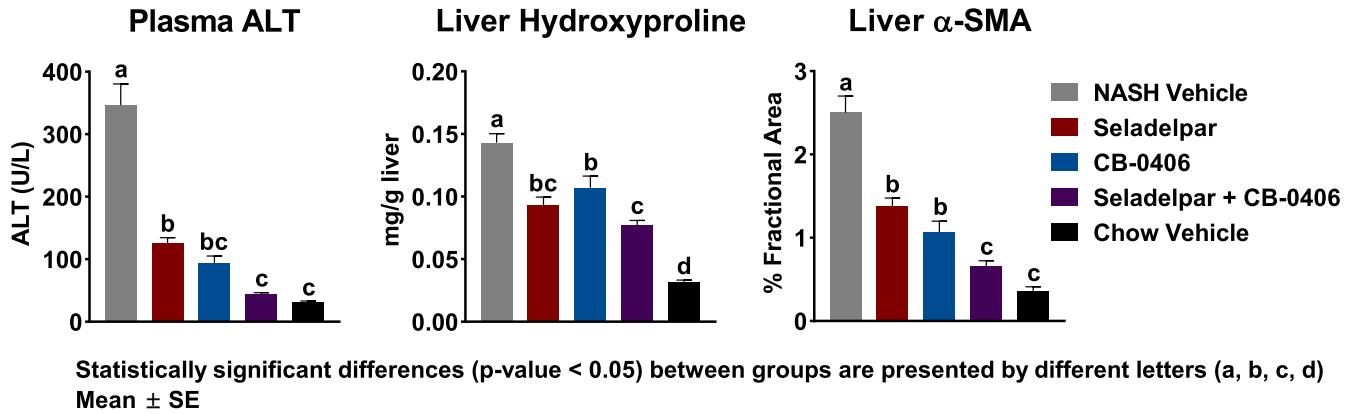


Figure: (abstract: PO-1797)

Method: NASH with advanced fibrosis was induced in male C57BL/6J mice by feeding a diet high in fat, fructose, and cholesterol for 56 weeks. Mice with biopsy-confirmed steatosis and fibrosis were randomized to receive daily vehicle, seladelpar (10 mg/kg), CB-0406 (100 mg/kg) alone or in combination for the last 12 weeks. Body composition, blood and liver biochemistry and histological parameters were assessed.

Results: Seladelpar and CB-0406 each resulted in significant decreases in body weight compared to vehicle. The combination led to greater weight loss than the monotherapies: -19% (combination), -11% (seladelpar), -3% (CB-0406), and +6% (vehicle). Weight loss in the seladelpar groups was associated with decreased fat mass without changes in food consumption or lean mass. Elevated liver enzymes (ALT/AST) were dramatically improved (all $p < 0.0001$) in the combination (-84%/-71%) followed by CB-0406 (-65%/-54%), seladelpar (-51%/-41%) vs. vehicle (+23%/+22%). A ≥ 2 -point improvement in the NAFLD Activity Score (NAS) was seen in 81%, 30%, 93% and 6% of mice for the seladelpar, CB-0406, combination and vehicle groups, respectively. Only the combination group (43%) showed a 4-point reduction in NAS. A >1 -point reduction in steatosis score was seen in 81% and 93% of mice for the seladelpar and combination groups, but in only 6% and 30% for the vehicle and CB-0406 groups. Significant reductions in liver fibrosis measured by hydroxyproline content were observed with seladelpar, its combination group ($p < 0.0001$) or CB-0406 ($p = 0.0003$) compared to the vehicle group. Morphometric measures of picro sirius red, collagen 1a1, α -SMA and galectin-3 staining demonstrated that the combination was more efficacious in reversing fibrosis than either monotherapy.

Conclusion: The combination of seladelpar and CB-0406 in a mouse model of NASH led to substantially greater reductions in fibrosis and NASH than either monotherapy. This combination may offer a novel treatment option for patients with NASH.

PO-1839

The Association of Dietary Factors and Physical Activity with Sarcopenia in Non-Alcoholic Fatty Liver Disease (NAFLD)

James Paik^{1,2}, Khalid W. Kabbara¹, Katherine Eberly¹, Michael Harring¹, Janus Ong³, Zobair Younossi^{1,2,4}. ¹Inova Health System, Department of Medicine, Center for Liver Disease, Falls Church, United States; ²Inova Health System, Beatty Obesity and Liver Research Program, Falls Church, United States; ³Univeristy of the Phillipines, College of Medicine, Manila, Philippines; ⁴Inova Health System, Medicine Service Line, Falls Church, United States
 Email: zobair.younossi@inova.org

Background and aims: The modern diet and physical inactivity have contributed to the epidemic of obesity, NAFLD and sarcopenia. We aimed to determine the association of dietary habits and physical activity with an increased risk of sarcopenia among adults with NAFLD.

Method: Self-reported diet and physical activity data and imputed dual-energy x-ray absorptiometry data for adults (aged 20-75 years) were obtained from the National Health and Nutrition Examination Surveys (NHANES 1999-2004). NAFLD was determined by US Fatty Liver Index (US-FLI) in the absence of other liver disease. Sarcopenia was defined using appendicular lean mass divided by BMI as defined the FNIIH criteria. Ideal diet level was defined as Healthy Eating Index (HEI) score ≥ 69.3 ; intermediate diet score of 56.9-69.3 and poor diet score < 56.9 . Physical activity (PA) level was determined as inactive (sedentary), intermediate, ideal (based on CDC definition of 150 minutes of moderate activity/week). Multiple imputation methods on publicly available imputed dual-energy x-ray absorptiometry (DXA) datasets were performed for all data analyses.

Results: Of 4, 435 adult NHANES participants [mean age 44.1 years; 48.6% male; 71.2% white, 10.6% black and 13.7% Hispanic], NAFLD prevalence was 29.6%; 15.7% of those with NAFLD had sarcopenia; only 6.3% met ideal diet with 18.4% reaching ideal PA. Among those without NAFLD (N = 2, 991), 4.9% had sarcopenia; 7.7% met ideal diet and 29.0% reached ideal PA (All $P < 0.05$). Compared to NAFLD without sarcopenia, NAFLD sarcopenia patients were older, female, Hispanic, obese (77.6% vs. 60.1%), hypertensive (74.7% vs. 65.3%) and diabetic (28.7% vs. 18.2%) (All $P < 0.05$) with significantly lower rates of ideal diet (2.4% vs. 7.0%) and lower ideal PA (22.7% vs. 39.1%) (All $P < .001$). After adjusting for all confounders (obesity, hypertension, hyperlipidemia, diabetes, and advanced fibrosis), NAFLD subjects with ideal diet and PA were less likely to have sarcopenia (Odds Ratio [OR] = 0.27 [95% confidence interval: 0.09-0.79] and 0.46 [0.30-0.72], respectively). These findings were not observed among adults without NAFLD. Finally, sarcopenia was independently associated with increased mortality among both with NAFLD (Hazard Ratio [HR] = 2.03 [1.28-3.22]) and non-NAFLD (HR = 1.53 [1.01-2.32]) subjects.

Conclusion: Poor diet and physical activity are associated with sarcopenia in NAFLD. Sarcopenia is an important predictor of mortality.

PO-1849

A3907, a novel orally available inhibitor of the apical sodium-dependent bile acid transporter, improves key clinical markers of non-alcoholic steatohepatitis in obese diet-induced and biopsy-confirmed mouse models

Peter Akerblad¹, Erik Lindström¹, Jan Mattsson¹, Patrick Horn¹, Pål Lundin¹, Sara Straniero², Bo Angelin², Kirstine Tølbøl³, Sanne Veidal³, Michael Feigh³, Arun Sanyal⁴. ¹Albireo Pharma, Inc.; ²Karolinska Institutet at Karolinska University Hospital Huddinge; ³Gubra Aps; ⁴Virginia Commonwealth University
 Email: peter.akerblad@albireopharma.com

Background and aims: Bile acids (BAs) are signalling molecules involved in lipid, glucose, and energy homeostasis; elevated BA levels are associated with non-alcoholic steatohepatitis (NASH). BA

POSTER PRESENTATIONS

transporter inhibition is a potential therapeutic option for treatment of NASH. To explore effects in NASH of systemic inhibition of apical sodium-dependent bile acid transporter (ASBT), we developed A3907, a potent ASBT inhibitor with high oral bioavailability. A3907 has potential to inhibit bile acid reuptake in the ileum, bile ducts, and kidney and increase BA elimination by faecal and urinary routes. Effects of A3907 were investigated in 2 obese diet-induced mouse models of NASH.

Method: Leptin-deficient *ob/ob* mice and diet-induced obese (DIO)-NASH mice were pre-fed GAN (Gubra-Amylin NASH) diet. Before treatment, animals underwent liver biopsy for histological confirmation of liver pathology (steatosis score ≥ 2 ; fibrosis stage ≥ 1 [*ob/ob*-NASH] or ≥ 2 [DIO-NASH]). A3907 or vehicle was given by oral gavage once daily for 10–16 weeks.

Results: In *ob/ob*-NASH mice, A3907 treatment (3–45 mg/kg) significantly reduced plasma transaminases, total cholesterol, and liver weight after 10 weeks vs vehicle. After 16 weeks in DIO-NASH mice, A3907 10–30 mg/kg significantly reduced plasma transaminases, total cholesterol, total BAs, and liver weight. Terminal histological assessment in both mouse models revealed that liver steatosis and percentage of hepatocytes with lipid droplets were reduced with A3907 vs vehicle. Markers of liver inflammation (eg, galectin-3) and number of inflammatory foci were also significantly reduced with A3907. Notably, A3907 significantly improved Non-alcoholic Fatty Liver Disease (NAFLD) Activity Score by ≥ 2 points vs vehicle in $>50\%$ of *ob/ob*-NASH mice at 30 mg/kg and $>60\%$ of DIO-NASH mice at 10 mg/kg. A3907 10, 30, and 45 mg/kg also significantly prevented fibrosis stage progression vs vehicle in $>50\%$ of *ob/ob*-NASH mice. In DIO-NASH mice, A3907 10 and 30 mg/kg significantly reduced liver fibrosis determined by histological staining vs vehicle. A3907 also reduced liver collagen 1a1 and alpha-smooth muscle actin levels in both models.

Conclusion: In *ob/ob*-NASH and DIO-NASH mice, A3907 treatment improved key plasma and liver histological markers of NASH. Importantly, A3907 improved NALFD Activity Score and demonstrated no worsening in fibrosis stage. These findings introduce A3907 as a novel intervention for treatment of NASH and fibrotic progression.

PO-1897

Men and women display different predictive biomarkers of NASH: a machine learning approach

Gerard Baiges¹, Elisabet Rodríguez-Tomás², Helena Castañe², Anna Hernández-Aguilera³, Salvador Fernández-Arroyo⁴, Jordi Camps³, Jorge Joven^{1,2,3}. ¹Institut d'Investigació Sanitària Pere Virgili, Reus, Spain; ²Rovira i Virgili University, Medicine and Surgery, Tarragona, Spain; ³Hospital Universitari Sant Joan de Reus, Reus, Spain; ⁴EURECAT, Centre for Omics Science, Reus, Spain
Email: gerardbaiges93@gmail.com

Background and aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a progressive disease, and it is considered one of the most important causes of liver transplantation. Unfortunately, there is currently no treatment or disease-modifying therapy, despite hundreds of studies being conducted. Predicting which patients with hepatic steatosis will suffer a progression to steatohepatitis (NASH) is difficult. However, there are a great needed of discerning those at highest risk of progressive liver disease to manage properly. In the big data era, using learning algorithms can help us to discover a biomarker with the capacity to discern each stage of the disease specific to sex. This approach is a way to identify the best sets of metabolites that are predictive of disease and are less invasive than hepatic biopsies.

Method: Fifty-nine women and forty-three men with morbid obesity candidates to bariatric surgery were classified into the non-NASH group (38 in women and 18 in men) and NASH group (21 in women and 25 in men). Biological samples such as plasma, liver, visceral (omental) and subcutaneous (abdominal) were used to perform a multi-omics (energy metabolism, one-carbon, lipidomics) analysis to build a predictive model, using machine learning algorithms, with the capacity to discern each stage of the disease.

Results: We found that our predictive model identifies a different set of metabolites depending on the sex. Concretely, the hepatic oxaloacetate and the visceral pentadecenoyl-carnitine were identified as the most important variable to predict NASH in women. By contrast, the hepatic DG 34:1, and pyruvate, alpha-ketoglutarate blood circulation was the main predictor of NASH in men.

Conclusion: The use of learning algorithms is a useful tool to work toward personalized medicine and help us to identify new ways of treatment and biomarker detection specific to sex and in the metabolic context we want.

PO-1916

Co-stimulatory signals mediated by ICOS/ICOS-L dyad influence the differentiation of liver NASH-associated macrophages (NAMs)

Naresh Naik Ramavath¹, Laila lavanya Gadipudi¹, Alessia Provera¹, Luca Casimiro Gigliotti¹, Elena Boggio¹, Nausicaa Clemente¹, Umberto Dianzani¹, Emanuele Albano¹, Salvatore Sutti¹. ¹University Of East Piedmont, Health Sciences, Novara, Italy
Email: lailalavanya1993@gmail.com

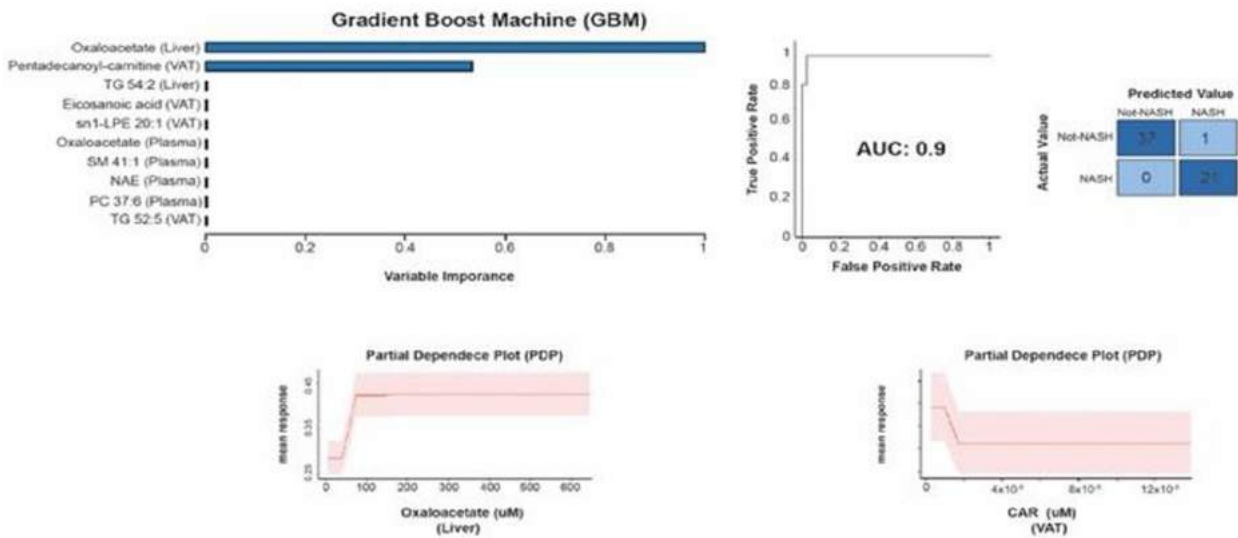
Background and aims: The Inducible T-cell Co-Stimulator (ICOS) present on T lymphocytes and its ligand ICOSL (B7 h) expressed on myeloid cells are member of the B7/CD28 family and play multiple roles in immunity by regulating T-cell activation/survival and antibodies production. Recent evidence indicates that reverse signalling involving ICOSL is also important in directing the differentiation of monocyte-derived cells. In this study, we have investigated the possible involvement of ICOS-ICOSL dyad in modulating macrophages functions during the evolution of non-alcoholic steatohepatitis (NASH).

Method: ICOS and ICOSL were investigated in experimental models of NASH based on mice feeding with choline/methionine deficient (MCD) or a cholesterol-enriched Western diets.

Results: In animal models of NASH, ICOS was selectively up-regulated on CD8+ T cells in parallel with an expansion of ICOSL-expressing CD11b+/F4-80+ monocytes/macrophages (MoMFs). Mice deficient for ICOSL receiving the MCD diet for 6 weeks had milder steatohepatitis. This effect was confirmed in mice fed with the Western diet for 24 weeks that also showed the lack of ICOSL greatly reduced the development of liver fibrosis. Recent studies have shown that NASH associated MoMFs display a specific phenotype characterized by the expression of the Triggering Receptor Expressed on Myeloid cells 2 (TREM2) and by the production of pro-fibrogenic mediators such as osteopontin (OPN) and galectin-3 (Gal-3). Liver TREM2, OPN and Gal-3 were strongly up-regulated in mice with NASH and the lack of ICOSL significantly reduced them without influencing liver MoMFs prevalence. Moreover, immunohistochemistry for OPN and Gal-3 confirmed the presence in NASH livers of diffuse crown-like macrophage aggregates positive for OPN and Gal-3 that were markedly reduced in ICOSL-/- mice.

Conclusion: Altogether these data indicate that ICOS present on CD8+ T cells provides critical signals to ICOSL-expressing liver MoMFs that allow them to maintain a pro-inflammatory and pro-fibrogenic phenotype that characterizes NASH-associated macrophages (NAMs) and suggest ICOS/ICOSL dyad as a possible target for therapeutic interventions.

Women



Men

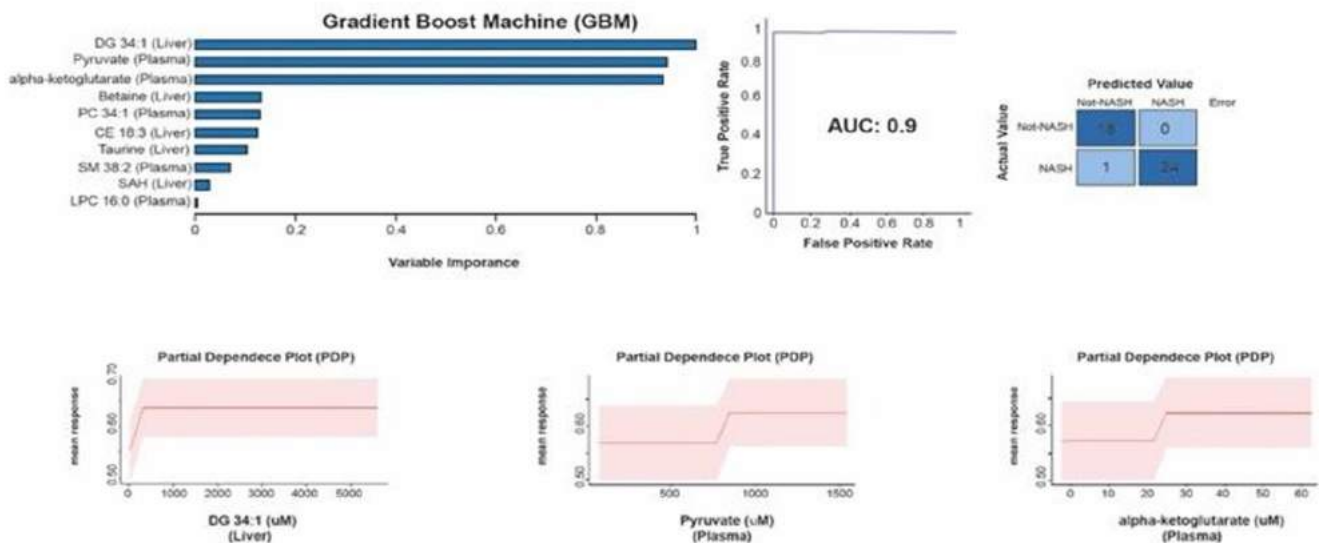


Figure: (abstract: PO-1897)

PO-1942

Blockade of IL-1 signaling in hepatocytes reduces tumor growth in a mouse model of NAFLD-related HCC

Nadine Gehrke¹, Beate Straub², Marcus-Alexander Wörns¹, Peter Galle¹, Jörn Schattenberg¹. ¹University Medical Center of the Johannes Gutenberg University Mainz, I. Department of Medicine, Mainz, Germany; ²University Medical Center of the Johannes Gutenberg University Mainz, Institute of Pathology, Mainz, Germany
Email: nadine.gehrke@unimedizin-mainz.de

Background and aims: Non-alcoholic fatty liver disease (NAFLD), especially its progressive form non-alcoholic steatohepatitis (NASH), represents an increasingly important cause of hepatocellular carcinoma (HCC); however, little is known about the molecular drivers involved. Given pathophysiological roles of IL-1 in inflammation and metabolism, we used hepatocyte-specific IL-1 receptor type 1 (IL-

1R1) knockout (*Il1r1*^{Hep-/-}) mice to examine the contribution of this pathway in NAFLD-associated hepatocarcinogenesis.

Method: Diethylnitrosamine (DEN, 25 mg/kg body weight) was given i.p. to 2-week-old, male *Il1r1*^{Hep-/-} mice and wild-type (WT) littermates. From 6 weeks of age the mice were fed either a high-fat, high-carbohydrate diet (HFD) or a control diet (n = 7–13/genotype and diet) until sacrifice at 24 weeks of age.

Results: All DEN-injected mice fed the HFD developed significant obesity, hyperlipidemia, and hyperglycemia; however *Il1r1*^{Hep-/-} mice were less susceptible to elevations of fasting glucose (378.2 vs. 444.3 mg/dl, p = 0.08) and HOMA-IR levels (31.4 vs. 49.7). Regarding liver pathology, IL-1R1 deficiency had no major impact on HFD-induced hepatomegaly, increase in serum transaminase activity and histologically confirmed macrovesicular steatosis. Macroscopic liver tumors arose with an incidence of 100% in both genotypes in response to DEN/HFD and an average of 15.1 vs. 18.1 nodules in

POSTER PRESENTATIONS

Il1r1^{Hep-/-} vs. WT livers. Remarkably, the average tumor size was 2.5-fold reduced in *Il1r1*^{Hep-/-} mice. Also histopathological examination of the left lateral liver lobe revealed a 2.7-fold reduction in dysplastic foci >1 mm in transgenic compared to WT mice ($p = 0.08$). In both genotypes, DEN/HFD induced an increase in intrahepatic F4/80⁺ macrophages, Ly6C⁺ monocytes and NK cells and a concomitant decline in the proportion of CD4⁺ and CD4⁺CD25⁺ T cells, irrespective of IL-1R1. By contrast, only WT mice presented a significantly elevated percentage of CD8⁺ T cells. Likewise, DEN/HFD led to increased levels of various pro-inflammatory and chemotactic cytokines, but upregulation of IL-1 α , TNF- α and TGF- β was significantly higher in *Il1r1*^{Hep-/-} vs. WT livers, whereas NF- κ B p65 activity was diminished ($p = 0.08$).

Conclusion: There is early evidence from this mouse model of NAFLD-driven HCC, that inhibition of the IL-1R1 pathway in hepatocytes leads to reduced tumor growth. It remains to be determined whether improved insulin sensitivity and/or inflammatory processes in *Il1r1*^{Hep-/-} mice are critical for reduced tumor burden.

PO-1986

The rs599839 A>G variant disentangles cardiovascular risk and hepatocellular carcinoma in NAFLD patients

Marica Meroni¹, Miriam Longo^{1,2}, Erika Paolini^{1,2}, Emilia Rita De Caro¹, Anna Alisi³, Luca Miele⁴, Giuseppina Pisano¹, Marco Maggioni¹, Giorgio Soardo⁵, Luca Valenti¹, Anna Ludovica Fracanzani¹, Paola Dongiovanni¹. ¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, General Medicine and Metabolic Diseases, Milan, Italy; ²Università degli Studi di Milano, Italy, Department of Pharmacological and Biomolecular Sciences, Milan, Italy; ³Bambino Gesù Children Hospital-IRCCS, Rome, Italy, Research Unit of Molecular Genetics of Complex Phenotypes, Italy; ⁴Area Medicina Interna, Gastroenterologia e Oncologia Medica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ⁵7Clinic of Internal Medicine-Liver Unit Department of Medical Area (DAME) University School of Medicine, Udine, Italy and Italian Liver Foundation AREA Science Park-Basovizza Campus, Trieste, Italy Email: paola.dongiovanni@policlinico.mi.it

Background and aims: Dyslipidemia and cardiovascular events are hallmark of non-alcoholic fatty liver disease (NAFLD), which ranges from steatosis to hepatocellular carcinoma (HCC). The rs599839 A>G variant, is localized in the CELSR2-PSRC1-SORT1 genetic cluster, which regulates both lipid handling and microtubule destabilization and spindle assembly during mitotic processes. The rs599839 variant has been previously associated with coronary artery disease (CAD), however its impact on metabolic traits and liver damage in NAFLD patients has not been investigated yet.

Method: We evaluated the effect of the rs599839 variant in 1380 biopsied NAFLD patients (Overall cohort) of whom 121 have HCC (NAFLD-HCC), in 500,000 individuals from the UK Biobank Cohort (UKBCC) and in 366 HCC samples from The Cancer Genome Atlas (TCGA). Hepatic PSRC1, SORT1 and CELSR2 expressions were evaluated by RNAseq in a subset of patients ($n = 125$).

Results: The rs599839 variant was associated with reduced circulating LDL, carotid intima-media thickness, carotid plaques, and hypertension ($p < 0.05$) in NAFLD patients and with protection against dyslipidemia in UKBCC. The G allele was associated with higher risk of HCC ($p < 0.05$) in the Overall cohort. Hepatic PSRC1, SORT1 and CELSR2 expressions were increased in NAFLD patients carrying the rs599839 variant ($p < 0.0001$). SORT1 mRNA levels negatively correlated with those of genes involved in lipoprotein turnover ($p < 0.0001$) and with circulating lipids. Conversely, PSRC1 expression was positively related to that of genes implicated in cell proliferation ($p < 0.0001$). In TCGA, PSRC1 over-expression promoted tumor stage and grade worsening and it correlated with genes involved in cell cycle progression ($p < 0.05$).

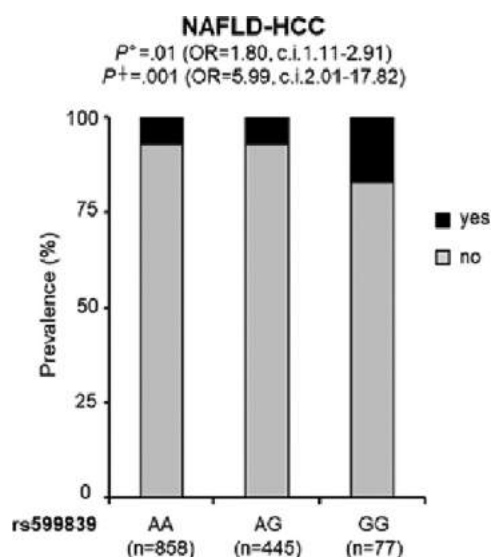


Figure: Association of the rs599839 variant with HCC (1380 NAFLD patients (Overall cohort) of whom 121 have HCC). Multivariable nominal logistic regression analysis adjusted for age, sex, BMI, T2D, presence of PNPLA3 I148M, TM6SF2 E167K and MBOAT7 T alleles at ° additive or +recessive model. CI: confidence interval.

Conclusion: In sum, the rs599839 A>G variant improves dyslipidemia thus protecting against CAD in NAFLD patients, but as one it might promote HCC development by modulating SORT1 and PSRC1 expressions which impact on lipid metabolism and cell proliferation, respectively.

PO-2033

TM6SF2/PNPLA3/MBOAT7 loss-of-function genetic variants impact on NAFLD development and progression both in patients and in in vitro models

Miriam Longo^{1,2}, Marica Meroni¹, Veronica Erconi¹, Fabrizia Carli³, Chiara Macchi⁴, Francesco Fortunato⁵, Dario Ronchi⁵, Silvia Sabatini³, Erika Paolini^{1,4}, Emilia Rita De Caro¹, Anna Alisi⁶, Luca Miele⁷, Giorgio Soardo⁸, Giacomo Comi^{5,9}, Luca Valenti⁵, Massimiliano Ruscica⁴, Anna Ludovica Fracanzani^{1,5}, Amalia Gastaldelli³, Paola Dongiovanni¹. ¹General Medicine and Metabolic Diseases, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, Milan, Italy; ²Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy, Milan, Italy; ³Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy, Pisa, Italy; ⁴Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy; ⁵Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁶Research Unit of Molecular Genetics of Complex Phenotypes, "Bambino Gesù" Children's Hospital IRCCS, Rome, Italy, Rome, Italy; ⁷Area Medicina Interna, Gastroenterologia e Oncologia Medica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Rome, Italy; ⁸Department of Medical Area (DAME), University of Udine and Italian Liver Foundation, Bldg Q AREA Science Park-Basovizza Campus, Trieste, Italy; ⁹Neuromuscular and Rare Diseases Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy Email: paola.dongiovanni@policlinico.mi.it

Background and aims: The I148M PNPLA3 and E167K TM6SF2 variants alongside the rs641738 polymorphism in MBOAT7/TMC4 locus represent the main genetic predictors of non-alcoholic fatty liver disease (NAFLD). We knocked-out MBOAT7 in HepG2 cells, homozygous for the I148M PNPLA3 (MBOAT7^{-/-}), which developed giant lipid droplets (LDs). We aimed to: 1) investigate the synergic impact of the 3 risk variants on liver disease severity and hepatocellular carcinoma (HCC) in NAFLD patients; 2) generate in

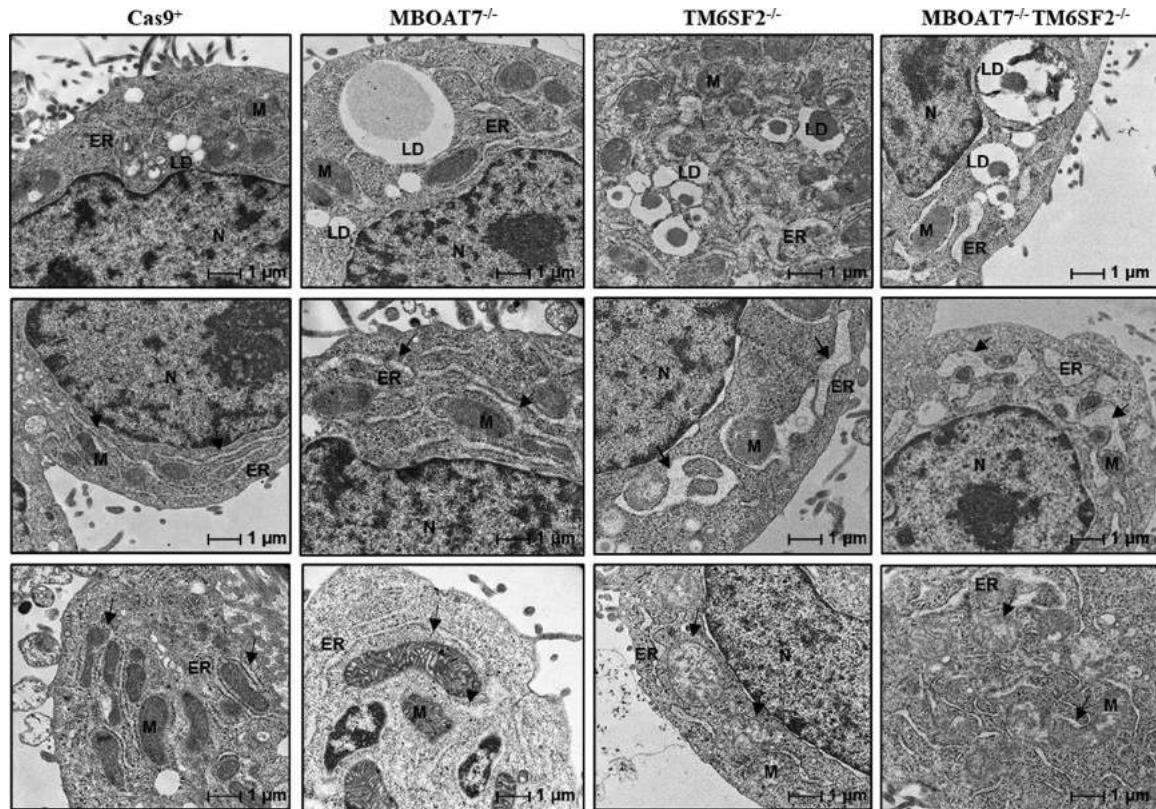


Figure: (abstract: PO-2033): Representative TEM images of LDs, ER tubules, and degenerative mitochondria (black arrows) obtained by ultrathin 70 nm sections of hepatocytes (bar scale: 1 μ m)

in vitro models of NAFLD by silencing *TM6SF2* in both HepG2 (*TM6SF2*^{-/-}) and *MBOAT7*^{-/-} cells (*MBOAT7*^{-/-}*TM6SF2*^{-/-}).

Method: 1380 biopsied NAFLD patients including 121 HCC were stratified by a semi-quantitative score ranging from 0 to 3 according to the number of *PNPLA3*, *TM6SF2* and *MBOAT7* at-risk variants. *TM6SF2* was silenced in HepG2 cells through CRISPR/Cas9. Organelles' morphology was assessed by transmission electron microscopy (TEM). Lipidomics was performed by LCMS-QTOF.

Results: At multivariate analysis adjusted for age, sex, BMI and diabetes, the co-presence of the 3 risk alleles correlated with the histological degree of steatosis ($p < 0.0001$), necroinflammation ($p < 0.0001$), ballooning ($p = 0.004$) and fibrosis ($p < 0.0001$). At nominal logistic regression analysis adjusted as above, patients carrying the 3 variants showed ~2-fold higher risk of fibrosis >2 ($p = 0.0003$), cirrhosis ($p = 0.0007$) and HCC ($p = 0.01$). *TM6SF2* silencing induced micro-vesicular LDs accumulation (median size: 0.87 μ m²) in *TM6SF2*^{-/-} cells, whereas the *MBOAT7*^{-/-}*TM6SF2*^{-/-} developed both micro/macro LDs (median size: 4.60 μ m²). Lipidomic analysis revealed that the amount of saturated/monounsaturated triacylglycerols was increased in cells lacking *TM6SF2* gene, while the polyunsaturated ones were reduced. *TM6SF2* deletion strongly affected endoplasmic reticulum (ER) and mitochondrial architecture and the compound knockout showed the highest levels of ER/oxidative stress and DNA damage ($p < 0.05$). *TM6SF2* deletion increased proliferative rate, more so in *MBOAT7*^{-/-}*TM6SF2*^{-/-} cells ($p < 0.05$), which represent the first model generated *in vitro* which may fully reproduce features of NAFLD individuals bearing all the 3 at-risk variants.

Conclusion: The co-presence of the 3 at-risk mutations impacts on NAFLD spectrum, in humans and experimental models. *TM6SF2* silencing alone or combined with I148M *PNPLA3* and *MBOAT7* deletion affects LDs' distribution and contributes to hepatocellular damage and proliferation.

PO-2055

The I148M *PNPLA3* variant mitigates Niacin beneficial effects: how the genetic screening in Non-alcoholic Fatty Liver Disease (NAFLD) patients gains value

Erika Paolini^{1,2}, Miriam Longo^{1,3}, Marica Meroni¹, Gemma Malaspina¹, Emilia De Caro¹, Annalisa Cespiati¹, Rosa Lombardi¹, Anna Ludovica Fracanzani¹, Paola Dongiovanni¹.

¹General Medicine and Metabolic Diseases, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, Milan, Italy; ²Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy, Milan, Italy; ³Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy, Milan, Italy

Email: paola.dongiovanni@policlinico.mi.it

Background and aims: The *PNPLA3* p.I148M variant is the major genetic predictor of NAFLD and nutrients modulate its impact on fat accumulation. Vitamin B3 (niacin) reduces triglycerides (TGs) synthesis and ROS production in NAFLD patients. However, the interplay between niacin and I148M genotype in the context of NAFLD has not been explored yet. Therefore, this study aims to: 1) assess the dietary and circulating levels of niacin in NAFLD patients stratified according to the presence of the I148M variant; 2) evaluate the beneficial effect of niacin in terms of lipid metabolism and oxidative stress in hepatoma cells (HepG2), carrying the I148M mutation, and in which steatosis was mimicked through palmitic acid (PA) exposure.

Method: We enrolled 172 patients with non-invasively assessed NAFLD. Dietary niacin was collected from a food questionnaire. Niacin serum levels were quantified by ELISA. Hepatic expression of genes related to NAD metabolism was evaluated by RNAseq in biopsied bariatric NAFLD patients (n = 125). HepG2 cells were treated with niacin 0.5 mM and/or PA 0.5 mM.

POSTER PRESENTATIONS

Results: At bivariate analysis NAFLD patients showed reduced dietary niacin ($p=0.01$). The p.I148M variant was correlated with lower levels of alimentary and circulating niacin ($p=0.01$ and $p<0.05$ vs non-carriers, respectively). At multivariate analysis, adjusted for sex, BMI, alimentary niacin and severe steatosis the p.I148M mutation was associated with reduced circulating niacin (beta = -18.01; CI: -35.6–0.57; $p=0.03$), suggesting that it may independently modulate niacin systemic availability. The hepatic expression of NAPRT, the first enzyme of NAD biosynthesis, was decreased in p. I148M carriers ($p=0.006$). In HepG2 cells, treatment with niacin and/or PA increased NADH levels ($p<0.05$), consistently with niacin's role as NAD precursor. Niacin alone or with PA reduced intracellular fat ($p<0.05$), upregulating the lipoproteins' export (MTTP; $p<0.05$ vs control) and the release of HDL rather than LDL was higher after niacin exposure ($p<0.05$). Niacin decreased ROS production even after PA stimulus ($p<0.05$ vs control) and ameliorated cell viability subsequently PA-induced lipotoxicity ($p<0.05$ vs PA).

Conclusion: Niacin levels are reduced in the presence of severe steatosis and more so in patients carrying the I148M variant. In HepG2 cells niacin supplementation reduces hepatic fat accumulation and oxidative stress.

	Estimate (β)	95% C.I.	P-value
Sex, Male	12.46	-7.48-32.41	0.21
BMI (Kg/m ²)	-1.49	-5.64-2.96	0.50
Alimentary Niacin	-0.10	-0.37-0.15	0.42
Steatosis >2	-5.46	-22.68-11.76	0.53
PNPLA3 I48M, yes	-19.74	-37.68-1.80	0.03

At multivariate analysis, adjusted for sex, BMI, alimentary niacin, and severe steatosis the presence of the p.I148M mutation is significantly associated with reduced circulating niacin levels in 172 NAFLD patients (beta = -18.01; CI: -35.6 - 0.57; $p=0.03$), suggesting that it may independently modulate niacin systemic availability.

Figure:

PO-2123

Liver Biopsy Graph Neural Networks for automated histologic scoring using the NASH CRN system

Jason Wang¹, Maryam Pouryahya¹, Kenneth Leidal¹, Harsha Pokkalla¹, Dinkar Juyal¹, Zahil Shanis¹, Aryan Pedawi¹, Quang Le¹,

Victoria Mountain¹, Sara Hoffman¹, Jackie Honerlaw¹, Murray Resnick¹, Michael Montalto¹, Andrew Beck¹, Katy Wack¹, Ilan Wapinski¹, Oscar Carrasco-Zevallos¹, Amaro Taylor-Weiner¹.

¹PathAI, Boston, United States

Email: amaro.taylor@pathai.com

Background and aims: Clinical trials in non-alcoholic steatohepatitis (NASH) require pathologic review of liver biopsies. Manual review is limited by inter- and intra-pathologist variability. While "black box" convolutional neural networks (CNNs) can standardize scoring of NASH histology, their application is limited by interpretability. Here, we describe a novel graph neural network (GNN) approach that combines interpretability with performance for NASH scoring.

Method: Whole-slide images (WSI) of 639 HandE and 633 trichrome NASH liver biopsies from clinical trial participants (EMINENCE, NCT02784444) were scored by 3 pathologists for NAFLD Activity (NAS 0–8) and its 3 components— inflammation (0–3), steatosis (0–3), and ballooning (0–2), and for fibrosis (0–4), respectively, and split into train, validation and test sets. A pathologist network annotated WSIs for tissue regions. Using the annotations on training set images, CNNs were trained to generate pixel-level predictions of 13 HandE and 5 trichrome classes (e.g., hepatocytes, bile duct etc.). WSIs were then converted into directed graphs via pixel-clustering (Birch method) and graph construction (treating each cluster as a node, directed edges were drawn between each node and its 5 nearest nodes). Each node was characterized by spatial and biological features (e.g., cluster size, bile duct pixels, etc.). GNNs were trained to grade biopsies for NAS and its 3 components (HandE), and fibrosis (trichrome). To account for inter-pathologist variability, we implemented a mixed-effects model to learn pathologist-specific biases during training (discarded during testing).

Results: GNN predictions were concordant with median pathologist scores (test set): linearly-weighted Cohen's kappa of 0.613 (NAS), 0.758 (steatosis), 0.584 (inflammation), 0.614 (ballooning), and 0.507 (fibrosis). Learned pathologist biases showed that scoring was consistently biased across tasks (Pathologist 1 scored lower than consensus, mean bias -0.459; Pathologist 3 scored higher, 0.495). In

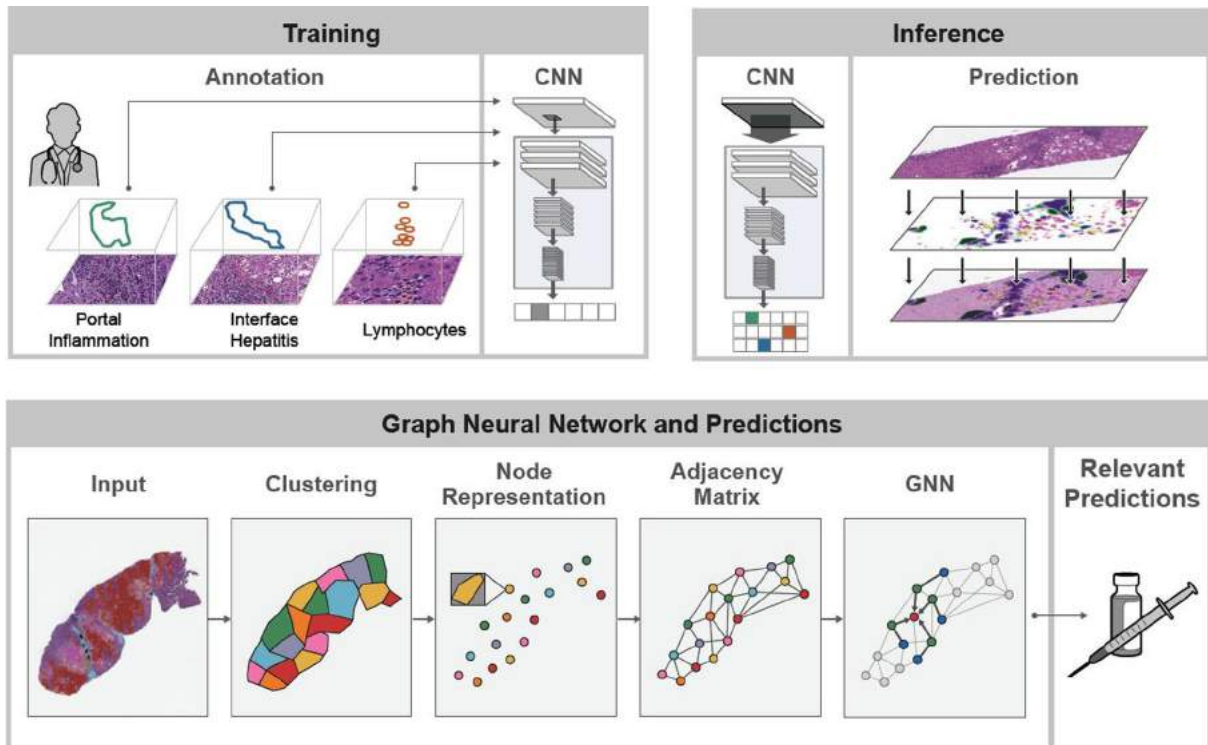


Figure: (abstract: PO-2123)

addition, we observed pathologist task-specific biases (inflammation saw minimal bias, fibrosis was highly biased).

Conclusion: Our approach recapitulates pathologist scorings for NAS, its 3 components, and fibrosis. Performance was comparable to that of published “black-box” models trained on larger datasets, demonstrating data efficiency. Our approach also enabled investigation of systematic biases among pathologists and NASH scoring tasks.

PO-2161

Human hepatocyte PNPLA3-148M exacerbates rapid non-alcoholic fatty liver disease development in chimeric mice

Mohammad Kabbani^{1,2}, Michailidis Eleftherios¹, Sandra Steensels³, Clifton Fulmer¹, Joseph Luna¹, Jérémie Le Pen¹, Matteo Tardelli³, Brandon Razooky¹, Inna Ricardo-Lax¹, Chenhui Zou³, Briana Zeck⁴, Ansgar Stenzel¹, Corrine Quirk¹, Lander Foquet⁵, Alison Ashbrook¹, William M. Schneider¹, Serkan Belkaya¹, Gadi Lalazar³, Yupu Liang¹, Meredith Pittman³, Lindsey Devisscher⁶, Hiroshi Suemizu⁷, Neil Theise⁴, Luis Chiriboga⁴, David Cohen³, Rob Copenhaver⁵, Markus Grompe⁵, Philip Meuleman⁶, Baran Ersoy³, Charles Rice¹, Ype de Jong^{1,3}. ¹The Rockefeller University, New York, United States; ²Hannover Medical School, Hannover, Germany; ³Weill Cornell Medicine, New York, United States; ⁴NYU Langone Health, New York, United States; ⁵Yecuris Corporation, United States; ⁶Ghent University, Gent, Belgium; ⁷Central Institute for Experimental Animals, Kawasaki, Japan

Email: ydj2001@med.cornell.edu

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is a rapidly emerging global health problem associated with metabolic syndrome and predisposing genetic polymorphisms, most strikingly an isoleucine to methionine substitution in patatin-like phospholipase domain-containing protein 3 (PNPLA3-I148M). Despite mechanistic studies in rodent models and cell lines, the role of the 148M variant in human NAFLD progression remains to be further elucidated. Here we established a NAFLD model to study the impact of hypercaloric feeding in liver chimeric mice with PNPLA3-148I or -148M human grafts.

Method: Livers of immunodeficient *Fah*^{-/-} mice (FNRG) were repopulated with primary human hepatocytes (PHH) from PNPLA3-148I or 148M donors. Once high human liver chimerism was achieved, mice were subjected to a Western-Style Diet (WD) consisting of sucrose in drinking water and a high fat (HFD). In addition, both PNPLA3 variants were overexpressed in PHH from a PNPLA3-148I homozygous donor prior to engraftment and chimeric mice were challenged with a WD or HFD.

Results: As early as 4 weeks on WD, humanized mice developed dyslipidemia, impaired glucose tolerance, and steatohepatitis

selectively in the human graft, followed by pericellular fibrosis after 8 weeks of WD feeding. The PNPLA3-148M variant, either from a homozygous 148M PHH donor or overexpressed in a homozygous 148I PHH background, caused microvesicular steatosis, more active steatohepatitis, and Mallory Denk body formation in chimeric livers of mice on hypercaloric diets.

Conclusion: PNPLA3-148I human hepatocytes develop steatosis and steatohepatitis with mild activity in chimeric mice on a hypercaloric diet. The PNPLA3-148M variant in human hepatocytes caused more active steatohepatitis. These models will facilitate mechanistic studies into the role of PNPLA3 in fatty liver disease progression. Human liver chimeric mice will also provide a platform to examine other human risk alleles associated with advanced fatty liver diseases.

PO-2186

Imaging by Desorption electrospray ionization mass spectrometry detects changes in lobular patterns of lipids in non-alcoholic fatty liver disease

Patcharamon Seubnooch¹, Pavitra Kumar¹, Mojgan Masoodi², Marie V. St-Pierre¹, David Bélet¹, Matteo Montani³, Umara Rafiqi³, Emmanuelle Claude⁴, Aurel Perren³, Jean-François Dufour^{1,5}. ¹Hepatology, Department for BioMedical Research, University of Bern, Bern, Switzerland; ²Institute of Clinical Chemistry, Inselspital, Bern University Hospital, Bern, Switzerland; ³Institute of Pathology, University of Bern, Bern, Switzerland; ⁴Waters Corporation, Wilmslow, United States; ⁵University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland

Email: jean-francois.dufour@dbmr.unibe.ch

Background and aims: Hepatic lipid accumulation is the hallmark of non-alcoholic fatty liver disease (NAFLD). The liver lobules display metabolic zonation and therefore lipidomics analysis of liver homogenates fails to provide information on the distribution of metabolites. However, a new mass spectrometry imaging technique called Desorption Electrospray Ionization (DESI-MS) does provide spatial metabolomics information and localization directly from tissue sections. Thus, our aim was to develop spatial lipidomics using DESI-MS to study hepatic lipids changes in NAFLD.

Method: Frozen liver sections from control (n = 5) or NAFLD mice (n = 5) fed a high fat diet (Teklad TD.120528) were analyzed using a DESI-MS (Waters Corporation, USA) in both positive and negative ionization modes over the mass range m/z 100 to 1200. Imaging was performed at 50 μm spatial resolution and 50 μm/s scan rate. The solvent consisted of methanol: water (98:2 v/v). The sensitivity and quality of imaging data were optimized via sprayer tip, geometric parameters of the sprayer source, sprayer parameters (nebulizing gas

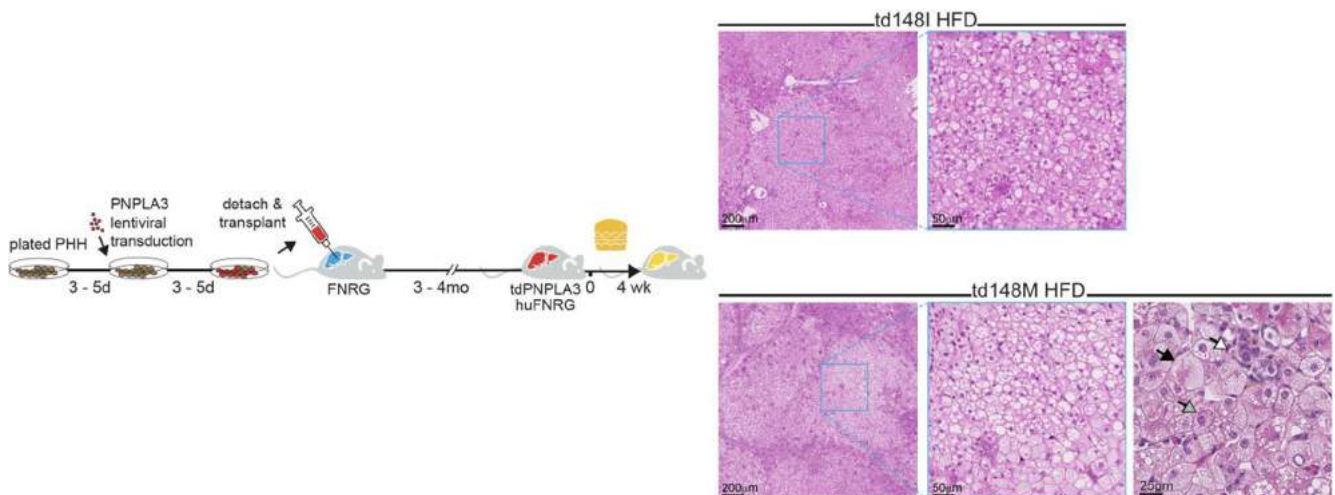


Figure: (abstract: PO-2161)

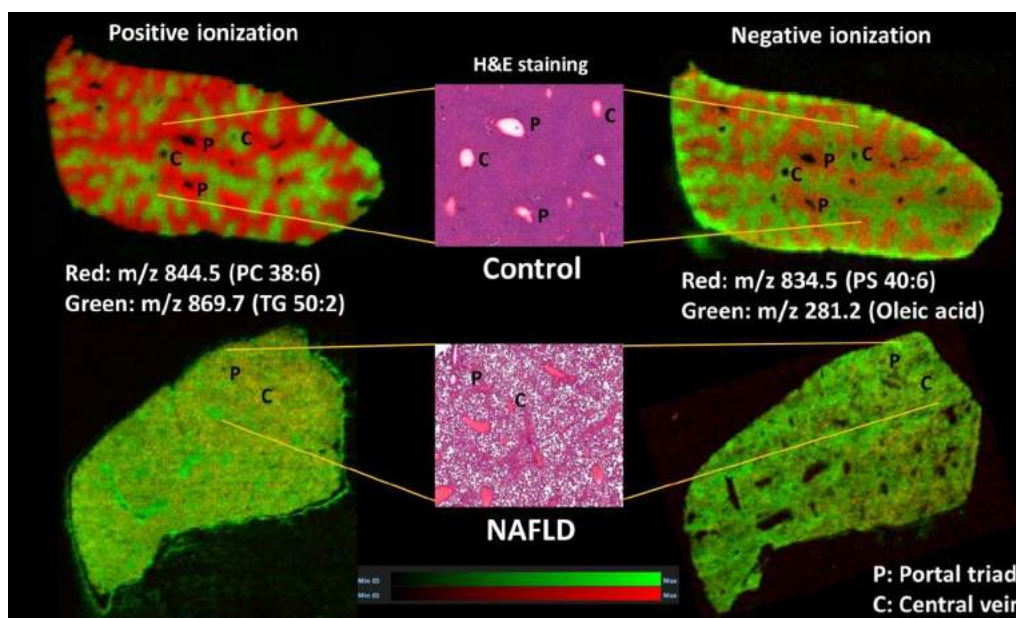


Figure: (abstract: PO-2186): Lipid metabolite distribution across the liver lobule.

and solvent flow rates) and mass spectrometry parameters to obtain the highest intensity.

Results: Oil Red O staining showed grade 3 steatosis in all NAFLD livers. Sirius Red staining showed a 4.5-fold increase in fibrosis in NAFLD ($p < 0.05$). We detected 1,102 metabolites out of which 866 were significantly different between control and NAFLD livers. Triacylglycerols (TGs), diacylglycerols (DGs) and unsaturated fatty acids were higher in NAFLD liver than in control liver by 3.9-fold, 14.0-fold and 2.9-fold ($p < 0.001$), respectively. Controls showed uneven distribution of TGs, DGs, phosphatidylcholines (PCs) and phosphatidylserines (PSs) across the liver lobule. NAFLD livers failed to show these zonation patterns (Figure 1). In particular, PCs were more abundant in the periportal zones than in the pericentral zones of controls, whereas PCs were evenly distributed in NAFLD livers. In fact, PCs were 5-fold ($p < 0.001$) less abundant in NAFLD periportal zones.

Conclusion: DESI-MS allows the determination of the spatial distribution of lipid species across the liver lobule. NAFLD triggers a more uniform lobular distribution of TGs, DGs, PCs and PSs.

PO-2210

A 3D *in vitro* screening-based discovery approach for selecting and prioritizing NASH drug candidates

Simon Ströbel¹, Radina Kostadinova¹, Jana Rupp¹, Katia Fiaschetti¹, Agnieszka Pajak¹, Katarzyna Sanchez¹, Manuela Bieri¹, Armin Wolf¹, Eva Thoma¹. ¹InSphero AG, Schlieren, Switzerland
Email: radina.kostadinova@insphero.com

Background and aims: Non-alcoholic steatohepatitis is a severe progressive disease characterized by lipid accumulation, inflammation and fibrosis in the liver. To date, there are no approved drugs for NASH treatment and drug development has been impeded by the lack of predictive *in vitro* models reflecting the complex pathology of NASH. The aim of the study was to develop a human 3D *in vitro* NASH spheroid microtissue, based on a scaffold-free co-culture of primary hepatocytes, Kupffer cells, liver endothelial cells, and hepatic stellate cells for high-throughput-compatible drug efficacy testing.

Method: Upon exposure to defined lipotoxic and inflammatory stimuli, such as free fatty acids and LPS in media containing high levels of sugar and insulin, our 3D NASH model displayed key disease pathophysiological features within 10 days of treatment. We established methods for assessing characteristic and quantifiable markers for NASH drug efficacy testing, including assays and end

points for measuring triglyceride assays, secretion of pro-inflammatory cytokines/chemokines (Luminex), and secretion of pro-collagen type I/III (HTRF/ELISA).

Results: We observed increases in intracellular triglyceride content as indicator of lipid accumulation and the secretion of inflammatory markers such as IL-6, MIP-1alpha, TNF-alpha, IL-10, MCP-1 and IL-8 in our NASH-induced model as compared to the untreated control. Further, we detected increased fibril collagens deposition and secretion of procollagen type I and III peptides under NASH conditions. Whole transcriptome analysis of NASH-induced microtissue versus control revealed activation of pathways and differential regulation of genes associated with key lipid metabolism, inflammation, and fibrosis induction. Treatment with the anti-NASH TGF-beta antibody and ALK5i (TGFβRI inhibitor) concentration dependently decreased secretion of pro-collagen type I/III. Decreased deposition of fibrosis based on quantification of Sirius-Red-stained tissues (PharmaNest) was observed in the presence of anti-TGF-beta antibody and ALK5i. Importantly, biochemical readouts for 3D models treated with NASH drug candidates (Selonsertib and Firsocostat) were indicative of disease progression and the results generally reflected documented clinical observations.

Conclusion: In summary, using this rapid, high-throughput-compatible 3D NASH model for drug candidate efficacy testing represents a promising approach for selection and decision making of the most effective drug candidates to move further in the development.

PO-2276

Ripk3 depletion improves mitochondrial bioenergetics and function in experimental NAFLD

Tawhidul Islam¹, Marta B. Afonso¹, Ricardo Amorim², Veronique Lenoir³, Vlad Ratziu^{4,5,6}, Paulo J. Oliveira², Rui E. Castro¹, Carina Prip-Buus³, Jérémie Gautheron^{6,7}, Cecília M. P. Rodrigues¹. ¹Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; ²Center for Neuroscience and Cell Biology (CNC), UC Biotech Building, Universidade de Coimbra, Coimbra, Portugal; ³Institut Cochin, Inserm, CNRS UMR8104, Université Paris Descartes, Paris, France; ⁴Assistance Publique-Hôpitaux de Paris (AP-HP), Pitié-Salpêtrière Hospital, Department of Hepatology, Paris, France; ⁵Sorbonne Université, Inserm, Centre de Recherche des Cordeliers (CRC), Paris, France; ⁶Institute of Cardiometabolism and Nutrition

(ICAN), Paris, France; ⁷Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine (CRSA), Paris, France
 Email: cmprodrigues@ff.ul.pt

Background and aims: Metabolic harmony between mitochondrial respiratory chain (MRC) activity and mitochondrial fatty acid oxidation is crucial to curb hepatic fat accumulation and restrain reactive oxygen species (ROS) overabundance. We have recently reported that receptor-interacting protein kinase 3 (RIPK3) acts as a lipid metabolism regulator contributing to liver damage, inflammation, fibrosis and carcinogenesis in non-alcoholic fatty liver disease (NAFLD). Here, we aimed to evaluate the role of RIPK3 in the interaction between lipid metabolism and mitochondria in experimental NAFLD.

Method: Wild-type (WT) and *Ripk3*^{-/-} 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 used for measuring MRC activities and evaluating of mitochondrial function. Mechanistic studies were performed in WT and *Ripk3*^{-/-} murine AML12 hepatocytes incubated with palmitic acid (PA).

Results: The CDAA diet resulted in decreased expression and activities of MRC complexes in WT mice, compared to CSAA-fed WT animals. Strikingly, *Ripk3*^{-/-} mice showed an overall protection against CDAA-induced MCR complex impairment, both at 32 and 66 weeks. Similarly, PGC1 α , NRF1, TFAM, NRF2 and MFN2 were down-regulated in CDAA-fed WT mice, but significantly increased in *Ripk3*^{-/-} animals. *Ripk3*-deficient mice also showed reduced mitochondrial DNA damage and increased SOD1, SOD2 and SIRT3 levels, contrasting the effect of the CDAA-diet. In WT AML12 cells, PA incubation increased cellular and mitochondrial ROS, preceding

altered mitochondrial morphology and membrane potential, and decreased oxygen consumption rates, a phenotype abrogated by *Ripk3* deficiency. Further, lipid droplet size and number were decreased in PA-loaded *Ripk3*^{-/-} AML12 cells, despite similar lipid overload, comparing to WT AML12 cells. Curiously, *Ripk3*^{-/-} cells exposed to PA also showed increased lipid droplet-associated PLIN5 levels, suggesting that RIPK3 signalling mediates the interaction between lipids and mitochondria.

Conclusion: Overall, impaired MRC complex activity and lipid overload correlate with mitochondrial dysfunction, ROS overproduction and altered mitochondrial metabolism in experimental NAFLD. RIPK3 deficiency restores MRC complex activity, increases ROS detoxification capacity, enhances mitochondrial bioenergetics and function, thus halting NAFLD.

Funding: FEDER LISBOA-01-0145-FEDER-029097, FCT PTDC/MED-FAR/29097/2017 and EU H2020 Marie Skłodowska-Curie 722619 grants.

PO-2322

Exposure to environmental contaminants is associated with sex-specific disturbances of hepatic lipid metabolism in non-alcoholic fatty liver disease

Matej Orešič¹, Partho Sen², Sami Quadri³, Panu Luukkonen³, Oddny Ragnarsdóttir¹, Sirkku Jäntti³, Anne Juuti³, Johanna Arola³, Hannele Yki-Järvinen³, Tuulia Hyötyläinen¹. ¹Örebro University, Sweden; ²University of Turku, Turku, Finland; ³University of Helsinki, Helsinki, Finland
 Email: matej.oresic@oru.se

Background and aims: Liver has a vital role in metabolism, distribution, and excretion of exogenous chemicals. The endocrine

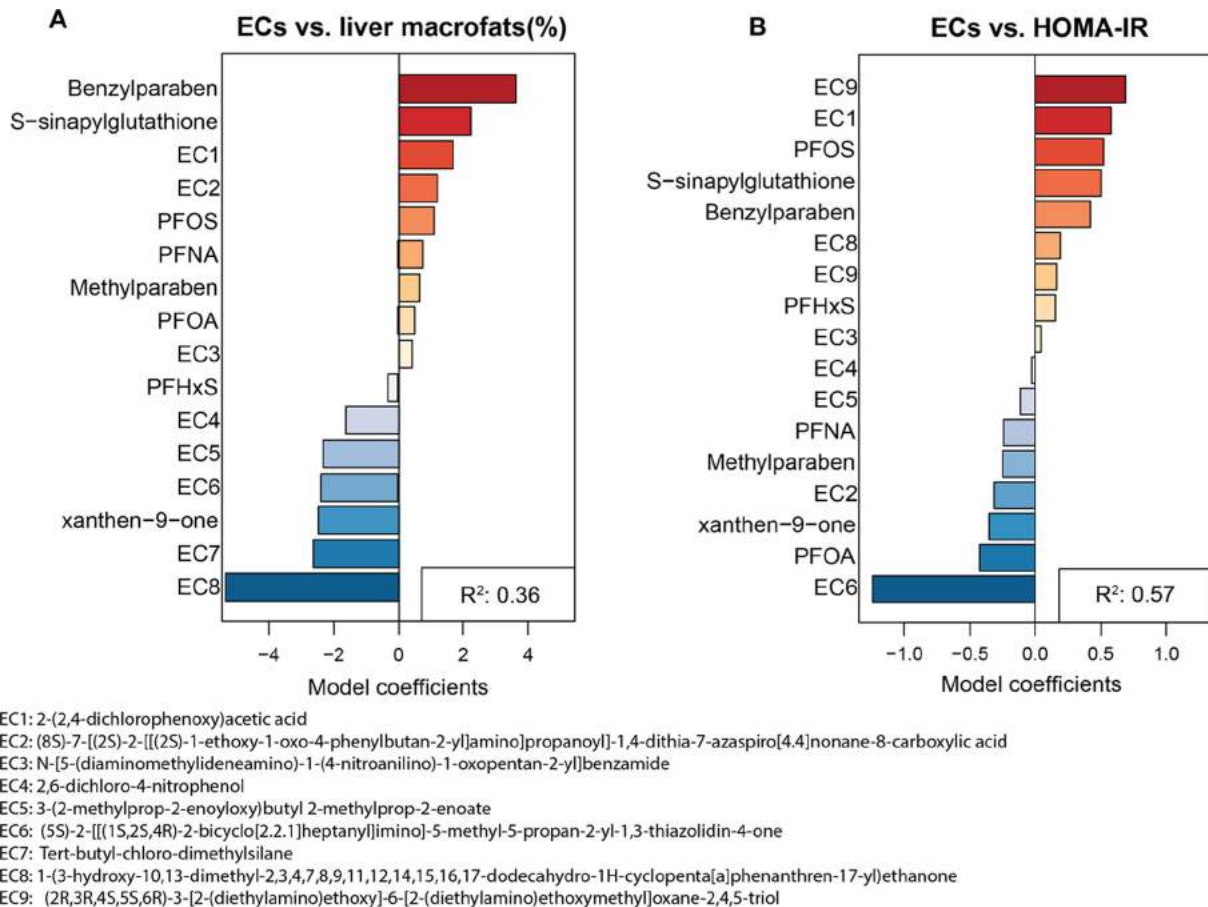


Figure: (abstract: PO-2322): Environmental contaminants (ECs) linked with liver fat % and HOMA-IR. A-B) Horizontal bar plots showing ranks (\pm model coefficients) of different ECs as predictors, using generalized linear regression modeling, adjusted for age and BMI as covariates.

POSTER PRESENTATIONS

disrupting chemicals (EDCs) may act as a 'second hit' in the progression of NAFLD, advancing the earlier stages of liver pathology such as steatosis to more severe stages. A specific class of EDCs that have been linked with NAFLD are perfluorinated alkyl substances (PFAS), a class of commonly used industrial chemicals that humans are widely exposed to. Due to their structural similarity with fatty acids, PFAS may disrupt hepatic lipid metabolism. Furthermore, functionally, PFAS share some features with bile acids, including similar enterohepatic circulation. Nevertheless, human data linking PFAS exposure and lipid metabolism in the liver are currently lacking. The principal aim of our study was to define the impact of PFAS exposure on hepatic metabolism, with specific focus on bile acid and lipid metabolism.

Method: In a well-characterized human NAFLD cohort of 105 individuals, we investigated the impact of PFAS exposure on liver metabolism in the individuals with NAFLD. Average BMI was 45.65 ± 5.99 kg/m², with liver fat content varying between 0% and 80%. We comprehensively characterized both hepatic (liver biopsy) and serum metabolome using four analytical platforms, and measured PFAS in serum. We investigated the association between the NAFLD (liver fat %, NASH grade, fibrosis stage, insulin resistance), PFAS exposure, and metabolome.

Results: PFAS exposure was associated with NAFLD (Figure) as well as with changes in hepatic lipid and bile acid metabolism. Importantly, we observed sex-specific association between chemical exposure and NAFLD, linked with sex-specific changes in both hepatic and circulating metabolome. We noticed differences not only in the exposure profiles between the males and females, but, notably, also the impact of the exposure, as characterized both with the impact on metabolome but also on clinical parameters was clearly different between the males and females.

Conclusion: Our results implicate that females may be more sensitive to the harmful impacts of PFAS. The results also suggest that the changes reported in the lipid metabolism due to PFAS exposure may be secondary to the interplay of PFAS and bile acids.

PO-2411

Hepatocyte-specific deletion of ERK5 worsens insulin resistance in a murine model of non-alcoholic fatty liver disease

Giovanni Di Maira¹, Giulia Lori¹, Benedetta Piombanti¹, Maria Letizia Taddei¹, Alessio Menconi¹, Paola Chiarugi¹, Cathy Tournier², Elisabetta Rovida¹, Fabio Marra¹. ¹University of Florence; ²University of Manchester
Email: giovanni.dimaira@unifi.it

Background and aims: The extracellular signal-regulated kinase 5 (ERK5) is a member of the mitogen-activated protein kinase family highly expressed in hepatocytes, macrophages and stellate cells. We recently generated hepatocyte-specific ERK5 knock-out mice (ERK5DHep). The aim of this study was to investigate the role of hepatocyte ERK5 in a murine model of NAFLD.

Method: ERK5DHep and control mice were fed with a high-fat diet (HFD) for 16 weeks. For glucose tolerance test (GTT) mice were injected with 1 g/kg BW glucose. Insulin tolerance test (ITT) was performed by injecting 0.8 U/kg BW of regular insulin. A murine hepatocyte cell line (MMH) was silenced using lentiviral vectors encoding shRNA for the ERK5 gene. Mitochondrial depolarization was assayed using the TMRE staining protocol. OXPHOS metabolism was measured by Seahorse.

Results: ERK5DHep mice exhibited impaired glucose tolerance and reduced insulin sensitivity in comparison to the control group. Bodyweight and food consumption were similar. MMH silenced for ERK5 showed reduced Akt activation following insulin stimulation. In MMH challenged with palmitic acid and then stimulated with insulin, ERK5 knockdown caused a complete abrogation of Akt activation, a reduction in the expression of the insulin receptor as well as an increase in the phosphorylation of IRS-1 at S307. All these events are associated with reduced sensitivity to insulin signaling.

Insulin receptor phosphorylation on S307 may be mediated by JNK, which was more phosphorylated in MMH/shERK5. Measurement of mitochondrial membrane potential indicated a strong depolarization in ERK5-silenced cells, which also showed an impairment of mitochondrial OXPHOS, indicating a profound impact of ERK5 deficiency on mitochondrial functions. In ERK5-silenced cells expression of peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1 α), a pivotal regulator of mitochondrial biogenesis and function, was up-regulated. Additionally, expression of TRIB3, which negatively regulates insulin signalling through inhibition of Akt and under the control of PGC-1 α , was higher in MMHshERK5 cells, and its expression was further enhanced by palmitic acid. Reduced expression of insulin receptor, and increased expression of PGC-1 α and TRIB3 were also observed in liver tissues from HFD-fed ERK5DHep mice.

Conclusion: We have elucidated novel pathways connecting the expression of ERK5 in hepatocytes to the regulation of insulin sensitivity through PGC-1 α , TRIB3, Akt, as well as through insulin receptor and IRS-1.

PO-2412

Combining non-selective beta blockers with FXR agonists towards ameliorating intestinal barrier dysfunction in NASH

Yasmeen Attia¹, Rasha Tawfiq², Olfat Hammam³, Mohamed Elmazar².
¹The British University in Egypt, Pharmacology; ²Faculty of Pharmacy, The British University in Egypt, Pharmacology; ³Theodor Bilharz Research Institute, Pathology
Email: yasmeen.attia@bue.edu.eg

Background and aims: Bacterial translocation (BT) is a critical trigger in the pathogenesis of non-alcoholic steatohepatitis (NASH) via activation of Toll-like receptors (TLRs). Hence, attempts to manipulate BT and the intestinal microbiome are novel insights to prevent NASH development and progression. The role of non-selective beta blockers (NSBBs) in decreasing gut permeability was highlighted in previous studies. Moreover, the pivotal role of farnesoid X receptor (FXR) in the maintenance of intestinal homeostasis is increasingly recognized along with its crucial involvement in the gut-liver axis. The present study aimed at investigating the effect of combining carvedilol (CAR), a NSBB, to obeticholic acid (OCA), an FXR agonist on BT and, therefore, NASH histopathological features.

Method: A combined experimental model of chronic colitis and dietary NASH was used to mimic the clinical presentation of NASH induced by intestinal barrier dysfunction. Eight-week-old male Swiss albino mice were fed a high fat diet for 13 weeks. Colitis was induced by dextran sulfate sodium (DSS) as 0.5% in drinking water applied in cycles each consisting of 7 days DSS followed by 10 days free drinking water. Treatments were started at week 10 at a dose of 5 mg/kg/day, p.o. for OCA and 10 mg/kg/day, p.o. for CAR, either alone or combined for 4 weeks. Intestinal permeability was evaluated using fluorescein isothiocyanate (FITC)-dextran test. Histopathological examination of liver and ileal samples was performed. Immunohistochemical analysis of ileal TLR-4, transforming growth factor (TGF)- β 1 expression, junctional adhesion molecule A protein (JAM-A) along with claudin-1 ileal expressions were also estimated.

Results: Histopathological changes of NASH observed in the control group were ameliorated in treated groups, especially the one which received a combination of OCA and CAR. Moreover, FITC-dextran fluorescence serum level was reduced in the combination-treated group compared to single treatments ($p < 0.05$). The expression of ileal TLR-4 and TGF- β 1 were lower in the OCA+CAR-treated group. Additionally, the ileal expression of JAM-A and claudin-1 were both increased after OCA+CAR treatment ($p < 0.05$).

Conclusion: Combining the NSBB, carvedilol, to OCA, decreased BT and mitigated the intestinal barrier dysfunction alongside NASH histopathological features in a combined model of chronic colitis and dietary NASH suggesting its potential use in NASH patients with disrupted intestinal homeostasis.

PO-2623

Myeloid-specific fatty acid transport protein 4 deficiency in mice induces a shift towards M2 macrophages that leads to aggravation of NASH after high-fat/high-cholesterol feeding

Deniz Göcebe¹, Chutima Jansakun¹, Simone Staffer¹, Sabine Tuma-Kellner¹, Sandro Altamura², Martina Muckenthaler², Uta Merle¹, Walee Chamulitrat¹. ¹Heidelberg Hospital University, Internal Medicine IV, Heidelberg, Germany; ²Heidelberg Hospital University, Pediatric Oncology, Hematology and Immunology, Heidelberg, Germany
Email: walee.chamulitrat@med.uni-heidelberg.de

Background and aims: Mutations of FATP4 are associated with blood lipids and insulin resistance, and these patients exhibit not only skin hyperkeratosis but also M2/Th2-related allergies and eosinophilia. We hypothesized that FATP4 deficiency in macrophages may contribute to the pathogenesis of NASH because this disease is also linked to type 2 immunity. We determined the effects of myeloid-specific Fatp4 deficiency on macrophage polarization and diet-induced NASH.

Method: LysM-Cre Fatp4-deficient mice (KO) with exon 3 deletion were generated. Complete blood counts from male and female control and KO mice were analysed. Cytokine release and gene expression were analysed in bone marrow-derived macrophages (BMDMs) from male mice with or without in vitro LPS for 24 h. Male and female control and KO mice were fed with high-fat (15%)/high-cholesterol (1.25%) (HFHC) diet for 16 weeks. Plasma cytokines, hepatic gene expression, and liver histology were analyzed.

Results: Male KO mice showed an increase in % monocytes and granulocytes while female KOs showed a decrease in % monocytes. BMDMs from male KO mice showed an increase in spontaneous release of M2/Th2 IL-4 and IL-13 as well as spontaneous and LPS-induced expression of MCP-1. This deficiency on the other hand attenuated LPS-induced expression and release of M1 TNF- α , IL-6, and IL-1b. After HFHC feeding, both male and female mutants showed a further elevation of plasma IL-4, IL-13, and MCP-1, while that of plasma IL-5 and IL-6 was observed only in female mutants. On the other hand, HFHC-induced elevation of plasma TNF- α was attenuated in both male and female mutants. Strikingly, HFHC feeding induced a marked increase of hepatic steatosis in male mutants but a massive hepatic infiltration of immune cells in female KOs. Both male and female KO mice showed an increase of HFHC-induced liver fibrosis and hepatic expression of MCP-1 protein. Correspondingly, male mutants showed increased mRNA expression of collagen 1a1, collagen 3a1, Timp1, Icam1, and Vcam1.

Conclusion: Myeloid-specific Fatp4 deficiency led to a shift from M1 towards M2 cytokines IL-4, IL-13 and MCP-1 at the level of BMDMs and HFHC-induced NASH. Such increase of Th2 immunity led to aggravated liver fibrosis in both male and female mutants. Hepatic steatosis and inflammatory IL-5/IL-6 was prominent in male and female mutants, respectively. Our findings may have some implications for patients with FATP4 mutations who consume HFHC-rich diets.

PO-2653

Blocking the CD47-SIRP α axis in non-alcoholic steatohepatitis enhances necroptotic hepatocyte uptake and improves hepatic fibrosis

Hongxue Shi¹, Xiaobo Wang¹, Brennan Gerlach¹, Arif Yurdagul², Bishuang Cai³, Sharon Zeldin¹, Luca Valenti⁴, Ira Tabas¹. ¹Columbia University Irving Medical Center, New York, United States; ²LSU Health Shreveport, Molecular and Cellular Physiology, Shreveport, United States; ³Icahn School of Medicine at Mount Sinai, New York, United States; ⁴University of Milan, Milano, Italy
Email: iat1@cumc.columbia.edu

Background and aims: Hepatocyte (HC) death is a key event during non-alcoholic steatohepatitis (NASH), but precisely how HC death contributes to NASH progression, particularly the most important

feature of liver fibrosis, remains incompletely understood. In general, cell death causes disease when clearance of dead cells by macrophages (M ϕ s) is impaired, leading to leakage of disease-causing factors. Whether poor clearance of dead HCs by liver M ϕ s in NASH contributes to disease progression is unknown. In other diseases, dead cell clearance can fail due to inappropriate activation of M ϕ SIRP α by CD47 on dead cells, which blocks cell engulfment by M ϕ s. In-vitro work has suggested that this scenario can occur when cells die by necroptosis, a form of cell death that has been implicated in NASH. We therefore hypothesized that expression of CD47 on necroptotic HCs (necHCs) in NASH activates SIRP α on NASH liver M ϕ s, leading to failed dead HC clearance and promotion of NASH.

Method: CD47 and SIRP α were assayed in tissue sections from human and mouse normal and NASH liver. For mouse NASH, male C57BL/6J mice were fed either a high-fat choline-deficient L-amino-defined (CDAA) diet for 12 weeks or a fructose-palmitate-cholesterol (FPC) diet for 16 weeks. We also generated a non-NASH necHC model by injecting mice with AAV8-TBG-mRipk3-2Fv, followed by treatment with a cross-linker to activate RIP3-induced necroptosis in HCs. For all mouse models, causation was tested by administering anti-CD47 or anti-SIRP α antibodies, followed by assessment of engulfment of necHCs by liver M ϕ s and NASH fibrosis. For *ex vivo* studies, the engulfment of human and mouse necHCs by primary human and mouse liver M ϕ s, respectively, was assayed in the absence or presence of anti-CD47 antibody.

Results: The necroptosis signaling markers RIP3 and p-MLKL were increased in human and mouse NASH liver compared with normal liver, and RIP3⁺ HCs showed poor association with liver M ϕ s. Interestingly, M ϕ -SIRP α and HC-CD47 were also increased in human and mouse NASH vs. control liver. *Ex vivo*, liver M ϕ s showed poor uptake of necHCs, and this was improved by addition of anti-CD47 or anti-SIRP α . As initial proof-of-concept *in vivo*, we used the inducible mRipk3-2Fv necHC model and showed that anti-CD47 treatment promoted engulfment of necHCs by liver M ϕ s and decreased profibrotic gene expression by hepatic stellate cells (HSCs). Most importantly, administration of anti-CD47 or anti-SIRP α antibody to both models of NASH mice enhanced necHC engulfment by liver M ϕ s and decreased HSC activation and liver fibrosis.

Conclusion: Increased expression of HC-CD47 and M ϕ -SIRP α expression occurs in NASH liver and is associated with poor clearance of necHCs, and blocking the CD47-SIRP α axis in NASH enhances necHC clearance and reduces liver fibrosis. These findings define a new mechanism contributing to NASH progression with potential therapeutic implications.

PO-2732

Core liver homeostatic networks: implications in therapeutic target discovery, pre-clinical studies, and innovative trial designs

Saeed Esmaili¹, Jacob George¹. ¹Westmead Institute for Medical Research, Storr Liver Centre, Westmead, Australia
Email: saeed.esmaili@sydney.edu.au

Background and aims: Findings about chronic complex diseases are always difficult to extrapolate from animal models to humans. These have led to efforts to develop more relevant pre-clinical models. We aimed to develop a framework using imperfect pre-clinical models for therapeutic target discovery. We reasoned that organs may have core network modules that are preserved between species and are predictably altered when homeostasis is disrupted. To explore this, we used pre-clinical models of fatty liver disease, human fatty liver, and human liver cancer datasets. We hypothesized that the mechanisms that maintain hepatic homeostasis in mice and humans are largely preserved.

Method: To test this idea, we challenged mice with diets containing different combinations of sucrose (HS) and cholesterol (Chol2%) with and without cholic acid (CA) for 8 weeks (6 diets). We applied weighted gene co-expression network analysis (WGCNA) on RNA_Seq; similar analyses were undertaken in healthy and diseased

POSTER PRESENTATIONS

human fatty liver and in liver cancer. Subsequently, we investigated the preservation of gene co-expression modules between datasets to find “core modules” for homeostasis.

Results: Histology indicated the presence of marked hepatic immune infiltration in diets that contained both CA and cholesterol. RNA sequencing of liver from mice fed the 6 diets followed by WGCNA reduced thousands of genes to a small number of transcriptionally coherent modules. Likewise, we performed WGCNA on human fatty liver and 3 human liver cancer datasets: TCGA, and ICGC (France, Japan). The core homeostatic disturbance in human HCC and fatty liver could be depicted by preserved modules. We termed these modules “core modules.” The core modules demonstrated disease specific behaviour (up- or down-regulation). Some of the components of core modules predicted liver cancer patient survival. We identified module eigengene quantitative trait loci (module-eQTL) for these predictive modules, targeting of which may improve patient outcomes.

Conclusion: Despite the dissimilarities between models, we highlight a framework for using pre-clinical models to understand fatty liver and liver cancer pathogenesis. In addition, we provided a network concept for understanding homeostatic perturbations. This approach can be developed for a core-based homeostatic network medicine approach and adopted for Complex Innovative trials Designs (CIDs).

PO-2858

Role of the nuclear receptor Farnesoid X Receptor in the immune functions of the intestine in the pathophysiological context of Non-alcoholic SteatoHepatitis

Margaux Nawrot¹, Simon Peschard¹, Emmanuelle Vallez¹, Emilie Dorchies¹, Olivier Molendi-Coste¹, Laurent Pineau¹, Anne Taillieux¹, David Dombrowicz¹, Bart Staels¹, Sophie Lestavel¹.
¹Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-, EGID, F-59000 Lille, France
Email: margaux.nawrot@univ-lille.fr

Background and aims: In metabolic disorders such as Non-alcoholic SteatoHepatitis (NASH), tight junctions of the intestinal epithelium are disorganised which leads to disrupted intestinal barrier and to intestinal inflammation which will spread in the whole organism as low grade inflammation. The bile acid nuclear receptor FXR (Farnesoid X Receptor) is recognized to play an important role in energy homeostasis. Whole body and intestinal FXR Knock-Out (^{int}FXR KO) mice are both protected against high fat diet-induced obesity and insulin resistance, although whole body FXR KO mice under normal diet show an increase of intestinal permeability. The aims of this study are to decipher whether the intestinal immune functions are under the control of epithelial FXR and whether that may participate to NASH pathogenesis.

Method: We have generated ^{int}FXR KO mice by crossing villin-Cre and FXR-floxed mice. We then analyzed the immune cell distribution in small intestine of ^{int}FXR KO and control mice under chow diet or high fat/high sucrose 1% cholesterol (HFHS) diet for 24 weeks. We performed an immunophenotyping on cells purified from the lamina propria and the intra-epithelial space by using a large panel of 18 appropriated antibodies to identify subtypes of immune cells by flow-cytometry (Fortessa 20X).

Results: Under chow diet, 10 week-old ^{int}FXR KO mice compared to their littermate controls displayed an increase of the population of T lymphocytes (LT) in the lamina propria of small intestine, which can be attributed to an increase of cytotoxic LT CD8 + cells parallel to a decrease of LT helpers CD4 + cells. At 32 week-old, we observed no more change in the amount of LT between the 2 genotypes, but rather

a change of quality of cytotoxic LT CD8 + population with an increase of resident T cells and a decrease of recruited T cells in the intestinal tissue of the ^{int}FXR KO mice. After 24 weeks of HFHS diet, the ^{int}FXR KO mice displayed an increase of LT CD8 + population in their intestinal intra-epithelial space compared to their littermate controls. **Conclusion:** We have shown that targeted intestinal FXR invalidation changes the intestinal immune profile under standard and HFHS diets, suggesting that FXR in the intestinal epithelium controls gut immunity. Molecular mechanisms remain to be deciphered and the impact of these intestinal modifications on NASH are under investigation.

PO-2883

The intestinal barrier is modified in mice suffering from non-alcoholic steatohepatitis

Simon Peschard¹, Margaux Nawrot¹, Laurent Pineau¹, Joel Haas¹, Olivier Molendi-Coste¹, David Dombrowicz¹, Bart Staels¹, Sophie Lestavel¹.
¹Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-, EGID, F-59000 Lille, France
Email: simon.peschard.etu@univ-lille.fr

Background and aims: Non-alcoholic steatohepatitis (NASH) is frequently observed in the context of obesity, type 2 diabetes and metabolic syndrome. Growing body of evidence highlights the importance of altered gut-liver dialogue in this pathology. We decided to study the intestinal barrier function in a well characterized NASH mouse model with a special focus on two of its components, the physical barrier with tight-junction proteins and the immunological barrier with the characterization of immune cells in the intestinal tissue.

Method: Eight week old C57Bl6/J male mice were fed for 24 weeks with a high fat/high sucrose diet supplemented with cholesterol to induce NASH, and compared to their littermate controls under chow diet. Liver and gut samples were collected for histological and transcriptomic analysis. Immunophenotyping was performed on cells purified from the lamina propria of the small intestine and colon by using a Percoll gradient after EDTA treatment and collagenase digestion. A panel of 18 antibodies was used to identify immune cell subtypes by flow cytometry (Fortessa X20). Results were analyzed using FlowJo software.

Results: After 24 weeks of NASH-diet and as expected, the histology of murine liver was consistent with the pathological history of the human disease, combining weight gain, hepatomegaly and increase of plasmatic markers of hepatic cytolysis. Liver histology shows an increase of steatosis and fibrosis in NASH mice compared to their controls. Moreover, an increase of F4/80, TNFalpha and IL-1beta mRNA expression was observed in the liver of NASH-diet fed mice. A decrease of almost all CD8+ lymphocyte populations was observed in the lamina propria of small intestine, with no change in CD4+ lymphocytes. Intestinal B lymphocytes, macrophages, dendritic cells and eosinophils were not affected by the NASH-diet. In colonic lamina propria of NASH mice, we observed an increase of TCRalpha/beta CD4+ cells and a decrease of TCRgamma/delta CD8+ cells. The expression of JAM-A, a protein of the tight junction complexes, is also decreased in the colon of NASH animals.

Conclusion: We have now shown that our NASH mouse model displays a modified intestinal immunological barrier and an altered expression of component of tight junctions. Whether these modifications are the leading cause of the hepatic dysfunctions remains to be elucidated. It will be now of importance to decipher the molecular mechanisms involved in the modifications of the intestinal barrier induced by the NASH-diet.

NAFLD: Therapy

PO-159

Target engagement and evidence of efficacy with PXL770, a novel direct AMP-Kinase activator, in a 4-week PK/PD trial in patients with NAFLD

Vlad Ratziu¹, Julie Dubourg², David Moller², Sébastien Bolze², Sophie Bozec², Pascale Fouqueray², Kenneth Cusi³, Stephen Harrison⁴. ¹Institute for Cardiometabolism and Nutrition, Paris, France; ²Poxel SA, Lyon, France; ³University of Florida, Division of Endocrinology, Diabetes and Metabolism, Gainesville, United States; ⁴Summit Clinical Research, San Antonio, United States
Email: vlad.ratziu@inserm.fr

Background and aims: NAFLD is characterized by hepatic lipid accumulation and progresses to non-alcoholic steatohepatitis NASH. Type 2 diabetes (T2D) and metabolic syndrome are common comorbidities and drivers of disease. AMPK activation improves insulin sensitivity, increases lipid oxidation, decreases hepatic de novo lipogenesis (DNL), improves inflammation, and reduces fibrogenesis. Metabolic dysfunction (including T2D) is associated with lower endogenous AMPK activity. PXL770 is a new direct allosteric AMPK activator. In human and mouse primary cells, PXL770 inhibits DNL in hepatocytes, cytokine release from macrophages and stellate cell activation. In NASH and T2D rodent models, it improves core NASH parameters including steatosis, inflammation, ballooning and fibrogenesis, and improves insulin sensitivity and glycemic control. Thus, PXL770 has potential to independently target the root causes and core features of NASH, while simultaneously improving insulin sensitivity and glycemic control. Here we sought to establish targets engagement, PK and safety of PXL770 in NAFLD patients.

Method: In a randomized, double-blind, parallel design clinical trial, 12 obese non-diabetic patients with NAFLD received PXL770 500 mg orally once daily and 4 received placebo for 4 weeks. NAFLD was diagnosed based on a fibroscan CAP >300 db/m and insulin resistance

(HOMA-IR >2.5). Hepatic fractional DNL (assessed by 2H incorporation into palmitate), in response to oral fructose challenge, was measured on days -1 and 28 using mass isotopomer distribution analysis. An OGTT was conducted on days -2 and 27. Additional plasma efficacy, safety parameters and PK concentrations were assessed at several time points.

Results: PXL770 treatment decreased the peak DNL by -21% (p = 0.005) and the AUC by -15% (p = 0.03) vs. baseline. Both mean total and incremental glucose AUC during the OGTT were improved vs. baseline with PXL770 by -10% (p = 0.023) and -25% (p = 0.03), respectively. In addition, significant improvements in several indices of insulin sensitivity were measured: HOMA-IR -37% (p = 0.0134), Matsuda +37% (p = 0.0136), OGIS +16% (p = 0.0123). Safety and tolerability were similar to placebo and PK parameters were similar to prior results with healthy subjects (terminal T1/2 ≈ 25 hr).

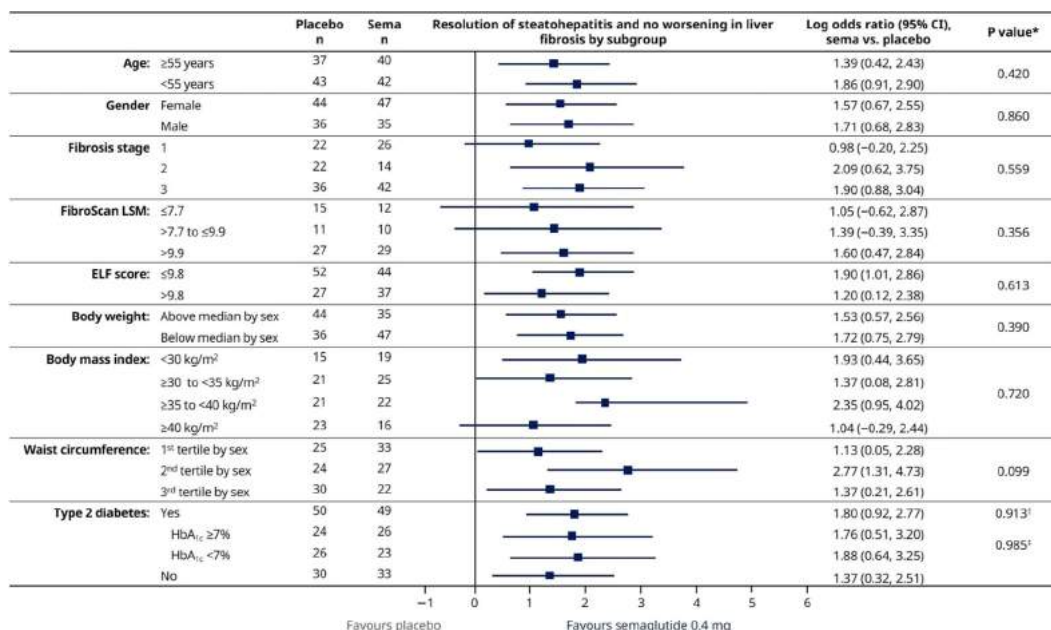
Conclusion: These results support the continued development of PXL770, the first direct AMPK activator to be studied in patients, and the potential utility of AMPK activation in NASH and other potential indications.

PO-230

Semaglutide in patients with non-alcoholic steatohepatitis: subgroup analysis of a randomised, placebo-controlled phase 2 trial

Sven Francque¹, Mette Kjaer², Steen Ladelund², Takeshi Okanoue³, Lyudmila Mateva⁴, Ichhya Shrestha², Stephen Harrison⁵. ¹Antwerp University Hospital, Antwerp, Belgium; ²Novo Nordisk A/S, Søborg, Denmark; ³Kyoto Prefectural University of Medicine, Kyoto, Japan; ⁴University Hospital St. Ivan Rilski, Sofia, Bulgaria; ⁵University of Oxford, Oxford, United Kingdom
Email: sven.francque@uza.be

Background and aims: Patients with non-alcoholic steatohepatitis (NASH) represent a heterogeneous group in which it is important to assess the efficacy of treatments across subpopulations. In a double-blind, placebo-controlled, phase 2 trial in patients with NASH and fibrosis stage (F) 1–3, significantly more achieved NASH resolution without worsening of fibrosis with the glucagon-like peptide-1



In all randomised patients (fibrosis stage 1–3). Patients without biopsy at 72 weeks are counted as non-responders. *p value for interaction between treatment and subgroup (Type 2 diabetes [yes or no]; †HbA_{1c} [≥7%, <7%, or non-type 2 diabetes]). CI, confidence interval; ELF, enhanced liver fibrosis; HbA_{1c}, glycated haemoglobin; LSM, liver stiffness measurement.

Figure: (abstract: PO-230)

POSTER PRESENTATIONS

receptor agonist semaglutide versus placebo (primary end point evaluated in patients with F2-3 only, 58.9% vs 17.2%; $p < 0.0001$). This *post-hoc* exploratory analysis of the trial (NCT02970942) assessed whether patient and disease characteristics influenced the effect of semaglutide versus placebo on NASH resolution.

Method: Adult patients with biopsy-confirmed NASH and fibrosis stage F1-3 were randomised to once-daily subcutaneous semaglutide 0.1, 0.2 or 0.4 mg, or placebo for 72 weeks. The primary end point of resolution of NASH with no worsening of fibrosis was evaluated across several subgroups based on gender, age, type 2 diabetes, body weight, body mass index, fibrosis stage, enhanced liver fibrosis score, and liver stiffness measurement by FibroScan. Subgroups based on baseline characteristics were analysed for heterogeneity (interaction) in treatment differences in the primary end point.

Results: A total of 320 patients were randomised to semaglutide 0.1 mg ($n = 80$), 0.2 mg ($n = 78$), 0.4 mg ($n = 82$) or placebo ($n = 80$). In all randomised patients (F1-3), NASH resolution without fibrosis worsening at 72 weeks was achieved by significantly more patients receiving semaglutide 0.4 mg compared with placebo (56.1% versus 20.0%; $p < 0.0001$). Semaglutide 0.4 mg was associated with a numerical benefit in regards to the proportion of patients with NASH resolution and no worsening of fibrosis across all subgroups (Figure). There were no significant treatment by subgroup interactions between semaglutide and placebo for achievement of NASH resolution without worsening of fibrosis at 72 weeks. Similar results were seen with semaglutide 0.1 and 0.2 mg (data not shown).

Conclusion: A consistent beneficial effect of semaglutide on the primary end point of NASH resolution without fibrosis worsening was observed across a variety of subgroups based on baseline characteristics, suggesting similar efficacy across a range of patients.

PO-231

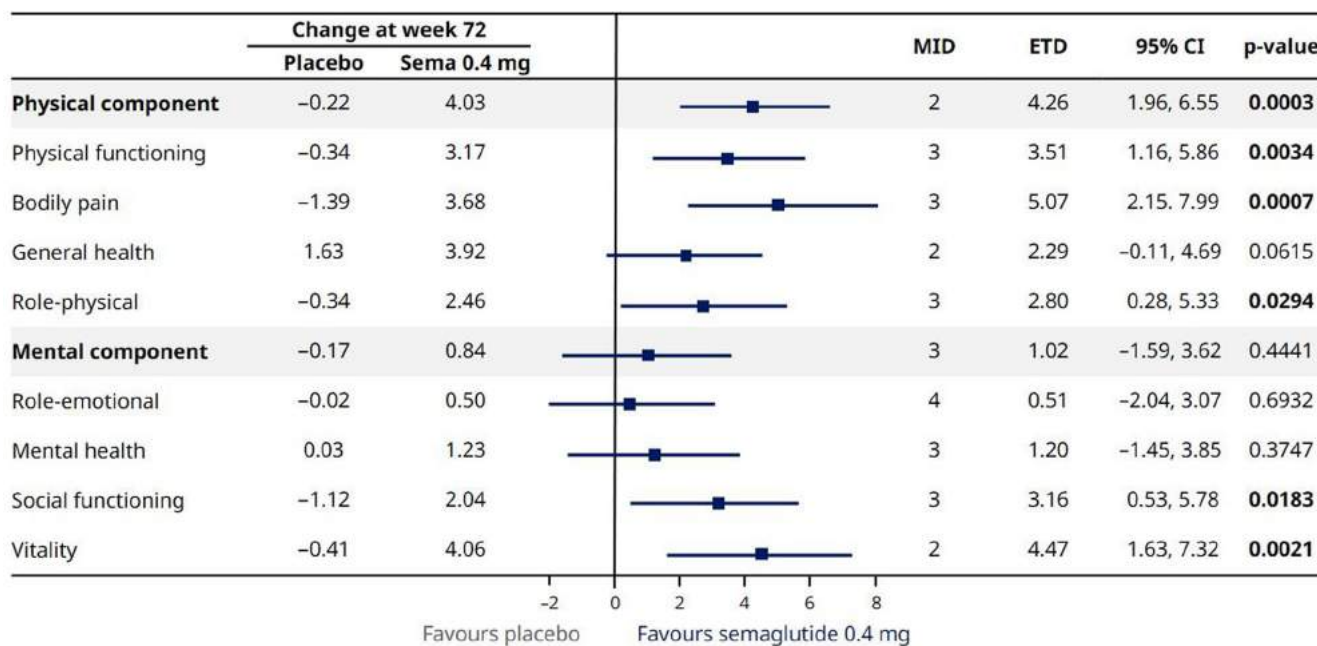
Effect of subcutaneous semaglutide on quality-of-life in patients with non-alcoholic steatohepatitis

Manuel Romero Gomez¹, Andrew Austin², João Diogo da Rocha Fernandes³, Steen Ladelund³, Anne-Sophie Sejling³, Ichhya Shrestha³, Arun Sanyal⁴. ¹UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain; ²University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; ³Novo Nordisk A/S, Søborg, Denmark; ⁴Virginia Commonwealth University School of Medicine, Richmond, VA, United Kingdom
Email: mromerogomez@us.es

Background and aims: Although often considered to be asymptomatic, non-alcoholic steatohepatitis (NASH) can have a detrimental effect on health-related quality of life (HRQoL). In a phase 2 trial, treatment with the glucagon-like peptide-1 receptor agonist semaglutide resulted in significantly more patients achieving NASH resolution without worsening of fibrosis compared with placebo, as well as improvements in fibrosis biomarkers, body weight and glycaemic control. Here, we report the effects of semaglutide on patient-reported outcomes of HRQoL in this trial (NCT02970942).

Method: A double-blind, placebo-controlled study randomised adult patients with biopsy-confirmed NASH and fibrosis stage (F) 1-3 to once-daily subcutaneous semaglutide 0.1, 0.2 or 0.4 mg, or placebo for 72 weeks. Changes from baseline in Short Form-36 (SF-36) individual sub-domains, and physical and mental component summary scores were assessed at week 72.

Results: A total of 320 patients were randomised to semaglutide 0.1 mg ($n = 80$), 0.2 mg ($n = 78$), 0.4 mg ($n = 82$) or placebo ($n = 80$). At 72 weeks, treatment with semaglutide 0.4 mg was associated with significantly greater improvements than placebo in the domains of bodily pain, physical functioning, role limitations due to physical health problems, social functioning and vitality (Figure). Numerically



Data for all randomised patients during the in-trial period, analysed using an ANCOVA model with missing data derived by multiple imputation from placebo group. Data for semaglutide 0.1 mg and 0.2 mg doses not shown (ETD versus placebo all non-significant, except social functioning for 0.1 mg dose, $p = 0.0022$). MID, which are defined as the smallest difference in score which patients perceive as beneficial, are from the SF-36 Manual and Interpretation Guide and refer to mean group differences rather than responder definitions for individuals. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; MID, minimum important difference; sema, semaglutide; SF-36, Short Form-36.

Figure: (abstract: PO-231)

greater but non-significant improvements were also seen in other domains. Estimated treatment differences between semaglutide 0.4 mg and placebo were larger than the minimum clinically important difference for all domains except role-physical. Physical component summary scores were also significantly improved with semaglutide 0.4 mg versus placebo; this improvement was significantly greater in patients with NASH resolution than without (mean [SD] change from baseline 3.0 [6.7] versus 1.2 [6.6]; $p = 0.014$). No significant differences in physical and mental components were observed between semaglutide 0.1 or 0.2 mg and placebo. There were no significant correlations observed between changes in SF-36 domains and NASH resolution or changes in body weight, enhanced liver fibrosis score or FibroScan-liver stiffness measurement.

Conclusion: This is the first evidence that once-daily subcutaneous semaglutide has a clinically important effect on HRQoL in patients with NASH and stage F1-3 fibrosis. Increased focus on and better understanding of patient-centered outcomes are needed in future research of treatments for NASH.

PO-337

Funded referral to a commercial weight loss provider is effective in achieving weight loss in Non-alcoholic fatty liver disease

Iain Hay¹, Sarah Roxburgh¹, Mairi Blair¹, Helen Cairns², Jude Morris², Matthew Priest², Ewan Forrest¹, Stephen Barclay¹. ¹Glasgow Royal Infirmary, Gastroenterology, Glasgow, United Kingdom; ²Queen Elizabeth University Hospital, Gastroenterology, Glasgow, United Kingdom

Email: iain.hay@nhs.scot

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is increasingly prevalent, affecting 30% of the population. EASL guidelines recommend a target of 7–10% weight loss. From 2016, patients with NAFLD were eligible for a funded 12 week weight loss programme with the commercial provider “Weight Watchers” (WW) via our health board. Those achieving 5% weight loss were eligible for a further 12 week programme. We sought to evaluate engagement, and outcomes of patients referred.

Method: Patients with NAFLD referred from liver clinics to WW between 2016 and 2020 were identified by Glasgow Weight Management Services, who provided data on attendance, completion and weight loss. Clinical data, including alcohol use, diabetes, adverse events, and liver stiffness measurements (LSM) were obtained from patient records. Patients were characterised as attenders if ≥ 1 session attended. Those still attending at time of data collection were excluded. Baseline parameters were compared according to attendance.

Results: 326 patients were included, of whom 168 (51.5%) attended ≥ 1 session (mean 8 (± 4)) and 84 (25.8%) completed 12 weeks. Attenders were older, and more likely to be female and diabetic (figure 1). 131/168 (77.9%) lost weight, 63/168 (37.5%) $\geq 5\%$ and 44/168 (26.2%) $\geq 7\%$. Similar rates of weight loss were seen in those with cirrhosis; $\geq 5\%$ (16/45, 35.6%) and $\geq 7\%$ (11/45, 24.4%). No patients with cirrhosis experienced decompensation. Amongst 24 attenders with pre and post LSMs, mean LSM fell from 10.3 kPa (± 3.0) to 8.25 kPa (± 4.0), $p = 0.029$.

Conclusion: An offer of funded commercial provider weight loss sessions had moderate acceptance amongst patients with NAFLD. Amongst attenders, 1 in 3 lost the target weight loss for ongoing funded sessions, and 1 in 4 achieved EASL recommended weight loss. Commercial weight loss providers may be a useful health intervention for patients with NAFLD. Further work to understand barriers to uptake amongst younger patients and men may help increase uptake.

	Total n = 326	Attended		p
		Yes (168)	No (158)	
Mean age (\pm SD)	56 (13)	58 (12)	53 (14)	0.0003
Male (%)	166 (50.9)	76 (45.2)	90 (57.0)	0.034
Any alcohol (%)	160 (49.1)	74 (44.0)	86 (54.4)	0.061
Type 2 Diabetes (%)	88 (27.0)	54 (32.1)	34 (21.5)	0.031
Mean Liver stiffness kPa (\pm SD)	11.2 (8.4)	10.8 (7.9)*	11.6 (8.9)^	0.27
Cirrhosis (%)	85 (26.1)	45 (26.8)	40 (25.3)	0.76

LSM available for 129* and 119^ patients.

PO-393

MET642, an FXR agonist with a unique chemotype, demonstrates a safe, sustained profile in a 14-day randomized study in healthy subjects

Richard Pencek¹, Kyoung-Jin Lee¹, Jonathan Lee¹, Hubert Chen¹.

¹Metacrine, Inc., San Diego, United States

Email: rpencek@metacrine.com

Background and aims: Farnesoid X receptor (FXR) agonists have been validated to benefit patients with non-alcoholic steatohepatitis (NASH), although improvements in therapeutic index for the class remain elusive. MET642 is a novel, non-bile acid FXR agonist with enhanced potency and sustained FXR engagement in preclinical studies. We conducted a double-blind, placebo (PBO)-controlled, single-ascending dose and 14-day multiple-ascending dose phase 1 study in healthy subjects to determine the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MET642.

Method: Healthy men and women aged 18–50 years-old were randomized to MET642 or PBO (6:2 allocation). The primary objective was to assess the safety and tolerability of MET642. Secondary objectives were to establish the PK and PD profiles of MET642, with PD assessed by plasma 7 α -hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19).

Results: Both single (10, 30, 100, 300 mg) and multiple (2.5, 5, 7.5, 10 mg) doses of MET642 were safe and well-tolerated. MET642 exhibited sustained PK and PD profiles with once-daily oral dosing. There were dose-dependent increases in maximum concentration (0.03–0.10 μ g/ml), exposure (0.4–1.7 μ g*h/ml) and elimination half-life (28–71 hrs) on the final day of dosing. MET642 repressed plasma C4 levels and final day area-under-the-curve (\downarrow 53–95%, Table) relative to PBO, with repression observed throughout 24 h post-dosing. Increased FGF19 levels were observed, although these results were not statistically significant. There were no serious adverse events, and all adverse events were mild-moderate in severity. MET642 was associated with isolated, transient increases in alanine aminotransferase in some participants, unaccompanied by clinical symptoms or adverse changes in other liver chemistries. MET642 did not increase low-density lipoprotein cholesterol (LDL-C) or cause generalized pruritus—two adverse events frequently seen in patients with NASH.

	PBO (n=8)	2.5 mg (n=6)	5 mg (n=6)	7.5 mg (n=6)	10 mg (n=6)
AUC ₀₋₂₄ (h* μ g/L)	597	280	49	80	28
% suppression		53%	92%	87%	95%
p values		<0.05	<0.001	0.01	<0.001

AUC data are the geometric least square mean for the final day study PK assessment.
p-values for comparisons of MET642 to placebo AUC are derived from type III sums of squares.

Figure: Comparison of final dose day plasma C4 area under the curve (AUC) for MET642 and placebo

Conclusion: MET642, a novel FXR agonist, demonstrated sustained target engagement and an encouraging safety and tolerability profile—including a lack of adverse LDL-C effects or pruritus—in healthy subjects after 14 days of daily oral dosing.

POSTER PRESENTATIONS

PO-435

Hyperammonemia and intrahepatic microcirculation disorders and its correction at the non-alcoholic steatohepatitis patients with initial stages of liver fibrosis

Tatiana Ermolova¹. ¹North-Western State Medical University Named After I.I.Mecnikov, Internal Medicine and Faculty, St.-Petersburg, Russian Federation
Email: t.v.ermolova@mail.ru

Background and aims: Ammonia is new potential therapeutic target for chronic liver diseases. Some experimental studies demonstrated effect of hypoammonemic drugs for decrease of activity of hepatic stellate cells, improvement of endothelial function, liver microcirculation and prevention of liver fibrogenesis. Aims of our study: are to estimate blood level of ammonia, intrahepatic microcirculation and efficacy of ornithine (Hepa-Merz) for correction of such disorders at the chronic liver diseases.

Method: We investigated 36 non-alcoholic steatohepatitis (NASH) and 35 HCV patients with initial fibrosis 0–2 stages. Level of ammonia was estimated by biochemical method (PocketChem BA, Arcray, Japan) in capillary blood at the patients and 29 healthy individuals (control). Intrahepatic hemodynamics are determined by polyhepatography (PHG)-modified hepatic impedansometry, non-invasive method for integral estimation of intrahepatic blood flow by checking of tissue resistance to weak electric current. PHG registers a blood flow in projection of zone of hepatic right, left lobes and spleen, integral body impedansography. For correction of blood flow disorders we used hypoammonemic drug ornithine (Hepa-Merz) in dosage 3 grams 2 times daily 4 weeks. Efficacy of LOLA we looked in 2 and 4 weeks via the control PHG and control of ammonia.

Results: Analysis of PHG demonstrated, that at all patients we revealed a liver microcirculation disorders- increased blood resistance, abnormal forms and amplitude of waves in sinusoidal level (out flow zone) at NASH patients and presinusoidal level (inflow zone) at viral patients. Level of ammonia in the NASH patients was 137.2 $\mu\text{mol/L}$, in control group-39.2 $\mu\text{mol/L}$ ($p < 0.001$). Hyperammonemia was higher at the NASH patients, compared with viral patients higher (102.3 $\mu\text{mol/L}$) ($p < 0.01$). Analysis of efficacy of Hepa-Merz showed, that it was effective for correction of hepatic hemodynamic disorders at all patients, in 2 weeks of the treatment we observed normalization or improvement of the wave form, in 4 weeks-wave amplitude. Level of ammonia was decreased in 2 weeks.

Conclusion: NASH patients with initial stages of liver fibrosis are characterized by hyperammonemia, which is more pronounced in comparison with viral hepatitis. NASH is accompanied by disorders of intrahepatic microcirculation disorders in out flow zone. LOLA improved liver microcirculation and decreases of blood ammonia level at the NASH and HCV patients.

PO-627

Hepatic magnesium accumulation upon cyclin M4 (CNNM4) silencing improves NASH

Jorge Simón¹, Naroa Goikoetxea¹, Marina Serrano-Macia¹, David Fernández Ramos^{1,2}, Diego Saenz de Urturi³, Jessica Gruskos⁴, Pablo Fernández Tussy¹, Sofia Lachiondo-Ortega¹, Irene González-Recio¹, Rubén Rodríguez Agudo¹, Virginia Gutiérrez de Juan¹, Begoña Rodríguez Iruetagoiena¹, Marta Varela-Rey¹, Paula Gimenez-Mascarell¹, María Mercado-Gómez¹, Beatriz Gómez Santos³, Carmen Fernández-Rodríguez¹, Fernando Lopitz Otsoa^{1,2}, Maider Bizkarguenaga^{1,2}, Sybille Dames⁵, Ute Schaeper⁵, Franz Martin-Bermudo^{6,7}, Guadalupe Sabio⁸, Paula Iruzubieta⁹, Javier Crespo⁹, Patricia Aspichueta^{3,10}, Kevan H. Chu⁴, Daniela Buccella⁴, Cesar Augusto Martín¹¹, Teresa Cardoso Delgado¹, Luis Alfonso Martínez-Cruz¹, María Luz Martínez-Chantar¹. ¹CIC

bioGUNE, BRTA, Liver Disease Laboratory, CIBERehd, Derio, Spain; ²CIC bioGUNE, BRTA, Precision Medicine and Metabolism Laboratory, Derio, Spain; ³University of Basque Country, Department of Physiology, Leioa, Spain; ⁴New York University, Department of Chemistry, New York, United States; ⁵Silence Therapeutics GmbH, Berlin, Germany; ⁶University Pablo de Olavide, University of Sevilla, CABIMER, Sevilla, Spain; ⁷CIBERDEM, Madrid, Spain; ⁸CNIC, ISCIII, Madrid, Spain; ⁹Marques de Valdecilla University Hospital, Instituto de Investigación Sanitaria Valdecilla, Gastroenterology and Hepatology Department, Clinical and Translational Digestive Research Group, Santander, Spain; ¹⁰Biocruces Health Research Institute, Barakaldo, Spain; ¹¹Instituto Biofisika (UPV/EHU), Department of Biochemistry, Bilbao, Spain
Email: mlmartinez@cicbiogune.es

Background and aims: Perturbations of intracellular magnesium (Mg^{2+}) homeostasis have implications for cell physiology. In particular, deficiencies of the cation have been identified in cirrhosis and liver cancer, whereas the supplementation of the cation has proved to reduce mortality derived from liver diseases. Among all magnesium proteins, the cyclin M family, CNNM, perform key functions in the transport of Mg^{2+} across cell membranes. Although they have been previously characterized to interact with phosphatases of regenerating liver (PRLs) involved in tumour development, the role of CNNMs in the liver remains poorly understood.

Method: Clinical characterization of serum Mg^{2+} levels and hepatic CNNM4 expression. Primary hepatocytes cultured under methionine and choline deprivation. In vivo rodent NASH models: 0.1% methionine and choline-deficient and choline-deficient high-fat diets. *Cnnm4* was silenced using siRNA, in vitro with DharmaFECT and in vivo with InvivoFectamine or siRNA conjugated to N-acetylgalactosamine.

Results: Patients with NASH showed hepatic CNNM4 overexpression and dysregulated Mg^{2+} levels in the serum. *Cnnm4* silencing ameliorated hepatic lipid accumulation, inflammation and fibrosis in the rodent NASH models. Mechanistically, CNNM4 knockdown in hepatocytes induced cellular Mg^{2+} accumulation, reduced endoplasmic reticulum stress and increased microsomal triglyceride transfer activity, which promoted hepatic lipid clearance by increasing the secretion of very-low-density lipoprotein. The conjugation of siRNA with GalNAc allows a stable and effective delivery to the liver.

Conclusion: Hepatic CNNM4 is a valuable therapeutic target for treating NASH.

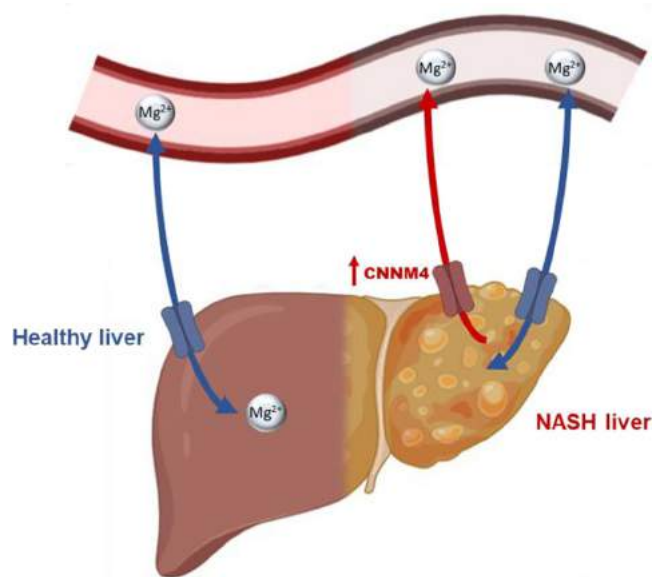


Figure:

PO-668

Safety and pharmacokinetics of DUR-928 in hepatic function impaired subjects

Jaymin Shah¹, Katherine Pozo², Deborah Scott², WeiQi Lin². ¹Durect, Clinical Pharmacology, Cupertino, United States; ²Durect, Clinical, Cupertino, United States
Email: jaymin.shah@durect.com

Background and aims: DUR-928 is an endogenous small molecule that epigenetically modulates the expression of genes that regulate lipid biosynthesis, inflammation, cell survival, and tissue regeneration. DUR-928 is in clinical development for the treatment of alcohol-associated hepatitis, COVID-19, and NASH. Animal studies with DUR-928 have shown high first-pass effect in the liver following oral dosing. The objective of this study was to assess the safety and pharmacokinetics (PK) of DUR-928 in subjects with hepatic impairment (HI).

Method: This was a Phase I open-label, study to assess the safety, tolerability, PK, and effect on biomarkers of DUR-928 in subjects with HI. The severity of HI was defined by Child-Turcotte-Pugh (CP) scores with mild HI being CP 5–6, moderate HI CP 7–9, and severe HI CP 10–15. This study enrolled 10 moderate HI, 7 severe HI, and 10 matched control subjects (MCS) with normal liver function, matched by age, gender and BMI. All subjects received a single oral dose of 200 mg DUR-928 and were followed for 7 days. Plasma concentrations of DUR-928 and its metabolite, 25HC, were determined for up to 48 hours post-dose.

Results: DUR-928 was well tolerated in all 27 subjects with no AEs or SAEs reported in the study. The exposure of DUR-928 (C_{max} and AUC) was increased with the severity of HI as compared to the MCS. Notably, the half-life of DUR-928 was increased and the clearance was decreased with the severity of HI as compared to the MCS. The clearance of DUR-928 was decreased by 70% and 88% in subjects with moderate HI and severe HI, respectively, as compared to the MCS. The mean time to maximum concentration of the drug (T_{max}) ranged from 2.8 to 4.3 hours across all study groups. Previously, we reported that C_{max} and AUC of DUR-928 in subjects with mild HI were not different from that in MCS, although the clearance of DUR-928 was slightly decreased. Cell death markers, cleaved CK-18 (M30) and full-length CK-18 (M65), were also measured in all subjects. Mean changes from baseline of M30 was –28% (p = 0.0001) in subjects with moderate HI and –15% (p = 0.0004) in subjects with severe HI at 12-hour post-dose. The change of M65 was –15% (p = 0.464) and –9% (p = 0.291) in subjects with moderate and severe HI, respectively, at 12-hour post-dose.

Conclusion: DUR-928 was well tolerated in all subjects with HI, including severe HI. As expected, HI resulted in higher exposure due to slower clearance of DUR-928 than MCS.

PO-757

Fenofibrate is safe and mitigates increases in serum triglycerides in NASH patients treated with the combination of the ACC inhibitor firsocostat and the FXR agonist cilofexor: A randomized trial

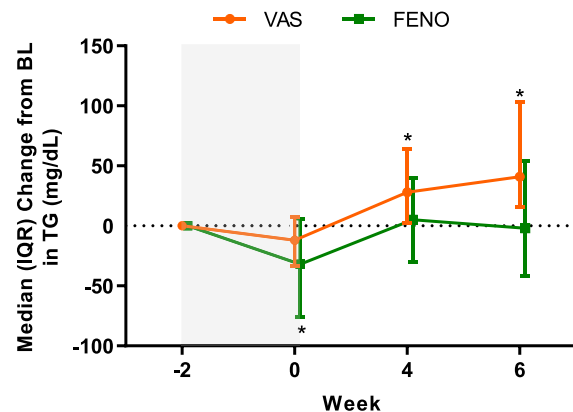
Eric Lawitz¹, Bal Raj Bhandari², Peter Ruane³, Anita Kohli⁴, Eliza Harting⁵, Catherine Jia⁵, Jay Chuang⁵, Ryan Huss⁵, Chuhan Chung⁵, Robert Myers⁵, Rohit Loomba⁶. ¹Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA, United States; ²Delta Research Partners, Bastrop, LA, USA, United States; ³Ruane Clinical Research, Los Angeles, CA, USA, United States; ⁴Arizona Liver Health, Chandler, AZ, USA; ⁵Gilead Sciences, Inc., Foster City, CA, USA, United States; ⁶University of California at San Diego, San Diego, CA, USA, United States
Email: ryan.huss@gilead.com

Background and aims: In patients with advanced fibrosis due to NASH, treatment with the FXR agonist cilofexor (CILO) and the acetyl-CoA carboxylase (ACC) inhibitor firsocostat (FIR) led to histologic and biochemical improvements but was associated with

hypertriglyceridemia in some patients. Our aim was to evaluate the safety and efficacy of fenofibrate (FENO) and icosapent ethyl (Vascepa[®], VAS) to mitigate increases in serum triglycerides (TG) in NASH patients treated with CILO+FIR.

Method: Patients with suspected NASH and fibrosis (by biopsy or liver stiffness by transient elastography ≥ 9.9 kPa or MRE ≥ 2.88 kPa) with TG ≥ 150 and < 500 mg/dL were randomized to treatment with VAS 2 g orally twice daily (n = 33) or FENO 145 mg orally once daily (n = 33) for two weeks, followed by the addition of CILO 30 mg and FIR 20 mg daily for 6 weeks (NCT02781584). Randomization was stratified by screening TG ($<$ vs ≥ 250 mg/dL). Safety parameters, lipids, and liver biochemistry were monitored.

Results: Overall, 69% of patients had diabetes and 82% were obese. At baseline (BL), median (IQR) TG were 177 mg/dL (154, 205) in the VAS group and 190 mg/dL (144, 258) in the FENO group, including 13% and 31% with TG ≥ 250 mg/dL, respectively. After two weeks of VAS or FENO monotherapy, median changes in TG were –12 mg/dL (–33, 7 [p = 0.0898 vs BL]) and –32 mg/dL (–76, 6 [p = 0.0121 vs BL]; Figure), respectively. Following 6 weeks of combination treatment with CILO +FIR, median change from BL in TG was +41 mg/dL (16, 103 [p < 0.0001 vs BL]) in the VAS group and –2 mg/dL (–42, 54 [p = 0.9206 vs BL]) in the FENO group. In patients with BL TG ≥ 250 mg/dL, changes at week 6 (W6) were +99 mg/dL (–29, 185) and –61 mg/dL (–128, –8), respectively. From BL to W6, median relative improvements in ALT (VAS: –16%; FENO: –37%), AST (–6%; –15%), and GGT (–13%; –34%) were observed in both groups. During combination therapy, treatment-emergent Grade 3 TG elevations (500–1000 mg/dL) were observed in 2 patients in each group, all with BL TG ≥ 250 mg/dL. Combinations were well tolerated; most adverse events (AEs) were Grade 1–2 and there were no discontinuations due to AEs. Prior to initiating CILO+FIR, one VAS-treated patient with BL TG of 2,540 mg/dL discontinued VAS after 8 days due to persistent TG elevation > 500 mg/dL.



Shaded area indicates 2-week pre-treatment period with VAS or FENO monotherapy. CILO+FIR added to VAS or FENO between Weeks 0 and 6. * p < 0.05 vs BL by Wilcoxon signed-rank test.

Figure: Serum triglycerides in patients treated with VAS or FENO in combination with CILO+FIR

Conclusion: In NASH patients with hypertriglyceridemia treated with the combination of CILO+FIR, icosapent ethyl and fenofibrate are well tolerated, but fenofibrate more effectively mitigates increases in serum triglycerides.

POSTER PRESENTATIONS

PO-787

Anti-fibrotic potential of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in preclinical models of fibrosis

Jung Kuk Kim¹, Jong Suk Lee¹, Seon Myeong Lee¹, Jae Hyuk Choi¹, Hyunjoon Kwon¹, Enu Jin Park¹, Sung Min Bae¹, Dae Jin Kim¹, Young Hoon Kim¹, In Young Choi¹. ¹Hanmi Pharm. Co., Ltd., Seoul, Korea, Rep. of South
Email: iychoi@hanmi.co.kr

Background and aims: Fibrosis due to NASH remains a major cause of liver-related mortality. However, no approved drug is available despite accelerated drug development. Although potential benefit of GLP-1RA has been proposed, semaglutide recently failed to improve fibrosis despite efficacy in NASH resolution, suggesting that additional mechanism is required to deliver therapeutic effects on fibrosis. To overcome these unmet needs of GLP-1RA, a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, has been developed. Here, we evaluated potential effect of HM15211 in animal models of fibrosis, and investigated underlying mechanism *in vitro*.

Method: Mice fed with AMLN diet were concomitantly treated with thioacetamide (AMLN/TAA mice) for 16 weeks. To establish diet-induced NASH and fibrosis model, mice were fed with choline-deficient and high fat diet (CD-HFD mice) for 16 weeks. HM15211 was subcutaneously administered during last 8 weeks, and acylated GLP-1 or GLP-1/GIP agonist were included. After treatment, hepatic hydroxyproline (HP) and collagen content were measured. Additional liver tissue samples were subjected to qPCR for evaluation of relevant marker gene expression. For mechanistic study, LX2 cell and rat primary hepatic stellate cell (HSC) were used.

Results: HM15211 treatment significantly reduced HP content (-53.1% vs. Veh.) and Sirius red positive area (-70.6% vs. Veh) in AMLN/TAA mice. Similarly, HM15211 treatment was associated with reduction of hepatic (-53.9, -41.4 and -51.9% vs. vehicle for alpha-SMA, TIMP-1 and collagen expression) and blood (-49.3, -48.0 and -49.1% vs. vehicle for TIMP-1, PIIINP and hyaluronic acid level) surrogate markers for fibrosis. In CD-HFD mice, HM15211 treatment showed greater reduction in hepatic HP and collagen contents (-4.2, -10.0, -31.2% vs. vehicle for acylated GLP-1, acylated GLP-1/GIP, HM15211) compared to acylated GLP-1 or GLP-1/GIP. Similar benefits of HM15211 were also observed when measuring hepatic expression of fibrosis markers such as TGF-beta and collagen. In LX2 cell and rat primary HSC, HM15211 treatment significantly reduced collagen production by TGF-beta via negatively affecting Smad signalling.

Conclusion: Based on these results, HM15211 may be a novel therapeutic option for liver fibrosis due to NASH. Hence, mechanistic studies highlight direct inhibitory effect of HM15211 on HSC activation. Human efficacy study is ongoing to assess the clinical relevance of these findings.

PO-838

Combination of an acetyl-CoA carboxylase inhibitor and fibroblast growth factor 19 reduced tissue triglyceride content and fibrosis in human precision-cut liver slices

Wen-Wei Tsai¹, Lee Borthwick², Jelena Mann², Jamie Bates¹, James L. Trevisakis¹. ¹Gilead Sciences, Foster City, United States; ²FibroFind LTD, Gateshead, United Kingdom
Email: wenwei.tsai1@gilead.com

Background and aims: Inhibition of the acetyl-CoA carboxylase (ACC) isozymes ACC1 and ACC2 results in inhibition of fatty acid synthesis and stimulation of fatty acid oxidation that may reduce lipotoxicity in non-alcoholic steatohepatitis (NASH). ACC inhibition also inhibits activation of hepatic stellate cells. Fibroblast growth factor 19 (FGF19) is secreted from the ileum in response to bile acid absorption. In the liver, FGF19 signals through FGF receptor 4 to reduce bile acid synthesis and regulate glucose and lipid metabolism. Combination of firsocostat (FIR), an ACC1/2 inhibitor (ACCi), and cilofexor, an FXR agonist that stimulates FGF19 release, led to

improvements in liver histology and biomarkers in patients with NASH. The aim of this study was to evaluate the effects of an ACCi and FGF19, alone or in combination, on lipid and fibrosis in human precision-cut liver slices (PCLS).

Method: Human PCLS were prepared from resected, non-fibrotic liver tissue of three donors and equilibrated for 24 h to allow the post-slicing stress period to elapse. PCLS were then stimulated with a mix of lipids conjugated to bovine serum albumin for 2 days. Subsequently, PCLS were stimulated with the same lipid cocktail plus transforming growth factor β 1 (TGF β 1)/platelet-derived growth factor $\beta\beta$ (PDGF $\beta\beta$) for a further 3 days. The ACCi (an analog of FIR), FGF19, or the combination were administered prophylactically from the time of lipid stimulation for a total of 5 days. PCLS culture media, including lipids, TGF β 1/PDGF $\beta\beta$, and compounds, were changed daily.

Results: Stimulation of the human PCLS with lipids and TGF β 1/PDGF $\beta\beta$ induced lipid accumulation and fibrosis as determined by an increase of tissue triglycerides, lipid droplets by Oil Red O staining (ORO) and positive area of alpha smooth muscle actin (α SMA) and Picrosirius Red (PSR) staining, without reducing cell viability. ACCi, FGF19, or the combination reduced tissue triglycerides in all three donors but only combination treatment consistently reduced ORO-positive area in all three donors. The combination of ACCi and FGF19 reduced α SMA-positive area in all donors and PSR-positive area in two out of three donors; however, ACCi or FGF19 alone had limited effect on α SMA or PSR.

Conclusion: The combination of an ACCi and FGF19 inhibited triglyceride accumulation and fibrosis in human PCLS stimulated with lipids and TGF β 1/PDGF $\beta\beta$ over 5 days. These data are consistent with improvements in steatosis and fibrosis observed in NASH patients treated with FIR and cilofexor combination therapy, and suggest a translational model to evaluate future NASH therapies.

PO-849

Treatment of a non-alcoholic steatohepatitis cirrhotic patients with resmetirom: baseline characteristics and effects on safety, biomarkers and imaging

Stephen Harrison¹, Naim Alkhouri², Rebecca Taub³, Manal Abdelmalek⁴, Guy Neff⁵. ¹Oxford, Hepatology, Oxford, United Kingdom; ²Arizona Liver Institute; ³Madrigal Pharmaceuticals, Research and Development, Conshohocken, United States; ⁴Duke University, Gastroenterology and Hepatology, Durham, United States; ⁵Covenant Research, Sarasota, United States
Email: rebeccataub@yahoo.com

Background and aims: MAESTRO-NAFLD-1 is a 52-week 1200 subject phase 3 randomized double blind placebo-controlled NASH clinical trial to study safety and biomarker effects of resmetirom, a selective thyroid hormone receptor beta agonist, in NASH patients with F1-F4 fibrosis identified using non-invasive biomarkers and imaging (NCT04197479). A goal of this "real life" NASH study is to identify non-invasive markers that correlate with individual patient response to resmetirom treatment. The 36-week Phase 2 resmetirom NASH study provided preliminary evidence of an association between MRI-PDFF (magnetic resonance imaging-proton density fat fraction) reduction and NASH resolution and fibrosis reduction on serial liver biopsy. This study includes an open label active treatment arm in NASH cirrhotic patients.

Method: MAESTRO-NAFLD-1 eligibility requires at least 3 metabolic risk factors, fibroscan kilopascals (kPa) consistent with \geq F1 fibrosis stage, and MRI-PDFF \geq 8% (no MRI-PDFF threshold required for NASH cirrhosis). The primary and key secondary end points of MAESTRO-NAFLD-1 include safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, and PRO-C3 (week 52). Baseline characteristics were compared between enrolled NASH cirrhotic patients and patients with liver biopsy documented NASH enrolled in the MAESTRO-NASH phase 3 trial. Initial analyses of safety, imaging and biomarkers were conducted in NASH cirrhotic patients.

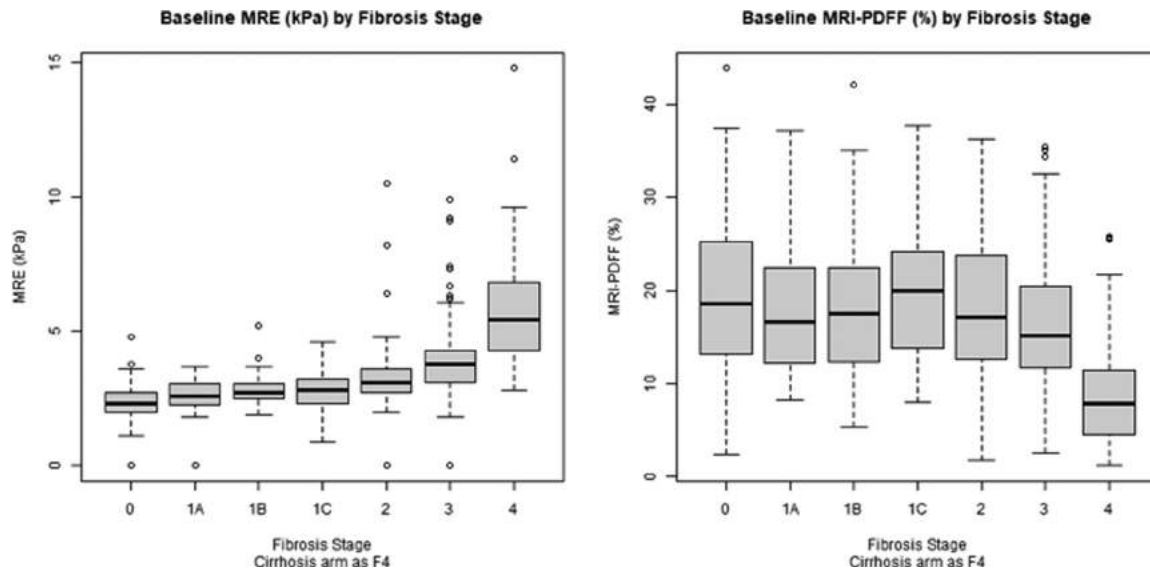


Figure: (abstract: PO-849)

Results: 108 well-compensated NASH cirrhotic patients were enrolled in the open label arm. Demographics include mean age 62.7 (9.0 (SD)), female 64%, BMI 35.5 (7.5), diabetes 66%, hypertension 71%, dyslipidemia >70%, mean ASCVD score 16%, hypothyroid 30%, 46.3% on statins, MRE (kPa 5.9 (2.2)), fibroscan (kPa 24.5 (15.1)), and mean MRI-PDFF of 7.9% (5%), consistent with F4 stage NASH. Cirrhotic compared to non-cirrhotic NASH patients (n >1000) had statistically significantly higher MRE (p < 0.0001) and lower MRI-PDFF (p < 0.0001) (Figure). In cirrhotic patients, 34.1% had PDFF ≤5% and 37.8% ≥8% at baseline, unrelated to steatosis grade on biopsy. At baseline NASH cirrhotic subjects with <8% compared with ≥8% PDFF had higher MELD (p = 0.0045), AST/ALT (p = 0.0001), MRE (p = 0.027), SHBG (p = 0.0003), and lower ALT (p = 0.002), platelets (p = 0.0059) and CAP (p = 0.037). In subjects with baseline PDFF ≥8%, resmetirom lowered PDFF by mean 30% and MRE by 0.4 kPa at week 16 (# with week 16 data will be expanded in presentation). In NASH cirrhotic subjects, resmetirom reduced LDL-C (20%), triglycerides (25%), and ApoB (19%) independent of baseline PDFF. Resmetirom was safe and well-tolerated.

Conclusion: NASH cirrhosis is associated with significantly higher MRE and lower PDFF than non-cirrhotic NASH. NASH cirrhotic subjects with lower baseline PDFF may represent a more advanced subtype.

PO-851

Study on multi-target engagement effect of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in animal model of NASH

Jong Suk Lee¹, Jung Kuk Kim¹, Seon Myeong Lee¹, Jae Hyuk Choi¹, Hyunjoon Kwon¹, Eun Jin Park¹, Jong Soo Lee¹, Dae Jin Kim¹, Sang Hyun Lee¹, In Young Choi¹. ¹Hanmi Pharm. Co., Ltd., Korea, Rep. of South
Email: iychoi@hanmi.co.kr

Background and aims: Since multiple biological pathways are involved in NASH progression, the approaches targeting multiple aspects should be required for effective treatment of NASH and eventually fibrosis. Recently, novel roles of incretin, especially glucagon and GIP in addition to GLP-1, have been demonstrated beyond metabolism such as inflammation and fibrosis. Thus, optimal use of these incretins simultaneously could be a promising strategy for NASH treatment. To address this and provide novel treatment option for NASH, HM15211, a long-acting Glucagon/GIP/GLP-1 triple agonist, was developed. Here, we evaluated potential benefits of

HM15211 by comparing its therapeutic effect with NASH drug candidates in high-fat diet induced mouse model of NASH.

Method: AMLN-diet induced NASH mice were administered either with HM15211 or NASH drug candidates (study 1: obeticholic acid (OCA), study 2: acylated GLP-1 or GLP-1/GIP agonist) for 12 weeks, followed by histological analysis. Additional liver tissue samples were subjected to qPCR analysis for related marker gene expression. For mechanistic study for anti-inflammation, THP-1 cell was used.

Results: In study 1, HM15211 treatment more efficiently normalized hepatic TG contents (-48.9%, -93.0% vs. vehicle for OCA, HM15211) and steatosis score compared to OCA (2.9, 2.1, 0.1 for vehicle, OCA, HM15211). Consistently, HM15211 treatment significantly reduced histological score for lobular inflammation (1.6, 1.1, 0.9 for vehicle, OCA, HM15211) and ballooning (1.4, 0.7, 0.0 for vehicle, OCA, HM15211) greater than OCA. Notably, while all individuals treated with HM15211 achieved NASH resolution criteria, only 14.3% achieved it after OCA treatment. In study 2, therapeutic effect of HM15211 was further compared with incretin analogs, and greater improvement in all sub-components of NAS was confirmed compared to acylated GLP-1 or GLP-1/GIP, highlighting potential benefits of multi-target engagement of HM15211 over other incretin analogs as well as FXR agonist for NASH treatment. Mechanistically, PMA-induced THP-1 cell adhesion and subsequent cytokine secretion such as TNF-alpha and IL-1beta were significantly attenuated by HM15211, explaining, at least in part, the underlying mechanism for its therapeutic effects observed *in vivo*.

Conclusion: Therefore, HM15211 may be a novel therapeutic option for NASH treatment. Efficacy study in biopsy proven NASH subjects is ongoing to assess the clinical relevance of these findings.

PO-889

Digital pathology with artificial intelligence analyses reveal new dynamics of treatment-induced fibrosis regression in non-alcoholic steatohepatitis

Nikolai V. Naoumov¹, Dominique Brees¹, Juergen Loeffler¹, Elaine Chng², Yayun Ren², Patricia Lopez¹, Dean Tai², Arun Sanyal³, Sophie Lamle¹. ¹Novartis Pharma AG, Basel, Switzerland; ²HistoIndex Pte. Ltd, Singapore; ³Virginia Commonwealth University School of Medicine, Richmond, United States
Email: nikolai.naoumov@novartis.com

Background and aims: Liver fibrosis is a dynamic process and a key prognostic determinant for clinical outcomes in non-alcoholic steatohepatitis (NASH). Current staging systems are static

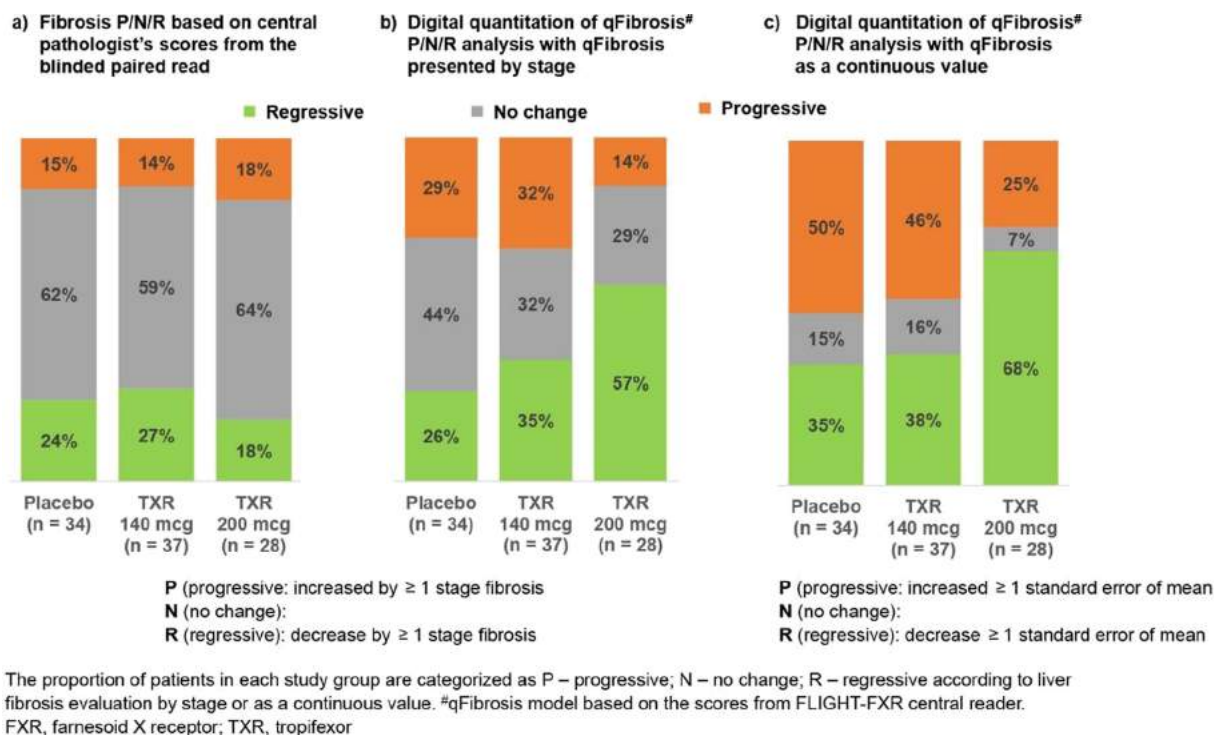


Figure: (abstract: PO-889): Changes in liver fibrosis between baseline and end of treatment

assessments of fibrosis and lack sensitivity in capturing fibrosis regression. Advances in second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy provide a standardized and reproducible approach for quantification of NASH features on a linear scale. The aim of this exploratory analysis was to understand the fibrosis dynamics and its relation to steatosis reduction after treatment with tropifexor (TXR), a non-bile acid farnesoid X receptor (FXR) agonist, in patients with NASH participating in FLIGHT-FXR study (NCT02855164).

Method: Unstained sections from 198 paired liver biopsies (baseline [BL] and end of treatment [EOT]) from 99 patients with NASH (fibrosis stage F2-F3) who received placebo (PBO; n = 34), TXR 140 µg (n = 37) or TXR 200 µg (n = 28) for 48 weeks were examined. Hepatic fat (qSteatosis) and liver fibrosis (qFibrosis) were quantitated using SHG/TPEF microscopy (Hepatology 2020;71:1953-66). Changes in septa morphology, collagen fiber parameters, and zonal distribution within liver lobules were also assessed quantitatively.

Results: TXR treatment led to dose-dependent reduction in qSteatosis (mean change: PBO, -0.25; TXR140, -0.6 [p = 0.047]; TXR200, -0.95 [p < 0.001]). There were strong correlations between qSteatosis and the results with magnetic resonance imaging-proton dense fat fraction (MRI-PDFF) at week 48 (r = 0.851) and for steatosis reduction BL to EOT (r = 0.709). qFibrosis analyses revealed fibrosis regression in a greater proportion of patients, than conventional microscopy (Figure). TXR led to a marked reduction in perisinusoidal fibrosis. Concomitant zonal quantitation of fibrosis and steatosis revealed that patients with greatest qSteatosis reduction had a marked reduction in perisinusoidal fibrosis. The changes of fibrous septa (thinning and reduction in collagen fiber parameters [number, length, width]) were greater with TXR200 vs placebo.

Conclusion: Following therapies that reduce hepatic lipid load and lipotoxicity, fibrosis regression is initially seen in the perisinusoidal regions, around areas of steatosis reduction. Digital pathology provides new insights in the dynamics of fibrosis regression, which are not captured by conventional staging systems.

PO-981

Aldafermin reduces hydrophobic bile acids in a 24-week, randomized, double-blind, placebo-controlled, multicenter study in patients with non-alcoholic steatohepatitis

Arun Sanyal¹, Lei Ling², Guy Neff³, Cynthia Guy⁴, Mustafa Bashir⁴, Angelo Paredes⁵, Juan Frias⁶, Ziad H. Younes⁷, James F. Trotter⁸, Nadege T. Gunn⁹, Sam Moussa¹⁰, Anita Kohli¹¹, Kristen Nelson¹², Mildred Gottwald¹², William Chang¹², Andrew Yan¹², Alex DePaoli¹², Hsiao Lieu¹², Stephen Harrison¹³. ¹Virginia Commonwealth University, Richmond, United States; ²NGM Biopharmaceuticals, South San Francisco, United States; ³Covenant Research and Clinics, Florida; ⁴Duke University, Durham, United States; ⁵Brooke Army Medical Center, San Antonio, United States; ⁶National Research Institute, Los Angeles, United States; ⁷Gastro One Research, Germantown, United States; ⁸Texas Digestive Disease Consultants, Dallas, United States; ⁹Pinnacle Clinical Research, Austin, United States; ¹⁰Adobe Clinical Research, Tucson, United States; ¹¹Arizona Liver Health, Chandler, United States; ¹²NGM Biopharmaceuticals, South San Francisco, United States, ¹³Pinnacle Clinical Research, San Antonio, United States
 Email: lling94080@yahoo.com

Background and aims: Higher serum bile acid levels are associated with an increased risk of cirrhosis and liver-related morbidity and mortality. Serum bile acids correlate with portal hypertension, and can predict decompensation, liver failure and transplant-free survival in chronic liver disease (Horvatits et al., 2017). Aldafermin, an engineered FGF19 analog, potently inhibits bile acid synthesis via the suppression of CYP7A1, which encodes the first and rate-limiting enzyme in the classic bile acid synthetic pathway. Here we report results from a secondary analysis of aldafermin on circulating bile acid profile in a 24-week, randomized, double-blind, placebo-controlled trial in patients with NASH.

Method: 78 subjects were randomized 1:2 to receive placebo (n = 25) or aldafermin 1 mg (n = 53) SC QD for 24 weeks at 9 US study sites. Key inclusion criteria included biopsy-proven NASH with NAS \geq 4, F2 or F3 fibrosis and absolute liver fat content \geq 8%. Fasting serum samples were collected at day 1 and week 24. Concentrations of

individual bile acids and 7 α -hydroxy-4-cholesten-3-one (a surrogate of hepatic CYP7A1 activity) were measured by mass spectrometry methods. Bile acid hydrophobicity indices were determined according to Heuman et al (J Lipid Res 1989).

Results: Aldafermin treatment reduced concentrations of deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), glycocholic acid (GCA) and glychenodeoxycholic acid (GCDCA), with changes of -0.6 $\mu\text{mol/L}$, -0.7 $\mu\text{mol/L}$, -0.6 $\mu\text{mol/L}$ and -0.9 $\mu\text{mol/L}$ at week 24 ($p < 0.001$ vs placebo for all comparisons), corresponding to relative changes of -70% , -56% , -60% and -25% , respectively, in subjects receiving aldafermin. In contrast, placebo-treated subjects had increases in these bile acids ($+83\%$, $+219\%$, $+87\%$ and $+51\%$ for DCA, GDCA, GCA and GCDCA, respectively). No reductions in tauroconjugated bile acids were seen with aldafermin treatment. Furthermore, aldafermin lowered total CA, total CDCA, total DCA, total primary bile acids and total secondary bile acids. The ratio of glycine to taurine conjugates (G/T ratio), as well as the ratio of (CA + DCA) to (CDCA + LCA), were decreased with aldafermin treatment.

Conclusion: Administration of aldafermin produced significant reductions in bile acids, and the major hydrophobic bile acids in particular. The preferential reduction of the more hydrophobic, glycine-conjugated bile acids, rather than the more hydrophilic, taurine-conjugated, bile acids by aldafermin resulted in a lower G/T ratio and reduced bile acid toxicity.

PO-1082

Atherosclerotic cardiovascular risk assessment in a 24-week, randomized, double-blind, placebo-controlled study of aldafermin

Nadege T. Gunn¹, Lei Ling², Guy Neff³, Cynthia Guy⁴, Mustafa Bashir⁴, Angelo Paredes⁵, Juan Frias⁶, Ziad H. Younes⁷, James F. Trotter⁸, Sam Moussa⁹, Anita Kohli¹⁰, Margery A. Connelly¹¹, Kristen Nelson¹², Mildred Gottwald¹², William Chang¹², Andrew Yan¹², Alex DePaoli¹², Hsiao Lieu¹², Stephen Harrison¹³. ¹Pinnacle Clinical Research, Austin, United States; ²NGM Biopharmaceuticals, South San Francisco, United States; ³Covenant Research and Clinics, United States; ⁴Duke University, United States; ⁵Brooke Army Medical Center, United States; ⁶National Research Institute, United States; ⁷Gastro One Research; ⁸Texas Digestive Disease Consultants; ⁹Adobe Clinical Research; ¹⁰Arizona Liver Health; ¹¹Labcorp; ¹²NGM Biopharmaceuticals; ¹³Pinnacle Clinical Research
Email: lling94080@yahoo.com

Background and aims: Aldafermin is an engineered FGF19 analogue that inhibits bile acid synthesis and regulates metabolic homeostasis. In a 24-week, randomized, double-blind, placebo-controlled study in NASH patients with serial liver biopsies, aldafermin treatment resulted in liver fat reduction, fibrosis improvement and NASH resolution. However, aldafermin increased serum cholesterol levels by inhibiting CYP7A1, which encodes the rate-limiting enzyme in the conversion of cholesterol to bile acids. Here we report results on cardiovascular risk assessment and key lipoproteins implicated in atherosclerosis from this study.

Method: 78 subjects were randomized 1:2 to receive PBO ($n = 25$) or aldafermin 1 mg ($n = 53$) SC QD for 24 weeks. Key inclusion criteria included biopsy-proven NASH with NAS ≥ 4 , stage 2–3 fibrosis and absolute liver fat content $\geq 8\%$. As pre-specified in the protocol, subjects were to start with rosuvastatin if statin naïve or switch to rosuvastatin if already on statin therapy, to treat LDL-C elevations of >10 mg/dL from baseline. Atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated per ACC/AHA guidance. Triglyceride and cholesterol content in the triglyceride-rich lipoproteins (TRL), and concentrations of apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1), were measured at baseline and week 24.

Results: At baseline, mean ASCVD risk scores were 15.0% and 11.6% in the aldafermin and placebo groups, respectively. At week 24, a greater reduction from baseline in the ASCVD risk score was observed in the

aldafermin group compared to placebo (-3.4% and -1.2% in absolute ASCVD score in aldafermin and placebo groups, respectively, $p = 0.032$ vs placebo). Both triglyceride and cholesterol content in TRL declined in subjects treated with aldafermin but not placebo (-27% and -17% for triglyceride and cholesterol content, $p = 0.006$ vs placebo for both comparisons). The aldafermin group, but not the placebo group, had reductions in the pro-atherogenic lipoprotein ApoB (-11% , $p = 0.002$ vs baseline) and increases in the anti-atherogenic lipoprotein ApoA1 ($+6\%$, $p = 0.037$ vs baseline). No significant change in other lipids and lipoprotein particles was seen in the aldafermin group compared to placebo at week 24. No patients experienced cardiovascular events during the study.

Conclusion: Aldafermin-associated cholesterol increase can be safely managed with a statin. At the end of treatment, an overall favorable cardiovascular risk profile was achieved in the aldafermin arm.

PO-1112

Analysis of non-invasive biomarker tests in the Phase 2 FASCINATE-1 Study of FASN Inhibitor TVB-2640

Marie O'Farrell¹, Katharine Grimmer¹, Cristina Alonso², Laura Millán², Bill McCulloch¹, Rohit Loomba³, George Kemble¹. ¹Sagimet Biosciences, San Mateo, United States; ²OWL Metabolomics, Derio, Spain; ³University College San Diego, San Diego, United States
Email: marie.ofarrell@sagimet.com

Background and aims: FASN synthesizes palmitate and is the last committed step in the de novo lipogenesis (DNL) pathway. FASN is an attractive target in NASH; not only does DNL cause steatosis and generate lipotoxins, but it is necessary for activation and fibrogenic activity of human liver stellate cells. TVB-2640 is an oral, first-in-class, small molecule reversible FASN inhibitor. In the Phase 2 study FASCINATE-1 (NCT03938246), TVB-2640 reduced liver fat by 9.6% at 25 mg ($p = 0.053$), and 28.1% at 50 mg ($p = 0.001$). MRI-PDFF responder rates (reduction $\geq 30\%$) were 11% in placebo, 23% at 25 mg, and 61% at 50 mg ($p = 0.001$). A comprehensive panel of non-invasive tests (NITs) was included to investigate biomarkers of FASN inhibition and response.

Method: The efficacy and biomarker analyses included 85 patients (27, 30, 28 for pbo, 25 mg and 50 mg respectively). Assays included metabolomic profiling of approx. 400 species, tripalmitin as a marker of FASN activity, ELF, ProC3, CK-18 M30 and M65, FGF21 and adiponectin. Genotyping of relevant SNPs was done in approx. 16 patients. The objective was to correlate liver fat response with NITs and gain insight into mechanism and patient response.

Results: TVB-2640 treatment reduced median tripalmitin levels by 25% (25 mg) and 55% (50 mg, $p < 0.001$) at wk 12 compared to baseline, evident by wk 4 (only 50 mg tested). MRI-PDFF responders had highest decreases in tripalmitin, indicating a FASN-mediated effect on liver fat. Metabolomic profiling showed that in placebo patients, very few metabolites were altered over time. TVB-2640 (50 mg) decreased levels of several diglycerides and triglycerides at wk 12, most notably species with shorter chains and greater saturation consistent with inhibition of FASN. A number of glycerophospholipids were also reduced. Palmitate is a building block for the ceramide and sphingomyelin classes which can mediate lipotoxicity. Several species were significantly decreased by TVB-2640 at 50 mg, but not at 25 mg. As previously shown, fibrosis markers ProC3 and TIMP1 decreased, and adiponectin and FGF21 increased with TVB-2640 treatment. Additional bioinformatics and SNP analysis is ongoing, to explore associations with changes in liver fat, tripalmitin and fibrosis markers.

Conclusion: FASCINATE-1 results show that TVB-2640 decreased liver fat and decreased markers of inflammation and fibrosis, consistent with mechanism and preclinical results. TVB-2640 will be tested in a Phase 2b liver biopsy study in NASH and liver histology end points will be assessed in conjunction with NIT analysis.

POSTER PRESENTATIONS

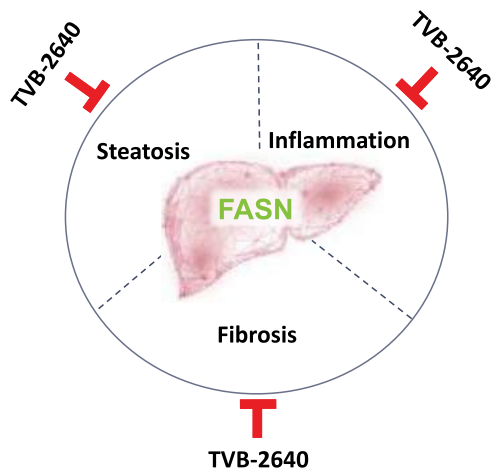


Figure:

PO-1198

Efficacy Signals Of 4-Week Oral DUR-928 in NASH Subjects

Eric Lawitz¹, Tarek Hassanein², Douglas Denham³, Michael Waters⁴, Brian Borg⁵, Gwenaelle Mille⁶, Deborah Scott⁶, Andy Mikszta⁶, John Culwell⁶, Dave Ellis⁶, James Brown⁶, WeiQi Lin⁶. ¹Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; ²Southern California Research Center; ³Clinical Trials of Texas; ⁴eStudySite; ⁵Southern Therapy and Advanced Research; ⁶Direct Email: lawitz@txliver.com

Background: DUR-928 is an endogenous sulfated oxysterol and an epigenetic regulator. It has been shown to stabilize mitochondria, reduce lipotoxicity, regulate inflammatory responses, promote cell survival, and stimulate hepatic regeneration in cultured cells and in animal models.

Recently, we reported that daily oral DUR-928 for 4 weeks was well tolerated in subjects with NASH and had overall improvement in liver enzymes, liver fat content by MRI-PDFF, serum lipid profiles, and certain biomarkers¹. Here we present further analysis of efficacy signals from this trial.

Method: A total of 65 subjects with F1-F3 NASH, defined by either liver biopsy or phenotype, with a baseline hepatic fat content $\geq 10\%$ by MRI-PDFF, completed this randomized, open-label, multi-center trial, of whom 62 also completed the 4-week follow-up period. All subjects received daily oral DUR-928 at 50 mg or 150 mg QD, or 300 mg BID (600 mg/day) for 4 weeks.

Results: In addition to overall improvement in multiple parameters in all 3 dose groups as reported earlier¹, hepatic stiffness by TE and MRE, measured before and after dosing, changed by -11% (TE) or -6% (MRE) in the 50 mg, -7% (TE) or 4% (MRE) in the 150 mg, and -2% (TE) or 0% (MRE) in the 600 mg groups.

At the end of 4-week dosing, plasma levels of pro-C3, a liver fibrosis marker, were decreased from baseline by -8% , -1% , and -5% in the 50 mg, 150 mg, and 600 mg groups, respectively. At 2-week post-dose follow-up, pro-C3 levels were -7% , 8% , and 1% from baseline in the 50 mg, 150 mg, and 600 mg groups, respectively.

Overall improvement was also observed in insulin resistance (by HOMA-IR) after 4-week DUR-928 treatment. At the end of dosing, HOMA-IR was -22% , -18% , and 1% from baseline in the 50 mg, 150 mg, and 600 mg groups, respectively. At 2-week post-dose follow-up, it was -10% from baseline in the 50 mg group, and 17% and 3% in the 150 mg and 600 mg groups, respectively.

Conclusion: Daily oral DUR-928 (50–600 mg) for 4 weeks in F1-F3 NASH subjects was well tolerated and resulted in overall improvement in liver enzymes, liver fat content by MRI-PDFF, serum lipid profiles, liver stiffness by TE and MRE, insulin resistance, and biomarkers (including the liver fibrosis marker, pro-C3). The results suggest that epigenetic regulation of gene expression and their signalling pathways is an attractive approach to treat NASH. Further

study of DUR-928 in subjects with metabolic disorders, such as NASH, is warranted.

Figure: 1.

Lawitz et al.: Safety and Efficacy Signals of Daily Oral DUR-928 for 4-Weeks in F1-F3 NASH. AASLD 2020 Poster No. 1693

PO-1314

The role of reduction in liver fat content (MRI-PDFF) and ALT in predicting treatment response in NASH: A secondary analysis of the randomized, controlled BALANCED trial

Rohit Loomba¹, Erik Tillman², Chen Hu³, Reshma Shringarpure⁴, Erica Fong⁴, Brittany de Temple⁴, Tim Rolph⁴, Andrew Cheng⁴, Kitty Yale⁴, Stephen Harrison⁵. ¹University of California, San Diego, Gastroenterology, San Diego, United States; ²Akero Therapeutics, South San Francisco, United States; ³Medpace Inc.; ⁴Akero Therapeutics; ⁵Pinnacle Clinical Research, San Antonio, United States Email: roloomba@health.ucsd.edu

Background and aims: Efruxifermin (EFX) treatment resulted in significantly greater reduction in liver fat content (LFC) as assessed by MRI-PDFF after 12 wks compared to placebo, and was associated with NASH resolution and fibrosis improvement at wk 16–20 liver biopsy assessment.¹ Because of the consistently large reductions of liver fat, this study provides a unique dataset to evaluate the utility of a decline in serum ALT of ≥ 17 U/L among MRI-PDFF responders ($\geq 30\%$ decline) for predicting histologic response in NASH when used alone or combined with normalization of liver fat ($\leq 5\%$ by MRI-PDFF) at wk 12. The aim of this secondary analysis of the BALANCED¹ trial was to examine the utility of a threshold response for ALT in predicting resolution of NASH among a treated population who achieved a $\geq 30\%$ relative reduction of liver fat.

Methods: This analysis included a subset of patients who had both MRI-PDFF at baseline and wk 12, and baseline and end-of-treatment liver biopsy (n=42). All 42 patients achieved a $\geq 30\%$ relative reduction in LFC at wk 12, and response to histologic end points was compared for ALT responders and ALT non-responders.

Results: Among the MRI-PDFF responders, the mean age, BMI, baseline NAS and LFC were 52y, 37 kg/m², 5.5 and 18.9% for ALT responders (N=28) and 54y, 36 kg/m², 5.4 and 19.6%, for ALT non-responders (N=14), respectively. ALT responders were twice as likely as ALT non-responders to achieve NASH resolution. Among ALT responders who also achieved normalization of LFC ($\leq 5\%$) the odds of achieving NASH resolution were even higher (Table 1). The AUROC (95% CI) of ALT decline by ≥ 17 U/L to predict NASH resolution was 0.7410 (0.5561, 0.9260). ALT responders were also more likely to achieve the composite end point of NASH resolution and fibrosis improvement.

Table 1: Odds Ratios for Predicting Histologic Responses by ALT Responder Status (MRI-PDFF responders with available post-treatment biopsies)

Marker	Histologic end point	Odds Ratio (95% CI)
ALT response	NASH Resolution	2.077 (0.554, 7.788)
ALT response and normalization of liver fat ($<5\%$)	NASH Resolution	2.667 (0.738, 9.629)
ALT response	NASH Resolution and Fibrosis improvement	2.842 (0.522, 15.465)

¹Harrison et. al. 2020. Hepatology, 72; 1S; 6A.

Conclusion: Among MRI-PDFF responders, a decline in serum ALT of at least 17 U/L is a robust marker in predicting NASH resolution for EFX and potentially other metabolic therapies with a potent anti-steatotic effect.

PO-1359

Anti-oxidant, anti-inflammatory, and anti-fibrotic properties of triterpenic acids and phenylpropanoids on in vitro models of non-alcoholic steatohepatitis

Noel Salvoza^{1,2}, Chiara Bedin³, Andrea Saccani³, Claudio Tiribelli¹, Natalia Rosso¹. ¹Fondazione Italiana Fegato Onlus, Basovizza, Italy; ²Philippine Council for Health Research and Development, Taguig, Philippines; ³ABRESEARCH srl, Brendola, Italy
Email: noel.salvoza@fegato.it

Background and aims: There is no approved pharmacological treatment for NASH. Preliminary data showed hepatoprotective properties of triterpenic acids ABRTA22 (TA) and phenylpropanoids ABRPP09 (PP) in animal models of steatosis but the molecular mechanisms underlying the beneficial effects are still elusive. We assessed the effects of both compounds in a well-established *in vitro* models of steatosis and early-stage NASH.

Method: Monocultures of human hepatocytes (HuH7) and simultaneous co-cultures (SCC) of human hepatocytes (HuH7) and hepatic stellate cells (LX2) were exposed to free fatty acid (FFA) alone or in combination with TA (10 nM; 50 nM; 100 nM) and PP (0.1 μM; 10 μM; 40 μM). Intracellular FFA accumulation was assessed by flow cytometry using Nile Red assay; the expression of genes involved in inflammation and fibrogenesis were quantified by RT-PCR. The generation of reactive oxygen species (ROS) and collagen deposition were also determined.

Results: Exposure of HuH7 cells to FFA induced a 40% (p < 0.001) increase in ROS generation and up-regulation of pro-inflammatory genes, IL-8 (1.7-fold, p < 0.05) and TNF-alpha (2.5-fold, p < 0.01). The exposure of SCC to FFA significantly increased both COL1A1 gene expression and extracellular collagen deposition. Co-treatment of either TA and PP and FFA resulted in a reduction of ROS generation but only PP showed a potent antioxidant effect at all concentrations (p < 0.05; p < 0.01 vs FFA). Addition of TA resulted in a non-significant reduction in IL-6 and IL-8 expressions but a significant down-regulation of TNF-alpha at 10nM and 50nM (p < 0.05). Likewise, PP reduced the expression of all the cytokines, with significant down-regulation in TNF-alpha at 0.1 μM and 10 μM (p < 0.05). Both compounds decreased COL1A1 gene expression (1.7-folds, p < 0.05 vs FFA) and extracellular collagen deposition (50%, p < 0.05 vs FFA) at the lowest concentration. In both models, treatment of TA or PP in the absence of FFA did not induce any effects in the extent of steatosis, inflammation, ROS generation, and collagen deposition.

Conclusion: Either triterpenic acids ABRTA22 (TA) or phenylpropanoids ABRPP09 (PP) reduces the FFA-related inflammation and ROS generation. Of notice, both compounds reduce collagen deposition suggesting their possible use in a clinical setting.

PO-1762

Correlation between changes in liver fat content and improvements in serum markers of liver injury, fibrosis, metabolism, and in histologic parameters following treatment with efruxifermin

Stephen Harrison¹, Peter Ruane², Bradley Freilich³, Guy Neff⁴, Rashmee Patil⁵, Cynthia Behling⁶, Chen Hu⁷, Reshma Shringarpure⁸, Brittany de Temple⁸, Erik Tillman⁸, Tim Rolph⁸, Andrew Cheng⁸, Kitty Yale⁹. ¹Pinnacle Clinical Research, San Antonio, United States; ²Ruane Clinical Research Group Inc, Los Angeles, United States; ³Kansas City Research Institute, Kansas City, United States; ⁴Covenant Research LLC, Sarasota, United States; ⁵South Texas Research Institute, Edinburg, United States; ⁶Pacific Rim Pathology, San Diego, United States; ⁷Medpace, Cincinnati, United States; ⁸Akero Therapeutics, South San Francisco, United States; ⁹Akero Therapeutics, South San Francisco, United States
Email: kyale@akerotx.com

Background and aims: Efruxifermin (EFX), a long-acting FGF21 analog, achieved the primary end point of significant reduction in liver fat in the Phase 2a BALANCED study.¹ This analysis evaluated the

association between changes in liver fat content (LFC) and markers of liver injury, fibrosis, metabolic parameters and histologic features following treatment with EFX.

Methods: Of 80 randomized patients, 68 had available MRI-PDFF assessments at baseline and Wk 12. Correlations between change in LFC and change in markers of interest at Wk 12 were performed in patients with non-missing values for both parameters at baseline and Wk 12. Markers of glycemic control were assessed in the subset of patients with Type 2 Diabetes (T2D, n = 35). MRI-PDFF responders, defined by a ≥30% reduction in liver fat at Wk 12, were eligible for a liver biopsy; post-treatment biopsies were available for 42 patients.

Table 1: Results

A. Correlation Between Relative (%) Reduction from Baseline in LFC and % Change from Baseline for Serum Markers		
Marker	Spearman Correlation Coefficient	P Value
<i>All Patients with non-missing Wk 12 values (N = 67)</i>		
ALT	0.5315	<0.0001
Pro-C3	0.5824	<0.0001
Pro-C3/C3M Ratio	0.4560	0.0001
Triglycerides	0.5986	<0.0001
<i>Patients with Type 2 Diabetes (N = 35)</i>		
Adiponectin	-0.6426	<0.0001
HbA1c	0.6064	0.0001
B. LFC Normalization and Improvements in NASH Histology		
Change in LFC	Histologic End point	Odds Ratio (95% CI) ^a P value ^b
LFC normalization	NASH Resolution	4.083 (1.122, 14.863) 0.0365
LFC normalization	NAS Reduction by ≥4	6.429 (1.662, 24.860) 0.0068

^aWald 95% CI;

^bFisher's exact test

¹Harrison et al. 2020. Hepatology, 72; 1S; 6A.

Results: All EFX-treated patients with MRI-PDFF at Wk 12 (n = 48) demonstrated ≥30% relative reduction in LFC compared to 2 patients on placebo.¹ Magnitude of reduction in LFC at Wk 12 correlated significantly with extent of reduction in ALT, Pro-C3, Pro-C3/C3-M ratio and triglycerides (**Table 1A**), and for patients with T2D, with extent of improvements in adiponectin and HbA1c. Patients who normalized LFC (≤5%) had significantly higher odds of achieving NASH resolution (NAS=0 for ballooning, ≤1 for inflammation) or improvement in NAS by ≥4 (**Table 1B**).

Conclusions: Treatment with EFX resulted in a significant reduction in LFC which correlated with improvements in markers of liver injury, fibrosis, metabolic parameters and histologic features. EFX treatment has the potential to significantly improve all aspects of the pathophysiology of NASH with fibrosis.

PO-1819

KS-356, a novel inhibitor of TGF-beta superfamily signaling, improves obesity and obesity-related hepatic steatosis by inhibition of TGF-beta/Smad3 signaling pathway in high-fat diet-induced mice

Kisoo Pakh¹, Sang Gil Lee^{2,3}, Chanmin Joung², Sungeun Kim¹, Sang Geon Kim^{3,4}, Won-Ki Kim². ¹Korea University Anam Hospital, Department of Nuclear Medicine, Korea, Rep. of South; ²Korea University, Institute for Inflammation Control, Korea, Rep. of South; ³Seoul National University, College of Pharmacy and Research Institute of Pharmaceutical Sciences, Korea, Rep. of South; ⁴Dongguk University, College of Pharmacy, Korea, Rep. of South
Email:

Background and aims: Obesity-induced inflamed visceral adipose tissue (VAT) secretes pro-inflammatory cytokines thereby promoting

POSTER PRESENTATIONS

systemic inflammation and insulin resistance which further exacerbate obesity-associated non-alcoholic fatty liver disease (NAFLD). TGF- β /Smad3 signaling has a crucial role in the inflammatory events within the VAT. Here, we investigate whether KS-356, a novel anti-inflammatory synthetic small molecule compound, can inhibit TGF- β /Smad3 signaling thereby exhibiting therapeutic effect against inflamed VAT and subsequent NAFLD in high-fat diet-induced mice.

Method: NAFLD was induced by a high-fat diet (60% fat) for 20 weeks using the male C57BL/6 mice. KS-356 (50 mg/kg) was orally given daily for 20 weeks. In vivo VAT- and systemic inflammation were measured by using ^{18}F -fluorodeoxyglucose positron emission tomography and C-reactive protein levels. Both insulin tolerance- and glucose tolerance test were performed to assess the status of insulin resistance and glucose intolerance. Histological and molecular analyses were performed on harvested liver and VAT.

Results: KS-356 inhibited TGF- β /Smad3 signaling pathway and remarkably suppressed high-fat diet-induced VAT inflammation and its related systemic inflammation. Furthermore, KS-356 significantly improved insulin sensitivity with glucose homeostasis and reduced hepatic steatosis.

Conclusion: KS-356 mitigates the development of NAFLD through attenuation of VAT inflammation. Our novel findings support the potential use of KS-356 as a therapeutic drug for NAFLD.

PO-1851

Significant lipid lowering by ASC41 oral tablet, a liver targeted THR β agonist, in a phase I randomized, double-blind, placebo controlled single- and multiple-ascending dose study

Jinzi Wu¹, Melissa Palmer², Handan He³, Jiao Zheng⁴, Shengdan Nie⁴, Zhili Chen⁵. ¹Gannex Pharma Co., Ltd, Shanghai, China; ²Gannex Pharma Co., Ltd, Shanghai, China; ³Gannex Pharma Co., Ltd, R andamp, D department, Shanghai, China; ⁴People's Hospital of Hunan Province, Clinical Trial Research Center, Changsha, China; ⁵Gannex Pharma Co., Ltd, Clinical operation Department, Shanghai, China

Background and aims: ASC41 is a small molecule prodrug and selectively cleaved in hepatic tissue by the action of cytochrome P450 isozyme 3A4, to release a pharmacologically active metabolite, ASC41-A, which is a potent and selective thyroid hormone receptor beta (THR β) agonist. The aim of this study was to evaluate the safety, tolerability, pharmacokinetics and lipid lowering potential of ASC41 oral tablets in subjects with low-density lipoprotein cholesterol (LDL-C) >110 mg/dL.

Method: This phase I trial was a randomized, double-blind, placebo controlled single- and multiple-ascending dose study in 65 subjects with elevated LDL-C (>110 mg/dL). ASC41 has been formulated in commercially ready oral tablets developed in-house using proprietary technology. In the single-ascending dose (SAD) portion of the study, subjects were treated with 1 mg (n = 15), 2 mg (n = 15), 5 mg (n = 15), 10 mg (n = 10) or 20 mg (n = 10) ASC41 oral tablets or matching placebo tablets. In the multiple-ascending dose (MAD) portion of the study, subjects were treated with 1 mg (n = 15), 2 mg (n = 15) or 5 mg (n = 15) ASC41 oral tablets or matching placebo tablets, QD for 14 days. A washout period of at least 14 days was required between SAD and MAD portions of this study.

Results: In the SAD study, data suggested that ASC41 was safe and well tolerated up to a dose of 20 mg. ASC41 oral tablet formulation showed dose-proportional pharmacokinetic profiles from 1 mg to 20 mg. In the MAD study, data showed that after 14 days of oral QD dosing, subjects demonstrated clinically meaningful and statistically significant reductions in LDL-C and triglycerides compared to placebo, with no significant impact on HDL-C (table 1). ASC41 was tolerable and had a benign adverse event (AE) profile at all doses following 14-day treatment, without grade 3 or above AEs, no serious adverse events or premature discontinuations. In addition, ASC41 displayed dose-proportional pharmacokinetic profiles from 1 mg to 5 mg following 14-day QD dosing.

Table 1. Placebo-adjusted relative change (mean) from baseline after 14 days of once daily oral dosing of ASC41 tablets

	1 mg (n=12)	2 mg (n=12)	5 mg (n=12)
Placebo-adjusted LDL-C reduction	-0.42%	-11.94%	-19.99%
P-value vs placebo	p=0.947	p=0.052	p=0.002
Placebo-adjusted triglyceride reduction	-39.43%	-31.06%	-34.49%
P-value vs placebo	p=0.002	p=0.029	p=0.015
Placebo-adjusted TC reduction	-1.48%	-8.53%	-10.71%
P-value vs placebo	p=0.766	p=0.142	p=0.030
Placebo-adjusted HDL-C reduction	8.11%	-2.54%	-0.22%
P-value vs placebo	p=0.135	p=0.668	p=0.962

Conclusion: These data supported advancement of the ASC41 clinical program for the indication of NASH. The successful development of commercially-ready oral tablet formulation will accelerate ASC41 clinical development.

PO-1908

Significant Improvement of NAFLD Activity Scores and Liver Fibrosis by ASC41, a Selective THR- β Agonist, in High Fat Diet Induced NASH SD Rats

Jinzi Wu¹, Handan He², Xiaodong Li³, Bailing Yang¹, Eiketsu Sho⁴. ¹Gannex Pharma Co., Ltd; ²Gannex Pharma Co., Ltd, China; ³Gannex Pharma Co., Ltd, China; ⁴KCI Biotech (Suzhou) Inc., China
Email: lingjie.jiang@ascltis.com

Background and aims: Thyroid hormone receptor β (THR- β) agonism has been reported to be an effective strategy to reduce low-density lipoprotein-cholesterol (LDL-C) and triglycerides for non-alcoholic steatohepatitis (NASH) treatment. ASC41 is a small molecule, hepatic targeting, potent and selective thyroid hormone receptor beta (THR- β) agonist prodrug, which is converted to its pharmacologically active metabolite ASC41-A by CYP3A4 in the liver. A phase I clinical trial of ASC41 tablets conducted in China demonstrated clinically meaningful and statistically significant reductions in LDL-C and triglycerides compared to placebo.

The objective of this study was to evaluate efficacy of ASC41 on high fat diet (HFD) induced NASH male SD rats with streptozotocin (STZ) and diethylnitrosamine (DEN) injection.

Method: Rats with STZ and DEN injection were used to promote diabetes and liver fibrosis, respectively. Newborn rats received two STZ injections on the 2nd day and 7th day after birth, respectively. After a 2-week lactation, a DEN injection was given and followed by lactation for another 4 weeks. 10 newborn male rats receiving neither STZ nor DEN injection were defined as normal control animals. 50 male rats with STZ and DEN injections were selected and randomly divided into 5 groups as model+vehicle group, comparator group (MGL3196 5 mg/kg), ACS41 0.5 mg/kg, ACS41 1.5 mg/kg, ACS41 4.5 mg/kg. All rats were fed with HFD (60KCal% Fat + 1.25% Cholesterol + 0.5% cholate) by oral gavage for 8 weeks, and ASC41 and MGL3196 were given 1 week after HFD feeding, once per day for 7 weeks. LDL-c were measured. Livers were collected for pathological detection.

Results: ASC41 demonstrated dose-dependently reductions in liver steatosis, inflammatory cell infiltration, ballooning change and total non-alcoholic fatty liver disease activity score (NAS). ASC41 at 1.5 mg/kg and 4.5 mg/kg showed higher NAS reductions relative to MGL3196 at 5 mg/kg (p = 0.01 and P < 0.001) (Figure 1).

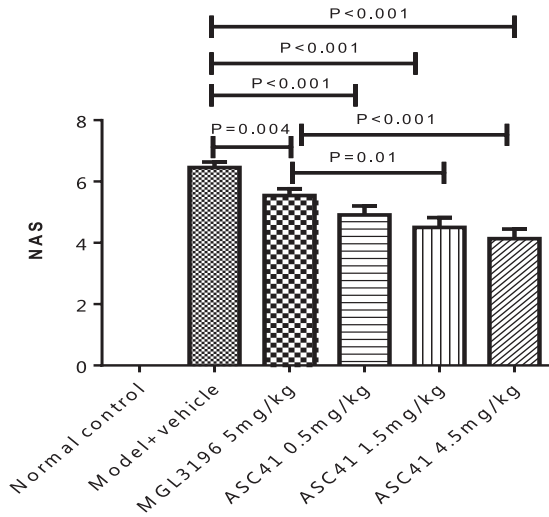


Figure 1: Improvement in NAS after 7-week treatment. NAS, non-alcoholic fatty liver disease activity score, was defined as the sum of steatosis, ballooning and inflammation score.

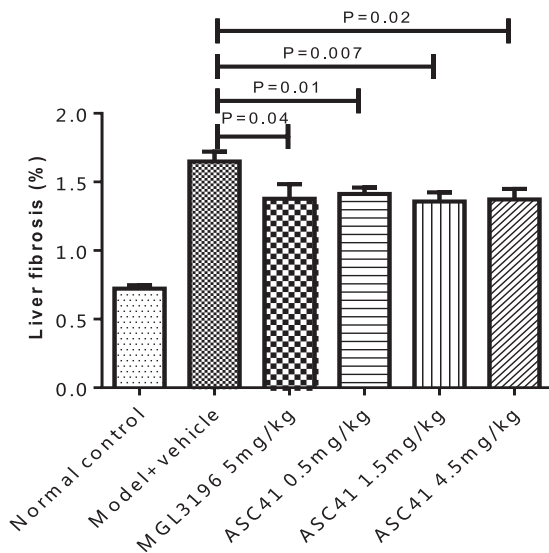


Figure 2: Improvement in fibrosis after 7-week treatment.

ASC41 at 0.5 mg/kg showed a 23.9% reduction in NAS score and a 14.4% reduction in liver fibrosis, similar to MGL3196 at 5 mg/kg (Figure 2). ASC41 at 1.5 mg/kg and 4.5 mg/kg both showed a significant decrease in serum LDL-C.

Conclusion: ASC41 demonstrated NAS reductions and anti-fibrotic benefits in the HFD+DEN+STZ rat NASH Model. The current efficacy data supported the advancement of ASC41 into clinical trials in human.

PO-1961

Significant improvement of NAFLD activity scores and liver fibrosis by ASC42, a novel non-steroidal FXR agonist, in high fat diet induced NASH mice

Jinzi J. Wu¹, Xiaodong Li¹, Handan He¹, Eiketsu Sho², Jinhua Chen¹.
¹Gannex Pharma Co., Ltd, Shanghai, China; ²KCI Biotech (Suzhou) Inc., Suzhou, China
 Email:

Background and aims: Farnesoid X receptor (FXR) agonists have shown to benefit patients with non-alcoholic steatohepatitis (NASH).

ASC42 is A novel non-steroidal, selective, potent FXR agonist and its phase I clinical trial is currently being conducted in the United States. The objective of this study was to evaluate the therapeutic efficacy of ASC42 on high fat diet induced NASH model in male C57BL/6 mice with streptozotocin (STZ) and diethylnitrosamine (DEN) injection.

Method: Mice with STZ and DEN injection were used to promote diabetes and liver fibrosis, respectively. Newborn mice received STZ injection on the 2nd day after birth. After a 2-week lactation, a DEN injection was given and followed by lactation for another 4 weeks. 10 newborn male mice receiving neither STZ nor DEN injection were defined as normal control animals. 50 male mice with STZ and DEN injection were randomly divided into 5 groups, the model+vehicle, comparator compound (OCA 30 mg/kg), ASC42 3 mg/kg, ASC42 10 mg/kg and ASC42 30 mg/kg. All rats were fed with HFD (60KCal % Fat + 1.25% Cholesterol + 0.5% cholate) by oral gavage for 8 weeks, and ASC42 and OCA were given 1 week after HFD feeding, once per day for 7 weeks. Livers were collected for pathological detection.

Results: ASC42 demonstrated dose-dependently reductions in liver steatosis, inflammatory cell infiltration, ballooning change and total non-alcoholic fatty liver disease activity score (NAS). ASC42 at 30 mg/kg showed a significantly higher NAS reduction relative to OCA at 30 mg/kg (p < 0.001). ASC42 at 3 mg/kg showed a 46.2% reduction in NAS score and a 15.2% reduction in liver fibrosis, similar to OCA at 30 mg/kg (Figures 1 and 2). Total glyceride in liver exhibited a dose-proportional decrease in ASC42-treated mice.

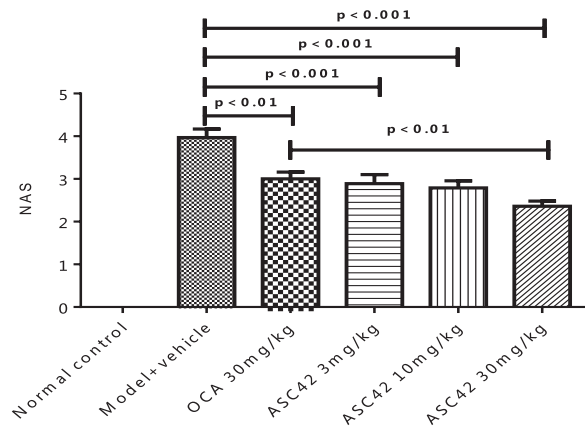


Figure 1: Improvement in NAS after 7-week treatment. NAS, non-alcoholic fatty liver disease activity score, was defined as the sum of steatosis, ballooning and inflammation score.

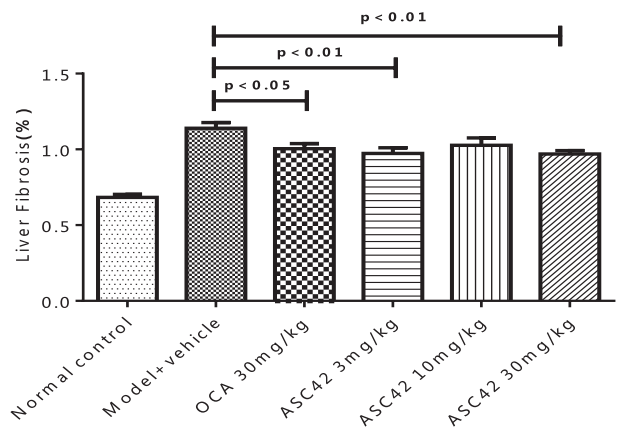


Figure 2: Improvement in fibrosis after 7-week treatment.

POSTER PRESENTATIONS

Conclusion: ASC42 demonstrated NAS reductions and anti-fibrotic benefits in the STZ+DEN+HFD rat NASH Model. These data supported the advancement of ASC42 into clinical trials in human.

PO-1992

Genetic ablation of TMEM86B (lysoplasmalogenase) modulates endogenous plasmalogens and is a potential therapy for non-alcoholic fatty liver disease

Sudip Paul^{1,2}, Anh Nguyen¹, Thy Duong¹, Graeme Lancaster^{2,3}, Peter Meikle^{1,2}. ¹Baker Heart and Diabetes Institute, Metabolomics, Melbourne, Australia; ²Faculty of Medicine, Nursing and Health Sciences, Clayton, Australia; ³Baker Heart and Diabetes Institute, Haematopoiesis and Leukocyte Biology, Melbourne, Australia
Email: sudip.paul@baker.edu.au

Background and aims: Plasmalogens are a sub-class of glycerophospholipids that possess important structural and functional roles. Their deficiency has been observed in multiple disease conditions including neurological, cardiometabolic and liver diseases. Accordingly, modulating endogenous plasmalogen levels has been suggested as a therapeutic strategy. However, an effective way to increase multiple endogenous plasmalogen species has not been established. Here, we evaluated lysoplasmalogenase (TMEM86B), a key plasmalogen catabolising enzyme, as a novel target for plasmalogen modulation. We also tested the potential of this plasmalogen modulation approach in protecting against non-alcoholic fatty liver disease (NAFLD).

Method: We generated global and hepatocyte-specific *Tmem86b* knockout mice and characterised their plasma and hepatic lipidomes. Hepatocyte-specific *Tmem86b* knockout (*Tmem86b*^{Liver KO}; *Tmem86b*^{flox/flox}, *Alb-Cre*) and floxed control (*Tmem86b*^{flox/flox}) mice were further exposed to chow and high-fat diet (40%kcal fat, 2% cholesterol and 20% fructose; HFHCF) for 4, 12 and 24 weeks. Metabolic, biochemical, histopathological, and liquid-chromatography mass-spectrometry based lipidomic analyses were performed. **Results:** Mice with a homozygous global inactivation of *Tmem86b* (*Tmem86b*^{KO}) were phenotypically normal but, importantly, had higher hepatic and plasma plasmalogens as well as higher lysoplasmalogens compared with wild-type (WT) mice. Similarly, *Tmem86b*^{Liver KO} had elevated hepatic and plasma plasmalogens and lysoplasmalogens compared with floxed control mice.

Importantly, fat mass gain was significantly lower in *Tmem86b*^{Liver KO} mice relative to control mice in response to a HFHCF diet. *Tmem86b*^{Liver KO} mice also had significantly lower levels of liver function markers in plasma as well as significantly lower liver weights, less hepatic injury and lower hepatic glycerolipid content compared with control mice following HFHCF diet exposure for 4, 12 and 24 weeks. Our data demonstrate that deletion of *Tmem86b* increases endogenous plasmalogen levels, and successively provides protection against exacerbated fat mass gain and liver pathologies associated with HFHCF diet feeding in mice.

Conclusion: The findings suggest that targeting TMEM86B may be an effective therapeutic strategy for the prevention and management of NAFLD.

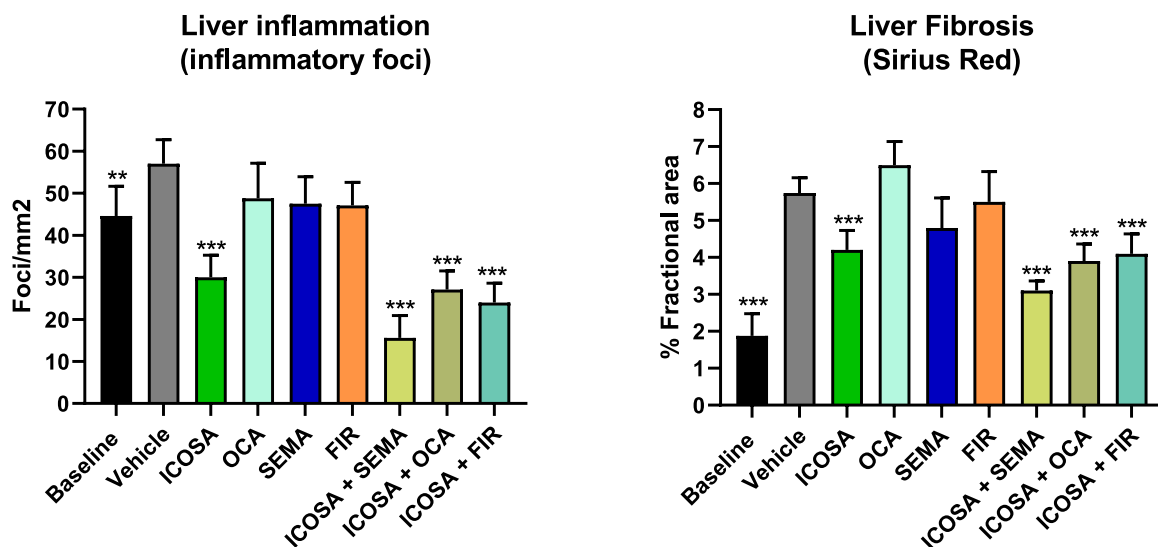
PO-2006

Anti-inflammatory and anti-fibrotic effects of icosabutate as mono- or combination therapy with a GLP-1 receptor agonist, a FXR agonist or an ACC inhibitor in a dietary mouse model of progressive fibrosis

David A. Fraser¹, Jacob Nøhr-Meldgaard², Tore Skjaeret¹, Sanne Veidal², Michael Feigh², Stephen Harrison³. ¹Northsea Therapeutics, Netherlands; ²Gubra ApS, Denmark; ³Radcliffe Dept of Medicine, University of Oxford
Email: david.fraser@northseatherapeutics.com

Background and aims: Icosabutate (ICOSA), a semi-synthetic eicosapentaenoic acid derivative, is currently in clinical development for the treatment of NASH with fibrosis (NCT04052516, results pending). To assess if additional anti-inflammatory and/or anti-fibrotic effects could be achieved via combination therapy, a comparison of ICOSA, firsocostat [FIR, a liver-targeted acetyl-coenzyme A carboxylase (ACC 1/2) inhibitor], semaglutide [SEMA, an injectable glucagon-like 1 (GLP-1) receptor agonist] or obeticholic acid [OCA, a farnesoid-X receptor agonist] as monotherapy was performed in a choline-deficient, L-amino acid defined high-fat dietary (CDAH-HFD) mouse model. The effect of combining ICOSA with either FIR, SEMA or OCA was simultaneously assessed.

Method: Male C57BL/6J mice were fed CDAH-HFD (A16092003, Research Diets) for 6 weeks before treatment start. A baseline group (n = 12) was terminated at study start. CDAH-HFD fed mice [n = 10–12 per group] received daily per oral (PO) treatment with vehicle (corn



Values expressed as mean of n = 9-12 + SEM, Dunnett's test one-factor linear model
: P < 0.01, *: P < 0.001 compared to Vehicle

Figure: (abstract: PO-2006)

oil), ICOSA (112 mg/kg), OCA (30 mg/kg), SEMA (30 nmol/kg SC), FIR (5 mg/kg) as monotherapy or combinations of ICOSA + either SEMA, OCA or FIR (all dosing as for monotherapy) for 8 weeks. Inflammation and fibrosis was assessed in terminal liver biopsy by IHC, biochemical and morphometric assays.

Results: SEMA induced a 26% loss of bodyweight ($p < 0.001$) relative to baseline as both mono- and combination therapy. As monotherapy, icosabutate was the only anti-inflammatory compound, reducing inflammatory foci by 47% ($p < 0.001$ vs vehicle, see figure) with no significant effect observed for other compounds. A similar pattern was observed with galectin-3 (a macrophage marker), where only icosabutate achieved a significant reduction (-28% , $p < 0.001$ vs vehicle). All ICOSA combinations achieved significant reductions of both inflammatory foci and galectin-3, the most pronounced effect achieved by ICOSA + SEMA (-73% and -45% for inflammatory foci and galectin-3 respectively, $p < 0.001$ vs vehicle). Icosabutate was also the only compound that induced a significant anti-fibrotic effect as monotherapy as measured by sirius red (SR)-morphometry (see figure) whilst both ICOSA and SEMA significantly reduced hydroxyproline (HYP) content (by 33 and 22% respectively, both $p < 0.001$ vs vehicle). All combination therapies achieved significant reductions in fibrosis, the most pronounced effects observed for ICOSA + SEMA (-46% and -45% for SR-morphometry and HYP respectively, both $p < 0.001$ vs vehicle).

Conclusion: As monotherapy, ICOSA is a more potent anti-inflammatory/anti-fibrotic compound than SEMA, OCA or FIR in a dietary mouse model of advanced fibrosis. The ability of SEMA to induce weight loss amplified the beneficial effects of ICOSA on inflammation and fibrosis and provides an attractive combination option for the treatment of fibrosing NASH in humans.

PO-2099

Development of a disease-mimicking model for NASH and liver fibrosis in a triple cell-type, spheroid-based liver-on-chip platform with microfluidics

Haysam Ahmed¹, Georgios Galaris¹, Karin Toet¹, Hossein Eslami Amirabadi¹, Elsbet Pieterman¹, Robert Ostendorf¹, Roeland Hanemaaijer¹, Bob van de Water², Ivana Bobeldijk¹, Evita van de Steeg¹, Geurt Stokman¹. ¹TNO, Metabolic Health Research, Leiden, Netherlands; ²Leiden Academic Centre for Drug Research, Division of Drug Discovery and Safety, Leiden, Netherlands
Email: geurt.stokman@tno.nl

Background and aims: Despite ongoing efforts there is currently no effective therapeutic treatment available for non-alcoholic steatohepatitis (NASH). Several drug candidates have failed clinical trials due to lack of efficacy, underlining the need for predictive preclinical models. To this end we developed a disease-mimicking *in vitro* model which closely resembles the pathophysiology of liver fibrosis induced by lifestyle factors.

Method: Primary human hepatocytes, Kupffer cells, and stellate cells were cultured in a matrix-free environment resulting in formation of uniformly-sized spheroids. Fatty acids, carbohydrates, and immunological factors were used to recapitulate development and progression of NASH. A novel, customized liver-on-chip was 3D-printed using proprietary material that has very low drug adsorption to circumvent the shortcomings of the widely used polydimethylsiloxane (PDMS). Spheroids were cultured under static conditions or subjected to continuous pump-driven flow. The effect of different experimental drugs on disease development was examined. Steatosis was determined by LipidTox accumulation. Expression of secreted protein markers of inflammation, fibrosis, hepatocyte function and viability was determined by specific ELISA's. Collagen deposition in the cell-matrix fraction was examined using a quantitative protein assay.

Results: Induction of NASH resulted in hepatocyte steatosis, expression of inflammatory cytokines, expression of secreted protein markers for fibrosis, and deposition of collagen in the

cell-matrix fraction of the liver spheroids. Exposure to fatty acids and carbohydrates under flow conditions resulted in a more homogenous distribution and size of lipid droplets per individual hepatocyte and per spheroid cross section, as compared to more variable droplet size under static conditions. Collagen deposition was about 3-fold higher than in controls in both static and flow conditions, and inhibited by treatment with an ALK5 inhibitor. Under static conditions, single drug treatment with PPAR agonists, FXR agonists, inhibitors of lipogenesis, or a pan-caspase inhibitor, showed varying effects on the degree of steatosis, expression of inflammatory or fibrosis markers, but had no significant effect on collagen deposition when compared to vehicle-treated NASH controls. In contrast, a combination treatment using drugs with different modes of action reduced collagen deposition compared to vehicle-treated NASH controls.

Conclusion: We present a disease-mimicking cell model for NASH and fibrosis that results in collagen production under static and flow conditions. The model is responsive to pharmacological interventions. We will further investigate the effect of microfluidic flow on the therapeutic efficacy of reference compounds and compounds currently in clinical trials as single or combination treatment.

PO-2163

Inhibition of integrin alphaVbeta1 and alphaVbeta6 by a small molecule inhibitor attenuated liver fibrosis and tumor formation in an advanced mouse NASH model

Dipankar Bhattacharya¹, Richard Chen², Min Lu², Lia Luus², Adrian Ray², Bryce Harrison², Bruce Rogers², Scott Friedman¹. ¹Icahn School of Medicine at Mount Sinai, Division of Liver Diseases, New York, United States; ²Morphic Therapeutic, Inc., Waltham, United States
Email: dipankar.bhattacharya@mssm.edu

Background and aims: Integrins alphaVbeta1 and alphaVbeta6 have been implicated in liver fibrosis due to their reported involvement in TGFbeta activation. Therefore, dual inhibition of both integrins may be more efficacious in non-alcoholic steatohepatitis (NASH). Here we tested a potent, selective, and orally bioavailable small molecule inhibitor of alphaVbeta1/beta6 in a mouse model of advanced NASH that progresses to hepatocellular carcinoma (HCC).

Method: NASH was induced in 8-week old male C57BL/6J mice ($n = 10$ /group) with Western Diet (WD), sugar water, and low-dose weekly carbon tetrachloride (CCl₄) injection for 12 weeks (WD_CCl₄) (doi: 10.1016/j.jhep.2018.03.011). Mice were then orally treated with vehicle (phosphate-buffered saline), a selective small molecule alphaVbeta1/beta6 dual inhibitor (MR-cpd3) (60 mg/kg), or obeticholic acid (OCA) (30 mg/kg) once daily for an additional 12 weeks. End points including liver histology, Picro-Sirius Red staining (PSR), tumor quantification, and gene expression were analyzed at the end of the study.

Results: Messenger RNA levels of integrin alphaV and beta6 were significantly elevated in the WD_CCl₄ model, associated with severe fibrosis and enhanced ductular reaction. Oral administration of MR-cpd3 or OCA resulted in reduced fibrosis as measured by PSR area and Collagen 1A1 mRNA levels ($p < 0.01$). Unlike OCA, which decreased NAFLD activity score (NAS), treatment with MR-cpd3 did not alter NAS, indicating a distinct mechanism of anti-fibrosis by the dual alphaVbeta1/beta6 inhibitor. Expression of alpha smooth muscle actin (alphaSMA) and platelet-derived growth factor receptor beta genes were also significantly downregulated by MR-cpd3 treatment ($p = 0.04$ and $p = 0.002$, respectively). Consistent with the mRNA and PSR staining results, collagen 1A1 ($p = 0.01$) and alphaSMA ($p = 0.0007$) protein levels are similarly decreased by MR-cpd3. While all vehicle-treated NASH animals developed HCC, MR-cpd3 and OCA administration resulted in an increased number of tumor free animals (36% and 20%, respectively). Oral administration of the MR-cpd3 did not affect body weight, food intake, or water consumption.

Conclusion: Treatment with a small molecule integrin alphaVbeta1/beta6 dual antagonist significantly diminishes liver fibrosis and progression to HCC in an advanced NASH model induced by

POSTER PRESENTATIONS

WD_CCL4, suggesting potential value in the treatment of human NASH.

This work was supported by a research contract from Morphic Therapeutic, Inc.

PO-2192

Neddylaton inhibition reduces liver steatosis in MAFLD mice models by promoting hepatic fatty acid oxidation via DEPTOR-mTOR axis

Marina Serrano-Macia¹, Jorge Simón Espinosa¹, María J. González Rellán², Naroa Goikoetxea¹, Mikel Azkargorta³, Fernando Lopitz Otsoa⁴, Diego Saenz de Urturi⁵, Rubén Rodríguez Agudo¹, Sofía Lachiondo-Ortega¹, María Mercado-Gómez¹, Maider Bizkarguenaga⁴, David Fernández Ramos⁴, Xabier Buque⁵, Guido Alessandro Baselli⁶, Luca Valenti⁶, Paula Iruzubieta⁷, Javier Crespo⁷, Erica Villa⁸, Jesus Maria Banales⁹, Jose Marin^{10,11,12}, Matías A. Avila¹³, Patricia Aspichueta⁵, James D. Sutherland¹⁴, Rosa Barrio¹⁴, Ugo Mayor¹⁵, Felix Elortza³, Dimitris Xirodimas¹⁶, Ruben Nogueiras², Teresa Cardoso Delgado¹, María Luz Martínez-Chantar¹. ¹Center for Cooperative Research in Biosciences (CIC bioGUNE), Liver Disease Lab, Derio, Spain; ²Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), Department of Physiology, Santiago de Compostela, Spain; ³Center for Cooperative Research in Biosciences (CIC bioGUNE), Proteomics Platform, Derio, Spain; ⁴Center for Cooperative Research in Biosciences (CIC bioGUNE), Precision Medicine and Metabolism Lab, Derio, Spain; ⁵University of the Basque Country UPV/EHU, Department of Physiology, Faculty of Medicine and Nursing, Leioa, Spain; ⁶Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Transfusion Medicine and Hematology, Milan, Italy; ⁷Marqués de Valdecilla University Hospital, Gastroenterology and Hepatology Department, Santander, Spain; ⁸Azienda Ospedaliero-Universitaria and University of Modena and Reggio Emilia, Department of Gastroenterology, Modena, Italy; ⁹Biodonostia Health Research Institute, Department of Liver and Gastrointestinal Diseases, San Sebastian, Spain; ¹⁰University of Salamanca, Experimental Hepatology and Drug Targeting, Salamanca, Spain; ¹¹University of Salamanca, IBSAL, CIBEREHD, Physiology and Pharmacology, Salamanca, Spain; ¹²Experimental Hepatology and Drug Targeting (HEVEPHARM), University of Salamanca, Biomedical Research Institute of Salamanca (IBSAL), CIBERehd, Salamanca, Spain; ¹³Center for Applied Medical Research (CIMA), Hepatology Programme, Pamplona, Spain; ¹⁴Center for Cooperative Research in Biosciences (CIC bioGUNE), Ubiquitin-like And Development Lab, Derio, Spain; ¹⁵University of the Basque Country (UPV/EHU), Department of Biochemistry and Molecular Biology, Leioa, Spain; ¹⁶Centre de Recherche en Biologie cellulaire de Montpellier (CRBM-CNRS), Montpellier, France
Email: mserrano@cicbiogune.es

Background and aims: Metabolic-associated fatty liver disease (MAFLD) is a complex liver disease and comprehends a group of conditions being the massive accumulation of fat in the liver the main feature. Mechanistic target of rapamycin (mTOR) pathway plays an essential role in lipid metabolism and development of MAFLD. In recent years, the regulation of DEP domain-containing mTOR-interacting protein (DEPTOR), a negative regulator of mTOR pathway, has been involved in the alteration of lipid homeostasis. It is known that DEPTOR is degraded by SCF (Skp1-Cullin-F box proteins) E3 ubiquitin ligase, which needs to be neddylated to be active. Neddylation is a reversible ubiquitin-like post-translational modification upregulated in many diseases, including MAFLD. Therefore, we decided to evaluate the potential use of Pevonedistat (MLN4924), a neddylation inhibitor, in MAFLD therapy through regulation of mTOR signaling.

Method: Neddylation inhibition was evaluated in mouse isolated hepatocytes. Moreover, male adult C57BL/6 mice (3-month old) fed either with 0.1% methionine and choline deficient diet (0.1%MCD diet) or with a choline-deficient high fat diet (CD-HFD) were used.

After 2 weeks of 0.1%MCD diet or 3 weeks of CD-HFD, mice were treated during 2 or 3 more weeks, depending on the diet, with Pevonedistat (60 mg/Kg) by oral gavage each 4 days. The effects of neddylation specific inhibition were also evaluated in male adult C57BL/6 AlfpCre mice infected with AAV-DIO-shNEED8 and maintained on CD-HFD for 6 weeks. Finally, the impact of hepatic neddylation in patients with MAFLD as well as the potential use of NEDD8 serum levels for MAFLD diagnostic purposes were evaluated. **Results:** Neddylation inhibition using Pevonedistat, as well as silencing Nedd8 (neural precursor cell expressed, developmentally down-regulated 8) reduced lipid accumulation in oleic acid-stimulated mouse primary hepatocytes. Likewise, pharmacological neddylation inhibition and Nedd8 hepatic knockdown ameliorates liver steatosis preventing lipid peroxidation, hepatic oxidative stress and inflammation in mouse models of diet induced MAFLD. Increased Deptor levels and concomitant repression of mTOR signalling when neddylation is inhibited, is associated with augmented fatty acid oxidation and reduced lipid content. Deptor silencing in isolated mouse hepatocytes abolishes the anti-steatotic effects mediated by neddylation inhibition. Finally, serum NEDD8 levels correlate with hepatic neddylation both during disease progression in the clinical setting and during disease regression by therapeutic approaches in pre-clinical models.

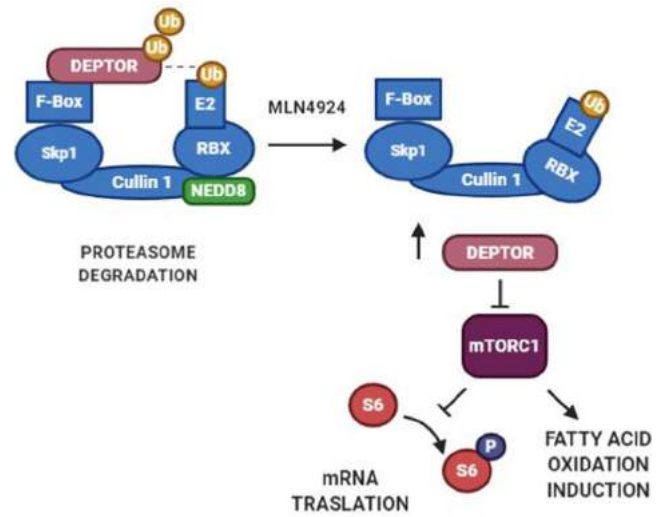


Figure:

Conclusion: Overall, upregulation of DEPTOR, driven by neddylation inhibition, is proposed as a novel effective target and therapeutic approach to tackle MAFLD. Besides, the results obtained enable to pose serum NEDD8 as a potential non-invasive biomarker in MAFLD.

PO-2287

Oral LPCN 1144 treatment significantly reduced liver fat and key liver injury markers in biopsy confirmed NASH subjects: Results of a Phase 2 randomized controlled study

Kongnara Papangkorn¹, Kilyoung Kim², Benjamin Bruno³, Nachiappan Chidambaram¹, Mahesh Patel⁴, Anthony DelConte⁵, Michael Charlton⁶, Mary Rinella⁷, Arun Sanyal⁸. ¹Lipocine Inc, Randd, Salt Lake City, United States; ²Lipocine Inc, Product Development, Salt Lake City, United States; ³Lipocine Inc, Clinical Affairs, Salt Lake City, United States; ⁴Lipocine Inc, Salt Lake City, United States; ⁵Saint Joseph's University, Philadelphia, United States; ⁶University Of Chicago Medicine, Hepatology, Chicago, United States; ⁷Northwestern Medicine Digestive Health Center, Hepatology, Chicago, United States; ⁸Virginia Commonwealth University, Internal Medicine, Richmond, United States
Email: kk@lipocine.com

Background and aims: Non-alcoholic Steatohepatitis (NASH) is a common cause of liver disease and is on a trajectory to become the

most common indication for liver transplantation in Western Europe and the United States. In large multi-ethnic cross-sectional studies, low testosterone (T) levels are independently predictive of fatty liver. Hepatic steatosis (measured by MRI-PDFF), together with serum transaminase levels, specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are predictive of liver pathology and histology in NASH subjects. LPCN 1144 is an oral prodrug of endogenous Testosterone (T) under development for treatment of noncirrhotic NASH. Therapy with d-alpha tocopherol has previously been shown to improve biochemical (ALT) and histological features of NASH albeit in a non-diabetic population. Currently, LPCN 1144 is being investigated for safety and efficacy in a 36-week randomized, double-blind, paired biopsy, placebo-controlled phase 2 LIFT ("Liver Fat intervention with oral Testosterone") study (NCT04134091). Here, we present the topline results post 12 weeks of treatment.

Method: Fifty-six adult male NASH subjects with F1-F3 fibrosis were randomized 1:1:1 to three arms (Treatment A: n = 18 with an oral dose of 142 mg T equivalent twice daily, Treatment B: n = 19 with an oral dose of 142 mg T equivalent formulated with 238 mg of d-alpha tocopherol acetate twice daily, and Placebo: n = 19 with matching placebo twice daily). The primary end point was change from baseline (BL) in hepatic fat fraction via MRI-PDFF. Change from BL of ALT, and AST were secondary end points post 12 weeks of treatment.

Results: Baseline levels of hepatic fat fraction, ALT, and AST for all groups were 19.2%, 51.4 U/L, and 33.3 U/L, respectively. As shown in the Figure, both treatment arms met the primary end point of liver fat reduction with statistical significance compared to placebo (p < 0.001). Approximately two thirds of patients treated with either LPCN 1144 treatment experienced greater than 30% reduction in liver fat. Both ALT and AST were significantly (p < 0.05 vs placebo) reduced with either LPCN 1144 treatment. Furthermore, Treatment B comprising d-alpha tocopherol amplified reduction of the liver injury markers in this population. During the 12 weeks of treatment, the observed rate and severity of Treatment Emergent Adverse Events in both the treatment arms were comparable to the placebo arm.

Treatment	Hepatic fat fraction†			ALT			AST		
	N	Absolute CBL (%)	Relative CBL (%)	N	Absolute CBL (U/L)	Relative CBL (%)	N	Absolute CBL (U/L)	Relative CBL (%)
Placebo	18	-1.7	-9.3	17	+1.8	+11.5	17	+2.8	+7.1
A	17	-8.0***	-39.9***	16	-9.4*	-4.2	16	-4.9*	-4.8
B	17	-9.4***	-46.8***	19	-22.4***	-33.2***	19	-10.4***	-20.4**

* < 0.05, ** < 0.01, *** < 0.001 vs placebo; † Hepatic fat fraction with baseline ≥ 5% liver fat; CBL: Change from baseline

Figure:

Conclusion: LPCN 1144 treatment substantially and significantly improved the key non-invasive markers of liver health in male patients with biopsy confirmed NASH with fibrosis. LPCN 1144's treatment potential for NASH resolution and/or fibrosis improvement is under evaluation in the ongoing LIFT trial.

PO-2290

Aminotransferase improvements in patients with non-alcoholic steatohepatitis are associated with fibrosis regression in the REGENERATE study

Mary Rinella¹, Jean-François Dufour^{2,3}, Quentin Anstee⁴, Zobair Younossi⁵, Rohit Loomba⁶, Arun Sanyal⁷, Thomas Capozza⁸, Tanya Granston⁹, Martin Bonacci¹⁰, Aldo Trylesinski¹⁰, Vlad Ratziu¹¹.
¹Feinberg School of Medicine, Northwestern University, Chicago, United States; ²University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; ³University of Bern, Bern, Switzerland; ⁴Newcastle University, Newcastle upon Tyne, United Kingdom; ⁵Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, United States; ⁶University of California, San Diego, La Jolla, United States; ⁷Virginia Commonwealth University, Richmond, United States; ⁸Intercept Pharmaceuticals, Inc., New York, United States; ⁹Intercept Pharmaceuticals, Inc., San Diego, United States; ¹⁰Intercept Pharmaceuticals, Inc., London, United Kingdom; ¹¹Sorbonne Université, Paris, France

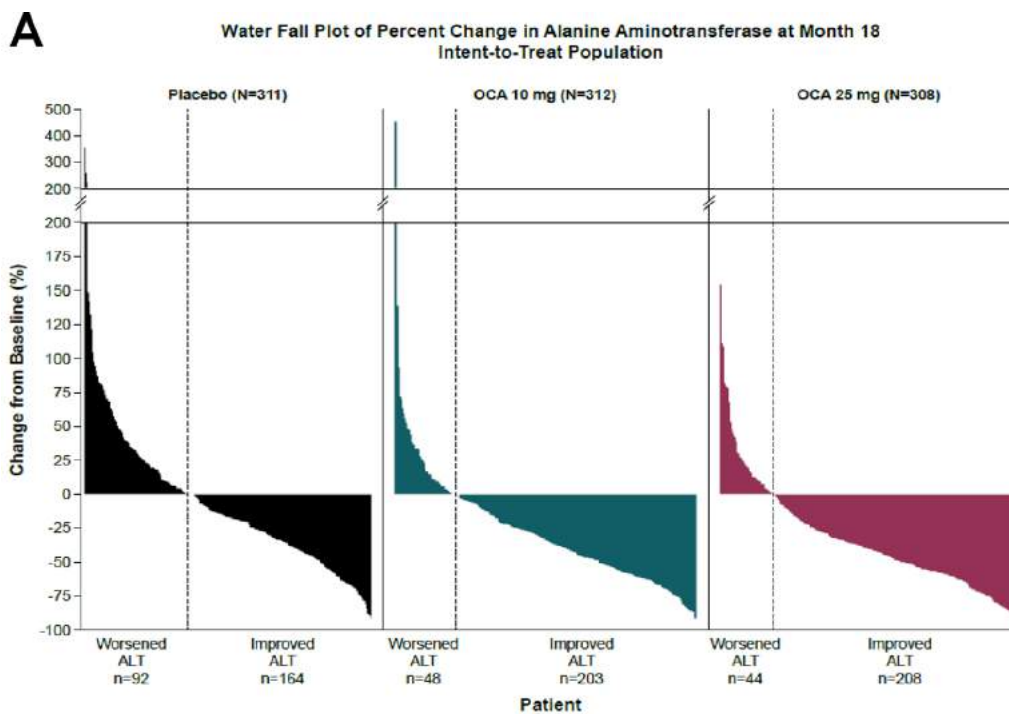
Email: marurinella68@gmail.com

Background and aims: The interim analysis of the REGENERATE study showed obeticholic acid (OCA) 25 mg treatment significantly improved liver histology in patients with non-alcoholic steatohepatitis (NASH) and fibrosis. Elevations in aminotransferases are associated with adverse liver-related outcomes in NASH. Here, we evaluate the utility of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as markers of treatment response to OCA in patients with NASH.

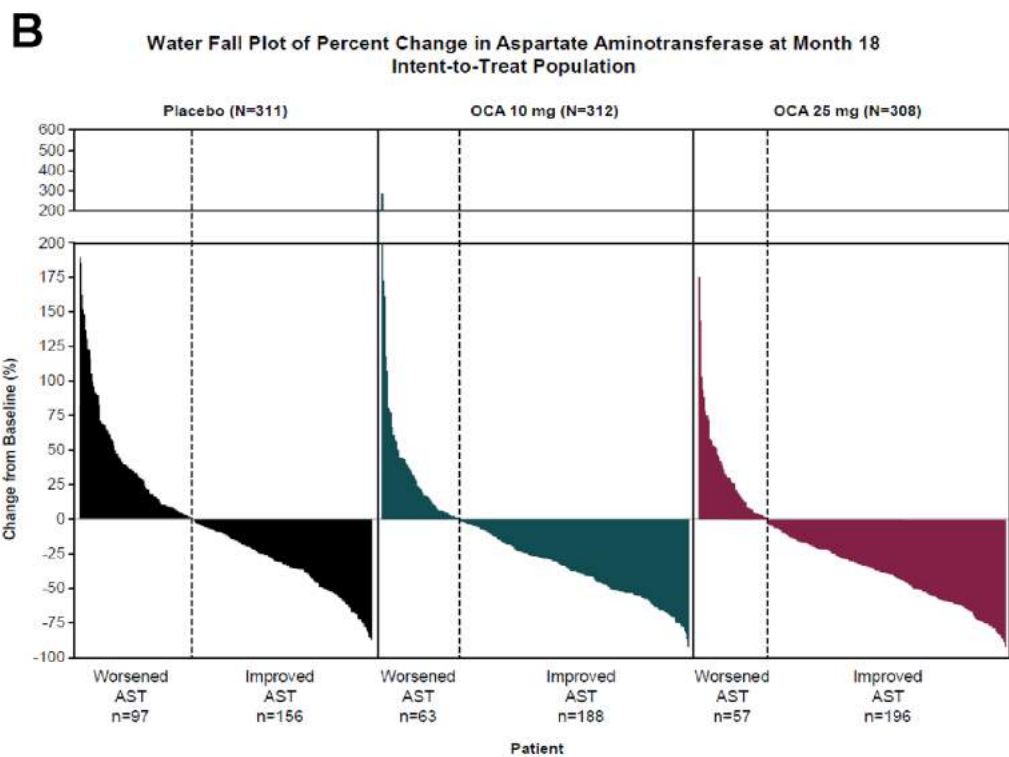
Method: Changes in ALT (upper limit of normal [ULN] = 55 U/L) and AST (ULN = 34 U/L) were assessed systematically at 1, 3, 6, 12, and 18 months in 931 NASH patients with stage 2 or 3 fibrosis randomized 1:1:1 to placebo (PBO), OCA 10 mg, or OCA 25 mg in REGENERATE (intent-to-treat population). Least-square mean (LSM) and 95% confidence intervals (CIs) of percentage change from baseline in ALT and AST were analyzed using a mixed-effect repeated-measures model.

Results: Baseline characteristics were well-balanced across treatment arms: ALT 79 ± 53 U/L; AST 58 ± 36 U/L; 44% F2, 56% F3. Aminotransferase values were >ULN for ALT in 60% (7% >3xULN), and for AST in 74% (9% >3xULN) of patients. Rapid, progressive, and dose-dependent improvement in ALT and AST was seen across PBO, OCA 10 mg, and OCA 25 mg arms, which at Month 18 was: ALT LSM change (95% CI), respectively, -4.9% (-10.7-0.9), -23.2% (-28.9- to -17.4) and -31.9% (-37.7- to -26.1) and in AST, -8.7% (-12.1- to -5.2), -13.4% (-16.8- to -9.9), and -19.4 (-22.8- to -15.9). ALT and AST LSM reductions in OCA arms vs PBO were seen regardless of patient ULN status at baseline. In all patients, ALT/AST reduction was associated with probability of fibrosis regression at Month 18, ranging from approximately 20%, 95% CI (14-27) to 45% (37-54) with any reduction in ALT (>0%-100%) and between approximately 20%, 95% CI (25-38) to 43% (35-57) with any reduction in AST (>0%-100%). Interestingly, even with increases of ≤40% in AST or ALT there was still a small probability of fibrosis regression (<20%). Analysis of changes in ALT and AST in individual patients showed that more patients had improvements on OCA than PBO at Month 18 (FIG 1).

Conclusion: OCA resulted in consistent dose-dependent improvement of ALT and AST. Patients with reductions in ALT or AST were up to twice as likely to have fibrosis improvement than those whose ALT or AST increased. The REGENERATE study is ongoing and will continue through clinical outcomes for verification and description of clinical benefits of OCA in treatment of NASH.



Patients with unchanged ALT at Month 18: placebo, n=1; OCA 10 mg, n=4; OCA 25 mg, n=1.



Patients with unchanged AST at Month 18: placebo, n=4; OCA 10 mg, n=2; OCA 25 mg, n=0.

Figure: (abstract: PO-2290): Individual patient changes from baseline at Month 18 by patient for A. ALT, B. AST

PO-2297

BIO89-100 demonstrated robust reduction in liver fat fraction and liver fat volume (LFV) and favorable tolerability with weekly (QW) and every 2 weeks (Q2W) dosing in a Phase 1b/2a placebo-controlled proof of concept study in NASH

Rohit Loomba¹, Eric Lawitz², Juan Frias³, Grisell Ortiz Lasanta⁴, Bridgette Boggess Franey⁵, Linda Morrow⁶, Chao-Yin Chen⁷, Leo Tseng⁷, Will Charlton⁷, Hank Mansbach⁷, Maya Margalit⁸.

¹University of California at San Diego, NAFLD Research Center, La Jolla, CA, United States; ²Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, United States; ³National Research Institute, Los Angeles, CA, United States; ⁴FDI Clinical Research, San Juan, Puerto Rico; ⁵Prosciento Clinical Research Unit, Chula Vista, CA, United States; ⁶Prosciento Inc., Chula Vista, CA, United States; ⁷89bio Inc., San Francisco, CA, United States; ⁸89bio Inc., Herzliya, Israel
Email: maya.margalit@89bio.com

Background and aims: FGF21 is an endogenous hormone regulating carbohydrate, lipid and energy metabolism. FGF21 analogs improve liver and metabolic abnormalities in non-alcoholic steatohepatitis (NASH). BIO89-100 is a glycoPEGylated FGF21 with promising tolerability and pharmacodynamic effects and potential for QW or Q2W dosing.

Method: This Phase 1b/2a trial enrolled 81 subjects with liver fat $\geq 10\%$ by MRI-PDFF and either biopsy-confirmed NASH (BC-NASH) or phenotypic NASH (PNASH: central obesity with either type 2 diabetes mellitus or with evidence of liver injury by ALT or FibroScan elastography score above defined thresholds). Subjects were randomized to 12 weeks of treatment at one of 6 doses (3, 9, 18 or 27 mg QW; 18 or 36 mg Q2W) or placebo (PBO). Key end points were safety, tolerability, pharmacokinetics, change in liver fat fraction measured by MRI-PDFF and liver and metabolic markers.

Results: Baseline characteristics were generally similar between pooled BIO89-100 v. pooled PBO groups, and between BC-NASH v. PNASH subjects. At week 13, all BIO89-100 dose groups showed significant relative reduction v. PBO of up to 70% ($p < 0.001$) in MRI-PDFF. Up to 88% of BIO89-100 subjects achieved $\geq 30\%$ MRI-PDFF reduction v. baseline ($p < 0.001$). Decreased steatosis was accompanied by decreased LFV of up to 305 ml and up to 65% v. baseline ($p < 0.001$). (Table 1) Significant decreases in ALT vs. PBO were observed with BIO9-100, maximal with 27 mg QW (30U/L decrease from baseline, $p < 0.001$), also prominent in the subgroup ($n = 17$) with baseline ALT $> 45U/L$ (35U/L decrease from baseline, $p < 0.05$). Metabolic benefits of BIO89-100 included significant reductions in triglycerides (TG; up to 28% in overall population, up to 49% in the subgroup [$n = 15$] with baseline TG ≥ 200 mg/ml), non-HDL cholesterol and LDL-C and increased adiponectin (up to 61%).

There were no deaths or related serious adverse events; one BIO89-100 treated subject discontinued due to a related adverse event (AE: localized skin rash). Mild increased appetite was the most common treatment-related AE. The frequency of gastrointestinal AEs was comparable to PBO.

Conclusion: In subjects with NASH, BIO89-100 led to significant and clinically meaningful reductions in liver fat fraction and volume assessed by MRI-PDFF with concurrent metabolic benefits and a favorable safety and tolerability profile. A Phase 2b study in NASH is planned and there is an ongoing proof of concept study in patients with severe hypertriglyceridemia.

Table 1: MRI-PDFF and LFV Summary

Measure	Placebo (n=19)	BIO89-100 Weekly (QW)				BIO89-100 Once every two weeks (Q2W)	
		3mg (n=6)	9mg (n=12)	18mg (n=11)	27mg (n=10)	18mg (n=14)	36mg (n=9)
Relative change in MRI-PDFF vs baseline	+10%	-37%**	-50%**	-36%**	-60%**	-43%**	-50%**
Relative reduction in MRI-PDFF vs placebo		-47%**	-60%**	-46%**	-70%**	-53%**	-60%**
Absolute change in MRI-PDFF vs baseline	+1.4%	-7.5%*	-10%**	-7.5%**	-13.5%**	-9.0%**	-9.7%**
Proportion of subjects with $\geq 30\%$ relative reduction in MRI-PDFF	0%	60%*	82%**	50%**	86%**	69%**	88%**
Relative change in liver fat volume vs baseline	+12%	-46%**	-53%**	-36%**	-65%**	-46%**	-56%**
Relative change in liver fat volume vs placebo		-58%**	-65%**	-48%**	-77%**	-59%**	-68%**
Absolute change in liver fat volume vs baseline (ml)	+22	-205*	-228%**	-148*	-305%**	-211%**	-249%**

* $p < 0.01$; ** $p < 0.001$ vs placebo. N based on subjects randomized. Least square mean based on MRI analysis set (N=75) and responder based on subjects with MRI at Week 13. Levels of liver fat in the BIO89-100 and placebo groups at baseline were 21.2% (on a pooled basis) and 21.8%, respectively. Baseline liver fat levels and changes in liver fat were similar in biopsy-confirmed NASH and phenotypic NASH subjects.

PO-2312

Novel liver-specific thyromimetics for the treatment of steatohepatitis

Andrea Perra¹, Marta Anna Kowalik¹, Marina Serra¹, Massimiliano Runfola², Simona Rapposelli², Amedeo Columbano¹.

¹Università degli Studi di Cagliari, Biomedical Sciences, Cagliari, Italy;

²University of Pisa, Pharmacy, Pisa, Italy

Email: andrea.perra@unica.it

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is rapidly emerging as one of the most common causes of chronic liver disease and an important risk factor for HCC. Due to limited success of currently available therapeutic options, there is an urgent need to define new approaches for NAFLD-induced HCC. TR-beta1-selective thyromimetics possessing T3-related effects on lipid metabolism without overt cardiotoxic effects of thyroid hormone, may represent such a strategy. The aim of this study was to investigate whether a novel liver-directed TR-beta1 agonist, TG68, may dampen/attenuate fully established non-alcoholic steatohepatitis (NASH) and display an anti-fibrotic effect in a mouse model of NAFLD.

Methods: A nutritional model of NAFLD consisting of feeding a high fat diet (HFD) was used. C57BL/6 mice were fed a HFD for 18 weeks prior to the administration of the new thyromimetic TG68 at different concentrations, in drinking water for additional 2 weeks. The efficacy of TG68 was compared with Resmetirom (MGL-3196), that recently entered Phase 3 clinical trial for patients with non-alcoholic steatohepatitis (NASH). The effect of TG68 was evaluated by histological parameters, as well as by immunohistochemistry and qRT-PCR. Blood samples were collected for clinical chemistry and determination of serum lipid levels.

Results: TG68 significantly improved liver histology by reducing hepatic triglycerides and NASH score in HFD-fed mice, similar to what observed following treatment with MGL-3196. Such impact on liver steatosis was associated with breakdown of fatty acids as evaluated by increased fatty acid beta-oxidation. A reduction in serum ALT, AST and TGs was also reported. The anti-steatogenic effect was accompanied by activation of TR-beta-target genes, as confirmed by increased expression of deiodinase 1 following treatment with TG68. Administration of TG68 affected also inflammatory and fibrotic pathways.

Conclusion: Our results indicate that the novel, liver specific TR-beta1 agonist, TG68, significantly reduces HFD-induced NASH in mice and, therefore, may provide a novel therapeutic opportunity for NAFLD-induced HCC.

POSTER PRESENTATIONS

PO-2329

High prevalence of low normal or overtly hypogonadal levels of testosterone observed in histologically established NASH subjects in LiFT Study

Benjamin Bruno¹, Kilyoung Kim², Kongnara Papangkorn³, Nachiappan Chidambaram³, Mahesh Patel⁴, Anthony DelConte⁵, Arun Sanyal⁶. ¹Lipocine Inc, Clinical Affairs, Salt Lake City, United States; ²Lipocine Inc, Product Development, Salt Lake City, United States; ³Lipocine Inc, RandD, Salt Lake City, United States; ⁴Lipocine Inc, Salt Lake City, United States; ⁵Saint Joseph's University, Philadelphia, United States; ⁶Virginia Commonwealth University, Internal Medicine, Richmond, United States
Email: kk@lipocine.com

Background and aims: Non-alcoholic Steatohepatitis (NASH) is an advanced state of non-alcoholic fatty liver disease ("NAFLD") and can progress to fibrotic or cirrhotic liver and eventually hepatocellular carcinoma/liver cancer. About three to eight percent among non-alcoholic fatty liver (NAFL) population (30–40% of US population) progress to NASH. There is no FDA approved drug for NAFLD/NASH. Both estrogen and androgen receptors are expressed in the liver and influence hepatic metabolism and other pathways relevant to NASH. Moreover, a study of liver disease in men undergoing androgen deprivation therapy (ADT) suggests patients receiving ADT were significantly more likely to develop NAFLD. A previous single-arm study revealed that NAFL is highly prevalent in hypogonadal males (~66%). Furthermore, there is significant overlap in co-morbidities associated with NASH and hypogonadism in adult males. Currently, LPCN 1144 is being investigated for safety and efficacy in a phase 2 LiFT ("Liver Fat intervention with oral Testosterone") study (NCT04134091). Here, we report prevalence of hypogonadism and low testosterone (T) levels in the LiFT study.

Method: LiFT is a randomized, double-blind, placebo-controlled, multi-center, three-arm, 36-week study. 183 adult male subjects had biopsies in screening, and 56 biopsy-confirmed NASH subjects were randomized. Baseline data were analyzed to identify the prevalence of hypogonadism and low testosterone levels (using LC-MS/MS) in the study.

Results: 181 suspected NASH male subjects underwent biopsy and had either T measured or a historical diagnosis of hypogonadism. Over two thirds (128 of 181) of these subjects had total T levels <300 ng/dL (lower limit of normal) or history of hypogonadism, and 81% had low-normal T levels, <400 ng/dL. Of the 56 randomized subjects with histologically established NASH, 63% (35/56) had total T levels <300 ng/dL or history of hypogonadism, and 84% had T levels <400 ng/dL. Independently, mean T levels were 315 ng/dL for all biopsied subjects, and the randomized NASH subjects. 46% (16/35) of the hypogonadal, biopsy-confirmed NASH subjects had no prior diagnosis of hypogonadism despite having mean T levels <300 ng/dL (211 ± 70 ng/dL).

Conclusion: The LiFT study demonstrates a high prevalence of low-normal or overtly hypogonadal levels of T in biopsied patients with suspected or established NASH. A significant portion of NASH subjects may have undiagnosed hypogonadism or low T. Apparently, male adult NASH patients are likely to have compromised androgen signaling with possible associated symptoms of androgen deficiency such as sarcopenia, skeletal fragility, sexual/mood disorder, and/or anemia. Men with NAFLD/NASH should be routinely screened for hypogonadism and vice versa. The effect of oral T therapy on NASH is under investigation in the ongoing LiFT trial.

PO-2377

Canagliflozin and Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus (CaNAFLD)-A Secondary Analysis of Two Randomized Controlled Trials

Angel Borisov^{1,2}, Alexander Kutz³, Emanuel Christ², Tuyana Boldanova¹, Christine Bernsmeier¹, Markus Heim¹, Fahim Ebrahimi^{1,2}. ¹Clarunis Universitäres Bauchzentrum Basel

Standort Universitätsspital, Gastroenterology and Hepatology, Basel, Switzerland; ²Universitätsspital Basel, Endocrinology, Diabetes and Metabolism, Basel, Switzerland; ³Kantonsspital Aarau, Aarau, Switzerland

Email: f.ebrahimi@outlook.com

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among patients with type 2 diabetes (T2DM), however no approved pharmacological treatment exists. While sodium glucose cotransporter 2 inhibitors (SGLT2i) have shown to decrease glycemia, blood pressure, body weight, and albuminuria in patients with T2DM, data from large randomized clinical trials on liver-related outcomes are lacking.

Method: This is a secondary analysis of two randomized controlled cardiovascular and renal outcome trials: CANVAS (NCT01032629) and CANVAS-R (NCT01989754). Patients with T2DM and high cardiovascular risk were randomly assigned to receive canagliflozin or placebo and were followed for a duration of up to 6 years. The primary end point of this study was a composite of a reduction of alanine aminotransferase (ALT) levels more than 30% or ALT normalization (decrease <30IU/L). Secondary outcomes included achievement of weight reduction of 5% or 10%, and improvement of non-invasive fibrosis scores (NAFLD fibrosis score; FIB-4 score). Data were provided by Yale Open Data Access (Project ID 2020 4409).

Results: We included 10'135 patients with T2DM. The majority of patients was male (64.2%) with a mean age of 61.8 years and a 13.5 years mean duration of diabetes. Of those, 2781 patients (27.4%) had elevated ALT levels (>30 IU/L) at baseline. These patients had a higher body weight (94.9 kg vs. 88.4 kg), elevated diastolic blood pressure (79.1 mmHg vs. 77.2 mmHg), higher glycemic indices and lipid parameters when compared to patients with normal ALT levels. The rate of the primary outcome was achieved in 35.6% of patients receiving canagliflozin compared to 26.2% with placebo, yielding an odds ratio (OR) of 1.55 (95% CI, 1.42–1.65; p < 0.001). Treatment with canagliflozin was associated with lower NAFLD fibrosis and FIB-4 scores (p < 0.001). Weight reduction of more than 10% was achieved in 38.5% of patients with canagliflozin compared to 16.1% with placebo (OR 3.49; 95% CI, 2.94–4.15; p < 0.001).

Conclusion: In two large randomized controlled trials involving patients with T2DM and risk of metabolic liver disease, treatment with canagliflozin resulted in a significant improvement of liver-related outcomes when compared to placebo.

Non-invasive assessment of liver disease except NAFLD

PO-818

Transient splenic elastography predicts high-risk esophageal varices in patients with noncirrhotic portal hypertension

Joel Silva¹, Hélder Cardoso¹, Rui Gaspar¹, Guilherme Macedo¹. ¹São João University Hospital Center, Porto, Portugal
Email: jom_73@hotmail.com

Background and aims: Non-cirrhotic portal hypertension (NCPH) comprise a heterogeneous group of liver diseases that cause portal hypertension without cirrhosis, leading to a high risk of hemorrhage from esophageal varices. In contrast to cirrhotic portal hypertension, there are no non-invasive predictors of high-risk varices (HRV) described in the literature for NCPH. The aim of this study was to evaluate whether transient splenic elastography (TSE) or other non-invasive assessments of portal hypertension could predict HRV in patients with NCPH.

Method: Prospective, single center study of patients with NCPH who underwent a single timepoint evaluation with transient liver and spleen elastography, gastroscopy and laboratory tests. The study was

performed from January to September 2020. Patients were divided in two groups based on the presence of HRV. The relation between TSE, transient liver elastography, spleen size and platelet count to presence of HRV was evaluated.

Results: Of 42 patients with NCPH who met inclusion criteria, 50% (21/42) presented HRV. The etiology of NCPH was extrahepatic portal thrombosis in 20 (47.6%), idiopathic in 18 (42.9%) and adult polycystic liver disease in 4 (9.5%). In univariate analysis, TSE (median, 58.4 vs. 28.3, $p=0.009$) and spleen size (median, 17.5 vs. 14.5, $p=0.013$) associated with HRV. No statistically significant relationship was found between the presence of HRV and platelet count or transient liver elastography (TLE). In multivariate analysis, TSE was the only variable related to HRV (OR 1.21, 95% CI 1.02–1.38). TSE is able to predict HRV in our population (AUROC 0.878; 95% CI 0.751–1.000). TSE >35.4 kPa presents 93.3% sensitivity, 60% specificity, 90.9% negative predictive value, 73.7% positive predictive value, positive likelihood ratio of 2, 34 and negative likelihood ratio of 0.10.

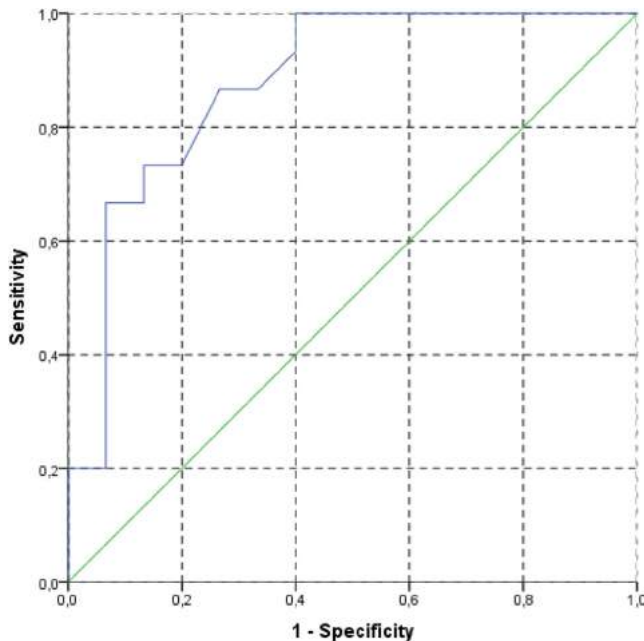


Figure: ROC curve for spleen transient elastography in prediction of high-risk varices in gastroscopy. AUROC was 0.878 (95%CI 0.751–0.985; $p<0.001$).

Conclusion: In our population of patients with NCPH, TSE is useful in predicting HRV. TLE, spleen size and platelet count are not related to HRV.

PO-1047

Jaundice detection by deep convolutional neural network using smartphone images

Tung-Hung Su¹, Jia-Wei Li², Shann-Ching Chen³, Pei-Ying Jiang¹, Jia-Hong Kao¹, Cheng-Fu Chou². ¹National Taiwan University Hospital, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taiwan; ²National Taiwan University, Department of Computer Science and Information Engineering, Taiwan; ³Compal Electronics, Taiwan
Email: tunghungsu@gmail.com

Background and aims: Jaundice usually indicates severe hepatic or biliary diseases and prompt management is needed. The degree of jaundice correlates with the severity of illness, and jaundice is easily confirmed by checking serum total bilirubin (T-Bil) level. Ideally, self-identification of jaundice is the key for its early detection, because a careful inspection may detect jaundice with a T-Bil >2 or 3 mg/dL. However, self-monitoring of jaundice is not easy for people without training, so a correct diagnosis is usually delayed. We aimed to

investigate the capability of early jaundice detection by smartphone images.

Method: We conducted a prospective study to enroll healthy volunteers and patients with jaundice. They all have recent data of T-Bil level as reference standard. The facial images were taken by smartphones with a color checker. These images were first normalized for brightness and color temperature, and followed by deep convolutional neural network based facial landmark detection and scleral segmentation. The average sRGB color of sclera were measured, and the color was converted to CIE LAB. A Support Vector Machine model using the LAB color of patient's both sclera was used to classify the presence of jaundice determined by a T-Bil 2 or 3 mg/dL, respectively. Overall, 80% of the images were used as the training set with a 10-fold cross-validation in the training phase. The remaining 20% of the images were used as the testing set.

Results: A total of 108 patients had been enrolled with 146 facial images being collected. There were 105, 10, and 31 scleral images with a T-Bil level <2, 2–3, and >=3 mg/dL, respectively. At the training phase, if the T-Bil level was set at 3 mg/dL, the area under the receiver operating characteristics curve (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) on the validation set are 0.983, 0.883, 0.978, 0.933, and 0.968, respectively. If the T-Bil level was set at 2 mg/dL, these values are 0.988, 0.867, 0.965, 0.925, and 0.959, respectively.

At the testing phase, if the T-Bil level was set at 3 mg/dL, the AUROC, sensitivity, specificity, PPV, and NPV on testing set are 0.979, 0.833, 0.958, 0.833, and 0.958, respectively. If the T-Bil level was set at 2 mg/dL, these values are 0.986, 0.909, 0.947, 0.909, and 0.947, respectively.

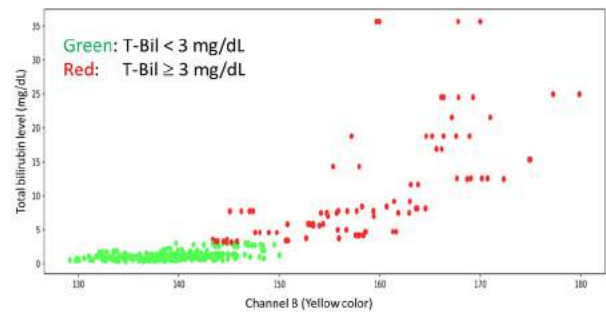


Figure:

Conclusion: Our data demonstrates the capability of jaundice detection by smartphone captured images with good performance. This platform may be applied in the scenario of self-monitoring or telemedicine.

PO-1091

CHES criteria for screening and monitoring of varices needing treatment: an international multicenter study

Chuan Liu¹, Jia Li², Qing-Lei Zeng³, Hong You⁴, Dong Ji⁵, Yu Jun Wong^{6,7}, Ye Gu⁸, Guo Zhang⁹, Yang Bu¹⁰, Fengmei Wang², Qin Wei¹¹, Lili Zhao², Shuang Li², Yan Wang⁸, Musong Li¹¹, Shengjuan Hu¹², Xiaoli Wu¹³, Jinlun Bao¹³, Yongning Xin¹⁴, Doudou Hu¹⁵, Zicheng Jiang¹⁶, Xiaoling Chi¹⁷, Yong Zhang¹⁸, Chunwen Pu¹⁸, Ming Lu¹⁹, Li Li¹⁹, Qibin He²⁰, Deqiang Ma²¹, Yuqian He²¹, Mingxin Zhang²², Huan Liu²², Chao Liu²³, Li Yang²⁴, Chaohui He²⁵, Shanghong Tang²⁶, Chunyan Wang²⁶, Wenjuan Wang⁹, Peng Hua²⁷, Liting Zhang²⁸, Ming-Hua Zheng²⁹, Dengxiang Liu³⁰, Pingcui Zhaoxi³¹, Xiaosong Yang³¹, Bianba Yangzhen³¹, Fuji Mao³², Chuan Song³², Jiafu Ao³³, Taiyun Zhao³³, Youfang Gao³³, Hao Hu³⁴, Jun Wu³⁴, Tinghong Li³⁵, Xiang Huiling³⁵, Zhujun Cao³⁶, Hailong Qi³⁷, Shengqiang Zhou³⁸, Guohong Ge³⁸, Jianbo Shao³⁸, Bingqiong Wang⁴, Ping Li², Tao Han³⁹, Lei Li⁴⁰, Minghui Li⁴¹, Wen Xie⁴¹, Wei Jiang⁴², Mingyi Xu⁴³, Bo Feng⁴⁴, Jilin Chen⁴⁵, Xiaozhong Wang⁴⁶, Hai Li⁴⁷, Hongxin Piao⁴⁸, Jiansong Ji⁴⁹, Chuxiao Shao⁵⁰, Tong Dang⁵¹, Yi Zhou⁵¹, Juan Tang⁵², Guochang He⁵², Li Dong⁵³, Jun Li⁵³, Xiqiao Zhou⁵⁴,

POSTER PRESENTATIONS

	Baveno VI criteria (PLT>150×10 ⁹ /L and LSM<20kPa)		Expanded-Baveno VI criteria (PLT>110×10 ⁹ /L and LSM<25kPa)		CHES criteria (PLT>110×10 ⁹ /L and LSM<19kPa)	
	Spared EGD	VNT missed	Spared EGD	VNT missed	Spared EGD	VNT missed
Real-world cohort (N= 1,274)	387 (30%) [†]	14/387 (3.6%)	675 (53%)	42/675 (6.2%)	585 (46%) [†]	29/585 (4.9%)
Multicenter cohort (N= 936)	210 (22%) [‡]	6/210 (2.9%)	412 (44%)	19/412 (4.6%)	379 (40%) [‡]	14/379 (3.7%)
International cohort (N= 306)	87 (28%) [§]	1/87 (1.1%)	175 (57%)	4/175 (2.3%)	132 (43%) [§]	2/131 (1.5%)
Anti-HBV cohort (N= 223)	80 (36%) [¶]	1 (1.3%)	126 (54%)	2/126 (1.6%)	125 (56%) [¶]	1 (0.8%)

Data are presented as n (%) or n/N (%), where N is the total number of related cases. LSM, liver stiffness measurement; PLT, platelet counts; EGD, esophagogastroduodenoscopy; VNT, varices needing treatment. [†]p < 0.001; [‡]p < 0.001; [§]p < 0.001; [¶]p < 0.001.

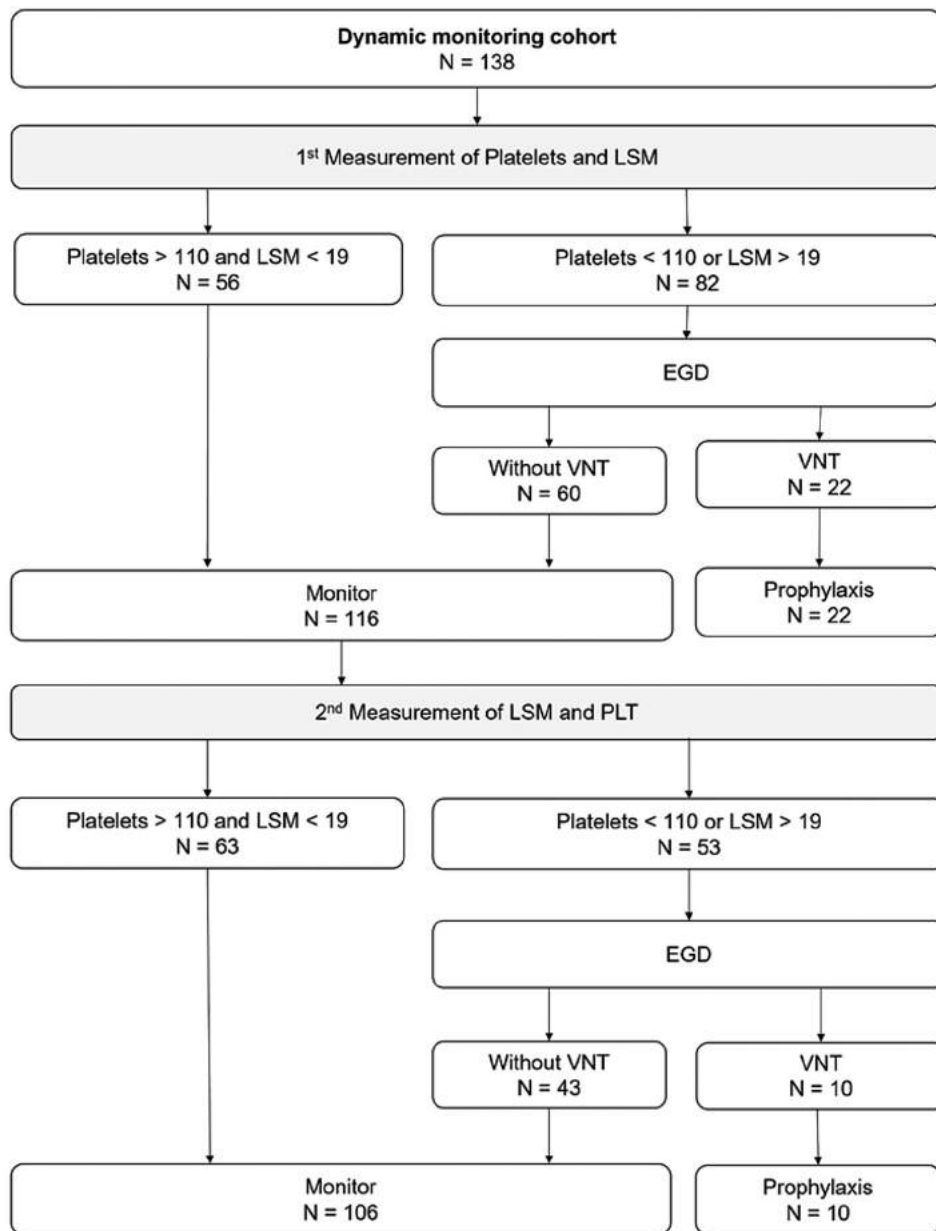


Figure: (abstract: PO-1091)

Guoxin Zhang⁵⁴, Kok Ban The⁶, Jing Tong⁵⁵, Yiling Yi⁵⁵, Liang Chen⁵⁶, Qing Xie³⁶, Don Rockey⁵⁷, Jiahong Dong⁵⁸, Xiaolong Qi¹. ¹CHES Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; ²Department of Gastroenterology and Hepatology, Tianjin Second People's Hospital, Tianjin, China; ³Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; ⁴Liver Research Center, Beijing Key Laboratory of Translational Medicine in Liver Cirrhosis, National Clinical Research Center of Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ⁵Department of liver diseases, fifth Medical Center of Chinese PLA General Hospital, Beijing, China; ⁶Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore, Singapore; ⁷Duke-NUS Medical School, Singapore; ⁸Portal Hypertension Center, The Sixth People's Hospital of Shenyang, Shenyang, China; ⁹Department of Gastroenterology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; ¹⁰Department of Hepatobiliary Surgery, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China; ¹¹Department of Gastroenterology, Baoding people's Hospital, Baoding, China; ¹²Department of Gastroenterology, Endoscopic center, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China; ¹³Department of Gastroenterology, Shannan People's Hospital, Shannan, China; ¹⁴Department of Hepatology, Qindao Municipal Hospital, Qingdao, China; ¹⁵Second Department of Gastroenterology, Qindao Municipal Hospital, Qingdao, China; ¹⁶Department of Infectious Diseases, Ankang Central Hospital, Ankang, China; ¹⁷Hepatology Department, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; ¹⁸affiliated Sixth People's Hospital of Dalian Medical University, Dalian, China; ¹⁹Department of Gastroenterology, Mengzi People's Hospital, Mengzi, China; ²⁰Department of Gastroenterology, Second Hospital of Nanjing, Nanjing Hospital of Chinese Medicine, Nanjing, China; ²¹Department of Infectious Diseases, Taihe Hospital, Hubei University of Medicine, Shiyan, China; ²²Department of Gastroenterology, The First Affiliated Hospital of Xi'an Medical University, Xi'an, China; ²³Department of Digestive Medicine, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China; ²⁴Division of Gastroenterology and Hepatology, Digestive Disease Institute, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China; ²⁵Department of Gastroenterology, The Fifth Affiliated Hospital of Zunyi Medical University, Zuhai, China; ²⁶Department of Gastroenterology, General Hospital of Western Theater Command PLA, Chengdu, China; ²⁷Department of Gastroenterology, Ankang Hospital of Traditional Chinese Medicine, Ankang, China; ²⁸Department of Hepatology, The First Hospital of Lanzhou University, Lanzhou, China; ²⁹NAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ³⁰Xingtai Institute of Cancer Control, Xingtai People's Hospital, Xingtai, China; ³¹The third People's Hospital of Tibet, Lasa, China; ³²The People's Hospital of Qingyang, Qingyang, China; ³³The People's Hospital of Bozhou, Bozhou, China; ³⁴The infectious disease hospital of Fuxin, Fuxin, China; ³⁵Tianjin Third Central Hospital, Tianjin, China; ³⁶Department of infectious disease, Ruijin hospital, Shanghai Jiao Tong university school of medicine, Shanghai, China; ³⁷The Second People's Hospital of Shizuishan, Shizuishan, China; ³⁸The Third people's hospital of Zhenjiang, Zhenjiang, China; ³⁹Department of Hepatology, Tianjin Third Central Hospital, Tianjin Medical University, Tianjin, China; ⁴⁰Department of Gastroenterology and Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China; ⁴¹Liver Diseases Center, Beijing Ditan Hospital, Capital Medical University, Beijing, China; ⁴²Department of Gastroenterology, Zhongshan Hospital Fudan University, Shanghai, China; ⁴³Department of Gastroenterology and Hepatology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁴⁴Hepatology Institute, Peking University People's Hospital, Beijing, China; ⁴⁵Department of Gastroenterology and Hepatology, Shanghai Public Health Clinical Center affiliated to Fudan University, Shanghai, China; ⁴⁶Department of Hepatology, Xinjiang Uygur Autonomous Region Traditional Chinese

Medicine Hospital; ⁴⁷Department of Gastroenterology, Tianjin Xiqing Hospital, Tianjin, China; ⁴⁸Infectious Disease Department, Affiliated Hospital of Yanbian University, Yanbian, China; ⁴⁹Department of Interventional Radiology, Lishui Central Hospital, Lishui, China; ⁵⁰Department of Hepatopancreatobiliary Surgery, Lishui Central Hospital, Lishui, China; ⁵¹Department of Gastroenterology, Second Affiliated Hospital of Baotou Medical University, Baotou, China; ⁵²The First People's Hospital of Zigong, Zigong, China; ⁵³Department of Infectious diseases, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; ⁵⁴Department of Gastroenterology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; ⁵⁵Department of Gastroenterology, The First Hospital of China Medical University, Shenyang, China; ⁵⁶Department of Hepatology, Shanghai Public Health Clinical Center, Shanghai, China; ⁵⁷Division of Gastroenterology and Hepatology, Medical University South Carolina, Charleston, United States; ⁵⁸Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Beijing, China Email: qixiaolong@vip.163.com

Background and aims: Baveno VI criteria and expanded-Baveno VI criteria have safely circumvented screening endoscopy among populations enriched with hepatitis C virus and alcoholic-related compensated cirrhosis. The study aimed to optimize the criteria in cohorts enriched with hepatitis B virus (HBV)-infected patients for single-use screening and dynamic monitoring of varices needing treatment (VNT).

Method: A total of six cohorts with compensated cirrhosis were enrolled, including: (1) a real-world cohort; (2) a multicenter validation cohort; (3) an international validation cohort; (4) a multicenter anti-HBV cohort; (5) a dynamic monitoring longitudinal cohort; (6) a multicenter, clinical practice cohort.

Results: We enrolled 3, 353 patients with compensated cirrhosis from 52 university hospitals in China and Singapore. In real-world cohort (65% [830/1, 274] HBV), Baveno VI criteria (platelets >150 × 10⁹/L and liver stiffness <20 kPa) would have spared 30% (387/1274) of esophagogastroduodenoscopy (EGD) and missed 3.6% (14/387) of VNT, while expanded-Baveno VI criteria (platelets >110 × 10⁹/L and liver stiffness <25 kPa) would have spared 53% (675/1, 274) of EGDs but missed 6.2% (42/675) of VNT. Meanwhile, using new CHES criteria (platelets >110 × 10⁹/L and liver stiffness <19 kPa) would have spared 46% (585/1, 274) of EGD and missed 4.9% of VNT (29/585). In the multicenter validation cohort, international validation cohort and anti-HBV cohorts, CHES criteria would have spared more EGD than Baveno VI criteria (Figure). Notably, employing CHES criteria in a dynamic monitoring longitudinal cohort would have spared 41% (56/138) and 54% (63/116) of EGD, and missed 1.8% (1/56) and 0% of VNT for the first and secondary monitoring, respectively (Figure). In the prospective clinical practice cohort-guided by CHES criteria, 75% (367/491) of EGD were spared after applying CHES criteria, with a VNT rate of 36% (45/124) in those undergoing EGD.

Conclusion: CHES criteria were superior to Baveno VI criteria and expanded-Baveno VI criteria for the screening and monitoring of varices in patients with predominantly HBV-related compensated cirrhosis.

PO-1668

Extracorporeal non-invasive assessment of the hepatobiliary function using novel bile acid derivatives with near-infrared fluorescence

Alvaro Temprano¹, Beatriz Sanchez de Blas², Ricardo A. Espinosa-Escudero², Candela Cives², Elisa Lozano³, Oscar Briz³, Concepcion Perez-Melero⁴, Francisco Bermejo⁵, Marta Romero⁶, Jose Marin⁷. ¹University of Salamanca, IBSAL, Biochemistry and Molecular Biology, Salamanca, Spain; ²University of Salamanca, IBSAL, Physiology and Pharmacology, Salamanca, Spain; ³University of Salamanca, IBSAL, CIBEREHD, Physiology and Pharmacology, Salamanca, Spain; ⁴University of Salamanca, IBSAL, Pharmaceutical Chemistry, Salamanca, Spain; ⁵University of Salamanca, Organic Chemistry, Salamanca, Spain; ⁶University of Salamanca, IBSAL,

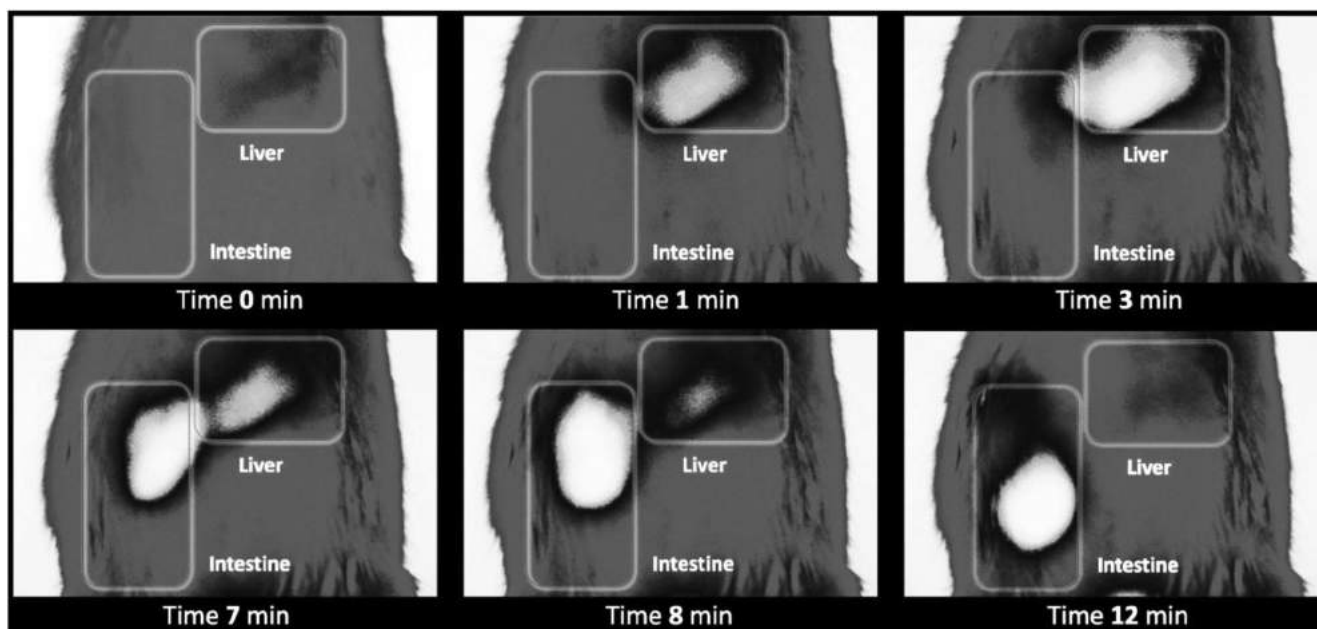


Figure: (abstract: PO-1668): Extracorporeal NIR fluorescence after NIRBAD1 administration to a control rat.

CIBEREHD, Biochemistry and Molecular Biology, Salamanca, Spain;
⁷University of Salamanca, IBSAL, CIBEREHD, Physiology and
 Pharmacology, Salamanca, Spain
 Email: jjgmarin@usal.es

Background and aims: A common feature in many liver diseases is impaired biliary secretion, which is not always evidenced by routine serum biochemical markers of liver function. Although normal bile acid (BA) uptake/secretion into bile accurately reflects healthy hepatobiliary function, serum levels can be affected by other factors altering BA pool size or enterohepatic circulation. We have aimed at developing a non-invasive strategy to carry out real-time evaluation of the hepatobiliary function based on the efficient liver handling of BAs and their derivatives.

Method: Using organic chemistry “click” technology, several BA species were linked to fluorochromes with near-infrared (NIR) emission wavelength, whose fluorescence can cross the abdominal wall and be extracorporeally detected. One of these compounds, named NIRBAD1 was chosen for preclinical evaluation. Selective NIRBAD1 uptake by hepatocytes has been investigated *in vitro* and *in vivo*. Extracorporeal determination of NIRBAD1 in rat liver was carried out with a high-sensitive (3.2 MP) CCD camera (Luminescent Image Analyzer LAS-4000 imaging system, Fujifilm Life Science).

Results: CHO cells were genetically manipulated to stably express hepatic BA transporters NTCP, OATP1B1, and OATP1B3. The uptake of 10 μM NIRBAD1 in the absence and the presence of 100 μM taurocholic acid (TCA) revealed that OATP1B3, and moderately OATP1B1, but not NTCP mediated TCA-inhibitible NIRBAD1 uptake. NIRBAD1 administration (i.v.) to anesthetized control rats was followed by its rapid disappearance from blood and secretion into bile. This time-course matched the dynamic of NIR fluorescence detected in the liver either directly by laparotomy or trans-abdominally in the intact animal (Figure). Serum markers of liver and kidney toxicity were not altered by NIRBAD1. The impaired hepatobiliary function was mimicked by phalloidin administration (i.v., 75 $\mu\text{g}/100\text{ g b.wt.}$). This procedure rapidly reduced (~50%) bile flow, which was accompanied by decreased NIRBAD1 bile output and a slower disappearance from blood. This was consistent with more prolonged retention in the liver. The half-life of extracorporeal NIR fluorescence was ≈ 5 min in controls, but longer (>2-fold) in phalloidin treated rats.

Conclusion: Novel BA derivatives with NIR fluorescence could be used as probes for the assessment of the hepatobiliary function by real-time extracorporeal non-invasive methods.

PO-1696

Diagnostic Accuracy of Transient Elastography in Diagnosing Clinically Significant Portal Hypertension in Patients with Chronic Liver Disease: A Systematic Review and Meta-analysis

Ashish Kumar¹, Anil Arora¹, Praveen Sharma¹,
 Shrihari Anikhindi¹, Naresh Bansal¹, Mandhir Kumar¹,
 Piyush Ranjan¹, Munish Sachdeva¹. ¹Sir Ganga Ram Hospital, Institute
 of Liver, Gastroenterology, and Pancreatico-Biliary Sciences, Delhi, India
 Email: ashishk10@yahoo.com

Background and aims: Transient elastography (TE) has been proposed as a promising non-invasive alternative to hepatic venous pressure gradient (HVPG) for diagnosing clinically significant portal hypertension (CSPH). However, previous studies have yielded conflicting results. We aimed to evaluate the correlation between liver stiffness measurement using TE and HVPG and the performance of TE in diagnosing CSPH (HVPG ≥ 10 mmHg).

Method: We conducted a systematic review and meta-analysis by searching PubMed and Scopus databases for relevant literature evaluating the clinical usefulness of TE for diagnosing CSPH in patients with chronic liver disease.

Results: Twenty-six studies (including 4337 patients with valid TE and HVPG readings) met our inclusion criteria. The median correlation coefficient of TE with HVPG was 0.70 (range 0.36 to 0.86). The weighted mean of optimal cut-off of liver stiffness value for diagnosing CSPH was 22.8 kPa (95% CI, 22.7–23.0 kPa). The summary sensitivity and specificity were 79% (95% CI, 74–84%) and 88% (95% CI, 84–91%), respectively. The area under the hierarchical summary receiver operating characteristic (HSROC) curve was 0.91 (95% CI, 0.88–0.93) according to the bivariate model. There was significant heterogeneity in the results, which was well explained by the variable liver stiffness cut-offs used in the studies. The meta-regression plot revealed that as the optimal cut-off increased, the sensitivity decreased, the specificity increased, and vice versa.

Conclusion: Liver stiffness measurement by TE correlates well with HVPG, and a liver stiffness cut-off value of 22.8 kPa shows a high accuracy for diagnosing CSPH. Thus, use of TE should be integrated into clinical practice for non-invasive diagnosis of CSPH.

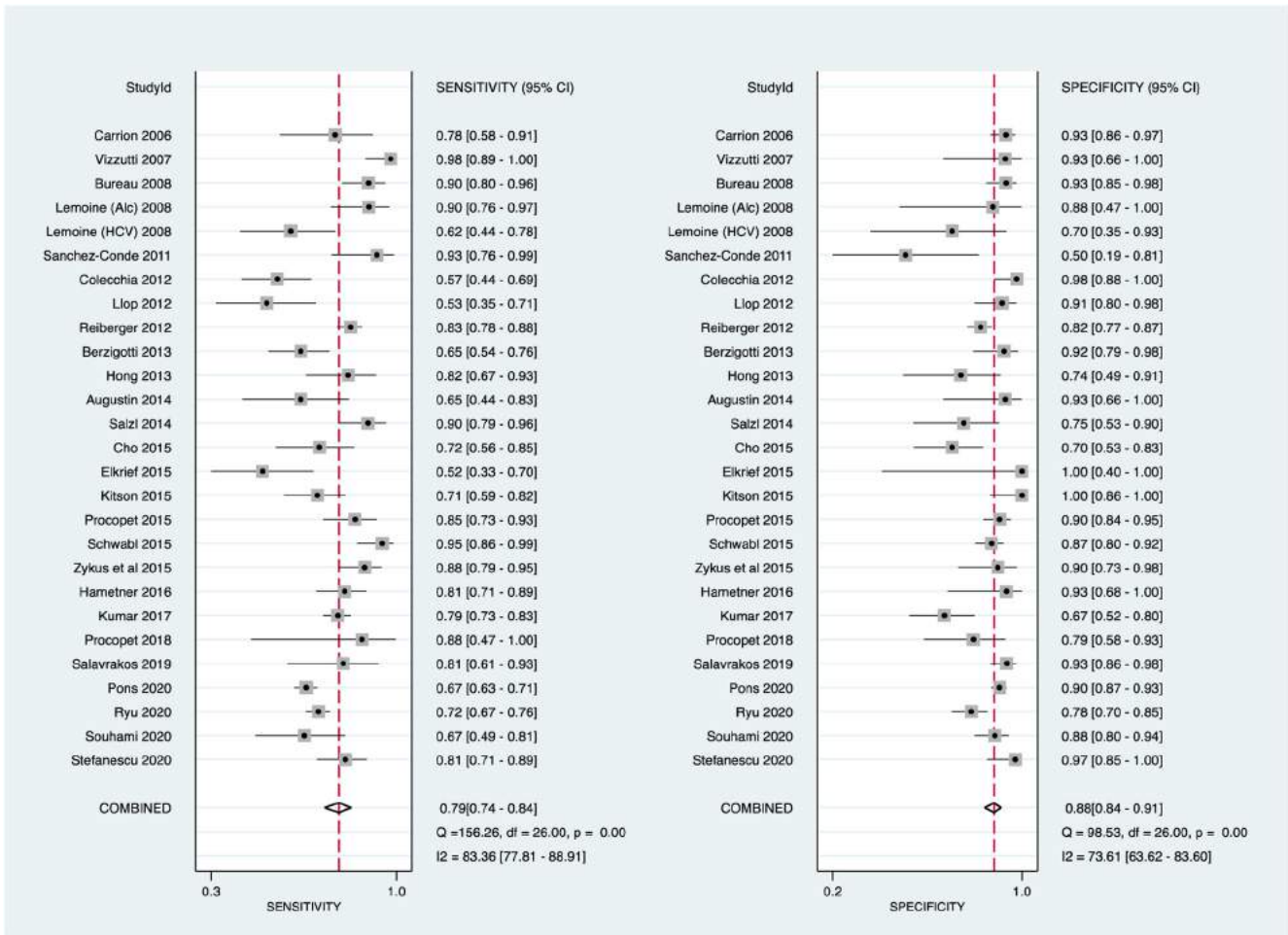


Figure: (abstract: PO-1696): Forest plot of sensitivity and specificity of TE for diagnosis of CSPH.

PO-1899

A novel liver-specific fibrosis biomarker, PRO-C18L, can predict response to antifibrotic treatment, with a peroxisome proliferator activated receptor - γ agonist, in patients with chronic hepatitis C
 Ida Villesen^{1,2}, Lasse Langholm¹, Diana Leeming¹, Zachary Goodman³, Keyur Patel^{4,5}, Morten Karsdal¹, Detlef Schuppan^{6,7}, Mette Juul Nielsen¹. ¹Nordic Bioscience, Fibrosis, Herlev, Denmark; ²University of Copenhagen, BRIC, Denmark; ³Inova Fairfax Hospital, Hepatic Pathology Consultation and Research, United States; ⁴University of Toronto, Division of Gastroenterology and Hepatology, Canada; ⁵Duke University, Durham, United States; ⁶Johannes Gutenberg University, University Medical Center, Mainz, Germany; ⁷Harvard Medical School, Beth Israel Deaconess Medical Center, United States
 Email: ifv@nordicbio.com

Background and aims: Fibrosis is characterized as excess accumulation of extracellular matrix (ECM) in a given organ. Recently the qualitative composition of the fibrotic liver ECM has emerged as a key determinant of prognosis and survival in advanced liver disease. Type XVIII collagen is a sinusoidal basement membrane collagen harbouring a liver-specific long isoform expressed primarily by hepatocytes, suggested to associate with a repair response to hepatic injury. Here we investigate if a novel biomarker for the liver isoform of type XVIII collagen, PRO-C18L, could predict responders to an antifibrotic treatment with peroxisome proliferator activated receptor (PPAR)- γ agonist: Farglitazar, in a retrospective cohort of patients with chronic hepatitis C (CHC).

Method: Plasma samples of 127 CHC patients with mild to moderate fibrosis (Ishak score 2–4) who had failed prior interferon- α treatment were included in the study (NCT 00244751). Patients received a daily doses of farglitazar 0.5 or 1.0 mg (n = 87), or placebo (n = 40) for 52 weeks. A baseline (BL) and end-of-treatment biopsy was taken and matched with blood sampling. The representative biopsies were centrally read using the Ishak score and patients were defined as regressors or progressors, characterized as at least one stage decrease or increase, respectively, in the Ishak fibrosis score at week 52, or as stable, defined as no change in Ishak score at week 52. Serological levels of PRO-C18L were analyzed at BL and at 52 weeks.

Results: 11/5 patients on placebo, 24/15 on Farglitazar progressed/regressed, respectively, while the rest remained stable. Patients with high BL levels of PRO-C18L (above 2.56 ng/ml) were found more prone to have a treatment response. This was shown by the change in PRO-C18L from BL to week 52. Thus, patients below median levels of PRO-C18L (<2.56 ng/ml) at BL showed no change with treatment (p = 0.6) while patients above median did (p = 0.05). These results were further supported by the histological assessment by the end of the study. Thus, when separating patients into tertiles based on BL level of PRO-C18L, the patients in the highest tertile had a significant proportion of regressors with treatment. This was not found in the lowest tertile.

Conclusion: The novel biomarker of hepatic repair response to injury, PRO-C18L, predicted responders to treatment at BL. PRO-C18L is there for a promising novel biomarker, to predict and follow the evolution of liver fibrosis with treatment.

POSTER PRESENTATIONS

PO-2094

Quantitate MR can identify paediatric patients with quiescent disease who may benefit from a change in treatment

Elizabeth Shumbayawonda¹, Kamil Janowski², Andrea Dennis¹, Helena Thomaidis-Brears¹, Matt Kelly¹, Maciej Pronicki³, Wiesława Grajkowska³, Małgorzata Woźniak², Piotr Pawliszak⁴, Elżbieta Jurkiewicz⁴, Rajarshi Banerjee¹, Piotr Socha². ¹Perspectum, Oxford, United Kingdom; ²Centrum Zdrowia Dziecka, Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, Warszawa, Poland; ³Centrum Zdrowia Dziecka, Department of Pathology, Warszawa, Poland; ⁴Centrum Zdrowia Dziecka, Department of Diagnostic Imaging, Warszawa, Poland
Email: elizabeth.shumbayawonda@perspectum.com

Background and aims: Autoimmune hepatitis (AIH) is monitored using liver biochemistry and histology, however, liver biopsy is invasive, and carries the risk of pain and bleeding. MR-derived iron corrected T1 (cT1) is a promising metric that has demonstrated utility in monitoring and predicting remission loss in AIH. cT1 interquartile range (IQR), a marker of disease heterogeneity, has also shown utility in patient management. The aim of this study was to investigate the utility of imaging markers to stratify those with active from those with quiescent disease and thus identify those who would not require a follow-up biopsy but may benefit from a change in treatment.

Method: In 21 biopsy-confirmed AIH paediatric patients (aged 13 ± 3 years) who had a repeat monitoring biopsy after ± 16 months, those with active disease were defined as having both lobular and portal inflammation >1 on monitoring biopsy. The number of patients in biochemical remission (ALT < 40 IU/L and AST < 40 IU/L) was assessed. The potential of both blood markers (AST, ALT, GGT, IgG, bilirubin, albumin, gamma globulins) and imaging markers (derived using LiverMultiScan®) to discriminate those who had active disease from those with quiescent disease was investigated. Accuracy of each biomarker was determined using area under the receiver operator characteristic curve (AUC).

Results: 9/21 patients had quiescent disease while 12/21 had active disease on monitoring biopsy. Moreover, 18/21 were in biochemical remission at follow-up. Patients with quiescent disease had lower mean cT1: 793 ± 47 ms compared to those with active disease cT1 of 819 ± 47 ms. cT1 IQR was the best imaging marker (AUC: 0.8 [0.57–1]) while GGT (AUC: 0.73 [0.5–0.96]) was the best blood marker to

identify those with quiescent disease. By combining blood with imaging markers (GGT + cT1 IQR), the diagnostic utility was improved to AUC: 0.84 [0.66–1] (Fig. 1). Moreover, when the definition of active disease was extended to include those with fibrosis >2, the combined marker of cT1 IQR and GGT performed the best with AUC: 0.8 [0.59–1], and thus highlighted the strength of combining imaging and blood markers in patient management.

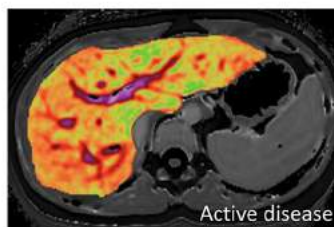
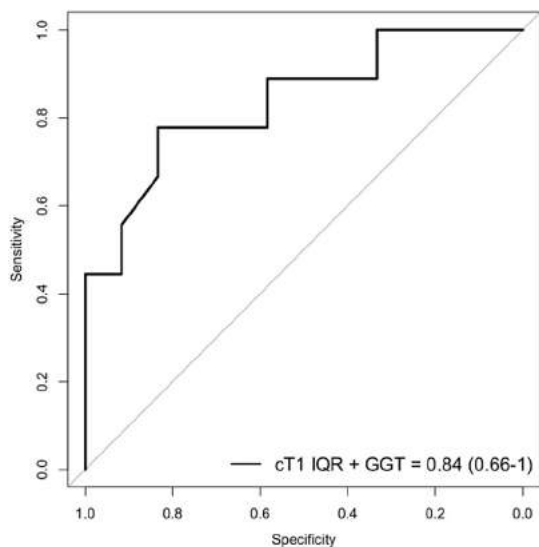
Conclusion: The combination of imaging and blood markers shows utility in identifying paediatric patients with quiescent disease, thus offering a potential non-invasive alternative to repeat biopsy. Further work exploring the utility of cT1 IQR in the AIH clinical pathway is warranted.

PO-2184

Serum miRNA profiling for the differential diagnosis of distal cholangiocarcinoma from pancreatic diseases

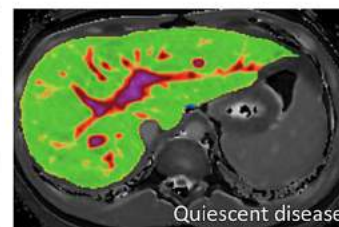
André F. Tomás¹, André L. Simão¹, Luis Muñoz-Bellvis², Ainhoa Lapitz³, Luis Bujanda⁴, Pedro Miguel Rodrigues³, Jesus Maria Banales³, Jose Marin⁵, Cecília M. P. Rodrigues¹, Rocio IR Macias⁵, Rui E. Castro¹. ¹Research Institute for Medicines (iMed. ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal; ²Service of General and Gastrointestinal Surgery, University Hospital of Salamanca, IBSAL, CIBERONC, Salamanca, Spain; ³Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute, Donostia University Hospital, University of the Basque Country (UPV/EHU), CIBERehd, Ikerbasque, San Sebastian, Spain; ⁴National Institute for the Study of Liver and Gastrointestinal Diseases (CIBERehd, Carlos III Health Institute), Madrid, Spain; ⁵Experimental Hepatology and Drug Targeting (HEVEPHARM), University of Salamanca, Biomedical Research Institute of Salamanca (IBSAL), CIBERehd, Salamanca, Spain
Email: adlsimao@ff.ulisboa.pt

Background and aims: When distal cholangiocarcinomas (dCCAs) cross the pancreatic head, it is clinically challenging to distinguish them from pancreatic ductal adenocarcinomas (PDACs) or even benign pancreatic diseases (BPDs) by using currently available imaging techniques or established biomarkers. Moreover, all these disease conditions share similar clinical symptoms. In that regard, serum microRNAs (miRNA/miRs) have been emerging as novel potential biomarkers for diseases. Thus, we aimed to profile global serum miRNA expression changes in human patients with dCCA, PDAC and BPDs in order to identify potential candidates for the



Active disease

AST: 55 IU/L
ALT: 87 IU/L
Fibrosis: 5
Portal inflammation: 3
Lobular inflammation: 2
cT1: 917 ms



Quiescent disease

AST: 21 IU/L
ALT: 20 IU/L
Fibrosis: 0
Portal inflammation: 0
Lobular inflammation: 1
cT1: 749 ms

Figure: (abstract: PO-2094): A. Diagnostic accuracy of individual blood and imaging markers to identify AIH patients with quiescent disease. B. cT1 maps for a patient with active disease (left) and quiescent disease (right).

differential diagnosis of these diseases, which would have a direct impact on their specific treatment.

Method: Serum samples were obtained from patients with histopathologic confirmation of dCCA (n = 35) or PDAC (n = 38), as well as from BPD patients (with cysts (n = 22) or with chronic pancreatitis (n = 20), or from healthy subjects (n = 45), with complete anthropometric, biochemical and clinical characterization. Serum miRNAs were isolated using the miRNeasy Serum Advanced Kit and sample pools from each group were analyzed using TaqMan Advanced miRNA Human Serum array cards. cel-miR-39-3p was used as an exogenous spike-in control. Selected miRNAs were validated by TaqMan Advanced Real-Time RT-PCR.

Results: Real time RT-PCR array analysis revealed distinct serum miRNA expression profiles between all groups of patients. Upon individual validation, miRNAs found to be mostly differentially expressed in dCCA included miR-95-3p and miR-154-5p, up- and down-regulated, respectively, comparing with PDAC, but also with BPD and healthy controls. Of note, miR-204-5p and miR-200c-3p were particularly elevated in BPD patients with cysts or with chronic pancreatitis, respectively, comparing with dCCA. In addition, the levels of these miRNAs were found to be independent of the patient gender or the presence of selected liver disease risk factors. Moreover, serum miR-154-5p levels negatively correlated with GGT, while both miR-204-5p and miR-200c-3p positively correlated with patients' age. Of note, in dCCA patients, miR-95-3p levels positively correlated with carbohydrate antigen19-9 (CA19-9), a non-specific tumor marker commonly used to help in the diagnosis of CCA and PDAC.

Conclusion: In conclusion, analysis of serum levels of specific miRNAs, including miR-95-3p and miR-154-5p, may allow for the differential diagnosis of dCCAs from both benign and malignant pancreatic diseases, as well as correlations with clinical features of patients. Further validation in independent cohorts could translate into the use of miRNAs as accurate biomarkers for dCCA early diagnosis. (OLD-HEPAMARKER, 0348_CIE_6_E; V Beca de Investigación Carmen Delgado/Miguel Pérez-Mateo, Spain; PTDC/MED-PAT/31882/2017, Portugal; COST Action CA18122, EUROCHOLANGIO-NET).

PO-2319

Validation of non-invasive criteria for diagnosis of clinically significant portal hypertension in compensated advanced chronic liver disease of different etiologies in an asian cohort

Ankur Jindal¹, Samagra Agarwal², Sanchit Sharma², Manoj Kumar¹, Anoop Saraya², Shiv Kumar Sarin¹. ¹Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India; ²AIIMS Hospital, Gastroenterology and Human Nutrition Unit, New Delhi, India
Email: shivsarin@gmail.com

Background and aims: Non-invasive diagnosis of clinically significant portal hypertension (CSPH) using simple classification criteria is important in centres where hepatic venous pressure gradient (HVPG) measurement is not routinely practiced. We aimed to validate the recently published non-invasive criteria to predict CSPH in compensated advanced chronic liver disease (cACLD) of different etiologies in an Asian cohort.

Method: In this retrospective study, consecutive patients of cACLD of different etiologies with anthropometry, liver stiffness measurement (LSM), HVPG and blood investigations records were included. CSPH was defined as HVPG>10 mm Hg. A LSM ≥25 kPa and LSM ≤15 kPa plus platelets ≥150 × 10⁹/L were evaluated as a non-invasive rule-in and rule-out criteria for CSPH respectively. The NASH-ANTICIPATE model (composite of BMI, platelets and LSM) was tested to evaluate CSPH in patients with NASH with BMI>30 kg/m².

Results: 626 patients (mean age:44.7 ± 13.5 years, 72.4% males) with alcohol (30.3%), non-alcoholic steatohepatitis (26.4%), hepatitis C (16.6%), hepatitis B (10.2%) related cACLD were included. CSPH was present in more than 80% patients of all etiologies except HBV (62.5%). Non-invasive rule-in criteria had a positive predictive value (PPV) >90% for all etiologies except in HBV (PPV- 80.8%) and in patients with HCV with BMI>30 kg/m² (PPV-75%). Non-invasive rule-out criteria were insufficient with 0-60% patients of different etiologies having CSPH despite satisfying both rule-out criteria. The NASH-ANTICIPATE model had a high specificity (100%) but a suboptimal sensitivity (68%) to detect CSPH in patients with obese NASH.

Conclusion: Utility of non-invasive rule-in criteria depends on prevalence of CSPH in population being assessed, with limited

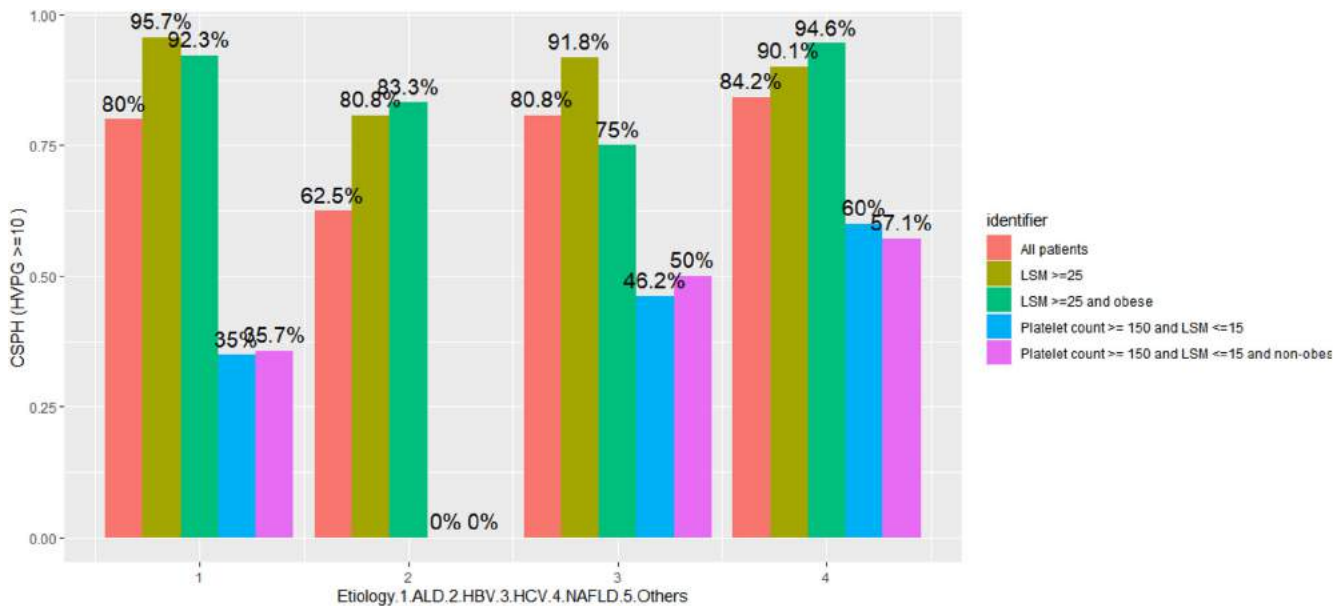


Figure: (abstract: PO-2319): Bar diagram showing overall prevalence of CSPH (red), prevalence of CSPH in patients with LSM>25 kPa (rule-in criteria), (dark green color), prevalence of CSPH in patients with rule out criteria and BMI>30 kg/m² (light green), prevalence of CSPH in patients with LSM<15 kPa and platelets less than 150000/mm³ (rule-out criteria) (blue color) and rule out criteria plus BMI<30 kg/m² (pink color) across different etiologies of cACLD.

POSTER PRESENTATIONS

value in HBV related CLD and in obese patients with HCV. Rule out criteria for CSPH are suboptimal for excluding CSPH across most etiologies and better criteria are needed before they can be used in clinical practice.

PO-2370

Evaluation of the newly proposed criteria for clinically significant portal hypertension using platelets and transient elastography

Kristian Podrug^{1,2}, Vladimir Trkulja³, Marko Zelenika⁴, Tomislav Bokun⁴, Tonci Bozin⁴, James O'Beirne⁵, Ivica Grgurevic⁶.

¹University Hospital centre Split, Department of Gastroenterology and Hepatology, Split, Croatia; ²University Hospital centre Split, Department of Gastroenterology and Hepatology, Split, Croatia; ³University of Zagreb School of Medicine, Department of Pharmacology, Zagreb, Croatia;

⁴University hospital Dubrava, Department of Gastroenterology, Hepatology and Clinical Nutrition, Zagreb, Croatia; ⁵University of Sunshine Coast, Department of Hepatology, Australia; ⁶University of Zagreb School of Medicine, University Hospital Dubrava, Department of Gastroenterology, Hepatology and Clinical Nutrition, Zagreb, Croatia
Email: kpodrug@gmail.com

Background and aims: New non-invasive criteria for diagnosing clinically significant portal hypertension (CSPH) have been proposed recently (Pons M. et al. Am Journal Gastroenterol 2020). We aimed to evaluate performance of the proposed criteria in a cohort of patients with compensated chronic liver disease.

Methods: We evaluated diagnostic performance of liver stiffness measurement (LSM) by transient elastography and Platelet count (Plt) for CSPH in a cohort of patients with available results of hepatic venous pressure gradient (HVPG) measurements and liver biopsy performed due to suspicion of compensated advanced chronic liver disease (cACLD). Newly proposed non-invasive criteria evaluated here were: $LSM \geq 25$ kPa for ruling-in, and $Plt \geq 150 + LSM \leq 15$ kPa for ruling-out CSPH. Only patients >18 years of age, who gave informed consent were included, whereas those with conditions known to affect results of LSM (ALT>5x ULN, liver congestion, extrahepatic biliary obstruction, infiltrative liver neoplasms) were not. Presence of cACLD was confirmed on liver biopsy in patients with bridging fibrosis or cirrhosis.

Results: The cohort included 76 patients [78.9% men, median age 62 (34–76) years, 30% obese, mostly suffering from alcoholic (36.8%) or non-alcoholic fatty liver (30.3%) disease], 61 (80.3%) of whom had cACLD, 40 (52.6%) had HVPG ≥ 10 mmHg (CSPH) and 43 (56.6%) had $Plt \geq 150$. $LSM \geq 25$ kPa had 88.9% (95% CI 73.9–96.9) specificity to rule-in, whereas $Plt \geq 150 + LSM \leq 15$ kPa had 100% (95% CI 73.5–100) sensitivity to rule-out CSPH. By these criteria it was possible to classify correctly 49/76 (64.5%) patients for the presence of CSPH. With increasing BMI, at any given value of Plt, higher LSM was needed for a certain probability of having CSPH.

Conclusion: By using these simple new non-invasive criteria almost 65% of patients could be classified correctly for the presence of CSPH. This might facilitate early recognition of CSPH among patients with cACLD and timely introduction of non-selective beta blockers considering the results from PREDESCI trial.

PO-2386

Dynamic liver function tests and liver elastography in cardiac amyloidosis-preliminary data from AmyKoS

Sandra Ihne¹, Oliver Goetze², Stefan Frantz³, Hermann Einsele⁴, Stefan Knop⁴, Stefan Stoerk³, Andreas Geier². ¹University Hospital of Würzburg, Department of Internal Medicine II/Hematology, Comprehensive Heart Failure Center (CHFC), Interdisciplinary Amyloidosis Center of Northern Bavaria, Würzburg, Germany;

²University Hospital of Würzburg, Internal Medicine II/Hepatology, Interdisciplinary Amyloidosis Center of Northern Bavaria, Würzburg, Germany; ³University Hospital of Würzburg, Internal Medicine I/ Cardiology, Comprehensive Heart Failure Center (CHFC), Interdisciplinary Amyloidosis Center of Northern Bavaria, Würzburg,

Germany; ⁴University Hospital of Würzburg, Internal Medicine II/ Hematology, Interdisciplinary Amyloidosis Center of Northern Bavaria, Würzburg, Germany
Email: ihne_s@ukw.de

Background and aims: Cardiac involvement (CA) indicates a poor prognosis in both light chain (AL) and transthyretin (ATTR) amyloidosis. Concomitant hepatic manifestation in AL amyloidosis clinically defined by elevated alkaline phosphatase (AP) levels and/or hepatomegaly even worsens outcome. Staging systems for CA are based on congestion-sensitive cardiac biomarkers NT-proBNP and troponin. We aimed to differentiate primary (amyloid deposition) from secondary liver affection (congestion) in amyloidosis. ATTR amyloidosis acts as example for secondary liver affection, AL amyloidosis is a model for both.

Method: Participants of the prospective amyloidosis cohort study AmyKoS with proven AL, ATTR and excluded systemic amyloidosis underwent detailed work-up including extensive laboratory tests, echocardiography, vibration controlled transient elastography (VCTE) and ¹³C-methacetin breath test (MBT).

Results: From November 2017 until April 2020, 79 patients with proven AL (n = 30; mean age 64.0 ± 8.1 years), ATTR (n = 29; mean age 74.9 ± 7.2 years) and excluded systemic amyloidosis (controls; n = 20; mean age 60.8 ± 11.7 years) were evaluated. CA was found in 17 AL (AL-CA; 57%) and 26 ATTR (ATTR-CA; 90%) amyloidosis patients.

AL-CA vs ATTR-CA vs controls showed heart failure with preserved ejection fraction with elevation of NT-proBNP 9601.3 ± 13988.5 pg/ml vs. 2782.6 ± 2290.8 pg/ml vs. 344.1 ± 685.8 pg/ml.

ESC criteria of acute heart failure (AHF) were fulfilled in 35% vs 35% vs. 0%, edema was apparent in 47% vs 31% vs 20%, and distended liver veins in 12 vs 12 vs 0%. Elevated AP levels (74.8 ± 22.7 vs 85.8 ± 41.0 vs 70.3 ± 18.5 U/l) were accompanied by reduced liver synthesis capacity.

VCTE revealed increased liver stiffness (5.0 ± 2.0 vs 7.9 ± 4.5 vs 4.4 ± 0.9 kPa, p = 0.008) in ATTR-CA associated with hypervolemia (Spearman's rho for edema 0.57, p = 0.009; distended hepatic veins 0.45, p = 0.047) and NT-proBNP (0.58; p = 0.007), but not with other standard parameters (e.g. NYHA stage, LVEF, cardiac output, wall thickness) and presence of AHF. Cumulative percentage dose of ¹³C recovery (cPDR) after 10–30 minutes in MBT correlates with AP and cardiac output, but not with parameters of hypervolemia.

Conclusion: Robust and generally applicable parameters for distinction of primary and secondary liver affection are needed in CA. Liver stiffness represents an indicator of hypervolemia and congestion; cPDR correlates with cardiac output, an acknowledged prognostic marker.

PO-2476

Development and multicenter external validation of FIB-6; a novel, machine-learning, simple bedside score to rule out severe liver fibrosis and cirrhosis in patients with chronic hepatitis C

Gamal Shihai¹, Reham Soliman², Nabil Mikhail³, Khaled Alswat⁴, Ayman Abdo⁵, Faisal Sanai⁵, Moutaz F.M. Derbala⁶, Necati Ormeci⁷, George Dalekos⁸, Said Ahmed Salim Al Busafi⁹, Waseem Hamoudi¹⁰, Alaa Sharara¹¹, Elsayed Tharwa¹², Samy Zaky¹³, Fathia El-Raie¹⁴, Mai Mabrouk¹⁵, Samir Marzouk¹⁶, Hidenori Toyoda¹⁷. ¹Mansoura-Damietta Road, Egyptian Liver Research Institute and Hospital, Shirbin, Egypt; ²Egyptian Liver Research Institute and Hospital, Tropical Medicine, Shirbin, Egypt; ³Egyptian Liver Research Institute and Hospital, Egypt; ⁴King Saud University, Hepatology, Riyadh, Kingdom of Saudi Arabia; ⁵King Abdulaziz Medical City, Medicine, Jeddah, Saudi Arabia; ⁶Hamad Hospital, Gastroenterology and Hepatology, Doha, Qatar; ⁷Ankara University School of Medicine, Gastroenterology, Ankara, Turkey; ⁸School of Medicine, University of Thessaly, Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; ⁹Oman, Gastroenterology and Hepatology, Oman; ¹⁰Jordan, Internal Medicine, Jordan; ¹¹Lebanon, Gastroenterology, Lebanon; ¹²Cairo, Hepatology, Cairo, Egypt; ¹³Cairo, Gastroenterology and Infectious Diseases, Cairo,

Egypt; ¹⁴Damietta, Hepatogastroenterology and Infectious Diseases, Damietta, Egypt; ¹⁵Misr University for Science and Technology, Biomedical Engineering, Egypt; ¹⁶Arab Academy for Science and Technology, Egypt; ¹⁷Ogaki Municipal Hospital, Gastroenterology
Email: g_shiha@hotmail.com

Background and aims: We developed and validated a non-invasive diagnostic index based on routine laboratory parameters for predicting the stage of hepatic fibrosis in patients with chronic hepatitis C (HCV).

Method: Machine learning with random forests algorithm was used to develop a non-invasive index using retrospective data of 7238 biopsy proven chronic hepatitis C (CHC) patients from two centers; derivation dataset (n = 1821) and validation set in the second center (n = 5417). ROC curve analysis was used to define cutoffs for different stages of fibrosis. Performance of the new score was externally validated in cohorts from two other sites in Egypt (n = 560) and in seven different countries (n = 1317). Results were also compared with three established tools (FIB-4, APRI, and AAR).

Results: Age, aspartate, and alanine aminotransferases, alkaline phosphatase, albumin (g/dL), and platelet count (/cm3) correlated with the biopsy-derived stage of liver fibrosis in the derivation cohort and were used to construct the model for predicting the fibrosis stage, resulting in an FIB-6 index. Applying the cutoffs from the ROC curve analysis of the derivation group in the validation groups indicated very good performance in ruling out cirrhosis (negative predictive value [NPV]=97.7%), severe fibrosis (NPV=90.2%), and significant

fibrosis (NPV=65.7%). In the external validation groups, FIB-6 demonstrated higher sensitivity and NPV than FIB-4, APRI, and AAR.
Conclusion: FIB-6 score is an accurate, simple, non-invasive test for ruling out advanced fibrosis and liver cirrhosis in chronic hepatitis C patients better than APRI, FIB-4 and AAR.

PO-2936

Improving the Accuracy of Non-Invasive Tests for Prediction of Cirrhosis in Chronic Hepatitis Delta: Insights from 230 Patients of the D-LIVR Study

Tarik Asselah¹, Maria Buti², David Yardeni³, Pietro Lampertico⁴, Rob Howard⁵, Ingrid Choong⁶, Johanna Wagstaff⁷, Ohad Etzion³.
¹Universite de Paris, Hepatology Department, Paris, France; ²Hospital Universitario Valle Hebron, Barcelona, Spain; ³Soroka University Medical Center, Department of Gastroenterology and Liver Diseases, Israel; ⁴University of Milan, Gastroenterology and Hepatology Division, Milan, Italy; ⁵Veridical Solutions, United States; ⁶Eiger BioPharmaceuticals, Inc, Palo Alto, United States; ⁷Eiger BioPharmaceuticals, Inc, Palo Alto, United States
Email: tarik.asselah@aphp.fr

Background and aims: Chronic Hepatitis Delta Virus (HDV) leads to the most severe form of viral hepatitis. In chronic HDV, factors associated with cirrhosis have not been well investigated. Few data are available regarding non-invasive methods to diagnose cirrhosis. This study aims to describe factors associated with cirrhosis in HDV and evaluate the performance of several commonly used non-

Parameter	No Cirrhosis (N=163)	Cirrhosis (N=67)	All Subjects (N=230)
Age (years)			
N	163	67	230
Mean (SE)	43.0 (0.87)	48.5 (1.37)	44.6 (0.75)
Median	42.00	51.00	43.50
Min, Max	19, 66	23, 69	19, 69
p-value		0.0008 [a]	
Baseline ALT (IU/L)			
N	156	64	220
Mean (SE)	98.9 (5.90)	114.0 (9.16)	103.3 (4.97)
Median	74.00	93.50	79.00
Min, Max	27, 501	34, 363	27, 501
p-value		0.1662 [a]	
Obesity (BMI > 30 kg/m ²)			
Yes	19 (11.7%)	16 (23.9%)	35 (15.2%)
No	105 (64.4%)	46 (68.7%)	151 (65.7%)
Missing	39 (23.9%)	5 (7.5%)	44 (19.1%)
p-value		0.0846 [c]	
Baseline HDV RNA (Log IU/mL)			
N	157	63	220
Mean (SE)	5.2 (0.09)	5.0 (0.12)	5.2 (0.08)
Median	5.27	5.12	5.26
Min, Max	2, 8	3, 7	2, 8
p-value		0.3713 [a]	
APRI > 2 and Fibroscan > 12.5 kPa			
Yes	5 (3.1%)	15 (22.4%)	20 (8.7%)
No	103 (63.2%)	40 (59.7%)	143 (62.2%)
Missing	55 (33.7%)	12 (17.9%)	67 (29.1%)
p-value		<.0001 [c]	
Fibroscan > 12.5 kPa and FIB-4 > 3.27			
Yes	6 (3.7%)	15 (22.4%)	21 (9.1%)
No	102 (62.6%)	40 (59.7%)	142 (61.7%)
Missing	55 (33.7%)	12 (17.9%)	67 (29.1%)
p-value		<.0001 [c]	

Figure: (abstract: PO-2936)

POSTER PRESENTATIONS

invasive scoring systems to diagnose or exclude cirrhosis in HDV, including aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis index based on four factors (FIB-4), Fibrotest™ and Stiffness (Fibroscan®).

Method: Demographic, histologic and clinical laboratory data from the first 230 randomized patients in the on-going Phase 3 HDV D-LIVR trial (NCT03719313) were evaluated. D-LIVR is the largest, global registrational study in HDV, investigating Lonafarnib, the first and only oral agent in development for HDV. All patients had a baseline liver biopsy to diagnose cirrhosis. The prediction of cirrhosis with non-invasive evaluation was based on established scales and cut-off values of APRI >2, FIB-4 >3.27, Fibrotest >0.74, Fibroscan >12.5 kPa.

Results: Patients with cirrhosis (n = 67) when compared to patients without cirrhosis (n = 163) were older (mean age 48.5 vs 43.0 years, $p = 0.0008$) with a trend toward obesity (BMI >30 kg/m²) (23.9% vs 11.7%, $p = 0.08$). There was no statistical difference between these two groups regarding baseline levels of ALT, glucose, albumin, bilirubin, HBsAg quantification, HDV RNA or HBV DNA. APRI >2, FIB-4 >3.27, Fibrotest >0.74 correlated with cirrhosis (r coefficient, p values). However, a large proportion of patients with cirrhosis (55–64%) were not identified as cirrhotic by these scores. Few (8–11%) patients without fibrosis were misclassified as having cirrhosis. Stiffness (Fibroscan >12.5 kPa) was correlated with cirrhosis (r coefficient, p values), however (41.8%) were missed by the scores and a large proportion (53.4%) of patients without fibrosis were misclassified as having cirrhosis. A combination of APRI <2 and Fibroscan <12.5 kPa correctly had a NPV of 96.9% for excluding cirrhosis. A combination of FIB-4 <3.27 and Fibroscan >12.5 had a NPV of 96.3% for excluding cirrhosis.

Conclusion: APRI, FIB-4, Fibrotest and Fibroscan are not accurate predictors of cirrhosis in chronic HDV patients. However, the combination of serum markers (APRI <2 or FIB-4 <3.27) and elasticity (Fibroscan <12.5 kPa) can exclude the presence of cirrhosis. For patients who do not meet these criteria, a liver biopsy may be

performed for the diagnosis of cirrhosis. Liver biopsy is currently the most reliable method for detection of cirrhosis in this population.

Keywords: APRI; Chronic hepatitis D; FIB-4; Cirrhosis.

Nurses and Allied Health Professionals

PO-190

Patients with LIVER CIRRHOSIS-SATISFACTION in a NURSE-LED outpatient clinic

Marie Louise Sjoedin Hamberg¹, Sabine Greve Danielsen¹, Lene Dupont¹, Hanne Bennick¹, Marthe Forbord Huss Joensson¹, Mette Lehmann Andersen¹, Ane Soegaard Teisner¹, Anne Kjaergaard Danielsen¹. ¹Herlev Gentofte Hospital, Dept. of Gastroenterology, Herlev, Denmark
Email: marie.louise.sjoedin.hamberg.01@regionh.dk

Background and aims: Patients with decompensated cirrhosis—regardless of etiology—often belong to an exposed and marginalized group of patients due to a broad variety of causes, e.g. the cognitive impact of hepatic encephalopathy (HE) and the stigmatization caused by the diagnosis alone. Consequently, for an outpatient there may be a corresponding need for easy access, continuity, frequent support and close follow-up. In 2017, to address this we implemented a nurse led outpatient clinic with a patient-centered approach. Since then we've continuously strived to increase patient participation and in 2020 we decided to conduct a survey to explore patient satisfaction within areas as involvement and level of information (fig.1).

Method: Patients with cirrhosis were recruited consecutively during their scheduled visits in the nurse-led clinic regardless of cause (e.g. medicine adjustments or paracentesis). All participants gave written consent and could only participate once. Data were collected using a

Results on patient satisfaction

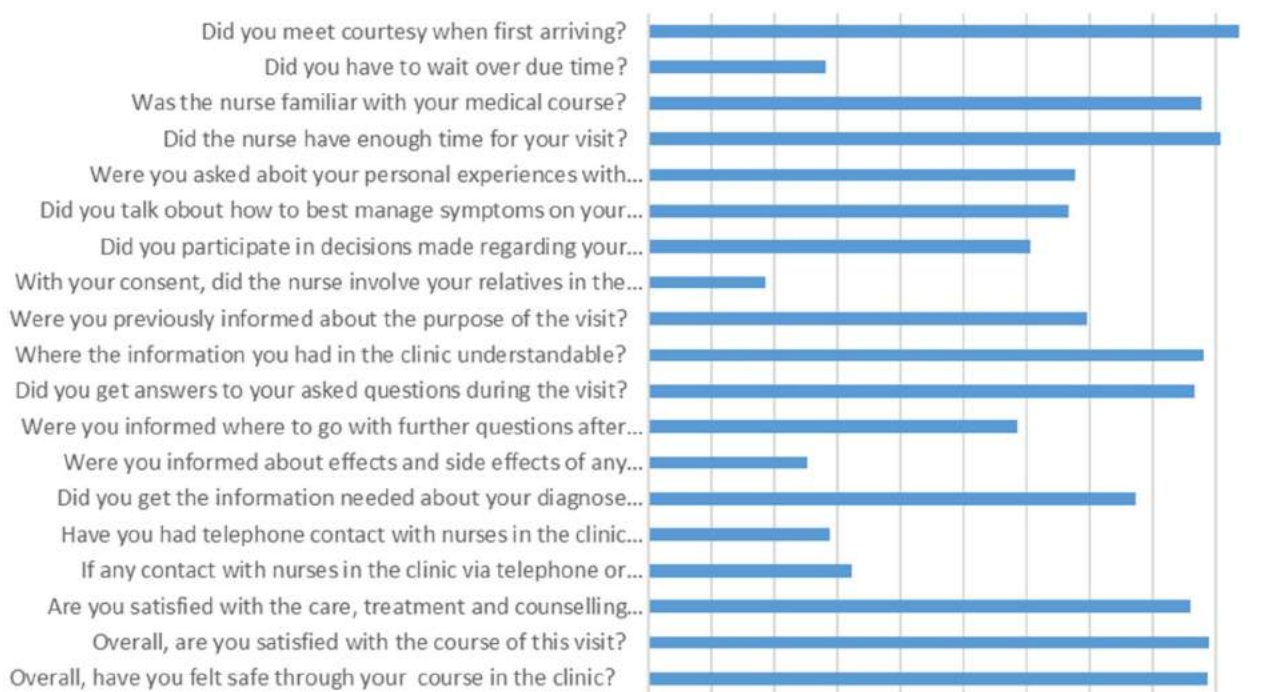


Figure: (abstract: PO-190): shows mean values of the 19 questions on satisfaction. Participants rated every question on a 5-point Likert scale ranging from Not at all to To a very large extent. Other options (not shown) were Don't know and Not relevant for me.

compound questionnaire with questions derived from a validated questionnaire on patient satisfaction. A research assistant with no prior knowledge of participants administered the final questionnaire with reference to the visit just completed. Besides primary outcome data on satisfaction (figure 1), demographic data, comorbidity, self-estimated health and data on treatment for liver cirrhosis were collected.

Results: 81 participants were screened over a 5-month period. 67 patients accepted participation, 60% men and 40% women. Distribution by age showed 60% over 66 years. Visits related to HE accounted for 42%, ascites issues for 36%. Educational background showed 51% with higher education, 35% were trained and only 3% had no education. A majority of 82% had retired or were off sick leave. Most of participants (66%) lived alone.

Patients demonstrated great readiness to participate (83%) and they expressed feeling safe and well known by nursing staff (figure 1). The information given was deemed useful and patients felt involved in decision making to some extent. Regarding involvement of relatives (question 8) and information on side effects of new medication (question 13) respectively 54% and 45% answered *not relevant*.

Conclusion: Concluding, results show a high degree of overall satisfaction. However, availability and ways of communication other than the physical visits (question 15 and 16) are areas to be developed. Knowing from literature that this group of patients commonly expresses gratefulness to a very large extend our positive results need to be acknowledged in this light.

PO-205

A new prediction equation for estimating body weight in cirrhotic patients with refractory ascites

Bruna Cherubini Alves¹, Moiséli Luchi da Cruz², Antonio de Barros Lopes³, Camila Saueressig¹, Valesca Dall'Alba^{1,2,4}.
¹Universidade Federal do Rio Grande do Sul, Graduate Program: Sciences of Gastroenterology and Hepatology, Porto Alegre, Brazil; ²Universidade Federal do Rio Grande do Sul, Undergraduate Course of Nutrition, Porto Alegre, Brazil; ³Hospital de Clínicas de Porto Alegre, Division of Gastroenterology and Hepatology, Porto Alegre, Brazil; ⁴Hospital de Clínicas de Porto Alegre, Division of Nutrition and Dietetics, Porto Alegre, Brazil
 Email: brunacherubini@gmail.com

Background and aims: Decompensated cirrhosis is marked by fluid retention, malnutrition, and high mortality. Ascites can impair the nutritional assessment, by overestimating body weight (W), under-diagnosing malnutrition. These factors may also compromise the adequate establishment of dietary needs. Dietetic guidances indicate subtracting 2.2–14 kg or 5–15% of the measured W according to the degree of ascites, however, there is a lack of evidence to substantiate these values. Thus, this study aims to develop a new prediction equation to estimate the dry W (DW) of patients with refractory cirrhotic ascites.

Method: Cross-sectional study, that included patients with decompensated cirrhosis undergoing large-volume paracentesis. Height (H) were measured and W, immediately before and after paracentesis. For the prediction of DW, a linear regression model was performed using as predictor variables: gender, H, and pre-paracentesis W (preW), as response variable: post-paracentesis W (postW). Three-way interaction was used to test the joint effect of these predictors. The capacity of this model to predict the postW was evaluated comparing it with the currently used predictions through the intraclass correlation coefficient (ICC) and the mean square error (MSE).

Results: Twenty patients were included, 16 were male. Moderate ascites was the most prevalent grade (n = 18). The mean (range) of ascitic fluid drained was 6.6 (0.45–16.0) L, and the difference of Wpre and Wpost was -6.8 (-0.7–15.7) kg. The prediction equation for estimating DW is presented in Table 1, in gender format. ICC values showed that all predictions measures were strongly correlated (r > 0.95). In comparison with current predictions, our model showed the

highest ICC (r = 0.97) and the lowest MSE (=7.70), comparing with the current predictions (MSE = 18.63, when the preW is adjusted from absolute values and MSE = 12.75 when adjusted from percentage values), indicating more accurate prediction.

Table 1: Prediction equations to estimate dry weight in patients with refractory cirrhotic ascites

Male	DW = -11.4 + 1.2 * Wpre + 0.125 * H - 0.002 * Wpre * H
Female	DW = -40.6 + 1.2 * Wpre + 0.331 * H - 0.030 * Wpre * H

Conclusion: This new prediction equation showed high reliability as a W adjustment tool for patients with refractory cirrhotic ascites. Further research is required to validate this prediction equation.

PO-511

Health status perception and patient experience in liver cancer patients participating in Nurse-led Educational Programs

Neus Llarch¹, Gemma Iserte², Núria Granel², Víctor Sapena³, Marco Sanduzzi Zamparelli⁴, Sergio Muñoz Martínez⁴, Marta Campos Gomez¹, Alejandro Forner³, Jordi Bruix³, María Reig³.
¹BCLC Group, ICMDiM. Hospital Clinic Barcelona, CIBERehd., Barcelona, Spain; ²BCLC Group, ICMDiM. Hospital Clinic Barcelona, Barcelona, Spain; ³BCLC Group, Liver Unit, ICMDiM. Hospital Clinic Barcelona, CIBERehd., Barcelona, Spain; ⁴BCLC Group, Liver Unit, Hospital Clinic Barcelona, Fundacio Clinic per la Recerca Biomèdica, Barcelona, Spain
 Email: nllarch@clinic.cat

Background and aims: Efficacy, security and experience are the 3 pillars of quality of care. Efficacy and security have been demonstrated in several studies, but the experience of patients in liver cancer has not yet been reported in the literature. Our aim is to evaluate the perceived health status and experience of liver cancer patients after being part of the BCLC-Educational Programs.

Method: Prospective study assessing patients' experience with the validated questionnaires IEXPAC and EQ-5D-3L. Population was distributed in two groups: patients with no previous contact with BCLC group (BCLC-Naive) and patients included in an educational program conducted by Advanced Practice Nurses. In this last group patient questionnaires were classified according to whether the assessment was done prior to the educational program (BCLC-experience) or during the follow-up in time-points 2, 6 or 12 months (BCLC-FUP).

Results: From February 2019 to December 2020, 116 patients were included (83.5% males, median age of 67, 96.7% with hepatocellular carcinoma and 3.3% cholangiocarcinoma) and they filled out 182 questionnaires. Some of the 65 patients who were in Educational Programs answered more than 1 questionnaire due to treatment migration.

At the time of this first analysis, we analyzed the 124 questionnaires corresponding to 51 BCLC-naive and 73 BCLC-experience patients. The health perception was 70/100 in both groups and the IEXPAC was 6.1 in BCLC-naive and 7 in BCLC-experience; respectively. The same score of IEXPAC and EQ-5D-3L was observed in ECOG-PS 0 patients (n = 44 BCLC-naive/n = 63 BCLC-experience patients) when analyzed separately.

The best scored IEXPAC items in the BCLC-experience questionnaires were "They ask me and help me to follow my treatment plan," "They are well-coordinated to offer me good care" and "They care about my well-being." The lowest scored items were "They encourage me to talk with other patients", "They help me find information online" and "I use the internet and mobile phone to check my medical history."

Conclusion: This is the first analysis worldwide of patient health status perception and experience in liver cancer. Patients' perception is 70/100. Patient Experience reflects the nurses' role, the impact of nurse intervention and the need to explore alternative channels of communication with patients.

This work was sponsored through a grant from PERIS IPIF19 SLT008/18/00182.88

POSTER PRESENTATIONS

PO-1193

Lifestyle changes after cured Hepatitis C patients and adherence of a nurse-led liver cancer screening program

Núria Granel^{1,2}, Gemma Iserte¹, Concepció Bartres³, Neus Llach⁴, Anna Pla³, Víctor Sapena⁴, Sabella Lens⁵, Ramón Vilana⁶, Nuñez Isabel⁷, Anna Darnell⁶, Ernest Belmonte⁶, Maria Ángeles García-Criado⁶, Alba Díaz⁸, Marco Sanduzzi Zamparelli², Carla Fuster⁸, Alejandro Forner⁴, Sergio Muñoz Martínez², Carmen Ayuso⁶, Luis Bianchi⁶, Jordi Rimola⁶, Ferran Torres^{9,10}, Xavier Forn⁵, Jordi Bruix⁴, Zoe Mariño⁹, María Reig⁴. ¹Hospital Clinic of Barcelona, BCLC Group, Liver Unit, ICMDiM, Barcelona, Spain; ²Clinic Foundation, BCLC Group, Liver Unit, Hospital Clinic of Barcelona, Barcelona, Spain; ³Hospital Clinic of Barcelona, Hepatitis Unit, Liver Unit, Barcelona, Spain; ⁴Hospital Clinic of Barcelona, BCLC Group, Liver Unit, ICMDiM, CIBERehd, Barcelona, Spain; ⁵Hospital Clinic of Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Hepatitis Unit, Liver Unit, Barcelona, Spain; ⁶Hospital Clinic of Barcelona, IDIBAPS, CIBERehd, University of Barcelona, BCLC Group, Radiology department, Barcelona, Spain; ⁷Hospital Clinic of Barcelona, IDIBAPS, Radiology Department, Barcelona, Spain; ⁸Hospital Clinic of Barcelona, IDIBAPS, CIBERehd, University of Barcelona, BCLC Group, Pathology Department, Barcelona, Spain; ⁹Hospital Clinic of Barcelona, IDIBAPS, Biostatistics and Data Management Platform, Barcelona, Spain; ¹⁰Autonomous University of Barcelona, Biostatistics Unit, Barcelona, Spain
Email: granel@clinic.cat

Background and aims: The eradication of hepatitis C virus (HCV) doesn't abolish the risk of hepatocellular carcinoma (HCC) development. Several factors are associated to it after achieving sustained virological response (SVR). Our aim is to describe lifestyle changes in patients with SVR after direct antiviral agents (DAA) and evaluate their adherence to a nurse-led HCC screening program.

Method: Single-centre, observational and prospective study. The screening program started within the 1st month of SVR and includes: ultrasound, laboratory, anthropometric measurements and questionnaires on lifestyle habits. All these procedures were done by the nurse and physician every 6 months until cancer development, death or lost to follow-up. This first analysis evaluated patients until the 4th year of follow-up.

Results: We included 182 patients, 2 of them were lost before the first US. The 180 analyzed patients were: males (51.6%), 65.9% were cirrhotic and 92.5% of them Child-Pugh A. Median body mass index (BMI) was 27.1 [24.9–29.6] and the waist-hip ratio 0.94 [0.89–1] in men and 0.84 [0.79–0.88] in women at the time of SVR. 19.2% of patients were smokers, 30.8% consumed alcohol, 48.8% coffee and 54.9% did physical activity at baseline. During the 54.7 [49.9–58.2] months median follow-up, 9 patients developed HCC (all were cirrhotic). Median time to HCC development was 30.7 [24.5–35.9] months. A total of 19 patients out of the 21 with cancer (7 out of 9 HCC and 11 out of 12 other cancers) had a baseline BMI >24. A significant increase in BMI [0.2 (CI95%: 0.02–0.38)] at 6 months was observed and this change was maintained in the following time-points.

There wasn't a significant change in coffee consumption but a trend for increasing physical activity was registered at 2 and 3 years of follow-up ($p=0.08$ and 0.09 , respectively). A significant increase in alcohol consumption in the same time intervals ($p=0.007$ and $p=0.02$; respectively) was observed, while the number of patients who didn't answer the alcohol related questions increased from 2.7% to 10.3% at 3 years of follow-up.

The adherence to the HCC screening program at 6 months, and 1, 2, 3 and 4 years were 98%, 97%, 92%, 90% and 80%, respectively.

Conclusion: The adherence to the nurse-led liver cancer screening program was very high. We observed an increase in the physical activity but also an increase of alcohol consumption and BMI which may represent an additional risk factor for HCC development at long term.

PO-1221

Importance of a clinical pharmacist specialized in hepatitis C treatment for the management of potential drug-drug interactions in a multidisciplinary ECHO® hepatitis C expert team

Yaroslav Filippov¹, Claire Wartelle-Bladou^{2,3}, Jocelyne Parent⁴, Valérie Martel-Laferrrière^{3,5,6}, Suzanne Brissette^{2,3}, Barbara Kotsoros², Suzanne Marcotte^{1,3}, Dominic Martel^{1,3}. ¹Centre hospitalier de l'Université de Montréal (CHUM), Département de pharmacie, Montreal, Canada; ²CHUM, Service de médecine des toxicomanies, Montreal, Canada; ³Centre de recherche du CHUM (CRCHUM), Montreal, Canada; ⁴Université de Montréal, Réseau universitaire intégré de santé et de services sociaux (RUISS), Montreal, Canada; ⁵CHUM, Microbiologie, infectiologie, Montreal, Canada; ⁶Université de Montréal, Faculté de médecine, département de microbiologie, infectiologie et immunologie, Montreal, Canada
Email: dominic.martel.chum@ssss.gouv.qc.ca

Background and aims: ECHO® CHUM hepatitis C program was launched in 2017. This "hub and spokes" model enables linking of an interdisciplinary hepatitis C virus (HCV) expert team with community-based healthcare professionals. De-identified clinical cases are presented during teleclinics. A clinical pharmacist specialized in HCV treatment is part of the ECHO® expert panel. We sought to evaluate the prevalence and severity of potential drug-drug interactions (DDIs) between direct-acting antivirals (DAAs) and co-medications in cases discussed throughout the program.

Method: Cases presented between April 2017 and March 2020 were included. Data were collected prospectively using case presentation forms and recommendations issued by the hub. Occurrence and severity of potential DDIs for each available DAA regimen were determined using two online interaction checkers. Cases were excluded in case of missing information on co-medications. Subgroup analyses were done using the Chi-square test.

Results: Overall, 75 cases were discussed during the study period and 73 patients were included. Most patients (77%) were past or active intravenous drug users or had a psychiatric illness (56%). The median number of comedications per patient was 4 and 36 (49%) patients were on at least five drugs. In total, 49 patients (67%) were at risk for at least one potential DDI with any available DAA, including 13 (18%) taking contraindicated comedications. Patients on five or more drugs had a higher likelihood of DDI with any DAA (92% (95%CI 78–98) vs. 45% (95% CI 30–63); $p<0.0001$). Nevertheless, the number of potential DDIs per antiviral regimen was low (less than 16%). Among the 139 different comedications in the study, 24 (17%) could present a potential DDI with any DAA regimen while 6 (4%) were identified as contraindicated. Drugs most frequently involved with DDIs were proton pump inhibitors, antipsychotics, statins and antiretrovirals. Out of the 63 pharmacological interventions from the hub, 41% pertained to the management of DDIs, while 29% and 18% of recommendations regarded comorbidities and adverse events/adherence respectively.

Conclusion: Assessment of DDIs is key in HCV care. Most cases discussed in this ECHO® program led to various pharmacological recommendations. A pharmacist with clinical expertise in HCV treatment should be part of the interdisciplinary expert ECHO® team. As most DDIs can be managed, they should not be a barrier to the initiation of HCV treatment.

PO-1353

Randomized controlled study: investigation of the effect of exercise on liver function tests, fatigue and quality of life in patients with liver cirrhosis

Hülya Keskin¹, Aynur Türeyen², Ulus Akarca³. ¹Mardin Artuklu University Health Science Faculty, Nursing Department, Mardin, Turkey; ²EGE University Nursing Faculty, Internal Medicine Nursing Department, Izmir, Turkey; ³EGE University Faculty Of Medicine, Department of Gastroenterology, Izmir, Turkey
Email: hulya_k@hotmail.com

Background and aims: This randomized controlled study aimed to determine the effect of the exercise program to be applied in patients with cirrhosis on the patient's biochemistry parameters, quality of life, fatigue level, depression, and quality of sleep.

Method: The study population consisted of 84 patients, including the physical exercise group (PE, n = 27), the breathing exercise group (BE, n = 29), and the no intervention group (NI, n = 28). An exercise program (5 minutes warm-up, 30 minutes walking, 5 minutes cooldown) and a 10-minute breathing exercise were requested 7 days a week for 3 months in PE and BE patients, respectively. The patients were trained on how to perform the exercises and all the patients were followed up by phone calls on the exercise days and on the same days for the NI group to motivate the patients. Personal Information Form, 6-Minute Walking Test, Body Mass Index (BMI) Assessment Form, SF-36 Quality of Life Scale, Biochemistry Parameters Assessment Form, Child-Pugh Score Assessment Form, Beck's Depression Inventory, Fatigue Severity Scale, Pittsburgh Sleep Quality Index (PSQI) were completed by face-to-face interviews at the beginning and the end of the study period. Differences between the data at the onset and at the end within the groups were tested by the Wilcoxon test. Comparisons of the differences of the groups were performed with GLM repeated measures. SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and R 4.0.2 software (R software, version 4.0.2, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; <http://r-project.org>) were used for the statistical analyzes.

	Baseline		Study end	p value
	X ± SD			
6MWT	PE	426,1±72,3	523,1±93,3	<0,001
	NI	453,6±54,3	433,6±69,4	
	BE	445,9±79,2	467,8±84,1	
LDH	PE	206,7±44,1	182,1±31,9	0,004
	NI	226,8±66,3	212,2±67,3	
	BE	200,4±58,5	199,9±55,6	
T.Protein	PE	73,2±6,1	75,1±4,7	0,05
	NI	72,1±7	73,4±7	
	BE	74±6,2	73,3±5,2	
Physical functioning	PE	80,6±20,4	97,6±6,1	<0,001
	NI	79,6±21,3	81,6±17,6	
	BE	79,7±20,7	90±18,4	
Role Physical	PE	66,7±48	85,2±36,2	0,035
	NI	82,1±39	67,9±47,6	
	BE	62,9±48,5	75±42,3	
Role Emotional	PE	54,3±49,9	70,4±46,5	0,038
	NI	75±44,1	50±50,9	
	BE	58,6±50,1	62,1±49,4	
Vitality	PE	49,1±21,8	74,3±19,8	<0,001
	NI	50±18,5	43,8±20,2	
	BE	50,2±16,2	64,7±20,7	
Mental Health	PE	60,9±15,9	79,1±13,7	<0,001
	NI	57,9±17,6	49,4±21,2	
	BE	64,1±17,4	72,7±16,1	
Social Functioning	PE	65,7±29,3	95,4±13,5	<0,001
	NI	78,6±17,6	75±26,1	
	BE	76,3±25,7	84,5±25,8	
Bodily Pain	PE	76,5±22,5	87±22,3	0,010
	NI	77,7±20,5	70,5±20	
	BE	71,9±28,6	80,2±23,8	
General Health	PE	54,6±20,2	72±21,1	<0,001
	NI	45±14,5	40,2±20,2	
	BE	53,4±16	63,8±21,3	
Fatigue Severity Scale Total Score	PE	4,2±1,4	2,5±1,4	0,002
	NI	4,3±1,3	4,3±1,4	
	BE	4,6±1,5	3,8±1,6	
Beck Depression Inventory Total Score	PE	32,7±9,4	25,8±8,2	<0,001
	NI	30,5±6,7	32,1±6,6	
	BE	34,4±13,5	27,5±6,6	
PSQI total score	PE	6,7±2,7	4±2,4	<0,001
	NI	6,8±3,1	6,8±2,8	
	BE	6,5±3	4,6±2,6	

Figure:

Results: As shown in the table, significant changes were found in some liver function tests, 6-MWT, all sub-dimensions of quality of life, total sleep quality scores, depression, and fatigue levels of the patients at the end of the study, comparing to the beginning of the study. Most of the positive effects were seen in the PE group, suggesting that PE has a favorable effect on the quality of life, well-being, sleep quality, and depression in cirrhotic patients.

Conclusion: Implementing non-pharmacological, inexpensive, and easily applicable exercise programs contribute positively to the management of patients with cirrhosis. Nurses should be trained to teach patients how to exercise and how to maintain an exercise program.

PO-1525

Nurse intervention optimizes the care of patients with hepatocellular carcinoma under systemic treatment

Gemma Iserte¹, Neus Llarch¹, Núria Granel¹, Víctor Sapena², Marta Campos Gomez², Marco Sanduzzi Zamparelli³, Sergio Muñoz Martínez³, Alejandro Forner^{1,2}, Jordi Bruix^{1,2}, María Reig^{1,2}. ¹Hospital Clinic i Provincial de Barcelona, Oncologia Hepàtica BCLC, Barcelona, Spain; ²CIBERehd, BCLC Group, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain; ³Fundació, BCLC Group, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain
Email: giserte@clinic.cat

Background and aims: Telephone visits have been part of Nurse Educational Programs for years and are a follow-up tool for liver cancer patients. This tool allows a fluid communication between the patient and the multidisciplinary team, as well as the early identification of treatment side effects, optimizing the management of patients. The aim of this study is to evaluate the impact of advanced practice nurse intervention (APN) managing unscheduled phone visits in patients with advanced hepatocellular carcinoma (HCC) in second and/or third line oral treatment.

Method: A retrospective, observational and descriptive study of patients who started second and/or third line treatment in a tertiary referral center (BCLC) from 01/2017 to 01/2020, and their phone calls received until 07/2020 or until discontinuation of treatment.

Results: Forty-one patients with advanced HCC started second or third line treatment; 20 of these patients received treatment with regorafenib and 23 with cabozantinib (2 patients received regorafenib in second line and later cabozantinib in third line). 408 phone calls were registered, 25% of which belonged to confinement period for COVID19 (March 14–June 21, 2020).

In our cohort (36% in regorafenib and 49% in cabozantinib), APNs resolved 100% of administrative consultations and 43% of phone calls related to health problems including potential toxicities of medication or cirrhosis decompensations. In second line cabozantinib patients, APNs resolved up to 73.5% of phone calls related to potential drug toxicity. In only 3.3% of phone calls related to health, patients were referred to the emergency department.

Conclusion: Telephone consultations managed by the APNs have a positive impact on the outpatient management of patients with HCC in systemic treatment and have been key to maintaining these treatments active during the COVID19 restrictions. The number of patients referred to the emergency department has been low, avoiding unnecessary saturation of the emergency services.

Public Health

PO-251

Definition of healthy ranges for alanine aminotransferase levels: a 2020 update

Serena Pelusi¹, Luca Valenti¹, Cristiana Bianco¹, Ferruccio Ceriotti², Alessandra Berzuini¹, Laura Iogna Prat³, Roberta Trotti¹, Guido Alessandro Baselli¹, Roberta D'Ambrosio⁴, Massimo Colombo⁵, Emmanuel Tsochatzis³, Mirella Fraquelli⁴, Daniele Prati¹. ¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, ²Department of Transfusion Medicine and Hematology, ³Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milan, Clinical Laboratory, Italy; ⁴Royal Free Hospital and UCL, London, UK, UCL Institute for Liver and Digestive Health; ⁵Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milan, Italy, Department of Gastroenterology and Hepatology, CRC "A.M. and A. Migliavacca" Center for Liver Disease; ⁵IRCCS San Raffaele Hospital, Liver Center, Milan, Italy Email: serenapelusi@libero.it

Background and aims: The changing epidemiology of liver disease, and modifications in the recommended analytical methodology call for a re-evaluation of the upper reference limits (URL) of alanine aminotransferase (ALT).

The aim of this study was to examine the determinants of ALT and to redefine the URL.

Method: We examined 21, 296 apparently healthy blood donors (age 18–65). The URL were tested for the ability to predict severe liver fibrosis estimated by liver stiffness in a subset of 447 participants with dysmetabolism.

ALT levels were measured by the new International Federation of Clinical Chemistry (IFCC) standardized test. Serum ALT values were fitted by generalized linear models. Sex-specific ALT-URL were estimated by the 95th centile in individuals without risk factors for liver disease.

Results: Independent predictors of ALT levels were male sex, higher body mass index, glucose, cholesterol, triglycerides and ferritin levels, hypertension, and younger age ($p < 0.001$). Updated URL were identified at 42 U/L in males ($n = 4, 855$), and 30 U/L in females ($n = 4, 340$), approximately 30% lower than those recommended by IFCC. Due to the higher sensitivity compared to the currently available thresholds, the updated URL conferred the ability to detect steatosis and liver fibrosis in individuals with dysmetabolism (OR 2.61, 1.24–5.47, $p = 0.006$ and OR 4.90, 1.50–15.96, $p = 0.008$, respectively), though with a limited accuracy.

Conclusion: Metabolic alterations are the major ALT determinants in healthy individuals. Updated ALT-URL at 40/32 in males/females predict liver disease related to dysmetabolism. Using the new IFCC standardized method, ALT thresholds are substantially higher than with the previous one. The limited awareness that both laboratory techniques are still in use should be regarded as a possible source of medical errors.

PO-260

Risk factors for chronic hepatitis B among 0.5 million Chinese adults

Elizabeth Hamilton¹, Ling Yang¹, Iona Millwood¹, Zhengming Chen¹. ¹Big Data Institute, Nuffield Department of Population Health, The University of Oxford, Oxford, United Kingdom Email: elizabeth.hamilton@univ.ox.ac.uk

Background and aims: Hepatitis B Virus (HBV) is one of the most common chronic viral infections in the world, and is an important public health issue in China, where approximately one-third of all global cases occur. It causes up to 80% of liver cancers in China, which is a leading cause of morbidity and mortality. Although there has been large progress in reducing childhood HBV infection with

universal vaccination at birth, the infection burden and associated disease among adults, particularly those in middle-age, has remained high. Despite this, robust evidence regarding risk factors for chronic HBV in Chinese adults is limited. We therefore aimed to describe HBV prevalence and examine cross-sectional factors associated with chronic HBV in a large cohort of middle-aged adults in China.

Method: The China Kadoorie Biobank (CKB) is a cohort of 0.5 million adults aged 30–79 years recruited from ten geographically diverse sites in China between 2004 and 2008. Participants underwent an interview-administered questionnaire at baseline including questions about demographic, socioeconomic, behavioral and lifestyle factors, and Hepatitis B surface antigen (HBsAg) was measured. Logistic regression models were constructed to estimate adjusted odds ratios for associations between baseline factors and HBsAg positivity.

Results: The overall prevalence of HBsAg was 3.0%, which varied markedly by region—Haikou had the highest prevalence at 5.5%, while Sichuan had the lowest prevalence at 1.7%. After multivariate adjustment, factors associated with higher risk of HBsAg positivity included male sex, younger age, no formal education, working in a factory, history of blood transfusion and poor self-rated health. Factors associated with lower risk of being HBsAg positive included having a household fridge, higher waist-hip-ratio and reporting occasional or regular alcohol intake.

Conclusion: A rigorous understanding of risk factors for HBsAg persistence in Chinese adults may help inform targeted screening and timely treatment among high-risk adults, to prevent progression to cirrhosis and liver cancer. Future work will include investigation of genetic determinants of chronic HBV.

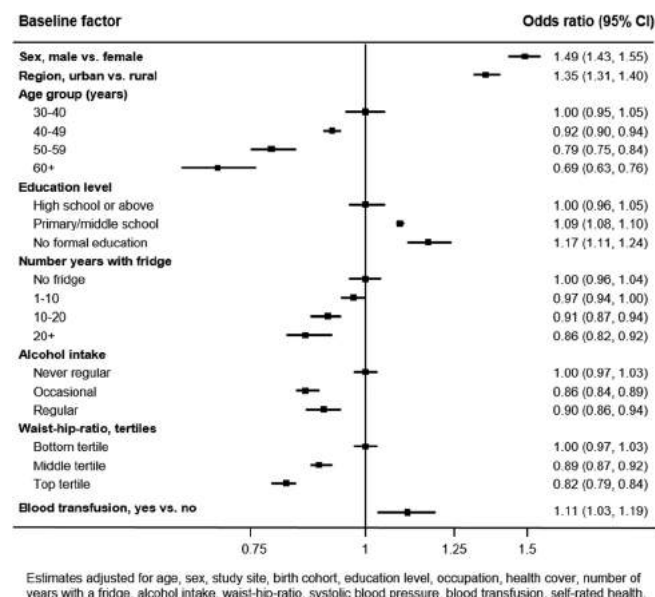


Figure: Select factors associated with chronic hepatitis B infection in 0.5 million Chinese adults

PO-424

Simplified test and treat protocols for population level screening and elimination of hepatitis B and hepatitis C in Uzbekistan

Erkin Musabaev¹, Shakhlo Sadirova¹, Shokhista Bakieva¹, Krestina Brigida¹, Homie Razavi², Rick Dunn², Kathryn Razavi-Shearer². ¹Research Institute of Virology, Tashkent, Uzbekistan; ²Center for Disease Analysis Foundation, Lafayette, United States Email: drmusabaev1956@gmail.com

Background and aims: An estimated 3.5 million people are infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) in Uzbekistan. This study tested the feasibility of eliminating HBV and HCV if the

testing and treatment protocols were simplified to support a national program.

Method: Nurses were trained to use rapid HCV antibody and hepatitis B surface antigen (HBsAg) to screen patients at polyclinics. Rapid creatinine and human immunodeficiency virus (HIV) tests were used to test HBsAg+ patients before they were referred to General Practitioners (GPs) for treatment. Core antigen/polymerase chain reaction (PCR), creatinine and AST-to-Platelet-Ratio Index (APRI) was collected for HCV+ cases. Cirrhotic patients were referred to a specialist while other patients were referred to GPs who were trained by specialists to treat patients. A centralized registry was used to collect patient data as they moved from screening to prescription refill.

Results: More than 60,000 people were screened over six months at polyclinics. 70% of HBV+ were linked to care and 86% of patients received a prescription. 57% of HCV+ were linked to care and 84% of viremic patients received a prescription in spite of lower patient engagement with healthcare systems due to COVID-19. There were large geographic variations in HBV and HCV prevalence across Tashkent and nationally.

Conclusion: A simplified test/treat protocol can be used to screen, link to care and treat large numbers of HCV+ and HBsAg+ patients using nurses and GPs who are accessible throughout the country. Patients with advanced liver disease still require consultation with a liver specialist. The study also highlighted hotspots in the country that could be prioritized in a national program.

PO-425

Modelling the potential effectiveness of different screening and treatment strategies for hepatitis c during pregnancy in Ukraine

Nadia Hachicha Maalej¹, Intira Jeannie Collins², AE Ades³, Karen Scott², Ali Judd², Elizabeth Chappell², Yazdan Yazdanpanah^{1,4}, Sylvie Deuffic-Burban¹. ¹Université de Paris, Inserm UMR 1137 IAME, France; ²Medical Research Council Clinical Trials Unit, University College London, United Kingdom; ³School of Social and Community Medicine, University of Bristol, United Kingdom; ⁴Service de Maladies Infectieuses et Tropicales, Hôpital Bichat-Claude Bernard, Paris, France
Email: nadia.hachicha@inserm.fr

Background and aims: Ukraine has a concentrated epidemic with ~2 million people living with HCV. There is a high burden in key subgroups, including people who have injected drugs, and among people living with HIV. Pregnant women with HCV RNA have a risk of vertical transmission (VT) of about 5%, and almost twofold higher in HCV/HIV-coinfected women with unsuppressed HIV. Results from a recent Phase I clinical trial reported good safety of direct-acting antiviral (DAA) regimen from the second trimester of pregnancy with high maternal HCV cure by delivery and no VT. We explored the potential impact of different HCV screening and treatment strategies during pregnancy on maternal cure and VT in Ukraine.

Method: A Markov model simulated a hypothetical cohort of 570,000 pregnant women per year. The model assessed the short-term effectiveness of five different HCV screening and treatment strategies ranging from (S0) standard of care (SOC) of targeted screening and deferred treatment to after end of breastfeeding, (S1) optimal targeted screening (WHO recommendations) and deferred treatment to (S4) universal antenatal screening and DAAs during pregnancy for all women with HCV RNA. This models parameters are based on data from the literature, data from a survey of pregnant/post-partum women in Ukraine and assumptions (top of figure). Probabilities of VT were based on estimates from a Bayesian model using data from three European HCV cohorts. Key outcomes were proportions of HCV RNA women diagnosed and cured by delivery and infants with VT.

Results: S0 would detect 79% women with HCV RNA in pregnancy and 0% cured by delivery (bottom of figure). This compares to 94% diagnosed and 0% cured in S1 with WHO optimal targeted screening and deferred treatment. While S4, universal screening of all pregnant women and DAAs during pregnancy, would result in the highest

proportion of women diagnosed and cured by delivery (71%), and result in the lowest risk of VT (4.7% vs 11.5% in S0 and S1).

Conclusion: This is one of the first models to explore the potential benefits of different HCV screening and treatment strategies in pregnancy in a high-burden middle-income country setting, which will be critical in informing future care and policy as more safety/efficacy data emerge. Universal screening and treatment would achieve positive maternal and infant outcomes although our model does not take into account costs, or spontaneous HCV clearance in children.

PO-504

Innovative linkage model to re-engage lost-to-follow-up individuals in the national hepatitis C elimination program of Georgia

Amiran Gamkrelidze¹, Alexander Turdziladze¹, Maia Tsreteli¹, Vladimer Getia¹, Ana Aslanikashvili¹, Lia Gvinjilia², Tinatin Kuchuloria², Irina Tskhomelidze², Shaan Shadaker³, Paige A. Armstrong³, Maia Japaridze⁴, Sonjelle Shilton⁴. ¹National Center for Disease Control and Public Health Georgia, Tbilisi, Georgia; ²The Task Force for Global Health, Tbilisi, Georgia; ³National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC, Division of Viral Hepatitis, Atlanta, United States; ⁴Foundation for Innovative New Diagnostics, Switzerland
Email: a.gamkrelidze@ncdc.ge

Background and aims: In 2015, Georgia launched a national hepatitis C virus (HCV) elimination program with the goal of reducing the country's HCV prevalence by 90%. By implementing systematic screening, and expanding harm reduction services and diagnostic capacity, 72% of the adult population had been screened for HCV by the end of 2020. However, referral of anti-HCV positive individuals for viremia testing, and subsequent enrollment in the treatment program, remains a challenge. In 2019, the National Center for Disease Control and Public Health partnered with the Foundation for Innovative New Diagnostics (FIND) to pilot a project to promote linkage to care for individuals who screened positive for HCV antibody (anti-HCV) but did not receive a viremia test.

Method: Anti-HCV positive individuals lost-to-follow-up residing in the 5 largest regions in Georgia were included in the pilot. Individuals with no documented viremia test results were randomly selected from the national database. Selected individuals were located and counselled via phone or home visit by trained epidemiologists and primary healthcare physicians and referred to an HCV care and treatment facility. If the first attempt was unsuccessful, one repeat attempt was made to contact the individual. Incentives were provided to the regional health personnel for each patient that was successfully linked to care, defined as anyone who presented for viremia testing.

Results: In December 2019, out of 7,130 antibody positive persons without viremia testing, a total of 5,313 (75%) were followed-up, of which 3,859 (73%) were reached. The remaining could not be reached, had moved, or emigrated. Of those contacted, 2,972 (77%) presented for viremia testing, of whom 1,685 (57%) were positive for HCV RNA or core antigen. Overall, 887 (53%) persons with chronic HCV infection were linked to care and enrolled in the HCV treatment program, which differed geographically; 46% of persons from urban areas were enrolled, compared to 57% of those in rural areas.

Conclusion: As Georgia nears elimination goals, ensuring all patients who screen positive for anti-HCV are linked to care is increasingly important. This pilot demonstrates the effectiveness of incentive-based active case follow-up. The project also demonstrates that individuals considered lost-to-follow-up can be re-engaged in HCV care. Lessons learned from this project are particularly relevant during the COVID-19 pandemic, when disruptions of care can compromise progress toward hepatitis elimination.

POSTER PRESENTATIONS

HCV screening and treating strategies	Uptake of screening strategies		Uptake of treatment
	Absence of HCVRF*	At least one HCVRF*	
S0=current standard of care with limited risk-based screening targeting HIV+ women (assumption: 100% screened for HIV during pregnancy and thus aware of their HIV status) and no treatment in pregnancy (SOC)	75%	87% when HIV+, 79% otherwise	0%
S1=S0+optimal screening of all women with HCV risk factors (HCVRF*)	75%	96% ¹	0%
S2=S1+DAA treatment in pregnancy for HCV-positive women with VT risk factors (VTRF) (i.e. HIV-co-infection, high HCV viral load>6 log-IU/ml)	75%	96% ¹	77% ¹ of +VTRF
S3=S2+Universal screening of all pregnant women and targeted treatment of women with VTRF	96% ¹	96% ¹	77% ¹ of all HCV+ women
S4=S3+Universal treatment of all HCV-positive women during pregnancy	96% ¹	96% ¹	

*HCVRF, HCV risk factors²: Persons who have received medical or dental interventions in health-care settings where infection control practices are substandard, Persons who have received blood donors for HCV was initiated or in countries where serological testing of blood donations for HCV is not routinely performed, People who inject drugs (PWID), Persons who have had tattoos, body piercing or scarification procedures done where infection control practices are substandard, Children born to mothers infected with HCV, Persons with HIV infection, Persons who use/have used intranasal drugs, Prisoners and previously incarcerated persons; +VTRF, VT risk factors once screened: presence of HIV infection and/or high HCV viral load>6 log-IU/ml, treatment is assumed to start from 7th month of pregnancy

(1) Acceptability of HCV screening and DAA treatment among pregnant and post-partum women in Ukraine: 96% were in favour of free universal HCV screening in pregnancy with little variation by HCV and HIV status; 77% of women would take DAAs in pregnancy if there was clear evidence they were safe

(2) WHO guidelines 2016

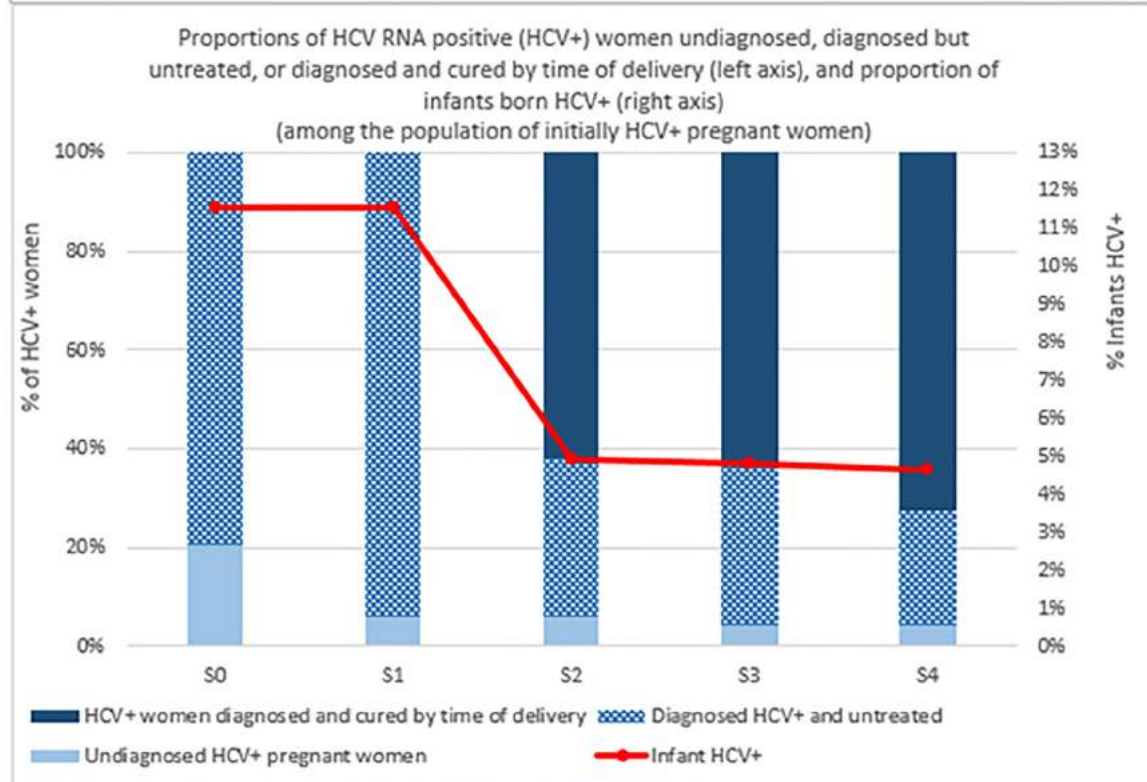


Figure: (abstract: PO-425)

PO-533

Healthcare restrictions due to COVID-19 impaired liver care, lowered patient satisfaction and increased liver-related mortality

Lukas Hartl^{1,2}, Georg Semmler^{1,2}, Benedikt S. Hofer^{1,2,3}, Nawa Schirwani¹, Mathias Jachs^{1,2}, Benedikt Simbrunner^{1,2,3}, David JM Bauer^{1,2}, Teresa Binter^{1,2}, Katharina Pomej^{1,2}, Matthias Pinter^{1,2}, Michael Trauner¹, Mattias Mandorfer^{1,2}, Thomas Reiberger^{1,2,3}, Bernhard Scheiner^{1,2}. ¹Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ²Medical University of Vienna, Hepatic Hemodynamic Lab, Vienna, Austria; ³Medical University of Vienna, Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Vienna, Austria

Email: thomas.reiberger@meduniwien.ac.at

Background and aims: The first wave of COVID-19 necessitated re-allocation of health care resources. We compared (i) chronic liver disease (CLD) patient perceptions on care quality and (ii) trends in elective and emergency admissions prior to (12/2019–02/2020), and during (03/2020–05/2020) healthcare restrictions.

Method: A tele-survey of outpatients (cohort-1) was conducted and written questionnaires (cohort-2) were distributed to in- and outpatients. All admissions to the Vienna General Hospital, Division of Gastroenterology/Hepatology (12/2019–05/2020) were assessed.

Results: In cohort-1, 279 (cirrhosis: 73.1%, hepatocellular carcinoma [HCC]: 14.7%, liver transplant recipients [LT]: 12.2%) and in cohort-2, 138 patients (non-cirrhosis: 31.9%, cirrhosis: 45.7%, HCC: 15.9%, LT: 6.5%) were included. 32.6% of cohort-1 and 72.5% of cohort-2 had

tele-medical contact during COVID-19. 57.3% of cohort-1 patients trying to reach their treating physician found this to be difficult or impossible. 32.1% of cohort-2 patients felt insufficiently informed about potential consequences of COVID-19 on CLD and 33.1% were concerned about negative effects of the pandemic on their CLD. Satisfaction with treatment declined significantly in cohort-1 (VAS 0–10: 9.0 ± 1.6 to 8.6 ± 2.2 ; $p < 0.001$) and non-significantly in cohort-2 (8.9 ± 1.6 to 8.7 ± 2.1 ; $p = 0.182$).

The number of hospital admissions was lower during COVID-19, but percentages of emergency (+6.3%) and intensive care unit (ICU; +6.7%) admissions significantly increased compared to pre-COVID-19. Non-electively admitted cirrhotic patients had higher Model for End-Stage liver disease (MELD; 25.5 [IQR14.2] vs. 17.0 [8.8] points; $p = 0.003$), Δ MELD (difference to last MELD; 3.9 ± 6.3 vs. 8.7 ± 6.4 points; $p = 0.008$), CLIF-C acute decompensation (AD; 61.5 ± 11.5 vs. 54.0 ± 11.7 points; $p = 0.011$) and Δ CLIF-C AD score (12.6 ± 8.3 vs. 5.0 ± 8.6 points; $p < 0.001$) than pre-COVID-19. Admitted patients more often progressed to severe/refractory ascites (63.3% vs. 30.6%; $p = 0.012$), required immediate ICU admission more frequently (26.7% vs. 5.6%; $p = 0.034$) and had higher 30-day liver-related mortality (30.0% vs. 8.3%; $p = 0.028$).

Conclusion: COVID-19 profoundly impacted on liver care. Patient satisfaction decreased and reaching physicians in emergency situations was often difficult, resulting in hospitalization of sicker CLD patients and increased liver-related mortality. Strategies for improved tele-medical care and early treatment of complications are crucial.

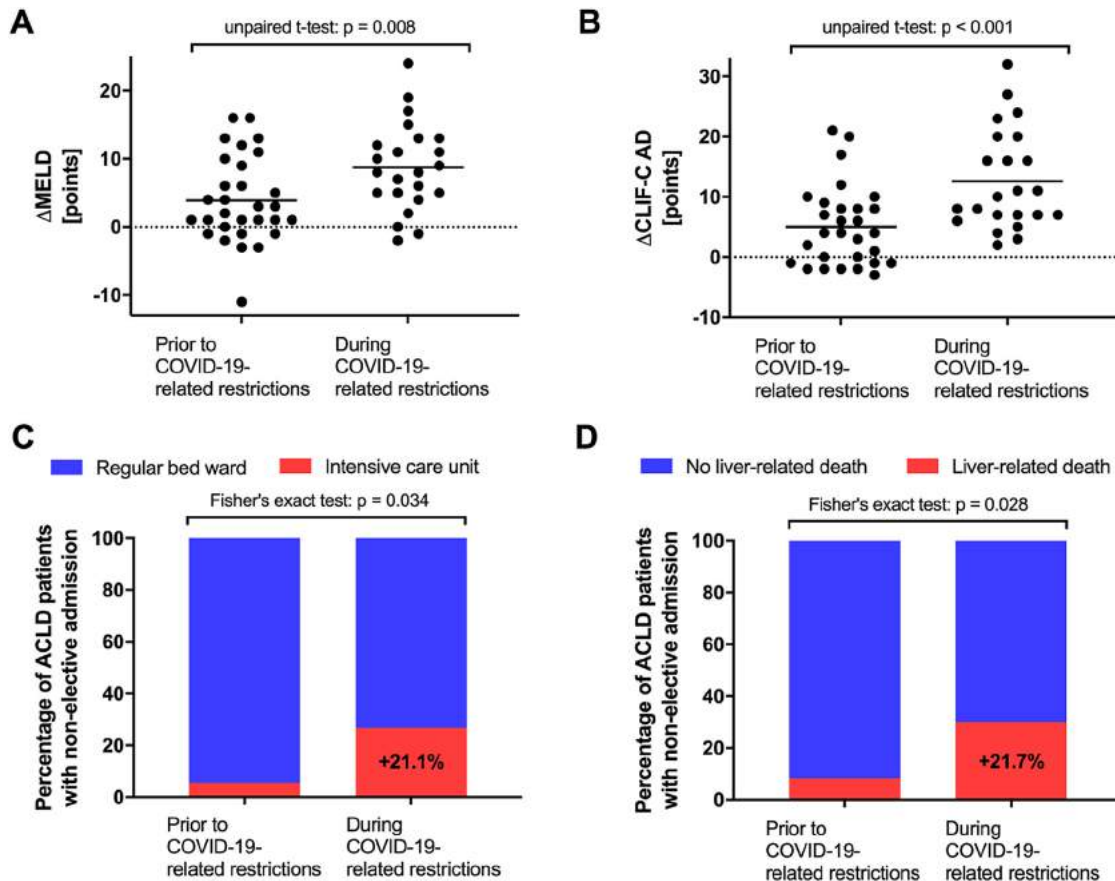


Figure: (abstract: PO-533)

POSTER PRESENTATIONS

PO-539

Promoting Hepatitis Virus Screening Test at Worksite in Japan Using Nudge Theory compared with Full Subsidies

Masaaki Korenaga¹, Jun Fukuyoshi², Keiko Korenaga³, Tatsuya Kanto¹.
¹National Center for Global Health and Medicine, The Hepatitis Information Center, Ichikawa, Chiba, Japan; ²Keio University, Department of Preventive Medicine and Public Health; ³Funabashi Central Hospital, Funabashi, Chiba, Japan
Email: dmkkorenaga@hospk.ncgm.go.jp

Background and aims: Despite the importance of hepatitis screening for decreasing liver cancer mortality, screening rates remain low in Japan. Previous studies show that full subsidies increase screening uptake, but full subsidies are costly and difficult to implement in low resource settings. Alternatively, applying nudge theory to the message design could increase screening at lower costs. This study examined the effects of both methods in increasing hepatitis virus screening rates at worksites.

Method: About 1,500 employees from a Japanese transportation company received client reminders for an optional hepatitis virus screening before their general health checkups. Groups A and B received a client reminder designed based on the principles of 'Easy' and 'Attractive', while the Control Group received a client reminder not developed using nudge theory. Additionally, hepatitis virus screening was offered to the Control Group and Group A for a co-payment of JPY 612, but was fully subsidized for Group B. The hepatitis virus screening rates among the groups were compared and the risk ratios of Group A and Group B to the Control Group were also calculated. To adjust for unobservable heterogeneity per cluster, the regression analysis was performed using generalized linear mixed models.

Results: The screening rate was 21.2%, 37.1%, and 86.3% for the Control Group, Group A, and Group B, respectively. And the risk ratio for Group A was 1.753 and that of Group B was 4.079. The odds ratio for Group A was 3.031 and that of Group B was 28.324, estimated using generalized linear mixed models. However, the cost-effectiveness (incremental cost-effectiveness ratio (ICER)) of the nudge-based reminder with the full subsidies was lower than that of only the nudge-based reminder.

Conclusion: While fully subsidized screening led to the highest hepatitis screening rates, modifying client reminders using nudge theory significantly increased hepatitis screening uptake at lower costs per person.

PO-640

Using the copula method to accurately estimate the impact of body mass index and alcohol consumption on liver disease

Daniel Ohrenstein¹, Laura Webber¹, Maria Buti², Helena Cortez-Pinto³, Peter Jensen⁴, Pierre Nahon⁵, Francesco Negro⁶, Nick Sheron⁷, Marieta Simonova⁸, Shira Zelba-Sagi⁹, Lise Retat¹, Jeffrey Lazarus¹⁰.
¹HealthLumen, London, United Kingdom; ²Hospital Universitari Vall d'Hebron, Department of Internal Medicine, Barcelona, Spain; ³University of Lisbon, Centro de Nutrição e Metabolismo, Lisbon, Portugal; ⁴Aarhus University, Department of Clinical Epidemiology, Aarhus, Denmark; ⁵Université Paris, Hospital Jean-Verdier, Paris, France; ⁶University Hospitals of Geneva, Department of Pathology and Immunology, Geneva, Switzerland; ⁷University of Southampton, Population Hepatology Research Group, Southampton, United Kingdom; ⁸Military Medical Academy, Department of Gastroenterology, Sofia, Bulgaria; ⁹University of Haifa, Department of Nutrition, Haifa, Israel; ¹⁰Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain
Email: lise.retat@healthlumen.com

Background and aims: To project the burden of non-communicable disease (NCD) such as liver disease we must calculate the joint relative risks (JRRs) associated with risk factors such as body mass index (BMI) and alcohol consumption. These JRR calculations rely on the estimated prevalence of the risk factors, and the prevalence estimates are ideally based on longitudinal data. Unfortunately, studies to collect longitudinal data are costly and time-consuming, whereas cross-sectional studies are easily accessible and often have larger sample sizes. In the absence of longitudinal data, joint prevalence distributions are calculated using approximate methods. The validated copula method (often used in finance) is applied here.

Method: The copula method uses a multidimensional inverse cumulative density function to estimate a joint distribution from univariate BMI and alcohol prevalence distributions and their correlation coefficient (see Figure 1). JRRs for chronic liver disease (CLD) were estimated with data from two cross-sectional epidemiological studies: The National Health and Nutrition Examination Survey from the United States and the Health Survey for England. These estimates were validated against published values that were calculated using longitudinal data.

Results: Estimates of the JRRs for CLD generated via the copula method were found to be in accordance with the literature. For moderate drinkers (1–14 cl/week), we calculated JRRs of 0.8, 1.1 and 1.3 for healthy, overweight and obese BMIs respectively, all within the confidence intervals reported. For heavy drinkers (>15 cl/week), we

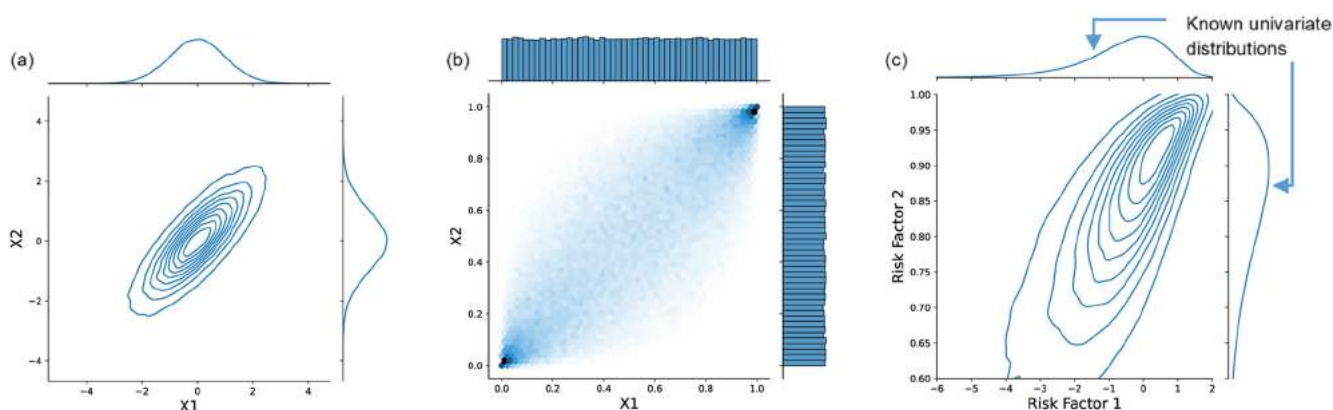


Figure: (abstract: PO-640): (a) Sample from a multivariate Gaussian with correlation η (the correlation between the two risk factors). (b) The sample is transformed using the inverse Gaussian cumulative distribution function (CFD) to generate a sample with uniform marginals while retaining the correlation—this distribution is the copula. (c) Transform this sample with the univariate CDFs for each risk factor to generate the estimated joint distribution. This process ensures the approximate distribution has the appropriate correlation and marginals.

calculated JRRs of 3.5, 4.5 and 4.8 for healthy, overweight and obese BMIs respectively, again in line with previous work.

Conclusion: This study demonstrated that the copula method is a valid and useful tool for estimating JRRs for liver disease. This approximation provides the flexibility to model interaction effects between multiple interacting risk factors and is applicable to other NCDs. Furthermore, the ability to make such an estimation with cross-sectional data (without relying on expensive longitudinal studies) is clearly advantageous to epidemiological modelling and public health applications.

PO-739

Micro-elimination of Hepatitis C in prisons of Punjab, India

Kanudeep Kaur¹, Sanjay Sarin¹, Praveen Kumar Sinha², Virendra Singh³, Sonjelle Shilton⁴, Gagandeep Singh Grover⁵.

¹Foundation for Innovative New Diagnostics, New Delhi, India; ²Additional Director General of Prisons, Department of Prisons, Punjab, Chandigarh, India; ³Post Graduate Institute of Medical Education and Research, Department of Hepatology, Chandigarh; ⁴Foundation for Innovative New Diagnostics, Geneva, Switzerland; ⁵Directorate of Health Services, Department of Health and Family Welfare, Chandigarh, India
Email: kanudeep.kaur@finddx.org

Background and aims: The State of Punjab, India, has a population of 27.7 million with an estimated anti-HCV prevalence of >20% in high-risk group of prisoners. However, very few prisoners are diagnosed and treated for HCV while incarcerated. The Punjab Department of Health Services (DHS) and Punjab Department of Prisons in partnership with FIND (Foundation for Innovative New Diagnostics) embarked on a program to eliminate HCV among inmates in 9 central prisons that contain over 80% of the total prison population in Punjab.

Method: Anti-HCV antibody rapid diagnostic test (RDT) was performed at the time of admission of inmates. Inmates with positive HCV RDT results received reflex blood draw for HCV RNA testing and pre-treatment investigations. Liver staging was determined by APRI score (non-cirrhotic is APRI <2 and cirrhotic as APRI >2). Non-cirrhotic patients were initiated on treatment dispensed by the prison pharmacist and overseen by the prison medical officer trained by DHS. Cirrhotic cases were referred to specialist for further evaluation. Post Graduate Institute of Medical Education and Research, Chandigarh, a tertiary referral hospital is conducting OPD via telemedicine to effectively manage the complicated cases remotely due to COVID-19. Twelve weeks after completion of therapy, another HCV RNA test was done to evaluate for SVR12.

Results: From 20th November 2019 to 31 December 2020, 14240 prisoners had been screened for HCV, of those 3201 (22%) were HCV antibody positive, 2883 (90%) received an RNA test, of which 2036 tested positive for HCV RNA. Of the HCV RNA positive 1282 (63%) have been initiated on treatment to date, with 322 (40%) completing SVR testing and 295 (92%) achieving SVR. The majority (96.8%) of cases were non-cirrhotic and HIV/HCV co-infection accounted for 5% of those who screened positive.

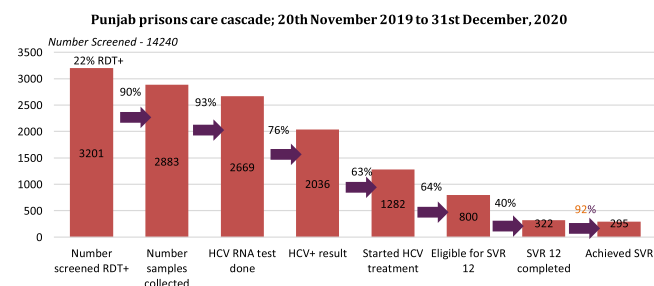


Figure:

Conclusion: To date the project screened 88% of the prison population for HCV and linked 63% of those confirmed for infection to treatment. This shows that micro-elimination in Punjab Prisons is

feasible. Increased efforts are being made to ensure treatment continuation and SVR testing post release as well as to facilitate telemedicine such that complicated cases which would once have been referred to tertiary hospital can be managed in the prisons due to Covid-19 related pressures on the health care system. The experience gained by the prison system through this project builds capacity to expand HCV care to district and sub-district correctional facilities in the future.

PO-785

RECONVOCC : Can we recouvene chronic hepatitis C patients who were lost to follow-up ?

Armand Abergel¹, Francois Bailly², Jérôme Gournay³, Frederic Faure¹, Sarra Oukil¹, Brigitte Chanteranne¹, Isabelle Rosa⁴, Juliette Foucher⁵, Catherine Guillemard⁶, Magdalena Meszaros⁷, Jean-Pierre Bronowicki⁸, Valérie Canva⁹, Isabelle Portal¹⁰, Veronique Loustaud-Ratti¹¹, Cécile Henquell¹², Leon Muti¹, Géraldine Lamblin¹, Maud Reymond¹, Eymeric Chartrain¹, Mathilde Huguet¹, Benjamin Buchard¹. ¹Chu Clermont-Fd : Site Estaing, Hepatology, Clermont-Ferrand, France; ²Hospital La Croix-Rousse-HCL, Hepatology, Lyon, France; ³Chu Nantes-Hotel Dieu, Hepatology, Nantes, France; ⁴Hospital Center Intercommunal De Créteil, Hepatology, Créteil, France; ⁵Hospital Center University De Bordeaux, Hepatology, Bordeaux, France; ⁶Hospital Center University Of Caen Normandie, Caen, France; ⁷Chu Montpellier St Eloi, Hepatology, Montpellier, France; ⁸Nancy Regional and University Hospital Center (CHRU), Nancy, France; ⁹Chu De Lille, Lille, France; ¹⁰Hospital Timone, Hepatology, Marseille, France; ¹¹Limoges University Hospital Dupuytren 1, Hepatology, Limoges, France; ¹²CHU Gabriel-Montpied, Virology, Clermont-Ferrand, France
Email: aabergel@chu-clermontferrand.fr

Background and aims: Hepatitis C virus (HCV) elimination by 2030, as targeted by the World Health Organization (WHO), requires that 90% of people with chronic hepatitis C (CHC) be diagnosed and 80% treated. France is one of the countries engaged in this viral elimination strategy. In the RECONVOCC study we assessed the effectiveness of a recall strategy. This project was initiated by the "Federation des Pôles de Référence Hépatites" (FPRH) and the main objective was to recall patients with CHC who were lost to follow-up in 14 French academic centers.

Method: The study population consists of patients HCV positive seen in 14 hospitals from 2003 to 2018 who were not cured. The patient should be lost to follow-up for over 18 months and be born after 1934. RECONVOCC takes place in 2 phases. The first, based on patient databases and medical records identified eligible patients including those tested in the virology department and followed by non hepatologists. To contact them and obtain information on HCV status, several methods were used such as townhall databases, hospital entry offices, health insurance databases, contacting patients or general practitioners or gastroenterologists or other specialists by phone or by letter... The second part corresponds to the inclusion of patients in the care process with data collection. The case report form used is REDCAP.

Results: Out of a total of 38387 patients identified as HCV positive, approximately 2/3 came from the hepatology department. To date RECONVOCC's investigative work identifies 560 patients still carrying HCV. Of the 194 patients included in the eCRF, 62% (121/194) were men. Mean age was 56 ± 13 years. 142/194 (72%) were treatment naïve. Thirty per cent of patients (58/194) had clinically significant fibrosis (F2-F3-F4). 46% (89/194) of patients were intravenous drug abusers. Genotypes 1a (30%) and 1b (15%) were the most frequent. 94 (48%) patients had a known co-morbidity. The most commonly cited reason for stopping hepatology monitoring were the lack of information for 39% of patients included and the low severity of liver fibrosis. The average duration of the follow-up break was more than 6 years. Until now 120 patients have already started treatment.

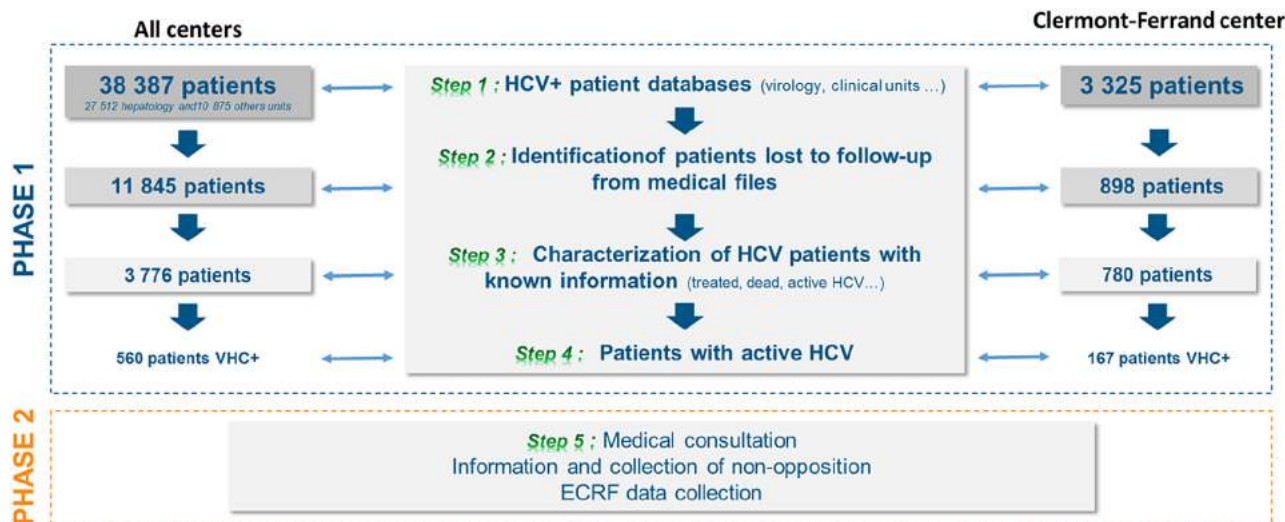


Figure: (abstract: PO-785): Distribution of RECONVOCC patients in December 2020

Conclusion: This work shows that there is still a high number of patients infected with the HCV who have not yet benefited from treatment with direct antiviral agents. Patients who were lost to follow-up should be reconvened to achieve HCV elimination in 2030. The study is still underway. This study was supported by Abbvie.

PO-821

Usefulness of FIB-4 as a screening test for chronic liver disease in a university hospital

Adele Delamarre¹, Victor Legal¹, Marie Irlés-Depe¹, Marie Decraecker¹, Paul Hermabessiere¹, Gautier Boillet¹, Juliette Foucher¹, Marie-Lise Bats¹, Nathalie Ong¹, Marie-Christine Beauvieux¹, Véronique Gilleron¹, Victor de Lédighen¹. ¹CHU Bordeaux, Pessac, France
Email: victor.deledighen@chu-bordeaux.fr

Introduction: It is unclear whether the identification of individuals at risk of cirrhosis using non-invasive tests can be used in tertiary centers. We prospectively tested whether automatically calculated fibrosis-4 index (FIB-4) could improve the identification of individuals with unknown liver disease.

Methods: From September 2019 to March 2020, FIB-4 was automatically calculated in all patients (18–70 yrs) who attended the University Hospital and had a blood sample with platelets and transaminases. Patients from intensive care, oncology, gynecology or hepatology units were excluded. In case of FIB-4 >2.67, all medical records were reviewed to exclude patients for whom a cause of false positive FIB-4 was found (known thrombopenia or cytopenia, known chronic liver disease, acute event with elevated transaminases or thrombopenia). At last, all other patients were proposed to attend our hepatology unit for clinical examination and liver stiffness measurement. At the end, patients were classified as having liver disease when liver stiffness measurement LSM (FibroScan®) was >6 kPa (and its cause), no liver disease, or unknown (patients who did not attend our unit).

Results: A total of 16, 100 FIB-4 were automatically calculated in the LIS (GLIMS). Main results are indicated on Figure. FIB-4 was >2.67 in 1, 165 patients (7.3%). Among them, 809 were considered to have false positive FIB-4. Therefore, 356 patients had an elevated FIB-4 result that needed a second step (2.2% from 16 100 patients). These patients came from the main following units: Emergency (n = 158), cardiology (n = 52), internal medicine (n = 46), gastroenterology (n = 18) and

endocrinology (n = 17). At this time (the study is going on), 107 patients (30.1%) already attended our hepatology unit. Among them, 50 patients had LSM ≤6 kPa and were considered as “no liver disease.” However, among these patients, 14 (28%) had elevated AUDIT questionnaire (>8) and were referred to GP. A total of 57/107 patients (53.3%) were considered having a chronic liver disease. These patients came from emergency (n = 19), cardiology (n = 14), and endocrinology (n = 6) units. Main causes of chronic liver disease were: alcoholic liver disease (n = 24, 42.1%), NAFLD (n = 15, 26.3%), heart failure (n = 12, 21.1%). At last, 25/57 patients (43.9%) had LSM > 15 kPa.

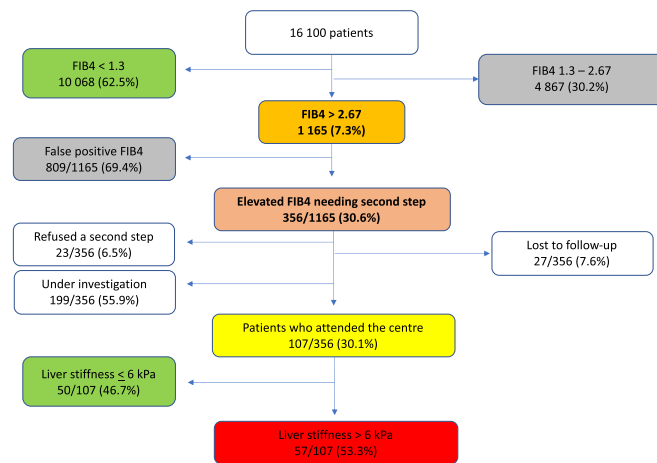


Figure:

Conclusion: In this study, conducted in a general population without known chronic liver disease, we found that automatically calculated FIB-4 allows the identification of individuals with suspected severe liver disease in 30.6% of cases. After liver stiffness measurement, 53.3% of these patients had chronic liver disease (liver stiffness ≥6 kPa). Automatically calculated FIB4 should be implemented in all hospitals because it allows detection of patients with severe liver disease without overloading the units since only 30% of patients require a confirmatory examination.

Financial support : Gilead Sciences.

PO-1035

A novel approach to age cohort screening for hepatitis C in the primary care setting of a large urban health care setting with linkage to care

David Bernstein¹, Tanya Louis¹, Nitzan Roth¹, Sanjaya Satapathy¹.

¹Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, United States

Email: dbernste@northwell.edu

Background and aims: New York (NYS) mandates the offering of hepatitis C testing for adults born between 1945–1965 and the CDC recently updated its screening guidelines to recommend one time screening of all people aged 18 and above. Despite these recommendations, it is estimated that more than 50% recommended candidates for HCV screening are not screened and therefore many with underlying disease are not identified. When patients with HCV are identified, current direct acting anti-viral therapy is curative in >95% of patients and is available to all in NYS. Northwell Health, the largest health system in New York State provides primary care services in 10 counties with a population of >10million people. HCV is under-diagnosed in this service area and most primary care providers are not appropriately screening for HCV. We hypothesize that the use of patient navigators to educate primary care providers about HCV screening will improve diagnosis and linkage of care of newly diagnosed HCV patients to treating physicians.

Method: Training materials and databases were developed and nurse educators were trained in all aspects of HCV infection. Nurse educators visited primary care practices to discuss the NYS law mandating HCV screening for all people born between 1945–1965 and revisited these practices to reinforce study goals and establish a process for screening and linkage to care to health care providers.

Results: From the time period April 1, 2018 to March 1, 2020, 31062 previously unscreened adult patients born between 1945–1965 in outpatient family medicine, geriatrics, internal medicine and OB/GYN offices had HCV antibody testing with reflex testing to HCVRNA by PCR if HCV AB was positive. 30383 tests were negative. 679 patients had a positive HCV AB (2.1%) and 155 (0.49%) were HCVRNA positive. Of the 679 who tested positive, 57.1% were female, 42.9% male, 54% Caucasian, 17% Black, 16% Latino and 8% Asian. 155/679 HCV AB positive patients were HCVRNA positive (22.8%). Of the 155 HCVRNA positive patients, 49% (76) successfully completed DAA therapy and had a sustained virological response, 27.1% (42) are currently on DAA therapy, 13.5% (21) were linked to a treating physician and declined DAA therapy when offered, 6.5% (10) expired before seeing a HCV treatment provider and 3.9% (6) were lost to follow-up.

Conclusion: In this large, diverse health care system, 2.1% of the previously unscreened patients born between 1945–1965 are HCV AB positive and 0.49% have active disease. The use of patient navigators increased the linkage to care with all patients referred to a treatment provider. Despite increased screening and highly effective HCV therapies, 13.5% of patients still declined curative HCV therapy. Better education regarding the safety and affordability of HCV therapies is needed to overcome societal misconceptions still held by a significant percentage of HCV positive patients in our community.

PO-1158

Baseline characteristics of a large multi-site chronic HBV electronic health record-based cohort in the UK

Cori Campbell^{1,2}, Tingyan Wang^{1,2}, Eleanor Barnes^{1,3},

Philippa Matthews^{1,3,4}. ¹Peter Medawar Building for Pathogen

Research, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; ²NIHR Oxford Biomedical Research Centre, Big Data

Institute, University of Oxford, Oxford, United Kingdom; ³Oxford

University Hospitals NHS Foundation Trust, Oxford, United Kingdom;

⁴Department of Infectious Diseases and Microbiology, John Radcliffe

Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford,

United Kingdom

Email: corijcam@gmail.com

Background and aims: Nearly 300 million people worldwide are chronically infected with hepatitis B virus (HBV), which is the leading cause of global liver cancer deaths. The UK HBV population is not well characterised but understanding the burden of disease is crucial to optimise case finding and clinical service provision.

Method: We included CHB patients from QResearch, a primary-care database in England of individual-level patient records from 1727 general practices, aged ≥18 years with a diagnostic record of CHB between 1999 and 2019. Baseline was defined as the first record of CHB.

Figure:

Characteristics	n (%), ormean (SD)
Total	7952 (100)
Follow-up, years	7.3 (5.8)
Age, years	
18–24	647 (8.1)
25–34	2810 (35.3)
35–44	2443 (30.7)
45–54	1277 (16.1)
55–64	534 (6.7)
65–74	241 (3.0)
Male	4823 (60.7)
Townsend deprivation quintile	
1 st (most deprived)	459 (5.8)
2 nd	722 (9.1)
3 rd	1211 (15.3)
4 th	2021 (25.5)
5 th (least deprived)	3516 (44.3)
Missing	23 (0.3)
Ethnicity	
Black African	1803 (22.7)
Chinese	865 (10.9)
South Asian	1307 (16.4)
Other	800 (10.1)
White	1894 (23.8)
Missing	1283 (16.1)
Alcohol, units/day	
Non-drinker	2564 (32.2)
<1	408 (5.1)
1–2	186 (2.3)
3–6	80 (1.0)
≥7–9	25 (0.4)
Missing	4687 (58.9)
Smoking, cigarettes/day	
Non-smoker	2902 (36.5)
Ex-smoker	662 (8.3)
<10	8648 (10.9)
10–19	179 (2.3)
≥20	84 (1.1)
Missing	3257 (41.0)
BMI, kg/m ²	
<18.5	98 (1.2)
18.5–24.9	1263 (15.9)
25–29.9	1248 (15.7)
≥30	742 (9.3)
Missing	4601 (57.9)
Diabetes	463 (5.8)
Hypertension	757 (9.5)
Ischaemic heart disease	151 (1.9)
Chronic kidney disease	140 (1.8)
Alcoholic liver disease	41 (0.5)
NAFLD	137 (1.7)
Cirrhosis	232 (2.9)
Varices/ascites	133 (1.7)
End-stage liver disease	25 (0.3)

Results: We identified 7952 CHB patients (61% male). Mean follow-up was 7.3 years. At baseline, 74% of patients were aged <45 years, 44% were residing in the most deprived geographical regions, and >50% were non-white. 1.8%, 2.9% and 3.7% of patients had record of non-alcoholic fatty liver disease (NAFLD), cirrhosis and varices/ascites,

POSTER PRESENTATIONS

respectively. Prevalence of extra-hepatic comorbidities was low, however 9.5% and 5.8% of patients had hypertension and diabetes, respectively. Sex and ethnicity were significantly associated with deprivation ($p < 0.001$). Within 3 years of diagnosis 145 (1.8%) patients were on antiviral treatment.

Conclusion: The UK CHB morbidity burden is concentrated in young, deprived, non-white individuals among whom a minority are treated. Further research is required to identify factors associated with different disease outcomes and to assess benefits of wider treatment.

PO-1330

Performance of screening strategies for primary prophylaxis of variceal bleeding in patients with compensated cirrhosis: a cost-effectiveness analysis

Shanshan Lin¹, Chuan Liu¹, Zonglin He², Ye Gu³, Yan Wang³, Qing Yang³, Jianbo Shao⁴, Guohong Ge⁴, Shengqiang Zhou⁴, Guo Zhang⁵, Wenjuan Wang⁵, Xing Wang⁶, Bin Wu⁶, Wai-Kit Ming², Xiaolong Qi¹. ¹CHES Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; ²School of Medicine, Jinan University, Guangzhou, China; ³Portal Hypertension Center, The Sixth People's Hospital of Shenyang, Shenyang, China; ⁴Department of Liver Disease, The Third People's Hospital of Zhenjiang, Zhenjiang, China; ⁵Department of Gastroenterology, The People's Hospital of Guangxi

Zhuang Autonomous Region, Nanning, China; ⁶Department of Gastroenterology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China
Email: qixiaolong@vip.163.com

Background and aims: Screening tools including esophagogastroduodenoscopy (EGD) and non-invasive methods (Baveno VI criteria) have been recommended to be performed in clinical practice in order to identify the high-risk patients and prevent the first episode of variceal bleeding in compensated cirrhosis. In this study, we aimed to examine the cost-effectiveness of screening tools, and to provide evidence-based information for decision and policy making.

Method: We developed an analytic decision model in which Markov models were embedded. Clinical parameters were derived from published literature and meta-analysis. Meanwhile, medical costs were collected in Chinese yuan from multi-level hospitals in China and converted into US dollars at an exchange rate of 6.53 yuan per dollar. Deterministic and probabilistic sensitivity analyses are followed. Our model was calculated over a five-year horizon.

Results: Patients categorized in the no screening scenario faced both the highest total cost of \$1421 per patient and the lowest life expectancy of 4.74 years per patient, and therefore the no screening strategy was dominated and excluded. Screening with Baveno VI criteria had the cheapest medical cost of \$1022 per patient, and

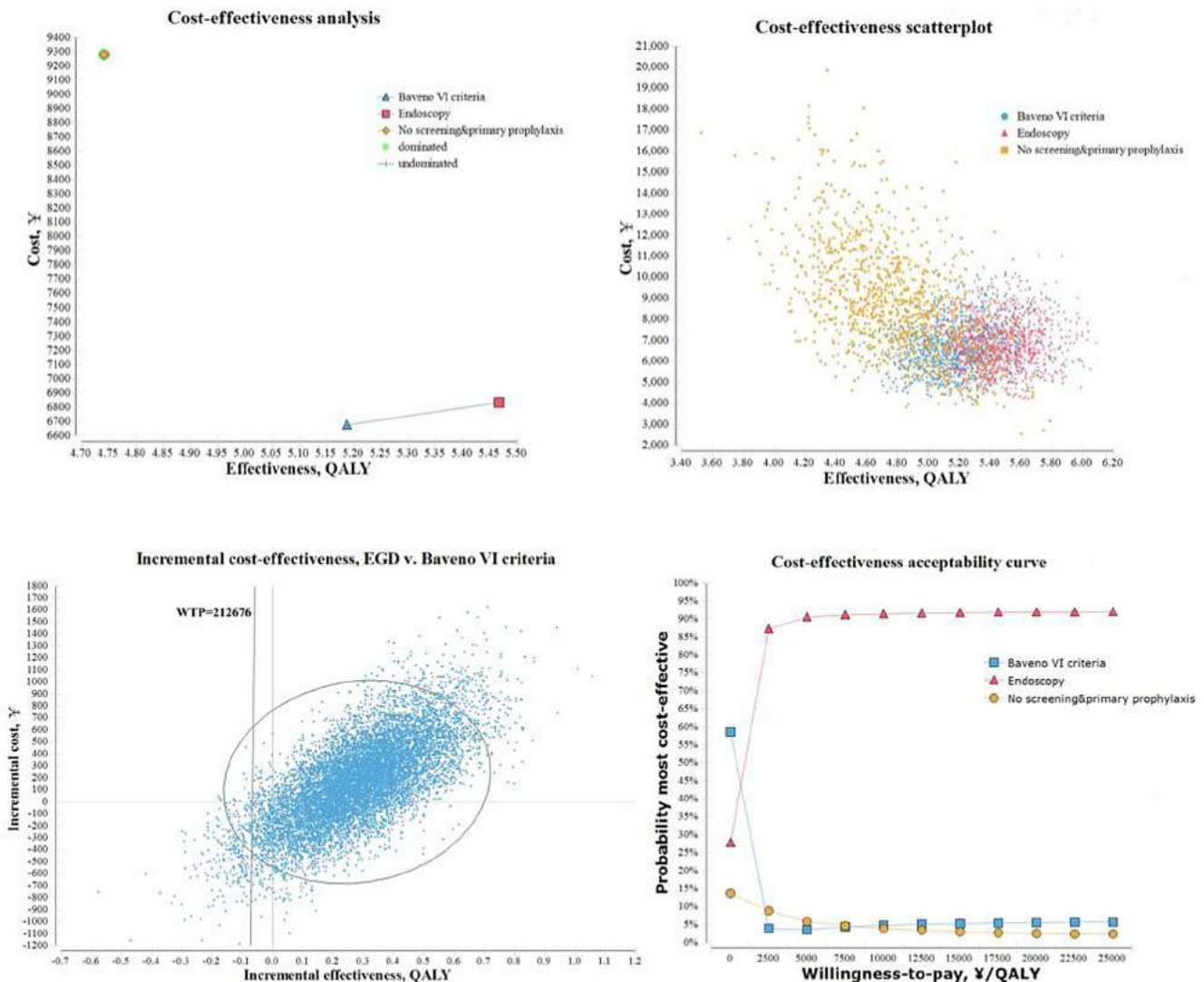


Figure: (abstract: PO-1330)

patients who underwent EGD screening gained the highest life expectancy of 5.47 years per patient. Compared to the Baveno VI criteria strategy, the incremental cost-effectiveness ratio of EGD strategy was \$89.28 per quality-adjusted life-year. The results were sensitive to the probability of low-risk patients detected by EGD. In terms of cost-effectiveness ratio, the strategies of EGD and Baveno VI criteria were both cost-effective according to the threshold. Additionally, the possibility of selecting EGD screening is 93.4%, however, if the capability of Baveno VI criteria of detecting high-risk patients improved or the willingness-to-pay was lower than \$91.4 per patient per quality-adjusted life-year, screening with Baveno VI criteria will emerge as a preferred strategy.

Conclusion: Scenarios of screening with EGD or Baveno VI criteria are both cost-effective. The preference of decision depends on the variation of key parameters and the willingness-to-pay of decision makers. The consideration of spared endoscopy rate and dynamic follow-up will improve the screening value of Baveno VI criteria in routine practice.

PO-1341

Active search to retrieve lost-to follow-up HCV patients (RELINK-C strategy): health and economic value

Joan Martínez-Camprecios^{1,2}, Raquel Domínguez-Hernández³, Cristina Marcos-Fosch¹, Ariadna Rando^{4,5}, Mar Riveiro-Barciela^{1,6}, Francisco Rodríguez Frias^{6,7,8}, Miguel Ángel Casado⁹, Rafael Esteban^{1,6}, Maria Buti^{1,6}. ¹Hospital Universitari Vall d'Hebron, Liver Unit, Internal Medicine Department, Barcelona, Spain; ²Universitat Autònoma de Barcelona, Medicine department, Bellaterra, Spain; ³Pharmacoeconomics and Outcomes Research Iberia (PORIB), Health Economics, Madrid, Spain; ⁴Hospital Universitari Vall d'Hebron, Department of Microbiology, Barcelona, Spain; ⁵Universitat Autònoma de Barcelona, Department of Microbiology, Bellaterra, Spain; ⁶CIBERehd, Instituto Carlos III, CIBERehd, Barcelona, Spain; ⁷Clinical Laboratories Hospital Universitari Vall d'Hebron, Biochemistry Department, Barcelona, Spain; ⁸Hospital Universitari Vall d'Hebron, Liver Pathology Unit, Biochemistry and Microbiology Departments, Barcelona, Spain; ⁹Pharmacoeconomics and Outcomes Research Iberia (PORIB), CEO, Madrid, Spain

Email: rdominguez@porib.com

Background and aims: Spain is on track to eliminate Hepatitis C (HCV) infection by 2030 after treating more than 140, 000 chronic infected individuals in the last six years. This public health challenge

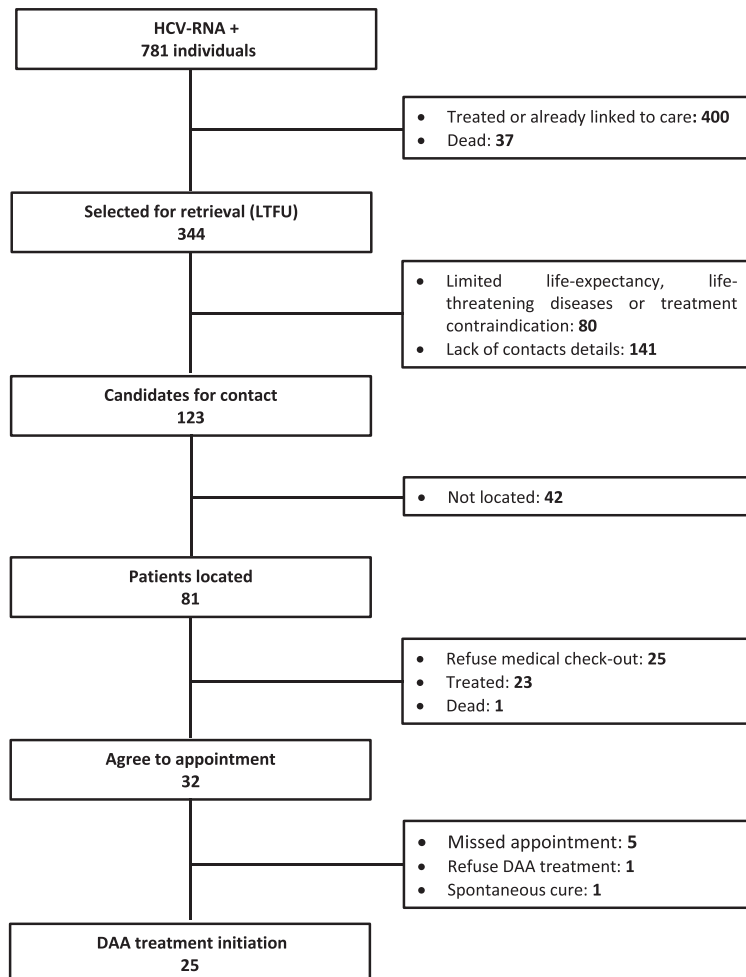


Figure 1. Flowchart of HCV viremic cases from year 2019, patients selected for retrieval or lost to follow-up (LTFU), candidates for contact, patients located and patients who finally initiate direct-acting antiviral (DAA) treatment.

Figure: (abstract: PO-1341)

POSTER PRESENTATIONS

is leading physicians and authorities to design new strategies in order to increase diagnosis of unknown HCV cases or to retrieve untreated or lost-to-follow-up (LTFU) patients. The aim of this study was to retrieve LTFU HCV viremic patients who could benefit from treatment (RELINK-C strategy) and to evaluate its effectiveness and economic value.

Method: The RELINK-C strategy is based on a retrospective search (January to December 2019) for HCV-RNA+ve cases from the central laboratory department of the Barcelona north health area (450, 000 inhabitants) followed by medical records review. Individuals who were LTFU or with an unresolved infection were selected for retrieval. Candidates were contacted by phone (5 maximum attempts) for diagnosis and treatment assessment. Cost of RELINK-C was estimated along with lifetime health and economic outcomes of RELINK-C vs non-intervention through a Markov model based on candidates for HCV treatment with available contact information.

Results: 781 HCV-RNA+ve cases were detected. Of those, 344 (44%) were LTFU and selected for retrieval and among them, 123 were candidates for contact. Reasons for not contacting 80 of the cases were limited life expectancy, life-threatening diseases or HCV treatment contraindication and patients lack of contact details among 141 cases. Upon the phone calls, 81 patients were located, of whom 32 agreed to an appointment with the physician (25 refused medical check out, 23 were already treated and 1 had died). Finally, 27 patients attended the appointment and 25 started DAA treatment (1 spontaneous cure, 1 refused treatment) (Figure 1).

The investment associated to RELINK-C strategy (search and diagnosis) was €13, 877. Model based on the 123 patients, excluding 23 patients already treated, 1 death and 1 spontaneous cure, showed that treating 25 patients in RELINK-C strategy vs no patients treated in non-intervention decreases mortality by 23% and liver complications by 22–27% (greater impact on decompensated cirrhosis), generating €278, 534 savings associated to liver complications management.

Conclusion: RELINK-C enabled 25 of the 81 located patients to receive HCV treatment and has shown to be an efficient strategy to help in achieving Hepatitis C elimination.

PO-1374

Optimizing diagnostic algorithms to advance HCV elimination in Italy: A cost effectiveness evaluation

Andrea Marcellusi¹, Francesco Saverio Mennini², Murad Ruf³, Claudio Galli⁴, Alessio Aghemo⁵, Maurizia Brunetto⁶, Massimo Andreoni², Sergio Babudieri⁷, Loreta Kondili⁸. ¹Tor Vergata University of Rome, Rome, Italy; ²Tor Vergata University of Rome, Rome, Italy; ³Gilead Sciences Europe Ltd, Public Health, Medical Affairs, Uxbridge, United Kingdom; ⁴Abbott Diagnostics Infectious Diseases, Rome, Italy; ⁵Humanitas Research Hospital, Milan, Italy; ⁶University of Pisa, Pisa, Italy; ⁷University of Sassari, Sassari, Italy; ⁸Istituto Superiore di Sanità, National Center for Global Health, Rome, Italy
Email: loreta.kondili@iss.it

Background and aims: Italy is the country with the greatest burden of hepatitis C virus (HCV) infection in Western Europe. There is a political will for HCV elimination and 71.5 million euros have been allocated to a free-of-charge screening in the 1969–1989 birth cohorts and the key populations. We aimed to evaluate the cost effectiveness of different diagnostic algorithms considering the complete patient journey from screening to treatment completion, within the available screening budget in Italy.

Method: A Cost-effectiveness analysis, simulating six screening diagnostic algorithms to detect HCV active infection in the targeted birth cohort (1969–1989) was conducted (Figure). A Markov model for liver disease progression with a 20-years' time horizon and health care system perspective was used. The diagnosis of active HCV infection is made by the detection of antibodies (HCV-Ab), either by rapid or phlebotomy-based assays, followed by HCV-RNA or HCV core antigen (HCV-AG) confirmatory testing either on a second sample (2 visits) or by Reflex testing (1 visit). The rate of individuals that will end up as undiagnosed and unlinked to care has been evaluated by the estimates of false negatives by each assay and by the patient re-attendance drop-off at each screening step based on literature data. Age, fibrosis stage, treatment effectiveness, DAA costs and liver disease costs were used to evaluate the quality-adjusted life-years (QALY) and the incremental cost-effectiveness ratios (ICER) of

Six testing options for active HCV infection: Allocation in the decision tree

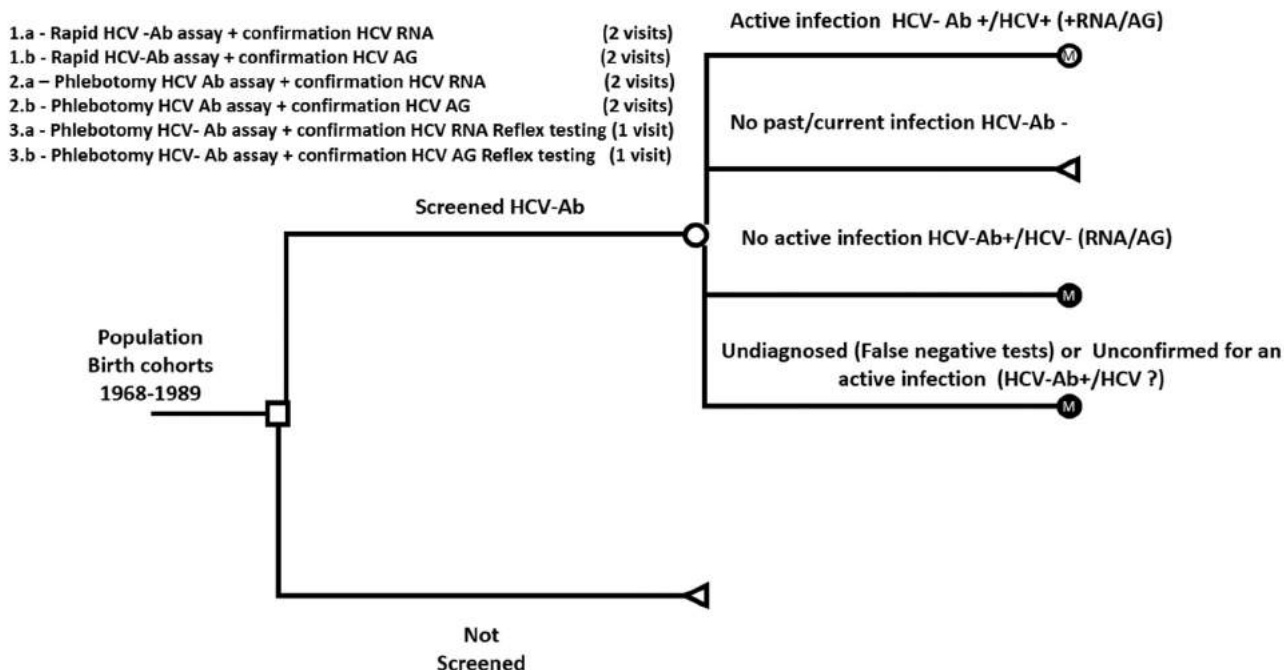


Figure: (abstract: PO-1374)

different diagnostic algorithms. The reference option was considered the algorithm that produced the lowest QALYs. The cost effectiveness threshold was 25.000 €/QALY.

Results: The reference option resulted the Rapid HCV-Ab+HCV-AG (859, 361 QALYs). The highest effectiveness (QALYs = 974, 458) was obtained by HCV RNA Reflex testing followed by HCV-AG Reflex testing. HCV RNA Reflex testing produced a highly cost-effective ICER (873€/QALY) with € 66, 274.00 screening costs (lower than the dedicated screening fund). Reflex testing (single visit) versus two patients' visits diagnostic algorithms, likely due to lesser patient attendance drop-off, yielded always higher QALYs with a very low ICERs (560 and 635 €/QALY for HCVAG and HCV-RNA, respectively). Reflex testing (both HCV RNA and AG HCV) was highly cost-effective in 100% of the 5, 000 probabilistic simulations

Conclusion: Reflex testing using either HCV RNA or HCV-AG is the most cost effective and sustainable with the dedicated screening fund in Italy. Our data confirm the EASL clinical practice guidelines recommending Reflex testing as it has the highest cost effectiveness compared to the other screening pathways.

PO-1421

The 2010 HIV outbreak among people who inject drugs in Athens, Greece could have been prevented if the undetected 2009 HCV outbreak had been detected: A mathematical modeling study

Ilias Gountas¹, Georgios Nikolopoulos², Giota Touloumi³, Anastasios Fotiou⁴, Angelos Hatzakis³, Kyriakos Souliotis¹. ¹University of Peloponnese, Faculty of Social and Political Sciences, Greece;

²University of Cyprus, Medical School, Cyprus; ³National and Kapodistrian University of Athens, Department of Hygiene, Epidemiology and Medical Statistics, Medical School; ⁴Athens University Mental Health, Neurosciences, and Precision Medicine Research Institute (UMHRI), National Monitoring and Documentation Centre for Drugs, Greece

Email: eliaoun@gmail.com

Background and aims: Several studies on People Who Inject Drugs (PWID) have shown that when hepatitis C virus (HCV) prevalence increases, the PWID community is at increased risk for a Human Immunodeficiency Virus (HIV) outbreak. This relationship has been

confirmed in Athens, Greece; an HCV and an HIV outbreak emerged among PWID of Athens in 2009 and 2010, respectively. The HCV outbreak was not detected at all, while that of HIV was identified in 2011. The main HIV-interventions started in early 2012. Public health interventions to the PWID population are beneficial for more than one disease. In the case of Athens, given that HCV and HIV share common transmission routes, HIV-interventions reduced HIV incidence by 78% and indirectly HCV incidence by 64.8%. This study aims to assess what the courses of the HCV and HIV outbreaks and their economic consequences would have been if HCV outbreak had been detected and integrated interventions had started 1- or 2- years earlier.

Method: A dynamic, stochastic, individual-based model was used to simulate HCV and HIV transmission among PWID. The model was calibrated to reproduce the observed HCV and HIV epidemiological parameters among PWID of Athens, Greece. We examined the effect of non-detection, 1- or 2-years earlier detection scenarios, and compared them to the status quo scenario. The time-horizon of the analysis was 2002–2019 so as to capture the second-order transmission effects.

Results: Under the status-quo scenario and during 2009-2019, the cumulative HCV and HIV cases were 6480 (95% Credible intervals (CrI) 6000, 6900) and 1360 (95% CrI: 400, 2600), respectively. If the HCV outbreak had been detected and the integrated interventions initiated 1- or 2- years earlier, 440 and 970 new HCV cases and 740 and 1110 new HIV cases could be averted by 2019, respectively (Figure). Under the non-detection scenario, 2800 and 7030 additional PWID would have been infected with HCV and HIV compared to the status quo by 2019, respectively. Concerning the costs of treating the new cases for both diseases, if there was an efficient notification system to detect the HCV outbreak, 40.9–65.8 million euros could have been saved.

Conclusion: HCV prevalence can quantify the intensity of injecting risk behaviors among PWID. If the HCV outbreak had been detected and promptly responded, the HCV outbreak would have been substantially blunted, the HIV outbreak would have been prevented and 40.9–65.8 million euros could have been saved

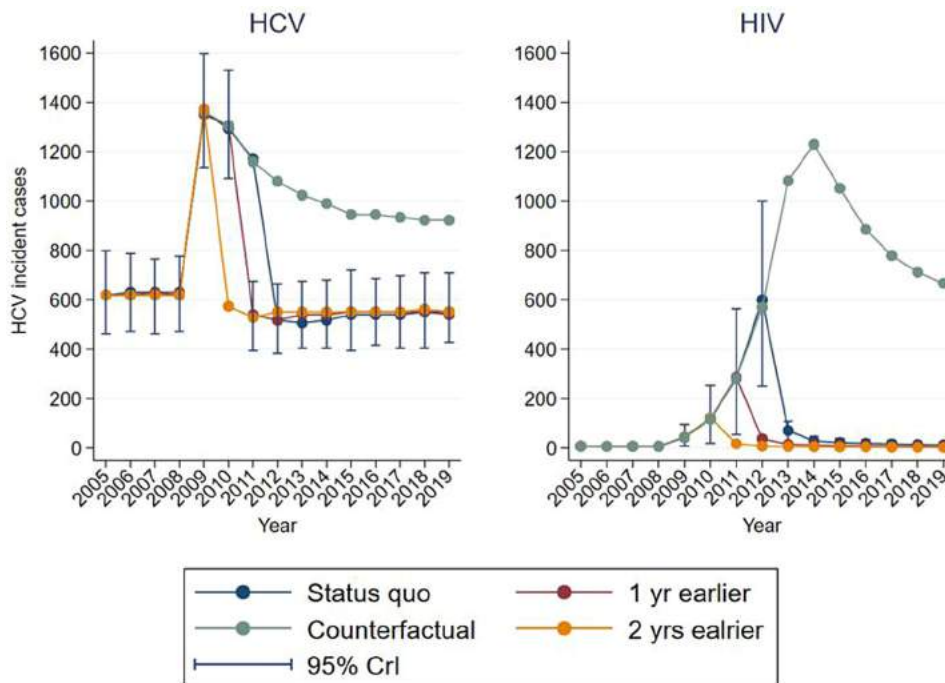


Figure: (abstract: PO-1421)

POSTER PRESENTATIONS

PO-1426

A discrete choice experiment about patients' and clinicians' preferences for the meet-test-treat approach to HCV management

Massimo Andreoni¹, Nicola Coppola², Antonio Craxi³, Stefano Fagioli⁴, Ivan Gardini⁵, Alessandra Mangia⁶, Felice Alfonso Nava⁷, Patrizio Pasqualetti⁸. ¹Infectious Diseases, Roma, Italy; ²Infectious Diseases, Department of Mental Health and Public Medicine, Italy; ³Department of Gastroenterology, Italy; ⁴Gastroenterology and Transplant Hepatology; ⁵EpaC Onlus; ⁶Liver Unit; ⁷Penitentiary Medicine and Drug Abuse Unit; ⁸Department of Public Health and Infectious Disease, Roma, Italy
Email: patrizio.pasqualetti@uniroma1.it

Background and aims: The meet-test-treat strategy could help reduce the incidence of chronic hepatitis C virus (HCV), increasing the proportion of diagnosed infected subjects and improving their access to treatment. The aim of this study was to investigate the opinion of relevant target populations on the practicability, effectiveness and best modalities of this approach, in Italy.

Method: An online cross-sectional survey was delivered to hospital patients with HCV, patients from drug addiction services (SerD), hospital physicians and SerD healthcare providers (SerD HCP). The questionnaires were divided into four sections: 1. socio-demographic characteristics, 2. characteristics of the care pathway (possible answers were ranked in order of importance), 3. discrete choice experiment (DCE) comparison of possible care pathways, 4. DCE comparison of treatment characteristics.

Results: The survey was completely answered by 190 hospital clinicians, 142 SerD HCPs, 372 hospital patients, and 131 SerD patients. For hospital clinicians, the most important attributes of a diagnostic-therapeutic pathway were a high compliance to treatment (relative importance [RI] 22%) and a short time to treat (RI 19%), while a 4-month delay of treatment was not acceptable. For SerD HCPs, although the care setting was not deemed important in comparison with other attributes, a significant preference for "inside the service" versus "outside the service" was present (preference weight = +0.09; 95% CI: +0.01–0.16). Among hospital patients, the most important attribute was the time of Meet-Test-Treat (RI 26%). For addicted subjects followed-up by SerD, the most important attribute of a diagnostic therapeutic pathway was compliance to test (RI 23%). Finally, SerD patients showed a significant preference for being cared for HCV within the SerD versus being cared in other centers (preference weight = +0.29; 95% CI: +0.19–0.38). SerD patients, in comparison with hospital patients, were less interested in the absence of adverse events, while they considered more important the low number of pills per day.

Conclusion: In the perspective of HCPs and of lay people, the diagnostic process should be rapid and thorough, and treatment should be tolerable. SerD patients should be met and cared in healthcare structures familiar to them.

PO-1431

Value assessment of sofosbuvir-based regimens for (chronic) hepatitis C in Spain

Rafael Esteban^{1,2}, Raquel Domínguez-Hernández³, Miguel Ángel Casado⁴. ¹Hospital Universitari Vall d'Hebron, Liver Unit, Internal Medicine Department, Barcelona, Spain; ²CIBERehd, Instituto Carlos III, CIBERehd, Barcelona, Spain; ³Pharmacoeconomics and Outcomes Research Iberia (PORIB), Health Economics, Madrid, Spain; ⁴Pharmacoeconomics and Outcomes Research Iberia (PORIB), CEO, Madrid, Spain
Email: rdominguez@porib.com

Background and aims: The treatment of chronic hepatitis C virus (HCV) with direct-acting antivirals has undergone a spectacular revolution, contributing to the World Health Organization (WHO) global strategy of HCV elimination by 2030. The aim of the study was to estimate the clinical and economic value of Sofosbuvir (SOF)-based regimens for a target population of 85, 959 chronic HCV patients,

from the Spanish National Health System (NHS) perspective, treated with SOF-based regimens during 2015–2019, compared to previous therapeutic strategies (PTS; peginterferon and ribavirin in double/triple therapy with telaprevir or boceprevir).

Method: To assess the impact of the SOF-based regimens, a previously developed lifetime Markov model was adapted simulating the disease evolution of HCV. In SOF-based regimens, all patients (100%) were treated regardless of their fibrosis stage with sustained virological response (SVR) of 93–98%, obtained from real-world data. In PTS, only \geq F2 patients were treated according to clinical practice (38%) with an average SVR of 61% taken from published literature. The results reported included the number of patients with HCV-related mortality, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver transplantation (LT) avoided cases; total costs and quality-adjusted life years (QALYs) were calculated applying an annual 3% discount rate.

Results: Compared to PTS, during lifetime, SOF-based regimens reduced DC by 89% (-14, 372 cases), HCC by 77% (-9, 473 cases) and LT by 84% (-1, 878 cases), decreasing the cost associated to liver complications management in €770 million. SOF-based regimens also decreased liver-related mortality by 82% (-15, 810). Besides, SOF-based regimens gained 310, 765/QALYs, saving €274 million (considering drugs, monitoring, and management of HCV complications).

Conclusion: For Spain, which is on a path to achieving HCV elimination within the next decade following WHO goals, SOF based regimens offer value in terms of lowering HCV-related liver disease burden and generating significant cost savings for the Spanish NHS.

PO-1480

Epidemiological evaluation of the liver cirrhosis in Albania: comparison with the historical data and indications to antiviral treatment appropriateness

Xhimi Tata^{1,2}, Adriana Babameto³, Liri Cuko³, Leonardo Baiocchi⁴, Luigina Ferrigno⁵, Maria Giovanna Quaranta⁵, Loreta Kondili⁵. ¹Istituto Superiore di Sanità, National Center for Global Health, Rome; ²University Nostra Signora del Buon Consiglio, Tirana, Albania; ³University Hospital Center of Tirana, Liver Unit, Tirana, Albania; ⁴Tor Vergata University of Rome, Rome, Italy; ⁵Istituto Superiore di Sanità, National Center for Global Health, Rome, Italy
Email: loreta.kondili@iss.it

Background and aims: Albania is a developing Mediterranean country, previously reported to be highly endemic for HBV infection. In Albania, HBV infection has been the main risk factor of liver cirrhosis affecting mainly young age individuals. HBV vaccination (in the newborns since 1995 and in high risk groups since 2000) and changes in the dietary habits/alcohol intake might have changed the weight of etiological factors of liver cirrhosis in the recent years. The aim of this study was to evaluate the prevalence of viral hepatitis infections (HBV, HDV, HCV) and of alcohol abuse in Albanian patients with liver cirrhosis, consecutively admitted during the year 2019 to the Liver Unit of the University Hospital Centre of Tirana, compared with previous data. The final goal is to properly address targeted public health interventions regarding diagnosis and antiviral treatment appropriateness.

Method: Demographic, alcohol abuse, clinical, virological and treatment data of patients consecutively admitted to the hospital during the study period, in the Albania's most important tertiary liver-care centre, were prospectively collected. Available data, collected in the same manner, during the years 1995 and 2005 were also evaluated. Chi square test were used for non-parametric variables; $p < 0.05$ was considered significant.

Results: The prevalence of viral hepatitis markers and of alcohol intake was evaluated in 120, 99 and 106 Albanian patients with cirrhosis admitted to the hospital during 2019, 2005 and 1995 respectively. A decrease of HBsAg prevalence (27% vs 70 vs. 78%) ($p < 0.05$), increase of alcoholic liver disease (HBsAg and anti-HCV

negative) (56% vs 21% vs 17%) ($p < 0.05$) and unchanged HCV prevalence (14% vs 11% vs 11%) were observed in patients admitted to the hospital during 2019/2020 vs 2005 vs 1995 respectively. HDV infection was tested only in 12.5% of HBsAg positive patients of them 50% were anti-HDV positive. HCC was diagnosed in 9% of overall patients, of them 73% HBV correlated. Of the 32 patients with HBV liver cirrhosis, 19% were treated with Tenofovir with unknown HBV DNA measurements during the hospital admission, the remaining HBsAg patients were diagnosed for the first time with cirrhosis and were untreated. 38% of patients with HCV infection were relapsers of previous DAA treatment, the remaining were HCV RNA negative following a DAA treatment in the cirrhosis stage.

Conclusion: Alcohol abuse was the main etiological factor of liver cirrhosis, as in several European countries. Despite the decreasing prevalence by anti-HBV vaccination, HBV infection remain an important etiological factor of liver cirrhosis and of HCC development. Hepatitis Delta is not properly diagnosed in Albanian patients. The increase of awareness of alcohol induced liver damage, early diagnosis and appropriate HBV and HCV treatment before reaching severe liver damage is of a paramount importance in Albania.

Changes in the prevalence of HBV, HCV and alcohol abuse over time in Albanian patients with liver cirrhosis

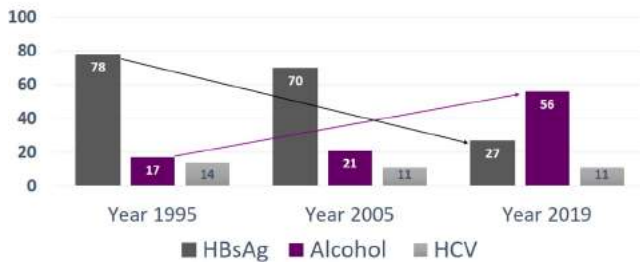


Figure:

PO-1551

The Impact of COVID-19 Pandemic on Patients with Chronic Liver Disease (CLD): Data from the Global Registry

Zobair Younossi^{1,2,3}, Yusuf Yilmaz⁴, Mohammed El-Kassas⁵, AJAY KUMAR Duseja⁶, Saeed Sadiq Hamid⁷, Gamal Esmat⁸, Nahum Méndez-Sánchez⁹, Wah-Kheong Chan¹⁰, Ashwani Singal¹¹, Brian Lam^{1,2,3}, Sean Felix³, Elena Younossi³, Manisha Verma^{2,3}, Jillian Price³, Fatema Nader^{1,2,3}, Issah Younossi³, Andrei Racila^{1,2,3}, Maria Stepanova^{1,2,3}. ¹Inova Health System, Medicine Service Line, Falls Church, United States; ²Inova Health System, Department of Medicine, Center for Liver Diseases, Falls Church, United States; ³Inova Health System, Beatty Liver and Obesity Research Program, Falls Church, United States; ⁴Marmara University, Department of Gastroenterology, School of Medicine, Turkey; ⁵Helwan University, Endemic Medicine Department, Faculty of Medicine, Egypt; ⁶Postgraduate Institute of Medical Education and Research, Department of Hepatology, India; ⁷Aga Khan University, Department of Medicine, Pakistan; ⁸Cairo University, Professor of Tropical Medicine and Hepatology, Faculty of Medicine, Egypt; ⁹Autonomous National University of Mexico, Liver Research Unit, Mexico; ¹⁰the First Affiliated Hospital of Wenzhou Medical University, NAFLD Research Center, Department of Hepatology, China; ¹¹University of South Dakota and Avera Transplant Institute, United States
Email: zobair.younossi@inova.org

Background and aims: The pandemic of COVID-19 is responsible for morbidity and mortality worldwide. Patients with pre-existing chronic diseases incur substantial burden from both the infection and disruption of life caused by the pandemic mitigation measures. The aim was to assess the impact of COVID-19 pandemic on patients with CLD.

Method: CLD patients who were previously enrolled in our Global Liver Registry were invited to complete COVID-19 survey with 23

items. Questions included whether patients were infected with COVID-19, details of the illness for those infected, and the overall pandemic-related disruption of life.

Results: 1994 CLD patients completed the survey [20% chronic hepatitis B (CHB), 18% chronic hepatitis C (CHC), and 62% non-alcoholic fatty liver disease (NAFLD); age 48 ± 13 years, 53% male]. Of the survey completers, 8.2% ($n = 164$) had COVID-19. Of those, 82% were diagnosed by a laboratory test, 92% had at least one symptom, and 76% received treatment for their symptoms. COVID-19 infected patients were ill for mean 13 ± 11 days, 62% received antivirals, and 21% were hospitalized. No patients reported the need for mechanical ventilation. Of all survey completers, 11% reported that pandemic had an impact on their liver disease; these rates were not different between those who were and were not infected ($p = 0.37$). COVID-19-infected patients' self-reported health scores due the pandemic were lower (6.6 ± 2.2 on a 1–10 scale with 10 being perfect health) than in those not infected (7.4 ± 2.2) ($p < 0.0001$). Life Disruption Event Perception (LDEP) questionnaire revealed that 78% of COVID-19 infected patients and 65% of patients without COVID-19 reported worsening in at least one aspect of their daily life (food/nutrition, exercise, social life, vocation/education, financial situation, housing, or healthcare) ($p = 0.0005$). The most profound worsening was reported for social life (70% and 57%), exercise (49% vs. 39%) and financial situation (39% vs. 30%) (all $p < 0.02$). The need for continued supportive care was independently associated with having had COVID-19 infection after adjustment for location, demographic parameters, etiology of liver disease, and non-liver comorbidities (odds ratio = 1.96 (1.23–3.11), $p = 0.0045$).

Conclusion: Patients with CLD experienced a substantial burden of COVID-19 pandemic on their daily lives. Social, financial and exercise aspects were the most commonly impacted. The need for supportive care in CLD was associated with COVID-19 infection.

PO-1572

Screening and treatment of Hepatitis C virus in Hungarian prisons: 13 years of experience

Gabor Horvath¹, Michael Makara², Krisztina Nemesi², Ferenc Schneider³, Ildiko Bali⁴, Judit Enyedi⁵, Judit Gervain⁶, Viktor Jancsik⁷, Miklos Lesch⁸, Klara Werling⁹, Bela Lombay¹⁰, Zsolia Muller⁶, Arpad Patai³, Zoltán Peterfi¹¹, Olga Szabo¹², Janos Szlavik², Tamás Tóth¹³, Marta Varga¹⁴, Judit Gacs², Eszter Ujhelyi¹⁵, Anna Nemes Nagy¹⁶. ¹hepatology Center of Buda, Budapest, Hungary; ²Szent László Hospital, Budapest, Hungary; ³Markusovszky University Teaching Hospital, Szombathely, Hungary; ⁴Balassa János Hospital of Tolna County, Szekszárd, Hungary; ⁵Markhot Ferenc Teaching Hospital and Clinic, Eger, Hungary; ⁶Szent György Hospital, Székesfehérvár, Hungary; ⁷Gyula Kenézy Hospital-Clinic, Debrecen, Hungary; ⁸Szabolcs-Szatmár-Bereg County Hospitals Jóna András Teaching Hospital, Nyíregyháza, Hungary; ⁹Semmelweis University, 1st Dept of Surgery and Interventional Gastroenterology Teaching Clinic, Budapest, Hungary; ¹⁰Central Hospital and University Teaching Hospital of Borsod-Abaúj-Zemplén County, Miskolc, Hungary; ¹¹Pécs University, Clinical Center, Pécs, Hungary; ¹²Nyíró Gyula Hospital, Infectology, Budapest, Hungary; ¹³Semmelweis University, 1st Department of Internal Medicine and Oncology, Budapest, Hungary; ¹⁴Réthy Pál Hospital and Clinic, Békéscsaba, Hungary; ¹⁵Mikromikrmed Kft, Budapest, Hungary; ¹⁶Hungarian Prison Service, Department of Health, Budapest, Hungary
Email: horvath.gabor@hepatologia.hu

Background: The proportion of people infected with HCV in prisons can be up to ten times higher compared to the general population, primarily due to the high rate of prior intravenous drug use among inmates.

Aims: In Hungary, a hepatitis C screening campaign and treatment for screened patients began in prisons in 2007. We summarize the results collected in the last 13 years and our experience with the treatment.

POSTER PRESENTATIONS

Method: Between 2007 and 2019, screening for anti-HCV antibodies and HCV PCR was performed on a voluntary basis in Hungarian prisons several times a year. Treatments were performed under the guidance of hepatologists who visited the institutions monthly. Patients were supervised by prison medical staff. Data were collected from Hepatology Centers, the Health Registry of Prisons, and the Hepreg computer program.

Results: HCV screening programs and treatments are in place in 84% of Hungarian prisons. A total of 29,395 patients underwent anti-HCV screening during the study period. Anti-HCV positive result was detected in 2075 cases, or 7% of the participants. HCV PCR positivity was confirmed in 1252 cases, representing 4.26% of the screened inmates. 792 (63%) patients from the HCV PCR positive population were put on treatment. Data were collected from 527 patients, including 380 on interferon-based therapy and 147 on direct-acting antiviral (DAA) treatment. Only 144 patients received full treatment, while 39% of IFN-based treatments and 8.8% of DAA treatments were terminated prematurely. On the results available at the end of treatment (EOT) + 24 weeks, sustained virologic response (SVR) rate was 86%.

Conclusion: We wish to demonstrate that the “test and treat” policy is feasible and effective at micro-eliminating HCV from a high risk group, prison inmates, where the proportion of prior intravenous drug users is excessively high.

Table 1: Data of treated patients from 2012

Number of patients	527
sex (male/female)	498/29
mean age	36.49 years
Ratio of drug abusers	100%
High ALT	281 (53%)
mean virus titer	1.612 363 IU/L
Genotyping	446
G1	2.5%
G1a	48%
G1b	25%
G3	12%
G4	0.5%
Cannot be determined (HCV PCR<500 IU/L)	12%
Treatments	
IFN-based	380
DAA	147
Full duration	144
early discontinuation	162
IFN-based	149
DAA	13

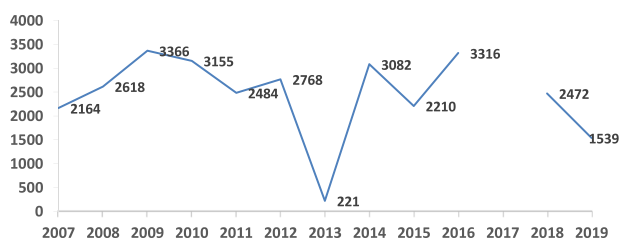


Figure 1. Number of inmates participating in HCV screening between 2007–2019

Table 2: Results of screening tests between 2007 and 2019

Number of screening tests	29,395
anti-HCV positive	2,075 (7%*)
HCV PCR positive	1,252 (4.26%*)
Treatment started	792 (63%*)

Table 3: SVR results (EOT+Week 24 HCV PCR)

	Treatment continued in 2012 no result	2012	2013	2014	2015	2016	2017	2018	2019	Total
No result Abbott HCV below 12 IU/ml	76	19	8	37	59	74	16	8	85	382
negative				1		1				2
positive		4	3	34	29	17	7	12	23	129
Total	76	24	11	77	90	95	25	21	108	527

PO-1593

The “Caserta Model”: a way for HCV free Hospitals, a simplified procedure for HCV micro-elimination

Vincenzo Messina¹, Arnolfo Petruzzello², Elena Tripaldelli³, Angela Annicchiarico⁴, Tommaso Sguglia⁴, Mario Massimo Mensorio⁵, Alfredo Matano⁴, Patrizia Cuccaro⁶, Paolo Maggi⁷, Nicola Coppola⁸. ¹A.O. S. Anna e S. Sebastiano di Caserta, UOC Malattie Infettive, Caserta, Italy; ²A.O. S. Anna e S. Sebastiano di Caserta, Patologia Clinica, Caserta, Italy; ³A.O. S. Anna e S. Sebastiano di Caserta, Patologia Clinica, Caserta, Italy; ⁴A.O. S. Anna e S. Sebastiano di Caserta, DIREZIONE SANITARIA, Caserta, Italy; ⁵A.O. S. Anna e S. Sebastiano di Caserta, DIREZIONE SANITARIA, Caserta, Italy; ⁶A.O. S. Anna e S. Sebastiano di Caserta, DIREZIONE SANITARIA, Caserta, Italy; ⁷A.O. S. Anna e S. Sebastiano di Caserta, UOC Malattie Infettive, Caserta, Italy; ⁸università della campania, UOC Malattie Infettive, Napoli, Italy
Email: vincenzomessina.ce@libero.it

Background and aims: the patients evaluated or recovered for surgery care are usually tested for HCV infection. HCV Ab positive patients are often not referred to a specialist evaluation for further analysis and diagnosis or treatment when necessary. The aim of the present study was to evaluate in S. Anna and S. Sebastiano Hospital of Caserta the prevalence of HCV Ab positive patients and HCV active infection, the awareness of HCV infection and the prevalence of those already treated with DAA in all tested patients

Method: evaluate all patient observed near S. Anna e S. Sebastiano Hospital resulted HCV Ab positive between January 2019 and December 2019 and tested for HCV Ab. Every monthly results record was evaluated in the following month by a specialist who, after consulting the regional care database (SaniArp) examined first the patients single position excluding by the recall list those died and those already treated with DAA, than contacted by phone call every HCV Ab positive patient for an active counselling. All the contacted patients were invited to have a free of charge specialistic consultation as a part of the ongoing care pathway.

Results: between January 2019 and December 2019, 14396 patients were overall tested for HCV Ab for any care in our hospital. 529 were HCV Ab positive, 199 female and 329 male (median age 69; IQR 54–78) 252 were admitted in medical units (pneumo 1, geriatrics 4, medicine 19, nephrol 21, emergency 13, resuscitation 6, neurol 2, heart 39, oncology 12, infectious dis. 92, gastro 14, outpatients 29) and 277 in surgery units (Fig. 1 eye 45, E.N.T 8, orthop 16, dental 48, neuro 22, vascular 16, heart 11, elective 67, urology 23, emergency 12, gynec 9). From the regional record 243 resulted already treated with DAA and were excluded by a recall, while 10 resulted died during hospitalization. If we exclude from the evaluation those admitted in Infectious diseases and Gastroenterology (106) the global prevalence of HCV Ab detection was 2.9% and resulted higher in surgery units 1.9% than in medical ones 1%. All patients contacted and invited for consultation accepted to be evaluated. About the HCV Ab positivity 145 were unaware of their condition, 73 were aware but unsure what to do because of the constantly ALT normal levels, 68 resulted HCV RNA negative and overall 194 were linked to DAA care.

Conclusion: an extensive HCV Ab testing during hospital care especially in surgery units and active surveillance on the testing results could be a simple and effective procedure for identify HCV Ab

positive patients and enhance the linkage to care. It could be assumed as an innovative simplified procedure for micro-elimination of HCV infection.

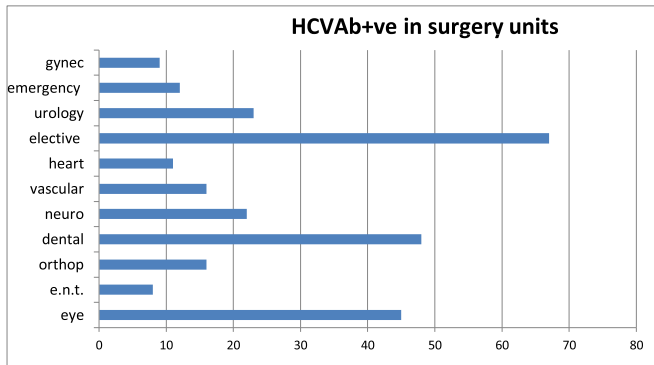


Figure:

PO-1624

Planning the Hepatitis C elimination in Cyprus: A modeling study

Ilias Gountas¹, Ioanna Yiasemi², Evi Kyprianou², Christos Mina², Chrysanthos Georgiou³, Petros Katsioloudes⁴, Andri Kouroufexi⁵, Anna Demetriou⁶, Elena Xenofontos⁷, Georgios Nikolopoulos¹.

¹University of Cyprus, Medical School, Cyprus; ²Cyprus National Addictions Authority, Cyprus Monitoring Centre; ³Nicosia General Hospital; ⁴Evangelistria Medical Centre; ⁵Pharmaceutical Services, Ministry of Health; ⁶Health Monitoring Unit, Ministry of Health; ⁷Department of Internal Medicine, Limassol General Hospital
Email: eliagoun@gmail.com

Background and aims: Hepatitis C virus (HCV) infection is a major global public health problem. In the Republic of Cyprus, the prevalence of chronic HCV (CHC) among the general population is estimated at 0.6%, while the CHC prevalence among people who inject drugs (PWID) is estimated at 43%. The direct-acting antivirals (DAAs) that are capable to eliminate HCV, are not yet available in Cyprus. However, when DAAs become available, a long-term strategic plan to guide elimination efforts will be needed to maximize treatment effect. The aim of the study is to determine the programmatic targets to eliminate HCV in the Republic of Cyprus.

Method: A dynamic, stochastic, individual-based model of HCV transmission, disease progression, and of cascade of care was calibrated to data from the Republic of Cyprus. The model stratifies the population into two groups: infected general population and PWID population. We assumed that the ongoing HCV transmission is limited to the PWID group. PWID moves to the infected general population if they are infected when they stop injection. A variety of test, prevention, and treatment strategies concerning the general population, PWID, or both were examined. The time horizon of our analysis was until 2034.

Results: Under the status quo scenario, the model predicted that 75 (95% Credible intervals (CrI): 60, 91) and 575 (95% CrI: 535, 615) liver-related deaths and new infections would occur by 2034, respectively. Launching an expanded treatment program, without screening interventions, would result in modest outcomes regarding CHC prevalence (16.6% reduction in 2034 compared to 2020) and liver-related deaths (10 deaths would be prevented compared to the status quo scenario by 2034).

Implementing a test and treat strategy in the general population, without any intervention in the PWID population, would be sufficient to achieve the mortality target but not the incidence target.

To achieve HCV elimination in Cyprus, 3080 (95% CrI: 3000, 3200) patients need to be diagnosed and treated by 2034 (2680 from the general population and 400 from PWID) (Figure) and harm reduction coverage among PWID should be increased by 3% per year (from 25% in 2020 to 67% in 2034).

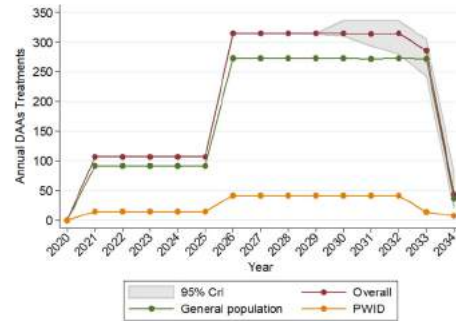


Figure:

Conclusion: Elimination of HCV is a demanding public health strategy, which requires significant interventions both among the general population and in high-risk groups. To achieve the elimination targets, 3080 (95% CrI: 3000, 3200) patients need to be diagnosed and treated between 2021–2034.

PO-1666

Telemedicine improve HCV elimination among Italian people who use drugs: an innovative therapeutic model to increase the adherence to treatment into addiction care centers.

Valerio Rosato¹, Riccardo Nevola¹, Vincenza Conturso², Pasquale Perillo¹, Teresa Le Pera², Ferdinando Del Vecchio², Ernesto Claar¹, ¹Ospedale Evangelico Betania, Liver Unit, Napoli, Italy; ²A.S.L. Napoli 1 Centro, DS32 SerD, Napoli, Italy
Email: valeriosato@gmail.com

Background and aims: HCV infection is very common among people who use drugs (PWUDs), who are usually considered “difficult-to-treat” patients due to adherence or reinfection concerns. Despite the high tolerability and efficacy of direct antiviral agents (DAAs), the linkage-to-care still remains an important gap for HCV elimination in Southern Italy. In this observational prospective study, we evaluated an innovative tailored remote model of care in order to reduce time to treat and improve the adherence to treatment of PWUDs.

Method: PWUDs with HCV were enrolled from January 2017 to December 2020 from one addiction care center in Southern Italy, where a complete hepatologic assessment, including blood chemistry, ultrasound and transient elastography examination, was provided. DAAs treatment was tailored on clinical features, performing also a daily administration during outpatient visit, and remote monitored by hepatologic specialists through phone or video calls. Adherence was evaluated on the accomplishment of therapy or on the percentage of visits attend.

Results: From a total of 690 active PWUDs, 135 had an active HCV infection and were enrolled in study. The characteristics of populations are reported in table. The median time from HCV diagnosis to treatment start was no longer than 3 weeks. We recorded 6 cases of drop-out and only one case of reinfection, obtaining a sustained virological response at week 12 (SVR12) in 98, 5% of cases with only 2 treatment failure.

POSTER PRESENTATIONS

Table:

Characteristics of population	
N. of pts	135
Age, mean ± SD	50 ± 7
Male, n (%)	129 (95, 6)
Current workers, n (%)	45 (33, 3)
<i>Ways of drug administration, n (%)</i>	
intravenous	114 (84, 5)
intranasal	8 (5, 9)
smoke	13 (9, 6)
<i>Current OST, n (%)</i>	
Methadone, n (%)	66 (48, 9)
Buprenorphine, n (%)	19 (14)
Benzodiazepine, n (%)	31 (22, 9)
<i>HCV Genotype, n (%)</i>	
1a	60 (44, 4)
1b	8 (5, 9)
2	3 (2, 2)
3	57 (42, 3)
4	7 (5, 2)
HBCAb	58 (42, 9)
Alanine transaminase IU/ml, mean ± SD	73 ± 71
Aspartate transaminase IU/ml, mean ± SD	59 ± 64
Gamma glutamyl transferase IU/ml, mean ± SD	73 ± 76
<i>Stage of liver disease*</i>	
No or mild Fibrosis (F 0–1)	86 (63, 7)
Moderate or advanced fibrosis (F 2–3)	27 (20)
Cirrhosis (F 4)	22 (16, 3)
Diabetes mellitus type 2	9 (6, 6)
<i>Antiviral treatment, n (%)</i>	
Sofosbuvir + Velpatasvir	63 (46, 6)
Glecaprevir + Pibrentasvir	72 (53, 4)
Ribavirin, n (%)	7 (5, 1)
<i>Adherence to treatment, n (%)</i>	
Drop-out	6 (4, 4)
Adherence <90%	9 (6, 6)
Reinfection	1 (0, 7)
SVR 12, n (%)	133 (98, 5)

OST: opioid substitution therapy; SVR 12: Sustained Virological Response at week 12

*Evaluated with transient elastography: F0–1 (<7, 1kPa), F2–3 (7, 1–13 kPa), F4 (>13, 1kPa)

Conclusion: We obtained a high SVR12 (98, 6%), providing a complete hepatologic assessment within addiction care center, tailoring the drug administration and performing a remote hepatologic stewardship. Our therapeutic model should improve the time to treat and the adherence to treatment in PWUDs.

PO-1713

Liver Transplant Wait-List Trends in Young American Adults

George Philip¹, Jennifer Flemming², Harriet Richardson³, Lawrence Hookey⁴. ¹Queen's University, Kingston, Canada; ²Queen's University, Medicine, Kingston, Canada; ³Queen's University, Public Health Sciences, Kingston, Canada; ⁴Queen's University, Medicine, Kingston, Canada
Email: George.philip@queensu.ca

Background and aims: Cirrhosis refers to end stage liver disease and it is the final common pathway for all chronic liver diseases (CLDs). Recent data illustrates that mortality secondary to cirrhosis is increasing in the United States (US) and is highest among young adults. Whether these trends are also occurring in Liver Transplant (LT) wait-list candidates however has not been well established. This study aimed to describe the epidemiology of LT wait-listing trends in

*Evaluated with transient elastography: F0–1 (<7, 1kPa), F2–3 (7, 1–13 kPa), F4 (>13, 1kPa)

the US over the past two decades stratified by age at listing, cirrhosis etiology, and sex.

Methods: We conducted a retrospective population-based study from 2002–2018, examining all adult LT wait-listed patients in the US. Patients ≥ 20 years at the time of LT listing were identified from the Scientific Registry of Transplant Recipients (SRTR) database. Annual standardized incidence proportions were calculated from US census data. Poisson regression was used to assess changes in the annual incidence of LT wait-listing stratified by age, sex, and cirrhosis etiology and described by incidence rate ratios (IRR).

Results: A total of 216, 936 unique individuals were included. The median age at LT wait-listing was 57 years (Range: 20–83; IQR: 51–62), with 68% being male, and 11, 312 individuals (5.2%) were <40 years at listing. The most common etiologies of cirrhosis were HCV, alcohol-related liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). The age and sex standardized incidence proportion of LT wait-listing more than doubled in both young and older adults over the study period (<40: 0.16/100, 000 in 2002 to 0.28/100, 000 in 2018; ≥ 40: 2.2/100, 000 in 2002 to 4.34/100, 000 in 2018). Using poisson regression, the etiologies with the highest annual IRR were ALD (<40: IRR 1.11, 95% CI 1.10–1.12, p < .001; ≥ 40 IRR 1.06, 95% CI 1.06–1.07, p < .001) and NAFLD (<40: IRR 1.13, 95% CI 1.10–1.15, p < .001; ≥ 40: IRR 1.16, 95% CI 1.15–1.16, p < .001). The rate of waitlisting for ALD in young females was higher than males (IRR 1.11, 95% CI 1.10–1.12, p < .001) Conversely, the listing rate for NAFLD was lower in young females compared to young males (IRR 0.97, 95% CI 0.97–0.98, p < .001).

Conclusion: The incidence of LT wait-listing is increasing in both young and older adults in the US driven primarily by ALD and NAFLD. In young adults, rates of listing are increasing most in young women with ALD and men with NAFLD. These data support ongoing efforts to identify young adults with ALD and NAFLD where public health interventions can prevent the development of cirrhosis and liver-related complications.

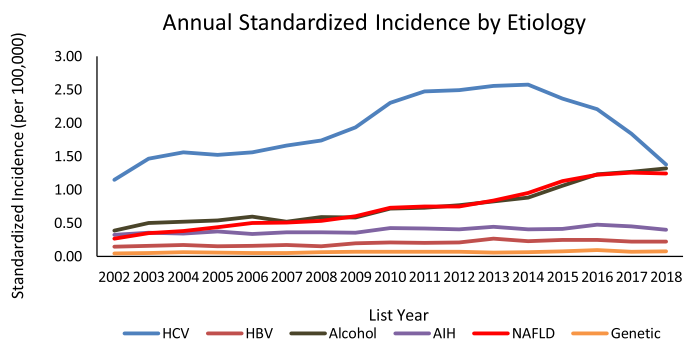


Figure:

PO-1813

General population testing for hepatitis B in Australia: a cost-effectiveness analysis

Yinzong Xiao^{1,2}, Nick Scott^{1,3}, Alexander Thompson^{2,4}, Margaret Hellard^{1,2,3}, Jess Howell^{1,4}. ¹Burnet Institute, Melbourne, Australia; ²University of Melbourne, Parkville, Australia; ³Monash University, Clayton, Australia; ⁴St. Vincent's Hospital Melbourne, Fitzroy, Australia
Email: yinzong.xiao@student.burnet.edu.au

Background and aims: In Australia, an estimated 0.9% of the population were living with chronic hepatitis B (CHB) in 2018, but only around 68% were diagnosed, well below the national and WHO targets, which are to achieve a diagnosis coverage of 80% by 2022 and 90% by 2030, respectively. Current practice of CHB testing is primarily voluntary testing promoted by symptoms or risk assessment, leading to missed opportunities of CHB diagnosis due to its asymptomatic nature, and inadequately implemented risk assessment in primary care. Testing for CHB in general population via opportunistic testing

(e.g. testing people present to a GP) may provide a viable solution. This study used a Markov model to assess the economic impacts of a general population CHB testing strategy in Australia.

Method: The model calculated costs, disability-adjusted life-years (DALYs) and incremental cost-effectiveness ratio (ICER) among people living with CHB in Australia in 2018–2030 in two scenarios compared to status quo: using a general population testing strategy to achieve 1) national diagnosis coverage target by 2022; or 2) WHO diagnosis coverage target by 2030. A healthcare funders perspective was taken; total costs include testing costs (regardless of results), implementation costs (assumed to either cost nothing if via opportunistic testing, or cost A\$85 per person screened), and direct medical costs of disease management. The general population testing strategy was assumed to have a 0.9% positive rate.

Results: Compared to status-quo, reaching the national or WHO diagnosis targets through a general population testing program (if via opportunistic testing) required an additional A\$319 million (+19%) or A\$333 million (+20%) between 2018–2030, respectively, and had ICERs of A\$37, 528 and A\$37, 541 per DALY averted, respectively. The ICERs for both scenarios remained under A\$50, 000 per DALY averted when testing positive rate was above 0.63%. If the testing program has a unit implementation cost of A\$85 per person tested, total costs increased to A\$2, 160 million and A\$2, 184 million for achieving national and WHO diagnosis coverage targets, respectively, with ICERs of A\$60, 138 and A\$60, 145 per DALY averted, but were below A\$50, 000 if the test positivity rate was above 1.12%.

Conclusion: A general population hepatitis B testing strategy is likely to be cost-effective compared with current testing practice in Australia to reach national and WHO diagnosis coverage targets.

PO-1817

Decreased hepatitis B and C testing in Ontario, Canada during the first wave of the COVID-19 pandemic

Erin Mandel¹, Adriana Peci², Kirby Cronin^{2,3}, Harry Janssen^{1,4}, Vanessa Tran^{2,5}, Mia Biondi^{4,6}, Jordan Feld^{1,4,7}. ¹University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ²Public Health Ontario Laboratory, Toronto, Canada; ³Public Health Agency of Canada, National Microbiology Laboratory, Canada; ⁴University Health Network, Viral Hepatitis Care Network (VIRCAN) Study Group, Toronto Centre for Liver Disease, Canada; ⁵University of Toronto, Department of Laboratory Medicine and Pathobiology, Toronto, Canada; ⁶Western University, Arthur Labatt Family School of Nursing, London, Canada; ⁷University of Toronto, Institute of Medical Sciences, Toronto, Canada
Email: erin.mandel@uhnresearch.ca

Background and aims: The COVID-19 pandemic has significantly disrupted care across many clinical areas with particular impact on the screening for, and management of, chronic medical conditions. We examined trends in hepatitis B (HBV) and C (HCV) testing in Ontario, Canada to determine how the first wave of COVID-19 impacted management of these chronic conditions.

Method: We extracted de-identified data from the provincial public health laboratory in Ontario, Canada for HBV and HCV testing from January 1, 2019 until August 31, 2020. Total and unique test volumes were evaluated for hepatitis B surface antigen (HBsAg), HBV DNA, HCV antibody (Ab) and HCV RNA testing stratified by age, sex, region and test indication. Prenatal HBV screening was evaluated separately. Changes in testing volumes were analysed by comparing percent and absolute changes over time.

Results: COVID-19 first emerged in Ontario in late January 2020 with near-immediate impact on health service provision. We compared testing volumes from February-August 2019 to those from February-August 2020. Compared to 2019, HCV Ab testing (screening) in 2020 decreased 30% and HCV RNA testing decreased 36%. Pre-treatment HCV RNA testing decreased by 43% and post-treatment sustained virologic response testing decreased by 36%. For HBV, HBsAg testing decreased 29% and HBV DNA testing by 33%. While pre-treatment HBV DNA decreased by 38%, on-treatment monitoring decreased by

only 14%. Trends were consistent when testing volumes were stratified by age, region, and sex; however, prenatal HBV testing volumes remained stable. Test volumes for all tests were increasing prior to 2019 with increased awareness of viral hepatitis elimination targets. No non-prenatal test type returned to pre-pandemic levels by August 2020, recovering to 75% for HCV Ab, 64% for HCV RNA, 77% for HBsAg and 82% for HBV DNA compared to tests in 2019.

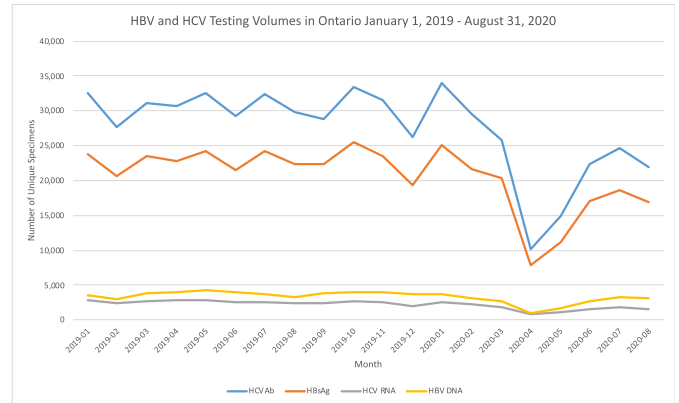


Figure:

Conclusion: Significant decreases in HBV and HCV testing occurred in Ontario during the first wave of the COVID-19 pandemic. Screening for HCV as well as pre- and post-treatment RNA testing were greatly affected and did not return to pre-pandemic testing levels by the end of the first wave. HBV screening and pre-treatment testing were similarly reduced, but HBV on-treatment monitoring was not as severely impacted. Strategies to maintain and ultimately increase screening, diagnosis and treatment initiation will be required to ensure the pandemic does not derail progress toward viral hepatitis elimination in Canada.

PO-1862

Predictors of loss to follow-up in an outpatient cirrhotic population

Joana Vieira Barbosa^{1,2}, Qua Tran³, Brian Malinn¹, Rosa L. Yu⁴, Michael Curry¹, Michelle Lai¹. ¹Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology and Hepatology, Boston, United States; ²Lausanne University Hospital and University of Lausanne, Division of Gastroenterology and Hepatology; ³Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Pharmacy Department, Boston, United States; ⁴Beth Israel Deaconess Medical Center, Harvard Medical School, Department of Internal Medicine, Boston, United States
Email: jvieirab@bidmc.harvard.edu

Background and aims: Cirrhosis is a major cause of morbidity and mortality with an increasing burden over the last decades. Due to the high risk of liver-related complications, periodic surveillance is key in the management of these patients. However, adherence to surveillance programs is suboptimal and measures to anticipate loss to follow-up (LTFU) are lacking. The aim of our study was to investigate the factors associated with loss to FU in an outpatient cirrhotic population, screened in a tertiary liver center.

Method: We analyzed data from all adult patients with cirrhosis evaluated in the Beth Israel Deaconess Medical Center outpatient Liver Clinic from 2018 to 2020. Patients with cirrhosis were identified from our internal electronic database, using International Classification Diseases-10 codes. Deceased patients or those with a previous diagnosis of hepatocellular carcinoma (HCC) were excluded. The outcome of interest was LTFU, defined as the absence of liver appointment and/or abdominal ultrasound in the last 9 months. Analysis was performed using logistic regression and results were reported as odds ratio (OR) and 95% confidence interval (95% CI).

POSTER PRESENTATIONS

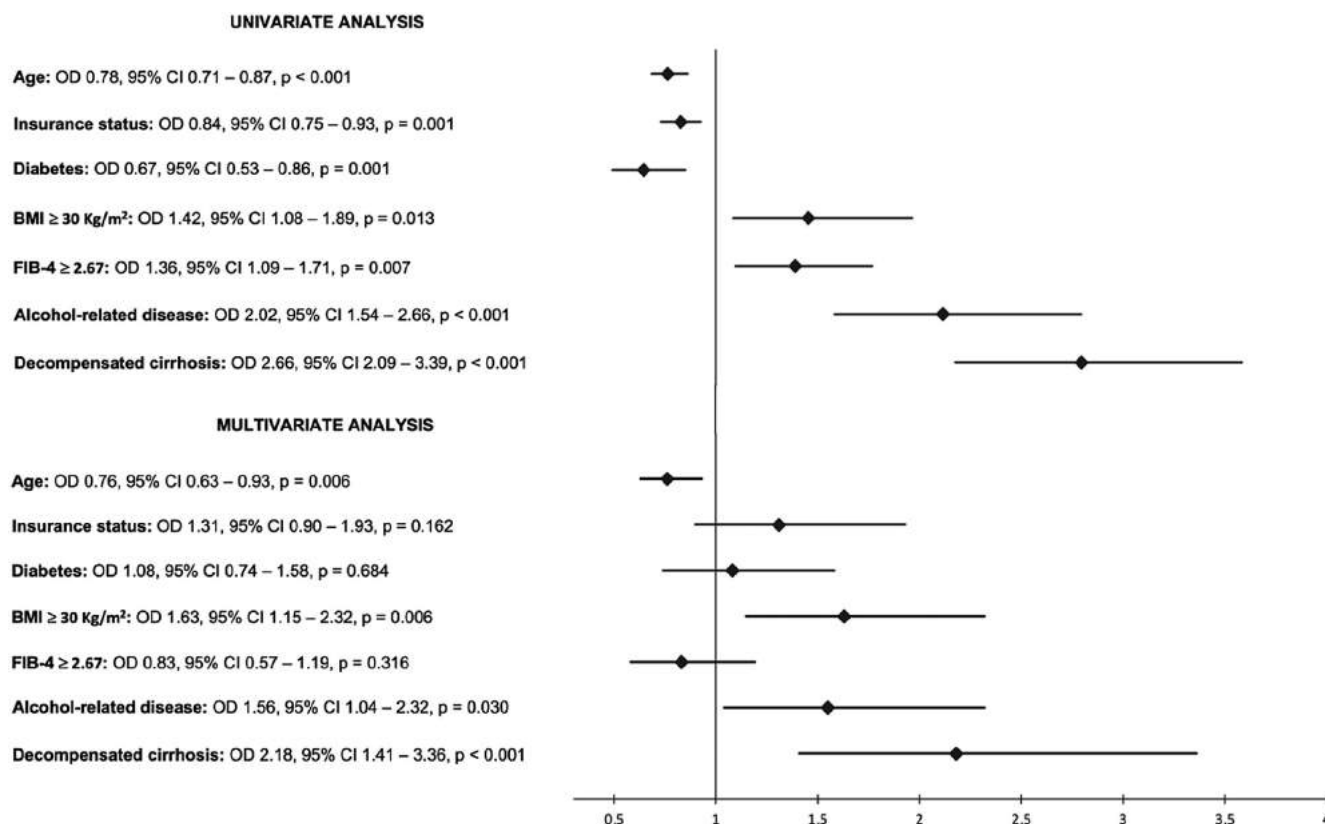


Figure: (abstract: PO-1862)

Results: Of 1742 consecutive adult patients with cirrhosis (57% male, mean age 61 ± 12 years), 461 (26.5%) were LTFU. Patients LTFU were younger (mean age: 59 vs 62 years, p < 0.001), more likely to be obese (BMI ≥ 30 kg/m²: 50% vs 41%, p = 0.013), have alcohol-related cirrhosis (46% vs 29%, p < 0.001), and have decompensated cirrhosis (34% vs 16%, p < 0.001) compared to patients without LTFU. In univariate analysis, clinical factors significantly associated with LTFU included age, insurance status, diabetes, BMI ≥ 30 kg/m², FIB-4 score ≥ 2.67, alcohol-related cirrhosis and decompensated cirrhosis. In multivariate logistic regression including all the above clinical factors, only younger age (OR 0.76, 95% CI 0.63–0.93, p = 0.006), BMI ≥ 30 kg/m² (OR 1.63, 95% CI 1.15–2.32, p = 0.006), alcohol-related cirrhosis (OR 1.56, 95% CI 1.04–2.32, p = 0.030) and decompensated cirrhosis (OR 2.18, 95% CI 1.41–3.36, p < 0.001) independently, significantly predicted LTFU (Figure 1).

Conclusion: In a large population of patients with cirrhosis, younger age, obesity, alcohol-related cirrhosis and liver decompensation were significant predictors of LTFU. Implementation of a targeted intervention program in this high-risk population to optimize surveillance rates and management is warranted.

PO-1877

Feasibility, effectiveness, and lessons learned from the introduction of decentralised HCV testing and treatment at primary healthcare clinics in three regions in Malaysia

Sonjelle Shilton¹, Jessica Markby¹, Xiaohui Sem¹, Sasikala Siva², Rozainanee Binti Mohd Zain³, Caroline Menetrey², Fazidah Binti Yuswan⁴, Nazrila Hairizan Binti Nasir⁴, Isabelle Andrieux-Meyer², Philippa Easterbrook⁵, Muhammad Radzi Abu Hassan⁶. ¹Foundation for Innovative New

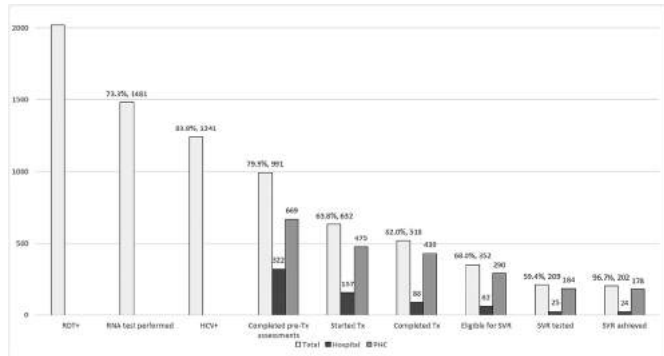
Diagnosics; ²Drugs for Neglected Diseases initiative; ³Institute for Medical Research; ⁴Ministry of Health Malaysia; ⁵World Health Organization; ⁶CRC Hospital Sultanah Bahiyah
Email: sonjelle.shilton@finddx.org

Background and aims: To achieve the global targets for elimination of hepatitis C virus (HCV), substantial scale-up in access to testing and treatment is needed. This will require decentralisation of testing and treatment to primary care settings and task-shifting to non-specialists. A Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) study was carried out in Malaysia to evaluate the feasibility and effectiveness of decentralised HCV testing using rapid diagnostic tests (RDTs) and treatment in primary healthcare clinics (PHCs) among high-risk populations.

Method: This observational study was conducted between December 2018 and December 2019 at 25 PHCs in three regions. Patients were tested based on routine clinical indications for an HCV test, in accordance with national guidelines. Each PHC was linked to one or more hospitals, for referral of patients for confirmatory testing, pre-treatment assessment bloods and a FibroScan to assess the presence of cirrhosis. Confirmation of HCV viremia by RNA testing was performed on plasma samples sent from hospitals to a reference laboratory in Kuala Lumpur using the Roche cobas® 4800 HCV assay. The majority of non-cirrhotic patients were referred back to PHCs for treatment.

Results: A total of 15366 adults were screened at the 25 PHCs during the study period. Of the 2020 HCV antibody-positive, 73.3% (1481/2020) had a confirmatory viral load test, 83.8% (1241/1481) were HCV RNA-positive, 79.9% (991/1241) completed pre-treatment assessments, 63.8% (632/991) had treatment initiated, 82.0% (518/632) completed treatment, 68.0% (352/518) were eligible for a sustained virological response (SVR) cure assessment, 59.4% (209/352) had a SVR cure assessment, and SVR was achieved in 96.7% (202/209)

patients. There were significant differences in treatment initiation (71.0%, 475/669 versus 48.8%, 157/322; $p < 0.001$) and treatment completion (90.5%, 430/475 versus 56.1%, 88/157; $p < 0.001$) according to whether patients were treated at PHCs or at hospitals respectively. Comparable SVR rates ($>95\%$) were achieved in those treated at PHCs and at hospitals.



RDT, rapid diagnostic test; SVR, sustained virological response; Tx, treatment

Figure:

Conclusion: This study demonstrated the effectiveness and feasibility of a simplified decentralised HCV testing and treatment model in primary healthcare settings, targeting high-risk groups in Malaysia. There were good outcomes across the cascade of care, and decentralisation of treatment at PHCs improved uptake and completion of treatment.

PO-1903

SEAL program-Early detection of liver fibrosis and cirrhosis by screening of the general population

Nagel Michael¹, Anita Arslanow¹, Marc Nguyen-Tat¹, Marcus-Alexander Wörns¹, Matthias Reichert², Franz Josef Heil³, Dagmar Mainz³, Gudula Zimmer⁴, Burkhard Zwerenz⁵, Johannes Jäger⁶, Harald Binder⁷, Erik Farin-Glattacker⁷, Bogatyreva Lioudmila⁷, Fichtner Urs⁷, Graf Erika⁷, Stelzer Dominikus⁷, Reyn van Ewijk⁸, Julia Ortne Dr.⁹, Louis Velthuis⁹, Frank Lammert², Galle Peter R.¹ Prof. Dr.¹Department of Internal Medicine I, University Medical Center Mainz, Mainz, Germany; ²Saarland University Medical Center, Department of Internal Medicine II; ³German Gastroenterology Association (bng); ⁴General Practitioners' Association Saarland, Germany; ⁵General Practitioners' Association Rhineland-Palatinate, Germany; ⁶Saarland University, Center for General Medicine; ⁷University of Freiburg, Institute of Medical Biometry and Statistics; ⁸Johannes Gutenberg University Mainz, Department of Economics; ⁹Johannes Gutenberg University Mainz, Department of Controlling
Email: michael.nagel@unimedizin-mainz.de

Background and aims: Most patients with liver cirrhosis are detected at a late stage of their disease. In approximately 75%, diagnosis is based on the development of complications such as ascites or bleeding. At this stage causative treatment interventions are less successful or impossible. Screening for liver health and disease is not included in standard medical check-up programs. The SEAL program (Structured Early Detection of Asymptomatic Liver Cirrhosis) investigates the feasibility, effectiveness and cost-benefit assessment of a general screening for liver fibrosis and cirrhosis.

Method: As part of the SEAL program, 16, 000 insured persons from a large German health insurance company will be offered additional testing of liver enzymes as part of a nationwide primary care program (check-up 35) in two German states, i.e. Rhineland-Palatinate and Saarland. In case of elevated transaminases, the APRI score as a liver fibrosis risk score is calculated. If the APRI score is suggestive for liver disease, patients are referred to a gastroenterologist for further differential diagnostic assessment. Patients suspected to have relevant liver fibrosis are referred to a liver center for further hepatologic workup. End points include data on the epidemiology of

elevated liver enzymes, cost-benefit assessments and prevalence of liver fibrosis in a general population.

Results: To date, more than 12000 patients have been enrolled. The average age of patients is 62 years. Of the examined patients, 11% and 6% presented with increased ALT and AST values with a maximum of 3828 U/l and 434 U/l, respectively. In 499 patients a known liver disease was already present at inclusion. Nevertheless, 11% of patients without known liver disease had pathologically elevated transaminases. 307 patients showed elevated transaminases and a conspicuous APRI score above 0.5, 76% of whom had no known liver disease. Up to now, referral for further diagnostics has been initiated in 245 patients

SEAL Program – Diagnostic Algorithm

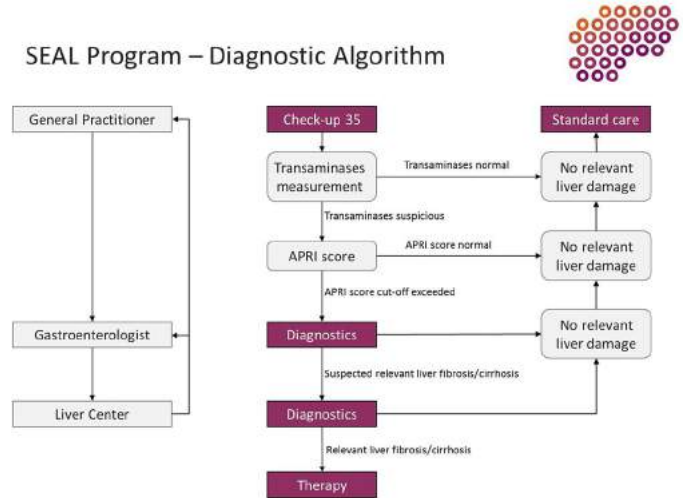


Figure:

Conclusion: The establishment of an early diagnosis of liver diseases is controversially discussed by professionals and in the literature. The initial data indicates that a relevant group of the population suffers from an increase in transaminases. The SEAL project will provide further data on feasibility, effectiveness and cost-benefit assessment in the German health care system and will contribute substantial evidence to the meaningfulness of such a measure.

PO-1936

A global systematic review of efforts to accelerate the elimination of hepatitis C virus (HCV) through micro-elimination

Jeffrey Lazarus¹, Camila Picchio¹, Christopher Byrne², Javier Crespo³, Massimo Colombo⁴, Graham Cooke⁵, Gregory Dore⁶, Jason Grebely⁶, John Ward⁷, Trenton White¹, John Dillon^{2,8}. ¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain; ²Division of Molecular and Clinical Medicine, University of Dundee School of Medicine, Ninewells Hospital, Dundee, United Kingdom; ³Gastroenterology and Hepatology Department, University Hospital Marques de Valdecilla. Research Institute Valdecilla-IDIVAL, Santander, Spain; ⁴Department of Medicine, Humanitas Hospital, Rozzano, Italy; ⁵Division of Infectious Diseases, Faculty of Medicine, Imperial College London, London, United Kingdom; ⁶The Kirby Institute, UNSW Sydney, Sydney, Australia; ⁷Coalition for Global Hepatitis Elimination, The Task Force for Global Health, Atlanta, United States; ⁸Department of Gastroenterology, Ninewells Hospital and Medical School, Dundee, United Kingdom
Email: Jeffrey.Lazarus@isglobal.org

Background and aims: Despite the availability of highly effective therapies, many countries have yet to develop programmes to reach the targets for hepatitis C virus (HCV) elimination. Micro-elimination aims to reduce this gap through targeted efforts among specific sub-populations. This review reports on the effectiveness of the micro-elimination approach, which population cohorts were targeted most frequently by micro-elimination initiatives, and to evaluate to what

POSTER PRESENTATIONS

extent the initiatives reported follow the criteria proposed for a successful micro-elimination approach to HCV.

Method: A search of the published literature was carried out in PubMed/Medline between 2013 and 2020. A grey literature search and manual search of relevant conference abstracts between 2017–2019 was performed. Inclusion criteria included studies published after 2013 with measurable outcomes that were published in English or Spanish where the main objective of the study was micro-elimination in a specific sub-population. Reviews and mathematical modelling studies were excluded. Data from publications that met the inclusion criteria were extracted and summarised based on the four criteria defining HCV micro-elimination: having a plan, the presence of achievable time-bound targets, a multistakeholder process, and ongoing monitoring.

Results: Thirty published manuscripts met the inclusion. The majority (80%) of studies came from high-income settings (Figure), included persons who are incarcerated (26%) or people who use drugs (16%), and 86% reported at least three out of four of the key components of micro-elimination. A total of 93% of the manuscripts included a clear plan for achieving micro-elimination in their intended target population and reported monitoring their outcomes. Twenty-six manuscripts reported treatment outcomes in the study population to calculate the sustained virologic response (SVR), which ranged from 15% to 100% with a median SVR of 86.5% in the included manuscripts.

Conclusion: Micro-elimination is a strategic approach to achieving the WHO elimination targets that should be adapted to local contexts and epidemiological profiles. Despite the demonstrated effectiveness of this approach in several settings, we found little published data on micro-elimination efforts, particularly in low- and middle-income countries. Existing literature highlights the micro-elimination interventions that can be scaled-up to eliminate HCV in target sub-populations and help launch national programmes.

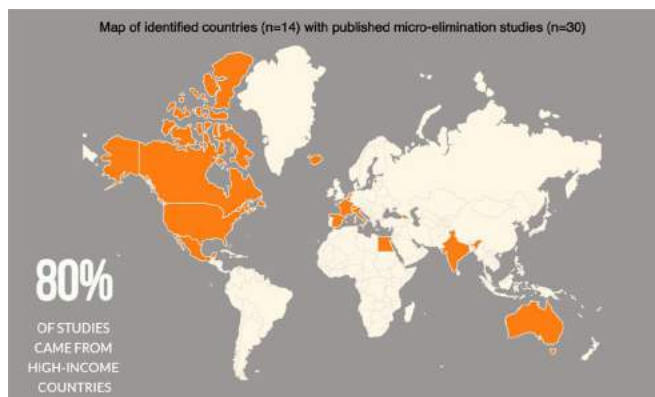


Figure:

PO-1990

The unmet needs of living with non-alcoholic steatohepatitis (NASH) in Europe and Canada: results from a multi-country survey

Jeffrey Lazarus¹, Fabienne Marcellin², Camelia Protopopescu², Aldo Trylesinski³, José Luis Calleja Panero⁴, Carrieri Patrizia².

¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain; ²Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France; ³Intercept Pharmaceuticals, London, United Kingdom; ⁴Liver Unit, Puerta de Hierro University Hospital, Universidad Autonoma de Madrid, CIBERehd, Madrid, Spain

Email: Jeffrey.Lazarus@isglobal.org

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is increasing worldwide and trends are closely related to those of obesity epidemics. Non-alcoholic steatohepatitis (NASH) is

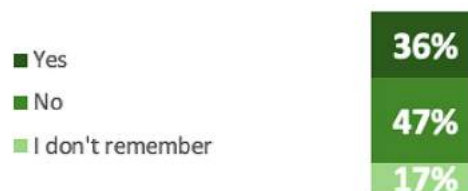
characterized by the presence of inflammation, ballooning and steatosis. The strongest driver of clinical outcomes is fibrosis, present in ~85% of NASH and 10% of NAFLD patients. Currently, healthier lifestyles and multidisciplinary care can improve the prognosis. Little is known about patients' knowledge of and experience with NASH and related care. We conducted a multi-country survey to better document NASH patients' knowledge, care, expectations and unmet needs.

Method: We recruited 1411 adults with NASH in Canada, France, Germany, Italy, Spain and the United Kingdom (UK), who were registered on the online patient community platform Carecity. Participants were invited to answer a questionnaire detailing their knowledge of and experience with NASH and related care. The dataset was weighted to enable inter-country comparison.

Results: The number of participants (54% men) per country ranged from 218 (Italy) to 276 (UK). Sex-age distributions were similar across all countries. Twenty-three percent of the participants reported feeling overwhelmed when diagnosed with NASH. Despite 19% reporting 3 or more comorbidities, 61% did not know their liver fibrosis status and 30% reported that it had been over a year since their last fibrosis assessment (Figure). Seventy-one percent of those without comorbidities thought their NASH was at an early stage. Even if 88% of participants were recommended lifestyle changes by their physician to manage NASH, only 14% reported being able to fully adhere to these. Thirty-two and 34% reported little to no understanding about liver fibrosis or cirrhosis consequences, respectively and 57% reported having little to no understanding of the signs indicative of deteriorating NASH. Only 14% reported having a good understanding of how NASH progresses over time.

Conclusion: Despite the negative clinical outcomes of NASH, patients' information about the disease, its associated risks and management were found to be very insufficient. Conducting multi-target campaigns to inform healthcare professionals and people at potential risk about the importance of regular screening and promoting patient educational programmes to support behavioural changes to prevent NAFLD progression should be urgently included in the international clinical and public health agenda.

Patient recall of physician's explanation of fibrosis stages



Time since last fibrosis stage check

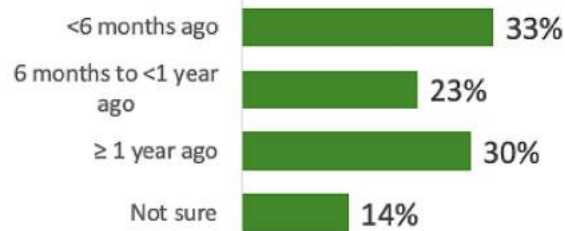


Figure:

PO-2014

The emergency department, a new setting for HBV screening in populations with limited linkage to the health care system in a high-income country

Jordi Llaneras¹, Ana Barreira², Ariadna Rando Segura³, Juan Bañares⁴, Beatriz Meza¹, Lourdes Ruiz⁴, Joana Rita Marques⁴, Arnau Monforte⁴, Olimpia Orozco¹, Mar Riveiro Barciela^{2,5}, Fernando Rodrigo-Velásquez³, Francisco Rodríguez-Frías³, Maria Arranz¹, Rafael Esteban^{2,5}, Maria Buti^{2,5}. ¹Emergency Department, Hospital Vall Hebron, Barcelona, Spain; ²Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; ³Biochemistry and Microbiology Department, Hospital Vall Hebron, Barcelona, Spain; ⁴Department of Internal Medicine, Hospital Vall Hebron, Barcelona, Spain; ⁵Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain
Email: jllaneras@vhebron.net

Background and aims: Universal vaccination against hepatitis B virus (HBV) has led to a significant reduction in hepatitis B-related complications. Despite this, there is still a significant number of people with HBsAg infection who are diagnosed at late stage of the disease. The emergency department (ED) offers the possibility of HBV screening, especially in population limited linkage to health care system.

Method: Prospective single-centre study in academic hospital involving screening and linkage to specialty care of hepatitis B. HBsAg screening was performed in individuals (>16 years) presenting to the ED requiring phlebotomy for medical reasons.

Results: Of the 7, 259 patients who were screened during one year (Feb-20 to Feb-21) in the ED, 43 (0.6%) patients were HBsAg positive. The median age was 64 years and 67% were male. Baseline characteristics of HBsAg positive patients are shown in the table. Risk factors for HBV infection were observed in less than 5% of cases and the majority (97%) were HBeAg negative. There were no cases of HIV, HCV or HDV co-infection. Caucasian race (81%) was predominant followed by African American (8%). Sixteen (37%) subjects were unaware of their infected status. Twenty-two (81%) patients with known HBV infection were already followed-up by a Liver specialist, and the remaining 5 (19%) had abandoned controls. No HBsAg-positive patients aged <40 years were born in Spain, country with an established HBV vaccination program in newborns and adolescent. The 3 cases HBsAg positive <40 years were from Sub-Saharan Africa and Eastern Europe. 14 (33%) patients had cirrhosis assessed by FIB-4 >3.25. Ten of new diagnosis patients were linked to care. Patients who were not referred were due to low life expectancy, severe cognitive impairment, or severe social problems.

Figure:

	HBsAg positive (N = 43)
Male, n (%)	29 (67%)
Age (years), Md (IQR)	67 (52–81)
Caucasian, n (%)	35 (81%)
PWID, n (%)	1 (2%)
Alcohol consumption, n (%)	7 (16%)
Prior transfusion of blood products, n (%)	2 (5%)
Surgical interventions in childhood, n (%)	4 (9%)
Psychiatric disorder, n (%)	9 (21%)
Patients' infection unawareness, n (%)	15 (35%)
ALT (U/L), Md (IQR)	24 (14–36)
MELD-NA, Md (IQR)	11 (9–16)
FIB-4, Md (IQR)	2.02 (1.21–4.35)
Late diagnosis (FIB-4 >3.25), n (%)	14 (33%)
Fibrosis F3-F4, n (%)	7 (24%)
HBeAg, n (%)	1 (29%)
antiHDV, n (%)	0 (0%)
Patients with new diagnosis referred to hepatologist, n (%)	10 (23%)

Conclusion: Despite vaccination programs, HBsAg persists in general population as a silent infection, mainly in those groups with limited access to the Health Care system. Current migratory movements favour the re-emergence of HBV infection in young patients in the absence of new-born vaccination programs. Screening for HBV infection in emergency departments can be a useful tool to rescue patients with unknown HBV infection and ensure appropriate follow-up.

PO-2032

Disclosure of non-alcoholic steatohepatitis (NASH) diagnosis and fear of discrimination: results from a multi-country survey

Jeffrey Lazarus¹, Fabienne Marcellin², Achim Kautz³, Vanessa Hebditch⁴, Aldo Trylesinski⁵, José Luis Calleja Panero⁶, Carrieri Patrizia². ¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain; ²Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France; ³UG, Cologne, Germany; ⁴British Liver Trust, Bournemouth, United Kingdom; ⁵Intercept Pharmaceuticals, London, United Kingdom; ⁶Liver Unit, Puerta de Hierro University Hospital, Universidad Autonoma de Madrid, CIBERehd, Madrid, Spain
Email: Jeffrey.Lazarus@isglobal.org

Background and aims: People with non-alcoholic steatohepatitis (NASH) may experience stigma and discrimination, not only due to co-occurrence of stigmatised conditions such as obesity, diabetes and poor social conditions, but also because of possible representations of this liver disease, often erroneously related to unhealthy alcohol use. We conducted a multi-country survey to better document how and to what extent people living with NASH disclose their diagnosis.

Method: We enrolled 1411 adult individuals with NASH in Canada, France, Germany, Italy, Spain and the United Kingdom (UK). Participants completed an online questionnaire that collected data on their experience with their disclosure of NASH diagnosis and fear of discrimination. To enable inter-country comparisons, the dataset was weighted-with respect to a general distribution-by age and gender of people with NASH.

Results: The number of participants per country ranged from 218 (Italy) to 276 (UK). Most participants were men (54%). A fifth (19%) reported three or more comorbidities, and 32% reported insufficient understanding about liver fibrosis consequences. Three in four (74%) felt confident about explaining how lifestyle changes can impact the development of cirrhosis. In terms of how well they were able to explain their disease to others, 17%, 48% and 37% reported not at all well, quite well and very well, respectively. With regard to NASH diagnosis disclosure, 84% reported disclosing it to their close family, 61% to friends, 32% to co-workers and 25% to their supervisor. However, only 41% felt comfortable speaking about NASH with their family. As for the fear of alcohol-related discrimination, very few (13%) reported avoiding the term “non-alcoholic” when speaking about NASH.

Conclusion: Overall, people diagnosed with NASH disclosed their disease to others, even in the workplace, and did not avoid associating it with alcohol use when referring to it. Considering the prevalence of overweight/obesity in NASH patients in the countries included, a NASH diagnosis may change their self-identity from a person living with a physically stigmatised condition to one living with liver disease. As lifestyle changes remain difficult for people with NASH, multidisciplinary care and therapeutic education are needed to reverse the course of the disease.

POSTER PRESENTATIONS

PO-2039

Anticipated timing of hepatitis C virus elimination in the Netherlands and the impact of COVID-19

Marleen van Dijk¹, Sylvia Brakenhoff², Cas J. Isfordink^{3,4}, Wei-Han Cheng⁵, Robert De Knecht², Sophie Willems⁶, Marc van der Valk⁴, Joost Ph Drenth¹. ¹Radboudumc, Gastroenterology and Hepatology, Nijmegen, Netherlands; ²Erasmus Medical Centre, Rotterdam, Netherlands; ³University Medical Centre Utrecht, Gastroenterology and Hepatology, Utrecht, Netherlands; ⁴Amsterdam Infection and Immunity Institute, Amsterdam University Medical Centre, Amsterdam, Netherlands; ⁵Abbvie Pharmaceuticals, Health Economics and Outcomes Research, Chicago, United States; ⁶Amsterdam University Medical Centre, Gastroenterology and Hepatology, Amsterdam, Netherlands

Email: marleen.vandijk@radboudumc.nl

Background and aims: The Netherlands has committed itself to eliminate hepatitis C virus (HCV) infection, according to the World Health Organization (WHO) elimination targets. A recent analysis suggested that elimination will only be reached by 2035 in the Netherlands. Recently, a nationwide HCV elimination project (CELINE) has harvested new data on the Dutch HCV epidemic. Therefore, this study aims to provide an updated analysis on elimination progress in the Netherlands.

Method: A previously published Markov model was used to map the path to HCV elimination. Prevalence data from 2016, treatment data from 2000–2019 and unpublished CELINE data were used as inputs. In the “Status Quo” scenario, we assumed a 10% decrease in diagnosis and treatment levels in 2020, as compared to 2019. From 2021 onwards, diagnosis and treatment levels stayed constant. In the “Gradual Decrease” scenario, starting in 2020, we assumed an annual decrease of 10% in both diagnoses and treatments. Finally, a two-year delay in elimination as a result of COVID-19 was modelled. We assumed a decrease of 42% in both diagnosis and treatment levels for 2020 and 2021. We anticipated that these levels would either rise again to “Status Quo” values in 2022 and remain constant afterwards (“Two-year COVID-19 Delay”), or would increase to “Status Quo” values in 2022, followed by an annual decrease of 10% (“Post-recovery Gradual Decrease”). WHO mortality, diagnosis, and treatment targets for 2030 were considered; the incidence target was disregarded, due to the very low incidence in the Netherlands (≤ 5 per 100,000).

Results: Following the “Status Quo” and “Gradual Decrease” scenarios, the Netherlands would reach the WHO targets by 2027 and 2032, respectively. The “Two-year COVID-19 Delay” would result in elimination by 2028, and the “Post-recovery Gradual Decrease” scenario would result in elimination by 2030 (see Table). The annual number of treatments needed in 2020–2030 was 381.

Conclusion: The Netherlands is on track to reach HCV elimination by 2030. COVID-19 does not seem to have a profound impact on the WHO HCV elimination goals. This might be because HCV incidence is so low and because the threshold of 381 annual treatments is more than met in the majority of years. It is, however, vital that HCV elimination remain high on the agenda.

Figure:

Year of achieving WHO elimination target	Status Quo	Gradual Decrease	Two-year COVID-19 Delay	Post-recovery Gradual Decrease
Liver-related mortality	2020	2020	2022	2022
Diagnosis	2027	2032	2028	2030
Treatment	2026	2028	2026	2027

PO-2047

HCV screening of immigrants at arrival: an opportunity to linkage to care of a population with limited access to health care system

Mar Riveiro Barciela^{1,2,3}, Begoña Treviño⁴, Nuria Serre⁴, Ariadna Rando Segura^{5,6}, Fernando Salvador⁴, Ana Barreira^{1,3}, Adriana Palom^{1,7}, Elena Vargas Accarino^{1,7}, Diana Pou⁴, Luisa Roade^{1,2,3}, Israel Molina⁴, Francisco Rodríguez-Frías⁵, Maria Buti^{1,2,3}. ¹Universitat Autònoma de Barcelona, Department of Medicine; ²Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBEREHD); ³Hospital Universitario Vall d'Hebron, Liver Unit, Department of Internal Medicine; ⁴Vall d'Hebron-Drassanes PROSICS Barcelona, Tropical Medicine and International Health Unit; ⁵Hospital Universitario Vall d'Hebron, Biochemistry and Microbiology Department; ⁶VHIR-Vall d'Hebron Institut de Recerca; ⁷VHIR-Vall d'Hebron Institut de Recerca, Liver Unit

Email: mar.riveiro@gmail.com

Background and aims: Several studies have shown that the prevalence of Hepatitis C virus (HCV) is higher in immigrants than autochthonous population. Besides migrants have a limited access to the Health Care system. Centers that attend these subjects at their arrival could play an important role in the HCV screening and the linkage to care of these individuals.

Method: All migrants attending the Drassanes Center that runs the International Health Program of Catalonia Health Institute were tested for anti-HCV antibodies between January and December 2020. In anti-HCV-positive serum samples, a reflex HCV-RNA test was automatically performed. HCV-RNA-positive subjects were evaluated by the Liver Unit for assessment of antiviral therapy

Results: HCV screening was carried out in 820 individuals: 60.7% were male, mean age 33 ± 14 years. The vast majority (99.4%) of individuals were not aware of their HCV status. The anti-HCV prevalence was 2.1% (18 cases), with 4 (25%) out of 16 subjects testing positive for HCV-RNA (0.49% of the overall cohort). Most prevalent origin of screened subjects and the prevalence of anti-HCV by regions were: East Europe (Number of tested subjects = 23, rate of anti-HCV positivity = 13%), Southern Asia (72, 8.3%), Central Africa (48, 8.3%), West Africa (119, 1.7%), Central America (71, 1.4%), North Africa (122, 0.8%), South America (248, 0.4%), Central Europe (112, 0%), and Western Asia (17, 0%). Countries with the highest rate of anti-HCV antibodies were: Ukraine (2/8, 25%), Equatorial Guinea (4/28, 14.3%) and Pakistan (5/48, 10.4%). In the figure countries with screened individuals and with positive anti-HCV patients are summarized. Only 4 (22%) HCV-positive individuals were aware of the HCV infection. Anti-HCV prevalence differed according to the region of origin ($p < 0.001$) and baseline AST (46 vs 28, $p = 0.01$), though age (33.7 vs 33.4, $p = 0.91$), male sex (66.7% vs 60.6%, $p = 0.40$), mean ALT (41 vs 26, $p = 0.261$), platelets (265 vs 262, $p = 0.84$), APRI (0.49 vs 0.31, $p = 0.215$) and FIB-4 score (1.11 vs 0.8, $p = 0.206$) were similar. All 4 HCV-RNA-positive individuals are currently under therapy and to date the adherence has been high.

Conclusion: Screening of HCV at arrival allows to detect a high rate of HCV infections in migrant population from Central Asia, Sub-Saharan Africa and Eastern Europe. The majority of them were unaware of HCV infection. Despite that, adherence to linkage to care is high.

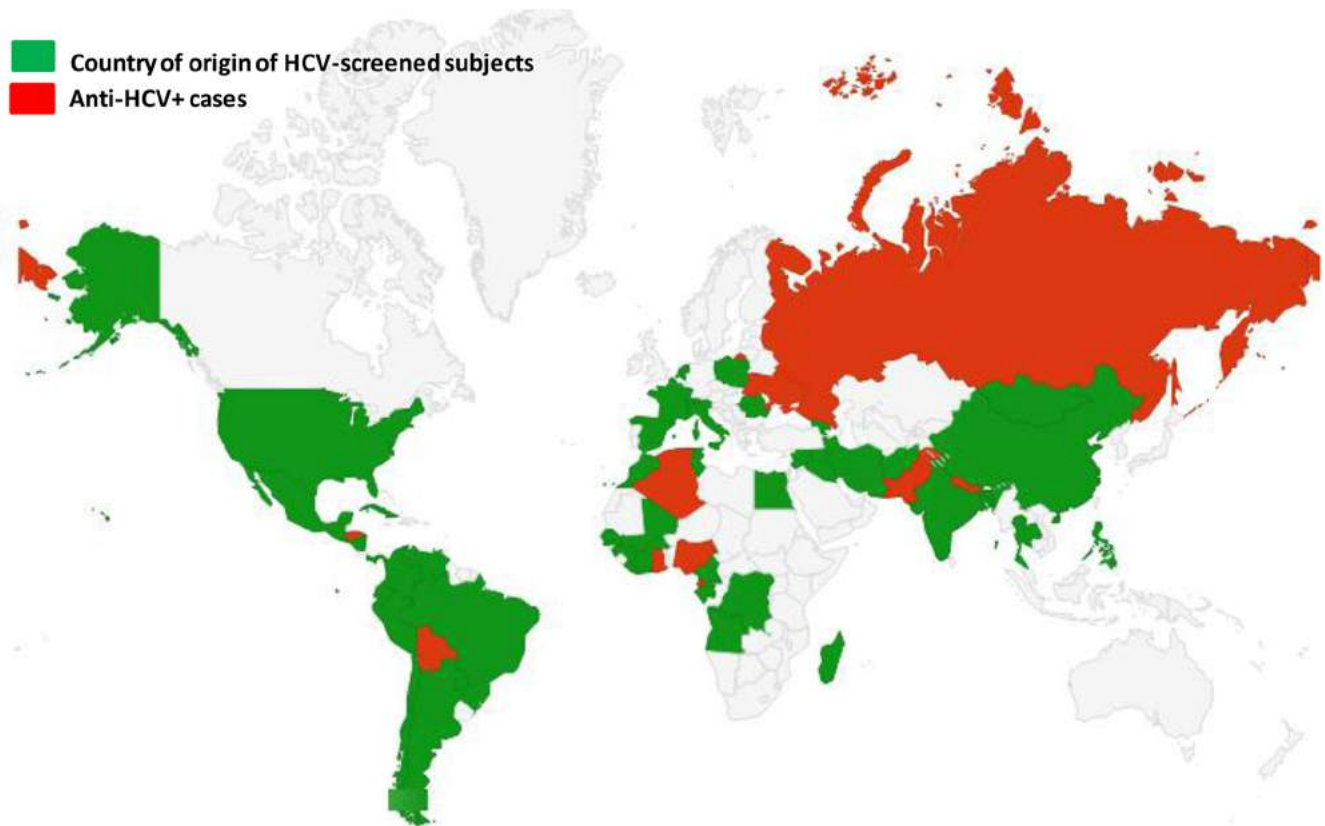


Figure: (abstract: PO-2047)

PO-2059
Characterizing stigma related to non-alcoholic fatty liver disease (NAFLD) and obesity: a Twitter discourse analysis

Jeffrey Lazarus¹, Shira Zelber-Sagi^{2,3}, Christine Kakalou⁴, Adam Palayew⁵, Christina Karamanidou⁴, Christos Maramis⁴, Pantelis Natsiavas⁴, Marcela Villota¹, Camila Picchio¹, Carrieri Patrizia⁶. ¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain; ²Department of Gastroenterology Tel Aviv Medical Center, Tel Aviv, Israel; ³School of Public Health, University of Haifa, Haifa, Israel; ⁴Institute of Applied Biosciences, Centre for Research and Technology Hellas, Thessaloniki, Greece; ⁵McGill Department of Epidemiology, Biostatistics, and Occupational Health, Montreal, Canada; ⁶Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France
 Email: Jeffrey.Lazarus@isglobal.org

Background and aims: Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are stigmatised conditions, partly due to “non-alcoholic” being in the name, but also because obesity is the most common comorbidity. Stigma is pervasive in social media and can contribute to reduced care-seeking and poorer health outcomes for those with NAFLD and NASH. We examined how stigma concerning NAFLD, NASH and obesity manifest on the social media platform Twitter.

Method: We retrieved Twitter data from May to December 2019 by using self-developed software and lexicon for NAFLD, NASH and stigmatising obesity terms. Next, three experts independently annotated a random data sample. We initially identified stigma and

obesity tweets that intersected with NAFLD/NASH, but due to the limited number of posts identified, we conducted a secondary analysis with a new subset of data with tweets only referring to obesity. Over 5, 000 tweets of the obesity dataset were annotated as either positive, neutral or negative (stigmatising); this corpus was used as a training set for a self-made Natural Language Processing software, which was used to identify sentiment clusters on 193, 747 randomly sampled tweets, exploiting a machine learning approach.

Results: After omission of tweets that were not in English (<10%), we retrieved 16, 835 tweets for NAFLD and 2, 376 for NASH from around the world (Figure). Upon sampling a subsection of these tweets (1, 130 for NAFLD and 535 for NASH), we found that there was limited NAFLD and NASH discourse on Twitter relating to obesity (NAFLD: 14.1%; NASH: 8.0%) and stigma (NAFLD: 2.2%; NASH: 0.5%) and that, overall, tweet content involved scientific discourse (NAFLD: 11.8%; NASH: 16.7%) and general liver information (NAFLD: 43.5%; NASH: 24.8%). By contrast, for the analysis of the 193, 747 classified obesity tweets, the algorithm classified 40% of tweets as relevant and, of this group, 85.2% were negative (stigmatising), 13.7% were neutral and 1.0% were positive.

Conclusion: NAFLD related tweets mostly indicate an unmet need for information. The stigmatising content of tweets related to obesity was frequent and its dissemination on social media can exacerbate stigmatising attitudes. As obesity-related stigma is associated with reduced engagement in care and lifestyle modification, which is the recommended treatment for NAFLD, interventions to further investigate and potentially reduce stigma in social media should be included in the liver health agenda.

POSTER PRESENTATIONS

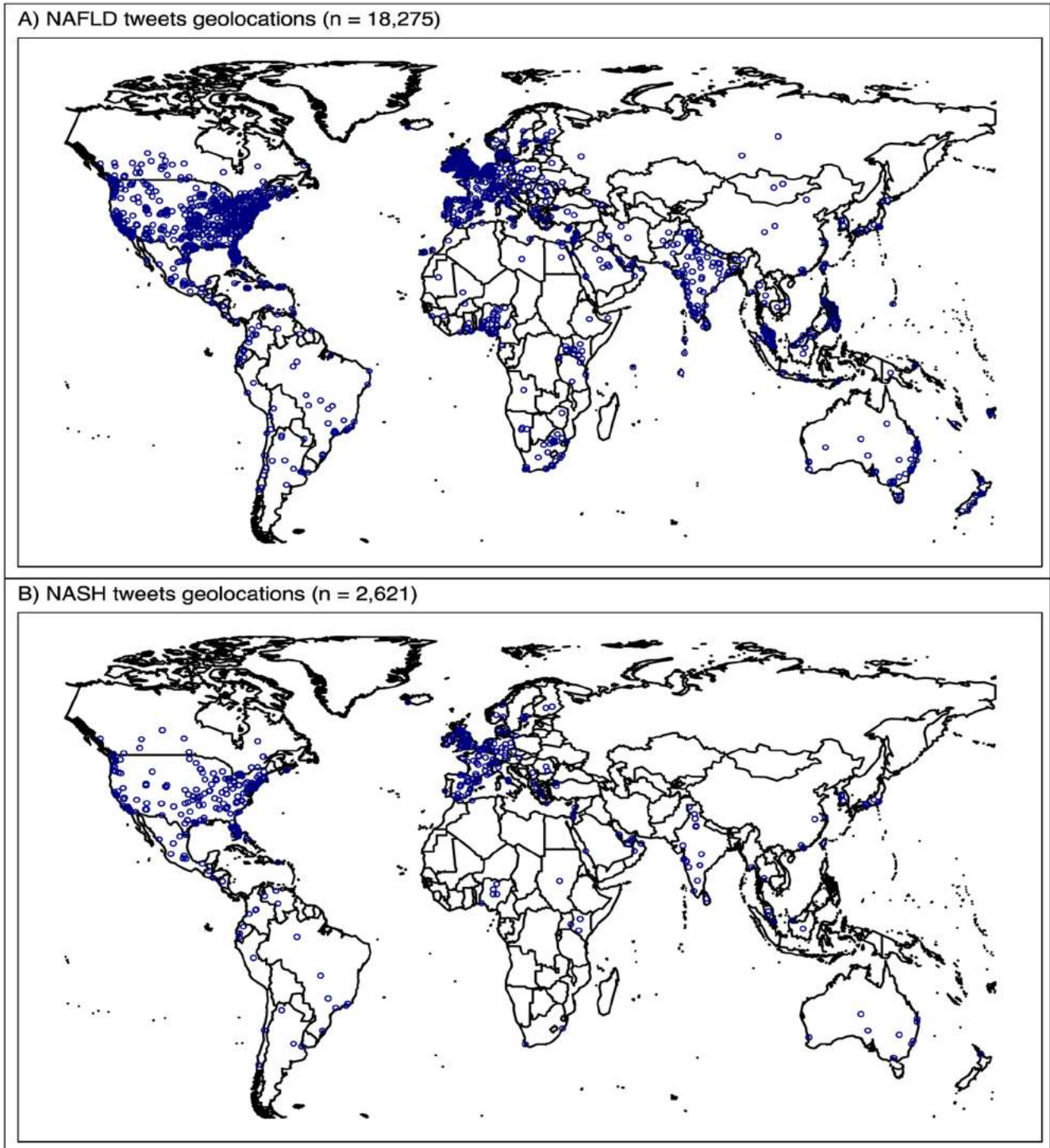


Figure: (abstract: PO-2059) Geographic distribution of: A) NAFLD and B) NASH tweets

PO-2081
Feasibility, effectiveness, and lessons learnt from decentralized HCV testing and treatment models among the general population in Delhi, India

Sonjelle Shilton¹, Jessica Markby¹, Sanjay Sarin², Divya Soni², Mugil Murya², Preetishirin Katapur², Navneet Tewatia², Babu Entoor Ramachandran², Alex Tyshkovskiy^{3,4}, Sandeep Migalni⁵, Philippa Easterbrook⁶, Shiv K. Sarin⁷, Ekta Gupta⁷. ¹Foundation for

Innovative New Diagnostics, Geneva, Switzerland; ²Foundation for Innovative New Diagnostics, New Delhi, India; ³Belozersky Institute of Physico-Chemical Biology, Moscow, Russian Federation; ⁴Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, United States; ⁵Delhi Department of Health Services, New Delhi, India; ⁶World Health Organization Global Hepatitis Program, Geneva, Switzerland; ⁷Institute of Liver and Biliary Sciences, New Delhi, India
Email: sonjelle.shilton@finddx.org

Figure: (abstract: PO-2081)

Site description	Total screened		RDT+		RNA test performed		HCV+		Started Tx		Completed Tx		SVR tested		SVR achieved	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Total	37425	100	771	2.06	704	91.31	605	85.94	493	81.49	446	90.47	347	77.80	333	95.97
Adjusted <i>P</i> value				1.00		1.00		1.00		1.00		1.00		1.00		1.00
Per arm																
1	21792	100	669	3.07	627	93.72	535	85.33	458	85.61	415	90.61	323	77.83	309	95.67
2	9822	100	40	0.41	21	52.50	19	90.48	14	73.68	12	85.71	9	75.00	9	100.00
3	5811	100	62	1.07	56	90.32	51	91.07	21	41.18	19	90.48	15	78.95	15	100.00
<i>P</i> value (Pearson Chi squared test)				1.34E-57		0.10		0.94		0.02		0.99		1.00		0.99
Adjusted <i>P</i> value				9.39E-57		0.72		1.00		0.14		1.00		1.00		1.00

Background and aims: India has a significant burden of hepatitis C virus (HCV) infection and has committed to achieving national elimination by 2030. This will require a substantial scale-up in access to testing and treatment. The “HEAD-Start Project” in Delhi compared the feasibility and effectiveness of three different models of decentralised HCV testing and treatment among the general population.

Method: A prospective observational study was conducted using HCV rapid diagnostic tests (RDTs) to were used to screen the general population at either:—Arm 1: 5 district hospital (DH) outpatient clinics (one-stop shop for testing and treatment), Arm 2: 15 polyclinics (PCs) with referral to DH for viral load (VL) testing and treatment), and Arm 3: 62 screening camps (SCs) with referral to DH for treatment.

Results: Between January and September 2019, 37, 425 participants were screened for HCV, 21, 792 (58%) in Arm 1, 9, 822 (26%) in Arm 2, and 5, 811 (16%) in Arm 3. The median (IQR) age of participants was 35 (26–48) years, with 50.4% male and 49.6% female. Positivity rates were 2.1% (Arm 1, 3.1%; Arm 2, 0.4%; and Arm 3 1.1%; adjusted *p* <0.001 (comparing all arms)). Arm 1 also had consistently high levels of uptake of VL (98.3%), and treatment (85.4%), in contrast to lower VL uptake (51.2%) in Arm 2, and lower treatment uptake in Arm 3 (38.5%).

Conclusion: Delivery of testing and treatment at a single site (district hospitals) resulted in a higher yield of HCV seropositive cases and treatment uptake compared with decentralised testing sites of polyclinics and testing camps and referral for VL and/or treatment to the DGH. Lessons for implementation and scale-up include opportunity for higher case-finding yield among outpatients at district hospitals with good linkage to care, as well as potential for future provision of HCV testing with treatment at polyclinics.

PO-2093

Micro-elimination of hepatitis C achieved in HIV co-infected persons in Slovenia: analysis of HCV infection in a national HIV cohort

Jasna Cernosa¹, Zala Pirnat¹, Janez Tomažič^{1,2}, Tomaz Vovko¹, Blaž Pečavar¹, Gabriele Turel¹, Maja Plesko¹, Manja Kordis¹, Barbara Kokosar Ulcar¹, Mateja Zalaznik¹, Jelka Meglič¹, Mario Poljak³, Jeffrey Lazarus⁴, Mojca Maticic^{1,2}. ¹UKC-Clinic for Infectious Diseases and Fever Conditions, Ljubljana, Slovenia; ²Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; ³Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia; ⁴ISGlobal, Barcelona, Spain
Email: jasnacernosa@gmail.com

Background and aims: In Slovenia, management of all persons infected with the human immunodeficiency virus (HIV) among whom men who have sex with men (MSM) predominate, has been centralised at one medical centre, where regular hepatitis C virus (HCV) screening has been performed since the mid-1990s. With the advent of direct-acting antivirals, a national “test-and-treat” strategy for HCV elimination in this sub-population was launched. The aim of this study was to evaluate epidemiological, virological and clinical characteristics of HIV/HCV co-infected and compare them with an HIV mono-infected cohort.

Method: All HIV-infected persons in Slovenia that tested anti-HCV positive were identified from the national HIV cohort registry at the Clinic for Infectious Diseases, University Medical Centre Ljubljana, and included retrospectively. Those who presented with HCV RNA positivity were further analysed. Demographic, virological and clinical data were extracted from their medical records and compared to a control group of 90 randomly selected HIV mono-infected patients, currently managed at the same clinic.

Results: Of 704 HIV-infected persons, 52 (7.4%) presented as anti-HCV. Twelve were excluded: 6/52 (11.5%) died prior to HCV treatment, 2/52 (3.8%) were lost to follow-up and 4/52 (7.7%) spontaneously cleared HCV with no reinfection. Of 40 HIV/HCV RNA positive (82.5% males), 38/40 (95%) were successfully treated for HCV and 2/40 (5%) are currently receiving treatment. Genotype 1 was predominant (19/38, 50%), followed by genotypes 4 (11/38, 28.9%), 3 (7/38, 18.4%), 1+4 (1/38, 2, 6%) and 2a/2c (1/38, 2.6%). At first presentation, HCV/HIV coinfection was detected in 14/40 (35%); HCV was diagnosed prior to HIV infection in 4/40 (10%), and during HIV infection in 22/40 (55%). HCV reinfection was detected in 7/40 (17.5%): 4/7 (57.1%) MSM, 2/7 (28.6%) injected drugs, and 1/7 (14.3%) reported both. Compared to HIV-mono-infected, HIV/HCV coinfection were significantly younger at first presentation (*p*=0.000859), when they significantly less frequently presented with HIV latency period (*p*=0.199) and end-stage HIV infection (*p*=0.0077), and they more frequently reported injecting drug use (30% vs. 7.2%) whereas significantly fewer were MSM (*p*=0.0052).

Conclusion: In Slovenia, HCV micro-elimination in HIV-infected persons was achieved in 2018. However, regular screening of persons living with HIV, particularly those at high-risk of infection or reinfection still needs to continue.

POSTER PRESENTATIONS

PO-2097

Impact of COVID-19 pandemic on referral of patients with liver disease to a liver transplant center

Giacomo Germani¹, Monica Pellone¹, Alberto Ferrarese¹, Alberto Zanetto¹, Sarah Shalaby¹, Giovanni Carretta², Daniele Donato², Umberto Cillo³, Paolo Feltracco⁴, Paolo Persona⁴, Eugenio Serra⁴, Martina Gambato¹, Marco Senzolo¹, Francesco Paolo Russo¹, Patrizia Burra¹. ¹Padova University Hospital, Multivisceral Transplant Unit, Padova, Italy; ²Padova University Hospital, Directional Hospital Management, Padova, Italy; ³Padova University Hospital, Hepatobiliary Surgery and Liver Transplant Center; ⁴Padova University Hospital, Anesthesia and Intensive Care Unit, Padova, Italy
Email: germani.giacomo@gmail.com

Background and aims: Access to liver transplantation (LT) can be affected by several barriers resulting in delayed referral and increased risk of mortality. Therefore, hub-and-spoke networks have been implemented in order to manage patients with liver disease. However, the COVID-19 pandemic may have significantly changed this scenario, as most of medical resources have been allocated for the care of patients with SARS-CoV-2 infection. This study aimed to assess the influence of COVID-19 pandemic on referrals of patients with liver disease to a LT Center.

Method: An integrated referral program was developed since October 2017 at Multivisceral Transplant Unit, Padova University Hospital. All consecutive adult patients with liver disease referred for the first time using this referral program from October 2017 to December 2020 were prospectively collected. Clinical characteristics were analyzed overall and according to era of referral (pre-COVID-19 era:10.2017–02.2020; COVID-19 era:03.2020–12.2020).

Results: 231 patients with liver disease were referred over the study period (men 61%, mean \pm SD age: 54 \pm 10 years). End-stage liver disease was the most common underlying condition (78.3%), followed by acute liver injury/acute liver failure (17.3%). During COVID-19 pandemic, the rate of referred patients showed a stable trend, if compared with the previous period (5.1 patients/month vs. 6.1 patients/month), also when only in-patient referrals were considered (pre-COVID-19 era vs. COVID-19 era: 2.9 vs. 3.2 patients/month). Considering 181 patients with cirrhosis, underlying etiology ($p=0.22$), severity of liver disease (MELD score: 21 \pm 7 vs. 20 \pm 8; $p=0.44$), and inpatient referrals (42% vs. 51%; $p=0.34$) did not differ between pre-COVID-19 and COVID-19 eras. There was a decreasing rate of ICU admission for cirrhosis-related complications during COVID-19 pandemic (22% vs. 34%; $p=0.3$), with an increased in-hospital transplant-free mortality (41% vs. 30%; $p=0.3$). The overall rate of ICU admission of inpatients showed a decreasing, although not statistically significant trend during COVID-19 pandemic (18.7% vs. 31.7%; $p=0.16$).

Conclusion: Our results did not show a significant decrease in the number of referrals and type of indications during the COVID-19 pandemic; however, the in-hospital transplant free mortality showed an increasing trend, which could be the consequence of a decreasing rate of ICU admissions. Taken together, these factors confirmed the importance of a referral network for the care of patients with liver disease, but also how the COVID-19 pandemic may influence the short-term outcome of patients with liver disease.

PO-2103

Changhua-Integrated Program to Stop Hepatitis C Infection (CHIPS-C) of Taiwan

Tsung-Hui Hu¹, Wei-Wen Su², Chi-Chao Yang³, Chi-Chieh Yang⁴, Sam Li-Sheng Chen⁵, Yen-Po Yeh⁶, Hsiu-Hsi Chen⁷. ¹Kaohsiung Chang Gung Memorial Hospital, and Chang Gung University College of Medicine, Kaohsiung, Taiwan, Taiwan; ²Changhua Christian Hospital, Changhua, Taiwan, Changhua, Taiwan; ³Changhua Hospital, Ministry of Health and Welfare, Changhua, Taiwan; ⁴Show Chwan Memorial Hospital, Changhua, Taiwan, Changhua, Taiwan; ⁵School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taipei,

Taiwan, Taipei, Taiwan; ⁶Changhua County Public Health Bureau, Changhua, Taiwan, Changhua, Taiwan; ⁷Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
Email: dr.hu@msa.hinet.net

Background and aims: Taiwan government has set an ambitious target of achieving 80% of treatment coverage for the patients with HCV by the year 2025. We selected a demonstration region, Changhua County, which is located in the central part of Taiwan, has 27 townships comprising a total of 1,289,000 residents. The prevalence rate of hepatitis C virus (HCV) infection was 3.4% in the population aged more than 40 years based on previous study. We developed a novel integrated model of HCV treatment delivery by combining the micro-elimination approach for special and general populations of patients since 2019 in Changhua country, led by the county's health authority.

Method: The present program is quite different from the previous screening models held by single or elective hospital in the past. There will be two population targets. For general population, HCV RNA screening will be conducted in 27 township health centers for those anti-HCV were positive (3803 patients since 2012 surveillance) but without tests of viremia. Furthermore, we plan to screen new 40,000 residents in three years and identify approximately 1360 (40,000 \times 3.4%) patients infected with HCV who have not been discovered. For the focused populations, the patient lists of special populations were all already established in the system of Changhua County Public Health Bureau. The screening and treatment will further be performed in hemodialysis centers (ESRD), prison (prisoners), health centers (DM and CKD), and hospitals (ESRD, CKD, DM, HIV-HCV co-infection, and IV drug users).

Results: The achievement of HCV micro-elimination: defined as the definition of HCV elimination by WHO criteria as diagnosis more than 90% and treatment more than 80% of the population. Until now, micro-elimination was achieved in four special populations. They are dialysis patients in 31 hemodialysis centers (prevalence 11.0% of 3657 patients, 100% diagnosed and 94% treated); HIV infected patients in five responsible hospitals (prevalence 44.55% of 855 patients, 99.77% diagnosed, and 89.66% treated); intravenous drug addicts with replacement therapy in five responsible hospitals (prevalence 90.34% of 384 patients, 99.74% diagnosed, and 95.54% treated); prisoners (prevalence 39.77% of 3258 patients, 92.38 diagnosed, 90.97% treated). We have also achieved micro-elimination of diabetes or chronic kidney disease population (prevalence 6.1% of 14309 patients, 91.9% diagnosed, and 91.1% treated) in 27 local health centers of the county. For the patients of diabetes and chronic kidney disease, who have been registered in all hospitals of the county as 92175 patients (prevalence rate 6.7%), 73% were screened for HCV, and 81% of documented HCV were treated until now.

Conclusion: It is expected to accelerate the achievement of hepatitis C eradication via the novel community model established in this project (led by public authority instead of hospital).

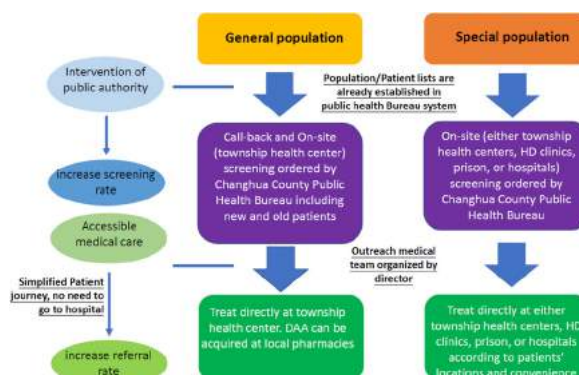


Figure:

PO-2108

The global non-alcoholic fatty liver disease (NAFLD) preparedness index: are countries ready to tackle the challenge?

Jeffrey Lazarus^{1,2}, Henry Mark², Adam Palayew^{2,3}, Carrieri Patrizia⁴, Massimo Colombo^{2,5}, Mattias Ekstedt⁶, Gammal Esmat⁷, Jacob George⁸, Giulio Marchesini Reggiani^{9,10}, KATJA Novak¹¹, Ponsiano Ocama¹², Vlad Ratziu¹³, Homie Razavi¹⁴, Manuel Romero Gomez¹⁵, Marcelo Silva¹⁶, Frank Tacke¹⁷, Emmanuel Tsochatzis¹⁸, Marcela Villota^{1,2}, Yusuf Yilmaz^{19,20}, Zobair Younossi²¹, Shira Zelber-Sagi^{22,23}, Helena Cortez-Pinto²⁴, Quentin Anstee²⁵. ¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain; ²EASL International Liver Foundation, Geneva, Switzerland; ³Department of Epidemiology, University of Washington, Seattle, United States; ⁴Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France; ⁵Department of Medicine, Humanitas Hospital, Rozzano, Italy; ⁶Department of Gastroenterology and Hepatology, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; ⁷Endemic Medicine and Hepatology Department, Faculty of Medicine, Cairo University, Cairo, Egypt; ⁸Storr Liver Centre, Westmead Institute of Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia; ⁹IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ¹⁰Università degli Studi di Bologna, Bologna, Italy; ¹¹University Medical Center Ljubljana, Department of Gastroenterology, Ljubljana, Slovenia; ¹²Makerere University College of Health Sciences, Kampala, Uganda; ¹³Sorbonne Université, Pitié-Salpêtrière Hospital, Paris, France; ¹⁴Center for Disease Analysis Foundation, Colorado, United States; ¹⁵Digestive Diseases and Ciberehd. Virgen del Rocío University Hospital. Institute of Biomedicine of Seville, University of Seville, Seville, Spain; ¹⁶Hospital Universitario Austral, Buenos Aires, Argentina; ¹⁷Charité University Medicine Berlin, Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum and Campus Charité Mitte, 13353, Berlin, Germany; ¹⁸UCL Institute for Liver and Digestive Health,

Royal Free Hospital and UCL, London, United Kingdom; ¹⁹Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Turkey; ²⁰Liver Research Unit, Institute of Gastroenterology, Marmara University, Istanbul, Turkey; ²¹Center for Liver Diseases, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia, United States; ²²University of Haifa, Faculty of Social Welfare and Health Sciences, School of Public Health, Mount Carmel, Haifa, Israel; ²³Department of Gastroenterology, Tel-Aviv Medical Centre, Tel-Aviv, Israel; ²⁴Clinica Universitária de Gastreenterologia, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; ²⁵Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
Email: Jeffrey.Lazarus@isglobal.org

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally, causing a substantial burden of ill health. However, it is widely absent within national health policies and strategies. This global study aimed to assess how prepared countries are to address NAFLD.

Method: Liver health experts from 162 countries were invited to participate in a survey covering relevant national policies and strategies, guidelines, civil society engagement, clinical management and epidemiologic data. Where feasible, survey data were validated against documents and where needed clarifications sought from country experts. Data were coded into 6 domains (policies, guidelines, civil awareness, epidemiology, detection and management) and responses categorised as high-, medium- or low-level based on predefined criteria. Multiple correspondence analysis (MCA) was conducted and the coordinates along the first dimension were used as raw untransformed scores for each country. Three reference standards (high, medium and low) were included to contextualize responses, with overall policy scores ranging from 0 to 100.

Results: Experts from 102 countries completed the survey (median experts per country team = 5; min = 1, max = 9, IQR = 4). No country was in the high-level for all 6 domains. For 5 domains, the smallest

Figure: Global NAFLD policy index score and country rank (n = 102).

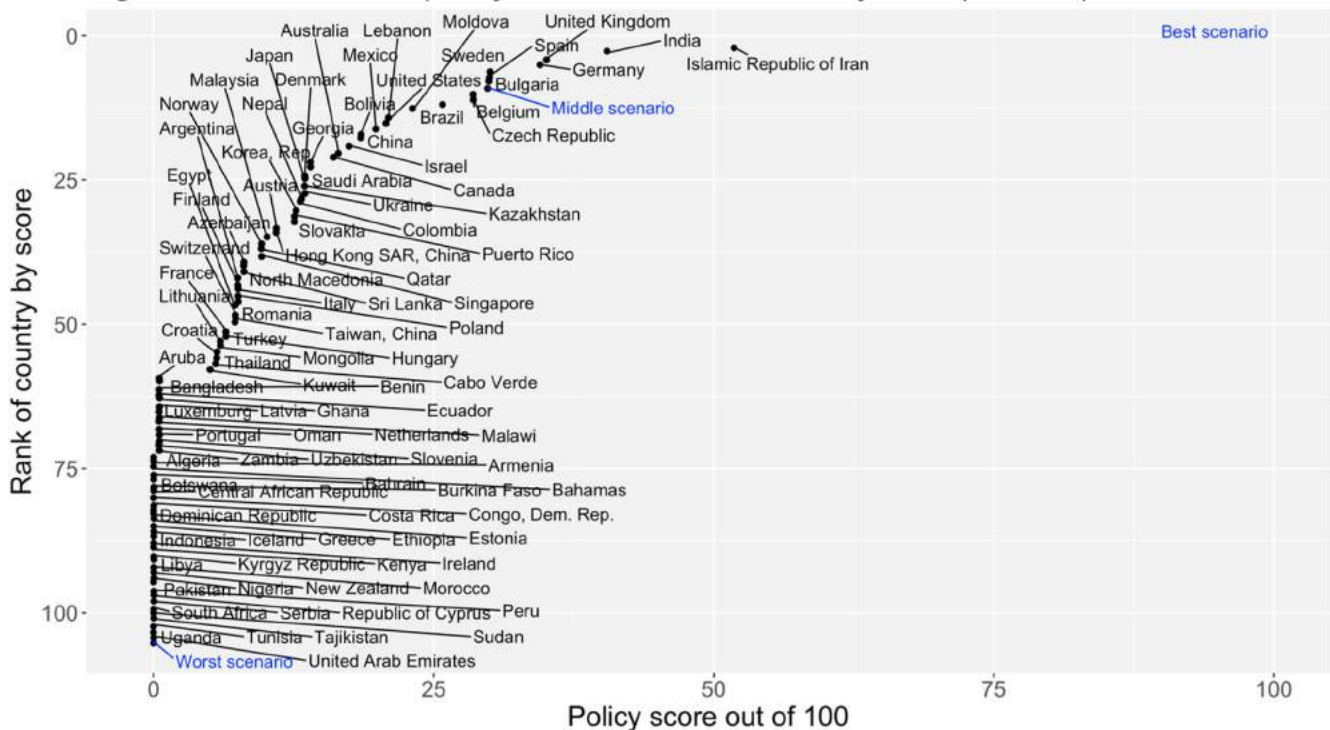


Figure: (abstract: PO-2108)

POSTER PRESENTATIONS

proportion of countries were in the high-level category while the largest proportion were in the low-level, the exception being the guidelines domain, where the smallest proportion of countries were in the medium-level. For the policies domain, all countries were in the low-level. For detection, Belgium, the Czech Republic, India, Iran, Lebanon and Moldova were in the high-level. For the epidemiology domain, Australia, Germany, Iran and Spain were in the high-level. The first dimension of the MCA explained 55.9% of the variation. Iran (51.8) had the highest overall preparedness score, followed by India (40.5) and the United Kingdom (35.1). Thirty-two countries (31%) had a preparedness score of zero (Figure).

Conclusion: No country was found to be well prepared to address NAFLD, with a large proportion of countries having an overall score of zero. Our findings highlight the need for greater attention for NAFLD within national health agendas. As positive scores do not necessarily indicate policy adoption, e.g., into routine clinical practice, these results can assist countries in identifying priority actions to improve their preparedness.

PO-2127

The road to hepatitis C virus elimination: entering the final stretch or chasing a moving finish line?

Ragnheidur H. Fridriksdottir¹, Sigurdur Olafsson^{1,2}, Valgerdur Runarsdottir³, Ingunn Hansdottir^{3,4}, Thorarinn Tyrfinngsson³, Thorvardur J. Löve^{2,5}, Ottar M. Bergmann¹, Einar S. Björnsson^{1,2}, Birgir Johannsson⁶, Bryndis Sigurdardottir⁶, Arthur Löve^{2,7}, Guðrún Erna Baldvinsdóttir⁷, Ubaldo Benitez Hernandez⁵, Maria Heimisdóttir⁸, Magnús Gottfredsson^{2,5,6}. ¹Landspítali-National University Hospital of Iceland, Department of Gastroenterology and Hepatology, Reykjavik, Iceland; ²University of Iceland, Faculty of Medicine, School of Health Sciences, Reykjavik, Iceland; ³SAA National Center for Addiction Medicine, Reykjavik, Iceland; ⁴University of Iceland, Faculty of Psychology, School of Health Sciences, Reykjavik, Iceland; ⁵Landspítali-National University Hospital of Iceland, Department of Science, Reykjavik, Iceland; ⁶Landspítali-National University Hospital of Iceland, Department of Infectious Diseases, Reykjavik, Iceland; ⁷Landspítali-National University Hospital of Iceland, Department of Virology, Reykjavik, Iceland; ⁸Icelandic Health Insurance, Reykjavik, Iceland
Email: sigurdol@landspitali.is

Background and aims: The World Health Organization (WHO) set goals of eliminating hepatitis C virus infection (HCV) as a major health threat by 2030. In 2016, a nationwide program, Treatment as Prevention for Hepatitis C (TraP HepC) was initiated in Iceland, offering treatment with direct acting antivirals (DAAs) to all infected during 36 months (phase 1) followed by a second phase (ongoing) to reach remaining patients and all new and/or reinfections without restrictions. In addition, diagnostic efforts were scaled up and access to needles and syringes were improved. During the first 36 months >95% of all diagnosed in the country received treatment with DAAs and WHO service coverage targets were reached.

Method: We compared patient characteristics receiving first treatment with DAAs during phase 1 of TraP HepC (1/2016–2/2019) with those who subsequently entered the program (2/2019–12/2020; phase 2) using the nationwide clinical data collected in the TraP HepC program.

Results: During phase 1, a total of 835 infections were diagnosed in 791 individuals. Of those 729 (92%) were evaluated, and 782 treatments initiated for 705 individuals. In the second phase 140 individuals were evaluated and 127 treatments were initiated. During phase 1, 77 (11%) patients had more than one treatment initiations compared to 44 (35%) during phase 2. Mean age was lower in period 2 (45 vs 39 years). Proportion of patients with country of birth outside Iceland increased from 13% to 28%. Homelessness affected 7% and 17% in phase 1 and 2, respectively. Similarly, 84% gave history of IDU and 39% had injected recently (within 6 months) in phase 1, whereas during phase 2, 79% of patients reported IDU and 61% recent

injection. In phase 2, 46% were treated for acute infection (one positive PCR) compared to 6% in phase 1. In phase 2, 83% of patients born in Iceland had injected recently.

Conclusion: Although treatment responses have been excellent overall, a small population of patients who are prone to reinfections due to relapsing injection drug use and sharing of needles pose a significant challenge to elimination of HCV in the country. Furthermore, imported cases constitute an increasing proportion of new cases. Currently, patients are increasingly started on treatment immediately following diagnosis to reduce subsequent spread of HCV. In order to succeed, elimination programs need to be adaptable and responsive to changing needs of people who inject drugs and people with different backgrounds.

PO-2131

A clinical and molecular epidemiological survey of hepatitis C in Blantyre, Malawi suggests an historic mechanism of transmission

Alexander Stockdale^{1,2}, Benno Kreuels^{3,4}, Isaac T. Shawa^{1,5}, James Meiring⁶, Deus Thindwa^{1,7}, Niza Silungwe¹, Karen Chetcuti⁸, Elizabeth Joekes², Maurice Mbewe¹, Pratiksha Patel¹, Rabson Kachala⁹, Priyanka Patel¹, Jane Mallewa^{5,10}, Peter Finch^{5,10}, Chris Davis¹¹, Rajiv Shah¹¹, Lily Tong¹¹, Anna da Silva Filipe¹¹, Emma Thomson¹¹, Anna Maria Geretti², Melita Gordon^{1,2}. ¹Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi; ²University of Liverpool, Liverpool, United Kingdom; ³Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; ⁴University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ⁵College of Medicine, Blantyre, Malawi; ⁶University of Oxford, United Kingdom; ⁷London School of Hygiene and Tropical Medicine, United Kingdom; ⁸College of Medicine, Blantyre, Malawi; ⁹Ministry of Health Malawi, Lilongwe, Malawi; ¹⁰Queen Elizabeth Central Hospital, Blantyre, Malawi; ¹¹Centre For Virus Research, Bearsden, United Kingdom
Email: a.stockdale@liverpool.ac.uk

Background and aims: Hepatitis C virus (HCV) is a leading cause of liver disease worldwide. There are no previous representative community HCV prevalence studies from southern Africa (with the exception of island nations) and very limited genotypic data. Epidemiological data are required to inform an effective public health response.

Method: We conducted a community census-based random sampling serological survey, and a hospital-based study of prospectively enrolled patients with cirrhosis and hepatocellular carcinoma (HCC) in Blantyre, Malawi. We tested participants with a 4th generation HCV antigen/antibody ELISA (Monolisa, Bio-Rad), confirmed with PCR (GeneXpert, Cepheid), used line immunoassay (Inno-LIA HCV, Fujiribio) for RNA-negative participants. We did target-enrichment whole-genome HCV sequencing (NextSeq, Illumina).

Results: Among 96,386 censused individuals, we randomly selected 1661 people aged ≥16 years for HCV testing and sampled in participants' homes. Population-standardised HCV RNA prevalence was 0.2% (95% CI 0.1–0.5). Among 238 prospectively recruited hospital patients, HCV RNA prevalence was 1.9% in patients with cirrhosis and 5.0% with HCC. Mapping showed that HCV RNA+ patients were from peri-urban areas surrounding Blantyre. Community and hospital HCV RNA+ participants were older than comparator HCV RNA negative populations (median 53 vs 30 years for community, $p=0.01$ and 68 vs 40 years for hospital, $p<0.001$). Endemic HCV genotypes were 4v (50%), 4r (30%) and 4w (10%).

Conclusion: In the first representative census-based community serological study in southern Africa, HCV was uncommon in the general population, centred on peri-urban areas, and was attributable for <5% of liver disease. HCV was observed among older people, suggesting an historic mechanism of transmission. Genotype 4r, which has been associated with treatment failure with ledipasvir and daclatasvir, is endemic.

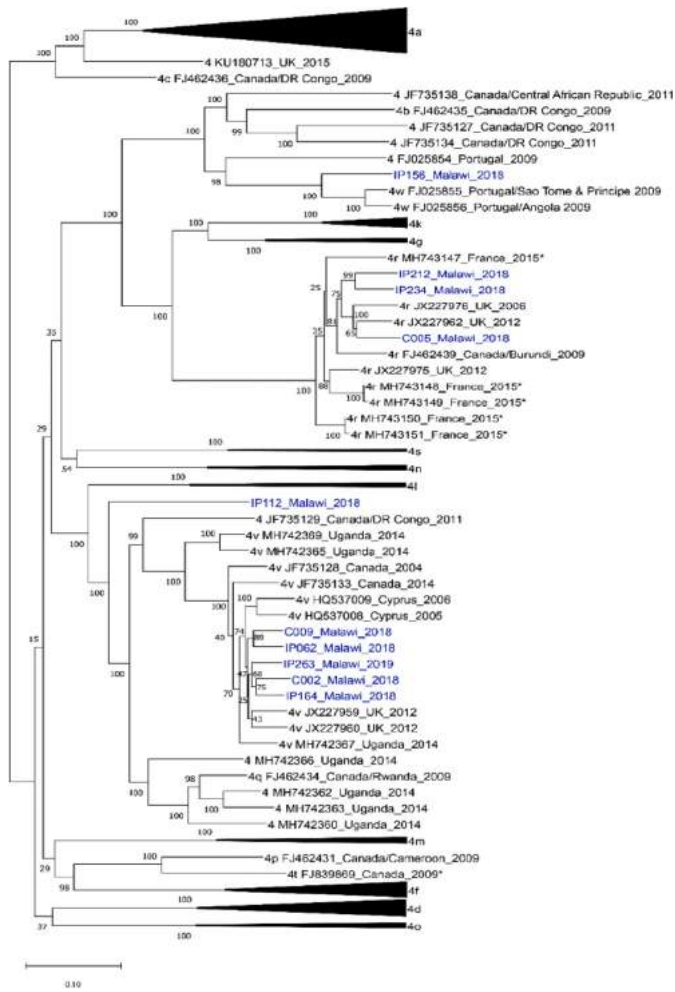


Figure: Maximum likelihood phylogenetic tree: full-length hepatitis C sequences from Malawi aligned to 117 genotype 4 sequences

PO-2152

Modelling clinical outcomes of NASH in the United States stratified by presence of type 2 diabetes

Zobair Younossi^{1,2}, Radhika Tampi², Gail Fernandes³, Joe Yang³, Adnan Alsumali³, Hardik Goswami³, Fatema Nader⁴. ¹Inova Health System, Department of Medicine, Falls Church, United States; ²Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States; ³Merck, Kenilworth, United States; ⁴Center for Outcomes Research in Liver Diseases, DC, United States
Email: zobair.younossi@inova.org

Background and aims: Certain populations with non-alcoholic steatohepatitis (NASH) are at higher risk of progression, leading to increased rates morbidity and mortality. We aim to estimate the clinical outcomes of the prevalent NASH population in the U.S. as of 2019 and compare outcomes stratified by presence or absence of type 2 diabetes (T2DM).

Method: We used a Markov cohort model to compare the clinical outcomes of NASH patients with T2DM to those with NASH without T2DM. Nine health states were included—four liver fibrosis stages (F0-F3), compensated and decompensated cirrhosis (CC and DCC), hepatocellular carcinoma (HCC), first year post-liver transplant (1yPLT) and post liver transplant beyond first year (PLT) states. Three mortality states were used including background all-cause mortality, cardiovascular mortality, and liver-related mortality. The time horizon was 20 years with 1-year cycles. Prevalence of NASH and T2DM as well as transition probabilities were taken from literature. Health utility values were derived from utility scores from patients

with NASH and used to calculate quality-adjusted life years (QALYs) which were discounted 3% annually.

Results: Total NASH prevalence in the adult U.S. population was 11.2 million. Within this population, 5.3 million (47%) had diagnosed T2DM. Over the twenty-year horizon, NASH patients without T2DM accounted for 61.4 thousand LTs, 1.1 million liver-related deaths, 0.87 million cardiovascular deaths, and 50 million QALYs accumulated. The proportion of the NASH population with T2DM accounted for 46.2 thousand LTs, 1.2 million liver-related deaths, 0.9 million cardiovascular deaths, and 40 million QALYs accumulated.

Conclusion: Although the proportion of NASH patients without T2DM is larger than proportion of NASH with T2DM, liver-related and cardiovascular mortality is higher in patients with NASH and T2DM. In addition, the NASH with T2DM is expected to accumulate fewer QALYs than NASH without T2DM. Overall, presence of T2DM in NASH is associated with worse outcomes

Figure: Table: Clinical outcomes of total NASH cohort when stratified by presence of T2DM

	Cohort Size	Liver Transplants	Liver Related Deaths	Cardiovascular Deaths	QALYs
NASH without T2DM	5,914, 752 (52.7%)	61,473 (57.1%)	1,132, 808 (47.5%)	870, 327 (49.3%)	50, 141, 675
NASH with T2DM	5,301, 294 (47.3%)	46,201 (42.9%)	1,251, 795 (52.4%)	895, 953 (50.7%)	40, 407, 165
Total NASH Cohort	11,216, 046				

PO-2288

Etiology of Cirrhosis in Turkey: A National Cohort Study

Abdullah Emre Yıldırım¹, Enver Ucbilek², M. Berk Oruncu³, Ilker Turan⁴, Mehmet Demir⁵, Aydin Koksali⁶, Ahmet Uyanikoglu⁷, Nimet Yilmaz⁸, Mesut Akarsu⁹, Mukaddes Tozlu⁶, Ufuk Avcioglu¹⁰, Busra Haktaniryan³, Murat Aladag¹¹, Ramazan Yolacan¹², Bilal Toka¹³, Ayse Kefeli¹⁴, Asli Ciftcibasi Ormeci¹⁵, Ferid Hacıyev⁹, Hatice Rizaoglu Balci², Mustafa Alper Yurci¹⁶, Hatice Yasemin Balaban¹⁷, Sami Fidan¹⁸, FEYZA Gunduz¹⁹, Genco Gencdal²⁰, Cem Simsek¹⁷, Berat Ebik²¹, Bilger Cavus¹⁵, Eylem Karatay²², Gulden Can Sezgin¹⁶, Serkan Yaras², Umit Karabulut¹¹, Huseyin Savas Gokturk²³, Ali Uzel¹¹, Nazim Ekin²¹, Sezgin Barutcu¹, Arif Mansur Cosar¹⁸, Caglayan Keklikkiran¹⁹, Kerim Deniz Batu¹⁹, Huseyin Alkim²⁴, Sencan Acar⁶, Yasar Yogun²⁵, Murat Harputluoglu¹¹, Kendal Yalcin¹², Fulya Günsar⁴, Orhan Sezgin², Ulus Akarca⁴, Sabahattin Kaymakoglu¹⁵, Abdullah Zeki Karasu⁴, Osman Cavit Ozdogan¹⁹, Ramazan Idilman³. ¹Gaziantep University, Gastroenterology; ²Mersin University, Gastroenterology, Turkey; ³Ankara University, Gastroenterology; ⁴Ege University, Gastroenterology; ⁵Mustafa Kemal University, Gastroenterology; ⁶Sakarya University, Gastroenterology; ⁷Harran University, Gastroenterology; ⁸Sanko University, Gastroenterology; ⁹Dokuz Eylul University, Gastroenterology; ¹⁰19 Mayıs University, Gastroenterology; ¹¹Inonu University, Gastroenterology; ¹²Dicle University, Gastroenterology; ¹³Meram Saglik Bilimleri University, Gastroenterology; ¹⁴Gaziosmanpasa University, Gastroenterology; ¹⁵Istanbul University, Gastroenterology; ¹⁶Erciyes University, Gastroenterology; ¹⁷Hacettepe University, Gastroenterology; ¹⁸Karadeniz Technical University, Gastroenterology; ¹⁹Marmara University, Gastroenterology; ²⁰Memorial Atasehir Hospital, Gastroenterology; ²¹Gazi Yasargil Training and Research Hospital, Gastroenterology; ²²Istanbul Gaziosmanpasa Training and Research Hospital, Gastroenterology; ²³Baskent University, Gastroenterology; ²⁴Sisli Hamidiye Etfal Training and Research Hospital, Gastroenterology; ²⁵Gezbe Fatih Training and Research Hospital, Gastroenterology
Email: enucbilek@hotmail.com

POSTER PRESENTATIONS

Background and aims: The aim of the present study was to determine the recent changing trends in the etiology and other clinical features of cirrhotic patients in Turkey.

Method: The study group included cirrhotic patients who were admitted to outpatient hepatology clinics in 24 tertiary centers of Turkey between July 2019 and December 2020. Cirrhosis was defined clinically, biochemically, radiologically and histologically when available. International Classification of Diseases-10 codes were used to identify cirrhosis and its complications. Data were entered in an electronic case report form (CRF) from each center and reviewed retrospectively. Etiology of cirrhosis in present data set is compared with the historical cirrhosis series.

Results: A total of 4836 cirrhotic patients, with at least 6 months of follow-up were included to the study. The mean age was 61.5 ± 13.7 years and the patients were predominantly male (55%). Forty-five per cent of the patients had compensated and 55% of the patients had decompensated cirrhosis: 48% of the patients were classified as Child-Pugh class A, 38% as Child-Pugh class B and 14% as Child-Pugh class C. Ascites (54%) was the most common decompensating event, followed by hepatic encephalopathy (15%), variceal bleeding (15%) and hepatorenal syndrome (1.8%). The mean MELD and MELD Na scores were 11.4 ± 5.0 and 11.9 ± 5.8 , respectively. Twenty-one percent of the patients had high MELD score (>15), and 19% were on the transplant waiting list.

Chronic viral hepatitis was the most common cause of cirrhosis (43.2%). Hepatitis B virus (HBV) infection was the main etiology in the overall cohort (31.2%), followed by cryptogenic cirrhosis (CC, 19.2%), hepatitis C virus (HCV) infection (12.0%), non-alcoholic fatty liver disease (NAFLD)-related cirrhosis (11.9%), alcohol-related liver disease (9.6%), autoimmune liver diseases (6.2%) and miscellaneous (9.9%). Interestingly, the proportion of CC was higher than expected. On admission, 517 patients (10.6%) had HCC and 123 (2.5%) had an extrahepatic malignancy. Female breast cancer (16%), colon cancer (14%) and hematologic malignancy (14%) were the most common extrahepatic malignancies.

Conclusion: HBV and HCV are the main etiology of cirrhosis in Turkey. The prevalence of HBV-related cirrhosis is declining (when compared to historic control it was nearly 45%), while the prevalence of HCV and NAFLD-related cirrhosis are increasing.

PO-2387

Implementation of a coordinated hepatocellular carcinoma screening program in an outpatient liver center

Joana Vieira Barbosa^{1,2}, Qua Tran³, Brian Malinn⁴, Rosa L. Yu⁵, Michael Curry⁴, Michelle Lai⁴. ¹Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology and Hepatology; ²Lausanne University Hospital and University of Lausanne, Division of Gastroenterology and Hepatology, Lausanne, Switzerland; ³Beth Israel Deaconess Medical Center, Harvard Medical School, Pharmacy Department, Boston, United States; ⁴Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Division of Gastroenterology and Hepatology, Boston, United States; ⁵Beth Israel Deaconess Medical Center, Harvard Medical School, Department of Internal Medicine, Boston, United States

Email: jvieirab@bidmc.harvard.edu

Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide. Although guidelines recommend regular HCC screening in all patients with cirrhosis, adherence is often suboptimal and measures to optimize HCC surveillance are lacking. We aimed to investigate the feasibility and success rate of implementing a targeted HCC screening program to improve patient surveillance.

Method: We analyzed data from consecutive adult patients with cirrhosis evaluated in the Beth Israel Deaconess Medical Center outpatient Liver Clinic from 2018 to 2020. Patients with cirrhosis were identified from our internal electronic database, using International Classification Diseases-10 codes. Patients with a

previous diagnosis of HCC or deceased were excluded. Loss to follow-up (LTFU) was defined as the absence of liver appointment and/or abdominal ultrasound in the last 9 months. Patients with LTFU and their primary providers were contacted by postal mail and electronic mail via a secure patient portal with a response card to send back with either request to schedule an appointment or to inform us that they are followed elsewhere.

Results: Out of 1742 consecutive adult patients with cirrhosis, there were 461 (26.5%) LTFU. Among those LTFU, 273 (59.2%) were male, mean age was 59 ± 12 years and 312 (67.7%) were of Caucasian race. We obtained 51 (11.1%) mail replies from patients and 56 (12.1%) mail replies from primary providers. Over a period of 7 months since the implementation of the HCC screening program, a total of 82/461 (17.8%) were successfully rescheduled, of whom 30/82 (36.6%) had presented with a decompensated cirrhosis at their last visit. 25/461 (5.4%) patients responded declining to reschedule likely due to getting care elsewhere. We observed no significant differences in demographic variables including age, sex, ethnicity, insurance or marital status, or clinical parameters, such as BMI, diabetes, hypertension, dyslipidemia, FIB-4 values, etiology of cirrhosis or rates of decompensated cirrhosis, between patients successfully rescheduled versus those unable to FU.

Conclusion: Implementation of a coordinated HCC screening intervention using postal and electronic mail resulted in 18% rate of response from patients previously LTFU, with 77% of patients not responding. Additional outreach strategies—such as telephonic contact—to increase response rates and improve outcomes warrant further investigation in further studies.

PO-2424

An interactive, country specific, online tool to assess the cost-effectiveness of different hepatitis C testing pathways to inform hepatitis C elimination

Madeline Adee¹, Yueran Zhuo^{1,2,3}, Tiannan Zhan¹, Rakesh Aggarwal⁴, Muhammad Radzi Abu Hassan⁵, Jagpreet Chhatwal^{1,3}, Sonjelle Shilton⁶. ¹Massachusetts General Hospital Institute for Technology Assessment, Boston, United States; ²Mississippi State University College of Business; ³Harvard Medical School; ⁴Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; ⁵Clinical Research Centre, Hospital Sultanah Bahiyah, Malaysia; ⁶Foundation for Innovative New Diagnostics

Email: madee@mgh.harvard.edu

Background and aims: In order to meet the World Health Organization goal of eliminating hepatitis C virus (HCV) as a public health threat by 2030, HCV testing must be scaled up. However, most countries do not have widespread testing programs in place, and cost is a burden to implementation. We created an interactive online tool to allow countries to assess the cost-effectiveness of custom testing pathways, and we present a case study evaluating alternative testing pathways in Malaysia.

Method: We utilized a previously validated microsimulation model of HCV disease progression, where states are defined by METAVIR stages F0-F4, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver-related death (LRD). We adapted this model to simulate the epidemiology of HCV in different countries. Country-specific model results are then run in an online tool, where users can input HCV antibody and viremia prevalence, target screening rate, and direct-acting antiviral (DAA) cost. Users can compare custom diagnostic pathways—with sequential steps of screening, confirmation, liver staging, and monitoring—where they can specify the test used, cost, and patient follow-up rate for each step of each pathway. In a high-risk cohort of 10,000 people with a viremia prevalence of 11.5% in Malaysia, we evaluated three testing pathways: (P1) patients moved at each step, (P2) patients moved at each step with higher follow-up, and (P3) one-stop shop. We compared them to no screening (NS). All persons in the cohort received antibody screening, and subsequent follow-up rates were pathway specific. Cost per

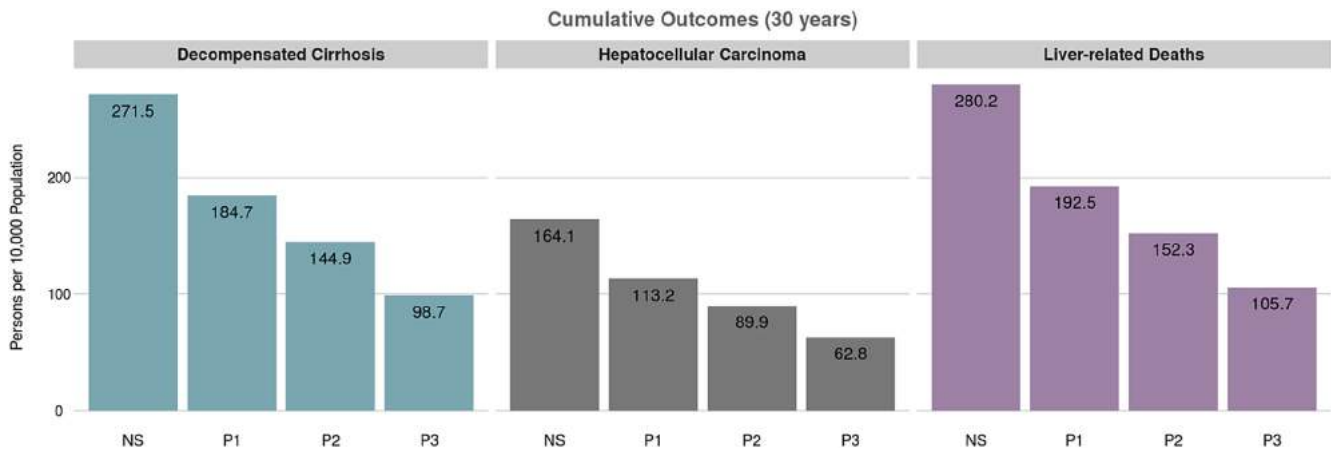


Figure: (abstract: PO-2424)

course of treatment was \$300 (USD), and results were analyzed over a 30-year time horizon.

Results: The one-stop shop pathway (P3), which eliminated loss to follow for confirmation testing by completing RNA testing on site immediately for all antibody positive, was cost-saving compared to the other pathways and to no screening. Per cohort of 10,000 people in the general population of Malaysia, this pathway would result in saving \$7.2 million (USD), gaining 1,882 QALYs, and prevent 173 cases of DC, 101 cases of HCC, and 175 HCV-related deaths compared to no screening (Figure). The majority of cost-savings comes from averted HCV sequelae management costs.

Conclusion: Our interactive tool can help identify optimal HCV testing pathways under different settings of HCV epidemiology, costs of different tests, patient follow-up rates, and on-site availability of diagnostics.

PO-2483

The impact of universal hepatitis B vaccine on the trend of hepatitis B virus attributable liver cancer from Global Burden of Disease Study 2017

Wen-Qiang He¹, Li Chenxi². ¹University of New South Wales; ²Independent Researcher, Australia
Email: wen-qiange@unsw.edu.au

Background and aims: Few studies have reported that the neonatal vaccination against hepatitis B virus (HBV) has reduced the risk of liver cancer. We aim to understand the trends of HBV-attributable liver cancer overall and by age as well as the impact of universal neonatal HBV vaccine on HBV-attributable liver cancer by age, in particular among children, adolescents and young adults.

Method: We retrieved data from Global Burden Disease study to estimate trends of HBV-attributable liver cancer by region and age from 1990 to 2017 and Hepatitis B 3rd dose (HepB3) vaccine data from World Health Organization to assess its impact on these trends for children (0–14 years), adolescents and young adults (15–29 years), adults (30–64 years) and elders (65+ years). Change of cancer cases, age-standardized incidence rate (ASR), and estimated annual percentage change (EAPC) were used to quantify the trends of HBV-attributable liver cancer.

Results: Although the global number of HBV-attributable liver cancer has increased from 219,830 (95% UI: 201,200–241,570) in 1990 to 403,960 (95% UI: 378,260–434,130) in 2017, it decreased among children (from 2,080 to 1,430), adolescents and young adults (from 10,890 to 9,090). In terms of ASR, overall reduction was observed globally by an average of –0.45% (95% CI: –0.62 to –0.29) per year in the same period with the highest reduction in adolescents and young adults at EAPC of –3.02 (95% CI: –3.57 to –2.46). As for six regions by HepB3 vaccine coverage, apart from the ten countries without universal

vaccination against HBV till the end of 2017, the average national HepB3 vaccine coverage and year of vaccination of the rest 185 countries or territories was 84% (range: 20% to 98.6%) and 18 years (range: 3 to 31 years). Over the period, decrease of cancer cases was only observed from countries with vaccine coverage greater than 80% for children (from 1,435 to 731) and adolescents and young adults (from 9,175 to 6,815). The ASR has decreased from all the five regions with universal HBV vaccination program, while it has increased in the region without universal vaccination and the highest increase was found among children with EAPC of 1.97 (95% CI: 1.71–2.23).

Conclusion: Significant reduction of HBV-attributable liver cancer among children was mainly due to the universal HBV vaccination. However, the increasing trend of HBV-attributable liver cancer in region without universal HBV vaccination suggested the necessity of introducing universal immunization against HBV.

PO-2586

Uptake of Direct Acting Antivirals for treatment of hepatitis C in human immunodeficiency virus/hepatitis C co-infected children and adolescents in the Russian Federation

Fariyah Malik¹, Giuseppe Indolfi², Inga Latysheva³, Evgeny Voronin³, Rebecca Lundin⁴, Nataliia Levina⁵, Claire Thorne¹, Anna Turkova⁶.
¹UCL Great Ormond Street Institute of Child Health, London, United Kingdom; ²University of Florence and Meyer Children's University-Hospital, Department Neurofarba, Firenze, Italy; ³Republican Clinical Hospital of Infectious Diseases, Saint-Petersburg, Russian Federation; ⁴Hospital Burlo Garofolo, Institute for Maternal and Child Health, IRCCS, Trieste, Italy; ⁵Fondazione Penta Onlus, Padova, Italy; ⁶Medical Research Council Clinical Trials Unit, University College London, London, United Kingdom
Email: fariyah.malik.18@ucl.ac.uk

Background and aims: Direct acting antivirals (DAAs) have revolutionised hepatitis C (HCV) treatment in adults and children. HIV/HCV co-infected children are at risk of advanced disease progress and are identified by professional society guidelines as a priority group for HCV treatment. The Russian Federation (RF) Paediatric HIV Programme is committed to treating all HIV/HCV children and adolescents once drugs are approved for them. For adolescents ≥12 years, Glecaprevir/Pibrentasvir (G/P) became available through the government programme in late 2019. Within the Russian European Alliance for research (REACH), we aimed to explore HCV therapeutic management practices and policies for children and adolescents with HIV/HCV co-infection and to evaluate treatment availability and utilisation.

Method: A web-based survey was distributed to clinicians 20 AIDS centres in October 2020, with a 95% response rate. The survey collected aggregated data on numbers of HIV/HCV co-infected

POSTER PRESENTATIONS

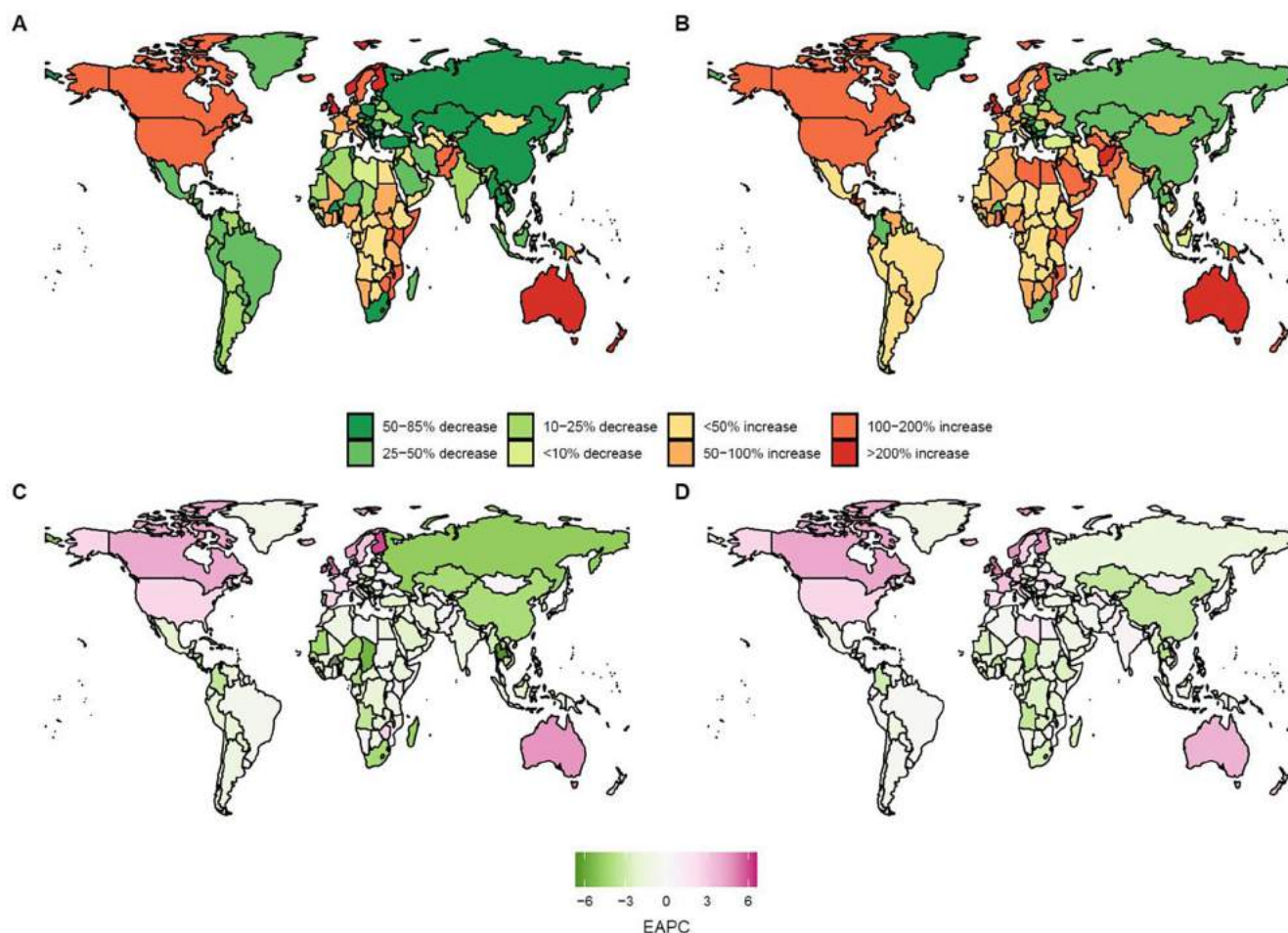


Figure: (abstract: PO-2483) **The trends of HBV-attributable liver cancer among children, adolescents and young adults.** The change of cancer cases from 1990 to 2017 for children (A), adolescents and young adults (B). The EAPC for children (C), adolescents and young adults (D). HBV, hepatitis B virus; EAPC, estimated annual percentage change.

children (<18 years) under current care by age group, sex, HCV genotype (GT), and HCV treatment history, plus details of policies or guidelines for identification, monitoring and treatment of paediatric HCV.

Results: 125 HIV/HCV co-infected children were in follow-up (61 female), ranging from 0 to 39 per centre. 29 children (23%) were aged <6 years, 26 (21%) 6- <12 years and 70 (56%) 12-17 years. Most were vertically infected (n = 92, 74%). Genotype GT was available for 94 (75%) children, of whom 60 (64%) had GT1, 32 (34%) GT3 and 2 (2%) GT2. 10 clinics used DAAs only (53%), 5 clinics interferon- or DAA-based treatments (26%), and 2 did not treat children for HCV (table 1). DAAs were only prescribed for adolescents ≥ 12 years. 50 (71%) HIV/HCV coinfected adolescents were treated with G/P.

Table:

	Number of AIDS centres where DAAs are indicated for treatment of adolescents n = 19	Number of HIV/HCV coinfected adolescents having received DAAs n = 70
Sofosbuvir	3 (16%)	1 (1%)
Daclatasvir	2 (11%)	0
Sofosbuvir/ Ledipasvir	3 (16%)	0
Sofosbuvir/ Velpatasvir	4 (21%)	0
Glecaprevir/ Pibrentasvir	15 (79%)	50 (71%)

Conclusion: DAA treatment uptake was high for HIV/HCV coinfected adolescents in the RF. Most of those in care at responding clinics were treated soon after approval of pangenotypic formulations. Access to treatment for younger children needs expansion as DAAs are licensed for these age groups.

PO-2596 Hepatitis C Virus Microelimination is Feasible During COVID-19 Pandemic in Centers for Addiction Treatment Users

Silvia Acosta-López¹, Esther Rodríguez Candelaria¹, Luz Goretti Santiago Gutiérrez², Juan Carlos Fernández Molina³, Pilar Díaz Ruiz⁴, Magdalena Lara⁵, María del Carmen Martínez-García³, Ana Laserna Ramos², David Rodríguez Galloway², Rosa Lidia González-Guerra³, Angelina Rodríguez Pérez², Ruth Suarez Darias¹, Antonio González Rodríguez¹, Teresa De la Rosa Vilar², Francisco Andrés Pérez Hernández¹. ¹Hospital Universitario Nuestra Señora de Candelaria, Liver Unit, Santa Cruz de Tenerife, Spain; ²San Miguel Adicciones, San Miguel Adicciones, San Cristóbal de La Laguna, Spain; ³ANTAD, ANTAD, Santa Cruz de Tenerife, Spain; ⁴Hospital Universitario Nuestra Señora de Candelaria, Pharmacy, Santa Cruz de Tenerife, Spain; ⁵Hospital Universitario Nuestra Señora de Candelaria, Microbiology Department
Email: sacostalopez9@gmail.com

Background and aims: To eliminate hepatitis C (HCV) infection is necessary to implement protocols in high prevalence but low adherence populations, like the centers for addiction treatment users (CAT). We have previously reported high sustained viral response (SVR) in this population with the Fast-Track Consultation Protocol (FT). Covid-19 pandemic (C19) has elicited to modifications of the health assistance and, consequently, HCV elimination. The aim of this study is to analyse the differences in diagnosis, adherence and response to HCV treatment in CAT users after the onset of C19.

Method: FT include screening and treatment supervision in CAT and hospital assistance in a single day (diagnosis and prescription). During pandemic, telemedicine and treatment dispensation at CAT were started. Demographic, clinical variables, adherence to treatment and SVR were included. Differences between pre-Covid19 pandemic (pC19) (March 2019 to February 2020) and covid pandemic (C19) (March 2020 to February 2021) in terms of SVR were analysed by using non-parametric tests.

Results: No significant differences between the two studied groups were identified in demographic and clinical variables and, interestingly, in the prevalence of active drug consumption or the presence of psychiatric disorders (table 1). During pC19, 390 patients were included and 33% were HCV positives; during C19, 115 patients were included (11% HCV positives). 139 patients started treatment in pC19, while 41 patients were treated during the C19 (8 were on treatment at the time of this analysis). 90.6% and 93.8% patients completed the treatment in pC19 and C19, respectively (p = .440). SVR was achieved in 90.6% of patients and 87.9% of patients in the pC19 and C19 groups, respectively (p = .632).

Conclusion: HCV elimination in CAT users has been feasible during C19 by adapting the FT protocol. It has achieved similar rates of adherence to treatment and SVR than in the pC19 and is not affected by basal vulnerability conditions.

Figure: Table 1: Differences in demographic and clinical features between pC19 and C19 groups.

	pC19 (n = 139) N (%)	C19 (n = 41) N (%)	p value
Gender (M:F)	126:13	34:7	.167
Age	49.5 [SD = 6.9]	47.5 [SD = 7.4]	.235
Liver Fibrosis			.286
F0-2	82 (59)	25 (65.8)	
F3-4	57 (41)	13 (34.2)	
Active Drug Consumption* (yes)	72 (51.8)	25 (61)	.373
Homeless (yes)	16 (11.5)	3 (7.3)	.019
Psychiatric disorders (yes)	40 (28.8)	10 (24.4)	.693
Psychotropic drug (yes)	72 (51.8)	18 (43.9)	.477

M: male. F: female.

*Intranasal or intravenous administration

PO-2689

Proportion, characteristics, and outcome of chronic hepatitis B who are 'linked to care' in Korea: A nationwide retrospective longitudinal study

Young Cheol Ju¹, Dae Won Jun^{1,2}, Eileen Yoon², Sang Bong Ahn³, Yun Jin Kim⁴, Mindie Nguyen⁵. ¹Graduate school of Biomedical Science and Engineering, Hanyang University, Department of Translational Medicine; ²Hanyang University Hospital, Hanyang University College of Medicine, Department of Internal Medicine; ³Nowon Eulji Medical Center, Eulji University College of Medicine, Department of Internal Medicine; ⁴Biostatistical Consulting and Research Laboratory, Medical Research Collaborating Center, Hanyang University; ⁵Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA

Email: noshin@hanyang.ac.kr

Background and aims: Apart from the prevalence of chronic hepatitis B (CHB), linkage to care rate is less well characterized. We aimed to characterize the proportion of CHB patients who have been linked to care, their characteristic and long-term outcomes.

Method: This was a retrospective longitudinal cohort study using the Korean National Health Insurance Service database data from 2002 to 2018. Our operational definition of in-care CHB patients includes those who had at least two clinic or hospital visits that were associated with a CHB diagnostic code during study period (2002–2006). The period from 2007 to 2018 was used for long-term follow-up of this selected population.

Results: Of the estimated 1,545,377 CHB patients during the study period, 553,085 patients (35.8%) were found to be linked to care, with lower rate in men (35.7% in men vs. 36.0% in women) (p = 0.006). The linkage to care rate was highest in the 40–49 year age group (48.5%), and lowest in the 20–29 year age group (29.4%). Interestingly, linkage to care rate was higher in the rural than metropolitan area (39.1% vs. 35.7%, p < 0.0001). The 15-year cumulative incidence of hepatocellular carcinoma and overall survival rates among linked to care CHB patients were 18.2% and 93.8%, respectively.

Conclusion: Two thirds (64.2%) of CHB Koreans are under inadequate care. Those who are male, dwelling in metropolitan, not in life transitioning period need to be focused for improvement of linkage to care rate in Korean CHB population.

PO-2861

Projecting the prevalence of obesity- and alcohol- related non-communicable diseases in France, the Netherlands and Romania from 2020 to 2030 using multi-risk microsimulation methods

Lise Retat¹, Timothy Coker¹, Laura Webber¹, Maria Buti², Helena Cortez-Pinto³, Peter Jepsen⁴, Jeffrey Lazarus⁵, Nick Sheron⁶, Pierre Nahon⁷, Francesco Negro⁸, Marieta Simonova⁹, Shira Zelber-Sagi¹⁰. ¹HealthLumen, Modelling Department, London, United Kingdom; ²Liver Unit, Department of Internal Medicine, Hospital Universitario Vall d'Hebron, Barcelona, Spain; ³Centro de Nutrição e Metabolismo, University of Lisbon, Lisbon, Portugal, Lisbon, Portugal; ⁴Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; ⁵Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Spain; ⁶Population Hepatology Research Group, University of Southampton, Southampton, UK; ⁷Université Paris, Hospital Jean-Verdier, Paris, France, France; ⁸Department of Pathology and Immunology of the University Hospitals of Geneva, Geneva, Switzerland, Switzerland; ⁹Department of Gastroenterology, HPB Surgery and Transplantology, Military Medical Academy, Sofia, Bulgaria; ¹⁰School of Public Health, Department of Nutrition, Health and Behavior, University of Haifa, Haifa, Israel
Email: lise.retat@healthlumen.com

Background and aims: Obesity prevalence is increasing across Europe, contributing to increasing liver and cardiovascular disease, already adversely affected by levels of alcohol consumption. Quantifying the epidemiological and economic burden of these risk factors will provide evidence for governments and other stakeholders to design and implement appropriate interventions and policies. This study quantifies the burden of liver diseases, and coronary heart disease (CHD), impacted by body mass index (BMI) and alcohol as joint risk factors, in France, Netherlands and Romania from 2020 to 2030.

Method: A validated multi-risk microsimulation model was employed [1]. Dynamic, representative virtual populations of the three countries were generated based on population data. Country-specific epidemiological and cost data for chronic liver diseases (CLD), liver cancer, and CHD were extracted from published sources. Morbidity and costs of diseases were projected to 2030 based on trends in increasing obesity and static alcohol consumption. The impact of an illustrative scenario in which BMI is reduced by 1% and alcohol consumption by 5% was assessed.

POSTER PRESENTATIONS

Results: For France, obesity is projected to increase by over 10% between 2020 to 2030. Cumulative incidence was estimated to increase from 12741, 10730, 14083 cases in 2020 to 136132, 123390, 164297, of CLD, liver cancer, cirrhosis cases respectively in 2030. Under the intervention scenario, the reduced burden in disease incidence corresponds to direct cost savings in 2030 of €376.67 m (liver cancer) and €518.96 m (cirrhosis). In the Netherlands, obesity is projected to increase across all age groups for both sexes by 2030. The cases avoided for each disease category under the intervention scenario were projected to lead to direct cost savings in 2030 of €7.1 m (CLD), €6.4 m (liver cancer), €9.95 m (cirrhosis). In Romania, obesity is projected to decrease between 2020 and 2030. Under the intervention scenario, this would lead to around 91, 200 and 10, 000 liver cirrhosis and CLD cases avoided.

Conclusion: We demonstrate the effect of rising obesity rates on liver diseases, assuming no changes in current alcohol consumption, as well as the associated economic burden to the French, Dutch and Romanian healthcare systems. These data suggest that policies designed to impact on both risk factors may be of benefit.

[1] Pérez-Ferrer et al. Inequalities in smoking and obesity in Europe predicted to 2050: Findings from the EConDA project. *Scand J Public Health*. 2018 Jul;46 (5):530–540. doi: 10.1177/1403494818761416.

PO-2872

COVID-19 pandemic and the impact on hospitalization of alcohol related liver disease-A retrospective cohort study in a secondary care setting

Wei Jin Lim¹, Yen Miao¹, Ka Kit Li¹, Heidi Whitsey¹, Jithin Jith¹, Michael Taylor¹. ¹University Hospitals of Leicester, Gastroenterology, United Kingdom

Email: lwjin90@hotmail.com

Background and aims: The COVID 19 pandemic has put unprecedented pressure on health care system around the world. Data have suggested strategies used in controlling infection such as lockdown have been associated with an increase in alcohol usage. In addition, evidence has also suggested an increase in avoidance to seek medical care due to COVID concerns. The downstream effects of such behaviours may inevitably result in increased morbidity and mortality of patient with alcohol related liver disease (ARLD). Our study aims to describe the characteristics of ARLD patients hospitalised in the COVID 19 pandemic year comparing to the year before, in a teaching hospital setting.

Method: Hospital admission for alcoholic related liver disease between April to September month for year 2019, and year 2020 were obtained. Information for baseline characteristic, prognostic scoring, morbidity and mortality were obtained from local Sunquest ICE and Nervecentre software. Data were tabulated and analysed. Chi-Square test of independence was applied for statistical significance.

Results: Number of ARLD admissions increased by 50% from 102 in year 2019, to 153 in year 2020. Incidence of alcoholic hepatitis increased from 30.4% to 69.2% ($p < 0.001$), with incidence of first presentation ARLD increased from 5.9 to 37.9% ($p < 0.001$). Only 2 (1.3%) contracted COVID 19 infection. There are no statistically significant differences in CLIF-C acute decompensation score, acute-on-chronic liver failure grade, Glasgow alcoholic hepatitis score, and overall 6-months mortality rate.

Conclusion: Our study has shown an increase in decompensated alcohol related liver disease hospitalization rate and alcoholic hepatitis during the COVID 19 pandemic. Our data add to the increasing evidence of the co-lateral damage created in the wake of the on-going pandemic and highlight the challenges ahead as a result of increasing incidence of patient with ARLD. COVID 19 pandemic presents a valuable learning opportunity for us to re-evaluate and reshape how hepatology services may be delivered to improve the outcome of patient with ARLD during the post pandemic recovery phase.

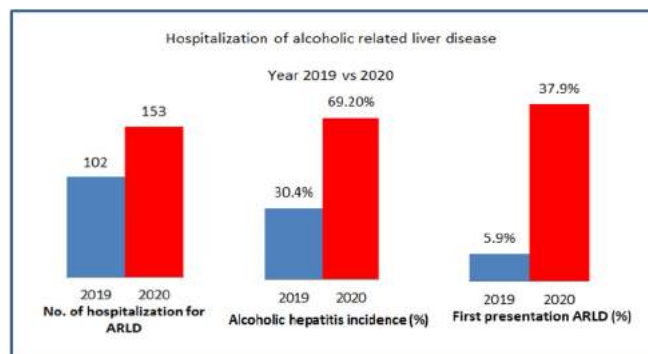


Figure:

PO-2904

Impact of Universal Automated Hepatitis C Screening with Treatment and Cure in a Primary Care Based Practice

Su Wang¹, Ruth Brogden¹, Binghong Xu¹, Jaymie Yango¹, Naomi Fox², Eric Handler³, Mary Adedeji¹. ¹RWJBarnabas Health, Center for Asian Health and Viral Hepatitis Programs, Florham Park, United States; ²Saint Barnabas Medical Center, Nursing Education and Research, Livingston, United States; ³Saint Barnabas Medical Center, Emergency Department, Livingston, United States

Email: su.wang@rwjbh.org

Background and aims: Liver cancer is the third most common cancer death in the world and viral hepatitis being a leading cause. An estimated 2.4 million people in the United States (US) are living with hepatitis C (HCV), but more than half are not yet aware. Injection drug use remains a major drive of transmission, and in the US, acute HCV incidence has been highest in those 20–29 years of age. In response to the changing epidemiology, the US Centers for Disease Control and Prevention (CDC) updated their HCV screening recommendations for all adults to be tested at least once except in settings where the prevalence of HCV infection is $< 0.1\%$. We sought to scale up HCV screening in a 577-bed community hospital with an Emergency Department (ED) of 100, 000 yearly visits, by modifying our electronic medical record (EMR) to automate HCV screening and provide linkage-to-care (LTC).

Method: The EMR modified to automate test orders for hepatitis screening beginning March 2018. HCV testing was triggered by year of birth (1945–1965) then expanded to universal (age > 18) in January 2020 and from the ED initially and then adding the inpatient units. When the test order is placed (HCV Ab with reflex to HCV RNA), nurses are notified of patient eligibility. Alerts of HCV positive results are sent to staff, and the patient navigator (PN) also receives a real-time secure text message. The PN reaches out and works individually with patients to arrange LTC for evaluation and treatment.

Results: From Mar 2018 to Mar 2021, a total 50, 873 of HCV screenings were conducted with 259 (0.5%) found to have current HCV infection and 128 (49.4%) were newly diagnosed. LTC rate was 86.9%. Starting January 2021, individuals born outside the 1945–65 birth cohort made up 75.8% of those screened and 41.0% of the infected. Totally 110 HCV infections were found via universal screening, 31 (28.2%) are younger than the birth cohort, and 14 (12.7%) are older. Of those LTC, 47 HCV patients were seen at PCP. Genotypes 1a and 1b are the most common. We initiated 39 HCV therapy and 34 were cured (confirmed sustained virologic response at 12 weeks).

Conclusion: The ongoing opioid epidemic necessitates more universal HCV screening strategies to identify individuals living with hepatitis C infection across the lifespan. Our study demonstrated that close to half of those infected were born outside of the original CDC recommended birth cohort and included people both younger and older. Scaling up screening through automated EMR based screening and utilizing frontline primary care practices are ways of integrating hepatitis services. Such approaches will be critical to reduce liver cancer rates and eliminate hepatitis.

Rare liver diseases (including paediatric and genetic)

PO-106

Social outcomes in patients with biliary atresia: a systematic review

Emma Alexander¹, William Greaves², Hrisheekesh Vaidya³, Charlotte Burford¹, Vandana Jain¹, Marianne Samyn¹. ¹King's College Hospital, United Kingdom; ²UCL Medical School, United Kingdom; ³Northwick Park Hospital, United Kingdom
Email: emma.alexander5@nhs.net

Background and aims: Biliary atresia is the most common indication for liver transplant in childhood. Following improved medical outcomes for children with biliary atresia, a new clinical and research focus is on promoting long-term well-being and quality of life. We therefore aimed to systematically review the social outcomes of patients with biliary atresia (BA).

Method: A systematic review of Medline, EMBASE, Global Health, Maternity and Infant Care Database was conducted in April 2020, supplemented by reference searching, with NHLBI scoring for quality appraisal. Protocol registered on PROSPERO (CRD42020178846).

Results: 55 studies met inclusion criteria (39 cohort, 11 cross-sectional, five case-control), including 5, 156 participants from 16 countries. BA post liver transplant (LT) (18 studies), native liver survival (NLS) (16 studies), mixed LT/NLS (16 studies) and 5 of other cohorts (e.g. listed for LT) were incorporated. Study outcomes included; education (n = 39), employment (n = 19), pregnancy (n = 24), and social functioning (n = 25). Patients with BA had lower school functioning scores than controls, with no difference when comparing those with and without LT. The need for additional educational support ranged between 2% and 48% of children. Adult patients with BA were employed at high rates (range 60–100%), with no difference between post-LT and NLS cohorts when compared in 1 study. Successful pregnancies were reported in 19 studies, with mostly small sample sizes. In 6/7 NLS studies mentioning pregnancy, complications included derangement in liver function and variceal bleeding secondary to portal hypertension. Social functioning scores did not significantly differ from healthy controls when compared in 7/9 studies.

Conclusion: Existing evidence on social outcomes for children and adolescents with BA is predominantly from non-controlled, single centre studies and based on parental surveys. The current findings suggest that school functioning is lower compared to peer groups and not influenced by having a liver transplant. Employment outcomes are encouraging and pregnancy considered an at-risk period. These findings provide justification for routine psychosocial assessment of these patients during follow-up and larger multi-centre collaborations in order to develop the evidence base for future patients.

PO-299

Clinical and radiological characterisation of Polycystic Liver Disease

Benjamin Giles¹, Alison Dimmer¹, Zeshan Riaz¹, Joanna Dowman¹, Andrew Fowell¹, Richard Aspinall¹. ¹Portsmouth Hospitals University NHS Trust, Gastroenterology and Hepatology, Portsmouth, United Kingdom
Email: r.j.aspinall@doctors.org.uk

Background and aims: Patients with Polycystic Liver Disease (PLD) have a wide range of symptom severity and disease course but little is known about the clinical impact of PLD in the United Kingdom. The aim of our study was to examine the spectrum of PLD including severity, cyst phenotype, symptoms and treatment in a large, secondary care population over a 10-year period.

Method: We systematically searched radiology reports from 2011–2020 at a major acute hospital serving a catchment population of 675,000. “Polycystic” and “multiple cysts” were used as search terms to identify patients, excluding those without liver or renal cysts. Electronic patient records were interrogated to collect demographics, clinical information and radiology. Images were reviewed to confirm numbers and sizes of cysts.

Results: We identified 484 patients with multiple liver cysts; 211 with isolated PLD and 273 with both liver and kidney cysts. Of the available imaging, 133/234 (57%) met the accepted definition of PLD (>10 liver cysts). Overall, 39/484 (8%) had symptoms from hepatic cysts whereas 26/133 (20%) meeting the PLD definition were symptomatic with abdominal pain being the most common symptom (85%). The mean age of first reporting PLD symptoms was 56 (range 36–84 years). Females were a higher proportion of both symptomatic patients (72%) and those requiring treatment (82%). Symptoms correlated with cyst number, occurring in 0–10 cysts 6/101 (6%), 11–20 cysts 6/42 (14%), >20 cysts 20/91 (22%) respectively. Cyst size similarly impacted symptoms and 218/229 (95%) of patients with small (<5 cm) liver cysts were asymptomatic. The mean largest cyst size was 4.0 cm (range 0.3–14.8) in asymptomatic people and 8.6 cm (range 4.3–21.0) in those with symptoms. Only 16/484 (3%) received targeted treatment for hepatic cysts with fenestration being the most common procedure performed, followed by resection and liver transplantation. No patients received somatostatin analogues during the study period.

Conclusion: This is the largest systematic study of a PLD population from the UK and describes the clinical spectrum of disease. We found patients with multiple simple liver cysts rarely became symptomatic or required treatment. However, defined PLD was more severe in females with a higher rate of symptoms and need for specialist treatment. Symptomatic disease increased when multiple hepatic cysts exceeded 10 in number or grew larger than 5 cm. Our data informs the natural history of PLD including the need to access appropriate care for symptomatic disease and highlights the importance of the recently established UK PLD Registry [<https://clinicaltrials.gov/ct2/show/NCT04645251>].

PO-323

Liver phenotype of adults with alpha-1 antitrypsin deficiency in the UK Biobank and in an international, multi-center cohort

Malin Fromme¹, Carolin Victoria Schneider¹, Vítor Pereira², Karim Hamesch¹, Monica Pons Delgado^{3,4}, Matthias C. Reichert⁵, Federica Benini⁶, Paul Ellis⁷, Katrine Thorhaug⁸, Mattias Mandorfer⁹, Barbara Burbaum¹, Vivien Woditsch¹, Joanna Chorostowska-Wynimko¹⁰, Jef Verbeek¹¹, Frederik Nevens¹¹, Joan Genesca^{3,4}, Marc Miravittles¹², Alexa Nuñez¹², Benedikt Schaefer¹³, Heinz Zoller¹³, Sabina Janciauskiene¹⁴, Nélia Abreu², Luís Jasmins², Rui Gaspar¹⁵, Catarina Gomes¹⁶, Kai Markus Schneider¹, Michael Trauner⁹, Aleksander Krag⁸, Bibek Gooptu^{17,18}, Douglas Thorburn¹⁹, Aileen Marshall¹⁹, John R. Hurst²⁰, David Lomas²⁰, Frank Lammert⁵, Nadine Gaisa²¹, Virginia Clark²², Griffiths Bill²³, Christian Trautwein¹, Alice Turner⁷, Noel G. McElvaney²⁴, Pavel Strnad¹. ¹University Hospital RWTH Aachen, Medical Clinic III, Gastroenterology, Metabolic diseases and Intensive Care, Aachen, Germany; ²Centro Hospitalar do Funchal, Department of Gastroenterology, Madeira, Portugal; ³Universitat Autònoma de Barcelona, Liver Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; ⁴Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; ⁵Saarland University Medical Center, Saarland University, Department of Medicine II, Homburg, Germany; ⁶Spedali Civili and University, Gastroenterology Unit, Department of Medicine, Brescia, Italy; ⁷University of Birmingham, Institute of Applied Health Research, Birmingham, United Kingdom; ⁸Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; ⁹Medical University Vienna, Division of

POSTER PRESENTATIONS

Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria; ¹⁰National Institute of Tuberculosis and Lung Diseases, Department of Genetics and Clinical Immunology, Warsaw, Poland; ¹¹University Hospitals KU Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium; ¹²Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Hospital Campus. CIBER de Enfermedades Respiratorias (CIBERES), Pneumology Department, Barcelona, Spain; ¹³Medical University Innsbruck, Department of Internal Medicine I, Innsbruck, Austria; ¹⁴Medical University Hannover, Clinic for Pneumology, Hannover, Germany; ¹⁵Faculty of Medicine of Porto University, Gastroenterology Department, Centro Hospitalar de São João, Porto, Portugal; ¹⁶Centro Hospitalar Vila Nova de Gaia/Espinho, Gastroenterology Department, Gaia, Portugal; ¹⁷University of Leicester, NIHR Leicester BRC-Respiratory and Leicester Institute of Structural and Chemical Biology, Leicester, United Kingdom; ¹⁸Royal Free Hospital, London Alpha-1 Antitrypsin Deficiency Service, London, United Kingdom; ¹⁹Royal Free Hospital, Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, London, United Kingdom; ²⁰University College London, UCL Respiratory, Division of Medicine, London, United Kingdom; ²¹University Hospital RWTH Aachen, Institute of Pathology; ²²University of Florida, Division of Gastroenterology, Hepatology, and Nutrition, Gainesville, Florida, United States; ²³Cambridge University Hospitals NHS Foundation Trust, Department of Hepatology, Cambridge, United Kingdom; ²⁴Royal College of Surgeons in Ireland, Beaumont Hospital, Irish Centre for Genetic Lung Disease, Dublin, Ireland
Email: malin.fromme@rwth-aachen.de

Background and aims: Alpha-1 antitrypsin deficiency (AATD) is caused by mutations in the *SERPINA1* gene and leads to lung and liver disease. While the susceptibility to liver disease in individuals homozygous for the Pi*Z variant (genotype Pi*ZZ) is well established, the effects of the more prevalent Pi*S variant remain to be investigated. To analyze the most relevant AATD genotypes on a population-based level, we evaluated individuals of the United Kingdom Biobank (UKB) and corroborated the results in an international cohort.

Method: We examined 17 006 Pi*MZ, 1014 Pi*SS, 864 Pi*SZ, 138 Pi*ZZ individuals, and 422 506 non-carriers in the UKB. The presence of the ICD10 diagnoses liver fibrosis/cirrhosis (K74.0-2, -6) and primary liver cancer (C22.0) was assessed and compared to known genetic liver disease modifiers. The confirmatory cohort consisted of 1104 systematically evaluated subjects from ten European countries and the US with available liver stiffness measurements (LSM).

Results: Pi*MZ and Pi*SZ individuals presented with elevated AST values, however Pi*ZZ subjects showed the highest AST values. All five genotypes displayed significantly higher ALT values than non-carriers. Mean ALP values were the highest in Pi*SZ subjects. Pi*SS individuals harbored slightly elevated ALT values, but no other abnormalities.

The ICD10 diagnosis fibrosis/cirrhosis (A) was 20 times more frequent in Pi*ZZ participants (21.7[8.8–53.7], $p < 0.0001$) and moderately enriched in Pi*SZ (3.1[1.2–8.2], $p = 0.027$) and Pi*MZ subjects (1.7[1.2–2.2]; $p = 0.001$). The odds of having primary malignant neoplasm of the liver (B) was significantly increased in Pi*ZZ and Pi*SZ individuals. For both ICD codes, the genotypes Pi*ZZ and Pi*SZ conferred similar or greater risk factors than known genetic liver disease modifiers. LSM values from the international cohort confirmed the intermediate liver fibrosis burden of Pi*SZ subjects compared to non-carriers and Pi*ZZ individuals.

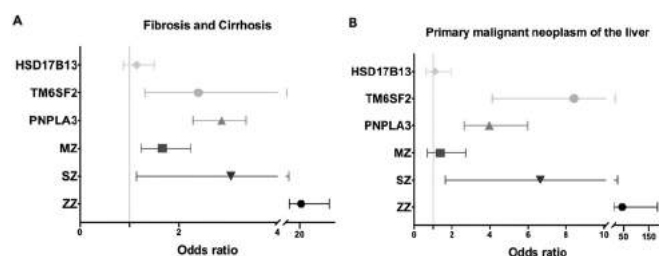


Figure: Adjusted odds ratios of ICD10 diagnoses in Pi*MZ, Pi*SZ, and Pi*ZZ subjects; and homozygous carriers of *PNPLA3* p.I148M (rs738409), *HSD17B13*:T (rs72613567), or *TM6SF2* p.E167K (rs5854926) variants, all compared to corresponding non-carriers.

Conclusion: Our study defines the liver phenotype of the most common AATD genotypes and enables evidence-based clinical management. For the first time, it provides reliable data on Pi*SZ individuals as well as AATD-associated predisposition to liver cancer.

PO-561

Recent portal venous system thrombosis associated with Cytomegalovirus disease: results of a multicenter study

Chloé De Broucker¹, Aurélie Plessier², Isabelle Ollivier Hourmand³, Sébastien Dharancy⁴, Jean Paul Cervoni⁵, Christophe Bureau⁶, Philippe Sogni⁷, Odile Gorla⁸, Olivier Corcos⁹, Kamal Zekrini², Payance Audrey², Hortense Davy², Nadhira Fidouh¹⁰, Yazdan Yazdanpanah¹⁰, Dominique Valla², Rautou Pe². ¹Hôpital de Poissy Saint Germain, Service de maladies infectieuses et tropicales, Poissy, France; ²Hôpital Beaujon, Hepatology, Clichy, France; ³CHU Caen, Service d'hépatogastro-entérologie et nutrition, Caen; ⁴CHRU Lille, Service d'hépatologie, Lille, France; ⁵CHU Besançon, Service d'hépatogastro-entérologie, Besançon, France; ⁶Hôpital Rangueil, Service d'hépatologie, Toulouse Cedex 9, France; ⁷Hôpital Cochin, Service d'Hépatologie, Paris, France; ⁸CHU Rouen, Service d'hépatogastro-entérologie, Rouen, France; ⁹Hôpital Beaujon, Gastroenterology, Clichy, France; ¹⁰Hôpital Bichat, Service de maladies infectieuses et tropicales, Paris, France

Email: pierre-emmanuel.rautou@aphp.fr

Background and aims: Recent non-malignant non-cirrhotic portal venous system thrombosis (PVT) is a rare condition. Among risk factors for PVT, cytomegalovirus (CMV) disease is usually listed based on few reported cases. The aim of this study was to determine characteristics and outcome of patients with PVT associated with CMV disease.

Method: We conducted a French multicenter retrospective study comparing patients with recent PVT and CMV disease ("CMV positive"; $n = 23$) with patients with recent PVT for whom CMV testing was negative ("CMV negative"; $n = 53$) or unavailable ("CMV unknown"; $n = 299$). Diagnosis of CMV disease was based on: anti-CMV IgM with low avidity of IgG or IgG seroconversion ($n = 13$); organ injury with a detectable CMV deoxyribonucleic acid (DNA) on biopsy ($n = 1$); significant plasma CMV DNA in immunodepression ($n = 1$); detectable anti-CMV IgM ($n = 8$).

Results: As compared with patients from the "CMV negative" and "CMV unknown" groups, patients from the "CMV positive" group were younger (51, 47 and 36 years-old, respectively), had more frequently fever (19%, 20% and 48%, respectively), higher heart rate (80, 76 and 105 beat per minute, respectively), higher lymphocyte count (1.6, 1.7 and 3.1 G/L, respectively) and higher serum ALT levels (30, 43 and 99 UI/L, respectively) ($p \leq 0.01$ for all comparisons). Frequency of immunosuppression, of abdominal inflammation, extension and localization of PVT were similar between the three groups. Thirteen out of 23 "CMV positive" patients had another risk factor for thrombosis. Besides CMV disease, number of risk factors for thrombosis was similar between the 3 groups. Prothrombin gene mutation was more frequent in "CMV positive" patients (22%) than in the "CMV negative" (4%, $p = 0.01$) and "CMV unknown" (8%, $p = 0.03$)

groups. Complete recanalization at 24 months was not associated with CMV status (hazard ratio = 1.957 in multivariate analysis, p = 0.225).

Conclusion: In patients with recent PVT, signs of viral syndrome should raise suspicion of CMV disease. CMV disease does not seem to influence thrombosis extension nor recanalization. More than half “CMV positive” patients have another risk factor for thrombosis, with a particular link with prothrombin gene mutation. Identification of CMV infection does not deter from performing an extensive screening for risks factors for thrombosis and should not influence decision on the duration of anticoagulation.

PO-570

Portal vein recanalization for severe portal hypertension related to chronic non-cirrhotic extrahepatic portal vein obstruction: long term results

Artru Florent¹, Naik Viotti-Violi², Christine Sempoux³, Joana Sofia Vieira Barbosa¹, Arnaud Hocquelet², Fabio Becce², Eleni Moschouri¹, Rafael Duran², Montserrat Fraga Christinet¹, Darius Moradpour¹, Pierre-Emmanuel Rautou⁴, Alban Denys². ¹Centre hospitalier universitaire vaudois, Gastroentérologie et hépatologie, Lausanne, Switzerland; ²Centre hospitalier universitaire vaudois, Radiodiagnostic et radiologie interventionnelle, Lausanne, Switzerland; ³Centre hospitalier universitaire vaudois, Institut universitaire de pathologie, Lausanne, Switzerland; ⁴Hôpital Beaujon, service d'hépatologie, Clichy, France
Email: flo_artru@hotmail.com

Background and aims: We aimed to evaluate the long-term outcome of patients with chronic non-cirrhotic extrahepatic portal vein obstruction (CNC-EHPVO) with severe portal hypertension who underwent portal vein recanalization (PVR) and to determine factors predicting PVR failure and stent dysfunction.

Method: This retrospective study included all patients who underwent PVR without TIPSS insertion in the context of CNC-EHPVO at Lausanne University Hospital, Switzerland between 01.2000 and 12.2019. Stent dysfunction was defined as complete occlusion of the stent or new onset of portal hypertension-related symptoms.

Table 1: Main characteristics of patients at recanalisation procedure

	Overall cohort (N = 31)
Indication for recanalization, N (%)	
GI bleeding	13 (42)
Abdominal pain	7 (23)
Prior to abdominal surgery	4 (12)
Portal cholangiopathy	3 (10)
Ascites	1 (3)
Other	3 (10)
Pattern of CNC-EHPVO according to Marot [1], N (%)	
1	16 (52)
2	12 (38)
3	3 (10)
Extension of thrombosis, N (%)	
Limited to portal vein	3 (10)
Splenic or mesenteric vein	13 (42)
Both splenic and superior mesenteric vein	15 (48)
Complete occlusion of the portal vein, N (%)	27 (87)
Duration between diagnosis and recanalisation, months	9 (2–49)

[1] PMID 30503174.

Results: 31 patients were included. Risk factors for CNC-EHPVO were thrombotic disorder (N = 12, 39%), pancreatitis (N = 10, 32%) and abdominal surgery (N = 9, 29%). Main characteristics at the time of PVR are presented in Table 1. PVR was successful in 27 patients (87%). PVR failure was associated with extension within the intrahepatic portal tract (Marot et al [1], p = 0.005) and recanalisation for recurrent abdominal pain (p = 0.02). Adverse events occurred in 6 patients (20%) without any fatal event. A majority of patients (N = 21; 78%) were anticoagulated after successful PVR. Long-term anticoagulation was administered in 18 patients (67%). After a median follow-up of 50 months (22–76), 7 patients developed stent dysfunction. Five of them underwent a second PVR with 3 successful procedures. Five-year survival free of stent dysfunction was 70% (95% CI: 51–89). Partial occlusion before PVR (p = 0.002), PVR for recurrent abdominal pain (p = 0.03) and higher hemoglobin level (p = 0.04) were associated with stent dysfunction at 5 years while anticoagulant therapy was not.

Conclusion: In selected patients with CNC-EHPVO and severe portal hypertension, PVR was feasible and safe. Complications of CNC-EHPVO are controlled in almost 3/4 of the patients at 5 years.

PO-737

Genetic haemochromatosis, a common disorder but are General Practitioners still unaware? A qualitative study

Gerri Mortimore^{1,2}, Amelia Woodward³. ¹University of Derby, Health and Social Care, Derby, United Kingdom; ²Haemochromatosis UK, Education Programme Manager, Spalding, United Kingdom; ³University of Derby, Research, Derby, United Kingdom
Email: g.mortimore@derby.ac.uk

Background: Genetic haemochromatosis (GH) is the most common genetic disorder in Caucasians¹. This is confirmed by data from the UK Biobank study which revealed that approximately 380, 000 people in the UK have GH². Despite its prevalence, Freedom of Information requests from UK hospital Trusts revealed that only 20, 698 are currently being treated in the UK³ and only 1:5000 people are diagnosed with it^{4, 5}, despite research indicating that 1:113 people have GH in Northern Ireland and Scotland, and 1:150 people in England and Wales²

GH causes the body to absorb excess iron which can lead to systematic iron overload within internal organs such as the liver, pancreas, heart, and joints; eventually causing inflammation and tissue damage. If left untreated it may lead to cirrhosis of the liver and a ten-fold risk of hepatocellular carcinoma in men⁶. Early symptoms of GH are non-specific such as fatigue, abdominal and joint pain and as such, may be considered inconsequential by General Practitioners (GP's), resulting in a delay in diagnosis and treatment, which consists of lifelong therapeutic venesections

To date there has been little research examining patient's thoughts and experiences of being diagnosed and treated for GH, a disorder which, if diagnosed late, can cause significant harm

AIMS: A phenomenological study to explore patient experiences of living with genetic haemochromatosis and the effect of this on their lives and family.

Method: Data was collected using semi-structured interviews with a sample of 22 male and female patients with haemochromatosis who responded to a poster advertising the study. Patients had been diagnosed between 1–30 years. The interview using broad themes covered their experience of diagnosis and treatment. The interviews were recorded and transcribed verbatim. Analysis of the data was conducted using a thematic analysis

Results: There were number of common themes that came out of the interviews around the diagnostic process. Most of the patients interviewed talked about experiencing a delay, in some cases of many years, from first presentation of symptoms to their GP to final diagnosis. Many of the patients felt that GPs lacked knowledge of genetic haemochromatosis and talked about how GPs were unable to give them any detailed information about the disease. Several

POSTER PRESENTATIONS

patients were only diagnosed once they saw a locum doctor not their normal family GP.

Conclusion: Early detection and treatment for GH depends on increased knowledge of GPs. This qualitative study identified that patients perceive there to be gaps in understanding GH diagnosis and treatment. Ensuring GPs are aware of GH and the strategies for diagnosis could result in improved patient care. These findings indicate that improved education for GPs regarding GH may be beneficial to improve patient care for this condition and potentially reduce delays in diagnosis and life-saving treatment

PO-891

An innovative treatment for Primary Hyperoxaluria Type 1 based on specific gene correction and hepatic direct cell reprogramming

Virginia Nieto-Romero^{1,2}, Aida García-Torralba^{1,2}, Andrea Molinos-Vicente^{1,2}, Ramon García-Escudero³, Eduardo Salido⁴, Jose Segovia^{1,2}, Maria Garcia-Bravo^{1,2}. ¹Biomedical Innovation Unit, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT) and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; ²Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD, UAM), Unidad Mixta de Terapias Avanzadas, Madrid, Spain; ³Molecular Oncology Unit (CIEMAT), Biomedical Research Institute i+12, University Hospital 12 de Octubre, and Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain; ⁴Hospital Universitario de Canarias, Universidad La Laguna. Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Pathology Department, Tenerife, Spain
Email: virginia.nieto@externos.ciemat.es

Background and aims: Liver transplantation is nowadays the only definitive curative treatment for many inherited metabolic liver disorders such as Primary Hyperoxaluria Type 1 (PH1). This is a rare genetic disorder caused by alanine:glyoxylate aminotransferase (AGT) deficiency, a hepatic enzyme involved in glyoxylate metabolism. Due to the shortage of liver donors, developing new therapeutic approaches for the treatment of these diseases is essential.

Liver cell replacement therapy appears as a promising alternative to liver transplant. However, the use of primary human hepatocytes or hepatocyte like cells generated from iPSCs, is limited by the difficulty to expand and generate completely functional mature hepatocytes, in addition to the safety issues in the case of iPSCs.

Method: To face this challenge we propose the combination of site-specific gene correction and direct cell reprogramming for the generation of autologous phenotypically healthy induced hepatocytes (iHeps) from PH1 patient skin-derived fibroblasts. Following this strategy would be possible to obtain high amounts of corrected hepatocyte-like cells, avoiding the potentially tumorigenic steps of iPSC generation.

Results: We obtained AGXT gene corrected cells by two different CRISPR/Cas9 based strategies. In a first strategy, accurate specific point mutation correction (c.853T-C) was achieved by homology-directed repair (HDR) with ssODN harboring the wild-type sequence. In the second strategy, an enhanced version of AGXT cDNA was inserted near the transcription start codon of the endogenous gene, constituting an almost universal correction strategy for PH1 mutations.

Direct reprogramming of fibroblasts into iHeps was conducted by lentiviral overexpression of hepatic transcription factors and in vitro culture in defined media. Transcriptome analysis of iHeps generated from healthy donors, as well as from PH1 and gene corrected patient-derived fibroblasts, has demonstrated the hepatic identity of the resulting iHeps. Demonstration of in vitro and in vivo functionality and disease phenotype reversion of gene corrected-PH1 iHeps is ongoing.

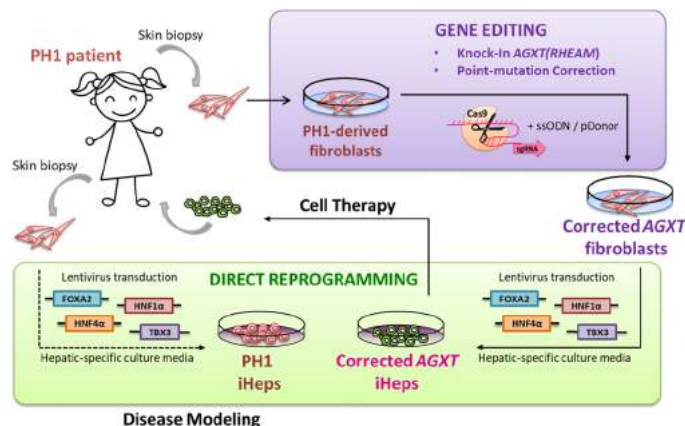


Figure:

Conclusion: The development of these advanced therapies will set up an alternative cellular source to replace endogenous deficient hepatocytes with autologous functional corrected cells for many genetic liver disorders. In addition, patient-derived iHeps would be a useful tool as in vitro disease model.

PO-996

Non-invasive biomarkers for assessment of esophageal variceal bleeding risk in patients with non-cirrhotic portal hypertension

Hangfei Xu¹, Yu Wang², Zhenhua Fan³, Hui Liu⁴, Fuliang He², Yongping Yang⁵, Fuquan Liu³, Ji-Dong Jia², Huiguo Ding¹. ¹Beijing You'an Hospital, affiliated with Capital Medical University, Department of Gastroenterology and Hepatology, Beijing, China; ²Beijing Friendship Hospital, affiliated with Capital Medical University, Department of Hepatology, Beijing, China; ³Beijing Shijitan Hospital, affiliated with Capital Medical University, Department of Interventional Therapy, Beijing, China; ⁴Beijing You'an Hospital, affiliated with Capital Medical University, department of pathology, Beijing, China; ⁵The Fifth Medical Center, Chinese PLA General Hospital, Comprehensive liver cancer Department, Beijing, China
Email: dinghuiguo@ccmu.edu.cn

Background and aims: To verify the value of Baveno VI criteria and expanded Baveno VI criteria in rolling out the high-risk varices (HRV) in patients with non-cirrhotic portal hypertension (NCPH), and to explore the predictiveness of liver stiffness \times spleen diameter/platelet count score (LSPS) and platelet count/spleen diameter ratio (PSR) for the risk of esophageal varices (EV) bleeding in patients with NCPH.

Method: One hundred and eleven patients of NCPH were enrolled at three tertiary medical centres, and 204 patients with hepatitis B cirrhosis served as controls. Of NCPH, 70 cases of idiopathic non-cirrhotic portal hypertension (INCPH) and 41 cases of chronic non-tumoral non-cirrhotic portal vein thrombosis (PVT) were included. According to the severity of EV under endoscopy, it was divided into low-risk varices (LRV) (no/mild EV) and HRV (moderate/severe EV). The ability of Baveno VI criteria and expanded Baveno VI criteria to exclude the presence of HRV was validated in NCPH and hepatitis B cirrhosis patients. LSPS and PSR were calculated for all patients. And diagnostic applicability was assessed by the area under the receiver operator curve (AUC).

Results: Based on gold standard of endoscopy, among INCPH/PVT patients who met the Baveno VI criteria and expanded Baveno VI criteria, the respective risk of missing HRV was 50%/30% and 53.8%/50%. In INCPH patients, there was no evidence for statistically significant difference in PLT, spleen diameter, LSM, LSPS and PSR between LRV and HRV. The assessment of the risk of EV bleeding was insufficiency with respective AUC of LSPS and PSR of 0.564 (95%CI 0.426–0.703, $P=0.372$) and 0.592 (95%CI 0.457–0.727, $P=0.202$). In PVT patients, there were significant differences in PLT, spleen diameter, LSPS and PSR between two groups. The AUC of LSPS and

PSR were 0.796 (95%CI, 0.651–0.941, P=0.003) and 0.833 (95%CI, 0.706–0.961, P=0.001), respectively. In patients with hepatitis B cirrhosis, the Baveno VI and expanded Baveno VI criteria have a lower risk of missing HRV of 0% and 5.4%, respectively. The respective AUC of LSPS and PSR were 0.867 and 0.789 (p <0.05).

Conclusion: The Baveno VI and expanded Baveno VI criteria have a higher risk of missing HRV in INCPH and PVT patients. LSPS and PSR may be useful in assessing the risk of EV bleeding in PVT patients.

PO-1108

Hepatic venous pressure gradient in non-cirrhotic portal hypertension – is it worth measuring?

Hangfei Xu¹, Yu Wang², Zhenhua Fan³, Hui Liu⁴, Fuliang He², Peng Li¹, Yuening Zhang¹, Yongping Yang⁵, Fuquan Liu³, Ji-Dong Jia², Huiguang Ding¹. ¹Beijing You'an Hospital, affiliated with Capital Medical University, Department of Gastroenterology and Hepatology, Beijing, China; ²Beijing Friendship Hospital, affiliated with Capital Medical University, Department of Hepatology, Beijing, China; ³Beijing Shijitan Hospital, affiliated with Capital Medical University, Department of Interventional Therapy, Beijing, China; ⁴Beijing You'an Hospital, affiliated with Capital Medical University, department of pathology, Beijing, China; ⁵The Fifth Medical Center, Chinese PLA General Hospital, Comprehensive liver cancer Department, Beijing, China
Email: dinghuiguang@ccmu.edu.cn

Background and aims: Hepatic venous pressure gradient (HVPG) ≥10mmHg is the independent predictor of hepatic decompensation events in cirrhosis. High HVPG signals increased risk of mortality. Non-cirrhotic portal hypertension (NCPH), especially prehepatic or presinusoidal portal hypertension, often have a normal or mildly elevated HVPG. A proportion of NCPH patients still have high HVPG (≥10mmHg). The difference of clinical characteristics and outcomes between high HVPG and low HVPG (<10mmHg) is unknown.

Method: 64 cases of NCPH patients with HVPG were enrolled in three tertiary medical centres. Based on HVPG, 26 patients were classified into high HVPG group, 38 patients were in low HVPG group. Baseline characteristics and follow-up date (variceal bleeding, ascites, liver transplantation and death) was compared between two groups.

Results: Between both groups of patients, mean age, gender characteristics, ALT, AST, albumin, bilirubin and liver stiffness measurement were not significantly different. The Child-Pugh score in high HVPG group was higher compared with those in low HVPG group (7 (6–8) vs 5 (5–7); P=0.008). At presentation, the prevalence of ascites in high HVPG group is significantly higher than low HVPG group (72% vs 32.4%; P=0.002), while the degree of esophageal varices, variceal bleeding at baseline was similar in the 2 groups. The median follow-up period was 14.8 months (IQR 12.5–20.9) in high HVPG group and 16.4 months (IQR 14.4–23.5) in low HVPG group (p = 0.262). Overall, the 3-year probability of liver transplantation-free survival was similar in high HVPG group compared with low HVPG group (95.5% vs 97.2% P = 0.76). Among all patients, no one developed uncontrolled ascites during follow-up. The 1-, 2-year actuarial probability of being free of bleeding were 86.4%, 86.4% in high HVPG group and 84.1%, 73.6% in low HVPG group respectively, showing no significant difference (p = 0.62).

Conclusion: Despite that some patients have higher HVPG, the value of HVPG in patients with NCPH to predict mortality and assess the progression of portal hypertension is limited.

PO-1243

Direct oral anticoagulants (DOACs) for off-label use in patients with Budd Chiari Syndrome (BCS)

Georg Semmler^{1,2}, Katharina Pomej^{1,2}, David JM Bauer^{1,2}, Lorenz Balcar^{1,2}, Benedikt S. Hofer^{1,2,3}, Benedikt Simbrunner^{1,2,4}, Matthias Pinter^{1,2}, Michael Trauner¹, Mattias Mandorfer^{1,2}, Thomas Reiberger^{1,2,4}, Bernhard Scheiner^{1,2}. ¹Medical University of

Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Vienna, Austria; ³Medical University of Vienna, Christian Doppler Lab for Portal Hypertension and Liver Fibrosis, Vienna, Austria; ⁴Medical University of Vienna, Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Vienna, Austria

Email: thomas.reiberger@meduniwien.ac.at

Background and aims: Budd Chiari Syndrome (BCS) is a rare vascular liver disease with long-term anticoagulation by vitamin-K antagonists (VKAs) being recommended by current guidelines. Direct oral anticoagulants (DOACs) do not interfere with INR/MELD and do not require routine monitoring, but their use in BCS is off-label. Here we report our experience with DOACs in BCS.

Method: 14 patients with BCS were considered for this longitudinal cohort study. Data on the clinical course on anticoagulant therapy and efficacy/safety of DOACs were longitudinally collected.

Results: Mean age at BCS presentation was 37.2 ± 16.8 years. Overall, 78.6% (11/14) had previous/current hepatic decompensation, and 92.9% (13/14) showed signs of clinically significant portal hypertension (CSPH; n = 12 splenomegaly, n = 11 varices, n = 9 ascites, n = 4 variceal bleeding). 62.5% (5/8) had concomitant portal vein thrombosis/splanchnic-vein-thrombosis, four were JAK-2 positive (2 suffering from essential thrombocytosis and 2 were additionally carrying the Factor-V-Leiden-mutation), and one patient suffered from anti-phospholipid-syndrome.

During a median follow-up of 98 (22–267) months, eight patients (57.1%) received DOAC treatment (edoxaban: n = 6, apixaban: n = 1, dabigatran: n = 1) for a median of 26 (6–69) months. 75.0% (6/8) patients were switched from LMWH (n = 3) or VKA (n = 3) to DOAC after disease stabilization/improvement, while 25.0% (2/8) of BCS patients were directly started with DOAC. Complete response was achieved or maintained in 7/8 patients including two patients with TIPS prior to DOAC initiation.

Three major bleedings (37.5%) occurred during DOAC therapy (n = 2 upper-GI-bleeding, n = 1 HCC rupture) but DOAC treatment was continued in all patients after bleeding control. Two deaths (n = 1 spontaneous bacterial peritonitis, n = 1 HCC) occurred while on DOAC therapy.

Conclusion: DOACs seem to be effective and safe for long-term anticoagulation in patients with BCS, but confirmation by larger prospective studies is needed.

PO-1244

The prevalence of PSYCHIATRIC comorbidities in WILSON'S DISEASE

Merjem Begic¹, Samantha Graf¹, Daniel König¹, Benjamin Vyssoki¹, Karin Kozbial², Albert Stättermayer², Petra Munda², Peter Ferenci².

¹Medical University of Vienna, Department of Psychiatry and Psychotherapy, Division of Social Psychiatry, Vienna, Austria; ²Medical University of Vienna, Department of Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria
Email: merjem.begic@meduniwien.ac.at

Background and aims: Psychiatric manifestations may precede neurological signs and hepatic symptoms in the early stages of Wilson disease (WD). Furthermore, some patients may develop psychiatric problems after initiation of treatment. Data on the frequency of psychiatric symptoms vary worldwide. Our goal was to determine the prevalence of psychiatric comorbidities in patients with WD currently undergoing treatment at the University Hospital of Vienna.

Method: From August 2020 until January 2021, all adult patients with WD were invited to participate in our prospective clinical trial. The patients who signed their consent were asked to complete three questionnaires (Beck Anxiety Inventory [BAI], Beck Depression Inventory [BDI] and WHO Disability Assessment Schedule 2.0

POSTER PRESENTATIONS

[WHODAS 2.0], followed by a structured interview (Mini-International Neuropsychiatric Interview [MINI]).

Results: Twenty-four patients (13 male [m] and 11 female [f]) with WD, with a mean age of 41.5 years, m/f = 43.8/38.7 years, were included. Sixteen patients (m/f = 7/9; 66, 7%) presented primarily with hepatic symptoms, and 8 patients (m/f = 6/2; 33%) with neurologic symptoms. In eighteen patients (m/f = 10/8; 75%) the testing revealed psychiatric comorbidities: 8 (m/f = 6/2) had a psychiatric diagnosis, 10 patients (m/f = 4/6) showed symptoms of psychiatric disorders of subclinical relevance such as mild anxiety disorder and 5 patients (m/f = 4/1) had light to moderate depression. The most common psychiatric comorbidities were major depression (m/f = 3/1; 16.6%), generalized anxiety disorder (m/f = 2/1; 12.5%), agoraphobia (m/f = 2/1; 12.5%) and panic disorder (m/f = 1/1; 8.3%). All 3 Patients with generalized anxiety disorder and 2 patients (m/f = 1/1) with agoraphobia also had major depression. In 2 male patients with major depression, psychotic disorder was documented. Out of these one was later admitted to the psychiatric clinic. Hypomania was observed in 2 patients (m/f = 1/1), and social phobia in 1 male patient. 6 patients did not meet the criteria for a psychiatric diagnosis.

Conclusion: With a high prevalence rate of psychiatric comorbidities (75%) in patients with WD, the study underscores the importance of adequate screening and treatment of such disorders. Concomitant psychiatric treatment could substantially increase therapy adherence and quality of life in patients with WD.

PO-1285

An integrated analysis of long-term clinical safety in maralixibat-treated participants with Alagille syndrome

Rakesh Raman¹, Will Garner¹, Pamela Vig¹, Ed Tucker¹. ¹Mirum Pharmaceuticals, Foster City, United States
Email: rraman@mirumpharma.com

Background and aims: Maralixibat (MRX) is an apical sodium-dependent bile acid transport inhibitor that interrupts enterohepatic recirculation of bile acids, thus reducing pruritus and cholestasis. The safety database of MRX comprises over 1600 participants, which includes participants with Alagille syndrome (ALGS). In this analysis, we present an overview of clinical safety for an integrated population of MRX-treated participants with ALGS.

Method: An analysis of safety data, which included a review of treatment-emergent adverse events (TEAEs) and laboratory data, was conducted across an integrated safety population comprising five Phase 2 clinical studies of MRX-treated participants with ALGS (N = 86). Doses of MRX ranged from 66.5 micrograms/kg once daily to 380 micrograms/kg twice daily. A data cut was taken on 1 December 2019.

Results: Of the 86 participants, the median duration of exposure to MRX was 32.3 months (range 0.03–60.9 months), including 19 participants who so far have received treatment for ≥4 years. Most TEAEs were mild to moderate in severity. A total of 22 participants had a serious adverse event (AE); 3 were related to MRX. Ten participants had an AE leading to discontinuation of MRX. The most common AEs were diarrhea and abdominal pain. These events were mostly transient in nature (median duration of 2 days and 1 day, respectively), mild to moderate in severity, and resolved with no action taken with MRX. Review of laboratory data showed asymptomatic spontaneous rises in serum alanine aminotransferase (ALT) in some participants; however, these appeared to be consistent with the natural history of ALGS and were not dose dependent. The increases were not associated with concomitant rises in aspartate aminotransferase, bilirubin, or clinical sequelae. No other clinically significant trends were observed, including for fat-soluble vitamins.

Conclusion: A long-term analysis of the safety data across the integrated ALGS population revealed most TEAEs to be mild to moderate in severity. Diarrhea and abdominal pain were the most common AEs, were mostly transient in nature, and resolved without any action taken. ALT rises were not associated with clinical sequelae and appeared to be consistent with the natural history of the disease.

This analysis demonstrates that >4 years of treatment with MRX is well tolerated and has an acceptable safety profile. Forty-one patients from this ALGS population continue to receive ongoing MRX treatment.

PO-1354

Wilson Disease is associated with prevalent neuropsychiatric comorbidity

Eva Pfister¹, Kirsten Müller-Vahl², Carolin Fremer², Imeke Goldschmidt¹, Norman Junge¹, Eva Bültmann³, Amelie Stalke^{1,4}, Ulrich Baumann¹. ¹Paediatric Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany; ²Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany; ³Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany; ⁴Department of Human Genetics, Hannover Medical School, Hannover, Germany
Email: pfister.eva-doreen@mh-hannover.de

Background and aims: To characterize a single centre cohort of children with Wilson disease (WD) with a focus on clinical and radiological findings, and long-term outcome of neuropsychiatric comorbidity.

Methods: All patients diagnosed with WD in childhood at Hannover medical School born after 1970 were retrospectively reviewed. Follow-up was carried out through an outpatient visit or structured telephone interview. In a subgroup of patients aged <18 years prospective specific neuropsychiatric assessment including Paediatric Quality of Life Inventory™, Children's Color Trail Test™, Global Assessment Scale for Wilson's Disease, Mini International Neuropsychiatric Interview for children and adolescents, and Global Dystonia Severity Rating Scale was performed. All cranial MRIs were systematically reviewed and re-evaluated.

Results: Data from 93 paediatric WD patients (n = 58 female, n = 81 genetically confirmed) was included. Presenting features of WD were elevated liver enzymes (n = 34), acute liver failure (n = 25), chronic liver disease (n = 15), and primary neuropsychiatric manifestation (n = 4; between the ages 5 and 17 years). 15 patients were asymptomatic at the time of diagnosis. Over time, 26 patients received liver transplantation (LTx). Within the long-term period of up to 40 years, 9 patients died, 11 were lost to follow-up, while 73 patients (7–48, median 21 years) are still alive.

The most recent medication of these 73 patients is D-Penicillamine (n = 39), Rentine (n = 7), D-Penicillamine + Zinc (n = 3) and Zinc monotherapy (n = 3). 4 patients were non-compliant. 17 patients receive immunosuppressive therapy after LTx. During follow-up 17/71 patients reported neurological-only, 4/71 psychiatric-only, and 4/71 neurological and psychiatric symptoms despite Wilson-specific therapy. Cranial MR showed pathological findings in 18/36 patients. Typical WD associated changes were detected in basal ganglia and brain stem, in patients with impaired liver synthetic function abnormalities in the pallidum were also noted. In addition, in 11 children we found an age-atypical accentuation of white matter changes and cerebellar fissures as a sign of a slight reduction in the volume of the cerebellum. In the prospective specific neuropsychiatric assessment conducted in 15 paediatric patients, abnormalities in at least one test were detected in each.

Conclusion: WD can manifest with neuropsychiatric symptoms as early as preschool age. Mild and clinically undiagnosed neuropsychiatric symptoms are common in paediatric WD patients and may be missed on general assessment. Children and adolescents may have radiological features including but not limited to copper deposition in basal ganglia. Despite use of current therapies, patients develop neurological and/or psychiatric complications. Current therapeutic options in childhood appear to be insufficient to address this comorbidity.

PO-1500

Dose adjustment of chelators based on urinary copper excretion after a drug free holiday-the first step to personalized medicine in patients with Wilson disease

Karin Kozbial¹, Albert Staettermayer¹, Alexander Pilger², Petra Munda³, Michael Trauner³, Peter Ferenci³. ¹Medical University of Vienna, Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Department of Laboratory Medicine, Vienna; ³Medical University of Vienna, Department of Gastroenterology and Hepatology, Vienna, Austria
Email: karin.kozbial@meduniwien.ac.at

Background and aims: In Wilson disease (WD) increased serum “free copper (Cu)” is considered to be toxic and is commonly calculated by subtracting ceruloplasmin (CPL)-bound Cu from the total serum Cu concentration (non-CPL plasma copper [NCC]). Unfortunately, correct estimation of NCC by current immunological methods is difficult, and with ≥20% negative NCC results of questionable value. Another approach to estimate “free Cu” is the 24-h urinary Cu excretion after an intentional drug holiday (U24CuDF).

The aim of the study was to investigate the feasibility of dose adjustment of chelators in long-term treated patients with WD based on U24CuDF.

Method: U24CuDF was measured repeatedly in 19 patients with WD on long-term treatment (>5 years) with chelators (D-Penicillamine (D-PA): 8, trientine-2HCl (TRI):10; combination of D-PA/zinc:1; m/f:11/8; mean age: 40.4 years (SD±9.9); hepatic:17, neurologic 2; cirrhosis: 4). Urine was collected on the third day of an intentional drug holiday. Urinary Cu concentrations were measured by graphite furnace atomic absorption spectrometry. Treatment was adapted depending on U24CuDF: if U24CuDF was <50 µg on subsequent visits chelator dose was decreased; if it was >50 µg the dose remained unchanged or was increased.

Results: U24CuDF (median:42.5 µg/24 h [range:11.3–167]) was lower than Cu excretion measured on drug intake (375 µg/24 h [85–1495], p < 0.001). In 11 patients (57.9%) U24CuDF was <50 µg/24 h, in 8 (42.1%) it was >50 µg. In 9 of the 11 patients with normal U24CuDF D-PA dose was reduced (1500 mg/d to 1250 mg/d in 1, 1500 to 1000 in 2, 1000 to 750 in 2, and 750 to 500 in 4). Follow-up of >one year was available in 6: in four U24CuDF remained <50 µg, in two values were slightly above 50 µg. No change in clinical parameters was noted. Two patients with severe psychiatric symptoms with an initially normal U24CuDF had values >50 µg/24 h during follow-up visits, dose was not changed. One of them was hospitalized repeatedly, the other died one month after the last visit (probably suicide).

Seven of the 8 patients with U24CuDF>50 µg were on TRI; in 3 of them the dose was increased, however no follow-up is yet available. The other patients continued the previous therapy.

Conclusion: U24CuDF is a useful parameter for dose adjustment in WD patients on long-term treatment with chelators. It may be a first step to individualize treatment in these patients. Furthermore it helps to identify patients with insufficient drug adherence. Further prospective studies are needed.

PO-1522

Voices of Italian patients with Wilson’s disease: results from a quality survey

Massimo Zuin¹, Giuseppe Maggiore², Georgios Loudianos³, Gabriella Nebbia⁴, Raffaele Iorio⁵, Fabiola Didato⁵, Salvatore Dilorenzo⁶, Margherita Matarazzo⁵. ¹ASST Santi Paolo e Carlo, Milano, Italy; ²Ospedale Bambino Gesù, Rome, Italy; ³Ospedale Microcitamico, Cagliari, Italy; ⁴IRCCS Cà Granda Ospedale Maggiore Policlinico-Clinica Pediatrica, Milano, Italy; ⁵University of Naples Federico II, Dipartimento di Scienze Mediche Traslazionali, Napoli, Italy; ⁶Italian Association of Wilson’s Disease, Maduria, Italy

Background and aims: Wilson’s disease (WD) is a rare autosomal recessive disorder in which defective biliary excretion of copper leads

to its accumulation, particularly in the liver and brain. Early diagnosis and adherence to life-long therapy is needed for disease control, although often problematic. Disease characteristics and prospected life-long medical care may impact on disease experience and patient’s quality of life. The aim of this work is to investigate different aspects related to WD patients in Italy, including disease experience and quality of life.

Method: A qualitative survey proposed by the Italian Association of WD Patients was distributed within the WD patients’ network.

Results: 151 patients participated to the survey and 125 (83%), including 52% women and 69% over 18, provided complete questionnaires. The disease was found to have been accidentally diagnosed in most patients (69%) by abnormal liver function tests. Surprisingly, 42% of these patients were misdiagnosed even if they presented some typical symptoms that could appear to be suspected WD disease. The timing of diagnosis was variable: pediatric cases were diagnosed within 12 months from the symptom onset, thanks to family screening. On the other hand, adults received a delayed diagnosis, ranging from 2 to 5 years. As expected, D-Penicillamine was used as initial treatment in 66% of patients, while Zinc and Trientine were used in 22% and 12% of patients, respectively. However, at the time of the survey, the proportion of patients on Penicillamine was almost halved due to adverse events, leading to a switch of patients on Trientine or on Zinc therapy. Regarding therapy satisfaction, 76% of patients were not satisfied with ongoing therapy and suggested how it might be an ideal therapy (Fig. 1). WD had a negative impact on school performance in 41% of students and led to change/interruption of job-activities in 36% of adults. Finally, when the quality of life was evaluated, 26% of patients considered it sufficient or limited, mainly due to daily fatigue and anxiety.

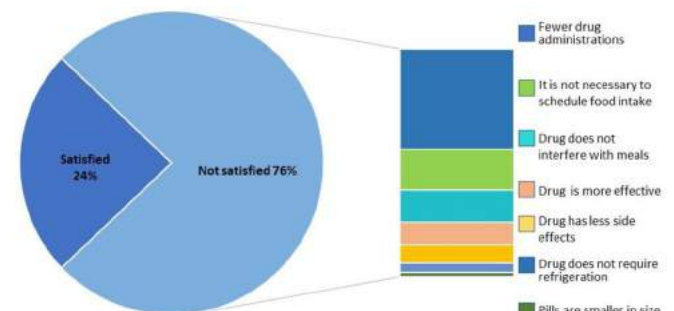


Fig. 1: Satisfaction of therapy and characteristics of an ideal therapy suggested by WD patients

Conclusion: 1) There is a need to strengthen the medical specialists’ knowledge regarding the WD as part of their general training. 2) The development of new therapies, more effective and easier to tolerate is desirable with the aim to ameliorate WD patients’ quality of life.

PO-1641

Long-term treatment with odevixibat improves multiple sleep parameters in patients with progressive familial intrahepatic cholestasis: a pooled responder analysis from the phase 3 PEDFIC studies

Richard Thompson¹, Pier Luigi Calvo², Winita Hardikar³, Patrick Horn⁴, Elke Lainka⁵, Cara Mack⁶, Quanhong Ni⁴, Lise Kjems⁴. ¹Institute of Liver Studies, King’s College London; ²Regina Margherita Children’s Hospital, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Turin, Italy; ³Royal Children’s Hospital; ⁴Albireo Pharma, Inc.; ⁵University Duisburg-Essen; ⁶Children’s Hospital Colorado, University of Colorado School of Medicine
Email: lise.kjems@albireopharma.com

Background and aims: Patients with progressive familial intrahepatic cholestasis (PFIC) may experience severe pruritus that results in considerable sleep disturbance. In the phase 3 PEDFIC 1 (P1) and

POSTER PRESENTATIONS

PEDFIC 2 (P2) studies, odevixibat reduced serum bile acids (sBA), improved pruritus, and was generally well tolerated in patients with PFIC. Using pooled data from these studies, we describe changes in several sleep parameters in patients who responded to odevixibat treatment (Rs) vs treatment non-responders (NRs).

Table:

Change from baseline to weeks:	sBA or Pruritus Response			
	Yes (n = 48)		No (n = 28)	
	n	Mean	n	Mean
% Days with scratching associated with bleeding				
1-4	47	-16.8	28	-6.5
21-24	34	-30.9	22	3.2
45-48	18	-41.5	2	12.5
% Days needing help falling asleep				
1-4	47	-23.1	28	-10.4
21-24	34	-56.1	22	-4.9
45-48	18	-73.0	2	-1.8
% Days needing soothing				
1-4	47	-22.5	28	-6.0
21-24	34	-58.8	22	7.8
45-48	18	-74.6	2	4.2
% days sleeping with caregiver				
1-4	47	-23.1	28	-3.1
21-24	34	-48.5	22	3.1
45-48	18	-69.1	2	0.0
Number of awakenings				
1-4	47	-3.1	28	1.3
21-24	34	-1.9	22	1.5
45-48	18	-11.0	2	-4.3
Value at timepoint:				
CGIC, moderately or very much better, %				
4	42	57.1	26	30.8
24	32	59.4	21	33.3
48	18	88.9	4	25.0
CaGIC, moderately or very much better, %				
4	39	48.7	28	25.0
24	27	70.4	21	23.8
48	15	93.3	3	33.3

Method: P1 was a 24-week, randomized, placebo-controlled study in children with PFIC1 or PFIC2, and P2 is an ongoing, 72-week, extension study in patients with any type of PFIC. Across these studies, 77 patients have received odevixibat and are included in this pooled analysis. Patient sleep was evaluated based on caregiver report using the PRUCISION scale and via the clinician- or caregiver-reported Global Impression of Change (CGIC or CaGIC, respectively) sleep scales. Treatment response was defined as an sBA response (sBAs <65 or <102 $\mu\text{mol/L}$ for patients with PFIC1 and PFIC2, respectively) or a pruritus response (a ≥ 1 -point drop from baseline in pruritus score).

Results: Mean decreases in caregiver-reported percentage of days with scratching associated with bleeding, needing help falling asleep, and needing soothing were greater among Rs vs NRs (Table). At week 48, clinicians and caregivers reported that $\geq 88\%$ of Rs had moderately or very much better sleep since starting odevixibat (Table).

Conclusion: Patients with PFIC and odevixibat treatment response had substantial improvements in caregiver- and clinician-reported

sleep. These effects occurred rapidly and continued over time. The improvement in sleep is likely linked to the improved pruritus observed in patients who responded to odevixibat.

PO-1665

Substantial clinical benefits with odevixibat treatment across progressive familial intrahepatic cholestasis genetic deficiencies: subgroup analysis of serum bile acids, pruritus, and safety using pooled data from the PEDFIC 1 and 2 studies

Richard Thompson¹, Patrick Horn², Roderick H.J. Houwen³, Florence Lacaille⁴, Quanhong Ni², Philip Stein², Mary Elizabeth Tessier⁵, Carrie Thompson², Jennifer Vittorio⁶, Lise Kjems². ¹Institute of Liver Studies, King's College London, London, United Kingdom; ²Albireo Pharma, Inc., Boston, United States; ³Wilhelmina Children's Hospital and University Medical Center, Utrecht, Netherlands; ⁴Hôpital Universitaire Necker-Enfants Malades, Paris, France; ⁵Baylor College of Medicine/Texas Children's Hospital, Houston, United States; ⁶Columbia University Medical Center, New York, United States

Email: lise.kjems@albireopharma.com

Background and aims: Odevixibat is an ileal bile acid transporter inhibitor in development to treat cholestatic liver diseases. The phase 3 PEDFIC 1 (P1) and PEDFIC 2 (P2) studies assessed odevixibat in patients with progressive familial intrahepatic cholestasis (PFIC) via serum bile acid (sBA) response and change in pruritus. We describe a pooled analysis of these outcomes in patients with PFIC1 (familial intrahepatic cholestasis 1 [FIC1] deficiency) or PFIC2 (bile salt export pump [BSEP] deficiency). For those with PFIC2, BSEP subtype was also examined (subtype 1: at least 1 p.D482G or p.E297G mutation; subtype 2: at least 1 missense mutation but not p.D482G or p.E297G). **Method:** This 48-week subgroup analysis included pooled data from P1 (consisting of a 24-week, placebo-controlled treatment period in patients with PFIC1 or PFIC2) and P2 (an ongoing, 72-week, open-label extension study in patients from P1 or new patients with any type of PFIC, where all patients receive odevixibat). sBA response (ie, $\geq 70\%$ reduction from baseline or sBAs $\leq 70 \mu\text{mol/L}$), change in pruritus based on positive pruritus assessments (PPAs) at the patient level (ie, scratching score ≤ 1 or a ≥ 1 -point drop from baseline on the PRUCISION instrument), and treatment-emergent adverse events (TEAEs) were assessed.

Results: Of 77 patients who received odevixibat, 20 had PFIC1 (26%) and 51 (66%) had PFIC2. BSEP subtype 1 or 2 were present in 13 (26%) and 36 (71%) patients with PFIC2, respectively (2 additional patients with BSEP subtype 3 were not included in this analysis). During the analysis period, $\geq 50\%$ of patients met sBA response criteria, regardless of genotype (Figure; panel A). Mean PPAs were above 60% for patients with PFIC2 (including BSEP subtypes 1 and 2); mean PPAs for patients with PFIC1 were 48% (Figure; panel B). Incidence of TEAEs in odevixibat-treated patients with PFIC1 or PFIC2 (80% each) and BSEP subtype 1 and 2 (77% and 86%, respectively) in the pooled population was comparable to that of placebo-treated patients in P1 (85%). Most TEAEs were mild or moderate, self-limiting, and considered by the investigator as not related to study drug.

Conclusion: Patients with PFIC1 or PFIC2 had substantial benefits with odevixibat treatment, including reductions in sBAs and improvement in pruritus symptoms. Long-term treatment with odevixibat was well tolerated, regardless of PFIC classification or BSEP subtype.

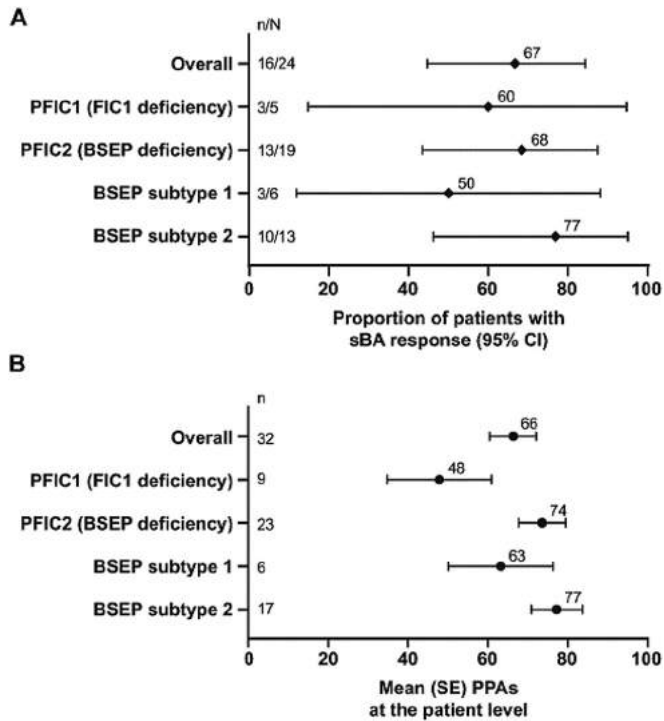


Figure:

PO-1718

Genetic analysis and phenotypic correlation in ductal plate malformation

Meha Bhuva¹, Richard Sandford², Griffiths Bill¹. ¹Addenbrooke's Hospital, Hepatology, United Kingdom; ²Addenbrooke's Hospital, Clinical Genetics, United Kingdom
Email: mehajb@aol.com

Background and aims: Ductal plate malformation (DPM) includes polycystic liver disease (PCLD), multiple biliary hamartomas (MBH), congenital hepatic fibrosis (CHF) and Caroli disease. We sought to identify the genetic basis of a cohort of hitherto undefined DPM.

Method: 34 unrelated adults with presumed congenital liver disease underwent extended genetic analysis via a clinical exome panel (PKD1, PKD2, PKHD1, SEC63, PRKCSH, GANAB, ALG8, DNAJB11, LRP5). Clinical details and phenotypic correlation were analysed.

Results: Of the 34 patients screened, genetic variants were identified in 20:

Heterozygous variants in GANAB (n = 4: 3 females, 1 male, mean age 56) were associated with a variety of mild PCLD phenotypes (with/without renal cysts, with Caroli's and with MBH). Variants were pathogenic in 2 cases and VUS in 2 cases (both deleterious).

Heterozygous variants in PRKCSH (n = 2: both female, mean age 62) were associated with PCLD without renal cysts including 1 VUS (deleterious) and 1 novel pathogenic variant in a patient considered for liver transplantation.

Heterozygous variants in the SEC63 (n = 4: 3 female, 1 male, mean age 60) were associated with largely asymptomatic PCLD mostly without renal cysts including 3 pathogenic (all novel) and one VUS (deleterious).

PKD1 (n = 3) and PKD2 (n = 2) heterozygous gene variants (4 pathogenic/2 novel) were associated with polycystic kidney and liver disease. All 5 were female (mean age 48) and with significant FH. Variants in PKHD1 (n = 5: 4 male, 1 female, mean age 67) were mostly compound heterozygous and had a variety of phenotypes including CHF (n = 2, both liver transplanted), CHF/MBH (n = 1, portal hypertension), MBH/Caroli (n = 1, kidney transplanted) and PCLD without renal cysts (n = 1).

No genetic variants were identified in 14/34 including 3 CHF, 3 MBH and 8 PCLD patients.

Conclusion: Patients with DPM display a spectrum of disease phenotypes ranging in severity from asymptomatic, incidental diagnosis to end-stage liver disease. We identified the genetic cause in nearly 60% of a previously undefined cohort of DPM patients and discovered several novel variants. Of note, a significant proportion had meaningful variants in GANAB, PRKCSH and SEC63. PRKCSH and SEC63 variants were associated with isolated PCLD. GANAB and PKHD1 mutations were associated with mixed phenotypes, the latter found in mostly males and with a strong propensity for CHF. GANAB and SEC63 phenotypes were mild. Our findings support the use of bespoke gene panels in suspected DPM.

PO-1722

Epidemiology and burden of Progressive Familial Intrahepatic Cholestasis: Systematic review

Tracey Jones-Hughes¹, Joanna Campbell¹, Louise Crathorne¹, Velichka Valcheva². ¹Roboleo and Co Ltd, York, United Kingdom; ²Albireo Pharma, VP Medical Affairs Europe
Email: tracey@roboleo.com

Background and aims: Progressive familial intrahepatic cholestasis (PFIC) is a rare but severe group of liver disorders of autosomal recessive inheritance, affecting an estimated 1 in 50,000 children worldwide. PFIC is characterized by severe pruritus and malabsorption, with rapid progress and ultimately liver failure. For children and their parents, PFIC is an extremely distressing disease. Significant pruritus can lead to severe cutaneous mutilation and, without surgery or liver transplant (LT), PFIC is typically fatal by age 20. The aim of this study was to conduct a systematic review of published evidence on the epidemiology and burden of PFIC.

Method: Databases including MEDLINE and Embase were searched for publications on PFIC prevalence, incidence or natural history, and the economic burden or health-related quality of life of patients with PFIC. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results: Three systematic reviews and twenty-two studies were eligible for inclusion for the epidemiology of PFIC including a total of 2,603 patients. Where reported, study periods ranged from 3 to 33 years. Local population prevalence of PFIC was reported in three studies, ranging from 9.0% to 12.0% of children admitted with cholestasis, acute liver failure, or splenomegaly.

The most detailed data come from the NAPPED study where findings for PFIC2 patients show a serum bile acid concentration below 102 μmol/L predicted native liver survival of >15 years following surgical bile diversion.

Burden of disease was mainly reported through health-related quality of life (HRQL), rates of surgery and survival. Rates of biliary diversion and liver transplant varied widely depending on study period, sample size and PFIC type, with many patients having multiple surgeries and progressing to liver transplant. This renders data unsuitable for comparison.

Conclusion: Using robust and transparent methods, this systematic review summarises our current knowledge of PFIC. The epidemiological overview is highly mixed and dependent on presentation and PFIC subtype. Only two studies reported HRQL and mortality results were variable across different subtypes. Lack of data and extensive heterogeneity severely limit understanding of this disease area, particularly variation around and within subtypes.

POSTER PRESENTATIONS

PO-1758

Circulating Fn14 is associated with pathogenic TH17 polarization in children with sclerosing cholangitis and inflammatory bowel disease

Simon Lam¹, Immaculeta Osuji², Annika Yang vom Hofe², Ruchi Singh², Cyd Castro Rojas², Astha Malik², Jonathan Dillman³, Divya Sharma⁴, Rebekah Karns², Rana Herro⁵, Alexander Miethke².
¹Alberta Children's Hospital, Pediatric Gastroenterology, Hepatology and Nutrition, Calgary, Canada; ²Cincinnati Children's Hospital Medical Center, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Cincinnati, United States; ³Cincinnati Children's Hospital Medical Center, Radiology, Cincinnati, United States; ⁴University of Cincinnati College of Medicine, Pathology, Cincinnati, United States; ⁵Cincinnati Children's Hospital Medical Center, Immunobiology, Cincinnati, United States
 Email: simon.lam@albertahealthservices.ca

Background and aims: Sclerosing cholangitis (SC) including primary sclerosing cholangitis (PSC) and autoimmune sclerosing cholangitis (ASC) are highly associated with inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC), and SC-IBD may represent a unique IBD phenotype. We previously reported Th17.1 polarization in liver tissue, using both liver RNAs-seq and multi-parameter immunofluorescence, to segregate with SC-IBD. In the present study, we aim to discover biomarkers that selectively segregate with SC-IBD.

Method: Circulating plasma proteins were assayed by Slow Off-rate Modified Aptamer (SOMAscan) technology on children in 2 separate cohorts of SC-IBD and healthy controls (HC) (A: SC-IBD = 17, mean age = 15.4 years, male = 10, UC = 8; HC = 13, mean age = 17.8 years, male = 7; B: SC-IBD = 11, mean age = 16.1 years, male = 9, UC = 8; HC = 8, mean age = 14.1 years, male = 3). Significantly differentially expressed proteins determined by Wilcoxon Rank Sum test and corrected using a false discovery rate of <5% in cohort A were validated in cohort B using logistic regression. Spearman rank order correlation was used to correlate significant circulating plasma proteins and liver biochemistries.

Results: Of 1305 circulating plasma proteins assayed, 215 proteins were nominally significant between SC-IBD and HC in cohort A. Pathways related to TH1 and TH2 cell differentiation, TNF, and IL-17 signaling pathways were upregulated in children with SC-IBD. Ten of these 215 proteins were validated in cohort B with increased concentrations of CXCL8, TIMP1, FGF23, FCGR3B, PIGR, SCARB2, TNFRSF1A and Fn14, while ACY1 and CTSD were the only proteins with decreased concentrations in SC-IBD compared to HC. SC-IBD had a 3.7-fold increase in Fn14 compared to HC, highest among all validated proteins (Table 1). Concentrations of circulating Fn14 correlated with AST (rs = 0.40, p = 0.03) and GGT (rs = 0.37, p = 0.04).

Table 1: Mean concentrations[†] of significantly differentially expressed circulating plasma proteins in children with SC-IBD compared to HC assayed by SOMAscan

Protein	HC	SC-IBD	Fold Change (SC-IBD/HC)	Corrected p value
Fn14	377	1398	3.71	<0.001
SCARB2	441	872	1.98	<0.001
PIGR	12040	18706	1.55	<0.001
TNFRSF1A	1423	1962	1.38	<0.001
CXCL8	2407	3229	1.34	<0.001
TIMP1	482	500	1.04	<0.001
FCGR3B	2225	2265	1.02	<0.001
ACY1	16734	16609	0.99	<0.001
CTSD	1462	1421	0.97	<0.001

[†]Concentrations of proteins expressed as relative fluorescent units (RFU) calibrated to a standard curve

Conclusion: Large scale plasma proteomic analysis discovered circulating Fn14 to segregate with pediatric SC-IBD and to correlate with biomarkers of SC liver disease. Fn14 was previously shown to promote TH17 polarization in autoimmune conditions like rheumatoid arthritis. The role of Fn14 in driving hepatic TH17.1 requires further investigations.

PO-1809

Efficacy, safety, and tolerability of seladelpar in patients with compensated liver cirrhosis due to primary biliary cholangitis (PBC): a pooled analysis of phase 2 and phase 3 studies

Stuart C. Gordon¹, Palak Trivedi², Christopher Bowlus³, Galambos Michael⁴, Aparna Goel⁵, Aliya Gulamhusein⁶, Cynthia Levy⁷, Guy Neff⁸, Carmen Stanca⁹, Douglas Thorburn¹⁰, Bruce Bacon¹¹, Brian Borg¹², Yvonne Doerffel¹³, Lisa Forman¹⁴, Bradley Freilich¹⁵, Liana Gheorghe¹⁶, Maria Sarai González¹⁷, Stephen Harrison¹⁸, Jonathan Huang¹⁹, Sook-Hyang Jeong²⁰, Seung Up Kim²¹, John Lake²², Joseph Odin²³, Won Young Tak²⁴, Hillel Tobias²⁵, John M. Vierling²⁶, Ke Yang²⁷, Alexandra (Sasha) Steinberg²⁷, Yun-Jung Choi²⁷, Charles McWherter²⁷, Marlyn J. Mayo²⁸.
¹Henry Ford Health System, Detroit, United States; ²University Hospital Birmingham, Birmingham, United Kingdom; ³University of California Davis Medical Center, Sacramento, United States; ⁴Digestive Healthcare of Georgia, Atlanta, United States; ⁵Stanford Hospital, Stanford, United States; ⁶Toronto General Hospital, Toronto, Canada; ⁷University of Miami, Miami, United States; ⁸Covenant Research, Sarasota, United States; ⁹NYU Langone Health, New York, United States; ¹⁰Royal Free Hospital, London, United Kingdom; ¹¹Saint Louis University School of Medicine, St. Louis, United States; ¹²Jackson Liver and GI Specialists, Jackson, United States; ¹³Charite, Berlin, Germany; ¹⁴University of Colorado, Aurora, United States; ¹⁵Kansas City Research Institute, Kansas City, United States; ¹⁶Fundeni Clinical Institute, Bucharest, Romania; ¹⁷Consultorio de la Doctora Maria Sarai Gonzalez Huevo, Metepec, Mexico; ¹⁸Pinnacle Clinical Research, San Antonio, United States; ¹⁹University of Rochester, Rochester, United States; ²⁰Seoul National University Bundang Hospital, Bundang-Gu, Seongnam-Si, Korea, Rep. of South; ²¹Severance Hospital Yonsei University Health System, Seodaemun-Gu, Korea, Rep. of South; ²²University of Minnesota, Minneapolis, United States; ²³Mount Sinai Hospital, New York, United States; ²⁴Kyungpook National University Hospital, Daegu, Korea, Rep. of South; ²⁵Concorde Medical Group, New York, United States; ²⁶Baylor College of Medicine, Houston, United States; ²⁷CymaBay Therapeutics, Newark, United States; ²⁸University of Texas Southwestern, Dallas, United States
 Email: ychoi@cymabay.com

Background and aims: Patients with PBC and compensated cirrhosis can progress to decompensation with its associated complications, liver transplantation or death. PBC patients with an incomplete response or intolerance to UDCA have an unmet need to slow disease progression. Seladelpar, a selective PPAR delta agonist, has shown potent anti-cholestatic and anti-pruritic activity in PBC studies. We now report a pooled analysis from two studies assessing the efficacy, safety, and tolerability of seladelpar in PBC patients with compensated cirrhosis.

Method: Eligible PBC patients with an inadequate response or intolerance to UDCA (ALP $\geq 1.67 \times$ ULN) were enrolled into an open-label phase 2 study (EudraCT 2016-002996-91) or a placebo (Pbo)-controlled phase 3 study (EudraCT 2018-001171-20). Cirrhosis was diagnosed using liver biopsy, imaging tests, or liver elastography. Patients received oral Pbo, seladelpar 5 mg or 10 mg once daily + UDCA if tolerated. Efficacy analyses at 3 months included composite response (ALP $< 1.67 \times$ ULN, ALP decrease of $\geq 15\%$ and total bilirubin [TB] \leq ULN), ALP % change, ALP \leq ULN, and changes in liver function. Safety was assessed for 3 months.

Results: Of 384 enrolled patients, 53 had compensated cirrhosis (Child-Pugh A: Pbo [n = 7], 5 mg [n = 22], and 10 mg [n = 24]). Baseline characteristics included: 92% female, mean age 58 yrs, 94%

on UDCA, ALP 287 U/L, TB 0.92 mg/dL, ALT 50 U/L, AST 49 U/L, GGT 228 U/L, albumin 3.96 g/dL, and platelets $197 \times 10^3/\mu\text{L}$. After 3 months, 39 patients were treated. The composite end point was met in 50% (9/18) of 5 mg and 63% (10/16) of 10 mg groups compared to none in Pbo (0/5). Reductions in ALP in the 5 mg (-31%, -82 U/L) and 10 mg groups (-41%, -114 U/L) were greater than Pbo (-2.6%, -8.7 U/L). ALP was normalized in 3 patients in each seladelpar group (17–19%) but none in Pbo. Changes in ALT were -15%, -6%, and -32% in Pbo, 5 and 10 mg groups, respectively. Total bilirubin, platelets, albumin, and INR remained stable. One patient in 10 mg discontinued due to AE (pruritus). Three patients had an SAE: 2 on 5 mg (febrile neutropenia, procedural pain) and 1 on 10 mg (angina pectoris), all unrelated to study drug. Efficacy, tolerability, and safety in patients with compensated cirrhosis were comparable to that of non-cirrhotic patients.

Patients with PBC and Compensated Liver Cirrhosis

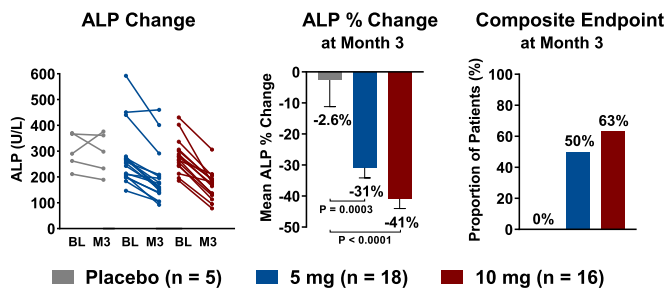


Figure:

Conclusion: Seladelpar appeared safe and was well tolerated and may provide an effective treatment option for patients with compensated liver cirrhosis due to PBC.

PO-1811

Odevixibat effects on cholestasis-related parameters: Analysis of pooled data from the PEDFIC 1 and PEDFIC 2 studies in children with progressive familial intrahepatic cholestasis

Richard Thompson¹, Reha Artan², Ulrich Baumann³, Piotr Czubkowski⁴, Buket Dalgiç⁵, Ozlem Durmaz⁶, Emmanuel Gonzales⁷, Tassos Grammatikopoulos^{1,8}, Girish Gupte⁹, Patrick Horn¹⁰, Alain Lachaux¹¹, Patrick McKiernan¹², Hasan Ozen¹³, Sanjay Rajwal¹⁴, Bertrand Roquelaure¹⁵, Ekkehard Sturm¹⁶, Henkjan Verkade¹⁷, Qifeng Yu¹⁰, Lise Kjems¹⁰. ¹Institute of Liver Studies, King's College London; ²Akdeniz University; ³Hannover Medical School; ⁴The Children's Memorial Health Institute; ⁵Gazi University Faculty of Medicine; ⁶Istanbul University; ⁷Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U 1193; ⁸King's College Hospital NHS Trust, Pediatric Liver, GI and Nutrition Centre; ⁹Birmingham Women's and Children's NHS Foundation Trust; ¹⁰Albireo Pharma, Inc.; ¹¹Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant; ¹²UPMC Children's Hospital of Pittsburgh; ¹³Hacettepe University Faculty of Medicine; ¹⁴Leeds Teaching Hospitals NHS Trust, Leeds Children's Hospital; ¹⁵CHU, Hospital de la Timone; ¹⁶University Children's Hospital Tübingen; ¹⁷University of Groningen, Beatrix Children's Hospital/University Medical Center Groningen
Email: lise.kjems@albireopharma.com

Background and aims: Odevixibat, an ileal bile acid transporter inhibitor, is in development to treat cholestatic liver diseases. In the phase 3 PEDFIC 1 (P1) and PEDFIC 2 (P2) studies, odevixibat treatment reduced serum bile acids (sBAs) and improved pruritus in patients with progressive familial intrahepatic cholestasis (PFIC). Using pooled data from these studies, we analysed changes in parameters of cholestasis, pruritus, and hepatic laboratory markers and compared patients who responded to odevixibat treatment (Rs) with non-responders (NRs).

Method: P1 was a 24-week, randomized, placebo-controlled study in children with PFIC1 or PFIC2, and P2 is an ongoing, 72-week extension study in patients with any type of PFIC. In this pooled analysis, spanning 48 weeks, 77 patients have received odevixibat (PFIC1, n = 20; PFIC2, n = 51; PFIC3, n = 5; MYO5B deficiency, n = 1; overall median exposure: 37 weeks). Two responder definitions were examined: 1) sBA response (ie, sBAs <65 or <102 $\mu\text{mol/L}$ for PFIC1 and PFIC2, respectively) and 2) sBA response or pruritus response (ie, a ≥ 1 -point drop from baseline in PRUCISION score).

Results: Rates of sBA Rs and sBA or pruritus Rs were 31% and 57%, respectively, at weeks 0–24, 48% and 60% at weeks 25–36, and 59% and 65% at weeks 37–48. Among all odevixibat-treated patients, mean change from baseline (CFB) to week 48 in alanine aminotransferase (ALT) and total bilirubin was -82 U/L and -18 $\mu\text{mol/L}$, respectively. In general, Rs had greater mean CFB (ie, improvements) vs NRs in these hepatic laboratory parameters with long-term odevixibat treatment (Table) that started as early as week 4 and increased over time.

Table:

Liver Enzyme Levels	sBA Response		sBA or Pruritus Response	
	Yes	No	Yes	No
	n (%)	Mean (SE)	n (%)	Mean (SE)
ALT, U/L				
Baseline	24 (39)	124 (33)	38 (63)	82 (18)
CFB→wk 4	23 (39)	-28 (37)	36 (16)	21 (24)
CFB→wk 24	19 (40)	-67 (42)	28 (11)	-10 (27)
CFB→wk 48	15 (63)	-112 (57)	9 (22)	-32 (48)
Total bilirubin, $\mu\text{mol/L}$				
Baseline	24 (39)	27 (7)	38 (63)	74 (16)
CFB→wk 4	23 (39)	-8 (4)	36 (9)	-10 (11)
CFB→wk 24	19 (40)	-23 (8)	28 (10)	-19 (7)
CFB→wk 48	15 (63)	-25 (11)	9 (14)	-6 (9)

^aResponder rate $([n/(n + m)] \times 100)$.

Conclusion: Patients with PFIC who responded to odevixibat treatment had sustained improvements in cholestasis-related parameters that were not observed to the same extent in treatment non-responders.

PO-1828

Genetic mutation and cystic fibrosis-associated liver disease at the time of diagnosis in children: A correlational study

Alejandra Marisela Sabillon-Mendoza¹, Rubén Peña Velez¹, Flora Zarate¹, Jaime Ramirez¹. ¹Instituto Nacional de Pediatría, Gastroenterología y Nutrición, Ciudad de México, Mexico
Email: alesabillon@yahoo.com

Background and aims: It is estimated that 10 to 15% of patients with cystic fibrosis have liver disease (CFLD), this negatively impacts the evolution of the disease, it has been reported that dysfunction of the transmembrane conductance regulator (CFTR) has a direct effect on the cholangiocyte function, finally the spectrum of complications ranges from cholestasis, progressive fibrosis, biliary obstruction to focal biliary cirrhosis. Around 2000 mutations in CFTR have been determined and classified according to their functional defect, however, none of them have been associated with CFLD, accepting that this is due to the interaction of environmental factors,

POSTER PRESENTATIONS

medications, infections and malnutrition. Our objective was to determine if there is a correlation between the most frequent CF mutations and liver disease in children at the time of diagnosis.

Method: Retrospective, observational and analytical study, 82 files of children diagnosed with cystic fibrosis were reviewed, 43 had a certain mutation, the diagnosis of liver disease was based on analytical, imaging or histopathology tests, an APRI index was performed to establish grade fibrosis.

Results: 82 records of children diagnosed with cystic fibrosis, the male gender predominated in 54%, the median age at the time of diagnosis was 10 months, it was observed that 59% of the children presented elevation of ALT by cut-off point for gender, the ultrasound was altered in 39%. There was an association between changes in USG and elevation of ALT ($p = 0.024$). This led to the performance of liver biopsies in five patients, finding variable degrees of fibrosis and macro and microvesicular steatosis.

The APRI index was correlated with other variables of liver and canalicular injury, finding a correlation as shown in Table 1.

Figure:

	APRI index	"p" value
ALT	0.612	$p < 0.001$
GGT	0.594	$p < 0.001$
DB	0.359	$p < 0.001$
FA	0.047	$p = 0.675$
INR	0.195	$p = 0.80$

Of the patients with an APRI index greater than 0.5, 3 had a *F508del* mutation, 2: *6542X*, 1: *N1303K*, those with an APRI index greater than 1.5, a patient with a *F508del* mutation and another with a *p. Phe1078Ile* mutation. The analysis of variance between the mutations showed a difference in the degree of liver injury $p = 0.03$ according to the genetic variant.

Conclusion: At diagnosis there is liver injury in 59% of children with CF, and some degree of fibrosis was observed in 29% of children. Larger studies are needed to look at the influence of the genetic mutation on the development of liver disease. In this study, we observed greater liver damage in the *F508del*, *6542X* mutations.

PO-1833

Odevixibat therapy improves clinically meaningful end points in children with progressive familial intrahepatic cholestasis: Data from the PEDFIC 1 and PEDFIC 2 trials

Richard Thompson¹, Lorenzo D'Antiga², Emmanuel Gonzales³, Saul Karpen⁴, Lise Kjems⁵, Kathleen Loomes⁶, Cara Mack⁷, Quanhong Ni⁵, Henkjan Verkade⁸, Patrick Horn⁵. ¹Institute of Liver Studies, King's College London; ²Azienda Ospedaliera Papa Giovanni XXIII; ³Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U 1193; ⁴Emory University School of Medicine; ⁵Albireo Pharma, Inc.; ⁶Children's Hospital of Philadelphia; ⁷Children's Hospital Colorado, University of Colorado School of Medicine; ⁸University of Groningen, Beatrix Children's Hospital/University Medical Center Groningen
Email: patrick.horn@albireopharma.com

Background and aims: Odevixibat, an ileal bile acid transporter inhibitor, is in development to treat cholestatic liver diseases. Here, we describe key outcomes with odevixibat in children with progressive familial intrahepatic cholestasis (PFIC) based on pooled analysis of data from the phase 3 PEDFIC 1 (P1; NCT03566238) and PEDFIC 2 (P2; NCT03659916) studies.

Method: This pooled analysis covers up to 48 weeks of odevixibat treatment from P1 and through the planned P2 interim data cut (median duration of exposure as of 15 July 2020: 37 weeks; range: 1–108 weeks). The following outcomes are described: change in serum bile acids (sBAs), change in pruritus score (measured using the

PRUCISION scale; range: 0–4), evaluation of growth and sleep parameters, and safety monitoring. Mean values are shown.

Results: Across the P1 and P2 studies, 77 patients received odevixibat. At baseline, sBAs and pruritus scores were 250 $\mu\text{mol/L}$ ($n = 77$) and 2.9 ($n = 76$), respectively. Four weeks after starting odevixibat, sBAs had decreased by 88 $\mu\text{mol/L}$ ($n = 68$) and pruritus score decreased by 0.7 ($n = 75$). At the end of the analysis period, sBAs had decreased from baseline by 213 $\mu\text{mol/L}$ in patients with available data ($n = 24$) and pruritus score dropped by 1.4 ($n = 32$). Height Z scores increased from -1.9 at baseline ($n = 75$) to -0.8 at week 48 ($n = 20$; Figure, panel A). Similar improvements were observed for weight Z scores (baseline: -1.1 [$n = 75$]; week 48: -0.0 [$n = 21$]; Figure, panel B). Odevixibat-treated patients had changes from baseline to weeks 37–48 in observer-reported percentage of days seeing blood due to scratching [-25%], needing help falling asleep [-52%], needing soothing [-51%], and sleeping with caregiver [-40%]. Overall, drug-related treatment-emergent adverse events (TEAEs) were reported in 32 of 77 (42%) patients, but no drug-related serious TEAEs were reported. Four patients had TEAEs leading to treatment discontinuation.

Conclusion: In children with PFIC, odevixibat treatment for up to 48 weeks was well tolerated and associated with clinically meaningful effects on sBAs, pruritus, growth, and sleep parameters.

PO-1843

Pretreatment serum bile acid parameters and predictability of response to odevixibat, an ileal bile acid transport inhibitor, in children with progressive familial intrahepatic cholestasis

Henkjan Verkade¹, Folkert Kuipers¹, Quanhong Ni², Velichka Valcheva², Patrick Horn², Jan Mattsson², Per-Goran Gillberg², Lise Kjems². ¹University of Groningen, Beatrix Children's Hospital/University Medical Center Groningen; ²Albireo Pharma, Inc.
Email: h.j.verkade@umcg.nl

Background and aims: Odevixibat, an orally administered, selective inhibitor of the ileal bile acid transporter, reduced serum bile acids (sBAs) and pruritus in children with progressive familial intrahepatic cholestasis (PFIC) type 1 or 2 in the phase 3, 24-week, double-blind PEDFIC 1 study. Here, we evaluated whether pretreatment sBA parameters could predict response to odevixibat using data from PEDFIC 1.

Method: This analysis included children with PFIC aged 0.5–18 years with elevated sBAs and significant pruritus who were treated with odevixibat 40 $\mu\text{g/kg/day}$ ($n = 23$) or 120 $\mu\text{g/kg/day}$ ($n = 19$) in PEDFIC 1. We analysed pretreatment sBA composition using liquid chromatography–tandem mass spectrometry, quantifying serum concentrations of total BAs, primary (cholate, chenodeoxycholate) and secondary (deoxycholate, lithocholate) BAs, and ursodeoxycholate (UDCA). We also quantified pretreatment serum concentrations of 7 α -hydroxy-4-cholesten-3-one (C4). Pretreatment parameters were analysed in treatment responders (Rs; ie, patients with sBAs ≤ 70 $\mu\text{mol/L}$ or reduced $\geq 70\%$ and/or a ≥ 1 -point drop in observer-reported pruritus score from baseline to end of treatment) vs non-responders (NRs).

Results: Median baseline UDCA concentration was 55.6 $\mu\text{mol/L}$ in the 31/42 patients who used UDCA as treatment and 0.2 $\mu\text{mol/L}$ in the 9/42 patients who did not use UDCA. Proportion of Rs was 16/23 and 8/19, respectively, in the 40 and 120 $\mu\text{g/kg/day}$ dose groups; groups were combined for analysis (overall Rs, 24/42 [57%]). The fraction of Rs was similar with (56%) and without UDCA use (60%). Before starting odevixibat, Rs and NRs had median total sBA concentrations of 194.1 and 269.3 $\mu\text{mol/L}$, respectively, composed of primary BAs (182.7 and 205.9 $\mu\text{mol/L}$), secondary BAs (0.3 and 0.3 $\mu\text{mol/L}$), and UDCA (52.9 and 28.8 $\mu\text{mol/L}$). Median pretreatment serum C4 concentrations were 2.0 ng/ml in Rs and 3.3 ng/ml in NRs.

Conclusion: Response to odevixibat treatment in patients with PFIC type 1 or type 2 was not associated with pretreatment serum

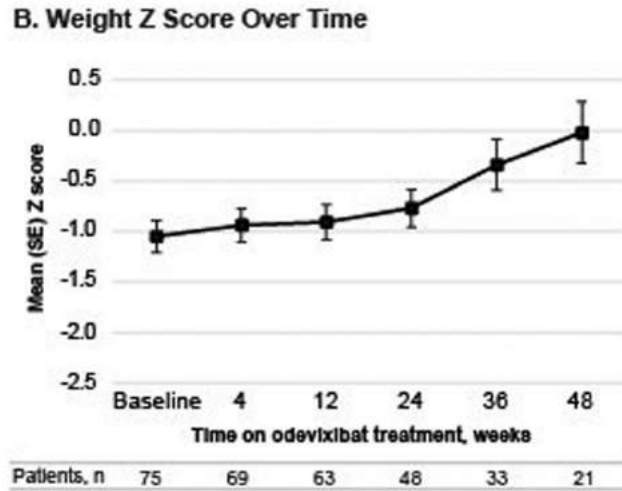
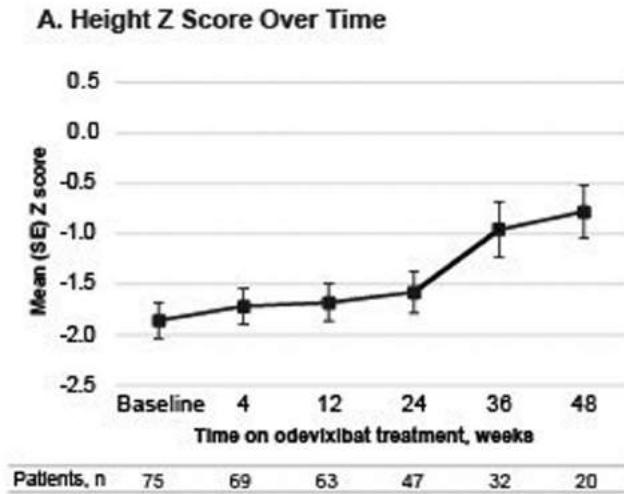


Figure: (abstract: PO-1833)

concentrations of total, primary, or secondary BAs, or of C4, a marker for BA synthesis rate. Neither UDCA use nor pretreatment serum concentration of UDCA was associated with subsequent response to odevixibat. Interestingly, the low relative serum concentration of secondary BAs before treatment apparently did not preclude subsequent response to odevixibat in these patients.

PO-2040

Single-centre experience with follow-up of patients with acute porphyria

Barbora Nováková¹, Jaromír Petrtýl¹, Iva Subhanová², Daniela Záhorská³, Libor Vitek², Pavel Martásek³, Radan Bruha¹.
¹First Faculty of Medicine, Charles University and General University Hospital in Prague, 4th Department of Internal Medicine-Department of Hepatogastroenterology, Prague 2, Czech Republic; ²First Faculty of Medicine, Charles University and General University Hospital in Prague, Institute of Medical Biochemistry and Laboratory Diagnostics, Prague 2, Czech Republic; ³First Faculty of Medicine, Charles University and General University Hospital in Prague, Department of Paediatrics and Inherited Metabolic Disorders, Prague 2, Czech Republic
 Email: cizkova.barbora@gmail.com

Background and aims: Acute porphyria is a rare metabolic disease, typically autosomal dominant inherited. It manifests itself in acute attacks, triggered by various stimuli, leading to many life-threatening complications. According to the rarity of acute porphyria, even single center follow-up studies are not so common. Therefore, we aim to present information about the patients diagnosed between 1959 and 2018 with acute porphyria in our center including type of porphyria, clinical symptoms, family history and genetics.

Method: We surveyed our clinical and laboratory data plus the results of genetic screening.

Results: 215 patients and relatives were diagnosed with acute porphyria (Acute intermittent porphyria (n = 86), Porphyria variegata (n = 68), Hereditary coproporphyria (n = 59), undefined type (n = 2)). At least 48% of patients have shown to be symptomatic (n = 104). 93% of symptomatic patients had abdominal manifestation, in 35% combined with neurological and in 7% with psychiatric symptoms, 20% had all three symptoms (abdominal, neurological and psychiatric) and 4% patients had neuropsychiatric symptoms only. Acute attack was induced by medicaments (23%) or by other causes (stress 16%, infection 12%, and hormonal changes 9%) and in 40% remained unknown. Importantly, two or more acute attacks were present in at least 62% of symptomatic acute porphyria cases (n = 64) including

10% of recurrent attacks (n = 10), see Figure. Cutaneous symptoms were present in at least 75% of cases of Porphyria variegata and in 17% of Hereditary coproporphyria cases. 51% of patients reported positive family history of acute porphyria (42 multi-member families, n = 174). The clinical penetrance of acute porphyria in patients diagnosed genetically by family screening was 17%.

Clinical manifestation of acute porphyria (N=215)

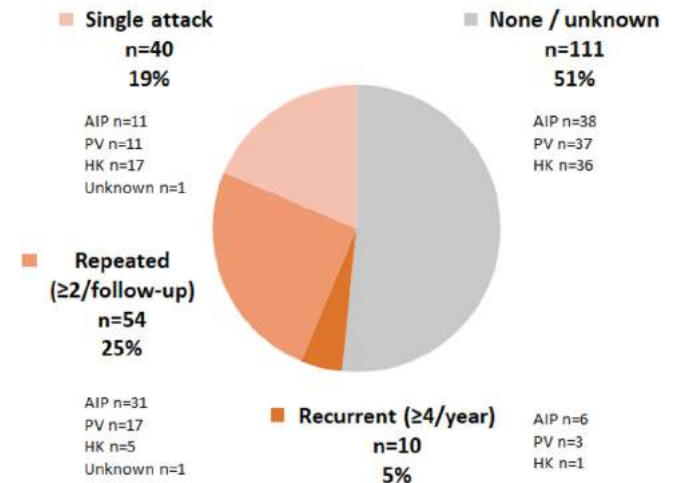


Figure:

Conclusion: Based on long term follow-up of patients with acute porphyria at least 62% of symptomatic cases developed repeated attacks, mostly manifested by abdominal symptoms. Nevertheless, the clinical penetrance of acute porphyria diagnosed by family screening is low.

PO-2090

A 3-proteomic score to improve the clinical management of childhood liver cancer

Juan Carrillo¹, Marina Simon-Coma¹, Mikel Azkargorta², Laura Royo¹, Laura Guerra³, del Rio Alvaro¹, Mario Failli⁴, Rosa Hernansaiz⁵, Hirokazu Kimura⁶, Marta Garrido⁷, Francisco Hernandez Oliveros⁸, Eduard Porta-Pardo⁹, Irene Oi-Lin Ng¹⁰, Montserrat Domingo-Sàbat¹,

POSTER PRESENTATIONS

Manuel Lopez-Santamaria³, Bruce Morland¹¹, Piotr Czauderna¹², Margaret Childs¹³, Rudolf Maibach¹⁴, Alfonso Valencia¹⁵, Felix Elortza², Margarita Sala¹⁶, Marie-annick Buendia¹⁷, Akira Akuchi⁶, Julio Saez-Rodriguez⁵, Diego Di Bernardo⁴, Maria-Rosa Sarrias¹⁸, Carolina Armengol¹, ¹IGTP Institut Germans Trias i Pujol, Childhood Liver Oncology Group (c-LOG), Badalona, Spain; ²CIC bioGUNE-Centro de Investigación Cooperativa en Biociencias, Proteomics Platform, Derio, Spain; ³Hospital Universitario La Paz, Pathology Department, Madrid, Spain; ⁴Tigem, Pozzuoli, Italy; ⁵Heidelberg University, Institute for Computational Biomedicine, Heidelberg, Germany; ⁶Osaka University, Department of Molecular Biology and Biochemistry, Suita, Japan; ⁷La Vall d'Hebron, Pathology Department, Barcelona, Spain; ⁸Hospital Universitario La Paz, Pediatric Surgery Department, Madrid, Spain; ⁹Josep Carreras Leukaemia Research Institute (IJC), Badalona, Spain; ¹⁰The University of Hong Kong, Department of Pathology, Hong Kong; ¹¹Women's and Children's Hospital, Department of Oncology, North Adelaide, Australia; ¹²Medical University of Gdańsk, Department of Surgery and Urology, Gdańsk, Poland; ¹³Nottingham Clinical Trials Unit, United Kingdom; ¹⁴Stiftung 'International Breast Cancer Study Group IBCSG', Bern, Switzerland; ¹⁵Barcelona Supercomputing Center-Centre Nacional de Supercomputació, Barcelona, Spain; ¹⁶Hospital Universitari de Girona Doctor Josep Trueta, Girona, Spain; ¹⁷INSERM, Villejuif, France; ¹⁸IGTP Institut Germans Trias i Pujol, Innate Immunity Group, Badalona, Spain Email: jcarrillo@igt.pcat

Background and aims: Hepatoblastoma (HB) is the main liver tumor in childhood. However, it is a rare tumor with an annual incidence of 1 case per million children. Therapeutic options for advanced tumors are limited, with a 3-year event free survival (EFS) below 35% (Semeraro et al, Eur J Cancer 2013). Gene expression and methylation studies have improved our knowledge on HB and revealed up to three HB molecular prognostic subtypes (Cairo-Armengol et al, Cancer cell 2008; Carrillo-Reixach et al, J Hepatol, 2020). Therefore, our aim is to perform the first proteomic study of HB and identify new prognostic biomarkers and dysregulated pathways.

Method: In total, 184 pediatric patients with liver cancer were included. A training set of 22 tumor and non-tumor snap-frozen samples from 14 HB patients were profiled by 2D-DiGE-MALDI-TOF and Label Free. Pathway analysis was performed using random walk and restart and fast-gene set enrichment analysis. Prognostic biomarkers were identified by supervised analysis using R and validated by immunohistochemistry (IHC) in an independent set of 509 FFPE samples from 170 pediatric patients with liver cancer. Impact of the prognostic biomarkers in other cancers was performed using the TCGA database. Tumor growth studies of selected biomarkers was assessed *in vivo* and *in vitro* using HB cell lines and xenografts.

Results: We identified 173 tumor deregulated proteins ($p < 0.05$, $FC \geq 1.5$). Overexpressed proteins were involved on the activation of cell-cycle, extracellular matrix, EIF2, PI3 K/Akt and mTOR pathways whereas underexpressed proteins belonged to pathways related to hepatic functions. The unsupervised analysis revealed two tumor clusters (PC-1, PC-2) associated with the C1/C2 transcriptomic subtypes ($p < 0.03$) and pathological features of poor prognosis ($p < 0.05$). The supervised analysis comparing PC-2 vs PC-1 tumors identified 341 differently expressed proteins ($p < 0.01$, $FC \geq 1.5$). We selected 3 proteins (CKAP4, C1QBP and CRYL1) which its differential expression was validated by Western blot in PC-2 vs PC-1 tumors but also as compared with non-tumor liver samples ($p < 0.0015$). A 3-protein score was defined by combining the 3 biomarkers and it was significantly associated to patient survival in the training ($p = 0.0083$) and in the validation set using IHC ($p = 1.59 \times 10^{-14}$). Moreover, the 3-protein score was an independent prognostic factor (HR:12.02, IC:4.19–34.51, $p < 0.0001$) for pediatric liver cancer patients and also for adult HCC, cholangiocarcinoma, lung, kidney, prostate, thyroid and thymus cancer patients. Finally, *in vitro* and *in vivo*

experiments showed that the inhibition of CKAP4 impaired significantly tumor growth ($p < 0.05$).

Conclusion: We identified a prognostic 3-protein score that could be easily applied at the clinical practice to improve clinical management of childhood liver cancer and other adult tumors.

PO-2120

Treatment with seladelpar in patients with primary biliary cholangitis (PBC) and prior experience with obeticholic acid (OCA) or fibrates

Aliya Gulamhusein¹, Guy Neff², Aparna Goel³, Marlyn J. Mayo⁴, Carmen Stanca⁵, Christopher Bowlus⁶, Lisa Forman⁷, Pietro Invernizzi⁸, Frederik Nevens⁹, Ehud Zigmund¹⁰, Eli Zuckerman¹¹, Ke Yang¹², Yun-Jung Choi¹², Alexandra (Sasha) Steinberg¹², Charles McWherter¹², Kris Kowdley¹³. ¹Toronto General Hospital, Toronto, Canada; ²Covenant Research, Sarasota, United States; ³Stanford Hospital, Stanford, United States; ⁴University of Texas Southwestern, Dallas, United States; ⁵NYU Langone Health, New York, United States; ⁶University of California Davis Medical Center, Sacramento, United States; ⁷University of Colorado, Aurora, United States; ⁸ASST di Monza-Azienda Ospedaliera San Gerardo, Rozzano, Italy; ⁹UZ Leuven, Leuven, Belgium; ¹⁰Tel Aviv Sourasky Medical Center PPDs, Tel Aviv-Yafo, Israel; ¹¹Lady Davis Carmel Medical Center, Haifa, Israel; ¹²CymaBay Therapeutics, Newark, United States; ¹³Liver Institute Northwest, PLLC, Seattle, United States Email: asteinberg@cymabay.com

Background and aims: Up to 40% of PBC patients (pts) taking ursodeoxycholic acid (UDCA) therapy do not achieve their biochemical treatment response. In this population, OCA or fibrates are often initiated as second-line therapy. Seladelpar, a potent and selective PPAR delta agonist, has shown potent anti-cholestatic and anti-inflammatory activity in PBC studies. This is a pooled analysis of 2 clinical studies to evaluate seladelpar in PBC patients who were previously treated with OCA or fibrates.

PBC patients with prior experience with OCA and Fibrates

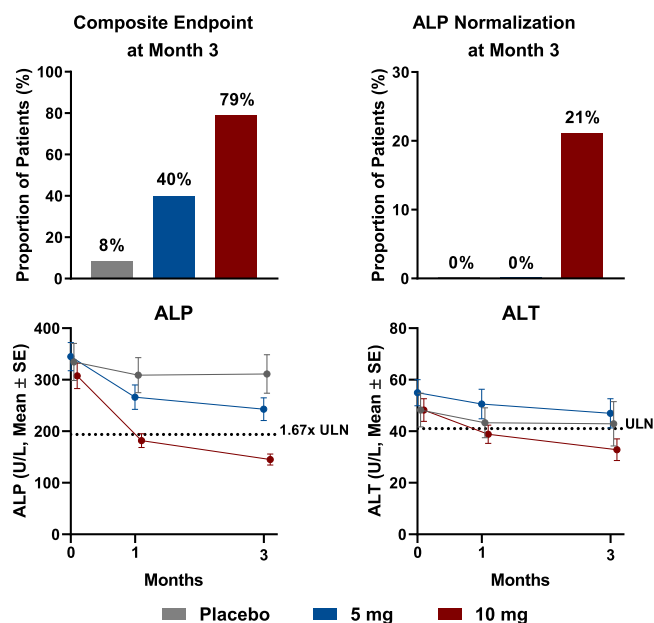


Figure:

Method: Pts with PBC who had an inadequate response to UDCA/intolerance to UDCA and an ALP ≥ 1.67 x upper limit of normal (ULN) were enrolled into an open-label Phase 2 study (EudraCT 2016-002996-91) or a placebo-controlled Phase 3 study (EudraCT 2018-001171-20). Analyses were performed on pts treated with OCA or fibrates prior to the study entry. Efficacy was assessed on pts treated

with either seladelpar 10 mg, 5 mg, or placebo (Pbo) for 3 months, by analysing a composite responder rate (ALP <1.67 × ULN, ALP decrease ≥15% and TB ≤ULN), ALP ≤1–ULN, ALP % change from baseline, and other markers of liver function. Safety was assessed over 1 year.

Results: A total of 71 (18%) of 384 enrolled pts in Phase 2 and Phase 3 studies had prior experience with OCA (47), fibrates (16), or both (8). In the 10 mg, 5 mg, and Pbo groups mean baseline values, respectively, were: ALP 307 U/L, 345 U/L, and 334 U/L; ALT 48 U/L, 55 U/L, and 48 U/L; total bilirubin of 0.77 mg/dL, 0.85 mg/dL, and 0.71 mg/dL. 51 pts were treated for 3 months: 10 mg n = 19, 5 mg n = 20 and Pbo n = 12. The composite end point was met in 79%, 40% and 8% pts in the 10 mg, 5 mg, and Pbo groups, respectively. ALP normalized in 21% pts in the 10 mg group, and 0% in the 5 mg or Pbo groups. Mean changes in ALP were –45%, –31%, and –9% in the 10 mg, 5 mg, and Pbo groups. Mean total bilirubin changes were –9%, –3% and +3%, and mean ALT changes were –21%, –13%, and –7%. Safety analysis was performed in 71 pts. Four pts had an SAE (3 pts on 5 mg and 1 pt on Pbo), all unrelated; treatment was discontinued due to AE in 2 pts: (1) ALT/AST elevation and (2) gastroesophageal reflux disease, both on 5 mg. AE of pruritus was noted in 7%, 15%, and 18% in the 10 mg, 5 mg, and Pbo groups, respectively.

Conclusion: In PBC pts with prior treatment with OCA or fibrates and ALP ≥1.67 × ULN, seladelpar appeared to be safe, well tolerated and showed meaningful and dose dependant improvement in biochemical markers of cholestasis.

PO-2204

Modeling phenotypic heterogeneity of Glycogen Storage Disease type Ia liver disease in mice by somatic CRISPR/Cas9-mediated gene editing

Martijn Rutten¹, Terry Derks², Nicolette Huijman¹, Trijnie Bos³, Niels Kloosterhuis¹, Kees van de Kolk⁴, Karin Wolters¹, Mirjam Koster¹, Rachel Thomas⁵, Alain de Bruin^{1,5}, Bart van de Sluis¹, Maaik Oosterveer¹. ¹University Medical Center Groningen, Pediatrics, Groningen, Netherlands; ²Beatrix Children's Hospital, University Medical Center Groningen, Section of Metabolic Diseases, Groningen, Netherlands; ³University Medical Center Groningen, Laboratory Medicine, Groningen, Netherlands; ⁴University Medical Center Groningen, The Central Animal Facility, Gronsai (Groningen Small Animal Imaging Facility), Groningen, Netherlands; ⁵Utrecht University, Dutch Molecular Pathology Center, Faculty of Veterinary Medicine, Utrecht, Netherlands
Email: m.g.s.rutten@umcg.nl

Background and aims: Patients with Glycogen Storage Disease type Ia (GSD Ia) primarily present with life-threatening hypoglycemia and display severe liver disease characterized by hepatomegaly. Despite strict dietary management, long-term complications still occur, amongst which liver tumor development. Variations in residual glucose-6-phosphatase (G6PC) activity likely contribute to phenotypic heterogeneity in biochemical symptoms and complications between patients. In addition, the molecular mechanisms that contribute to this heterogeneity remain largely unresolved. Incomplete insight into the relationship between residual G6PC activity and mechanisms poses major challenges to provide optimal healthcare and quality of life for GSD Ia patients. The currently available GSD Ia animal models are not suitable to systematically investigate the relationship between hepatic G6PC activity and phenotypic heterogeneity, or the contribution of gene-gene interactions in the liver. To meet these needs, we generated and characterized a novel hepatocyte-specific GSD Ia mouse model using somatic CRISPR/Cas9-mediated gene editing.

Method: Male hepatocyte-specific Cas9-expressing mice (ROSA26-LSL-Cas9 knock-in mice × Alb-Cre mice) were injected with various titers (0.1–1.0 × 10¹¹ particles) of adenovirus particles containing three sgRNAs targeting G6pc exon 1 in comparison to mice administered control adenovirus (empty vector, 1.0 × 10¹¹ particles).

Animals were sacrificed 4 weeks or 18 months after virus injection for organ and blood collection.

Results: Hepatic G6pc editing reduced hepatic G6PC activity up to 98% and resulted in fasting hypoglycemia, hypertriglyceridemia, hepatomegaly, hepatic steatosis, and an increased liver tumor incidence. This approach was furthermore successful to simultaneously modulate hepatic G6PC and ChREBP, a transcription factor that is activated in GSD Ia and protects against hepatic steatosis under these conditions. Importantly, it also allowed us to model a spectrum of GSD Ia phenotypes in terms of hepatic G6PC activity, fasting hypoglycemia, hypertriglyceridemia, hepatomegaly and hepatic steatosis.

Conclusion: In conclusion, we show that somatic CRISPR/Cas9-mediated gene editing of hepatic G6pc in mice opens new perspectives for translational research on GSD Ia. This approach will likely contribute to novel and personalized treatments for GSD Ia and other genetic liver diseases.

PO-2324

Incidence and impact of PYLEPHEBITIS in PYOGENIC LIVER ABSCESS

Nicolas Drilhon¹, Paul Janvier², Geoffrey Rossi², Francois Durand², Agnes Lefort², Olivier Roux². ¹Hospital Beaujon AP-HP, 92, Clichy, France; ²Hospital Beaujon AP-HP, Clichy, France
Email: nicolas.drilhon@gmail.com

Background and aims: Prevalence of pylephlebitis in patients with pyogenic liver abscess (PLA) remains unclear and its treatments debated. We aimed at describing the prevalence of pylephlebitis and its impact on PLA management and outcomes in a large cohort of patients treated for PLA.

Method: All the 332 patients hospitalized for PLA in our tertiary care center were screened from January 2010 to May 2018. Patients with history of chronic liver disease, liver transplantation or at risk for another cause of portal vein thrombosis (i.e.: acute pancreatitis or abdominal surgery in the last 15 days, local neoplasia) were excluded. All CT-scans were individually reviewed by an expert radiologist. Poor outcome was defined as primary treatment failure (PTF), death within 3 months after the diagnosis, or recurrence.

Overall, 96 patients (68% male, median age 62 years) with PLA were included. A microbiological documentation was found in 68 (71%): and *E. coli* (20/68 isolates, 29%) and *Klebsiella* spp. (18/68 isolates, 26%) were the most frequent micro-organisms found. Median duration of antibiotic treatment was 28 days and drainage was performed in 75 patients. Thirty-eight patients (40%) had portal or hepatic vein thrombosis: among them 27 (71%) had portal, 13 (34%) had hepatic vein thrombosis and 2 (5%) had both. Patients with pylephlebitis had more abscess at diagnosis (median number 2 vs 1, p = 0, 02) than patients without. Among patients with pylephlebitis, 17 (45%) received curative anticoagulation (AC) treatment, including 4 (11%) already receiving AC for another indication at diagnosis. Twenty-one (20%) patients had poor outcomes (14 had PTF, 4 died, 3 recurrences) with a median follow-up of 143 days. Pylephlebitis was not associated with poor outcomes (HR = 1.3, CI95% [0, 5–3, 4], p = 0, 581).

Conclusion: The prevalence of pylephlebitis in patient with PLA was 40%, mainly involving portal vein and 45% of patients with pylephlebitis received curative AC therapy. Pylephlebitis was not associated with a poor outcome.

PO-2392

Liver Involvement is rare during COVID-19 Infection in Children

Cigdem Arıkan¹, Esra Polat², Hacer Akturk³, Sirin Guven², Fidan Khalilova³. ¹Koc University School of Medicine, Pediatric Gastroenterology Hepatology/KUTTAM, Istanbul, Turkey; ²SBU Sancaktepe Training and Teaching Hospital, Pediatric Gastroenterology Hepatology, Istanbul; ³Koc University School of Medicine
Email: cigdemarikanmd@yahoo.com

POSTER PRESENTATIONS

Several studies reported deranged liver enzyme levels ranging from 14% to 74% COVID-19 patients. However, there is no sufficient data which described liver test abnormalities in children with COVID-19. We evaluated the frequency of liver test abnormalities and clinical characteristics of children with COVID-19.

Methods: Medical records of 726 patients (mean \pm SME 114.5 \pm 2.5 months; male/female: 375/351) with laboratory-confirmed COVID-19 between April 2020 and September 2021 were reviewed and clinical characteristics, liver tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total bilirubin (TBIL) and lactate dehydrogenase (LDH) at admission and peak during follow-up retrieved retrospectively. Children who had not liver tests were excluded from study. Patients categorized according to clinical status (asymptomatic, mild, moderate and severe disease). AST ALT elevations classified as less than 2 \times upper limit of normal (ULN), 2–5 \times ULN and more than 5 \times ULN. Comorbidities, outcome and frequency of liver injury were analyzed by SPSS.

Results: 425 children included into the study and AST, ALT, GGT and LDH abnormalities detected in 17.6%, 9.5%, 0.6% and 18.7% of children during follow-up. AST and ALT elevation were lower than 2 ULN in 94.7 and 90.3%, respectively. None of them showed more than 5 \times ULN. Most of them had asymptomatic or mild disease (96.7%). In terms of disease severity, we did not find significant difference between normal and abnormal liver test groups. Liver test abnormalities were not found related to disease severity, presence of comorbid conditions (immunosuppression, malignancy, transplantation), antibiotic-antiviral treatment, age and gender (table 1). Absolute lymphocyte count was significantly low in children with moderate and severe disease compared to mild and asymptomatic children (1400 \pm 338 vs 3178 \pm 117p = 0.013). Progressive liver disease or liver failure was not observed and all of them alive.

Table 1:

	Asymptomatic-mild n = 363	Moderate-severe n = 62	p
Age (months)	109.7 \pm 2.5	115.1 \pm 8.9	0.56
AST IU	30 \pm 2.5	22 \pm 2	0.27
ALT IU	22.5 \pm 2	18 \pm 2.6	0.59
GGT IU	21 \pm 6	26 \pm 3.2	0.73
LDH IU	413 \pm 114	392 \pm 128	0.69
TBIL mg/dl	1.2 \pm 0.2	1.3 \pm 0.3	0.86

Data are given mean \pm SEM.

Conclusion: Liver test abnormalities detected in minority of patients in this cohort. This could be related to milder course of COVID -19 in children, lack of comorbid conditions such as hypertension, diabetes, coronary heart disease.

PO-2628

Novel Copper Protein Speciation method for calculating Serum Non Ceruloplasmin Copper: A comparative analysis

Timothy Morley¹, C. Omar Kamlin¹, Heidi Goenaga-Infante², Koenraad D'Hollander³, Stuart McDougall⁴. ¹Orphalan, United Kingdom; ²National Measurement Laboratory LGC group, United Kingdom; ³IDDI, Belgium; ⁴Quotient Sciences, United Kingdom
Email: tim.morley@orphalan.uk

Background and aims: US and European guidelines recommend calculated serum non-ceruloplasmin-bound copper (NCC; free copper index) for the diagnosis and management of Wilson disease (WD) with a target range of 50 to 150 mcg/L. Standard of care involves incubating patient serum with EDTA to chelate Copper (Cu) from proteins other than ceruloplasmin (Cp). This ultrafiltrate captures NCC complexes and may result in an underestimation of NCC. As a result, the immunological and enzymatic assays used to determine NCC are not universally adopted by clinicians. The aim of this study is to compare standard of care EDTA ultra-centrifugation (NCC-EDTA)

method with a novel Cu protein speciation (NCC-CuSp) assay in WD patients.

Method: NCC CuSp quantification is a two step process; inductively coupled mass spectrometry (ICP-MS) to measure total Cu followed by liquid chromatography (LC) ICP-MS to calculate the relative amount of caeruloplasmin bound copper (Cp-Cu) as a percentage of total Cu in the sample. LC-ICP-MS determines Cp-Cu indirectly by the speciation of copper containing proteins (Cp, albumin and α -2-macroglobulin). The relative concentration of Cp-Cu is calculated [(% Abundance of Cu-Cp) / ([Total Serum Cu]) where Cp-Cu is determined from peak area of Cp-Cu as a percentage of total Cu peak area. NCC-CuSp = Total Cu minus Cp-Cu. WD patients enrolled in a clinical trial had blood samples taken for NCC evaluation by both methods at screening and 9 visits every 4 weeks thereafter. Paired data were compared using Bland Altman (BA) analysis, where the standard deviation (SD) of the difference of paired measurements was calculated based on a mixed model, taking into account repeated measures for each subject.

Results: 511 paired samples were available from 73 patients. The BA plot (figure 1a) shows a mean difference of 10.04, with (2SD) limits of agreement (-32.97, 53.05) microgram/L; these limits capture 489 out of 511 observations (Fig. 1a). In the scatter plot (Fig. 1b), the diagonal line has slope 1, indicating a higher NCC-CuSp value compared to NCC-EDTA for observations below the diagonal. Within the target range of 50 to 150 mcg/L, 264 (52%) and 360 (70%) of the 511 samples were detected with NCC-EDTA and NCC-CuSp respectively. Of the 360 NCC-CuSp in the range, only 234 (65%) were paired with NCC-EDTA; 126 (35%) registering as <50 mcg/L (red box).

Conclusion: Agreement between NCC-EDTA and NCC-CuSp is moderate. On average, compared with NCC-CuSp, NCC-EDTA produces lower NCC values; falling more frequently below the 50–150 mcg/L range, and this may be important for clinical decision making.

PO-2667

Three-fold increased risk for death in Budd-Chiari syndrome compared to matched controls-population-based cohort study

Fredrik Åberg¹, Linnea Widman², Rupesh Rajani³, Hannes Hagström^{3,4}. ¹Helsinki University Hospital and University of Helsinki, Department of Transplantation and Liver Surgery., Helsinki, Finland; ²Karolinska Institutet, Biostatistics Core Facility, Sweden; ³Karolinska University Hospital, Stockholm, Sweden; ⁴Karolinska Institutet, Department of Medicine, Huddinge, Sweden
Email: hannes.hagstrom@ki.se

Background and aims: Patients with Budd-Chiari syndrome (BCS) have a high risk of overall and liver-specific mortality, but this has not been quantified on a population level nor compared against the general population.

Method: We performed a register-based study, identifying all patients in Sweden with a recorded diagnosis of BCS in the nationwide Patient Register between 1987 and 2016. Cases with BCS were matched by age, sex and living location with up to ten reference individuals from the general population. Data on cause-specific mortality was obtained from the Causes of Death Register. Cox regression was used to investigate rates of all-cause and cause-specific mortality.

Results: A total of 478 patients with BCS were matched with 4603 reference individuals. 56% were men and median age was 57.7 years. 39% of patients with BCS had a recorded diagnosis of a precipitating risk factor, and 13% had an underlying liver disease. During a median follow-up of 5.1 years, 248 (52%) of patients with BCS died compared with 1416 (31%) of reference individuals.

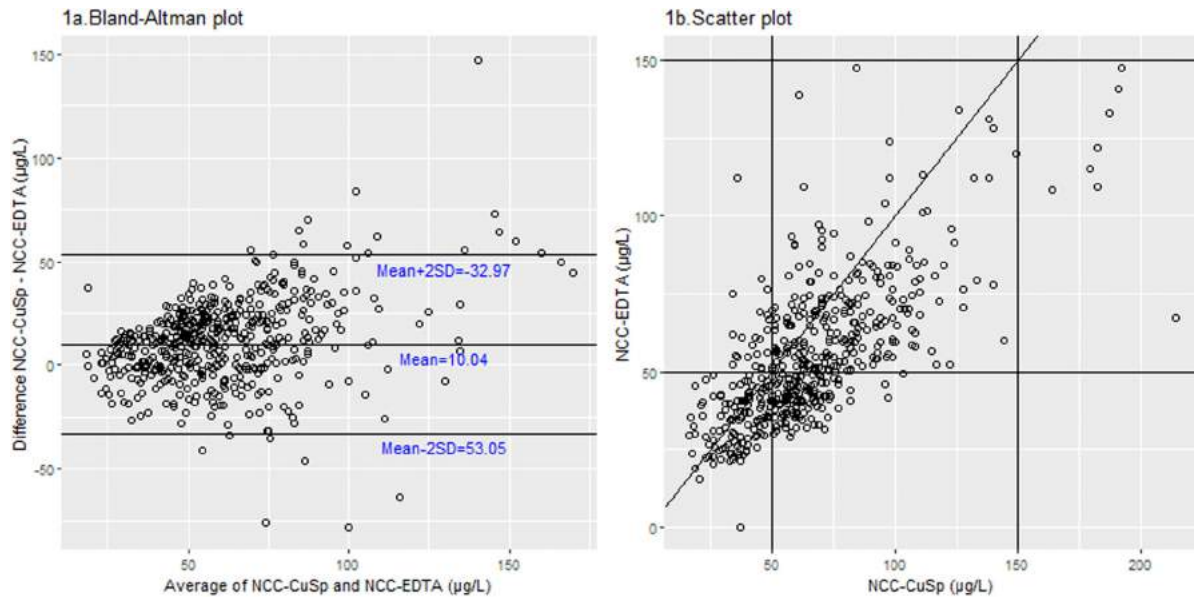


Figure: (abstract: PO-2628) NCC Data (paired) in Bland Altman plot and individual in scatter plot

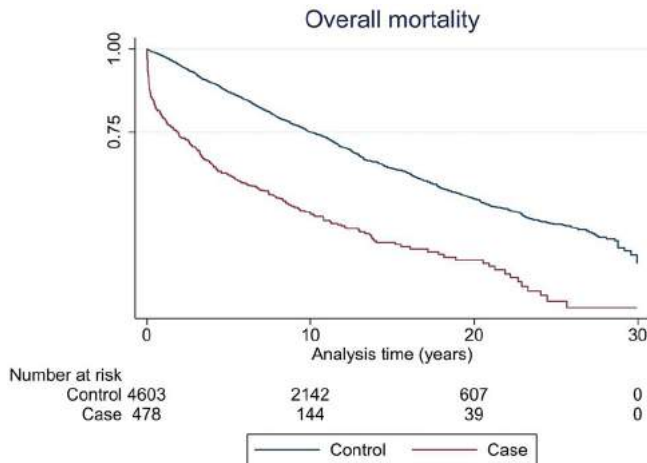


Figure: Kaplan-Meier curve of the risk of overall mortality in patients with Budd-Chiari (cases) and matched reference individuals (controls).

The incidence of overall mortality was 71/1000 person-years (PY) in BCS compared with 29/1000 PY:s in reference individuals. This translated to an adjusted hazard ratio (aHR) of 3.0 (95%CI = 2.6–3.5, figure 1). The rate of liver-related death was particularly high (incidence rate 6.9/1000 vs 0.2/1000; aHR = 47.6, 95%CI = 16.5–137.4), but the most common cause of death was cardiovascular disease (incidence rate 25/1000 vs 13/1000; aHR = 2.2, 95%CI = 1.7–2.9). 33 patients with BCS (6.9%) underwent liver transplantation.

Conclusion: Patients with BCS in Sweden during the study period had a 3-fold higher risk of death compared to general population reference individuals. While the risk of liver disease mortality was in relative terms highest, most patients died from cardiovascular causes.

PO-2697

Defining the range of healthy volunteer non ceruloplasmin copper using a new Copper Protein Speciation assay

Timothy Morley¹, C. Omar Kamlin¹, Heidi Goenaga-Infante², Maria Estela del Castillo², Koenraad D'Hollander³. ¹Orphalan, United Kingdom; ²National Measurement Laboratory LGC group, United Kingdom; ³IDDI, Belgium
 Email: tim.morley@orphalan.uk

Background and aims: US and European guidelines recommend calculated non-ceruloplasmin-bound copper (NCC; free copper index) for the diagnosis and management of Wilson Disease (WD). A serum sample from collected blood is incubated with EDTA to chelate copper (Cu) from proteins other than ceruloplasmin followed by calculation of NCC using either immunological or enzymatic technologies to determine ceruloplasmin concentration. These methods are unreliable and not universally adopted by clinicians. The aim of this study is to produce normative data for a novel NCC copper protein speciation assay (NCC-CuSp).

Method: NCC-CuSp quantification is a two-step process; inductively coupled mass spectrometry (ICP-MS) to measure total Cu followed by liquid chromatography (LC) ICP-MS to calculate the relative amount of ceruloplasmin bound copper (Cp-Cu) as a percentage of total Cu in the sample. LC-ICP-MS determines Cp-Cu indirectly by the speciation of copper containing proteins (Cp, albumin and alpha-2-macroglobulin). The relative concentration of Cp-Cu is calculated [(% Abundance of Cu-Cp) / ([Total Serum Cu]) where Cp-Cu is determined from peak area of Cp-Cu as a percentage of total Cu peak area. NCC-CuSp = Total Cu minus Cp-Cu. Blood samples from 50 healthy adult volunteers were obtained for determining NCC-CuSp using ICP-MS/LC-CIP-MS and descriptive statistics generated. Normality of the data was tested using a Shapiro-Wilk test. Reference interval limits were calculated using a nonparametric method (2.5th and 97.5th percentiles). This method makes no assumption about the probability distribution of the observed values. The confidence interval (CI) for the lower and upper limits were calculated using bootstrapping.

Results: Fifty volunteers; 25 females and males with a mean (range) age of 40 (21–62) and 40 (20–78) years of whom 60% were Hispanic, participated. Results of the copper speciation are shown in the table. As the hypothesis of normality was rejected, the reference interval was calculated using a non-parametric method. Outliers were consistently present by subgroup (gender, age, race). Two outlying observations (NCC = 310 and 213 mcg/L) were identified using Cook's distance and removed. The lower and upper (90% CI) reference limits are 41.2 (34.5, 42.4) and 148.7 (144.5, 184) mcg/L respectively.

POSTER PRESENTATIONS

Figure:

	Mean	Median	Q1	Q3	Min	Max	Standard deviation
Total Copper (ng/ml)	1163	1145	987	1303	724	1960	278.7
Cp-Cu relative abundance (ng/ml)	1081	1065	911	1220	414	1870	287.7
Alb-Cu relative abundance (ng/ml)	70	58.2	47.5	74.6	33.3	295	43.8
NCC (mcg/L)	82.2	72.8	56.7	85.3	40	310	45.0

Conclusion: A reference interval was established for the novel NCC-CuSp assay based on the results from 50 healthy volunteers. This may be an appropriate safe target range for patients with WD and provide clinicians a target to aim for through dose titration of WD therapies.

PO-2770

Optimization of CRISPR/Cas9 technology for a safer treatment of rare metabolic disorders

Laura Tamayo^{1,2}, Ibon Tamayo^{2,3}, África Vales^{1,2}, Cristina Olague^{1,2}, Sergio López-Manzaneda^{4,5,6,7}, Isabel Ojeda-Pérez^{5,7,8}, Jose Segovia^{5,7,9}, Juan R. Rodríguez-Madoz^{2,10}, Eduardo Salido^{11,12,13}, Nerea Zabaleta^{1,2,14,15,16,17}, Gloria González-Aseguinolaza^{1,2}. ¹CIMA (Center for Applied Medical Research) University of Navarre, Gene Therapy and Regulation of Gene Expression, Pamplona, Spain; ²Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain; ³CIMA (Center for Applied Medical Research) University of Navarre, Bioinformatics core, Pamplona, Spain; ⁴ICM Institute for Brain and Spinal Cord, Thérapie Cellulaire et Génique des Maladies Neurologiques de l'Enfant et de l'Adulte-NeuroGenCell, Equipe CARTIER, Paris, France; ⁵Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Cell Differentiation and Cytometry Unit, Hematopoietic Innovative Therapies Division, Madrid, Spain; ⁶Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; ⁷Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD, UAM), Unidad Mixta de Terapias Avanzadas, Madrid, Spain; ⁸Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; ⁹Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; ¹⁰CIMA (Center for Applied Medical Research) University of Navarre, Cell Therapy Program, Pamplona, Spain; ¹¹Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain; ¹²University of La Laguna, San Cristóbal de La Laguna, Spain; ¹³Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER); ¹⁴Grousbeck Gene Therapy Center, Boston; ¹⁵Schepens Eye Research, Boston, United States; ¹⁶Mass. Eye and Ear, Boston, United States; ¹⁷Harvard Medical School, Boston, United States

Email: ltorella@alumni.unav.es

Background and aims: Gene therapy is the most attractive approach for rare life-threatening monogenic disorders. To date, liver-kidney transplantation is the unique curative therapy for Primary Hyperoxaluria type I (PH1), an inherited disorder associated with mutations in the AGXT gene, that causes a deficiency in hepatic alanine-glyoxylate aminotransferase (AGT). Consequently, oxalate, an insoluble metabolic substrate, accumulates in kidneys causing end-stage renal failure and systemic oxalosis.

The inhibition of glycolate oxidase (GO), the enzyme implicated in the synthesis of glyoxylate (precursor of oxalate), has been proven to be an efficacious strategy as substrate reduction therapy (SRT) for PH1. Our goal is to develop CRISPR/Cas9-based SRT by editing the *Hao1* gene, encoding GO. Recently, we showed in a PH1 mouse model that CRISPR/Cas9-mediated *Hao1* gene disruption prevented oxalate accumulation and kidney damage, with no signs of toxicity. We have further improved this strategy by 1) increasing the on-target editing

precision using two gRNAs 64-base pair (bp) apart; and 2) combining the two gRNAs and the nickase version of SaCas9 (D10AnSaCas9), to reduce the off-target effect.

Methods: Two *Hao1*-specific gRNAs were used in combination with CRISPR/SaCas9 or its nickase-version, both under the control of a liver-specific promoter. They were delivered using an AAV serotype 8. Lastly, a vector co-expressing the nickase together with the two gRNAs was created to decrease the vector dose and increase the safety. Twelve-week-old male *Agxt1*^{-/-} mice were administered intravenously with a single dose of AAV-CRISPR vectors and untreated age-matched *Agxt1*^{-/-} mice were used as control. 4 weeks after treatment, animals were sacrificed, and livers harvested for molecular and histological analysis.

Results: Simultaneous double-strand-breaks led to predictable on-target genome editing since most of the edited sequences had a precise deletion of 64-bp. These modifications led to a decrease in *Hao1* mRNA levels with an overall depletion of GO protein expression. However, the use of two gRNAs might increase the risk of unwanted off-target events. The administration of the same two gRNAs in presence of a nickase Cas9 had equal GO depletion efficacy while greatly reducing the off-target potential, proven by the absence of on-target editing with a nickase/sgRNA complex. Lastly, the combination of the dual-nickase gRNA system in a single vector decreased the effective minimal dose 3-fold.

Conclusion: We have developed a safe and efficient CRISPR/SaCas9 SRT for targeted gene disruption by combining two gRNAs binding nearby sequences of *Hao1* and Cas9 nickase in a single vector. The therapeutic effect of this optimized vector in PH1 mice is under evaluation. This strategy could potentially be applied for the treatment of other inherited hepatic metabolic disorders that can benefit from SRT.

PO-2902

Impact of SarsCov2 pandemic on vascular liver diseases

Anna Baiges¹, Eira Cerda Reyes¹, Caroline Amicone², Tellez Luis³, Angela Puente⁴, Elba Llop⁵, Edilmar Alvarado⁶, Filipa Rocha⁷, Lara Orts⁸, Oliva Ros⁸, Pamela Vizcarrá⁸, Maria José Serrano⁸, M. Àngels Falgà⁸, Marta Magaz¹, Pol Olivás¹, Fabián Betancourt Sánchez¹, Valeria Perez¹, Fanny Turon¹, Payance Audrey², Odile Gorla², Rautou Pe², Virginia Hernandez-Gea¹, Aurélie Plessier², Juan Carlos Garcia Pagan¹, Jose Ignacio Fortea⁴. ¹Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS and CIBERehd, Spain, Barcelona, Spain; ²DHU Unity, Pôle des Maladies de l'Appareil Digestif, Service d'Hépatologie, Centre de Référence des Maladies Vasculaires du Foie, Hôpital Beaujon, AP-HP, Clichy, France; ³Gastroenterology and Hepatology Department, Hospital Ramon y Cajal, Universidad de Alcalá, Madrid, Spain; ⁴Digestive Diseases Department, Marqués de Valdecilla University Hospital. IDIVAL. Santander, Spain; ⁵Liver Unit, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain; ⁶Gastroenterology Department, Hospital Santa Creu i Sant Pau, Barcelona, Spain; ⁷Hospital da Luz Lisboa; ⁸Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain
Email: abaiges@clinic.cat

Background and aims: Vascular liver diseases (VLD) are represented mainly by portosinusoidal vascular disease (PSVD), non-cirrhotic splanchnic vein thrombosis (SVT) and Budd Chiari syndrome (BCS). It is unknown whether patients with VLD represent a high risk population for complications and greater mortality from SarsCov2 infection.

Our objective was to assess the prevalence and severity of SarsCov2 infection among patients with VLD.

Method: Retrospective international study analyzing the prevalence and severity of SarsCov2 infection in VLD between March 2020-March 21. Patients from Spain and France were included.

The Spanish VLD database includes 550 patients, of whom we were able to contact 495 (90%): 147 patients with PSVD, 277 with SVT and 71 with BCS. Similarly, the French VLD database comprises 700 patients of whom 489 were contacted (70%): 121 PSVD, 281 SVT and 87 BCS. We compared our data to that of the general population (GP).

Results: In the Spanish cohort 57 patients presented SarsCoV2 infection (11.5% of patients with VLD vs 6.5% of Spanish GP): 25 PSVD, 31 SVT and 1 BCS. Regarding age distribution, the prevalence of SarsCoV2 in PSVD between 30–39, 40–49, 50–59, 60–69 and 70–79 years of age was 15%, 24%, 32%, 12% and 5% compared to 7%, 6.5%, 6.4%, 5.3% and 4.5% in GP. In patients with SVT, the prevalence was 6%, 16%, 11%, 12% and 12%.

In the French cohort, 71 patients presented with SarsCoV2 infection (14.5% of patients with VLD vs 8.4% in French GP): 22 PSVD, 41 SVT and 8 BCS. Regarding age distribution, the prevalence of SarsCoV2 in patients with PSVD between 15–44, 45–64 and 65–75 years was 12%, 19%, 22% compared to 7%, 11% and 10.5% in French GP. In patients with SVT, the prevalence was 15%, 17% and 5% and in BCS of 15–44 years and 45–64 years the prevalence was 9% and 12%.

In terms of infection severity, in Spain 11 patients (20%) required hospital admission compared to 7.3% in GP; 1 patient required ICU (1.7% vs 0.7% in GP) and 3 patients died (5.2% vs 1.5% in GP), all of them with SVT. In France, 8 patients required hospital admission (11%), 3 ICU (4%) and 2 patients died (2.8% vs 1.8% in GP), one with PSVD and one with SVT.

We were not able to identify baseline factors (previous decompensation, comorbidity, underlying thrombophilia) correlating with the risk and severity of SarsCoV2 infection.

Conclusion: Patients with vascular liver disease have a higher prevalence of SarsCov2 infection and associate a higher mortality.

Viral Hepatitis A, B, C, D, E: Virology

PO-175

A cell-based cccDNA reporter assay combined with functional genomics identifies YBX1 as HBV cccDNA host factor and antiviral target

Gaëtan Ligat¹, Eloi Verrier¹, Laura Heydmann¹, Katharina Doernbrack², Julija Miller², Anne Maglott-Roth³, Frank Jühling¹, Hussein El Saghire¹, Naoto Fujiwara⁴, Sen-Yung Hsieh⁵, Yujin Hoshida⁴, David E. Root⁶, Patrick Pessaux^{1,7}, Atish Mukherji¹, Catherine Schuster¹, Laurent Brino³, Michael Nassal², Thomas Baumert^{1,7}. ¹Université de Strasbourg, Inserm, Institut de Recherche sur les Maladies Virales et Hépatiques UMRS 1110, Strasbourg, France; ²Department of Internal Medicine II/ Molecular Biology, University Hospital Freiburg, Freiburg, Germany; ³IGBMC, Plateforme de Criblage Haut-débit, Illkirch, France; ⁴Liver Tumor Translational Research Program, Simmons Comprehensive Cancer Center, Division of Digestive and Liver Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, United States; ⁵Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Taiwan; ⁶Broad Institute of Massachusetts Institute of Technology and Harvard, United States; ⁷Institut Hospitalo-Universitaire, Pôle Hépatite-digestif, Nouvel Hôpital Civil, Strasbourg, France
Email: thomas.baumert@unistra.fr

Background and aims: Chronic hepatitis B virus (HBV) infection is a leading cause of liver disease and hepatocellular carcinoma (HCC). A key feature of HBV replication is the synthesis of the covalently close circular (ccc)DNA, not targeted by the current treatment and whose elimination would be crucial for viral cure. To date, little is known about cccDNA formation. One major challenge to address this urgent

question is the absence of robust model for the study of cccDNA biology.

Method: We established a cell-based HBV cccDNA reporter assay and performed a loss-of-function screen targeting 239 genes encoding for the human DNA damage response machinery.

Results: Overcoming the limitations of current models, the reporter assay enables to quantify cccDNA levels using a robust ELISA as a readout. A loss-of-function screen identified 27 candidate cccDNA host factors, including Y box binding protein 1 (YBX1), a DNA binding protein regulating transcription and translation. Validation studies in authentic infection models including primary human hepatocytes revealed a robust decrease in HBV marjers and cccDNA levels following silencing or treatment with drugs targeting YBX1, providing proof-of-concept for the targetability of YBX1 for new antiviral therapy. Chromatin immunoprecipitation qPCR assays confirmed that YBX1 was recruited to HBV genome. In patients, YBX1 expression robustly correlates with both HBV load and liver disease progression, confirming its clinical impact for the HBV life cycle.

Conclusion: Our cell-based reporter assay enables the discovery of HBV cccDNA host factors as antiviral targets. YBX1 is a previously undiscovered HBV host-dependency factor targetable for antiviral therapy not only relevant for the HBV life cycle but also for the pathogenesis of virus-induced liver disease and cancer.

PO-258

Helicases DDX5 and DDX17 regulate hepatitis B virus transcriptional fidelity and RNA processing in infected human primary hepatocytes

Fleur Chapus^{1,2}, Guillaume Giraud¹, Caroline Charre^{1,2,3}, Chloe Goldsmith^{1,2}, Maria Guadalupe Martinez^{1,2}, Judith Fresquet¹, Audrey Diederichs^{1,2}, Maelle Locatelli^{1,2}, Hélène Polveche^{4,5}, Caroline Scholtes⁶, Hector Hernandez-Vargas², Rivoire Michel⁷, Cyril Bourgeois^{2,5}, Fabien Zoulim^{1,2,3}, Barbara Testoni¹. ¹Inserm U1052-Cancer Research Center of Lyon, Cancer Initiation and Tumor cell Identity, Lyon, France; ²University of Lyon, UMR_S1052, CRCL, Lyon, France; ³Croix Rousse Hospital, Hospices Civils de Lyon, Department of Hepatology, Lyon, France; ⁴CECS, I-Stem, Corbeil-Essonnes, France; ⁵Ecole Normale Supérieure de Lyon, Inserm U1210-CNRS-UMR5239, Lyon, France; ⁶Croix Rousse Hospital, Hospices Civils de Lyon, Department of virology, France; ⁷Centre Leon Berard, Inserm U1032, Lyon, France
Email: barbara.testoni@inserm.fr

Background and aims: Unaffected by current antiviral therapies, covalently closed circular DNA (cccDNA) is responsible for Hepatitis B virus (HBV) persistence in infected hepatocytes and represents the key molecule for viral life cycle. cccDNA is a stable chromatinized episome and the template for the six viral mRNAs. Transcription from cccDNA has several peculiar features, among which the fact that all viral RNAs use a common polyadenylation signal (PAS). Mechanisms and factors determining HBV RNA 3' end processing are still poorly defined. This study, therefore, aimed to precisely map the 3' end of HBV transcripts and to decipher the molecular events regulating HBV mRNA transcriptional fidelity.

Method: RNA extracted from HBV-infected HepG2-NTCP cells and primary human hepatocytes (PHHs) was subjected to HBV-adapted 3' RACE followed by MinION Nanopore single molecule sequencing. These experiments were combined with RT-qPCR and Northern blot analysis of HBV transcripts, together with chromatin- and RNA-immunoprecipitation (ChIP, CLIP) and functional inactivation of candidate proteins by RNA interference (RNAi).

Results: Single molecule sequencing analysis precisely indicated that the majority of HBV mRNAs ended 13 nucleotides downstream of the PAS in both infected PHH and HepG2-NTCP cells. However, in HepG2-NTCP cells, a significant proportion of HBV transcripts displayed a transcriptional readthrough of hundreds of base pairs downstream of this PAS. This readthrough was correlated with a higher expression of the DDX5 and DDX17 RNA helicases in HepG2-NTCP cells compared

POSTER PRESENTATIONS

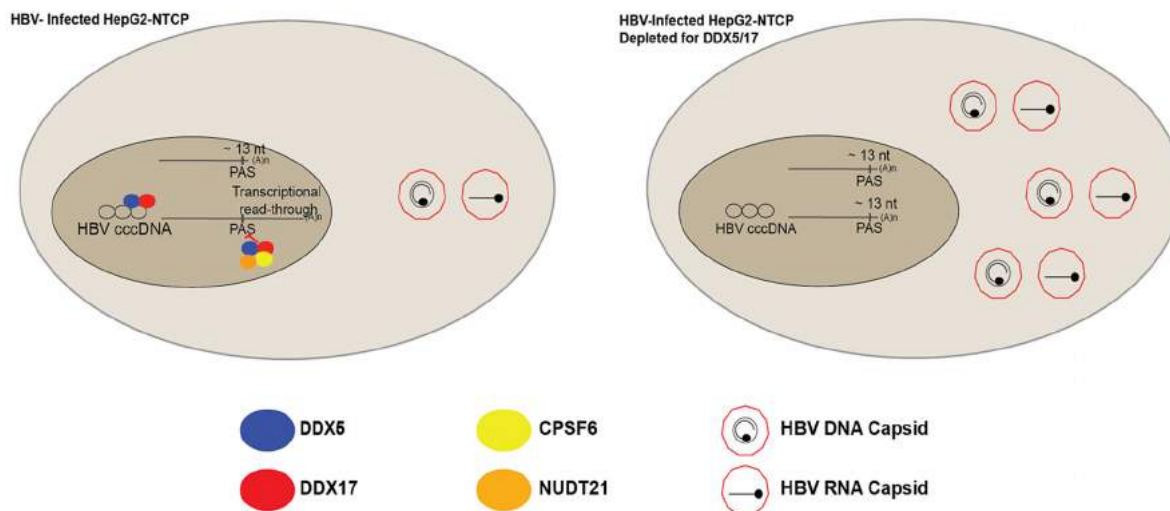


Figure: (abstract: PO-258)

to PHHs. Accordingly, RNAi for both helicases triggered an increase in electromobility of HBV RNAs in Northern Blotting without any significant effects on global RNAs levels suggesting a shortening of viral transcripts that was confirmed by the disappearance of the transcriptional readthrough after MinION sequencing. Combination of ChIP and CLIP-qPCR experiments showed that both DDX5 and DDX17 were recruited to cccDNA and RNAs and were required for the recruitment of the termination complex components CPSF6 and NUDT21, known to favor transcriptional readthrough. Finally, repression of DDX5 and DDX17 increased intracellular encapsidated DNA levels suggesting an increased HBV replication.

Conclusion: Altogether, our data suggest that optimal viral replication requires a fine tune regulation of the 3' end processing of HBV mRNAs and point to a pivotal role of DDX5/17 helicases and the terminator complex components NUDT21 and CPSF6 in the HBV transcription termination process.

PO-469

Study of the effect of the hepatitis D virus on the hepatitis B virus quasispecies in mice models by a next-generation sequencing approach

Beatriz Pacín^{1,2}, Gracián Camps³, David Tabernero^{1,4}, María Francesca Cortese^{1,2}, Josep Gregori^{1,2}, Marta Vila^{1,2}, Rosario Casillas^{1,2}, Selene García^{1,2}, Ariadna Rando¹, Josep Quer^{2,4}, Rafael Esteban^{4,5}, Mar Riveiro Barciela^{4,5}, Maria Buti^{4,5}, Gloria González-Aseguinolaza³, Francisco Rodriguez Frias^{1,4}.

¹University Hospital Vall d'Hebron, Liver Pathology Unit, Departments of Biochemistry and Microbiology, Barcelona, Spain; ²Vall d'Hebron Research Institute (VHIR), Liver Unit, Liver Disease Laboratory-Viral Hepatitis, Barcelona, Spain; ³University of Navarra, Center for Applied Medical Research (CIMA), Pamplona, Spain; ⁴Instituto de Salud Carlos III (Institute of Health Carlos III), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd, Network Center For Biomedical Research in Hepatic and Digestive Diseases), Madrid, Spain; ⁵University Hospital Vall d'Hebron, Liver Unit, Department of Internal Medicine, Barcelona, Spain
Email: david.tabernero@ciberehd.org

Background and aims: Hepatitis B virus (HBV) replication does not significantly activate innate immune responses and is strongly affected by the co-infecting hepatitis D virus (HDV), which induces a profound type I Interferon (IFN) response. However, few data about the effects of this interaction over HBV quasispecies (QS) are available. The aim of this study was to analyse, in vivo, the influence of HDV over HBV QS variability, and potential role of IFN response.

Method: HBV and HDV replication competent genomes were delivered to the mouse liver using adeno-associated viruses (AAV-HBV and AAV-HDV). As control an AAV carrying the luciferase reporter gene was used (AAV-Luc). Eight-week-old C57BL/6 (WT) (n = 6) and IFN alpha receptor knock out (IFNaR KO) (n = 8) male mice were divided into two different groups (n = 3/4) that were co-infected with AAV-HBV and AAV-Luc (HBV_mi) or AAV-HBV and AAV-HDV (HBV_HDV). Intrahepatic RNA was obtained from all mice at day 21 after AAV injection. The HBV-RNA QS was analyzed by next-generation sequencing in 2 independent amplicons including the 5' and 3' ends of HBV X gene (HBX) transcripts: nucleotides (nt) 1255-1611 (5' HBX) and 1596-1912 (3' HBX). The nt changes relative to the master sequences were assessed.

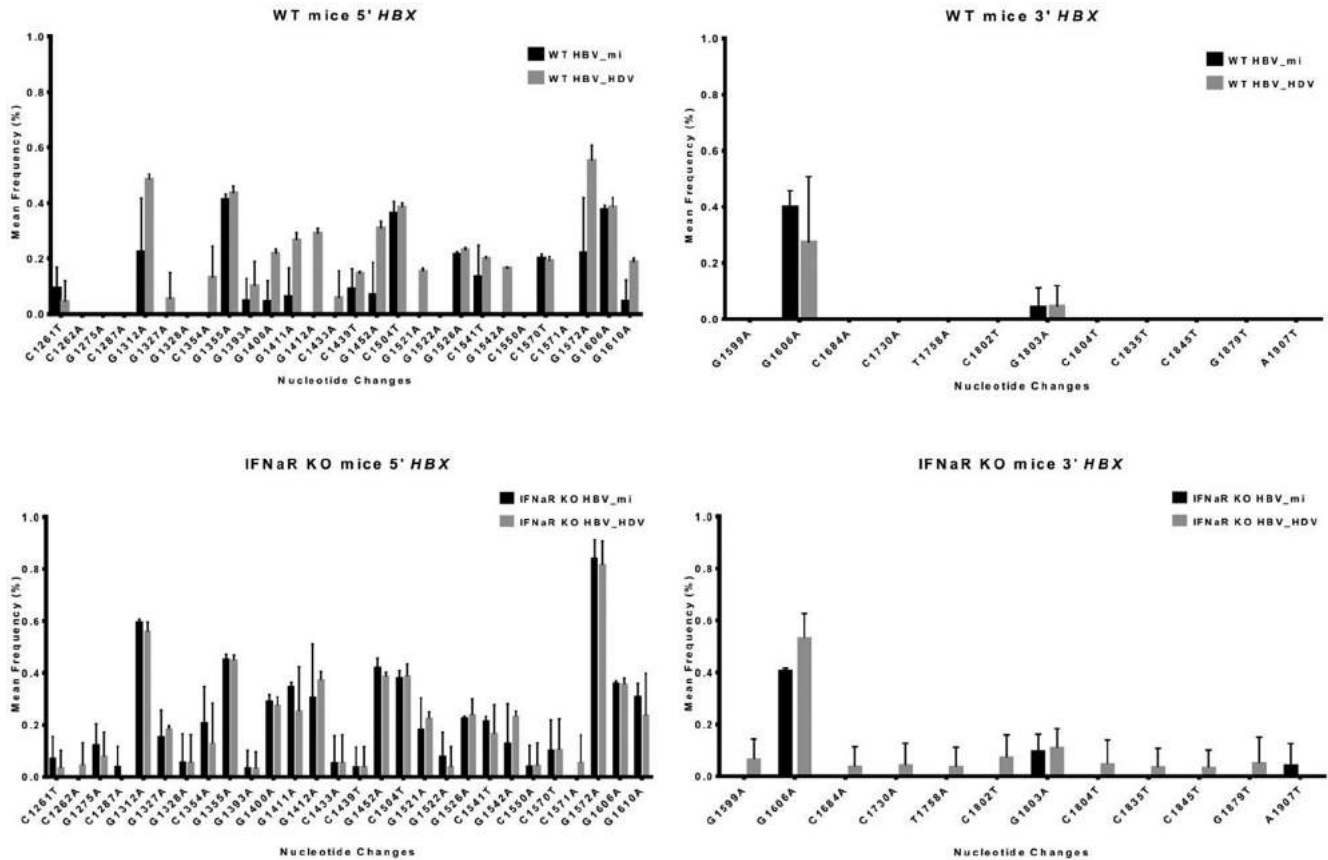
Results: A median of 111467 (interquartile range 83999-232731) and 218852 (155171-293022) sequence reads/sample were obtained from 5' and 3' HBX respectively. Analysis of both 5' and 3' HBX amplicons showed that most identified nt changes accumulated in 5' HBX (figure). This analysis showed a total of 22 nt changes in WT mice, all present in HBV_HDV and only 16 (72.7%) in HBV_mi. Of 14/16 (87.5%) mean frequencies were HBV_mi <HBV_HDV, while in 2 (12.5%) HBV_mi >HBV_HDV. IFNaR KO mice showed a total of 39 nt changes, 37 (94.9%) in HBV_HDV and 28 (71.8%) in HBV_mi. 26/39 (66.7%) nt changes were observed in HBV_mi and HBV_HDV [11/26 (42.3%) mean frequencies were HBV_mi <HBV_HDV, in 15/26 (57.7%) HBV_mi >HBV_HDV].

Conclusion: The HBV_HDV WT mice showed higher rates of HBX nt changes in comparison to HBV_mi, indicating that HDV enhanced HBV QS variability. Interestingly, those differences were reduced in IFNaR KO animals. The 3' HBX showed a higher trend to sequence conservation than 5' HBX, which could be explained by the importance to preserve the essential regulatory sequence motifs included in that region. Funding: Instituto de Salud Carlos III (grant PI18/01436), co-financed by the European Regional Development Fund (ERDF).

PO-526

Real life kinetics of new HBV markers during treatment of chronic hepatitis D with bulevirtide

Charlotte Pronier^{1,2}, BOMO Jeremy², Juliette Besombes¹, Anita Levacher³, Segolene Brichler^{4,5}, Philippe Gripon², Caroline Jezuquel³, Dominique Guyader³, Vincent Thibault^{1,2}. ¹CHU Pontchaillou, Virology, RENNES, France; ²Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) UMR_S 1085, 2IIEF, RENNES, France; ³CHU Pontchaillou, Hepatology, RENNES, France; ⁴AP-HP, Avicenne, Clinical Microbiology, Bobigny, France; ⁵Paris



Nucleotide changes identified in each amplicon, with their mean frequencies and standard deviations (error bars) in each group of mice:
 • Upper graphs, C57BL/6 (WT) mice with HBV mono-infection (WT HBV_mi) vs. HBV/HDV co-infection (WT HBV_HDV). Left graph shows nucleotide changes between positions 1255 – 1611 (5' HBX) and right graph between positions 1596 – 1912 (3' HBX).
 • Bottom graphs, interferon alpha receptor knock out (IFNαR KO) mice with HBV mono-infection (IFNαR KO HBV_mi) vs. HBV/HDV co-infection (IFNαR KO HBV_HDV). Left graph shows nucleotide changes at 5' HBX and right graph at 3' HBX.

Figure: (abstract: PO-469)

13 University, Sorbonne Paris Cité, Inserm, U955, Creteil, France
 Email: charlotte.pronier@chu-rennes.fr

Background and aims: Bulevirtide is a first-in-class entry inhibitor for the treatment of chronic hepatitis D virus (HDV) and hepatitis B virus (HBV) infections. We report the interim results of real life kinetics of new HBV markers on chronically infected HDV patients treated with this recently approved treatment.

Method: Nine HDV RNA positive adult patients, mainly men, with compensated liver disease were treated with bulevirtide (2 mg/d SC), pegylated interferon alpha (PegIFNα) and NUC. Kinetics of HBV markers were evaluated at initiation of treatment and then at months 1, 2, 3, 6, 9 and up to 1 year during treatment.

Results: Among these 9 patients infected by genotype 1 HDV except one, most of them were cirrhotics and overweight with a median age of 35 years. Duration of 12, 9 and 3 months of treatment was evenly distributed in three thirds among patients. At initiation of bulevirtide, median ALT was 131 IU/L (IQR 144) and viral markers were as follows. Median HDV viral load (VL) was 7.23 log IU/ml (IQR 2.53). HBV-DNA was <10 IU/ml and HBV-RNA was negative in all patients except one. Median HBsAg was 4.04 log IU/ml (IQR 0.2). HBcrAg was positive in all patients except one (median 4.3 log U/ml; IQR 2). Median anti-HBc IgG level was 62.5 COI (IQR 59.47). No patient had anti-HBs antibodies and all were HBeAg negative, except one. HDV-VL decreased significantly throughout each visit and 7 patients achieved HDV-RNA indetectability. During follow-up, HBsAg titers remained unchanged, HBcrAg status did not change while anti-HBc IgG and ALT tended to decrease overtime. In 3 patients, PegIFNα was stopped

after 1 year of treatment following 6 months of HDV-RNA indetectability (n = 1) or secondary to adverse events (n = 2).

Conclusion: Kinetics of viral markers in patients treated by bulevirtide appears highly heterogeneous between individuals and their predictive values remain to be defined. The ongoing follow-up of these markers continues and will be scrutinized after bulevirtide discontinuation. These preliminary results will have to be confirmed in larger cohort of patients.

PO-611

Adaptation of hepatitis C virus to efficient infection of mouse hepatocytes

Julie Sheldon¹, Qingong Yuan¹, Melina Winkler¹, Nicola Frericks¹, Yudi Zhang¹, Richard Brown², Arnaud Carpentier¹, Natascha Gödecke³, Sara Behme³, Katharina Rox⁴, Florian Vondran⁵, Stefan Pöhlmann⁶, Dagmar Wirth³, Thomas Pietschmann¹. ¹Twincore, Hannover, Germany; ²Paul Ehrlich Institute, Langen (Hessen), Germany; ³Helmholtz Centre for Infection Research, Model Systems for Infection and Immunity, Braunschweig, Germany; ⁴Helmholtz Centre for Infection Research, Chemical Biology, Braunschweig, Germany; ⁵Medizinische Hochschule Hannover, Klinik für Allgemein-, Viszeral-, und Transplantationschirurgie, Hannover, Germany; ⁶German Primate Center, Göttingen, Germany
 Email: julie.sheldon@twincore.de

Background and aims: Approximately 71 million people suffer from a chronic infection with the hepatitis C virus (HCV). Despite effective treatment, viral transmission remains high and a prophylactic vaccine

POSTER PRESENTATIONS

is not available. The absence of an immune competent HCV animal model limits vaccine research and development. HCV has a narrow species tropism, and naturally infects only humans. However, replication is error-prone giving rise to a vast spectrum of variants (quasispecies) facilitating viral adaptation to changing environments. Here we exploited this property for the generation of a virus population with high replication fitness in primary mouse hepatocytes (PMH).

Method: We used a step-wise adaptation procedure culturing HCV between human (Huh-7.5) and mouse liver cells expressing HCV entry factors (MLT-5H) and then further passaged the virus population in primary mouse hepatocytes from entry factor transgenic mice (hOC^{hep}) in the presence of a janus kinase signalling inhibitor (ruxolitinib, rux).

Results: HCV adaptation increased infectious virus production in the MLT-5H and hOC^{hep} PMH + rux by more than 1,000-fold compared to the parental virus. In contrast, infection efficiency of primary human hepatocytes, human pluripotent stem cell-derived hepatocytes, and primary macaque hepatocytes remained similar to parental HCV, suggesting that adaptation was specific to mouse hepatocytes. Mouse-adapted HCV (MAD-HCV) was susceptible to directly-acting antivirals and depended on expression of human hCD81 and hOccludin for infection of PMH cells. MAD-HCV was sensitive to interferon as replication was not detectable in hOC^{hep} PMH without rux treatment and because genetic ablation of interferon signalling enhanced virus propagation. Individual or combined knock out of *mCd302* and *mCr11*, two recently discovered liver cell-expressed murine restriction factors, also increased permissiveness to MAD-HCV.

Conclusion: This step-wise adaptation procedure is a novel paradigm for exploring the viral determinants that govern species tropism. Moreover, MAD-HCV is an interesting starting point for development of a robust HCV animal model.

PO-626

assembly dynamics and infection efficacy of hepatitis b virus surface protein exchanges in the eight hepatitis d virus genotypes

Wenshi Wang^{1,§,*}, Florian Lempp^{1,2,§}, Franziska Schlund¹, Lisa Walter¹, Charlotte Decker¹, Zhenfeng Zhang¹, Yi Ni^{1,2}, Stephan Urban^{1,2,*}. ¹Department of Infectious Diseases, Molecular Virology, University Hospital Heidelberg, Heidelberg, Germany, Heidelberg, Germany; ²German Centre for Infection Research (DZIF), partner site Heidelberg, Heidelberg, Germany

[§]contributed equally

Email: stephan.urban@med.uni-heidelberg.de

Background and aims: Chronic hepatitis D virus (HDV) infections cause the most severe form of viral hepatitis. HDV requires hepatitis B virus (HBV) envelope proteins for hepatocyte entry, particle assembly and secretion. Eight HDV and eight HBV genotypes are presently distinguished. However, comprehensive data of replication competence of the different HDV genotypes is scarce. Furthermore, it is unknown to what extent combination with different HBV envelopes affect virion assembly and infectivity.

Methods: We subcloned cDNAs of all HDV and HBV genotypes and performed combinatorial studies on replication competence, assembly dynamics and infection efficacy using Northern Blot, Western Blot, qPCR, in-cell ELISA, quantitative infection and infection inhibition assays.

Results: The eight 1.1-fold HDV genotypic cDNA clones initiated HDV replication in transfected Huh7 cells with noticeable differences regarding replication efficacy. The eight HBV-HBsAg-encoding constructs all supported secretion of subviral particles, however profound variations in envelope protein stoichiometry and secretion efficacy were observed. Co-transfection of all HDV/HBV combinations supported particle assembly, however, the respective pseudo-typed HDVs differed with respect to assembly kinetics and infectivity. All HDVs elicited robust and comparable innate immune responses. The

most productive combinations did not correlate to the natural geographic distribution arguing against an evolutionary adaptation of HDV ribonucleoprotein complex to HBV envelopes. We further observed HBV envelope-dependent differences in the activity of the EMA approved entry inhibitor bulevirtide/Hepcludex (formerly myrcludex), however >90% inhibition and full blockade could be achieved at therapeutically applied doses. Possible differences in assembly inhibition by Lonafarnib were also investigated and will be presented.

Conclusions: Different genotypes of HDV replicate with variable efficacies. Genotypic variations in HDV and also HBV-envelopes are major determinants for HDV egress, entry efficacy and consequently entry inhibition by Hepcludex or assembly interference by Lonafarnib. These differences possibly influence HDV pathogenicity, immune responses and the efficacy of drug regimens.

PO-700

Farnesoid X receptor alpha ligands inhibit in vitro HDV replication and virion secretion and infectivity

Benoît Lacombe¹, Julie Lucifora², Camille Ménard¹, Anne-Flore Legrand¹, Michelet Maud², Adrien Foca¹, Pauline Abrial¹, Vincent Lotteau¹, Patrice Andre^{1,3}, David Durantel², Christophe Ramière^{1,3}. ¹CIRI, Centre International de Recherche en Infectiologie, INSERM U1111, LYON, France; ²Cancer Research Center of Lyon (CRCL), INSERM U1052, LYON, France; ³Université de Lyon, Université Claude Bernard Lyon 1, LYON, France

Email: christophe.ramier@inserm.fr

Background and aims: Hepatitis delta virus (HDV) is a satellite of hepatitis B virus (HBV), both using the Sodium Taurocholate Co-Transporting Polypeptide (NTCP), the main transporter of bile acids (BA) in the liver, to enter hepatocytes. Links between BA and HBV infection are not limited to the entry step as we previously showed that some ligands of the farnesoid X receptor alpha (FXR), the nuclear receptor of BA, acted as inhibitors of HBV replication. Regarding HDV, excepting the role of NTCP in viral entry, putative links between BA metabolism and HDV replication have not been yet explored. We thus wanted to determine whether FXR also played a role in HDV life cycle.

Method: *In vitro* HDV mono-infection or HDV/HBV co-infection and super-infection were performed in differentiated HepaRG cells and primary human hepatocytes (PHH). Cells were treated with several FXR ligands: 6-ECDCA, a BA analog and two synthetic ligands, GW4064 and tropifexor. The impact on distinct forms of HDV RNAs was analysed by quantitative PCR and Northern Blot. Analysis of HDV proteins was performed by immunofluorescence (IF) and Western Blot (WB). Viral secretion was studied by HDV RNA quantification in supernatants and infection of naive Huh7.5-NTCP cells.

Results: In HDV/HBV super-infection models, a 10-day treatment with 10 μ M of GW4064 decreased total intracellular HDV RNA by 60% and 40% in HepaRG cells and PHH, respectively. Northern blot showed that both HDV genomic and antigenomic RNAs were affected by treatment. IF staining and WB showed that FXR ligands also decreased intracellular amounts of delta antigens, by around 75% for both small and large forms. Importantly, this inhibitory effect of FXR ligands on HDV replication was also observed in HDV mono-infected HepaRG cells. The specificity of action was confirmed as FXR ligands GW4064, 6-ECDCA and tropifexor showed comparable efficacy and their effects were lost in FXR loss-of-functions experiments. Finally, in HBV/HBV co-infected HepaRG cells, HDV secretion was decreased by 60% and virion specific infectivity by >95%.

Conclusion: FXR ligands inhibit *in vitro* HDV replication, independently of their previously identified antiviral properties against HBV, as well as virion secretion and specific infectivity. Mechanisms underlying this inhibitory effect are under investigation. As current therapeutic strategies are limited for HDV-infected patients, FXR may represent a new and attractive target for HDV antiviral therapy.

PO-820

Viral factors and host response in chronic HDV infection

Thais Leonel¹, Ester García-Pras¹, Sergio Rodríguez-Tajes¹, Mireia García-López¹, Sabela Lens¹, Zoe Mariño¹, Yabetse G. Tessema¹, Françoise Berby², Barbara Testoni², Francisco Rodríguez-Frías³, Fabien Zoulim², Xavier Fornis¹, Sofía Pérez-del-Pulgar¹. ¹Hospital Clínic, University of Barcelona, IDIBAPS, CIBERehd, Liver Unit, Barcelona, Spain; ²INSERM U1052-Cancer Research Center of Lyon (CRCL), University of Lyon, UMR_S1052, Lyon, France; ³Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, CIBERehd, Department of Biochemistry and Microbiology, Barcelona, Spain
Email: sofiapp@clinic.cat

Background and aims: Chronic hepatitis delta is the most severe form of viral hepatitis and a risk factor for cirrhosis and hepatocellular carcinoma. Little is known about the pathobiology of HBV/HDV infection, due in part to limited experimental models to study HBV and HDV infection and the lack of studies using liver tissue samples from HBV/HDV infected patients. The aim of this study was to explore viral and host factors contributing to chronic hepatitis delta pathogenesis.

Methods: Thirty-seven anti-HDV positive patients were included in the study. Intrahepatic and serological HBV and HDV replication markers were determined in prospectively collected liver biopsies and serum samples. To investigate the host response towards HDV, we performed Nanostring gene expression analysis on formalin-fixed paraffin-embedded liver samples.

Results: The median age of the patients was 50 years; 68% were male, 70% had liver cirrhosis and 51% were on nucleos (t)ide analog (NA) treatment. All patients had detectable HBsAg (median levels 6251 IU/ml) and 94% were HBeAg negative. Serum HDV-RNA assessment revealed ongoing HDV infection in 25 (68%) patients (HDV+), whereas the remaining 12 (32%) had undetectable HDV-RNA (HDV-). The percentage of patients receiving NA therapy was similar between HDV+ and HDV- patients (48% and 58%, respectively). Serum HDV-RNA concentration correlated with HBsAg ($r=0.54$, $p=0.010$) and HBcrAg ($r=0.49$, $p=0.041$) but not with HBV-DNA levels. Only 4 (16%) HDV+ patients had circulating 3.5 kb HBV-RNA (none of the HDV- patients). In contrast, 3.5 kb HBV-RNA in the liver was detected in 88% of HDV+ versus 43% of HDV- patients ($p=0.038$) and its presence was associated with detectable HBcrAg levels ($p=0.018$). Preliminary gene expression analysis based on a small number of patients (7 HDV+ and 4 HDV-) showed an upregulation of genes related IFN response and proinflammatory pathways in HDV+ patients. Likewise, the immune cell signature of the liver was consistent with an enhanced adaptive and innate infiltrate and a profile of CD8+ T cell exhaustion.

Conclusion: Our results suggest that HBV pregenomic RNA might preferentially be translated into HBcrAg rather than packaged and retrotranscribed in HDV+ patients. HDV appears to elicit an IFN and proinflammatory response, which is not capable of eliminating HDV but could modulate HBV replication. A dysfunctional adaptive immune response may contribute to HDV persistence.

PO-852

Identification of novel host factors in the patho-biology of Hepatitis B Virus (HBV) infection

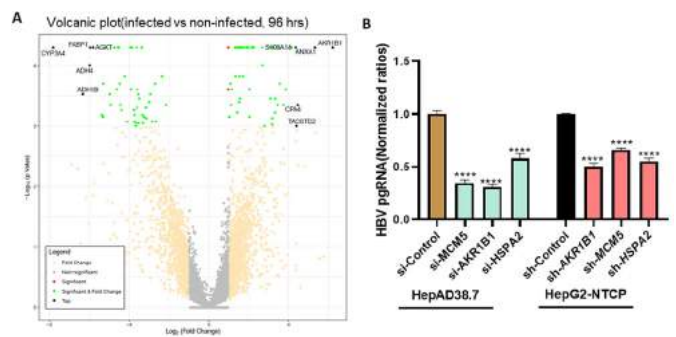
Collins Oduor Owino^{1,2,3}, Balakrishnan Chakrapani Narmada², Giridharan Periyasamy², Pablo Bifani¹, DasGupta Ramanuj². ¹National University of Singapore, Microbiology and Immunology, Singapore, Singapore; ²Genome Institute of Singapore, Singapore, Singapore; ³University of Nairobi, Centre for Biotechnology and Bioinformatics, Nairobi, Kenya

Background and aims: Even though there is an effective vaccine, HBV infection remains a major threat to global health with over 250 million people chronically infected. The pathogenesis of HBV infection and how it hijacks the host machinery is yet to be fully elucidated. Transcriptomic analysis of HBV infected cells has offered a

valuable tool in identifying HBV-host cell interactions. However, majority of these studies have been carried out in cell models that only partly mimic the complex human liver environment, such as rat primary hepatocytes or hepatoma cells. Therefore, one key caveat in the understanding of host cell factors that influence HBV pathology has been the lack of physiologically relevant, disease models.

Method: We hypothesized that host-specific genes that are induced by HBV infection may play important roles in HBV life cycle. Therefore, first we employed whole transcriptomic sequencing of HBV infected primary human hepatocytes (PHH) to identify host gene dysregulation during HBV infection. Next, we employed RNA interference technology to evaluate and validate the function of top-upregulated host factors on HBV gene expression and replication in HepAD38.7 and HepG2-NTCP. Lastly, we explored the expression profiles of these host factors in publicly available micro-array datasets of HBV patients; GSE65359, GSE83148 and GSE14520.

Results: Whole transcriptomic sequencing (WTS) in HBV-infected PHH identified multiple host pathways that might play a role during HBV infection including those in epithelial-mesenchymal transition (EMT), Aurora Kinase pathway, and matrisome interactions. Reassuringly, we also identified pathways previously identified to be deregulated during HBV infection including p38 MAPK, cell cycle genes involved in G2/M checkpoint and bile acid metabolism. Gene set enrichment analysis (GSEA) identified numerous upregulated genes during HBV infection including *NXF1*, *SRPK1* and *CDK1* all of which have been previously described to modulate HBV infection. The top-upregulated genes were validated by loss-of function studies and evaluated the effect of loss of function on surface antigen and identified novel factors potentially involved in HBV infection cycle. We report that RNAi-mediated knockdown of *HSPA2*, *AKR1B1* and *MCM5* in HepG2-NTCP live infection model inhibited HBV replication and gene expression. Finally, transcriptomic data analysis microarray datasets of different patient cohorts collectively reveal that expression of these host factors is indeed significantly associated with CHB, liver disease and HBV related HCC.



A: volcano plot showing differential gene expression in HBV infected PHH, B: cells harvested 3 days post-transfection (left) and 10 days post-infection (right), and quantified HBV pgRNA. Data presented as the mean normalized ratio +/- SD between control and si/sh samples, of 3 independent experiments

Figure:

Conclusion: Here, we utilized PHH models combined with functional elucidation in orthogonal infection models to identify potential HBV host factors. Altogether this study offers novel insights into the mechanisms of HBV infection as well as a new perspective in the development of host-directed therapies (HDT).

POSTER PRESENTATIONS

PO-861

Exploring host liver responses to Hepatitis B Virus at single cell resolution

Bal Krishnan Chakrapani Narmada¹, Niranjan Shirgaonkar¹, Giridharan Periyasamy^{1,2}, Seng-Gee Lim³, Ramanuj Dasgupta¹.

¹Genome Institute of Singapore, A*STAR, Singapore, Singapore;

²Experimental Drug Development Centre, A*STAR, Singapore, Singapore;

³National University of Singapore, Department of Medicine, Singapore, Singapore

Email: chakrapaninb@gis.a-star.edu.sg

Background and aims: Chronic Hepatitis B infection can persist in the host liver without causing alarming symptoms for decades and there is much ambiguity in the early processes of the viral life cycle-entry, nuclear transport, HBV cccDNA formation and its implications for liver cancers. HBV-associated hepatocellular carcinoma (HCC) has recently been shown to have multiple, distinct evolutionary clones within a single tumour which could be monoclonal or polyclonal in the nature of HBV infection. Also, the genetic factors in hepatocytes that render susceptibility/resistance to infection at early stage and factors that allow chronic infection remain largely underexplored. We aim to identify the factors affecting host susceptibility and response in patient intrahepatic tissues using single-cell RNA-sequencing technology. This enables investigation of the impact of HBV on specific cell subsets or cell states that help reconstitute the host's transcriptomic changes observed at the single-cell population level which may not otherwise be detectable at the bulk population level.

Method: One core biopsy from chronic HBV patient livers, who underwent Nucleoside analogues or Interferon treatment, were freshly dissociated into single cells using Collagenase P. Single cell RNA-seq was performed using 10X Genomics 3' v3 on liver core biopsies from 14 chronic HBV patients, who were either resistant to treatment and carried a high Hepatitis B surface antigen (HBsAg) load (Non-S Loss) or those who have responded to treatment and have lost HBsAg (S Loss). Datasets were aggregated using CellRanger aggr, hierarchical clustering analysis, data normalization, filtering was performed using Seurat and specific marker gene sets were used to annotate the cell types and subtypes.

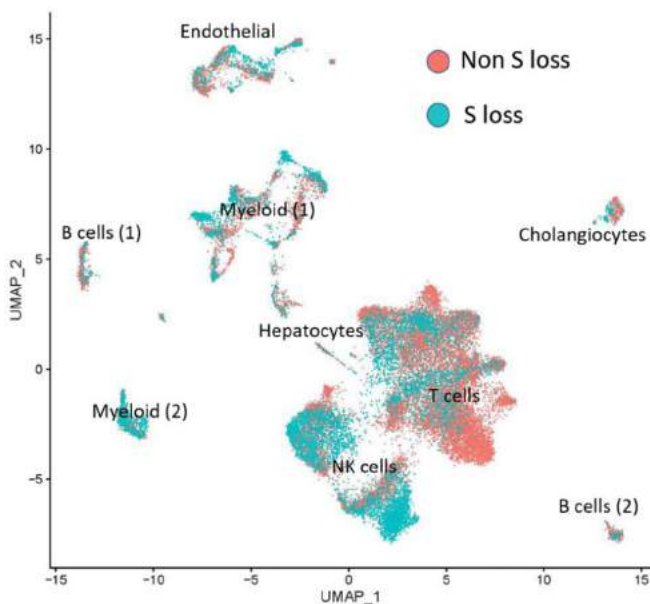


Figure:

Results: Unique cell-type/cell-state signatures emerged in S Loss patients from their single cell transcriptomic profiling. We also found evidence for the loss of certain cytotoxic immune cell clusters in S Loss patients upon achievement of functional cure compared to the

Non-S Loss chronic HBV patients. Specific phenotypic signatures were observed in the Cytotoxic T cells (CD8+), regulatory T cells, and NKT cells which are currently being validated by independent flow cytometry and spatial analysis. Figure 1 shows an UMAP of the liver cell types based on their HBsAg status upon treatment, Non-S Loss and S Loss, and key cell types unique to each of the conditions.

Conclusion: Creating an atlas of cell types and cell subtypes heterogeneity in chronic HBV patients, responding to or resistant to therapies, will inform us of valuable host-specific cell signatures. These specific signatures will serve to develop effective prognostic biomarkers enhancing prediction of patient response and designing better therapeutics against HBV.

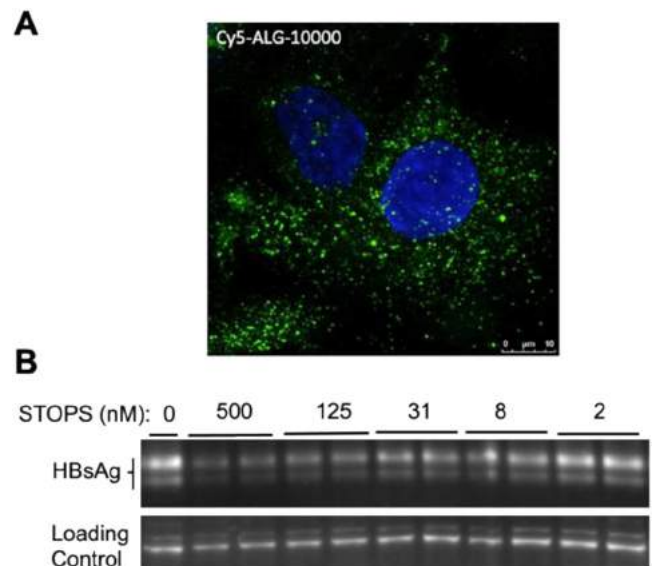
PO-1305

Mechanism of Action of Hepatitis B Virus S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPSTM) Molecules

Cheng Kao¹, Yuchun Nie¹, Suping Ren¹, Rajendra Pandey², Jin Hong¹, Julian Symons¹, Leonid Beigelman², Lawrence Blatt¹. ¹Aligos Therapeutics, Biology, So. San Francisco, United States; ²Aligos Therapeutics, Chemistry, So. San Francisco, United States
Email: chekao@gmail.com

Background and aims: Functional cure of chronic hepatitis B requires the elimination of serum hepatitis B virus surface antigen (HBsAg). We have developed a series of single-stranded oligonucleotides containing novel chemistry named STOPSTM that significantly reduce HBsAg produced by HBV-infected hepatocytes in vitro. This project aims to elucidate the mechanism whereby STOPSTM cause the reduction of HBsAg.

Method: STOPSTM and siRNAs were transfected into HepG2.2.15 cells that contain integrated HBV genomes using Lipofectamine RNAiMax. Proteins from HepG2.2.15 cell lysates that bind STOPSTM were identified using affinity chromatography, tandem mass spectrometry, and searches of the human proteome database. Fluorophore-labeled ALG-10000 in cells was visualized using a Leica SP6 microscope. HBsAg and other HBV proteins were quantified using ELISA and Western blotting. HBV nucleic acids were quantified using a Quantigene and real-time polymerase chain reaction assays.



STOPSTM molecules localize to the cytoplasm of HepG2.2.15 cells (A) and reduces intracellular HBsAg levels in a concentration-dependent manner (B).

Figure:

Results: STOPS molecule ALG-10000 was identified in a screen of chemically-modified oligonucleotides for the ability to reduce HBsAg production by HepG2.2.15 cells. ALG-10000 also inhibited HBV infection of primary human hepatocytes. In addition to reducing HBsAg production, ALG-10000 could reduce the level of HBV E-antigen, HBV polymerase, the Core protein, total HBV RNA, and secreted rcDNA in HepG2.2.15 cells. ALG-10000 localized to the cell cytoplasm but did not significantly co-localize with or bind to the HBsAg, indicating that STOPS acts through host-encoded factors. Five host proteins that function in RNA processing, translation, and protein folding/degradation were identified to bind ALG-10000: SRSF1, HNRNPA2B1, GRP78, RPLP1, and RPLP2. Silencing RNAs targeting these host factors reduced the levels of HBsAg and other HBV molecules known to be affected by STOPS. Finally, introduction of ALG-10000 or the knockdown of GRP78, RPLP1 and RPLP2 in cells resulted in increased ubiquitination of HBsAg and proteasome-mediated degradation of HBsAg.

Conclusion: STOPS reduce HBsAg production by sequestering select host proteins required for HBV RNA processing, translation and protein degradation.

PO-1450

Secreted hepatitis B virus (HBV) RNA associates to extracellular vesicles in supernatant of infected hepatocytes

Delphine Bousquet^{1,2}, Doohyun Kim¹, Annie Adrait³, Yohann Couté³, Maria Guadalupe Martinez¹, Alexia Paturel^{1,2}, Aaron Hamilton⁴, Marintha Heil⁴, Massimo Levrero^{1,2,5,6}, Barbara Testoni¹, Fabien Zoulim^{1,2,5}. ¹INSERM U1052-, Cancer Research Center of Lyon (CRCL), Lyon, France; ²University of Lyon, UMR_S1052, CRCL, Lyon, France; ³Univ. Grenoble Alpes, CEA, INSERM, IRIG, BGE, Grenoble, France; ⁴Roche Molecular Diagnostics, Pleasanton, United States; ⁵Croix Rousse hospital, Hospices Civils de Lyon, Department of Hepatology; ⁶Sapienza University of Rome, Department of Internal Medicine-DMISM and the IIT Center for Life Nanoscience (CLNS), Rome, Italy
Email: fabien.zoulim@inserm.fr

Background and aims: Chronic Hepatitis B virus (HBV) infection remains a global health burden, since current antiviral strategies are unable to eliminate the virus from infected hepatocytes and, thus, achieve a complete cure. Non-invasive biomarkers are necessary to improve patients' management and the evaluation of new therapies. This study aims at characterizing the compartments containing extracellular HBV RNA, which was recently proposed as a new surrogate marker of cccDNA transcriptional activity.

Method: Supernatants from HBV-infected HepG2-NTCP cells and Primary Human Hepatocytes treated or not with lamivudine were collected and processed through sucrose/iodixanol gradient separation, to allow physical separation of extracellular vesicles (EVs) and viral particles according to their buoyant density. Viral and EVs-associated proteins were analyzed by Western Blotting and ELISA, while HBV RNAs were detected by specific droplet digital (dd)PCR and correlated with intracellular viral replicative parameters (HBV-DNA, cccDNA, 3.5 kb HBV-RNA). Nanoparticle tracking analysis (NTA) and mass spectrometry (MS)-based proteomics were used to further characterize the viral and non-viral components.

Results: ELISA and western blotting assays for HBs and HBc proteins, together with HBV-DNA quantification after gradient separation showed that virions were found in fractions corresponding to a density of 1,17–1,20 g/ml. CD9 expression, marker of exosomes/EVs, was detected only in lower density fractions (1,07–1,15 g/ml), which were deprived of HBc. ddPCR analysis using assays spanning the 5' region of 3.5Kb RNA or the HBx region suggested that 3.5 Kb RNA is the predominant but not the only viral RNA specie in cell supernatants. HBV-RNAs distribution across gradient fractions showed no significant differences between Lamivudine-treated vs untreated samples. Interestingly, HBV-RNAs were detected not only in virion-like particles and non-enveloped capsids, but also in lighter fractions, suggesting that EVs could also carry secreted HBV-RNA. NTA analysis

confirmed that these fractions were indeed containing EVs in size spanning from 30 to 150 nm and MS analysis revealed a significant enrichment for exosomal proteins (CD63, CD9, TSG101 or HSC70).

Conclusion: Our results show evidence for EV containing HBV RNAs and will help understanding the molecular biology of serum HBV RNA secretion. This knowledge will aid the development and interpretation of serum HBV RNAs as a novel biomarker for chronic HBV infection.

This work is supported by the French National Research Agency Investissements d'Avenir program (CirB-RNA project-ANR-17-RHUS-0003).

PO-1451

Characterization of circulating hepatitis B virus (HBV) RNA in chronic hepatitis B (CHB) patients

Doohyun Kim¹, Delphine Bousquet^{1,2}, Marie-Laure Plissonnier¹, Alexia Paturel^{1,2}, Hyoseon Tak¹, Françoise Berby¹, Isabelle Bordes¹, Aaron Hamilton³, Marintha Heil³, Massimo Levrero^{1,2,4,5}, Barbara Testoni¹, Fabien Zoulim^{1,2,4}. ¹INSERM U1052-Cancer Research Center of Lyon (CRCL), Lyon, France; ²University of Lyon, UMR_S1052, CRCL, Lyon, France; ³Roche Molecular Diagnostics, Pleasanton, United States; ⁴Croix Rousse hospital, Hospices Civils de Lyon, Department of Hepatology, Lyon, France; ⁵Sapienza University of Rome, Department of Internal Medicine-DMISM and the IIT Center for Life Nanoscience (CLNS), Rome, Italy

Background and aims: Circulating HBV RNA (cirB-RNA) is emerging as a promising non-invasive biomarker for cccDNA transcriptional activity. However, the molecular characteristics and circulating particles containing cirB-RNA *in vivo* remain to be fully defined.

Method: A protocol based on a Iodixanol/Sucrose density gradient ultracentrifugation was set up to separate components of human serum according to their buoyant density. Each density fraction was analysed for HBV DNA/RNA by qPCR and specific droplet digital (dd) PCR. Viral and extracellular vesicles (EVs)-associated proteins were analysed by ELISA and Western Blotting. Nanoparticle tracking analysis (NTA) allowed to detect and quantify EVs content. 5'RACE PCR was used to discriminate cirB-RNA species in patients' serum.

Results: Sera from 7 untreated [4 HBeAg (+) and 3 HBeAg (-)] and 1 HBeAg (+) entecavir-treated CHB patients were subjected to density ultracentrifugation. Among the 10 fractions obtained, specific distribution of Dane particles, non-enveloped nucleocapsids and subviral particles was determined by ELISA and Western Blotting for viral proteins, together with quantification of HBV DNA. cirB-RNA was mainly detected in core-associated virion-like particles, but in 2 log₁₀ less amount than HBV DNA. However, cirB-RNA was the predominant species in lower density fractions (1.17–1.18 g/ml) deprived of viral proteins. The enrichment for EVs in these fractions was confirmed by NTA and detection of CD9 and CD81 EVs markers by western blotting. Distribution of cirB-RNA did not differ significantly in HBeAg (+) vs HBeAg (-) patients and in the entecavir-treated patient. Interestingly, in a serum with low HBsAg expression (570 IU/ml), cirB-RNA was mainly detected in the EVs-enriched fractions. Lastly, 5' RACE analysis identified pgRNA, spliced pgRNA and HBx transcripts as the three main categories of cirB-RNA in patients' serum.

Conclusion: Our results indicate that, in CHB patients' serum, EVs-enriched compartment contributes to the circulation of HBV-RNAs besides virion-like particles. Moreover, different HBV-RNA transcripts in addition to pgRNA can be detected *in vivo*. Altogether, these data could significantly contribute to the characterization of cirB-RNAs as new viral biomarker.

This work is supported by the French National Research Agency Investissements d'Avenir program (CirB-RNA project-ANR-17-RHUS-0003).

PO-1631

A cell culture model of primary human hepatocytes derived from HBV-infected humanized mice for antiviral drug evaluation

Jan-Hendrik Bockmann^{1,2}, Lena Allweiss^{1,2}, Katja Giersch¹, Tassilo Volz¹, Marc Lutgehetmann^{2,3}, Maura Dandri^{1,2}. ¹University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany; ²German Center for Infection Research (DZIF), Hamburg-Lübeck-Borstel-Riems partner site; ³University Medical Center Hamburg-Eppendorf, Department of Medical Microbiology, Virology and Hygiene, Hamburg, Germany
Email: j.bockmann@uke.de

Background and aims: Primary human hepatocytes (PHH) isolated from liver chimeric mice have emerged as an alternative hepatocyte supply for in vitro HBV infection studies. However, high HBV amounts are needed, infection rates remain variable and HBV requires days to build stable cccDNA levels. Our aim was to establish a reproducible in vitro model where stably HBV infected PHHs are isolated from the liver of chronically HBV infected chimeric mice and can be readily used for antiviral studies. Here, we comparatively assessed the antiviral effects of lamivudine and interferon (IFN) in vitro on all viral parameters, including epigenetic silencing of HBV cccDNA and its association with the SMC5/6 complex (Allweiss, Giersch et al., Gut 2021).

Method: PHHs were isolated from USG (uPA/SCID/beige/IL2RG^{-/-}) mice after 12 weeks of HBV infection by collagenase perfusion, seeded on collagen-coated 24-well plates and cultured for 21 days in Williams' medium E with DMSO. One day after seeding, treatment with 1000 IU/ml IFN- α -2a or 1 μ M lamivudine was performed. RNA and DNA were isolated from the same wells and HBV DNA, pgRNA and expression of interferon-stimulated genes (ISGs) in cell lysates, as well as HBeAg and HBsAg in supernatants were determined by RT-PCR and CLIA. Furthermore, chromatin immunoprecipitation (ChIP)-qPCR was performed using antibodies for NSE4, a component of the SMC5/6 complex.

Results: HBsAg (mean 2.2×10^2 IU/ml) and HBeAg (mean 2.5×10^2 S/CO) remained stable up to 21 days after seeding. Compared to untreated cells, 14 days of IFN treatment led to a significant reduction of HBV DNA (3.2-fold; $p = 0.010$) and pgRNA (28.4-fold; $p = 0.024$), as well as HBeAg (5.8-fold; $p = 0.0012$) and HBsAg (6.7-fold; $p = 0.0025$). As expected, LAM treatment reduced intracellular HBV DNA (d14: 3.9-fold; $p = 0.001$) but not viral proteins. Vigorous inductions of human ISGs were detected only in IFN treated samples (day7: OAS1: 37-fold, $p < 0.0001$; CXCL10: >500-fold, $p = 0.0002$), which remained enhanced up to day 21. ChIP-qPCR analysis showed a strong association of NSE4 to the cccDNA (8-fold relative increase) only in interferon treated cells, indicating epigenetic cccDNA suppression.

Conclusion: PHHs exposed to long-term HBV infection in USG mice maintain stable HBV replication and innate immune responses in culture similar to those determined in vivo. This model can expand preclinical testing of drugs, including those targeting cccDNA activity and intrinsic innate responses.

PO-1688

Molecular mechanisms underlying the antiviral activity of a TLR2 agonist on HBV replication in hepatocytes

Manon Desmares^{1,2}, Brieux Chardes^{1,2}, Caroline Pons^{1,2}, Michelet Maud^{1,2}, Rivoire Michel^{3,4}, Anna Salvetti^{1,2}, Julie Lucifora^{1,2}, David Durantel^{1,2}. ¹INSERM, U1111, International Center for Research in Infectiology (CIRI), Lyon, France; ²University de Lyon (UCBL1), Lyon, France; ³INSERM, U1032, Lyon, France; ⁴Centre Léon Bérard, Lyon, France
Email: david.durantel@inserm.fr

Background and aims: Pegylated interferon-alpha (peg-IFN) is yet used in clinics, some time in first line, to treat chronically HBV-infected patients, despite its poor safety profile and relative weak efficacy at inducing HBsAg loss. If an immune-stimulator is argued to be an instrumental component of future combination therapies aiming at curing HBV infections, it would be interesting to find

alternatives to peg-IFN. We have previously identified the TLR2 agonist Pam3CSK3, as one of the best agonist to reduce HBV replication, including cccDNA level and activity, in infected hepatocytes (Lucifora et al., Scientific Rep. 2018). Yet the detailed mode of action (MoA) of this potential anti-HBV asset remained elusive. The aim of this study was to precisely decipher the MoA of Pam3CSK4 in vitro, by determining the kinetic of antiviral events, identifying the upstream and most relevant step of blockade of HBV replication, working-out its specificity of action, discovering host-effectors involved in the long-lasting antiviral phenotypes.

Method: We used experimentally-HBV-infected differentiated HepaRG cells and primary human hepatocytes (PHH), as well as rather standard molecular and cellular virologic methods to decipher the MoA of Pam3CSK4. This included RNA-seq analyses for the identification of antiviral host-effectors and loss-of-functions studies to validate them.

Results: Pam3CSK4 strongly and durably (no rebound within 5-weeks off drug) inhibited HBV replication by engaging the TLR2 innate receptor and canonical NF- κ B pathway. The overall long-lasting antiviral phenotype is the double consequence of an immediate effect on HBV RNA biogenesis, by both reduction of RNA transcription and acceleration of RNA decay, as well as a reduction of cccDNA level; the latter phenotype, which kinetically occurs second, reinforce the first, as cccDNA is the main template of HBV RNA synthesis. RNA-seq analyses and loss-of-function approaches allowed the investigation of two host-effectors, respectively MCPIP1 and FEN-1, as involved in the reduction of HBV RNA accumulation and cccDNA level.

Conclusion: Using relevant cell culture models, we have uncovered the MoA of Pam3CSK4, a TLR2 ligand, which is currently under preclinical evaluation in a liver-deliverable and nanoparticulate form for the treatment of chronic HBV infections.

PO-1707

Cloning and in vivo characterization of a new hepatitis D virus genotype 1 strain from a patient achieving sustained virus response to interferon alpha treatment

Katja Giersch¹, Nora Goldmann², Lennart Hermanussen¹, Lennart Hendricks¹, Tassilo Volz¹, Jan-Hendrik Bockmann^{1,3}, Lena Allweiss^{1,3}, Ansgar Lohse¹, Jörg Petersen⁴, Marc Lutgehetmann^{3,5}, Dieter Glebe^{2,3}, Maura Dandri^{1,3}. ¹University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Hamburg, Germany; ²Justus Liebig University, Institute of Medical Virology, National Reference Center for Hepatitis B Viruses and Hepatitis D Viruses, Gießen, Germany; ³German Center of infection research (DZIF), Hamburg-Lübeck-Borstel-Riems and Giessen-Marburg-Langen partner sites, Germany; ⁴IFI Institute for Interdisciplinary Medicine at Asklepios Clinic St. Georg, Hamburg, Germany; ⁵University Medical Center Hamburg-Eppendorf, Department of Medical Microbiology, Virology and Hygiene, Hamburg, Germany
Email: kgiersch@uke.de

Background and aims: Pegylated interferon alpha (pegIFN α) is commonly used for the treatment of hepatitis D virus (HDV) infected patients. However, the mode of action (MoA) of IFN in HDV infected cells remains elusive and only a minority of patients responds to therapy. Previous experimental studies mostly relied on a particular cell culture-derived strain of HDV genotype 1 (AJ000558) (Kuo, Chao, Taylor J Virol. 1989) that resulted insensitive to IFN α in vitro (Zhang et al, J Hep 2018). Contrarily, we showed that a patient-derived HDV-1 strain (HDV-1p) responded to pegIFN α in human liver chimeric mice (Giersch et al, Sci Rep 2017). Our aim was to clone and characterize this IFN sensitive HDV-1 isolate to study the antiviral effects of IFN in infected human hepatocytes.

Method: The HDV-1p strain was obtained from a patient later achieving sustained HDV response to IFN therapy. The isolate was passaged in chimeric mice, sequenced and cloned as genome-sense tandem dimer in pcDNA3.1 (+). HDV was generated by co-

transfection of HuH7 cells with plasmids encoding the HDV-1p dimer and hepatitis B virus (HBV) surface proteins. Infectivity of HDV-1p particles was tested *in vitro* using NTCP-expressing HepG2 cells and in HBV infected human liver chimeric mice. HBV/HDV-1p infected mice received pegIFN α twice a week (25 ng/g) for 4 weeks. Mice infected with the HDV (AJ000558) strain were used for comparison. Serum and liver viral loads were analyzed by qRT-PCR, immunofluorescence (IF) staining and RNA *in situ* hybridization.

Results: HDV stocks produced *in vitro* showed high infectivity in NTCP-expressing HepG2 cells. In HBV infected humanized mice stable HDV viremia (median 3×10^7 copies/ml) was determined 6 weeks post HDV-1p super-infection and around 42% of human hepatocytes displayed HDV antigen (HDAg). PegIFN α reduced HDV (>2log) and HBV viremia (2log) in HBV/HDV-1p infected mice. Strong decrease of all intrahepatic HDV markers led to substantial HDAg negativization (4% HDAg positive cells). In contrast, pegIFN α lowered HBV viremia (2log) in HBV/HDV-1 (AJ000558) infected mice, but did not affect HDV markers in serum and liver, even after extending treatment to 9 weeks.

Conclusion: As an alternative to the commonly used HDV strain, we identified and cloned an IFN α sensitive patient derived HDV-1 isolate (HDV-1p) suitable to dissect the MoA of IFN in HDV infection and for assisting the design of therapies aiming to accelerate HDV loss and achieve HDV cure.

PO-1711

Inducers of the NF- κ B pathways impair Hepatitis Delta virus (HDV) replication and strongly decrease progeny infectivity and spreading

Michelet Maud^{1,2}, Dulce Alfaiate³, Brieux Chardes^{1,2}, Suzanne Faure-Dupuy⁴, Thomas Engleitner⁵, Caroline Pons^{1,3}, Rayan Farhat^{1,2}, Tobias Riedl⁴, Anne-Flore Legrand^{1,2}, Rivoire Michel⁶, Fabien Zoulim⁷, Mathias Heikenwälder⁴, Anna Salvetti^{1,2}, David Durantel^{1,2}, Julie Lucifora^{1,2}. ¹INSERM, U1111, International Center for Research in Infectiology (CIRI), Lyon, France; ²University of Lyon (UCBL1), Lyon, France; ³Hospices Civils de Lyon, Lyon, France; ⁴Heidelberg University, Heidelberg, Germany; ⁵Technische Universität München, München, Germany; ⁶Centre Léon Bérard, Lyon, France; ⁷Cancer Research Center of Lyon, Lyon, France
Email: julie.lucifora@inserm.fr

Background and aims: Hepatitis Delta Virus (HDV) super-infection of chronically Hepatitis B Virus (HBV)-infected patients is the most aggressive forms of chronic viral hepatitis, with an accelerated progression towards fibrosis/cirrhosis and an increased risk of liver failure, hepatocellular carcinoma, and death. At least 25 million of people would be co-infected with both viruses, ranking this co-infection as one of the most prevalent and most clinically challenging worldwide. While HDV infection is not susceptible to available direct anti-HBV drugs, suboptimal responses are obtained with IFN- α based therapies, and the number of investigational drugs remains limited.

Method: We recently established *in vitro* models of HDV super/co-infection of HBV-infected cells based on primary human hepatocytes (PHH) and the HepaRG cell line that are relevant to explore new therapeutics, including immune therapeutics.

Results: Using those models, we analyzed the effect of several innate immune-stimulators on HDV replication in chronically infected cells. We further characterized the anti-HDV effects of Pam3CSK4, an agonist of TLR1/2 and BS1, an agonist of the Lymphotoxin Beta Receptor (LT β R) that both induced dose dependent reductions of total intracellular HDV RNAs, as well as HDV proteins levels. Off-drug rebound experiments revealed a long-lasting antiviral activity suggesting an irreversible effect on HDV replication and transcription templates. Both molecules negatively affect HDV progeny release and dramatically decrease their specific infectivity.

Conclusion: Immune-modulators inducing NF- κ B pathways in hepatocytes can strongly inhibit HDV replication, and could be

further developed as efficient therapeutic approaches for HBV/HDV chronically infected patients.

PO-1907

Viral interference in a hepatitis C virus and hepatitis E virus co-infection system

Thomas Burkard¹, Nora Moeller², Kathrin Resner², Leonard Knegeendorf², Martina Friesland², Ruth Bröring³, Patrick Behrendt^{2,4}, Heiner Wedemeyer⁴, Daniel Todt^{1,5}, Eike Steinmann¹. ¹Ruhr-University Bochum, Molecular and Medical Virology, Bochum, Germany; ²TWINCORE Centre for Experimental and Clinical Infection Research; a joint venture between the Medical School Hannover (MHH) and the Helmholtz Centre for Infection Research (HZI), Institute for Experimental Virology, Hannover, Germany; ³University Hospital of Essen, Clinic for Gastroenterology and Hepatology, Essen, Germany; ⁴Hannover Medical School, Hepatology and Endocrinology, Department of Gastroenterology, Hannover, Germany; ⁵European Virus Bioinformatics Center (EVBC), Jena, Germany
Email: thomas.burkard@rub.de

Background and aims: Despite the advent of direct acting antivirals (DAAs) Hepatitis C virus (HCV) continues to constitute a global health problem with an estimated 71 million people being chronically infected, while Hepatitis E virus (HEV) on the other hand is the major cause of acute hepatitis establishing chronic courses only in immunocompromised patients. Clinical and virological information about HCV/HEV co-infections are limited and it is not known whether HCV and HEV influence each other's replication in the hepatocytes. In this study, we aimed to simulate HCV/HEV co-infections in a cell culture model system to assess their mutual influence on each other.

Method: We used state-of-the art tissue culture models for HEV and HCV. We assessed replication via transfection of subgenomic viral RNA harboring luciferase or fluorescence reporter, which enabled flow-cytometric or luminescence-based detection of both replicons. Furthermore, coinfection and superinfection experiments with authentic virus were performed and analyzed via indirect immunofluorescence.

Results: A novel model system to investigate interaction between HCV and HEV was established. Co-transfection of HCV and HEV RNA at the same time allowed quantification and visualization of viral replication of both viruses, while an exclusion phenotype was observed when HCV cells were super-transfected or infected with HEV. This phenotype could be linked to the activity of the HCV protease non-structural protein 3/4A (NS3/4A), whose overexpression alone inhibited HEV replication and infection. Treating HCV-positive cells with sofosbuvir or telaprevir restored the susceptibility to HEV.

Conclusion: This novel experimental model system of HCV/HEV co-infections revealed that, despite possible co-replication and co-infection, HCV interferes with the replication of HEV. This exclusion phenotype was found to be linked to HCV protease NS3/4A. These findings provide new insights into the pathogenesis of HCV-HEV co-infections.

PO-1917

Significant in-Vitro and in-Vivo inhibition of HBsAg and HBV pgRNA with ASC42, a novel non-steroidal FXR agonist

Jinzi Wu¹, Xiaodong Li¹, Handan He¹, Qiong Zhou². ¹Ascletris Bioscience Co., Ltd, Hangzhou, China; ²WuXi AppTec (Shanghai) Co., Ltd, China

Background and aims: Activation of franesoid X receptor (FXR) may inhibit hepatitis B virus (HBV) replication. The objective of this study was to validate the anti-HBV efficacy of a FXR agonist ASC42 via *in vivo* and *in vitro* studies.

Method: Primary human hepatocyte (PHH) cells with HBV infection and AAV/HBV mouse model were used to evaluate ASC42's anti-HBV efficacy. PHH cells were infected by HBV and were treated with ASC42 for 6 days. Mice were intravenously injected with rAAV8-1.3 HBV and were administered with ASC42 for 28 days. The control compound

POSTER PRESENTATIONS

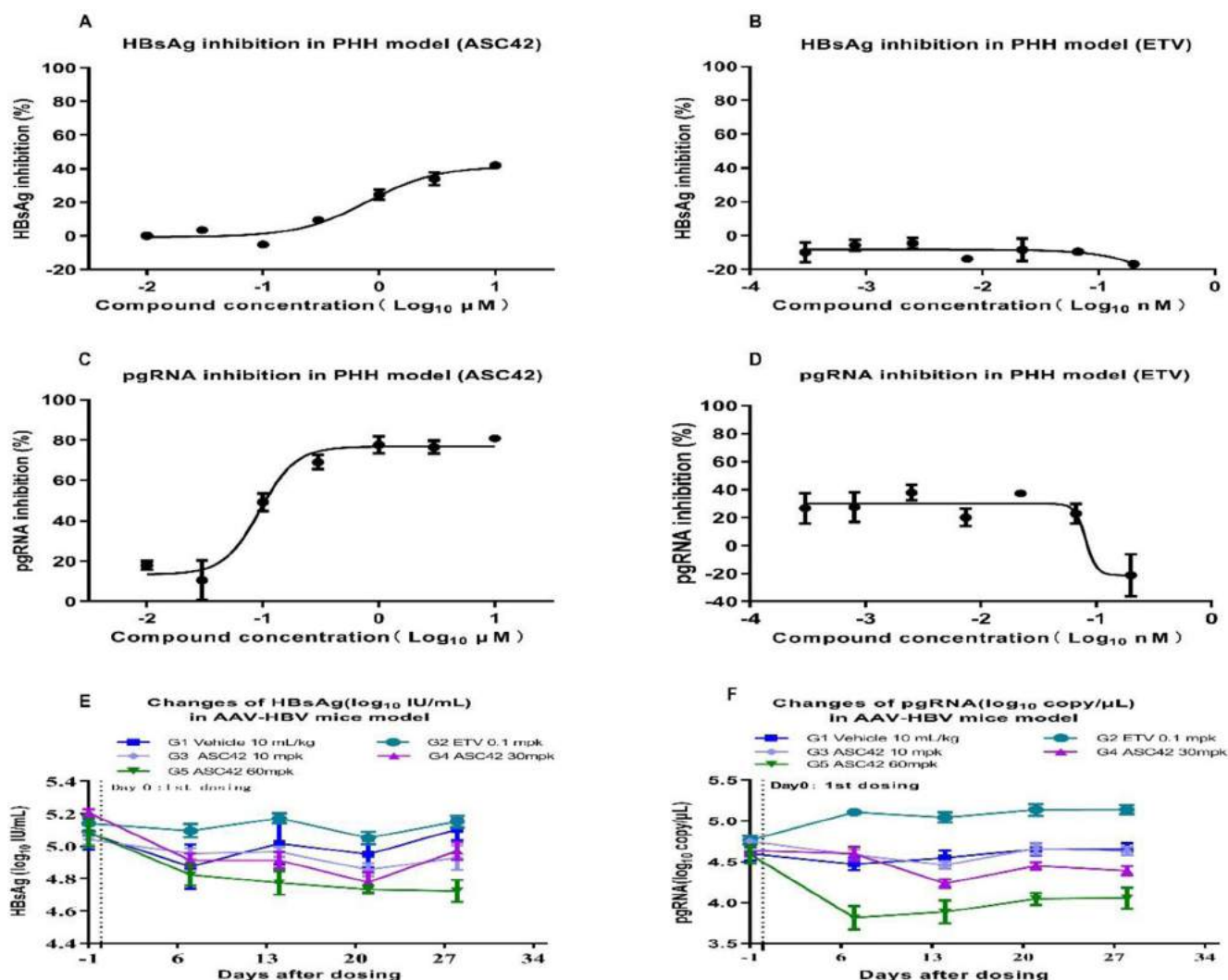


Figure 1. (abstract: PO-1917) ASC42 inhibits HBsAg and HBV pgRNA in PHH model and AAV/HBV mice model.

was entecavir (ETV) in both studies. HBsAg, HBV pgRNA and HBV DNA were measured in culture medium and in mouse plasma.

Results: In PHH model, the control compound ETV showed the expected inhibitory activity on HBV DNA, but had no inhibition on HBV pgRNA and HBsAg, while ASC42 inhibited HBsAg, HBV pgRNA, and HBV DNA dose-dependently, with EC₅₀ of 0.79 μM, 0.09 μM and 0.62 μM, respectively (Figure 1A–D). In AAV-HBV mice model, after ETV (0.1 mg/kg) monotherapy, HBV DNA in mouse plasma decreased significantly, while HBV pgRNA and HBsAg showed no obvious reduction. ASC42 demonstrated a dose-dependent inhibition of HBV pgRNA, HBsAg, HBV DNA in mouse plasma. High-dose group of ASC42 (60 mg/kg) inhibited HBV pgRNA, HBsAg, and HBV DNA by 0.60 log₁₀ copy/μL ($p < 0.01$), 0.38 log₁₀ IU/μL ($p = 0.002$), and 0.77 log₁₀ copy/μL ($p < 0.05$), respectively, relative to vehicle control group (Figure 1E–F).

Conclusion: These in-vitro and in-vivo studies demonstrated that ASC42, a FXR agonist, significantly inhibited HBV DNA, HBV pgRNA and HBsAg, indicating that ASC42 has therapeutic potential to functional cure of HBV infection. The results support the advancement of ASC42 into clinical trials in human.

PO-1928

Unexpected rising in the circulation of HBV complex profiles with HBsAg vaccine-escape mutations in HBV genotype-D: potential implications for HBsAg detection/quantification and vaccination strategies

Lorenzo Piermatteo¹, Mohammad Alkhatib¹, Maria Concetta Bellocchi¹, Rossana Scutari¹, Ada Bertoli^{1,2}, Luca Carioti¹, Lavinia Fabeni³, Miriam Lichtner⁴, Massimo Marignani⁵, Caterina Pasquazzi⁵, Nerio Iapadre⁶, Giustino Parruti⁷, Giuseppina Cappiello⁸, Massimo Andreoni⁹, Loredana Sarmati⁹, Francesca Ceccherini Silberstein¹, Valentina Svicher¹, Romina Salpini¹.
¹University of Rome "Tor Vergata", Experimental Medicine, Rome, Italy; ²Polyclinic Tor Vergata Foundation, Virology Unit, Rome, Italy; ³National Institute for Infectious Disease, IRCCS L. Spallanzani, Virology and Biosafety Laboratories Unit, Rome, Italy; ⁴"Sapienza" University, Public Health and Infectious Disease, Rome, Italy; ⁵S. Andrea Hospital, Infectious Diseases, Rome, Italy; ⁶"San Salvatore Hospital", L'Aquila, Italy; ⁷Pescara General Hospital, Infectious Diseases Unit, Pescara, Italy; ⁸"S. Pertini" Hospital, Microbiology and Virology Unit, Rome, Italy; ⁹Tor Vergata University Hospital, Infectious Diseases, Rome, Italy
 Email: lorenzo.piermatteo@uniroma2.it

Background and aims: Vaccine-escape mutations can alter HBsAg recognition by antibodies challenging vaccine efficacy, promoting immunosuppression-driven HBV-reactivation and impairing HBsAg

detection. Here, we investigate the circulation of vaccine-escape mutations, single or in complex mutational profiles, over time and their impact on serological parameters in HBV genotype-D.

Method: This study includes HBsAg sequences from 947 viremic HBV genotype-D infected patients (pts) collected from 2005 to 2019. 21 vaccine-escape mutations are analyzed (Lazarevic, 2014). Next generation sequencing (NGS) is performed by Illumina in a subset of 21 pts to evaluate the intra-patient prevalence of mutations.

Results: Median (IQR) HBV-DNA is 3.5 (2.6–5.0) logIU/ml and 4.2% of pts is HBsAg-negative despite HBV-DNA positivity. Overall, 17.7% (168/947) of pts harbors ≥ 1 vaccine escape mutation with the highest prevalence in subgenotype-D3 (23% for D3 vs 13.6% for other subgenotypes, $P < 0.001$). Among them, 17.3% (29/168) show complex profiles with ≥ 2 vaccine-escape mutations.

NGS shows that vaccine-escape mutations, either single or in complex profiles, occur with an intra-patient prevalence $>90\%$ in 81% of pts analyzed, suggesting their fixation in viral population. Notably, the proportion of pts with complex profiles of vaccine-escape mutations increased over time: from 0.4% (1/237) in 2005–2009 to 3.0% (12/396) in 2010–2014 and to 5.1% (16/314) in 2015–2019, $p = 0.007$, suggesting a progressive increase in the circulation of viral strains with enhanced capability to evade humoral responses. Moreover, the presence of complex mutational profiles correlates with lower HBsAg levels: median (IQR) 40 (0–2905) IU/ml for pts with vs 1688 (348–6090) without complex profiles ($p = 0.0007$).

Focusing on HBsAg-negativity, the presence of complex mutational profiles also correlates with HBsAg-negativity despite HBV-DNA positivity (34.8% with ≥ 2 vaccine-escape mutations vs 6.7% and 2.3% with a single or no vaccine-escape mutations is HBsAg-negative, $p = 0.007$ and < 0.0001).

Conclusion: A noteworthy fraction of HBV genotype-D infected pts harbors complex profiles of vaccine-escape mutations detected as predominant species. These profiles correlate with lower HBsAg quantification and HBsAg-negativity despite ongoing viral replication. These mutations should be considered for a proper clinical interpretation of HBsAg results and their circulation should be taken into account for the development of novel vaccine formulation.

PO-1950

An antibody microarray identifies epidermal growth factor receptor as a novel host factor of hepatitis E virus

Jil Alexandra Schrader¹, Volker Kinast¹, Ruth Bröring², Florian Vondran³, Eike Steinmann¹. ¹Ruhr-University Bochum, Molecular and Medical Virology, Bochum, Germany; ²University Hospital Essen, Department for Gastroenterology and Hepatology, Essen, Germany; ³Medizinische Hochschule Hannover, Klinik für Allgemein-, Viszeral-, und Transplantationschirurgie, Hannover, Germany
Email: jil.schrader@rub.de

Background and aims: Hepatitis E virus (HEV), a (+)-single-stranded RNA virus, is the most common cause of viral hepatitis with more than 20 Mio cases per year. Despite more than 3 Mio symptomatic cases and almost 70 000 death annually, HEV is a long-neglected, still under-reported, -diagnosed and -investigated health burden. Deciphering virus-host-interactions will not only be essential for a detailed understanding of HEV pathogenesis but also endorse the development of novel antiviral strategies targeting viral host factors.

Method: Human hepatoma cells and an antibody-based microarray with 613 phosphosite- and 265 pan-specific antibodies were used to detect differences in protein expression and phosphorylation in cell signaling pathways, caused by HEV replication. Resulting hits were validated in infection assays via siRNA mediated knock down, FDA-approved inhibitors as well as by ectopic expression and knock-out of the respective protein.

Results: More than 120 changes, including 54 overlapping hits, in protein expression and phosphorylation were detected 12 h and 48 h post HEV challenge. HEV replication induced a phosphorylation of several kinases e.g. mitogen-activated protein kinases as well as the

EGF-Receptor (EGFR). A subsequent siRNA-mini screen of 28 candidates revealed a significant decrease of one half in HEV susceptibility upon EGFR knockdown when compared to control infections. Selective inhibition of EGFR with FDA-approved drugs reduced HEV entry in both hepatoma cells and primary human hepatocytes down to 20%. Of note, viral replication was not affected by pharmacological inhibition of EGFR. In line, CRISPR/Cas9 knock-out of EGFR in HepG2 cells decreased the susceptibility for HEV by one half, but had no effect on viral replication. In contrast, stable EGFR expression in hepatoma cells lead to a three-fold increased HEV susceptibility and the effect could be reversed by treatment with EGFR-specific modulators during the virus inoculation.

Conclusion: An antibody microarray technology uncovered that HEV causes a brought mobilization of host cell pathways. An siRNA screen of 28 selected hits validated and specified the effects of the tested genes/proteins. EGFR was identified as a potential novel host factor, playing a role in the entry process of HEV. A detailed analysis of the corresponding, but also further pathways, will define their role for the pathogenesis of HEV and may help to facilitate the development of anti-HEV therapies.

PO-1980

Quantified integrated hepatitis B virus DNA in relation to other viral markers in chronic hepatitis B patients

Robin Erken^{1,2}, Vladimir Loukachov², Karel van Dort², Anne van den Hurk², Bart Takkenberg¹, Sophie Willemse¹, Neeltje Kootstra². ¹Amsterdam UMC, locatie AMC, Gastroenterology and Hepatology, Amsterdam, Netherlands; ²Amsterdam UMC, locatie AMC, Experimental Immunology, Amsterdam, Netherlands
Email: r.erken@amc.uva.nl

Background and aims: ext to the formation of cccDNA, the hepatitis B virus (HBV) can also integrate in the host genome of the hepatocyte. The effect of integrated HBV DNA on the production of viral proteins and viral replication is still unknown, especially since there is no standardized method for the detection of integrated HBV DNA. The aim of our study was to design a PCR detecting and quantifying integrated HBV DNA and analyse the relation between HBV integration and virological activity.

Method: Total DNA of HepG2.2.15 cells were used for validation of the multistep Alu-PCR that detects integrated HBV: Integrated HBV DNA was amplified using a specific forward primer for each HBV ORF (S, X, or C) and an Alu reverse primer with a tag sequence. HBV-Alu PCR products were amplified by a nested PCR with a downstream forward HBV ORF primer (S, X or C) and a reverse tag primer. A second nested PCR was performed using HBV ORF specific primers and a detection probe.

Pre-treatment liver tissue samples were available from chronic hepatitis B patients with either a high ($>20,000$, $n = 38$) or low ($<20,000$, $n = 97$) viral load, and controls ($n = 25$). Patients were previously included in two prospective studies investigating the effect of combination treatment with interferon and tenofovir or adefovir. The different integrated HBV-DNA ORF levels were measured in liver tissue and normalized using the $2^{-\Delta\Delta Ct}$ method. Integrated HBV-DNA levels between groups were compared using a Mann-Whitney U test. Association between the integrated HBV-DNA levels, virological markers, liver damage markers was performed using a Spearman correlation test and corrected for multiple testing.

Results: Integrated HBV DNA sequences of ORF S and X but not C were detected and quantified in patients with chronic hepatitis B but not in control samples. ORF S and X integrants correlated with HBV DNA, HBsAg and ALT levels in serum/plasma as well as to HAI scores of liver tissue, all $p < 0.02$. The strongest correlations were found between ORF X and: ORF S ($\rho = 0.655$, $p < 0.001$) or plasma HBV DNA ($\rho = 0.526$, $p < 0.001$). Integrated HBV DNA levels did not differ between HBeAg negative and -positive patients although a clear trend ($p = 0.0501$) of lower ORF S levels in HBeAg negative patients was seen.

POSTER PRESENTATIONS

Conclusion: Our Alu-PCR protocol was effective in quantifying the ORF S and X of integrated HBV DNA in chronic HBV patients. Levels of ORF S and X integrants correlated with viral markers in plasma.

PO-2105

Hepatitis B virus surface antigen expression determines hepatic immunity and Kupffer cell functions in HBV-transgenic mice

Stefan Schefczyk¹, Simon Merz², Xufeng Luo¹, Martin Trippler¹, Matthias Hardtke-Wolenski¹, Ruth Broering¹. ¹Essen University Hospital, Department of Gastroenterology and Hepatology, Essen, Germany; ²LaVision BioTec GmbH, Bielefeld, Germany
Email: stefan.schefczyk@uni-due.de

Background and aims: One of the most frequent causes for liver related morbidity and mortality is the chronic Hepatitis B virus (HBV) infection. Pathogenesis of this infection is driven by the adaptive as well as the innate immune system. The present project aims to investigate how HBV surface antigen (HBsAg) affects the hepatic innate and adaptive immune responses, utilizing different HBV-transgenic mouse strains, which show I) inflammation and tumour progression (Alb/HBs), II) Kupffer cell (KC)-mediated interferon responses (HBV-s-mut) or III) neither inflammation nor interferon responses (HBV-s-rec).

Method: F4/80 positive KC were prepared after two-step perfusion of murine livers (wildtype, Alb/HBs, HBV-s-mut and HBV-s-rec) followed by MACSbead separation. KC were used in a phagocytosis assay using zymosan bioparticles and analysed by flow cytometry. KC were further visualized using light sheet fluorescence microscopy (LSFM) in ECi cleared mouse liver samples.

Results: In term of KC cell count, the HBV-s-mut mouse showed a higher number of KC compared to the other mouse strains. The total KC phagocytic activity was altered in the different HBV-transgenic mouse strains. Scilicet, the Alb/HBs-derived KC showed a significantly decreased phagocytosis activity and the HBV-s-rec-derived KC showed an overall distinct phagocytosis activity. Two populations of F4/80 positive KC (dim and bright) could be identified and independently analysed. Within the F4/80 bright population only the HBV-s-rec showed a significantly altered, namely decreased phagocytosis activity. In the F4/80 dim population the Alb/HBs-derived KC showed a decreased phagocytosis activity, whereas the HBV-s-rec-derived KC showed an altered phagocytosis activity with significantly increased activity at very early (15–60 min) and very late time points (upon 210 min). The HBV-s-mut-derived KC, either total F4/80, dim or bright populations showed phagocytic activities and capacities comparable to the wildtype KC populations. LSFM visualized distinct distribution pattern of the two F4/80 populations within the liver of wildtype and HBV-transgenic mice.

Conclusion: The data led to suggest, that the accumulation of the HBsAg in Alb/HBs mice leads to a decreased phagocytosis activity in F4/80 dim population. Interestingly, the production and release of viral particles in HBV-s-rec mice led to an increased phagocytosis pattern in HBV-s-rec-derived F4/80 dim KC. Finally, despite the increased KC number and the known, consistent IFN response in KC from HBV-s-mut mice didn't affect the phagocytosis activity.

PO-2135

A specific deletion pattern in the preS1- and preS2-domain is associated with treatment induced HBsAg loss in chronic hepatitis B

Maria Pfefferkorn¹, Danilo Deichsel¹, Madlen Matz-Soja^{1,2}, Thomas Berg¹, Florian van Bömmel¹. ¹Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; ²Leipzig University, Faculty of Medicine, Rudolf Schönheimer Institute of Biochemistry, Leipzig, Germany
Email: Maria.pfefferkorn@medizin.uni-leipzig.de

Background and aims: HBsAg consists of the S (small; SHBs), the preS2 (middle, MHBs) and the preS1 (large; LHBs) proteins, and the proportions of those proteins changes during the development of

HBsAg loss under nucleos (t)ide analogue (NA) treatment. We have investigated whether changes in HBsAg composition during development of functional cure is associated with genomic variants in the coding s gene of HBV.

Method: Patients achieving HBsAg loss (n = 15) and patients without serologic response including HBeAg or HBsAg loss (w/o SR; n = 23) during NA treatment were retrospectively analyzed. Proportions of HBsAg proteins were quantified in sera collected before and during treatment. The complete HBV s gene was sequenced in all available serum samples (n = 164) of patients with HBsAg loss and in minimum three sequential samples of patients w/o SR.

Results: Among patients with HBsAg loss, 53% (n = 8) showed wildtype s gene before and during NA treatment, whereas 40% (n = 6) developed a double deletion of aa 1–6 and aa 88–129. These deletions are located in the N-terminal regions of the preS1- (LHBs) and the preS2- (MHBs) domain and include the start ATG of both proteins. In samples with the deletions aa 1–6 and aa 88–129, HBV DNA and HBsAg levels were significantly lower as compared to samples with wt. In patients with subsequent HBsAg loss LHBs and MHBs became undetectable 3.9 (0–9) and 11.4 (0–53) months before the loss of total HBsAg. The occurrence of the double deletion lead to a strong decrease of MHBs (%), but not LHBs (%). In patients w/o SR, 74% (n = 17) showed wildtype s genes in all analyzed samples and no patient showed the double deletion of aa 1–6 and aa 88–129.

Conclusion: In many patients with HBsAg loss during antiviral treatment a double deletion in the start ATG of the preS1- and preS2-domain was found which is associated with decreased MHBs ratios and possibly with decreased HBV replication. The relevance of those mutations for HBV replication and the process of HBsAg loss need to be studied further.

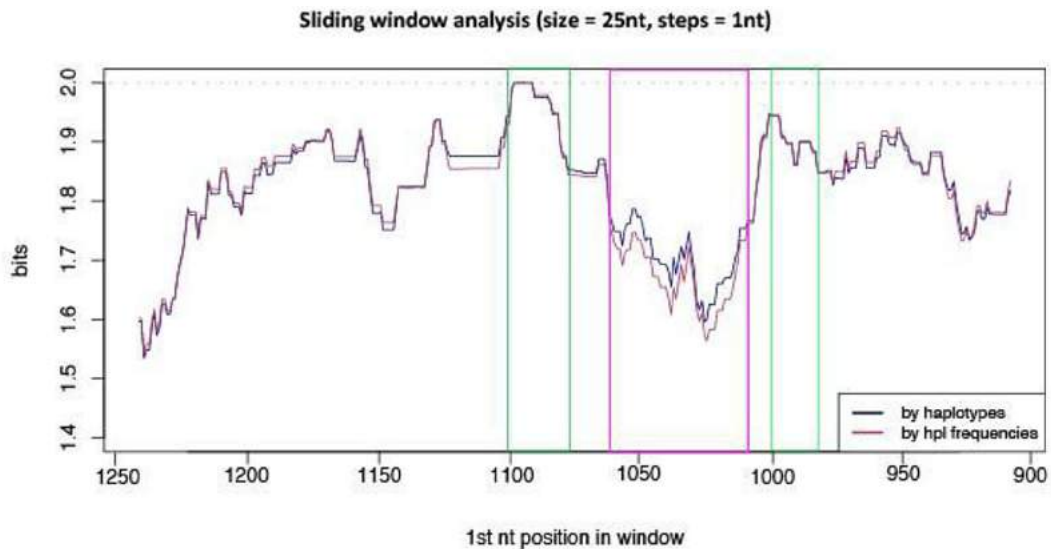
PO-2145

Conservation, variability and evolution of Hepatitis Delta virus in antigen coding region

Beatriz Pacín^{1,2}, Maria Francesca Cortese^{1,2}, Josep Gregori², Marta Vila^{1,2}, Selene Garcia-Garcia^{1,2}, David Tabernero^{1,3}, Rosario Casillas^{1,2}, Ariadna Rando¹, Adriana Palom⁴, Mar Riveiro Barciela^{3,4}, Francisco Rodríguez-Frías^{1,2,3}, Maria Buti^{3,4}. ¹Vall D'hebron University Hospital, Biochemistry and Microbiology/Liver Pathology Unit, Barcelona, Spain; ²Vall D'hebron Research Institute, Barcelona, Spain, Liver Unit, Barcelona, Spain; ³Instituto De Salud Carlos III, Madrid, Spain, Centro De Investigación Biomédica En Red, Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; ⁴Vall D'hebron University Hospital, Liver Unit, Internal Medicine Department., Barcelona, Spain
Email: beatriz.pacin@vhir.org

Background and aims: Hepatitis delta virus HDV affects around 5% of hepatitis B virus infected patients causing the most severe form of chronic viral hepatitis. HDV RNA genome encodes just for a protein that exists in two length-dependent isoforms (S- and L-HDAg) following an edition of the canonical stop codon. The HDV is characterized by a high evolutionary rate resulting in a complex viral population (quasispecies, QS) that could influence viral replication and clinical evolution. Mutations in L-HDAg related to escape from adaptive immune response had been associated with more severe hepatitis. Here we analyzed by next generation sequencing (NGS) the L-HDAg quasispecies to identify highly conserved regions and mutations that potentially affect HDV evolution.

Method: Ten patients with chronic hepatitis delta (CHD) were enrolled in the study and followed up for an average period of 1.5 years. HDV RNA was extracted from two plasma samples per patient (at inclusion and follow-up). A region in HDAg gene located between nucleotide (nt) 910 to 1270 (amino acid, aa 111–215) was analyzed by NGS (MiSeq Illumina, San Diego, USA). Conservation was calculated by analyzing QS information content. Amino acid substitutions were identified by aligning sample QS with its genotype sequence.



Sliding window of QS conservation in multiple alignment of HDAG nucleotide sequences. The sliding window analysis is the result of the mean information content (bits) of the 25-nt long windows with a displacement between them of 1nt obtained by multiple alignment of all haplotypes (blue line) and taking into account their relative frequencies (red line). Green boxes show the highly conserved regions, whereas the highly variable region is highlighted in pink.

Figure: (abstract: PO-2145)

Results: A median of 31384, 5 reads/sample was obtained. Two highly conserved regions were observed between nt 1404–1383 (corresponding to aa 159–172) and nt 1502–1483 (aa 191–197) of L-HDAG, whereas high variability was observed between nt 1480–1423 (aa 171–190) (Figure). Of note, conservation index did not change over the time in none of the studied patients. A total of 37 mutated aa positions were identified. Remarkably, in 5/10 patients, 7 aa changes (K113S, V144I/T, P148R, V149 T/A, S159A, T180S, V188M/I) were positively selected over time and located within CD8+ T-cells epitopes. Of note, in 3/5 patients, more than 2 aa changes at epitopes were observed.

Conclusion: The HDAG gene seems to be relatively conserved during the time. The HDAG editing domain was highly conserved, agree with its essential role. Other hyper-conserved region was observed, which might suggest an important function in HDV replication. However, some aa changes located into CD8 immune epitopes were selected, suggesting a possible immune escape mechanism as one of the HDV evolution factor. Funding: Instituto de Salud Carlos III (grant PI17/02233), co-financed by the European Regional Development Fund (ERDF).

PO-2293

Low anti-HBc levels are associated with lower risk of virological relapse after discontinuation of nucleos (t)ide analogue therapy in HBe antigen negative patients.

Valerie Ohlendorf¹, Maximillian Wuebbolding^{1,2,3}, Paul Gineste⁴, Christoph Hoener zu Siederdisen¹, Birgit Bremer¹, Heiner Wedemeyer^{1,2}, Markus Cornberg^{1,2,3}, Benjamin Maasoumy^{1,2,3}. ¹Hannover Medical School, Clinic for Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ²German Center for Infection Research (DZIF), Braunschweig, Germany; ³Centre for Individualised Infection Medicine (CiIM), a joint venture of Helmholtz Centre for Infection Research and Hannover Medical School, Hannover, Germany; ⁴Abivax, Paris, France
Email: ohlendorf.valerie@mh-hannover.de

Background and aims: EASL guidelines suggest that treatment with nucleos (t)ide analogue (NA) can be stopped in HBeAg negative

patients after three years of viral suppression. However, relapse must be expected in more than half of the patients. Recently, a low level of serum anti-HBc at the time of NA cessation has been linked to a higher risk of relapse in a cohort of predominantly HBeAg positive patients. In this study we investigated the association of serum anti-HBc with relapse after stop of NA therapy in HBeAg negative patients. **Method:** Serum levels of anti-HBc, HBsAg and HBcrAg were determined in 136 HBeAg negative patients, participating in a prospective, multicenter therapeutic vaccination trial (ABX-203, NCT02249988), before Stop of NA therapy or vaccination (baseline). Importantly, vaccination showed no impact on relapse. Virological relapse was defined as HBV DNA >2,000 IU/ml. Anti-HBc levels were compared between relapsers and off-treatment responders using the Mann-Whitney U test. Optimal anti-HBc thresholds were determined by the Youden-Index. Correlation between anti-HBc, HBsAg and HBcrAg was tested with Spearman correlation.

Results: Median age of the patients was 53 years and 75% (n = 102/136) of patients were male. The majority of patients was treated with entecavir (n = 90/136; 66%), while the rest received tenofovir. Median anti-HBc, HBsAg and HBcrAg at baseline was 490 IU/ml, 784 IU/ml and 1585 U/ml, respectively. No significant correlation was found between baseline anti-HBc and HBsAg (r = 0.016, p = 0.85) or anti-HBc and HBcrAg (r = -0.011; p = 0.90). Relapse after NA discontinuation occurred in 68 out of 136 patients (50%). Median anti-HBc was significantly higher among relapsers when compared to off-treatment responders (520 IU/ml vs. 330 IU/ml, p = 0.0098). A baseline anti-HBc-level of 325 IU/ml was determined as optimal cut-off value to predict relapse. Relapse occurred in 35% of patients with an anti-HBc level <325 IU/ml, while this was the case in 60% of those with values ≥325 IU/ml (p = 0.0103; sensitivity 50%, specificity 75%; Figure).

POSTER PRESENTATIONS

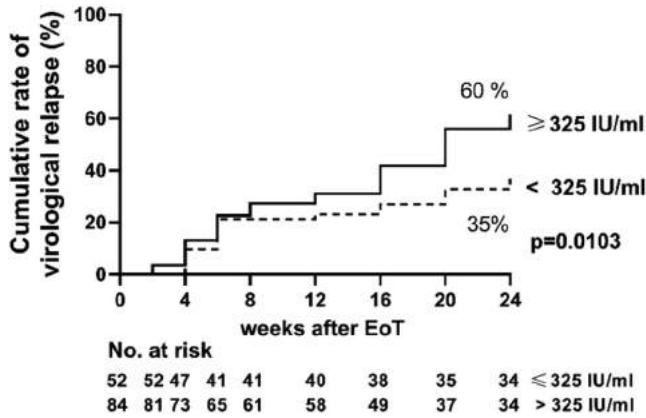


Figure: Cumulative relapse rate after NA cessation according to end of treatment (EoT) by serum anti-HBc baseline levels.

Conclusion: In contrast to cohorts of predominantly HBeAg positive patients, lower serum anti-HBc levels are associated with a significantly lower risk of relapse after NA cessation in HBeAg negative patients. As anti-HBc showed no correlation with other virological markers we suggest that it should be further explored when establishing prediction models in the future.

PO-2474

Novel HBV cure strategy: Leveraging HBV pol for infected cell-specific killing-*In vivo* proof-of-concept

Serhat Gumrukcu^{1,2}, Tung Nguyen^{1,2}, Michael Bobardt³, Philippe Gallay³. ¹Seraph Research Institute, Los Angeles, United States; ²Enochian Biosciences Inc, Los Angeles, United States; ³The Scripps Research Institute, Department of Immunology and Microbiology, La Jolla, United States

Email: drs@seraphinstitute.org

Background and aims: Despite effective treatment and vaccination, Hepatitis B virus (HBV) persists as a global cause of chronic liver disease and mortality responsible for ~ 900, 000 deaths annually. Thus, an effective cure strategy is urgently needed. Current strategies focusing on reducing HBV (ccc)DNA or interrupting viral replication have not been successful. We hypothesized that inducing apoptosis in HBV-infected hepatocytes by "hijacking" HBV *pol* could effectively eradicate infection.

Method: A unique, proprietary vector construct expressing a non-functional, non-coding (nc)RNA (HBV Hijack RNA), under liver-specific thyroxine binding globulin (TGB) promoter was packaged in AAV8 particles. HBV Hijack RNA is designed using negative strand of human caspase-9 (casp-9) cDNA flanked by 2 HBV *epsilon* signals (HBV *pol*-specific recognition sequence). HBV *pol*/RT recognizes HBV Hijack RNA and reverse transcribes it to double stranded (ds) DNA expressing casp-9 driven by a strong promoter, to induce apoptosis. We have previously reported *in vitro* and *in vivo* studies validating our proposed mechanism of action. To investigate killing kinetics *in vivo*, we established a xenograft model by transplanting bioluminescent-tagged HBV *pol*-expressing HepG2 cells (2×10^5 cells in 0.1 ml serum-free medium with 50% Matrigel) into nude mice. Once xenografts were detectable, mice were treated with test AAV8 expressing HBV Hijack RNA, or control AAV8 expressing GFP. Along with cage-side general health observations, tumor size was measured daily by an *in vivo* imaging system (IVIS). On day 30 after AAV treatment, mice were sacrificed for evaluation of their liver tissues by immunohistochemistry. The same model was used for dose escalation and toxicity studies.

Results: In the kinetics study, bioluminescence measurements showed daily reduction in the target tissue size, starting 2 days after AAV administration. On day 8 there was no visible signal in mice treated with the test vector. Daily growth of target cells was observed in controls (Figure). No liver or treatment-related toxicity was

observed in test vector-treated mice or recrudescence xenograft growth by day 30. Necropsy and dose escalation results will be presented.

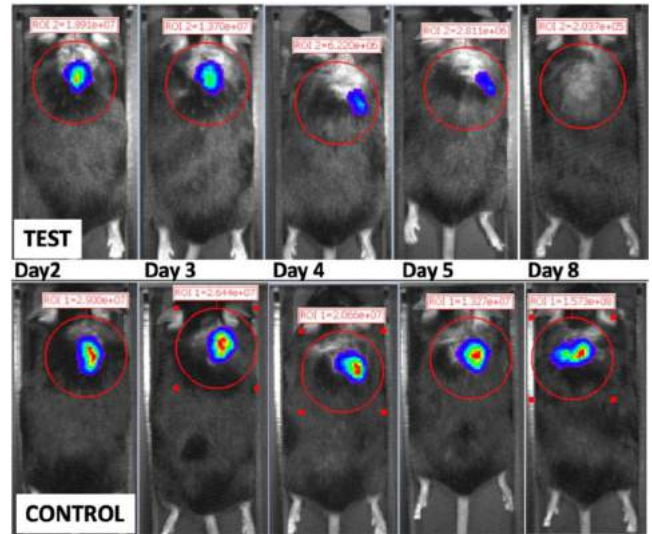


Figure:

Conclusion: HBV Hijack RNA rapidly cleared HBV-target cells in mice without recrudescence or toxicity by day 30 post-treatment. HBV Hijack RNA could be a promising strategy to cure HBV infection.

PO-2684

Mitochondrial stress in patients with chronic hepatitis b and advanced fibrosis

Dimitri Loureiro^{1,2}, Issam Tout^{1,2}, Morganer Roinard^{1,2}, Ahmad Sleiman^{1,2}, Boyer Nathalie^{1,2}, Stephanie Narguet^{1,2}, Nathalie Pons-Kerjean³, Corinne Castelnau^{1,2}, Nathalie Giuly^{1,2}, Vassili Soumelis⁴, Jamel El Benna², Patrick Soussan⁵, Richard Moreau^{1,2}, Valérie Paradis^{1,2}, Abdel Mansouri^{1,2}, Tarik Asselah^{1,2}. ¹Hospital Beaujon AP-HP, Hepatology, Clichy, France; ²Center Recherche Sur L'inflammation, U1149, Paris, France; ³Hospital Beaujon AP-HP, Service de Pharmacie, Clichy, France; ⁴Hospital _ Saint-Louis Ap-Hp, Laboratoire d'Immunologie et Histocompatibilité, Paris, France; ⁵Université de Paris, U1135, Paris, France
Email: dimitri.loureiro@inserm.fr

Background and aims: Mitochondrial DNA is particularly sensitive to oxidative stress and hepatitis B virus (HBV) increases hepatic stress. We postulated that it may cause oxidative damage to mitochondrial DNA, resulting in mitochondrial dysfunction which might account for fibrosis progression in chronic hepatitis B infection (CHB).

Method: 136 treatment-naïve CHB mono-infected patients were included. Liver mitochondrial DNA (mtDNA) damage was screened by long PCR and sequencing and levels by Slot blot. The expression of the main genes of cytochrome *c* oxidase subunits, mitophagy, mitochondrial peptidases and chaperonins, TNF α and IL6 were investigated by RT-qPCR and Western-blotting. Patients with advanced fibrosis (F3-F4 Metavir score; n=41) were compared to patients with mild-moderate fibrosis (F0-F2;n=86). *In vitro*, HBV and HBx were expressed in HepG2 cells and the superoxide anion formation was assessed by MitoSox and mtDNA levels by Slot blot.

Results: Whereas 100% of patients with F3-F4 fibrosis exhibited multiple mtDNA deletions, 50% of those with F0-F2 fibrosis ($\kappa^2 = 6.8$; $p < .001$) carried a single mtDNA deletion. Significant decreases were observed in F3-F4 compared to F0-F2 for the mRNAs of MT-CO1 (0.55 ± 0.36 and 1.20 ± 0.75 , $p < .001$), HSPA9 (0.70 ± 0.28 and 1.06 ± 0.37 , $p < .001$), HSPD1 (0.83 ± 0.36 and 1.10 ± 0.44 , $p < .05$), Lon Peptidase 1, LONP1 (0.83 ± 0.22 and 1.06 ± 0.33 , $p < .05$), Parkinson-juvenile

disease protein 2, PRKN (0.45 ± 0.26 and 1.12 ± 0.57 , $p < .0001$), and Phosphatase and Tensin-Induced Putative Kinase-1, PINK1 (0.59 ± 0.17 and 1.06 ± 0.26 , $p < .0001$). Liver TNF α mRNA was 1.72 ± 0.2 and 0.99 ± 0.2 ($p < .05$) and IL6 mRNA was 7.82 ± 0.90 and 1.14 ± 0.26 ($p < .05$) in F3-4 and F0-F2, respectively. Protein levels significantly decreased in F3-F4 compared to F0-F2 for MT-CO1, LONP1, PRKN and PINK1. *In vitro*, both HBV or HBx expression significantly ($p < .05$) increased mitochondrial superoxide formation, depleted mtDNA, decreased MT-CO1 expression, increased 3-Nitrotyrosine (3-NT) residues within respiratory chain complexes and inhibited complex I at 24 and 48 h post-transfection.

Conclusion: Diverse mtDNA damages were associated with alterations in mitochondrial function, mitochondrial unfolded protein response, mitophagy and inflammation in patients with CHB and advanced fibrosis. *In vitro*, the accumulation of 3-NT on mitochondrial proteins points out a role of the superoxide anion reacting with NO to form mtDNA- and protein-damaging peroxy-nitrite. In addition to the damage caused by reactive species; decreased levels of mitochondrial transcripts lead to mitochondrial dysfunction. Modulating mitochondrial function is therefore an attractive therapeutic strategy to block the progression of fibrosis and prevents CHB.

Viral hepatitis A-E: Clinical aspects

PO-1844

Global burden of acute hepatitis and its association with socioeconomic development status, 1990–2019

Dan-Yi Zeng¹, Jing-Mao Li², Jia You¹, Mei-Zhu Hong³, Yueyong Zhu¹, Jin-Shui Pan¹. ¹First Affiliated Hospital of Fujian Medical University, Hepatology, Fuzhou, China; ²Xiamen University, School of Economics, Xiamen, China; ³Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China
Email: dr_ezhu@163.com

Background and aims: Acute viral hepatitis (AVH) represents an important global health problem, however, progress in understanding AVH has been eclipsed by the priority of combating persistent HBV and HCV infections. An improved understanding of the burden of AVH is needed to inform strategies for global intervention.

Method: Age-standardized incidence rate and disability-adjusted life years (DALYs) rate of AVH were extracted from GBD 2019, which were stratified by sex, level of Socio-demographic Index (SDI), and country and territory. The association between burden of AVH and socioeconomic development status, represented in SDI, was also described.

Results: In 2019, there was an age-standardized incidence rate of 3615.9 (95% CI 3360.5–3888.3) and an age-standardized DALYs rate of 58.0 (47.3–70.0) per 100 000 person-years, in terms of 4 major AVH. Among major AVH, acute hepatitis A caused the heaviest burden. There was a significant downward trend in age-standardized DALYs rates due to the major AVH from 1990 to 2019. Globally, several regions or countries located in West and Central Africa shouldered the highest age-standardized incidence rates of AVH in 2019. Stratified using SDI, the high SDI, and high-middle SDI locations recorded the lowest incidence rate and DALYs rate of AVH, whereas the low-middle SDI, and low SDI locations possessed the highest-burden of AVH.

Conclusion: Pronounced association exists between socioeconomic development status and burden of AVH. Data of GBD 2019 are valuable for policymakers to implement cost-effective interventions for AVH.

Viral hepatitis B-D: Clinical aspects except therapy

PO-218

Incidence and resolution of steatohepatitis in patients receiving entecavir for chronic hepatitis B

Xiu-Juan Chang¹, Yiwen Shi², Wang Jing³, Huabao Liu⁴, Yan Chen¹, Xiao-Ning Zhu⁵, Yong-Ping Chen⁶, Zu-Jiang Yu⁷, Qing-Hua Shang⁸, Lin Tan⁹, Qin Li¹⁰, Li Jiang¹¹, Guang-Ming Xiao¹², Chen Liang¹³, WEI Lu¹⁴, Xiao-Yu Hu¹⁵, Qing-Hua Long¹⁶, Lin-Jing An¹, Zi-Yuan Zou², Vincent Wai-Sun Wong¹⁷, Yongping Yang¹, Jianguo Fan². ¹Chinese PLA General Hospital, the Fifth Medical Center of Chinese PLA General Hospital, Department of Liver Disease, Beijing, China; ²Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Department of Gastroenterology, Shanghai, China; ³Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Department of liver diseases, Luzhou, China; ⁴Traditional Chinese Medicine Hospital of Chongqing, Department of liver diseases, Chongqing, China; ⁵Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Department of Liver Disease, Luzhou, China; ⁶Liver Research Center, the First Affiliated Hospital of Wenzhou Medical University, Department of Infectious and Liver Diseases, Wenzhou, China; ⁷the First Affiliated Hospital of Zhengzhou University, Department of Infectious Disease, Zhengzhou, China; ⁸ the 960th Hospital of Chinese PLA, Center of Therapeutic Liver Disease, Taian, China; ⁹Fuyang 2nd People's Hospital, Liver Disease Department, Fuyang, China; ¹⁰Fuzhou Infectious Diseases Hospital, Department of liver diseases, Fuzhou, China; ¹¹Southwest Hospital, Army Military Medical University, Department of Infectious Diseases, Chongqing, China; ¹² Guangzhou 8th People's Hospital, Department of Infectious Diseases, Guangzhou, China; ¹³Shanghai Public Health Clinical Center, Department of Hepatic Diseases, Shanghai, China; ¹⁴Tianjin Second People's Hospital, Department of liver diseases, Tianjin, China; ¹⁵Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Department of Infectious Diseases, Chengdu, China; ¹⁶Yichun People's Hospital, Department of Infection and Liver Disease, Yichun, China; ¹⁷The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China
Email: fanjianguo@xinhua.com.cn

Background and aims: Although concomitant non-alcoholic steatohepatitis (NASH) is common in chronic hepatitis B (CHB) patients, the outcome of NASH in CHB patients remains unclear. This study was aimed to evaluate the incidence and resolution rate of NASH in CHB patients during antiviral treatment.

Method: This was a sub-study of a multicenter prospective study on HBV treatment outcomes including patients with or without NASH. The histopathological features of NASH were examined using paired liver biopsies at baseline and week 72. Finally, 297 of 1000 CHB patients (30%) had concomitant steatosis, 182 (18.2%) had NASH.

Results: After 72-week entecavir treatment, concomitant steatosis and NASH decreased to 18% (129/727) and 10% (73/727), respectively. Among patients with NASH, the scores of hepatic steatosis, ballooning, lobular inflammation and fibrosis stages all improved (all $P < 0.001$), and 63 of 136 patients (46%) achieved NASH resolution. By multivariable analysis, baseline body mass index (BMI) < 23 kg/m² (OR = 2.4, 95% CI: 1.112–5.255, $P = 0.012$) and no weight gain at follow-up (OR = 5.4, 95% CI: 1.443–19.896, $P = 0.026$) were significantly associated with NASH resolution. The rates of serum HBeAg loss, HBeAg seroconversion, undetectable HBV DNA and ALT normalization were similar between patients with or without NASH ($p = 0.303, 0.652, 0.498$ and 0.736 , respectively). Among patients who had no or bland steatosis at baseline, 22 cases (3.7%) had incident NASH. Baseline BMI ≥ 23 kg/m² (OR = 12.5, 95%CI: 2.813–55.606, $P = 0.001$) and weight gain (OR = 5.1, 95%CI: 1.674–15.694, $P = 0.005$) were predictors of NASH development.

POSTER PRESENTATIONS

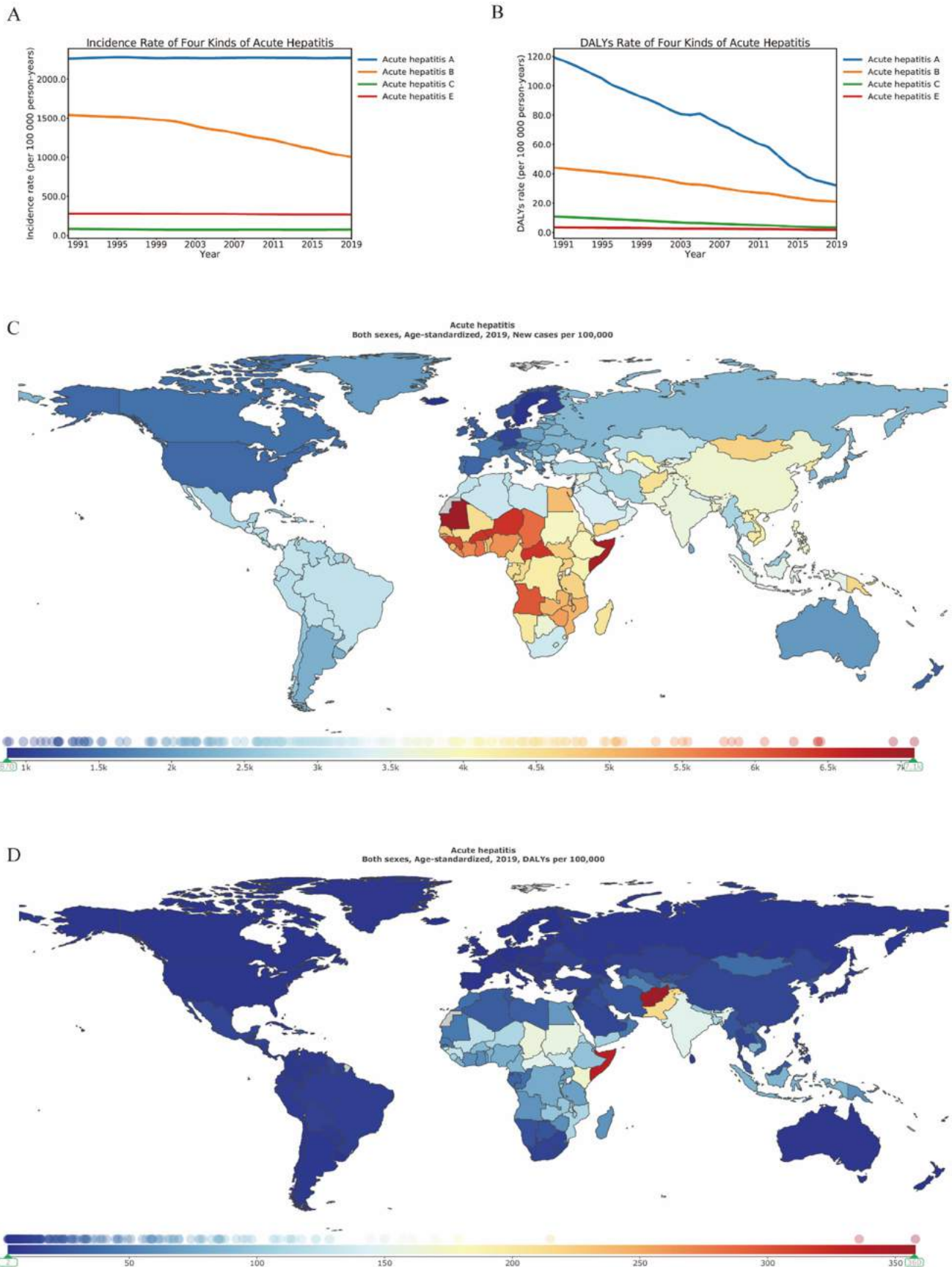


Figure 1: (abstract: PO-1844) Burden of AVH for 204 countries and territories.

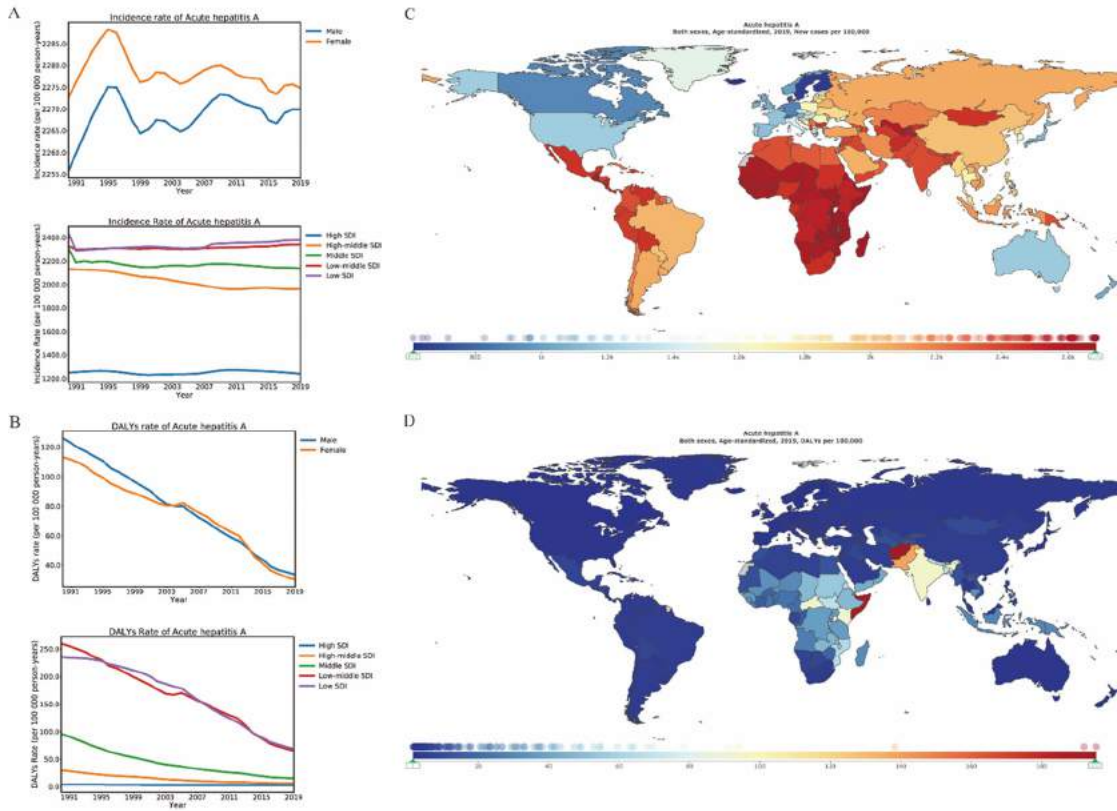


Figure 2: (abstract: PO-1844) Burden of AHA for 204 countries and territories

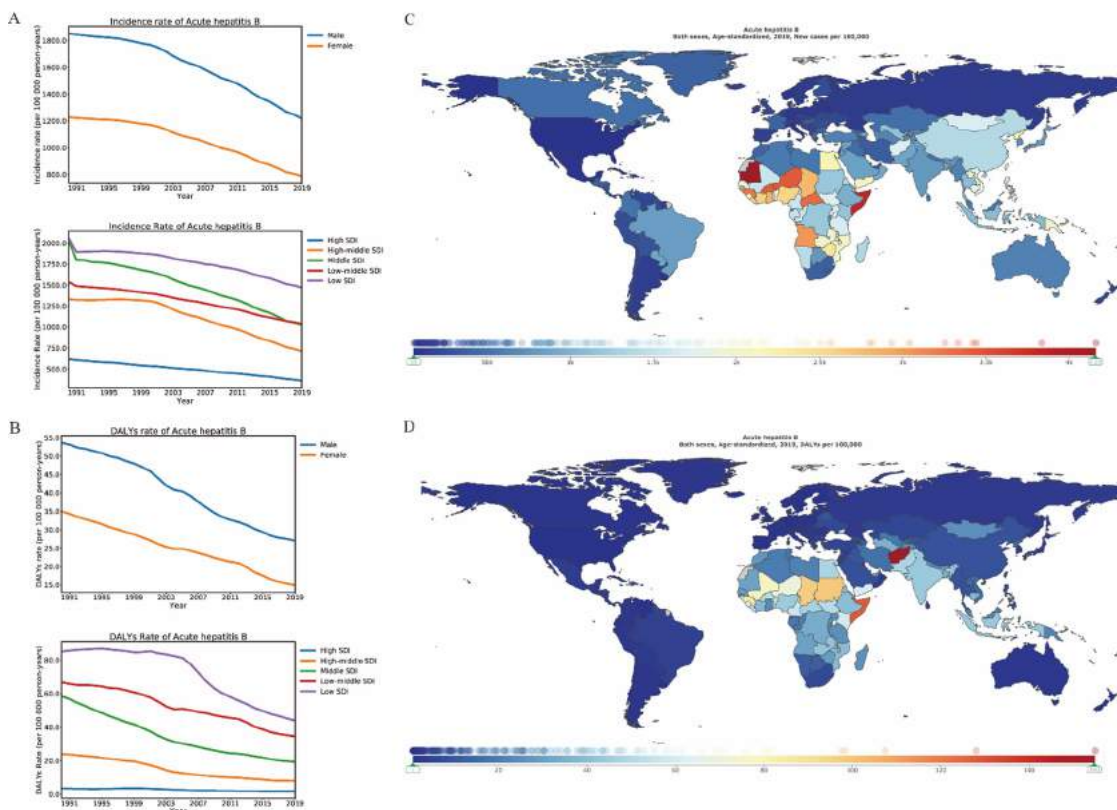


Figure 3: (abstract: PO-1844) Burden of AHB for 204 countries and territories.

POSTER PRESENTATIONS

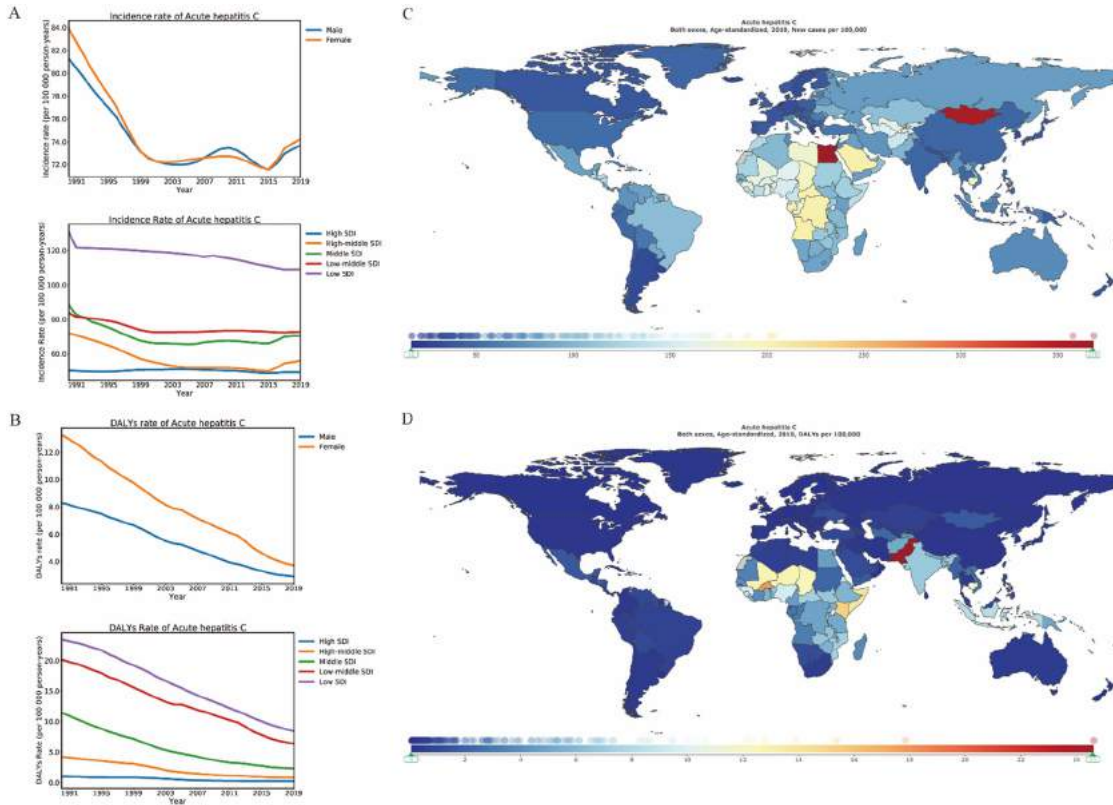


Figure 4: (abstract: PO-1844) Burden of AHC for 204 countries and territories

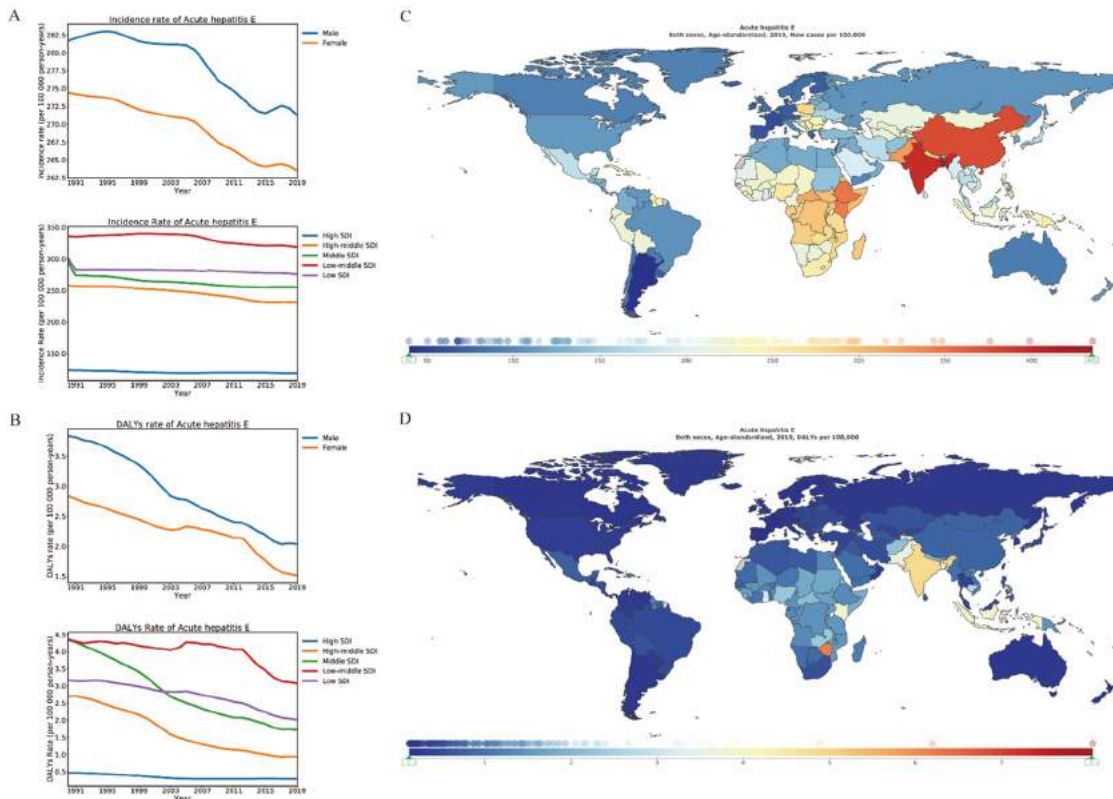


Figure 5: (abstract: PO-1844) Burden of AHE for 204 countries and territories.

Table: Risk factors associated with the outcomes of NASH

	Events	OR	95%CI	P value
NASH resolution				
BMI \geq 23	40%	Ref		
BMI<23	61%	2.42	1.11, 5.26	0.012
Weight gain	17%	Ref		
No weight gain	51%	5.36	1.44, 19.90	0.026
NASH resolution without worsening of fibrosis				
BMI \geq 23	37%	Ref		
BMI<23	56%	2.23	1.04, 4.79	0.040
Weight gain	17%	Ref		
No weight gain	47%	4.46	1.21, 16.48	0.025
NAS decrease \geq2 points				
BMI \geq 23	80%	Ref		
BMI<23	95%	5.16	1.10, 24.12	0.037
Weight gain	61%	Ref		
No weight gain	88%	5.01	1.59, 15.80	0.006
NASH improvement without worsening of fibrosis				
BMI \geq 23	53%	Ref		
BMI<23	73%	2.50	1.10, 5.68	0.028
Weight gain	33%	Ref		
No weight gain	63%	3.45	1.18, 10.09	0.024

Conclusion: CHB patients had a high proportion of NASH resolution during antiviral treatment, especially in lean patients without weight gain. The value of weight management in CHB patients during antiviral treatment deserves further evaluation.

PO-266

Liver volume measurement predicts development of hepatic encephalopathy in chronic hepatitis b patients

Jin-Wook Kim², Sumi Kim³. ¹College of Medicine, Seoul National University, Seoul, Korea, Rep. of South; ²Seoul National University Bundang Hospital, Department of Medicine, Seongnam, Korea, Rep. of South; ³Seoul National University College of Medicine, Korea, Rep. of South

Email: jwook2112@gmail.com

Background and aims: Potent antiviral therapy has improved the prognosis of chronic hepatitis B (CHB), but some patients still experience disease progression. Liver volume represents overall hepatic functional reserve and has been used for preoperative planning for hepatic resection. The aim of this study was to determine whether CT-measured liver volume can predict complications of HBV-associated liver cirrhosis such as varix bleeding, ascites, and hepatic encephalopathy development.

Method: This study is the retrospective cohort study which included 223 HBeAg-negative CHB patients who received at least two CT scans in a tertiary referral hospital in South Korea. Liver volume was measured on portal venous phase contrast-enhanced CT images. To adjust the effect of body build, liver volume index was calculated, dividing CT-measured liver volume by formula liver volume. Clinical, demographic, and laboratory parameters were independent variables. Varix bleeding, ascites, and hepatic encephalopathy development were dependent variables. By performing multiple logistic regression, independent predictors for complications development were identified.

Results: Platelet count ($\times 10^9/L$) was an independent predictor for varix bleeding (odds ratio [OR] = 0.943; $p = 0.001$). Age and sex had significant correlation with ascites development (OR = 1.065 and 3.673 in age and sex, respectively; $p = 0.018$ and 0.047). Liver volume didn't show any significant results with varix bleeding and ascites. However, age and liver volume were identified as predictors of hepatic encephalopathy (OR = 1.057 and 10.942 in age and liver volume index, respectively; $p = 0.015$ and 0.021).

Figure: Predictors of hepatic encephalopathy development by multiple logistic regression model

Characteristic	Exp (B)	95% CI for exp (B)	P
Age	1.057	1.011–1.106	0.015
Male sex	1.609	0.605–4.277	0.341
Nucleotide Analogue	1.094	0.428–2.795	0.851
AFP (ng/ml)	1.046	0.988–1.108	0.121
Albumin (g/dl)	0.673	0.201–2.248	0.520
Bilirubin (mg/dl)	0.842	0.388–1.829	0.665
PT INR	35.253	0.361–3439.715	0.127
Platelet ($\times 10^9/L$)	1.002	0.995–1.009	0.543
Volume Index*	10.942	1.335–89.708	0.021

AFP, alpha-fetoprotein; PT, prothrombin time; CI, confidence interval

Conclusion: Liver volume was able to predict future development of hepatic encephalopathy in HBeAg-negative CHB patients.

PO-408

Circulating HBV RNA correlates with intrahepatic covalently closed circular DNA (cccDNA) transcriptional activity in untreated and NUC-treated chronic hepatitis B (CHB) patients

Barbara Testoni¹, Caroline Scholtes^{1,2}, Marie-laure Plissonnier¹, Françoise Berby¹, Floriana Facchetti³, François Villeret⁴, Alessandro Loglio³, Beth Scott⁵, Ling Wang⁵, Aaron Hamilton⁵, Marantha Heil⁵, Pietro Lampertico^{3,6}, Massimo Llevero^{1,4,7}, Fabien Zoulim^{1,4,8}. ¹INSERM U1052–Cancer Research Center of Lyon (CRCL), Lyon, France; ²Croix Rousse Hospital, Hospices Civils de Lyon, Department of Virology, Lyon, France; ³Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy; ⁴Croix Rousse hospital, Hospices Civils de Lyon, Department of Hepatology, Lyon, France; ⁵Roche Molecular Diagnostics, Pleasanton, CA, United States; ⁶University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; ⁷Sapienza University of Rome, Department of Internal Medicine-DMISM and the IIT Center for Life Nanoscience (CLNS), Rome, Italy; ⁸University of Lyon, UMR_S1052, CRCL, Lyon, France

Email: fabien.zoulim@inserm.fr

Background and aims: Quantification of Hepatitis B virus (HBV) RNA in blood circulation (cirB-RNA) across chronic hepatitis B (CHB) phases and during long-term nucleos (t)ide analogues (NUC) treatment and its correlation with intrahepatic viral markers and HBcrAg, the other emerging biomarker of cccDNA transcription, is still lacking.

Method: 122 untreated and 30 NUC-treated CHB patients with paired liver biopsy and serum sample, were analyzed for serum HBV DNA, quantitative (q)HBsAg, HBcrAg and alanine aminotransferase (ALT) levels. Liver cccDNA and 3.5Kb RNA were assessed by qPCR and droplet digital PCR (ddPCR) and cccDNA transcriptional activity was calculated as 3.5Kb RNA/cccDNA ratio. Liver histology scores were also available. cirB-RNA was quantified by the Roche HBV RNA investigational assay for use on the cobas® 6800 System (LLOQ 10 cp/ml; linearity range 10 to 10^7 cp/ml; LLOD ~3 cp/ml).

Results: All untreated HBeAg (+) patients, 74% of HBeAg (-) chronic hepatitis (CH) and 21% of HBeAg (-) chronic infection (CI) patients had detectable cirB-RNA. The 39 cirB-RNA (-) patients (23 HBeAg (-) CI and 16 HBeAg (-) CH) had lower cccDNA (median 0.06 vs 0.3 cp/cell, $p < 0.0001$), 3.5Kb RNA (0.03 vs 10.3, $p < 0.0001$) and 3.5Kb RNA/cccDNA (0.79 vs 8.9, $p = 0.002$) as compared to the cirB-RNA (+) ones. No significant difference was found in qHBsAg levels, while both HBcrAg (median 5.4 vs 2.6 LogU/ml, $p < 0.0001$) and serum HBV DNA (6.2 vs 2.7 LogIU/ml, $p < 0.0001$) were significantly higher in cirB-RNA (+) patients. In HBeAg (-) patients, cirB-RNA significantly correlated with serum HBV DNA ($R = 0.81$, $p < 0.0001$), HBcrAg ($R = 0.73$, $p < 0.0001$), intrahepatic 3.5Kb RNA ($R = 0.77$, $p < 0.001$) and cccDNA

POSTER PRESENTATIONS

transcriptional activity ($R = 0.78$, $p < 0.0001$), but not with HBsAg and cccDNA levels. A subgroup of cirB-RNA (+) patients with increased cccDNA (0.1 vs 0.03 cp/cell), serum HBV DNA levels (4 vs 2.7 logIU/ml) and fibrosis score was identified among HBeAg (-) HBcrAg (-) patients.

All NUC-treated patients (median treatment duration of 2.6 years) had detectable intrahepatic cccDNA and RNA by ddPCR, albeit at low levels (2×10^{-3} and 10×10^{-3} cp/cell, respectively). HBcrAg was quantifiable in 77% and cirB-RNA in 40% of patients. cirB-RNA (+) patients showed higher 3.5Kb RNA (0.04 vs 0.002, $p = 0.009$) and cccDNA transcriptional activity (24.1 vs 0.4, $p = 0.04$) levels compared to cirB-RNA (-) ones, but no significant difference in cccDNA amount.

Conclusion: Our results support the notion that cirB-RNA detected by Roche HBV RNA investigational assay reflects the transcriptional activity of intrahepatic cccDNA in both untreated and NUC-treated CHB patients.

This work is supported by the French National Research Agency Investissements d'Avenir program (CirB-RNA project-ANR-17-RHUS-0003)

PO-415 exosomes with mir-574 transfer anti-hbv activity mediated by the interferon from macrophage to hbv-infected hepatocyte

Wenyu Wu¹, Di Wu¹, Weiming Yan¹, Xiaoyang Wan¹, Dong Xi¹, Xiaoping Luo¹, Meifang Han¹, Qin Ning¹. ¹Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Department and Institute of Infectious Disease, Wuhan City, Hubei Province, China
Email: qning@vip.sina.com

Background and aims: Interferon alpha (IFN- α) has proven to be clinically effective in the treatment of chronic hepatitis B (CHB) due to its capability to reduce hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) covalently closed circular DNA (cccDNA). However, the underlying mechanisms are not well defined. The purpose of this study is to explore the role of exosomes in the antiviral process of IFN

Method: We investigated the anti-HBV activities of exosomes both from pegylated IFN- α (PegIFN- α) treated patients and the supernatants of IFN- α -treated THP-1 (the human leukemia monocyte cell line) derived macrophages. Then, we identified three upregulated miRNAs in exosomes through miRNA sequencing. By luciferase reporter assay, we found hsa-miR-574-5p reduced pregenomic RNA (pgRNA) and polymerase mRNA levels by binding to the nucleotides 2750–2757 position of HBV genomic sequence.

Results: Exosomes from patients and the supernatants exhibited anti-HBV activities including the suppression of supernatant HBsAg, HBeAg, and HBV DNA levels as well as intracellular HBV cccDNA in HBV related cell lines. MicroRNA sequencing revealed that PegIFN- α treatment upregulated exosomal hsa-miR-193a-5p, hsa-miR-25-5p, and hsa-miR-574-5p that could partially inhibit HBV replication and

transcription. The luciferase reporter assay confirmed that hsa-miR-574-5p reduced pgRNA and polymerase mRNA levels by binding to the 2750–2757 position of HBV genomic sequence.

Conclusion: Exosomes can transfer IFN- α -related miRNAs from macrophages to HBV-infected hepatocytes, thereby suppressing HBV replication and expression.

PO-420 A 3-antigen prophylactic hepatitis B virus vaccine confers rapid onset of protection in young adults, age 18–45, compared to a single-antigen hepatitis B virus vaccine

Francisco Diaz-Mitoma¹, Timo Vesikari², Joanne Langley³, Nathalie Machluf¹, Johanna Spaans¹, Bebi Yassin-Rajkumar¹, David Anderson¹, Vlad Popovic¹. ¹VBI Vaccines Inc, Massachusetts, United States; ²Nordic Research Network, Finland; ³Departments of Pediatrics and Community Health and Epidemiology, Canadian Center for Vaccinology, Canada
Email: fdiazmitoma@vbivaccines.com

Background and aims: Vaccination rates against Hepatitis B Virus (HBV), a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma worldwide, remain low in adults. Adults or children who were not immunized as infants against HBV remain at risk of becoming infected. According to the European Centre for Disease Prevention and Control, 25 to 34-year-olds are the most affected age group for both acute and chronic HBV infections, accounting for 30% of reported cases in 2017 by the 30 EU/EEA Member States. HBV vaccines that are more immunogenic than conventional vaccines, and optimally designed to provide robust and rapid seroprotection, are needed. The overall aim of our clinical trials was to evaluate the speed to seroprotection, immunogenicity, and safety of a 3-antigen (pre-S1/S2/S) prophylactic HBV vaccine in adults less than 45 years of age.

Method: Four phase 3 studies assessing kinetics of seroprotection rates (SPR; % of subjects with anti-HBs ≥ 10 mIU/ml) in healthy adults aged 18–45 years, vaccinated at months 0, 1 and 6 with 10 μ g of a 3-antigen HBV vaccine (3A-HBV) vs. 20 μ g of a single-antigen HBV vaccine, Engerix-B® (1A-HBV), were completed between 2008 and 2020: (1) PROTECT study in Europe, U.S., and Canada, subset age 18–44, $n = 299$; (2) CONSTANT study in Europe, U.S., and Canada, $n = 2,838$; (3) SG-005-05 study in Vietnam, $n = 379$; (4) 38-13-040 study in Russia, $n = 99$. Additionally, one phase 4, open-label single-arm study (SciB018) was conducted with 10 μ g of 3A-HBV in adults aged 20–40 years in Israel, $n = 91$.

Results: In these 5 studies of healthy, young adults age 18–45 years, vaccination with 3A-HBV achieved a more rapid onset of protection compared to 1A-HBV, with SPRs of 87.2–100.0% (vs. 39.0–89.4%) after 2 doses and 99.2–100.0% (91.1–98.3%) after 3 doses (Figure 1). Rates of mild or moderate injection site pain and tenderness, and myalgia were higher for 3A-HBV than 1A-HBV. No new or unexpected safety signals were observed, and safety and tolerability were consistent with the known profile of study vaccines.

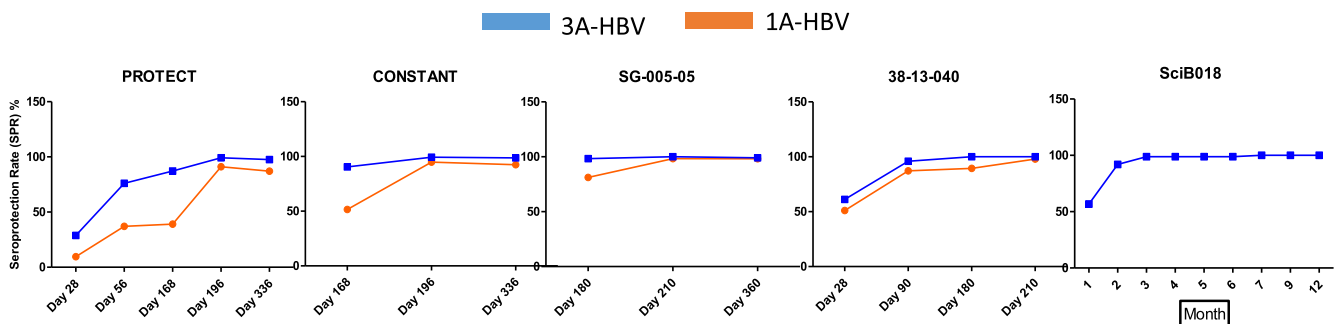


Figure 1: (abstract: PO-420)

Conclusion: The 3-antigen prophylactic HBV vaccine rapidly and consistently achieved high rates of seroprotection against hepatitis B in young and healthy adults in multiple clinical studies conducted across different regions of the world.

PO-460

Persistent High HBsAg Levels Predict Lower Risk of Hepatocellular Carcinoma in HBeAg-seropositive Chronic Hepatitis B Patients

Hsin-Che Lin^{1,2}, Rachel Wen-Juei Jeng^{3,4}, Jessica Liu¹, Mei-Hsuan Lee⁵, Richard Batrla-Utermann⁶, Sheng-Nan Lu⁷, Li-Yu Wang⁸, San-Lin You⁹, Chien-Jen Chen¹, Hwai-I Yang¹. ¹Academia Sinica, Genomics Research Center, Taipei, Taiwan; ²Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; ³Linkou Chang Gung Memorial Hospital, Department of Gastroenterology and Hepatology, Taoyuan, Taiwan; ⁴Chang Gung University, College of Medicine, Taiwan; ⁵National Yang-Ming University, Institute of Clinical Medicine, Taiwan; ⁶Roche, Bau 663, Diagnostics, Basel, Switzerland; ⁷Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ⁸Mackay Medical College, Taiwan; ⁹Fu Jen Catholic University, Department of Public Health, College of Medicine, Taiwan

Background and aims: The longitudinal changes of HBsAg level (qHBsAg) and the application in HBeAg positive patients for prediction of hepatocellular carcinoma (HCC) development remain to be studied. Our study aimed to investigate the association between qHBsAg trajectory and risk of HCC in HBeAg positive chronic hepatitis B (CHB) patients.

Method: HBeAg positive CHB patients from the REVEAL-HBV cohort (N = 524) who had 2 or more qHBsAg measurements before HBeAg clearance were included. Group-based trajectory modeling (GBTM) was used to identify distinctive groups of longitudinal qHBsAg up to 11-years of follow-up. Serum qHBsAg was measured using Roche Elecsys HBsAg II quant assay (range, 0.05–52,000 IU/ml; Roche Diagnostics, Mannheim, Germany). Development of HCC was ascertained by follow-up examinations and computerized data linkage with National Cancer Registry and National Death Certification profiles. Multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models. Statistic procedures were performed with SAS 9.4. A P value less than .05 was considered statistically significant.

Results: A total of 319 HBeAg positive patients who remained HBeAg positive throughout the follow-up duration were included and 9 groups were classified through GBTM. Four groups with less than 5 patients were excluded for further analysis. Remaining groups were then divided into (A) Persistently high group: HBsAg levels persistently >10⁴ IU/ml without decline (n = 72), (B) Declining group: low HBsAg levels at baseline or HBsAg level declining to <10⁴ IU/ml during observation period (n = 233). Age at baseline, sex and observation duration showed no difference between these two groups, while percentage of abnormal ALT level, genotype C and basal core mutation were significantly higher in declining group (p < 0.05). The annual incidence of HCC in persistently high HBsAg group and declining HBsAg group were 0.37% and 1.16%, respectively (p = 0.03). Univariate analysis showed baseline age over 40, abnormal ALT level and declining HBsAg group were associated with higher risk of subsequent development of HCC. In the multivariate analysis, age over 40 [HR: 4.4 (2.5–7.9), p = <.001], abnormal ALT level [HR: 2.7 (1.4–5.1), p = <.001] and declining HBsAg group [HR: 2.6 (1.1–6.1), p = 0.03] were confirmed to be independent predictors of following development of HCC.

Figure:

Univariate/Multivariate Analysis of HCC Risk in HBeAg-Positive Patients						
	Univariate Analysis			Multivariate Analysis		
	HR	CI	P value	HR	CI	P value
Age						
≥40	4.48	2.51–7.99	<.001	4.43	2.48–7.90	<.001
<40						
ALT						
Abnormal	2.95	1.65–5.26	<.001	2.73	1.44–5.15	<.001
Normal						
HBsAg						
Persistent high						
Declining group	3.31	1.43–7.68	<.001	2.60	1.11–6.09	0.03

Conclusion: A group of HBeAg positive patients with lower HCC risk could be identified by their persistently high HBsAg levels through repeated monitoring.

PO-529

Clinical importance of a new, high-sensitivity HBcrAg assay for monitoring chronic hepatitis B and HBV reactivation

Takako Inoue¹, Shigeru Kusumoto², Etsuko Iio³, Shintaro Ogawa³, Takanori Suzuki⁴, Shintaro Yagi⁵, Atsushi Kaneko⁶, Kentaro Matsuura⁴, Katsumi Aoyagi⁶, Yasuhito Tanaka⁷. ¹Nagoya City University Hospital, Department of Clinical Laboratory Medicine, Japan; ²Nagoya City University Graduate School of Medical Sciences, Department of Hematology and Oncology, Japan; ³Nagoya City University Graduate School of Medical Sciences, Department of Virology and Liver Unit, Japan; ⁴Nagoya City University Graduate School of Medical Sciences, Department of Gastroenterology and Metabolism, Japan; ⁵Advanced Life Science Institute, Inc., Research and Development Department, Japan; ⁶Fujirebio Inc., Research and Development Division, Japan; ⁷Kumamoto University, Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Japan
Email: tinoue@fg8.so-net.ne.jp

Background and aims: Hepatitis B core-related antigen (HBcrAg) is one of the useful biomarkers that have an important role in chronic hepatitis B (CHB). A fully automated high-sensitive chemiluminescent enzyme immunoassay for detection of HBcrAg has been newly developing in Japan. Our aims of this study are to demonstrate the clinical utility of new HBcrAg assay for monitoring CHB and early detection of hepatitis B virus (HBV) reactivation.

Method: A new high-sensitive HBcrAg assay (iTACT-HBcrAg, Fujirebio, Inc., Figure) is more inexpensive than HBV DNA test, and can measure HBcrAg within 30 minutes. The sensitivity of iTACT-HBcrAg (2.1 Log IU/ml) is approximately 10-fold higher than that of a conventional HBcrAg assay (G-HBcrAg) (2.8 Log IU/ml). The fundamental assessment of iTACT-HBcrAg was satisfactory. The clinical performance of iTACT-HBcrAg was compared with other HBV markers. 1) Of our CHB patients, serial sera, available from 161 HBeAg-negative CHB patients with persistently undetectable HBV DNA, were measured by iTACT-HBcrAg and G-HBcrAg. 2) Serial sera from 13 HBV-reactivated patients were measured by iTACT-HBcrAg and ultra-high-sensitivity hepatitis B surface antigen (HBsAg) immune complex transfer-chemiluminescent enzyme immunoassay (lower limit of detection; 0.0005 IU/ml, ICT-CLEIA) for comparison with HBV DNA detection. The study protocol was approved by the appropriate institutional ethics review committees.

Results: 1) At the last visit where HBV DNA was undetectable in 161 NA-treated patients, HBcrAg was detectable by G-HBcrAg in the sera of 75.2% (121/161) patients and detectable by iTACT-HBcrAg in the sera of 97.5% (157/161) patients; that is, 75.2% (121/161) patients had ≥2.8 Log U/ml and were detectable by G-HBcrAg, and 22.4% (36/161) patients had 2.1–2.8 Log U/ml, which were undetectable by G-HBcrAg.

POSTER PRESENTATIONS

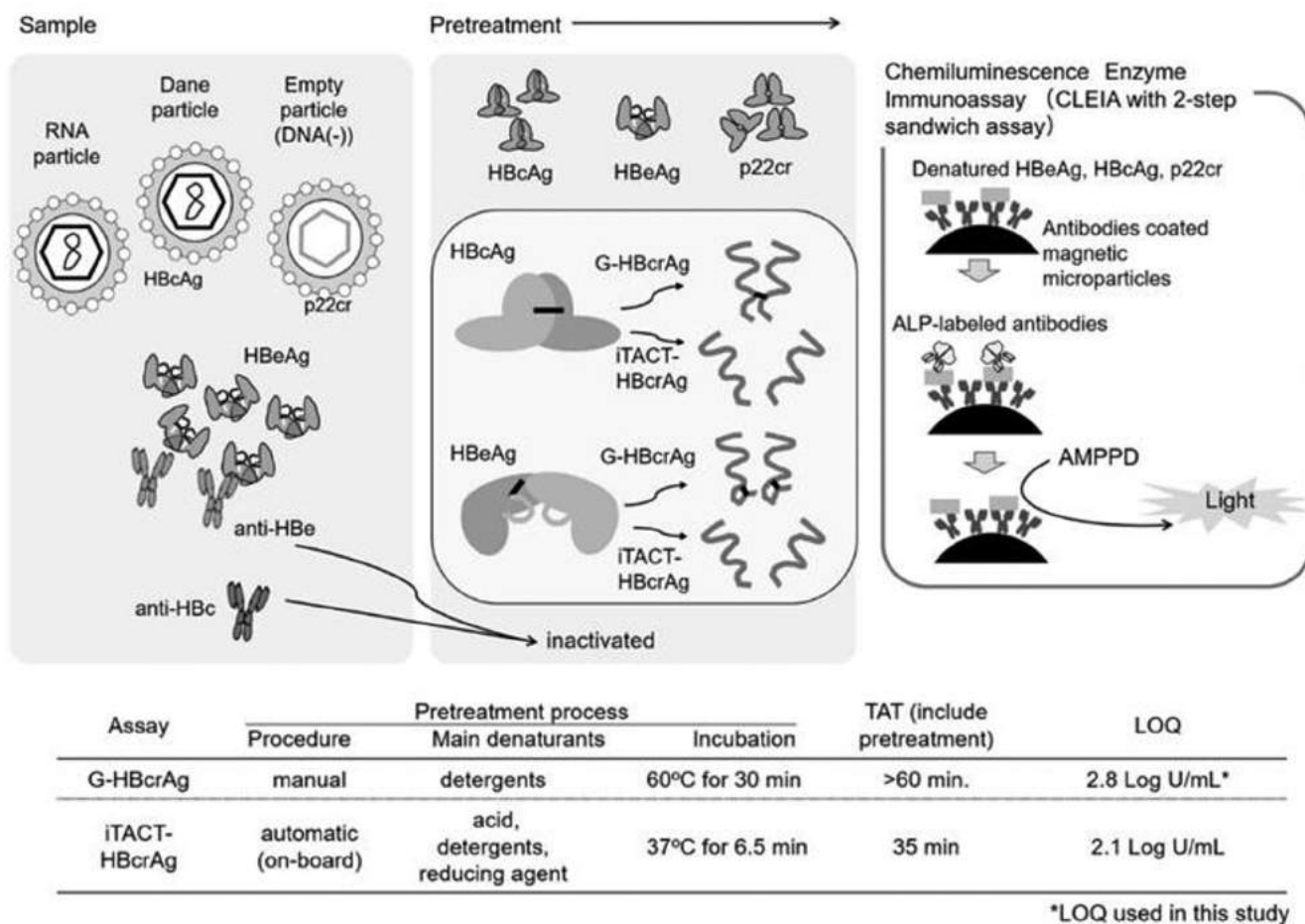


Figure: (abstract: PO-529)

2) In our HBV-reactivated patients, the primary diseases were hematologic malignancies (10 patients), benign hematologic disease, autoimmune disease and solid cancer (1 patient each). Nine and 2 of 13 HBV-reactivated patients were HBcrAg-positive by iFACT-HBcrAg before and at HBV DNA positivity, respectively. Seven and 4 were HBcrAg-positive by iFACT-HBcrAg before and at being HBsAg-positive by ICT-CLEIA, respectively.

Conclusion: iFACT-HBcrAg should be of increased benefit for monitoring anti-HBV treatments for HBeAg-negative patients and HBV reactivation at early phase.

PO-665

Transcriptomic analyses reveal variation of liver inflammation across phases of chronic hepatitis B infection

Ricardo Ramirez¹, Noe Montanari², Nicholas Van Buuren¹, Michael Doukas², Abhishek Aggarwal¹, Christina Moon¹, Scott Turner¹, Lauri Diehl¹, Li Li¹, Andre Boonstra², Becket Feierbach¹.
¹Gilead Sciences, Inc., Foster City, United States; ²Erasmus MC, Rotterdam, Netherlands
 Email: ricardo.ramirez@gilead.com

Background and aims: Chronic Hepatitis B (CHB) disease stages are based on serum measurements of HBeAg, viral load, and ALT. With the potential use of immune modulators for HBV cure, understanding the landscape of liver inflammation across CHB disease phases may help identify key patient populations. Though ALT is a useful marker of liver damage, it is an indirect measurement of liver inflammation. To delineate the patterns of inflammation found in CHB patients, we present a transcriptomic analysis of HBV infected liver biopsies

representing the four stages of natural history as well as comorbidities: fibrosis, non-alcoholic steatohepatitis (NASH), and Hepatitis D Virus (HDV) infection.

Method: RNA-Seq was performed on 103 FFPE core needle liver biopsies from 94 CHB patients and 9 healthy liver donors for cell type deconvolution and gene set analyses by EPIC and GSVA, respectively. The HBV biopsy set includes 15 immune tolerant (IT), 16 immune active (IA), 23 inactive carrier (IC), 17 HBeAg negative (ENEG), 5 fibrotic, 10 NASH, and 8 HDV samples. IT and healthy samples were re-sequenced using a novel whole exome plus HBV targeted sequencing assay. In addition, we imaged 39 corresponding biopsies using a custom 12-plex immunofluorescent assay (Ultivue InSituPlex).

Results: Although Healthy and IT liver transcriptomes clustered together, cell deconvolution found a significant increase in B-cell and T-cell estimates within the IT. IA, IC, and ENEG cohorts all showed an additional increase in B-cell, T-cell, and monocyte gene markers as compared to the IT group. IFN, TNF and IL-6 signaling pathways were significantly upregulated in chronic hepatitis (IA, ENEG) but not in chronic infection (IT, IC) samples. There was no significant correlation between liver HBV mRNA and immune cell estimates. HBV/HDV samples had the highest activity of the cytokine signaling pathways and immune cell content.

Conclusion: Our dataset represents the most comprehensive view of CHB, with samples from healthy livers, all phases of HBV chronic infection, and HBV combined with additional liver disease. All phases tend to have higher inflammation than healthy livers. Though characterized by low ALT levels, biopsies from IT and IC patients present gene signatures indicative of immune cell infiltration. HDV/

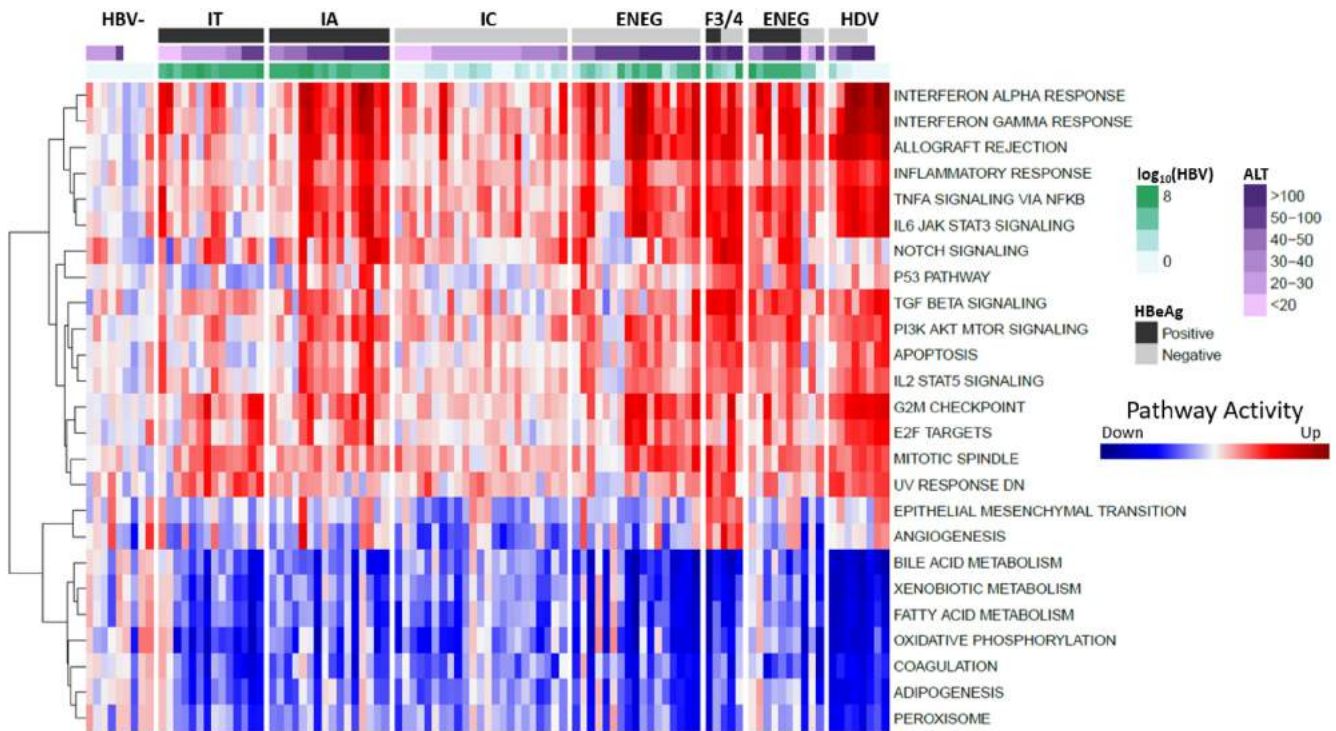


Figure: (abstract: PO-665)

HBV co-infection results in significant inflammatory disease, potentially exceeding inflammation caused by HBV infection combined with fibrosis or steatosis.

PO-676
An episode of detectable serum hepatitis B virus-DNA level does not affect risk of hepatic decompensation among untreated compensated cirrhosis patient with viral load of <2,000 IU/ml

Hye Won Lee¹, Soo Young Park², Yu Rim Lee², Jae Seung Lee¹, Seung Up Kim¹, Jun Yong Park¹, Do Young Kim¹, Sang Hoon Ahn¹, Beom Kyung Kim¹. ¹Yonsei University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; ²Kyungpook National University, Department of Internal Medicine, Daegu, Korea, Rep. of South
 Email: beomkkim@yuhs.ac

Background and aims: Whether antiviral therapy (AVT) is necessary for hepatitis B virus (HBV)-infected compensated cirrhosis patients with low-level viremia (LLV) is still controversial. Herein, we evaluated their natural history.

Method: From three academic teaching hospitals, we enrolled untreated compensated cirrhosis patients having persistently serum HBV-DNA <2,000 IU/ml; LLV group was defined as patients having detectable serum HBV-DNA (20~2,000 IU/ml) episode at least one time, whereas maintained virological response (MVR) group as remaining patients having persistently undetectable serum HBV-DNA (<20 IU/ml) during the whole follow-up. In case of serum HBV-DNA ≥2,000 IU/ml, AVT was commenced. The study end point was development of cirrhotic complication event (CCE) such as ascites, spontaneous bacterial peritonitis, hepato-renal syndrome, variceal hemorrhage, hepatic encephalopathy, deterioration of liver function into Child-Pugh class B, and liver transplantation.

Results: Among 567 patients finally analyzed, all belonged to Child-Pugh class A. Cumulative CCE risks at 1, 3, 5, and 7 years were also comparable between LLV (n=391) and MVR (n=176) groups; 2.2%, 7.5%, 12.8%, and 13.7% vs. 2.4%, 7.8%, 12.3%, and 14.6%, respectively (p=0.880). After adjusting for other key variables, LLV (vs. MVR) group was not associated with CCE risk with adjusted hazard ratio (HR) of 1.290 (95% confidence interval [CI] 0.712~2.338; p=0.402). Through

inverse probability of treatment weighting analysis, similar outcome was also re-produced with p=0.767; those of LLV vs. MVR groups at 1, 3, 5, and 7 years were 3.2%, 8.1%, 10.9%, and 10.9% vs. 3.1%, 7.2%, 12.8%, and 13.9%, respectively (HR 1.097, 95% CI 0.534~2.254; p=0.801).

Conclusion: An instantaneous LLV episode among untreated patients with compensated cirrhosis does not increase the risk of hepatic decompensation, compared to MVR status. Thus, the benefit from prompt AVT for such a LLV group should be re-evaluated.

Key words: Compensated cirrhosis, hepatitis B virus, low-level viremia, decompensation, antiviral therapy

PO-813
Prognosis of severe HBV reactivation in Western countries: role of the MELD score

Edoardo Poli¹, Isaac Ruiz², Lucy Meunier³, Jérôme Dumortier⁴, Lucia Parlati⁵, Paul Carrier⁶, Nicolas Carbonell⁷, Benjamin Buchard⁸, Carmen Vinaixa⁹, Ilias Kounis¹, Lea Duhaut¹, Rodolphe Sobesky¹, Eleonora De Martin¹, Bruno Roche¹, Philippe Ichai¹⁰, Anne Marie Roque-Afonso¹¹, Didier Samuel¹, Audrey Coilly¹. ¹Centre Hépatobiliaire, Paul Brousse Hospital, Hepatology, Villejuif, France; ²Centre Hospitalier de l'Université de Montréal, Hepatology and Liver Transplantation, Montréal, Canada; ³CHU Montpellier-Hôpital Saint Eloi, Pôle Digestif, Montpellier, France; ⁴Hospices Civils de Lyon, Hepatology, Lyon, France; ⁵Hôpital Cochin, Hepatology, Paris, France; ⁶CHU Dupuytren, Hepatology and Gastroenterology, Limoges, France; ⁷Hôpital Saint Antoine, Hepatology and Gastroenterology, Paris, France; ⁸CHU Estaing, Hepatology and Gastroenterology, Clermont-Ferrand, France; ⁹Hospital Universitari i Politècnic la Fe, Hepatology and Gastroenterology, Valencia, Spain; ¹⁰Centre Hépatobiliaire, Paul Brousse Hospital, Intensive Care Unit, Villejuif, France; ¹¹Centre Hépatobiliaire, Paul Brousse Hospital, Virology, Villejuif, France
 Email: edoardo.poli88@gmail.com

Background and aims: Severe reactivation of hepatitis B virus (HBV) can lead to death or liver transplantation. While trigger events are quite well understood, prognostic factors for short-term liver transplant (LT) -free survival in these patients, particularly in Western countries, are poorly known. MELD score has been

POSTER PRESENTATIONS

demonstrated to be an interesting prognostic score in an Asian cohort, but a “grey zone” of patients with MELD between 28 and 32 still represent a challenge for the indication and the timing of an urgent LT (Fung J. Hepatology 2020).

Method: All patients hospitalized for HBV reactivation with a viral load ≥ 4 log IU/ml between January 2014 and April 2020 were included in this retrospective multicenter study. Patients with other causes of ACLF were excluded. The primary outcome was to determine factors associated with 12-week risk of death or need for LT.

Results: Sixty-one patients have been included in our study, 47 (77%) males with a median age of 51 years (IQR 40–62), 15 (25%) presenting an extensive hepatic fibrosis ($\geq F3$) at liver biopsy. Trigger events for HBV reactivation have been identified in 41 (67%) patients. During hospitalization, 17 (28%) patients developed hepatic encephalopathy and 20 (33%) have been transferred to an ICU. On admission, mean HBV serum viral load was 6.94 log IU/ml (IQR 5.85–7.96). All patients have been treated with tenofovir (72%) or entecavir (28%). Median follow-up was of 847 days (IQR 305–1440) and overall LT-free survival was of 46%. The 12-week LT-free survival was of 62%, 8 patients died and 15 were transplanted because of hepatic failure within 12 weeks.

Univariate analysis is shown in table 1. At multivariate analysis, MELD score of admission was associated with a higher risk of death or need of LT within 12 weeks (HR 1.13, CI 1.07–1.20; $p < 0.001$).

The AUC of MELD score to predict 12-week mortality or need for LT was 0.757. Mortality or need for LT at 12 weeks was low (<20%) for MELD ≤ 20 and high (>70%) for MELD ≥ 25 , with a “grey zone” for patients having a MELD = 20–25.

Table:

	Overall cohort n = 61	Transplanted or dead within 12 weeks n = 23	Survivors at 12 weeks without LT n = 38	p
Gender, males	47 (77)	19 (83)	28 (74)	0.420
Age, years	51 (40–62)	57 (50–64)	46 (36–59)	0.054
MELD score	20.1 (16.0– 25.6)	25.6 (20.3– 31.0)	17.3 (14.0– 23.0)	<0.001
ALT, IU/L	1057 (393– 2563)	607 (298– 1352)	1260 (807– 2718)	0.068
Admission HBV DNA, log IU/ml	6.94 (5.85– 7.96)	7.51 (5.87– 8.15)	6.69 (5.69– 7.64)	0.250
Intensive care unit HE during hospitalization	20 (33)	16 (70)	4 (11)	<0.001
Ascites during hospitalization	17 (28)	16 (70)	1 (3)	<0.001
	14 (23)	10 (43)	4 (11)	0.003

Conclusion: Our study confirm that admission MELD score can predict the short-term mortality and need for LT in patients with severe HBV reactivation, with lower thresholds in Western countries compared to an Asian cohort. Patients with MELD ≥ 25 should be evaluated for LT.

PO-915

METABOLIC dysfunction associated FATTY LIVER disease and adverse clinical outcomes in patients with CHRONIC HEPATITIS B

Laurens van Kleef¹, Hannah S.J. Choi², Willem Pieter Brouwer¹, Bettina Hansen², Keyur Patel², Robert De Man¹, Harry Janssen², Robert De Nègret¹, Milan Sonneveld¹. ¹Erasmus MC, University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands;

²Toronto General Hospital, University Health Network, Toronto Center for Liver Disease, Toronto, Canada

Email: laurensvankeef@gmail.com

Background and aims: A recent consensus document has defined metabolic dysfunction associated fatty liver disease (MAFLD) as hepatic steatosis together with overweight, diabetes and/or a

combination of other metabolic risk factors. The prevalence and clinical relevance of this novel diagnosis is unknown among patients with chronic hepatitis B (CHB). We therefore studied the association between presence of MAFLD (with or without steatohepatitis) and adverse clinical outcomes in patients with CHB.

Method: We performed a retrospective, long term follow-up cohort study at two tertiary hospitals. All consecutive patients with CHB who underwent liver biopsy were enrolled. Biopsies were reassessed for the presence of steatosis, degree of fibrosis and presence of steatohepatitis (based on NAFLD activity score ≥ 3 and/or histopathologist interpretation). Patients were classified as no fatty liver disease, fatty liver disease without metabolic dysfunction, and MAFLD with or without steatohepatitis and associations with event-free hepatocellular carcinoma (HCC)-free and transplant-free survival were explored.

Results: We analyzed 1076 CHB patients of whom 296 (27.5%) had MAFLD. Median follow-up was 9.8 years (IQR: 6.6–14.0) and 107 events occurred in 78 patients, comprising death (n = 43), HCC (n = 36), liver decompensation (n = 21) and liver transplantation (n = 7). Patients with superimposed MAFLD had reduced event free ($p < 0.001$, figure), HCC free ($p < 0.001$) and transplant free survival ($p < 0.001$), and findings were consistent in multivariate analysis after adjusting for age, gender, HBeAg status, advanced fibrosis at enrolment and antiviral treatment. Among patients with MAFLD, presence of steatohepatitis did not increase the risk of adverse outcomes ($p = 0.21$ –0.95). Among patients without MAFLD, presence of fatty liver disease was not associated with reduced event free survival when compared to patients without fatty liver disease ($p = 0.56$).

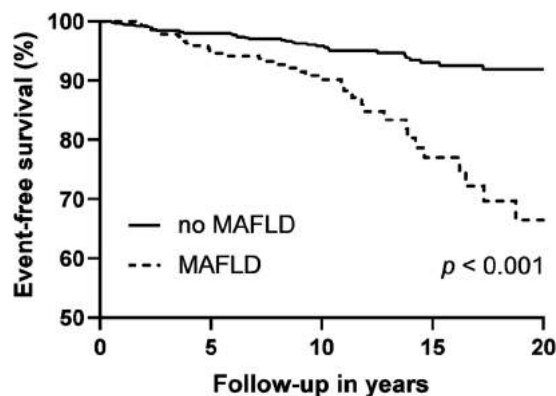


Figure 1. Association of MAFLD with event-free survival (Kaplan-Meier).

Conclusion: In this multicenter study, presence of MAFLD in CHB patients was associated with an increased risk for liver related clinical events and death. Concomitant presence of steatohepatitis did not increase the risk of adverse outcomes. Our findings highlight the importance of metabolic health in patients with CHB and suggest that the prognostic value of a liver biopsy to assess presence of steatohepatitis among patients with MAFLD may need to be reassessed.

PO-947

Immunogenetic diversity predicts viral control in chronic HBV (CHB) patients after discontinuation of direct antiviral treatment

Marianne Tuefferd¹, Marjolein Crabbe², Tsung-Hui Hu³, Chi-Yi Chen⁴, Rong-Nan Chien⁵, Wei Kuo-Liang⁶, Cheng-Yuan Peng⁷, Wan-Long Chuang⁸, Wei-Wen Su⁹, Liang Kung-Hao^{10,11}, Anna Shen¹², Yu-Shuang Lin¹², Alessandro Di Cara¹³, Jacques Bollekens¹⁴, Chau-Ting Yeh¹¹, Kurt Spittaels¹⁴, Jeroen Aerssens¹. ¹Janssen

Pharmaceutica, Johnson and Johnson Pharmaceutical Research and Development, Infectious Diseases Biomarker, Beerse, Belgium; ²Janssen Pharmaceutica, Johnson and Johnson Pharmaceutical Research and Development, Quantitative Sciences, Beerse, Belgium; ³Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ⁴Chia-Yi Christian Hospital, Chia-Yi, Taiwan; ⁵Linkou Chang Gung Memorial Hospital and University, Taoyuan, Taiwan; ⁶Chiayi Chang-Gung Memorial Hospital, Chiayi, Taiwan; ⁷China Medical University Hospital, Taichung, Taiwan; ⁸Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ⁹Chang-Hua Christian Hospital, Chang-Hua, Taiwan; ¹⁰Taipei Veterans General Hospital, Medical Research Department, Taipei, Taiwan; ¹¹Chang Gung Memorial Hospital, Liver Research Center, Linkou, Taiwan; ¹²Janssen Pharmaceutica, Johnson and Johnson Pharmaceutical Research and Development, Taipei, Taiwan, ¹³QuartzBio, part of Precision for Medicine, Geneva, Switzerland; ¹⁴Janssen Pharmaceutica, Johnson and Johnson Pharmaceutical Research and Development, Infectious Diseases, Translational Medicine, Beerse, Belgium
Email: mtueffe1@its.jnj.com

Background and aims: Importance of specific human leukocyte antigen (HLA) genotypes as risk factor for many disease-related traits has been well investigated. Recently, it was shown that higher HLA genetic diversity may positively influence cancer immunotherapy efficacy and HIV-1 control. Here we studied whether the genetic build-up of the HLA region in chronic hepatitis B patients (CHB) may predict viral control after discontinuation of direct antiviral treatment.

Method: A multi-center, prospective study enrolled 186 CHB patients in their last year treatment regimen with direct antivirals that were followed for up to 2 years after treatment discontinuation. Virological relapse (VR) was defined as HBV DNA ≥ 2000 IU/ml. Clinical relapse (CR) was defined as VR with serum ALT ≥ 80 IU/L. Sustained clinical response (SCR) was defined as absence of VR during the entire follow-up period. DNA samples were collected for HLA-typing. Beside allelic association, HLA evolutionary divergence (HED) score (Pierini et al., MBE, 2018), considering the influence of allele diversity on amino-acid composition, was derived.

Results: Of the cohort, 161 patients experienced VR of whom 110 also had a CR. Six patients experienced hepatic flare without VR, and 23 were considered as SCR. Allelic association revealed HLA-B*51, HLA-C*07 and HLA-C*15 alleles as predictive for onset of VR and SCR. No specific allele was associated with onset of CR. High HED score in both class I and class II regions were protective against early onset of VR and CR and predictive for SCR. Performance of the regression models was improved when adding immunogenetic composite markers to established clinical covariates. For instance, odds ratios for contributors in a signature for SCR varied from 10.66 [3.01–44.42] (low HBsAg at treatment end) to 2.34 [0.36–14.12] (HLA-B*51 alleles), 7.68 [1.29–46.66] (HLA-C*15 alleles), 5.38 [1.51–21.62] (high HED score class I) and to 11.49 [3.08–57.35] (high HED score class II). The Receiver Operating Characteristic (ROC) curve AUC increased from 0.66 to 0.79 to predict onset of VR, from 0.67 to 0.70 to predict onset of CR, and from 0.67 to 0.89 to predict SCR.

Conclusion: The study shows the importance for the first time of HLA class I and the significance of high HLA evolutionary diversity for long term viral control in CHB patients. Host immunogenetic markers can be measured easily in clinic and are major contributors in predicting patient outcome when cessation of direct antiviral treatment is considered.

PO-1000

Association of Vitamin D receptor's CdX-2 polymorphism and related haplotypes in patients with chronic hepatitis B infection in the inactive carrier and chronic hepatitis phases: a case-control study

Prooksa Ananchuensook¹, Sirinporn Suksawatamnuay², Panarat Thaimai², Supachaya Sriphoosanaphan^{1,2}, Kessarinn Thanapirom^{1,2}, Piyawat Komolmit^{1,2}. ¹Chulalongkorn University, Thailand; ²King Chulalongkorn Memorial Hospital, Thailand
Email: prooksa.anan@gmail.com

Background and aims: Vitamin D receptor (VDR) partly regulates host immune system. The association between VDR polymorphisms and severe flare-up hepatitis, cirrhosis and hepatoma in patients with chronic HBV infection were reported in previous studies. Patients with HBV inactive carrier (IC) and chronic hepatitis (CH) phases shows different disease's natural history and risk of complications. We hypothesize that VDR polymorphisms initially influence the host immune status which represented two different phases and consequently leading to HBV-related events.

Method: Patients with chronic HBV infection were enrolled from February to August 2020. The IC phase was defined as HBV viral load (VL) $< 2,000$ IU/ml twice for six months apart, without a previous history of HBV treatment. The CH phase was defined as persistent HBV VL $> 2,000$ IU/ml with evidence of hepatic inflammation or fibrosis. Six common VDR genes' single nucleotide polymorphisms (SNP) including CdX-2, GATA, FokI, BsmI, ApaI, and TaqI, were studied using TaqMan real-time PCR assay. The difference in allele, genotype, and haplotype frequencies in between groups and linkage disequilibrium (LD) mapping were analyzed using a haplotype inference application.

Results: Among 324 enrolled patients, there were 163 and 161 patients in IC and CH respectively. The proportion of male patients is lower in IC (46.0% vs. 68.3%, $p < 0.001$). The mean vitamin D levels were not statistically different between groups. The proportion of alleles frequency of CdX-2 in IC and CH was 53.7% and 62.7% for G allele and 46.3% and 37.3% for A allele which was statistically significant ($p = 0.019$). The proportion of GG genotype of CdX-2 was less frequently found in IC compared to CH (27% vs 41%, $p = 0.028$). AA haplotype (CdX-2/GATA) and AAC haplotype (CdX-2/GATA/FokI) were significantly associated with IC with odd ratio (OR) 1.43, $p = 0.025$ and 1.98, $p < 0.001$ respectively. By multivariate analysis, CdX-2 G/A genotypes was independently associated with IC, with adjusted OR 1.83, $p = 0.019$. The SNPs' LD mapping revealed high LD scores of CdX-2/GATA and GATA/FokI only in CH group.

Figure: Univariate and multivariate analysis of factors associated with HBV inactive carrier (IC) phase.

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p value	OR (95%CI)	p value
Age	0.99 (0.96–1.02)	0.806		
Gender (male)	0.39 (0.25–0.62)	$< 0.001^*$	0.40 (0.25–0.63)	$< 0.001^*$
CdX-2 genotype				
G/G	–	0.029*	–	0.045*
G/A	1.84 (1.12–3.02)	0.016*	1.83 (1.10–3.04)	0.019*
A/A	1.98 (1.03–3.77)	0.038*	1.85 (0.95–3.58)	0.068
Vitamin D level	1.00 (0.98–1.02)	0.608		

*Significant p value

Conclusion: The results suggest that CdX-2 G/A genotypes was independently associated with IC status in Thai patients with chronic HBV infection. The difference in LD of the CdX-2/GATA and GATA/FokI haplotypes in between groups might represent a non-random selection in either group resulting in the variation of immune control.

POSTER PRESENTATIONS

PO-1115

Clinical aspect of coronavirus disease 2019 (COVID-19) on HBV infected patients in term of Health Insurance Review and Assessment service data

Young Kul Jung¹, Gi Hyen Seo², Tae Hyung Kim¹, Sun Young Yim³, Young-Sun Lee⁴, Ji Hoon Kim⁴, Yeon Seok Seo³, Hyung Joon Yim¹, Jong Eun Yeon⁴, Kwan Soo Byun⁴, Soon Ho Um³. ¹Korea University Ansan Hospital, Internal Medicine, Ansan-si, Korea, Rep. of South; ²Health Insurance Review and Assessment Service, Korea, Rep. of South; ³Korea University Anam Hospital, Korea, Rep. of South; ⁴Korea University Guro Hospital, Korea, Rep. of South
Email: 93cool@hanmail.net

Background and aims: Several reports announced chronic liver diseases and cirrhosis are risk factors for COVID (coronavirus disease)-19 infection and poor outcomes. However, there is no large data to report the specific clinical course of COVID-19 patients with chronic hepatitis B virus (HBV) infection. In this study, we aimed to report the clinical course of COVID-19 patients with HBV infection, to provide a reference for clinical treatment of the patients, and also to know whether the use of antiviral agents affects the clinical course.

Method: We performed a nationwide population-based cohort study using the Korean Health Insurance Review and Assessment database. Claim records were screened for 19,160 individuals who were diagnosed by the test of COVID-19 until November 2020.

Results: Of the 19,160 patients diagnosed with COVID-19, 675 (3.5%) patients had HBV infection. Among them, 138 (20.4%) patients were receiving antiviral therapy for the purpose of treating hepatitis B. The Mean age was 52.6 years for COVID-19 infection patients and 59.3 years for HBV infected patients; the HBV infected patients were elderly and showed higher rates of concomitant diseases such as diabetes, hypertension, and lung diseases compared with non-HBV infected patients ($p < 0.001$). During the observation period (about 10 months), 1,524 (8.2%) of overall COVID-19 patients died and 91 HBV-infected patients (13.5%) died of COVID-19 disease ($p < 0.001$). For 675 HBV-infected patients, the mean hospital stay was 19.9 days; of whom 85 patients (12.6%) were admitted to the intensive care unit, 13 patients (1.9%) had liver failure, 54 patients (8%) had acute respiratory failure, and 34 (5%) patients showed acute renal failure. When the overall risk of mortality was assessed for HBV-infected patients with antiviral drugs and without the antiviral drug, the Crude odds ratio (OR) was 1.72 (95% confidence interval (CI), 1.39–2.11), $P < 0.001$ and 1.96 (95%CI, 1.30–2.87; $p = 0.001$), respectively; which showed that the HBV-infected patients with or without the antiviral treatment had a higher risk of death when exposed to COVID-19. However, after age, sex, and comorbid diseases were corrected, the adjusted OR was 0.97 (95% CI, 0.76–1.23; $p = 0.823$) and 1.01 (95% CI, 0.63–1.59; $p = 0.952$), respectively, and these indicated no difference in mortality risk compared to other patients. In addition, there was no difference in intensive care unit admission rate or hospital stay length after correction.

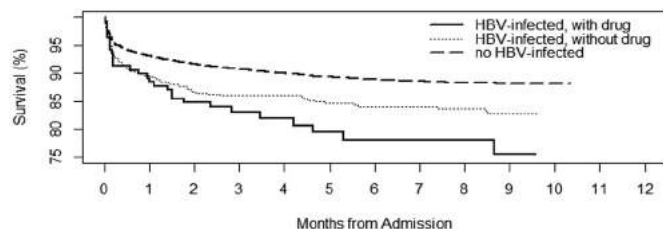


Figure:

Conclusion: In COVID-19 infected patients with chronic liver diseases or cirrhosis caused by HBV infection, they showed a slightly higher mortality rate than those without the diseases. However, in the case of patients treated with the antiviral agent for HBV infection, it can be seen that their mortality rate from COVID-19 does not increase further if there is no cirrhosis or other comorbidity.

PO-1257

Combination drug interactions of hepatitis B virus (HBV) small interfering RNA (siRNA) and antisense oligonucleotides (ASO) in vitro and in vivo

Hua Tan¹, Kang Hyunsoon¹, Yuchun Nie¹, Rajendra Pandey², John Cortez², Vivek Rajwanshi², David Smith², Lawrence Blatt², Leonid Beigelman², Julian Symons², Jin Hong². ¹Aligos Therapeutics, Virology, South San Francisco, United States; ²Aligos Therapeutics, South San Francisco, United States
Email: htan@aligos.com

Background and aims: Clinical studies have shown that siRNA's and ASO's targeting HBsAg knockdown are attractive therapeutic options for the treatment of chronic hepatitis B (CHB). We explored the combinations of an siRNA, ALG-125903 (unconjugated form of ALG-125755) and an ASO, ALG-020579 (unconjugated form of ALG-020572) in vitro in dual combinations with each other as well as with other anti-HBV agents such as nucleoside analogs (NA) and Capsid Assembly Modulators (CAM). We also explored the benefits of combining HBV siRNA (GalNac conjugated ALG-125755) and ASO (GalNac conjugated ALG-020572) constructs in the AAV-HBV model to maximize HBsAg reduction by utilizing their non-overlapping cellular pathways.

Method: In vitro combination studies were performed using the HepG2.2.15 cell line. ALG-125903 and ALG-020579 were transfected using RNAiMAX into cells in a checkerboard fashion and HBsAg in the supernatant was measured by ELISA (enzyme-linked immunosorbent assay) 4 days post transfection. ALG-125903 or ALG-020579 combinations with CAM and NA were tested similarly with secreted HBV DNA as the end point. Data were analyzed with MacSynergy II software. In vivo, ALG-125755 and ALG-020572 were administered subcutaneously (SC) in AAV-HBV mice as single agents as well as in combination. In the combination group, ALG-125755 was dosed as a single dose of 5 mg/kg on day 0 and ALG-020572 as repeat doses of 5 mg/kg on days 0, 7 and 14. Serial blood collections occurred every 5 days until day 60 for HBsAg ELISA and ALT assays.

Results: Combination of ALG-125903 and ALG-020579 in vitro exhibited minor synergy with a synergy volume of 46.01 mM²%. Combination of ALG-125755 and ALG-020572 in vivo demonstrated additive effects in HBsAg knockdown without change in serum ALT levels in mice. When tested in pairwise combinations with NA and CAM in vitro, HBV siRNA ALG-125903 or ASO ALG-020579 demonstrated significant synergy (synergy volume of >100 mM²%), synergy (25–100 mM²%) or additivity (0–25 mM²%), respectively. No antagonistic effects were observed.

Conclusion: The HBV siRNA, ALG-125755, in combination with the ASO, ALG-020572, demonstrated additive to minor synergy in vitro and in vivo. Further investigation of the strategy to combine HBV siRNA and ASO compounds in CHB clinical trials is warranted.

PO-1309

Alanine aminotransferase flares and seroclearance in chronic hepatitis B virus patients

Shahed Iqbal¹, Yuqing Zhang², Ruidong Li³, Vlad Malkov², Vithika Suri⁴, John Flaherty⁴, Anuj Gaggar⁴, Jeffrey Wallin¹. ¹Gilead Sciences, Inc., Biomarker Sciences, FOSTER CITY, United States; ²Gilead Sciences, Inc., Clinical Data Science, FOSTER CITY, United States; ³Gilead Sciences, Inc., Research Bioinformatics, FOSTER CITY, United States; ⁴Gilead Sciences, Inc., Clinical Research, FOSTER CITY, United States
Email: shahed.iqbal1@gilead.com

Background and aims: Steep increase in alanine aminotransferase (ALT flares) levels in chronic hepatitis B (CHB) patients have been found to be associated with declines in hepatitis B surface antigen (HBsAg) levels and seroclearance (SC). ALT flares can be a marker of immune response to therapy as well as a prognostic marker for CHB.

Method: Adult (≥ 18 years) CHB patients were identified from the IQVIA Ambulatory EMR database using International Classification of

Disease (ICD)(ICD 9: 070.22–23, 070.32–33 or ICD 10: B18.0, B18.1) or SNOMED (61977001) codes. Patients with HIV disease, cancer, long-term steroid use, chronic liver disease, other hepatitis virus infections, and those who were pregnant were excluded. ALT flares were defined as 5XULN (females: ≥ 125 IU/L, males: ≥ 175 IU/L). Patients with subsequent negative HBsAg tests or positive hepatitis B surface antibody tests were considered to have SC. Dispensing records provided information on approved hepatitis b antiviral use. Multivariate (age, sex, race, BMI, diabetes, cardiovascular disease) stepwise Cox proportional hazard models were used to determine association between ALT flares and SC by antiviral use.

Results: CHB patients (N = 12, 653) diagnosed between 2001–2020 were included (mean age: 49.7 years, 48% men). Patients included Caucasian (39%), Asian (27%), African American (10%) and other races (2%). Around 4% (n = 531) of patients had SC (median time to SC = 820 [121–4516] days) and 189 (1.5%) had ALT flares. Among those with flares, 17 (9.0%) had flares occurring prior to SC. Patients with ALT flares had shorter time to SC (median: 1.7 vs. 2.3 years) and had SC 2X more often when compared to those without flares (Odds Ratio [OR], 95% confidence interval [95% CI] = 2.3[1.4–3.8]). This association was significant in an adjusted model among CHB patients with antiviral use (Hazard Ratio [HR], 95% CI = 3.5[1.4–8.9]) but not among those without antiviral use (HR [95% CI] = 1.5[0.6–4.0]). Race, BMI, having diabetes, or cardiovascular disease were associated with SC (Table).

Table: Association between variables and seroclearance by antiviral use

Variable	Antiviral use (N = 2207)			No antiviral use (N = 10, 446)		
	HR	95% CI	p-value	HR	95% CI	p value
ALT flare	3.5	(1.4–8.9)	0.009	1.5	(0.6–4.0)	0.431
Age ≥ 45 vs. <45 years				1.6	(1.2–2.1)	0.002
BMI ≥ 30 vs. <30				1.5	(1.1–2.0)	0.003
African American vs. others				1.5	(1.1–2.0)	0.013
Caucasian vs. others	2.4	(1.3–4.5)	0.006			
Diabetes mellites				1.6	(1.2–2.3)	0.004

HR = Hazard Ratio; CI = Confidence Interval.

Conclusion: In this large cohort of CHB patients, ALT flares prior to SC were relatively uncommon. Whether antiviral use is associated with therapeutic flares in a subgroup of patients requires additional research. Further elucidation of underlying pathophysiology and role of other associated factors could provide insight to CHB disease progression and functional cure.

PO-1340

Association between chronic hepatitis B infection and COVID-19: A nationwide case-control study

Seong Hee Kang¹, Han Seul Ki¹, Moon Young Kim¹, Soon Koo Baik¹.
¹Yonsei University Wonju College of Medicine, Internal Medicine, Wonju, Korea, Rep. of South

Email: shkang14@yonsei.ac.kr

Background and aims: Few studies have reported the impact of coronavirus disease 2019 (COVID-19) in patients with chronic hepatitis B (CHB). We measured the association between underlying CHB and antiviral use with infection rates among patients who underwent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing.

Method: In total, 204, 418 patients >20 years old who were tested for SARS-CoV-2 between January and June 2020 were included. For each case patient with a positive SARS-CoV-2 test, random controls were selected from the target population who had been exposed to

someone with COVID-19 but had a negative SARS-CoV-2 test result. We merged claim-based data from the Korean National Health Insurance Service database collected January 1, 2015 and August 18, 2020. End points examined were SARS-CoV-2 infection rate and severe clinical outcomes of COVID-19.

Results: The proportion of underlying CHB was lower in COVID-19 positive patients (n = 267, 3.5%) than in COVID-19 negative controls (n = 2482, 5.4%). Underlying CHB was significantly associated with a lower SARS-CoV-2 positivity rate, after adjusting for comorbidities (adjusted odds ratio [aOR] 0.65; p < 0.001). Among patients with confirmed COVID-19, underlying CHB tended to confer a 66% greater risk of severe clinical outcomes of COVID-19, although this value was statistically insignificant. Antiviral agent treatment including tenofovir and entecavir was associated with a reduced SARS-CoV-2 positivity rate (aOR 0.49; p < 0.001), while treatment was not associated with severe clinical outcomes of COVID-19.

Conclusion: Patients with CHB who received antiviral agents had a reduced risk of SARS-CoV-2 infection, and no statistically significant indication that they experienced enhanced risk of severe clinical outcomes of COVID-19 was observed.

PO-1385

Risk of Hepatitis B Virus Reactivation in Patients Treated with PD-1 or PD-L1 Inhibitor for Non-Hepatocellular Cancer

Sun Yoo¹, Jonggi Choi¹, Danbi Lee¹, Ju Hyun Shim¹, Kang Mo Kim¹, Young-Suk Lim¹, Han Chu Lee¹.
¹Asan Medical Center, University of Ulsan College of Medicine, Department of Gastroenterology, Seoul, Korea, Rep. of South
Email: jkchoi0803@gmail.com

Background and aims: Hepatitis B virus (HBV) reactivation is a well-known complication of chronic hepatitis B (CHB) patients undergoing treatment with immunosuppressive agents or cytotoxic chemotherapy. However, the risk of HBV reactivation of Immune checkpoint inhibitors (ICIs) is not as well understood so far.

Method: This retrospective case series included non-hepatocellular carcinoma (HCC) cancer patients treated with ICIs who were referred to Asan Medical Center in Seoul, Korea, between January 1, 2015 and September 30, 2020. The primary outcome was the incidence of HBV reactivation.

Results: Among 102 Hepatitis B surface antigen (HBsAg) positive patients, 3 patients (2.9%) developed HBV reactivation with a median onset of 54 weeks (range, 38–141 weeks) after ICIs treatment. In all three cases, antiviral agent was not administered prior to ICI treatment. Two of them experienced grade 4 hepatitis and the other experienced grade 2 hepatitis due to HBV reactivation, and all three patients recovered to normal levels of liver function within median of 4 weeks (ranges, 1–6 weeks) after antiviral agent administration. No HBV related fatal outcome occurred.

Conclusion: HBV reactivation is a rare event in cancer patients treated with ICIs. No reactivation event was observed in patients who had antiviral prophylaxis prior to ICI treatment. No fatal hepatic adverse event occurred during ICI treatment. Therefore, with screening and regular monitoring for hepatitis B and antiviral prophylaxis, ICIs could be safely administered to cancer patients with HBV infection.

PO-1510

Serum markers of HBV cccDNA transcriptional activity-HBcAg and pre-genomic HBV RNA, pre-treatment HDV RNA and HDV genotype are useful markers in predicting treatment responses to pegylated interferon in HDV infection

Ivana Carey¹, Mark Anderson², Christiana Moigboi¹, Bo Wang¹, Gavin Cloherty², Geoffrey Dusheiko¹, Kosh Agarwal¹.
¹King's College Hospital, Institute of Liver Studies, London, United Kingdom; ²Abbott Diagnostics, Department of Infectious Diseases, Abbott Park, United States

Email: ivana.kraslova@kcl.ac.uk

Table 1: (abstract: PO-1385): Details of patients with HBV reactivation

Patient No.	Patient Characteristics				Baseline			At reactivation			Outcome		
	Age	Gender	Cancer type	ICIs type	HBeAg	HBV DNA (IU/ml)	Antiviral prophylaxis	Onset from first dose of ICIs (weeks)	HBV DNA (IU/ml)	Peak ALT (U/L)		Management	Antiviral treatment
1	55	M	Lung cancer	Pembrolizumab	Positive	Undetectable	No	54	3.9×10^6	1177	Delayed ICIs until LFT normalization	TDF	Normalized ALT and HBV DNA within 4 weeks
2	60	F	Ovarian cancer	Pembrolizumab	Negative	Undetectable	No	38	2.6×10^4	174	Maintained ICIs with antiviral treatment	TAF	Normalized ALT within 1 week
3	56	M	Renal cell carcinoma	Nivolumab + Ipilimumab	Positive	NA	No	141	3.8×10^6	1768	Delayed ICIs until LFT normalization	TDF	Normalized ALT and HBV DNA within 6 weeks

Abbreviations: HBV hepatitis B virus, HBeAg Hepatitis B e antigen, ICIs Immune checkpoint inhibitors, ALT alanine aminotransferase, LFT liver function test, TDF tenofovir disoproxil fumarate, TAF tenofovir alafenamide, NA not available

Background and aims: Hepatitis delta virus (HDV) requires HBsAg for propagation. A response to pegylated-interferon (Peg-IFN) treatment is achieved in less than 50% of patients, and unless HBsAg loss is achieved patients are at a risk of late HDV relapse. Novel serum biomarkers-HBcrAg and pre-genomic HBV RNA (pgRNA)-are non-invasive biomarkers that correlate with intrahepatic cccDNA transcriptional activity. The role of new biomarkers in predicting the response to Peg-IFN is not clear. We aimed to compare baseline and post treatment virological serum biomarkers (HBV DNA, HBsAg levels, HBcrAg and pgRNA concentrations, HDV genotypes and HDV RNA viral load) in HDV-positive responders versus non-responders (NR) to Peg-IFN.

Methods: Serum samples of 33 HDV RNA-positive patients (median age 38 yrs, 21 (63%) males, 2 (6%) HBeAg+, 12 (36%) with compensated cirrhosis) were tested at the start and 3 years after completing therapy for the following markers: HBsAg levels by Abbott Architect [IU/ml], HBV DNA by TaqMan Roche [IU/ml], HBcrAg by CLEIA Fujirebio [\log_{10} U/ml] and pgRNA by real-time PCR Abbott Molecular Diagnostic assay (LLQD = $1.65 \log_{10}$ U/ml), HDV RNA by in-house real-time PCR assay (LLQD = 640 copies/ml) and HDV genotypes by direct sequencing. FIB4 scores were calculated at the same time-points from biochemical and haematological results. The outcome was correlated with the concentrations of these biomarkers. All results are shown as medians.

Results: 3 years post Peg-IFN therapy, 15 (45%) patients were HDV RNA negative (responders), (2 patients with HBsAg loss), whereas 18 patients had detectable HDV RNA (NR). Age, HBV DNA (13 vs. 28 IU/ml, $p = 0.22$), HBsAg (6801 vs. 8326 IU/ml, $p = 0.16$) and FIB4 scores (1.42 vs. 1.54, $p = 0.2$) at baseline were similar in responders and NR. However, eventual responders had significantly lower HBcrAg (3.1 vs. 4.3, $p < 0.01$), pgRNA (1.7 vs. 2.3, $p = 0.04$) and HDV RNA (23, 300 vs. 671, 000, $p = 0.016$) levels at baseline than NR. Responders were less likely to have cirrhosis (13% vs. 55%, $p = 0.03$), were more likely male (87% vs. 53%, $p = 0.03$) and were infected with HDV genotype 5 (93% vs. 27%, $p < 0.01$). In NR, although HBV DNA, HBsAg and HDV RNA did not change significantly from the start of treatment, we observed a decline in HBcrAg (4.3 vs. 3.4, $p < 0.01$), pgRNA (2.3 vs. 1.72, $p < 0.01$) and FIB4 score (1.54 vs. 1.31, $p = 0.05$); in contrast HBsAg (6801 vs. 452, $p < 0.01$), as well as HBcrAg (3.1 vs. 2.2, $p < 0.01$), pgRNA (1.7 vs. 0, $p < 0.01$) and FIB4 (1.42 vs. 0.89, $p < 0.01$) reduced significantly in responders.

Conclusion: Lower baseline HDV RNA levels, HDV genotype 5 and lower concentrations of markers of cccDNA transcriptional activity were associated with response to Peg-IFN in HDV infection. Lower concentrations of markers of cccDNA transcriptional activity-HBcrAg and pg HBV RNA-may be of greater utility than HBsAg in differentiating the likelihood of long-term response in HDV infection.

PO-1519 Endoscopic surveillance of esophageal varices could be refined in HBV compensated cirrhotics taking Tenofovir or Entecavir: an 11-year real-life study

Elisa Farina^{1,2}, Alessandro Loglio¹, Giulia Tosetti¹, Mauro Viganò³, Carmine Gentile^{2,3}, Riccardo Perbellini¹, Marta Borghi¹, Floriana Facchetti¹, Sara Colonia Uceda Renteria⁴, Maria Grazia Rumi³, Massimo Primignani¹, Pietro Lampertico^{1,2}. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; ²Università degli Studi di Milano, CRC "A.M. e A. Migliavacca" per lo Studio e la Cura delle Malattie del Fegato, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Milan, Italy; ³San Giuseppe Hospital, Division of Hepatology, Milan, Italy; ⁴Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Virology Unit, Milan, Italy
Email: elisa.farina@unimi.it

Background and aims: Long-term effective oral therapies improve liver parameters in CHB patients, but the effect on esophageal varices (EV) changes is unknown. We evaluated the risk of EV development/

progression in HBV monoinfected compensated cirrhotics taking TDF/ETV in a real-life setting.

Method: 186 Caucasian HBV monoinfected, HCC-free, compensated cirrhotics without high-risk varices (HRV) were enrolled in a longitudinal study from TDF/ETV start to June 2020 (or liver-transplantation). Blood exams and abdominal US were performed every six months, endoscopy according to Baveno (every two or three years in patients without EV or with low risk EV (LRV), respectively). **Results:** At TDF/ETV start: 61 (21–83) years-old, 80% males, 60% HBV-DNA undetectable, 63% NUCs previously exposed, 73% normal ALT, 56% BMI >25 kg/m², 40% platelets <150,000/mm³, Liver stiffness 8.7 (2.5–60) kPa, spleen length 11 (7–20) cm, 25 (13%) with LRV. During 136 (26–170) months of TDF/ETV, all achieved virological response, 99% normalized ALT, 37 (20%) developed HCC, 4 (2%) non-neoplastic portal vein thrombosis. Overall, 666 endoscopies were performed, median 3 [2–7] per patient: the 11-year cumulative risk of EV development/progression was 5.1% (95%CI 3–10%); no patient bled. In 25 patients with LRV, EV disappeared in 11 (44%), remained stable in 12 (48%) and progressed to HRV in 2 (8%), after 17 and 77 months, post HCC diagnosis in the second case. Of 161 patients without EV, 7 (4%) developed LRV after 53 (24–67) months (3 concurrent to HCC, p < 0.001), but only 1 subsequently progressed to HRV at HCC onset (at the second follow-up endoscopy). In patients without EV at entry, baseline platelet count (HR 0.97, p=0.004) and spleen length (HR 1.34, p=0.032) were associated with LRV development at univariate analysis, only platelet count (HR 0.96, p=0.028) at multivariate analysis. Baseline platelet count ≤90,000/mm³ (AUROC 0.70) had 98.05% specificity, 42.86% sensitivity, 50% PPV, 97.42% NPV, accuracy 95.65% for LRV onset during NUC treatment. Overall, in patients without EV at NUCs start, none developed EV after two consecutive follow-up endoscopies.

Conclusion: In compensated HBV cirrhotics under TDF/ETV, the 11-year risk of developing/progressing EV is negligible, thus challenging the current surveillance rules in patients without EV at baseline.

PO-1605

Detection of novel biomarkers in HBV-associated chronic hepatitis, liver fibrosis/cirrhosis, and hepatocellular carcinoma utilizing transcriptome sequencing technology

Dandan Zhao¹, Wen Zhao¹, Lu Li¹, Liu Lingdi¹, Yuemin Nan¹. ¹Third Hospital of Hebei Medical University, Department of Traditional and Western Medical Hepatology, Shijiazhuang, China
Email: nanyuemin@163.com

Background and aims: The purpose of this study was to assess novel biomarkers in patients with chronic hepatitis B (CHB), HBV-associated Liver fibrosis (LF)/liver cirrhosis (LC), and HBV-associated hepatocellular carcinoma (HCC).

Method: Transcriptome sequencing technology of liver tissue was performed on 4 healthy controls, 5 patients with CHB, 5 patients with LF/LC and on 5 patients with HCC. By using bioinformatics analysis, the hub mRNAs were identified. Quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) and ELISA were then used to investigate the expression level of screened targets in the four groups.

Results: STEM analysis indicated that a total 25 mRNAs showed a gradually increasing trend in the group of healthy control, CHB, LF/LC and HCC; among them, by using WGCNA, the 9 hub mRNAs (SHC1, SLAMF8, IL32, ITGB2, MANF, TC2N, SYNPO, UGP2, EFEMP1) were identified. We used qRT-PCR in 5 liver tissue samples in each group to investigate the expression of selected mRNAs; which found 8 mRNAs showed the same trend. Then we utilized qRT-PCR in 80 PBMC samples and found 3 mRNAs (SHC1, SLAMF8, IL32) showed the same trend. Further validation with a retrospective cohort (n=200) by ELISA utilizing plasma showed that SHC1, SLAMF8 and IL32 levels were significantly higher in HCC patients (10.7 ng/ml, 8.4 ng/ml, 78.3 pg/ml, respectively) than in LF/LC patients (9.7 ng/ml, 7.0 ng/ml, 62.3 pg/ml, respectively), CHB patients (7.5 ng/ml, 6.1 ng/ml, 50.2 pg/ml, respectively), and healthy volunteers (4.4 ng/ml, 5.1 ng/ml,

32.3 pg/ml, respectively). ROC curve analysis revealed that plasma SHC1, SLAMF8 and IL32 could be used to differentiate HCC, LF/LC, CHB and healthy controls from each other. Further, a diagnostic model PSSI (PLT, SHC1, SLAMF8, IL32) was built to discern HCC from LF/LC with high accuracy (auROC = 0.976), LF/LC from CHB (auROC = 0.982), as well as CHB from healthy controls (auROC = 0.998).

Conclusion: In summary, our study has identified that SHC1, SLAMF8 and IL32 may serve as novel targets for the diagnosis of liver diseases. Moreover, the combination of PLT, SHC1, SLAMF8 and IL32 confers significant benefit to diagnostic accuracy in differentiating HCC from LF/LC, CHB, as well as healthy controls.

PO-1622

Efficacy of hepatitis B virus vaccines HBVaxpro40 and Fendrix in patients with chronic liver disease in clinical practice

Diana Horta¹, Anna Agusti², Montserrat Forne², Agnès Raga², Pablo Ruiz-Ramirez², Juana Maria Hernandez², Maria Esteve². ¹Hospital Universitario Mútua de Terrassa, Gastroenterology and Hepatology, Terrassa, Spain; ²Hospital Universitario Mútua de Terrassa, Terrassa
Email: diana.horta.s@gmail.com

Background and aims: Chronic liver disease results in a lower response rate to the hepatitis b virus (HBV) vaccine at the standard dose. The use of the adjuvanted vaccine Fendrix and adsorbed Vaxpro40 in chronic liver disease is scarce. Prospective observational study in clinical practice using HBVaxpro40 and Fendrix. Aims: 1) to evaluate the effectiveness of HBV vaccines HBVaxpro 40 and Fendrix in patients with chronic liver disease 2) to assess the kinetics of anti-HBs at six months.

Method: Non-cirrhotic and cirrhotic liver disease patients with HBV-negative serologic tests were prospectively included. Liver disease was assessed by abnormal liver blood tests (minimum 6 months), elastography, non-invasive markers of fibrosis, ultrasound and biopsy (when available). Patients were vaccinated with HBVaxpro 40 (0, 1 and 6 months) or Fendrix (0, 1, 2 and 6 months) depending on availability. Clinical, blood tests and anti-Hbs levels were collected at 2 and 6 months. A multivariate analysis was performed to evaluate variables associated to vaccine response. Classic response was defined as anti-HBs ≥10 IU/L and non-classic response as anti-HBs ≥100 IU/L.

Results: 103 patients were included (mean age 62.4 years; 56.3% males; 36.9 liver cirrhosis, 89.5% of whom were Child A). The aetiology of chronic liver disease was 33% alcohol, 27.2% metabolic, 23.3% virus c hepatitis and 16.5% autoimmune/primary biliary cholangitis. 73 patients were vaccinated with HBVaxpro40 and 30 with Fendrix. There were no significant differences between the two vaccines protocols. The overall response rate was 76.7% (anti-HBs ≥10 IU/L) and 56.2% (anti-HBs ≥100 IU/L). At six months, the overall response rate was 73.3% (anti-HBs ≥10 IU/L) and 46.5% (anti-HBs ≥100 IU/L). In the univariate analysis, male gender, cirrhosis and ultrasound signs of portal hypertension were associated with a lower response rate to vaccination.

In the multivariate analysis, liver cirrhosis increased 10.2 times the likelihood of non-response to the vaccine (OR, 10.2; 95% CI, 3.18–32.71; p < 0.001).

Vaccination response at two months

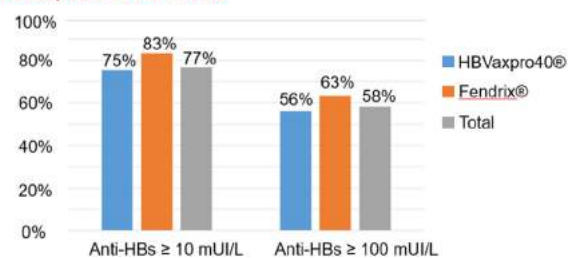


Figure 5:

POSTER PRESENTATIONS

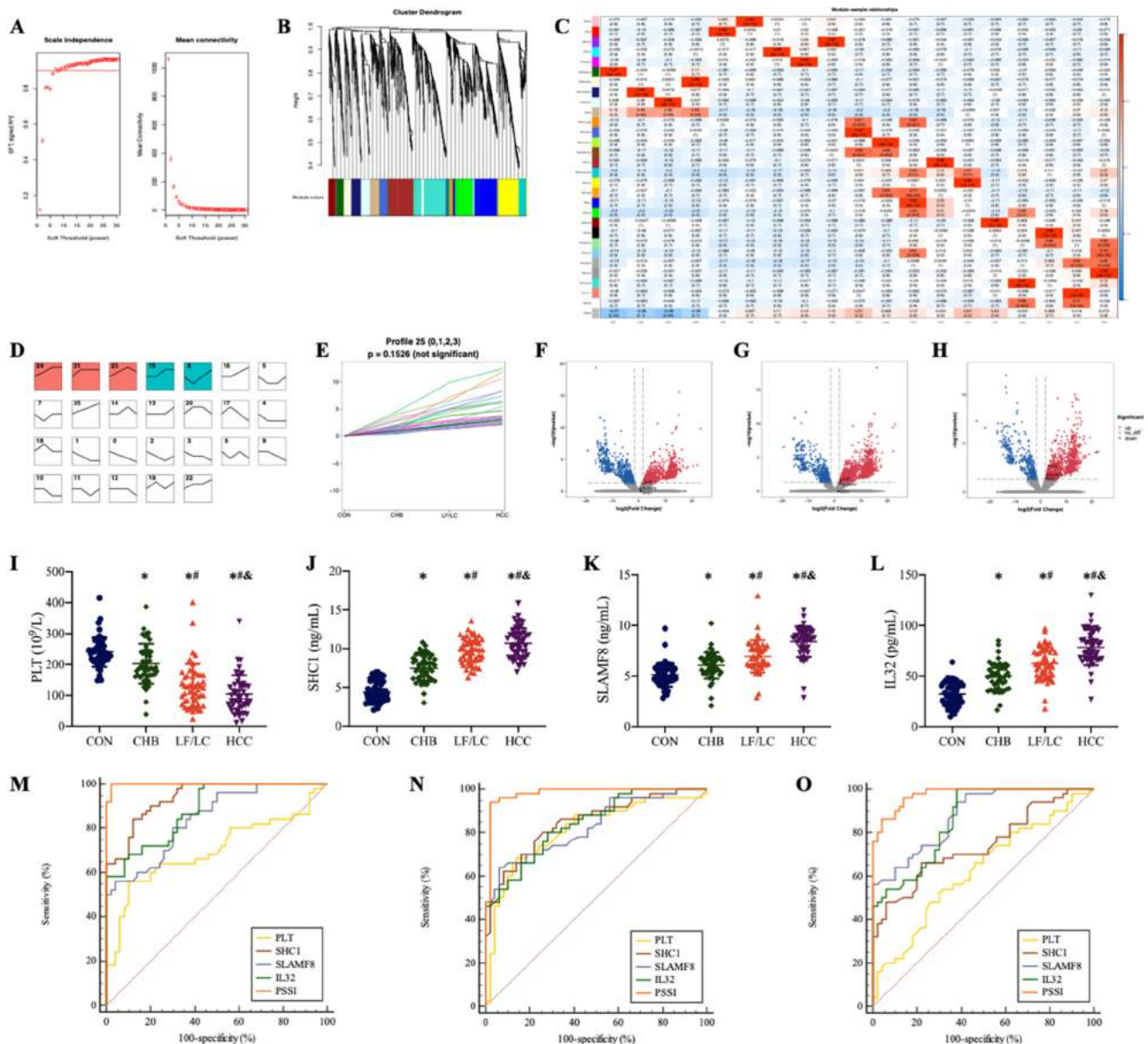


Figure: (abstract: PO-1605)

Conclusion: HBVaxpro40 and Fendrix are good HBV vaccinations in patients with chronic liver disease in early stages.

PO-1725

Health-related quality of life and stigma related to chronic hepatitis B: a systematic literature review

Vera Gielen¹, Stuart Kendrick¹, Rishabh Pandey², Ruchika Mittal², Kajal Thapa², Lee Evitt¹. ¹GlaxoSmithKline Research and Development, Brentford, London, United Kingdom; ²Parexel International, Bengaluru, India

Email: vera.x.gielen@gsk.com

Background and aims: Chronic hepatitis B (CHB) is associated with substantial morbidity and mortality burden. However, impact of health-related quality of life (HRQoL) is less well considered. Many factors including stigma may have an impact on HRQoL. A systematic literature review (SLR) was conducted to assess HRQoL, health utility values (HUVs; value given to a health state with '0' representing death; '1' perfect health) and impact of stigma in CHB.

Methods: SLR methodology was employed. Major databases (Embase; MEDLINE; Cochrane) were searched for literature published Jan-2004 to Feb-2020.

Results: Of 2385 abstracts reviewed, 104 studies were found to be relevant (HRQoL, n = 80; HUVs, n = 16; stigma, n = 22). Generic (e.g. SF-36; EQ-5D), liver-disease specific (CLDQ; LDSI; LDQOL) and hepatitis B specific instruments (HBQoL; HQLQ) were used. HBQoL was the most commonly used hepatitis B specific instrument. CHB patients with or without complications reported worse HRQoL for physical and emotional functioning, fatigue, worry and depression vs healthy participants. CHB patients with cirrhosis, liver transplant, and hepatocellular carcinoma (HCC) reported worse HRQoL vs patients without complications. CHB patients without complications had significant improvement in physical health and less improvement in vitality and mental health, emotional and social functioning with nucleos (t)ide analogues; no improvement was observed with interferon treatment. Mean HUVs (range) in states of CHB (carriers: 0.75–0.81; compensated cirrhosis: 0.56–0.89; decompensated cirrhosis: 0.30–0.85; first year post-transplant: 0.54–0.63; subsequent

years post-transplant: 0.62–0.86; HCC: 0.32–0.85) were reported. Stigma impacts willingness to screen, seeking care, diagnosis acceptance, interpersonal relationships and employment among CHB patients and caregivers; higher education, old age and better social status is associated with less stigma.

Conclusion: Patients with CHB have impaired HRQoL particularly in mental health, emotional and social functioning with limited or no improvement on these domains with current treatments. Impact on these in clinical practice and trials should be further evaluated with disease specific instruments like HBQoL that focus on psychological well-being and stigma. Social awareness and education to avoid stigma and considering patients' concerns and perception into clinical practice might further reduce the CHB health burden.

Funding: GSK (Study 209774).

PO-1788

The incidence and predictors of HCC in REVEAL chronic hepatitis B patients with incident spontaneous HBsAg loss

Rachel Wen-Juei Jeng^{1,2}, Mei-Hung Pan³, Jessica Liu³, Mei-Hsuan Lee⁴, Richard Batrla-Utermann⁵, Sheng-Nan Lu⁶, Li-Yu Wang⁷, Chien-Jen Chen³, Hwai-I Yang³. ¹Linkou Chang Gung Memorial Hospital, Department of Gastroenterology and Hepatology, Taiwan; ²Chang Gung University, College of Medicine, Taiwan; ³Academia Sinica, Genomic Research Center, Taiwan; ⁴National Yang-Ming University, Institute of Clinical Medicine, Taiwan; ⁵Roche Diagnostics, Basel, Switzerland; ⁶Kaohsiung Chang Gung Memorial Hospital, Department of Gastroenterology and Hepatology, Taiwan; ⁷Mackay Medical College, Taiwan
Email: hiyang@gate.sinica.edu.tw

Background and aims: HBsAg loss is an ideal end point for chronic hepatitis B (CHB) treatment. Age >50 and cirrhosis at time of HBsAg loss has been reported as predictors for HCC by meta-analysis. However, information on the incidence and predictors of HCC in incident cases of spontaneous HBsAg loss within untreated long-term follow-up CHB cohort is limited. **Aim:** To investigate the HCC incidence and risk factors in CHB patients who underwent newly spontaneous HBsAg seroclearance

Method: A total of 633 patients who newly cleared serum HBsAg out of 4155 CHB patients in REVEAL cohort were enrolled. Patients with HCC diagnosed prior to HBsAg seroclearance were excluded (n = 1). HCC diagnosis was ascertained by follow-up examinations and computerized data linkage with National Cancer Registry and National Death Certification profiles by the end of 2017. Multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models. Statistic procedures were performed with SAS 9.4. A P value less than .05 was considered statistically significant.

Results: A total of 29 patients were diagnosed of HCC during a median (IQR) follow-up duration of 17.5 (0.1–25.5) years after HBsAg seroclearance. The 5-, 10-, 15- and 20-year cumulative incidence of HCC was 1%, 3%, 4% and 5%, respectively. The median age of HBsAg seroclearance was 55.3 year-old; those with subsequent HCC development were slightly older than those without (58.7 vs. 55.1, P = 0.075). Patients diagnosed with cirrhosis before HBsAg seroclearance had a higher incidence of HCC development than those without cirrhosis (annual incidence: 1.37% vs. 0.2%). Older age [Crude HR (95% CI): 1.05 (1.01–1.09), P = 0.015], cirrhosis [Crude HR (95% CI): 6.91 (3.12–15.25), P < 0.0001] are significant factors in univariate analysis while cirrhosis is the only independent predictors of HCC in the multivariate cox regression analysis [adjusted HR (95% CI): 4.02 (1.11–14.66), P = 0.035]. Older age at time of HBsAg loss is the only predictor of HCC in patients without cirrhosis [HR (95% CI): 1.05 (1.00–1.10)] while there's no predictors of HCC in cirrhotic patients before HBsAg loss.

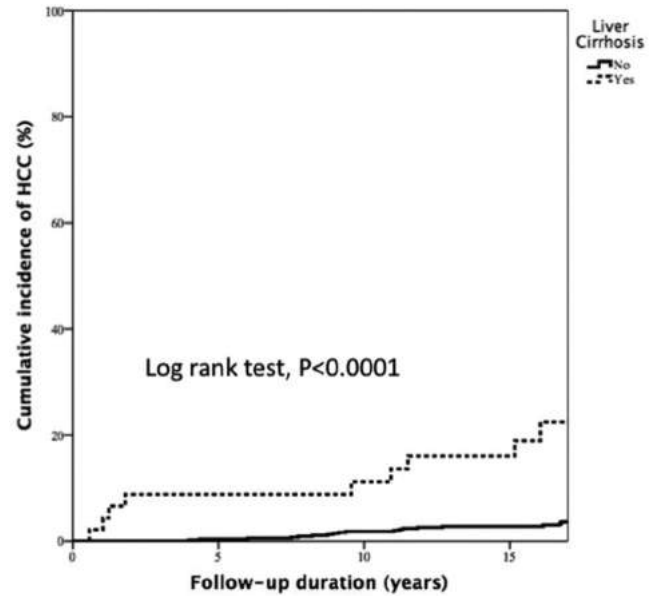


Figure:

Conclusion: This is the largest cohort with the longest follow-up duration reporting the HCC incidence and risk factors in CHB patients with newly spontaneous HBsAg seroclearance. Cirrhosis before HBsAg loss is predictive for subsequent HCC development while increasing age is the only risk factor for patients without cirrhosis.

PO-1789

Characterization of the Liver Immune Microenvironment in Chronic HBV Infected Patient Liver Biopsies

Nicholas Van Buuren¹, Ricardo Ramirez¹, Scott Turner¹, Diana Chen¹, Vithika Suri¹, Abhishek Aggarwal¹, Christina Moon¹, Sam Kim¹, Cameron Soulette¹, Dmytro Korniyev¹, Neeru Bhardwaj^{1,2}, Maria Buti³, Henry Chan⁴, Patrick Marcellin⁵, Jeffrey Wallin¹, Anuj Gaggar¹, Lauri Diehl¹, Hongmei Mo¹, Li Li¹, Becket Feierbach¹. ¹Gilead Sciences Inc, Foster City, United States; ²Foundation Medicine, Cambridge, United States; ³Hospital Universitari Val d'Hebron, Barcelona, Spain; ⁴The Chinese University of Hong Kong, China; ⁵Hopital Beaujon, Clichy, France
Email: nick.vanbuuren@gilead.com

Background and aims: Our current knowledge of the interaction between chronic HBV (CHB) infection and the liver immune microenvironment largely comes from animal models and patients with hepatocellular carcinoma (HCC). Here, we describe the liver immune microenvironment from CHB-infected, non-HCC patients from the GS-US-174-0149 clinical trial.

Method: Matching FFPE and fresh frozen liver biopsies were collected from immune active patients within the open-label Phase 4 study GS-US-174-0149. We applied bulk RNA-Seq to 53 CHB liver biopsies from 46 patients including eight longitudinal pairs from Baseline and Week 96. The xCell algorithm as well as gene set variance analysis was used to characterize and quantify the immune microenvironment of each sample. Twenty-eight of the 53 samples had matched FFPE biopsies subjected to multiplex immunofluorescence (mIF) using the Neogenomics MultiOmyx™ platform. The biopsies were stained with a custom 12-plex panel including cell segmentation, immune and viral biomarkers. Finally, corresponding serum samples were screened using the MSD Human V-plex Screen Service to identify peripheral correlates for the immune microenvironment.

Results: Unsupervised clustering of the transcriptome revealed two unique liver immune signatures from the CHB biopsies. We classified these signatures as Immune High and Immune Low based on the quantification of gene signatures from the liver immune infiltrate.

Immune High

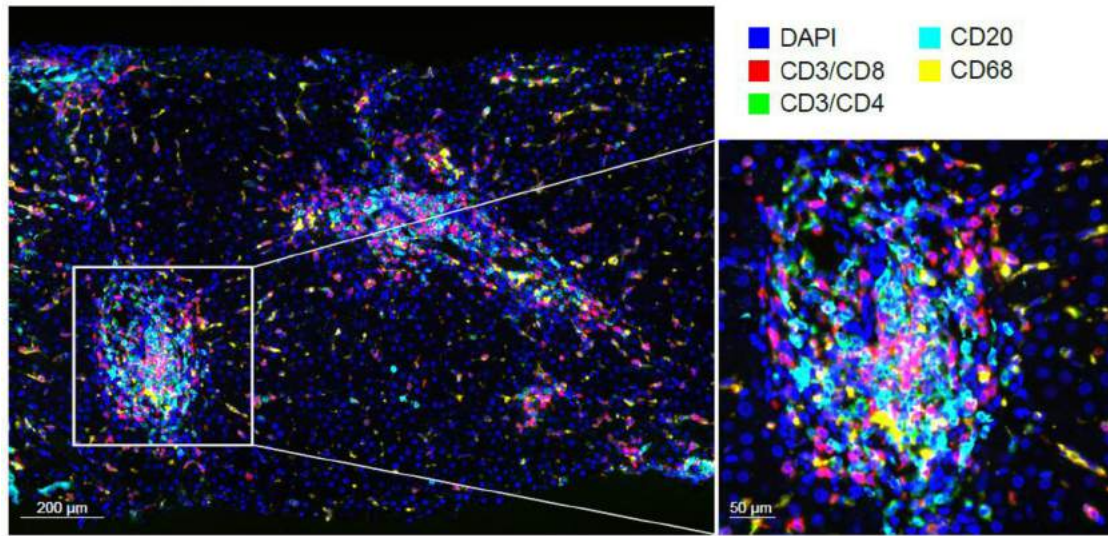


Figure: (abstract: PO-1789)

mIF analysis demonstrated the formation of periportal lymphoid aggregates in Immune High samples (Figure). In addition, single-plex IHC demonstrated that Immune High samples had significantly elevated expression of the PD-1 and PD-L1. High and Low immune microenvironments were independent of patient HBeAg status, serum viral biomarkers or liver antigen burden. Finally, we screened corresponding peripheral samples and identified elevated levels of ICAM-1 and IP-10 as serum biomarkers that strongly correlated with the Immune High gene signature.

Conclusion: We utilized transcriptomics and mIF to investigate the CHB liver immune microenvironment. Our data identified different levels of immune cell infiltrates that were independent of viral load and HBeAg status. These findings could have implications for treatment modalities designed to augment an anti-viral immune response.

PO-1810

A non-invasive model to predict liver histological lesions in chronic hepatitis B patients with persistently normal alanine aminotransferase and detectable viremia

Qiankun Hu¹, Wei Xu¹, Qianqian Wang¹, Qiang Li¹, Chenlu Huang¹, Shuai Tao¹, Xun Qi¹, Yi Zhang¹, Xinyan Li¹, Xuhua Jiang¹, Jie Song¹, Liang Chen¹, Yuxian Huang^{1,2}. ¹Shanghai Public Health Clinical Center, Fudan University, Department of Liver Diseases, Shanghai, China; ²Huashan Hospital, Fudan University, Department of Infectious Diseases, Shanghai, China

Background and aims: This study aimed to develop a non-invasive model to predict significant liver histological changes (SLHC), which is the histological indication for antiviral therapy in chronic hepatitis

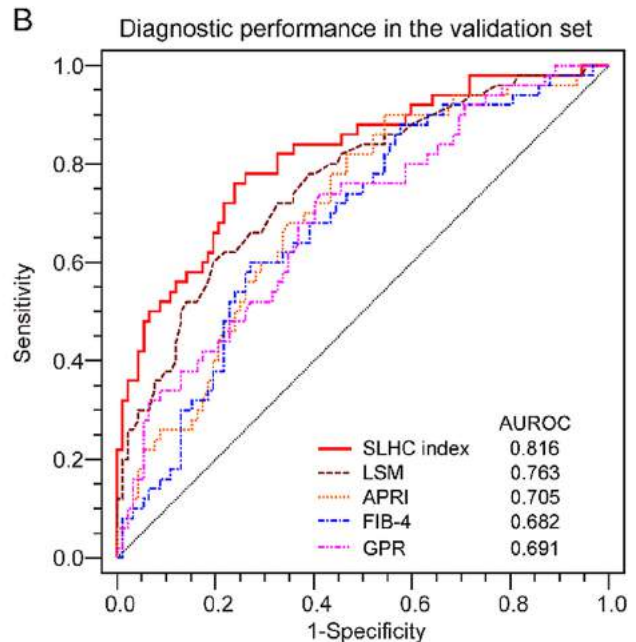
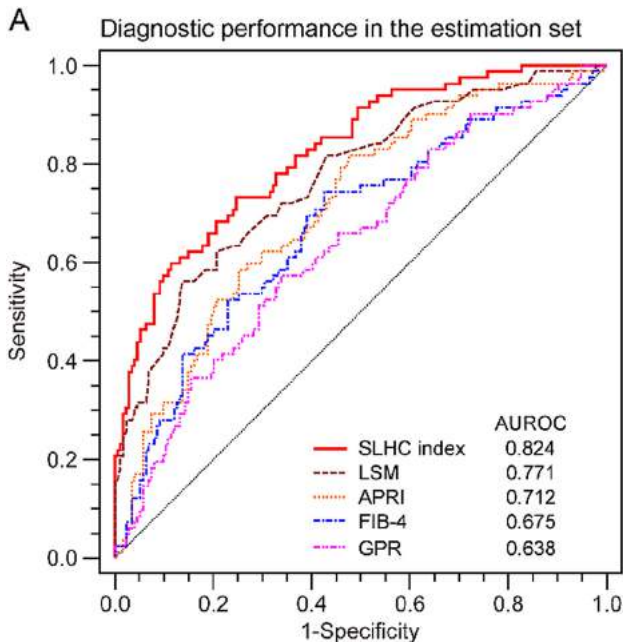


Figure: (abstract: PO-1810): Comparison of the diagnostic performance of the SLHC index with other non-invasive models in the estimation set (A) and validation set (B).

B (CHB) patients with persistently normal alanine aminotransferase (PNALT) and detectable HBV DNA.

Method: 398 CHB patients with PNALT and detectable HBV DNA who underwent liver biopsy were divided into the estimation set (n = 256) and the validation set (n = 142). Logistic regression analysis was performed to identify independent predictors of SLHC. Then a novel model index was developed to predict SLHC.

Results: 82 (32.0%) patients and 50 (35.2%) patients had SLHC in the estimation set and validation set, respectively. Multivariate analysis identified aspartate aminotransferase (AST), cholinesterase (ChE) and liver stiffness measurement (LSM) as independent predictors for SLHC (all p < 0.05). The SLHC index consisting of AST, ChE and LSM was developed to predict SLHC, which yielded an AUROC of 0.824 and 0.816 in the estimation set and validation set, respectively. More importantly, compared with other established non-invasive models, the SLHC index presented significantly better diagnostic performance in identifying patients with or without SLHC.

Conclusion: The SLHC index provided a high accuracy in predicting histological indication for antiviral therapy in CHB patients with PNALT and detectable HBV DNA.

PO-1876

Novel shapelet patterns for time series classification (TSC) for AFP and ALT to predict HCC in patients with chronic hepatitis B on antiviral treatment

Vicki Wing-Ki Hui^{1,2}, Guozhong Li³, Shiwen Li⁴, Terry Cheuk-Fung Yip^{2,5}, Yee-Kit Tse^{2,5}, Vincent Wai-Sun Wong^{2,5}, Grace Lai-Hung Wong^{2,5}, Bryon Koon-Kau Choi⁴. ¹The Chinese

University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong; ²Medical Data Analytic Centre (MDAC); ³Hong Kong Baptist University, Department of Computer Science, Hong Kong; ⁴Hong Kong Baptist University, Department of Computer Science; ⁵The Chinese University of Hong Kong, Department of Medicine and Therapeutics Email: wonglaihung@cuhk.edu.hk

Background and aims: Alpha-fetoprotein (AFP) is the most widely used biomarker for hepatocellular carcinoma (HCC) surveillance, which is criticized for its high false-positive rate in patients with raised alanine aminotransferase (ALT) levels. Time-series shapelets are discriminative subsequences, recently found effective for time series classification (TSC). We aimed to identify novel shapelets for accurate TSC of ALT and AFP levels to predict HCC in patients with chronic hepatitis B (CHB) who had received antiviral treatment.

Method: This was a territory-wide retrospective observational cohort study in Hong Kong. We identified CHB patients who received entecavir or tenofovir treatment. Serial serum AFP and ALT levels from baseline (start of antiviral) to 6 months prior HCC (HCC group) or to last visit (no HCC group) were analyzed. A novel efficient shapelet discovery method was adopted to identify novel shapelets of the time series of AFP alone or AFP and ALT to predict HCC.

Results: 35, 516 CHB patients were included; mean age was 51.6 ± 12.7 years; 21865 (61.6%) patients were male and 2, 429 (6.8%) patients had clinical evidence of cirrhosis. 1, 571 HCC occurred in a 49.1 ± 31.2 months of follow-up. Two representative shapelets of AFP alone and AFP and ALT are showed in Figure 1. The accuracy of the shapelet patterns for TSC increased from 64.31% for AFP alone, to 84.31% for combining AFP and ALT.

Conclusion: Novel shapelet patterns for TSC of serum AFP and ALT levels achieve higher accuracy than those of AFP alone to predict HCC in CHB patients.

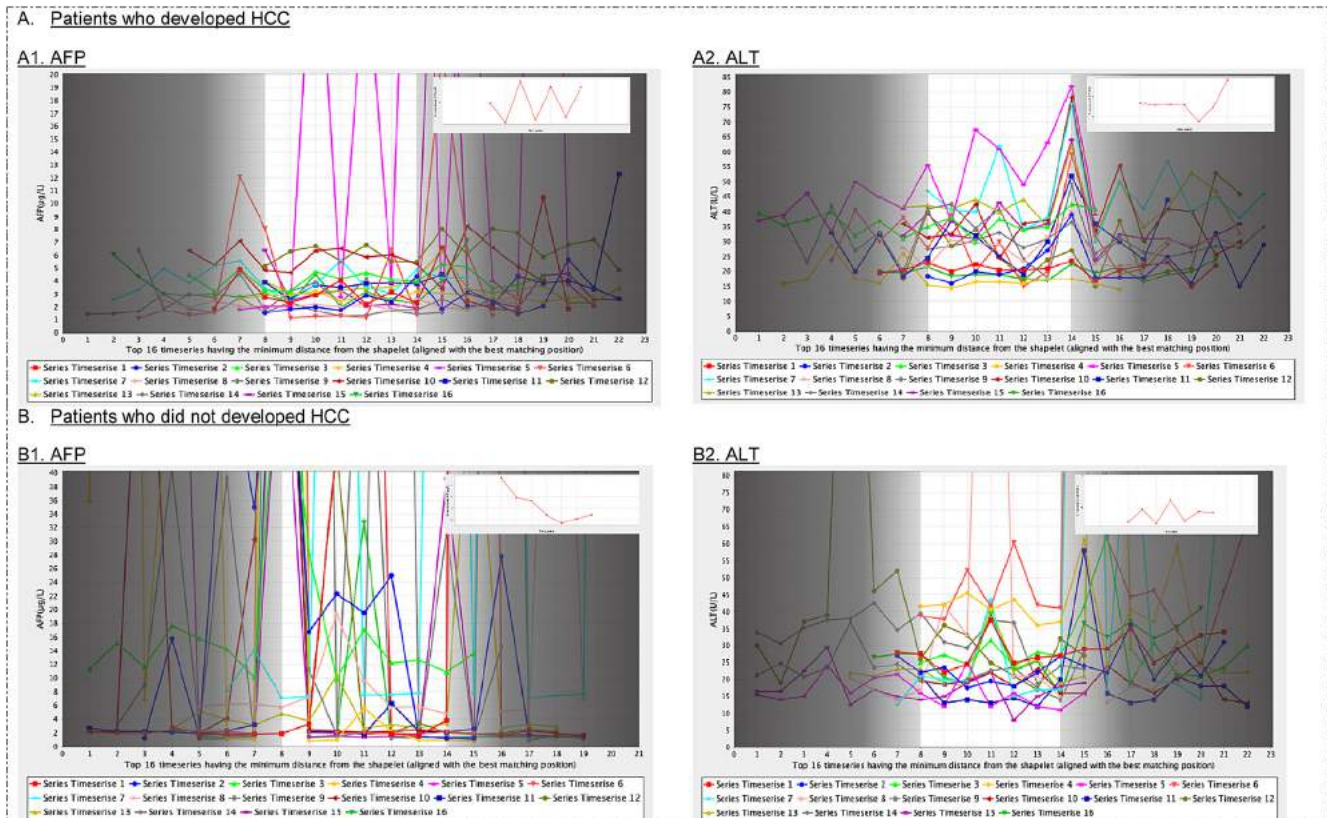


Figure: (abstract: PO-1876) The most heavy-weighted shapelet for A. patients who developed HCC and B. patient who did not developed HCC. (A) Patients who developed HCC; (B) Patients who did not developed HCC.

POSTER PRESENTATIONS

PO-1982

Association between plasma miRNA-200-3p and transcriptional activity of hepatic cccDNA in chronic hepatitis B

Vladimir Loukachov^{1,2}, Karel van Dort^{1,2}, Bart Takkenberg³, Henk Reesink⁴, Neeltje Kootstra^{1,2}. ¹Amsterdam UMC, location AMC, Experimental Immunology, Amsterdam, Netherlands; ²Amsterdam Infection and Immunity Institute, Amsterdam, Netherlands; ³Amsterdam UMC, location AMC, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands; ⁴Leiden University Medical Center (LUMC), Department of Gastroenterology and Hepatology, Leiden, Netherlands
Email: v.loukachov@amsterdamumc.nl

Background and aims: Chronic hepatitis B (CHB) infection is a serious health problem worldwide and with the current treatment a functional cure is only achieved in 3–7% of the patients due to persistence of covalently closed circular DNA (cccDNA) in the liver, resulting in ongoing production of HBsAg and HBV-RNA. At present only pegylated interferon can target this cccDNA pool, however several experimental therapies are under investigation. Since cccDNA is best determined in liver tissue, surrogate markers in plasma are of interest to monitor the effect of these new therapies. As miRNA are promising biomarkers in numerous diseases, in this study the plasma levels of various miRNAs expressed in CHB patients were compared with the respective hepatic cccDNA levels and degree of HBV transcriptional activity.

Method: For this study pretreatment plasma samples of 54 CHB patients, either HBeAg negative (n = 30) or positive (n = 24), were available for analysis. RNA was isolated from plasma and the expression levels of the specific miRNAs were measured using qPCR. DNA and RNA was isolated from liver tissue samples and cccDNA and pregenomic RNA (pgRNA) levels were measured by qPCR. Transcriptional activity of cccDNA was defined as the pgRNA/cccDNA ratio. Association between miRNA expression levels, cccDNA levels and cccDNA transcriptional activity was performed using a Spearman correlation test.

Results: The plasma expression levels of miR-122-5p, miR-10b-5p, miR-192-5p, miR-194-5p, miR-30c-5p, let-7e-5p, miR-125b-5p, miR-146b-5p, miR-193b-3p and miR-215 were associated with hepatic cccDNA levels (p < 0.01) but no correlation was observed for cccDNA transcriptional activity. Next, the HBeAg negative and positive groups were analyzed separately. In the HBeAg positive patients expression levels of let-7e-5p, miR-122-5p and miR-143-3p (p < 0.05) were found to be associated with cccDNA levels, however no correlation was observed for the cccDNA transcriptional activity. In the HBeAg negative patients no correlation between the expression levels of miRNAs and cccDNA was found, however the expression levels of plasma miR-200a-3p level was correlated (p = 0.01) with cccDNA transcriptional activity in the liver.

Conclusion: The expression levels of various miRNAs in plasma was associated with hepatic cccDNA levels in CHB patient. Plasma expression levels of miR-200a-3p was associated with HBV transcriptional activity in the liver in HBeAg negative CHB patients only.

PO-1996

HBV reactivation can be predicted by combined highly-sensitive HBV markers: implications for an optimized management of HBsAg-negative/anti-HBc-positive oncohematological patients

Mohammad Alkhatib¹, Romina Salpini¹, Vincenzo Malagnino², Carlotta Cerva², Lorenzo Piermatteo¹, Arianna Battisti¹, Ada Bertoli¹, Maria Cantonetti³, William Arcese³, Francesca Ceccherini Silberstein¹, Carlo Federico Perno⁴, Massimo Andreoni², Loredana Sarmati², Valentina Svicher¹. ¹University of Rome "Tor Vergata", Department of Experimental Medicine, Rome, Italy; ²University of Rome "Tor Vergata", Clinical Infectious Disease, Department of System Medicine, Rome, Italy; ³University of Rome "Tor Vergata", Department of Hematology, Stem Cell Transplant Unit, Rome, Italy; ⁴IRCCS Bambino Gesù' Pediatric Hospital, Department of Diagnostic and Laboratory Medicine, Rome, Italy
Email: mohammad-alkhatib@hotmail.com

Background and aims: HBV-reactivation (HBV-R) is still a challenging issue in HBsAg-negative/anti-HBc-positive patients with oncohematological diseases. Here, we examine the role of HBV markers in predicting HBV-R in these patients.

Method: This study includes 107 HBsAg-negative/anti-HBc-positive oncohematological patients, receiving anti-HBV prophylaxis for ≥18 months after stopping immunosuppression (EASL guidelines) and prospectively monitored every 3 months. 61/107 patients completed prophylaxis and were monitored for a median time of 41 (35–47) months after prophylaxis completion. The role of HBV markers in predicting HBV-R is evaluated by testing 831 serum samples for highly-sensitive HBsAg (Fujirebio, HS-HBs; lower limit of quantification [LLOQ]: 5mIU/ml), HBV-DNA (Roche, LLOQ: 20IU/ml), quantitative anti-HBs and anti-HBc (Fujirebio). HBV-R is defined as serum HBV-DNA ≥20IU/ml (Seto, 2016).

Results: At baseline, all patients have undetectable HBV-DNA and 67.3% is anti-HBs positive (median [IQR]: 152[47–976]mIU/ml). HBV-R occurs in 17/107 (15.9%) patients: 6 during and 11 after completing prophylaxis (up to 27 months after prophylaxis completion).

At HBV-R, median (IQR) HBV-DNA is 44 (27–40509)IU/ml, ALT >ULN for 44% (median [IQR]: 81[49–541]U/L), and ≥1 immune-escape mutation is detected in 50% of patients.

By serological markers analysis, the combination of anti-HBc >3COI and anti-HBs persistently or declining to <50mIU/ml is a predictive factor for HBV-R (OR[95%CI]: 9.1[2.7–30.2]; 63% of patients with vs 15% without this combination experiences HBV-R, P < 0.001). This combination predicts HBV-R also in the subset of patients completing prophylaxis (OR[95%CI]: 8.8[2.0–38]; 55% of patients with vs 14% without this combination experiences HBV-R, P = 0.005).

Furthermore, by monitoring of virological markers, the positivity, confirmed in ≥2 time-points, to HS-HBs (detection failed by routinely used HBsAg-assays) and/or to HBV-DNA (detected below LLOQ) strongly increases HBV-R risk after completing prophylaxis (OR[95%CI]: 24[3.7–157.4]; 50% of patients positive to HS-HBs and/or HBV-DNA vs 4% never positive to these markers experiences HBV-R, P = 0.001).

Conclusion: HBV-R frequently occurs in anti-HBc-positive/HBsAg-negative oncohematological patients, particularly after completing prophylaxis and selects for viral strains with enhanced potential to evade humoral response. The integrated monitoring of accurate HBV-markers can guide to identify patients at higher HBV-R risk who need an extended prophylaxis.

PO-2134

The association of serum hepatitis B core antibody and liver inflammation in HBeAg-negative chronic hepatitis B patients with normal ALT and detectable HBV DNA

Kefang Yao¹, Jian Wang², Xiaomin Yan², Guiyang Wang², Yali Xiong², Shengxia Yin², Xin Tong², Rui Huang², Chao Wu^{1,2}. ¹Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University; ²Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School
Email: dr.wu@nju.edu.cn

Background and aims: The association of serum hepatitis B core antibody (anti-HBc) levels and liver inflammation is not clear in HBeAg-negative chronic hepatitis B (CHB) patients with normal alanine aminotransferase (ALT) and detectable HBV DNA. We attempted to evaluate the association of serum anti-HBc levels and liver inflammation in these patients.

Method: A total of 117 HBeAg-negative CHB patients with normal ALT and detectable HBV DNA who underwent liver biopsy were included. Serum anti-HBc levels were detected by commercial immunoassays (Abbott GmbH and Co. KG). The association between liver inflammation and anti-HBc levels was analyzed.

Results: Approximately 43.6% (51/117) of the HBeAg-negative CHB patients with normal ALT and detectable HBV DNA showed significant liver inflammation (≥G2). Serum anti-HBc levels significantly

correlated with liver inflammation grades ($r=0.511$, $p<0.001$). Multivariate logistic analysis showed that serum anti-HBc levels were independently associated with significant liver inflammation (OR 1.513, 95%CI 1.112–2.058, $p=0.008$). The receiver operating characteristic (ROC) curve indicated that serum anti-HBc levels could predict significant liver inflammation (AUC = 0.773, $P < 0.001$) with the cut-off values of 10.87 S/CO.

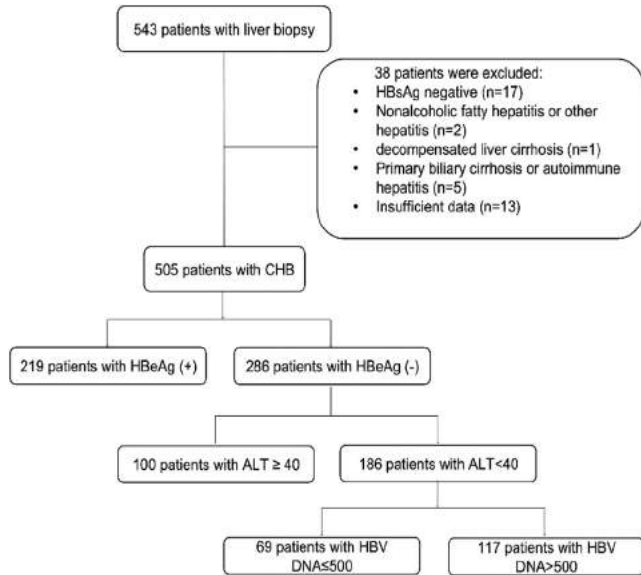


Figure 1: Flow diagram of patient selection.

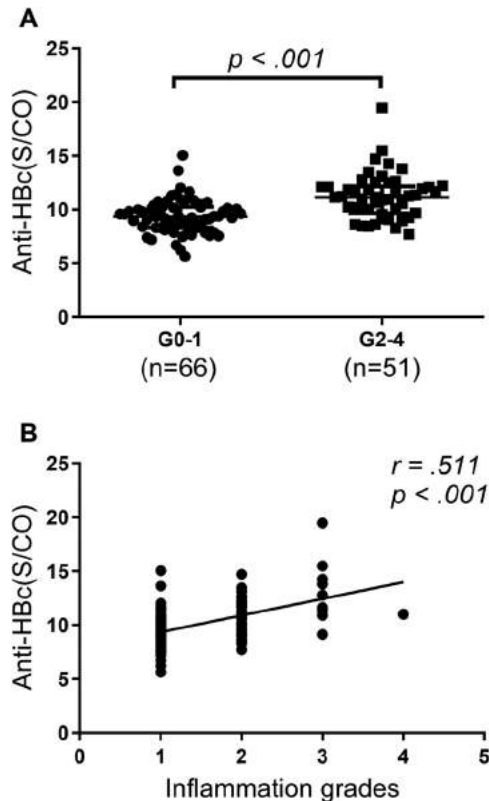


Figure 2: Proportion of patients with different immune status of entire CHB patients (A) and distribution of CHB patients with different gray zones (B).

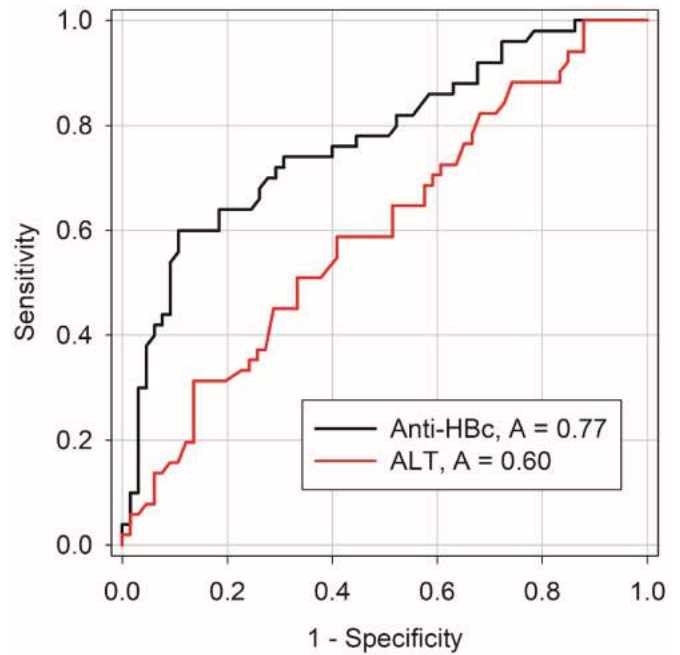


Figure 3: Distribution of CHB patients with different immune status according to age (A) and sex (B).

Conclusion: A significant proportion of HBsAg-negative CHB patients with normal ALT and detectable HBV DNA showed significant liver inflammation. The anti-HBc levels could be used to predict significant liver inflammation in HBsAg-negative CHB patients with normal ALT and detectable HBV DNA.

PO-2261

Changing demographic-clinic-pathologic profiles of newly diagnosed carriers of chronic hepatitis B virus infection across two decades: a single Italian reference center report

Gabriele Ricco¹, Patrizia Bleve¹, Barbara Coco¹, Daniela Cavallone¹, Piero Colombatto¹, Filippo Oliveri¹, Veronica Romagnoli¹, Antonio Salvati¹, Ferruccio Bonino², Maurizia Brunetto^{1,2,3}.
¹University Hospital of Pisa, Hepatology Unit, Pisa, Italy; ²National Research Council, Biostructure and Bioimaging Institute, Naples, Italy; ³University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy
 Email: maurizia.brunetto@unipi.it

Background and aims: Hepatitis B Virus (HBV) epidemiology burden is rapidly evolving worldwide. We studied the viral, clinical, pathologic and demographic characteristics of two cohorts of consecutive chronic hepatitis B surface antigen (HBsAg) carriers who presented at a single Italian reference center across the last 2 decades.

Method: All [1847, 70.0% native-born and 30.0% Immigrants] HBsAg carriers evaluated at the Hepatology Unit of the University Hospital of Pisa, Italy from January 2000 to December 2019 were included in the analysis and grouped according to decade of first evaluation [856 (46.3%) between 2000 and 2009 (first cohort, 1C), 991 (53.7%) between 2010 and 2019 (second cohort, 2C). Groups comparison included the characteristics listed in the Table by χ^2 or Mann-Whitney nonparametric test.

Results: The 2 cohorts differed significantly ($p < 0.001$) for: gender (higher female number in 2C, 28–38%, higher in immigrants); origin

POSTER PRESENTATIONS

and HBV genotype [increased immigrants rate in 2C, (14.7–43.3%) and increased non-D genotype in 2C, (18.7–33.2%)]; HBV infection phase [more HBeAg negative infection in 2C (ENI, 30.6–46.9%); coinfections (lower HCV, higher HDV in 2C); liver disease severity (cirrhosis from 28.9 to 17.8% from 1C to 2C); non-viral disease co-factors [higher overweight (27.6–36.6%) and metabolic syndromes (9.6–16.2% in 2C)]; previous therapy [untreated (78.5–88.7% in 2C)]. The HCC prevalence decreased not significantly (6.3% in 1C, 4.3% 2C). Primary infections raised (3.1–4.5%) in non-vaccinated Italians with HBV-genotypes prevalent in immigrants.

		2000-2009 (1 st cohort)	2010-2019 (2 nd cohort)	P
		n= 856 (46.3)	n= 991 (53.7)	
Gender	F / M	244 (28.5) / 612 (71.5)	377 (38.0) / 614 (62.0)	<0.001
Origin	Italian/Immigrants	730 (85.3) / 126 (14.7)	562 (56.7) / 429 (43.3)	<0.001
Genotype	D / non-D	438 (81.3) / 101 (18.7)	407 (66.8) / 202 (33.2)	<0.001
Infection Phase	HBeAg- infection	253 (30.6)	442 (46.9)	<0.001
	Grey Zone ^a	52 (6.3)	112 (11.9)	
	HBeAg- CHB	412 (49.8)	267 (28.3)	
	HBeAg+ CHB	103 (12.5)	112 (11.9)	
	HBeAg+ infection	7 (0.8)	10 (1.1)	
Coinfections	Absent	753 (88.0)	904 (91.2)	<0.001
	HDV	35 (4.0)	46 (4.7)	
	HCV	45 (5.3)	30 (3.0)	
	HDV+HCV	18 (2.1)	4 (0.4)	
	HIV	5 (0.6)	7 (0.7)	
Cirrhosis	n (%)	247 (28.9)	176 (17.8)	<0.001
Overweight	n (%)	236 (27.6)	363 (36.6)	<0.001
Insuline-Res/ Diabetes	n (%)	82 (9.6)	161 (16.2)	<0.001
Naïve	n (%)	672 (78.5)	879 (88.7)	<0.001

^aGrey Zone: HBeAg positive/HBeAg negative individuals with viremia persistently <20000 IU/mL and normal ALT.

Figure:

Conclusion: The HBV infection epidemiology significantly changed in Italy over the last decades driven by the effective national policy of HBV burden control and increasing immigration from highly endemic areas. Tracing the dynamics of these changes will foster the most appropriate healthcare strategies for an effective control of HBV infection, higher adherence to general vaccination and timely antiviral treatment.

PO-2366

Non-alcoholic fatty liver disease in chronic hepatitis B patients: patients' characterization and impact on disease progression

Yana Davidov¹, Fadi Abu Baker^{1,2,3}, Ilan Green³, Orna Mor⁴, Yael Gozlan⁴, Ziv Ben Ari¹. ¹Sheba Medical Center, Hepatology, Ramat Gan, Israel; ²Hillel Yaffe Medical Center, Hadera, Israel; ³Leumit Health Care Services, Holon, Israel; ⁴Sheba Medical Center, Virology Lab., Ramat Gan, Israel

Email: Fa_fd@hotmail.com

Background and aims: Concomitant non-alcoholic fatty liver disease (NAFLD) is common in patients with chronic hepatitis B (CHB) infection, although its impact on liver-related outcomes remains controversial. We aimed to evaluate the effect of NAFLD on the course, phenotype, management and outcome of patients with CHB. **Method:** We performed a large retrospective cohort study utilizing the Leumit-Health-Service database in Israel. Electronic reports of 692106 members were reviewed between 2000 and 2019 and patients with CHB diagnosis based on ICD-9-CM codes and serology results were included. Patients with excessive alcohol consumption (>2 drinks per day) were excluded. CHB phase was determined in concordance with the EASL guidelines based on HBeAg status, ALT, HBV viral load and pathology results when available. Patients who had liver imaging during follow-up period were included for final analysis. Accordingly, patients diagnosed with NAFLD by imaging were included in the CHB-NAFLD group, while those with CHB but without NAFLD comprised the control group. We evaluated demographics, risk factors, habits, laboratory results, disease course and treatment. Outcome including cirrhosis and hepatocellular carcinoma (HCC) based on relevant ICD-9-CM as well as the rate of advanced fibrosis (FIB-4 >2.65 and/or APRI >1.5) based on laboratory

data at the end of the study period were compared between both groups.

Results: A total of 1166 patients with CHB were included. Of these, 179 (15.35%) had a diagnosis of NAFLD and were included in the CHB-NAFLD group. Patients in the CHB-NAFLD group were significantly older (44.6 ± 12.6 vs. 39 ± 14.2; P < 0.001) and had a more prominent male predominance (64.6% vs. 57.4%; P = 0.069). As expected, obesity (BMI > 30) (46.6% vs. 24.4%; P < 0.01) and diabetes mellitus (DM) (35.8% vs. 17.4%; P < 0.01) were significantly higher in CHB-NAFLD patients. CHB-NAFLD group was distinguished by higher levels of ferritin (165 ± 84 vs. 101 ± 19; P < 0.01) and triglycerides (150 ± 85 vs. 116 ± 71; P < 0.01). The HBeAg negative chronic infection phase was predominant in both groups. The vast majority of CHB-NAFLD patients (96.9%) were HBeAg negative at time of diagnosis. CHB-NAFLD patients had higher rates of HBeAg negative hepatitis (34.2% vs. 25%; P = 0.001). Moreover, HBeAg seroclearance rate was lower in these patients (1.7% vs. 4.4%; P = 0.029). Interestingly, patients with CHB-NAFLD had comparable outcome to the control group as the rate of cirrhosis (2.8% vs 1.9%; P = 0.003), advanced fibrosis (6.2% vs. 5.8%; P = 0.435) and HCC didn't differ significantly between the groups. In multivariate analysis, DM (HR 2.845, CI 1.146–7.061; P = 0.0024) but not NAFLD, was independently associated with cirrhosis and advanced fibrosis development.

Conclusion: Concomitant NAFLD and CHB is distinctive by features of the metabolic syndrome and HBeAg negativity but has similar outcome to CHB without NAFLD.

PO-2484

Nomogram for predicting significant liver injury in chronic hepatitis B patients with immune tolerance

Chun-yan Wang¹, Ya Deng², Chang Guo¹, Dong Ji^{1,2,3}. ¹Fifth medical center of chinese PLA general hospital, Department of liver diseases, Beijing, China; ²Southern Medical University, The Second School of Clinical Medicine, Guangzhou, China; ³Peking University 302 Clinical Medical School, Beijing, China

Email: jidg302@126.com

Background and aims: While current guidelines advise against starting antiviral treatment for immune-tolerant CHB (IT-CHB) patients, some new data have shown that about 10% to 49% IT-CHB patients had significant liver injury (liver inflammation grade ≥G2 and/or liver fibrosis stage ≥S2) by liver biopsy (LB) proven. Whether IT-CHB patients should be treated with antiviral therapy still remains under debate. The aim of our study is to identify the high-risk factors of significant liver injury in IT-CHB patients and establish a nomogram prediction model.

Methods: IT-CHB patients who underwent LB at the Fifth Medical Center of the PLA General Hospital, from August 2002 to December 2017, were retrospectively enrolled. The criteria of IT-CHB met the definition of AASLD 2018 hepatitis B guidance. The eligible patients were assigned to two groups based on significant liver damage (≥G2/S2) or not. High-risk factors were identified by univariate and multivariate logistic regression, and then were incorporated into a nomogram model. The discrimination and calibration of the novel nomogram were assessed by concordance index (C-index) and calibration with 1000 bootstrap sampling.

Results: A total of 382 IT-CHB patients were enrolled, with an average age of 33.3 ± 10.2 years, males accounted for 68.3%, 57.9% had family history of hepatitis B, median HBV DNA was 8.4 log₁₀ IU/ml, and 21.5% had significant liver damage. Logistic regression analysis showed that age (OR = 1.074, 95%CI: 1.043 ~ 1.107, p < 0.001), HBV DNA load (OR = 0.442, 95%CI: 0.314 ~ 0.624, p < 0.001), AST (OR = 1.096, 95%CI: 1.051 ~ 1.142, p < 0.001) and PLT (OR = 0.992, 95%CI: 0.986 ~ 0.998, p = 0.006) were independent high-risk factors associated with significant liver injury. Based on the above factors, a nomogram model was established, which achieved good C-index of 0.845, and had well-fitted calibration curves. The area under ROC was 0.845 (95%CI: 0.795 ~ 0.895), which was significantly better than

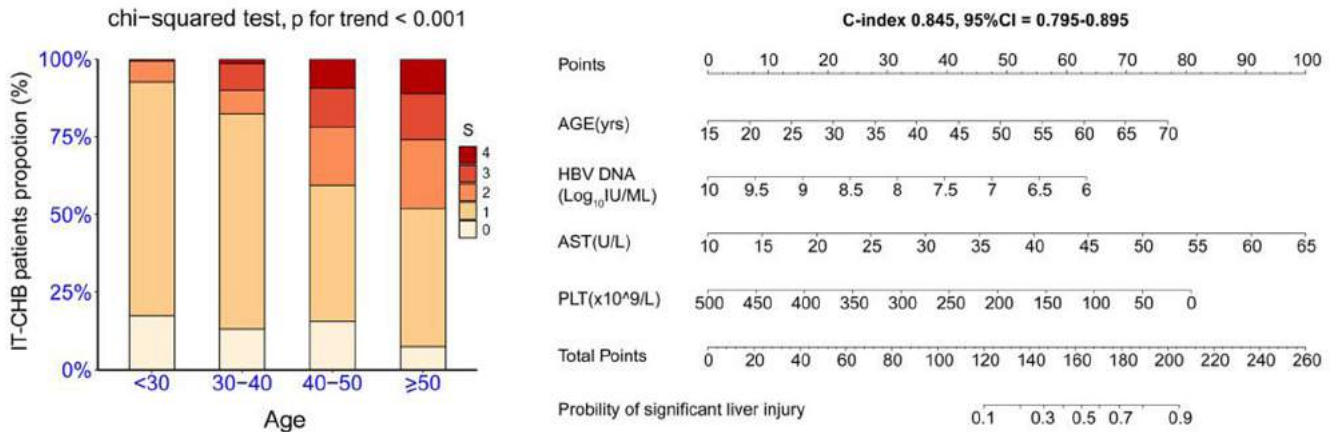


Figure: (abstract: PO-2484)

APRI (0.781, 95%CI: 0.723 ~ 0.840) and FIB-4 (0.802, 95%CI: 0.746 ~ 0.859).

Conclusions: The proportion of IT-CHB patients with significant liver injury is not rare. Incorporating age, HBV DNA, AST, and PLT, the established nomogram model achieved good prediction accuracy, and can be used to predict significant liver damage in IT-CHB patients individually, reduce the need of LB, and provide a reference for precise antiviral treatment.

Key words: Hepatitis B; chronic; immune tolerance; IT-CHB; nomogram; significant liver injury

PO-2575

Restoration of HBV-specific immune responses with therapeutic vaccine BRII-179 (VBI-2601) in chronic HBV patients in a phase 1b/2a study

Haiyan Ma¹, Tien Huey Lim², Apinya Leerapun³, Martin Weltman⁴, Ji-Dong Jia⁵, Young-Suk Lim^{6,7}, Pisit Tangkijvanich⁸, Wattana Sukeepaisarnjaroen⁹, Nina Le Bert¹, Yun Ji¹⁰, Dong Li¹⁰, Yao Zhang¹⁰, Robert Hamatake¹⁰, Simone Strasser¹¹, Chunming Li¹⁰, Huiquo Ding¹², Jung-Hwan Yoon¹³, Stace Nigel¹⁴, David Anderson¹⁵, Li Yan¹⁰, Antonio Bertoletti¹, Qing Zhu¹⁰, Man-Fung Yuen¹⁶. ¹Duke-NUS Medical School, Singapore; ²Middlemore Hospital, New Zealand; ³Maharaj Nakorn Chiang Mai Hospital, Thailand; ⁴Nepean Hospital, Kingswood, Kingswood, Australia; ⁵Beijing Friendship Hospital, Beijing, China; ⁶Asan Medical Center, Seoul, Korea, Rep. of South; ⁷Asan Medical Center, University of Ulsan College of Medicine, Korea, Rep. of South; ⁸King Chulalongkorn Memorial Hospital, Bangkok, Thailand; ⁹Srinagarind Hospital, Khon Kaen, Thailand; ¹⁰Brii Biosciences, Durham, United States; ¹¹Royal Prince Alfred Hospital, Camperdown, Australia; ¹²Beijing You 'an Hospital, Beijing, China; ¹³Seoul National University Hospital, Seoul, Korea, Rep. of South; ¹⁴Capital and Coast District Health Board, Wellington, New Zealand; ¹⁵VBI Vaccines, Cambridge, United States; ¹⁶The University of Hong Kong, Hong Kong, China
Email: mfyuen@hku.hk

Background and aims: Functional cure of chronic HBV infection without life-long treatment requires a restoration of compromised HBV-specific T and B cell immunity. Therapeutic vaccines based on the major structural (core and S) and non-structural proteins (polymerase) have been tested in chronic HBV (CHB) patients but have shown scarce immunogenicity. BRII-179, also known as VBI-2601, is a virus-like particle-based therapeutic vaccine produced in CHO cells using the same manufacturing process as Sci-B-Vac®, a preventative vaccine. BRII-179 is a new formulation and higher dose of all three HBV envelope proteins (Pre-S1, Pre-S2, and S). Safety, immunogenicity, and early antiviral activity of BRII-179 admixed with IFN-alpha as co-adjuvant were assessed in a phase 1b/2a study in CHB patients.

Method: This randomized, open-label, controlled study included two dose levels, 20 mcg BRII-179 (Part 1; n = 25) and 40 mcg BRII-179 (Part 2 n = 24). Non-cirrhotic CHB patients, virally suppressed under nucleos (t)ide analog (Nrtl) therapy were randomized 1:2:2 into 3 cohorts in Part 1 and 1:1 to 2 cohorts in Part 2 to receive 4 monthly intramuscular injections of BRII-179 admixed with or without 3 MIU IFN-alpha. Antibody and cellular responses to surface antigens, as well as evolution of circulating HBsAg were monitored.

Results: Both dose levels of BRII-179 (20 mcg and 40 mcg) with/without IFN-alpha administered through intramuscular injection were safe and well-tolerated across all cohorts without severe adverse event. BRII-179 induced anti-HBs antibody response in >30% patients in all treated cohorts, however, moderate anti-PreS1 or anti-PreS2 antibody responses were only observed in patients receiving BRII-179 admixed with IFN-alpha. BRII-179 also restored and/or boosted S-, Pre-S1-, Pre-S2-specific IFN-gamma producing T cells in the majority of treated patients evaluated. Overall, no or minimal reduction of HBsAg was observed after 4 doses of BRII-179 treatment.

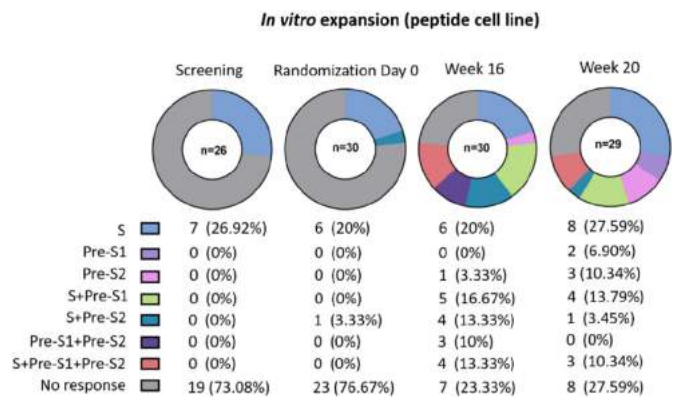


Figure:

Conclusion: In CHB patients under Nrtl therapy, BRII-179 with and without IFN-alpha co-adjuvant exhibited a good safety and tolerability profile. A limited number of doses of BRII-179 containing S, Pre-S1 and Pre-S2 antigens induced B and T cell responses in CHB patients. Restoration of HBV immune responses did not modify the HBsAg level during the study. These data support further clinical evaluation of BRII-179 as an immunomodulator in combination with other treatment modalities for functional cure.

POSTER PRESENTATIONS

PO-2637

In HBeAg-negative patients within grey zone, serum HBV-RNA levels are higher and more commonly detected, while intrahepatic markers are similar

Adriana Palom¹, Mar Riveiro Barciela^{1,2}, Sofía Pérez-del-Pulgar^{2,3}, Luisa Roade¹, David Tabernero^{2,4}, Alison Kuchta^{2,3}, Thais Leonel^{2,3}, Mireia García-López^{2,3}, Ariadna Rando^{2,4}, Francisco Rodríguez-Frías^{2,4}, Rafael Esteban^{1,2}, Maria Buti^{1,2}. ¹Hospital Universitari Vall Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain, Liver Unit, Barcelona, Spain; ²Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas, Madrid, Spain; ³Hospital Clínic, University of Barcelona, IDIBAPS, Liver Unit, Barcelona, Spain; ⁴Hospital Universitari Vall d'Hebron, Barcelona, Spain, Liver Pathology Unit (Biochemistry and Microbiology departments, Clinical Laboratories), Barcelona, Spain
Email: mbuti@vhebron.net

Background and aims: Serum hepatitis B virus RNA (HBV-RNA) has been reported to be a surrogate marker of intrahepatic cccDNA in HBeAg-positive patients. However, there are scarce data on HBeAg negative subjects. The aim of the study was to evaluate the correlation between HBV-RNA and intrahepatic HBV markers in HBeAg negative patients within the grey zone (HBV-DNA >2000 IU/ml).

Method: Collaborative study that included 74 HBeAg negative patients in the grey zone (HBV-DNA >2000 IU/ml plus normal or slightly increased ALT) and were classified according to the EASL guidelines after the performance of a liver biopsy as CHB (N = 22) and IC (N = 52). HBV-RNA was determined by an automated standardized technique (Cobas[®] HBV-RNA test Roche; LLQ 10 cop/ml, LLD 6.6 cop/ml), as well as qHBsAg and HBcrAg. In a subgroup of patients (N = 22) intracellular markers were also quantified in fresh-frozen liver biopsies.

Results: 74 naïve HBeAg negative patients were included: 38 (51.5%) male, age 47 ± 14 years, 58% Caucasian, 30% African. HBV-RNA could be performed in 63 subjects. HBV-RNA was detected in all CHB and in 72% IC (p = 0.01), with higher median levels in the CHB group (2.3 vs 0.8 log₁₀ IU/ml, p < 0.001). Overall, CHB subjects had higher levels of liver stiffness (LS), ALT and HBV markers (HBV-DNA, qHBsAg, HBcrAg). The marker with the highest AUROC for CHB identification was HBV-RNA (0.868), followed by HBcrAg (0.774), HBV-DNA (0.754), APRI (0.700) and LS (0.663). 93% of subjects with HBV-RNA <1 log₁₀ IU/ml were ICs. A high correlation between HBV-RNA and HBcrAg (R = 0.815) and HBV-DNA (0.797) was observed. No correlation was found with qHBsAg (R = 0.264). In the 22-patient subgroup with a fresh liver biopsy (7 CHB and 15 ICs), no significant differences were observed in intracellular levels of HBV-RNA, HBV-DNA, cccDNA or cccDNA transcriptional activity between CHB and IC (table). Overall, there was a positive correlation between HBcrAg and intracellular HBV-DNA (R = 0.64, p = 0.003) and with intracellular HBV-RNA (R = 0.5, p = 0.03) but not with plasmatic HBV-RNA or other intracellular markers. In CHB subjects, a trend was observed between plasmatic HBV-RNA and cccDNA (R = 0.795), absent in ICs (R = -0.148).

	CHB (N = 7)	IC (N = 15)	p value
<i>Serum HBV markers</i>			
DNA (log IU/ml)	5.4 (4.9–5.8)	3.9 (3.8–4.1)	<0.001
qHBsAg (Log IU/ml)	4.3 (4.2–4.6)	3.5 (3.1–3.8)	0.004
HBcrAg (Log U/ml)	3.7 (2.6–4.4)	2.6 (2.3–2.8)	0.046
RNA (cop/ml)	2.4 (1.3–4.4)	1.3 (0.5–1.6)	0.019
<i>Intrahepatic HBV markers</i>			
DNA (cop/cell)	2.6 (0.0–12.2)	1.0 (0.7–2.2)	0.237
RNA (cop/25 ng total RNA)	79.0 (25.1–405.5)	56.2 (9.8–136.2)	0.400
cccDNA (cop/cell)	0.8 (0.4–2.4)	1.2 (0.5–1.5)	0.694
cccDNA transcriptional activity	104.1 (58.0–5682.0)	101.7 (6.3–214.1)	0.718

Median (IQR)

Conclusion: In HBeAg negative subjects within the grey zone, those with CHB present higher HBV-RNA and HBcrAg levels than ICs, while intrahepatic markers are similar.

PO-2834

HBsAg protein composition differs across stages of hepatitis B and hepatitis Delta: a validation cohort study

Luisa Roade^{1,2}, Sara Sopena Santistevé^{2,3}, Maria Pfefferkorn⁴, Mar Riveiro Barciela^{1,2}, Adriana Palom¹, Marta Bes^{2,5}, Rosario Casillas³, David Tabernero^{2,3}, Francisco Rodríguez-Frías^{2,3}, Thomas Berg⁴, Rafael Esteban^{1,2}, Florian van Bömmel⁴, Maria Buti^{1,2}. ¹Hospital Universitari Vall d'Hebron, Liver Unit, Barcelona, Spain; ²Instituto de Salud Carlos III, Madrid, Spain, Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas, Spain; ³Hospital Universitari Vall d'Hebron, Biochemistry and Microbiology Unit, Clinical Laboratories, Barcelona, Spain; ⁴Leipzig University medical center, Division of Hepatology, Department of Medicine, Leipzig, Germany; ⁵Banc de Sang i Teixits, Transfusion Safety Laboratory, Barcelona, Spain
Email: mbuti@vhebron.net

Background and aims: The components of the hepatitis B virus (HBV) surface antigen (HBsAg) small, medium and large surface proteins (SHBs, MHBs and LHBs) were proposed as novel tool to differentiate stages of chronic hepatitis B (CHB), including chronic hepatitis delta virus co-infection (CHD). We aimed to validate these findings independently in a well-characterized cohort with CHB or CHD infection, and at assessing a possible impact of HBV genotypes (GT).

Method: We performed a retrospective analysis in serum samples of 216 patients from an academic hospital in Barcelona (Spain). This population included 160 treatment-naïve patients with HBeAg negative chronic HBV infections: 86 chronic HBV infection/inactive carriers (ICs), 39 low viremic-LV subjects (normal ALT, HBV DNA >2000 IU/ml and absence of fibrosis), 35 HBeAg negative CHB; as well as 56 CHD patients (47 with detectable HDV RNA). MHBs and LHBs proteins were measured by ELISA in serum samples stored at -20°C. The proportion of each component was calculated based on total HBsAg levels (log₁₀ ng/ml; Siemens Healthcare, Enzygnost HBsAg 6.0). Results of IC were compared with those obtained in CHB and LV subjects analyzed altogether.

Results: Patients with HBeAg negative CHB had higher total HBsAg levels than IC patients (3.9 vs 3.4 log₁₀ IU/ml, p = 0.002). No differences in HBsAg levels were observed between CHB and ICs with HBsAg ≥1,000 IU/ml (p = 0.555). However, IC patients with HBsAg ≥1,000 IU/ml had significantly lower LHBs proportions compared to CHB patients (p = 0.036), regardless of HBV DNA levels. In both CHB and ICs, proportions of LHBs differed according to HBV genotype (GT) (Figure). Thus, HBV GT D patients showed higher LHBs levels as compared to GTA. In CHD patients, HBsAg levels were higher in those with detectable HDV RNA (p = 0.011). These patients also had higher LHBs ratios than those with undetectable HDV RNA (median 6.2 vs 3.2, p = 0.047). The LHBs proportion was similar between CHD patients with undetectable HDV RNA and ICs (median 3.2% vs. 3.4%, p = 0.289). No differences in MHBs proportions were found across all patient groups (p = 0.086).

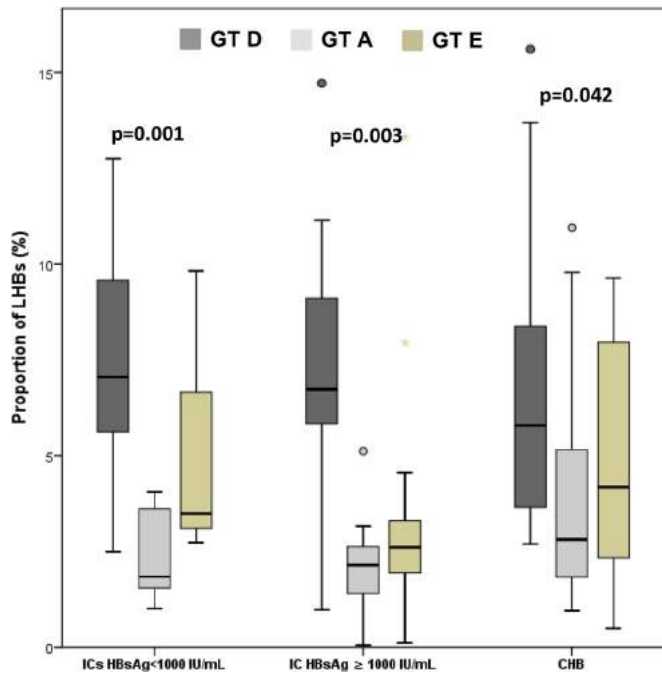


Figure:

Conclusion: Our results validated previous findings that ICs have lower LHBs ratios compared to patients with HBeAg negative CHB. They support the quantification of HBsAg components as a valuable clinical tool for CHB, and possibly also for CHD patients. HBV GT has a significant impact on LHBs proportion that needs to be further researched.

Viral hepatitis B-D: therapy

PO-43

Preliminary pharmacokinetics and safety in healthy volunteers of VIR-3434, a monoclonal antibody for the treatment of chronic hepatitis B infection

Sneha V. Gupta¹, Andre Arizpe¹, Marie C. Fanget¹, Sanjay Dholakiya¹, Ling Shen¹, Phil Pang¹, Chin Tay¹, Daniel Cloutier¹, Erik Mogalian¹, Edward Gane². ¹Vir Biotechnology, San Francisco, United States; ²University of Auckland, Auckland Clinical Studies, Auckland, New Zealand

Email: sgupta@vir.bio

Background and aims: VIR-3434 is a fully human, monoclonal antibody in development for the treatment of chronic hepatitis B virus (HBV) infection with three distinct modes of action: 1) entry inhibition via neutralization of all 10 HBV genotypes in vitro, 2) reduction of circulating HBsAg-containing particles in vivo, and 3) potential therapeutic vaccination via Fc engineering. Preliminary blinded pharmacokinetic (PK) and safety data from a Phase 1 study evaluating VIR-3434 in healthy volunteers is presented herein

Method: This is an ongoing randomized, double-blind, placebo-controlled Phase 1 single ascending dose study evaluating VIR-3434 in healthy volunteers (Part A) and participants with chronic HBV infection who are receiving nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy (Parts B-C). In Part A, healthy adults were randomized 3:1 to receive a single dose of VIR-3434 or placebo. Doses of 90, 300, and 900 mg were administered subcutaneously (SC), and doses of 900 and 3,000 mg were administered intravenously (IV). Subjects were followed for safety, tolerability, PK, and immunogenicity for 24 weeks following study drug administration.

Results: Forty-one subjects (n = 8 per cohort, with 1 subject replaced for non-safety related reasons) were enrolled and received VIR-3434 or placebo. Preliminary PK data for the 90–900 mg SC cohorts (N = 18) and blinded safety data for all cohorts (N = 41) are reported here. VIR-3434 was absorbed after SC injection with a median T_{max} of 7 days and has a half-life of approximately 28 days. Based on available data, exposure (C_{max} and AUC) increased in a dose proportional manner across the range of 90–900 mg. Intersubject variability within each cohort was generally low (CV ~35%). VIR-3434 was well tolerated across doses of 90–3,000 mg. A total of 24/41 (59%) subjects experienced adverse events (AEs), which were predominantly Grade 1. No serious adverse events (SAEs) were reported, and no clinically significant effects on laboratory parameters or electrocardiograms were observed.

Conclusion: VIR-3434 was well tolerated in healthy volunteers following single doses of up to 3,000 mg. VIR-3434 demonstrated favorable PK properties in healthy volunteers supportive of SC dosing and continued development for the treatment of chronic HBV infection. Additional data from this ongoing study, including PK from IV doses, will be presented.

PO-80

End-of-treatment HBsAg, HBcrAg and HBV RNA levels predict sustained response and HBsAg loss in chronic hepatitis B patients

Sylvia Brakenhoff¹, Robert De Knecht¹, Margo J.H. van Campenhout¹, Annemiek Van der Eijk², Willem Pieter Brouwer¹, Florian van Bömmel³, Andre Boonstra¹, Bettina Hansen^{4,5}, Thomas Berg³, Harry Janssen⁴, Robert De Man¹, Milan Sonneveld¹. ¹Erasmus MC, University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; ²Erasmus MC, University Medical Center, Viroscience, Rotterdam, Netherlands; ³Leipzig University Medical Center, Division of Hepatology, Department of Medicine II, Leipzig, Germany; ⁴Toronto General Hospital, University Health Network, Toronto Center for Liver Disease, Toronto, Canada; ⁵University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada
Email: s.brakenhoff@erasmusmc.nl

Background and aims: We recently demonstrated that high end-of-treatment (EOT) HBV RNA, HBsAg and HBcrAg levels are associated with an increased risk of off-treatment ALT flares. We aimed to assess the relationship between EOT serum hepatitis B biomarkers with sustained response and HBsAg loss.

Method: We studied chronic hepatitis B patients who participated in 3 global randomised controlled trials of peginterferon-based therapy (99-01 [PEG-IFN vs PEG-IFN + lamivudine], PARC [PEG-IFN vs PEG-IFN + ribavirin] and ARES [entecavir with PEG-IFN add-on]). Serum HBsAg, HBV RNA and HBcrAg were quantified at EOT. Associations between serum biomarkers and treatment response were assessed using continuous data and after categorisation (low vs high; <3/>3 log for HBsAg, undetectable/detectable for HBV RNA, and for HBcrAg <3/>3 log HBeAg-negative and <6/>6 log for HBeAg-positive patients). SCALE-B score (comprising HBsAg and HBcrAg) was calculated and categorised (<260, 260–320, ≥320). Treatment response was defined as sustained response (SR; HBV DNA levels <2,000 IU/ml 6 months after EOT) and HBsAg loss. We excluded patients who were HBsAg-negative at EOT.

Results: We included 344 patients with EOT data; 230 HBeAg-positive and 114 HBeAg-negative. Patients were predominantly Caucasian (77.0%) and had genotype A/B/C/D in 23/7/13/52%. SR was achieved in 57/311 (18.3%) and HBsAg loss in 6 (1.8%) patients. Lower HBsAg (OR 0.480, 95% CI 0.371–0.621, p < 0.001), HBV RNA (OR 0.119, 95% CI 0.017–0.807, p = 0.029) and HBcrAg (OR 0.658, 95% CI 0.565–0.767, p < 0.001) levels were associated with higher probability of SR (Figure) and HBsAg loss. Combinations of biomarkers improved prediction. Among 65 patients with both high HBV RNA and HBsAg levels, 2 (3.1%) achieved SR, compared to 23/36 patients (63.9%) with both low levels (p < 0.001; Figure). HBsAg loss was exclusively observed in patients with both low levels of HBsAg and HBV RNA

POSTER PRESENTATIONS

(7.3% vs 0.0%, $p = 0.004$). Findings were consistent when data was stratified based on HBeAg-status and in multivariate analysis adjusted for potential predictors including HBeAg-status and EOT response (HBV DNA <200 IU/ml).

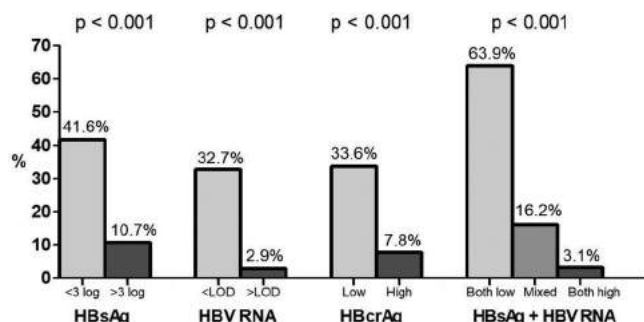


Figure: Rates of sustained response (HBV DNA <2,000 IU/ml 6 months after treatment withdrawal), according to HBsAg, HBcrAg and HBV RNA levels at end-of-treatment.

Conclusion: Lower EOT HBsAg, HBcrAg and HBV RNA levels are associated with higher probability of sustained response and HBsAg loss after therapy cessation. Combinations of biomarkers improved response prediction, supporting the use of combined biomarkers as treatment end points in HBV trials.

PO-111

One-year safety results of the Nuc-Stop Study, an open-label study on stopping antiviral therapy in HBeAg negative chronic hepatitis B

Asgeir Johannessen¹, Dag Henrik Reikvam², Soo Aleman³, Nega Berhe⁴, Nina Weis⁵, Lars Heggelund⁶, Lars Normann Karlsen⁷, Pascal Brugger-Synnes⁸, Hans Erling Simonsen⁹, Jan Svendsen¹⁰, Olav Dalgard¹¹, ¹Sykehuset i Vestfold, Tønsberg, Norway; ²Oslo University Hospital Ullevål, Oslo, Norway; ³Huddinge Hospital, Sweden; ⁴Addis Ababa University, Addis Ababa, Ethiopia; ⁵Hvidovre Hospital, Hvidovre, Denmark; ⁶Drammen sykehus, Norway; ⁷Stavanger Universitetssjukehus-SUS, Norway; ⁸Ålesund Sykehus, Norway; ⁹Nordland Hospital, Bodø, Bodø, Norway; ¹⁰Vestre Viken-Baerum Hospital, Norway; ¹¹Akershus University Hospital, Lørenskog, Norway
Email: johannessen.asgeir@gmail.com

Background and aims: Antiviral therapy effectively reduces the risk of complications in chronic hepatitis B (CHB). However, treatment is indefinite as a functional cure, defined as loss of hepatitis B s-antigen (HBsAg), rarely occurs with antiviral therapy. Stopping antiviral therapy may trigger an immune response which induces HBsAg loss, but there is concern about the safety of this intervention. Here we present one-year safety results of the Nuc-Stop Study, a randomized, multicentre, open-label trial of stopping antiviral therapy in hepatitis B e-antigen (HBeAg) negative CHB patients.

Method: HBeAg negative CHB patients with at least 24 months of full viral suppression were eligible for inclusion. Patients with past or present evidence of cirrhosis were excluded. All study participants stopped antiviral therapy and were randomized to either low threshold (alanine aminotransferase [ALT] >80 U/L and viral load >2000 IU/ml) or high threshold (ALT >100 U/L for >4 months or ALT >400 U/L for >2 month) for re-start of therapy. Patients in both groups re-started therapy in case of a severe flare, defined as ALT >800 U/L or any ALT flare with INR ≥ 1.4 or bilirubin >38 mmol/L.

Results: A total of 127 patients were included at 11 centres in Norway, Sweden, Denmark and Ethiopia; 86 (67.7%) were men and median age was 43 years (range 25–66). Median duration of antiviral treatment prior to inclusion was 45 months (interquartile range 32–76), and most patients were receiving either tenofovir disoproxil fumarate (TDF; $n = 90$; 70.9%) or entecavir ($n = 30$; 23.6%). During the initial 12 months after treatment cessation, 108 patients (85.0%) experienced virological relapse (viral load >2000 IU/ml) and 44

(34.6%) had clinical relapse (ALT >80 U/L and viral load >2000 IU/ml). Nine patients (7.1%) had a severe flare (maximum ALT 2600 U/L), one of whom had bilirubin >38 mmol/L. The occurrence of a severe flare was neither associated with age, sex nor duration of previous antiviral treatment; however, all nine occurred among patients who stopped TDF therapy. No other serious adverse events related to treatment interruption were observed.

Conclusion: Stopping long-term nucleoside analogue therapy was safe among non-cirrhotic HBeAg negative CHB patients, although one in ten patients stopping TDF therapy experienced a severe flare.

PO-247

On-treatment HBsAg kinetics can predict HBsAg loss after nucleos(t)ide analogues interruption in HBeAg negative patients

Teresa Broquetas^{1,2,3}, Juan-Jose Hernandez⁴, Montserrat Garcia-Retortillo^{1,2,3}, Lidia Canillas^{1,3}, Marc Puigvehí^{1,2,3}, Nuria Cañete Hidalgo^{1,2,3}, Susana Coll^{1,2,3}, Ana Viu^{1,3}, Esther Garrido^{1,3}, Judit Romero^{1,3}, Xavier Bessa^{1,2,3}, Jose A. Carrión^{1,2}. ¹Hospital del Mar, Liver Section, Gastroenterology Department, Barcelona, Spain; ²Universitat Autònoma de Barcelona, Medicina, Bellaterra, Spain; ³IMIM, Barcelona, Spain; ⁴Laboratori de Referència de Catalunya, Spain
Email: 95565@parcdesalutmar.cat

Background and aims: Studies in Asian and Caucasian patients with HBeAg-negative chronic hepatitis B (CHB) have shown that nucleos(t)ide analogues (NA) withdrawal after a long-term viral suppression, can improve HBsAg loss rates. However, there are not well-established conditions during therapy to select patients who will benefit from this strategy. The aim of the study was to evaluate HBsAg kinetics before and after treatment interruption.

Method: Single centre, longitudinal, ambispective study in non-cirrhotic CHB HBeAg-negative patients analysing HBsAg levels before and after NA withdrawal. Patients were eligible if they had been under NA therapy for at least 3 years. HBsAg levels were evaluated before NA initiation, at 1 and 3 years of therapy, at end of treatment, and at weeks 12, 24, 36, 48, 72 and 96 post-treatment. We report the results 48 weeks after NA interruption.

Results: From December 2017 to October 2019, 75 patients were evaluated, 17 (23%) declined participation, and serum samples were suboptimal in 6. Therefore, HBsAg kinetics before and after NA interruption were evaluated in 52, 75% males, median age of 52 years, treatment duration of 8.2 years, 65% with TDF, and 56% infected by genotype D. During 48 weeks after NA interruption, 6 (11.5%) patients lost HBsAg. Multivariate analysis showed that on-treatment HBsAg decline was independently associated with HBsAg loss after NA interruption (OR = 0.10; 95%CI = 0.016–0.632; $p = 0.014$). Patients with an HBsAg decline >1 log₁₀ IU/ml ($n = 10$) showed lower HBsAg levels before interruption (114 vs. 1277; $p = 0.001$) despite before NA initiation were similar (3330 vs. 3891; $p = ns$). Therefore, 50% of patients with HBsAg decline >1 log₁₀ IU/ml or HBsAg <100 before NA interruption achieved HBsAg loss during the first year after treatment withdrawal ($p = 0.001$).

Conclusion: Kinetics of HBsAg during antiviral treatment can predict the frequency of HBsAg loss after NA interruption. Half of the patients with a significant HBsAg decline (>1log IU/ml) or HBsAg <100IU/ml during therapy can eliminate HBsAg during the first year after NA withdrawal.

PO-397

Novel hepatitis B virus gene expression inhibitor in clinical development

Yixin Zhou¹, Wenqiang Wu¹, Shikui Chen¹, Zhou Yu¹, Neha Nagpal², Suneet Agarwal², Vadim Bichko¹, John Mao¹, Yanbin Hu³, Fei Sun³, Qiong Zhou³, Charles Z. Ding³, Shuhui Chen³. ¹Fujian Cosunter Pharmaceutical Co., Ltd., Fuzhou, China; ²Boston Children's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, United States; ³Domestic Discovery Service Unit, WuXi AppTec (Shanghai) Co., Ltd., Shanghai, China
Email: vbichko@gmail.com

Background and aims: The currently used therapies for chronic hepatitis B virus (HBV) infection seldom achieve hepatitis B serum surface antigen (HBsAg) loss. However, HBsAg loss is considered one of the ultimate end points, leading to restoration of the immune function and achieving virus control. GST-HG131 is a small-molecule inhibitor of hepatitis B virus (HBV) gene expression that significantly reduces the levels of hepatitis B surface antigen (HBsAg) and HBV DNA in vitro and in HBV mouse models. Here we report preclinical characterization of GST-HG131, which is currently under phase I clinical evaluation.

Methods: Effects on HBsAg, hepatitis B e-antigen (HBeAg), HBV DNA and RNA were determined in HepG2.2.15 cells and in primary human hepatocytes (PHH), using ELISA, qPCR and northern blotting. Terminal nucleotidyl transferase 4B (TENT4B) binding and inhibition assays were done as previously described (Nagpal et al, Cell Stem Cell 2020 4;26 (6):896–909). The in vivo antiviral efficacy was assessed in the AAV-HBV mouse model.

Results: GST-HG131 potently inhibited secretion of HBsAg (EC₅₀ = 3.4 ± nM), HBeAg (EC₅₀ = 8 nM, and HBV DNA (EC₅₀ = 3.3 ± 1.7 nM) from HepG2 2.15 cells in the absence of cytotoxicity (CC₅₀ >100 microM), and was additive with Entecavir. The antiviral effects of GST-HG131 were not significantly affected (EC50 fold shift = 1.5) by 50% human serum. Secretion of both HBsAg and HBeAg by PHH was also strongly inhibited, with the EC₅₀ values of 18 and 19 nM, respectively). In cell culture experiments, GST-HG131 significantly reduced the level of HBV 2.4/2.1 kb RNAs, as well as 3.5 kb pre-genomic RNA, albeit to a lesser extent, in a concentration-dependent manner. It was shown that GST-HG131 binds recombinant TENT4B, and potently inhibits its enzymatic function in vitro, disrupting polyadenylation tail of mRNAs. No significant cytotoxicity was observed

in nine human cell lines and primary cells (CC₅₀ >10 microM). HBV inhibition by GST-HG131 was specific, as no other tested DNA and plus-/minus-strand RNA viruses were inhibited. In the AAV/HBV model, GST-HG131 demonstrated a robust dose-dependent reduction in serum HBsAg (~1 log₁₀), following 28 days of dosing. Combination with Tenofovir resulted in additivity. GST-HG131 was well-tolerated, no significant effect on animal body weight was observed.

Conclusions: GST-HG131 is a novel, orally-bioavailable inhibitor of HBV gene expression. It has an excellent antiviral potency in vitro, efficacy in vivo, and is well-tolerated in rodents. The molecular mechanism of GST-HG131 antiviral action, including strong inhibition of HBsAg secretion, involves binding to and inhibition of TENT4B, leading to shortening of poly-adenylation tail of HBV mRNAs, and thus accelerating its degradation. Further development of GST-HG131 for chronic HBV infections is warranted. Currently GST-HG131 is undergoing phase I clinical evaluation.

PO-430

High probability of reactive HBV-specific CD8 cells after stopping nucleos(t)ide analogue treatment forecast rapid HBsAg decrease in eAg (-) chronic hepatitis B

Julia Peña Asensio^{1,2}, Henar Calvo^{2,3}, Joaquin Miquel^{2,3}, Eduardo Sanz de Villalobos^{2,3}, Alejandro González Praetorius^{2,4}, Miguel Torralba^{2,5,6}, Juan Ramón Larrubia^{2,3,6}. ¹University of Alcalá, Departamento de Biología de Sistemas, Alcalá de Henares, Spain; ²Guadalajara University Hospital, Translational Hepatology Unit, Guadalajara, Spain; ³Guadalajara University Hospital, section of Gastroenterology and Hepatology, Guadalajara, Spain; ⁴Guadalajara University Hospital, Section of Microbiology, Guadalajara, Spain; ⁵Guadalajara University Hospital, Service of Internal Medicine, Guadalajara, Spain; ⁶University of Alcalá, Department of Medicine and Medical Specialties, Alcalá de Henares, Spain
Email: juan.larrubia@uah.es

Background and aims: Restoration of a reactive cytotoxic T cell response (RCTCR) during eAg (-) chronic hepatitis B (CHBeAg (-)) treatment with nucleos (t)ide analogue (NUC) could lead to functional cure. We developed a model to predict RCTCR with variables involved in T cell exhaustion. We tested the model as treatment stopping rule.

Method: In NUC treated CHBeAg (-), we checked for peripheral HBV-specific RCTCR detection. We performed a logistic regression model (LRM) to predict RCTCR probability, based on patients' age (infection

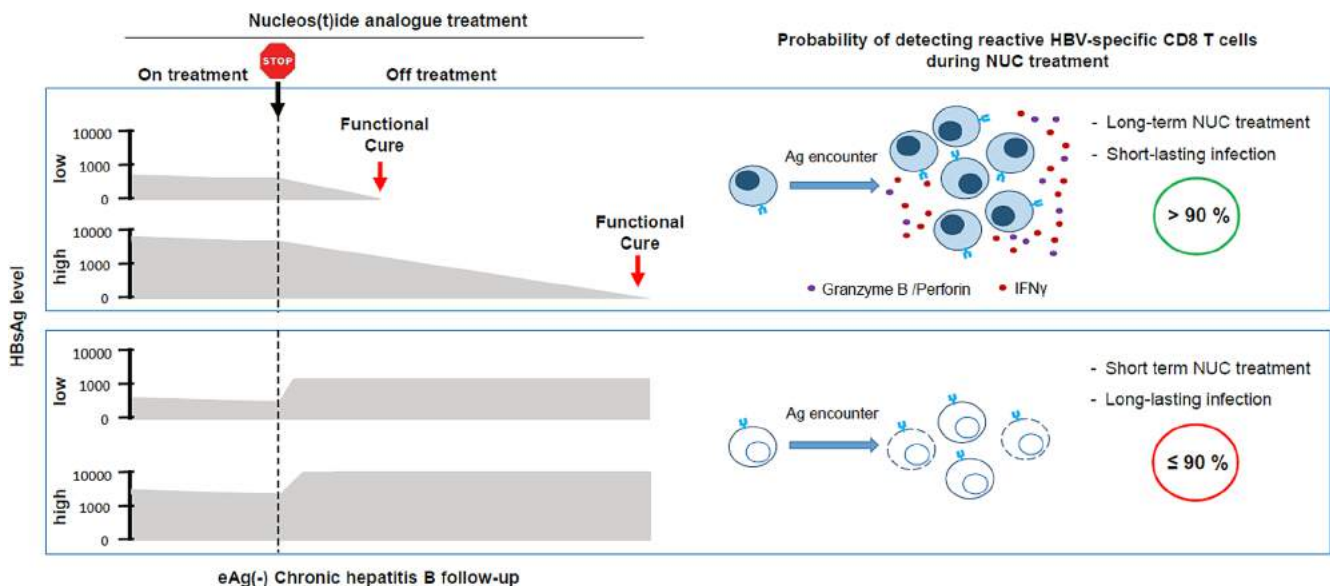


Figure: (abstract: PO-430)

POSTER PRESENTATIONS

length), NUC treatment duration and HBsAg level (antigenic pressure). We stopped NUC treatment and assessed >50% HBsAg decline during follow-up, according to RCTCR probability.

Results: We observed a negative correlation between HBsAg and both treatment duration and patients' age. We found higher HBsAg level in short-term (ST) than in long-term (LT) treated cases. HBV-core18-27 and HBV-pol455-63 RCTCRs were more frequent, and interferon- γ secreting cells were more prevalent in LT group. Peripheral HBV-env183-91-specific CD8 cells were deleted in both groups. LRM predicted HBV-core18-27 RCTCR presence which, correlated positively with treatment duration and negatively with age but not with HBsAg level. LRM explained 55% of the observed variability. After stopping treatment, HBsAg decline during 24-month median follow-up was faster in patients with RCTCR probability >90%, independently of HBsAg level at treatment stop, although HBsAg loss was higher in cases with HBsAg <1000 IU/ml.

Conclusion: Short-term Ag exposure rather than its level and long-lasting NUC treatment impact on RCTCR presence. High probability of RCTCR detection after NUC treatment withdrawal associates with rapid HBsAg reduction.

PO-482

Viral response and safety following discontinuation of treatment with the core inhibitor vebicorvir and a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg positive or negative chronic hepatitis B virus infection.

Edward Gane¹, Mark Sulkowski², Xiaoli Ma³, Tuan Nguyen⁴, Hie-Won Hann⁵, Tarek Hassanein⁶, Magdy Elkhatab⁷, Sing Chan⁸, Ronald Nahass⁹, Michael Bennett¹⁰, James Park¹¹, Ira Jacobson¹¹, Maurizio Bonacini¹², Julie Ma¹³, Ran Yan¹³, Steven J. Knox¹³, Luisa Stamm¹³, Alnoor Ramji¹⁴, Steven-Huy B. Han¹⁵, Walid Ayoub¹⁶, Natarajan Ravendhran¹⁷, Paul Yien Kwo¹⁸, Douglas Dieterich¹⁹, Ho Bae²⁰, Eugene R. Schiff²¹, Jacob Lalezari², Scott Fung²², Man-Fung Yuen²³. ¹Auckland Clinical Studies, Ltd., Auckland, New Zealand; ²Johns Hopkins School of Medicine, Baltimore, United States; ³Office of Xiaoli Ma, Philadelphia, United States; ⁴T Nguyen Research and Education, Inc., San Diego, United States; ⁵Thomas Jefferson University Hospital, Philadelphia, United States; ⁶Southern California Research Center, Coronado, United States; ⁷Toronto Liver Centre, Toronto, Canada; ⁸Sing Chan MD, New York, United States; ⁹Infectious Disease Care, Hillsborough, United States; ¹⁰Medical Associates Research Group, San Diego, United States; ¹¹New York University Langone Medical Center, New York, United States; ¹²Quest Clinical Research, San Francisco, United States; ¹³Assembly Biosciences, Inc, South San Francisco, United States; ¹⁴Providence Health Care Research Institute, Vancouver, Canada; ¹⁵Pfeger Liver Institute, University of California, Los Angeles, United States; ¹⁶Cedars-Sinai Medical Center, Los Angeles, United States; ¹⁷Digestive Disease Associates, Catonsville, United States; ¹⁸Stanford University Medical Center, Stanford, United States; ¹⁹Icahn School of Medicine, Mount Sinai Hospital, Department of Medicine, Division of Liver Diseases, New York, United States; ²⁰Asian Pacific Liver Center, Los Angeles, United States; ²¹Schiff Center for Liver Diseases, University of Miami School of Medicine, Miami, United States; ²²University of Toronto, Toronto, Canada; ²³The University of Hong Kong, Medicine, Hong Kong Email: lstamm@assemblybio.com

Background and aims: Vebicorvir (VBR) is a 1st-generation core inhibitor being developed for chronic HBV infection (CHBV). In Study 201, Nrtl-suppressed eAg pos or eAg neg CHBV patients (pts) with F0-F2 fibrosis were randomized to VBR or placebo +Nrtl for 24 wks. Eligible pts then received VBR+Nrtl in Study 211. VBR+Nrtl resulted in deep on-treatment viral suppression assessed by high sensitivity assays. VBR+Nrtl was discontinued if total HBV nucleic acid (DNA +pgRNA) was <20 U/ml and eAg negative or levels \leq 5 IU/ml for \geq 6 mths at Wk 52 or later. Here we report off-treatment (off-Rx) viral response and safety after VBR+Nrtl discontinuation (DC) in Study 211. **Method:** The primary end point in Study 211 was sustained virologic response (SVR; HBV DNA <20 IU/ml, COBAS TaqMan v2.0) 24 wks off-

treatment. eAg and sAg were measured by Abbott Architect (LLOQ = 0.11 IU/ml, 0.05 IU/ml, respectively) and crAg by Lumipulse G (LOD = 1 kU/ml). Safety was assessed by adverse events (AEs) and labs. Nrtl was restarted per protocol-specified criteria or investigator/pt preference.

Results: Of the pts in Study 211, 18 of 43 eAg pos and 23 of 26 eAg neg pts discontinued VBR+Nrtl. In these 41 pts, the mean age was 46 yrs, 71% male, 78% Asian, 80% on TFV and 20% on ETV. At time of DC, the mean duration of VBR treatment was 76 wks and Nrtl was 6 yrs; the eAg pos pts had mean eAg 1.1 IU/ml, crAg 247 kU/ml and sAg 6595 IU/ml and the eAg neg pts had mean crAg 7.0 kU/ml and sAg 2808 IU/ml. No pt achieved SVR. Of the 18 eAg pos pts, 17 (94%) relapsed early at off-treatment (off-Rx) Wk 4 and 1 pt (6%) relapsed at off-Rx Wk 12. Of the 23 eAg neg pts, 16 (70%) relapsed early at off-Rx Wk 4, and 3 (13%) and 4 (17%) pts relapsed later at off-Rx Wk 12 and 16, respectively. Univariate logistic regression identified ETV use ($p < 0.001$) and lower crAg ($p = 0.03$) as associated with later relapse after off-Rx Wk 4. The current mean time off-Rx was 19 wks with 29/41 (71%) pts restarting Nrtl with subsequent decline in HBV DNA. Off-Rx, 14/41 (34%) pts had AEs, most Grade 1 or 2. The most common AE was ALT elevation in 4/41 (10%) pts. No pt had confirmed ALT flare ($\geq 10 \times$ ULN) or hepatic decompensation. Two unrelated SAEs were reported, hemorrhage following surgery and seizure.

Conclusion: While VBR+Nrtl DC was well-tolerated, SVR was not achieved. Data suggest crAg level may be important in future DC criteria. Other studies with VBR+Nrtl in multi-drug combinations will evaluate potential finite treatment regimens.

PO-655

Activation of inducible caspase 9 allows efficient depletion of adoptively transferred HBV-specific T cells

Alexandre Klopp¹, Martin Pule², Ulrike Protzer³, Karin Wisskirchen³. ¹Institute of Virology, Helmholtz Zentrum München/Technical University Munich, School of Medicine, Munich, Germany; ²Cancer Institute, University College London, London, United Kingdom; ³Institute of Virology, Helmholtz Zentrum München/Technical University Munich, School of Medicine, Munich, Germany Email: alexandre.klopp@tum.de

Background and aims: Adoptive T-cell therapy with T cells that express either an HBV-specific chimeric antigen receptor (S-CAR) or T-cell receptor (TCR) represents a promising therapeutic strategy for treatment of chronic hepatitis B and HBV-associated cancer. However, side effects such as cytokine release syndrome or hepatotoxicity are not excluded. Inclusion of a safeguard mechanism, which allows depletion of transferred T cells on demand, would thus be an interesting means to increase safety of T-cell therapy.

Method: In this study, T cells were generated by retroviral transduction to co-express an HBV-specific receptor and in addition a safeguard molecule, namely inducible Caspase 9 (iCasp9), herpes simplex virus thymidine kinase (HSV-TK), or the CD20-based molecule RQR8. First, comparative experiments including the different safeguard molecules were performed and iCasp9 proved to be the most efficient and practical approach to deplete HBV-specific cells. It was further evaluated *in vitro* and *in vivo*.

Results: *In vitro*, co-expression of iCasp9, slightly reduced receptor expression but did not alter T cell functionality. HBV-specific T cells were specifically activated to secrete IFN γ and kill HBV⁺ target cells. Real-time cytotoxicity assays using HBV-replicating HepG2.2.15 hepatoma cells revealed that induction of iCasp9 by addition of an iCasp9 dimerizer to activate caspase 9 function halted cytotoxicity of HBV-specific T cells within less than one hour.

In vivo, iCasp9 expressing S-CAR T cells were injected into AAV-HBV-infected Rag2IL2rg^{-/-} mice followed by the dimerizer at day four. By day seven, numbers of S-CAR⁺ T cells in both liver and spleen were reduced by 3log₁₀ in comparison to mice in which depletion of HBV-specific T cells had not been induced. After iCasp9 induction, the remaining S-CAR T cells were mostly unfunctional as determined by

restimulation with HBsAg and intracellular cytokine staining. Depletion of transferred T cells halted hepatotoxicity but also reduced the antiviral effect of S-CAR T cells.

Conclusion: In conclusion, T cells co-expressing iCasp9 and HBV-specific receptors efficiently recognize and kill HBV-replicating cells. Induction of cell death via iCasp9 is efficient *in vitro* and *in vivo*, leading to a strong depletion of transduced T cells and prevention of cytotoxicity.

PO-715

One-year safety and efficacy of tenofovir alafenamide (TAF) in chronic hepatitis B (CHB): a Hellenic multicenter ReAl-life CLinical Study (HERACLIS TAF)

George Papatheodoridis¹, Konstantinos Mimidis², Spiliotis Manolakopoulos^{1,3}, Nikolaos Gatselis⁴, Ioannis Goulis⁵, ANDREAS Kapatais⁶, Emmanouil Manesis⁷, Themistoklis Vasileiadis⁸, Christos Triantaris⁹, Demetrios N. Samonakis¹⁰, Vasilis Sevastianos¹¹, Stylianos Karapatanis¹², Ioannis Elefsiniotis¹³, Melanie Deutsch³, Theodora Mylopoulou², Margarita Papatheodoridi¹, Hariklia Kranidioti³, Polyxeni Agorastou⁵, Theofanie Karaoulani⁶, Anastasia Kyriazidou⁸, Konstantinos Zisimopoulos⁹, George Dalekos⁴.

¹Medical School of National and Kapodistrian University of Athens, Department of Gastroenterology, Laiko General Hospital of Athens, Athens, Greece; ²Democritus University of Thrace, A Department of Internal Medicine, Alexandroupolis, Greece; ³Medical School of National and Kapodistrian University of Athens, 2nd Department of Internal Medicine, Hippokratio General Hospital of Athens; Athens, Greece; ⁴Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Department of Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; ⁵Hippokratio Hospital, Aristotle University of Thessaloniki, 4th Department of Internal Medicine, Thessaloniki, Greece; ⁶General Hospital Nikaia-Piraeus Agios Panteleimon, General Hospital of Western Attica Agia Varvara, Athens, Greece; ⁷Euroclinic SA, Liver Unit, Athens, Greece; ⁸Aristotle University of Thessaloniki, "Papageorgiou" Hospital, Thessaloniki, 3rd Department of Internal Medicine, Thessaloniki, Greece; ⁹University Hospital of Patras, Department of Gastroenterology, Patras, Greece; ¹⁰Department of Gastroenterology and Hepatology, University Hospital of Heraklion Crete, Heraklion, Greece; ¹¹Evangelismos General Hospital, Athens; 4th Department of Internal Medicine and Liver Outpatient Clinic, Athens, Greece; ¹²General Hospital of Rhodes, 1st Department of Internal Medicine, Rhodes, Greece; ¹³General and Oncology Hospital of Kifisia Agioi Anargyroi, University Department of Internal Medicine, Athens, Greece

Email: gepapath@med.uoa.gr

Background and aims: In the registrational trials, TAF compared to tenofovir disoproxil fumarate (TDF) was shown to have similar efficacy and improved safety in renal function and bone mineral density (BMD) parameters, but CHB patients with significant renal and/or bone disorders were not included. In Greece, TAF has been reimbursed since 02/2018 for CHB patients with estimated glomerular filtration rate (eGFR) <60 ml/min, serum phosphate <2.5 mg/dl or osteoporosis (T-score <-2.5). This study assessed the safety and efficacy of one-year TAF therapy in CHB patients treated in Greek tertiary liver centers.

Method: Adult (≥18 years old) CHB patients who started TAF between 02/2018–10/2019 at 13 clinics participating in the HERACLIS-TAF registry were included. Main exclusion criteria were coinfection with HDV, active malignancy and bisphosphates use in the last 6 months. Clinical and laboratory characteristics were recorded at onset and 6 and 12 months of TAF. MDRD formula was used for eGFR (ml/min) estimation.

Results: TAF was initiated in 176 patients: age 64 ± 12 years, 71% males, 85% undetectable HBV DNA, 86% ALT<40, 45% eGFR<60, 94% nucleos (t)ide analogue (NA) experienced (91% directly switched to TAF from another NA–81% from TDF; 3% NA discontinuation >2 months). At month-12 of TAF, HBV DNA was undetectable (<15 IU/ml)

in 97% and ALT was <40 IU/L in 96% of cases. In cases switching to TAF from other NA, median ALT decreased from onset to month-12 of TAF (23 to 21 IU/L, P < 0.001). Mean eGFR had decreased from previous NA onset (74 ± 28) to TAF onset (65 ± 27, P < 0.001) and then increased at 6 (69 ± 26, P < 0.001) or 12 months of TAF (71 ± 29, P < 0.001). eGFR difference between 12 months and onset of TAF was ≥0 in 71% and ≥10 in 65% of cases; eGFR difference >0 was not associated with any patients' characteristic, while eGFR difference >10 was associated with BMI>25 [OR:2.4 (1.1–5.1), P=0.024] and no hemodialysis. In cases starting TAF with phosphate <2.5, mean phosphate levels increased from onset to month-12 (2.1 to 2.7, P < 0.001). Mean BMD did not change significantly from onset to month-12 of TAF (T-score: -2.1 to -1.9, P = 0.164).

Conclusion: In mostly NA experienced CHB patients with renal and/or bone disorders/risks, one year of TAF achieves maintenance of virological suppression and improvement of ALT, eGFR and serum phosphate levels. eGFR improvement >10 ml/min can be achieved in >2/3 of non-hemodialysis patients and seems to be associated with BMI >25 kg/m².

PO-774

A combination of gapmers and/or siRNA as potential gene therapy strategy against HBV infection: in vitro results.

Maria Francesca Cortese^{1,2}, Selene Garcia-Garcia^{1,2}, Beatriz Pacín^{1,2}, Rosario Casillas^{1,2}, David Taberner^{1,3}, Roser Maria Ferrer-Costa⁴, Mar Riveiro Barciela^{3,5}, Maria Buti^{3,5}, Francisco Rodríguez-Frías^{1,2,3}. ¹Vall D'hebron University Hospital, Biochemistry and Microbiology/Liver Pathology Unit, Barcelona, Spain; ²Vall D'hebron Research Institute, Liver Unit, Spain; ³InstitutoDe Salud Carlos III, Centro DeInvestigación Biomédica En Red, Enfermedades Hepáticas y Digestivas (CIBERehd), Spain; ⁴Vall D'hebron University Hospital, Department of Biochemistry, Spain; ⁵Vall D'hebron University Hospital, Liver Unit, Internal Medicine Department, Barcelona, Spain
Email: maria.cortese@vhir.org

Background and aims: Hepatitis B virus (HBV) infection cannot be eradicated due to the persistence of its covalently closed circular DNA, which supports HBV proteins expression, contributing to hepatocellular carcinoma development. Gene silencing could be a valuable strategy and HBX gene, thanks to its co-terminal localization, an optimal target. Here we present a gene therapy strategy based on antisense locked nucleic acid (LNA) Gapmer (GP) and siRNA targeting HBX hyper-conserved regions.

Method: HepG2-NTCP cells were treated with DMSO 2.5% at least 14 days and later infected with HBV at 500 multiplicities of genome equivalents by centrifugation at 37°C for 1 h and incubating overnight. Infected cells were treated with GP (GP1 and/or GP4 at 50nM, Qiagen) and/or siRNA (50nM) using TransIT-X2 at 48 h or 5d post infection (pi). A scrambled control gapmer was used in each experiment. Cells and supernatants were collected after 72 h of treatment. Pregenomic RNA (pgRNA) was extracted from cells through RNAeasy Plus mini kit (Qiagen) and quantified by RT-qPCR using TaqMan probe (Roche, Lightcycler@480). HBsAg and HBeAg were quantified in supernatants by chemiluminescent enzyme assay (Roche, COBAS@8000).

Results: Early after infection (at 48hpi), GP1 treatment allowed an inhibition of more than 70% for both pgRNA, HBeAg and HBsAg (respectively 75.5 ± 9.9; 74.7 ± 6.4 72.4 ± 7.7%). Differently, GP4 showed an inhibition between 7.4 and 13 percentage points lower than GP1 (62 ± 17; 66.1 ± 11.2 and 64.7 ± 12% for respectively pgRNA, HBeAg and HBsAg). When GP were introduced at late timepoint (5 dpi), the inhibition of pgRNA decreased for both GP1 and GP4 (respectively 53.5 ± 29% and 58.5 ± 17%). The efficiency was lower if considering viral proteins expression (less than 48% for both GP). Of note, the combination of both GP or GP with a siRNA increased the inhibition efficiency of pgRNA (69.1 ± 16.5%; 66.7 ± 12.2%; 63.8 ± 21% for respectively GP1+GP4; GP1+siRNA; GP4+siRNA), just partially improving viral proteins inhibition.

POSTER PRESENTATIONS

Conclusion: Gapmers seem to be valuable molecules to inhibit HBV expression *in vitro*. Their limited efficiency after the establishment of a productive infection (5 dpi) could be improved by combining GP with each other or with siRNA targeting the same hyper-conserved region. Further experiments are required to confirm these results and other delivery systems should be tested to improve treatment efficiency. Funding: Instituto de Salud Carlos III (grant PI18/01436), co-financed by the European Regional Development Fund (ERDF).

PO-797

Tenofovir alafenamide in blocking mother-to-child transmission of hepatitis B virus: A multi-center, prospective clinical study

Guorong Han¹, Guanlun Zhou¹, Tong Sun², Xiucui Luo³, Jinxia Xu⁴, Chao Chen¹, Wen Xu³, Su'e Jiang⁴, Chenxu Wang¹. ¹The Affiliated Nanjing Hospital of Nanjing University of Chinese Medicine; ²The Fifth People's Hospital of Wuxi; ³The Maternal and Child Health Hospital of Lianyungang; ⁴The Maternal and Child Health Hospital of Huai'an
Email: hgr518@163.com

Background and aims: Few data are available regarding the administration of tenofovir alafenamide (TAF) during pregnancy for the prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV). This prospective study aimed to evaluate the efficacy and safety of TAF for preventing MTCT of HBV.

Method: In this ongoing, multi-center, prospective study, chronic HBV-infected pregnant women aged from 20 to 35 years old, positive for Hepatitis B e-antigen and with HBV DNA level at least 1×10^6 IU/ml, received oral TAF (25 mg/day) from gestational weeks 24–28 until postpartum week 4. All infants received HBV immunoprophylaxis. The participants, including mothers and infants, were followed up until postpartum week 28. The primary measurement was MTCT rate. The key secondary measurement was the safety of TAF for mothers and infants. The other assessments were the dynamic changes of HBV DNA, liver and renal function of mothers.

Results: To date, 91 mothers were enrolled, 2 of them were unable to get TAF due to the COVID-19 outbreak and dropped out after enrollment. 84 mothers delivered, and 86 infants (two sets of twins) were born. 54 mothers (56 infants) were followed up to postpartum week 28. TAF therapy was initiated at a mean gestational age of 25.04 (± 0.96) weeks with the mean treatment duration of 14.3 (± 1.2) weeks before delivery. 96.4% (81/84) mothers discontinued the TAF treatment, the median [interquartile range, IQR] time was 5.9 [4.5, 9.8] weeks postpartum. The HBsAg positive rate was 0% at 7 months in 56 infants, among whom no growth retardation was detected at that time. No infant (0/86) had congenital defects. 84 mothers were tolerated during TAF treatment and had no drug-related serious adverse events. At delivery, 82.1% (69/84) mothers achieved an HBV DNA level < 200000 IU/ml, and 20.2% (17/84) mothers achieved an HBV DNA level < 500 IU/ml. There were no significant changes on the mean (\pm SD) serum phosphate between baseline (1.20 ± 0.10 mmol/L) and at delivery (1.22 ± 0.13 mmol/L, $p = 0.85$). The serum creatinine at delivery (51.97 ± 8.65 μ mol/L) was higher than baseline (45.97 ± 5.60 μ mol/L, $p < 0.05$), but all within the normal range. None of the mothers had ALT flares on TAF treatment during pregnancy, however, 9 of 81 mothers who stopped TAF treatment after delivery had mild ALT flare.

Conclusion: TAF therapy initiated during the second trimester for HBV-infected pregnant women with HBeAg positive and HBV DNA level $> 1 \times 10^6$ IU/ml was effective in preventing MTCT, and there were no safety concerns for mothers and infants with 28 weeks of follow-up after delivery. (ClinicalTrials.gov number, NCT04065230).

PO-811

Unreliable estimation of fibrosis regression during treatment by liver stiffness measurement in patients with chronic hepatitis B

Dong Ji¹, Yan Chen¹, Yongping Yang¹. ¹5th Medical Center of Chinese PLA General Hospital, Department of Liver Diseases
Email: yongpingyang@hotmail.com

Background and aims: Little reliable evidence has been reported regarding usefulness of liver stiffness measurement (LSM) for monitoring the hepatic fibrosis changes during treatment. We aimed to assess the association between changes in LSM and histological outcomes in patients with chronic hepatitis B (CHB).

Method: In this prospective multicenter study, 727 treatment-naïve patients receiving entecavir-based therapy, who underwent paired biopsies at treatment baseline and week 72, were analyzed. Changes in LSM were defined as $\geq 30\%$ decrease, minor change and $\geq 30\%$ increase. Multivariate logistic regression was used to estimate odd ratios (ORs) of changes in LSM on clinical outcomes accounting for regression to the mean (RtM). A new on-treatment LSM threshold was established by receiver operating curve.

Results: Overall regression of fibrosis, improvement of inflammation, significant histological response, virologic response, ALT normalization and HBeAg seroconversion were 51.2%, 74.4%, 22.0%, 86.0%, 83.5% and 7.6%, respectively. The association between changes in LSM and improvement of inflammation was non-linear ($p = 0.012$). LSM decrease $\geq 30\%$ was associated with regression of fibrosis (OR 1.501, 95% CI 1.073–2.099, $P = 0.018$), significant histological response (OR 1.726, 95% CI 1.124–2.652, $P = 0.013$) and ALT normalization (OR 2.149, 95% CI 1.229–3.757, $P = 0.007$). After adjusting for RtM, LSM increase $\geq 30\%$ became negatively associated with the above three outcomes. A new on-treatment LSM cutoff value of 5.4 kPa was established for indicating the significant histological response.

Conclusion: Changes in LSM is unreliable to estimate regression of fibrosis during treatment, the established cutoff value of on-treatment LSM can optimize monitoring strategy for histological outcomes in CHB patients.

PO-824

Preliminary on-treatment data from a phase 2 study evaluating VIR-2218 in combination with pegylated interferon alfa-2a in participants with chronic hepatitis B infection

Man-Fung Yuen¹, Young-Suk Lim², Daniel Cloutier³, Ling Shen³, Andre Arizpe³, Phil Pang³, Chin Tay³, Vaidehi Thanawala³, Sneha V. Gupta³, Andrea Cathcart³, Edward Gane⁴. ¹Queen Mary Hospital, The University of Hong Kong, Hong Kong; ²Asan Medical Center, University of Ulsan College of Medicine, Gastroenterology, Seoul, Korea, Rep. of South; ³Vir Biotechnology, San Francisco, United States; ⁴University of Auckland, Auckland Clinical Studies, Auckland, New Zealand
Email: dcloutier@vir.bio

Background and aims: VIR-2218 is a novel synthetic small interfering ribonucleic acid (siRNA) therapeutic in development for functional cure of chronic hepatitis B virus infection (CHB). Pegylated interferon alfa-2a (Peg-IFN α) is an approved immunomodulator for the treatment of CHB; however, $< 10\%$ of patients achieve HBsAg loss after 48 weeks of treatment. We hypothesize that combining VIR-2218 with Peg-IFN α may increase the rates of HBsAg loss in CHB patients. We present here the preliminary on-treatment 12-week data.

Method: In this Phase 2 open-label study, noncirrhotic, virologically suppressed CHB participants were enrolled. Study treatment included 200 mg of subcutaneous (SC) VIR-2218 every 4 weeks for 6 doses, either alone (Cohort 1), in combination with 24 weeks of 180 mcg SC Peg-IFN α administered concurrently (Cohort 3), or in combination with 12 weeks of 180 mcg SC Peg-IFN α starting on week 12 of VIR-2218 treatment (Cohort 2). Through week 12, Cohort 2 participants have only received VIR-2218. Participants will be followed for at least 24 weeks after completing study treatment.

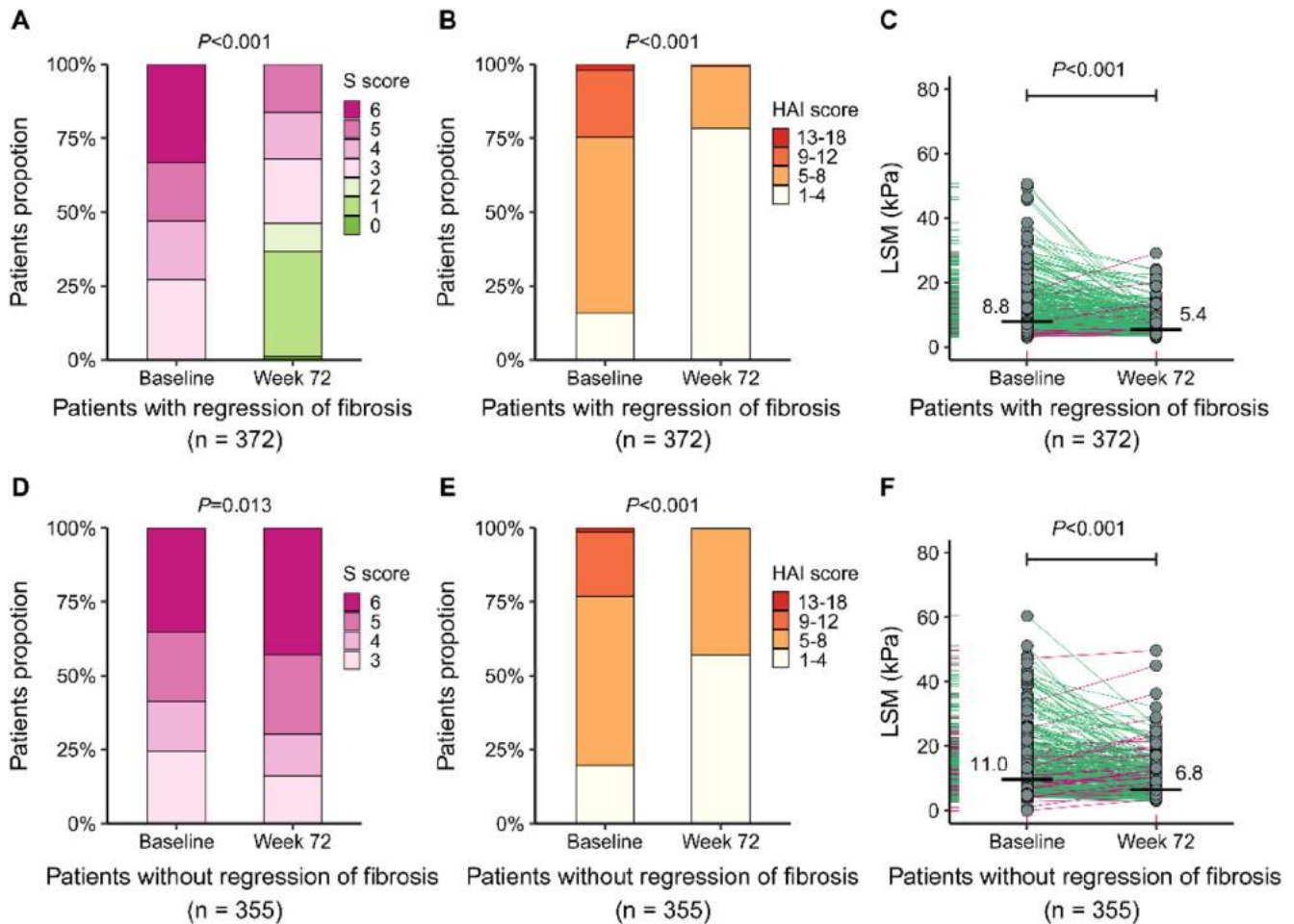


Figure: (abstract: PO-811)

Results: To date, 27 participants have been enrolled, of which 14 have completed at least 12 weeks of treatment. At week 12, the mean HBsAg decline for the 10 participants (3 HBeAg+, 7 HBeAg-) receiving VIR-2218 alone is 1.0 (Cohort 1) and 1.1 (Cohort 2) \log_{10} IU/ml, respectively, and 1.8 \log_{10} IU/ml for the 4 participants (1 HBeAg+, 3 HBeAg-) receiving VIR-2218 with Peg-IFNa (Cohort 3). Earlier and steeper HBsAg declines were observed in Cohort 3, with a mean reduction of $\geq 1 \log_{10}$ IU/ml by week 4. Some participants receiving Peg-IFNa and VIR-2218 combination experienced asymptomatic ALT elevations (grade 2-3) concurrent with HBsAg decline ($\geq 1 \log_{10}$ IU/ml). ALT elevations were not associated with functional changes of the liver (bilirubin, PT or INR). No serious AEs have been reported.

Conclusion: The initial data from this ongoing study show that co-administration of VIR-2218 with Peg-IFNa results in a more rapid and substantial HBsAg decline compared to either VIR-2218 alone or what has been shown with Peg-IFNa alone. In other published studies, Peg-IFNa plus NRTI was associated with $< 0.5 \log_{10}$ IU/ml HBsAg declines, on average, over the first 12 weeks. This data supports the hypothesis that the antiviral activity of VIR-2218 can be potentiated by immunomodulators, such as Peg-IFNa. Additional data beyond 12 weeks, as available, will be presented at the congress.

PO-853

A novel therapeutic vaccine achieves functional cure in a mouse model of chronic hepatitis B

Rena Walsh^{1,2}, Stephen Locarnini^{1,2}, Rachel Hammond^{1,2}, Michiko Hyakumura^{1,2}, Chee Leng Lee^{1,2}, Joan Ho^{1,2}, Ronald Farquhar¹, Aileen Rubio¹, Hans Netter^{1,2}, ¹ClearB Therapeutics, Concord, United States; ²Victorian Infectious Diseases Reference Laboratory, Molecular Research and Development, Melbourne, Australia
Email: rwalsh@clearbtherapeutics.com

Background and aims: We have previously reported hepatitis B virus (HBV) specific antibody responses in patients associated with HBsAg loss and functional cure [Walsh, Ret al 2019. Liver Int 39 (11) pp2066]. This 'clearing' anti-HBs antibody response is defined by an antibody clearance profile (CP) associated with the occupation of key loop 1 and 2 epitopes within the HBsAg "a" determinant, which is distinct from the anti-HBs profile elicited following standard HBV prophylactic vaccination. We generated three bio-nano particles (BNPs) of

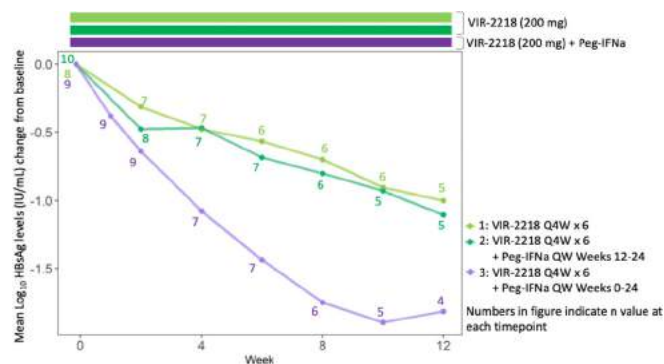


Figure:

POSTER PRESENTATIONS

HBsAg modified with multiple repeats of these key CP epitopes (CP-BNPs). This study investigated whether CP-BNP vaccination cleared HBV infection in association with the generation of the clinically observed CP-specific antibody responses, in a chronic hepatitis B (CHB) murine model.

Method: CBA/CaJ mice (Jackson Laboratory, Maine, USA) were hydrodynamically injected (HDI) in the tail vein with an infectious HBV clone (genotype A2adw2), and CHB established [Chou H-H et al 2015. PNAS 112 (7) pp2175]. Animals were vaccinated by subcutaneous injection across three fortnightly doses with aluminium hydroxide-adjuvanted CP-BNPs. The effect of the therapeutic vaccine to influence functional cure, compared to placebo CHB-infected mice, was assessed by 1) serological HBsAg, anti-HBs antibody and HBV DNA load; and 2) immunohistochemistry anti-HBs and anti-HBc staining of liver sections.

Results: Therapeutic vaccination of persistently HBV infected mice with the CP-BNP vaccine formulation (CLB-101/401/501) resulted in >3 log IU/ml reduction in serum HBV DNA and HBsAg to undetectable levels, as well as the development of a vaccine-elicited 'clearing' anti-HBs response. Liver compartment analysis confirmed clearance of HBV positive cells following serum HBsAg clearance and seroconversion. In comparison, persistent CHB infection was maintained in placebo mice. Vaccination with the standard prophylactic vaccine (Engerix B) at an equivalent human dose did not result in significant virological effects.

Conclusion: A novel HBsAg therapeutic vaccine developed by targeting CP antibody epitopes identified from CHB functionally cured patients demonstrated viral control, HBsAg clearance from serum and liver compartments, and seroconversion, in a mouse CHB model. These findings support the clinical development of the CLB-101/401/501 trivalent vaccine for the treatment of CHB.

PO-942

Discovery and characterization of EDP-721, a novel hepatitis B virus RNA destabilizer

Michael Vaine¹, Tessa Cressey¹, Anand Balakrishnan¹, Victor Dellisola¹, Joe Panarese¹, Dexter Davis¹, Nate Kenton¹, Samuel Bartlett¹, Yat Sun Or¹, Bryan Goodwin¹, Kai Lin¹. ¹Enanta Pharmaceuticals, Inc, Watertown, United States
Email: mvaine@enanta.com

Background and aims: Available therapies for chronic hepatitis B virus (HBV) infection are effective at reducing both the circulating viral load and the risk for developing hepatocellular carcinoma. However, these therapies rarely result in viral clearance and require lifelong treatment. One barrier to a functional cure for chronic HBV (CHB) is the abundance of circulating surface antigen (HBsAg) which is believed to play an immunosuppressive role. Here we report the discovery of EDP-721, a potent and selective inhibitor of the non-canonical poly (A) RNA polymerase-associated domain containing proteins 5 and 7 (PAPD5 and PAPD7). These host factors play a central role in the post-transcriptional stabilization of HBV RNA and their inhibition results in the destabilization of viral transcripts leading to reduced production of viral proteins, including HBsAg. We show that EDP-721 is effective at reducing HBV RNA and protein in both *in vitro* and *in vivo* models of HBV infection.

Method: The activity and selectivity of EDP-721 was determined biochemically against PAPD5, PAPD7, PAP α , PAPD1, and PAPD4. Antiviral activity was assessed in the 2.2.15 cell line, which stably expresses HBV, as well as in cells permissive to HBV infection including, HepG2-NTCP and primary human hepatocytes. *In vivo* efficacy studies were conducted in mice infected with an adeno-associated virus (AAV) vector delivering an HBV genome.

Results: EDP-721 inhibits the catalytic activity of PAPD5 and PAPD7 with a half-maximal inhibitory concentration (IC₅₀) of 4 nM and 32 nM, respectively. No inhibition of the poly (A) polymerases PAP α , PAPD1, or PAPD4 was observed at concentrations up to 10 mM. *In vitro*, EDP-721 prevents production of HBsAg with EC_{50s} of 160 pM,

223 pM, and 360 pM in 2.2.15 cells, HepG2-NTCP cells, and primary human hepatocytes, respectively. This antiviral activity results from a reduction in the length of HBV mRNA poly (A) tails and subsequent degradation of HBV RNAs. We demonstrate that EDP-721 is pan-genotypic and has additive to synergistic activity with nucleos (t)ide analogs and HBV core inhibitors. *In vivo*, EDP-721 reduces circulating HBsAg levels by up to 3 logs with 14 days of dosing in an AAV-HBV mouse model.

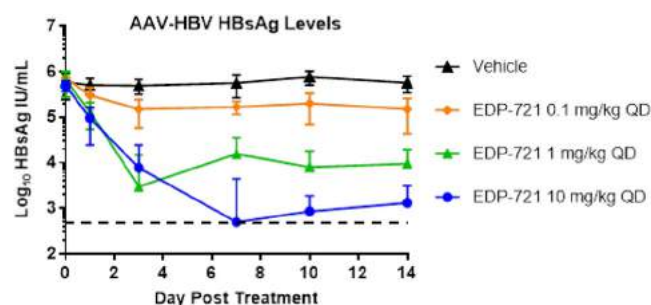


Figure:

Conclusion: EDP-721 is a potent and selective HBV RNA destabilizer that leads to robust reductions in viral proteins including, HBsAg, and has the potential to be a key component of a regimen enabling a functional cure for CHB.

PO-990

Safety of tenofovir alafenamide administered before or in early phase of pregnancy in women with active chronic hepatitis B and the effectiveness in preventing perinatal hepatitis B virus infection: a multicenter prospective study

Qing-Lei Zeng¹, Guangming Li², Ying-Hua Feng³, Guofan Zhang⁴, Wei Li⁵, Jiang-Hai Xu⁶, Zhi-Qin Li¹, Yi-Hua Zhou⁷, Zu-Jiang Yu¹. ¹The First Affiliated Hospital of Zhengzhou University, Department of Infectious Diseases and Hepatology, Zhengzhou, China; ²The Sixth People's Hospital of Zhengzhou City, Department of Hepatology, Zhengzhou, China; ³The Sixth People's Hospital of Kaifeng City, Department of Hepatology, Kaifeng, China; ⁴The First Affiliated Hospital of Nanyang Medical College, Department of Infectious Diseases, Nanyang, China; ⁵Henan Provincial People's Hospital, Department of Infectious Diseases, Zhengzhou, China; ⁶The Fifth People's Hospital of Anyang City, Department of Hepatology, Anyang, China; ⁷Nanjing Drum Tower Hospital, Nanjing University Medical School, Department of Experimental Medicine and Jiangsu Key Laboratory for Molecular Medicine, Nanjing, China
Email: zengqinglei2009@163.com

Background and aims: We previously demonstrated that tenofovir alafenamide (TAF) administered from gestational weeks 24–35 to delivery in inactive chronic hepatitis B virus (HBV)-infected pregnant women with HBV DNA >200,000 IU/ml is safe and can completely prevent mother-to-child transmission (MTCT) of HBV. Here we report the safety data of TAF administration initiated before gestation or from early phase of pregnancy in mothers with active chronic hepatitis B (CHB) and the effectiveness in preventing MTCT.

Method: In this multicenter prospective study, mothers and expectant mothers with newly diagnosed and previously diagnosed treatment-experiencing CHB who chose and switched to TAF therapy were enrolled and followed until postpartum months 12. Infants received standard immunoprophylaxis and were followed until 12 months of age.

Results: In total, 60 mothers were eligible, 51 of them were enrolled, and 19 (37%) mothers switched from non-TAF regimens to TAF. The mean TAF initiation time was 2.6 (\pm 14) weeks of pregnancy, and 24 (47%) of them started TAF before pregnancy from a mean of -10 (\pm 7) weeks. The mean age, alanine aminotransferase, and HBV DNA levels at TAF initiation for mothers were 29.2 (\pm 4.6) years, 113.3 (\pm 93.8) U/L,

and $5.1 (\pm 3) \log_{10}$ IU/ml, respectively. TAF was well tolerated for mothers during a mean treatment duration of $79 (\pm 20)$ weeks, and the most common adverse event was nausea (21.6%). Notably, one (2%) mother who exposed to pesticide during early pregnancy and initiated TAF from gestational weeks 12 undergone induced abortion at gestational weeks 22 due to the diagnosis of cleft lip and palate for the fetus. A total of 50 living infants were born at a mean gestational age of $39.2 (\pm 1.2)$ weeks, the prenatally potential TAF exposure duration were $36 (\pm 14.7)$ weeks, no infants had birth defects at birth, and 35 (70%) infants received breast milk. Notably, 1 (2%) infant was diagnosed with hearing impairment at 1 week and was identified as conductive hearing impairment due to secretory otitis media at 3 months. Additionally, 1 (2%) infant was reported the cutaneous hemangioma (Figure) at 4 weeks. Hepatitis B e antigen seroconversion occurred in 2 (4%) mothers, however, viral breakthrough occurred in 2 (4%) other mothers after 6 months of switchover from previous entecavir to TAF. The infants' physical and neurological development at birth, 7 months, and 12 months were comparable with the China national and World Health Organization standards. None of 50 infants was infected with HBV at 7 months.



Figure: Infantile hemangioma (lower right, size: 15×25 mm) on the left arm. The upper left one was the BCG vaccination site.

Conclusion: TAF administered before or in early phase of pregnancy in women with active CHB was generally safe for both mothers and infants, and reduced the MTCT rate to 0%, however, the abnormalities with ambiguous cause should be noticed and future large-scale studies are needed.

PO-1004

Safety, tolerability and pharmacokinetics (pk) of single and multiple doses of alg-010133, an s-antigen transport inhibiting oligonucleotide polymer (stops) for the treatment of chronic hepatitis B

Edward Gane¹, Man-Fung Yuen², Jeysen Yogaratnam³, Kha Le³, Jennifer Vuong³, Westland Christopher³, Vikrant Gohil³, Christian Schwabe⁴, Kosh Agarwal⁵, Alina Jucov⁶, JyanWei Liu³, Tse-i Lin³, Lawrence Blatt³, Sushmita Chanda³, Matthew McClure³, John Fry³. ¹University of Auckland, Faculty of medicine, Auckland, New Zealand; ²Queen Mary Hospital, Hong Kong; ³Aligos Therapeutics, South San Francisco, United States; ⁴Auckland Clinical Studies, Auckland, New Zealand; ⁵King's College Hospital, London, United Kingdom; ⁶Arensia Exploratory Medicine, Chisinau, Moldova
Email: jeysen.yogaratnam@hotmail.com

Background and aims: To evaluate the safety, PK and antiviral activity of ALG-010133, a STOP molecule designed to reduce hepatitis B surface antigen (HBsAg) in chronic hepatitis B (CHB) patients.

Method: This is a three-part, multicenter, double-blind, randomized, placebo-controlled study. In Parts 1 and 2, each cohort consisted of 8 healthy volunteers (HV) randomized to ALG-010133 or placebo in a 3:1 ratio. Each cohort in Parts 1 and 2 received a single or three-weekly subcutaneous (SC) doses, respectively. Part 3 is evaluating cohorts (N=10 each; 8 ALG-010133, 2 placebo) of virologically suppressed CHB patients who will receive study drug weekly for 12 weeks. Safety assessments (adverse events (AEs), vital signs, electrocardiogram (ECG) and laboratories), viral markers (Part 3) and plasma/urine PK samples (Parts 1 and 2) were collected throughout study conduct. Reported here are preliminary blinded results in Parts 1 and 2. Available Part 3 data will also be presented at the conference.

Results: In Part 1, 7 cohorts (N=56 HVs) received a single 20, 50, 75, 125, 160 or 200 mg (100 mg/ml and 200 mg/ml) SC dose of ALG-010133/placebo. In Part 2, 2 cohorts (N=16 HVs) received three weekly 120 or 180 mg SC doses. There were no serious AEs, premature discontinuations, or dose-limiting toxicities. All treatment emergent AEs (TEAEs) were mild (Grade 1) or moderate (Grade 2) except for one Grade 3 injection site reaction (ISR) that occurred in a subject in the 200 mg cohort. The most commonly occurring (≥ 3 subjects) TEAEs in Part 1 were injection site bruising (n=11), ISRs (erythema/rash; n=7), headache (n=7), nausea (n=4) and diarrhea/loose stools (n=3) and, in Part 2, ISRs (n=3). There was no dose relationship to severity or frequency of AEs. All treatment-emergent laboratory abnormalities were Grade ≤ 2 with the exception of three (Grade 3, n=2; Grade 4, n=1) exercise-related creatine kinase elevations. No clinically significant PE, vital signs, or ECG abnormalities were reported. ALG-010133 exposures increased in a greater than dose-proportional manner with moderate variability after single doses. Median t_{max} was 2–10 hours. Plasma ALG-010133 achieved steady state and did not accumulate with weekly dosing over 3 weeks. Doses of 100–200 mg are projected to result in antiviral activity.

Conclusion: ALG-010133 was generally safe and well tolerated in HV as single and multiple SC doses up to 200 and 180 mg, respectively. The PK exposures achieved are expected to result in antiviral activity, supporting the ongoing evaluation in CHB patients.

POSTER PRESENTATIONS

PO-1109

Baseline serum exosome-derived miRNAs predict HBeAg seroconversion in chronic hepatitis B patients treated with peginterferon

Qiankun Hu¹, Qianqian Wang¹, Qiang Li¹, Yi Zhang¹, Shuai Tao¹, Xueyun Zhang², Xiaoqin Liu², Xinyan Li¹, Xuhua Jiang¹, Chenlu Huang¹, Wei Xu¹, Xun Qi¹, Liang Chen¹, Yuxian Huang^{1,2}.

¹Shanghai Public Health Clinical Center, Fudan University, Department of Liver Diseases, Shanghai, China; ²Huashan Hospital, Fudan University, Department of Infectious Diseases, Shanghai, China

Background and aims: Peginterferon (Peg-IFN) is one of the first-line treatment options for HBeAg-positive chronic hepatitis B (CHB) patients, whereas the clinical application is compromised by the limited serological response rates and frequent side effects. This study aimed to explore the predictive value of baseline serum exosome-derived miRNAs for HBeAg seroconversion in CHB patients treated with Peg-IFN.

Method: 120 treatment-naïve, HBeAg-positive CHB patients who received Peg-IFN therapy were enrolled. Serological response was defined as HBeAg seroconversion after 48 weeks of Peg-IFN treatment. Next-generation sequencing (NGS) was performed to screen the differentially expressed serum exosomal miRNAs, which were further validated by qRT-PCR in a confirmation cohort. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the predictive efficacy of selected serum exosomal miRNAs.

Results: Thirty-three patients (27.5%) achieved HBeAg seroconversion after a 48-week course of Peg-IFN therapy. Forty serum exosome-derived miRNAs were differentially expressed in the identification cohort. Validation analysis revealed that the expression levels of serum exosomal miR-194-5p ($p < 0.001$) and miR-22-3p ($p < 0.001$) were significantly downregulated in the response group compared to the non-response group. Multivariate analysis identified baseline serum exosomal miR-194-5p ($p = 0.019$), miR-22-3p ($p = 0.023$), alanine aminotransferase (ALT) ($p = 0.035$) and HBV DNA ($p = 0.038$) as independent predictors for HBeAg seroconversion. The predictive performances of serum exosomal miR-194-5p (AUROC = 0.77) and miR-22-3p (AUROC = 0.75) were superior to ALT (AUROC = 0.70) and HBV DNA (AUROC = 0.69). The combined detection of serum exosomal miR-194-5p and miR-22-3p further improved the predictive performance to 0.82.

Conclusion: Pretreatment serum exosomal miR-194-5p and miR-22-3p may serve as novel biomarkers to predict HBeAg-positive CHB patients who are likely to experience HBeAg seroconversion after treatment with Peg-IFN.

PO-1196

ALG-125755, a Small Interfering RNA (siRNA) Against Hepatitis B Virus (HBV) Effectively Inhibits Hepatitis B Surface Antigen (HBsAg) Secretion in HBV Cell Models and the AAV-HBV Mouse Model

Jin Hong¹, Saul Martinez Montero¹, Tilani De Costa¹, Yuchun Nie¹, Hua Tan¹, Rajendra Pandey¹, Vivek Rajwanshi¹, Aneerban Bhattacharya¹, Cheng Kao¹, Kang Hyunsoon¹, Elen Rosler¹, Sucheta Mukherjee¹, Kusum Gupta¹, David Smith¹, Lawrence Blatt¹, Julian Symons¹, Leonid Beigelman¹. ¹Aligos Therapeutics, South San Francisco, United States

Email: jhong@aligos.com

Background and aims: The current standard of care for chronic hepatitis B (CHB) fails to reduce HBsAg needed to attain a “functional cure.” HBV siRNA therapies have been shown to be effective in reducing HBsAg in CHB patients. In this study, we applied multiple stabilization chemistries, including unique end capping, to distinct HBV siRNA sequences and achieved significant improvements in depth and duration of HBsAg knockdown over their parent compounds in the serum of AAV-HBV mouse model. ALG-125755, a

GalNAc conjugated form of the siRNA ALG-125903 that utilizes these chemistries was selected for further development.

Method: HBV siRNAs were profiled for HBsAg release in HepG2.2.15 cells, a commonly used genotype D HBV cell model, PLC/PRF/5 cells containing integrated partial HBV genome, and a primary human hepatocyte (PHH) live HBV infection model. Unconjugated siRNAs were transfected using Lipofectamine® RNAiMAX. For PHH cells, infection with HBV at 200 MOI (ge) occurred 4 days prior to the transfection of siRNA. The secreted HBsAg was quantified by ELISA. In the AAV-HBV mouse model, HBV siRNAs conjugated with GalNAc were administered subcutaneously (SC) with blood collections every 5 days for HBsAg and ALT assessments.

Results: ALG-125755 targets a highly conserved region of the HBV genome in the Small HBsAg open reading frame and can cleave 4 HBV transcripts including both 2.4 kb and 2.1 kb transcripts encoding HBsAg. The sequence demonstrates $\geq 99\%$ homology to HBV genotypes A-J. In HepG2.2.15, ALG-125903 showed an EC50 of 24 pM in inhibiting HBsAg release. This sequence also demonstrated similar potency in HBV-infected PHH and PLC/PRF/5 cells. A single 5 mg/kg, SC dose of ALG-125755 reduced HBsAg by 1.5 log₁₀ IU/ml in the serum of AAV-HBV mice, 0.5 log₁₀ IU/ml greater than its unoptimized parent. ALG-125918, containing a novel end cap to the antisense strand of another HBV siRNA, improved maximum HBsAg reduction by 0.5 log₁₀ IU/ml from its parent following a single SC dose of 5 mg/kg. Importantly, this modification significantly improved the durability of HBsAg knockdown which was stable for 90 days in AAV-HBV mice after a single dose.

Conclusion: Multiple novel GalNAc conjugated HBV siRNA sequences containing unique optimized stabilization patterns and novel chemistries demonstrated significant and durable HBsAg knockdown in the AAV-HBV mouse model. Among these, ALG-125755 has been selected for further development.

PO-1240

Pharmacokinetics of ATI-2173, a novel active site polymerase inhibitor nucleotide, in a Phase 1b clinical trial

Katherine Squires¹, Lauren Ogilvie¹, Jade Huguette², Alina Jucov³, Igor Anastasiy⁴, Nelli Ghicavii⁵, Rebeca Melara², Martin Constantineau², Douglas Mayers¹. ¹Antios Therapeutics, Inc, Atlanta, United States; ²Altasciences Company, Inc., Laval, Quebec, Canada; ³Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, Chisinau, Moldova; ⁴Arensia Exploratory Medicine, Kyiv, Ukraine; ⁵Arensia Exploratory Medicine, Chisinau, Moldova

Email: logilvie@antiostherapeutics.com

Background and aims: ATI-2173 is a novel phosphoramidate liver-targeted prodrug of clevudine-5'-triphosphate that functions as an active site polymerase inhibitor nucleoside (ASPIN). Unlike nucleoside inhibitors, the triphosphate is a non-competitive, non-chain terminating inhibitor that distorts the active site of the HBV polymerase. ATI-2173 demonstrated improved pharmacokinetics in animal models as compared to its parent molecule, clevudine, and was assessed for safety, tolerability, pharmacokinetics, and antiviral activity in a phase 1b clinical trial.

Method: The phase 1b portion of the ANTT101 study, a randomized, double-blind, placebo-controlled trial of ATI-2173 in HBV-infected subjects, was conducted at clinical sites in Moldova and Ukraine. Seventeen HBV-infected subjects were given 10 mg, 25 mg, or 50 mg ATI-2173 once a day for 28 days. Pharmacokinetics visits were conducted on days 1, 2, 3, 7, 10, 14, 21 and 28 on treatment and days 2, 3, 4, 7, 10, and 14 off treatment. A validated UHPLC method with MS/MS detection was used to measure plasma concentrations of ATI-2173 and Clevudine (1–1000 ng/ml), intermediate metabolite M1 (1–500 ng/ml). PK analysis was performed using noncompartmental methods.

Results: ATI-2173 was rapidly absorbed, with median T_{max} observed at 0.5–1.0 hours post-dose, after which plasma levels rapidly declined

and were quantifiable for up to 6 hours. ATI-2173 was generally dose proportional with no indication of accumulation. Clevudine was quantifiable in the plasma through 2 to 24 hours post-dose on Day 1 and through 312 hours post-dose in all subjects on Day 28, with total exposure (AUC) being higher on Day 28 versus Day 1. Clevudine AUC₂₄ following daily dosing of 10 mg, 25 mg, and 50 mg ATI-2173 for 28 days was 5%, 13%, and 34% of the plasma exposures historically seen with the 30 mg dose of clevudine, respectively. "M1," an intermediate metabolite, is also being evaluated for PK. The mean 28-day viral load reduction with all three dose levels was $-2.7 \log_{10}$ IU/ml.

Conclusion: ATI-2173 is a novel ASPIN to treat chronic HBV infection. ATI-2173 at doses of 10 to 50 mg orally per day had potent antiviral activity against chronic HBV with greatly decreased systemic exposure to the active nucleoside clevudine. The 25 and 50 mg doses of ATI-2173 have been advanced into a phase 2a study in combination with tenofovir in both HBV mono-infected and HBV/HDV co-infected populations.

PO-1251

Phase 1 results for ATI-2173, a novel active site polymerase inhibitor nucleotide, in HBV-infected subjects

Douglas Mayers¹, Alina Jucov², Igor Anastasiy³, Nelli Ghicavii², Lauren Ogilvie¹, Katherine Squires¹, Abel De La Rosa¹. ¹Antios Therapeutics, Inc., Atlanta, United States; ²Arensia Exploratory Medicine, Chisinau, Moldova; ³Arensia Exploratory Medicine, Kyiv, Ukraine
Email: logilvie@antiostherapeutics.com

Background and aims: ATI-2173 is a novel phosphoramidate liver-targeted prodrug of clevudine-5'-triphosphate that functions as an active site polymerase inhibitor nucleoside (ASPIN). ATI-2173 was designed to enhance the antiviral HBV activity and significantly reduce systemic exposure to the parent nucleoside, clevudine. ANTT101 included a phase 1b 28-day study of ATI-2173 in treatment-naïve subjects with chronic HBV-infection eligible for treatment under EASL guidelines.

Method: The phase 1b portion of the ANTT101 study was a randomized, double-blind, placebo-controlled trial of ATI-2173 in chronic HBV-infected subjects conducted at sites in Moldova and Ukraine. Predominantly HBeAg-negative, HBsAg-positive subjects (n = 25) were randomized 6:2 to doses of 10 mg, 25 mg, 50 mg ATI-2173 or placebo (PBO) orally once a day for 28 days. Safety labs and pharmacokinetics were evaluated on days 1, 2, 3, 7, 10, 14, 21, and 28 on-treatment and days 2, 3, 4, 7, 10, 14, and 28 off-treatment. Antiviral activity was measured at baseline and on days 7, 14, 21, and 28 on-treatment and days 4, 10, and months 1, 3 and 6 off-treatment. HBV DNA was measured using a Roche Cobas 6800 (LLOQ = 10 IU/ml). HBsAg was measured using a Roche Elecsys (LLOQ = 0.05 IU/ml).

Results: ATI-2173 was generally safe and well tolerated. There were no apparent dose-related adverse events (AE) or serious adverse events. The most common AE was headache. One subject withdrew on day 3 for personal reasons and was replaced. Viral load responses at day 28 for 10 mg (N = 6), 25 mg (N = 5), 50 mg (N = 6) or PBO (N = 7) doses of ATI-2173 were -2.7 , -2.7 , -2.7 and $+0.2 \log_{10}$ IU/ml, respectively. There was no change in HBsAg at day 28. After treatment, 3/6 subjects in the 10 mg cohort, 4/5 subjects in the 25 mg cohort, 5/6 subjects in the 50 mg cohort, and 0/7 in the PBO cohort were BLQ (<10 IU/ml). Of the subjects who were BLQ, 9/9 remain BLQ at 4 weeks, 4/9 remain BLQ at 12 weeks, and 1/4 remains BLQ at 12 weeks off-treatment.

Conclusion: ATI-2173 is a novel ASPIN with potent activity ($-2.7 \log_{10}$ IU/ml) against HBV at 28 days of treatment. 65% of ATI-2173 treated subjects were BLQ at EOT. Sustained off-treatment responses were noted 1- to 6-months post ATI-2173 discontinuation. The 25 mg and 50 mg doses of ATI-2173 have been advanced into a phase 2a study in combination with tenofovir in both HBV mono-infected and HBV/HDV co-infected populations.

PO-1270

Safety and efficacy of switching to besifovir dipivoxil maleate in virologically-suppressed chronic hepatitis B patients with tenofovir disoproxil fumarate: 24-week interim analysis

Hyung Joon Yim¹, Ji Hoon Kim², Yeon Seok Seo³, Won Kim⁴, Jae Young Jang⁵, Sae Hwan Lee⁶, Yun Soo Kim⁷, Chang Wook Kim⁸, Hyoung Su Kim⁹, Jae-Jun Shim¹⁰, Eun Young Cho¹¹, In Hee Kim¹², BYUNG SEOK Lee¹³, Jeong-Hoon Lee¹⁴, Byung Seok Kim¹⁵, Jeong Won Jang¹⁶, HYUN WOONG Lee¹⁷, Jung Hyun Kwon¹⁸, Moon Young Kim¹⁹, Do Seon Song²⁰, Eileen Yoon²¹, Jung Gil Park²². ¹Korea University Ansan Hospital, Internal Medicine; ²Korea University Guro Hospital, Internal Medicine, Seoul, Korea, Rep. of South; ³Korea University Anam Hospital, Internal Medicine; ⁴Seoul National University Boramae Medical Center, Internal Medicine; ⁵Soonchunhyang University Seoul Hospital, Internal Medicine; ⁶Soonchunhyang University Cheonan Hospital, Internal Medicine; ⁷Gachon University Gil Medical Center, Internal Medicine, Incheon, Korea, Rep. of South; ⁸Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Internal Medicine, Seoul, Korea, Rep. of South; ⁹Kangdong Sacred Heart Hospital of Hallym University Medical Center, Internal Medicine, Korea, Rep. of South; ¹⁰KyungHee University Hospital, Internal Medicine, Seoul, Korea, Rep. of South; ¹¹Wonkwang University College of Medicine, Internal Medicine, Iksan, Korea, Rep. of South; ¹²Jeonbuk National University Hospital, Internal Medicine, Jeonju, Korea, Rep. of South; ¹³Chungnam National University School of Medicine, Internal Medicine, Daejeon, Korea, Rep. of South; ¹⁴Seoul National University Hospital, Internal Medicine, Seoul, Korea, Rep. of South; ¹⁵Daegu Catholic University Medical Center, Internal Medicine, Daegu, Korea, Rep. of South; ¹⁶Seoul St. Mary's Hospital, The Catholic University of Korea, Internal Medicine, Seoul, Korea, Rep. of South; ¹⁷Gangnam Severance Hospital, Internal Medicine, Seoul, Korea, Rep. of South; ¹⁸Incheon St. Mary's Hospital, The Catholic University of Korea, Internal Medicine, Incheon, Korea, Rep. of South; ¹⁹Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, Internal Medicine, Wonju, Korea, Rep. of South; ²⁰The catholic university of korea, ST. Vincent's Hospital. A, Internal Medicine, Suwon, Korea, Rep. of South; ²¹Inje University Sanggye Paik Hospital, Internal Medicine; ²²Yeungnam University, College of Medicine, Internal Medicine
Email: gudwns21@korea.ac.kr

Background and aims: Long-term viral suppression is needed for the management of chronic hepatitis B (CHB). Although tenofovir disoproxil fumarate (TDF) shows high antiviral efficacy, its extended use is associated with renal toxicity and bone mineral density reduction. Therefore, we aimed to evaluate the efficacy and safety of besifovir dipivoxil maleate (BSV) for 48 weeks in CHB patients after switching therapy from TDF to BSV.

Method: We are currently performing a randomized, active-controlled, open-label, multicenter study to evaluate safety and non-inferior efficacy of switching from TDF to BSV for 48 weeks compared to continuing TDF in virologically suppressed patients (HBV DNA <20 IU/ml). The primary end point was the proportion of patients who achieve a sustained undetectable HBV DNA level <20 IU/ml at 48 weeks. We evaluated renal and bone-related outcomes for safety analysis.

Results: A total of 153 patients were enrolled. An interim analysis was conducted on a subset of 142 patients (70 switched to BSV, 72 maintaining TDF) at week 24. Baseline characteristics were similar between the two groups. At 24 weeks, high rates of virologic response were maintained 98.6% and 100% in BSV and TDF groups, respectively (95% CI - 4.33 to 1.39; p = 0.493). None of the patients developed virologic breakthrough. The mean eGFR significantly improved by 4.20% in the BSV group (p = 0.003) whereas it changed only by 1.00% in the TDF group (p = 0.482). Patients who switched to BSV experienced improvements in bone turnover biomarkers while those who maintaining TDF worsened, and had increased T-score of bone mineral density at spine (p < 0.001). FIB-4 score declines in the BSV group was larger than in TDF group (p = 0.005).

POSTER PRESENTATIONS

Conclusion: In this interim analysis, patients who switched from TDF to BSV maintained efficacy in viral suppression without virological breakthrough with significant improvements in bone safety at 24 weeks.

PO-1286

No emergent core inhibitor resistance in patients with chronic hepatitis B virus infection treated with Vebicorvir in combination with a nucleos (t)ide reverse transcriptase inhibitor

Man-Fung Yuen¹, Stephen Locarnini², Peter Revill³, Ran Yan⁴, Lea Ouyang⁴, Dawei Cai⁴, William Delaney⁴, Katie Kitrinov⁴, Alexander Thompson⁵, Fabien Zoulim⁶, Mark Sulkowski⁷. ¹The University of Hong Kong, Department of Medicine, Hong Kong; ²VIDRL Doherty Institute, Research and Molecular Development, Melbourne, Australia; ³VIDRL, Royal Melbourne Hospital at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia; ⁴Assembly Biosciences, South San Francisco, United States; ⁵St. Vincent's Hospital and the University of Melbourne, Department of Gastroenterology, Fitzroy, Australia; ⁶Viral Hepatitis Laboratory, Cancer Research Center of Lyon, Lyon, France; ⁷Johns Hopkins University School of Medicine, Baltimore, United States
Email: ryan@assemblybio.com

Background and aims: Vebicorvir (VBR, ABI-H0731) is a 1st generation hepatitis B virus core inhibitor in development for the treatment of chronic hepatitis B virus infection (cHBV). In the Phase 2 Study 201, virologically suppressed cHBV patients were randomized in a blinded manner to VBR or placebo with nucleos (t)ide reverse transcriptase inhibitor (NrtI) for 24 weeks after which eligible patients entered the open-label extension Study 211 to receive VBR+NrtI. On treatment, VBR+NrtI led to deeper virologic suppression as assessed by high sensitivity HBV DNA and pgRNA assays. The aim of this study was to investigate whether any treatment emergent core inhibitor or NrtI substitutions were observed after treatment discontinuation.

Method: 41 patients discontinued VBR+NrtI; all patients experienced virologic rebound and were included in the study. Sanger sequencing of RNA at HBV core and the pol/RT region was attempted for all patients at Study 201 baseline and DNA was sequenced for the first 2 consecutive off treatment visits with HBV DNA >20 IU/ml. Sequence evaluations were conducted across core and the pol/RT region, focusing on core inhibitor binding pocket substitutions and NrtI resistance mutations.

Results: 28 and 22 patients were successfully sequenced at all 3 timepoints for HBV core and pol/RT, respectively. There were 13 and 19 patients without baseline sequences for core and pol/RT, respectively, due to low viral loads. Overall, no core inhibitor substitutions were observed in 32/41 (78%) patients at all timepoints tested. Y38F and Y118F substitutions were each detected off treatment in 1 patient missing a baseline sequence; both substitutions remained stable between off treatment timepoints (≥4 weeks) (Table 1). Seven patients had core inhibitor substitutions at baseline (Y38H/F, P25S, D29E and I105 T); no enrichment of these substitutions was observed off treatment. NrtI resistance mutations were detected off treatment in 4 patients missing baseline sequences. All NrtI mutations reverted towards wildtype off treatment, with no enrichment/development of NrtI mutations.

Table: Summary of core inhibitor Substitutions Observed

Subject	Baseline	Off Treatment 1	Off Treatment 2
1	no baseline	Y38F	Y38F
2	no baseline	Y118Y/F	Y118Y/F
3	Y38F	Y38F	Y38F
4	Y38H/Y	Y38Y/H	Y38
5	Y38Y/F	Y38F/Y	Y38F/Y
6	Y38Y/H	Y38Y/H	Y38
7	P25P/S	P25	P25
8	D29D/E	D29D/E	D29D/E
9	I105T	I105T	I105T

Conclusion: Overall, most patients (78%) had no core inhibitor substitutions detected by Sanger sequencing. For patients harboring a core inhibitor substitution (22%), no enrichment compared to baseline was observed after treatment was removed.

PO-1386

Capsid assembly modulator ALG-000111 and its prodrug ALG-000286 display excellent in vitro and in vivo antiviral activity

Yannick Debing¹, Dieudonné B. Kum¹, Cheng Liu², Jerome Deval², Hannah Vanrusselt³, Abel Acosta Sanchez³, Qingling Zhang², Sucheta Mukherjee², Dinah Misner², Sushmita Chanda², Raymond F. Schinazi⁴, Julian Symons², Lawrence Blatt², Leonid Beigelman², Pierre Raboisson¹, Sandrine Vendeville¹, David Smith², Andreas Jekle². ¹Aligos Belgium BV, Leuven, Belgium; ²Aligos Therapeutics, Inc., South San Francisco, United States; ³Novalix, Leuven, Belgium; ⁴Emory University, Atlanta, United States
Email: ydebing@aligos.com

Background and aims: Hepatitis B virus (HBV) capsid assembly is a promising target for the treatment of chronic hepatitis B. Class II capsid assembly modulators (CAMs) induce rapid HBV core protein (HBc) assembly into empty capsids, thus inhibiting HBV RNA encapsidation and formation of infectious HBV particles. CAMs can also block cccDNA establishment by blocking viral DNA release from the capsid after entry. As a part of our efforts to advance multiple structurally diverse CAMs, we report on ALG-000111, a novel Class II CAM with excellent antiviral activity and efficacy in the AAV-HBV mouse model.

Method: HBV DNA antiviral activity was determined in HepG2.117 cells using qPCR, with and without 40% human serum. Optimized assays were performed to assess inhibition over several logs and longevity of the antiviral effect after compound removal. Activity was also studied in HBV-infected primary human hepatocytes, both the primary effect on HBV DNA and the secondary effect on cccDNA establishment. Further characterization was performed using biochemical quenching assays, electron microscopy visualization, and immunofluorescent HBc staining. ADME properties were evaluated in vitro, whereas in vivo antiviral efficacy was assessed in the AAV-HBV mouse model.

Results: ALG-000111 and its prodrug ALG-000286 potently inhibited HBV DNA production in HepG2.117 cells with EC50/EC90 values of 0.88/4.34 nM and 2.06/9.23 nM respectively. An optimized protocol allowed the determination of EC99/EC99.9 values of 4.81/15.3 nM and 10.4/39.7 nM respectively. Inclusion of 40% human serum resulted in a modest 7-fold shift in antiviral activity. Rebound assays showed a significant retention of antiviral activity, with strong inhibition observable up to 10 days after compound removal. ALG-000111 also displayed significant antiviral activity in HBV-infected primary human hepatocytes with EC50/EC90 values of 0.98/3.22 nM on HBV DNA. Additionally, the formation of cccDNA was blocked, indicated by potent reductions in secreted HBsAg and intracellular HBV RNA (EC50/EC90 values of 41.7/651 nM and 34.0/189 nM respectively). ALG-000111 induced empty capsid formation in

biochemical quenching assays and by electron microscopy. Immunofluorescent imaging revealed a tendency for cytoplasmic HBc accumulation. ALG-000111 was stable in SGF/SIF and in liver microsomes and hepatocytes across species. The compound displayed low CYP450-mediated drug-drug interaction potential and high permeability across Caco-2 monolayers. Evaluation of the prodrug ALG-000286 in the AAV-HBV mouse model resulted in a strong reduction in HBV DNA with a mean maximum 3.7 log₁₀ IU/ml drop in HBV DNA following 4 weeks of PO dosing at 30 mg/kg BID.

Conclusion: With sub-nanomolar activity and deep knockdown of HBV DNA in cell-based assays and the AAV-HBV mouse model, ALG-000286 is a promising Class II CAM candidate for further development.

PO-1416

Pharmacokinetics and safety of JNJ-73763989, an RNA interference therapy for hepatitis B virus, in moderately hepatically impaired participants

Thomas Kakuda¹, Atef Halabi², Carine Guinard-Azadian³, Katja Nedoschinsky³, Julius Nangosyah³, Emmanuel Njumbe Ediage³, Peter Verboven³, Michael Biermer³. ¹Janssen BioPharma Inc., South San Francisco, United States; ²Clinical Research Services Kiel GmbH, Kiel, Germany; ³Janssen Pharmaceutica NV, Beerse, Belgium
Email: tkakuda@its.jnj.com

Background and aims: JNJ-73763989 comprises hepatitis B virus (HBV)-specific, liver-targeted N-galactosamine-conjugated short interfering RNA (siRNA) triggers, JNJ-73763976 and JNJ-73763924, which silence HBV RNA transcripts from host-integrated HBV DNA and episomal DNA. JNJ-73763989 administered subcutaneously (SC) as 3 monthly doses 100–400 mg + a nucleos (t)ide analogue daily, demonstrated HBsAg decline ≥ 1 log₁₀ IU/ml in chronic HBV patients that was sustained in 39% of patients for up to 48 weeks off treatment (Gane EJ, et al. EASL 2020). Here, pharmacokinetics (PK), safety/tolerability of JNJ-73763989 in participants with moderate hepatic impairment (Child-Pugh B) for reasons other than HBV infection were evaluated and compared to healthy participants with normal liver function.

Method: 73763989HPB1002 (NCT04208386) was a Phase 1 single-dose, open-label, parallel study. Eight Child-Pugh B participants and 8 healthy participants matching for sex, age (± 10 years) and body weight (± 10 kg) were enrolled and received a single 200 mg SC dose of JNJ-73763989. Plasma and urine concentrations of JNJ-73763976 and JNJ-73763924 were collected over 72 hours and analyzed using liquid chromatography coupled to a fluorescence detector. PK parameters were estimated using non-compartmental analysis (WinNonlin, Certara, Princeton NJ). Safety/tolerability were assessed throughout.

Results: PK parameters are summarized (table). JNJ-73763976 geometric mean ratio for C_{max} was 1.4- and AUC 1.3-fold higher in Child-Pugh B participants vs case controls; for JNJ-73763924, 2.2- and 2.0-fold higher. Half-life and amount of drug renally excreted were slightly higher for both analytes in Child-Pugh B participants. There were no deaths, serious adverse events (AEs) or discontinuations. Overall, 2 participants, 1 in each group, reported ≥ 1 treatment-emergent AE (TEAE). TEAEs were mild/moderate and not related to JNJ-73763989. All TE graded laboratory abnormalities were mild/moderate, except for transient platelet reductions from grade 2 at screening to grade 3 in 2 Child-Pugh B participants. There were no relevant cardiovascular findings.

Liver status	JNJ-73763976		JNJ-73763924	
	Child-Pugh B 8	Healthy participants 8	Child-Pugh B 8	Healthy participants 8
C _{max} (ng/mL)	1,640 (1,087)	1,068 (565)	444 (355)	190 (75)
t _{max} (h)	7.00 (0.25–12.00)	9.00 (4.00–12.00)	6.00 (0.25–12.00)	8.00 (0.50–12.00)
AUC _{0-∞} (ng·h/mL)	26,569 (13,132)	18,237 (6,192)	6,410 (3,605)	2,862 (694)
AUC _{0-t} (ng·h/mL)	26,711 (13,085)	18,273 (6,194)	6,335 (4,172), [n=6]	3,023 (634), [n=7]
t _{1/2} (h)	6.93 (3.76)	5.39 (1.75)	7.11 (5.74), [n=6]	4.34 (1.55), [n=7]
Ae (% dose)	34.4 (14.1)	26.6 (7.47)	29.1 (13.6)	21.2 (5.83)

C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; AUC, area under the plasma concentration-time curve from time 0 to the time of the last measured concentration (AUC_{0-∞}) or extrapolated to infinity (AUC_{0-t}); t_{1/2}, half-life; Ae, amount of drug excreted.
Mean (SD) except for t_{max}, median (range)

Figure:

Conclusion: JNJ-73763976 and JNJ-73763924 exposures were higher in participants with moderate hepatic impairment. A single 200 mg dose of JNJ-73763989 was well tolerated in participants without and with moderate hepatic impairment.

PO-1419

First real-life experiences with 2 mg bulevirtide for the treatment of hepatitis delta-data from a tertiary reference centre in Germany

Caroline Zöllner¹, Katrin Lutz¹, Münevver Demir¹, Frank Tacke¹. ¹Charité-University Medicine Berlin, Department of Hepatology and Gastroenterology, Campus Virchow Klinikum and Charité Campus Mitte, Berlin, Germany
Email: caroline.zoellner@charite.de

Background and aims: Hepatitis B/D coinfection poses a high risk for the progression to severe liver disease. In July 2020, bulevirtide (2 mg/day) was approved in the European Union for the treatment of chronic hepatitis delta. The drug blocks the bile salt transporter NTCP, which is also the entry receptor for Hepatitis B and D viruses. Here we describe the first sixteen weeks of therapy with bulevirtide in hepatitis delta patients who were included in an early access programme in a tertiary care centre in Germany.

Method: We included patients with active hepatitis B/D coinfection who were eligible for the early access programme. The main exclusion criteria were liver cirrhosis Child-Pugh Score B or C, thrombocytopenia below 50/nl, hepatocellular carcinoma or planned pregnancy. All included patients (n = 8) received detailed information and training for drug administration.

Results: All patients (n = 8) were under concomitant therapy with nucleoside/nucleotide analogues. None had a concomitant interferon treatment, mostly due to patients' reticence or contraindications. One patient dropped out shortly after inclusion because of a newly diagnosed hepatocellular carcinoma, and seven patients completed at least 16 weeks of therapy (table). Mean ALT values before treatment (baseline) were 78 U/l and declined to 39 U/l after 16 weeks. Mean HDV-RNA was 10, 902, 457 cop/ml at baseline and dropped to 3, 740, 569 cop/ml. One patient showed no significant biochemical or viral response and was discontinued. We observed no relevant side effects apart from asymptomatic elevation of bile acids.

Table: HDV-RNA in the first 16 weeks of therapy (cop/ml)

	Baseline	Week 4	Week 8	Week 12	Week 16
Pat. 1	13,200	non detectable	non detectable	<3,000	<3,000
Pat. 2	541,000	non detectable	non detectable	<3,000	5,380
Pat. 3	>24,500,000	6,240,000	>24,500,000	>24,500,000	>24,500,000
Pat. 4	>24,500,000	5,030,000	1,150,000	255,000	665,000*
Pat. 5	>24,500,000	>24,500,000	1,980,000	1,060,000	980,000
Pat. 6	2,260,000	24,9000	118,000	29,500	27,600
Pat. 7	<3,000	5,230	<3,000	NA	<3,000

*HDV-RNA for this patient was not available at week 16 but at week 20
The linear range in our laboratory is from 3,000 to 24,500,000 copies

POSTER PRESENTATIONS

Conclusion: These are the first real life data on bulevirtide therapy in Germany. Overall, we observed a favorable safety profile as well as a marked biochemical and virological response in the majority of our patients. However, middle- and long-term data are needed to evaluate the impact of bulevirtide on clinical end points in hepatitis delta patients.

PO-1448

Excellent virological and clinical responses maintained over 3 years of continuous Bulevirtide treatment in patients with HDV compensated cirrhosis and clinically significant portal hypertension

Alessandro Loglio¹, Peter Ferenci², Sara Colonia Uceda Renteria³, Christine Y.L. Tham⁴, Heidemarie Holzmann⁵, Marta Borghi¹, Riccardo Perbellini¹, Elena Trombetta⁶, Silvia Giovanelli⁷, Laura Porretti⁶, Daniele Prati⁷, Ferruccio Ceriotti³, Antonio Bertoletti⁴, Pietro Lampertico^{1,8}. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Gastroenterology and Hepatology, Milano, Italy; ²Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ³Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Virology Unit, Milan, Italy; ⁴Duke-NUS Medical School, Singapore, Singapore; ⁵Medical University of Vienna, Center for Virology, Vienna, Austria; ⁶Foundation IRCCA Ca' Granda Ospedale Maggiore Policlinico, Flow Cytometry Service, Milan, Italy; ⁷Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Transfusion Medicine and Hematology, Milan, Italy; ⁸University of Milan, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, Milan, Italy
Email: ale.loglio@gmail.com

Background and aims: Treatment with Bulevirtide (BLV) for 48 weeks in compensated HDV cirrhotic patients is safe and effective, but its long-term effects in a real-life setting even after dose reduction/discontinuation have not been investigated yet.

Method: Three difficult-to-treat compensated HDV cirrhotic patients with clinically significant portal hypertension added BLV 10 mg/day (high dose) to ongoing TDF. Case 1: 69 years, female, HDV-RNA 23, 600 IU/ml, HBsAg 10 IU/ml, ALT 140 U/L; Case 2: 51 years, male, HDV-related autoimmune hepatitis, small esophageal varices, platelets 74, 000/mm³, HDV-RNA 392, 000 IU/ml, ALT 232 U/L; Case 3: 58 years, female, HDV-RNA 104, 803 IU/ml, ALT 244 U/L. HDV-RNA was quantified by RoboGene 2.0 (LLOQ 6 IU/ml). In first two patients, HDV/HBV-specific T cells were analyzed in blood by direct ex-vivo IFN- γ ELISPOT methods, up to last follow-up

Results: In Case 1, HDV-RNA became undetectable by week 36 and ALT normalized by week 20. After BLV withdrawn (week 52), HDV-RNA became rapidly detectable, peaked at week 16 (13, 655 IU/ml), and then declined at week 32 (421 IU/ml), remaining stable <1, 000 IU/ml afterwards. ALT level increased from week 14 to 30 (41–333 U/L) and then declined to persistent normal values. At 101-weeks off therapy: HDV-RNA 87 IU/ml, ALT 26 U/L, HBsAg 0.49 IU/ml. Two patients were treated continuously for 3 years: undetectable HDV-RNA and normal ALT levels were achieved after 28 and 12 weeks in Case 2, and 52 and 28 weeks in Case 3. Virological and biochemical response were maintained through the following 2 years of therapy, even after BLV dose reduction to 5 and 2 mg/day. At last visit: both patients had undetectable HDV-RNA and ALT 22 U/L. In one patient, virological response was associated with an excellent clinical response: esophageal varices disappeared, histological/lab features of autoimmune hepatitis resolved, AFP normalized, platelets and albumin improved. Overall, no safety issues were recorded, as bile salt increase was asymptomatic. Circulating HDV/HBV-specific T cells were tested in 2 patients at baseline and every 2 months during and off-therapy: no changes were observed, neither after HDV reactivation (Case 1) nor in 2.5 years of BLV continuative treatment (Case 2).

Conclusion: Continuous administration of BLV for 3 years provides excellent virological and clinical response in HDV cirrhotic patients with clinically significant portal hypertension.

PO-1449

Tenofvir reduces the severity of COVID-19 infection in chronic hepatitis B patients

Beatriz Mateos Muñoz¹, Maria Buti², Inmaculada Fernández Vázquez³, Marta Hernández Conde⁴, Vanesa Bernal Monterde⁵, Fernando Diaz⁶, Rosa Morillas⁷, Luisa Garcia-Buey⁸, Esther Badia-Aranda⁹, Mireia Miquel¹⁰, Alberto Amador¹¹, Sergio Rodriguez-Tajes¹², Lucía Ramos Merino¹³, Antonio Madejón¹⁴, Montserrat García-Retortillo¹⁵, Juan Arenas¹⁶, Joaquín Cabezas¹⁷, Jesús González Santiago¹⁸, Conrado Fernández-Rodríguez¹⁹, Patricia Cordero²⁰, Moises Diago²¹, Antonio Mancebo²², Albert Pardo²³, Manuel Rodríguez²⁴, Elena Hoyas²⁵, José Juan Moreno²⁶, Juan Turnés²⁷, Miguel Angel Simón²⁸, Cristina Marcos-Fosch², José Luis Calleja Panero⁴, Rafael Bañares⁶, Sabela Lens¹², Javier Crespo¹⁷, Manuel Romero Gomez²⁹, Enrique Rodríguez-Santiago¹, Santiago Moreno Guillén¹, Agustín Albillos¹. ¹Hospital Universitario Ramón y Cajal, CIBERehd, IRYCIS, Universidad de Alcalá, Madrid, Spain; ²Hospital Universitario Valle Hebrón Hospital, CIBERehd, Hepatology Department, Barcelona, Spain; ³Hospital Universitario 12 de Octubre, Gastroenterology Department, Madrid, Spain; ⁴Hospital Universitario Puerta de Hierro, Gastroenterology Department, Majadahonda, Spain; ⁵Hospital Miguel Servet, Gastroenterology Department, Zaragoza, Spain; ⁶Hospital Universitario Gregorio Marañón, Gastroenterology Department, Madrid, Spain; ⁷Hospital Germans Trias i Pujol, IGTP, CIBERehd, Hepatology Unit, Badalona, Spain; ⁸Hospital Universitario La Princesa, Gastroenterology Department, Madrid, Spain; ⁹Hospital de Burgos, Gastroenterology Department, Burgos, Spain; ¹⁰Hospital Parc Tauli, CIBERehd, Gastroenterology Department, Sabadell, Spain; ¹¹Hospital Universitario Bellvitge, IDIBELL, Liver Unit, Barcelona, Spain; ¹²Hospital Clinic Barcelona, IDIBAPS, Ciberehd, Liver Unit, Barcelona, Spain; ¹³Hospital La Coruña, Infectious Diseases, La Coruña, Spain; ¹⁴Hospital Universitario La Paz, Gastroenterology Department, Madrid, Spain; ¹⁵Hospital del Mar, Gastroenterology Department, Barcelona, Spain; ¹⁶Hospital Universitario de Donostia, Gastroenterology Department, Donostia, Spain; ¹⁷IDIVAL-Instituto de Investigación Valdecilla. Hospital Universitario de Valdecilla Hospital, Gastroenterology Department, Santander, Spain; ¹⁸Hospital Universitario de Salamanca, IBSAL, Gastroenterology Department, Salamanca, Spain; ¹⁹Hospital Universitario Fundación de Alcorcón, Gastroenterology Department, Alcorcón, Spain; ²⁰Hospital Universitario Virgen de la Macarena, Gastroenterology Department, Sevilla, Spain; ²¹Hospital General de Valencia, Gastroenterology department, Valencia, Spain; ²²Hospital Universitario de Albacete, Gastroenterology Department, Madrid, Spain; ²³Hospital Joan XXIII, Gastroenterology Department, Tarragona, Spain; ²⁴Hospital Universitario Central de Asturias, Gastroenterology Department, Oviedo, Spain; ²⁵Hospital Virgen de Valme, Gastroenterology Department, Sevilla, Spain; ²⁶Complejo asistencial de Segovia, Internal Medicine Department, Segovia, Spain; ²⁷Hospital de Pontevedra, Gastroenterology Department, Pontevedra, Spain; ²⁸Hospital Clínico de Zaragoza, Gastroenterology Department, Zaragoza, Spain; ²⁹UCM Digestive Diseases, Virgen del Rocio University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain
Email: agustin.albillos@uah.es

This abstract is under embargo until the beginning of the press conference it is being presented in on Wednesday 23 June 2021 at 09:00 EDT/15:00 CET.

It will be uploaded to the conference website once the embargo has lifted.

69 weeks) were recruited. The patients all had post-treatment follow-up for at least 4 months. All patients fulfilled the stopping criteria of the Asia-Pacific Association for the Study of the Liver of 2012. The propensity score-matching method was used by creating a ratio of 1:3 to adjust age, sex, cirrhosis, HBV DNA at entry, treatment and consolidation duration and end-of-treatment (EOT) HBsAg. Thus, 31 and 93 patients who discontinued TDF with (Group I) and without (Group II) switching to TAF were included in this study.

Results: There were no significant differences in terms of clinical features or HBsAg levels between the two groups. In the Group I and Group II patients, the incidences of virological relapse at post-treatment 12 and 24 weeks were 50.5% versus 36.6% and 71.4% versus 59.1% ($p = 0.211$), respectively, and the clinical relapse rates were 34.4% versus 30.1% and 62.1% versus 52.7% ($p = 0.259$), respectively. There was no significant difference in virological and clinical relapse rates between the two groups. Multivariate analysis showed that old age, NA-naïve status and lower EOT HBsAg levels were independent predictors of virological and clinical relapse.

Conclusion: HBV relapse rate might be comparable between HBeAg-negative CHB patients who discontinued TDF with or without switching to TAF.

PO-1661

Outcomes and characteristics of hepatocellular carcinomas (HCC) in Caucasian chronic hepatitis B (CHB) patients treated with long-term entecavir (ETV) or tenofovir disoproxil fumarate (TDF) therapy

George Papatheodoridis¹, George Dalekos², Ramazan Idilman³, Vana Sypsa⁴, Maria Buti⁵, José Luis Calleja Panero⁶, Ioannis Goulis⁷, Milan Sonneveld⁸, Florian van Bömmel⁹, Spiliou Manolakopoulos^{1,10}, Alessandro Loglio¹¹, Margarita Papatheodoridi¹, Nikolaos Gatselis², Marta López-Gómez⁶, Savvoula Savvidou⁷, Sylvia Brakenhoff⁸, ANNA Samakidou², Cihan Yurdaydin³, Rafael Esteban⁵, Harry Janssen¹², Thomas Berg⁹, Pietro Lampertico¹¹. ¹Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko," Department of Gastroenterology, Athens, Greece; ²General University Hospital of Larissa, Department of Medicine and Research Laboratory of Internal Medicine, Expertise Center of Greece in Autoimmune Liver Diseases, Larissa, Greece; ³Ankara University School of Medicine, Department of Gastroenterology, Ankara, Turkey; ⁴Medical School of National and Kapodistrian University of Athens, Department of Hygiene, Epidemiology and Medical Statistics, Athens, Greece; ⁵Valle Hebron and Ciberehd, Hospital General Universitario, Barcelona, Spain; ⁶IDIPHIM CIBERehd, Hospital U Puerta de Hierro, Madrid, Spain; ⁷Aristotle University of Thessaloniki Medical School, 4th Department of Internal Medicine, Thessaloniki, Greece; ⁸Erasmus MC, University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ⁹University Clinic Leipzig, Section of Hepatology, Clinic for Gastroenterology and Rheumatology, Leipzig, Germany; ¹⁰Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Hippokratio," 2nd Department of Internal Medicine, Athens, Greece; ¹¹Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC "AM e A Migliavacca" Center for Liver Disease, Milan, Italy; ¹²Toronto General Hospital, Toronto Centre for Liver Disease, Toronto, ON, Canada
Email: gepapath@med.uoa.gr

Background and aims: HCC can develop in CHB patients under long-term oral antiviral therapy even in reduced rates, but the characteristics of this occurrence have not been adequately studied. This study aimed to assess patient and tumour characteristics as well as outcomes in adult Caucasian CHB patients, with or without compensated cirrhosis, who developed HCC during long-term therapy with ETV or TDF.

Method: In total, 1951 adult Caucasian CHB patients treated with ETV/TDF were included in the PAGE-B cohort (baseline age 53 ± 14 years, males 71%, HBeAg-positive 18%, cirrhosis 28%). Patients with

PO-1628

Comparison of hepatitis B virus relapses between hepatitis B e antigen-negative chronic hepatitis B patients who discontinue tenofovir disoproxil fumarate with or without switching to alafenamide

Chien-Hung Chen¹, Rachel Wen-Juei Jeng^{2,3}, Tsung-Hui Hu⁴, Yen-Chun Liu³, Jing-Houng Wang⁴, Chao-Hung Hung⁴, Sheng-Nan Lu⁴, Rong-Nan Chien². ¹Chang Gung Memorial Hospital, Internal Medicine, Kaohsiung, Taiwan; ²Linkou Chang Gung Memorial Hospital, Internal Medicine, Taoyuan, Taiwan; ³Chang Gung University, College of Medicine, Taiwan; ⁴Kaohsiung Chang Gung Memorial Hospital, Internal Medicine, Kaohsiung, Taiwan; ⁵Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
Email: e580306@ms31.hinet.net

Background and aims: Previous studies showed that hepatitis B virus (HBV) relapse after the cessation of tenofovir disoproxil fumarate (TDF) occurs much earlier than that after the cessation of entecavir. Prior study showed the clinical relapse pattern goes along with the ended-up nucleos(t)ide analogues (Peng CW AASLD 2020 abstract). Tenofovir alafenamide (TAF) is a new prodrug of tenofovir, TAF was non-inferior to TDF in efficacy. However, the incidence of HBV relapse after the cessation of TAF therapy remains unclear. The aim of this study is to compare HBV relapse rates between hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients who discontinued TDF with or without switching to TAF.

Method: A total of 442 HBeAg-negative patients who received TDF monotherapy and 31 HBeAg-negative patients who received TDF at the start treatment and switching to TAF at least 12 weeks (range 20–

POSTER PRESENTATIONS

decompensated cirrhosis or coinfections were excluded. HCC surveillance was based on ultrasonography ± AFP at least every 6 or 12 months in patients with and without cirrhosis, respectively. During a median follow-up of 8.8 years after ETV/TDF onset, HCC was diagnosed in 155 (7.9%) patients at a median of 3.8 (0.1–13.5) years. Patient characteristics at baseline and at HCC diagnosis, HCC therapeutic interventions and outcomes were analysed.

Results: In the 155 patients with HCC, mean age was 63 ± 8 years at ETV/TDF onset and 67 ± 9 years at HCC diagnosis, whereas 87% were males, 10% were HBeAg-positive and 69% had cirrhosis at baseline. HCC was diagnosed within Milan criteria in 84% of cases, whereas 80%, 12% and 8% of cases were classified as BCLC stage 0-A, B and C, respectively. Potentially curative intervention was provided in 72% of patients. No patient or tumour characteristic or type of intervention differed in patients with HCC diagnosed in ≤2 and >2 (or ≤5 and >5) years after ETV/TDF onset, except for mean age at HCC diagnosis (61 ± 9 vs 66 ± 8 vs 71 ± 7 years in patients with HCC diagnosed in ≤2 vs >2–5 vs >5 years after ETV/TDF onset, $P < 0.001$). Cumulative rates of 1-, 3-, 5-year overall survival were 87%, 63%, 49% and liver transplantation free survival 81%, 55%, 43%, respectively. Overall survival was not associated with any of the patient characteristics, but it was better in patients treated with curative interventions (HR:3.2, 95%CI:1.8–5.7; $P < 0.001$).

Conclusion: In treated Caucasian CHB patients, with or without compensated cirrhosis, who are under HCC surveillance, HCCs are usually diagnosed within Milan criteria and in early BCLC stage allowing potentially curative therapies in most cases. The probability of 5-year overall survival after HCC diagnosis is almost 50% and is affected only by curative intervention but not by patient characteristics.

PO-1699

Discovery and preclinical profile of VNRX-9945, a potent, broadly active core protein inhibitor for the treatment of hepatitis B virus (HBV) infection

Glen Coburn¹, Bin Liu¹, Christopher Benetatos¹, Jiangchao Yao¹, Steve Boyd¹, Tom Haimowitz¹, Stephen Condon¹, Tony Drager¹, Susan Emeigh Hart¹, Daniel Pevear¹, Christopher Burns¹. ¹Venatorx Pharmaceuticals, Inc., Malvern, United States
Email: coburn@venatorx.com

Background and aims: A functional cure for chronic hepatitis B virus (HBV) infection remains the ultimate goal of HBV therapy. To achieve this objective, combinations of direct-acting antivirals, oligonucleotide agents that promote antigen knockdown and immune modulators, are likely required to further suppress viral replication and eliminate infected hepatocytes. Here we report on the discovery and preclinical profile of VNRX-9945, a potentially best-in-class core protein inhibitor for the treatment of chronic HBV infection.

Method: VNRX-9945 was identified through multiple iterative cycles of medicinal chemistry followed by rigorous profiling in a battery of antiviral, ADME, pharmacokinetic and *in vitro* safety assays. The *in vitro* antiviral properties of VNRX-9945 were evaluated in several HBV replication assays using quantitative polymerase chain reaction (qPCR) to measure extracellular HBV DNA. The pharmacokinetics, safety and tolerability of the compound were extensively studied in both rats and cynomolgus monkeys following single and repeat doses of VNRX-9945 for up to 28-days. Finally, the *in vivo* antiviral activity of VNRX-9945 was demonstrated in the AAV-HBV mouse model of HBV infection.

Results: VNRX-9945 binds to the dimer-dimer interface of the HBV core protein and accelerates the formation of normal sized capsids that are devoid of the HBV pgRNA and polymerase. The compound is a potent inhibitor of HBV replication with an $EC_{50} = 2$ nM ($EC_{90} = 12$ nM) in both HepG2.2.15 and HepAD38 cells with a modest shift (~5-fold) in activity in the presence of human serum. VNRX-9945 demonstrates potent activity against genotypes A-H and is broadly active against the majority of amino acid polymorphisms localized to

the core inhibitor binding site. Addition of VNRX-9945 to primary human hepatocytes at the time of infection not only blocked normal capsid assembly but also inhibited *de novo* formation of covalently closed circular DNA (cccDNA) with an $EC_{50} = 100$ nM. Oral administration of a solution of VNRX-9945 to mice, rats, dogs and monkeys resulted in linear exposures up to doses of 600 mg/kg. Administration of VNRX-9945 to rats and monkeys for up to 28 days resulted in no adverse effects or target organ toxicity. Finally, repeat dosing of VNRX-9945 (10–100 mg/kg bid) resulted in potent suppression of HBV DNA to below the lower limit of quantification in the AAV-HBV mouse model of infection.

Conclusion: VNRX-9945 is one of the most potent core inhibitors reported to date with demonstrated activity against both capsid assembly and *de novo* cccDNA formation in naïve primary hepatocytes. The antiviral, pharmacokinetic and safety profile supports the inclusion of VNRX-9945 in future combination therapies that are optimized to achieve a functional cure for chronic HBV. VNRX-9945 is being advanced rapidly into clinical development as a potential best-in-class core protein inhibitor.

PO-1775

GST-HG141, a novel clinical-stage hepatitis B virus capsid assembly modulator

Dong Zhang¹, Wenqiang Wu¹, Shikui Chen¹, Zhou Yu¹, Vadim Bichko¹, John Mao¹, Jiang Zhigan², Haiying He², Jian Li², Shuhui Chen². ¹Fujian Cosunter Pharmaceutical Co., Ltd., Fuzhou, China; ²Domestic Discovery Service Unit, WuXi AppTec (Shanghai) Co., Ltd., Shanghai, China
Email: vbichko@gmail.com

Background and aims: Capsid assembly process, a critical step in the hepatitis B virus (HBV) life cycle, has recently emerged as a key target for the treatment of chronic hepatitis B. The capsid assembly modulators (CAMs) have been validated in the clinic and have a potential for HBV cure. Here we report preclinical characterization of GST-HG141, a novel HBV CAM, including molecular mechanism (s) of its antiviral action and the resistance profile *in vitro*. Currently GST-HG141 is under phase I clinical evaluation.

Methods: A purified, recombinant, c-terminally truncated HBV core protein (aa 1–150) was used in the biochemical quenching assay, size-exclusion chromatography and transmission electron microscopy (TEM), to determine the effects on HBV capsid assembly *in vitro*. Effects on secreted HBV DNA were determined in HepG2.2.15 cells using qPCR. Western, southern and northern blots were performed to detect HBV capsids and HBV capsid-associated DNA and RNA, respectively. *In vivo* antiviral efficacy was assessed in the AAV-HBV mouse model.

Results: In the biochemical quenching assay, GST-HG141 induced HBV core protein assembly ($EC_{50} = 0.93 \pm 0.11$ μM). GST-HG141 also induced formation of intact capsids, demonstrated by the size-exclusion chromatography experiments. TEM studies confirmed that treatment with GST-HG141 did not affect the capsid morphology. In the GST-HG141-treated HepG2.2.15 cells, a dose-dependent reduction of capsid-associated HBV DNA was observed. However, a shift from T=4 towards T=3 capsid formation was not observed, in contrast to other class I CAMs. The HBV DNA secretion in HepG2.2.15 cells was potently inhibited ($EC_{50} = 8.16 \pm 3.65$ nM). In the transient transfection assays, GST-HG141 retained potent antiviral activity against HBV genotypes A-D (EC_{50} of 26–228 nM), and against nucleos (t)ide- and CAM-resistant mutants. The resistance profile of this drug was different from that of other CAMs. No significant cytotoxicity was observed in human cell lines and primary cells ($CC_{50} > 50$ microM). The antiviral effect of GST-HG141 was HBV-specific, no other tested viruses were inhibited. In the AAV/HBV model, GST-HG141 robustly and dose-dependently reduced serum (~3.0 log₁₀) and liver (0.9 log₁₀) HBV DNA. Combination with Tenofovir resulted in additivity. GST-HG141 was well-tolerated, no significant effect on animal body weight was observed.

Conclusion: GST-HG141 is a novel, orally-bioavailable HBV CAM. It accelerates HBV capsid assembly in vitro, leading to formation of “empty” capsids, devoided of genetic material. However, its mode of action and resistance profile appear to be distinct from other class I CAMs in development. GST-HG141 has an excellent antiviral potency in vitro, as well as efficacy in vivo, and is well-tolerated in rodents. Further development of GST-HG141 for chronic HBV infections is warranted. Currently it is undergoing phase I clinical evaluations.

PO-1781

HCC incidence is low after HBsAg seroclearance in off-Nuc patients

Rachel Wen-Juei Jeng^{1,2,3}, Yen-Chun Liu^{1,2,3}, Chien-Wei Peng^{1,2,3}, Yi-Cheng Chen^{1,2,3}, Rong-Nan Chien^{1,2,3}, Yun-Fan Liaw^{2,3}. ¹Linkou Chang Gung Memorial Hospital, Department of Gastroenterology and Hepatology, Taiwan; ²Chang Gung University, College of Medicine, Taiwan; ³Linkou Chang Gung Memorial Hospital, Liver Research Unit, Taiwan

Email: liveryfl@gmail.com

Background and aims: Hepatocellular carcinoma (HCC) incidence is low in chronic hepatitis B (CHB) patients with HBsAg seroclearance during natural history or antiviral therapy. Studies showed that 2.29% of CHB patients would develop HCC after HBsAg loss. However, the long-term outcome in patients with HBsAg loss after stopping nucleos (t)ide analogues (Nuc) therapy is unknown. **Aim:** To investigate the HCC incidence in CHB patients who had HBsAg loss after stopping Nuc

Method: Patients with finite Nuc therapy and had HBsAg loss after stopping Nuc were recruited. Age at treatment, end-of-treatment and HBsAg loss, as well as gender, cirrhosis, HBV genotype (GT), treatment duration were compared. Of a total of 1681 patients in the Chang Gung Memorial Hospital off-Nuc cohort, HBsAg loss was confirmed in 157 patients. Excluding patients with HBsAg loss during Nuc (N = 18), or HCC occurrence during (N = 8) or after stopping Nuc but before HBsAg loss (N = 5) and follow-up less than 6 months (N = 4), a total of 122 CHB patients were recruited.

Results: A total of 122 CHB patients with off-Nuc HBsAg loss were analysed. The median treatment duration was 2.7 (0.8–8.2) years, 90% were male, 41.8% were cirrhosis, GT-B: 68.9%, GT-C: 31.1%. Before HBsAg loss, 40 patients (32.8%) had clinical relapse without retreatment. The median time from end-of-treatment to HBsAg loss was 3.7 (0–16.7) years. During a median follow-up of 4.6 (0.5–18.6) years after HBsAg loss, 3 male patients developed HCC at month 10 (age 47, non-cirrhotic), 16 (age 61, cirrhotic), 52.5 (age 63, cirrhotic) after HBsAg loss. There’s no difference of HBV genotype, treatment duration, presence of clinical relapse between patients with and without HCC. The HCC occurrence was numerically higher in patients with cirrhosis (2/51, 3.9%) than non-cirrhosis (1/71, 1.4%) but the difference was non-significant statistically (p = 0.57).

Conclusion: This seemed to be the first report of HCC development after HBsAg loss in patients who had stopped finite Nuc therapy. The HCC rate of 3 (2.5%) in 122 patients is low, even in cirrhotic patients, and was similar to that reported in patients who lost HBsAg spontaneously or during antiviral therapy.

PO-1791

Hepatic decompensation and hepatocellular carcinoma after stopping nucleos (t)ide analogue therapy: Results from a large, global, multi-ethnic cohort of patients with chronic hepatitis B (RETRACT-B study)

Grishma Hirode^{1,2}, Bettina Hansen^{1,2}, Chien-Hung Chen³, Tung-Hung Su⁴, Grace Lai-Hung Wong⁵, Wai-Kay Seto⁶, Stijn Van Hees⁷, Margarita Papatheodoridi⁸, Sylvia Brakenhoff⁹, Sabela Lens¹⁰, Hannah S.J. Choi¹, Rong-Nan Chien¹¹, Jordan Feld^{1,2}, Xavier Forns¹⁰, Milan Sonneveld⁹, George Papatheodoridis⁸, Thomas Vanwolleghem⁷, Man-Fung Yuen⁶, Henry Chan⁵, Jia-Hong Kao⁴, Yao-Chun Hsu¹², Markus Cornberg¹³, Rachel Wen-Juei Jeng¹¹, Harry Janssen^{1,2}. ¹Toronto General Hospital,

University Health Network, Toronto Centre for Liver Disease, Toronto; ²The Toronto Viral Hepatitis Care Network (VIRCAN), Toronto Centre for Liver Disease, Toronto, Canada; ³Kaohsiung Chang Gung Memorial Hospital, Taiwan; ⁴National Taiwan University Hospital, Taiwan; ⁵The Chinese University of Hong Kong, Hong Kong; ⁶The University of Hong Kong, Hong Kong; ⁷Antwerp University Hospital, Antwerp, Belgium; ⁸Medical School of National and Kapodistrian University of Athens, Greece; ⁹Erasmus MC, University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ¹⁰Hospital Clinic Barcelona, IDIBAPS and CIBEREHD, Barcelona, Spain; ¹¹Chang Gung Memorial Hospital, Taiwan; ¹²E-Da Hospital/I-Shou University, Taiwan; ¹³Hannover Medical School, Germany
Email: grishma.hirode@gmail.com

Background and aims: Despite improvements in management of chronic hepatitis B (CHB), risk of progression to cirrhosis and HCC remains. There is discordance between guidelines regarding the safe discontinuation of nucleos (t)ide analogue (NA) therapy. We aim to analyze rates of liver-related complications (LRC) after NA cessation. **Method:** Cohort study of virologically suppressed, end-of-therapy HBeAg negative patients with CHB who stopped NAs between 2001 and 2020 from 12 participating centers across North America, Europe and Asia. Survival analysis techniques were used to analyze cumulative incidence of off-treatment LRC (hepatic decompensation and/or HCC) and differences by patient characteristics. LRC was considered related to treatment cessation if diagnosed off-treatment or within 6 months of starting retreatment. Patient was considered cirrhotic at cessation if cirrhosis was diagnosed at any time prior to NA cessation.

Results: Among 1528 included patients, 35 developed LRC after NA cessation: 18 hepatic decompensation and 17 HCC. Cumulative rate of LRC at 1- and 4-years of off-treatment follow-up was 1.4% and 3.5%. In the LRC group, mean age was 58 ± 11 years, most were male (77%), Asian (91%), Entecavir-treated prior to cessation (66%), infected with HBV genotype B (51%) (genotype C [17%], D [2.9%], A [0%]), and mean HBsAg level at cessation was 2.5 ± 0.7 log₁₀IU/ml. Median off-treatment follow-up was 15 (IQR: 7–37) months. Patients with LRC (vs no LRC) were older at cessation (≥50 years: 80% vs 63%), more often cirrhotic at cessation (37% vs 11%) and had a higher proportion of start-of-therapy (SOT) HBeAg positive disease (29% vs 14%), resulting in higher cumulative incidence of LRC among these groups (Figure). Higher LRC incidence was mainly driven by decompensation for SOT HBeAg positive disease (vs SOT HBeAg negative: adjusted hazard ratio [aHR] 4.3, p=0.001) while it was driven by both decompensation and HCC for patients aged ≥50 years (vs <50 years: aHR 3.8, p=0.007) and cirrhotics at cessation (vs non-cirrhotics at cessation: aHR 4.7, p<0.001). There were no significant between-group differences for other patient characteristics. In the LRC group, 4/35 had off-treatment HBsAg loss, and 2/4 had HBsAg loss after the LRC had been diagnosed. Among those without LRC, 109/1493 had off-treatment HBsAg loss.

Conclusion: Regardless of off-treatment HBsAg loss, older, cirrhotic, and/or SOT HBeAg positive patients should be carefully assessed prior to stopping NAs to prevent deterioration to LRC.

POSTER PRESENTATIONS

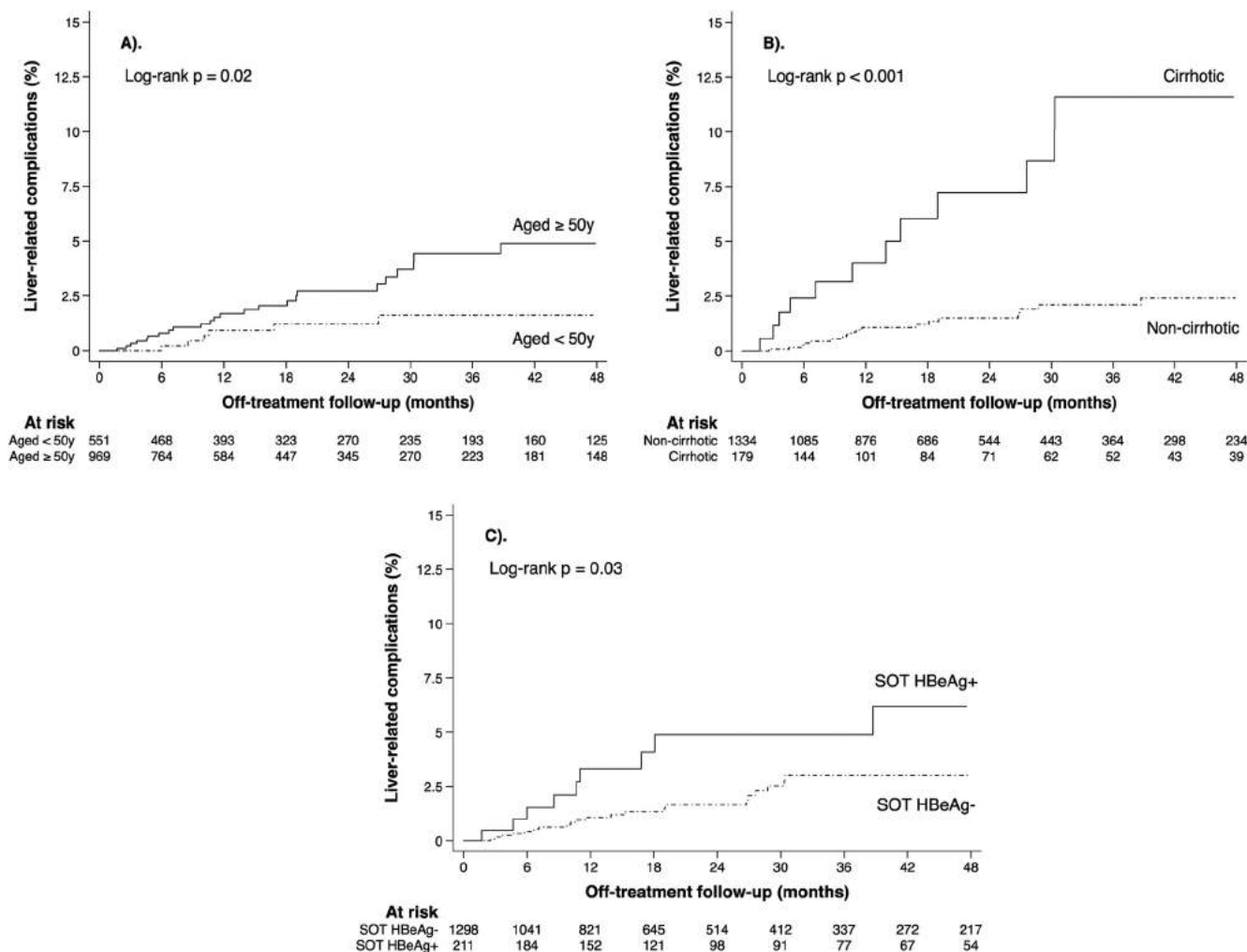


Figure: (abstract: PO-1791): Cumulative incidence of LRC by A) age at cessation, B) cirrhosis status at cessation and C) SOT HBeAg status. LRC, liver-related complications; SOT, start-of-therapy.

PO-1837

HBsAg, anti-HBs and ALT kinetic characterization during NAP-based combination therapy of HBeAg negative chronic hepatitis B infection

Leeor Hershkovich¹, Louis Shekhtman^{1,2}, Michel Bazinet³, Victor Pântea⁴, Gheorge Placinta⁴, Iruie Moscalu⁵, Valentin Cebotarescu⁴, Lilia Cojuhari⁴, Pavlina Jimbei⁶, Liviu Iarovoi⁴, Valentina Smesnoi⁶, Tatiana Musteata⁶, Alina Jucov^{4,5}, Scott Cotler¹, Andrew Vaillant³, Harel Dahari¹. ¹Loyola Univeristy Chicago, The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Maywood, United States; ²Northeastern, University, Network Science Institute, Boston, United States; ³Replicor Inc., Montreal, Canada; ⁴State University of Medicine and Pharmacy, Department of Infectious Diseases, Chişinău, Moldova; ⁵Republican Clinical Hospital, ARENSIA Exploratory Medicine, Chişinău, Moldova; ⁶Toma Ciorbă Infectious Clinical Hospital, Chişinău, Moldova
Email: harel.dahari@gmail.com

Background and aims: The interplay among serum hepatitis B surface Antigen (HBsAg), anti-HBs, and alanine aminotransferase (ALT) during combination therapy with REP 2139-Mg or REP 2165-Mg, pegylated interferon alpha-2a (IFN) and tenofovir disoproxil fumarate (TDF) has not been analyzed in detail. Here we characterize HBsAg, anti-HBs and ALT kinetics during 48-week triple therapy.

Method: Serum samples of 20 chronic HBV-infected participants who received 48 weeks of triple therapy (following 24 weeks of TDF monotherapy) from the REP 401 study (Bazinet et al. Gastroenterology 2020; 158:2180–94) were analyzed for HBsAg (Abbott Architect, LLoQ 0.05 IU/ml), anti-HBs (Abbott Architect, seroconversion cutoff = 10 IU/ml) and ALT. HBV DNA was not analyzed since it became ≤ 2.1 log IU/ml in 19/20 participants during TDF monotherapy. Distinctions between HBsAg phases were defined as at least a 2-fold change in slope. A single-phase decline was defined as monophasic, and two-phase declines were defined as biphasic. Patients with an overall reduction from baseline in HBsAg < 1 log at EOT were defined as non-responders (NR).

Results: Three HBsAg kinetic patterns were found: NR ($n = 4$, Fig. 1a), monophasic decline ($n = 12$, Fig. 1b) and biphasic decline ($n = 4$, Fig. 1c). HBsAg decline (9 ± 2 wk) was delayed in NR vs monophasic/biphasic decline (3 ± 3 wk, $p = 0.001$). Rate of HBsAg decline in monophasic participants was 0.52 ± 0.22 log IU/ml/week, all reaching $< \text{LLOQ}$ by week 18 ± 8 . The 1st phase decline in biphasic participants (0.25 ± 0.15 log IU/ml/week) was slower ($p = 0.02$) versus monophasic participants followed by a slower phase decline of 0.03 ± 0.02 log IU/week with only one patient reaching $< \text{LLOQ}$ at EOT (Fig. 1c). Anti-HBs was not detected in 17/20 participants at baseline. Early (14 ± 5 wk, Fig. 1b) seroconversion (0.23 ± 0.09 log/mIU/wk) accompanied 11/12 HBsAg monophasic HBsAg declines. Only 1/4 HBsAg biphasic (Fig. 1c) and none of the NR participant (Fig. 1a) experienced

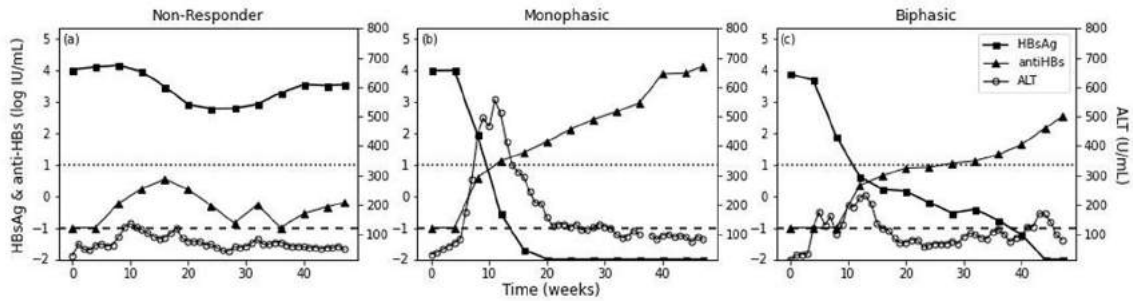


Figure 1. Representative patients based on HBsAg response kinetic patterns during 48-week combination therapy with TDF, IFN and REP. (a) non-responder, (b) monophasic, and (c) biphasic. Horizontal dashed line represents HBsAg LLoQ (log 0.1 IU/mL); horizontal dotted line represents anti-HBs seroconversion (log 10 IU/mL).

Figure: (abstract: PO-1837)

seroconversion by EOT (Fig. 1a). ALT kinetics were independent of HBsAg decline. Transient increases in ALT (baseline 39 ± 19 U/ml) reached a 12.0 ± 10.4 -fold peak above mean baseline ALT, followed by decline (2.9 ± 2.4 -fold from baseline) at EOT. ALT flares coincided with HBsAg decline in 19/20 participants and with anti-HBs seroconversion in monophasic decline. There was no difference in kinetic patterns between REP 2139-Mg and REP 2165-Mg.

Conclusion: Longer (>6 weeks) delay in HBsAg decline may predict non-responders to combination therapy. Concomitant ALT flare and anti-HBs seroconversion with a rapid decline in HBsAg suggest that NAP-based therapy leads to specific anti-HBV immune responses yet to be identified.

PO-1841

Earlier and more frequent virological and clinical relapse after cessation of tenofovir disoproxil fumarate versus entecavir therapy: Results from a large, global, multi-ethnic cohort of chronic hepatitis B patients (RETRACT-B study)

Hannah S.J. Choi¹, Grishma Hirode^{1,2}, Chien-Hung Chen³, Tung-Hung Su⁴, Grace Lai-Hung Wong⁵, Wai-Kay Seto⁶, Stijn Van Hees⁷, Margarita Papatheodoridis⁸, Sylvia Brakenhoff⁹, Sabela Lens¹⁰, Arif Sarowar¹, Rong-Nan Chien¹¹, Jordan Feld¹, Xavier Forn¹⁰, Milan Sonneveld⁹, George Papatheodoridis⁸, Thomas Vanwolleghem⁷, Man-Fung Yuen⁶, Henry Chan⁵, Jia-Horng Kao⁴, Yao-Chun Hsu¹², Markus Cornberg¹³, Bettina Hansen¹, Rachel Wen-Juei Jeng¹¹, Harry Janssen¹. ¹University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ²The Toronto Viral Hepatitis Care Network (VIRCAN), Toronto, Canada; ³Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ⁴National Taiwan University Hospital, Taipei, Taiwan; ⁵The Chinese University of Hong Kong, Sha Tin, Hong Kong; ⁶The University of Hong Kong, Pokfulam, Hong Kong; ⁷Antwerp University Hospital, Edegem, Belgium; ⁸Medical School of National and Kapodistrian University of Athens, Athens, Greece; ⁹Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ¹⁰Hospital Clínic Barcelona, IDIBAPS and CIBEREHD, Barcelona, Spain; ¹¹Chang Gung Memorial Hospital, Taoyuan, Taiwan; ¹²Fu-Jen Catholic University Hospital/E-DA Hospital, New Taipei, Taiwan; ¹³Hannover Medical School, Hanover, Ghana
Email: sjchoi0731@gmail.com

Background and aims: Whether tenofovir disoproxil fumarate (TDF) and entecavir (ETV) differentially affect relapse across different patient subpopulations following treatment discontinuation remains unclear. We aimed to study the association between drug type and relapse in a global multi-centre cohort of chronic hepatitis B (CHB) patients who discontinued either TDF or ETV therapy.

Method: We investigated outcomes in CHB patients who stopped either TDF or ETV therapy between 2001 and 2020 from 12

participating centres across North America, Europe, and Asia. All included patients were HBeAg-negative at discontinuation. Rates and risk of virological (VR; HBV DNA ≥ 2000 IU/ml) and clinical (CR; HBV DNA ≥ 2000 IU/ml and ALT $\geq 2 \times$ ULN) relapse were analyzed using multivariable Cox regression stratified by site, adjusting for age, sex, race, total treatment duration, treatment history, HBeAg status at the start of therapy (SOT), and HBsAg level at the end of therapy (EOT).

Results: Of 1386 CHB patients included, 416 had been treated with TDF and 970 with ETV. No significant differences in age, sex, and EOT HBsAg levels and no proportional differences in cirrhosis and HBeAg status at SOT were observed between the two groups. The TDF group had fewer Asian patients (81% vs 94%), more patients previously treated with other NAs (27% vs 11%) or (peg-)interferon (10% vs 6%), and higher median ALT at EOT compared with the ETV group (0.7 vs $0.5 \times$ ULN); all $p < 0.05$. Overall, 995/1386 (72%) and 561/1386 (41%) patients experienced VR and CR, respectively, during a median off-treatment follow-up of 17 months; 838/995 (84%) VRs and 354/561 (63%) CRs occurred within 12 months of cessation. TDF vs ETV was associated with a higher rate of VR in the first 12 months overall (hazard ratio [HR]: 2.0, $p < 0.01$) and across different races and HBeAg status at SOT; the difference became negligible over time (HR: 0.79, $p = 0.37$) (Fig.). Among Asian patients, the risk of VR associated with TDF was further increased in males ($p < 0.05$) and those with HBsAg ≥ 1000 IU/ml ($p < 0.01$). TDF was also associated with consistently higher rates of CR compared with ETV throughout follow-up (Fig.). TDF was an independent predictor of CR (HR: 1.63, $p < 0.01$), adjusting for the factors aforementioned.

Conclusion: VR was very frequent after ETV or TDF treatment discontinuation. VR and CR were observed earlier and more frequently in individuals treated with TDF vs ETV, adjusting for race, age, sex, treatment history, HBeAg status at SOT, and HBsAg levels at EOT. Only among TDF-treated Asian patients, the risk of VR was further increased with male sex and/or HBsAg ≥ 1000 IU/ml at EOT.

POSTER PRESENTATIONS

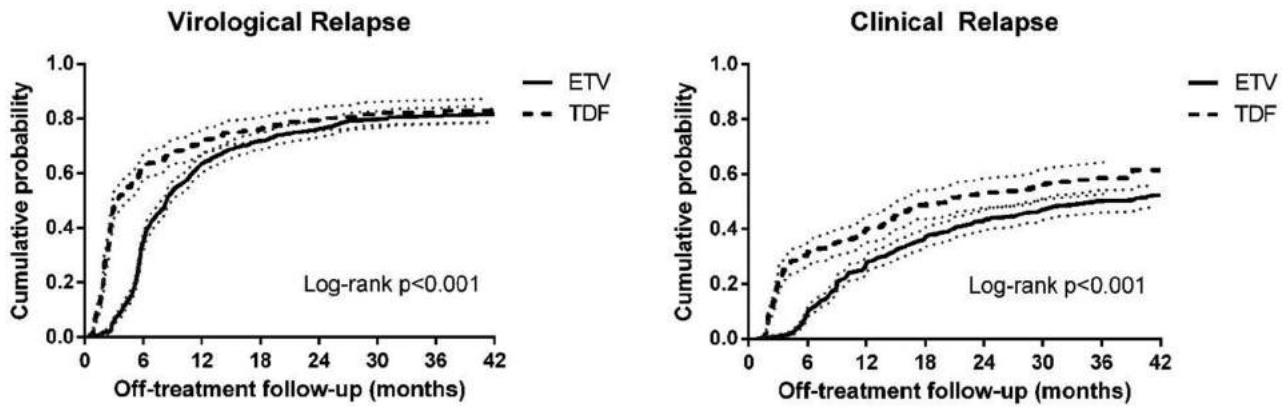


Figure: (abstract: PO-1841)

PO-2089

HIF1 α -mediated RelB/APOBEC3B downregulation allows Hepatitis B virus persistence

Tobias Riedl¹, Suzanne Faure-Dupuy¹, Maude Rolland², Svenja Schuehle¹, Zoheir Hizir², Silvia Calderazzo¹, Xiaodong Zhuang³, Jochen Wettengel⁴, Martin Lopez², Sandra Prokosch¹, Danijela Heide¹, Corinna Leuchtenberger¹, Martin Schneider¹, Bernd Hessling¹, Benjamin Stottmeier⁵, Isabel Wessbecher⁵, Peter Schirmacher⁵, Jane McKeating³, Ulrike Protzer⁴, David Durantel⁶, Julie Lucifora⁶, Emmanuel Dejaradin², Mathias Heikenwälder¹. ¹German Cancer

Research Center, Heidelberg, Germany; ²University of Liège, Liège, Belgium; ³University of Oxford, Oxford, United Kingdom; ⁴Helmholtz Zentrum München-Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), München, Germany; ⁵University Hospital Heidelberg, Heidelberg, Germany; ⁶Cancer Research Center of Lyon, Lyon, France
Email: t.riedl@dkfz.de

Background and aims: New therapeutic strategies against Hepatitis B virus (HBV) focus, among others, on the activation of the immune system to enable the infected host to eliminate HBV. Hypoxia inducible factor 1 alpha (HIF1 α) stabilisation has been associated with impaired immune responses. HBV pathogenesis triggers chronic hepatitis-related scarring, leading *inter alia* to modulation of liver

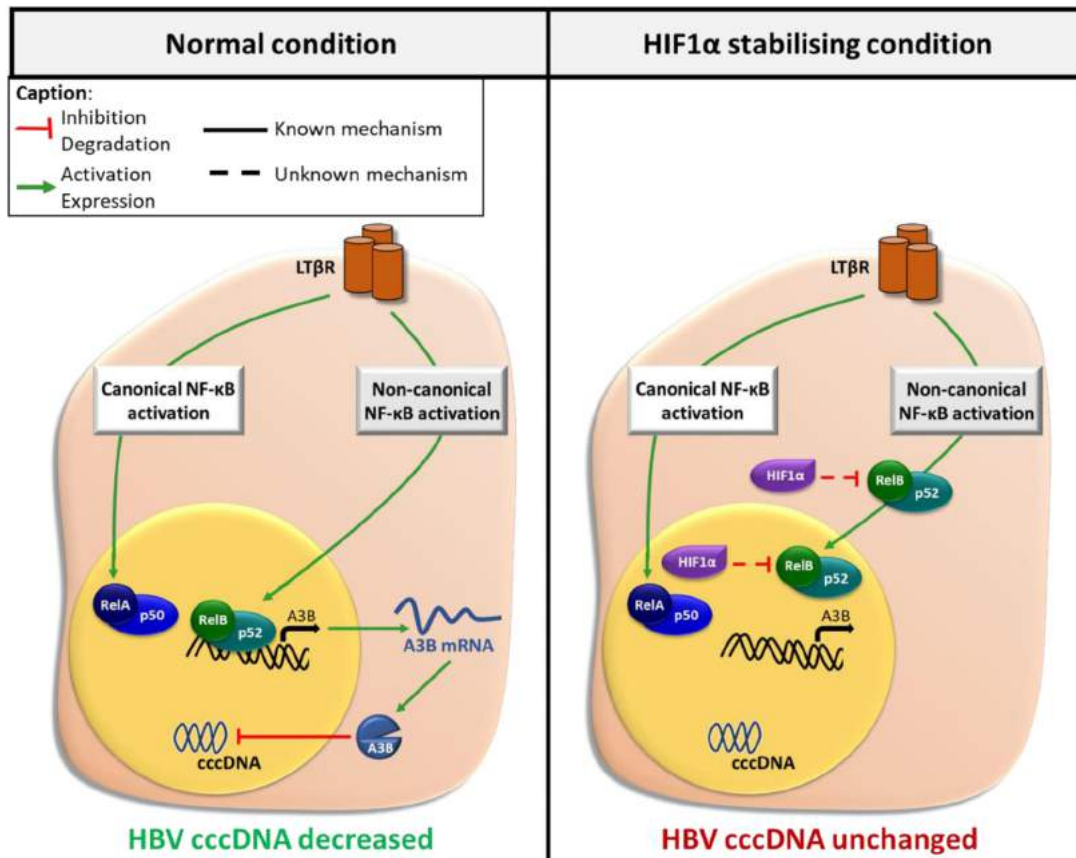


Figure: (abstract: PO-2089)

oxygenation and transient immune activation, both factors playing a role in HIF1 α stabilisation. We addressed whether HIF1 α interferes with immune-mediated induction of the cytidine deaminase APOBEC3B and subsequent covalently closed circular DNA (cccDNA) decay.

Method: Liver biopsies of chronic HBV patients (CHB) were analysed by IHC, and *in situ* hybridization. The effect of HIF1 α induction/stabilisation on differentiated HepaRG or mice \pm HBV \pm LT β R-agonist (BS1) was assessed *in vitro* and *in vivo*. Induction of A3B and subsequent effects were analysed by RT-qPCR, immunoblotting, ChIP, ICC, and mass-spectrometry.

Results: Analysing CHB highlighted that areas with high HIF1 α levels and low A3B expression correlated with high HBcAg, potentially representing a reservoir for HBV survival in immune-active patients. *In vitro*, HIF1 α stabilisation, strongly impaired A3B expression and anti-HBV effect. Interestingly, HIF1 α knock-down was sufficient to rescue the inhibition of A3B-upregulation and -mediated antiviral effects, whereas HIF2 α knock-down had no effect. HIF1 α stabilisation decreased the level of RelB protein but not its mRNA, which was confirmed *in vivo*. Noteworthy, this function of HIF1 α was independent of its partner ARNT.

Conclusion: In conclusion, inhibiting HIF1 α expression or stabilisation represents a novel anti-HBV strategy in the context of immune-mediated A3B induction. High HIF1 α , mediated by hypoxia or inflammation, offers a reservoir for HBV survival *in vivo*, and should be considered as a restricting factor in the development of novel immune therapies.

PO-2106

T-cell engagers that bind HBV envelope proteins enable T cells to control the infection and to target hepatoma in mice

Oliver Quitt¹, Shanshan Luo¹, Marten Meyer², Forough Golsaz-Shirazi³, Eva Loffredo-Verde¹, Zhe Xie¹, Julia Festag¹, Jan H. Bockmann¹, Lili Zhao¹, Daniela Stadler¹, Wen-Min Chou¹, Raindy Tedjokusumo¹, Nadja Bulbuc², Fazel Shokri³, Sandra Lüttgau⁴, Mathias Heikenwälder¹, Felix Bohne¹, Gerhard Moldenhauer⁴, Frank Momburg², Ulrike Protzer¹. ¹German Research Centre for Environmental Health/Technical University of Munich, Institute of Virology, München, Germany; ²German Cancer Research Centre, Antigen Presentation and T/NK Cell Activation Group, Clinical Cooperation Unit Applied Tumor Immunity, Heidelberg, Germany; ³Teheran University of Medical Sciences, Department of Immunology, Tehran, Iran; ⁴German Cancer Research Centre, Department of Translational Immunology, Heidelberg, Germany
Email: oliver.quitt@tum.de

Background and aims: Hepatitis B virus (HBV) infection is a global health problem responsible for 880,000 deaths per year. Current antiviral therapies control but rarely eliminate the virus, and leave chronic HBV carriers at risk to develop hepatocellular carcinoma (HCC). Lacking or dysfunctional virus-specific adaptive immune responses prevent immune control of HBV and allow the virus to persist. Therefore, alternative treatment strategies aim at restoring anti-viral T-cell immunity to achieve HBV elimination in chronically infected patients.

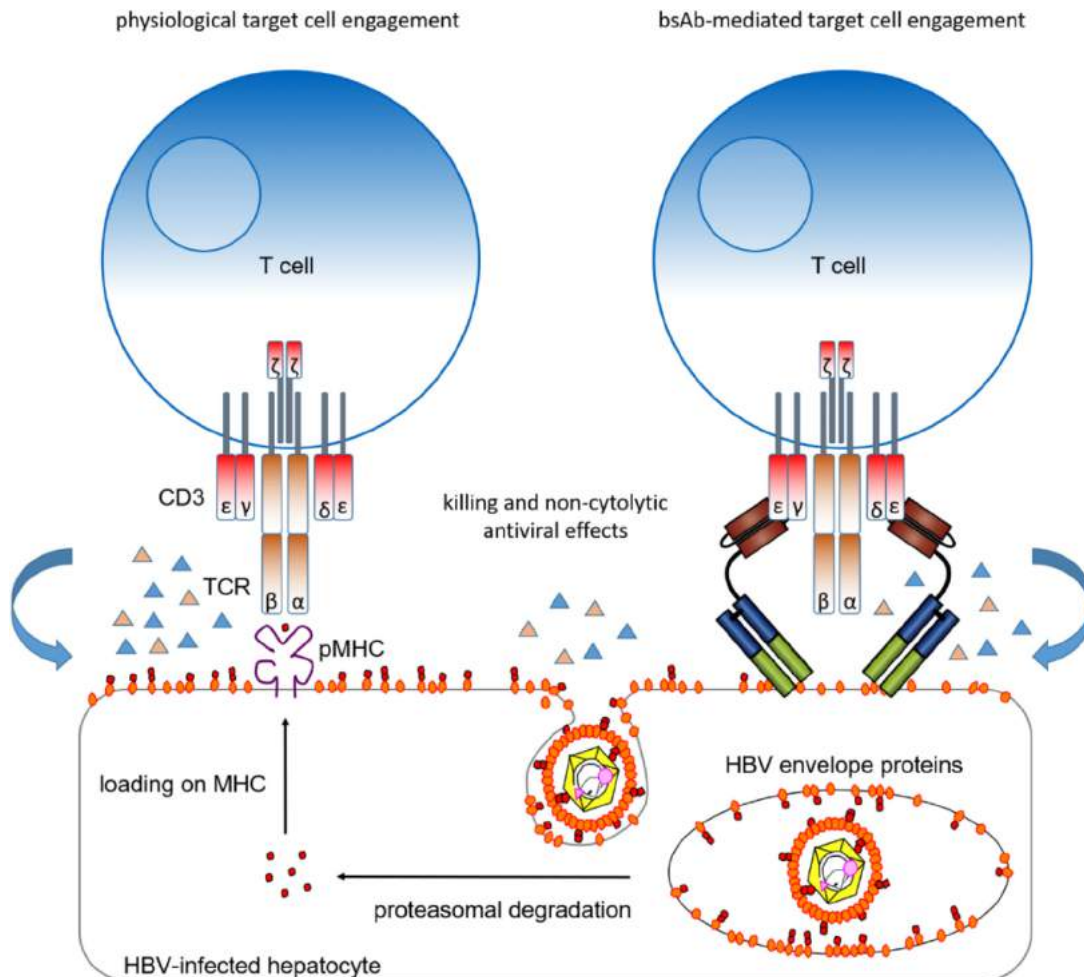


Figure: (abstract: PO-2106)

POSTER PRESENTATIONS

Method: We constructed bispecific T-cell engager antibodies (bsAbs) that are designed to induce anti-viral immunity through simultaneous binding of HBV envelope proteins (HBVenv) on infected hepatocytes and CD3 and 28 on T cells. The constructs were employed in co-cultures with peripheral blood mononuclear cells (PBMC) and HBV-infected target cells and the redirected T-cell response was determined by detection of pro-inflammatory cytokines, viability of target cells and the quantification of viral DNAs. To study the efficacy of bsAbs *in vivo*, we established a tumor transplant model with human effector and HBVenv-positive hepatoma cells in immune-deficient Rag2^{-/-}/IL2Ryc^{-/-} mice.

Results: T-cell engager antibodies synergistically activated T cells to become polyfunctional effectors that in turn elicited potent anti-viral effects by killing infected cells and via non-cytolytic, cytokine-mediated antiviral mechanisms. In mice, the antibodies attracted T cells to tumors expressing HBVenv resulting in T-cell activation, infiltration into the tumor and reduction of tumor burden.

Conclusion: This study demonstrates that the administration of HBVenv-targeting bsAbs facilitates a robust T-cell redirection towards HBV-positive target cells and provides a feasible and promising approach for the treatment of chronic hepatitis B (CHB) and HBV-associated HCC.

PO-2243

Control of APOBEC3B induction and transcription-independent Hepatitis B virus episome decay by NF- κ B and miR-138-5p

Suzanne Faure-Dupuy¹, Tobias Riedl¹, Maude Rolland², Zoheir Hizir², Florian Reisinger¹, Katharina Neuhaus¹, Svenja Schuehle¹, Caroline Remouchamps², Nicolas Gillet³, Maximilian Schöning¹, Mira Stadler¹, Jochen Wettengel⁴, Romain Barnault⁵, Romain Parent⁵, Linda Schuster¹, Rayan Farhat⁵, Sandra Prokosch¹, Corinna Leuchtenberger¹, Rupert Öllinger⁴, Thomas Engleitner⁴, Karsten Rippe¹, Roland Rad¹, Kristian Unger^{6,7}, Darjus Tschaharganeh¹, Daniel Lipka¹, Ulrike Protzer⁴, David Durantel⁵, Julie Lucifora⁵, Emmanuel Dejardin², Mathias Heikenwälder¹. ¹German Cancer Research Center, Heidelberg, Germany; ²University of Liège, Liège, Belgium; ³NAMUR, Asse, Belgium; ⁴Helmholtz Zentrum München-Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), München, Germany; ⁵Cancer Research Center of Lyon, Lyon, France; ⁶LMU University Clinics, Department of Radiation Oncology, Munich, Germany; ⁷Helmholtz Zentrum München, Radiation Cytogenetics, Neuherberg, Germany
Email: m.heikenwaelde@dkfz-heidelberg.de

Background and aims: Immune-mediated induction of cytidine deaminase APOBEC3B (A3B) expression leads to hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) decay. Here, we aimed to decipher the signalling pathway (s) and regulatory mechanism (s) involved in A3B induction and related HBV control.

Method: Differentiated HepaRG (dHepaRG) knocked-down for NF- κ B signalling components, transfected with siRNA or micro RNAs (miRNA), and primary human hepatocytes \pm HBV, were treated with

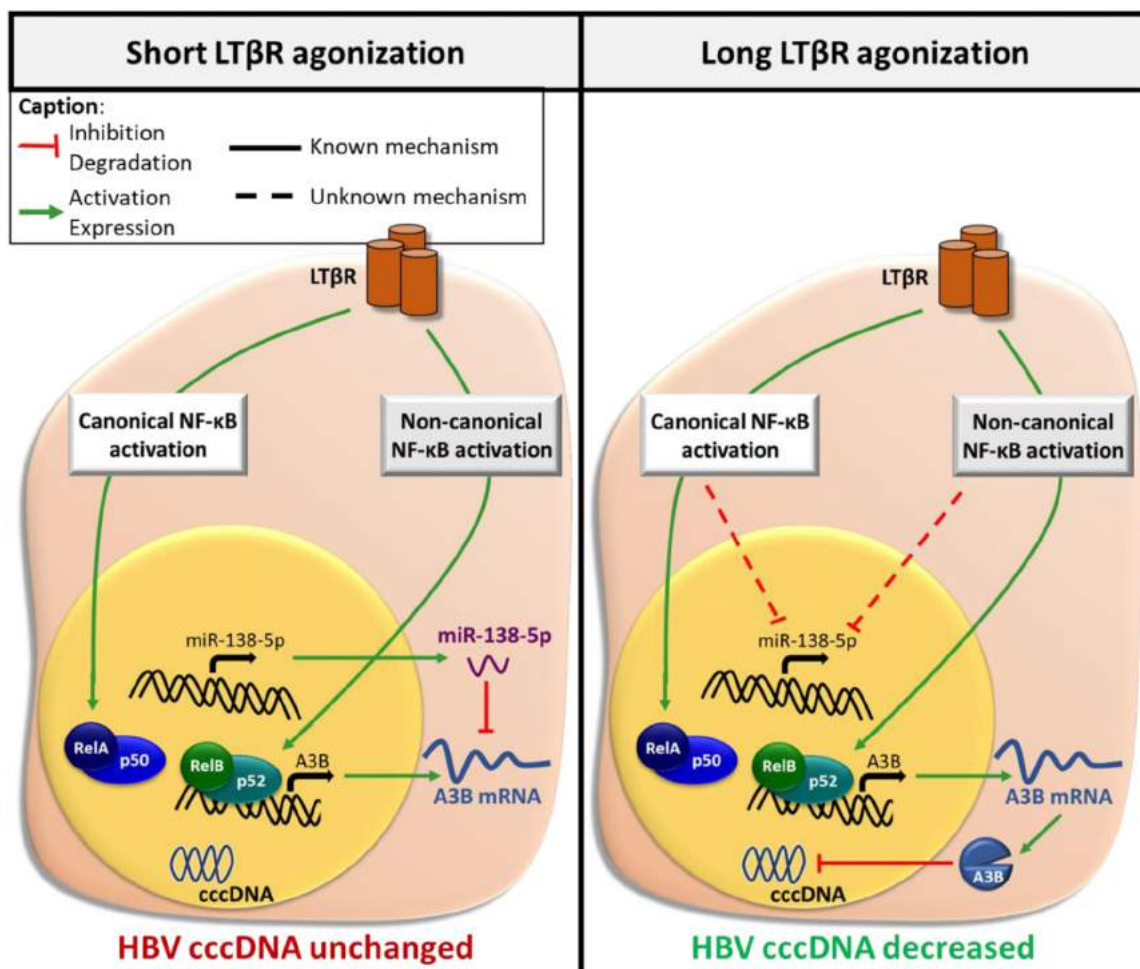


Figure: (abstract: PO-2243)

LT β R-agonist (BS1). Induction of A3B and subsequent effects were assessed by RT-qPCR, immunoblotting, luciferase activity, ChIP, EMSA, targeted-bisulfite-, miRNA-, RNA-, genome-sequencing, and mass-spectrometry.

Results: We found that canonical and non-canonical NF- κ B signalling pathways are mandatory for A3B induction and anti-HBV effects. The degree of immune-mediated A3B production is independent of A3B promoter demethylation but is controlled post-transcriptionally by the micro RNA 138-5p expression (hsa-miR-138-5p), promoting A3B mRNA decay. Hsa-miR-138-5p over-expression reduced A3B levels and its antiviral effects. Of note, established infection inhibited BS1-induced A3B expression through epigenetic modulation of A3B promoter. Twelve days of treatment with a lymphotoxin beta receptor-specific agonist BS1 is sufficient to reduce the cccDNA pool by 80% without inducing mutational load to the genomic DNA. Interestingly, the A3B-mediated effect on HBV is independent of the transcriptional activity of cccDNA as well as of rcDNA synthesis.

Conclusion: Altogether, A3B represents the only described enzyme to target both transcriptionally active and inactive cccDNA. Thus, inhibiting hsa-miR-138-5p expression should be considered in the combinatorial design of new therapies against HBV, especially in the context of immune-mediated A3B induction.

PO-2269

HBsAg, HBcrAg, and HBV RNA in outcomes and after NA discontinuation in HBeAg negative patients with chronic hepatitis B: results from the Toronto STOP Study

Arif Sarwar¹, Scott Fung¹, David Wong¹, Colina Yim¹, Seham Noureldin¹, Jiayun Chen¹, Karen Rother², Mina Farag¹, Thomas Berg², Jordan Feld^{1,3}, Florian van Bömmel², Bettina Hansen^{1,4}, Harry Janssen¹, ¹University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ²University Hospital Leipzig, Department of Gastroenterology and Rheumatology, Section of Hepatology, Leipzig, Germany; ³McLaughlin-Rotman Centre for Global Health, Toronto, Canada; ⁴University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada
Email: arif.sarwar@uhnresearch.ca

Background and aims: Novel biomarkers such as HBcrAg and HBV RNA have been shown to predict sustained response after NA discontinuation, however more understanding of these biomarkers during relapse and follow-up is needed. In this randomized controlled study, we studied the outcomes and kinetics of novel HBV biomarkers after NA discontinuation.

Method: HBV RNA, HBsAg, and HBcrAg levels were measured in 67 HBeAg negative patients, randomized into stop (n = 45) or continue (n = 22) NA therapy and followed for 72 weeks. HBV RNA was quantified using real time PCR (limit of detection: 160 cp/ml) and HBcrAg using CLEIA assay (limit of detection 3 log U/ml). Virological relapse (HBV DNA >2000 IU/ml), clinical relapse (HBV DNA >2000 and ALT >1.5x ULN), retreatment, and biomarker levels were assessed.

Results: For the 45 patients that discontinued NA, mean HBV RNA at end-of-treatment (EOT) was 1.92 log U/ml (1.8), with 32/45 (71%) patients undetectable. Mean HBcrAg was 3.36 log U/ml (0.83) with 22/45 (49%) patients undetectable at EOT. Virological relapse was observed in 39/45 (87%) stop patients, with clinical relapse occurring in 31/45 (69%) patients. In total 17/45 (38%) patients were retreated according to a standardized retreatment protocol, with 1/45 (2%) stop NA patients achieving HBsAg clearance. Presence of detectable HBcrAg at EOT (>3 log U/ml) was significantly associated with increased rates of retreatment. (p < 0.005, HR: 4.83), while no significant associations were found with HBV RNA and HBsAg at EOT. HBcrAg levels over time remain stable in patients not retreated, with retreated patients exhibiting a non-significant increase in HBcrAg levels by end of follow-up. No patients experienced adverse liver related outcomes or death.

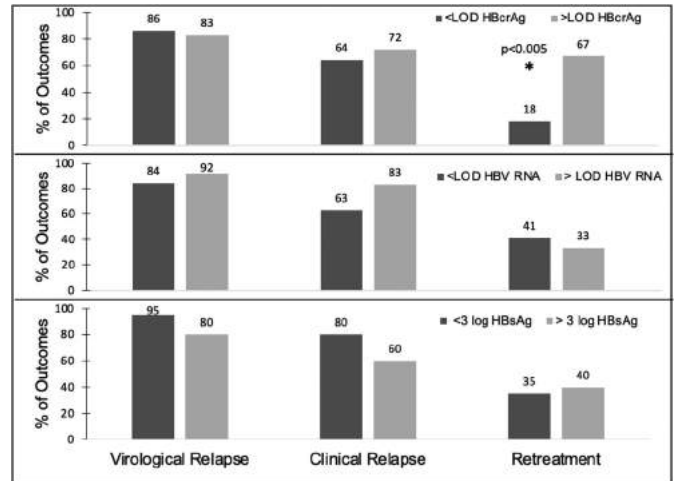


Figure: Relapse and retreatment outcomes for stop patients (n = 45) based on HBcrAg, HBV RNA, and HBsAg levels at end of treatment. Limit of detection (LOD) for HBV RNA and HBcrAg was 160 cp/ml and 3 log U/ml, respectively

Conclusion: While HBsAg and HBV RNA show low predictive value in our randomized controlled study, HBcrAg shows potential predictive value for retreatment after NA discontinuation, with lower levels of HBcrAg associated with lower rates of retreatment. As 45% of our patients had undetectable levels at EOT, optimizing HBcrAg testing would improve sensitivity and further understanding of treatment management in future studies.

PO-2338

Switching from tenofovir disoproxil fumarate and/or other oral antivirals to tenofovir alafenamide in virally suppressed chronic hepatitis B patients with hepatic impairment: final 2 year efficacy and safety results from a phase 2, open-label study

Young-Suk Lim¹, Chun-yen Lin², Jeong Heo³, Ho Bae⁴, Wan-Long Chuang⁵, Tak Yin Owen Tsang⁶, Claire Fournier⁷, Aric Josun Hui⁸, Huy Trinh⁹, Susanna Tan¹⁰, Yang Zhao¹⁰, John F. Flaherty¹⁰, Vithika Suri¹⁰, Anuj Gaggar¹⁰, Diana Brainard¹⁰, Stephen Ryder¹¹, Harry L.A. Janssen¹², ¹Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Rep. of South; ²Chang Gung University and Chang Gung Memorial Hospital, Taoyuan City, Taiwan; ³Pusan National University School of Medicine, Pusan, Korea, Rep. of South; ⁴Asian Pacific Liver Center, Los Angeles, United States; ⁵Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; ⁶Chinese University of Hong Kong, Hong Kong; ⁷Service d'Hépatologie, CHUM, Montreal, Quebec, Canada; ⁸Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong; ⁹San Jose Gastroenterology; ¹⁰Gilead Sciences Inc., Foster City, United States; ¹¹Biomedical Research Centre in Gastrointestinal and Liver Disorders at Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom; ¹²Erasmus MC, Rotterdam, Netherlands
Email: vithika.suri@gilead.com

Background and aims: We have previously shown that in hepatically impaired (chronic hepatitis B) CHB patients, switching to tenofovir alafenamide (TAF) from tenofovir disoproxil fumarate (TDF) and/or other oral antivirals (OAVs) maintains high rates of viral suppression with stable bone and renal safety parameters through 48 weeks. Here we present our final 2-year (Week 96) results.

Method: In this Phase 2 study (NCT03180619), virally suppressed CHB patients (HBV DNA <LLOQ x \geq 6 months and <20 IU/ml at screening) with Child-Turcotte-Pugh (CTP) scores \geq 7 and \leq 12 at screening (or previously documented to be \geq 7) while receiving TDF and/or other OAVs for \geq 48 weeks were enrolled and switched to TAF 25 mg QD for 96 weeks. Safety assessments including changes in bone (hip and spine BMD) and renal (CrCL by Cockcroft-Gault

POSTER PRESENTATIONS

[eGFR_{CC}], serum creatinine) parameters, viral suppression, and serological and biochemical responses were serially assessed. **Results:** Of 31 patients enrolled, mean age was 55 y (29% ≥60 y), 68% male, 81% Asian, and 90% HBeAg-negative; median (Q1, Q3) CTP and MELD scores were 6 (5, 8) and 10 (7.5, 14.2), respectively, median eGFR_{CC} 98.5 ml/min; 19% had osteoporosis on spine DXA. Twenty-five (81%) patients completed 96 weeks of TAF treatment (6 discontinued early: 2-withdrew consent, 1-adverse event [AE; Grade 2 creatinine increase], 1-investigator decision, and 2-death [respiratory failure and aspiration pneumonia-both not treatment-related]). Week 96 efficacy/safety results are summarized in the Table. 96% of patients on TAF treatment had HBV DNA <20 IU/ml with a high proportion having normal ALT levels. Bone and renal parameters remained stable. TAF was well tolerated with no patients having a Grade 3 or 4 AE or a serious AE related to treatment.

n/N (%), or median (Q1, Q3)	TAF 25 mg QD	
	Missing = Failure	Missing = Excluded
Efficacy		
HBV DNA <20 IU/mL	24/31 (77)	24/25 (96) ^a
ALT normal (2018 AASLD criteria) ^{b,c}	18/31 (58)	18/25 (72)
ALT normal (Central lab criteria) ^{b,d}	22/31 (71)	22/25 (88)
HBeAg loss ^e	2/30 (7)	2/24 (8)
qHBeAg, log ₁₀ change (IU/mL)		-0.15 (-0.32, -0.08)
CTP score change		0 (-1, 0)
MELD score change		-0.6 (-1.3, 0.0)
Bone safety		
Hip BMD, % change		+0.15 (-1.167, 2.677)
Spine BMD, % change		-0.13 (-2.192, 2.736)
CTX, % change (ng/mL) ^f		-6.3 (-25.0, 7.1)
P1NP, % change (ng/mL) ^g		-3.8 (-19.3, 25.4)
Renal safety		
sCr, change (mg/dL)		0.02 (-0.05, 0.90)
sPO ₄ , change (mg/dL)		-0.1 (-0.4, 0.3)
eGFR _{CC} , change (mL/min)		-2.4 (-11.4, 10.7)
RBP/Cr, % change ^h		-22.5 (-42.7, 14.7)
β2MG/Cr, % change ⁱ		-20.5 (-52.5, 27.3)

^a1 patient had HBV DNA ≥20 IU/ml but <69 IU/mL; ^bALT normal is proportion with ALT ≤ULN at Week 96 regardless of baseline ALT level; ^cULN ≤35 U/L males, ≤25 U/L females; ^dULN ≤43 U/L men and ≤35 U/L for men ≥65y, ≤34 U/L women and ≤32 for women ≥65y; ^eNo patient had HBeAg seroconversion; ^fSerum C-type collagen sequence (bone resorption marker); ^gSerum procollagen type 1 N-terminal propeptide (bone formation marker); ^hUrine retinol binding protein/creatinine ratio (proximal tubular marker); ⁱUrine beta-2 microglobulin/creatinine ratio (proximal tubular marker). BMD, bone mineral density by DXA scan; sCr, serum creatinine; eGFR_{CC}, estimated creatinine clearance (Cockcroft-Gault method); sPO₄, serum phosphorus.

Conclusion: At 2 years, CHB patients with hepatic impairment who were switched to TAF maintained high rates of viral suppression and normal ALT values while bone and renal parameters remained stable.

PO-2395

Switching from tenofovir disoproxil fumarate and/or other oral antivirals to tenofovir alafenamide in virally suppressed CHB patients with moderate or severe renal impairment or ESRD on HD: final week 96 efficacy and safety results from a phase 2 study

Harry LA Janssen¹, Pietro Lampertico², Chien-Hung Chen³, Jeong Heo⁴, Claire Fournier⁵, Sang Hoon Ahn⁶, Tak Yin Owen Tsang⁷, Carla S. Coffin⁸, Yi-Hsiang Huang⁹, Giulio Marchesini Reggiani¹⁰, Aric Josun Hui¹¹, Magdy Elkhatab¹², Chi-Yi Chen¹³, Syed-Mohammed Jafri¹⁴, Susanna Tan¹⁵, Yang Zhao¹⁵, Vithika Suri¹⁵, John F. Flaherty¹⁵, Anuj Gaggar¹⁵, Diana Brainard¹⁵, Wan-Long Chuang¹⁶, Kosh Agarwal¹⁷, Edward Gane¹⁸, Young-Suk Lim¹⁹. ¹Erasmus Universiteit Rotterdam, Rotterdam, Netherlands; ²University of Milan, Milan, Italy; ³National Taiwan University Hospital, Taipei City, Taiwan; ⁴Pusan National University School of Medicine, Korea, Rep. of South; ⁵Service d'Hépatologie, CHUM, Canada; ⁶Yonsei University College of Medicine, Seoul, Korea, Rep. of

South; ⁷Chinese University of Hong Kong, Central Ave, Hong Kong; ⁸University of Calgary; ⁹Taipei Veterans General Hospital, Taipei, Taiwan; ¹⁰University of Bologna, Italy; ¹¹Alice Ho Miu Ling Nethersole Hospital, Hong Kong; ¹²Toronto Liver Centre, Canada; ¹³Chia-Yi Christian Hospital, Taiwan; ¹⁴Henry Ford Health System, United States; ¹⁵Gilead Sciences Inc., Foster City, United States; ¹⁶Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan; ¹⁷Institute of Liver Studies, King's College Hospital, United Kingdom; ¹⁸University of Auckland, New Zealand; ¹⁹Asan Medical Center, University of Ulsan College of Medicine, Korea, Rep. of South
Email: vithika.suri@gilead.com

Background and aims: We have previously shown in renally impaired (RI) chronic hepatitis B (CHB) patients, including those with end-stage renal disease (ESRD) on hemodialysis (HD), that switching to tenofovir alafenamide (TAF) from tenofovir disoproxil fumarate (TDF) and/or other oral antivirals (OAVs) maintains high rates of viral suppression with stable bone and renal safety parameters at Week 48. Here we present the final Week 96 results. **Method:** In this Phase 2 study (NCT03180619), virally suppressed CHB patients (HBV DNA <LLOQ × ≥6 months and <20 IU/ml at screening) with moderate or severe RI or with ESRD on HD at screening while receiving TDF and/or other OAVs for ≥48 weeks were enrolled and switched to TAF 25 mg QD for 96 weeks. Safety assessments including adverse events (AEs) and changes in bone (hip and spine BMD) and renal (creatinine clearance by Cockcroft-Gault [eGFR_{CC}], serum phosphorus, and serum creatinine -except in ESRD patients) parameters, viral suppression, and serological and biochemical responses were serially assessed.

Table. Final Results at Week 96: Efficacy and Bone and Renal Parameters

n/N (%), or median (Q1, Q3)	Moderate – Severe RI ^a		ESRD on HD ^b	
	M = F ^c	M = E ^d	M = F	M = E
HBV DNA <20 IU/mL	65/78 (83)	65/65 (100)	13/15 (87)	13/13 (100)
HBV DNA <20 IU/mL and target not detected (sLLOD)	54/78 (69)	54/65 (83)	10/15 (67)	10/13 (77)
Normal ALT (2018 AASLD criteria) ^{e,f}	58/78 (74)	58/65 (89)	13/15 (87)	13/13 (100)
Normal ALT (Central lab criteria) ^{e,g}	64/78 (82)	64/65 (98)	13/15 (87)	13/13 (100)
HBeAg loss ^h	0/13	0/9	1/3 (33)	1/3 (33)
HBeAg loss	0/78	0/66	0/15	0/13
qHBeAg, log ₁₀ IU/mL change		-0.10 (-0.16, -0.01)		-0.11 (-0.17, -0.02)
Hip BMD, % change		+0.94 (-1.285, 2.282)		-1.54 (-3.620, 1.721)
Spine BMD, % change		+1.21 (-1.230, 3.452)		-1.32 (-3.459, 1.910)
CTX, % change (ng/mL) ⁱ		-18.9 (-35.0, 0.0)		-9.9 (-38.6, 23.9)
P1NP, % change (ng/mL) ^j		-13.8 (-29.3, 8.0)		-20.8 (-28.7, 16.5)
sCr, change (mg/dL)		-0.04 (-0.120, 0.080)		NA
sPO ₄ , change (mg/dL)		0.1 (-0.2, 0.4)		NA
eGFR _{CC} , change (mL/min)		+1.0 (-2.8, 4.5)		NA
RBP/Cr, % change ^k		-38.5 (-62.5, 29.5)		NA
β2MG/Cr, % change ^l		-57.0 (-77.0, 62.0)		NA

^aModerate to severe renal impairment: eGFR_{CC} 15 - <60 mL/min at screening;

^bESRD on HD: eGFR_{CC} <15 mL/min maintained on chronic hemodialysis

^cM=F, missing equal failure analysis; ^dM=E, missing equal excluded analysis (i.e. observed data)

^eALT value within normal range at Week 96 regardless of baseline ALT level; ^fULN ≤35 U/L males and ≤25 U/L females

^gULN ≤43 U/L men and ≤35 U/L for men ≥65y; ≤34 U/L women and ≤32 for women ≥65y

^hOnly includes patients HBeAg positive at baseline; ⁱSerum C-type collagen sequence (bone resorption marker); ^jSerum procollagen type 1 N-terminal propeptide (bone formation marker)

^kUrine retinol binding protein/creatinine (renal tubular marker); ^lUrine beta-2 microglobulin/creatinine (renal tubular marker)

Abbreviations: eGFR_{CC}, estimated creatinine clearance (Cockcroft-Gault method); ESRD, end-stage renal disease; BMD, bone mineral density by DXA scan; LLOD, lower limit of detection; NA, not applicable (hemodialysis patients)

Results: Of 93 patients (mod-severe RI 78; ESRD on HD 15) enrolled, most (74%) were male and Asian (77%), with 51% ≥65 y, 83% HBeAg-negative, 34% with cirrhosis, and median ALT 17 U/L. Up to 24% had osteoporosis at hip and/or spine, with most having comorbidities (HTN 60%, CV disease 22%, DM 25%). Twelve (13%; 11 mod-severe RI and 1 ESRD) patients discontinued the study early (5-withdrew consent, 3-deaths [none treatment-related], 2-AE, and 2-investigator decision). Key efficacy/safety results at Week 96 are summarized in the Table. Viral suppression (HBV DNA<20IU/ml) was maintained in all patients remaining on treatment (i.e. missing equals excluded); a

high proportion had target not detected. Overall, TAF was well tolerated with no Grade 3 or 4 AEs or serious AEs related to study treatment. Relative to baseline levels, switching to TAF resulted in small median % increases in hip/spine BMD in those with moderate to severe RI, and small median decreases in ESRD patients. 2 patients with mod-severe RI had a bone fracture (ankle, rib). Median eGFR_{CG} increased while urinary markers of proximal tubular function progressively decreased in moderate to severe RI patients.

Conclusion: Renally-impaired CHB patients, including ESRD patients on HD, who were switched to TAF from TDF and/or other OAVs maintained high rates of viral suppression, and bone and renal parameters remained stable or slightly improved after 2 years of treatment.

PO-2422

Safety, efficacy, and pharmacodynamic (PD) activity of 12 weeks treatment with oral RIG-I agonist, inarigivir (IRIG), plus 48 weeks of tenofovir alafenamide in adult patients with chronic hepatitis B: a phase 2 collaboration study

Young-Suk Lim¹, Aric J. Hui², Jeong-Won Jang³, Won-Young Tak⁴, Sang Hoon Ahn⁵, Byoung Kuk Jang⁶, Tak Yin Owen Tsang⁷, Won Kim⁸, Jenny Yang⁹, Diana Chen⁹, Circe McDonald⁹, Liao Zhang⁹, Anuj Gaggar⁹, Bing Gao⁹, Kwan Soo Byun¹⁰, Kwan Sik Lee¹¹, Hyung Joon Yim¹², Henry L.Y. Chan¹³. ¹Asan Medical Center, University of Ulsan College of Medicine Seoul-Korea, Seoul, Korea, Rep. of South; ²Alice Ho Miu Ling Nethersole Hospital, Hong Kong; ³The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Rep. of South; ⁴Kyungpook National University Hospital, Kyungpook National University School of Medicine, Korea, Rep. of South; ⁵Yonsei University College of Medicine, Korea, Rep. of South; ⁶Keimyung University Dong Sang Hospital, Korea, Rep. of South; ⁷Princess Margaret Hospital, Hong Kong; ⁸Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Korea, Rep. of South; ⁹Gilead Sciences Inc., Foster City, United States; ¹⁰Korea University College of Medicine, Korea University Guro Hospital, Korea, Rep. of South; ¹¹Gangnam Severance Hospital, Yonsei University College of Medicine, Korea, Rep. of South; ¹²Korea University Ansan Hospital, Ansan-si, Gyeonggi-do-Korea, Korea, Rep. of South; ¹³Prince of Wales Hospital, Hong Kong
Email: jenny.yang@gilead.com

Background and aims: IRIG, RIG-I agonist, has demonstrated antiviral activity in CHB patients. The MOA of IRIG suggests a direct antiviral and an immune modulatory pathway. This study evaluated safety, efficacy, and PD activity of IRIG ≤400 mg ± TAF in CHB pts.

Method: IA CHB pts were enrolled into 4 cohorts: 48WK TAF alone or TAF+IRIG 50, 200, and 400 mg QD for 12WK; and virally suppressed (VS) cohort of 12WK IRIG 100 mg. Safety included AEs and lab abnormalities. Primary obj: %pts with HBsAg ≥-0.5 log₁₀ IU/ml at WK12. Secondary obj: change from BL in immune PD biomarkers. Final WK48 data and immunological characterization of 400 mg cohort to be presented.

Results: 102 IA and 21 VS Asian CHB pts enrolled. Table shows BL and mean change at WK12 of viral markers. More TAF and IRIG 50 mg pts at BL had GT C (≥75%), higher HBV DNA and ALT vs IRIG 200 mg and 400 mg. No difference at WK12 in HBV DNA decline observed; TAF and IRIG 50 mg had numerically greater decline in HBsAg vs IRIG ≥200 mg. In VS pts, no change in HBsAg with IRIG 100 mg observed. Prelim WK12 safety showed, no G4 AEs; 3 IRIG and 1 TAF pts had G3 AEs. Majority of IRIG 400 mg pts had slight increase in ALT at WK16 (mean (SD) change in ALT=9 (65) U/L); similar trends were not observed at lower doses. AEs reported by 41% (46/111) IRIG and 58% (7/12) TAF pts. Frequent (>1 pt) AE related to study drug were: ALT increase (n = 5), constipation, dizziness, and headache (n = 2 each) all in IRIG pts. PD analysis demonstrates minimal changes to ISG expression with IRIG 50 mg and 200 mg. Peripheral cytokine and HBV-specific T cell response was similar between TAF and IRIG 50 mg.

Conclusion: No dose dependent changes in HBV DNA or HBsAg were observed with IRIG ≤400 mg+NUC. IRIG was generally safe and well tolerated at doses ≤400 mg for 12WK. IRIG development has been discontinued due to IRIG-related hepatotoxicity.

Table: (abstract: PO-2422):

	TAF (N = 12)	IRIG 50 mg (N = 30)	IRIG 200 mg (N = 30)	IRIG 400 mg (N = 30)	IRIG 100 mg VS Patients (N = 21)
HBV DNA, mean log ₁₀ IU/ml (range)	7.1 (3.9–8.8)	7.1 (3.8–9.4)	6.3 (3.5–8.8)	6.6 (3.7–9.2)	<1.3
HBsAg, mean log ₁₀ IU/ml (range)	4.1 (2.8–4.8)	3.9 (2.2–5.1)	3.4 (1.9–4.9)	3.5 (1.5–5.1)	3.2 (2.1–4.2)
ALT, mean U/ml (range)	163 (48–630)	104 (31–439)	74 (25–154)	73 (26–461)	23 (8–52)
Mean WK12 Change (range)					
HBV DNA, log ₁₀ IU/ml	-4.2 (-6.4, -2.6)	-4.2 (-6.4, -2.3)	-4.0 (-5.5, -1.7)	-3.9 (-6.1, -2.4)	N/A
HBsAg, log ₁₀ IU/ml	-0.44 (-1.62, 0.02)	-0.24 (-0.96, 0.08)	0.02 (-0.46, 1.02)	-0.03 (-0.86, 1.06)	-0.02 (-0.12, 0.06)
ALT, U/L	-117 (-611, 13)	-57 (-403, 160)	-38 (-135, 46)	-12 (-196, 47)	7 (-5, 50)

PO-2429

Safety and efficacy of oral TLR8 agonist, selgantolimod, in viremic adult patients with chronic hepatitis B

Harry L.A. Janssen¹, Young-Suk Lim², Hyung Joon Kim³, Cheng-Hao Tseng⁴, Carla S. Coffin⁵, Magdy Elkashab⁶, Sang Hoon Ahn⁷, Anh-Hoa Nguyen⁸, Diana Chen⁸, Jeffrey Wallin⁸, Susanna Tan⁸, Jenny Yang⁸, Anuj Gaggar⁸, Diana Brainard⁸, Scott Fung¹, Yoon Jun Kim⁹, Jia-Horng Kao¹⁰, Wan-Long Chuang¹¹, Anna Brooks^{12,13}, P. Rod Dunbar^{12,13}. ¹Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, University Health Network, Canada; ²Asan Medical Center, University of Ulsan College of Medicine, Korea, Rep. of South; ³Chung-Ang University College of Medicine, Korea, Rep. of South; ⁴E-Da Hospital, Taiwan; ⁵University of Calgary, Cumming School of Medicine, Canada; ⁶Toronto Liver Centre, Canada; ⁷Yonsei University College of Medicine, Korea, Rep. of South; ⁸Gilead Sciences Inc., Foster City, United States; ⁹Seoul National University Hospital, Department of Internal Medicine and Liver Research Institute, Korea, Rep. of South; ¹⁰National Taiwan University Hospital, Taiwan; ¹¹Kaohsiung Medical University Hospital, Taiwan; ¹²School of Biological Sciences, University of Auckland, Auckland, New Zealand; ¹³Maurice Wilkins Centre Auckland, University of Auckland, Auckland, New Zealand
Email: harry.janssen@uhn.ca

Background and aims: Selgantolimod (GS-9688, SLGN) is an oral, Toll-like receptor 8 agonist in clinical development for the treatment of chronic hepatitis B (CHB). Here we present the results through week 48 on the safety and efficacy of 24 weeks of SLGN treatment in viremic CHB patients.

Method: In this multicenter, double-blind, phase 2 study, viremic CHB patients were randomized (2:2:1) to SLGN 3 mg, 1.5 mg, and placebo (PBO) once a week for 24 weeks in combination with tenofovir alafenamide. Safety assessments included monitoring of treatment emergent adverse events (TEAE) and laboratory abnormalities. The primary efficacy end point was the proportion of patients with ≥1 log₁₀IU/ml decline in HBsAg levels from baseline at week 24. Exploratory end points include changes in pharmacodynamic (PD) markers (e.g. IL-12p40 and IL-1RA) and changes in peripheral T- cell, myeloid and NK-cell subsets.

Results: 67 patients (39 HBeAg-positive) were randomized. Baseline characteristics were similar across groups: majority were Asian (98.5%), male (58%) with a median (IQR) age of 47 (35–54) years, HBsAg level of 4.1 (3.5–4.7) log₁₀IU/ml, and HBV DNA level of 7.5 (5.4–8.3) log₁₀IU/ml. No patients achieved the primary end point of ≥1 log₁₀IU/ml decline in HBsAg levels at week 24; however, 3 (6%) patients in the SLGN-treated achieved HBsAg decline ≥0.5 log₁₀IU/ml compared to none in the placebo group. At week 48, 4 (7.4%) patients

POSTER PRESENTATIONS

in the SLGN-treated group (including the 3 subjects at week 24) while none in the placebo group achieved HBsAg decline ≥ 0.5 log₁₀IU/ml. Most frequent ($\geq 10\%$ SLGN-treated) TEAE (SLGN v PBO) were: nausea (26% v 0%), headache (15% v 15%), vomiting (17% v 0%), fatigue (15% v 0%), and dizziness (11% v 0%). Grade ≥ 3 TEAE were observed in 0 (SLGN) v 7.7% (PBO) subjects; 1 subject (SLGN 3 mg) discontinued study due to TEAE of vomiting and abdominal pain. Most patients treated with SLGN showed decline of immune cell subsets in the circulation 4 h after dosing, concurrent with increases of circulating IL-12p40 and IL-1RA. Cell populations that decreased in the circulation included effector and memory T cell subsets. These parameters reverted to baseline values at 24 h post-dosing.

Conclusion: Oral SLGN up to 3 mg once weekly for 24 weeks is safe and well-tolerated. SLGN can induce sustained HBsAg declines of ≥ 0.5 log₁₀IU/ml in some patients out to Week 48. Further evaluation of SLGN in combination with immunomodulatory and antiviral agents is planned.

PO-2619

Effects of tenofovir alafenamide fumarate treatment in pregnant women on maternal viral load reduction and preventing mother-to-infant HBV transmission

Huey-Ling Chen^{1,2}, Chien-Nan Lee³, Ming-Wei Lai⁴, Ming-Chieh Tsai⁵, Rong-Nan Chien^{6,7}, Wan-Hsin Wen^{8,9}, Kai-Chi Chang¹, Chun-Jen Liu¹⁰, Yen-Hsuan Ni¹, Mei-Hwei Chang¹. ¹National Taiwan University College of Medicine and Hospital, Department of Pediatrics, Taipei, Taiwan; ²College of Medicine, National Taiwan University, Department and Graduate Institute of Medical Education and Bioethics, Taipei, Taiwan; ³National Taiwan University College of Medicine and Hospital, Department of Obstetrics and Gynecology, Taipei, Taiwan; ⁴Chang Gung Memorial Hospital, Linkou Branch, Division of Pediatric Gastroenterology, Department of Pediatrics; Liver Research Center, Taiwan; ⁵Hsinchu Cathay General Hospital, Department of Internal Medicine, Hsinchu City, Taiwan; ⁶Chang Gung Memorial Hospital, Liver Research Center, Linkou, Taiwan; ⁷Keelung Chang Gung Memorial Hospital, Liver Research Unit, Taiwan; ⁸Cardinal Tien Hospital, Department of Pediatrics, New Taipei City, Taiwan; ⁹College of Medicine, Fu-Jen Catholic University, School of Medicine, New Taipei City, Taiwan; ¹⁰National Taiwan University College of Medicine and Hospital, Internal Medicine, Taipei, Taiwan
Email: hueyling@ntu.edu.tw

Background and aims: Short-term antiviral therapy for pregnant women with chronic hepatitis B virus (HBV) infection and high viral load has been recommended to prevent maternal transmission. Data of using tenofovir alafenamide fumarate (TAF) treatment for such purpose is limited. This study is the interim analysis of a clinical trial using TAF for preventing mother-to-infant transmission of HBV, in comparison with mothers using tenofovir disoproxil fumarate (TDF) treatment.

Method: This prospective, multicenter clinical trial recruited 57 HBV-infected pregnant women seropositive for HBsAg and HBeAg, and with HBV viral load above 1,000,000 IU/ml. Enrolled subjects received TAF 25 mg daily since third trimester until 2 weeks postpartum in 2019–2021. Maternal and children outcomes were compared with 53 pregnant women received TDF 300 mg daily during 2016–2018.

Results: The maternal age of delivery in the TAF group was 35.56 \pm 4.41 years and in the TDF group 34.56 \pm 3.65 years ($p = 0.20$). The HBV DNA levels decreased from 7.87 \pm 0.57 Log₁₀IU/ml at baseline, to 3.96 \pm 1.10 Log₁₀IU/ml at delivery in the TAF group; and from 8.30 \pm 0.36 Log₁₀IU/ml to 4.47 \pm 0.86 Log₁₀IU/ml in the TDF group. The mean reduction of HBV DNA levels was comparable between the TAF group (3.90 \pm 0.90 Log₁₀IU/ml) and TDF group (3.83 \pm 0.83 Log₁₀IU/ml, $p = 0.67$). The percentage of the mothers to achieve HBV DNA level below 6.0 log₁₀IU/ml at the time of delivery were 94.7% (54/57) in the TAF group versus 96.2% (51/53) in the TDF group ($p = 1.00$). Of the mother in the TAF group, one experienced with nausea and one with dry eyes.

All symptoms subsided spontaneously. In the TDF group, two mothers experienced nausea, one with skin itching and one with mild diarrhea. Of the 62 newborns delivered in the TAF group, the average gestation age was 38.25 \pm 1.83 weeks; and 38.66 \pm 1.33 weeks of the 55 newborns in the TDF group ($p = 0.17$). The mean body weight 2958 \pm 519.9 gram in the TAF group and 3052 \pm 431.3 g ($p = 0.30$) in the TDF group. Of the 32 infants in the TAF group followed up to 12 months, none were HBsAg positive (0/32), versus 1.8% (1/55, $p = 1.00$) in the TDF group. No major and minor congenital anomalies were identified in the infants.

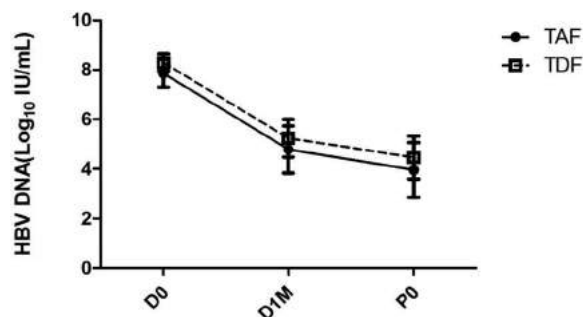


Figure:

Conclusion: The effects of TAF treatment for highly viremic HBV-infected pregnant women were comparable with TDF treatment in terms of maternal HBV DNA reduction and in preventing mother-to-infant transmission.

PO-2735

Durability of hepatitis B surface antigen seroclearance induced by peginterferon alpha-based regimens

Rui Lu¹, Feng-ping Wu¹, Yixin Liu¹, Yikai Wang¹, Yan Tian¹, Yaping Li¹, Mei Li¹, Zicheng Jiang², Xue Mei Li², Juanjuan Shi¹, Xin Zhang¹, Xiaoli Jia¹, Shuangso Dang¹. ¹The Second Affiliated Hospital of Xi'an Jiaotong University, Department of Infectious Diseases, Xi'an, China; ²The Ankang Central Hospital, Department of Infectious Diseases, Ankang, China
Email: dang212@126.com

Background and aims: Durability of Hepatitis B surface antigen (HBsAg) seroclearance induced by Peginterferon -alpha (Peg-IFN alpha)-based regimens has not been well elucidated yet. The study was to observe the durability of HBsAg seroclearance induced by Peg-IFN alpha-based regimens.

Method: In this prospective, two-centre, observational study, 212 subjects with HBsAg seroclearance induced by Peg-IFN alpha-based regimens were enrolled from November 2015 to March 2021 at the Second Affiliated Hospital of Xi'an Jiaotong University and Ankang Central Hospital, China. From the date of cessation of Peg-IFN alpha-based regimens, all subjects were evaluated for hepatitis B virus (HBV) markers, HBV DNA, and liver functions every 1–3 months during the follow-up. The primary end point was HBV recurrence which was defined as the reappearance of either HBsAg, HBV DNA, or both at least 2 times in an interval of 4–8 weeks during the follow-up after treatment cessation. The second end points included the dynamics of HBsAb, alanine aminotransferase (ALT) flares, and the incidence of liver cirrhosis and hepatocellular carcinoma (HCC).

Results: After a median of 72 (42–120) weeks of follow-up, 2 subjects were lost of follow-up. A total of 28 subjects experienced HBsAg recurrence, while no subject experienced HBV DNA seroreversion. Intention-To-Treat analysis showed that the HBsAg recurrence rate was 13.6% (28/212). Among 119 patients with HBsAg seroconversion at the cessation, 20.4% (24/119) of the subjects experienced HBsAb disappearance. The median HBsAb level decreased from 1.76 log₁₀ mIU/ml at baseline to 1.33 log₁₀ mIU/ml at the end of follow-up. No

patient suffered from ALT flares, as well as developed into liver cirrhosis or HCC during the follow-up.

Characteristics	Patients in all (n = 212)
Age, years, mean ± SD	35.2 ± 11.3
Male, n (%)	124 (58.3)
<i>Characteristics before HBsAg clearance</i>	
Therapy regimens	
Peg-IFN alpha alone, n (%)	101 (43.8)
Adding on Peg-IFN alpha to NA, n (%)	93 (47.9)
NA de novo combination with Peg-IFN alpha, n (%)	18 (8.3)
Peg-IFN alpha types	
Peg-IFN alpha-2a, n (%)	88 (41.7)
Peg-IFN alpha-2b, n (%)	124 (58.3)
HBsAg levels at the initial of Peg-IFN alpha, log ₁₀ IU/ml, mean ± SD	
HBsAb-negative, n (%)	199 (93.8)
HBsAb-positive, n (%)	13 (6.3)
HBV DNA negative, n (%)	137 (64.6)
HBeAg-positive, n (%)	42 (19.8)
ALT at the initial of Peg-IFN alpha, IU/ml, IQR	15.0 (23.0, 34.8)
AST at the initial of Peg-IFN alpha, IU/ml, IQR	24.0 (19.0, 30.0)
Treatment duration before HBsAg loss, weeks, IQR	24.0 (12.0, 48.0)
Consolidation treatment time after HBsAg loss, weeks, IQR	12.0 (6.0, 16.0)
<i>Characteristics at discontinuation of Peg-IFN alpha</i>	
Patients with HBsAg seroconversion, n (%)	119 (56.3)
HBsAb levels, log ₁₀ mIU/ml, mean ± SD	1.2 ± 0.9

Conclusion: HBsAg seroclearance induced by Peg-IFN alpha-based treatment was durable during long-term follow-up.

PO-2738

Functional cure based on pegylated interferon α in long-term nucleoside analog suppressed HBeAg negative chronic hepatitis B: A multicenter real-world study (everest project in china), a sequential report the predictors for HBsAg loss

Ze-Qian Wu¹, Dong-Ying Xie¹, Lei Fu², Wenhua Zhang³, Jia Wei⁴, Jia Shang⁵, Guojun Li⁶, Ying Guo⁷, Jiahong Yang⁸, Yujuan Guan⁹, Jiabin Li¹⁰, Jiabao Chang¹¹, Guangyu Huang¹², Yanzhong Peng¹³, MInghua Lin¹⁴, Zeng Yilan¹⁵, Jia Li¹⁶, Jiaji Jiang¹⁷, Yongfang Jiang¹⁸, Ye Gu¹⁹, Jiawei Geng²⁰, Zhi-liang Gao¹. ¹Third Affiliated Hospital of Sun Yat-sen University, Department of Infectious Diseases; ²Xiangya Hospital Central South University, Changsha, China; ³Gansu Wuwei Cancer Hospital, Wuwei, China; ⁴Affiliated Hospital of Yunnan University, Kunming, China; ⁵Henan Provincial People's Hospital, Zhengzhou, China; ⁶The Third People's Hospital of Shenzhen, Shenzhen, China; ⁷The third people's hospital of Taiyuan, Taiyuan, China; ⁸ People's Hospital of Deyang City, Dengyang, China; ⁹Guangzhou Eighth People's Hospital, Guangzhou, China; ¹⁰The First Affiliated Hospital of Anhui Medical University, Hefei, China; ¹¹The Second Hospital of Nanjing, Nanjing, China; ¹²The Fourth Affiliated Hospital Zhejiang University School Of Medicine, Yiwu, China; ¹³Peking University Shenzhen Hospital, Shenzhen, China; ¹⁴MengChao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China; ¹⁵Chengdu Public Health Medical Center, Chengdu, China; ¹⁶Tianjin Second People's Hospital, Tianjin, China; ¹⁷The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; ¹⁸The Second Xiangya Hospital of Central South university, Changsha, China; ¹⁹The Sixth People's Hospital of Shenyang, Shenyang, China; ²⁰The First People's Hospital of Yunnan Province, Kunming, China
Email: gaozli@mail.sysu.edu.cn

Background and aims: Add-on or switch to pegylated interferon α (PegIFNα) in nucleoside analog (NA) suppressed chronic hepatitis B (CHB) patients are effective strategies to improve HBsAg loss. We sought to investigate efficacy of “add-on” or “switch to” strategy and predictors for HBsAg loss by pegIFNα.

Method: The Everest Project is a multicenter real-world study that focused on functional cure of CHB in China (NCT04035837). Patients who had experienced effective NA therapy for more than one year, presented as HBV DNA<100 IU/ml, HBeAg negative and HBsAg<1500 IU/ml were recruited. “Add-on” or “switch to” strategy for 48 weeks or up to 96 weeks was decided by patients. Interim data on those who have completed 48 weeks of treatment were analyzed. mITT population included 5055 patients and PP population included 3517 patients.

Results: In the PP analysis, 82% patients were male, the mean age was 41.1 years and the mean baseline of HBsAg was 386.7 IU/ml. The HBsAg loss rate were 10.3%, 23.0%, 28.9% and 32.8% at 12, 24, 36 and 48 weeks, respectively. Common clinical indicators as predictors for HBsAg loss were identified by subgroup analysis. HBsAg loss rate at 48 weeks were 55.3%, 31.2%, 22.8%, 16.8% and 8.4% for different baseline HBsAg stratification (0.05–100, 100–200, 200–500, 500–1000 and 1000–1500 IU/ml, respectively). HBsAg loss rate at 48 weeks of patients with HBsAg, 500 IU/ml at 24 weeks was significantly higher than those with HBsAg ≥500 IU/ml (36.7% vs. 1.2%, p <0.0001). For patients with HBsAg decline >1 log₁₀ IU/ml from baseline to 24 weeks, the HBsAg loss rate at 48 weeks was 57.5%, while 8.7% for those HBsAg decline ≤1 log₁₀ IU/ml (p <0.0001). According to different ALT stratification at 12 weeks (≥5 × ULN, 2–5 × ULN, 1–2 × ULN and, 1 × ULN), HBsAg loss rate at 48 weeks were 47.0%, 40.5%, 33.8% and 24.6%, respectively. It was worth noting that 66.6% (1146/1721) of the patients who did not achieved HBsAg loss at 48 weeks achieved HBsAg≤100 IU/ml, which may be the advantage patients for further functional cure. PegIFNα treatment was well-tolerated.

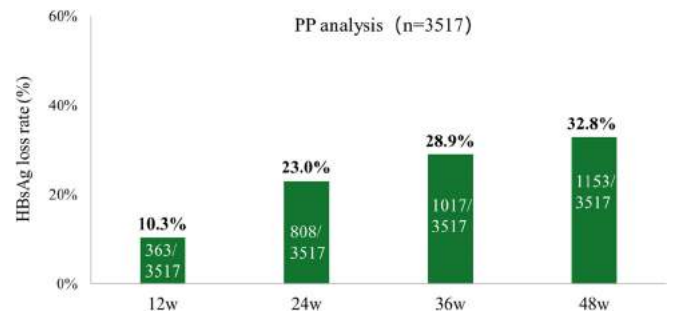


Figure: HBsAg loss rate at different time points in PP analysis.

Conclusion: Functional cure could be well achieved in NA-suppressed HBeAg negative chronic hepatitis B by pegIFNα strategy. Lower HBsAg at baseline, lower HBsAg at 24 weeks, a rapid decline of HBsAg and ALT elevations at 12 weeks are predictors for functional cure over the course of 48 weeks. There are still good chances of functional cure for more than half of the patients who had not achieved HBsAg loss by prolonged treatment or retreatment.

PO-2759

Short-term peginterferon alpha re-treatment induced a high functional cure rate in patients with hepatitis B surface antigen recurrence after cessation of peginterferon alpha-based regimens

Feng-ping Wu¹, Rui Lu¹, Yixin Liu¹, Yikai Wang¹, Yan Tian¹, Yaping Li¹, Mei Li¹, Wenjun Wang¹, Zicheng Jiang², Xue Mei Li², Song Zhai¹, Xin Zhang¹, Xiaoli Jia¹, Shuangsoo Dang¹. ¹The Second Affiliated Hospital of Xi'an Jiaotong University, Department of Infectious Diseases, Xi'an, China; ²The Ankang Central Hospital, Department of Infectious Diseases, Ankang, China
Email: dang212@126.com

Background and aims: Little is known about the efficacy of peginterferon alpha (peg-IFN- alpha) in the re-treatment of patients with hepatitis B surface antigen (HBsAg) recurrence after being clinically cured by peg-IFN alpha-based regimens. This study was aimed to evaluate the efficacy of peg-IFN α-2b in the re-treatment of

POSTER PRESENTATIONS

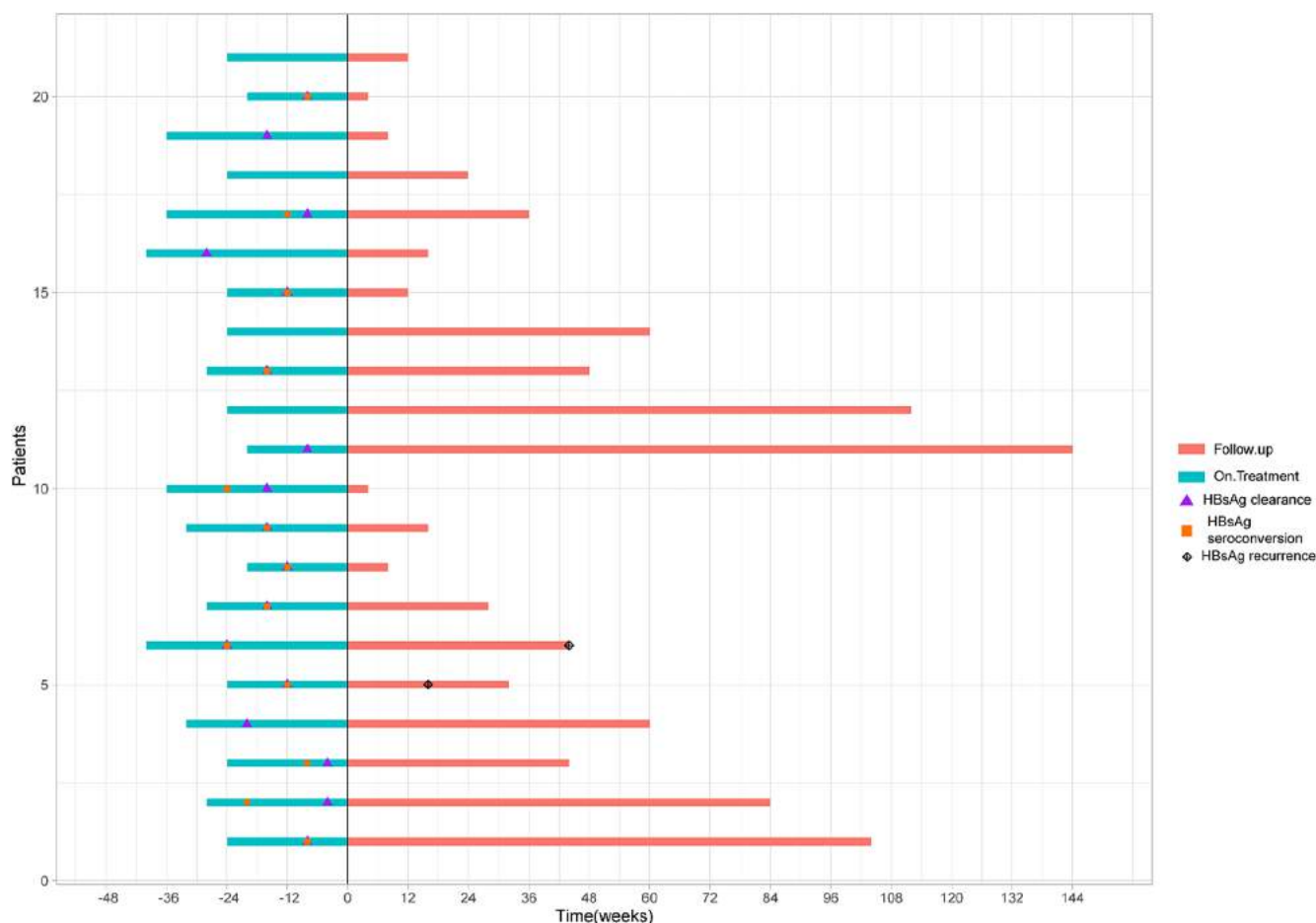


Figure: (abstract: PO-2759)

patients with HBsAg recurrence after cessation of peg-IFN alpha -based regimens.

Method: In this real-world, two-center, observational study, a total of 21 patients with HBsAg recurrence after cessation of peg-IFN alpha -based regimens were prospectively enrolled. All patients received an individualized peg-IFN alpha -2b (PegBeron, 180 µg, subcutaneous injection, once weekly, Chinese-made) re-treatment. The hepatitis B virus (HBV) vaccine could be injected after HBsAg clearance. The primary end point was HBsAg clearance.

Results: All patients had HBsAg levels of <4 IU/ml and hepatitis B virus deoxyribonucleic acid (HBV DNA) levels of <20 IU/ml. The median (mean) baseline HBsAg levels were 0.88 (1.31) IU/ml. After a median (mean) of 24 (28) weeks of peg-IFN alpha-2b re-treatment, 17 patients (81.0%, 17/21) achieved HBsAg clearance again and 13 patients (61.9%, 13/21) achieved HBsAg seroconversion. Unfortunately, 2 patients experienced HBsAg recurrence again during a median (mean) of 28 (42.7) weeks of follow-up. Generally, the peg-IFN alpha-2b and HBV vaccine therapy were well tolerated.

Conclusion: High rate of HBsAg clearance can be achieved by short-course of peg-IFN alpha-2b re-treatment in patients with HBsAg recurrence after cessation of peg-IFN alpha-based regimens.

PO-2822

Inhibition of hepatitis B surface antigen by RNA interference therapeutic AB-729 in chronic hepatitis B patients correlates with suppression of all HBsAg isoforms and HBV RNA

Emily P. Thi¹, Man-Fung Yuen², Edward Gane³, Heather Sevinsky¹, Karen Sims¹, Mark Anderson⁴, Angela M. Lam¹, Michael J. Sofia¹, Gavin Cloherty⁴, Gaston Picchio¹. ¹Arbutus Biopharma Inc.,

Warminster, United States; ²Queen Mary Hospital, Hong Kong; ³Auckland Clinical Studies, New Zealand; ⁴Abbott Diagnostics, Abbott Park, United States
Email: ethi@arbutusbio.com

Background and aims: Therapeutic strategies to develop a cure for chronic hepatitis B (CHB) must address the high antigenemia that contributes to viral persistence and HBV immune tolerance. AB-729 is an N-Acetylgalactosamine-conjugated short interfering RNA (siRNA) therapeutic, currently in clinical development in combination with other agents for treatment of CHB. AB-729, a single trigger agent, blocks all HBV RNA transcripts including HBx, resulting in suppression of viral replication and all HBV antigens including hepatitis B surface antigen (HBsAg). Here we report the effect of AB-729 on novel HBV markers in nucleos (t)ide suppressed (HBV DNA-) or untreated (HBV DNA+) CHB subjects receiving single or repeat doses of AB-729. **Method:** Longitudinal plasma samples from CHB subjects receiving a single dose (60–180 mg, n = 22) or undergoing repeat dosing (60 mg every 4 weeks for 6 doses, n = 7 or 60 mg every 8 weeks for 3 doses, n = 7) were assessed for total HBV RNA and pregenomic RNA (pgRNA) by quantitative reverse-transcription polymerase chain reaction, and HBsAg isoforms and HBsAg immune complex by chemiluminescent immunoassays (Abbott Diagnostics).

Results: Following AB-729 single or repeat dosing, total HBsAg declines correlated significantly with reductions in total HBV RNA, pgRNA, Large (LHBs) and Middle (MHBs) HBsAg isoforms in HBV DNA- or HBV DNA+ subjects (p < 0.0001, two-tailed Pearson correlation). In HBV DNA- or HBV DNA+ “slow responders” (<0.3 log₁₀ HBsAg decline 4 weeks after AB-729 dose initiation), 0.46 to 1.44 log₁₀ reduction in total HBV RNA or pgRNA was observed in 4/5

subjects which was comparable to subjects with early HBsAg decline (0.02 to 0.99 log₁₀ HBV RNA decrease). Similar suppression of LHBS or MHBS was noted in all subjects undergoing AB-729 single or repeat dosing. No changes in immune complex levels were observed up to 24 weeks after AB-729 dosing initiation.

Conclusion: To our knowledge, this is the first assessment of HBsAg isoforms and immune complex in CHB subjects administered single or repeat doses of an HBV-targeting GalNAc-siRNA. Total HBsAg decline correlated with decreases in circulating HBV RNA species and both HBsAg isoforms. Early reduction in HBV RNA was observed in both "slow responders" who showed delayed HBsAg decline as well as in subjects who exhibited early HBsAg inhibition, confirming rapid target engagement by AB-729 in all CHB subjects. The significance of fast vs. slow HBsAg decline is currently being explored.

PO-2823

Inhibition of hepatitis B surface antigen in chronic hepatitis B subjects by RNA interference therapeutic AB-729 is accompanied by upregulation of HBV-specific T cell activation markers

Bhavna Paratala¹, Jang-June Park¹, Sharie C. Ganchua¹, Edward Gane², Man-Fung Yuen³, Amy C.H. Lee¹, Chris Moore¹, Angela M. Lam¹, Heather Sevinsky¹, Karen Sims¹, Deana Antonello¹, Michael J. Sofia¹, Gaston Picchio¹, Emily P. Thi¹. ¹Arbutus Biopharma Inc., Warminster, United States; ²Auckland Clinical Studies, New Zealand; ³Queen Mary Hospital, Hong Kong

Email: ethi@arbutusbio.com

Background and aims: Therapeutic strategies aimed at reducing antigenemia, particularly hepatitis B surface antigen (HBsAg), may potentiate HBV-specific immune restoration in chronic hepatitis B (CHB). AB-729 is a single trigger N-Acetylgalactosamine (GalNAc)-conjugated siRNA targeting all HBV transcripts, currently in clinical development in combination with other agents for the treatment of CHB. Here we report immunological assessments in nucleos(t)ide analog-suppressed CHB subjects receiving single or repeat doses of AB-729.

Method: Longitudinal plasma samples from subjects receiving a single injection of AB-729 (60–180 mg, n = 16) were assessed for cytokines/chemokines using a multiplex Luminex assay. Longitudinal plasma or peripheral blood mononuclear cell samples from subjects (n = 6 or 5) undergoing repeat dosing of 60 mg AB-729 every 4 weeks (Q4W) for 6 doses were assessed using Luminex, interferon gamma (IFNγ) T-cell fluorospot, T-cell proliferation assay and flow cytometry.

Results: Following a single dose of AB-729, transient elevation of 2 to 6-fold over pre-dose baseline levels in plasma IFNγ, IL-17a, CD163, CXCL9 and CXCL13 were observed in some subjects (60 mg, 90 mg n = 3/6 each). In one subject receiving AB-729 60 mg Q4W, a 1.7 log₁₀ reduction in HBsAg preceded a 9-fold elevation in IFNγ at Week 28, which coincided with increase in IFNγ-producing HBV-specific T-cells (Figure). This was preceded by mild elevations in serum alanine aminotransferase (ALT, Grade 1), which resolved by Week 28. In 3/5 subjects, elevated HBV-specific T-cell proliferation was observed by Week 8 and increases in IFNγ-producing HBV-specific T-cells coincided with ≥1.7 log₁₀ HBsAg reduction. Mild to moderate ALT elevations (n = 2/5 Grade 1, 2/5 Grade 2) preceded or coincided with IFNγ-producing HBV-specific T-cells. No changes were observed in any subjects for inflammatory cytokine IP-10, or other liver safety markers.

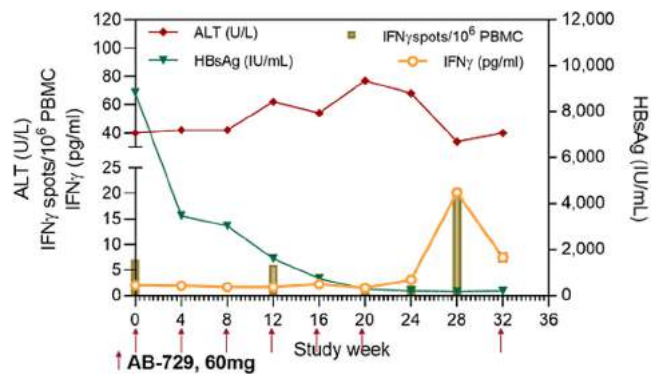


Figure:

Conclusion: We believe this represents the first immunological assessment of CHB subjects with prolonged HBsAg suppression following repeat doses of an HBV-targeting GalNAc-siRNA. Our findings suggest that AB-729-induced reductions in HBsAg results in increased HBV-specific immune responses in a subset of CHB subjects, accompanied by mild to moderate ALT elevations. These results strengthen the hypothesis that long-term HBV antigen suppression can promote immune reawakening in CHB and suggest AB-729 combinations with immunomodulatory agents may be beneficial.

PO-2844

A phase 2 study testing FXR agonist Vofanefoxor in treatment naive patients with chronic hepatitis B (CHB): preliminary week 16 results

Pietro Scalfaro¹, Jeong Heo², Chun-Jen Liu³, Chao-Wei Hsu⁴, Wan-Long Chuang⁵, Tsung-Hui Hu⁶, Wai-Kay Seto⁷, Virginie LE Meaux¹, Jacky Vonderscher¹, Raphaël Darteil¹, Hugo Girma¹, Marion Odoul¹, Artin Karapet⁸. ¹ENYO Pharma SA, Clinical Operations, Lyon, France; ²Pusan National University Hospital, BUSAN, Korea, Rep. of South; ³National Taiwan University Hospital, Taipei, Taiwan; ⁴Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; ⁵Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan; ⁶Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ⁷Queen Mary Hospital, Hong Kong; ⁸LyonaPharm Consulting, Lyon, France

Email: ps@enyopharma.com

Background and aims: The nuclear farnesoid X receptor (FXR) is a key factor regulating bile acid homeostasis and a target for metabolic liver diseases. FXR is also involved in hepatitis B virus (HBV) replication. The FXR agonist Vofanefoxor (V) impacted HBsAg levels in vitro and after a few weeks administration to CHB patients. We evaluate the safety and antiviral effect in CHB and report preliminary results after 16 weeks (W16) of treatment.

Method: In this ongoing multi-center, randomized, open-label Phase 2 trial (NCT04365933) treatment naive CHB patients with HBsAg ≥300 IU/ml and HBV DNA ≥20'000 IU/ml for HBeAg+ and ≥2'000 for HBeAg- were randomized to a combination of oral V 200 mg QD with sc pegylated interferon alpha2a (peg-IFN 180 mcg QW) to which entecavir (0.5 mg QD, ETV) was added (arm 1) or not (arm 2). Non-CHB or worsening liver disease were excluded. The experimental treatment to W16 is followed by an ongoing 24 week maintenance with ETV. Virology and safety assessments were collected every 2 weeks. The primary end point was the number of adverse events (AE) and the HBsAg decline from baseline (BL) to W16.

Results: Enrolled patients (n = 20) had a mean age of 48.3 years, 56% were male and 100% Asian. AE were mostly mild (47%) or moderate (37%), 11 patients had isolated ALT/AST flares (5–10x ULN) resolving with dosing interruptions. All (10/10) HBeAg- patients had a pronounced significant DNA and HBsAg decline, whereas HBeAg+ (n = 5) showed less response both for DNA and HBsAg: -3.7 (0.4) log₁₀ IU/ml (mean, SE, p < 0.001) vs. -0.4 (0.7, p = 0.53) and -0.9 (0.1,

POSTER PRESENTATIONS

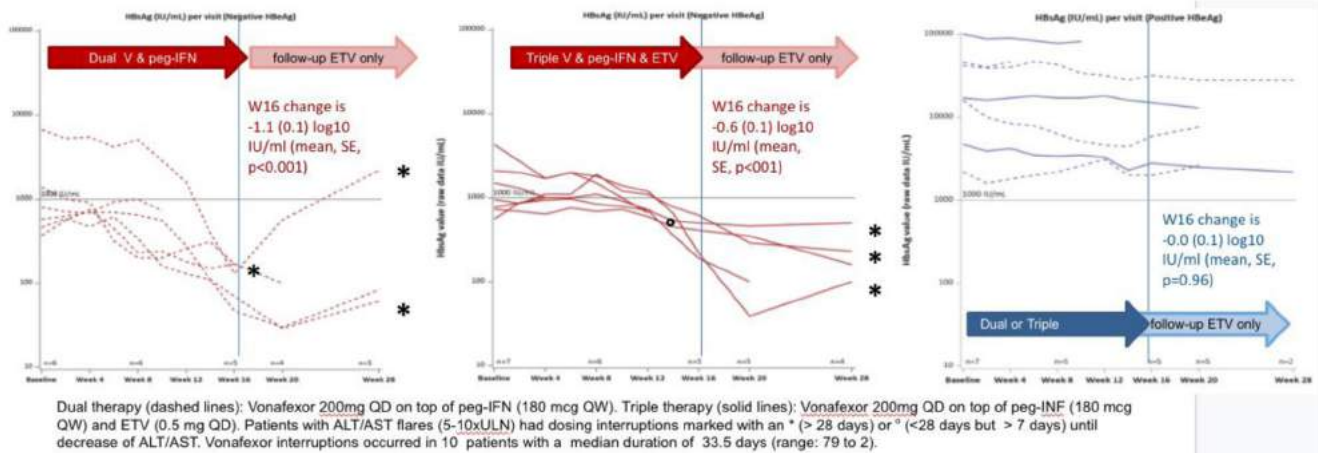


Figure: (abstract: PO-2844)

$p < 0.001$) vs. -0.0 (0.1 , $p = 0.96$) resp. In addition and surprisingly HBsAg declines were more pronounced with dual (arm 2) over triple treatment (arm 1) Figure. Dosing interruptions with insufficient treatment duration explained HBsAg flares seen during follow-up in some patients.

Conclusion: Vofaxefor combined with peg-IFN induces a marked HBsAg decline in HBeAg- treatment naive CHB patients. No relationship between transaminase flares and viral response was found. Additional data is being collected during the ongoing follow-up period. The mechanism is investigated as to the cellular pathways involving FXR and the innate immunity.

PO-2853

The incidence of hepatocellular carcinoma in patients with hepatitis B cirrhosis during long-term antiviral therapy: A real world cohort study

Ying Han¹, Huiguo Ding², BIN Xu¹, Yanmin Liu¹, Lei Li². ¹Beijing You'an Hospital affiliated with Capital Medical University, Second Department of Liver Disease Center, Beijing, China; ²Beijing You'an Hospital affiliated with Capital Medical University, Department of Gastroenterology and Hepatology, Beijing, China
Email: gladyshanying@163.com

Background and aims: In the era of antiviral therapy, the incidence and risk factors of hepatocellular carcinoma (HCC) in patients with hepatitis B cirrhosis in different clinical stages need to be further clarified.

Method: This is a retrospective-prospective cohort study between June 2014 to June 2020. The enrolled hepatitis B cirrhotic patients received TDF or ETV monotherapy for more than 12 months from June 2014 to December 2018 at outpatient or inpatient department. The average follow-up time is 2 years The end point of follow-up: (1) occurrence of hepatocellular carcinoma, (2) death or liver transplantation.

Results: A total of 9601 hepatitis B cirrhotic patients were included, male/female 6593/3008, 47.57 ± 13.13 years old. Of them, compensated (CC) and decompensated cirrhotic (DCC) patients were 2844 and 6757, respectively. Total 445 (6.6%: 445/6757) of enrolled patients were development to HCC during follow-up. Of them, 334 (4.9%: 334/6757) in DCC and 111 (3.9%: 111/2844) in CC patients respectively. The 6-year cumulative incidence of HCC were significantly difference between DCC (60.07%) and CC (43.70%). Interesting, the 2, 3, 4, 5, 6-year cumulative incidence of HCC in ETV vs TDF treatment cirrhotic patients were 4.35% vs 1.85%, 7.35% vs 3.82%, 11.62% vs 7.65% and 19.98% vs 15.66%, 55.99% vs 56.52%. The 2, 3, 4, 5, 6-year cumulative mortality of ETV combined/sequential TDF treatment were lower than ETV monotherapy (0.20% vs 0%, 0.58%

vs 0.15%, 0.90% vs 0.18%, 1.55% vs 0.25%, 2.81% vs 0.46%, 12.75% vs 2.50%), $P = 0.040$. The 6-year cumulative mortality were significantly difference between DCC (15.22%) and CC (2.91%), $P = 0.028$.

Conclusion: Whether it is CC or DCC patients, ETV or TDF antiviral treatment can significantly reduce the incidence of HCC. After antiviral treatment, the cumulative mortality rate has been reduced, especially in CC patients. Compared with ETV, ETV combined/sequential TDF treatment seems to reduce the cumulative mortality in patients with cirrhosis more significantly.

PO-2879

A single dose of the GalNAc-siRNA, AB-729, results in prolonged reductions in HBsAg, HBcrAg, HBV DNA and HBV RNA in the absence of nucleos(t)ide analogue therapy in HBeAg negative subjects with chronic hepatitis B infection

Edward Gane¹, Heather Sevinsky², Man-Fung Yuen³, Mark Anderson⁴, Gavin Cloherty⁴, Emily P. Thi², Tosh Wattamwar², Michael J. Sofia², Kevin Gray², Deana Antonello², Timothy Eley², Gaston Picchio², Karen Sims². ¹University of Auckland, Auckland, New Zealand; ²Arbutus Biopharma, United States; ³Queen Mary Hospital, Hong Kong; ⁴Abbott Laboratories, United States
Email: hsevinsky@arbutusbio.com

Background and aims: AB-729 is an N-Acetylgalactosamine (GalNAc)-conjugated single trigger RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens. AB-729 is currently in clinical development in combination with other antiviral agents for the treatment of chronic hepatitis B (CHB). Here we report additional pharmacodynamic (PD) results following a single dose of AB-729 in HBV DNA+ subjects with CHB.

Method: AB-729-001 is an on-going study examining AB-729 in healthy (Part 1) and CHB subjects (Parts 2/3). In Part 2 Cohort D, 6 non-cirrhotic, HBeAg negative CHB subjects with HBV DNA $> 1,000$ IU/ml not on treatment received a single 90 mg subcutaneous dose of AB-729. Safety and PD assessments, including HBV DNA, HBsAg, HBV RNA and HBcrAg, were assessed.

Results: One subject was excluded as predose Day 1 results revealed a spontaneous HBV flare. To date, mean HBsAg and HBV DNA levels through Week 36 remained below baseline levels ($-0.81 \log_{10}$ and $-0.69 \Delta \log_{10}$ IU/ml, respectively). One subject's maximum HBV DNA decline of $1.31 \log_{10}$ occurred at Week 32. In 2 subjects with apparent HBV DNA rebound at Weeks 24 and 28, a second decline of $> 0.8 \log_{10}$ from baseline occurred without addition of any other therapy (Figure). HBV RNA became unquantifiable or undetectable post-dose in 5/5 subjects. 2/3 subjects with quantifiable HBcrAg at baseline reached unquantifiable levels post-dose. The remaining

subject achieved 1 log₁₀ decline in HBcAg that was maintained at Week 36. Amongst these 5 subjects there were no serious adverse events (AEs), discontinuations due to AEs, or Grade 2, 3 or 4 lab abnormalities. Ten TEAEs (9 mild, 1 moderate) were observed; only 1 was related to AB-729 (mild injection site bruising).

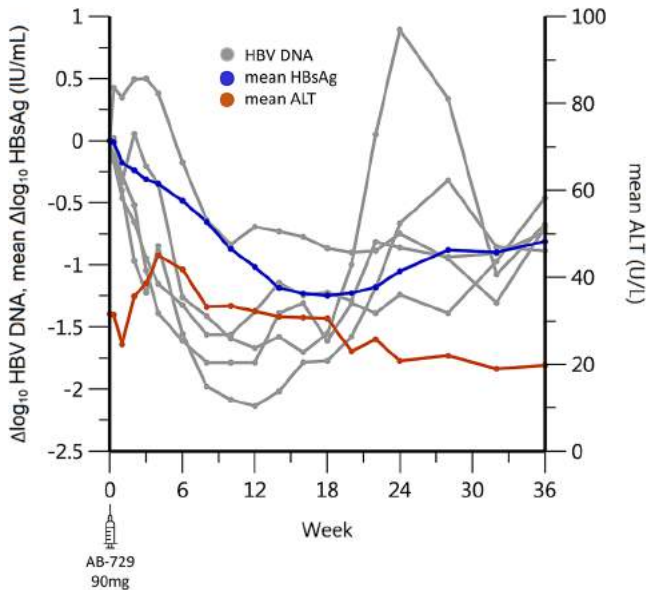


Figure: Individual $\Delta\log_{10}$ HBV DNA, mean $\Delta\log_{10}$ HBsAg and mean ALT over time in HBV DNA+ CHB subjects following a single dose of AB-729 90 mg

Conclusion: AB-729 90 mg single dose reduces all measured viral markers, including HBsAg, HBV DNA, HBV RNA and HBcAg, with suppression below baseline levels up to 36 weeks post-dose. Development of AB-729 continues, including repeat dosing at varying dosing intervals, in combination with other antiviral agents.

Viral hepatitis C: Clinical aspects except therapy

PO-68

Prospective independent confirmation of guideline defined hepatitis C screening strategies within the “Check-Up” examination in the primary care setting

David Petroff¹, Ingmar Wolfram², Olaf Bätz³, Katrin Jedrysiak³, Jan Kramer³, Thomas Berg⁴, Johannes Wiegand⁴. ¹University of Leipzig, Clinical Trial Centre, Leipzig, Germany; ²Primary Care Physician, Paderborn, Germany; ³LADR Laboratory Group Dr Kramer and Colleagues, Geesthacht, Germany; ⁴Department of Medicine II, Leipzig University Medical Center, Division of Hepatology, Leipzig, Germany
Email: johannes.wiegand@medizin.uni-leipzig.de

Background and aims: Adequate screening strategies for unknown infections are fundamental for hepatitis C virus (HCV) elimination. In 2015, we investigated HCV prevalence (anti-HCV 0.95%, HCV-RNA 0.43%) and screening strategies in 21 000 patients in an urban primary care setting based on a guideline adapted questionnaire for HCV risk scenarios. Presence of one of the risk factors iv drug abuse (IVDU), blood transfusion before 1992 (BT), immigration, or elevated ALT diagnosed 83% of unknown HCV-RNA positive cases by screening only 26% of the population (Wolfram, J Hepatol 2015). The aim of the present project was to perform a second independent screening and prospectively verify these results. In addition to a second urban area we included a rural region to analyse potential differences.

Method: Anti-HCV and ALT were included in a routine check-up (“Check-Up”) in the metropolitan area of Hamburg and rural area of Schleswig-Holstein together with a questionnaire covering 15 guideline adapted risk scenarios. HCV-RNA (PCR) was analysed in anti-HCV positive individuals. Risk factors were assessed by multivariate logistic regression.

Results: In Hamburg and Schleswig-Holstein, 4323 and 9321 individuals were recruited by 29 and 46 primary care practices, respectively. Baseline characteristics did not differ except for a slightly younger population in Hamburg (52.6 vs 56.6 years) and immigration being more prevalent (15.1% vs 5.9%). The anti-HCV prevalence was 0.56% and 0.49% and 0.1% of patients were HCV-RNA positive in both regions. In the total cohort (n = 13644), 52 of the 70 anti-HCV positive patients including eight HCV-RNA positive cases were so far unaware of the infection, which implies a number needed to screen of 262 to detect one unknown anti-HCV positive individual. At least one of the risk factors was present in 3000 patients (22% of the total cohort). This screening strategy identified 27 (52%) and 6 (75%) of the anti-HCV and HCV-RNA positive patients with unknown infections, reducing the number needed to screen to 111. The odds ratio (95% CI) for anti-HCV was 53.1 (27.9–96.5), 2.1 (0.8–4.4), 2.6 (1.4–4.6) and 1.4 (0.6–2.6) for IVDU, BT, immigration and elevated ALT, respectively.

Conclusion: Our second independent screening prospectively verifies the results of the first study. An anti-HCV screening in combination with a simply to capture risk questionnaire and ALT measurement should be included in the routine check up at the primary care level.

PO-72

Hepatitis C in Connecticut Community Clinics: Measuring the Impact of the Project ECHO Model in Treatment in Primary Care

Aaron Smith¹, Marwan Haddad². ¹Quinnipiac University, Frank H. Netter MD School of Medicine, North Haven, United States; ²Community Health Centers, Inc., Weitzman Institute, Middletown, United States

Email: aasmith@qu.edu

Background and aims: 3.5 million Americans are living with chronic hepatitis C virus (HCV), a viral infection of the liver which, prior to COVID-19, killed more people in the US than any other infectious disease. A significant barrier to treatment is a lack of training of primary care providers (PCPs). The Project Extension for Community Healthcare Outcomes (Project ECHO), a telemedicine model for training PCPs, has been used to address this barrier, with treatment outcomes comparable to those of gastroenterology (GI) specialists. Community Health Center, Inc. (CHC) in Connecticut has been operating a hepatitis C virus (HCV) ECHO program since 2012. This study aims to evaluate the program’s efficacy in changing provider behavior and increasing rates of treatment among HCV patients.

Method: This is a retrospective cohort study including the 2, 638 HCV patients in primary care at CHC from 2012 to 2019. A population analysis was conducted, comparing individuals in three treatment groups: patients treated in primary care, referred to GI, and neither. A multinomial logistic regression was used to create a predictive model for these groups. A Fisher’s exact test was used to compare patients treated in primary care who did and did not have an ECHO-trained PCP.

Results: Compared to the other two treatment groups, patients treated in primary care were more likely to have an ECHO-trained PCP, as well as be HIV-positive, and have opioid use disorder (OUD) and advanced fibrosis or cirrhosis. While 52.6% of patients treated in primary care had a PCP who was ECHO-trained, 81.3% of patients treated in primary care were prescribed medication by an ECHO-trained provider. Notably, having an ECHO-trained PCP was found to be a positive predictor of treatment in primary care (OR = 1.611; 95% CI = 1.332–1.949; p = <0.001), and a negative predictor for referral to a GI specialist (OR = 0.662; 95% CI = 0.526–0.832; p = <0.001).

POSTER PRESENTATIONS

Additionally, advanced fibrosis or cirrhosis (OR = 4.048; 95% CI = 3.143–5.212; $p < 0.001$), and OUD (OR = 2.45; 95% CI = 2.002–3; $p < 0.001$) were found to be significant positive predictors of treatment in primary care.

Conclusion: Not only were patients of ECHO-trained providers more likely to be treated in primary care, but ECHO-trained-providers were responsible for the great majority of treatment in primary care. Moreover, patients who were the most medically complicated, based on the presence of advanced liver disease and HIV, were more likely to be treated in primary care, and more likely to be treated by an ECHO-trained PCP. The success of this program suggests that the ECHO model can be extremely effective in increasing access to care, by creating a significant change in provider behavior and increasing treatment in primary care. If the United States hopes to achieve its nation-wide goal of HCV elimination, the ECHO model should be an integral part of a multi-faceted approach.

PO-131

From screening to therapy: Anti-HCV screening and linkage to care in a network of general practitioners and a private gastroenterology practice

David Petroff¹, Olaf Bätz², Katrin Jedrysiak², Jan Kramer², Hjördis Möller³, Renate Heyne³, Burkhard Jäger³, Thomas Berg⁴, Johannes Wiegand⁴. ¹University of Leipzig, Clinical Trial Centre, Leipzig, Germany; ²LADR Laboratory Group Dr Kramer and Colleagues, Geesthacht, Germany; ³Leberzentrum am Checkpoint, Berlin, Germany; ⁴Department of Medicine II, Leipzig University Medical Center, Division of Hepatology, Leipzig, Germany
Email: johannes.wiegand@medizin.uni-leipzig.de

Background and aims: Low rates of hepatitis C virus (HCV) diagnosis and sub-optimal linkage to care constitute barriers to eliminate HCV infection—a World Health Organisation goal for 2030. In 2012/13, we performed an HCV screening on top of a routine check-up in the primary care setting and observed an anti-HCV and HCV-RNA prevalence of 0.95% and 0.43%, respectively (Wolfram, J Hepatol 2015). However, anti-HCV positive patients may not receive further diagnostics and antiviral therapy, because they drop out during the referral pathway to the specialized care of gastroenterologists. Thus, clinical studies on linkage to care aspects are of major relevance to improve HCV elimination strategies: We used an existing network of primary care physicians and a specialized private practice of gastroenterology to investigate an ideal pathway from screening to referral of newly identified HCV patients with documentation of further diagnostic steps and initiation of therapy.

Methods: An anti-HCV and HCV-RNA screening was prospectively included in a routine check-up covered by statutory health care insurance in the primary care setting. Primary care physicians cooperated routinely with a private gastroenterology practice in Berlin. Anti-HCV positive patients were referred for further specialized diagnostics and treatment if indicated.

Results: Within 14 months, 17 primary care practices screened 1875 patients (46% male, age 50 ± 17 years). 12 individuals were anti-HCV positive (0.6%), six of them reported previous antiviral HCV therapy, leaving six newly discovered cases, of whom one was HCV-RNA positive (0.05% of the population). The main risk factor for being anti-HCV positive was a history of iv drug abuse (5/12 (42%) vs. 12/1863 (0.6%); $p < 0.001$). None of the 12 anti-HCV positive cases whom referral to secondary care was offered to showed up at the private gastroenterology practice. Thus, further clinical details of the pathway from screening to therapy could not be analyzed.

Conclusions: Although much effort was made to characterize linkage to care of newly diagnosed hepatitis C patients between primary and secondary care, the project failed its primary goals. The prevalence of anti-HCV and HCV-RNA positive patients was remarkably lower than in our primary screening project and did not allow detailed analysis of patient care pathways.

PO-388

Increased screening, tailored access, linkage to care and treatment for PWUD through a patient centered program

Alessandra Mangia^{1,2}, Rosa Cotugno¹, Maria Franca³, Antonio Canosa⁴, Valeria Piazzolla¹, Maria Squillante¹, Ernesto Agostinacchio⁵, Giovanna Cocomazzi¹, Loredana Ciaccia⁶, Egidio Visaggi⁷, Fausto Campanozzi⁸. ¹IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo; ²Liver Unit, Medical Sciences, San Giovanni Rotondo, Italy; ³SUD Department, Policoro; ⁴SUD Department, Termoli; ⁵Internal Medicine, Bari; ⁶IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo; ⁷Internal Medicine, Terlizzi; ⁸SUD Department, Torremaggiore
Email: a.mangia@tin.it

Background and aims: In Italy, rates of HCV testing and diagnosis are variable among PWUD. In Puglia in 2018, of 871 screened subjects, 38% had HCVAb*. Despite DAAs are associated with 95% SVR rates, addition center (SERD) physicians are often located in remote areas and are not allowed to prescribe DAAs. Notably, during the last year, and in concomitance with COVID-19 pandemic, a reduction in DAAs prescriptions has been observed. To increase all the steps of HCV cascade, a dedicated program including “ad hoc” transportation service, fast track access to care and treatment was offered to PWUD in our geographical area.

Method: Over 12 months period, 1500 individuals seen at 15 SERDs underwent HCV screening by OraQuick. For patients testing HCVAb positive, a fast track baseline evaluation was performed at our Unit allowed to prescribe DAAs. Patients were transported to our center on a dedicated “ad hoc” shuttle and, after a 5 hours baseline evaluation, were taken to pharmacists close to their SERDs in order to receive medications. Treatment and adherence were supervised by SERDs physicians and SVR12 assessed at our center after the follow-up. Scalability of the process was assessed based on the number of patients screened in our region in 2018, and on the number of PWUD diagnosed and treated at our center during 06/2018–07/2019.

Results: Of the 1500 individuals screened, 634 (42.2%) tested HCVAb positive. Active HCV infection was observed in 231 ongoing PWUD, 54% of whom on OAT. Baseline characteristics of 634 patients and HCV RNA status are reported in Table 1. Higher rates were on OAT and had liver stiffness results compatible with cirrhosis among HCV RNA positive than negative. Median interval between HCV RNA assessment and treatment start was 22 days (0–300). Patients received pangenotypic treatment for 12 weeks without RBV. In 222 patients who completed treatment SVR rate was 98.6%. Among GT3 infected, SVR12 was 98%. Overall, 9 patients discontinued treatment or were lost to follow-up, 6 of them between week 4 and 8. No reinfection was observed.

	HCV Ab+ve N = 634
Median age (yrs) range	48.1 (22–71)
Male gender	562 (88.6)
Current IVDU	180 (28.4)
Heroin alone	56 (31.2)
Cocaina alone	23 (12.7)
Heroin combined with alcol/others	101 (56.1)
OAT	221 (34.8)
HCV RNA reactive	231 (36.4)
Past HCV treatment	278 (44.0)
HIV positive	14 (2.2)
Mental Disorders	56 (8.8)
Liver stiffness >12.5 Kpa	147 (23.1)

Conclusion: Among PWUD, a patient tailored service led to an increase in screening and diagnosis. A rapid treatment start occurred in the vast majority of cases. SVR12 was high regardless of HCV GT. In patients with history of drug addiction and social instability, dedicated treatment programs allow to increase the number of HCV infected patients identified, diagnosed and successfully treated.

Funding: this work was supported by Gilead for the study “The Puglia micro-elimination” NCT03923595.

PO-453

The impact of unrestricted access to direct-acting antiviral among 1001 incarcerated hepatitis C virus-infected patients

Yu Jun Wong^{1,2}, Prem Harichander Thurairajah³, Rahul Kumar³, Ngai Moh Law¹, Sin Yoong Chong¹, Tiing Leong Ang¹, Jessica Tan¹, Eng Kiong Teo¹. ¹Changi General Hospital, Gastroenterology and Hepatology, Singapore, Singapore; ²Duke-NUS Medical School, Singapore; ³National University Hospital, Gastroenterology and Hepatology, Singapore, Singapore
Email: eugene.wong.y.j@singhealth.com.sg

Background and aims: Despite the disproportionately high prevalence of hepatitis C virus (HCV) amongst the incarcerated population, eradication remains challenging due to logistic and financial barriers. Although treatment prioritization based on disease severity is commonly practiced, the efficacy of such an approach remains uncertain. Recent modelling study showed that at least 630 HCV patients have to be treated annually in order for Singapore to achieved HCV elimination target by 2030 [1]. We aimed to compare the impact of unrestricted access to DAA among incarcerated HCV-infected patients in Singapore.

Method: In this retrospective study, we reviewed all incarcerated HCV-infected patients treated in our hospital during the restricted DAA era (2013–2018) and unrestricted DAA access era (2019). During restricted DAA era, DAA was reserved for patients with Genotype 1 HCV infection, HIV/HBV co-infection, cirrhosis, prior treatment experienced or contraindication to pegylated interferon. During unrestricted DAA era, all patients received DAA as first-line treatment. Study outcomes included the rate of SVR (both intention-to-treat (ITT) and per-protocol (PP) analysis), treatment completion and treatment default. Subgroup analysis was performed based on the presence of liver cirrhosis and HCV genotype.

Results: Total of 1001 HCV patients were treated during the study period. They were predominantly male (93%) with genotype-3 HCV infection (71%), and 38% were cirrhotic. More patients received DAA during unrestricted DAA era (95% vs 42%, p < 0.001). The overall SVR during the restricted DAA access era and unrestricted DAA access era were (ITT: 83.8%, PP: 92.1%) and (ITT: 92.1%, PP: 99.1%), respectively. Unrestricted access to DAA exponentially improved the treatment access among HCV-infected patients by 460% to 681 in the year 2019 alone, resulting in a higher SVR rate (99% vs 92%, p = 0.003), higher treatment completion rate (99% vs 93%, p < 0.001), lower treatment default rate (1% vs 9%, p < 0.001) and allowing more non-cirrhotic patients to be treated (non-cirrhotic: 74.4% vs 34.7%, p < 0.001). Our findings remained robust among subgroup analysis in patients with liver cirrhosis or genotype-3 HCV infection.

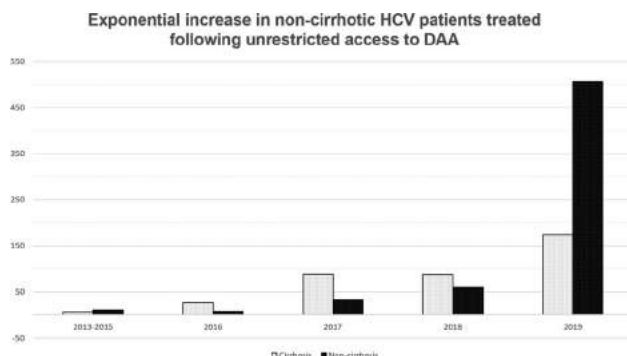


Figure: Exponential increase in non-cirrhotic HCV patients treated following unrestricted access to DAA.

Conclusion: In this large cohort of incarcerated HCV-infected patients, we demonstrated that unrestricted access to DAA is an

impactful strategy to allow rapid treatment up-scale in HCV micro-elimination.

Reference

Chaillon A, Thurairajah PH, Hsiang JC, *et al*. What is required for achieving hepatitis C virus elimination in Singapore? A modelling study. *J Gastroenterol Hepatol* 2020 [early view].

PO-525

Pooling plasma samples for hepatitis C RNA detection: a strategy to expand access to diagnostics

A. Aguilera¹, Sara Pereira¹, Ana Fuentes², Adolfo de Salazar³, Daniel Navarro¹, Maria Cea¹, Camila Picchio³, Jeffrey Lazarus³, Federico Garcia Garcia². ¹Complejo Hospitalario Universitario de Santiago (CHUS). Universidad de Santiago de Compostela (USC). Instituto de Investigación Sanitaria de Santiago (IDIS), Departamento de Microbiología, Santiago de Compostela, Spain; ²Hospital Universitario San Cecilio. Instituto de Investigación Ibs, Granada, Clinical Microbiology, Granada, Spain; ³Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona
Email: fe Garcia@ugr.es

Background and aims: Processing SARS-CoV-2 diagnostic tests has created an enormous workload for laboratories around the world, at the cost of processing many other tests. Yet the diagnosis of active hepatitis C virus (HCV) infection is the necessary first step for its elimination. In most countries, universal population screening and/or screening by age group have not been adopted due to cost and cost-effectiveness considerations. We propose a sample pooling diagnosis strategy to overcome this challenge, and to contribute to increasing the diagnostic capacity of clinical laboratories.

Method: A positive sample with known HCV RNA IU/ml was pooled 1/10, 1/100, 1/1000, 1/10 000, 1/1 00 000, and 1/10 00 000, and run by two commercially available diagnostic assays: CAP CTM v2 HCV and Cobas 6800 (Roche Diagnostics). The sensitivity of pooling was assessed as the last pool able to detect more than 15 IU/ml.

Results: As shown in Table 1, both tests were able to identify the positive sample when pooled in up to 10⁴ samples. We observed a one log decrease per 10-fold pooling factor in the amount of HCV RNA that the commercial assays were able to detect.

Table: Pooling of a positive sample (U = unknown) by two commercially available HCV-RNA detection tests

Samples	Pool	CAP CTM v2 HCV		Cobas 6800	
		IU/ml	Log10	IU/ml	Log10
U		61 0311	5.78	1 15 000	5.06
U+9 negative	10	51 389	4.71	14 700	4.16
U+99 negative	100	4642	3.67	1730	3.23
U+999 negative	1000	604	2.78	231	2.36
U+9999negative	10 000	94	1.97	43	1.63
U+99999 negative	1 00 000	<15	<1.18	<15	<1.18
U+999999	10 00 000	TND	-	TND	-
negative					

TND: target not detected.

Conclusion: The strategy of pooling samples for the diagnosis of active HCV infection has great advantages that can and should be exploited with the aim of eliminating HCV as a public health threat. From our study, we believe that a plausible size for countries with a low prevalence of chronic hepatitis C would be 100 samples, very similar to the number used earlier by blood banks and transfusion centers. Given current prices on the market and for a pool size of 100 samples, the price of pooled testing for HCV-RNA would be reduced to EUR 0.30 per patient screened. We believe that by substantially improving cost-effectiveness, this strategy enables and provides the necessary sustainability for use in large-scale diagnosis of HCV.

POSTER PRESENTATIONS

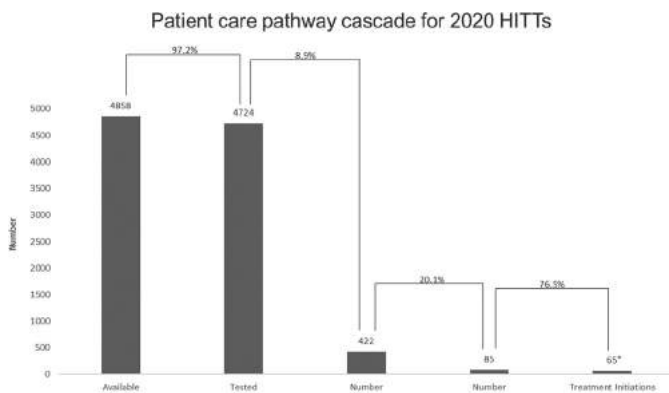
PO-637

Achieving hepatitis C micro-elimination in prisons through High Intensive Test and Treat (HITT) interventions

Sean Cox¹, Andrew Jones², Lee Christensen¹, Julia Sheehan¹, Kate Dorrington³, Andrew Milner³, Phil Troke³, Iain Brew⁴, Rachel Halford¹. ¹Hepatitis C Trust, London, United Kingdom; ²Gilead Sciences Ltd, Medical Affairs, London, United Kingdom; ³Gilead Sciences Ltd, London, United Kingdom; ⁴Practice Plus Group Health and Rehabilitation, United Kingdom
Email: andy.jones@gilead.com

Background and aims: National Health Service England plans to eliminate Hepatitis C in England by 2025, five years earlier than World Health Organisation goals. Achieving micro elimination in prisons is an essential component of this plan. Testing on prison admission has historically been low and, despite recent increases, there remains a large population who still require testing and treatment.

Method: Through a collaboration between The Hepatitis C Trust (HCT), Her Majesty's Prison and Probation Service, Prison Healthcare provider Practice Plus Group, Gilead Sciences and NHS England, we have developed a process to screen entire prisons over 1–5 days and rapidly initiate treatment. Prior to an intervention, HCT Peers engage with both staff and prisoners to raise awareness and reduce stigma. During the event, screening is performed using rapid point-of-care antibody tests followed by PCR-based assessment of positives. Testing acceptance is maximised by testing on the prison wings and provision of incentives: chocolate, toiletries, telephone credit. The aim is for treatment initiation to begin within 7 days (maximum 14 days) of PCR+ diagnosis.



* COVID-19 impacted prisons following the national lockdown and this effected the initiation of treatment following 3 HITTs which took place in March 2020

Figure:

Results: During 2020, HITTs were performed at 9 prisons with 4, 724 prisoners tested out of a potential 4, 858 (97%; range 96–100%). HCV antibody prevalence varied greatly with the highest being female

closed (19%), and high turnover male remand (11%), prisons, compared to Young Offenders Prisons (0.2%). The initial prisons engaged were those with pre-existing reception testing and treatment pathways. As a result, over half of patients who tested positive for HCV antibody were already on treatment, previously treated or had naturally cleared the virus. COVID-19 significantly impacted these interventions but procedures were developed to safely deliver HITTs during the pandemic.

Conclusion: HITT interventions have proven effective in testing entire prison populations with all prisons achieving the NHSE target of over 95% of residents tested. HCT Peers with their lived experience of HCV have proven essential to engage prisoners who previously refused testing. Viraemia rates were low in comparison to antibody rates due to the successful testing and treatment pathways in these prisons. Future HITTs are planned for prisons with historically low HCV screening and treatment rates, with the aim of increasing identification of RNA+ individuals.

PO-649

Impact of extending DAAs availability in France: a five-year overview (2015–2019) of data from French administrative healthcare databases (SNDS)

Stanislas Pol¹, Fayssol Fouad², Magali Lemaître², Ingrid Rodriguez³, Olivier Lada³, Françoise Roudot-Thoraval⁴. ¹Cochin (AP-HP), Paris, France; ²IQVIA, Courbevoie, France; ³Gilead, Boulogne-Billancourt, France; ⁴Henri-Mondor (AP-HP), Créteil, France
Email: fayssol.fouad@iqvia.com

Background and aims: Direct antiviral agents (DAAs) first became available in France in 2014 for the treatment of chronic hepatitis C (CHC) in patients with severe fibrosis (prioritized access); then in 2017, DAAs became available to all CHC patients (universal access). Lastly, in May 2019, universal prescription was granted, allowing every physician, including GPs, to prescribe pangenotypic DAAs. This study evaluated the impact of DAA availability on CHC treatment access and HCV screening in general and at-risk populations.

Method: Adult patients affiliated with the French national health insurance system (SNDS databases) who were screened or treated for CHC between 2015 and 2019 were included. Different algorithms were developed to identify at-risk subpopulations: migrants, inmates, HIV+ patients, psychiatric patients and drug users.

Results: In the general population, the proportion of screened patients increased by 1% between 2015 and 2019 (from 4.6% to 5.6%). The median interval between the last screening test and treatment initiation decreased from 64 days in 2015 to 37 days in 2019.

During the study period, 71, 466 patients began CHC treatment (median age 55; [48–62]; 59% male). The proportion of patients starting treatment increased by 44% between 2015 and 2017 and decreased in 2019. The median age decreased from 56 to 54 years and the proportion of female increased from 36% to 39% during the study

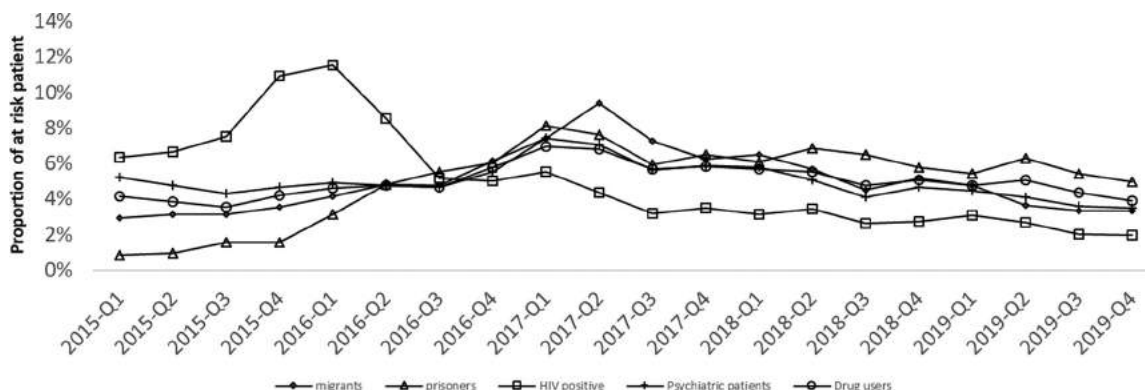


Figure: (abstract: PO-649): Time trend of the proportions of at-risk subpopulations among treated patients, 2015–2019.

period. Among the study population, only 2, 212 (3%) patients were treated at least twice.

Among treated patients, 54% were not at-risk patients. The main nonexclusive risk factors for CHC were psychiatric conditions (27%), drug use (21%) and HIV positivity (11%). Among treated patients, the proportion of HIV+ patients decreased from 19% to 8%, while the proportions increased, or remained stable, in other at-risk subpopulations. Depending on the year, between 51% and 57% of psychiatric patients had additional risk factors, mainly drug use with a 38% to 52% overlap.

Conclusion: To our knowledge, this study is the first describing the HCV treatment management in France between 2015 and 2019 using the SNDS databases to assess the impact of extending DAA availability. It highlights that DAA availability was associated with a screening increase since 2015 and a decrease in the time to treatment initiation. It also emphasizes that universal access in 2017 led to a surge in treatment initiations in the general population. Finally, this study is the first to use algorithms to identify and describe at-risk subpopulations using the SNDS databases, which will help to improve the HCV cascade of care in these subpopulations.

PO-690

Depist C pharma, an innovative outreach HCV screening project in pharmacy for drug users and general population

André-Jean Remy¹, Eric Puget¹, Olivier Albert¹. ¹Perpignan Hospital, Mobile Hepatitis Team, Perpignan, France
Email: andre.remy@ch-perpignan.fr

Background and aims: Hepatitis C testing is still insufficient in France. Beyond defined groups with risk behaviors, hepatitis C testing should now be directed at the general population. The French pharmacies territorial coverage is excellent, and pharmacists are increasingly involved in public health actions (therapeutic education, vaccination against the flu). French Public Health Act on Innovation thank to the "Article 51" allow enables health care teams to propose experiments aimed at improving the diagnostic and/or therapeutic management of a disease. This funding methods and organization is unprecedented. Our aim was to screen for hepatitis C in pharmacies with POCT performed by pharmacists.

Method: Pharmacist recruitment was done on a voluntary basis from different pharmacies on a population pool of 600, 000 inhabitants. Pharmacists received training and education appropriate to the POC testing. At request of the health authorities, screening was only proposed for patients with one or more risk factors (national health agency list). There were planned 10 tests per week per pharmacy over 12 months for a total of 5, 000 tests. Expected prevalence was 10%. Patients with positive POCT were tested for HCV viral load real-time and for liver fibrosis assessment by FIBROSCAN. They could be treated with HCV antiviral direct agents.

Results: 37 pharmacists representing 25 pharmacies were trained to POCT use and announcement of results during 4 half days session. 9 pharmacies were located in agglomeration, including 5 in working-class areas, 7 in rural area, 7 in seaside area and 2 in middle mountain area. After 15 months of experimentation: 29 pharmacies have completed at least one POCT; we observed a decrease in the number of tests performed during the flu vaccination campaign; 656 tests were performed including 45 positives or a serological prevalence of 6, 9%. 33 patients had a negative viral load with 1 or 2 risk factors and a Fibroscan mean value at 4, 5 KPa (fibrosis stage F1); 13 patients had positive HCV viral load (prevalence 2%) and 3 to 9 HCV risk factors, mean Fibroscan value at 8.6 KPa (fibrosis stage F2). They all were effectively treated and cured by direct antiviral agents.

Conclusion: We have demonstrated the feasibility of hepatitis c screening by POCT performed by pharmacists regardless of geographic location. Targeting screening by risk factors does not identify all patients. Pharmacists represent very interesting local *healthcare professional* who could invest in COVID19 screening by POCT.

PO-694

Clinical features and comorbidities pattern of HCV infected migrants as compared to native patients in care in Italy: a real life evaluation in the PITER cohort

Maria Giovanna Quaranta¹, Luigina Ferrigno¹, Xhimi Tata², Franca D'Angelo¹, Marco Massari³, Carmine Coppola⁴, Elisa Biliotti⁵, Alessia Giorgini⁶, Diletta Laccabue⁷, Alessia Ciancio⁸, Pierluigi Blanc⁹, Marzia Margotti¹⁰, Donatella Ieluzzi¹¹, Maurizia Brunetto¹², Francesco Barbaro¹³, Francesco Paolo Russo¹⁴, Ilaria Beretta¹⁵, Giulia Morsica¹⁶, Gabriella Verucchi¹⁷, Annalisa Saracino¹⁸, Loreta Kondili¹. ¹Italian National Institute of Health, National Center for Global Health, Roma, Italy; ²University of Tor Vergata, Nostra Signora del Buon Consiglio di Tirana, Tiranë, Albania; ³Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Italy, Infectious Diseases, Reggio Emilia, Italy; ⁴Gragnano Hospital, Naples, Italy, Department of Hepatology, Gragnano, Italy; ⁵Sapienza University, Rome, Italy, Hepatology Unit, Department of Clinical Medicine, Roma, Italy; ⁶ASST Santi Paolo e Carlo, Gastroenterology and Hepatology Unit, Milano, Italy; ⁷Maggiore Hospital, Unit of Infectious Diseases and Hepatology, Parma, Italy; ⁸University of Turin, Gastroenterology Unit, Torino, Italy; ⁹Santa Maria Annunziata Hospital, Infectious Disease Unit, Ponte a Niccheri, Bagno a Ripoli, Italy; ¹⁰University Hospital of Modena, Department of Internal Medicine, Modena, Italy; ¹¹University Hospital of Verona, Clinical Unit of Gastroenterology, Verona, Italy; ¹²University Hospital of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy; ¹³Azienda Ospedaliera di Padova, Infectious and Tropical Diseases Unit, Padova, Italy; ¹⁴University of Padua, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; ¹⁵San Gerardo Hospital, Division of Infectious Diseases, Monza, Italy; ¹⁶San Raffaele Hospital, Department of Infectious Diseases, Milan, Italy; ¹⁷Alma Mater Studiorum Bologna University, Department of Medical and Surgical Sciences, Bologna, Italy; ¹⁸Bari University Hospital, Division of Infectious Diseases, Bari, Italy
Email: loreta.kondili@iss.it

Background and aims: Direct-acting antivirals are highly effective for the treatment of hepatitis C virus (HCV) infection, regardless race/ethnicity and genotype. We aimed to evaluate socio-demographic, virologic and clinical features of HCV-infected migrants in care versus natives enrolled in the PITER cohort.

Method: Migrants were defined by birth's country and nationality different from Italy. Comparison between natives and migrants was performed by Mann-Whitney U test and Chi-squared test. Age and sex adjusted Odds Ratios were calculated by multiple logistic regression.

Results: Of 10, 669 consecutively enrolled patients in PITER, 301 (2.8%) were migrants. Migrants were younger (median age of 47 vs 62, p < 0.001), more frequently females (56.5% vs 45.3%, p < 0.001) and with higher HBsAg positivity (3.8 vs 1.4, p < 0.05). HCV genotype 1b was prevalent in both groups, while genotype 1a and 2 were more frequent in natives and genotype 4 in migrants (p < 0.05). Liver disease severity and the sustained virologic response (SVR) were similar.

Cardiovascular, endocrine, haematological and psychiatric disorders were more frequently reported in native respect to migrant patients (p < 0.05). In patients with F4 fibrosis who achieved the SVR, pre-existing cofactors for liver disease progression (such as steatosis, hypertension/cardiovascular disease, excessive alcohol drinking, obesity and/or diabetes) were more frequent in migrants (p < 0.05).

Conclusion: The diagnosis of comorbidities seems to be underestimated in migrants in care. In patients with liver disease progression risk factors, an increase of awareness regarding continuous follow-up after HCV eradication is required.

POSTER PRESENTATIONS

PO-745

Simulations of HCV vaccine trials reveal opportunities to re-evaluate vaccine efficacy

Alexander Gutfraind^{1,2}, Mary-Ellen Mackesy-Amiti³, Eric Tataru^{4,5}, Nicholson Collier^{4,5}, Scott Cotler¹, Kimberly Page⁶, Jonathan Ozik^{4,5}, Basmattee Boodram³, Marian Major⁷, Harel Dahari¹. ¹Loyola University Chicago, The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Maywood, United States; ²University of Illinois at Chicago, Division of Epidemiology and Biostatistics, School of Public Health, Chicago, United States; ³University of Illinois at Chicago, Division of Community Health Sciences, School of Public Health, Chicago, United States; ⁴University of Chicago, Consortium for Advanced Science and Engineering, Chicago, United States; ⁵Argonne National Laboratory, Decision and Infrastructure Sciences, Argonne, United States; ⁶University of New Mexico Health Sciences Center, Division of Epidemiology, Biostatistics and Preventive Medicine, Department of Internal Medicine, Albuquerque, United States; ⁷Food and Drug Administration, Division of Viral Products, Center for Biologics Evaluation and Research, Silver Spring, United States
Email: harel.dahari@gmail.com

Background and aims: Agent-based models (ABM) can identify challenges and help to develop robust HCV vaccine trial designs to increase the chance of reaching end points. In this study we use an ABM to perform in-silico simulations of HCV vaccine randomized clinical trials (RCT).

Method: To forecast RCT outcomes, we designed an ABM simulation representing 32, 000 PWID in metropolitan Chicago, Illinois, USA accounting for their networks and infections with HCV. The in-silico simulation represents recruitment, follow-up, and statistical analysis of a two-dose vaccine based on a completed trial (NCT01436357 or NEJM in press). The vaccine was assumed to have vaccine efficacy (aVE) of 60% in preventing chronic HCV but no effect on acute infections. We ran 3 trial simulations with different random seeds, collecting daily HCV-infection status of each in silico PWID in the trial, which allowed us to examine the effect of HCV testing frequency (e.g., weekly vs. monthly) and various statistical approaches (SA) of calculating the estimated vaccine efficacy (eVE): (SA #1) incidence rate ratio (IRR) of chronic HCV, intention to treat, (SA #2) IRR of chronic HCV, per protocol sample, (SA #3) IRR of chronic HCV among acute infected, (SA #4) Cox proportional hazard (CPH) model for the risk of chronic HCV, (SA #5) adjusted CPH model for the risk of chronic HCV (Table 1).

Table 1: Prevented chronic HCV infection in simulated vaccine trial analysis with assumed vaccine efficacy of aVE=60%

	Trial A		Trial B		Trial C	
	Study	Placebo	Study	Placebo	Study	Placebo
N total	1604	1603	1604	1603	1604	1603
HCV acute cases	79	60	52	74	65	63
HCV chronic cases	34	41	20	50	30	44
Statistical approaches (SA) of eVE (chronic HCV prevented)						
(1) 1-IRR, ITT	.19	.60	.31			
(2) 1-IRR, per protocol	.25	.62	.33			
(3) 1-IRR, among acute	.38	.41	.36			
(4) 1-HR (Cox regression)	.19	.60	.32			
(5) 1-aHR (Cox regression) †	.27	.55	.25			

IRR: incidence rate ratio; ITT: intention to treat; HR: hazard ratio; aHR: adjusted HR; eVE: estimated efficacy based on in silico trial simulation results; † adjusted for age, gender, race/ethnicity, drug use degree, friend HCV prevalence, daily injection intensity, network mean age, fraction receptive sharing.

Results: The HCV incidence in each arm was found to have a significant effect on eVE. In trial A, a higher rate of acute infections in the vaccine arm compared to the placebo arm increased the number of chronic infections, and reduced the eVE calculated by the crude IRR (SA #1). Covariate adjustment (SA #5) only partially mitigated the effect of unequal infection rates. Conversely, in Trial B there were more acute cases in the placebo arm resulting in an overestimated eVE. Trial C showed eVE<60% despite a balanced incidence. An analysis of time to viral clearance among persons infected showed a strong vaccine effect in all trials, with clearance rates 3 to 5 times higher in the vaccine compared to placebo condition. The simple IRR

method (SA #1) appears to give similar eVE as the more complex (unadjusted) Cox method (SA #4) in all trials. The incidence rate ratio for chronic infection among acute cases (SA #3), as well as the time to clearance, were found to be robust measures of vaccine performance, and could provide secondary end points. Analysis of the choice of weekly vs. monthly blood testing did not find a systematic difference in results.

Conclusion: The statistical methodology and end point have a significant effect on the success of vaccine trials, with some analysis establishing a much lower eVE than aVE, which suggest a re-evaluation of how vaccine trials for HCV should be evaluated.

PO-908

Diagnostic accuracy of dried blood spot and plasma separation card samples for testing hepatitis c virus rna

Agnes Malobela¹, Marie Amougou², Panos Iliopoulos³, Jean-Claude Mugisha⁴, Nino Berishvili⁵, Manana Sologashvili⁶, Emmanuel Fajardo¹, Francois Lamoury¹, Aurélien Macé¹, Maxwell Chirehwa⁷, Richard Njouom², Angelos Hatzakis³, Jules Kabahizi⁴, Claude Muvunyi⁴, Penny Buxton⁸, Sadaf Mohiuddin⁸, Maia Alkhazashvili⁵, Elena Ivanova¹. ¹Foundation for Innovative New Diagnostics, Geneva, Switzerland; ²Cameroon Pasteur Center, Yaoundé, Cameroon; ³Hellenic Scientific Society for the Study of AIDS and Sexually Transmitted Diseases, Athens, Greece; ⁴Rwanda Military Hospital, Kigali, Rwanda; ⁵National Center for Disease Control and Public Health, Tbilisi, Georgia; ⁶Hepa Plus, Tbilisi, Georgia; ⁷University of Cape Town, Cape Town, South Africa; ⁸National Reference Laboratory, Victoria, Australia
Email: elena.ivanova@finddx.org

Background and aims: Dried blood spots (DBS) have the potential to improve access to diagnostic testing for hepatitis C virus. A number of studies have shown good performance of centralized HCV RNA assays with DBS specimens. However, there was no standard protocol for DBS collection, storage and processing and the use of DBS samples was limited to "off-label" use. Here, we evaluated the performance of three centralized HCV RNA assays from capillary blood collected on DBS and Plasma Separation Cards (PSC) using manufacturers' protocols.

Method: Participants were enrolled at four sites located in Cameroon, Rwanda, Georgia, and Greece. Dried blood spot and Plasma Separation Card samples were prepared from capillary (fingerstick) and venous whole blood samples. Collected samples were tested locally and sent for further testing to the central laboratory facility at NRL Australia (Melbourne, Australia). The diagnostic accuracy of these sample types for detecting hepatitis C virus RNA was assessed using three platforms (Abbott m2000sp/rt, Roche cobas® 4800 and Roche cobas® 6800), with plasma tested using the respective plasma assays on each of the platforms, serving as the reference tests.

Table 1: Diagnostic accuracy of centralized HCV RNA assays using DBS and PSC samples

Index test and sample type	Sensitivity (%), (95% CI)	Specificity (%), (95% CI)
Abbott RealTime	95.2	95.6
DBS	(92.9–96.8)	(93.3–97.1)
Roche cobas® 4800	97.2	88.6
DBS	(95.2–98.3)	(85.4–91.2)
Roche cobas® 4800	95.2	99.6
PSC	(92.8–96.8)	(98.5–99.9)
Roche cobas® 6800	97.3	95.9
DBS	(95.4–98.5)	(93.7–97.3)
Roche cobas® 6800	96.9	99.8
PSC	(94.8–98.1)	(98.8–100)

Abbreviations: CI, confidence interval; DBS, dried blood spot; PSC, plasma separation card.

Results: A total of 946 participants were enrolled. The sensitivity and specificity of the Abbott RealTime assay was 95.2% and 95.6%, respectively, using capillary DBS samples. The sensitivity and

specificity of the Roche cobas® 6800 was 97.3% and 95.9%, respectively, on the DBS samples. Sensitivity and specificity were high on the Roche cobas® 4800 and 6800 assays using PSC samples. **Conclusion:** The diagnostic accuracy of DBS and PSC samples for detecting HCV RNA was high on all platforms evaluated, confirming that these sample types can be used as an alternative to plasma, to screen for HCV infection, thus facilitating access to testing.

PO-951

High rates of hidden HCV infections among hospitalized patients aged 55–85

Valeria Piazzolla^{1,2}, Giulia Paroni³, Marco Turchini⁴, Antonio Cisternino⁵, Francesca Bazzocchi⁶, Luigi Ciuffreda⁷, Franco Gorgoglione⁸, Leonardo Gorgoglione⁹, Mauro Casse¹⁰, Nicola Cascavilla¹¹, Vincenzo Palazzo¹², Antonio Greco¹³, Salvatore De Cosmo¹⁴, Mauro Salvatori¹⁵, Maurizio Leone¹⁶, Michele Fania¹⁷, Natale Sciannamè¹⁸, Filippo Aucella¹⁹, Evaristo Maiello²⁰, Maria Squillante², Antonio Laborante²¹, Lazzaro Di Mauro²², Francesco Longo²³, Alessandra Mangia². ¹Liver Unit, Medical Sciences, San Giovanni Rotondo; ²Liver Unit, Medical Sciences, San Giovanni Rotondo, Italy; ³Central Laboratory, Services, San Giovanni Rotondo; ⁴Thoracic Surgery, Surgery, San Giovanni Rotondo, Italy; ⁵Urology, Surgery, San Giovanni Rotondo, Italy; ⁶Abdominal Surgery, Surgery, San Giovanni Rotondo, Italy; ⁷Brest Surgery, Surgery, San Giovanni Rotondo, Italy; ⁸Orthopedics, Surgery, San Giovanni Rotondo, Italy; ⁹Neurosurgery, Surgery, San Giovanni Rotondo, Italy; ¹⁰Cardiosurgery, Surgery, San Giovanni Rotondo, Italy; ¹¹Hematology, Medical Sciences, San Giovanni Rotondo, Italy; ¹²Vascular Surgery Unit, Surgery, San Giovanni Rotondo, Italy; ¹³Geriatric Medicine, Medical Sciences, San Giovanni Rotondo, Italy; ¹⁴Internal Medicine, Medical Sciences, San Giovanni Rotondo, Italy; ¹⁵Neurology, Emergency, San Giovanni Rotondo, Italy; ¹⁶Neurology, Emergency, San Giovanni Rotondo, Italy; ¹⁷Dermatology, Medical Sciences, San Giovanni Rotondo, Italy; ¹⁸Gynecology, Surgery, San Giovanni Rotondo, Italy; ¹⁹Nephrology, Medical Sciences, San Giovanni Rotondo, Italy; ²⁰Oncology, Medical Sciences, San Giovanni Rotondo, Italy; ²¹Ophthalmology, Surgery, San Giovanni Rotondo, Italy; ²²Central Laboratory, Services, San Giovanni Rotondo, Italy; ²³Maxillo-facial Unit, Surgery, San Giovanni Rotondo, Italy
Email: a.mangia@tin.it

Background and aims: Given the millions of patients who remain unaware of their HCV infection and/or diagnosis, WHO solicits Countries to achieve elimination by 2030.

The Italian government started routine screening for HCV infection on January 2021 initially targeting subjects born between 1969 and 1989. In Italy, the most recent active HCV epidemiological estimate dates before the 2017 widespread DAA use and shows 1.7% prevalence with significant geographical differences. At the aim of achieving micro-elimination, we designed a hospital-wide project focusing on inpatients born from 1935 to 1985 to be conducted at our Institution.

Method: All inpatients aged up to 85, admitted from February 10, 2020 to February 9, 2021 underwent HCV screening. Patients were evaluated by III generation ELISA. Reflex HCV RNA test and genotyping were performed in HCVAb positive. Clinical history, diagnosis, laboratory data and concomitant medications were available for all.

Results: The HCV screening rate of inpatients was 100%. A total number of 11.146 were enrolled with a male prevalence of 54.5%. HCVAb positivity rate was 3.1% (95% CI, 3.06–3.10%) among the total population. The rate was significantly higher among male (3.4% vs 2.6%, p = 0.01). The HCVAb rate increased with age and was highest for patients born between 1944 and 1935 (5.2%). Overall, 81% of HCV RNA positive were 55 or older. The rate of HCV RNA positivity was 0.98%. Prevalence of HCVAb positivity by birth decades, and deaths by HCV RNA status are reported in the table. Overall, 18 patients died soon after diagnosis (1 due to COVID-19 infection). Among patients older

than 65, death rate was significantly higher than in those with active HCV infection. Although the proportion of HCV RNA positive patients was equal for Surgical and Medical departments, the rate of unaware patients with active HCV infection was higher among patients admitted to Orthopedic, Urologic, Abdominal, Cardiovascular, Thoracic, Maxillo-facial Surgery Units than among Medical Units (61% vs 55%).

Age cohorts	Number of subjects	HCV Abs positivity n, (%)	HCV RNA positivity n, (%)	Deaths among HCVAb n, (%)	Deaths among HCV RNA n, (%)
1975–1984	1432	24 (1.6)	6 (0.4)	0	0
1965–1974	1905	60 (3.1)	15 (0.8)	1	0
1955–1964	2546	64 (2.5)	16 (0.6)	1	0
1945–1954	2927	72 (2.4)	24 (0.8)	1	2
1935–1944	2341	124 (5.2)	46 (5.2)	3	10

Conclusion: The present study reveals a rate of active HCV infections among inpatients lower than that reported in the past in general population as a result of DAA use. The high rate of inpatients unaware of HCV infections, and the high number of deaths among subjects born from 1935 to 1965 suggest that –at least in Southern Italy– a targeted screening of these birth cohorts may be required to reduce the number of undiagnosed cases and hidden infections.

PO-955

Cost and effectiveness of treatment at Day 1 (Rapid Start) for hepatitis C and screening intensification in high-risk populations (TandT strategy) in France

Jean-Baptiste Trabut¹, Marc Bourlière², Ingrid Rodriguez³, Oliver Lada³, Martin Blachier⁴, Christophe Hezode³, Henri Leleu⁴. ¹Service d'addictologie, Hôpital Henri Mondor, France; ²Service d'hépatogastroentérologie, hôpital Saint-Joseph, Marseille, France; ³Gilead, Boulogne-Billancourt, France; ⁴Public Health Expertise, Paris, France
Email: Ingrid.rodriguez@gilead.com

Background and aims: France is committed to improving prevention, diagnosis, and treatment of hepatitis C (HCV) in line with the WHO objective of eliminating HCV by 2030. However, despite increasing attention to HCV screening, half of the patients screened with a positive serology are lost to follow-up (LTFU) before initiating treatment. This study estimates the impact on patient care of a “test and treat” (TandT) strategy which combines a targeted screening effort on elderly (>55 y/o) with an early treatment on day 1 for all patients (Rapid Start).

Method: A decision tree combined with a Markov model stimulating HCV natural history was used. The model simulates HCV screening and treatment cascade, as well as HCV progression for untreated patients whether undiagnosed or LTFU. Four at-risk populations were included: intravenous drug users (IDU), men who have sex with men (MSM), immigrants and elderly over 55 years. Epidemiology and screening cascade parameters were specific for each risk group. A sustain virologic response (SVR) rate of 100% was assumed. Three screening strategies were compared: (1) the current screening strategy (2) Rapid Start (3) Rapid Start and a 300% increase in screening individuals over 55 years in the general population. A one-year cycle was used. Outcomes included epidemiological and economic results.

Results: Between 2020 and 2030, compared to the current strategy, implementing a TandT strategy (Rapid Start + increased screening) would decrease undiagnosed patients by 22, 608 and increase treated patients by 5, 602 (Table 1). This strategy would be associated with a decrease in HCV complications with 1, 873 decompensated cirrhosis and 3, 949 HCC avoided. Such a strategy would also lead to an

POSTER PRESENTATIONS

increase of €348.75 m in treatment costs and of €0.49 m in screening costs. However, it would be compensated by a reduction in complication costs of €93.81 m and in indirect costs (absenteeism and presenteeism) of €516.06 m.

Table 1: Results of a TandT strategy in France

Versus current situation (2020–2030)	Rapid Start only (treatment on day 1 for all patients)	TandT: Rapid Start + increased screening targeted on individuals >55 y/o
<i>Main outcomes</i>		
Undiagnosed Reduction (2030)	13, 873	22, 608
Incident Cases Reduction	22, 124	22, 124
Treated Increase	-3, 958*	5, 602
<i>Avoided Complications</i>		
Decompensated Cirrhosis	736	1, 873
HCC	1, 513	3, 949
Liver Transplant	37	55
Liver-Related Deaths	851	1, 871
<i>Additional Costs (millions €)</i>		
Screening	-0.31	0.49
Treatment	111.18	348.57
<i>Avoided Costs</i>		
Complications	40.03	93.81
Indirect Costs	158.60	516.06

Conclusion: A TandT strategy would reduce both the epidemiological and economic burden of HCC in France by 2030.

PO-983

Concordance of SVR 4-12-24 timepoints in an era of reduced sustained virologic response (SVR) determination

Mark Sulkowski¹, Jordan Feld², Nancy S. Reau³, Liyun Ni⁴, Stacey Scherbakovsky⁵, Candido Hernández⁶, Kim Vanstraelen⁶, Kyle Hammond⁷, Bruce Kreter⁵, Vithika Suri⁸, Marc Bourliere^{9,10}, Alessandra Mangia¹¹. ¹Johns Hopkins University School of Medicine, Division of Infectious Diseases, Baltimore, United States; ²Toronto General Hospital, Toronto Centre for Liver Disease, University Health Network, Toronto, Canada; ³Rush University, Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Rush Medical College, Chicago, United States; ⁴Gilead Sciences, Biostatistics, Foster City, United States; ⁵Gilead Sciences, Global Medical Affairs, Foster City, United States; ⁶Gilead Sciences, Global Medical Affairs, Stockley Park, United Kingdom; ⁷Gilead Sciences, Medical Affairs, Foster City, United States; ⁸Gilead Sciences, Clinical Research, Foster City, United States; ⁹Hopital Saint Joseph, Hepato-Gastro-Enterologie, Marseilles, France; ¹⁰Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and; ¹¹Fondazione “Casa Sollievo della Sofferenza” IRCCS, San Giovanni Rotondo, Italy
Email: a.mangia@tin.it

Background and aims: Over the last 5 years the landscape of HCV treatment providers has evolved in response to the WHO call to action and simplified treatment algorithms. Non-specialist providers are seeing an increasing number of patients with mental health disorders, active injection drug use, and homelessness, many of whom have less severe liver disease. Often these patients are more difficult to engage, treat, and monitor, and more difficult to reach for confirmation of SVR. A high degree of concordance between SVR4, SVR12, and SVR24 helps validate the shift towards simplification, minimal monitoring, and acceptance of missing the traditional SVR12 timepoint. The most recent EASL guidance recognizes this shift with the statement that testing for SVR may be omitted in certain patients. Still, verifying effective cure reassures a health system that treating this vulnerable population is “worth” the effort.

Method: HCV RNA data from patients in the registrational ASTRAL-1, -2, and -3 clinical trials were evaluated. SVR was defined as patients

with HCV RNA less than the lower limit of quantification (15 IU/ml) at the aforementioned post-treatment visits, using the COBAS TaqMan HCV Test v2.0. Only patients with both SVR4 and SVR12 or SVR12 and SVR24 data were included in the concordance analysis.

Results: 1588 patients were evaluated in ASTRAL-1, -2, and -3. The overall SVR12 rate for all patients receiving 12 weeks of sofosbuvir/velpatasvir in ASTRAL 1–3 was 98% (n = 1015/1035; 13 relapses; 4 lost to follow-up; 1 discontinuation of drug; 1 withdrawal of consent; 1 death-unrelated). For the 13 relapses, 3 occurred between SVR4 and SVR12, while 10 occurred between treatment week 12 and SVR4. No relapses occurred between SVR12 and SVR24. Of the 1015 patients who had both SVR4 and SVR12 recorded, there was a 99.7% positive predictive value (PPV). For SVR12 and SVR24 concordance, the PPV was 100% for 993 patients. For both sets of concordance, the negative predictive value was 100%.

Conclusion: HCV treatment non-response with sofosbuvir/velpatasvir is infrequent and the absence of HCV RNA at SVR4 is highly predictive of HCV cure. This early time point to confirm HCV may be important when monitoring a vulnerable population at high risk to be lost to follow-up. These data support minimal monitoring of HCV treatment and follow-up, and the EASL guidance that testing for SVR can be omitted in certain patients without compromising the treatment paradigm.

PO-1007

A comprehensive HBsAg-positive patient centered screening strategy targeting microelimination of Hepatitis C virus in Chongqing, China

Dachuan Cai¹, Peng Hu¹, Dazhi Zhang¹, Hong Ren¹. ¹The Second Affiliated Hospital of Chongqing Medical University, Department for Infectious Diseases, Chongqing, China
Email: cqmucdc@cqmu.edu.cn

Background and aims: The exact prevalence of hepatitis B (HBV) and C viruses (HCV) coinfection is actually unknown. In regions where HBV is endemic, such as China with a HBsAg positive rate of 7.18%, the probability of coinfection increases due to a similar transmission route, especially in patients with high risk of HCV infection. The aim of the study was to explore the prevalence of HCV antibodies positive rate among HBsAg positive subjects, to investigate the HCV RNA positive rate in anti-HCV positive patients, and to evaluate HBV/HCV co-infection rate. All the patients with a positive HCV RNA have been informed about the possible sequelae of chronic HCV infection and available therapy in order to accelerate the micro-elimination of hepatitis C.

Method: 12, 500 HBsAg positive serum samples from the Second Affiliated Hospital of Chongqing Medical University between 2019.2–2020.1 have been collected. All samples were tested for anti-HCV. Furthermore, positive samples would be tested for HCV RNA. All patients with positive HCV RNA were followed up for suspicious transmission route of HCV and linkage to care. Chi-square accurate test and T-test were used for comparison.

Results: Forty four out of 10560 (0.4%) patients with positive HBsAg had detectable anti-HCV. There were 32 male (72.7%) and 12 females (27.3%), with statistical difference (p = 0.003). 17/44 (38.6%) were HCV RNA positive. 6/44 (13.6%) patients could not be contacted for investigation, suspected transmission routes of HCV for other 38 patients: surgical operation history [13/38 (34.2%)], intravenous drug use 10/38 [(26.3%), blood transfusion [8/38 (13.9%)], tooth extraction history [1/38 (2.6%)], paid blood donation [1/38 (2.6%)], hemodialysis [1/38 (2.6%)], sexual transmission [2/38 (5.3%)], dental treatment history [1/38 (2.6%)], others [11/38 (28.9%)]. Among 15 out of 38 patients with HCV RNA positive, 8 patients started anti-HCV treatment with DAA regimen, while the other 7 patients had not. The reason of not initiating treatment is 1 died, 4 for no awareness of the importance of anti-HCV treatment. After patient education, one patient started treatment and reached SVR12, 3 patients still refused anti-HCV treatment, 2 patients did not start HCV treatment for no

awareness of HCV infection, they agreed to start anti-HCV treatment after being informed of their condition and educated on prognosis of HCV infection and benefit of SVR.

Conclusion: HCV/HBV coinfection prevalence is lower compared with previous study result, and it is higher in male than female. Different from MTCT, HBV main transmission route, high risk behaviors in adults are the main transmission route of HCV in Chongqing, China, HBV and HCV didn't share the mutual transmission route, HBsAg positive population may not have high risk of HCV infection. It is possible to accelerate the micro-elimination of hepatitis C through patient education.

PO-1029

Acute hepatitis C virus infection: A prospective ten years observational study of HCV-mono- and HCV/HIV-coinfected patients

Christiana Graf¹, Lutz Thomas², Gaby Knecht², Christoph Stephan³, Peter Gute², Markus Bickel², Kai-Henrik Peiffer¹, Stefan Zeuzem¹, Julia Dietz¹, Christoph Sarrazin^{1,4}. ¹Goethe University Hospital, Department of Internal Medicine I, Frankfurt, Germany; ²Inferiologikum, Frankfurt, Germany; ³Goethe University Hospital, Department of Infectious Diseases, Frankfurt, Germany; ⁴St. Josefs-Hospital, Wiesbaden, Germany
Email: christiana.graf@kgu.de

Background and aims: Hepatitis C virus (HCV) infection has emerged as a sexually transmitted infection among human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) since several years in large urban centres worldwide. HIV coinfection is associated with lower rates of spontaneous clearance and HCV treatment response as well as with accelerated liver disease. This study evaluated epidemiological and clinical parameters of acute hepatitis C infection over time.

Method: This prospective, ongoing observational study has analysed clinical and epidemiological parameters of n = 161 patients with a proven acute HCV infection between 2009 and 2019, who were enrolled in three centres in Frankfurt. NS5B population-based sequencing was performed at the time of acute hepatitis C diagnosis (baseline) to re-evaluate the HCV genotype and for phylogenetic analyses.

Results: Overall, the majority of the patients were MSM (90%, 146/161) with a sexual HCV transmission route, of which n = 6 were HIV negative. In the remaining patients (n = 15/161), HCV transmission was attributable to infecting drug use, needle stick injuries or blood transfusions (non-MSM patients). In n = 155 patients with available baseline sequencing data, the prevalence of HCV genotypes was as follows: during the first five years of study, 80% (74/93) of the patients were infected with HCV GT1a, 4% each with GT1b or GT3a (4/93), 2% with GT2 (2/93) and 10% (9/93) had GT4d. However, in the last five years of study, HCV GT1a was detected in 74% (46/62) of patients, GT1b or GT3a in 1.5% of patients each and GT4d infection in 23% (14/62) of patients. Interestingly, MSM were mainly infected with HCV GT1a (82%, 115/140) or GT4d (16%, 23/140 with sequencing data available). In contrast, HCV genotypes were almost equally distributed in non-MSM patients. 42% (5/14 with sequencing data) were infected with HCV GT1a, 21% each (3/14) with GT1b or GT3a and 16% had GT2. Based on the comparison of HCV GT or NS5B sequences, 24 (15%) were diagnosed with a HCV reinfection, of which 14 patients had a genotype switch. The median time to reinfection was 3.2 years (range 0.6–10.3) and the overall HCV reinfection incidence rate was 2.2 per 100 person-years (PY). The incidence rate in MSM for a reinfection and for a first HCV infection declined in the period between 2017 and 2019 (1.2/100PY and 3.76/1000 PY) compared the DAA era between 2013 and 2016 (1.8/100 PY and 6.39/1000 PY) and to the interferon era (2008–2012; 1.6/100 PY and 6.5/1000 PY).

Conclusion: During the last 5 study years the prevalence of GT4 infections increased, while annual acute hepatitis C incidences decreased. Incidence of reinfections remains a frequent finding

among MSM in Germany, which may have implications for HCV elimination in MSM.

PO-1186

Detection of active hepatitis C by two-step point-of-care based strategy and linkage to care among excluded people using a mobile unit in Madrid, Spain

Pablo Ryan^{1,2,3}, Jorge Valencia¹, Guillermo Cuevas¹, Juan Torres^{1,2}, Jesús Troya¹, Jeffrey Lazarus⁴, Maria Jose Muñoz-Gomez⁵, Sonia Vázquez-Morón⁵, Salvador Resino-García⁵. ¹Hospital Universitario Infanta Leonor, Madrid, Spain; ²Complutense University of Madrid, Madrid, Spain; ³Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain; ⁴Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain; ⁵Instituto de Salud Carlos III, Majadahonda, Spain
Email: pabloryan@gmail.com

Background and aims: There is a considerable burden of hepatitis C virus (HCV) infection among people with social excluded, marginalized populations. We aimed to assess the effectiveness of a point-of-care (PoC) simplified model for screening of active HCV infection and its linkage to care among excluded people.

Methods: We carried out a prospective study in 2001 participants from Madrid, Spain. With a nurse and an educator, a mobile unit was used to screen active hepatitis C by a two-step PoC-based strategy (rapid HCV antibody test and an HCV RNA test for confirmation). Participants with active HCV were referred to the hospital the same day to evaluate and treat HCV with a navigator.

Results: Overall, 1621 (81%) participants were unexposed to HCV, 380 (18.9%) were positive for HCV antibodies, and 136 (6.8%) had active hepatitis C. Among the latter, 134 (98.5%) received the HCV screening results, 133 (97.8%) had an appointment at the hospital, 126 (92.8%) were attended at the hospital, and 105 (77.2%) started HCV treatment. People over 50 years and drug users, particularly people who inject drugs (PWID), were directly associated with active hepatitis C (p < 0.005). PWID were the only ones with HCV reinfections (4.3% in inactive PWID and 5.9% in active PWID). Furthermore, both having no economic resources and alcohol intake were also directly associated with active hepatitis C among PWID. Active PWID showed the lowest rates of attention in the hospital (91.8%) and those who started HCV treatment (70.4%).

Conclusion: HCV screening using a two-step PoC-based strategy and its linkage to care had excellent efficiency in identifying and treating excluded people with active hepatitis C. New approaches are needed to enhance rates of initiation of HCV treatment among PWID, particularly those who have problematic alcohol intake and who reported no economic resources.

PO-1339

Impact of the COVID-19 pandemic on hepatitis C virus screening in drug treatment settings in England and implications for testing protocols

Shayon Salehi¹, Tracey Kemp², Helen Hampton³, Stacey Smith⁴, Peter Smethurst⁵. ¹Gilead Sciences Ltd, Medical Affairs, London, United Kingdom; ²C G L Change Grow Live, United Kingdom; ³We Are With You, United Kingdom; ⁴Humankind, United Kingdom; ⁵Gilead Sciences Ltd, Patient Access to Care, United Kingdom
Email: shayon.salehi@gilead.com

Background and aims: Individuals who have ever injected drugs are at risk of hepatitis C virus (HCV) infection and subsequent liver disease. Protocols developed by drug treatment services (DTS) allow at-risk individuals to be tested and linked to appropriate care. This analysis assessed the impact of the COVID-19 pandemic on HCV testing in DTS.

Method: The number of HCV tests conducted across three DTS providers in England was recorded (August 2019 and through October 2020).

POSTER PRESENTATIONS

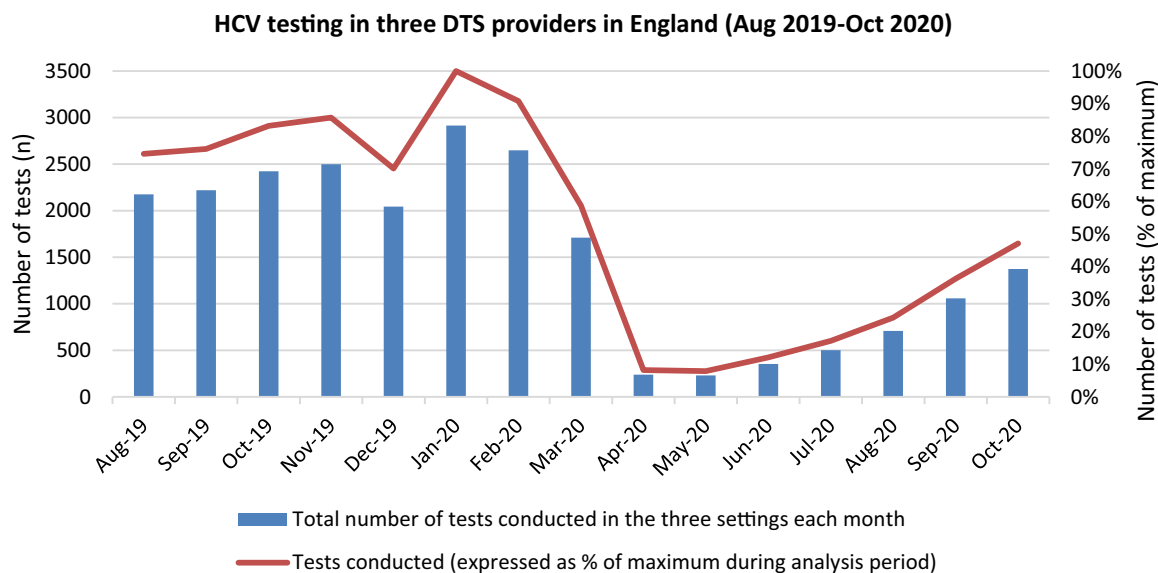


Figure: (abstract: PO-1339)

Results: During the period assessed, over 82,000 individuals accessed the services supported by the three providers. Of individuals accessing the service, 27–32% had a history of injecting drug use and 14.5–17% were current injectors. In the 7 months before the COVID-19 pandemic, the mean number of HCV tests conducted each month was 2418 (range: 2044–2915). A >88% reduction in HCV tests was observed (April–June 2020) following introduction of the U.K. COVID-19 restrictions in March 2020. By October 2020, the number of HCV tests/month had increased to 50% of the maximum pre-pandemic level following the adaptation of testing services including introducing postal tests.

Conclusion: Restrictions introduced in England to control the COVID-19 pandemic had a substantial negative impact on HCV testing. Rapid adaptation of services has increased the proportion of service users accessing tests, but more needs to be done to ensure those who need a test receives one. Continued adaptations should limit the impact future restrictions could have on HCV testing in this population.

PO-1397

Community-based linkage to care program targeting HCV elimination-Establishment of a model towards HCV elimination in China

Ming Li¹, Jingzhi Li², Xiaojuan Shang¹, Zhu Liu², Kefeng Xin¹, Ping Liu², Kewei Wang², Feng Wang², Mei Wang², Hui Zhao², Jingjing Yu². ¹No.2 People's Hospital of Fuyang City, The Second Infectious Department, Fuyang, China; ²Jingjiu Chengzhuang Community Health Center, Community Health Center, Fuyang, China
Email: 758529109@qq.com

Background and aims: Direct-Antiviral-Agents (DAAs) have been covered by Chinese Medical Insurance system currently. The barrier to eliminate Hepatitis C in China is to find out HCV patients and link to care. But for community doctors in rural areas and other under-developed places are hard to screen and treat HCV patients due to lacking of knowledge. An effective model is needed to screen, manage and follow-up with these populations.

Method: This program leads by Infectious doctors from No.2 people's hospital of Fuyang city and Community doctors from 6 communities of Jingjiu chengzhuang, from 2019 Jan, has been designed into 4 steps. First, infectious doctors provide education and online guidance for community doctors. Second, the residents be activated through materials advertisements, media, and community health classes which are conducted by community doctors in each community.

Those activities have been started earlier before screen and are continuing. Third, people be screened in communities and those with anti-HCV positive would be delivered to fixed doctors of No.2 people's hospital of Fuyang for further diagnose and treatment. Fourth, HCV patients on treatment or not both be followed up by community doctors. We planned to screen residents with age over 40 years old or with high risk (HCV family history, high risk behaviors) first, whom are from more than 40,000 rural and city communities' residents.

Results: by Jan 12th, 2020, 2679 residents had been screened. Age and gender information of 1851 had been collected. The mean age was 50 years old, 40% were male. 164/2679 (6.1%) subjects were seropositive for anti-HCV. 89/164 (54.3%) subjects detected HCV RNA, of which 67 subjects obtained HCV RNA detection through program team and 22 subjects obtained RNA detection by themselves. The HCV RNA positive rate was 42/89 (47.2%), of whom 40/42 (95.2%) patients initiated treatment. HCV GT1b was the most prevalent genotype (73.8%), followed by HCV GT2 (21.4%). 16.7% patients were diagnosed with cirrhosis. Up to now, 30 patients completed treatment, the SVR12 was 100% for those whom finished follow-up. The model with reinforced connection (Doctors education be held bi-monthly and team discussion be held monthly) between communities' doctors and fixed infectious doctors, to educate, screen and follow-up patients just in community which made none of the patients lost.

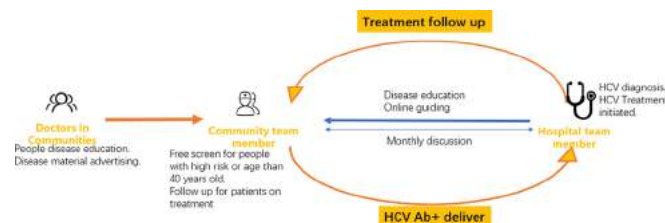


Figure:

Conclusion: It is the first large scale program to find out HCV patients and link to care in China mainland. It makes sense to screen patients with high risk. Community based program through reinforcing the connection of infectious doctors and community doctors improved screen rate and made most of those HCV patients linked to care, which is highly effective and necessary to large-scale applied towards HCV elimination in China.

PO-1691

Feasibility and effectiveness of models of hepatitis C viraemia testing at harm reduction sites in Georgia: a prospective 3 arm study

Sonjelle Shilton¹, Jessica Markby¹, Maia Japaridze^{2,3}, Violet Chihota¹, Shaun Shadaker⁴, Lia Gvinjilia⁵, Maia Tsereteli⁶, Maia Alkhazashvili⁶, Maia Butsashvili⁷, Ketevan Stvilia⁶, Alexander Asatiani⁶, Ekaterine Adamia⁸, Philippa Easterbrook⁹, Irma Khonelidze⁶, Amiran Gamkrelidze⁶. ¹Foundation for Innovative New Diagnostics; ²Foundation for Innovative New Diagnostics, HCV, Tbilisi, Georgia; ³Foundation for Innovative New Diagnostics, HCV, Tbilisi, Georgia; ⁴Centers for Disease Control and Prevention, Division of Viral Hepatitis National Center for HIV, Hepatitis, STD and TB Prevention; ⁵Task Force for Global Health; ⁶National Center for Disease Control and Public Health, Georgia; ⁷Health Research Union, Georgia; ⁸Ministry of Health, Labour and Social Affairs of Georgia, Georgia; ⁹Department of Global HIV, Hepatitis and STI Programmes, World Health Organization
Email: lgi1@cdc.gov

Background and aims: In 2015, Georgia began a hepatitis C virus (HCV) elimination programme. Although screening programmes have largely been decentralised for high-risk groups, viraemia testing remains a limiting factor for people who inject drugs (PWID). As part of HEAD-Start (Hepatitis C Elimination through Access to Diagnostics) Georgia, Foundation for Innovative New Diagnostics (FIND) in partnership with Georgia's National Centers for Disease Control and Public Health conducted a cluster, non-randomized interventional study to describe two models of viraemia testing that aim to address this gap and compare them to the current standard of care (SOC).

Method: We assigned 8 harm reduction sites (HRS) to one of three arms. Arm 1: GeneXpert HCV viral load on-site testing, Arm 2: centralised viraemia testing with HCV core antigen (centralised HCVcAg), or Arm 3: SOC with all anti-HCV positive referred to treatment centres for HCV RNA testing.

Results: Between May 2018 and September 2019, 1671 HCV-seropositive participants were enrolled (Arm 1, 620; Arm 2, 486; Arm 3, 565). Participants were predominantly male (95.4%), with a median age of 43 years (interquartile range [IQR]): 37, 50), and 1290 (77.2%) were currently injecting drugs. Significantly higher proportions of participants in Arms 1 (100.0%) and 2 (99.8%) had viraemia testing performed compared with Arm 3 (91.3%) (Arm 1 vs Arm 3; P < 0.001, Arm 2 vs Arm 3; P < 0.001) (Figure). Among viraemic participants, treatment uptake was similar across all arms (Arm 1, 84.0%; Arm 2, 79.5%; Arm 3, 88.4%). The time between screening and sample collection for viraemia testing was significantly longer in Arm 3 (median 1 [0, 4] days) compared with both Arm 1 (p < 0.001) and Arm 2 (p < 0.001) (median 0 [0, 0] days for both), and the overall time between screening to treatment initiation was longer for Arm 3 (67 [45, 94] days) compared with Arm 1 (57 [39, 87] days; P < 0.001) and Arm 2 (50 [38, 80] days; P < 0.001).

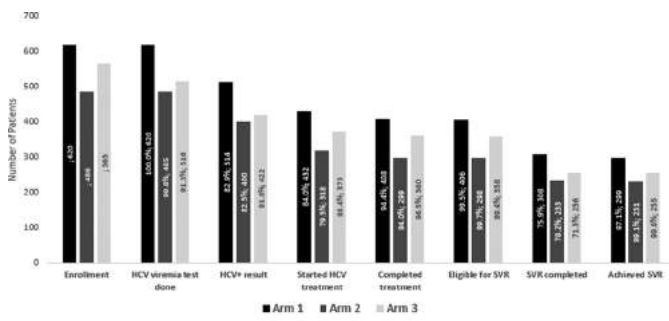


Figure: Retention of patients in the hepatitis C care cascade by study arm. Abbreviations: HCV = hepatitis C virus; SVR = sustained virologic response

Conclusion: Point-of-care viraemia testing and blood drawn on-site for HCVcAg testing resulted in more HCV seropositive patients receiving viraemic testing within a shorter timeframe compared with referral for blood collection using SOC. However, proportions of viraemic patients who were referred to treatment centres and subsequently initiated treatment were similar across all arms. These findings underscore the benefits of fully decentralised HCV care.

PO-1871

Screening, enhancement of access to care and prioritization of treatment of chronic hepatitis C infection in high-risk population in Hong Kong

Lung Yi Loey Mak^{1,2}, Cynthia Hui¹, Wai Man Vivien Tsui¹, Wai Pan To¹, KL Ko¹, Siu Yin Wong¹, Kevin Liu¹, Wai-Kay Seto^{1,2}, Man-Fung Yuen^{1,2}. ¹The University of Hong Kong, Medicine, Hong Kong, China; ²State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong, China
Email: loeymak@gmail.com

Background and aims: In the current era of highly effective direct acting antiviral (DAA) therapy, the one of the remaining obstacles to elimination of chronic HCV infection (CHC) is identification of high-risk groups for micro-elimination. In Hong Kong, people who inject drugs (PWIDs) are one of the targets. We aimed to provide linkage to care (LTC) for PWIDs with CHC who are undergoing drug rehabilitation.

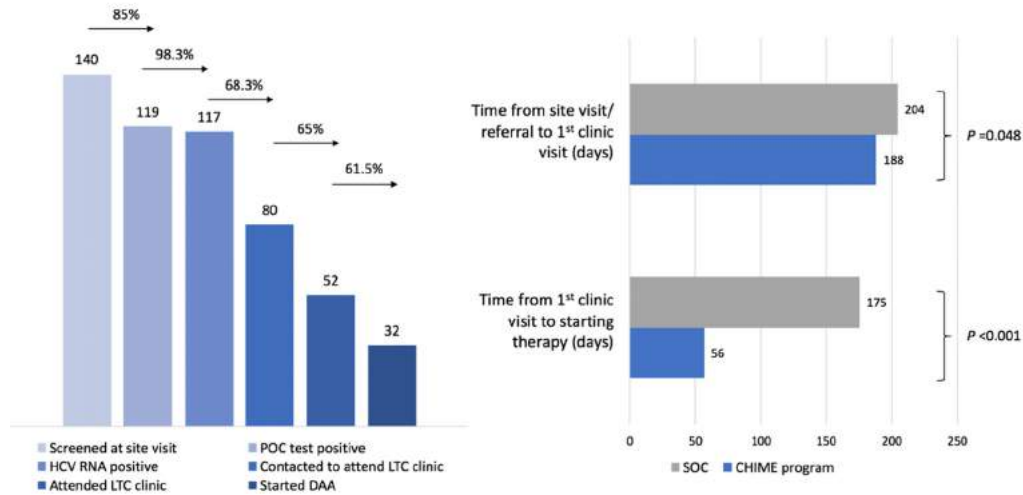
Method: Since late 2019, we initiated the Conquering Hepatitis v/a Micro-Elimination (CHIME) program and performed a prospective study by forming an outreach team to conduct site visits to halfway house or drug rehabilitation centers run by non-governmental organizations. We performed point-of-care (POC) test for antibody to HCV (anti-HCV), and blood takings were performed for subjects with positive POC results to check for HCV RNA. Subjects with confirmed active CHC were contacted to attend the LTC clinic for counselling, risk stratification and evaluation for DAA.

Results: In this interim analysis, 9 site visits were conducted and 140 PWIDs were screened which identified 117 subjects with CHC (83.6% HCV RNA positive) and 52 already attended the LTC clinic (Figure 1A). Compared to subjects who received standard-of-care (non-CHIME, n = 275, 10.5% PWIDs), PWIDs under the CHIME program were younger (median 61 vs 52, p < 0.001), with more male (56.4% vs 3.8%, p < 0.001), lower chance to expose to previous CHC treatment (16.4% vs 3.8%, p0.017), higher RNA viral load (1.2×10^6 vs 2.4×10^7 IU/ml, p = 0.006) and lower liver stiffness (11 vs 7.2 kPa, p < 0.001). CHIME patients had predominantly genotype 6 (63.5%) infection, with non-significantly higher prevalence of hepatitis B coinfection [7.8% vs 2.9% (non-CHIME patients), p = 0.1]. The time from site visit to first LTC visit and to starting treatment were shorter for CHIME patients compared to non-CHIME patients (Figure 1A). The rates of sustained virological response (SVR) were 90.6% and 95.3 respectively (p = 0.226). No significant differences in SVR were observed between different genotypes or PWIDs vs non-PWIDs. The treatment uptake rate was affected by COVID-19 (Figure 1B).

Conclusion: Micro-elimination is an effective strategy to identify subjects with CHC in places like Hong Kong where the overall prevalence of CHC in background population is low. The CHIME program successfully allowed PWIDs with CHC to be linked to care with significant shortening of waiting time and no compromise to treatment outcome.

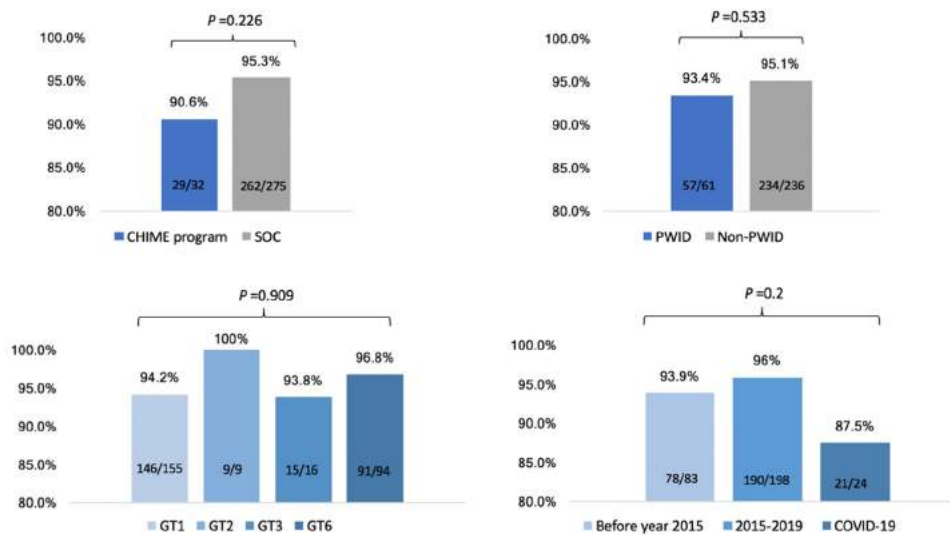
POSTER PRESENTATIONS

Figure 1A: left panel: number of subjects at each step of CHIME program; right panel: number of days required between site visit or referral to 1st clinic visit, and number of days from 1st clinic visit to starting therapy



DAA: direct acting antiviral agents, LTC: Linkage-To-Care, POC: point-of-care, SOC: standard of care

Figure 1B: Rates of sustained virological response in different subgroups



GT: genotype, PWID: people who inject drugs, SOC: standard of care

Figure: (abstract: PO-1871)

PO-1966

Hepatitis C Elimination in the Netherlands (CELINE): nationwide retrieval of lost to follow-up chronic hepatitis C patients

Marleen van Dijk¹, Cas J. Isfordink^{2,3}, Sylvia Brakenhoff⁴, Johannes E. Arends⁵, Robert De Knecht⁴, Marc van der Valk³, Joost Ph Drenth¹. ¹Radboudumc, Gastroenterology and Hepatology, Nijmegen, Netherlands; ²University Medical Centre Utrecht, Gastroenterology and Hepatology, Utrecht, Netherlands; ³Amsterdam

Infection and Immunity Institute, Amsterdam University Medical Centre, Internal Medicine, Division of Infectious Diseases, Amsterdam, Netherlands; ⁴Erasmus Medical Centre, Gastroenterology and Hepatology, Rotterdam, Netherlands; ⁵University Medical Centre Utrecht, Infectious Diseases, Utrecht, Netherlands
Email: marleen.vandijk@radboudumc.nl

Background and aims: Hepatitis C virus (HCV) prevalence in the Netherlands is estimated at 0.16%. Presumably, up to 30% of the diagnosed population has been lost to follow-up (LTFU) before being cured. Retrieval of LTFU patients has the potential to reduce the impact of the HCV epidemic. Therefore we initiated the nationwide

retrieval project CELINE, aiming to achieve HCV micro-elimination in previously diagnosed but LTFU HCV patients.

Method: LTFU patients were identified by consulting laboratory and patient records of up to 15 years old in hepatitis treatment centres and, when possible, public health or primary care laboratories and other hospitals. Subsequently, the Municipal Personal Records database was consulted to identify patients eligible for retrieval, defined as being alive and having a known Dutch residence. These patients were invited for a screening visit at their local hepatitis treatment centre. Primary end point was the number of LTFU patients successfully re-linked to care.

Results: So far, 29 centres have finished the identification phase and initiated the retrieval phase, whereas in a further 10 centres CELINE has been approved. Of 15, 558 potential ever chronically infected patients, 65% had already been cured or were still in care and only 8% (n = 1, 248) were LTFU and eligible for retrieval. Currently, 942 patients have been invited for re-evaluation: 24% of these had already been successfully treated elsewhere, 5% had either severe comorbidity, moved abroad or were deceased precluding treatment, 8% refused to be re-evaluated and in 45% contact has not (yet) been established. So far, 160 patients (17%) have been screened or have an outpatient care appointment scheduled. At their screening visit, patients were mostly male (69%), median 58 years old, LTFU for median 7 years (IQR 4–11) and intravenous drug use was the predominant HCV transmission route (68%). At re-evaluation, 86% tested HCV RNA positive and none HIV positive. Of those HCV RNA positive, 30% had a Fibroscan measurement indicating advanced fibrosis or cirrhosis (≥ 9.5 kPa). So far, 79% of RNA-positive retrieved patients have commenced HCV treatment.

Conclusion: The majority of ever diagnosed HCV patients in the Netherlands has already been cured, while only 8% is LTFU and eligible for retrieval. So far, we have re-linked 160 patients (17%) to care, with 30% of HCV RNA positive patients showing signs of at least advanced fibrosis. This demonstrates that retrieval of LTFU HCV patients is feasible and worthwhile.

PO-2048

Rapid point of care HCV testing allows high throughput HCV screening and rapid treatment uptake among PWID attending a medically supervised injecting room

Michael MacIsaac^{1,2}, Bradley Whitton¹, Jenine Anderson³, Shelley Cogger³, Kasey Elmore³, David Pemberton³, Matthew Penn³, Jacinta Holmes^{1,2}, Nico Clark⁴, Alexander Thompson^{1,2}, ¹St Vincent's Hospital Melbourne, Gastroenterology, Fitzroy, Australia; ²University of Melbourne, Department of medicine, Parkville, Australia; ³North Richmond Community Health, Richmond, Australia; ⁴North Richmond Community Health, Richmond, Australia
Email: michael.macisaac@svha.org.au

Background and aims: In order to achieve the WHO HCV elimination targets, efforts must focus on developing novel models of care that engage people who inject drugs (PWID) in HCV screening and treatment. We aimed to assess the feasibility of a new model of care incorporating the Xpert[®] HCV fingerstick point of care (POC) test, which provides a HCV RNA result within 1 hour, in PWID attending a medically supervised injecting room (MSIR) in Melbourne, Australia.

Method: This was a prospective cohort study, recruiting PWID attending a high volume (>100 client visits/day) MSIR across a 9-week period (November 2020–January 2021). Clients were offered HCV screening using the rapid Xpert[®] fingerstick POC test, as well as venepuncture for HBV/HIV screening, and liver elastography for fibrosis assessment. HCV RNA results were returned the same day if clients were still present at the MSIR, or via phone or at their next MSIR visit if they had departed. HCV treatment was prescribed immediately upon return of a positive HCV test, and medication was dispensed within 30 minutes and couriered to the MSIR. Clients commencing treatment will be followed up 4 weekly during treatment, and at SVR12. Primary end points are i) number of

clients screened; ii) number of clients commenced on DAAs. Testing rates were compared to a historical control period of standard of care venepuncture testing led by a blood-borne virus nurse.

Results: 228 PWID consented to HCV screening with the Xpert[®] POC test, averaging >25/week. By comparison, 61 clients were screened using standard of care venepuncture testing during the same time period 12-months prior (274% increase with POC testing). Fingerstick testing was well received by participants and was preferred to venepuncture testing. Median age was 43 yrs (IQR 38–48), 78% were male. 9 (4%) had cirrhosis. HBV and HIV co-infection rates were 2% and 3%, respectively. 64 (28%) returned a positive HCV RNA result; 60 (94%) were informed of their positive result, with most (67%) receiving their result on the same day. 56/64 (88%) of HCV RNA positive clients commenced DAA therapy; 13 (23%) started treatment on the same day as POC testing. Median time to treatment initiation was 1 day (IQR 0.5–10). 31/35 clients who have reached the 4th week of treatment have remained engaged in care. Further treatment outcomes will be presented at the ILC.

Conclusion: Supervised injecting rooms service a high volume of marginalised clients with risk factors for HCV. Our streamlined, real world model of care using fingerstick POC testing rapidly engages large numbers of PWID in HCV screening. Further, almost all HCV RNA positive clients were successfully linked to treatment. Novel fingerstick POC testing in high prevalence settings is likely to play a critical role in achieving WHO elimination targets.

PO-2095

Is elimination of hepatitis C across an entire prison network possible? A nurse-led test and treat model in 47 English prisons

Hannah Alexander¹, Andrew Jones², Kate Dorrington³, Andrew Milner³, Sean Cox⁴, Rob Cheetham¹, Phil Troke³, Iain Brew¹.
¹Practice Plus Group, Health and Rehabilitation Services, Reading, United Kingdom; ²Gilead Sciences Ltd, Medical Affairs, London, United Kingdom; ³Gilead Sciences Ltd, London, United Kingdom; ⁴Hepatitis C Trust, London, United Kingdom
Email: andy.jones@gilead.com

Background and aims: With a prevalence of approximately 6% in male, and 12% in female prisons, secure environments are a critical part of the plan to eliminate HCV in England by 2025. In October 2014 a national prison policy for blood-borne viruses (BBV) opt-out testing upon entry was implemented, but despite this, testing rates remained low until the end of 2018.

Method: Practice Plus Group (PPG) is the provider of healthcare to 47 English prisons with approximately 30,000 residents. In 2019, PPG partnered with the Hepatitis C Trust (HCT) and Gilead Sciences with the aim of increasing BBV screening, linkage to care and achieving elimination of HCV across their entire network. Each prison faces unique challenges to creating an effective pathway, such as the prison's size, age/design, security level and duration of residents' stay. For this reason, each prison needs to be supported to adapt a pathway to suit their needs. PPG Regional BBV Lead Nurses, and Gilead medical colleagues, are leading multi-stakeholder pathway optimisation workshops to identify local issues, create individualised pathways and drive service improvements. Most prisons have also transitioned to point-of-care antibody testing to increase uptake. We have developed an accredited training course for healthcare staff, whilst HCT Peers with a personal experience of HCV are engaging in all prisons to educate and reduce stigma amongst prisoners and prison officers.

Results: As a result of staff and resident education, modified testing methods and improved pathways, the HCV screening rate upon prison entry increased 2.2-fold in 12 months from 25% in December 2018 to 56% by December 2019. COVID-19 significantly impacted pathways from March 2020, but testing continued to improve to 62% in December 2020. Despite the impact of COVID-19 lockdowns on all English prisons, regular adaptation of pathways meant that new

POSTER PRESENTATIONS

admissions continued to be tested and treated throughout the entire of 2020.

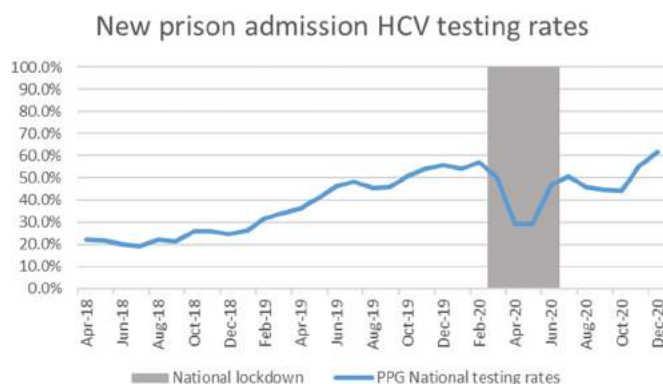


Figure:

Conclusion: BBV care pathways individualised for each prison, in combination with education and the use of Peers, has proven to be successful in doubling the testing of new receptions for HCV. The key to success has been the role of dedicated Regional BBV Lead Nurses in driving the improvements through the on-site prison healthcare staff.

PO-2193

Evaluation of hepatitis C virus (HCV) core antigen assay from venepuncture compared to HCV RNA in plasma: a cohort study from Pakistan

Saeed Sadiq Hamid¹, Adeel Abid¹, Muraduddin Gulab¹, Sultan Sallahuddin¹, Safia Awan¹, Gavin Cloherty². ¹Aga Khan University, Medicine, Karachi, Pakistan; ²Abbott Laboratories, Abbott Park, United States

Email: saeed.hamid@aku.edu

Background and aims: Diagnosis of Hepatitis C virus (HCV) infection can be a challenge due to cost and lack of access to centralized testing. There is an urgent need to use simple and affordable HCV testing methods. The aim of this study was to evaluate the sensitivity and specificity of Hepatitis C core antigen (HCVcAg) assay in a resource-limited setting.

Method: This was an observational cohort study of people living in an underdeveloped union council of a highly endemic, peri-urban district of Karachi, Pakistan. Between October 2019 and July 2020, subjects aged 12 years and above who screened positive for HCV antibody underwent a phlebotomy procedure. 10 ml of venous blood was taken for both HCV RNA testing (GeneXpert® IV, Cepheid, France) and HCV core antigen testing (Abbott® Diagnostics) to confirm active HCV infection. Abbott ARCHITECT®-i2000R Immunoassay Analyser was set up in a local hospital as a point-of-care facility for HCVcAg testing while samples for HCV RNA testing were transported 40 km to a central lab. Sensitivity and specificity of the HCVcAg assay (≥ 10 fmol/L) was evaluated at three different thresholds of HCV RNA, including ≥ 12 , ≥ 1000 IU/ml and ≥ 3000 IU/ml. Kappa (κ) statistic was calculated as a quantitative measure of agreement between the two diagnostic tests.

Results: 200 individuals (mean age 46 ± 14 years, 71% females) who screened positive for HCV antibody were included in the study. HCV RNA was detected in 119 (59.5%) participants. Sensitivity and specificity of HCVcAg in plasma at different thresholds of HCV RNA was very high (Table 1). Similarly, there was a strong agreement between HCV core antigen assay (≥ 10 fmol/L) with HCV RNA, resulting in κ values of 0.88, 0.93 and 0.96 for HCV RNA thresholds of ≥ 12 IU/ml, ≥ 1000 IU/ml and ≥ 3000 IU/ml respectively.

Table: Sensitivity and specificity of HCVcAg (≥ 10 fmol/L) compared to different HCV RNA thresholds.

	Detected	Undetected	Sensitivity (95% CI)	Specificity (95% CI)
HCV RNA Plasma (≥ 12 IU/ml)				
Detected	118	10	99.1% (95%–100%)	87.6% (78.4%–94%)
Undetected	1	71		
HCV RNA Plasma (≥ 1000 IU/ml)				
Detected	118	5	99.1% (95%–100%)	93.8% (86%–98%)
Undetected	1	76		
HCV RNA Plasma (≥ 3000 IU/ml)				
Detected	118	2	99.1% (95%–100%)	97.5% (91%–100%)
Undetected	1	79		

Conclusion: Sensitivity and specificity of HCVcAg assay came out to be very high in a highly endemic, resource-limited setting. The cheaper HCVcAg assay can therefore be as a confirmatory test in HCV elimination programs particularly for low-income countries.

PO-2218

Cost-effectiveness of a novel point of care core antigen rapid diagnostic test for hepatitis C

Madeline Adee¹, Huaiyang Zhong^{1,2}, Elena Ivanova³, Yueran Zhuo^{1,2,4}, Jagpreet Chhatwal^{1,2}, Sonjelle Shilton³. ¹Massachusetts General Hospital Institute for Technology Assessment; ²Harvard Medical School; ³Foundation for Innovative New Diagnostics; ⁴Mississippi State University College of Business

Email: madee@mgh.harvard.edu

Background and aims: Globally, fewer than 20% of the 71 million people living with hepatitis C virus (HCV) are aware of their status. Rapid diagnostic tests (RDT) at the point of care (POC) provide an opportunity to improve diagnosis rates by minimizing loss to follow-up and linking HCV positive individuals to treatment. An RDT that detects HCV core antigen (cAg) could be cheaper but also could have lower sensitivity compared to the molecular tests currently available. Our objective was to evaluate the performance and cost-effectiveness of using POC cAg RDT for HCV confirmation testing compared to lab-based RNA under different settings.

Method: We adapted a previously validated microsimulation model of the natural history of HCV to compare the outcomes of two HCV testing algorithms: (1) POC cAg RDT for confirmation (using a base-case sensitivity of 80%), followed by lab-based RNA confirmation for those with negative cAg tests, and (2) current standard of care algorithm with lab-based RNA confirmation only. Confirmed cases were treated with direct-acting antivirals after accounting for lost to follow-up in each algorithm. We simulated outcomes for 10,000 adults in Georgia and Malaysia, with an HCV prevalence of 5.4% and 1.5% respectively. The baseline characteristics of HCV patients in each country were determined based on different distributions of sex, HCV genotype, and METAVIR fibrosis stage. All costs were considered from a healthcare payers perspective.

Results: For Georgia, the diagnosis rate with the POC cAg algorithm was 95.4% vs 78.8% with the current standard. For Malaysia, the corresponding rates were 91.2% and 57.9%. Compared with the standard of care, the testing algorithm with POC cAg confirmation testing increased QALYs (207 for Georgia and 146 for Malaysia) and resulted in cost savings (\$232,000 for Georgia and \$504,000 for Malaysia) per 10,000 simulated people. POC cAg remained cost-saving over the wide range of values of model inputs. We also found that cost-savings begin to accrue for both countries after just the first year of treatment and continue to increase until eventually plateauing after 40 years. The majority of cost-savings come from averted HCV sequelae costs although testing costs are also saved (Figure).

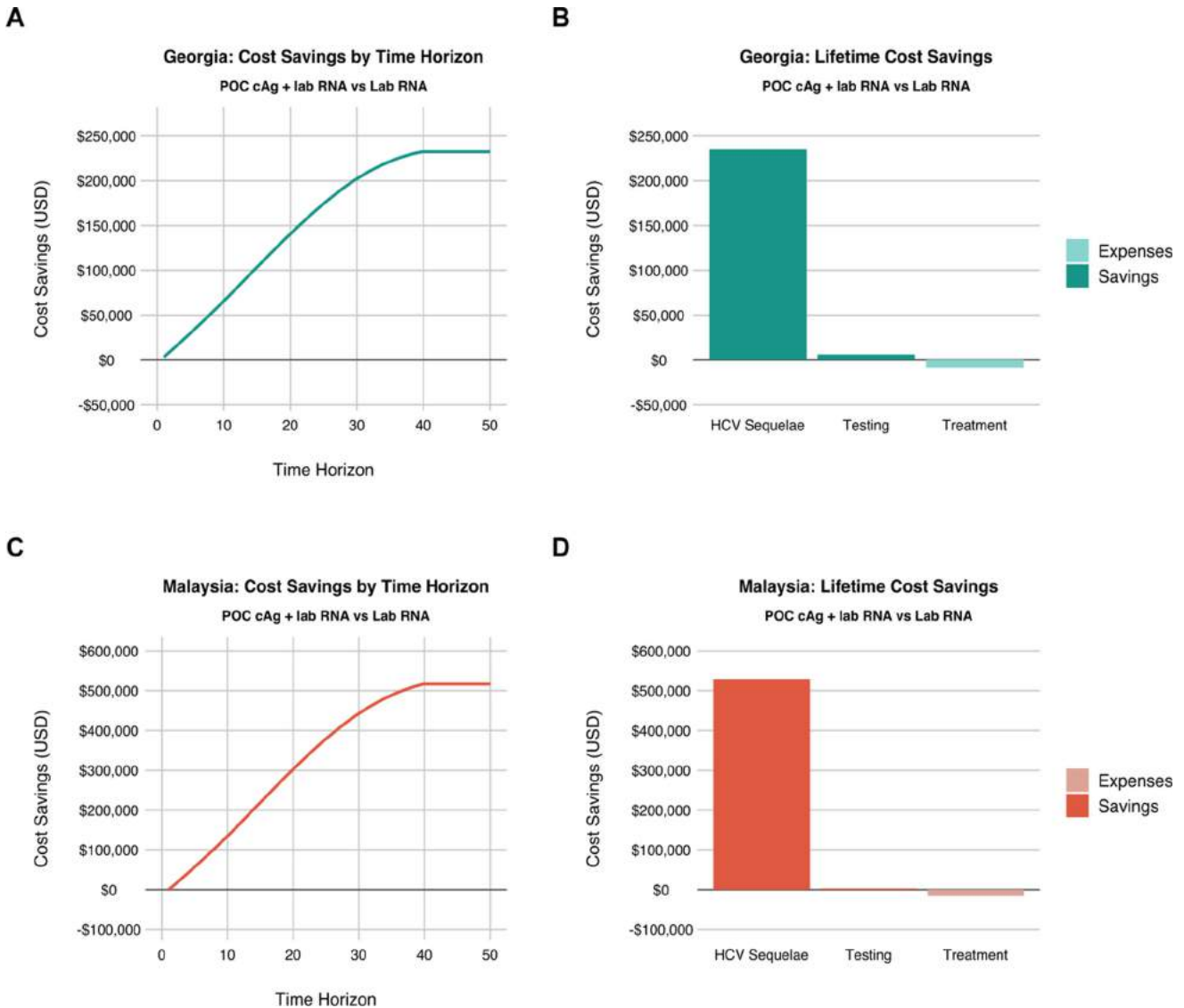


Figure: (abstract: PO-2218)

Conclusion: HCV testing with cAg RDT, which allows the majority of HCV-infected individuals to initiate treatment the same day as testing, could increase HCV diagnosis rate and result in cost savings.

PO-2352
Beating Hepatitis C together in challenging times: an evaluation of a multi-disciplinary approach to testing and treating homeless people temporarily housed during the COVID-19 pandemic

Rebecca Wilkinson¹, Elizabeth Nother², Tracey Stirrup², Mark Aldersley². ¹University of Southampton, School of Primary Care, Population Sciences and Medical Education, Southampton, United Kingdom; ²Leeds Teaching Hospitals NHS Trust, Hepatology, Leeds, United Kingdom

Email: markaldersley@nhs.net

Background and aims: Homeless people are at particularly high risk of hepatitis C virus (HCV); a recent survey of people who inject drugs found that prevalence of chronic HCV was twice as high (35%) in those who reported homelessness in the previous year. The COVID-19 pandemic resulted in severe disruption to HCV testing and treating in the UK but the provision of temporary accommodation to rough sleepers provided a unique opportunity for HCV care providers and

partners to engage with this vulnerable group at a time when they were potentially more stable. This evaluation aims to establish the impact of one such multi-disciplinary intervention in Leeds, where outreach work was done in hotels, hostels and on the street using a healthcare bus. A further aim is to establish the enablers and barriers to successfully HCV outreach work with the housed homeless in order to inform future service delivery.

Method: Following the UK wide lockdown, resulting in a reduction of face to face clinics, HCV care providers in Leeds decided to work together and take testing and treatment directly to homeless clients being temporarily housed. The Hepatitis C Trust peer support workers performed some of the antibody testing and incentives were provided, ranging from £5 shop vouchers, to drinks, sweets and care packages. To evaluate this intervention, a mixed methods approach was used which combined descriptive analysis of routinely collected data with qualitative information from the HCV care providers.

Results: Between May-September 2020, 78 people (including 41 who were previously unknown to the HCV service) were tested either during street outreach or at four venues that were housing homeless people in Leeds. Of these, 21 (26.9%) were found to have chronic HCV infection. All were offered and subsequently started on treatment. At

POSTER PRESENTATIONS

the time of analysis, 18 (85.7% of those starting) had completed treatment and 5 (23.8%) had confirmed SVR.



Figure: Hepatitis C testing at a hotel in Leeds housing homeless people.

Working with partners was found to facilitate access to this population group and also enabled a person-centered approach. The use of peers to maintain engagement with treatment was considered vital. Taking the service directly to the clients via the bus and offering immediate RNA testing were further facilitators.

Conclusion: Working together in a multi-disciplinary team has enabled progress towards HCV elimination by facilitating engagement with a particularly high-risk group at a time when services generally were severely disrupted.

PO-2359

Hepatitis B and C screening in hospitalized SARS-CoV-2 patients

Judith Gómez-Camarero¹, Raisa Quiñones², Rosa Sáiz Chumillas¹, Laura Alcoba Vega², Esther Badia-Aranda¹, Sandra Díez Ruiz², Noemi Gómez-Manero³, Raquel Vinuesa¹, Francisco Jorquera².

¹Hospital Universitario de Burgos, Servicio de Aparato Digestivo, Burgos, Spain; ²Complejo Asistencial Universitario de León, Servicio de Aparato Digestivo, León, Spain; ³Hospital Universitario de Burgos, Servicio de Medicina Interna, Burgos, Spain

Email: jgomcam@hotmail.com

Background and aims: Hepatitis B and C remain a global health challenge, with great morbidity and mortality. The WHO has proposed the elimination of viral hepatitis as a public health threat by 2030. In 2020, the arrival of SARS-CoV-2 pandemic stopped the screening and treatment of viral hepatitis. However, hospital admissions due to SARS-CoV-2 infection can be an opportunity to screen patients for hepatitis B and C and thus move towards viral hepatitis elimination. The aim of this study is to evaluate the results of a screening program in hospitalized COVID-19 patients.

Method: This is a prospective cohort study conducted in two Spanish hospitals (Hospital Universitario de Burgos and Complejo Asistencial Universitario de León). All patients admitted to our centers from March 1st to December 31st 2020 with a diagnosis of COVID-19 were tested for markers of hepatitis B (HBsAg, anti-HBc) and C (anti-HCV, HCV RNA) infection.

Results: In the study period, 4513 patients with COVID-19 were admitted to our centers: 57.7% were male, median age was 74 years. Data regarding HBV infection was available in 3159 (70%) patients, of whom 303 (9.6%) were anti-HBc + and 11 (0.35%) HBsAg +. From these, only 4 (0.13%) patients did not have a previous diagnosis of hepatitis B (median age 80 years, all APRI <0.5). Seven HBsAg + patients received high dose corticosteroids; only one received prophylaxis and another one was treated with entecavir because a mild reactivation (DNA HBV 69 900 IU/ml). Anti-HCV were available in 3152 (69.8%) patients, of whom 24 (0.72%) were positive. From these, 13 patients had a previous hepatitis C diagnosis: 10 patients

had been treated and presented SVR, 2 achieved spontaneous cure and 1 did not receive treatment because of his age. From the 11 previously unknown anti-VHC + patients, 9 had a negative HCV RNA. Overall, only 3 (0.1%) patients tested RNA HCV positive. However, none received HCV treatment (2 older than 90 years, 1 died from COVID-19).

Conclusion: Screening of hepatitis B and C infection in hospitalized COVID-19 patients seems to be an unsuccessful tool in our region. The low prevalence of infection after antiviral treatments, the high age of our population and the difficulties for the application of the protocol in the context of the pandemic limit the detection of potential HCV candidates for treatment. HBV screening in this context should be aimed to prevent reactivation under immunosuppressive treatments.

Viral Hepatitis C: Post SVR and long term follow up

PO-52

Persistent long-term risk of liver related complications in hepatitis C virus patients after antiviral therapy-Data from the German Hepatitis C-Registry (DHC-R)

Heiner Wedemeyer^{1,2}, Peter Buggisch³, Stefan Mauss⁴, Albrecht Stoehr³, Hartwig Klinker⁵, Klaus Boeker⁶, Gerlinde Teuber⁷, Yvonne Serfert², Markus Cornberg^{1,8}, Heinz Hartmann², Dietrich Hüppe⁹, Christoph Sarrazin^{10,11}, Karl-Georg Simon¹², Stefan Zeuzem¹¹, Thomas Berg¹³ and German Hepatitis C-Registry².

¹Hannover Medical School, Hannover, Germany; ²Leberstiftungs-GmbH Deutschland, Hannover, Germany; ³ifi-Institute for Interdisciplinary Medicine, Hamburg, Germany; ⁴Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; ⁵University Hospital Würzburg, Würzburg, Germany; ⁶Center of Hepatology, Hannover, Germany; ⁷Practice PD Dr. med. G. Teuber, Frankfurt, Germany; ⁸Centre for Individualised Infection Medicine (CIIM), Hannover, Germany; ⁹Gastroenterologische Gemeinschaftspraxis Herne, Herne, Germany; ¹⁰St. Josefs-Hospital, Medical Clinic 2, Wiesbaden, Germany; ¹¹Goethe University Hospital, Frankfurt, Germany; ¹²MVZ Dres. Eisenbach, Simon, Schwarz GbR, Leverkusen, Germany; ¹³University Hospital Leipzig, Leipzig, Germany

Email: wedemeyer.heiner@mh-hannover.de

Background and aims: Direct acting antivirals against hepatitis C improve the short-term outcome of patients with chronic hepatitis C. The long-term clinical course after interferon-free treatment of chronic hepatitis C has rarely been studied in large real-world cohorts. We here present data on 10, 448 patients being followed for up to 7 years after DAA therapy in the German Hepatitis C-Registry.

Method: The DHC-R (German Hepatitis C-Registry) is a national multicentre real-world registry currently including about 17, 700 patients recruited by more than 250 centres. Data were analysed as of Jan 01, 2021. The present analysis is based on patients treated with DAAs against since February 2014.

Results: About 1/3 (32%) of the patients had liver cirrhosis at baseline. 26% (2, 712/10, 448) had a follow-up of at least three years after end of treatment. Antiviral treatment containing ribavirin (RBV) were given to 2, 359 patients, while 8, 089 patients received a regimen without RBV. The overall sustained virological response rates were 95% (9, 951/10, 448) and 97% (9, 824/10, 157) in intention-to-treat and per protocol analysis, respectively. During long-term follow-up, 181 patients died. Liver-related clinical events (liver transplantation, hepatocellular carcinoma (HCC), hepatic decompensation or increase in MELD score by ≥ 3 points) occurred in 416 (5.7%) patients. The time course of event-free survival is shown in the figure. The overall incidence for de novo HCC was 0.6%/year. In patients with liver cirrhosis the annual HCC risk was 1.2% in the first two years after

treatment and 0.8% from year 3–7. In multivariate analysis, parameters associated with the development of liver-related end points in SVR patients with high significance ($p < 0.01$) were previous antiviral therapy, male sex, baseline hemoglobin, eGFR and alkaline phosphatase. Liver cirrhosis and treatment experience were the only factors being associated with de novo HCC development with high significance ($p < 0.01$).

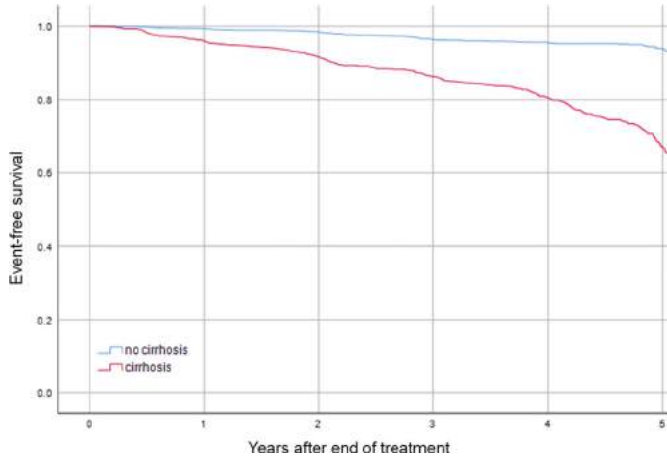


Figure: Kaplan-Meier curve analysis of liver related end point free survival of SVR patients with and without baseline liver cirrhosis during long-term follow-up.

Conclusion: This large real-world cohort confirmed that patients with chronic hepatitis C and liver cirrhosis are still at risk to develop complications of liver disease even beyond 3 years after HCV cure. We still strongly recommend a regular long-term monitoring in particular in treatment-experienced patients with liver cirrhosis.

PO-404
12 weeks treatment of Sofosbuvir/Velpatasvir in HCV negative recipients receiving renal transplantation from HCV positive donors

Ruoyang Chen¹, Dawei Li¹, Shaoyong Zhuang¹, Ming Zhang¹, Xiaodong Yuan¹. ¹Affiliated Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Urology, Shanghai, China
 Email:

Background and aims: To evaluate the efficacy and safety of Sofosbuvir/Velpatasvir prophylaxis in HCV negative recipients who received transplant kidney from HCV infected donors.

Method: This retrospective study included 26 consecutive HCV negative recipients between January 2019 and December 2020, who were treated with Sofosbuvir/Velpatasvir (400 mg/100 mg) once daily for 12 weeks after receiving transplant kidney from HCV infected donors (except for the first dose which was given 2 hours before renal transplant surgery). The primary end point was the proportion of patients with negative HCV RNA 12 weeks after the end of antiviral treatment.

Results: 16 patients completed 12 weeks of treatment and whole duration of follow-up. 7 patients completed Sofosbuvir/Velpatasvir treatment and are still under follow-up. The rest of 3 patients are still under 12 weeks of treatment. Among the 26 recipients, 22 recipients remained negative HCV Antibody (Ab) after transplantation. All patients had undetectable HCV RNA, including those who are still under treatment or follow-up, by the time we report. 3 patients experienced graft rejection, 6 patients experienced delayed graft function. However, none of them were related to study medication. The majority of adverse events reported in the study were mild and consistent with previous Sofosbuvir/Velpatasvir studies. Serious adverse events were reported in 6 patients, but none was considered

related to the drugs. Renal function remained stable during the whole study.

Table: Demographic and Clinical Characteristics of Recipient and Donor

Recipient Characteristics (n = 26)	
Median age (IQR), yr	42 (20–73)
Male, n (%)	19 (73.1%)
Cirrhosis, n (%)	0
Alanine aminotransferase level (U/L)	10.5 (3–70)
Serum creatinine level ($\mu\text{mol/L}$)	894 (373–1705)
Estimated glomerular filtration rate (ml/min)	7.715 (4–20.77)
Primary cause of renal failure, (n)	
IgA nephropathy	4
Polycystic kidney disease	3
Focal segmental glomerulosclerosis	3
Diabetic nephropathy	0
Hypertensive nephrosclerosis	1
Unknown	15
History of diabetes, (n)	2
Median time on dialysis before transplantation	330 (0–4340)
Median time on waitlist before transplantation	198 (29–865)
Donor Characteristics (n = 15)	
Male, n (%)	14 (93.3%)
Cause of death, (n)	
Donation after brain death	13
Donation after cardiac death	2
Median terminal serum creatine ($\mu\text{mol/L}$)	84.5 (24–194.5)

Conclusion: Sofosbuvir/Velpatasvir prophylaxis treatment was effective and safe in HCV uninfected recipients who received renal transplantation from HCV positive donors.

PO-578
Long-term follow-up in patients with hepatitis C virus treated with direct-acting-antivirals agents

Paula Fernandez Alvarez¹, María Guerra Veloz¹, Daniel Barranco Castro¹, Patricia Cordero Ruiz¹, Antonia Sáez Díaz², Francisco Bellido Muñoz¹, Angel Caunedo Alvarez¹, Isabel Carmona Soria¹. ¹Virgen Macarena University Hospital, Gastroenterology and Hepatology Department, Seville, Spain; ²Virgen Macarena University Hospital, Statistics Department, Seville, Spain
 Email: paulafer7@gmail.com

Background and aims: The introduction of the new direct-acting antivirals agents (DAA) has revolutionized the natural history of chronic HCV. The aim of this study was to determine risk factors associated with the developing of liver related events (LRE) in patients with prior advanced fibrosis who achieved sustained virological response (SVR).

Method: Observational retrospective single center study which included patients with chronic hepatitis C and advanced fibrosis (Fibroscan >10 kPa, APRI >1.5 and/or FIB-4 >3.25) treated with DAA between 2014 and 2017 that achieved SVR.

Results: A total of 321 patients were included, 68.8% (221) were male with a median age of 57 years. The median follow-up was 52 months (IQR 41–63). 13.7% of patients developed LRE, 10% (32) portal hypertension decompensation and 3.7% (12) HCC.

Patients with portal hypertension decompensation had higher basal Child-Pugh score (B 46.9 vs 6.9%, C 3.1 vs 0.3%; $p < 0.001$), basal MELD score (9.4 vs 7.8; $p < 0.001$), basal fibroscan value (26.5 vs 20.1; $p = 0.003$), basal APRI score (2.21 vs 1.13; $p < 0.001$), basal FIB-4 score (6.12 vs 2.62; $p < 0.001$) and more prior LRE (46.9 vs 5.9%; $p < 0.001$) in comparison with patient who did not develop liver decompensation. Furthermore, APRI and FIB-4 scores at first and second year were also higher in decompensated patients. In the multivariable analysis only the basal fibroscan value (OR 1.09 (1.029–1.175) $p = 0.005$) was associated with portal hypertension decompensation.

POSTER PRESENTATIONS

Patients who developed hepatocellular carcinoma (HCC) were older (67.6 vs 58.5; $p = 0.005$) and had higher rates of diabetes (50 vs 20.5%; $p = 0.025$), basal Child Pugh score (B 33.3 vs 10%, C 8.3 vs 0.3%; $p < 0.001$), genotype 3 (41.7 vs 12.6%; $p = 0.032$) and basal FIB-4 score (5.4 vs 2.8; $p < 0.011$) than those without HCC. During the follow-up patients who had higher APRI and FIB-4 scores at first and second year were more likely to develop HCC than those with low scores. In the multivariable analysis age (OR 1.13 (1.03–1.23) $p = 0.007$), presence of diabetes (OR 8.54 (1.32–55.15) $p = 0.024$) and the basal FIB-4 (OR 1.17 (1.04–1.32) $p = 0.009$) were related with the development of HCC.

During this period death occur in 22 patients (6.85%).

Conclusion: Patient's age, presence of diabetes and the baseline fibroscan and FIB-4 values were associated with the developing of LRE in a long-term follow-up. FIB-4 and APRI score measured at first and second year after SVR were not associated with LRE.

PO-602

Persistent perturbation of the circadian clock by chronic hepatitis C virus infection following cure with direct-acting antivirals

Frank Jühling^{1,2}, Atish Mukherji^{1,2}, Laurent Maily^{1,2}, Carla Eller^{1,2}, Clara Ponsolles^{1,2}, Katharina Herzog^{1,2}, Nouridine Hamdane^{1,2}, Xiaodong Zhuang³, Hiroshi Aikata⁴, Michio Imamura⁴, Jacinta Holmes⁵, Shu-Chi Wang⁶, Ming-Lung Yu^{7,8,9}, Raymond Chung¹⁰, Catherine Schuster^{1,2}, Emanuele Felli^{1,2,11}, Patrick Pessaux^{1,2,11}, Jane McKeating³, Kazuaki Chayama⁴, Thomas Baumert^{1,2,11,12}. ¹Université de Strasbourg, Strasbourg, France; ²Inserm, U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France; ³Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; ⁴Department of Gastroenterology and Metabolism, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; ⁵University of Melbourne, St Vincent's Hospital, Melbourne, Australia; ⁶Department of Medical Laboratory Science and Biotechnology, Center for Cancer Research and Liquid Biopsy, Kaohsiung Medical University, Kaohsiung, Taiwan; ⁷Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ⁸Hepatitis Research Center, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; ⁹Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; ¹⁰Liver Center, Gastroenterology Division, Massachusetts General Hospital and Harvard Medical School, Boston, United States; ¹¹Institut Hospitalo-Universitaire, Pôle Hépatite-digestif, Nouvel Hôpital Civil, Strasbourg, France; ¹²Institut Universitaire de France, Paris, France
Email: thomas.baumert@unistra.fr

Background and aims: Chronic HCV infection is a major cause of HCC. While viral cure by direct-acting anti-viral (DAA) agents decreases the overall HCC risk, large cohort studies revealed that HCC risk persists following cure especially in advanced fibrosis. The absence of reliable biomarkers to robustly predict HCC risk is a challenge for patient management. Despite significant research efforts, the molecular basis of HCV-induced HCC is still incompletely understood. The circadian clock (CC) is a well-known regulator of liver physiology and disease biology, while its clinical impact for HCV infection and hepatocarcinogenesis is unknown. Here, we aimed to investigate the role of the circadian clock in HCV-associated HCC risk. **Method:** To study the perturbation of the CC in patients, we performed ChIP-seq and RNA-seq from liver tissue of patients with chronic HCV-infection, cured patients and non-infected control patients and measured gene expressions and transcription factor recruitments of CC components at different stages of disease and pre- and post-cure. In addition, we performed perturbation studies in a human liver chimeric mouse model, primary human hepatocytes and HCV-permissive differentiated human hepatocellular carcinoma cells to unravel the regulation of affected CC-components in detail.

Results: We show that chronic HCV infection, a major cause of chronic liver disease (CLD) and HCC, results in marked epigenetic and

transcriptional perturbations of CC-controlled pathways driving the progression of CLD and HCC in patients. Our data show that HCV-induced epigenetic and transcriptional perturbations of CC-controlled pathways persist upon viral cure in patients with advanced fibrosis. The downstream network of disturbed genes, including many oncogenes as well as tumor suppressor genes, are associated with the hallmarks of cancer, and correlate with the outcome and risk to develop HCC. Mechanistically, virus-induced cytokine signaling impairs the CC-function by altering the expression of key CC components and downstream signaling.

Conclusion: Our results demonstrate that a human virus targets the CC and thereby drives fibrosis, a chronic inflammation-related disease, which is strongly linked with the development of cancer in advanced stages. Our findings provide novel opportunities for the discovery of urgently needed biomarkers and strategies for HCC surveillance and chemoprevention, and for HCC risk assessment in HCV-infected and cured patients.

PO-666

Characteristics and Survival Outcomes of Hepatocellular Carcinoma Developed After HCV SVR

Ming-Lun Yeh^{1,2}, Po-Cheng Liang¹, Pei-Chien Tsai¹, Shu-Chi Wang³, Jennifer Leong⁴, Eiichi Ogawa⁵, Dae Won Jun⁶, Cheng-Hao Tseng⁷, Charles Landis⁸, Yasuhito Tanaka⁹, Chung-Feng Huang^{1,2}, Jun Hayashi¹⁰, Yao-Chun Hsu⁷, Jee-Fu Huang^{1,2}, Chia-Yen Dai^{1,2}, Wan-Long Chuang^{1,2}, Mindie Nguyen^{11,12}, Ming-Lun Yu^{1,2}. ¹Kaohsiung Medical University Hospital, Department of Internal Medicine and Hepatitis Center, Taiwan; ²Kaohsiung Medical University, School of Medicine, Lipid Science and Aging Research Center, and Hepatitis Research Center, College of Medicine, and Center for Cancer Research and Center for Liquid Biopsy and Cohort Research, Taiwan; ³Kaohsiung Medical University, Department of Medical Laboratory Science and Biotechnology, Taiwan; ⁴Mt. Sinai Health System, Henry D. Janowitz Division of Gastroenterology, United States; ⁵Kyushu University Hospital, Department of General Internal Medicine, Japan; ⁶Hanyang University, Department of Gastroenterology, School of Medicine, Korea, Rep. of South; ⁷E-Da Hospital/I-Shou University, Division of Gastroenterology of Hepatology, Taiwan; ⁸University of Washington Medical Center, Department of Gastroenterology, United States; ⁹Kumamoto University, Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Japan; ¹⁰Haradai Hospital, Kyushu General Internal Medicine Center, Japan; ¹¹Stanford University Medical Center, Division of Gastroenterology and Hepatology, Department of Medicine, United States; ¹²Stanford University, Department of Epidemiology and Population Health, United States
Email: minglunye@gmail.com

Background and aims: The clinical presentation and survival of hepatocellular carcinoma (HCC) developed in patients post hepatitis C virus (HCV) eradication as compared to HCC developed in patients of remained viremia are not well studied. We aimed to investigate the characteristics and survival between HCV viremic and non-viremic patients at HCC diagnosis.

Method: A total of 1,389 HCV-related HCC patients, including 301 with HCC post HCV eradication (post-SVR HCC) and 1,088 with remained HCV viremia (viremic HCC) were retrospectively analyzed overall survival outcomes. A propensity score-matching method was also used to evaluate overall survival in these two groups.

Results: Post-SVR HCC patients demonstrated an older age, less obese, less cirrhosis, better liver function, lower alpha-fetoprotein levels, earlier tumor stages, and higher surgical rate for HCC as compared to viremic HCC at HCC diagnosis. A higher median overall survival was observed in post-SVR HCC patients than viremic patients (153.3 vs 55.6 months, $p < 0.01$), but post-SVR HCC was not independently associated with overall survival on multivariate analysis (adjusted HR: 1.05, 95% CI: 0.76–1.47). However, on sub-analysis, viremic HCC patients with subsequently HCV SVR by antiviral treatment showed a significantly higher median overall

survival than post-SVR HCC patients ($p < 0.01$). Multivariate analysis further identified a significantly lower mortality of viremic HCC with subsequent HCV SVR as compared to post-SVR HCC (adjusted HR: 0.18, 95% CI: 0.11–0.29). Similar findings were also observed in the propensity score-matched cohorts.

Conclusion: The better overall survival of patients with post-SVR HCC was related to their advantages in clinical and tumor characters at HCC diagnosis. However, HCV eradication after HCC development improved survival, too.

PO-689

Titer and breadth of anti-hepatitis C virus E2-glycoprotein antibodies in cirrhotic patients after direct antiviral agent therapy

Daniel Sepúlveda-Crespo¹, Cristina Díez², Víctor Hontañón³, Juan Berenguer², Juan González-García³, Luis Ibañez-Samaniego⁴, Elva Llop⁵, Leire Pérez-Latorre², Carmen Busca³, Antonio Oliveira⁶, Javier Martínez⁷, María Belén Yélamos⁸, Julián Gómez⁸, Salvador Resino¹, Isidoro Martínez¹. ¹Centro Nacional de Microbiología, Instituto de Salud Carlos III, Unidad de Infección Viral e Inmunidad, Majadahonda (Madrid), Spain; ²Hospital General Universitario "Gregorio Marañón," Unidad de Enfermedades Infecciosas/VIH, Madrid, Spain; ³Hospital Universitario "La Paz," Unidad de VIH; Servicio de Medicina Interna, Madrid, Spain; ⁴Hospital General Universitario "Gregorio Marañón," Servicio de Aparato Digestivo, Madrid, Spain; ⁵Hospital Universitario Puerta de Hierro, Servicio de Aparato Digestivo, Majadahonda (Madrid), Spain; ⁶Hospital Universitario "La Paz," Servicio de Aparato Digestivo, Madrid, Spain; ⁷Hospital Universitario Ramón y

Cajal, Servicio de Aparato Digestivo, Madrid, Spain; ⁸Universidad Complutense, Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Químicas, Madrid, Spain
Email: danisecre@hotmail.com

Background and aims: Several lines of evidence point to the participation of antibodies to the hepatitis C virus (HCV) in protection against HCV infection. We aimed to compare the titers, dynamic, and breadth of plasma antibodies against the HCV E2 glycoprotein, the main target of neutralizing anti-HCV antibodies (HCV-Abs), in HCV-monoinfected and HIV/HCV-coinfected individuals before HCV therapy (baseline) and following HCV clearance after direct-acting antiviral (DAA) therapy.

Method: We performed a prospective study in 50 HIV/HCV-coinfected patients (HIV/HCV-group) and 12 HCV-monoinfected patients (HCV-group) with advanced cirrhosis who received DAA therapy. Patients were assessed at baseline and 48 weeks after HCV treatment completion. Antibody titers against four purified E2 glycoproteins from 1a (H77), 1b (J4), 3a (S52), and 4a (ED43) genotypes were determined in plasma by ELISA assays and computed by the area under the curve (AUC) using GraphPad Prism 7.0. Statistical analyses were performed using SPSS version 21.0.

Results: All HIV/HCV-coinfected individuals were on suppressive ART, the median of CD4⁺ T-cells was 439 cells/mm³, the median of log₁₀ HCV-RNA was 6.2 IU/ml, and 18 of patients met acquired immune deficiency syndrome (AIDS) criteria at some point. Twenty-three HIV/HCV-coinfected patients were coinfecting with HCV genotype 1a, nine with genotype 1b, seven with genotype 3, and 10

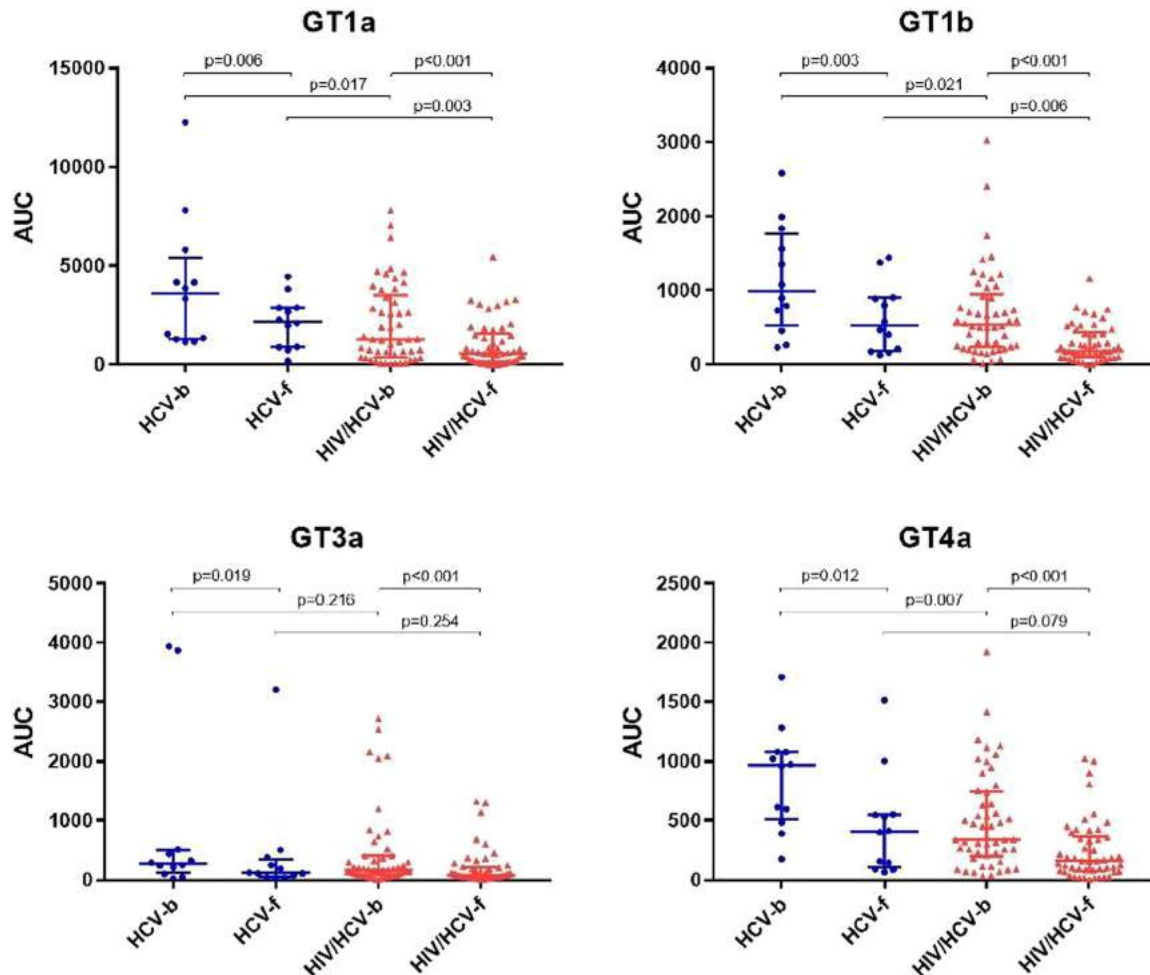


Figure: (abstract: PO-689)

POSTER PRESENTATIONS

with genotype 4. HCV-monoinfected patients also had a median log₁₀ HCV-RNA of 6.2 IU/ml. Nine were infected with HCV genotype 1a, one with genotype 1b, and two with genotype 3. We found that AUC values decreased by around 50% in HIV/HCV-group and the HCV group after treatment. The decreasing order was: 1a (H77) >1b (J4) >4a (ED43) >3a (S52) ($p < 0.05$; see Figure). The largest differences between independent groups (HIV/HCV-group vs. HCV-group) were found for 1a (H77), followed by 1b (J4), and 4a (ED43) at both baseline and the end of follow-up ($p < 0.05$; see Figure). The antibody titers were around 1.5–4-fold higher in the HCV-group than in HIV/HCV-group for the four genotypes analyzed at baseline and week 48 after HCV treatment completion ($p < 0.05$; see Figure).

Conclusion: The antibody response against HCV appears to be somewhat hampered by HIV coinfection. Furthermore, the decrease in antibody titers 48 weeks after completion of HCV treatment suggests that both mono and coinfecting patients may not be protected against HCV reinfection.

PO-697

Incidence of liver and non-liver related events and mortality in a large cohort of HCV cirrhotics with an SVR to DAA: a 5-year single center study

Roberta D'Ambrosio¹, Elisabetta Degaspero¹, Maria Paola Anolli¹, Ilaria Fanetti¹, Marta Borghi¹, Roberta Soffredini¹, Massimo Iavarone¹, Giulia Tosetti¹, Riccardo Perbellini¹, Angelo Sangiovanni¹, Pietro Lampertico^{1,2}. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; ²CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy
Email: roberta.dambrosio@policlinico.mi.it

Background and aims: As the long-term benefits of a sustained virological response (SVR) in hepatitis C virus (HCV) cirrhosis following direct-acting antivirals (DAA) remain undefined, we assessed the SVR impact on liver-related (LRE), non-liver related events (NLRE) and mortality in cirrhotics successfully treated with DAA.

Method: Consecutive SVR cirrhotics were enrolled in a longitudinal, single-center study, and divided into *Cohort A* (CPT-A without previous LRE), *Cohort B* (previous non-HCC LRE), *Cohort C* (previous HCC). Study end points were incidence and predictors of LRE, NLRE and mortality.

Results: 647 cirrhotics (65 years-old, 58% males, 89% CPT-A) were followed for 51 (8–68) months. In *Cohort A* (n=486), LREs 5-year cumulative incidences (CumI) were 7.6% for HCC, 1.4% for ascites and 1.2% for bleeding. Corresponding figures in *Cohort B* (n=91) were 19.3% for HCC, 2.9% for ascites, 7.7% for bleeding, 2.5% for encephalopathy. Only HCC developed in 70 *Cohort C* patients (5-year CumI: 68.7%). Independent predictors of LREs were male gender (HR 2.93, $p = 0.03$), diabetes (HR 2.49, $p = 0.02$), anti-HBc positivity (HR 2.20, $p = 0.04$) and pre-treatment liver stiffness (HR 1.05, $p = 0.01$) in *Cohort A*; anti-HBc positivity (HR 3.34, $p = 0.02$), γ GT (HR 1.01, $p = 0.001$) and platelets (HR 0.98, $p = 0.02$) in *Cohort B*. NLRE occurred in 70 (11%) patients (36 cerebro-cardiovascular, 33 non-HCC malignancies, 1 ESRD) across all cohorts, age being the only predictor. Overall, 50 patients died, (42% liver-related and 58% non-liver related causes), and 14 (2%) patients underwent liver transplantation (LT). HCC was the most frequent cause of liver-related death and LT. The 5-year CumI for the combined end point liver-related death and LT was 7.7%.

Conclusion: Despite HCV eradication, cirrhotics face a significant residual risk of HCC and non-liver-related complications.

PO-717

Non-invasive tests to predict liver-related events in a single-center cohort of 486 HCV cirrhotic patients treated with DAA

Elisabetta Degaspero¹, Roberta D'Ambrosio¹, Ilaria Fanetti¹, Riccardo Perbellini¹, Maria Paola Anolli¹, Marta Borghi¹, Roberta Soffredini¹, Pietro Lampertico^{1,2}. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; ²CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy
Email: elisabetta.degaspero@policlinico.mi.it

Background and aims: The association between non-invasive tests for fibrosis and liver-related events (LREs) after a sustained virological response (SVR) to direct-acting antivirals (DAA) in HCV cirrhotics remains undefined. We investigated their modifications following DAA and the association with LREs in a large cohort of cirrhotics.

Method: Consecutive compensated SVR cirrhotics treated between 2014 and 2019 in a single-Center were enrolled. LREs included hepatocellular carcinoma (HCC), ascites, variceal bleeding and encephalopathy; those occurring before SVR were excluded. LSM, Fibrosis-4 (FIB-4) and AST to Platelets Ratio index (APRI) were assessed at DAA start (baseline) and 12 months post-treatment (SVR48).

Results: Overall, 486 patients were analysed: median age 64 (24–92) years, 59% males, 19% diabetics. Compared to baseline, all tests significantly declined at SVR48: median LSM from 17.0 to 13.9 kPa, FIB-4 from 4.02 to 2.41, APRI from 1.7 to 0.49 ($p < 0.0001$ for all comparisons). After 51 (8–68) months from baseline, 41 (8%) patients developed a LRE (32 HCC, 6 ascites, 3 bleedings), 5-year cumulative incidence being 10.2% (95% C.I. 7–13%). By multivariate analysis, neither baseline nor SVR48 APRI, FIB-4, Δ APRI and Δ FIB-4 were associated with LREs. Conversely, both baseline (HR 1.05, $p = 0.01$) and SVR48 (HR 1.02, $p = 0.003$) LSM, but not Δ LSM, independently predicted LREs, together with diabetes, anti-HBc and male gender. By ROC curve analysis, baseline LSM >20.8 and SVR48 >16.1 kPa were the optimal cut-offs for LREs prediction: the 5-year cumulative incidence of LREs resulted 16.3% vs. 5.5% in patients with baseline LSM >or \leq 20.8 kPa ($p = 0.01$); the corresponding figures were 21% vs. 3.7% for SVR48 LSM >or \leq 16.1 kPa ($p = 0.003$).

Conclusion: In a large cohort of compensated HCV cirrhotics with an SVR to DAA, LSM but not FIB-4 or APRI score was associated with LREs.

PO-862

Mortality risk following HCV cure among people with HIV coinfection

Naveed Janjua^{1,2}, Stanley Wong¹, Younathan Abdia¹, Sofia Bartlett¹, Hector Velasquez¹, Makuza Jean Damascene², Hasina Samji¹, Dahn Jeong², Prince Adu¹, Margo Pearce², James Wilton¹, Maria Alvarez¹, Mawuena Binka¹, Terri Buller-Taylor¹, Mel Krajden¹. ¹BC Centre for Disease Control, Vancouver, Canada; ²The University of British Columbia, Vancouver, Canada
Email: naveed.janjua@bccdc.ca

Background and aims: Co-infection with Human Immunodeficiency Virus (HIV) is associated with higher morbidity and mortality compared to Hepatitis C Virus (HCV) mono-infection. Sustained virologic response (SVR) following HCV treatment is associated with reduced morbidity and mortality. We assessed all-cause, liver-, drug- and non-liver non-drug-related mortality following SVR among people with HIV co-infection (PWHI) compared to people with HCV mono-infection (PWHC) in a large population-based cohort in British Columbia (BC), Canada.

Method: We used data from the BC Hepatitis Testers Cohort, which includes ~1.3 million people tested for HCV since 1990, linked with data on medical visits, hospitalizations, prescription drugs and mortality. We followed PWHC and PWHI who achieved SVR following DAA treatment to death or December 31, 2019. We computed

mortality rates by HIV co-infection status and performed multi-variable proportional hazard modeling to assess the effect of HIV co-infection on all-cause, liver, drug-related and non-liver and non-drug-related mortality.

Results: There were 10, 101 people who achieved SVR following direct-acting antiviral treatment. PWHI: n = 811, person-years (PY) = 1, 774.2, deaths = 78; PWHC: n = 9, 290, PY = 19, 464.8, deaths = 474. Median follow-up time was 1.9 years (interquartile range 0.9–3.3; maximum = 5.4). The all-cause, liver, drug and non-liver and non-drug-related mortality rate among PWHI and PWHC was 44.0 vs. 24.4/1, 000PY, 5.1 vs. 9.1/1, 000PY, 20.9 vs. 4.5/1, 000PY, 18.0 vs. 11.9/1, 000PY, respectively. In the multivariable model, HIV co-infection was associated with higher all-cause (adjusted hazards ratio (AHR): 1.54, 95%CI: 1.18–2.00), drug-related (AHR: 1.86, 95%CI: 1.20–2.90) and non-liver and non-drug related mortality (AHR: 1.57, 95%CI: 1.05–2.35), while risk of liver-related mortality (AHR: 0.78, 95%CI: 0.39–1.54) was not significant different compared to HCV mono-infection.

Conclusion: After successful treatment, people with HIV co-infection have similar liver-related mortality as people with HCV mono-infection, but have higher all cause, drug- and non-liver, non-drug-related mortality. Higher drug-related and non-liver, non-drug related mortality indicate tailoring services based on syndemic conditions co-occurring with HIV and HCV infections, such as substance use and mental health support and care for chronic non-communicable conditions.

PO-881

Gender differences in microRNAs profile in HIV patients after HCV eradication with DAAs: potential biased consequences

Daniel Valle Millares¹, Óscar Brochado Kith¹, Alicia Gómez Sanz¹, Luz Martín Carbonero², Pablo Ryan³, Ignacio De los Santos⁴, Juan Miguel Castro Álvarez², Jesús Troya³, Mario Mayoral Muñoz², Guillermo Cuevas³, Paula Martínez¹, Jesús Sanz Sanz⁴, María Muñoz Muñoz⁵, María Ángeles Jiménez Sousa¹, Salvador Resino García¹, Verónica Briz¹, Amanda Fernández Rodríguez^{1,6}. ¹ISCIII, Majadahonda, Spain; ²IdiPAZ,

Madrid, Spain; ³Hospital Universitario Infanta Leonor, Madrid, Spain; ⁴Hospital de La Princesa, Madrid, Spain; ⁵INA-Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria, Madrid, Spain; ⁶Alfonso X el Sabio, Villanueva de la Cañada, Spain
Email: da.valle@isciii.es

Background and aims: Gender-specific consequences after HCV eradication are unexplored. MicroRNAs (miRNAs) play a crucial role in the immune response against viral infections. However, few have highlighted miRNA role in sex-biased disease or therapy response. This study aims to assess gender differences reflected in the miRNA expression of HIV/HCV-coinfected patients who achieve sustained virological response (SVR) with direct acting antivirals (DAAs).

Method: We conducted a prospective study of miRNA expression in PBMCs from 28 chronic HIV/HCV-coinfected patients (HIV/HCV group) at baseline and after achieving SVR with DAAs. Sixteen HIV-monoinfected patients were used as controls (HIV group). Identification of significant differentially expressed (SDE) miRNAs was performed with generalized linear model and mixed GLMs. We also explored putative dysregulated biological pathways.

Results: The HIV/HCV group at baseline showed differences in the miRNA profile concerning the HIV group (165 and 102 SDE miRNAs for males and females, respectively). Gender-stratified analysis of HIV/HCV group at baseline versus at SVR achievement showed higher differences in males (80 SDE miRNAs) than in females (55 SDE miRNAs). After SVR, HIV/HCV group showed similar values to HIV individuals, especially in females (1 SDE miRNA). However, ten miRNAs in males remained dysregulated, which were mainly involved in the cancer, fatty acid, and inflammatory pathways.

Conclusion: Our findings show gender-biased dysregulation in the miRNA expression profile of PBMCs after HCV eradication with DAA therapy. These differences were normalized in females, while miRNA profile and their target-related pathways of males remained different from HIV patients, which may be related to a high-risk of developing liver-related complications.

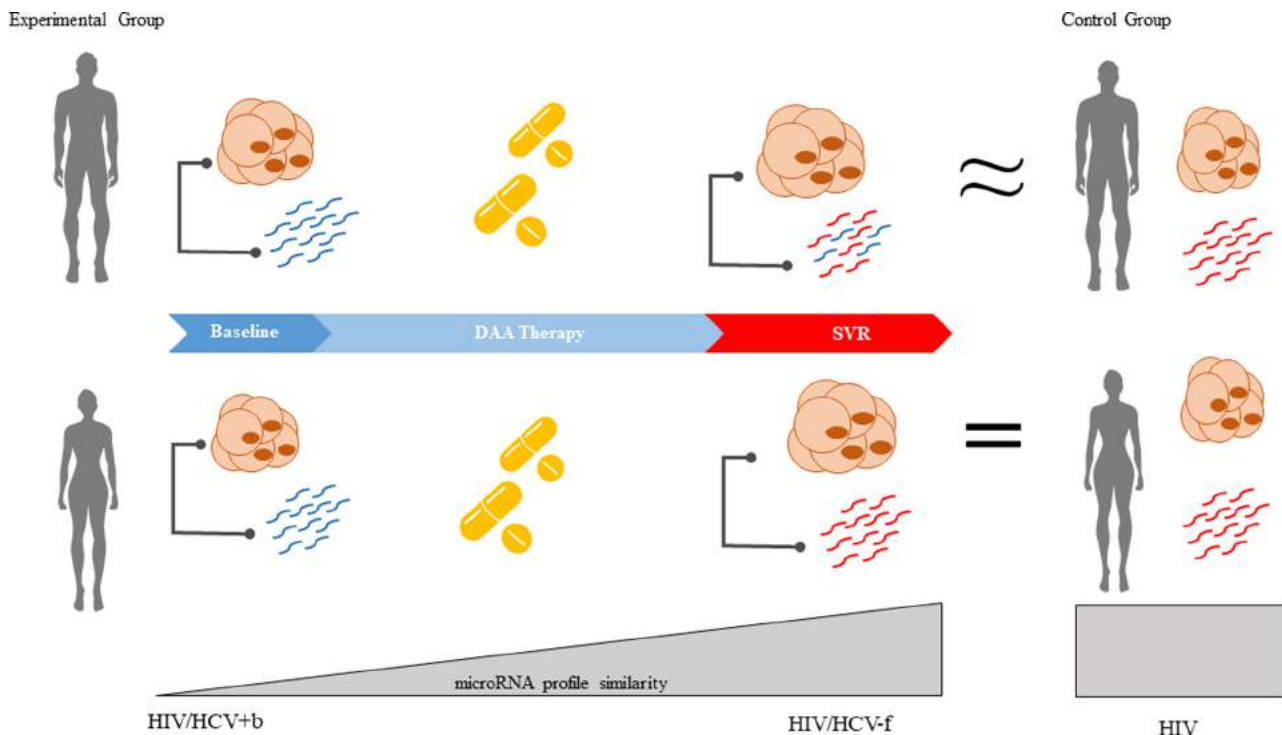


Figure: (abstract: PO-881)

POSTER PRESENTATIONS

PO-921

PIVKA-II levels predict hepatocellular carcinoma development in caucasian HCV cirrhotic patients treated with DAAs

Elisabetta Degasper¹, Riccardo Perbellini¹, Roberta D'Ambrosio¹, Sara Colonia Uceda Renteria², Ferruccio Ceriotti², Alberto Perego³, Corinna Orsini³, Marta Borghi¹, Massimo Iavarone¹, Mariangela Bruccoleri¹, Alessandro Rimondi¹, Angelo Sangiovanni¹, Pietro Lampertico^{1,4}. ¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; ²Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Clinical Laboratory, Milan, Italy; ³Fujirebio, Sweden, ⁴CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy
Email: elisabetta.degasper@policlinico.mi.it

Background and aims: Prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) has been associated with hepatocellular carcinoma (HCC), but its performance in HCV cirrhotics achieving a sustained virological response (SVR) to direct-acting antivirals (DAA) is unknown.

Method: In this single-center study, we tested a large cohort of HCV cirrhotics with an SVR for PIVKA-II and alpha-fetoprotein (AFP) (Fujirebio, Japan) at DAA start (baseline), end of treatment (EOT) and HCC diagnosis. PIVKA-II and AFP performances were evaluated at HCC diagnosis and as predictors of HCC.

Results: 400 patients (1,029 samples tested) were included: age 65 (24–92) years, 56% males, 91% Child-Pugh Turcotte (CPT) A, Liver Stiffness Measurement (LSM) 16.9 (12.0–75.0) kPa. During DAA, PIVKA-II did not change [35 (12–886) vs. 35 (16–867) mAU/ml, $p = 0.43$] while AFP significantly decreased [12 (1–537) to 6 (1–347) ng/ml, $p < 0.0001$]. After 52 (3–66) months from baseline, 34 (8.5%) patients developed *de-novo* HCC, the 5-year probability being 11.3% (95% CI 7–16%). At HCC diagnosis, 82% were BCLC 0-A, AFP was 9 (2–12, 868) ng/ml and PIVKA-II was 80 (22–1, 813) mAU/ml. The Youden cut-offs for HCC detection were PIVKA-II > 47 mAU/ml (76% Sn, 79% Sp, 25% PPV, 97% NPV) and AFP > 17 ng/ml (29% Sn, 97% Sp, 48% PPV, 97% NPV), with higher AUROC for PIVKA-II (0.82 vs. 0.6, $p = 0.03$). HCC features (size, nodule number, BCLC stage) did not differ according to PIVKA-II or AFP levels.

At multivariate analysis, baseline predictors of HCC were PIVKA-II (HR 1.01, $p < 0.001$), diabetes (HR 3.79, $p = 0.002$), bilirubin (HR 1.79, $p = 0.04$) and anti-HBc (HR 2.53, $p = 0.03$). Among EOT variables, PIVKA-II (HR 1.01, $p = 0.01$) and AFP (HR 1.01, $p < 0.001$) independently predicted HCC together with diabetes (HR 3.68, $p = 0.002$), GGT (HR 1.01, $p = 0.001$) and albumin (HR 0.31, $p = 0.01$). Optimal cut-offs for HCC prediction were calculated by ROC curve analysis. The 4-year cumulative probability of HCC was 24% vs. 2% in patients with EOT PIVKA-II > or £41 mAU/ml ($p < 0.0001$), and 26% vs. 9% for EOT AFP > or £15 ng/ml ($p = 0.02$). By combining the two markers at EOT, patients testing positive for both had a 38% 4-year estimated cumulative probability of HCC vs. 21% of patients with a single positive marker and 2% of patients with both negative markers ($p < 0.0001$).

Conclusion: In DAA-treated HCV cirrhotics, PIVKA-II was superior to AFP and independently predicted HCC, while the combination of biomarkers improved risk stratification.

PO-975

Long-term effect of hcv eradication with direct acting antiviral (daas) therapy on egyptian patients with mixed cryoglobulinemias (mc)

Mohamed Elnadry¹, Sayed Farouk Mohamed¹, Mohamed Mahmoud Abdelhalem¹, Kareem Elnoomany². ¹Al-Azhar University, Hepato-Gastroenterology and Infectious Diseases, Cairo, Egypt; ²Sheben Elkoom Fever Hospital, Hepato-Gastroenterology and Infectious Diseases, Monof, Egypt
Email: prof_nadry@yahoo.com

Background and aims: The highest prevalence of HCV infection worldwide was present in Egypt. Mass HCV treatment program was

started using DAAs since 2015 aiming to eradicate HCV infection by 2030. HCV is usually associated with variable types of MCs. The long-term impact of DAAs on MCs associated to HCV is still being researched. The aim of this study is to evaluate the long-term effect of DAAs on Egyptian patients with HCV-associated MCs.

Method: This prospective observational study included 80 patients with HCV-associated MC, 30 patients with cutaneous lesions, 30 patients with musculoskeletal manifestations (was defined by circulating cryoglobulin associated with systemic vasculitis symptoms) and 20 patients with renal involvement (was established by kidney biopsy). All patients fulfilled the inclusion criteria of the study and received DAAs from March to December 2017 in the form of a three-month course of Sofosbuvir/Daclatasvir ± Ribavirin regimen. Post-treatment follow-up ranged from 30 to 36 months.

Results: The mean age of the included HCV-MCs patients was 54.2 years ± 8.4 SD; 44 (55%) of them were females. Purpuric papules of the lower extremities was the most frequent cutaneous lesion 80% (24/30) while haemorrhagic crusts, and/or ulcers, lichen planus, and chronic urticaria were frequent in 10% (3/30), 3.33% (1/30), and 6.7% (2/30) of patients, respectively. Arthralgia was the most frequent in musculoskeletal manifestations 90% (27/30). Diffuse membranoproliferative glomerulonephritis was the most frequent lesion in patients with kidney involvement 90% (18/20). All patients reached SVR12. There were improvements in the presenting HCV-MCs clinical manifestations in variable degrees, ranging from complete response (clinical, and immunological) in 53.75% (43/80) patients and partial response (clinical, and immunological) in 33.75% (27/80) patients with no response (clinical and immunological) in 12.5% (10/80). Immunosuppressive therapies are required in 40% (12/30), 26.7% (8/30), 85% (17/20) of patients with cutaneous, musculoskeletal and kidney involvement, respectively. Cryoglobulins were detected (post treatment with DAAs) in 10% (3/30), 6.7% (2/30), and 25% (5/20) of HCV-patients with cutaneous, musculoskeletal and kidney involvement respectively.

Conclusion: Clearance of HCV led to resolution and improvement of most patients with cutaneous and musculoskeletal manifestation. In patients with HCV-induced MCs especially those with kidney involvement are still a difficult to treat group and most of them need immunosuppressive therapy.

PO-1176

Hepatitis C virus eradication improves cognition in patients with and without cirrhosis: results from a real-life prospective study

Luis Ibañez¹, Marta Rapado², Lucía Cabrero³, Cristina Navarrete¹, Seila García-Mulas¹, Adriana Ahumada¹, LAURA Marquez¹, María Dolores Pérez¹, Diego Rincón Rodríguez¹, Rafael Bañares¹, Rita Garcia Martinez¹. ¹Gregorio Marañón Hospital, Madrid, Spain; ²Instituto de Psiquiatria y Salud Mental Hospital Gregorio Marañón, Madrid, Spain; ³Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
Email: lisamaniego@gmail.com

Background and aims: HCV infection is associated with neuropsychiatric disturbances that impact on functioning and health-related quality of life (HRQoL). The potential reversibility in different stages of the liver disease is not well-known. We aimed to evaluate cognitive function, functioning and HRQoL at different stages of liver disease following HCV eradication.

Method: A random selection of consecutive patients attending the viral hepatitis clinic (April'15–March'17) were assessed before initiating treatment, 12 and 48 weeks after end of direct-acting antiviral agents (DAAs). A comprehensive neuropsychological assessment, functioning and HRQoL questionnaires were applied.

Results: One-hundred and thirty-six HCV-infected patients completed the follow-up, of whom 45 had cirrhosis (12% decompensated). One cirrhotic patient did not achieve virological response and was excluded from the analysis. Twenty-one percent of patients (Figure) had cognitive impairment before starting DAAs (34%

cirrhotic vs 14% non-cirrhotic, $p < 0.011$). Viral eradication was associated with improvement of cognitive performance and a decrease of cognitive impairment to 23% in cirrhotic and to 6% in non-cirrhotic patients ($p < 0.05$). Interestingly, age ($B = 0.11$ IC95% 0.03–0.19) and baseline cognitive impairment ($B = 3.58$, IC95% 1.54–5.62) were independently associated to higher cognitive benefit, regardless the stage of liver disease. Patients with cognitive impairment after eradication were more likely to be obese, with diabetes mellitus, arterial hypertension, cirrhosis, lower educational level and with higher anxiety and depression scores. Functioning and HRQoL also improved following HCV cure.

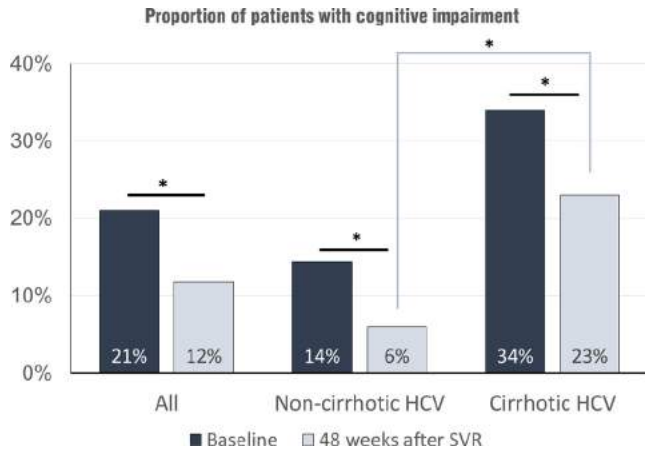


Figure:

Conclusion: HCV-infected patients develop cognitive impairment even with mild liver disease. Viral eradication improves cognitive performance independently of the degree of liver disease and is associated with improvement in functioning and HRQoL. Identification of HCV-patients through screening programs may reduce the burden of cognitive disturbances and improve HRQoL beyond the prevention of liver disease progression.

PO-1247

New onset steatosis but not persistent steatosis prevents hepatic fibrosis improvement after viral eradication by direct-acting antiviral therapy (DAAs) in patients with chronic hepatitis C: evaluation by CAP and LSM

Annalisa Cespiati¹, Salvatore Petta², Rosa Lombardi¹, Vito Di Marco², Vincenza Calvaruso², Giordano Sigon¹, Giovanna Oberti³, Cristina Bertelli³, Giuseppina Pisano³, Erika Fatta³, Federica Iuculano³, Luciano Crapanzano², Gerlando Gibilaro², Paolo Francione¹, Antonio Craxi², Silvia Fargion¹, Anna Ludovica Fracanzani¹. ¹Unit of Internal Medicine and Metabolic Disease, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ²Section of Gastroenterology and Hepatology, PROMISE, University of Palermo, Italy, Palermo, Italy; ³Unit of Internal Medicine and Metabolic Disease, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, Milan, Italy
Email: annalisa.cespiati@unimi.it

Background and aims: In patients with chronic hepatitis C (CHC) presence of steatosis before and after sustained virological response (SVR) has been demonstrated. A multifaceted behavior of hepatic steatosis has been related with metabolic alterations. Aim: to define the impact of post SVR steatosis on fibrosis improvement evaluated with Fibroscan in CHC patients after viral eradication by DAAs.

Method: 794 patients with CHC who achieved SVR, referring to 2 Italian Liver Units were enrolled. Data were collected the day of DAAs starting and six months after SVR. Fibroscan defined the presence of steatosis (by controlled attenuation parameter (CAP) ≥ 248 dB/m) and fibrosis (by liver stiffness measurement LSM).

Results: Mean age was 64 ± 16 , 50% males, genotype 1 in 73%, genotype 3 in 7%. Mean CAP and LSM values at baseline were 244 ± 60 dB/m and 10 ± 7.6 kPa. Patients with baseline steatosis 365 (46%) presented significantly higher baseline LSM values compared to their counterpart (10.6 ± 7.8 vs 9.4 ± 7.4 kPa; $p = 0.04$). New onset steatosis (CAP ≥ 248 dB/m) after SVR developed in 125 out of 429 (29%) without steatosis at enrollment, persistent steatosis in 243/365 (66%). LSM significantly reduced after SVR (10 ± 7.6 vs 8.2 ± 7.2 kPa, $p < 0.001$), even in presence of hepatic steatosis post SVR (10.3 ± 7.3 vs 8.2 ± 6.6 kPa; $p < 0.001$). However, when the analysis was differentiated between patients with persistence and new onset steatosis, a significantly reduction of LSM in patients with persistence (10.8 ± 7.8 vs 8.0 ± 5.7 kPa, $p < 0.001$) but not in those with new onset steatosis (9.4 ± 6.4 vs 8.7 ± 8.0 kPa, $p = 0.12$) was confirmed.

Conclusion: New onset steatosis but not persistence of baseline steatosis prevents fibrosis improvement after SVR, possibly because of a combined action of acute inflammation and metabolic alterations. Our finding may suggest the presence of two different type of post SVR steatosis. Further studies are warranted to better elucidate differences between entities.

PO-1404

Metabolomic changes in HIV/HCV coinfectd patients after DAAs therapy

Óscar Brochado-Kith¹, Ana Virseda¹, Juan Berenguer², David Rojo³, Juan Gonzalez⁴, Amanda Fernández Rodríguez¹, Cristina Diez², Victor Hontañón⁴, Teresa Aldámiz-Echevarría², Rafael Micán², Chiara Fanciulli², Carmen Busca⁴, Coral Barbas³, Salvador Resino-García¹, María Ángeles Jiménez Sousa¹. ¹ISCIII, Majadahonda, Spain; ²Gregorio Marañón Hospital, Madrid, Spain; ³CEMBIO, Alcorcón, Spain; ⁴Hospital Universitario La Paz, Madrid, Spain
Email: brochado1993@gmail.com

Background and aims: Changes in the metabolomic profile have been described during the different stages of cirrhosis. However, there is little information about what happens in patients coinfectd with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) after direct-acting antivirals (DAAs) therapy. Thus, we aimed to assess plasma metabolites changes and their association with liver cirrhosis markers before and after effective DAAs therapy in HIV/HCV coinfectd patients with advanced HCV-related cirrhosis.

Method: We performed a multicenter prospective study in 49 coinfectd patients with advanced cirrhosis assessed at baseline and 48 weeks after DAAs therapy completion. Metabolomics analysis was carried out by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Inflammatory plasma biomarkers were analyzed by ProcartaPlex Immunoassays. The statistical analysis was performed by partial least squares discriminant analysis and generalized linear mixed model correcting for multiple testing.

Results: At 48 weeks after HCV treatment completion, patients experienced significant reduction in taurocholic acid, 2, 3-butanediol, and lysoPC (18:0); while several phosphatidylcholines (lysoPC (16:1), lysoPC (18:1), lysoPC (20:4), and PC (16:0/9:0 (CHO))), 2-keto-n-caproic acid/2-keto-isocaproic acid and N-methylalanine increased, compared to baseline. We also found the decrease in plasma taurocholic acid was associated with a reduction in Child-Turcotte-Pugh (CTP) score (AMR = 3.39; q-value = 0.006) and liver stiffness measurement (LSM) (AMR = 1.06; q-value < 0.001), the increase in plasma levels of lysoPC (20:4) was related to a reduction in LSM (AMR = 0.98; q-value = 0.027), and the rise of plasma 2-keto-n-caproic acid/2-keto-isocaproic acid was associated with a reduction in CTP (AMR = 0.35; q-value = 0.004). Finally, changes in taurocholic acid were directly associated with inflammatory plasma biomarkers, while changes in lysoPC (20:4) were inversely associated (Figure 1).

POSTER PRESENTATIONS

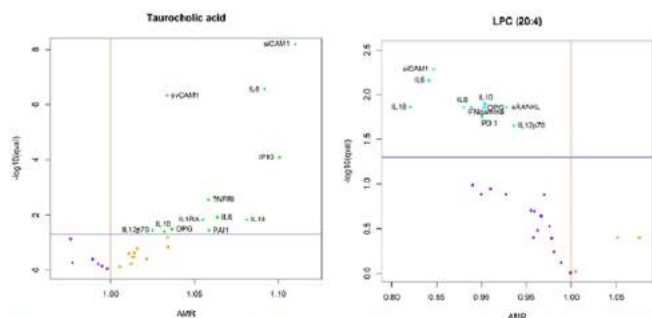


Figure 1: Association between changes in plasma metabolites and plasma markers related to inflammation from baseline to 48 weeks after DAA therapy.

Figure:

Conclusion: We found significant changes in plasma metabolites after HCV clearance with DAAs therapy in HIV/HCV coinfecting patients with advanced liver cirrhosis. A decrease in plasmatic levels of taurocholic acid and increases in levels of lysoPC (20:4) and 2-keto-n-caproic acid/2-keto-isocaproic acid were associated with decreases in CTP score and LSM. Additionally, plasma levels of taurocholic acid and lysoPC (20:4) could influence the inflammatory state.

PO-1415

Usefulness of dried blood spot samples for HCV genotyping to inform retreatment after recurrent viremia in people who inject drugs in the real world

Elisa Martró^{1,2}, Verónica Saludes^{1,2}, Anna Miralpeix^{3,4}, Mont Gálvez^{3,4}, Anna Not¹, Antoni E. Bordoy¹, Noemi Gonzalez⁵, Sergio Rodriguez-Tajes^{3,4,6}, Zoe Mariño^{3,4,6}, Juliana Reyes-Ureña^{2,7}, Xavier Major⁸, Joan Colom⁸, Xavier Forn^{3,4,6}, Sabela Lens^{3,4,6}.

¹Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol (IGTP), Microbiology Department, Laboratori Clínic Metropolitana Nord, Badalona, Spain; ²Biomedical Research Networking Centre in Epidemiology and Public Health (CIBERESP), Group 27, Madrid, Spain; ³Hospital Clínic, Liver Unit, Barcelona, Spain; ⁴IDIBAPS, Barcelona, Spain; ⁵Parc de Salut Mar, REDAN La Mina, Sant Adrià del Besòs, Spain; ⁶Biomedical Research Networking Centre in Hepatic and Digestive Diseases (CIBEREHD), Madrid, Spain; ⁷Center for Epidemiological Studies on HIV/AIDS and STIs of Catalonia (CEEISCAT), ASPCAT, Badalona, Spain; ⁸Public Health Agency of Catalonia (ASPCAT), Program for the Prevention, Control and Care of HIV, Sexually Transmitted Infections and Viral Hepatitis, Barcelona, Spain
Email: emartro@igtp.cat

Background and aims: We demonstrated that dried blood spot (DBS) samples are a reliable tool to diagnose viremic HCV infection among people who currently inject drugs (PWID) attending harm reduction services (HRS) in Catalonia. We aimed to assess the usefulness of DBS for HCV genotyping in HCV-RNA positive PWID after on-site treatment with pangenotypic antivirals in order to inform the retreatment regimen.

Method: Within the context of an ongoing micro-elimination study targeting current PWID in the largest HRS in Barcelona, PWID were followed up after treatment and HCV viral load was assessed in fingerstick capillary blood by GeneXpert®. DBS from HCV-RNA positive participants at follow-up (FU) weeks 12, 36, or 60 were compared with baseline DBS to assess reinfection vs. treatment failure by an in-house NS5B nested-PCR followed by Sanger sequencing. The epidemiological relationship between HCV-RNA positive participants was assessed by phylogenetic analysis. In those cases where sequencing failed, a commercial real-time PCR assay was used (Abbott Molecular), which identifies the following genotypes/subtypes: 1, 1a, 1b, 2, 3, 4, 5 and 6.

Results: Among the 45 FU DBS from RNA-positive patients after treatment (40 cases, including five with a subsequent re-treatment), two FU36 DBS samples with <500 IU/ml (the lower limit of detection) could not be genotyped. Among the rest, 25 DBS were successfully genotyped by sequencing and the other 18 were tested by the real-time PCR assay (in four of them no genotype was assigned due to relatively low viral loads). Genotyping results from FU vs baseline DBS samples evidenced the presence of reinfection in 37 cases (in four cases with the same HCV subtype); four of them also presented reinfection after re-treatment. Conversely, treatment failure was identified in three cases (one of them also failed to re-treatment). Most of the patients got reinfected with subtypes 1a or 3a and were often phylogenetically related to other viremic study participants.

Conclusion: HCV genotyping from DBS samples is useful to identify reinfections in PWID in cases with >1000 IU/ml and administer retreatment regimens accordingly. Phylogenetic analysis evidenced that reinfection often occurs from other HRS users. Therefore, reinforced harm reduction measures and strategies such as “treat your friends” should be considered in this setting (treating persons in the same injecting network at the same time) in order to minimize reinfection.

PO-1542

Metabolic comorbidities reduce the improvement of procoagulant imbalance in non-cirrhotic patients with chronic hepatitis C (CHC) after viral eradication with direct-acting antiviral agents (DAAs)

Giordano Sigon¹, Roberta D'Ambrosio², Marigrazia Clerici³, Giuseppina Pisano⁴, Veena Chantarangkul³, Annalisa Cespiati¹, Federica Iuculano¹, Rosa Lombardi¹, Flora Peyvandi⁵, Pietro Lampertico², Silvia Fargion¹, Armando Tripodi³, Anna Ludovica Fracanzani¹. ¹Unit of Internal Medicine and Metabolic Disease, Fondazione Ca Granda IRCCS, Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ²CRC AM e a Migliavacca Center for Liver Diseases, Gastroenterology and Hepatology, Fondazione Ca' Granda Irccs Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ³Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁴Unit of Internal Medicine and Metabolic Disease, Fondazione Ca Granda IRCCS, Ospedale Maggiore Policlinico, Milan, Italy; ⁵Unit of Internal Medicine Hemostasis and Thrombosis, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico, Milan, Italy
Email: gio.sigon@virgilio.it

Background and aims: A strong relationship between endothelial dysfunction, inflammation, procoagulant imbalance, liver damage, was described in non-cirrhotic CHC patients. An improvement in procoagulant imbalance was reported, after DAAs-sustained virologic response (SVR) in CHC patients with cirrhosis. Aims: 1) to assess procoagulant imbalance changes in CHC patients without advanced fibrosis after SVR, 2) to evaluate if metabolic alterations may interfere with coagulation improvement.

Method: We enrolled 104 non-cirrhotic patients with CHC and SVR. All patients were evaluated for clinical and biochemical parameters, procoagulant imbalance (endogenous thrombin potential (ETP) with/without thrombomodulin and protein C (PC) to factor VIII ratio), early atherosclerosis (carotid intima-media thickness (IMT)), liver damage (liver stiffness measurement (LSM) at enrolment, after 6 months and in a subgroup of 52 patients after 24 months. Controls for coagulation parameters were 188 healthy hospital employees.

Results: At baseline CHC patients show a procoagulant imbalance compared to controls (FVIII/PC 1.76 ± 0.76 vs 1.1 ± 0.3 , $p < 0.0001$). Pre-treatment indices of procoagulant imbalance were associated

with liver fibrosis (FVIII/PC ratio with NAFLD fibrosis score: coefficient 0.7 SE 0.1, $p < 0.0001$). After SVR a reduction of procoagulant imbalance (FVIII/PC 1.76 ± 0.76 vs 1.32 ± 0.54 , $p < 0.0001$) was observed in 86% of patients and remained stable at 24 months. A decrease of liver damage compared to pre-treatment (LSM: $5.1 + 1.7$ vs $6.5 + 5.5$; FIB-4: $2.1 + 2.8$ vs $1.7 + 0.7$, $p = 0.02$; ALT: $49 [31-75]$ vs $17 [14-22]$, $p < 0.0001$) was observed in 69%. At multivariate analysis procoagulant imbalance remained independently related to ALT levels (Coeff 0.02, ES 0.001, $p = 0.005$). The absence of coagulation improvement was independently related to baseline age (OR 0.9, IC95 0.8–0.97, $p = 0.009$), diabetes (OR 18.7, IC95, 1.6–217, $p = 0.02$) and dyslipidaemia (OR 222, IC95 10–5077, $p = 0.001$).

Conclusion: Non-cirrhotic CHC patients show a procoagulant imbalance that may play a role in the increased severity of fibrosis and endothelial dysfunction.

After HCV eradication by DAAs, a very early improvement of both procoagulant imbalance and liver fibrosis occurs strengthening the direct link between HCV, liver damage and coagulation modifications. Metabolic diseases may account for the lack of improvement of procoagulant imbalance and endothelial dysfunction.

PO-1561

Risk of hepatocellular carcinoma after HCV eradication: capturing the role of portal hypertension

Elton Dajti¹, Giovanni Marasco¹, Federico Ravaioli¹, Alberto Ferrarese², Davide Festi¹, Antonio Colecchia². ¹University of Bologna, Bologna, Italy; ²Borgo Trento University Hospital of Verona, Unit of Gastroenterology, Verona, Italy
Email: e_dajti17@hotmail.com

Background and aims: Hepatitis C virus (HCV) eradication with direct-acting antivirals (DAAs) reduces but does not eliminate the risk for hepatocellular carcinoma (HCC). The development of surveillance strategies for HCC after the sustained virologic response (SVR) is warranted. We aimed to evaluate the role of spleen stiffness measurement (SSM) in the prediction of HCC risk in a cohort of patients with advanced chronic liver disease (ACLD) treated with DAAs.

Method: This is a retrospective cohort study of 140 patients with HCV-related ACLD successfully treated with DAAs at our centre between 2015 and 2017. Patients with available liver stiffness (LSM) and SSM before and at six months (SVR24) after treatment were included. A Cox regression model investigated the association between SSM and HCC.

Results: During a median follow-up of 41.5 (interquartile range 32–49) months, 20 patients presented HCC. SSM at SVR24 predicted HCC development in univariate and adjusted multivariate analysis (Hazard Ratio: 1.025; 95%-Confidence-Interval: 1.001–1.050); the best cut-off for this purpose was 42 kPa. Only one out of the 45 (2.2%) patients with LSM-SVR24 ≤ 10 kPa developed HCC, so this was the category at lowest risk of HCC (incidence rate of 0.65%/year). In patients with LSM-SVR24 > 10 kPa, HCC incidence was not further influenced by LSM values (10–20 kPa vs > 20 kPa), but by SSM-SVR24 values (≤ 42 vs > 42 kPa) (Figure 1A). Based on these values, risk could be stratified as moderate (incidence rate 3.14%/year) in patients with LSM-SVR24 10–20 kPa and SSM-SVR24 ≤ 42 kPa and high (incidence rate 9.71%/year) in patients with LSM-SVR24 > 20 kPa or SSM-SVR24 > 42 kPa (Figure 1B).

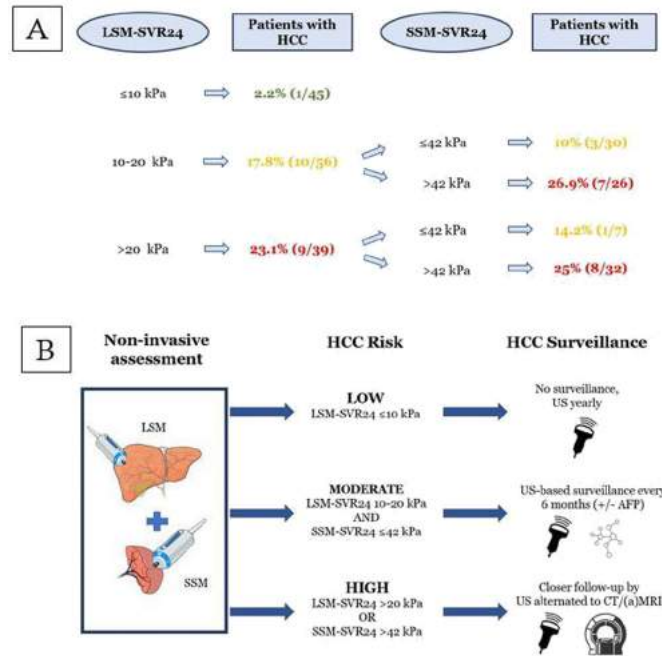


Figure: A new algorithm based on LSM and SSM values at SVR24 for the HCC risk assessment and the surveillance strategy after SVR achievement.

Conclusion: Portal hypertension, as evaluated by SSM, plays an essential role in liver carcinogenesis after DAA treatment. We proposed a new algorithm based on post-treatment values of LSM and SSM to stratify for the risk of HCC and to guide the surveillance strategy after SVR achievement.

PO-1918

The impact of hepatitis C virus eradication on hepatocarcinogenesis in haemophiliacs

Yosuke Inukai¹, Norihiro Imai¹, Kenta Yamamoto¹, Takanori Ito¹, Yoji Ishizu¹, Takashi Honda¹, Masatoshi Ishigami¹, Mitsuhiro Fujishiro¹. ¹Nagoya university graduate school of medicine, Gastroenterology and Hepatology, Aichi, Japan
Email: yokmok@med.nagoya-u.ac.jp

Background and aims: Haemophiliacs infected with hepatitis C virus (HCV) are known to develop cirrhosis and hepatocellular carcinoma (HCC) at a relatively younger age than non-haemophilic patients. Although recent progress in direct-acting-antivirals allow high rate of sustained virological response (SVR) against HCV, the clinical impact of HCV eradication in haemophiliacs remains unclear. The aim of this study is to compare the clinical outcomes after SVR against HCV in haemophiliacs with non-haemophilic patients.

Method: 699 patients who achieved SVR after HCV antiviral treatment were enrolled. Patients were divided into two groups; 78 haemophiliacs (H-group) and 621 non-haemophilic patients (NH-group). We evaluated the patient characteristics, clinical outcome and cumulative incidence of HCC after SVR.

Results: Compared with NH-group, patients in H-group were significantly younger, had more human immunodeficiency virus or hepatitis B virus co-infection and lower hepatic fibrosis score. No difference was found in the incidence of liver disease-related and overall death between the two groups during a mean follow-up of 7 years.

Four patients (5%) in H-group and 36 patients (6%) in NH-group were diagnosed as HCC after SVR. Multivariate analysis showed that male, age and cirrhosis were significant risk factors for incidence of HCC. There was no significant difference in the cumulative incidence of HCC after propensity score matching, adjusting for risk factors for HCC between the two groups.

POSTER PRESENTATIONS

Conclusion: Haemophilia is not a significant risk factor for hepatocarcinogenesis after SVR against HCV.

PO-1919

Long term follow-up in HCV infected patients with end stage chronic kidney disease after DAA therapy

Joan Martínez-Campanos^{1,2}, Raquel Muñoz Gómez³, María Carlota Londoño^{4,5}, Mercé Roget⁶, Miguel Serra⁷, Desamparados Escudero-García⁷, Laura Puchades⁷, Manuel Rodríguez⁸, Juan E. Losa-García⁹, María Luisa Gutierrez¹⁰, Isabel Carmona¹¹, Francisco Javier García-Samaniego Rey^{5,12}, Luis Enrique Morano Amado^{13,14}, Ignacio Martín-Granizo Barrenechea¹⁵, Marta Montero¹⁶, Martín Prieto¹⁷, Manuel Delgado¹⁸, Natalia Ramos Terrada¹⁹, Mar Riveiro Barciela^{1,5}, Maria Buti^{1,5}. ¹Hospital Universitario Vall d'Hebron, Liver Unit, Internal Medicine, Barcelona, Spain; ²Universitat Autònoma de Barcelona, Departamento de Medicina, Bellaterra, Spain; ³Hospital General Universitario 12 de Octubre, Gastroenterology, Madrid, Spain; ⁴Hospital Clinic/IDIBAPS, Liver Unit, Barcelona, Spain; ⁵Instituto Carlos III, Centro de Investigación Biomédica en Red de enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; ⁶Consorci Sanitari de Terrassa, Liver Unit, Terrassa, Spain; ⁷Hospital Clínico Universitario de Valencia, Digestive Medicine Service, Valencia, Spain; ⁸Hospital Universitario Central de Asturias, Gastroenterology, Oviedo, Spain; ⁹Hospital Universitario Fundación Alcorcón, Infectious Diseases, Madrid, Spain; ¹⁰Hospital Universitario Fundación Alcorcón, Gastroenterology, Madrid, Spain; ¹¹Hospital Universitario Virgen de la Macarena, Digestive Diseases, Sevilla, Spain; ¹²Hospital Universitario La Paz/IdiPaz, Liver Unit, Madrid, Spain; ¹³Hospital Universitario Álvaro Cunqueiro, Infectious Diseases and Internal Medicine, Vigo, Spain; ¹⁴RIS (Red Española de Investigación en SIDA); ¹⁵Hospital Universitario Álvaro Cunqueiro, Gastroenterology, Vigo, Spain; ¹⁶Hospital Universitario y Politécnico de la Fe, Infectious Diseases, Valencia, Spain; ¹⁷Hospital Universitario y Politécnico de la Fe, Liver Unit, Valencia, Spain; ¹⁸Complejo Hospitalario Universitario A Coruña, Coruña, Spain; ¹⁹Hospital Universitario Vall d'Hebron, Nefrology, Barcelona, Spain
Email: mbuti@vhebron.net

Background and aims: Direct acting antivirals (DAA) based on the combination of an NS5 inhibitor and protease Inhibitor are highly effective and safe in patients with end-stage chronic kidney disease (ESCKD). Currently there is scarce data regarding the impact of HCV cure on the long-term follow-up of kidney function. We assessed the evolution of renal function and development of renal and liver events in a real-life cohort of patients with ESCKD who received DAAs and were followed for a mean of 3, 9 ($\pm 1, 5$) years.

Method: Multicentric retrospective-prospective study including patients with chronic kidney disease stage 3b-5 and dialysis who had previously participated in Vie-KinD¹ study in which HCV GT 1 and 4 patients received OBV/PTV/r \pm DSV for 12–24 weeks. Data on long-term hepatic and renal function, clinical events and mortality were collected.

Results: 135 patients were included in Vie-KinD study. SVR was achieved in 93% of the cases. At the time of starting DAAs, mean age was 58 (± 11) years, 70% had hypertension, 24% diabetes, 14% dyslipidemia and 64 (47%) had advanced fibrosis (F3/F4 by transient elastography). Fifteen (11%) patients had CKD stage 3b, 20 (15%) stage 4 and 100 (74%) stage 5. 105 were under renal replacement (78%). 52 (38%) had history of kidney transplant.

69 patients were followed mean of 3, 9 ($\pm 1, 5$) years. At baseline, mean creatinine and estimated glomerular filtration rate (eGFR) were 5, 8 (± 3) mg/dl and 13 ($\pm 8, 6$) ml/min respectively. Three (4%) patients had CKD stage 3b, 11 (16%) stage 4 and 55 (80%) stage 5. During the follow-up, 21 patients (36, 2%) died (7 due to cardiovascular events, 10 other causes, 2 liver-related and 2 kidney-related cause), 3 (4.3%) developed liver decompensation and 2 (2.9%) hepatocarcinoma. 25 (36.2%) individuals (21 CKD stage 5, 4 stage 4; 19 on dialysis) received a kidney transplant within a mean of 1, 9 ($\pm 1, 2$) years after HCV cure.

Among the 44 (63, 8%) patients who didn't require kidney transplant, 33 were on dialysis at baseline and 34 at last follow-up. There were no changes on the mean creatinine (5, 9 $\pm 2, 9$ mg/dl, $p = 0, 4$) or eGFR values (15, 5 $\pm 14, 3$ ml/min, $p = 0, 5$), though in 5 (8, 6%) there was an improvement in the CKD stage.

Conclusion: Long-term follow-up of CKD stage 3b-5 patients who achieved HCV cure after DAA shown a high mortality mainly due to cardiovascular events and a stabilization of renal function. A small proportion of patients (<10%) had an improvement on the renal function after HCV cure.

PO-2008

Liver stiffness measurements for the prediction of liver-related outcomes in chronic hepatitis C patients after viral elimination

Yen-Chun Liu^{1,2}, Rachel Wen-Juei Jeng^{1,2}, Ya-Ting Cheng^{1,2}, Yi-Chung Hsieh^{1,2}, Yi-Cheng Chen^{1,2}, Chun-yen Lin^{1,2}, Rong-Nan Chien^{1,2}, Tai Dar-In^{1,2}, I-Shyan Sheen^{1,2}. ¹Chang Gung University, Taoyuan, Taiwan; ²Linkou Chang Gung Memorial Hospital, Gastroenterology and Hepatology, Taoyuan, Taiwan
Email: rachel.jeng@gmail.com

Background and aims: The utility of liver stiffness measurements (LSM) before or after direct acting antiviral agents (DAA) were reported to be predictive of liver-related adverse outcomes including HCC and hepatic decompensation. However, there's no comparison of the LSM's predictability at pre-DAA and SVR-24. The aim of the study was to compare predictive performances of LSM at different assessment timepoint (pre-DAA versus SVR-24) for liver-related adverse outcomes.

Method: Chronic hepatitis C patients achieved HCV elimination by interferon-free DAAs, whose LSM report by transient elastography (TE, Fibroscan) available at baseline and SVR-24, in Chang Gung Memorial Hospital were enrolled. The predictions for HCC and hepatic decompensation between baseline and SVR-24 LSM were compared by testing accuracy and AUROC. The cumulative de-novo HCC and decompensation incidences were calculated by Kaplan-Meier method.

Results: Among 951 patients enrolled, 19% had liver cirrhosis and 40% were males. The median follow-up duration was 22 months. The area under ROC curve for HCC and hepatic decompensation prediction by pre-DAA vs. SVR 24 were 0.821, 0.919 vs. 0.804, 0.924, respectively, both $p > 0.1$ (Figure). The optimal cut-off value for prediction of HCC and hepatic decompensation by Youden index was lower when adopting SVR-24 timepoint (10 and 16 kPa) than pre-DAA treatment (12 and 18 kPa). The 2-year cumulative incidence of HCC of patients with pre-DAA LSM > 12 kPa was 8% vs. 0.7% (LSM < 12 kPa), $P < 0.001$, similar to that using SVR 24 LSM > 10 kPa (8.7% vs. 1%). The 2-year cumulative incidence of hepatic decompensation of patients with pre-DAA LSM > 18 kPa was 10.8% vs. 0.3% (LSM < 18 kPa), $P < 0.001$, while that using SVR 24 LSM > 16 kPa was 13.6% vs. 0.4%.

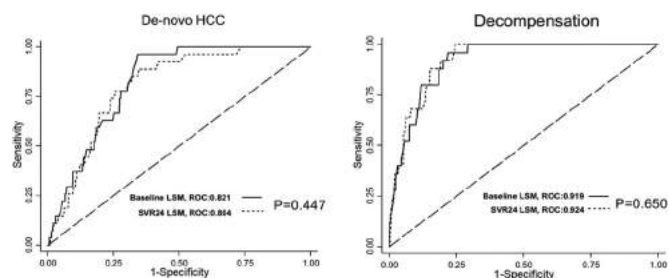


Figure:

Conclusion: The predictive performance of LSM for HCC and hepatic decompensation event are comparable at pre-DAA treatment or SVR-24 timepoints. The optimal cut-off value shall be adjusted according to the assessment timepoint.

PO-2418

Hepatitis C virus genotype 3 is associated with high risk of de novo portal vein thrombosis in cirrhotic patients after successful antiviral therapy: Russian long-term single center experience

Ekaterina Nabatchikova¹, Dzhamal Abdurakhmanov¹, Teona Rozina^{1,2}, Elena Nikulkina¹, Elena Tanashchuk¹, Sergey Moiseev^{1,2}. ¹*I.M. Sechenov First Moscow State Medical University (Sechenov University), The Department of Internal, Occupational Diseases and Rheumatology;* ²*M.V. Lomonosov Moscow State University*
Email: e.nabat4ikova@gmail.com

Background and aims: Portal vein thrombosis (PVT) is one of the most serious complications of liver cirrhosis, leading to the clinical decompensation and high risk of mortality. Successful antiviral therapy with direct-acting antivirals (DAAs) is reported to improve clinical outcomes in cirrhotic patients. However, data of the PVT risk after hepatitis C virus (HCV) eradication is not enough. The aim of our study was to assess incidence and risk factors of PVT in patients with HCV-related cirrhosis treated by DAAs.

Method: The prospective single-center cohort study included patients with HCV-related cirrhosis treated by DAAs between July 2015 and January 2020. Exclusion criteria was previous and present PVT. Patients who achieved sustained virological response underwent clinical, laboratory and imaging assessment every 3–6 months after the end of therapy (EOT).

Results: A total of 229 cirrhotic patients were enrolled. The median age was 54 (25; 60, 5) years, 48% were males, diabetes was present in 20%, obesity-in 33%, HCV genotype 3-in 25% and 30% were treatment-experienced. Child-Pugh class B/C were found in 28.4%. Baseline median MELD score was 11 (9; 13), liver stiffness (n = 131)-22.7 (16.1; 28.2) kPa, platelet count $100 \times 10^3/\text{ml}$ were in 52.8% of patients, albumin $\leq 35 \text{ g/l}$ -35.4%, bilirubin $\geq 34 \mu\text{mol/l}$ -18.3%, prothrombin time $\leq 60\%$ -19.7%, aspartate aminotransferase-platelet ratio index >2 -55.4%, fibrosis-4 score ≥ 3.25 -67.2%. Esophageal varices were in 61%, ascites-24.4%. The median follow-up time after EOT was 30 (18; 36) months. De novo PVT occurred in 8 (3, 5%) patients. The median time from EOT to PVT diagnosis was 24 (13.5; 30) months. The cumulative incidence of developing PVT was 0, 9% and 5, 9% at 1-, 3-years, respectively. At the univariate analysis, HCV genotype 3 (Hazard ratio (HR) 9.4; $p=0.008$), prothrombin time $\leq 60\%$ (HR 4.81; $p=0.027$), ascites (HR 6.14; $p=0.018$) and spleen size $\geq 81 \text{ cm}^2$ (HR 8, 47; $p=0, 046$) were significantly associated with the risk of PVT. At the multivariate analysis, only HCV genotype 3 (HR 7.19; $p=0.021$) was independent risk factor for PVT. By Kaplan-Mayer analysis, patients infected HCV genotype 3 have higher cumulative risk of PVT compared to patients with non-3 genotype (Figure).

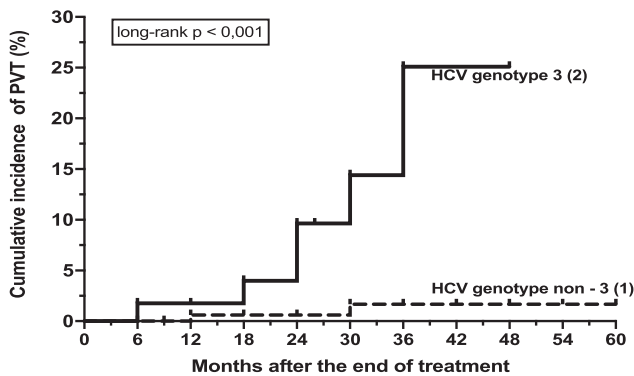


Figure: Cumulative incidence of PVT in DAAs treated cirrhotic patients with SVR.

Conclusion: Cirrhotic patients infected HCV genotype 3 have considerable cumulative risk of PVT occurrence and need more careful monitoring after antiviral therapy in order to prevent clinical decompensation.

PO-2708

Impact of direct-acting antiviral treatment on mortality related to extrahepatic manifestations: findings from a large population-based cohort in British Columbia, Canada

Dahn Jeong^{1,2}, Stanley Wong², Mohammad Ehsanul Karim^{1,3}, Sofia Bartlett^{2,4}, James Wilton², Makuza Jean Damascene^{1,2}, Hector Velasquez², Mawuena Binka², Prince Adu^{1,2}, Margo Pearce², Amanda Yu², Maria Alvarez², Hasina Samji^{2,5}, Younathan Abdia², Mel Krajden^{2,4}, Naveed Janjua^{1,2}. ¹*University of British Columbia, School of Population and Public Health, Vancouver, Canada;* ²*British Columbia Centre for Disease Control, Vancouver, Canada;* ³*Centre for Health Evaluation and Outcome Sciences, Vancouver, Canada;* ⁴*University of British Columbia, Department of Pathology and Laboratory Medicine, Vancouver, Canada;* ⁵*Simon Fraser University, Faculty of Health Sciences, Burnaby, Canada*
Email: dahn.jeong@bccdc.ca

Background and aims: Chronic hepatitis C virus (HCV) infection is associated with mortality due to extrahepatic manifestations (EHM). The sustained virologic response (SVR) following the highly effective direct-acting antivirals (DAA) has been linked to decreased all-cause and liver-related mortality. However, evidence on the impact of DAA on EHM-related mortality is lacking. This study assessed the impact of DAA treatment on reducing mortality related to EHM using a population-based linked administrative data.

Method: The British Columbia (BC) Hepatitis Testers Cohort includes ~1.3 million people tested for HCV since 1990 and is linked with administrative health data, including medical visits, hospitalizations and chronic disease registry. We compared three groups of individuals: treated and SVR, treated and no-SVR, and untreated. EHM mortality included deaths due to diabetes, rheumatoid arthritis, cardiovascular, cerebrovascular, renal and neurocognitive diseases. Individuals were followed from baseline to the earliest of 1) death due to EHM 2) other death or 3) end of study (2019/12/31). EHM mortality rates were computed, and incidence curves were generated for each group. To adjust for differences in baseline characteristics, we estimated the inverse probability of treatment weights (IPTW). We used IPTW-weighted multivariable subdistributional hazards model adjusting for competing risk and confounders.

Results: Study population included 10, 694 treated (10, 254 SVR, 440 no-SVR) and 10, 694 untreated individuals. People who never received treatment had the highest EHM mortality rate, with 29.4 per 1, 000 person-years of follow-up (PYFU) (95% confidence interval [CI] 27.2–31.8). Among those who received DAA treatment, those who didn't have SVR had an EHM mortality rate of 25.3 per 1, 000 PYFU (95% CI 16.7–38.5 per 1, 000 PYFU). Those who had SVR had the lowest EHM mortality rate, with 5.9 per 1, 000 PYFU (95% CI 5.0–6.9 per 1000 PYFU). Figures show the 5-year (A) survival probability and (B) cumulative incidence curves for deaths related to EHM. In the multivariable model, the treated and SVR group had the greatest reduction in EHM mortality (adjusted hazard ratio [aHR] 0.16, 95% CI 0.13–0.20), followed by the treated and no-SVR group (aHR 0.57, 95% CI 0.34–0.94) compared to the untreated group. Older age and history of other comorbid conditions including ischemic heart disease, heart failure, hypertension, end-stage renal disease, diabetes mellitus, cirrhosis were associated with increased risk of EHM-related mortality.

POSTER PRESENTATIONS

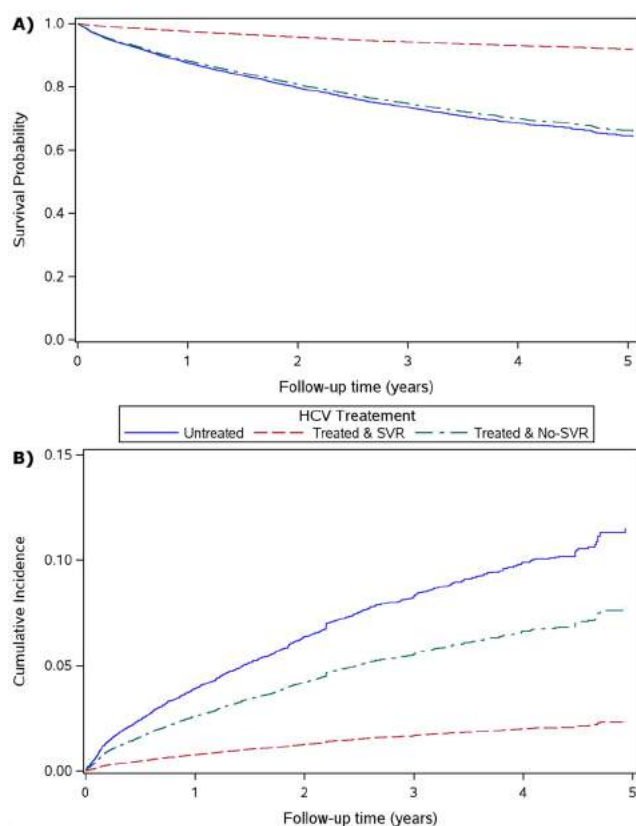


Figure:

Conclusion: Virologic cure of HCV following DAA treatment was associated with a significant reduction in mortality due to extrahepatic manifestations, with a 85% reduction in EHM mortality associated with SVR. This highlights the crucial need of providing diagnosis and treatment for people living with HCV infection to reduce extrahepatic mortality.

PO-2836

Higher all-cause mortality in individuals living with HIV cured of HCV by direct-acting antivirals compared to HIV mono-infection despite controlled HIV: Results from the ANRS-CO4 FHDH cohort

Maria Requena¹, Sophie Grabar^{1,2,3}, Dominique Costagliola¹, Karine Lacombe^{1,4}. ¹Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLSP), Paris, France; ²Hôpital Cochin, Unité de Biostatistiques et Epidémiologie, Paris, France; ³Université de Paris Descartes, Paris, France; ⁴Hôpital Saint-Antoine, Service de maladies infectieuses et tropicales, Paris, France
Email: maria.requena@iplsp.upmc.fr

Background and aims: Hepatitis coinfection contributes to the leading causes of mortality among people who live with HIV (PLWH). Since 2014, direct-antiviral agents (DAAs) have enabled a 95% cure rate and decreased hepatic complications in mono-infected patients with Hepatitis C virus (HCV). This study aimed to compare all-cause mortality in PLWH achieving HIV viral suppression (<200 copies/ml) cured of HCV by DAAs to all-cause mortality in virally suppressed HIV mono-infected individuals of the nationwide ANRS-CO4 French Hospital HIV Database (FHDH) cohort.

Method: Cured HCV PLWH with controlled HIV viral load who started DAAs between September 2013 and September 2018 were included. They were matched on age (± 5 years), gender, HIV transmission route (men who have sex with men -MSM- intravenous drug user -IVDU- or other), AIDS status, and BMI (± 1) to up to 10 HIV mono-infected patients with controlled HIV viral load, followed at the index date (date of HCV cure). Multivariable Cox proportional hazards models with robust variance estimates were used to compare mortality in

both groups accounting for age, gender, HIV transmission route, AIDS status, year of first HIV serology, CD4 nadir, and BMI.

Results: 3, 574 PLWH cured of HCV by DAAs and 28, 846 mono-infected PLWH were included. Median follow-up time was 2.0 years in DAA cured, interquartile range [1.1; 3.7], and 2.2 years [1.3; 2.9] in mono-infected PLWH. Median age was 52.6 years [47.2; 55.9] and 52.0 years [48.4; 56.3]; 2, 649 (74.1%) and 22, 085 (76.6%) were men, respectively. In DAA cured participants, 311 (8.7%) had cirrhosis. One hundred and ten deaths occurred in the DAA cured PLWH group and 384 in the HIV-mono-infected PLWH group, with respective three-year survival estimates of 96% (95% CI 95–97) and 98% (95% CI 98–98). HCV past coinfection was associated with a higher risk of all-cause death (hazard ratio HR = 1.72, 95% CI 1.04–2.84), as were IVDU (HR = 1.76, 95% CI 1.02–3.06) and CD4 nadir <200 cells/ml (HR = 2.83, 95% CI 1.40–5.71). The risk of death with cured HCV co-infection was higher after 18 months of follow-up (relative risk 0–18 months = 1.65, 95% CI 1.44–1.88, relative risk 18–36 months = 3.08, 95% CI 2.76–3.43).

Conclusion: Despite HCV cure and HIV viral suppression, HCV-coinfected PLWH cured by DAAs are at higher risk of all-cause mortality than mono-infected PLWH, even after controlling for CD4 nadir. The risk is increased after 18 months of follow-up.

PO-2946

Patients with cirrhosis show an improvement in dynamic liver function following the eradication of hepatitis C virus with direct acting antivirals

Jibran Mecci¹, Polychronis Kemos¹, Graham Foster¹. ¹Barts Health NHS Trust, Barts Liver Centre, London, United Kingdom
Email: alij16@hotmail.com

Background and aims: The introduction of direct acting antiviral (DAA) therapy in the treatment of hepatitis C virus (HCV) has revolutionised care for those with cirrhosis. Fibrosis and portal hypertension improve post eradication however, functional improvement has yet to be determined with reports of MELD score not showing overall improvement. We used indocyanine green (ICG) excretion to resolve this uncertainty.

Method: This was a prospective, longitudinal, observational trial, looking at a single cohort of patients with hepatic C cirrhosis treated at Bart's Health NHS trust. We included adult patients with cirrhosis (Fibroscan >11.5 kPa or APRI score >2 or liver biopsy or imaging report of cirrhosis) who were starting DAA treatment. Those unable to consent, pregnant or allergic to ICG were excluded. ICG excretion is solely by the liver and was measured by near infra-red spectroscopy (LiMON, PULSION medical systems, Munich, Germany) and stated as ICG retention at 15 minutes (ICGR15), with lower values showing better function. Data was captured at baseline, 4 weeks (± 2 weeks) post treatment and 1 calendar year (± 2 weeks). Correlations were determined and then inserted into a repeated measures analysis to determine to adjust for subject variance. Area under the curve (AUROC) estimation determined a cut-off value. The Declaration of Helsinki was adhered to (NCT02782247).

Results: Of the 52 patients willing to be enrolled, 43 had 2 or more investigations. Median age was 54 years old and most were male (58.1%). A history of heavy alcohol intake was reported in 27.2% with 25.6% being diabetic. Most cases were genotype 3 (58.1%) and Childs-Pugh A (88.5%) at enrolment. Fixed effects modelling showed a similar pattern though less marked with 5.38% initial improvement and 6.95% overall ($p < 0.001$, R^2 94.3%). Fibroscan readings improved by 6.53 kPa at 1 year ($p < 0.001$). We found an ICGR15 of 24.7% predicted an acceptable value of 15% at 1 year (AUROC: 0.88, 95% C.I: 0.68–1.00, $p < 0.001$, sensitivity = 83%, specificity = 93%).

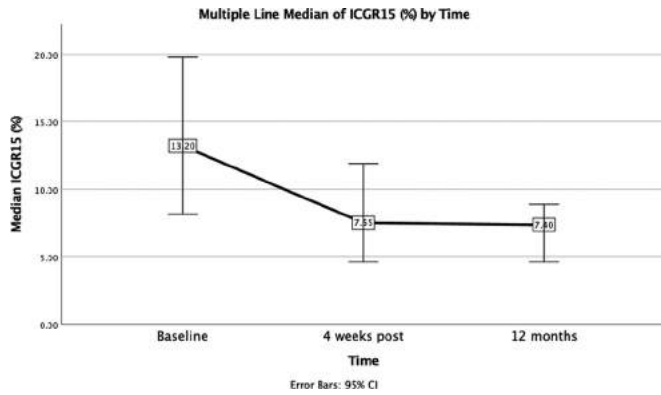


Figure: A line graph for the median percentage of ICG remaining after 15 minutes (ICG15) for all subjects over the course of the year with 95% confidence intervals, displayed.

Conclusion: We have demonstrated an improvement in dynamic liver function in patients with cirrhosis following HCV eradication.

Viral hepatitis C: Therapy and resistance

PO-51

Aiming for HCV elimination-Optimizing DAA therapy by characterisation of patients lost to follow-up (LTFU) in a large real world setting-Data from the German Hepatitis C-Registry (DHC-R)

Stefan Christensen^{1,2}, Peter Buggisch³, Albrecht Stoehr³, Gerlinde Teuber⁴, Hartwig Klinker⁵, Uta Merle⁶, Yvonne Serfert⁷, Markus Cornberg^{8,9}, Christoph Sarrazin^{10,11}, Karl-Georg Simon¹², Stefan Mauss¹³ and German Hepatitis C-Registry⁷. ¹CIM Münster, Muenster, Germany; ²Muenster University Hospital, Department of Gastroenterology and Hepatology, Muenster, Germany; ³ifi-Institute for Interdisciplinary Medicine, Hamburg, Germany; ⁴Practice PD Dr. med. G. Teuber, Frankfurt, Germany; ⁵University Hospital Würzburg, Würzburg, Germany; ⁶Heidelberg University Hospital, Heidelberg, Germany; ⁷Leberstiftungs-GmbH Deutschland, Hannover, Germany; ⁸Hannover Medical School, Hannover, Germany; ⁹Centre for Individualised Infection Medicine (CIIM), Hannover, Germany; ¹⁰St. Josefs-Hospital, Medical Clinic 2, Wiesbaden, Germany; ¹¹Goethe University Hospital, Medical Clinic 1, Frankfurt, Germany; ¹²MVZ Dres. Eisenbach, Simon, Schwarz GbR, Leverkusen, Germany; ¹³Center for HIV and Hepatogastroenterology, Düsseldorf, Germany
Email: christensen@cim-ms.de

Background and aims: Prevention, diagnosis and linkage to care are key factors to reach the goal of HCV elimination especially in vulnerable patient groups. A full course of direct acting antivirals

Baseline characteristics	mITT population N=6,990*	Lost before EOT N=432*	Lost after EOT N=476*	p ^{1**}	p ^{2**}
Male, n (%)	4,164 (59.6)	313 (72.5)	338 (71.0)	<0.001	<0.001
Age (years, mean ± SD)	52.5 ± 12.9	46.5 ± 13.2	46.4 ± 12.4	<0.001	<0.001
Psychiatric disorders, n (%)	1,040 (14.9)	48 (11.1)	63 (13.2)	0.030	0.350
HCV/HIV co-infection, n (%)	605 (8.7)	20 (4.6)	18 (3.8)	0.002	<0.001
Non-OST/NDU, n (%)	4,680 (67.0)	191 (44.2)	176 (37.0)	<0.001	<0.001
Non-OST/DU, n (%)	1,403 (20.1)	121 (28.0)	153 (32.1)	<0.001	<0.001
OST, n (%)	907 (13.0)	120 (27.8)	147 (30.9)	<0.001	<0.001

Baseline characteristics	Regression analysis			
	mITT population vs. lost before EOT		mITT population lost vs. lost after EOT	
	univariate	multivariate [#]	univariate	multivariate [#]
Sex male vs. female	<0.001	0.011	<0.001	0.026
Age (years)	<0.001	<0.001	<0.001	<0.001
Psychiatric disorders	0.032	0.001	0.329	
HCV/HIV co-infection	0.004	0.001	<0.001	<0.001
Non-OST/NDU vs. Non-OST/DU vs. OST	<0.001	<0.001	<0.001	<0.001

*if not otherwise indicated (specific lab data were not available for all patients); **depending on scale level Chi-Square Test / t-test, Median Test; [#]significant univariate parameters with at least 75% valid data; DU, former/current drug use and/or HCV transmission via drug abuse; HCV, hepatitis C virus; HIV, human immunodeficiency virus; EOT, end of treatment; mITT, modified intention-to-treat; NDU, no former/current drug use/other mode of HCV transmission; non-OST, patients without OST; OST, opioid substitution therapy; p¹, p-value not lost vs. lost before EOT; p², p-value not lost vs. lost after EOT; SD, standard deviation.

Figure: (abstract: PO-51): Baseline characteristics of interest and results with significant differences in regression analysis

POSTER PRESENTATIONS

(DAA) leads to HCV-cure in more than 90% of patients chronically infected. Simplifying all aspects associated with DAA treatment may facilitate access in particular for vulnerable patient groups. To characterise patients who went lost-to-follow-up (LTFU) before end of treatment (EOT) might help to identify those in need for alternative access strategies to DAA therapy.

Method: The DHC-R (German Hepatitis C-Registry) is a national multicentre real-world registry currently including about 17,700 patients recruited by more than 250 centres. Data were analysed as of Jan 01, 2020. The present analysis of patients with LTFU before and after EOT in comparison to patients with data on sustained virological response (SVR) 12/24 weeks after EOT (modified Intention-to-treat population, mITT) is based on 7,898 patients (ITT) treated with GLE/PIB, SOF/LDV, SOF/VEL, SOF/VEL/VOX and GZR/EBR (\pm ribavirin). LTFU before EOT was defined as reported lost before treatment was ended as scheduled, LTFU after EOT as lost after a full course of therapy without SVR12/24 data.

Results: In total, 11.5% (908/7,898) of the patients were reported as lost: 432 patients were lost before and 476 patients were lost after EOT. Thus, 6,990 were included in the mITT analysis. Baseline characteristics of interest are given in Table 1. The overall SVR rates were 86% (6,823/7,898) and 98% (6,823/6,990) in the ITT and mITT analysis, respectively. In multivariate regression analysis (Figure), being male or of younger age and having a history of drug abuse and/or an opioid substitution therapy (OST) has been associated with a higher risk of LTFU before and after EOT, HIV/HCV co-infected and patients with psychiatric disorders do have a lower risk of LTFU.

Conclusion: It is known that patients lost after EOT have a high probability of achieving SVR. In this analysis, we identified patient groups with a higher risk of LTFU before end of treatment. In the setting of good tolerability and high effectiveness of DAA therapy, alternative treatment approaches tailored to the target group such as less intense monitoring or in contrast, directly observed treatment (DOT) should be considered.

PO-81

Economic consequences of anti-HCV treatment of patients diagnosed through screening in Italy: a prospective modeling analysis.

Loreta Kondili¹, Andrea Marcellusi^{2,3}, Claudia Simonelli², Francesco Saverio Mennini^{2,3}. ¹Istituto Superiore di Sanità, Center for Global Health, Rome, Italy; ²Center for Economic and International Studies: Economic Evaluation and HTA (CEIS-EEHTA); ³Institute of Leadership and Management in Health, Kingston Business School
Email: loreta.kondili@iss.it

Background and aims: The World Health Organization (WHO) defined prevention and treatment targets for the elimination of the hepatitis C virus (HCV) as a public health threat by 2030. In Italy, the European country with the highest disease burden, challenges remain to achieve this goal, considering the significant portion of HCV-infected patients that are undiagnosed. Our aim is to evaluate the cost-consequences of the investment in anti-HCV treatment by the Italian National Health System (NHS) for patients that will be newly diagnosed through active HCV screening, to be implemented in Italy starting from 2020.

Method: A previously published Markov model was used to estimate the disease complications avoided and the associated savings over 20 years to treat a standardized population of 1,000 HCV-infected patients diagnosed as a result of the approved screening. Fibrosis stage and genotype distributions, treatment effectiveness, disease progression probabilities were obtained from the literature. Real-life medical expenses for disease management were estimated starting from a representative cohort of HCV treated patients in Italy (Italian Platform for the Study of Viral Hepatitis Therapies -PITER). The breakeven point in time (BPT) was defined as the time in years required for the initial investment in treatment to be recovered in terms of cumulative costs saved.

Results: For 1,000 standardized treated patients diagnosed through an active HCV screening, over a 20-year time horizon there are 589 avoided events of progression which are associated to €68.31 million net savings accrued by the Italian NHS. The initial investment in treatment is recouped in the form of savings from disease complications avoided in 4.8 years.

Conclusion: Investment in treatment of newly diagnosed patients will bring a significant reduction in disease complications which is associated to great economic benefits. This type of action can reduce the infection rate and clinical and economic disease burden of HCV infection in Italy, necessary to achieve the WHO elimination goals.

PO-153

Prevalence and origin of rare HCV Genotypes in DAA-naïve and DAA-experienced patients

Julia Dietz¹, Christiana Graf¹, Peter Buggisch², Beat Müllhaupt³, Kerstin Port⁴, Kai-Henrik Peiffer¹, Georg Dultz¹, Christophe Moreno⁵, Thomas Berg⁶, Christoph Berg⁷, Stefan Zeuzem¹, Christoph Sarrazin^{1,8}. ¹Goethe University Hospital, Department of Internal Medicine I, Frankfurt am Main, Germany; ²Institute for Interdisciplinary Medicine IFI, Hamburg, Germany; ³Swiss Hepato-Pancreato-Biliary Center and Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland; ⁴Department of Gastroenterology, Hepatology and Endocrinology, Medizinische Hochschule Hannover, Hannover, Germany; ⁵Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; ⁶Section of Hepatology, Department of Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany; ⁷Department of Gastroenterology, Hepatology, and Infectiology, University Hospital Tübingen, Tübingen, Germany; ⁸St. Josefs-Hospital, Wiesbaden
Email: julia.dietz@em.uni-frankfurt.de

Background and aims: Treatment of chronic hepatitis C virus (HCV) infection with direct acting antivirals (DAAs) is highly effective and high SVR (sustained virologic response) rates make global HCV eradication feasible. However, second generation DAAs are not available in all countries. Studies showed that rare HCV genotypes (GT) exist in certain countries and are associated with lower SVR rates. This study investigated the prevalence of rare HCV GT and resistance-associated substitutions (RASs) among European DAA-naïve and DAA-failure patients.

Method: The European resistance database contains samples from 7300 patients, 4499 of whom were DAA-naïve and 1258 had failed to an IFN-free DAA treatment. NS3, NS5A and NS5B population sequencing was conducted to determine the HCV GT and RASs conferring a >2-fold increased DAA susceptibility were analyzed.

Results: In total, rare HCV GT were detected in 2% (72/4499) of DAA-naïve patients and 5% (57/1258) of DAA failures. The frequencies of rare GT1 (1c, 1e, 1g, 1h, 1i, 1p) and GT6 (6a, 6e, 6f, 6m, 6n, 6r) were comparable in DAA-naïve (GT1, 17%; GT6, 15%) and DAA-experienced patients (GT1 and GT6, 11% each). In contrast, rare GT2 (2i, 2k, 2l, 2m) and GT5a were less common among DAA failures (4% each) compared to DAA naïve patients (15% each). Interestingly, the frequencies of rare GT3 (3b, 3g, 3h, 3i, 3k) and GT4 (4b, 4c, 4f, 4m, 4n, 4o, 4r, 4v) were higher in DAA failures (GT3, 25%; GT4, 47%) compared to DAA-naïve patients (GT3, 14%; GT4, 25%). Among DAA failures, rare HCV GT were more common after first generation DAA regimens (LDV/SOF, DCV/SOF, GZR/EBR, 3D) (79%, 45/57) compared to second generation pangenotypic regimens (VEL/SOF, G/P) (21%, 12/57). With regard to RASs, characteristic NS5A patterns were particularly evident in patients with rare GT4 (L28M, M31L/V) and rare GT3 (A30 K, L31M) and Y93H was rare in both GT. Patients with rare GT1, GT2 or GT4 mainly originated from sub-Saharan Africa, those with rare GT3 from India or Pakistan, those with GT5a from South Africa and patients with rare GT6 came from South-East Asia.

Conclusion: Rare HCV GT were detected in 2% of DAA-naïve and 5% of DAA failure patients. Rare HCV GT were more frequent after failure to

first generation DAA regimens compared to second generation regimens. Patients originated mainly from Africa or South Asia and the first-generation DAAs available in these countries may not be effective enough to achieve the goals of global HCV elimination.

PO-377

Risk of multiple drug-drug interactions (DDIs) in HCV patients receiving pangenotypic DAAs (pDAAs): A complex drug interaction scenario first time evaluated in German patients

Tim Umland¹, Andreas Hintz¹, Gero Niess², Mehtap Guendogdu², Frank Tacke³. ¹Alexander Apotheke, Hamburg, Germany; ²Gilead Sciences GmbH, Planegg, Germany; ³Charite-Campus Mitte Medizinische Klinik m.S. Hepatologie und Gastroenterologie, Berlin, Germany

Email: frank.tacke@charite.de

Background and aims: Previous studies have evaluated the risk of DDIs in HCV patients receiving pangenotypic DAAs (pDAAs), but all based on given drug pair interactions (DAA and one comedication). However, none has considered that HCV patients take multiple comedications and the presence of multiple DDIs can exist in the same patient involving more than one comedication. Our aim was to describe for the first time the prevalence of this situation and the linked risk of DDIs.

Method: Data were obtained using the German IMS LRx database (IQVIA) covering about 80% of statutory health insurance prescriptions. Patients (pts) with HCV therapy between Nov 2019 and Oct 2020 were included in the analysis. Comedication was evaluated and potential DDIs and contraindications regarding pangenotypic DAAs prescribed in HCV therapy (i. e. Sofosbuvir/Velpatasvir [SOF/VEL], and Glecaprevir/Pibrentasvir [GLE/PIB]) were assessed using the University of Liverpool Hep Drug Interactions database. This study focused on evaluating patients receiving more than one comedication linked to risk of DDIs and the pharmacokinetic outcome of the different identified DDIs, classified in: increase in comedication (linked to safety/tolerability issues), increase in DAA (potential safety/tolerability issue), and decrease in DAA level (potential efficacy issue).

Results: Comedication was analyzed for 4, 950 HCV patients, 3, 154 treated with GLE/PIB and 1, 796 with SOF/VEL. The proportion of males and median age were similar in both groups: 32% vs 31%, and 46 y vs 48 y, respectively. Overall, 173 (3.5%) patients treated with pDAAs received ≥2 comedications showing risk of DDIs, concretely: two (116), three (47), four (7), and five (3) comedications.

For GLE/PIB, 102 (3.2%) patients received ≥2 comedications with DDI risk: two (74), three (23), four (4), and five (1) comedications. For SOF/VEL, 71 (4%) patients received ≥2 comedications with DDI risk: two (42), three (24), four (3), and five (2) comedications. In terms of the outcome; for GLE/PIB, 39 (1.2%) patients resulted in a risk of DAA concentration decrease, 20 (0.6%) in an increase in comedications, and 2 (0.06%) in an increase in DAA concentration. There were 2 patients receiving each one 3 concomitant drugs linked to a decrease of DAA, but none contraindicated. For SOF/VEL, 18 (1.0%) patients resulted in a risk of DAA decrease, 11 (0.6%) in an increase in comedications, and none in an increase in DAA, and there were no patients receiving 3 or more concomitant drugs linked to a decrease in the DAA.

Conclusion: In Germany, the percentage of HCV patients treated with pDAAs and ≥2 comedications showing risk of DDIs is 3.5%. The most frequent outcome resulted from the multiple DDI context was a decrease in the DAA, having similar risk both pDAA.

PO-468

Direct antivirals can achieve a cure in all patients with chronic hepatitis C due to genotype 5. A French multicentre study.

Armand Abergel¹, Carine Nicolas¹, Helene Fontaine², Dominique Guyader³, Veronique Loustaud-Ratti⁴, METIVIER Sophie⁵, Tarik Asselah⁶, Dominique Thabut⁷, Marc Bourliere^{8,9,10}, Valérie Canva¹¹, Victor de Lédighen¹², Dominique Larrey¹³, Varaut Anne¹⁴, Laurent Alric¹⁵, Francois Bailly¹⁶, Géraldine Lamblin¹, Leon Muti¹, Laurent Poincloux¹, Eyméric Chartrain¹, Maud Reymond¹, Benjamin Buchard¹. ¹CHU Clermont-Ferrand, Medecine Digestive et Hepato-Biliaire, Clermont-Ferrand, France; ²Hopital Cochin, Service d'Hepatologie, Paris, France; ³CHU Rennes, Service d'Hepatologie, Rennes, France; ⁴CHU Limoges, Service d'Hepato-gastroenterologie, Limoges, France; ⁵CHU Toulouse, Service d'Hepatologie, Toulouse, France; ⁶Hopital Beaujon, Service d'Hepato-gastroenterologie, Paris, France; ⁷Hopital La Pitie Salpetriere, Service d'Hepato-gastroenterologie, Paris, France; ⁸Hopital Saint-Joseph, Service d'Hepato-gastroenterologie, Marseille, France; ⁹Department of Hepatology and Gastroenterology, Hôpital Saint Joseph, Marseille, France; ¹⁰Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques and Sociales de la Santé and; ¹¹CHU Lille, Service d'Hepatologie, Lille, France; ¹²CHU Bordeaux, Service d'Hepatologie, Bordeaux, France; ¹³CHU Montpellier, Service d'Hepato-gastroenterologie, Montpellier, France; ¹⁴Hopital Henri Mondor, Service d'Hepatologie, Créteil, France; ¹⁵CHU Toulouse, Service de Medecine interne, Toulouse, France; ¹⁶CHU Lyon, Service d'Hepatologie, Lyon, France

Email: cnicolas@chu-clermontferrand.fr

Background and aims: Genotype 5 (GT5) is found mainly in South and East Africa and in restricted areas of Belgium, France, Spain, Greece, Canada, Brazil, Syria... Prevalence of HCV GT5 in France is 2% and 14% in our area from central France. Migration from Syria can increase the prevalence of this genotype in European countries. As there are few data published on the response to treatment of these patients with new drugs. Our study aimed to evaluate the sustained virological response (SVR) in patients infected with HCV GT5 treated with direct-acting antivirals (DAA).

Methods: A cohort of 139 patients with HCV GT5 from 13 hospitals (central France = 101, other hospitals = 38) received all-oral DAA for 8, 12 or 24 weeks from 2014 to 2020. These patients were treated either in clinical trials (n = 39) or according to international guidelines (n = 100). The SVR was defined as an HCV RNA below the lower limit of quantification (LLOQ) 12 weeks after the end of treatment (SVR12).

Results: Baseline characteristics were: mean age 66 years, sex ratio 0.7 (M/F), fibrosis score: 62% ≥F2 (86/139) including 24% F4 (33/139), pre-therapeutic viremia >800,000 UI/ml: 65% (90/139) and ALT higher than the upper limit of normal: 54% (75/141). The average treatment duration was 12 weeks. Distribution of patients according to drug combinations was: sofosbuvir (SOF)/ledipasvir (LDV) ± ribavirine (RBV) 67, SOF/VEL (velpatasvir) 35, glecaprevir (GLE)/pibrentasvir (PIB) 16, SOF/DCV (daclatasvir) ± RBV 13, SOF/VEL/VOX (voxilaprevir) 4, SOF/SMP (simeprevir) 1 and grazoprevir (GZR)/elbasvir (EBR)/RBV 1. Seventy patients out of 139 were treatment-naïve (50%) and 69 had been treated with interferon (IFN) therapy (50%) (48 relapsers and 21 non-responders). Thirty-nine patients out of 139 were included in clinical trials (28%). At the end of treatment, 99% (100/101) of patients had HCV RNA <LLOQ for those treated for 12 weeks (W), 100% (13/13) for 8 weeks and 100% (8/8) for 24 weeks. The overall SVR12 result was 98% (136/139). Relapse occurred in 2 patients (SOF/DCV, SOF/LDV). Their profiles were different but both patients had prior treatment with IFN. One patient had been successfully retreated with the same DAAs (SOF/LDV) plus RBV for 24 weeks (instead of 12 weeks) and another had refused a new treatment. One patient had on-treatment virologic failure (SOF/VEL/VOX) between W8 and end of treatment (W12). No resistance to the DAAs received had been found (hepatitis C national reference center). The patient was naïve and had a good DAA adherence. A second 12-week SOF/VEL/VOX treatment resulted in a cure.

POSTER PRESENTATIONS

Conclusion: A high SVR12, 99% (138/139) in intention to treat and 100% (138/138) per protocol, was achieved in HCV GT5 patients treated with a DAA-regimen. This cohort shows that the combination treatments of SOF/LDV, SOF/VEL and GLE/PIB are very efficient in patients infected with HCV GT5.

PO-773

Frequency and impact of potential multiple drug-drug interactions (DDIs) associated with pangenotypic direct-acting antivirals in patients receiving opioid substitution therapy

Tim Umland¹, Andreas Hintz¹, Gero Niess², Mehtap Guendogdu², Frank Tacke³. ¹Alexander Apotheke, Hamburg, Germany; ²Gilead Sciences GmbH, Planegg, Germany; ³Charite-Campus Mitte Medizinische Klinik m.S. Hepatologie und Gastroenterologie, Berlin, Germany
Email: gero.niess@gilead.com

Background and aims: Pangenotypic direct-acting antivirals (pDAA) are an essential prerequisite in reaching the global goal of eliminating hepatitis C virus (HCV) infections by 2030. Treatment of HCV infections in current and former people who inject drugs (PWID) is a cornerstone of this effort. However, previous studies have shown that polypharmacy and potential drug-drug-interactions (DDI) are issues of concern in treating patients who receive opioid substitution therapy (OST pts). The aim of the present analysis was to evaluate the frequency, type and possible consequences of potential multiple DDI, i.e. more than 2 concurrent DDI, of pDAA with comedication in a large nationwide cohort of OST pts.

Method: Data were obtained using the German IMS LRx database (IQVIA) covering about 80% of statutory health insurance prescriptions. Anonymised prescription information was extracted for the time period from November 2019 to October 2020. In OST pts, the frequency of potential multiple DDI between prescribed comedications and Sofosbuvir/Velpatasvir (SOF/VEL) and Glecaprevir/Pibrentasvir (GLE/PIB), respectively, was evaluated on the basis of the University of Liverpool Hep Drug Interactions database. Comedication was analysed according to ATC classes and individual substance levels. Clinical outcomes related to potential multiple DDI were evaluated for each substance.

Results: In total, 95,243 OST pts were included in the analysis. In 52,889 patients, at least one comedication that could be evaluated for DDI was documented. For the majority of these patients, no potential DDI were observed with SOF/VEL (57.9%) or GLE/PIB (47.6%). About one third received comedication with only one potential DDI (SOF/VEL: 27.2%; GLE/PIB: 31.1%). The total number of patients with at least two potential DDI related to pDAA was lower for SOF/VEL (n = 7, 883; 14.9%) compared to GLE/PIB (n = 11, 242; 21.3%). Almost twice as many patients had three or more potential DDI related to GLE/PIB compared to SOF/VEL (8.0% vs. 4.4%). Possible consequences of DDI include a decreased antiviral efficacy or an increased risk of adverse drug reactions (ADRs).

Conclusion: Multiple DDI with pDAA are likely to occur in a subset of OST patients. Compared to SOF/VEL, GLE/PIB is more frequently associated with potential multiple DDI in this population. Since the relevance of clinical outcomes may differ, possible consequences of DDI should be evaluated carefully prior to initiation of pDAA treatment in OST pts.

PO-815

Efficacy and safety of 8- or 12 weeks of glecaprevir/pibrentasvir in patients with signs of portal hypertension

Robert Brown¹, Michelle Collins², Amanda Emmett², Andrew Topp², Margaret Burroughs², Rosa Ferreira², Jordan Feld³. ¹Center for Liver Disease and Transplantation, Weill Cornell Medical College, New York, United States; ²AbbVie Inc., North Chicago, United States; ³Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Canada
Email: rsb2005@med.cornell.edu

Background and aims: High efficacy and safety of 8-week glecaprevir/pibrentasvir (G/P) therapy was seen in hepatitis C (HCV)-infected, treatment-naïve (TN), compensated cirrhosis (CC) patients in EXPEDITION-8. However, the efficacy and safety of 8- or 12 weeks of G/P in patients with signs of portal hypertension (PHT) continues to be an area of exploration.

Method: Data for TN, CC, HCV GT 1–6 patients were derived from ad-hoc subgroup analyses of the EXPEDITION-8 study and from 9 pooled, phase II/III studies for patients receiving 8- and 12 weeks of G/P, respectively. Signs of PHT included at least one of the following at baseline: FibroScan ≥ 20 kPa, platelets $< 100 \times 10^9/L$, or medical history consistent with PHT. The primary efficacy end point was SVR12; adverse events consistent with hepatic decompensation were assessed.

Results: Of 343 patients receiving 8 weeks of G/P, 208 were identified with signs of PHT; out of 392 patients in the 12-week group, 224 PHT patients were identified. Baseline characteristics and delineation of patients by inclusion criteria are provided in the Table. In 8- vs 12 weeks, SVR12 was 97.6% (203/208) vs 98.7% (221/224) in the intention-to-treat analysis. Eight patients did not achieve SVR12; 3 experienced virologic failures (one on 8-week therapy), 4 were lost to follow-up and 1 discontinued therapy. Three cases of hepatic decompensation were reported: 2 nonserious cases of ascites (1 each in 8- vs 12 weeks) and 1 serious case of esophageal variceal bleeding in the 12-week group; none were assessed as related to G/P or led to discontinuation of therapy.

Table: Baseline demographics and inclusion criteria in portal hypertension patients receiving 8- and 12-weeks of glecaprevir/pibrentasvir^a

	8-Weeks N = 208 n (%)	12-Weeks N = 224 n (%)
Male	136 (65.4)	127 (56.7)
Age, years, median (range)	57 (32–84)	59 (28–88)
Genotype		
1a/1b	64 (30.8)/75 (36.1)	34 (15.2)/84 (37.5)
2	15 (7.2)	47 (21.0)
3	43 (20.7)	42 (18.8)
4-6	11 (5.3)	17 (7.6)
FibroScan	149 (43.4) ^b	159 (40.6) ^c
≥ 20 kPa		
Platelets $< 100 \times 10^9/L$	80 (23.3) ^b	102 (26.0) ^c
Medical history consistent with PHT	70 (20.4) ^b	53 (13.5) ^c

^aITT population

^bN = 343

^cN = 392

ITT, intention-to-treat; PHT, portal hypertension

Conclusion: Eight weeks of G/P was as effective as 12 weeks of therapy in HCV patients with signs of PHT. Adverse events related to hepatic decompensation were uncommon in both groups. Analysis is ongoing.

PO-987

SH229 plus daclatasvir for treatment of chronic hepatitis C virus infection in China: a single-arm, open-label, phase 3 study

Rui Hua¹, Fei Kong¹, Xiaofeng Wen², Xingxiang Yang³, Chenxin Meng⁴, Yongfang Jiang⁵, Wen Xie⁶, Xiaozhong Wang⁷, Xueji Han⁸, Yan Huang⁹, Jiefei Wang¹⁰, Qing Mao¹¹, Yujuan Guan¹², Jiayu Chen¹³, Yingjie Ma¹⁴, Hong Ma¹⁵, Qingfang Xiong¹⁶, Xuebing Yan¹⁷, Huiying Rao¹⁸, Yingren Zhao¹⁹, Tong Sun²⁰, Xiaorong Mao²¹, Jianqi Lian²², Liying Zhu²³, Yongning Xin²⁴, Guojiong Deng²⁵, Yifei Wang²⁶, Bin Xu²⁷, Hainv Gao²⁸, Youwen Tan²⁹, Yinong Ye³⁰, Dongliang Li³¹, Dongliang Yang³², Minghua Su³³, Cheng Li³⁴, Xian Shen³⁵, Qiong Wu³⁵, Xian Zhang³⁵, Zhiqiang Wang³⁵, Liwen Zhao³⁵, Yuexin Zhang³⁶, Guangming Li³⁴, Junqi Niu¹. ¹The First Hospital of Jilin University, Changchun, China; ²Liuzhou People's Hospital, Liuzhou, China; ³Sichuan Provincial People's Hospital, Chengdu, China; ⁴The Sixth People's Hospital of Shenyang, Shenyang, China; ⁵The Second Xiangya Hospital of Central South University, Changsha, China; ⁶Beijing Ditan Hospital Affiliated to Capital Medical University, Beijing, China; ⁷Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, Urumchi, China; ⁸Affiliated Hospital of Yanbian University, Yanbian, China; ⁹Xiangya Hospital, Central South University, Changsha, China; ¹⁰Shanghai Public Health Clinical Center, Shanghai, China; ¹¹First Affiliated Hospital of Army Medical University (Southwest Hospital), Chongqing, China; ¹²Guangzhou Eighth People's Hospital, Guangzhou, China; ¹³The 940th Hospital of Joint Logistics Support Force of PLA, Lanzhou, China; ¹⁴Zhengzhou People's Hospital, Zhengzhou, China; ¹⁵Beijing Friendship Hospital Affiliated with Capital Medical University, Beijing, China; ¹⁶The Second Hospital of Nanjing, Nanjing, China; ¹⁷Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; ¹⁸Peking University People's Hospital, Beijing, China; ¹⁹The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; ²⁰Wuxi Fifth People's Hospital, Wuxi, China; ²¹The First Hospital of Lanzhou University, Lanzhou, China; ²²Tangdu Hospital of the Fourth Military Medical University of Chinese People's Liberation Army, Xi'an, China; ²³The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China; ²⁴Qingdao Municipal Hospital, Qingdao, China; ²⁵Jiangyin People's Hospital, Jiangyin, China; ²⁶Tonghua Central Hospital, Tonghua, China; ²⁷Beijing You'an Hospital Affiliated with Capital Medical University, Beijing, China; ²⁸Shulan (Hangzhou) Hospital, Hangzhou, China; ²⁹The Third People's Hospital of Zhenjiang, Zhenjiang, China; ³⁰Foshan First People's Hospital, Foshan, China; ³¹The 900th Hospital of Joint Logistics Support Force of PLA, Fuzhou, China; ³²Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; ³³The First Affiliated Hospital of Guangxi Medical University, Nanning, China; ³⁴Zhengzhou Sixth People's Hospital, Zhengzhou, China; ³⁵Nanjing Sanhome Pharmaceutical Co., Ltd., Nanjing, China; ³⁶The First Hospital Affiliated to Xinjiang Medical University, Urumchi, China

Background and aims: SH229 is a novel potent, pan-genotypic HCV NS5B polymerase inhibitor in development for the treatment of chronic HCV infection. Data from a phase 2 study showed that SH229 plus daclatasvir was well tolerated and highly effective for Chinese patients infected with HCV, with a SVR12 rate of 90.2%, 95.2%, and 100% in patients receiving daclatasvir at a standard dose of 60 mg daily plus SH229 at a dose of 400, 600, or 800 mg, respectively. Here, we performed a phase 3 study to confirm the efficacy and safety of SH229 in combination with daclatasvir in Chinese patients with HCV infection.

Method: This single-arm, open-label, phase 3 study was conducted at 35 study centers in China. All patients with chronic HCV infection received 600 mg SH229 tablets plus 60 mg daclatasvir tablets once daily for 12 weeks. Patients were followed up at post-treatment weeks 4 and 12, and those who achieved SVR12 were followed up at post-treatment week 24. Plasma samples were collected for HCV RNA quantification in a central laboratory using Roche COBAS® AmpliPrep®/COBAS® TaqMan® HCV v2.0 test, which has a reported

lower limit of quantification (LLOQ) of 15 IU/ml. The primary end point was SVR12.

Results: A total of 327 patients were enrolled in the study, and 326 patients received at least one dose of SH229 plus daclatasvir, including 169 (51.8%) with HCV genotype 1, 95 (29.1%) with HCV genotype 2, 22 (6.7%) with HCV genotype 3, and 40 (12.3%) with genotype 6. 12.6% of patients had compensated cirrhosis at baseline, 7.1% failed prior interferon-based therapy, and 83.1% had the IL28B CC allele. The median baseline HCV RNA was 6.2 log₁₀ IU/ml. 99.4% of patients had pre-existing NS5A and/or NS5B resistance-associated substitutions (RASs) at baseline. Of the 326 patients who received at least one dose of study drugs, 321 (98.5% [95% CI 96.5%-99.5%]) achieved SVR12, which was superior to a historical SVR rate of 88% (p < 0.0001). The SVR12 rates was 100% (3/3) among patients with HCV genotype 1a, 98.8% (164/166) with genotype 1b, 100% (95/95) with genotype 2a, 93.8% (15/16) with genotype 3a, 100% (6/6) with genotype 3b, 97.1% (33/34) with genotype 6a, and 83.3% (5/6) with genotype 6n. The SVR12 rates were similar regardless of most baseline characteristics, such as viral load, prior HCV treatment history, IL28B genotype, and the presence of pre-existing RASs. The most common adverse event (≥10%) was only hypercholesterolemia. Serious adverse events were reported in 25 (7.7%) patients, none of which was judged to be related to SH229 plus daclatasvir treatment. The majority of adverse events were mild to moderate in intensity.

Conclusion: Treatment with the pan-genotypic regimen of SH229 plus daclatasvir for 12 weeks was highly effective and safe in Chinese patients infected with HCV genotype 1, 2, 3, or 6, suggesting this regimen could be a promising option for HCV treatment in China irrespective of genotype.

PO-1307

High rate of early HCV reinfection among PWID with high-risk practices and re-treatment efficacy

Sabela Lens^{1,2}, Anna Miralpeix¹, Mont Gálvez¹, Elisa Martró^{3,4,5}, Noemi Gonzalez⁶, Sergio Rodriguez-Tajes^{1,2}, Zoe Mariño^{1,2}, Veronica Saludes^{3,4,7}, Juliana Reyes^{4,7}, Xavier Major⁸, Joan Colom⁸, Xavier Forns^{1,2}. ¹Liver Unit, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Spain; ²Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Spain; ³Institut d'Investigació Germans Trias i Pujol (IGTP), Microbiology Department, Badalona, Spain; ⁴Center for Epidemiological Studies on HIV/AIDS and STIs of Catalonia (CEEISCAT), Spain; ⁵Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, Spain; ⁶REDAN La Mina. Institute of Neuropsychiatry and Addictions. Parc de Salut Mar, Barcelona, Spain; ⁷Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Spain; ⁸Program on Substance Abuse. Public health Agency of Catalonia (ASPCAT). Government of Catalonia, Spain
Email: slens@clinic.cat

Background and aims: Reported HCV reinfection rates in people who inject drugs (PWID) after antiviral therapy ranges between 2 and 10/100 persons/year. These differences mainly reflect heterogeneity in study populations with regards to risk behaviours. We analyzed the reinfection rate, associated factors and retreatment efficacy in PWID with ongoing high-risk practices in a harm reduction center (HRC) in Barcelona.

Method: HCV point-of-care screening for HCV-RNA (GeneXpert®), liver stiffness measurement (LSM), antiviral therapy delivery and sustained virological response (SVR) assessment were performed at the HRC. Dried blood spot was collected at baseline, FU12 and every 6 months in order to differentiate relapse vs reinfection by genotyping and phylogenetic analysis. Adherence was assessed by daily/weekly visits. The program included educative and harm-reduction interventions.

Results: 919 active drug injectors were prospectively enrolled. Of those accepting screening (386, 42%), 212 (55%) were HCV-RNA positive. Of the 168 (79%) individuals who already started treatment,

POSTER PRESENTATIONS

median age was 42 years, 86% were male, 45% foreigners, 33% homeless, 73% unemployed, 20% HIV+ and 62% had been imprisoned before. Advanced fibrosis (LSM>9.5 kPa) was present in 12%. In regard to high-risk practices, 72% were daily injectors at enrolment, 30% reported either syringe or paraphernalia sharing and 38% unprotected sexual relationships. All patients received a pangenotypic regimen. ITT and per protocol SVR12 were 61% (89/146) and 70% (87/123), respectively; only 5 patients had a relapse. There were 39 (32%) reinfections after a median follow-up of 14 months with most cases 28/39 (72%) occurring as early as FU12. The most frequent genotypes at reinfection were 1a and 3a (44%). Patients with reinfection were more frequently homeless (38% vs 18%), HIV+ (41% vs 10%), shared syringes (29% vs 11%) or had been imprisoned during treatment (18% vs 4%); all $p < 0.05$. Of those re-treated (30/37), 83% received the same antiviral regimen. At FU12 after re-treatment, a new reinfection was documented in 4/17 patients (23%), while the rest achieved SVR (Figure).

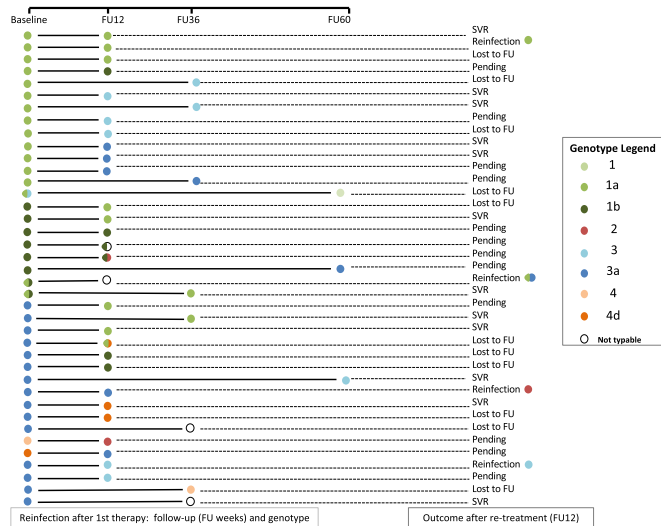


Figure:

Conclusion: This patient-centered circuit demonstrates that HCV treatment can be successfully delivered to active PWID with high-risk practices. However, the early high reinfection rate emphasizes the role of harm reduction interventions and prompt re-treatment initiation. Preliminary results of this cohort supports re-treatment strategies with the same antiviral regimen.

PO-1508

Injecting network structure determines the most efficient strategy to achieve Hepatitis C elimination in people who inject drugs

Chloe Brown¹, Martin Siegle², Mark Wright³, Salim Khakoo¹, Julie Parkes¹, Rachel Sacks-Davis⁴, Ryan Buchanan¹. ¹University of Southampton, Southampton, United Kingdom; ²University of Sussex, Brighton, United Kingdom; ³University Hospital Southampton, Southampton, United Kingdom; ⁴Burnet Institute, Australia
Email: rmb1d14@soton.ac.uk

Background and aims: Transmission of Hepatitis C (HCV) continues via sharing of injection equipment between people who inject drugs (PWID). Network-based modelling studies have produced conflicting results as to whether random treatment is preferable to targeting treatment at PWID with multiple partners. We hypothesise that differences in the modelled injecting network structure produce this heterogeneity, and aim to test how changing network structure affects HCV transmission and treatment effects.

Method: We create three different dynamic injecting network structures connecting 689 PWID (UK-net, AUS-net and USA-net) based on published empirical data. HCV within the networks is

transmitted via a susceptible-infected-susceptible model. At 5 years we compare prevalence of HCV in the three networks in three scenarios: 1) with no treatment, 2) with randomly targeted treatment and 3) with treatment targeted at PWID with the most injecting partnerships.

Results: Median HCV prevalence at 5 years without treatment differed significantly between the three networks (UK-net 42.8%; AUS-net 38.2%, $p < 0.0001$; USA-net 54.0%, $p < 0.0001$). In the treatment scenarios UK-net showed a clear benefit of targeted treatment (median 5-year prevalence 1.0% vs. 9.6% $p < 0.0001$), AUS-net showed a smaller benefit (0.15% vs. 0.44%, $p < 0.0001$) and USA-net showed no significant difference (29.3% vs. 29.2% random, $p = 0.0681$). In sensitivity analyses, targeted treatment was optimised in low prevalence, moderate treatment coverage conditions whereas random treatment was optimised in low treatment coverage, high baseline prevalence conditions.

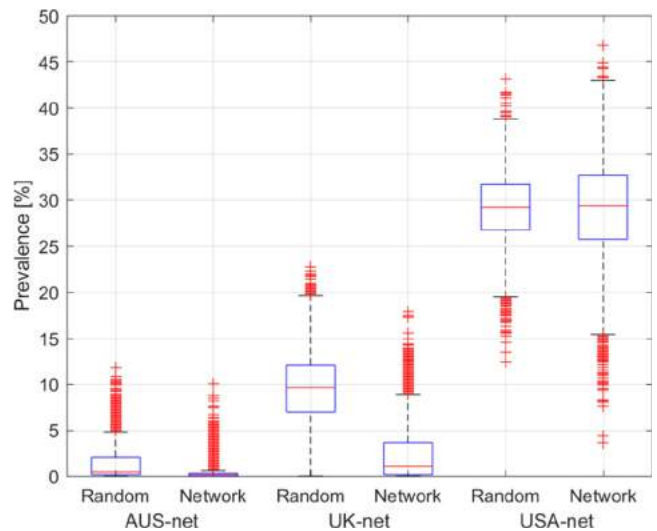


Figure: Box plots showing the distribution of HCV prevalence at 5 years from 1000 simulations in each network structure. Random and degree-based targeted ('network') strategies are compared in each network model. The ends of the boxes are the upper and lower quartiles, a horizontal line inside each box marks the median value and the whiskers extend to extreme values at most 1.5 × the inter-quartile range. Outliers beyond this range are indicated by crosses.

Conclusion: Network structure determines the transmission rate of HCV in PWID and the most efficient treatment strategy to achieve elimination. In real-world injecting network structures, the benefit of targeting HCV treatment at individuals with multiple injecting partnerships may have been underestimated.

PO-1533

Full dose Sofosbuvir-Velpatasvir in chronic Hepatitis C in patients with end stage renal disease.

Aadil Ashraf¹, Altaf Shah¹, Mushtaq Khan¹, Muzafar Maqsood Wani², Ghulam M. Gulzar¹, Jaswinder Singh¹, Shaheena Parveen¹, Nadeem Ahmad¹, Hilal Dar³, Riffat Abdul Aziz¹, Neeraj Dhar¹, Syed Mushfiq Shafi¹, Avinash Tiwari¹. ¹Skims Soura, Gastroenterology, Srinagar, India; ²Skims Soura, Nephrology, Srinagar, India; ³GMC Baramulla, Medicine, Baramulla, India
Email: draadilgastro@gmail.com

Background and aims: Successful treatment of HCV infection is associated with improved outcome in different clinical domains. Use of Direct Acting Anti Virals (DAAs) has been largely limited to patients with estimated Glomerular Filtration Rate (eGFR)>30 ml/min. This is largely related to paucity of data on safety of safety of Sofosbuvir which has a predominant renal excretion. We conducted study (one

of the largest in country) on efficacy of fixed dose combination of Sofosbuvir-Velpatasvir in End Stage Renal disease patients.

Method: The study was conducted in our hospital, SKIMS Soura. Patients with HCV infection (detectable RNA levels) with eGFR <15 ml/min and on hemodialysis were included in the study. All the patients were evaluated for liver disease. Patients with prior exposure to a DAA, portal vein thrombosis or hepatocellular carcinoma were excluded from the study. All the patients received open label combination of sofosbuvir and velpatasvir (400 mg/100 mg). The primary end point was to assess sustained virological response [SVR12] and secondary end point was to assess side effect profile of the patients.

Results: A total of 162 patients were enrolled in the study. Mean age in our study population was 43.08 ± 12.08 years. Mean creatinine in our study population was 7.01 ± 2.61 mg/dl. 125 (78%) among them were on regular hemodialysis sessions. 24 (14.8%) had evidence of liver disease with 4 patients having evidence of decompensated liver disease. 142 (87.6%) achieved Viral clearance at 4 weeks of therapy. 160 (98.7%) of the patients achieved End of treatment viral clearance and same number of patients maintained viral clearance 12 weeks after stopping the treatment (SVR12) (Fig. 1). Remaining 2 patients expired (1 due to massive anterior wall myocardial infarction, another patient died of Sepsis secondary to pneumonia). Mean bilirubin before start of therapy was 1.25 ± 1.1 mg/dl and at 12 weeks after therapy was 0.97 ± 0.09 mg/dl (*p* value 0.003). Mean Alanine Transaminase (ALT) before start of therapy was 77.51 ± 99.7 U/L and at 12 weeks after therapy was 37.4 ± 5.77 U/L (*p* value ≤ 0.0001). No significant difference was found in pre- and post-treatment Sr albumin, Sr creatinine, MELD scoring (in liver disease patients) (Fig. 2). The most common adverse effects noticed were nausea (20%), vomiting (18%), head ache (10%), weakness (7%).

Parameter	Baseline	SVR 12	p Value
Bilirubin (mg/dl)	1.25 ± 1.1	0.97 ± 0.09	0.003
ALT (U/L)	77.51 ± 99.7	37.4 ± 5.77	≤ 0.0001
Creatinine (mg/dl)	7.01 ± 2.61	6.9 ± 2.9	0.71
Albumin (mg/dl)	3.19 ± 0.44	3.25 ± 0.37	0.18
MELD	13.88 ± 3.66	12.93 ± 4.46	0.42

Comparison between different parameters.

Conclusion: We conclude that treatment with sofosbuvir-velpatasvir is a safe and effective treatment option in HCV infection in end stage renal disease.

PO-1553

Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015-December 2020

Tengiz Tsertsvadze^{1,2}, Amiran Gamkrelidze³, Nikoloz Chkhartishvili¹, Akaki Abutidze^{1,2}, Lali Sharvadze^{2,4}, Vakhtang Kerashvili¹, Maia Butsashvili⁵, David Metreveli⁶, Lia Gvinjilia⁷, Shaun Shadaker⁸, Tamar Gabunia⁹, Ekaterine Adamia⁹, Stefan Zeuzem¹⁰, Nezam Afdhal¹¹, Sanjeev Arora¹², Karla Thornton¹², Francisco Averhoff⁸, Paige A. Armstrong⁸. ¹Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; ²Ivane Javakishvili Tbilisi State University, Tbilisi, Georgia; ³National Center for Disease Control and Public Health, Tbilisi, Georgia; ⁴Clinic Hepa, Tbilisi, Georgia; ⁵Clinic NeoLab, Tbilisi, Georgia; ⁶Mrcheveli European Limbach Diagnostic Group, Tbilisi, Georgia; ⁷The Task Force for Global Health, Decatur, United States; ⁸Centers for Disease Control and Prevention, Division of Viral Hepatitis National Center for HIV, Hepatitis, STD and TB Prevention, Atlanta, United States; ⁹Ministry of IDPs from the Occupied Territories, Labour, Health, and Social Affairs of Georgia, Tbilisi, Georgia; ¹⁰University Hospital Frankfurt, Frankfurt am Main, Germany; ¹¹Beth Israel Deaconess Medical Center (BIDMC), Boston, United States; ¹²The University of New Mexico, Albuquerque, United States
Email: tt@aidcenter.ge

Background and aims: In April 2015, with the technical assistance of U.S. CDC and commitment from Gilead Sciences to donate direct acting antivirals (DAAs), Georgia launched the world's first HCV elimination program. Key strategies include nationwide HCV screening, active case finding, linkage to care, decentralized care, provision of treatment for all HCV persons, and effective prevention interventions. The initial goal of the program was to achieve the following targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress towards elimination targets 5 years into the elimination program.

Method: The program collects data on all persons registered with the treatment program. Treatment was provided with Sofosbuvir, Ledipasvir/Sofosbuvir or Velpatasvir/Sofosbuvir-based regimens. Data on persons tested for chronic HCV infection, and those deemed cured by sustained virologic response (SVR) were extracted as of December 2020.

Results: As of December 31, 2020 a total of 90,578 persons were diagnosed with chronic HCV infection, representing 60.4% of the estimated 150,000 adults living with HCV in Georgia. A total of 72,811 (80.4%) patients initiated treatment-56.8% of the estimated target population to be treated (128,250). Of the 51,208 patients who were evaluated for SVR, 50,644 (98.9%) tested negative for HCV by PCR, representing 41.6% of the estimated target population cured (121,837).

High cure rates were achieved for all HCV genotypes: 98.9% in genotype 1, 98.9% in genotype 2 and 98.3% in genotype 3, typically the most challenging to treat. Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 98.2% achieving SVR, and among patients with mild or no liver fibrosis (≤F2), SVR = 99.1%.

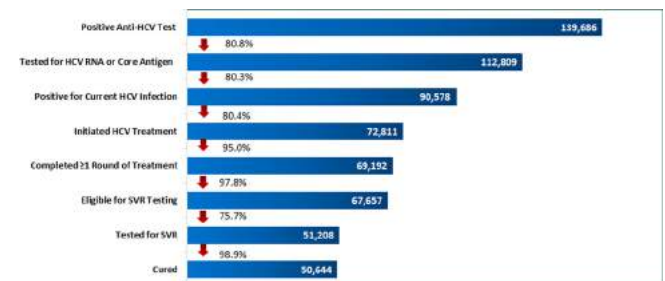


Figure: Hepatitis C care cascade as of December 31, 2020

Conclusion: Georgia has made substantial progress towards eliminating hepatitis C, with over 40% of persons with chronic HCV infection identified and cured. 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.

PO-1872

A costing analysis of a state-wide, nurse-led hepatitis C treatment model in prison

Anna Palmer¹, Tim Papaluca^{2,3}, Mark Stoope^{1,4}, Rebecca Winter^{1,2}, Alisa Pedrana^{1,4}, Margaret Hellard^{1,4,5,6,7}, David Wilson¹, Alexander Thompson^{2,3}, Nick Scott^{1,4}. ¹Burnet Institute, Disease Elimination Program, Melbourne, Australia; ²St Vincent's Hospital Melbourne, Department of Gastroenterology, Melbourne, Australia; ³The University of Melbourne, Department of Medicine, Parkville, Australia; ⁴Monash University, School of Population Health and Preventive Medicine, Melbourne, Australia; ⁵The Alfred Hospital, Department of Infectious Diseases, Melbourne, Australia; ⁶Peter Doherty Institute for Infection and Immunity, Parkville, Australia; ⁷The University of Melbourne, School of Population and Global Health, Parkville, Australia
Email: anna.palmer@burnet.edu.au

Background and aims: Hepatitis C is highly prevalent among prisoners. The simplicity of direct-acting antiviral (DAA) treatment

POSTER PRESENTATIONS

for hepatitis C makes it possible to use novel models of care to increase treatment uptake within prisons. We estimate the average non-drug cost of initiating a prisoner on treatment using real world data from the State-wide Hepatitis Program (SHP) in Victoria, Australia—a coordinated nurse-led model of care.

Method: Data were considered from prisoners presenting to the SHP (following antibody-positive diagnosis) during the initial evaluation period, November 2015 to December 2016. All costs associated with the SHP were estimated, including staffing salaries, medical tests, pharmacy costs and overhead costs. DAA costs were excluded as in Australia an unlimited number of treatments are available with costs covered by a federal government risk-sharing agreement with pharmaceutical companies. The average non-drug cost of treatment initiation through the SHP was compared to equivalent costs from primary and hospital-based models of care in the community.

Results: The total non-drug cost accumulated by 803 prisoners engaged in the SHP was A\$749,470 (uncertainty range: A\$728,905–794,111). 659/803 were infected, 424/659 had sentences long enough to be eligible for treatment, and 416/424 were initiated on treatment, resulting in an average cost of A\$1,802 (95% CI: A\$1,799–1,841) per prisoner initiated. A protocol change allowing prisoners with short sentences to start treatment reduced the average cost to A\$1,263 (95% CI: A\$1,263–1,287) per prisoner initiating treatment—11% and 56% cheaper than estimated equivalent costs in primary (A\$1,647) and hospital-based (A\$2,840) models of care in the community, respectively.

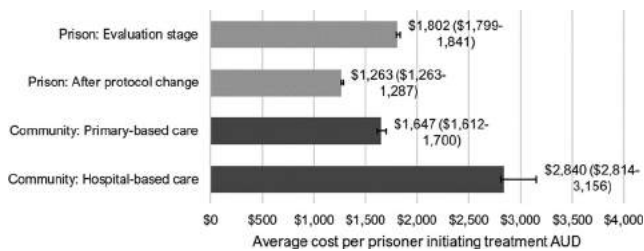


Figure:

Conclusion: Delivering hepatitis C treatment in prison using a nurse-led model of care is cheaper than delivering treatment in the community. These findings provide an economic rationale for implementing coordinated prison-based hepatitis C treatment programs.

PO-1962

Validation of a simple score to identify patients who can safely use protease inhibitor-based therapy for HCV infection

Lisette Krassenburg^{1,2}, Joy Peter³, Lucy Akushevich⁴, Rael Maan¹, Alnoor Ramji⁵, Heiner Wedemeyer⁶, Robert De Man¹, Harry Janssen², Bettina Hansen^{2,7}, Adriaan Van der Meer¹, David R. Nelson³, Michael W. Fried⁴, Jordan Feld². ¹Erasmus MC University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; ²Toronto General Hospital, University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; ³University of Florida, Department of Medicine, Gainesville, United States; ⁴University of North Carolina at Chapel Hill, Division of Gastroenterology and Hepatology, Chapel Hill, United States; ⁵University of British Columbia, Department of Medicine, Division of Gastroenterology, Vancouver, Canada; ⁶Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; ⁷University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada
Email: l.krassenburg@erasmusmc.nl

Background and aims: Although highly effective as part of direct-acting antivirals (DAAs), protease inhibitors (PI) have been associated with decompensation in people with cirrhosis. A simple tool to identify patients who can safely take PIs with a very low or no risk of

decompensation would be useful, particularly as treatment expands to primary care. We validated our previously developed score using only baseline albumin and platelets (plt) in the large HCV-TARGET real-world cohort.

Method: All patients treated with PI-based therapy in the HCV-TARGET and PRIORITIZE studies were included. Incidence of decompensation (ascites, spontaneous bacterial peritonitis, variceal bleed or encephalopathy) from treatment start to SVR12 was determined in patients with normal baseline bilirubin. Patients were categorized by previously identified thresholds of baseline albumin \geq 38 g/L and plt \geq 130 \times 10⁹/L.

Results: A total of 2894 patients were included, 2136 without cirrhosis, 590 with compensated cirrhosis and 168 with history of decompensation. Median (IQR) age was 59 (51–64) years, 1689 (58.3%) were male, 108 (3.7%) had Genotype 3 and 126 (4.4%) had prior liver transplantation. In patients with available virological outcomes, SVR was attained in 93.2% (94.5% CI 92.5–96.4) with compensated cirrhosis, 86.5% (95% CI 81.0–91.9) with decompensated cirrhosis and in 95.7% (95% CI 94.8–96.6) non-cirrhotic patients. Overall, 17 (0.6%) patients experienced decompensation during treatment, all of whom had cirrhosis (17/758, 2.2%). The most frequent symptom of decompensation was hepatic encephalopathy in 12 (70.6%) patients. No treatment-emergent decompensation occurred in 2136 patients without cirrhosis. In patients with compensated cirrhosis, no decompensation events occurred in patients with albumin \geq 38 and plt \geq 130 (0/219). Among patients with a history of prior decompensation, 31/168 (18.5%) had an albumin \geq 38 and plt \geq 130 at baseline, of whom 2 (6.5%) decompensated during treatment (Figure).

Compensated Cirrhosis (n=590)				
	Alb<3.8	Alb \geq 3.8	Total	
	0/0	0/1	0/7	
Plt<130	0/4	2/116 (1.7%)	1/150 (0.7%)	3/270 (1.1%)
Plt \geq 130	0/1	2/93 (2.2%)	0/219	2/313 (0.6%)
Total	0/5	4/210 (1.9%)	1/375 (0.3%)	5/590 (0.8%)
Cirrhosis with prior history of decompensation (n=168)				
	Alb<3.8	Alb \geq 3.8	Total	
	0/0	0/3	0/4	
Plt<130	0/0	9/65 (13.8%)	0/35	9/100 (9.0%)
Plt \geq 130	0/2	1/31 (3.2%)	2/31 (6.5%)	3/64 (4.7%)
Total	0/2	10/99 (10.1%)	2/67 (3.0%)	12/168 (7.1%)

Figure: Risk of decompensation among patients with cirrhosis starting DAA therapy

Conclusion: These results confirm that patients with baseline albumin \geq 38, plt count \geq 130 and compensated cirrhosis or without cirrhosis can safely be treated with PI-based therapy. Even patients with a history of prior decompensation meeting these thresholds have a low risk of treatment-related decompensation but should still preferably use non-PI-based therapy. This simple approach allows for identification of patients who can safely use PI-based therapy, a key to expanding treatment outside of specialty care to help achieve the WHO elimination goals by 2030.

PO-2020

Good practice hepatitis C screening and linkage to care initiatives at the SLTC Summit 2020: three out of four diagnosed patients able to start direct-acting antiviral treatment

Joaquín Cabezas^{1,2}, Daniella Cohen³, Chris Fraser⁴, Dominique Larrey⁵, Andreas Maieron⁶, Anthony Martinez⁷, Lucy McDonald^{8,9}, Candido Hernández¹⁰, Margaret O'Sullivan¹¹, André-Jean Remy¹², Jens Rosenau¹³, Pablo Ryan¹⁴, Tessa Windelinckx¹⁵, Ming-Lung Yu¹⁶. ¹Marqués de Valdecilla University Hospital, Santander, Spain; ²Valdecilla Research Institute, Santander, Spain; ³Maccabi Health Services, Tel Aviv-Yafo, Israel; ⁴Victoria Cool Aid Society-Community Health Centre, Victoria, Canada; ⁵University Hospital of Montpellier, Montpellier, France; ⁶University Hospital St. Pölten, Sankt Pölten, Austria; ⁷Erie County Medical Center, Buffalo, United States; ⁸St. Vincent's Hospital Melbourne, Fitzroy, Australia; ⁹University of Melbourne, Parkville, Australia; ¹⁰Gilead

Sciences Europe Ltd, Hayes, United Kingdom; ¹¹Brighton And Sussex University Hospitals NHS Trust, Brighton, United Kingdom; ¹²Hospital Centre of Perpignan, Perpignan, France; ¹³University of Kentucky Medical Center, Lexington, United States; ¹⁴Infanta Leonor Teaching Hospital, Madrid, Spain; ¹⁵Free-Clinic, Antwerp, Belgium; ¹⁶Kaohsiung Medical University, Kaohsiung City, Taiwan
 Email: candido.hernandez@gilead.com

Background and aims: The SLTC Summit is a Gilead-sponsored event initiated in 2017 and designed to facilitate the sharing of good practice examples of hepatitis C (HCV) screening and linkage to care (SLTC). We sought to evaluate patient cascade data derived from the 17 global examples of good practice presented in 2020.

Method: Key data from good practices initiatives presented during the SLTC Summit in 2020 were extracted and supplemented by additional data where possible. Six variables were analysed: prevalence of HCV Ab+ and HCV RNA+ from the screened population; proportion of HCV RNA+ among the HCV Ab+ population; proportion of HCV RNA+ patients able to start (direct-acting antiviral) DAA treatment; proportion of HCV RNA+ patients who were cured; proportion of patients who started treatment who were cured. Only initiatives that included these variables were included in the respective analyses. Some data included the period during the COVID-19 pandemic.

Results: Data from 13 initiatives in 10 countries (Australia, Austria, Belgium, Canada, France, Israel, Spain, Taiwan, UK and USA) were evaluable. Target populations included people who used drugs, people in prison, homeless people, sex workers, migrants, and the 'general population'. Complete care cascade data were not available for each initiative. Overall, 500, 353 people were screened for HCV and 7691 patients initiated DAA treatment. Of the programmes with evaluable datasets, an average of 76% (range 45%–100%) of people diagnosed as HCV RNA+ went on to start DAA treatment. See Table for detailed information.

Variable	Mean percentage across the initiatives (range)	Sample	Countries/cohorts
HCV Ab+ of those screened	29 (1–72)	7696/496,663	7/9
HCV RNA+ of those screened	21 (2–49)	1192/9753	7/9
HCV RNA+ among HCV Ab+	53 (30–82)	1164/2364	6/8
HCV RNA+ and starting DAA Tx	76 (45–100)	725/922	6/8
HCV RNA+ and achieving SVR	60 (31–85)	466/731	6/7
Starting DAA Tx and achieving SVR	75 (56–94)	705/1011	6/7

Conclusion: This analysis of good practice HCV screening and linkage to care initiatives from around the world, focused on high-risk populations, indicates that 3 out of 4 patients start DAA treatment after HCV RNA+ diagnosis. Despite the global impact of the COVID-19 pandemic it is important to maintain or even improve this ratio in order to achieve global HCV elimination goals.

PO-2021

Deferred direct-acting antiviral treatment in kidney transplantation from HCV-viremic donors into HCV-negative recipients

Giulia Pagano¹, Eulàlia Solà², Nuria Cañete^{1,3}, Teresa Broquetas^{1,3}, Jose A. Carrión^{1,4}, Marc Puigvehí^{1,3}, Susanna Coll^{1,3}, Esther Garrido^{1,3}, Ana Viu³, Judit Romero¹, MARIA JOSE Pérez², ANA Zapatero⁵, Xavier Bessa^{1,3}, Marta Crespo Barrio², Montserrat Garcia-Retortillo^{1,3}.

¹Hospital del Mar, Liver Section, Gastroenterology Department, Barcelona, Spain; ²Hospital del Mar, Nephrology Department, Barcelona, Spain; ³Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; ⁴Universitat Autònoma de Barcelona, Bellaterra, Spain; ⁵Hospital del Mar, Transplant Coordination, Barcelona, Spain
 Email: 97235@parcdesalutmar.cat

Background and aims: Outcomes of kidney transplantation (KT) from HCV-viremic donors into HCV-negative recipients has shown excellent results when prophylactic or early antiviral treatment is initiated. However, oral tolerance and drug-drug interactions (DDIs) can limit this strategy. Aim: To analyze the efficacy and safety of deferred direct-acting antiviral therapy with glecaprevir/pibrentasvir (GLE/PIB) in KT recipients from HCV-viremic donors.

Method: KT candidates testing negative for HCV who received a kidney from a HCV-viremic donor at a tertiary care center were included prospectively. HCV-RNA was determined in kidney recipients pre-KT, at day 3, 7 and 14 post-KT, immediately before antiviral treatment, at the end of treatment and at 12, 24 and 48 weeks after the end of treatment. Antiviral therapy with GLE/PIB had to be initiated per protocol within the 2nd and 4th week post- KT after achieving a correct oral tolerance and stability of immunosuppressant levels. Levels of immunosuppressants were registered at day 3, 7, 14 and 28 post-KT and monthly thereafter

Results: Eight KT recipients were included from 1/2020 to 9/2020, 7 of them were men with a median age of 56 years (range 48–62) and a follow-up period of 156 days (IQR: 50–277). The immunosuppressant regimens consisted in the combination of steroids plus tacrolimus and mycophenolate (n=4) or everolimus (n=4). HCV-RNA was detected 3 days after KT in 6 out of 8 patients (75%) and in 100% of patients one week after KT. Moderate and asymptomatic elevation in transaminases appeared in 7 out of 8 patients (87, 5%) and reached the maximum peak between the 11th and 27th day after KT. GLE/PIB was initiated the 19th day post-KT (range: 12–33 days). Tacrolimus levels after 2 and 4 weeks post-antiviral treatment initiation increased a 99% and 52% respectively and were associated with dose reduction of 22% and 13% at the same time points. Four patients have reached week 12 after the end of treatment and all of them achieved the SVR. There were no adverse events related to antiviral therapy in any recipient

Conclusion: Deferred antiviral therapy with GLE/PIB after KT from HCV-viremic donors into HCV-negative recipients is a safe and effective strategy and avoids the higher risk period for DDIs. However, a close monitoring of tacrolimus levels is required for an appropriate dose adjustment.

PO-2138

Safety and efficacy of direct acting antiviral therapy for chronic HCV infection in elderly people

Adriano De Santis¹, Daniela Maggi¹. ¹Università La Sapienza, Policlinico Umberto I, Gastroenterologia, Rome, Italy
 Email: daniela.maggi2@gmail.com

Background and aims: The mean age of patients with chronic HCV infection and the number of elderly patients with advanced liver disease is gradually increasing in many countries. Screening strategies concerning high-risk groups and leaving out the elderly population risk to be unsuccessful in a global eradication perspective. The elderly should be considered a Special Population to screen and treat like other subjects considered at high risk. This study aim is to evaluate the safety and efficacy of direct antiviral therapy in the elderly patient with chronic HCV infection.

Method: We retrospectively analyzed the efficacy and safety of DAAs in 137 HCV patients of 70 years or older treated in our center between 2015 and 2020. Eligibility for treatment was assessed according to current clinical practices. We evaluated personal and anamnestic data, Cumulative Illness Rating Scale (CIRS), ultrasound, elastometry and laboratory parameters. The pre-therapy data were compared with the data collected 6 months after the end of therapy.

POSTER PRESENTATIONS

Results: The mean age was 77 years. The CIRS severity scale is moderate-severe in 65% of patients and 40% of them have compensated cirrhosis. 73% of patients were taking two or more drugs. In 38% of cases, we had to change chronic therapy to avoid potentially serious drug interactions. One serious adverse event occurred (diverticular bleeding due to interaction with DOAC). Mild side effects occurred in 37% of patients. HCV RNA undetectability EOT was achieved in 97% of patients, while SVR 12 and SVR24 in 98% of patients. After treatment, we saw a reduction in the incidence of episodes of liver decompensation in cirrhotic patients. In all patients, we find a significant improvement in all ultrasound variables and a significant reduction in the elastographic measurements. No significant differences in outcomes were observed dividing the population into patients aged ≥ 80 and < 80 years.

Conclusion: The benefit of DAA therapy in the elderly patient mainly concerns liver disease and is strongly indicated in the cirrhotic patients. For non-cirrhotic patients, the therapy does not affect extrahepatic comorbidities but allows to end follow-up in 40% of patients with consequent savings in terms of resources. It also plays an important role in reducing the risk of hepatocellular cancer and all-cause mortality, if compared to untreated patients. Age should not be an a priori exclusion factor if the patient has a good performance status.

PO-2191

Directly observed therapy for hepatitis C alongside opioid agonist therapy as an effective microelimination strategy for PWIDs with a high risk for non-adherence in Vienna, Austria

Michael Schwarz^{1,2,3}, Angelika Schütz⁴, Cornelia Schwanke⁴, Caroline Schmidbauer^{1,2,3}, Eva Krabb⁴, Raphael Schubert⁴, Enisa Gutic¹, Roxana Pirker¹, Tobias Lang¹, Thomas Reiberger^{2,3}, Hans Haltmayer⁴, Michael Gschwantler^{1,5}. ¹Klinik Ottakring, Department of Internal Medicine IV, Division of Gastroenterology and Hepatology, Vienna, Austria; ²Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; ³Vienna HIV and Liver Study Group; ⁴Suchthilfe Wien gGmbH, Vienna, Austria; ⁵Sigmund Freud University Vienna, Vienna, Austria

Email: michael.gschwantler@gesundheitsverbund.at

Background and aims: Despite highly effective direct acting antivirals (DAAs), people who inject drugs (PWIDs) still show high hepatitis C virus (HCV) prevalence. Austria offers a national opioid agonist therapy (OAT) program for PWIDs with recent or ongoing intravenous drug use (IDU). However, a considerable subgroup of PWIDs on OAT, especially those with ongoing IDU, have a high risk of non-adherence to therapy with DAAs. Thus, the innovative Viennese concept of directly observed therapy (DOT) combines DAA therapy with OAT to improve adherence to antiviral treatment.

Method: From September 2014 until January 2021 PWIDs with a high risk for non-adherence to DAA therapy were included in the Viennese HCV elimination project using DOT. DAA regimens were selected according to genotype (GT), fibrosis stage, comedication, and reimbursement policy of insurances. PWIDs received HCV treatment

alongside their OAT under supervision of healthcare workers in a pharmacy or low-threshold facility.

Results: 523 PWIDs were included. 400 patients were male (76.5%), median age at baseline was 39.6 years. Coinfection with HIV or HBV was found in 23 (4.4%) and 7 (1.3%) patients, respectively. 52 (9.9%) had received prior HCV treatment. 259/414 patients (62.6%) reported ongoing IDU. Most common GTs were GT-1 (291, 55.6%) and GT-3 (197, 37.7%). Most frequently used DAA combinations were sofosbuvir/velpatasvir (201, 40.2%), glecaprevir/pibrentasvir (188, 36.0%) and sofosbuvir/ledipasvir (63, 12.1%). Stages of fibrosis measured through transient elastography were: F0/F1 207 (39.6%), F2 137 (26.2%), F3 71 (13.6%), F4 106 (20.3%).

Following the concept of DOT adherence to DAA treatment was excellent with only 98/25.864 (0.4%) scheduled visits missed by the patients. Sustained virologic response 12 weeks after treatment completion (SVR12) was achieved in 400/404 (99.0%; CI: 97.5–99.7%) patients according to modified intention to treat analysis (mITT), while 4/404 (1.0%) patients showed treatment failure (or reinfection before confirmed SVR12). 57 patients were lost to follow-up, 2 patients died due to reasons not related to DAA treatment before SVR12 was documented. By the time of submission, 60 patients remain on treatment or SVR12 surveillance. Over a median follow-up of 28 weeks (IQR 22) 21 (5.3%) reinfections were observed.

Conclusion: HCV treatment according to the concept of DOT achieved excellent SVR12 rates of 99% in PWIDs at high risk for non-adherence to DAA therapy.

PO-2205

Delivering elimination: rapid scale-up of hepatitis c virus treatment among people who inject drugs in Tayside, Scotland

Christopher Byrne^{1,2}, Lewis Beer², Sarah Inglis², Emma Robinson^{1,3}, Andrew Radley^{1,4}, Sharon Hutchinson⁵, David Goldberg⁵, Matthew Hickman⁶, John Dillon^{1,3}. ¹University of Dundee, Molecular and Clinical Medicine, Dundee, United Kingdom; ²University of Dundee, Tayside Clinical Trials Unit, Dundee, United Kingdom; ³NHS Tayside, Ninewells Hospital and Medical School, Dundee, United Kingdom; ⁴NHS Tayside, Public Health, Dundee, United Kingdom; ⁵Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, United Kingdom; ⁶University of Bristol, Population Health Sciences, Bristol, United Kingdom

Email: c.x.byrne@dundee.ac.uk

Background and aims: Tayside, in the North East of Scotland, had high levels of injection drug use and hepatitis c virus (HCV) infection. In 2017, rapid scale-up of HCV treatment for People Who Inject Drugs (PWID) commenced to achieve a substantial reduction of chronic HCV, thereby achieving elimination. Novel HCV care pathways in community settings were implemented. This study analyses outcomes for the treated cohort during the scale-up against programme targets. It also aims to: determine the most efficacious pathways and assess if any routinely collected data predict Sustained Virologic Response (SVR).

Method: All treatments were with Direct Acting Antivirals (DAA). Treatment was delivered through five novel pathways in addition to standard care: nurse-led outreach clinics, drug treatment centres;

Table 1: (abstract: PO-2205): Treatment initiations, sustained virologic response, by pathway: Tayside 2017–20

Treatment Pathway	Standard care	Drug treatment centres ^a	Community pharmacies ^a	Needle exchanges ^a	Nurse-led community clinics ^a	Prisons ^a	Total
Treatments initiated-n (%)	91 (12.8)	46 (6.4)	144 (20.2)	205 (28.8)	124 (17.4)	103 (14.4)	713 (100)
SVR-n (%)	74 (81.3)	34 (73.9)	129 (89.6)	156 (76.1)	101 (81.5)	79 (76.7)	573 (80.4)
SVR exc. unknown ^b -%	92.5	87.2	95.6	86.7	96.2	92.9	91.8

Abbreviations: SVR, sustained virologic response; exc., excluding.

^aNovel care pathway.

^bExcluding those without an SVR test, n = 624.

needle exchanges; community pharmacies; and prisons. Demographic and treatment outcomes were summarised using descriptive statistics. Multivariate analysis was by binary logistic regression.

Results: Treatment was initiated 713 times for 662 PWID, resulting in 573 SVRs. 74.2% were male, 51.9% self-reported injecting in twelve months prior to treatment. Overall and adjusted SVR rates are reported in table 1. Needle exchanges and community pharmacies treated 49% of patients. Community pharmacies had highest SVR rate. Completing treatment (OR, 6.21 [95% CI, 3.78 – 10.20], $p < .001$) and receiving treatment via a clinical trial of a novel pathway (OR, 2.13 [95% CI, 1.38–3.31], $p = .001$) were significant predictors of SVR.

Conclusion: Tayside exceeded its targets for the elimination scale-up programme. Needle exchanges and pharmacies delivered most PWID into care. Completing DAA treatment and receiving treatment through a pragmatic trial of a novel pathway increased odds of achieving SVR. Delivering HCV care in community settings is effective in reducing the population level burden of infection.

PO-2240

Real-time utility of response-guided DAA therapy for hepatitis C based on a mathematical modeling approach: database formation and machine learning methods

Stephanie Kriss¹, Alex Churkin², Asher Uziel¹, Jay Srinivas¹, Scott Cotler¹, Ohad Etzion³, Amir Shlomai^{4,5}, Danny Barash⁶, Harel Dahari¹. ¹Loyola University Chicago, Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Stritch School of Medicine, Maywood, United States; ²Sami Shamoon College of Engineering, Department of Software Engineering, Beer Sheva, Israel; ³Soroka University Medical Center, Beer Sheva, Israel; ⁴Rabin Medical Center, Petah-Tikva, Israel; ⁵Tel Aviv University, Tel Aviv, Israel; ⁶Ben-Gurion University of the Negev, Department of Computer Science, Beer Sheva, Israel
Email: harel.dahari@gmail.com

Background and aims: We recently reported (Sci Rep.2020;10 (1):17820) the first proof-of-concept clinical trial assessing in real-time the utility of response-guided therapy (RGT) with direct-acting antivirals (DAA) in chronic hepatitis C (CHCV), based on a mathematical modeling approach. Several retrospective studies have shown that mathematical modeling of viral kinetics predicts time to cure (TTC) of less than 12 weeks in the majority of individuals treated with sofosbuvir-based as well as other DAA regimens (Table 1). The aims of this study are to build a database of these studies and to evaluate machine learning (ML) methods for estimating missing datapoints to facilitate real-time modeling studies.

Method: Data from six studies exploring mathematical modeling of early HCV kinetics under DAA in CHCV-infected patients were gathered and analyzed (Table 1). Statistical analysis was conducted to examine associations between patient demographics (such as age, gender, liver disease severity) and estimated HCV kinetic parameters that are used to predict the individualized TTC. A linear-regression ML model was trained on part of our dataset ('train' set), to predict missing data-points on the untrained part ('test' set).

Results: Overall, 266 patients from the retrospective studies had a mean age of 66 ± 12 years, 133 (50%) were male, 113 patients (42%) had measured IL28B genotypes, 145 (55%) had cirrhosis, 52 (20%) had decompensated cirrhosis, 213 (80%) had HCV genotype-1, and 96 (36%) were treatment naïve (Table 1). Among the 266 patents, there was a significant ($p < 0.001$) difference in the mean serum viral clearance rate between patients with cirrhosis (7.4 ± 3.4) and patients without cirrhosis (10.0 ± 4.5). In the real-time study, patients had a mean age of 49 ± 15 years, all patients were non-cirrhotic, and all but one were treatment naïve. The gender, HCV genotype-1, and mean baseline HCV baseline viral load were comparable to patients baseline characteristics of the retrospective studies. Patients in the real-time study had a significantly ($p \leq 0.03$) lower viral clearance rate and lower infected cell death/loss rate compared to the patient in the retrospective studies (Table 1), which may partially be related to the difference in HCV quantification assay used in the real-time study (Cepheid, GeneXpert) compared to all retrospective studies (Roche

Cohort (PMID/doi)	N	HCV GT-1 - N (%)	Cirrhosis - N (%)	DAA	Time to Cure (w)	V ₀ (log IU/mL)	c	ε	δ
Sci Rep.2020* 33082372	11	7 (64%)	0	SOF/VEL, ELB/GRZ, SOF/LED	6 to 12	5.8 ± 0.5	6.2 ± 2.8	0.999 ± 0.002	0.34 ± 0.08
JID, 2020 32363394	44	20 (45%)	19 (43%)	P/G	4 to 12	6.4 ± 0.8	7.6 ± 3.1	0.998 ± 0.004	0.45 ^b
LiverInt2019 30499631	74	51 (69%)	70 (95%) ^a	SOF/SIM/RBV LED/DCV/ DSV/OBV/PVT	4 to 12	5.7 ± 0.6	5.7 ± 0.6	0.992 ± 0.003	0.53 ± 0.22
JVH, 2018, 10.1111/jvh.45_12923	26	26 (100%)	1 (4%)	SOF/DCV/ ASV/BCV	5.4 ± 1.8	6.7 ± 0.8	6 ^b	0.999 ± 0.001	0.54 ± 0.22
PLoS ONE, 2017 29216198	68	68 (100%)	24 (35%)	DCV/ASV	6 to 12	6.1 ± 0.4	14.9 ± 0.9	0.999 ± 0.001	0.40 ± 0.05
J HEP, 2016 26907973	54	48 (89%)	31 (57%)	SOF+LED, SOF+DCV, SOF+SIM	6 to 13	6.1 ± 0.3	6 ^b	0.997	0.45 ± 0.19

Table 1. Database characteristics and HCV kinetic parameter estimates. * real-time modeling-based study; SOF, sofosbuvir; VEL, velpatasvir; ELB, elbasvir; GRZ, grazoprevir; LED, ledipasvir; P/G, pibrentasvir-glecaprevir; DCV, daclatasvir; ASV, asunaprevir; BCV, beclabuvir; SIM, simeprevir; RBV, ribavirin; OBV, ombitasvir; PVT, paritaprevir; r, ritonavir; DSV, dasabuvir; V₀, baseline HCV RNA; c, virion clearance rate constant; ε, therapy effectiveness; ^aDecompensated cirrhosis among 70% of patients; ^bNo SD in viral kinetic parameter estimates indicates a fixed value.

Figure: (abstract: PO-2240)

POSTER PRESENTATIONS

CobasTaqMan). Preliminary ML efforts suggest that it is possible to predict missing data points in the dataset, such as “day 14” or “day 28,” with a very high accuracy (relative error around 0.04%).

Conclusion: ML provides a means to estimate missing dataset parameters to establish an accurate TTC prediction that will support the implementation of our individualized treatment approach on a world-wide scale.

PO-2275

Prevalence of resistance associated substitutions in hepatitis C virus NS5A against direct acting antivirals

Zain Ul Abideen¹, Shafiq Siddique², Azeem Butt³. ¹COMSATS University Islamabad, Biosciences, Islamabad, Pakistan; ²National University Of Medical Sciences (NUMS), Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan; ³COMSATS University Islamabad (CUI), Biosciences, Islamabad, Pakistan

Background and aims: The introduction of direct-acting antivirals (DAAs) has significantly increased the sustained virological response (SVR) rate in hepatitis C (HCV) patients however, resistance-associated substitutions (RASs) are reported to emerge and impair the DAAs' effectiveness against HCV particularly in cases such as cirrhosis. Identification and functional analysis of such RASs is therefore important in clinical settings to optimize treatment regimens thereby, increasing the SVR rates. We performed a meta-analysis to provide an update on prevalence of RASs in the HCV NS5A gene across all genotypes.

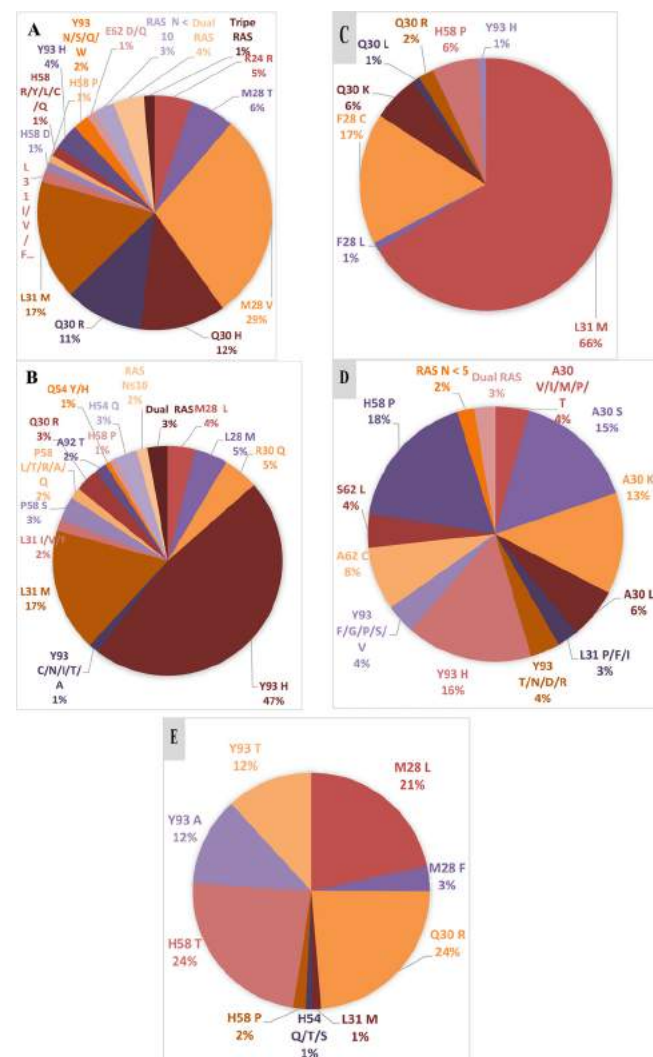


Figure: Prevalence of NS5A RASs across genotypes. (A) Prevalence of RASs in genotype 1a (B) Prevalence of RASs in genotype 1b. (C) Prevalence of RASs in genotype 2. (D) Prevalence of RASs in genotype 3. (E) Prevalence of RASs in genotype 6

Method: The current study was conducted as per PRISMA guidelines. Different databases were searched for studies reporting RASs in the HCV NS5A gene till July 2020. After the screening of 288 research publications, 67 studies were included in the meta-analysis. For modest heterogeneity fixed-effect model was used; otherwise, a random effect model was applied. The odds ratio (OR) and 95% confidence interval (CI) were calculated by comparing the prevalence of RASs between the different groups for the potential association.

Results: Overall, 9377 individuals (GT 1a, n = 2347; GT 1b, n = 4712; GT 2, n = 203; GT 3a, n = 1371; GT 3 others, n = 94; GT 4, n = 554; GT 6, n = 96), treatment naïve and treatment-experienced were included. M28V, Y93H, L31M, H58P, L28M, and P32S were the most observed RAS in HCV genotype 1a, 1b, 2, 3a, 4, and 6a, respectively. Significantly higher prevalence of Q30H, Q30R, and L31M were observed in genotype 1a treatment-experienced group while Y93H, L31M, and L28V were significantly higher in genotype 1b and 4 treatment-experienced groups respectively.

Conclusion: The presence of baseline mutation significantly hinders the efficacy of DAAs, indicating that it could be beneficial to offer resistance testing before initiating the DAA treatment regime in HCV patients.

PO-2295

Amino acid substitutions associated with treatment failure of hepatitis C virus infection

Carlos García-Crespo¹, Maria Eugenia Soria¹, Brenda Martínez-González¹, Lucía Vázquez-Sirvent¹, Rebeca Lobo-Vega¹, Ana Isabel de Ávila¹, Isabel Gallego¹, Qian Chen², Damir García-Cehic², Meritxell Llorens-Revull², Carlos Briones³, Jordi Gómez⁴, Cristina Ferrer-Orta⁵, Nuria Verdaguer⁵, Josep Gregori², Francisco Rodríguez-Frías⁶, Maria Buti², Juan Ignacio Esteban², Esteban Domingo^{1,7}, Josep Quer², Celia Perales^{1,2,8}. ¹Centro de Biología Molecular Severo Ochoa, Department of Interactions with the environment, Madrid, Spain; ²VHIR-Vall d'Hebron Institut de Recerca, Liver Unit, Internal Medicine Hospital Universitari Vall d'Hebron, Barcelona, Spain; ³Astrobiology Center, Department of Molecular Evolution, Torrejón de Ardoz, Spain; ⁴Instituto de Parasitología y Biomedicina López Neyra-CSIC, Department of Molecular Biology, Spain; ⁵Institute for Molecular Biology of Barcelona, Structural Biology Department, Barcelona, Spain; ⁶VHIR-Vall d'Hebron Institut de Recerca, Biochemistry and Microbiology Departments, Barcelona, Spain; ⁷Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain; ⁸IIS-Fundación Jiménez Díaz, Department of Clinical Microbiology, Madrid, Spain
Email: carlos.garciac@cbm.csic.es

Background and aims: Despite the high sustained virological response rates achieved with current directly-acting antiviral agents (DAAs) against hepatitis C virus (HCV), around 2% to 5% of patients do not achieve such a response. Identification of amino acid substitutions associated with treatment failure requires analytical designs, such as subtype-specific ultra-deep sequencing (UDS) methods for HCV characterization and patient management.

Method: By deep sequencing analysis of 220 subtyped HCV samples from infected patients who failed therapy, collected from 39 Spanish hospitals, we determined amino acid sequences of the DAA-target proteins NS3, NS5A and NS5B, by UDS of HCV patient samples, in search of resistance-associated substitutions (RAS).

Results: Using this procedure, we have identified six highly represented amino acid substitutions (HRSs) in NS5A and NS5B of HCV, which are not bona fide RAS. They were present frequently in basal and post-treatment virus of patients who failed therapy to different DAA-based therapies. Contrary to several RAS, HRSs belong to the acceptable subset of substitutions according to the PAM250

replacement matrix. Coherently, their mutant frequency, measured by the number of deep sequencing reads within the HCV quasispecies that encode the relevant substitutions, ranged between 90% and 100% in most cases. Also, they have limited predicted disruptive effects on the three-dimensional structures of the proteins harboring them.

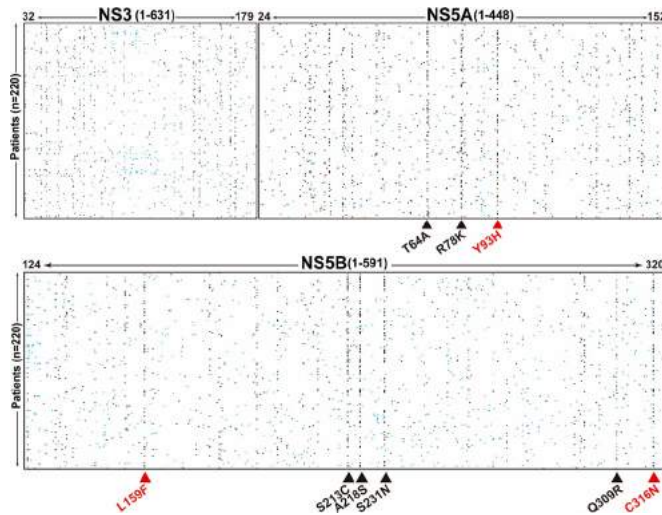


Figure:

Conclusion: The information on HRSs that will be gathered during sequencing should be relevant not only to help predict treatment outcomes but also to further understand HCV population dynamics, which appears much more complex than thought prior to the introduction of deep sequencing.

PO-2320

Efficacy and Safety of Sofosbuvir/Ledipasvir Combination or Nitazoxanide in Treatment of COVID-19: A Placebo-Controlled, Randomized Clinical Trial

Mohammed Medhat¹, Haidi Karam-Allah¹, Ahmad Al Shafie², Marwa Salama³, Dalia T. Kamal⁴, Hamdy Sayed², Azza M. Ezz Eldin⁴, Mohamed Badr⁵, Mohamed Samir Abd Elghafar⁶, Hossam El-deen Esmael¹, Ashima'a I. Ossimi⁷, Sameera Ezzat⁸, Ahmed Shamseldeem⁹, Inas Moaz⁸, Sahar M. Hassany¹, Sherief Abd-Elsalam³, Ehab F. Moustafa¹, Mohamed El Kassas¹⁰.
¹Assiut University Hospitals, Tropical Medicine and Gastroenterology Department, Assiut, Egypt; ²Faculty of Medicine, Helwan University, Endemic Medicine and Hepato-Gastroenterology Department, Cairo, Egypt; ³Faculty of Medicine, Tanta University, Tropical Medicine and Infectious diseases department, Tanta, Egypt; ⁴Faculty of Medicine, Assiut University, Clinical Pathology Department, Assiut, Egypt; ⁵Faculty of Medicine, Helwan University, Critical care medicine department, Cairo, Egypt; ⁶Faculty of Medicine, Tanta University, Anesthesia, Surgical Intensive Care and Pain Medicine Department, Tanta, Egypt; ⁷Faculty of medicine, Helwan University, Critical Care and Emergency Medicine Department, Cairo, Egypt; ⁸National Liver Institute, Menoufia University, Epidemiology and Preventive Medicine, Menoufia, Egypt; ⁹15 Mayo Hospital, Intensive Care, Cairo, Egypt; ¹⁰Faculty of Medicine, Helwan University, Endemic Medicine and Hepato-Gastroenterology Department, Cairo, Egypt
 Email: m_elkassas@hq.helwan.edu.eg

Background and aims: Despite several antiviral drugs have been evaluated as possible treatments for the COVID-19 pandemic, none of these drugs has proved to be effective against the SARS-CoV-2 virus. The journey to find a curative therapy for HCV is successful and

inspiring. We evaluated the possibility of repositioning for Sofosbuvir/Ledipasvir (SOF/LED) and Nitazoxanide (NTZ) as a possible treatment for COVID-19 infection.

Method: This multicenter open-label randomized controlled trial recruited patients with mild and moderate COVID-19 infection. Patients were randomly assigned in a 1:1:1 ratio to receive either the fixed combination of SOF/LED (400 mg and 90 mg, orally) once daily for 14 days, plus the standard of care therapy (SCT) for COVID-19 patients according to Egyptian Ministry of Health protocol (group 1), or NTZ (500 mg, orally) four times per day for 14 days plus the SCT (group 2), or to receive the SCT alone (group 3) for 14 days. NTZ was used in a dose of 500 mg q.id. as this dose was found to be able to present in both the plasma and the lung and can be maintained above the in vitro EC90 for the majority of the dosing period. Patients were excluded if they were less than 12 years old, had severe or critical COVID-19 infection, pregnant, had renal impairment with creatinine clearance <30 ml/min, with evidence of malignancies, and patients using favipiravir or lopinavir-ritonavir, as the co-administration of these drugs with sofosbuvir/ledipasvir has not been well studied. Follow-up by PCR was done at 5, 8, 11, and 14 days interval. The primary end point was the viral clearance.

Results: One-hundred and ninety patients were included. Viral clearance was significantly higher in the SOF/LED and NTZ groups compared to the standard of care group in all follow-up intervals (p <0.001). In the SOF/LED, 36.9% showed early viral clearance by day 5. By the end of the follow-up at 14 days, 83.1% of the SOF/LED group, 39.7% of the NTZ group, and 19.4% of the SCT groups developed negative PCR (Figure 1). Although there was a significant difference between the groups regarding age and sex, the Cox regression analysis showed that SOF/LED and NTZ were the only significant factors with the highest OR (17.88, 95% CI: 6.66–47.98 and 2.59, 95% CI: 1.11–6.07, respectively). No mortality or progression to severe COVID-19, ICU admission, or severe side effects were recorded.

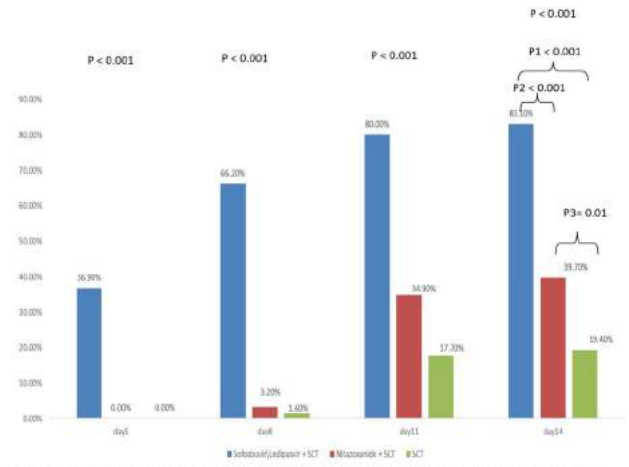


Figure: The cumulative incidence of negative RT-PCR following treatment at each follow follow-up time interval. P1; P value between Sofosbuvir/Ledipasvir plus SCT and SCT alone, P2; P value between Sofosbuvir/Ledipasvir plus SCT and Nitazoxanide plus SCT, P3; P value between Nitazoxanide plus SCT and SCT alone.

Conclusion: The addition of sofosbuvir/ledipasvir or nitazoxanide to the standard therapy resulted in an early and high viral clearance rate in mild and moderate COVID-19. These drugs appear to be promising and safe treatment in COVID-19 management.

Author Index

- Aagaard, Neils Kristian Muff, S194 (CS-1997)
- Aamann, Luise, S344 (PO-342)
- Aaron den Daas, Stijn, S330 (PO-2147)
- Abad, Laia, S334 (PO-624)
- Aban, Marites, S347 (PO-1045)
- Abbas, Nadir, S426 (PO-770)
- Abdallah, Dalaal, S407 (PO-2363)
- Abdelaal, Hala, S395 (PO-1505)
- Abdelhaleem, Mohamed Mahmoud, S784 (PO-975)
- Abdelmalek, Manal, S268 (OS-1034), S268 (OS-1044), S614 (PO-849)
- Abd-El salam, Sherief, S803 (PO-2320)
- Abdia, Younathan, S782 (PO-862), S789 (PO-2708)
- Abdo, Ayman, S636 (PO-2476)
- Abdulla, Ruba, S502 (PO-1752)
- Abdul Razzack, Aminah, S383 (PO-2305)
- Abdurakhmanov, Dzhamal, S789 (PO-2418)
- Abecia, Leticia, S301 (PO-1185)
- Abe, Hiroshi, S239 (OS-2686)
- Abe, Masanori, S425 (PO-376)
- Abergel, Armand, S461 (PO-351), S462 (PO-353), S647 (PO-785), S793 (PO-468)
- Åberg, Fredrik, S334 (PO-134), S692 (PO-2667)
- Abeysekera, Kushala, S273 (OS-183)
- Abid, Adeel, S776 (PO-2193)
- Abideen, Zain Ul, S802 (PO-2275)
- Abid, Shahab, S378 (PO-1987)
- Abofayed, Hiatem, S420 (PO-1822)
- Abou-Taleb, Ashraf, S293 (OS-2306)
- Abrahamowicz, Michał, S469 (PO-1459)
- Abrahamyan, Lusine, S228 (OS-1586)
- Abraides, Juan, S307 (PO-48)
- Abraides, Juan G., S235 (OS-213), S315 (PO-1099), S368 (PO-1064)
- Abramov, Andrey, S338 (PO-1684)
- Abrescia, Nicola G. A., S502 (PO-1752)
- Abreu, Nélia, S677 (PO-323)
- Abrial, Pauline, S698 (PO-700)
- Abril-Fornaguera, Jordi, S240 (OS-615)
- Abu-Omar, Jasmin, S213 (OS-513)
- Abutidze, Akaki, S797 (PO-1553)
- Aby, Elizabeth, S532 (PO-33)
- Abyzov, Anton, S572 (PO-1217)
- Acarli, Koray, S473 (PO-2211)
- Acar, Sencan, S671 (PO-2288)
- Accarino, Elena Vargas, S664 (PO-2047)
- Accolla, Roberto, S246 (OS-1399)
- Acevedo, Juan, S495 (PO-2799)
- Acharjee, Animesh, S263 (OS-1028)
- Acharya, Chathur, S403 (PO-418)
- Ackermann, Nora, S332 (PO-2358)
- Acosta-López, Silvia, S492 (PO-2594), S674 (PO-2596)
- Acosta Rivera, Mirelis, S243 (OS-295)
- Adam, Gerhard, S522 (PO-1745)
- Adamia, Ekaterine, S773 (PO-1691), S797 (PO-1553)
- Adam, Rene, S525 (PO-2408)
- Adam, René, S473 (PO-2211), S482 (PO-750)
- Adams, David, S423 (PO-60)
- Addolorato, Giovanni, S466 (PO-935)
- Adedeji, Mary, S676 (PO-2904)
- Adeel Hassan, Syed, S383 (PO-2305)
- Adee, Madeline, S672 (PO-2424), S776 (PO-2218)
- Adekunle, Femi, S424 (PO-254), S434 (PO-1664), S439 (PO-2327)
- Adelmeijer, Jelle, S343 (PO-187)
- Ades, AE, S643 (PO-425)
- Adrait, Annie, S701 (PO-1450)
- Adrien, Lannes, S566 (PO-944)
- Adu, Prince, S782 (PO-862), S789 (PO-2708)
- Aerssens, Jeroen, S718 (PO-947)
- Aerts, Isabelle, S242 (OS-906)
- Afdhal, Nezam, S334 (PO-134), S579 (PO-1714), S797 (PO-1553)
- Afonso, João, S296 (LBP-2891), S440 (PO-2701), S443 (PO-2801), S445 (PO-2887), S445 (PO-2898)
- Afonso, Marta B., S604 (PO-2276)
- Afonso, Milessa Silva, S401 (PO-2415)
- Agarwal, Banwari, S194 (GS-1997), S209 (OS-2060)
- Agarwal, Kosh, S285 (OS-887), S288 (OS-211), S721 (PO-1510), S741 (PO-1004), S756 (PO-2395)
- Agarwal, Samagra, S212 (OS-31), S371 (PO-1151), S378 (PO-1705), S381 (PO-2294), S438 (PO-2280), S635 (PO-2319)
- Agarwal, Suneet, S735 (PO-397)
- Aggarwal, Abhishek, S401 (PO-2415), S716 (PO-665), S725 (PO-1789)
- Aggarwal, Rakesh, S672 (PO-2424)
- Aggarwal, Reenika, S508 (PO-2742)
- Aggarwal, Sandeep, S259 (OS-1592)
- Aggelis, Nikolaos, S204 (LBO-2765), S360 (PO-2867)
- Aghemo, Alessio, S353 (PO-1767), S652 (PO-1374)
- Agiasotelli, Danai, S328 (PO-1501)
- Agorastou, Polyxeni, S737 (PO-715)
- Agostinacchio, Ernesto, S764 (PO-388)
- Ågren, Anna, S339 (PO-1787)
- Agudo, Rubén Rodríguez, S243 (OS-1948), S320 (PO-2043), S612 (PO-627), S624 (PO-2192)
- Aguilar-Bravo, Beatriz, S207 (OS-2028)
- Aguilar, Ferran, S325 (PO-552)
- Aguilera, A., S765 (PO-525)
- Aguilera, Victoria, S277 (OS-1172)
- Agusta Cipriano, Maria, S442 (PO-2761)
- Agusti, Anna, S723 (PO-1622)
- Aharon, Arnon, S419 (PO-1311)
- Ahlholm, Noora, S260 (OS-2362)
- Ahmadi, Mitra, S582 (PO-1927)
- Ahmad, Nadeem, S796 (PO-1533)
- Ahmed, Aijaz, S532 (PO-33)
- Ahmed, Haysam, S623 (PO-2099)
- Ahn, Sang Bong, S675 (PO-2689)
- Ahn, Sang Hoon, S287 (OS-2225), S717 (PO-676), S756 (PO-2395), S757 (PO-2422), S757 (PO-2429)
- Ahumada, Adriana, S239 (OS-2686), S784 (PO-1176)
- Aigner, Elmar, S542 (PO-1205), S552 (PO-2328), S570 (PO-1195), S573 (PO-1220)
- Ai, Jingwen, S359 (PO-2688)
- Aikata, Hiroshi, S780 (PO-602)
- Aiko, Mika, S335 (PO-698), S338 (PO-1761)
- Aimard, Alexis Monnet, S341 (PO-2382)
- Aithal, Guruprasad, S259 (OS-1592), S274 (OS-1381), S303 (PO-1379), S562 (PO-775), S573 (PO-1336)

*Page numbers for abstracts are followed by the abstract number(s) in parentheses.

- Ajayi, Omolola, S395 (PO-1441), S478 (PO-1422)
- Ajmera, Veeral, S577 (PO-1648)
- Akamatsu, Nobuhisa, S193 (GS-1213)
- Akarca, Ayse, S245 (OS-1145)
- Akarca, Ayse U., S448 (PO-718)
- Akarca, Ulus, S640 (PO-1353), S671 (PO-2288)
- Akarsu, Mesut, S472 (PO-2001), S671 (PO-2288)
- Akdogan Kayhan, Meral, S472 (PO-2001)
- Akerblad, Peter, S223 (OS-1847), S597 (PO-1849)
- Akers, Nicholas, S240 (OS-615)
- Akhavan, Sepideh, S191 (GS-1065)
- Akita, Tomoyuki, S532 (PO-19)
- Akkouche, Linda, S584 (PO-2030)
- Akturk, Hacer, S691 (PO-2392)
- Akuchi, Akira, S690 (PO-2090)
- Akushevich, Lucy, S798 (PO-1962)
- Akyildiz, Murat, S193 (GS-1213), S472 (PO-2001)
- Alabsawy, Eman, S209 (OS-2060)
- Aladag, Murat, S671 (PO-2288)
- Alam, Imtiaz, S583 (PO-1981)
- Alaparthi, Lakshmi, S395 (PO-1505)
- Alavi, Maryam, S515 (PO-767)
- Alazawi, William, S536 (PO-630)
- Albano, Emanuele, S598 (PO-1916)
- Alberto Costa Noronha Ferreira, Carlos, S216 (OS-1544)
- Alberto Ferrusquia, Jose, S345 (PO-835)
- Albert, Olivier, S767 (PO-690)
- Alberts, Catharina, S276 (OS-2750)
- Albillos, Agustin, S216 (OS-1544), S252 (OS-571), S269 (OS-1769), S307 (PO-48), S334 (PO-624), S347 (PO-1045), S746 (PO-1449)
- Albillos, Agustín, S277 (OS-1172)
- Albrechtsen, Nicolai J. Wever, S593 (PO-1407)
- Alcoba, Diego, S246 (OS-1399)
- Aldámiz-Echevarría, Teresa, S785 (PO-1404)
- Aldersley, Mark, S273 (OS-199), S777 (PO-2352)
- Aleman, Soo, S294 (LBP-2730), S734 (PO-111)
- Alén, Rosa, S250 (OS-1414)
- Alessandria, Carlo, S353 (PO-1767)
- Alexander Aghdassi, Ali, S535 (PO-566)
- Alexander, Emma, S677 (PO-106)
- Alexander, Graeme, S435 (PO-1790)
- Alexander, Hannah, S775 (PO-2095)
- Alexander Worns, Marcus, S521 (PO-1351)
- Alexopoulos, Sophoclis, S463 (PO-530)
- Alexopoulos, Theodoros, S328 (PO-1501), S350 (PO-1471)
- Alexopoulou, Alexandra, S328 (PO-1501), S350 (PO-1471)
- Alfaiate, Dulce, S703 (PO-1711)
- Alfonso Martinez-Cruz, Luis, S301 (PO-1185)
- Alfthan, Henrik, S229 (OS-2096)
- Aliabadi, Elmira, S454 (PO-2154), S456 (PO-2339)
- Alick Bonghanoy, Adrian, S305 (PO-2122)
- Ali Malek-Hosseini, Seyed, S473 (PO-2211)
- Ali, Nasima, S272 (OS-1756)
- Ali Shagrani, Mohammad, S279 (OS-1554)
- Alisi, Anna, S600 (PO-1986), S600 (PO-2033)
- Alizei, Elahe Salimi, S454 (PO-1983)
- Alkhatib, Mohammad, S704 (PO-1928), S728 (PO-1996)
- Alkhashvili, Maia, S768 (PO-908), S773 (PO-1691)
- Alkhouri, Naim, S200 (GS-2563), S265 (OS-1746), S314 (PO-832), S538 (PO-819), S539 (PO-825), S561 (PO-756), S563 (PO-836), S563 (PO-866), S567 (PO-1001), S575 (PO-1568), S578 (PO-1689), S614 (PO-849)
- Alkim, Huseyin, S671 (PO-2288)
- Allara, Elias, S245 (OS-1145)
- Allen, Sophie, S342 (PO-2851)
- Aller, Rocio, S255 (OS-2337), S584 (PO-2369)
- Aller, Rocío, S564 (PO-916)
- Allinder, Matthew, S434 (PO-1748)
- Allison, Michael, S256 (OS-538), S263 (OS-1028), S266 (OS-2831), S548 (PO-1747)
- Allison, Mike, S255 (OS-243), S564 (PO-919), S568 (PO-1056)
- Allweiss, Lena, S702 (PO-1631), S702 (PO-1707)
- Al-Mahtab, Mamun, S438 (PO-2280)
- Almeida, Joana Inês, S457 (PO-1154)
- Almeida, Nuno, S247 (OS-2190)
- Alnuaimi, Bader, S574 (PO-1453)
- Alonso, Cristina, S564 (PO-916), S574 (PO-1518), S617 (PO-1112)
- Alqahtani, Saleh, S468 (PO-1169), S495 (PO-2799), S544 (PO-1227)
- Alric, Laurent, S793 (PO-468)
- Al-Rubaiy, Laith, S442 (PO-2724)
- Alsaed, Mohamad, S193 (GS-1213)
- Alsawat, Khaled, S636 (PO-2476)
- Alsumali, Adnan, S671 (PO-2152)
- Altamura, Sandro, S607 (PO-2623)
- Altmann, Daniel M., S448 (PO-718)
- Alukal, Joseph, S365 (PO-1032), S366 (PO-1038)
- Alvani Gani, Rino, S438 (PO-2280)
- Alvarado, Edilmar, S252 (OS-571), S307 (PO-48), S378 (PO-1987), S694 (PO-2902)
- Álvares-da-Silva, Mario Reis, S495 (PO-2799)
- Alvarez-Alvarez, Ismael, S303 (PO-1389)
- Alvarez, Angel Caunedo, S779 (PO-578)
- Álvarez-Cancelo, Ana, S537 (PO-685)
- Alvarez, Carol, S476 (PO-982)
- Alvarez, Daniel, S346 (PO-864)
- Álvarez, Juan Miguel Castro, S783 (PO-881)
- Alvarez, Maria, S782 (PO-862), S789 (PO-2708)
- Álvarez-Navascués, Carmen, S516 (PO-1010)
- Alvarez-Ossorio, Angela Rojas, S342 (PO-2420)
- Alvarez, Paula Fernandez, S779 (PO-578)
- Álvarez-Velasco, Rut, S516 (PO-1010)
- Alvaro, del Rio, S240 (OS-615), S689 (PO-2090)
- Alvaro, Domenico, S425 (PO-376)
- Alves, Bruna Cherubini, S639 (PO-205)
- Alves, Paula M., S457 (PO-1154)
- Alves, Rogério, S495 (PO-2799)
- Alvisi, Margherita, S533 (PO-441)
- Amaddeo, Giuliana, S487 (PO-1153)
- Amado, Luis Enrique Morano, S788 (PO-1919)
- Amador, Alberto, S746 (PO-1449)
- Ambroise, Jérôme, S477 (PO-1207)
- Amer, Johnny, S220 (OS-2854)
- Amicone, Caroline, S694 (PO-2902)
- Amin, Irum, S233 (OS-2656)
- Amin, Janaki, S515 (PO-767)
- Amin, Oliver E., S451 (PO-1460)
- Amirabadi, Hossein Esлами, S623 (PO-2099)
- Amitrano, Lucio, S216 (OS-1544), S307 (PO-48)
- Amjad, Waseem, S322 (PO-2389)
- Amlani, Bharat, S356 (PO-2524)
- Ammar, Majeed, S512 (PO-75)
- Amor Chatterjee, Devnandan, S349 (PO-1165)
- Amorim, Ricardo, S604 (PO-2276)
- Amoroso, Antonio, S234 (OS-116)
- Amougou, Marie, S768 (PO-908)
- Ampuero, Javier, S255 (OS-2337), S269 (OS-1769), S342 (PO-2420), S540 (PO-831), S556 (PO-167), S584 (PO-2369)
- Amuzie, Dozie, S531 (PO-2627)
- Ananchuensook, Prooksa, S719 (PO-1000)
- Anand, Abhinav, S212 (OS-31)
- Anastasiy, Igor, S742 (PO-1240), S743 (PO-1251)
- Andersen, Jesper, S240 (OS-179), S497 (PO-133)
- Andersen, Jesper B., S505 (PO-1969)
- Andersen, Mette Lehmann, S638 (PO-190)
- Anders, Maria Margarita, S495 (PO-2799)
- Anderson, David, S358 (PO-2683), S386 (PO-2685), S714 (PO-420), S731 (PO-2575)
- Anderson, Jeff, S241 (OS-699)
- Anderson, Jenine, S775 (PO-2048)
- Anderson, Mark, S285 (OS-887), S721 (PO-1510), S760 (PO-2822), S762 (PO-2879)
- Anders, Simon, S393 (PO-793)
- Andersson Friis Liby, Ingaliil, S227 (OS-1088)
- Andersson, Maria, S284 (OS-2864)

Author Index

- Andrade, Raul J., S193 (GS-1213), S301 (PO-1185), S302 (PO-1335), S303 (PO-1389), S304 (PO-1406)
- Andreola, Fausto, S194 (GS-1997), S209 (OS-2060), S329 (PO-1585), S347 (PO-1045)
- Andreone, Pietro, S294 (LBP-2730)
- Andreoni, Massimo, S652 (PO-1374), S654 (PO-1426), S704 (PO-1928), S728 (PO-1996)
- Andre, Patrice, S698 (PO-700)
- Andres, Malena, S560 (PO-632)
- Andreu, Enrique J., S329 (PO-2058)
- Andreu-Oller, Carmen, S521 (PO-1420)
- Andrieux-Meyer, Isabelle, S660 (PO-1877)
- Ángeles Pérez-san-Gregorio, María, S533 (PO-381)
- Angelin, Bo, S223 (OS-1847), S597 (PO-1849)
- Angeli, Paolo, S346 (PO-918), S346 (PO-932), S355 (PO-2273), S469 (PO-1496), S473 (PO-2425)
- Angel, Peter, S219 (OS-2754)
- Angrisani, Debora, S466 (PO-935)
- Ang, Tiing Leong, S765 (PO-453)
- Anguita, Juan, S243 (OS-1948), S301 (PO-1185)
- Angus, Peter, S471 (PO-1971)
- Anikhindi, Shrihari Anil, S632 (PO-1696)
- An, Jihyun, S500 (PO-920), S528 (PO-895)
- An, Lin-Jing, S709 (PO-218)
- Anne van Os, Elise, S527 (PO-608)
- Anne, Varaut, S793 (PO-468)
- Annicchiarico, Angela, S656 (PO-1593)
- Annunziato, Francesco, S506 (PO-2375)
- Ann Wong, Jo, S394 (PO-1125)
- Anolli, Maria Paola, S782 (PO-697)
- Anstee, Quentin, S253 (OS-635), S256 (OS-538), S257 (OS-1556), S259 (OS-1592), S266 (OS-2831), S564 (PO-916), S564 (PO-919), S568 (PO-1056), S575 (PO-1568), S576 (PO-1575), S579 (PO-1714), S579 (PO-1777), S625 (PO-2290), S669 (PO-2108)
- Anstee, Quentin M., S255 (OS-243)
- Anthony, Daniel C., S418 (PO-1026)
- Antoine Allard, Marc, S482 (PO-750), S525 (PO-2408)
- Antoine, Corinne, S469 (PO-1459)
- Antonelli, Barbara, S524 (PO-2401)
- Antoniades, Charalambos, S306 (PO-2178)
- Antoniades, Charalambos G., S224 (OS-1946)
- Antoniello, Deana, S203 (LBO-2764), S761 (PO-2823), S762 (PO-2879)
- Antonini, Teresa, S350 (PO-1549)
- Antonio Almeyda-Farfán, José, S533 (PO-445)
- Antonio Diaz, Luis, S199 (GS-2309)
- Anton, Martina, S262 (OS-584)
- Antony, Fino, S394 (PO-1069), S396 (PO-1580)
- Antoran, Belén Ruiz, S269 (OS-1769)
- Anty, Rodolphe, S201 (LBO-2631)
- Ao, Jiafu, S629 (PO-1091)
- Aouinti, Safia, S352 (PO-1712)
- Aoyagi, Katsumi, S715 (PO-529)
- Apostolova, Nadezda, S401 (PO-1935), S595 (PO-1626)
- Arab, Juan Pablo, S199 (GS-2309), S323 (PO-2704)
- Arama, Sorin Stefan, S291 (OS-2717)
- Aransay, Ana María, S502 (PO-1752)
- Araujo, Melissa, S392 (PO-733)
- Araujo, Roberta, S199 (GS-2309)
- Arbib, Orly Sneh, S272 (OS-798)
- Arcese, William, S728 (PO-1996)
- Ardzinski, Andrzej, S281 (OS-595)
- Arefaine, Bethlehem, S222 (OS-2044), S330 (PO-2147), S333 (PO-2870)
- Arenas, Juan, S746 (PO-1449)
- Arena, Umberto, S506 (PO-2375)
- Arends, Johannes E., S774 (PO-1966)
- Arico, Francesco, S215 (OS-1864)
- Ari, Derya, S472 (PO-2001)
- Ariño Mons, Silvia, S207 (OS-2028)
- Ari, Ziv Ben, S730 (PO-2366)
- Arizpe, Andre, S288 (OS-211), S733 (PO-43), S738 (PO-824)
- Arikan, Cigdem, S193 (GS-1213), S472 (PO-2001), S691 (PO-2392)
- Armakolas, Athanasios, S511 (PO-2920)
- Armandi, Angelo, S253 (OS-635), S556 (PO-167)
- Armengol, Carolina, S240 (OS-615), S690 (PO-2090)
- Armstrong, Matthew, S332 (PO-2609), S342 (PO-2851)
- Armstrong, Paige A., S274 (OS-551), S643 (PO-504), S797 (PO-1553)
- Arnold, Dirk, S244 (OS-777)
- Arola, Johanna, S227 (OS-1088), S229 (OS-2096), S260 (OS-2362), S444 (PO-2830), S605 (PO-2322)
- Aronson, Sem J., S202 (LBO-2647)
- Arora, Anil, S632 (PO-1696)
- Arora, Gunisha, S212 (OS-1491)
- Arora, Sanjeev, S797 (PO-1553)
- Arora, Vinod, S381 (PO-2238)
- Arranz, Maria, S663 (PO-2014)
- Arrese, Marco, S199 (GS-2309), S389 (PO-477), S564 (PO-916), S574 (PO-1518)
- Arretxe, Enara, S564 (PO-916)
- Arroyo, Vicente, S209 (OS-2060), S325 (PO-552), S347 (PO-1045), S354 (PO-1930)
- Arroyo, Vincente, S194 (GS-1997)
- Arshad, Tamoore, S544 (PO-1227)
- Arslanow, Anita, S661 (PO-1903)
- Artan, Reha, S687 (PO-1811)
- Artaza Varasa, Tomás, S216 (OS-1544)
- Arvaniti, Pinelopi, S422 (PO-2681)
- Asatiani, Alexander, S773 (PO-1691)
- Asensio, Julia Peña, S447 (PO-235), S735 (PO-430)
- Asghar, Syed, S493 (PO-2687)
- Ashbrook, Alison, S603 (PO-2161)
- Ashraf, Aadil, S796 (PO-1533)
- Askgaard, Gro, S316 (PO-1375)
- Aslanikashvili, Ana, S274 (OS-551), S643 (PO-504)
- Aslan, Katrin, S246 (OS-1399)
- Aspichueta, Patricia, S389 (PO-477), S497 (PO-133), S591 (PO-1037), S612 (PO-627), S624 (PO-2192)
- Aspinall, Richard, S426 (PO-770), S677 (PO-299)
- Assante, Gabriella, S264 (OS-1524)
- Asselber, Tarik, S291 (OS-2717), S637 (PO-2936), S708 (PO-2684), S793 (PO-468)
- Assenat, Eric, S198 (GS-945)
- Asser Karsdal, Morten, S432 (PO-1512)
- Astbury, Stuart, S303 (PO-1379)
- Åström, Hanne, S488 (PO-1164)
- Atallah, Edmond, S303 (PO-1379)
- Atkinson, Stephen, S207 (OS-2158), S309 (PO-94)
- Atsukawa, Masanori, S239 (OS-2686)
- Attenberger, Ulrike, S213 (OS-513)
- Attia, Yasmeen, S407 (PO-2363), S606 (PO-2412)
- Attri, Sumeet, S356 (PO-2608)
- Aubé, Christophe, S198 (GS-945), S518 (PO-1209), S520 (PO-1263)
- Aucella, Filippo, S769 (PO-951)
- Audrey, Payance, S197 (GS-613), S678 (PO-561), S694 (PO-2902)
- Augustin, Salvador, S252 (OS-571), S255 (OS-2337), S584 (PO-2369)
- Augusto, Margarida, S398 (PO-1589), S399 (PO-1609)
- Aureli, Massimo, S505 (PO-1969)
- Aurrekoetxea, Igor, S497 (PO-133)
- Austin, Andrew, S610 (PO-231)
- Auzinger, Georg, S306 (PO-2178)
- Avallone, Antonio, S246 (OS-1399)
- Avcioglu, Ufuk, S671 (PO-2288)
- Avellini, Claudio, S448 (PO-718)
- Averhoff, Francisco, S797 (PO-1553)
- Avila, Matías A., S301 (PO-1185)
- Avila, Matías A., S243 (OS-1948), S320 (PO-2043), S624 (PO-2192)
- Avitabile, Emma, S311 (PO-345), S319 (PO-1932)
- Awan, Safia, S776 (PO-2193)
- Ayada, Ibrahim, S550 (PO-1951)
- Aymeric, Labourdette, S257 (OS-555)
- Ayoub, Walid, S361 (PO-2951), S496 (PO-2812), S736 (PO-482)
- Ayuso, Carmen, S640 (PO-1193)
- Azam, Zahid, S378 (PO-1987)
- Aziz, Bishoi, S228 (OS-1586)
- Aziz, Fatima, S329 (PO-2058)
- Aziz, Fátima, S194 (GS-1997), S209 (OS-2060)
- Aziz, Riffat Abdul, S796 (PO-1533)
- Azkargorta, Mikel, S334 (PO-624), S401 (PO-2113), S502 (PO-1752), S624 (PO-2192), S689 (PO-2090)

- Azzara, Anthony, S529 (PO-1606)
 Azzaroli, Francesco, S518 (PO-1124)
 Azzu, Vian, S263 (OS-1028)
- Baars, Matthijs J.D., S457 (PO-279)
 Babameto, Adriana, S654 (PO-1480)
 Babudieri, Sergio, S652 (PO-1374)
 Babuta, Mrihya, S206 (OS-1663),
 S594 (PO-1547)
 Bachmayer, Sebastian, S542 (PO-1205),
 S552 (PO-2328), S573 (PO-1220)
 Bacon, Bruce, S686 (PO-1809)
 Badenas, Celia, S271 (OS-1954)
 Badia-Aranda, Esther, S746 (PO-1449),
 S778 (PO-2359)
 Badlani, Disha, S499 (PO-677)
 Badr, Mohamed, S803 (PO-2320)
 Badrock, Jonathan, S420 (PO-1578)
 Bae, Ho, S736 (PO-482), S755 (PO-2338)
 Baerlecken, Niklas T., S423 (PO-60)
 Bae, Si Hyun, S504 (PO-1825)
 Bae, Sung Min, S417 (PO-855),
 S614 (PO-787)
 Baiges, Anna, S277 (OS-1172),
 S694 (PO-2902)
 Baiges, Gerard, S598 (PO-1897)
 Baik, Soon Koo, S327 (PO-984),
 S332 (PO-2547), S721 (PO-1340)
 Bail, Brigitte Le, S510 (PO-2865)
 Bailey, Adam, S418 (PO-1026)
 Bailly, Francois, S647 (PO-785),
 S793 (PO-468)
 Bailly, Sébastien, S238 (OS-1704)
 Baiocchi, Leonardo, S654 (PO-1480)
 Bajaj, Jasmohan, S207 (OS-2158)
 Bajaj, Jasmohan S., S220 (OS-119),
 S309 (PO-117), S403 (PO-418)
 Baker, Fadi Abu, S730 (PO-2366)
 Bakieva, Shokhista, S642 (PO-424)
 Balaban, Hatice Yasemin, S671 (PO-2288)
 Balabaud, Charles, S510 (PO-2865)
 Balagna, Roberto, S234 (OS-116)
 Balaji, Anu, S349 (PO-1165)
 Balakrishna, Deepika, S393 (PO-938)
 Balakrishnan, Anand, S740 (PO-942)
 Balaphas, Alexandre, S548 (PO-1772)
 Balaseviciute, Ugne, S240 (OS-615)
 Bala, Shashi, S594 (PO-1547)
 Balcar, Lorenz, S236 (OS-498),
 S270 (OS-507), S374 (PO-1249),
 S376 (PO-1316), S377 (PO-1613),
 S521 (PO-1312), S542 (PO-1205),
 S552 (PO-2328), S570 (PO-1195),
 S573 (PO-1220), S681 (PO-1243)
 Balcells, Cristina, S245 (OS-1145)
 Balci, Deniz, S472 (PO-2001)
 Balci, Hatice Rizaoglu, S671 (PO-2288)
 Baldassarre, Maurizio, S347 (PO-1045)
 Baldea, Victor, S398 (PO-1582)
 Baldvinsdóttir, Guðrún Erna,
 S670 (PO-2127)
 Balendran, Clare, S561 (PO-756)
 Bali, Ildiko, S655 (PO-1572)
 Ballard, J.W.O, S264 (OS-1524)
- Ballester-Ferré, María Pilar, S335 (PO-698)
 Ballester-Ferré, María-Pilar, S335 (PO-709)
 Ballester, José, S335 (PO-698),
 S335 (PO-709)
 Balsano, Clara, S353 (PO-1767)
 Baltacioglu, Feyyaz, S491 (PO-2223)
 Bamberg, Fabian, S535 (PO-566)
 Banales, Jesus Maria, S240 (OS-179),
 S497 (PO-133), S624 (PO-2192),
 S634 (PO-2184)
 Banares Canizares, Rafael, S194 (GS-1997),
 S209 (OS-2060)
 Bañares, Juan, S663 (PO-2014)
 Bañares, Rafael, S239 (OS-2686),
 S252 (OS-571), S307 (PO-48),
 S746 (PO-1449), S784 (PO-1176)
 Bandiera, Simonetta, S212 (OS-1491)
 Bandi, Juan Carlos, S495 (PO-2799)
 Bandukwala, Hozefa, S453 (PO-1653)
 Banerjee, Rajarshi, S403 (PO-2790),
 S408 (PO-629), S410 (PO-985),
 S634 (PO-2094)
 Bansal, Naresh, S632 (PO-1696)
 Bansal, Vikas, S353 (PO-1766)
 Bantel, Heike, S429 (PO-1294)
 Bao, Jinlun, S368 (PO-1094),
 S629 (PO-1091)
 Baptista, Pedro, S457 (PO-1154),
 S459 (PO-2234)
 Barash, Danny, S801 (PO-2240)
 Barashi, Neta, S419 (PO-1311)
 Barbaro, Francesco, S767 (PO-694)
 Barbas, Coral, S785 (PO-1404)
 Barbeta, Arianna, S471 (PO-1773)
 Barbier, Louise, S461 (PO-351),
 S462 (PO-353), S518 (PO-1209)
 Barbosa, Joana Sofia Vieira,
 S679 (PO-570)
 Barbosa, Joana Vieira, S659 (PO-1862),
 S672 (PO-2387)
 Barciela, Mar Riveiro, S663 (PO-2014),
 S664 (PO-2047), S696 (PO-469),
 S706 (PO-2145), S732 (PO-2637),
 S732 (PO-2834), S737 (PO-774),
 S788 (PO-1919)
 Barclay, Stephen, S611 (PO-337)
 Barclay, Stephen T., S489 (PO-1729)
 Barget, Nathalie, S259 (OS-1592)
 Baribault, Helene, S198 (GS-1645),
 S298 (PO-443), S312 (PO-442)
 Barkai, Laszlo, S226 (OS-894)
 Barnault, Romain, S754 (PO-2243)
 Barnes, Eleanor, S332 (PO-2609),
 S403 (PO-2790), S649 (PO-1158)
 Barn, Jeevan, S470 (PO-1523)
 Baronio, Giuseppe, S513 (PO-574)
 Barreira, Ana, S437 (PO-2015),
 S663 (PO-2014), S664 (PO-2047)
 Barrenechea, Ignacio Martin-Granizo,
 S788 (PO-1919)
 Barriaes, Diego, S243 (OS-1948)
 Barrio, Marta Crespo, S799 (PO-2021)
 Barrio, Rosa, S624 (PO-2192)
 Barritt, A. Sidney, S332 (PO-2609)
- Barrón Campos, Arcelia Carolina,
 S533 (PO-445)
 Bartels, Anna-Lena, S230 (OS-2782)
 Bartlett, Samuel, S740 (PO-942)
 Bartlett, Sofia, S782 (PO-862),
 S789 (PO-2708)
 Bartres, Concepció, S640 (PO-1193)
 Barutcu, Sezgin, S671 (PO-2288)
 Baselli, Guido, S261 (OS-297)
 Baselli, Guido Alessandro, S333 (PO-2870),
 S624 (PO-2192), S642 (PO-251)
 Bashir, Mustafa, S200 (GS-2563),
 S616 (PO-981), S617 (PO-1082)
 Bashyam, Maria, S354 (PO-1998)
 Basili, Stefania, S216 (OS-1544)
 Bassanelli, Chiara, S424 (PO-254),
 S434 (PO-1664), S439 (PO-2327)
 Bassegoda, Octavi, S252 (OS-571),
 S311 (PO-345), S319 (PO-1932),
 S329 (PO-2058)
 Bataller, Ramon, S199 (GS-2309),
 S307 (PO-48)
 Bates, Jamie, S614 (PO-838)
 Bathon, Melanie, S521 (PO-1420)
 Batrla-Utermann, Richard, S715 (PO-460),
 S725 (PO-1788)
 Bats, Marie-Lise, S648 (PO-821)
 Battisti, Arianna, S728 (PO-1996)
 Batu, Kerim Deniz, S671 (PO-2288)
 Bätz, Olaf, S763 (PO-68), S764 (PO-131)
 Baudin, Martine, S268 (OS-1034),
 S268 (OS-1044)
 Baudoin, Mael, S292 (OS-728)
 Bauer, David J.M., S213 (OS-925),
 S270 (OS-507), S362 (PO-309),
 S363 (PO-310), S364 (PO-532),
 S365 (PO-560), S374 (PO-1249),
 S376 (PO-1316), S377 (PO-1613),
 S383 (PO-2403)
 Bauer, David JM, S645 (PO-533),
 S681 (PO-1243)
 Bauer, Tanja, S446 (PO-147)
 Baumann, Anna, S423 (PO-60)
 Baumann, Ulrich, S202 (LBO-2647),
 S682 (PO-1354), S687 (PO-1811)
 Baumert, Thomas, S196 (GS-2069),
 S212 (OS-1491), S247 (OS-2190),
 S392 (PO-692), S695 (PO-175),
 S780 (PO-602)
 Baum, Seth J., S200 (GS-2563)
 Bauschen, Alina, S448 (PO-262)
 Bayard, Quentin, S242 (OS-906)
 Bayerl, Felix, S262 (OS-584)
 Bazinet, Michel, S750 (PO-1837)
 Bazzocchi, Francesca, S769 (PO-951)
 Bazzoli, Franco, S518 (PO-1124)
 Beach, Timothy, S233 (OS-2656)
 Beauvieux, Marie-Christine, S648 (PO-821)
 Bebars, Gihan, S293 (OS-2306)
 Becares, Natalia, S328 (PO-1387),
 S452 (PO-1598)
 Becce, Fabio, S679 (PO-570)
 Becchetti, Chiara, S466 (PO-1126),
 S467 (PO-1133)

Author Index

- Beck, Andrew, S254 (OS-1611),
S433 (PO-1644), S602 (PO-2123)
- Beckebaum, Susanne, S477 (PO-1119)
- Becker, Diana, S498 (PO-336),
S501 (PO-1304)
- Becker, Jeanette, S374 (PO-1249)
- Beck, Julia, S464 (PO-841)
- Beck, Stephen, S531 (PO-2627)
- Bedin, Chiara, S619 (PO-1359)
- Bedossa, Pierre, S400 (PO-1857),
S555 (PO-2692), S564 (PO-919),
S568 (PO-1056), S593 (PO-1504)
- Bedozza, Pierre, S255 (OS-243)
- Bee Leng Ong, Agnes, S233 (OS-1290)
- Beer, Lewis, S800 (PO-2205)
- Befeler, Alex, S327 (PO-968)
- Begic, Merjem, S681 (PO-1244)
- Begum, Neelu, S222 (OS-2044)
- Begum, Sofina, S404 (PO-799)
- Behling, Cynthia, S204 (LBO-2800),
S577 (PO-1648), S619 (PO-1762)
- Behme, Sara, S697 (PO-611)
- Behrendt, Patrick, S282 (OS-1062),
S423 (PO-60), S703 (PO-1907)
- Beigelman, Leonid, S700 (PO-1305),
S720 (PO-1257), S742 (PO-1196),
S744 (PO-1386)
- Beiroa, Daniel, S391 (PO-479)
- Bejjani, Anthony, S521 (PO-1420)
- Belén Rubio, Ana, S311 (PO-345),
S319 (PO-1932)
- Bélet, David, S603 (PO-2186)
- Beliz Ulas, Bahar, S549 (PO-1865)
- Belkaya, Serkan, S603 (PO-2161)
- Bellar, Annette, S317 (PO-1541)
- Bellocchi, Maria Concetta, S704 (PO-1928)
- Belmonte, Ernest, S640 (PO-1193)
- Belnou, Pierre, S194 (GS-1587)
- Bende, Felix, S398 (PO-1582)
- Bendtsen, Flemming, S593 (PO-1407)
- Benedicto, Ana, S595 (PO-1626)
- Benetatos, Christopher, S748 (PO-1699)
- Bengsch, Bertram, S245 (OS-1145),
S281 (OS-1021)
- Benhamed, Fadila, S528 (PO-1027)
- Benini, Federica, S677 (PO-323)
- Ben Khaled, Najib, S389 (PO-410)
- Benlloch, Salvador, S335 (PO-698)
- Benmassaoud, Amine, S215 (OS-1864),
S540 (PO-831)
- Benna, Jamel El, S708 (PO-2684)
- Bennett, Michael, S736 (PO-482)
- Bennick, Hanne, S638 (PO-190)
- Benninga, Marc, S547 (PO-1526)
- Beo, Vincent Di, S292 (OS-728)
- Berby, Françoise, S699 (PO-820),
S701 (PO-1451), S713 (PO-408)
- Berenguer Haym, Marina, S472 (PO-2121),
S473 (PO-2211)
- Berenguer, Juan, S781 (PO-689),
S785 (PO-1404)
- Beretta, Ilaria, S767 (PO-694)
- Beretta-Piccoli, Benedetta Terziroli,
S193 (GS-1213), S227 (OS-1088)
- Berg, Christoph, S792 (PO-153)
- Berger, Arthur, S377 (PO-1474)
- Bergmann, Ottar M., S670 (PO-2127)
- Bergna, Irene, S521 (PO-1351)
- Bergquist, Annika M., S227 (OS-1088),
S421 (PO-2285)
- Berg, Thomas, S286 (OS-1892),
S287 (OS-2225), S429 (PO-1294),
S472 (PO-2121), S544 (PO-1296),
S706 (PO-2135), S732 (PO-2834),
S733 (PO-80), S747 (PO-1661),
S755 (PO-2269), S763 (PO-68),
S764 (PO-131), S778 (PO-52),
S792 (PO-153)
- Berhe, Nega, S734 (PO-111)
- Berishvili, Nino, S768 (PO-908)
- Berliba, Elina, S203 (LBO-2764)
- Bermejo, Francisco, S631 (PO-1668)
- Bernabeu, Jesús Quintero, S271 (OS-1954)
- Bernales, Irantzu, S497 (PO-133)
- Bernal, William, S306 (PO-2178),
S343 (PO-187)
- Bernard Chabert, Brigitte, S201 (LBO-2631)
- Bernardo, Diego Di, S690 (PO-2090)
- Bernardo, Ganeko, S249 (OS-1355)
- Bernasconi, Davide, S425 (PO-376)
- Bernsmeier, Christine, S208 (OS-638),
S306 (PO-2178), S628 (PO-2377)
- Bernstein, David, S649 (PO-1035)
- Berryman, Victoria, S536 (PO-630)
- Berry, Philip, S441 (PO-2719)
- Bertelli, Cristina, S785 (PO-1247)
- Bertels, Sanne, S581 (PO-1895)
- Bert, Nina Le, S731 (PO-2575)
- Bertoia, Monica, S254 (OS-1780),
S434 (PO-1664)
- Bertoletti, Antonio, S731 (PO-2575),
S746 (PO-1448)
- Bertoli, Ada, S704 (PO-1928),
S728 (PO-1996)
- Berzigotti, Annalisa, S252 (OS-571),
S373 (PO-1230), S377 (PO-1474),
S540 (PO-831)
- Berzuini, Alessandra, S642 (PO-251)
- Besch, Camille, S461 (PO-351),
S462 (PO-353)
- Bes, Marta, S732 (PO-2834)
- Besombes, Juliette, S696 (PO-526)
- Bessa, Xavier, S280 (OS-1921),
S734 (PO-247), S799 (PO-2021)
- Bethencourt, Dácil Díaz, S492 (PO-2594)
- Bettencourt, Ricki, S577 (PO-1648)
- Betz, Briana, S571 (PO-1202)
- Beuers, Ulrich, S202 (LBO-2647),
S225 (OS-706), S248 (OS-138),
S429 (PO-1074), S429 (PO-1294),
S585 (PO-2485)
- Beumont-Mauviel, Maria, S289 (OS-1430)
- Beyeler, Franziska, S466 (PO-1126),
S467 (PO-1133)
- Beysen, Carine, S297 (LBP-2907)
- Bezerra, Jorge, S199 (GS-2283),
S442 (PO-2761)
- Bhandari, Bal Raj, S613 (PO-757)
- Bhardwaj, Ankit, S378 (PO-1705),
S378 (PO-1987)
- Bhardwaj, Neeru, S284 (OS-654),
S725 (PO-1789)
- Bhaskaran, Vasanthi, S529 (PO-1606)
- Bhat, Adil, S406 (PO-2010)
- Bhati, Chandra, S460 (PO-212)
- Bhat, Purnima, S358 (PO-2683),
S386 (PO-2685)
- Bhattacharya, Aneerban, S742 (PO-1196)
- Bhattacharya, Dipankar, S623 (PO-2163)
- Bhat, Vinyas, S567 (PO-1001)
- Bhoori, Sherrie, S448 (PO-718)
- Bhuva, Meha, S685 (PO-1718)
- Bianchi, Luis, S640 (PO-1193)
- Bianco, Cristiana, S261 (OS-297),
S642 (PO-251)
- Bichko, Vadim, S735 (PO-397),
S748 (PO-1775)
- Bickel, Markus, S771 (PO-1029)
- Bidault, Guillaume, S263 (OS-1028)
- Biddle-Snead, Charles, S254 (OS-1611)
- Bidmon, Hans Jürgen, S528 (PO-1357)
- Bieri, Manuela, S604 (PO-2210)
- Biermer, Michael, S289 (OS-1430),
S745 (PO-1416)
- Biewenga, Maaikje, S193 (GS-1213),
S428 (PO-872)
- Bifani, Pablo, S699 (PO-852)
- Bihan, Helene, S555 (PO-2692)
- Bihari, Chhagan, S340 (PO-2213),
S388 (PO-89)
- Bijnens, Tom, S581 (PO-1895)
- Bilbao, Jon, S249 (OS-1355)
- Biliotti, Elisa, S767 (PO-694)
- Billeter, Adrian, S262 (OS-584)
- Bill, Griffiths, S201 (LBO-2592),
S677 (PO-323), S685 (PO-1718)
- Billin, Andrew, S561 (PO-756),
S575 (PO-1568)
- Bindels, Laure, S588 (PO-470)
- Binder, Harald, S661 (PO-1903)
- Binka, Mawuena, S782 (PO-862),
S789 (PO-2708)
- Binquet, Christine, S469 (PO-1459)
- Binter, Teresa, S374 (PO-1249),
S645 (PO-533)
- Biondi, Mia, S659 (PO-1817)
- Biotrel, Marie-therese, S307 (PO-2888)
- Bioulac-Sage, Paulette, S510 (PO-2865)
- Bird, Thomas G., S508 (PO-2787)
- Birerdinc, Aybike, S395 (PO-1505),
S592 (PO-1235)
- Birgit, Kohnke-Ertel, S498 (PO-336)
- Bischofberger, Zita, S466 (PO-1126)
- Biswas, Rakish, S544 (PO-1227)
- Biswas, Subhrajit, S388 (PO-89)
- Bittermann, Therese, S463 (PO-364)
- Bitzer, Michael, S236 (OS-498)
- Bizkarguenaga, Maider, S564 (PO-916),
S612 (PO-627), S624 (PO-2192)
- Björnsson, Einar S., S670 (PO-2127)
- Blachier, Martin, S769 (PO-955)
- Blach, Sarah, S295 (LBP-2814)

- Blair, Mairi, S611 (PO-337)
- Blaise, Lorraine, S487 (PO-1153),
S495 (PO-2799), S518 (PO-1209),
S520 (PO-1263)
- Blanc, Jean-Frédéric, S198 (GS-945),
S510 (PO-2865)
- Blanco, Jesus Miguens, S220 (OS-1167)
- Blanc, Pierluigi, S767 (PO-694)
- Blank, Antje, S294 (LBP-2730)
- Blank, Valentin, S544 (PO-1296),
S560 (PO-751)
- Blasczyk, Rainer, S473 (PO-2821)
- Blas-García, Ana, S401 (PO-1935),
S595 (PO-1626)
- Blasi, Anabel, S343 (PO-187)
- Blatt, Lawrence, S700 (PO-1305),
S720 (PO-1257), S741 (PO-1004),
S742 (PO-1196), S744 (PO-1386)
- Blaya, Delia, S320 (PO-2043)
- Bleeker, Aycha, S531 (PO-2793)
- Bleve, Patrizia, S729 (PO-2261)
- Bloks, Vincent, S591 (PO-1150)
- Bloom, Stephen, S358 (PO-2683),
S386 (PO-2685)
- Blyth, Karen, S508 (PO-2787)
- Bobardt, Michael, S708 (PO-2474)
- Bobeldijk, Ivana, S623 (PO-2099)
- Bock, Kilian, S438 (PO-2259)
- Bockmann, Jan H., S753 (PO-2106)
- Bockmann, Jan-Hendrik, S702 (PO-1631),
S702 (PO-1707)
- Bodakci, Emin, S549 (PO-1865)
- Boddu, Ravan, S349 (PO-1165)
- Bode-Böger, Stefanie M., S194 (GS-1997),
S209 (OS-2060)
- Boehlig, Albrecht, S544 (PO-1296)
- Boeira, Paula, S322 (PO-2341)
- Boeker, Klaus, S778 (PO-52)
- Boettcher, Jan, S262 (OS-584)
- Boggio, Elena, S598 (PO-1916)
- Bogomolov, Pavel, S291 (OS-2717),
S294 (LBP-2730)
- Böhling, Nina, S213 (OS-513)
- Bohlooly-Y, Mohammad, S263 (OS-1028)
- Bohne, Felix, S753 (PO-2106)
- Boike, Justin, S382 (PO-2298)
- Boilesen, Astrid Elisabeth Bruun,
S593 (PO-1407)
- Boillet, Gautier, S648 (PO-821)
- Boillot, Olivier, S461 (PO-351),
S462 (PO-353)
- Boitard, Christian, S555 (PO-2692)
- Bojunga, Jörg, S306 (PO-2203),
S332 (PO-2358)
- Bokun, Tomislav, S636 (PO-2370)
- Boldanova, Tuyana, S628 (PO-2377)
- Bollekens, Jacques, S718 (PO-947)
- Bollerup, Signe, S276 (OS-2202)
- Bolze, Sébastien, S267 (OS-427),
S609 (PO-159)
- Bonacci, Martin, S557 (PO-313),
S625 (PO-2290)
- Bonaccorsi Riani, Eliano, S235 (OS-213),
S477 (PO-1207)
- Bonacini, Maurizio, S736 (PO-482)
- Bonaventura, Chiara Di, S506 (PO-2375)
- Bonder, Alan, S193 (GS-1213),
S226 (OS-894)
- Bongaerts, Anouk, S581 (PO-1895)
- Bonifacius, Agnes, S473 (PO-2821)
- Bonilla, Elvira, S303 (PO-1389)
- Bonilla, Eva Fernandez, S337 (PO-1643)
- Bonino, Ferruccio, S729 (PO-2261)
- Bonnardel, Johnny, S450 (PO-1333),
S453 (PO-1649)
- Bonneville, Anne, S523 (PO-1856)
- Boodram, Basmattee, S768 (PO-745)
- Boon, Nathalie, S327 (PO-1161)
- Boonstra, Andre, S716 (PO-665),
S733 (PO-80)
- Borand, Laurence, S289 (OS-865)
- Bordes, Isabelle, S701 (PO-1451)
- Bordoy, Antoni E., S786 (PO-1415)
- Borg, Brian, S578 (PO-1689),
S618 (PO-1198), S686 (PO-1809)
- Borghgraef, Peter, S450 (PO-1333)
- Borghgi, Marta, S722 (PO-1519),
S746 (PO-1448), S782 (PO-697),
S782 (PO-717), S784 (PO-921)
- Borgmann, Anthony, S382 (PO-2298)
- Borisov, Angel, S628 (PO-2377)
- Borman, Meredith, S315 (PO-1099)
- Borrelli, Marco, S466 (OS-1399)
- Borthwick, Lee, S614 (PO-838)
- Bosch, Jaime, S307 (PO-48), S334 (PO-624),
S373 (PO-1230), S378 (PO-1987),
S579 (PO-1714)
- Bosma, Piter, S202 (LBO-2647)
- Boss, Sofia Brites, S453 (PO-1653)
- Bossuyt, Patrick, S259 (OS-1592),
S564 (PO-919), S568 (PO-1056)
- Bossuyt, Patrick M., S255 (OS-243)
- Bos, Trijnie, S531 (PO-2793),
S691 (PO-2204)
- Bota, Simona, S380 (PO-2162)
- Böttler, Tobias, S262 (OS-584),
S281 (OS-1021), S429 (PO-1294),
S454 (PO-1983)
- Bouam, Samir, S194 (GS-1587)
- Bouattour, Mohamed, S198 (GS-945),
S495 (PO-2799)
- Boucheny, Camille, S350 (PO-1549)
- Boudaoud, Larbi, S197 (GS-613)
- Boudjema, Karim, S461 (PO-351),
S462 (PO-353), S473 (PO-2211)
- Boulter, Luke, S248 (OS-387),
S250 (OS-2934)
- Bourgeois, Cyril, S695 (PO-258)
- Bourke, Michele, S493 (PO-2612)
- Bourliere, Marc, S291 (OS-2717),
S292 (OS-728), S770 (PO-983),
S793 (PO-468)
- Bourlière, Marc, S769 (PO-955)
- Boursier, Jerome, S253 (OS-612),
S255 (OS-243), S257 (OS-555),
S259 (OS-1592), S536 (PO-614),
S540 (PO-831), S557 (PO-313),
S564 (PO-919), S565 (PO-941),
S566 (PO-944), S568 (PO-1056),
S584 (PO-2030)
- Bousquet, Delphine, S701 (PO-1450),
S701 (PO-1451)
- Bouzbib, Charlotte, S355 (PO-2194),
S551 (PO-2002)
- Bouzin, Caroline, S458 (PO-1356),
S477 (PO-1207)
- Bowedes, Frank, S215 (OS-755)
- Bowlus, Christopher, S433 (PO-1644),
S686 (PO-1809), S690 (PO-2120)
- Bowman, Andrew, S262 (OS-584)
- Boyd, Sonja, S444 (PO-2830)
- Boyd, Steve, S748 (PO-1699)
- Boyton, Rosemary J., S448 (PO-718)
- Bozec, Sophie, S267 (OS-427),
S609 (PO-159)
- Bozin, Tonci, S636 (PO-2370)
- Bozward, Amber, S303 (PO-1379)
- Braadland, Peder Rustøen, S421 (PO-2285)
- Braat, Arthur, S245 (OS-972)
- Braconi, Chiara, S495 (PO-2799)
- Brahmania, Mayur, S199 (GS-2309)
- Brainard, Diana, S489 (PO-1289),
S755 (PO-2338), S756 (PO-2395),
S757 (PO-2429)
- Brain, John, S420 (PO-1578)
- Brakenhoff, Sylvia, S664 (PO-2039),
S733 (PO-80), S747 (PO-1661),
S749 (PO-1791), S751 (PO-1841),
S774 (PO-1966)
- Brancale, Joseph, S334 (PO-134)
- Branchereau, Sophie, S242 (OS-906)
- Brandman, Danielle, S558 (PO-454)
- Brass, Clifford, S255 (OS-243),
S564 (PO-919), S568 (PO-1056)
- Braun, Marius, S272 (OS-798)
- Brauns, Elisa, S327 (PO-1161)
- Bravo, Miren, S243 (OS-1948),
S320 (PO-2043)
- Bravo, Susana, S391 (PO-479),
S591 (PO-1037)
- Brecht, Mary-Lynn, S361 (PO-2951)
- Breen, Leigh, S342 (PO-2851)
- Brees, Dominique, S615 (PO-889)
- Breinholt Kjær, Mikkel, S384 (PO-2529)
- Bremer, Birgit, S456 (PO-2339),
S707 (PO-2293)
- Breton, Michele, S442 (PO-2761)
- Breuhahn, Kai, S501 (PO-1304)
- Breure, Karen, S581 (PO-1895)
- Brevini, Teresa, S233 (OS-2656)
- Brew, Iain, S766 (PO-637), S775 (PO-2095)
- Briand, Francois, S595 (PO-1727)
- Briand, François, S582 (PO-1927)
- Brichler, Segolene, S696 (PO-526)
- Bricogne, Christopher, S236 (OS-2792)
- Brigida, Krestina, S642 (PO-424)
- Brino, Laurent, S695 (PO-175)
- Briones, Carlos, S802 (PO-2295)
- Brismar, Torkel, S269 (OS-1627)
- Brissette, Suzanne, S640 (PO-1221)
- Briz, Oscar, S631 (PO-1668)
- Briz, Verónica, S783 (PO-881)

Author Index

- Brocca, Alessandra, S355 (PO-2273), S469 (PO-1496)
- Brochado-Kith, Óscar, S785 (PO-1404)
- Brochard, Alexandre, S510 (PO-2865)
- Broering, Ruth, S706 (PO-2105)
- Brogden, Ruth, S676 (PO-2904)
- Broisat, Alexis, S582 (PO-1927)
- Brol, Maximilian, S332 (PO-2358)
- Bronowicki, Jean-Pierre, S647 (PO-785)
- Brooks, Anna, S757 (PO-2429)
- Broqua, Pierre, S268 (OS-1034), S268 (OS-1044), S595 (PO-1727)
- Broquetas, Teresa, S280 (OS-1921), S734 (PO-247), S799 (PO-2021)
- Bröring, Ruth, S703 (PO-1907), S705 (PO-1950)
- Brosnan, M. Julia, S564 (PO-919), S568 (PO-1056)
- Brotherston, Sophie, S420 (PO-1578)
- Brouwer, Willem Pieter, S718 (PO-915), S733 (PO-80)
- Brown, Chloe, S796 (PO-1508)
- Brown, Elizabeth, S395 (PO-1505), S587 (PO-283), S592 (PO-1235)
- Brown, James, S618 (PO-1198)
- Brown, Richard, S697 (PO-611)
- Brown, Robert, S794 (PO-815)
- Bruccoleri, Mariangela, S492 (PO-2364), S784 (PO-921)
- Bruce, Kenneth, S406 (PO-1763)
- Brugger-Synnes, Pascal, S734 (PO-111)
- Brugières, Laurence, S242 (OS-906)
- Bruha, Radan, S564 (PO-916), S574 (PO-1518), S689 (PO-2040)
- Bruijnen, Rutger, S245 (OS-972)
- Bruins Slot, Alexandra, S359 (PO-2753)
- Bruix, Jordi, S492 (PO-2242), S495 (PO-2799), S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
- Brujats, Anna, S378 (PO-1987)
- Brunet, Eduard, S345 (PO-835)
- Brunetti-Pierri, Nicola, S202 (LBO-2647)
- Brunetto, Maurizia, S294 (LBP-2730), S491 (PO-2223), S652 (PO-1374), S729 (PO-2261), S767 (PO-694)
- Bruno, Benjamin, S296 (LBP-2886), S624 (PO-2287), S628 (PO-2329)
- Bruno, Marco, S225 (OS-706), S281 (OS-1024)
- Bruns, Tony, S226 (OS-894), S387 (PO-2938), S405 (PO-1558)
- Brunt, Elizabeth, S593 (PO-1504)
- Brustowsky, Angélique, S555 (PO-2692)
- Bruzzzone, Chiara, S564 (PO-916)
- Buccella, Daniela, S301 (PO-1185), S612 (PO-627)
- Buchanan, Ryan, S796 (PO-1508)
- Buchard, Benjamin, S647 (PO-785), S717 (PO-813), S793 (PO-468)
- Buchholtz, Kristine, S561 (PO-756)
- Bucsics, Theresa, S213 (OS-925), S364 (PO-532)
- Bucur, Roxana, S508 (PO-2742)
- Buelow, Robin, S535 (PO-566)
- Buendia, Marie-annick, S240 (OS-615), S690 (PO-2090)
- Buggisch, Peter, S778 (PO-52), S791 (PO-51), S792 (PO-153)
- Bugianesi, Elisabetta, S253 (OS-635), S255 (OS-243), S256 (OS-538), S259 (OS-1592), S261 (OS-297), S266 (OS-2831), S540 (PO-831), S556 (PO-167), S564 (PO-916), S564 (PO-919), S568 (PO-1056), S579 (PO-1777)
- Buijs, Jorie, S225 (OS-706)
- Bujanda, Luis, S634 (PO-2184)
- Bujko, Anna, S453 (PO-1649)
- Bukong, Terence, S205 (OS-1293)
- Bulbuc, Nadja, S753 (PO-2106)
- Buller-Taylor, Terri, S782 (PO-862)
- Bültmann, Eva, S682 (PO-1354)
- Bum Cho, Sung, S305 (PO-1947)
- Bündgens, Bennet, S227 (OS-1088)
- Buonaguro, Luigi, S246 (OS-1399)
- Buque, Xabier, S389 (PO-477), S497 (PO-133), S591 (PO-1037), S624 (PO-2192)
- Burak, Kelly, S315 (PO-1099), S368 (PO-1064)
- Burbaum, Barbara, S677 (PO-323)
- Bureau, Christophe, S197 (GS-613), S201 (LBO-2631), S252 (OS-571), S307 (PO-48), S377 (PO-1474), S678 (PO-561)
- Bureau, Cristophe, S277 (OS-1172)
- Bureau, Morgane, S292 (OS-728)
- Burford, Charlotte, S677 (PO-106)
- Burgos-Santamaria, Diego, S252 (OS-571)
- Burkard, Thomas, S703 (PO-1907)
- Burkhardt, Barbara, S391 (PO-663)
- Burns, Christopher, S748 (PO-1699)
- Burns, Lisa, S529 (PO-1606)
- Burra, Patrizia, S193 (GS-1213), S466 (PO-935), S469 (PO-1496), S473 (PO-2425), S488 (PO-1238), S668 (PO-2097)
- Burriel, Miquel Serra, S252 (OS-571)
- Burroughs, Margaret, S794 (PO-815)
- Burt, Alastair, S266 (OS-2831)
- Burton, Alice, S231 (OS-1299)
- Burza, Maria Antonella, S193 (GS-1213)
- Busafi, Said Ahmed Salim Al, S636 (PO-2476)
- Busca, Carmen, S781 (PO-689), S785 (PO-1404)
- Busoms, Cristina Molera, S271 (OS-1954)
- Busschots, Dana, S581 (PO-1895)
- Buti, Maria, S284 (OS-654), S286 (OS-1892), S287 (OS-2225), S437 (PO-2015), S637 (PO-2936), S646 (PO-640), S651 (PO-1341), S663 (PO-2014), S664 (PO-2047), S675 (PO-2861), S696 (PO-469), S706 (PO-2145), S725 (PO-1789), S732 (PO-2637), S732 (PO-2834), S737 (PO-774), S746 (PO-1449), S747 (PO-1661), S788 (PO-1919), S802 (PO-2295)
- Butler, Andrew, S233 (OS-2656)
- Butsashvili, Maia, S773 (PO-1691), S797 (PO-1553)
- Butt, Azeem, S802 (PO-2275)
- Büttner, Reinhard, S501 (PO-1629)
- Buuren, Nicholas Van, S284 (OS-654), S716 (PO-665)
- Buxton, Penny, S768 (PO-908)
- Bu, Yang, S368 (PO-1094), S629 (PO-1091)
- Byrne, Chris, S538 (PO-719), S541 (PO-1030), S562 (PO-769), S567 (PO-1020)
- Byrne, Christopher, S661 (PO-1936), S800 (PO-2205)
- Bystrianska, Natalia, S407 (PO-2914)
- Byun, Kwan Soo, S720 (PO-1115), S757 (PO-2422)
- Caballol, Berta, S492 (PO-2242)
- Cabezas, Joaquín, S746 (PO-1449)
- Cabezas, Joaquín, S798 (PO-2020)
- Cabibbo, Giuseppe, S495 (PO-2799)
- Cable, Ed, S596 (PO-1797)
- Cabrero, Lucía, S784 (PO-1176)
- Cacciato, Valentina, S448 (PO-718)
- Cacciottolo, Tessa, S548 (PO-1747)
- Caciolli, Lorenzo, S395 (PO-1441)
- Cadahía-Rodrigo, Valle, S516 (PO-1010)
- Cai, Bishuang, S607 (PO-2653)
- Cai, Dachuan, S770 (PO-1007)
- Cai, Dawei, S290 (OS-2299), S744 (PO-1286)
- Caillo, Ludovic, S352 (PO-1712)
- Cairns, Helen, S611 (PO-337)
- Cairo, Stefano, S240 (OS-615)
- Cai, Xinting, S535 (PO-566)
- Cai, Yan-Yan, S483 (PO-1147)
- Calderaro, Julien, S198 (GS-945), S487 (PO-1153)
- Calderazzo, Silvia, S752 (PO-2089)
- Caldwell, Stephen, S208 (OS-845), S433 (PO-1644), S578 (PO-1689)
- Calenda, Charles D., S206 (OS-1663), S594 (PO-1547)
- Cales, Paul, S377 (PO-1474)
- Caliskan, Ali Riza, S193 (GS-1213)
- Calleja, José Luis, S255 (OS-2337)
- Callejo-Pérez, Ana, S437 (PO-2015)
- Calvaruso, Vincenza, S785 (PO-1247)
- Calvino, Valeria, S355 (PO-2273), S469 (PO-1496)
- Calvo, Henar, S447 (PO-235), S735 (PO-430)
- Calvo, Pier Luigi, S683 (PO-1641)
- Camma, Calogero, S540 (PO-831)
- Campani, Claudia, S506 (PO-2375)
- Campanozzi, Fausto, S764 (PO-388)
- Campbell, Cori, S649 (PO-1158)
- Campbell, Joanna, S685 (PO-1722)
- Campinoti, Sara, S395 (PO-1441), S478 (PO-1422)
- Campreciós, Genís, S499 (PO-541)
- Camps, Gracián, S696 (PO-469)
- Camps, Jordi, S598 (PO-1897)
- Candelaria, Esther Rodríguez, S674 (PO-2596)

- Candinas, Daniel, S467 (PO-1133)
 Cañete Hidalgo, Nuria, S280 (OS-1921)
 Cañete, Nuria, S307 (PO-48),
 S799 (PO-2021)
 Canillas, Lidia, S280 (OS-1921),
 S734 (PO-247)
 Canivet, Clémence M., S565 (PO-941),
 S566 (PO-944)
 Cannan, Elise, S471 (PO-1971)
 Cano, L., S525 (PO-2408)
 Canosa, Antonio, S764 (PO-388)
 Canter, Timothy, S394 (PO-1125)
 Cantonetti, Maria, S728 (PO-1996)
 Canva, Valérie, S647 (PO-785),
 S793 (PO-468)
 Cao, Gary, S529 (PO-1606)
 Caon, Elisabetta, S596 (PO-1753)
 Cao, Ping, S368 (PO-1094)
 Cao, Zhujun, S629 (PO-1091)
 Capone, Manuela, S506 (PO-2375)
 Capozza, Thomas, S254 (OS-1780),
 S566 (PO-980), S577 (PO-1588),
 S625 (PO-2290)
 Cappiello, Giuseppina, S704 (PO-1928)
 Cara, Alessandro Di, S718 (PO-947)
 Caraceni, Paolo, S347 (PO-1045),
 S353 (PO-1767)
 Carambia, Antonella, S451 (PO-1472)
 Carapeta, Sara, S475 (PO-2890)
 Carayannopoulos, Leon, S391 (PO-663),
 S587 (PO-283)
 Carballo Folgoso, Lorena, S516 (PO-1010)
 Carballo, Sebastian, S548 (PO-1772)
 Carbonell, Nicolas, S201 (LBO-2631),
 S717 (PO-813)
 Carbone, Marco, S226 (OS-894),
 S387 (PO-2938), S425 (PO-376)
 Carbonero, Luz Martín, S783 (PO-881)
 Cardoso Delgado, Teresa, S301 (PO-1185),
 S389 (PO-477), S502 (PO-1752)
 Cardoso, Hélder, S443 (PO-2801),
 S628 (PO-818)
 Cardoso, Joana, S475 (PO-2890)
 Card, Timothy, S562 (PO-775)
 Carey, Ivana, S285 (OS-887), S721 (PO-1510)
 Cariotti, Luca, S704 (PO-1928)
 Carla, Cremonese, S332 (PO-2358)
 Carli, Fabrizia, S600 (PO-2033)
 Carlos Garcia Pagan, Juan, S216 (OS-1544),
 S307 (PO-48)
 Carlota Londoño, Maria, S423 (PO-60),
 S431 (PO-1484)
 Carlton, Jill, S423 (PO-127)
 Carmona, Isabel, S788 (PO-1919)
 Carney, Daniel, S393 (PO-938)
 Carobbio, Stefania, S263 (OS-1028)
 Caro, Emilia Rita De, S600 (PO-1986)
 Carolle Ntandja Wandji, Line,
 S206 (OS-1619)
 Carol, Marta, S311 (PO-345),
 S319 (PO-1932)
 Carpentier, Arnaud, S697 (PO-611)
 Carrafiello, Gianpaolo, S492 (PO-2364),
 S524 (PO-2401)
 Carrasco-Zevallos, Oscar, S254 (OS-1611),
 S433 (PO-1644), S602 (PO-2123)
 Carrat, Fabrice, S191 (GS-1065),
 S226 (OS-894), S239 (OS-2686),
 S292 (OS-728)
 Carretta, Giovanni, S668 (PO-2097)
 Carrier, Paul, S717 (PO-813)
 Carrillo, Juan, S240 (OS-615),
 S689 (PO-2090)
 Carrión, Jose A., S280 (OS-1921),
 S734 (PO-247), S799 (PO-2021)
 Carroll, James, S552 (PO-2326),
 S553 (PO-2343)
 Carsana, Emma, S505 (PO-1969)
 Cartier, Mariano, S346 (PO-864)
 Caruso, Stefano, S242 (OS-906)
 Carvalhais, Natalia Alves Souza,
 S509 (PO-2839)
 Carvalho, Ana, S475 (PO-2890)
 Casadei Gardini, Andrea, S514 (PO-591)
 Casado, Miguel Ángel, S651 (PO-1341),
 S654 (PO-1431)
 Casagrande, Edoardo, S448 (PO-718)
 Casanova, Franc, S335 (PO-698),
 S335 (PO-709), S338 (PO-1761)
 Casar, Christian, S522 (PO-1745)
 Casas, Meritxell, S307 (PO-48),
 S345 (PO-835)
 Casazza, Giovanni, S491 (PO-2181)
 Cascante, Marta, S243 (OS-1948)
 Cascavilla, Nicola, S769 (PO-951)
 Cases, Paula, S335 (PO-698),
 S338 (PO-1761)
 Casillas, Rosario, S696 (PO-469),
 S706 (PO-2145), S732 (PO-2834),
 S737 (PO-774)
 Cassese, Mauro, S769 (PO-951)
 Cassiman, David, S280 (OS-2590)
 Cassinotto, Christophe, S259 (OS-1592)
 Castañe, Helena, S598 (PO-1897)
 Castano-García, Andrés, S516 (PO-1010)
 Castaño González, Luis A.,
 S497 (PO-133)
 Castedal, Maria, S284 (OS-2864)
 Castel, Hélène, S214 (OS-1266)
 Castellana, Donatello, S301 (PO-1185)
 Castellote Alonso, José, S307 (PO-48)
 Castelnau, Corinne, S708 (PO-2684)
 Castelo, Janire, S243 (OS-1948)
 Castera, Laurent, S555 (PO-2692)
 Castet, Florian, S241 (OS-699),
 S521 (PO-1420)
 Castoldi, Angela, S450 (PO-1333)
 Castro, Daniel Barranco, S779 (PO-578)
 Castro, Rui E., S604 (PO-2276),
 S634 (PO-2184)
 Castven, Darko, S501 (PO-1304)
 Casulleras, Mireia, S325 (PO-552)
 Catalano, Donna, S206 (OS-1663)
 Catalina, Maria-Vega, S194 (GS-1997),
 S209 (OS-2060)
 Cathcart, Andrea, S287 (OS-44),
 S288 (OS-211), S738 (PO-824)
 Catrysse, Leen, S591 (PO-1150)
 Cauchy, Francois, S518 (PO-1209),
 S520 (PO-1263)
 Caussy, Cyrielle, S574 (PO-1453)
 Cavallone, Daniela, S729 (PO-2261)
 Cavallo, Rossana, S234 (OS-116)
 Caviglia, Gian Paolo, S253 (OS-635)
 Cavit Ozdogan, Osman,
 S491 (PO-2223)
 Cavus, Bilger, S671 (PO-2288)
 Cayon, Lorena, S537 (PO-685)
 Cazzagon, Nora, S226 (OS-894),
 S227 (OS-1088), S387 (PO-2938),
 S425 (PO-376)
 Cazzanti, Manuela, S217 (OS-874)
 Cea, Maria, S765 (PO-525)
 Cebotarescu, Valentin, S750 (PO-1837)
 Celada Sendino, Miriam,
 S516 (PO-1010)
 Celine, Dorival, S292 (OS-728)
 Céline, Dr Guichon, S350 (PO-1549)
 Cerdan, Sebastian, S250 (OS-1414)
 Ceriotti, Ferruccio, S492 (PO-2364),
 S524 (PO-2401), S642 (PO-251),
 S746 (PO-1448), S784 (PO-921)
 Cernosa, Jasna, S667 (PO-2093)
 Cerva, Carlotta, S728 (PO-1996)
 Cervera, Marta, S311 (PO-345),
 S319 (PO-1932)
 Cervoni, Jean Paul, S678 (PO-561)
 Cesari, Maurizio, S346 (PO-918),
 S346 (PO-932)
 Cespiati, Annalisa, S261 (OS-297),
 S601 (PO-2055), S785 (PO-1247),
 S786 (PO-1542)
 Chadwick, Kristina, S529 (PO-1606)
 Chaffaut, Cendrine, S312 (PO-433)
 Chakraborty, Sutirtha, S455 (PO-2173)
 Chambers, Edward, S490 (PO-2070)
 Chambers, Jenny, S440 (PO-2657)
 Chamulitrat, Walee, S607 (PO-2623)
 Chan, Adelyne, S230 (OS-1171)
 Chanda, Sushmita, S741 (PO-1004),
 S744 (PO-1386)
 Chang, Devon Y., S563 (PO-866)
 Chang, Jiabao, S759 (PO-2738)
 Chang, Johannes, S213 (OS-513)
 Chang, Kai-Chi, S758 (PO-2619)
 Chang, Mei-Hwei, S199 (GS-2283),
 S758 (PO-2619)
 Chang, Ting, S201 (LBO-2592)
 Chang, William, S410 (PO-985),
 S616 (PO-981), S617 (PO-1082)
 Chang, Xiu-Juan, S709 (PO-218)
 Chan, Henry, S268 (OS-931), S285 (OS-900),
 S725 (PO-1789), S749 (PO-1791),
 S751 (PO-1841)
 Chan, Henry L.Y., S757 (PO-2422)
 Chan, Henry LY, S287 (OS-2225)
 Chan, Lap Kwan, S278 (OS-1396)
 Chan, Sing, S736 (PO-482)
 Chantarangkul, Veena, S786 (PO-1542)
 Chantar, Maria Luz Martinez,
 S249 (OS-1355)
 Chanteranne, Brigitte, S647 (PO-785)

Author Index

- Chan, Wah-Kheong, S257 (OS-555), S259 (OS-1592), S569 (PO-1106), S655 (PO-1551)
- Chao, Yee, S518 (PO-1142)
- Chappell, Elizabeth, S643 (PO-425)
- Chapus, Fleur, S695 (PO-258)
- Chardes, Brioux, S702 (PO-1688), S703 (PO-1711)
- Chardot, Christophe, S242 (OS-906)
- Chargi, Najiba, S359 (PO-2753)
- Charles, Edgar, S395 (PO-1505), S587 (PO-283), S592 (PO-1235)
- Charles Nault, Jean, S487 (PO-1153), S495 (PO-2799), S518 (PO-1209), S520 (PO-1263)
- Charlton, Michael, S265 (OS-2450), S593 (PO-1504), S624 (PO-2287)
- Charlton, Will, S627 (PO-2297)
- Charre, Caroline, S695 (PO-258)
- Chartrain, EymERIC, S647 (PO-785), S793 (PO-468)
- Chatha, Yash, S567 (PO-1001)
- Chaudhary, Ravinder, S330 (PO-2313)
- Chaudhary, Sardar, S318 (PO-1623), S319 (PO-1654)
- Chaudhary, Sudrishti, S406 (PO-2010)
- Chau, Gar-Yang, S483 (PO-1090), S523 (PO-1801)
- Chaumette, Tanguy, S246 (OS-1399)
- Chayama, Kazuaki, S780 (PO-602)
- Chazouillères, Olivier, S226 (OS-894), S437 (PO-2230)
- Cheetham, Rob, S775 (PO-2095)
- Chen, Chao, S368 (PO-1094), S738 (PO-797)
- Chen, Chao-Yin, S627 (PO-2297)
- Chen, Chien-Hung, S747 (PO-1628), S749 (PO-1791), S751 (PO-1841), S756 (PO-2395)
- Chen, Chien-Jen, S715 (PO-460), S725 (PO-1788)
- Chen, Chi-Yi, S718 (PO-947), S756 (PO-2395)
- Chen, Diana, S287 (OS-2225), S446 (PO-216), S447 (PO-240), S448 (PO-846), S725 (PO-1789), S757 (PO-2422), S757 (PO-2429)
- Chen, Dongbo, S479 (PO-250), S531 (PO-1887)
- Chen, Eric, S508 (PO-2742)
- Cheng, Alexandra, S314 (PO-607)
- Cheng, Andrew, S204 (LBO-2800), S618 (PO-1314), S619 (PO-1762)
- Cheng, Dangxiao, S508 (PO-2742)
- Cheng, Di, S507 (PO-2694)
- Chen, Genwen, S304 (PO-1885)
- Cheng, Qiuyu, S299 (PO-559)
- Cheng, Shuangping, S368 (PO-1094)
- Cheng, Tsung-Yi, S483 (PO-1090)
- Chen, Guofeng, S300 (PO-679)
- Cheng, Wei-Han, S664 (PO-2039)
- Cheng, Wendy, S289 (OS-1430)
- Cheng, Ya-Ting, S788 (PO-2008)
- Chen, Hao, S368 (PO-1094)
- Chen, Hongsong, S479 (PO-250), S531 (PO-1887)
- Chen, Hsiu-Hsi, S668 (PO-2103)
- Chen, Hubert, S611 (PO-393)
- Chen, Huey-Ling, S758 (PO-2619)
- Chen, Hui, S198 (GS-1645)
- Chen, Jian, S391 (PO-663)
- Chen, Jiayu, S795 (PO-987)
- Chen, Jiayun, S755 (PO-2269)
- Chen, Jilin, S629 (PO-1091)
- Chen, Jin, S534 (PO-534)
- Chen, Jinhua, S621 (PO-1961)
- Chen, Jitao, S368 (PO-1094)
- Chen, Li, S499 (PO-677)
- Chen, Liang, S631 (PO-1091), S726 (PO-1810), S742 (PO-1109)
- Chen, Minshan, S247 (OS-2679)
- Chen, Pu, S479 (PO-250), S531 (PO-1887)
- Chen, Qian, S802 (PO-2295)
- Chen, Richard, S623 (PO-2163)
- Chen, Ruoyang, S779 (PO-404)
- Chen, Sam Li-Sheng, S668 (PO-2103)
- Chen, Shann-Ching, S629 (PO-1047)
- Chen, Shikui, S735 (PO-397), S748 (PO-1775)
- Chen, Shubo, S359 (PO-2688)
- Chen, Shuhui, S735 (PO-397), S748 (PO-1775)
- Chen, Sui-Dan, S538 (PO-719), S567 (PO-1020)
- Chen, Tao, S299 (PO-559)
- Chen, Ting-Chun, S523 (PO-1801)
- Chen, Tingyao, S298 (PO-537)
- Chen, Wei-Ming, S483 (PO-1147)
- Chenxi, Li, S673 (PO-2483)
- Chen, Xin, S499 (PO-677)
- Chen, Yan, S709 (PO-218), S738 (PO-811)
- Chen, Yi-Cheng, S749 (PO-1781), S788 (PO-2008)
- Chen, Yi-Tzen, S518 (PO-1142)
- Chen, Yong-Ping, S538 (PO-719), S567 (PO-1020), S709 (PO-218)
- Chen, Zhengming, S642 (PO-260)
- Chen, Zhenhuai, S359 (PO-2688)
- Chen, Zhili, S620 (PO-1851)
- Chen, Zhongwei, S562 (PO-769)
- Cheon, Gab Jin, S332 (PO-2547)
- Cheon, Jaekyung, S526 (PO-2712)
- Chermak, Faiza, S559 (PO-569)
- Cherqui, Daniel, S482 (PO-750), S525 (PO-2408)
- Cherradi, Sara, S196 (GS-2069), S247 (OS-2190)
- Chetcuti, Karen, S670 (PO-2131)
- Cheung, Wa, S512 (PO-75)
- Chevret, Sylvie, S216 (OS-1544), S312 (PO-433)
- Chhatwal, Jagpreet, S672 (PO-2424), S776 (PO-2218)
- Chhim, Kearena, S289 (OS-865)
- Chhun, Samsorpea, S289 (OS-865)
- Chiara Frigo, Anna, S346 (PO-918), S346 (PO-932)
- Chiarugi, Paola, S606 (PO-2411)
- Chiche, Laurence, S510 (PO-2865)
- Chidambaram, Nachaiappan, S296 (LBP-2886)
- Chidambaram, Nachiappan, S624 (PO-2287), S628 (PO-2329)
- Chien, Elaine, S440 (PO-2657)
- Chien, Rong-Nan, S718 (PO-947), S747 (PO-1628), S749 (PO-1781), S749 (PO-1791), S751 (PO-1841), S758 (PO-2619), S788 (PO-2008)
- Chihota, Violet, S773 (PO-1691)
- Childs, Margaret, S690 (PO-2090)
- Chimakurthi, Chenchu, S427 (PO-770)
- China, Louise, S211 (OS-2779), S328 (PO-1387), S452 (PO-1598)
- Chinburen, Jigjidsuren, S241 (OS-699), S499 (PO-541)
- Chin Cho, Hyun, S305 (PO-1947)
- Chinnaratha, Asif, S524 (PO-2075)
- Chiosa, Andrei, S477 (PO-1119)
- Chirehwa, Maxwell, S768 (PO-908)
- Chiriboga, Luis, S603 (PO-2161)
- Chiu, Tim, S281 (OS-595)
- Chi, Xiaoling, S562 (PO-769), S629 (PO-1091)
- Chkhartishvili, Nikoloz, S797 (PO-1553)
- Chlopicki, Stefan, S342 (PO-2833), S417 (PO-899)
- Chng, Elaine, S400 (PO-1857), S615 (PO-889)
- Choe, Byung-Ho, S199 (GS-2283)
- Cho, Eun Ju, S286 (OS-1892), S288 (OS-691)
- Cho, Eun Young, S743 (PO-1270)
- Cho, Hyunsoon, S479 (PO-409)
- Choi, Bryon Koon-Kau, S727 (PO-1876)
- Choi, Dae Hee, S332 (PO-2547)
- Choi, Hannah S.J., S718 (PO-915), S749 (PO-1791), S751 (PO-1841)
- Choi, In Young, S417 (PO-855), S614 (PO-787), S615 (PO-851)
- Choi, Jae Hyuk, S417 (PO-855), S614 (PO-787), S615 (PO-851)
- Choi, Ji Won, S263 (OS-768)
- Choi, Jonggi, S721 (PO-1385)
- Choi, Jong Young, S504 (PO-1825)
- Choi, Seong Il, S263 (OS-768)
- Choi, Won-Mook, S516 (PO-857)
- Choi, Yun-Jung, S596 (PO-1797), S686 (PO-1809), S690 (PO-2120)
- Chokkalingam, Anand, S489 (PO-1289)
- Chokshi, Shilpa, S208 (OS-2158), S222 (OS-2044), S264 (OS-1524), S321 (PO-2185), S330 (PO-2147), S333 (PO-2870), S395 (PO-1441), S478 (PO-1422)
- Cholankeri, George, S323 (PO-2417)
- Cho, Michael, S334 (PO-134)
- Chong, Sin Yoong, S765 (PO-453)
- Choong, Ingrid, S637 (PO-2936)
- Choon See, Teik, S233 (OS-2656)
- Choo, Su-Pin, S243 (OS-295)
- Chorostowska-Wynimko, Joanna, S677 (PO-323)
- Chou, Cheng-Fu, S629 (PO-1047)

- Choudhri, Sahil, S567 (PO-1001)
 Choudhury, Ashok, S438 (PO-2280)
 Choudhury, Gourab, S201 (LBO-2592)
 Choudhury, Shakti, S381 (PO-2238)
 Chouik, Yasmina, S350 (PO-1549)
 Chou, Wen-Min, S753 (PO-2106)
 Cho, Yeonhee, S205 (OS-1293),
 S206 (OS-1663)
 Christaki, Maria, S204 (LBO-2765),
 S360 (PO-2867)
 Christ-Crain, Mirjam, S306 (PO-2178)
 Christ, Emanuel, S628 (PO-2377)
 Christensen, Anne Illeemann,
 S316 (PO-1375)
 Christensen, Lee, S766 (PO-637)
 Christensen, Peer Brehm, S276 (OS-2202)
 Christensen, Stefan, S791 (PO-51)
 Christianson, Dawn, S201 (LBO-2592),
 S294 (LBP-2580)
 Christian Torp, Nikkolaj, S207 (OS-1726)
 Christinet, Montserrat Fraga, S679 (PO-570)
 Christofori, Gerhard, S247 (OS-2190)
 Christopher, Westland, S741 (PO-1004)
 Chröis, Karoline, S593 (PO-1407)
 Chua, Conan, S455 (PO-2307)
 Chuang, Jay, S265 (OS-1746),
 S578 (PO-1689), S613 (PO-757)
 Chuang, Wan-Long, S718 (PO-947),
 S755 (PO-2338), S756 (PO-2395),
 S757 (PO-2429), S761 (PO-2844),
 S780 (PO-666)
 Chu, Janet, S558 (PO-454)
 Chu, Kevan H., S612 (PO-627)
 Chulanov, Vladimir, S294 (LBP-2730)
 Chul Yoon, Byung, S402 (PO-2695)
 Chumillas, Rosa Sáiz, S778 (PO-2359)
 Chung, Chuhan, S254 (OS-1611),
 S265 (OS-1746), S433 (PO-1644),
 S575 (PO-1568), S578 (PO-1689),
 S579 (PO-1714), S613 (PO-757)
 Chung, Goh Eun, S288 (OS-691)
 Chung, Raymond, S587 (PO-283),
 S780 (PO-602)
 Chung, Sungwon, S288 (OS-691)
 Church, Karen, S347 (PO-1045)
 Churkin, Alex, S801 (PO-2240)
 Ciaccia, Loredana, S764 (PO-388)
 Ciancio, Alessia, S767 (PO-694)
 Cichoż-Lach, Halina, S319 (PO-1708)
 Cicinnati, Vito, S477 (PO-1119)
 Ciconelle, Ana, S408 (PO-301)
 Cilla, Marta, S215 (OS-1864)
 Cillo, Umberto, S466 (PO-935),
 S469 (PO-1496), S473 (PO-2425),
 S488 (PO-1238), S668 (PO-2097)
 Ciociola, Ester, S261 (OS-297)
 Cippitelli, Annalisa, S252 (OS-571)
 Cisternino, Antonio, S769 (PO-951)
 Citterio, Davide, S521 (PO-1420)
 Ciuffreda, Luigi, S769 (PO-951)
 Cives, Candela, S631 (PO-1668)
 Claar, Ernesto, S657 (PO-1666)
 Claret, Marc, S591 (PO-1037)
 Clària, Joan, S325 (PO-552), S354 (PO-1930)
 Clark, Nico, S775 (PO-2048)
 Clark, Virginia, S677 (PO-323)
 Clark, William, S508 (PO-2787)
 Claude, Emmanuelle, S603 (PO-2186)
 Cleary, Sean, S508 (PO-2742)
 Clemente, Nausicaa, S598 (PO-1916)
 Clerbaux, Laure-Alix, S588 (PO-470)
 Clerc, Romain, S582 (PO-1927)
 Clerici, Marigrazia, S786 (PO-1542)
 Clifford, Cathal, S493 (PO-2612)
 Clifford, Gary, S276 (OS-2750)
 Cloherty, Gavin, S285 (OS-887),
 S289 (OS-1430), S721 (PO-1510),
 S760 (PO-2822), S762 (PO-2879),
 S776 (PO-2193)
 Cloutier, Daniel, S287 (OS-44),
 S288 (OS-211), S733 (PO-43),
 S738 (PO-824)
 Cobbold, Jeremy, S259 (OS-1592),
 S272 (OS-1756), S403 (PO-2790)
 Coburn, Glen, S748 (PO-1699)
 Cockell, Simon, S256 (OS-538),
 S266 (OS-2831)
 Coco, Barbara, S729 (PO-2261)
 Cocomazzi, Giovanna, S764 (PO-388)
 Coen, Muireann, S406 (PO-1763)
 Coenraad, Minneke, S336 (PO-1051)
 Coffin, Carla, S315 (PO-1099),
 S368 (PO-1064)
 Coffin, Carla S., S756 (PO-2395),
 S757 (PO-2429)
 Cogger, Shelley, S775 (PO-2048)
 Cohen, Daniella, S798 (PO-2020)
 Cohen, David, S603 (PO-2161)
 Cohen, Jonathan, S588 (PO-475)
 Cohen-Naftaly, Michal,
 S272 (OS-798)
 Coilly, Audrey, S355 (PO-2194),
 S461 (PO-351), S462 (PO-353),
 S482 (PO-750), S525 (PO-2408),
 S717 (PO-813)
 Cojuhari, Lilia, S750 (PO-1837)
 Coker, Ahmet, S473 (PO-2211)
 Coker, Timothy, S675 (PO-2861)
 Colagrande, Stefano, S506 (PO-2375)
 Cola, Marco, S355 (PO-2273)
 Cole, Alex, S354 (PO-1998)
 Cole, Andrew G., S281 (OS-595)
 Cole Barret, Stephen, S212 (OS-1491)
 Colecchia, Antonio, S787 (PO-1561)
 Cole, Tom, S245 (OS-1145)
 Colin, Cyrille, S574 (PO-1453)
 Collaud, Fanny, S202 (LBO-2647)
 Colledan, Michele, S513 (PO-574)
 Colledge, Danni, S283 (OS-2826)
 Colli, Agostino, S491 (PO-2181)
 Collier, Jane D., S403 (PO-2790)
 Collier, Nicholson, S768 (PO-745)
 Collins, Intira Jeannie, S643 (PO-425)
 Collins, Michelle, S794 (PO-815)
 Colliva, Carolina, S457 (PO-279)
 Coll, Susana, S734 (PO-247)
 Coll, Susanna, S280 (OS-1921),
 S799 (PO-2021)
 Colombatto, Piero, S491 (PO-2223),
 S729 (PO-2261)
 Colombo, Massimo, S642 (PO-251),
 S661 (PO-1936), S669 (PO-2108)
 Colome-Tatche, Maria, S232 (OS-943)
 Colom, Joan, S786 (PO-1415),
 S795 (PO-1307)
 Colonno, Richard, S290 (OS-2299)
 Colucci, Nicola, S492 (PO-2242)
 Colucci, Nicolas, S548 (PO-1772)
 Columbano, Amedeo, S500 (PO-1118),
 S627 (PO-2312)
 Comi, Giacomo, S600 (PO-2033)
 Concepcion-Masip, Teresa,
 S492 (PO-2594)
 Conde, Marta Hernández, S266 (OS-2831),
 S746 (PO-1449)
 Condon, Stephen, S748 (PO-1699)
 Conesa, Ana, S335 (PO-709)
 Congly, Stephen, S315 (PO-1099),
 S368 (PO-1064)
 Congregado, Daniela Mestre, S497 (PO-133)
 Connelly, Margery A., S617 (PO-1082)
 Constantineau, Martin, S742 (PO-1240)
 Constantinescu, Alexandrina,
 S199 (GS-2283)
 Conti, Filomena, S461 (PO-351),
 S462 (PO-353), S551 (PO-2002)
 Conturso, Vincenza, S657 (PO-1666)
 Cooke, Graham, S661 (PO-1936)
 Cools, Laura, S527 (PO-608)
 Cooreman, Michael, S268 (OS-1034),
 S268 (OS-1044)
 Copara, Roberto, S249 (OS-1355)
 Copeland, Christopher, S206 (OS-1663)
 Copenhagen, Rob, S603 (PO-2161)
 Coppola, Carmine, S767 (PO-694)
 Coppola, Nicola, S654 (PO-1426),
 S656 (PO-1593)
 Corbett, Gareth, S233 (OS-2656)
 Corbic, Michele, S197 (GS-613)
 Corcoran, Eleanor, S222 (OS-2044)
 Corcos, Olivier, S678 (PO-561)
 Cordero, Julio, S393 (PO-793)
 Cordero, Patricia, S746 (PO-1449)
 Cordi, Sabine, S509 (PO-2839)
 Cordoba-Jover, Bernat, S218 (OS-1478)
 Corey, Kathleen, S587 (PO-283)
 Cornberg, Markus, S370 (PO-1146),
 S454 (PO-1983), S454 (PO-2154),
 S456 (PO-2339), S707 (PO-2293),
 S749 (PO-1791), S751 (PO-1841),
 S778 (PO-52), S791 (PO-51)
 Cornillet, Martin, S227 (OS-1088)
 Cornu, Isabelle, S377 (PO-1474)
 Cororuge, Marion, S194 (GS-1587)
 Corpechot, Christophe, S226 (OS-894),
 S387 (PO-2938), S425 (PO-376),
 S461 (PO-351), S462 (PO-353)
 Correig-Blanchar, Xavier, S250 (OS-1414)
 Correnti, Margherita, S505 (PO-1969)
 Corrigall, Douglas, S209 (OS-2060)
 Corrigall, Dr Douglas, S194 (GS-1997)
 Cortellini, Alessio, S245 (OS-1145)

Author Index

- Cortese, Maria Francesca, S696 (PO-469), S706 (PO-2145), S737 (PO-774)
Cortez, John, S720 (PO-1257)
Cortez-Pinto, Helena, S255 (OS-243), S347 (PO-1045), S564 (PO-919), S568 (PO-1056), S646 (PO-640), S669 (PO-2108), S675 (PO-2861)
Cosar, Arif Mansur, S671 (PO-2288)
Costagliola, Dominique, S790 (PO-2836)
Costa, Montserrat, S354 (PO-1930)
Costa, Tilani De, S742 (PO-1196)
Costentin, Charlotte, S238 (OS-1704), S257 (OS-555), S565 (PO-941)
Cotler, Scott, S750 (PO-1837), S768 (PO-745), S801 (PO-2240)
Cotrau, Radu, S398 (PO-1582)
Cottrell, Neil, S353 (PO-1766)
Cotugno, Rosa, S764 (PO-388)
Coulouarn, Cedric, S505 (PO-1969)
Coupland, Paul, S232 (OS-943)
Couté, Yohann, S701 (PO-1450)
Cox, I. Jane, S347 (PO-1045)
Cox, Sean, S766 (PO-637), S775 (PO-2095)
Crabbe, Marjolein, S718 (PO-947)
Cramp, Matthew, S322 (PO-2341)
Crapanzano, Luciano, S785 (PO-1247)
Crathorne, Louise, S685 (PO-1722)
Craxi, Antonio, S540 (PO-831), S654 (PO-1426), S785 (PO-1247)
Craxi, Lucia, S466 (PO-935)
Crespo, Gonzalo, S277 (OS-1172)
Crespo, Javier, S255 (OS-2337), S269 (OS-1769), S497 (PO-133), S537 (PO-685), S564 (PO-916), S574 (PO-1518), S584 (PO-2369), S612 (PO-627), S624 (PO-2192), S661 (PO-1936), S746 (PO-1449)
Cressey, Tessa, S740 (PO-942)
Creteur, Jacques, S194 (GS-1997), S209 (OS-2060)
Crick, Keziah, S233 (OS-2656)
Cristofaro, Ludovica, S383 (PO-2381)
Cristoferi, Laura, S226 (OS-894), S425 (PO-376)
Crocé, Saveria Lory, S353 (PO-1767)
Cronin, Kirby, S659 (PO-1817)
Crooks, Colin, S316 (PO-1375)
Crothers, Hannah, S426 (PO-770)
Crouch, Emilie, S196 (GS-2069), S212 (OS-1491), S247 (OS-2190)
Crysler, Oxana, S243 (OS-295)
Csak, Timea, S594 (PO-1547)
Csernalabics, Benedikt, S281 (OS-1021)
Cubero, Francisco Javier, S334 (PO-624)
Cubillo Gracian, Antonio, S243 (OS-295)
Cuccaro, Patrizia, S656 (PO-1593)
Cuconati, Andrea, S281 (OS-595)
Cueto-Sanchez, Alejandro, S304 (PO-1406)
Cuevas, Guillermo, S771 (PO-1186), S783 (PO-881)
Cuevas Pérez, Javier, S516 (PO-1010)
Cui, Jiawei, S463 (PO-530)
Cuko, Liri, S654 (PO-1480)
Culver, Emma, S229 (OS-1728), S418 (PO-1026), S426 (PO-770), S437 (PO-2230)
Culwell, John, S618 (PO-1198)
Cuñarro, Juan, S391 (PO-479)
Cunliffe, William, S494 (PO-2755)
Cure, Sandrine, S557 (PO-313)
Curran, Chris, S489 (PO-1729)
Curry, Michael, S326 (PO-675), S659 (PO-1862), S672 (PO-2387)
Curto, Anna, S325 (PO-552)
Cusi, Kenneth, S267 (OS-427), S294 (LBP-2580), S564 (PO-916), S574 (PO-1518), S609 (PO-159)
Czauderna, Carolin, S501 (PO-1304), S521 (PO-1351), S521 (PO-1420)
Czauderna, Piotr, S690 (PO-2090)
Czernichow, Sebastien, S555 (PO-2692)
Czeszewski, Linda, S528 (PO-1357)
Czlonkowska, Anna, S280 (OS-2590)
Czubkowski, Piotr, S193 (GS-1213), S687 (PO-1811)
Czyzyska-Cichon, Izabela, S417 (PO-899)
da Cruz, Moiséli Luchi, S639 (PO-205)
Dagna, Lorenzo, S229 (OS-1728)
Dahari, Harel, S750 (PO-1837), S768 (PO-745), S801 (PO-2240)
Dai, Chia-Yen, S780 (PO-666)
Dajti, Elton, S787 (PO-1561)
Dalby Hansen, Camilla, S313 (PO-487)
Dalekos, George, S226 (OS-894), S227 (OS-1088), S286 (OS-1892), S387 (PO-2938), S422 (PO-2681), S423 (PO-60), S636 (PO-2476), S737 (PO-715), S747 (PO-1661)
Dale, Martin, S263 (OS-1028)
Daley, Ann, S579 (PO-1777)
Dalgard, Olav, S734 (PO-111)
Dalgiç, Buket, S687 (PO-1811)
Dall'Alba, Valesca, S639 (PO-205)
Dalvi, Priya, S501 (PO-1629)
Daly, Ann K., S256 (OS-538), S266 (OS-2831)
Damascene, Makuza Jean, S782 (PO-862)
D'Ambrosio, Roberta, S261 (OS-297), S642 (PO-251), S782 (PO-697), S782 (PO-717), S784 (PO-921), S786 (PO-1542)
Dames, Sybille, S612 (PO-627)
Damgaard, Lars, S561 (PO-756)
Dam, Gitte, S344 (PO-342)
Damle Vartak, Dr. Amruta, S219 (OS-2754)
Dancert, Nathan, S540 (PO-950)
Dandri, Maura, S702 (PO-1631), S702 (PO-1707)
Danese, Anna, S232 (OS-943)
D'Angelo, Franca, S767 (PO-694)
Dang, Shuangsoo, S758 (PO-2735), S759 (PO-2759)
Dang, Tong, S629 (PO-1091)
Daniel Jensen, Morten, S436 (PO-1799)
Danielsen, Anne Kjaergaard, S638 (PO-190)
Danielsen, Sabine Greve, S638 (PO-190)
Danta, Mark, S515 (PO-767)
D'Antiga, Lorenzo, S202 (LBO-2647), S279 (OS-1554), S688 (PO-1833)
Danylenko, Oleksandr, S385 (PO-2655)
Dao, Thong, S312 (PO-433), S520 (PO-1263)
Dao, Thông, S201 (LBO-2631)
Dar, Hilal, S796 (PO-1533)
Darias, Ruth Suarez, S674 (PO-2596)
Dar-In, Tai, S788 (PO-2008)
Darnell, Anna, S640 (PO-1193)
da Rocha Fernandes, João Diogo, S610 (PO-231)
Darrell, Kristen, S476 (PO-982)
Darteil, Raphaël, S761 (PO-2844)
Dasgupta, Ramanuj, S700 (PO-861)
Da Silva, Eduardo Barroso Garcia, S475 (PO-2890)
da Silva Filho, Maurício Ricardo Moreira, S408 (PO-301)
da Silva Filipe, Anna, S670 (PO-2131)
Da Silva, Geraldine, S430 (PO-1428), S431 (PO-1486)
Da Silva Lima, Natalia, S389 (PO-477)
da Silva Lima, Natália, S591 (PO-1037)
Datta, Shouren, S489 (PO-1729)
Datz, Christian, S542 (PO-1205), S552 (PO-2328), S570 (PO-1195), S573 (PO-1220)
Daubon, Thomas, S502 (PO-1752)
Dauguet, Nicolas, S509 (PO-2839)
Daumerie, Aurelie, S477 (PO-1207)
Davenport, Andrew, S194 (GS-1997), S209 (OS-2060)
Davidov, Yana, S730 (PO-2366)
Davidson, Brian R., S451 (PO-1460)
Davidson, Nicholas O., S564 (PO-916)
Davies, Nathan, S194 (GS-1997), S209 (OS-2060), S329 (PO-1585), S347 (PO-1045)
Davies, Susan, S233 (OS-2656), S263 (OS-1028)
Davies, Susan E., S548 (PO-1747)
Davis, Chris, S670 (PO-2131)
Davis, Dexter, S740 (PO-942)
Davy, Hortense, S678 (PO-561)
Dayangac, Murat, S472 (PO-2001)
Dear, James, S301 (PO-1185)
De, Arka, S360 (PO-2832)
de Ávila, Ana Isabel, S802 (PO-2295)
de Barros Lopes, Antonio, S639 (PO-205)
Debing, Yannick, S744 (PO-1386)
de Blas, Beatriz Sanchez, S631 (PO-1668)
Debray, Dominique, S193 (GS-1213)
De Broucker, Chloé, S678 (PO-561)
de Bruijne, Joep, S245 (OS-972), S359 (PO-2753)
de Bruin, Alain, S531 (PO-2793), S591 (PO-1150), S691 (PO-2204)
Decaens, Thomas, S238 (OS-1704)
De Carmen Fernández-Martínez, Nerina, S533 (PO-445)
De Caro, Emilia, S601 (PO-2055)
de Carvalho Ribeiro, Marcelle, S206 (OS-1663)

- De Castro, Tiago, S248 (OS-334)
 Decker, Charlotte, S698 (PO-626)
 Deckmyn, Olivier, S191 (GS-1065)
 De Coppi, Paolo, S478 (PO-1422)
 De Cosmo, Salvatore, S769 (PO-951)
 Decraecker, Marie, S559 (PO-569),
 S583 (PO-1981), S648 (PO-821)
 De Fatima Higuera De La Tijera, Maria,
 S199 (GS-2309)
 Degasperis, Elisabetta, S782 (PO-697),
 S782 (PO-717), S784 (PO-921)
 De Giorgio, Massimo, S513 (PO-574)
 de Gottardi, Andrea, S221 (OS-1979)
 De Greef, Vitaline, S509 (PO-2839)
 Degroote, Helena, S227 (OS-1088),
 S277 (OS-1172)
 de Groot, Eric, S547 (PO-1526)
 de Haas, Robbert J., S343 (PO-187)
 Deichsel, Danilo, S706 (PO-2135)
 De Jardin, Emmanuel, S752 (PO-2089),
 S754 (PO-2243)
 de Jong, Niels, S244 (OS-777)
 de Jong, Ron, S393 (PO-938)
 de Jong, Ype, S603 (PO-2161)
 de Juan, Virginia Gutiérrez, S612 (PO-627)
 De Knecht, Robert, S550 (PO-1951),
 S774 (PO-1966)
 Dela, Flemming, S593 (PO-1407)
 Delahaye, Jared, S455 (PO-2173)
 Delamarre, Adele, S226 (OS-894),
 S559 (PO-569), S565 (PO-941),
 S648 (PO-821)
 Delamarre, Adèle, S583 (PO-1981)
 Delaney, William, S290 (OS-2299),
 S744 (PO-1286)
 Delarocque-Astagneau, Elizabeth,
 S292 (OS-728)
 De la Rosa Vilar, Teresa, S674 (PO-2596)
 del Campo Herrera, Enrique,
 S302 (PO-1335), S304 (PO-1406)
 Del Campo, Laura, S216 (OS-1544)
 del Carmen Martínez-García, María,
 S674 (PO-2596)
 del Castillo, María Estela, S693 (PO-2697)
 DelConte, Anthony, S296 (LBP-2886),
 S624 (PO-2287), S628 (PO-2329)
 Delecroix, Elodie, S586 (PO-2739)
 Deledicque, Sylvie, S586 (PO-2739)
 de Lédinghen, Victor, S191 (GS-1065),
 S226 (OS-894), S253 (OS-612),
 S257 (OS-555), S259 (OS-1592),
 S377 (PO-1474), S536 (PO-614),
 S559 (PO-569), S565 (PO-941),
 S583 (PO-1981), S648 (PO-821),
 S793 (PO-468)
 Deleuze, Jean-François, S242 (OS-906)
 Delgado, Igotz, S497 (PO-133)
 Delgado, Manuel, S788 (PO-1919)
 Delgado, Monica Pons, S677 (PO-323)
 Delgado, Teresa, S591 (PO-1037)
 Delgado, Teresa Cardoso, S243 (OS-1948),
 S320 (PO-2043), S497 (PO-133),
 S612 (PO-627), S624 (PO-2192)
 Deligiannis, Ioannis K., S232 (OS-943)
 Della Torre, Emanuel, S229 (OS-1728)
 Dell'Era, Alessandra, S307 (PO-48)
 Dellestable, Caroline, S352 (PO-1730)
 Dellisola, Victor, S740 (PO-942)
 del Mar Lozano, María, S495 (PO-2799)
 De los Santos, Ignacio, S783 (PO-881)
 Delphine, Degré, S327 (PO-1161),
 S385 (PO-2621)
 Del Pilar Chantada, María, S591 (PO-1037)
 Del Prete, Luca, S513 (PO-574)
 Del Rosario Herrero Maceda, Maria,
 S533 (PO-445)
 Deltenre, Pierre, S385 (PO-2621)
 De Man, Robert, S245 (OS-972),
 S281 (OS-1024), S428 (PO-872)
 de Martel, Catherine, S276 (OS-2750)
 Demelash, Abeba, S476 (PO-982)
 Demetriou, Anna, S657 (PO-1624)
 DeMicco, David, S563 (PO-836)
 de Miguel, Ignacio, S218 (OS-1478)
 Demir, Mehmet, S671 (PO-2288)
 Demir, Münevver, S745 (PO-1419)
 Demory, Alix, S487 (PO-1153)
 De Munck, Kitty, S581 (PO-1895)
 De Munck, Toon, S554 (PO-2673)
 Deneau, Mark, S193 (GS-1213)
 Deng, Guojiong, S795 (PO-987)
 Deng, Junge, S507 (PO-2694)
 Deng, Kangjian, S531 (PO-1887)
 Deng, Mingming, S368 (PO-1094)
 Deng, Xiaogeng, S507 (PO-2694)
 Deng, Ya, S730 (PO-2484)
 Deng, Ying, S368 (PO-1094)
 Denham, Douglas, S618 (PO-1198)
 Denk, Gerald, S389 (PO-410)
 Denk, Helmut, S318 (PO-1651)
 Dennis, Andrea, S408 (PO-629),
 S634 (PO-2094)
 Denys, Alban, S679 (PO-570)
 de Paiva, Wesley Borges, S408 (PO-301)
 DePaoli, Alex, S410 (PO-985),
 S429 (PO-1074), S616 (PO-981),
 S617 (PO-1082)
 De Ponti, Aurora, S219 (OS-2754)
 De Prijck, Sofie, S450 (PO-1333),
 S453 (PO-1649)
 Derbala, Moutaz F.M., S636 (PO-2476)
 der Eijk, Annemiek Van, S733 (PO-80)
 Derks, Terry, S691 (PO-2204)
 der Meer, Adriaan Van, S798 (PO-1962)
 Dermer, Shari, S571 (PO-1202)
 De Rudder, Maxime, S458 (PO-1356)
 de Salazar, Adolfo, S765 (PO-525)
 Desbalmes, Christopher, S364 (PO-532)
 Des Grottes, Marraud, S559 (PO-569),
 S583 (PO-1981)
 Deshmukh, Shalaka, S198 (GS-1645)
 Desmares, Manon, S702 (PO-1688)
 De Smet, Vincent, S388 (PO-223),
 S527 (PO-375)
 De Somer, Thomas, S581 (PO-1895)
 Despotis, Grigorios, S204 (LBO-2765),
 S360 (PO-2867)
 Destro, Marie, S257 (OS-555)
 de Temple, Brittany, S204 (LBO-2800),
 S618 (PO-1314), S619 (PO-1762)
 Detlefsen, Sönke, S207 (OS-1726),
 S321 (PO-2331)
 de Toni, Enrico, S389 (PO-410)
 Deuffic-Burban, Sylvie, S643 (PO-425)
 de Urturi, Diego Saenz, S612 (PO-627),
 S624 (PO-2192)
 Deutsch, Melanie, S737 (PO-715)
 Deval, Jerome, S744 (PO-1386)
 de Veer, Rozanne, S226 (OS-894),
 S430 (PO-1428), S431 (PO-1486)
 de Villalobos, Eduardo Sanz, S447 (PO-235),
 S735 (PO-430)
 Devisscher, Lindsey, S450 (PO-1333),
 S603 (PO-2161)
 Devoogdt, Nick, S582 (PO-1927)
 Devos, Marlies, S581 (PO-1895)
 Devshi, Dhruvi, S207 (OS-2158)
 Dewidar, Bedair, S589 (PO-716)
 de Wit, Koos, S248 (OS-138)
 Dewyse, Liza, S388 (PO-223), S527 (PO-375)
 de Zoete, Marcel R., S457 (PO-279)
 Dgyves, Mario, S567 (PO-1001)
 Dhaliwal, Amritpal, S342 (PO-2851)
 Dhanda, Ashwin, S322 (PO-2341)
 Dhar, Ameet, S354 (PO-1998)
 Dharancy, Sebastien, S206 (OS-1619),
 S461 (PO-351), S462 (PO-353),
 S469 (PO-1459), S678 (PO-561)
 Dhar, Neeraj, S796 (PO-1533)
 Dhillon, Amandeep K., S421 (PO-2285)
 Dholakiya, Sanjay, S733 (PO-43)
 D'Hollander, Koenraad, S280 (OS-2590),
 S692 (PO-2628), S693 (PO-2697)
 Diago, Moises, S746 (PO-1449)
 Dianzani, Umberto, S598 (PO-1916)
 Diao, Shiqi, S359 (PO-2688)
 Diaz, Alba, S448 (PO-718)
 Díaz, Alba, S311 (PO-345), S319 (PO-1932),
 S640 (PO-1193)
 Díaz, Antonia Sáez, S779 (PO-578)
 Diaz, Fernando, S746 (PO-1449)
 Diaz, Luis Antonio, S323 (PO-2704)
 Díaz-Mejía, Nely, S437 (PO-2015)
 Diaz-Mitoma, Francisco, S714 (PO-420)
 Diaz-Moreno, Irene, S502 (PO-1752)
 Diaz-Quintana, Antonio, S502 (PO-1752)
 Di Bisceglie, Adrian, S424 (PO-210)
 Dickinson, Klara, S593 (PO-1504)
 Di Cola, Simone, S353 (PO-1767)
 Di Costanzo, Francesco, S243 (OS-295)
 Didato, Fabiola, S683 (PO-1522)
 Didier, Samuel, S209 (OS-2060)
 Diederichs, Audrey, S695 (PO-258)
 Diego Riveros Zalamea, Juan,
 S502 (PO-1752)
 Dieguez, Carlos, S249 (OS-1355),
 S389 (PO-477), S391 (PO-479)
 Diéguez, Carlos, S591 (PO-1037)
 Diehl, Lauri, S401 (PO-2415), S716 (PO-665),
 S725 (PO-1789)
 Dienes, Hans-Peter, S318 (PO-1651)
 Diestelhorst, Jana, S423 (PO-60)

Author Index

- Dieterich, Douglas, S736 (PO-482)
Dieter, Lütjohann, S547 (PO-1667)
Dietz, Julia, S771 (PO-1029), S792 (PO-153)
Diez, Cristina, S785 (PO-1404)
Diez, Cristina, S781 (PO-689)
Digigow, Reinaldo, S451 (PO-1472)
Di Giorgio, Angelo, S202 (LBO-2647)
Digkilia, Antonia, S521 (PO-1420)
Dijkstra, Jelmer, S527 (PO-778)
di Lazzaro Filho, Ricardo, S408 (PO-301)
Dili, Alexandra, S458 (PO-1356), S477 (PO-1207)
Dillman, Jonathan, S686 (PO-1758)
Dillon, John, S292 (OS-1390), S661 (PO-1936), S800 (PO-2205)
Dilorenzo, Salvatore, S683 (PO-1522)
Di-Luoffo, Mickael, S509 (PO-2839)
Di Marco, Vito, S785 (PO-1247)
Di Martino, Vincent, S469 (PO-1459), S584 (PO-2030)
Dima, Simona, S477 (PO-1119)
di Matteo, Mario, S500 (PO-1118)
Di Mauro, Lazzaro, S769 (PO-951)
Dim, Bunnet, S289 (OS-865)
Dimmer, Alison, S677 (PO-299)
Dimopoulou, Vassiliki, S511 (PO-2920)
Ding, Charles Z., S735 (PO-397)
Ding, Dora, S556 (PO-167), S579 (PO-1714)
Ding, Huiguo, S680 (PO-996), S681 (PO-1108), S731 (PO-2575), S762 (PO-2853)
Ding, Jlanhong, S501 (PO-1352)
Ding, Xiao, S287 (OS-44)
Dinh, Duy, S429 (PO-1074)
Diniz, Mariana O., S451 (PO-1460)
Dinkelborg, Katja, S282 (OS-1062)
Diogo da Rocha Fernandes, João, S398 (PO-1589), S399 (PO-1609)
Dioguardi Burgio, Marco, S572 (PO-1217)
Dirchwolf, Melisa, S466 (PO-1126), S467 (PO-1133)
Disse, Emmanuel, S574 (PO-1453)
Di-Tommaso, Sylvaine, S510 (PO-2865)
Dixon, Selena, S423 (PO-127)
Di Zeo-Sánchez, Daniel E., S302 (PO-1335)
d Müller, Timo, S249 (OS-1355)
Dobosz, Ewelina, S417 (PO-899)
Dobrev, Gergana, S393 (PO-793)
Dodge, Jennifer, S191 (GS-1072)
Dodge, Stephen, S566 (PO-980), S577 (PO-1588)
Doerffel, Yvonne, S686 (PO-1809)
Doernbrack, Katharina, S695 (PO-175)
Dolot, Andrii, S385 (PO-2655)
Dolu, Süleyman, S472 (PO-2001)
Dombrowicz, David, S608 (PO-2858), S608 (PO-2883)
Domenech, Gema, S194 (GS-1997), S209 (OS-2060)
Domingo, Esteban, S802 (PO-2295)
Domingo-Sabat, Montserrat, S240 (OS-615), S689 (PO-2090)
Domínguez-Hernández, Raquel, S651 (PO-1341), S654 (PO-1431)
Dominikus, Stelzer, S661 (PO-1903)
Donakonda, Sainitin, S262 (OS-584)
Donato, Daniele, S668 (PO-2097)
Donato, Maria Francesca, S193 (GS-1213)
Donghia, Rossella, S215 (OS-1864)
Dongiovanni, Paola, S261 (OS-297), S600 (PO-1986), S600 (PO-2033), S601 (PO-2055)
Dong, Jiahong, S631 (PO-1091)
Dong, Jian, S298 (PO-537)
Dong, Li, S629 (PO-1091)
Dongre, Ashok, S592 (PO-1235)
Dong, Tang, S368 (PO-1094)
Dong, Xuan, S483 (PO-1147)
Dong Yang, Ju, S361 (PO-2951)
Donnadieu-Rigole, Hélène, S352 (PO-1712)
Donnelly, Mhairi, S493 (PO-2687)
Donovan, Michael, S241 (OS-699)
Doornebal, Ewald, S321 (PO-2185)
Dorchies, Emilie, S608 (PO-2858)
Dore, Gregory, S515 (PO-767), S661 (PO-1936)
Doris, Mayr, S389 (PO-410)
Dorko, Kenneth, S476 (PO-982)
Dorrington, Kate, S766 (PO-637), S775 (PO-2095)
Dorsey, Bruce D., S281 (OS-595)
Dosso, Sara De, S236 (OS-498)
Doss, Wahid, S293 (OS-2306)
Doukas, Michael, S716 (PO-665)
Dourakis, P. Spyridon, S328 (PO-1501), S511 (PO-2920)
Dourthe, Cyril, S510 (PO-2865)
Dousot, Alexandre, S469 (PO-1459)
Dow, Ellie, S292 (OS-1390)
Downman, Joanna, S677 (PO-299)
Downey, Lianne, S470 (PO-1523)
Downward, Lewis, S474 (PO-2842)
Doyle, Alexander, S318 (PO-1623)
Doyle, Joseph, S358 (PO-2683), S386 (PO-2685)
Drager, Tony, S748 (PO-1699)
Draijer, Laura, S547 (PO-1526)
Dreier, Torsten, S217 (OS-874)
Drenth, Joost Ph, S423 (PO-60), S437 (PO-2230), S664 (PO-2039), S774 (PO-1966)
Driever, Ellen, S343 (PO-187)
Drilhon, Nicolas, S691 (PO-2324)
Drinnan, Michael, S266 (OS-2831)
Duan, Zhongping, S438 (PO-2280)
Dübel, Stefan, S423 (PO-60)
Dubourg, Julie, S267 (OS-427), S609 (PO-159)
Duclos-Vallée, Jean-Charles, S312 (PO-433), S482 (PO-750)
Ducreux, Michel, S246 (OS-1674)
Dudek, Michael, S262 (OS-584)
Duffin, Kevin, S255 (OS-243), S564 (PO-919), S568 (PO-1056)
Dufour, Jean-François, S255 (OS-243), S564 (PO-919), S568 (PO-1056)
Dufour, Jean-François, S236 (OS-498), S262 (OS-584), S466 (PO-1126), S467 (PO-1133), S521 (PO-1420), S603 (PO-2186), S625 (PO-2290)
Dugot-Senant, Nathalie, S510 (PO-2865)
Duhamel, Alain, S201 (LBO-2631)
Duhaut, Lea, S717 (PO-813)
Du, Juan, S506 (PO-2601)
Dultz, Georg, S792 (PO-153)
Dulundu, Ender, S491 (PO-2223)
Duman, Serkan, S549 (PO-1865)
Dumortier, Jérôme, S226 (OS-894), S461 (PO-351), S462 (PO-353), S574 (PO-1453), S717 (PO-813)
Dunbar, P. Rod, S757 (PO-2429)
Duncan, Ian, S559 (PO-580)
Duncan, Katherine, S318 (PO-1623), S319 (PO-1654)
Dündar, Ziya, S472 (PO-2001)
Dunn, Rick, S642 (PO-424)
Dunn, Winston, S489 (PO-1289)
Duong, François H.T., S196 (GS-2069), S247 (OS-2190)
Duong, Thy, S622 (PO-1992)
Dupont, Lene, S638 (PO-190)
Dupuy, Jean-William, S510 (PO-2865)
Durand, François, S194 (GS-1997), S197 (GS-613), S209 (OS-2060), S347 (PO-1045), S691 (PO-2324)
Durand, François, S216 (OS-1544), S277 (OS-1172)
Durand, Sarah, S196 (GS-2069), S247 (OS-2190), S392 (PO-692)
Duran-Güell, Marta, S325 (PO-552)
Duran, Rafael, S679 (PO-570)
Durantel, David, S698 (PO-700), S702 (PO-1688), S703 (PO-1711), S752 (PO-2089), S754 (PO-2243)
Durbán, Lucía, S335 (PO-698), S335 (PO-709)
Durebex, Christelle Veyrat, S249 (OS-1355)
Durier, Christine, S289 (OS-865)
Durmaz, Ozlem, S687 (PO-1811)
Duseja, AJAY KUMAR, S360 (PO-2832), S438 (PO-2280), S655 (PO-1551)
Dusheiko, Geoffrey, S285 (OS-887), S721 (PO-1510)
Du, Simo, S566 (PO-980), S577 (PO-1588)
Dutartre, Dan, S559 (PO-569)
Dutkowski, Philipp, S466 (PO-1126), S467 (PO-1133)
Dutra, Bruna, S420 (PO-1822)
Duursma, Suzan, S215 (OS-755)
Duvoux, Christophe, S461 (PO-351), S462 (PO-353), S473 (PO-2211)
Duwe, Lea, S240 (OS-179)
Dyson, Jessica, S419 (PO-1364), S420 (PO-1578), S423 (PO-60), S426 (PO-770), S493 (PO-2687)
Dzen, Lucile, S268 (OS-1034), S268 (OS-1044)
Eapen, C.E., S438 (PO-2280)
Easterbrook, Philippa, S660 (PO-1877), S666 (PO-2081), S773 (PO-1691)
Eaton, John, S226 (OS-894)

- Eaton, Simon, S347 (PO-1045)
- Ebadi, Maryam, S193 (GS-1213)
- Ebbo, Mikael, S229 (OS-1728)
- Ebeid, Fatma, S293 (OS-2306)
- Eberly, Elisabeth, S468 (PO-1169)
- Eberly, Katherine, S597 (PO-1839)
- Ebert, Christina, S587 (PO-283)
- Ebert, Matthias, S236 (OS-498)
- Ebik, Berat, S671 (PO-2288)
- Ebrahimi, Fahim, S628 (PO-2377)
- Eche, Thomas, S487 (PO-1153)
- Eddowes, Peter, S259 (OS-1592)
- Ediage, Emmanuel Njumbe, S745 (PO-1416)
- Ed, Schwalbe, S513 (PO-573)
- Edwards, Lindsey A., S220 (OS-1167), S347 (PO-1045), S406 (PO-1763)
- Efe, Cumali, S193 (GS-1213), S472 (PO-2001)
- Effenberger, Maria, S262 (OS-584)
- Egecioglu Norlin, Jenny, S399 (PO-1831)
- Egger, Matthias, S542 (PO-1205), S552 (PO-2328), S573 (PO-1220)
- Egia-Mendikute, Leire, S243 (OS-1948), S502 (PO-1752)
- Eguchi, Yuichiro, S267 (OS-681)
- Eguileor, Álvaro, S320 (PO-2043)
- Ehlken, Hanno, S230 (OS-2782)
- Ehmer, Ursula, S498 (PO-336)
- Ehrenmann, Phillipp, S454 (PO-1983)
- Ehrlich, Dusko, S406 (PO-1763)
- Eichelter, Jakob, S592 (PO-1369)
- Eigenbauer, Ernst, S364 (PO-532), S365 (PO-560)
- Eilenberg, Magdalena, S592 (PO-1369)
- Einsele, Hermann, S636 (PO-2386)
- Eiz-Vesper, Britta, S473 (PO-2821)
- Ekin, Nazim, S671 (PO-2288)
- Ekstedt, Mattias, S255 (OS-243), S260 (OS-2362), S557 (PO-313), S564 (PO-919), S568 (PO-1056), S669 (PO-2108)
- Eksteen, Bertus, S424 (PO-210)
- El-Akel, Wafaa, S293 (OS-2306)
- Elefsiniotis, Ioannis, S737 (PO-715)
- Eleftherios, Michailidis, S603 (PO-2161)
- Elemshaty, Wafa, S494 (PO-2786), S497 (PO-2893)
- Elewaut, Dirk, S453 (PO-1649)
- Eley, Timothy, S203 (LBO-2764), S762 (PO-2879)
- Elghafar, Mohamed Samir Abd, S803 (PO-2320)
- Elguezabal, Natalia, S243 (OS-1948)
- El Jamaly, Hydar, S551 (PO-2074)
- Elkashab, Magdy, S757 (PO-2429)
- El-Kassas, Mohammed, S495 (PO-2799), S655 (PO-1551)
- Elkhashab, Magdy, S257 (OS-555), S578 (PO-1689), S736 (PO-482), S756 (PO-2395)
- Elkhesheh, Ahmed, S234 (OS-161)
- El-Khoureiry, Anthony, S243 (OS-295)
- Elkrief, Laure, S277 (OS-1172), S312 (PO-433)
- Ellen Cvijic, Mary, S395 (PO-1505)
- Eller, Carla, S780 (PO-602)
- Ellik Melekoglu, Zeynep, S549 (PO-1865)
- Elliott, Hunter, S433 (PO-1644)
- Ellis, Dave, S618 (PO-1198)
- Ellis, Paul, S677 (PO-323)
- Elmazar, Mohamed, S407 (PO-2363), S606 (PO-2412)
- Elmore, Kasey, S775 (PO-2048)
- Elnadry, Mohamed, S784 (PO-975)
- Elnoomany, Kareem, S784 (PO-975)
- Elortza, Felix, S334 (PO-624), S502 (PO-1752), S624 (PO-2192), S690 (PO-2090)
- Elortza, Félix, S401 (PO-2113)
- Elosua, Roberto, S347 (PO-1045)
- El-Raie, Fathia, S636 (PO-2476)
- El-Rayes, Bassel, S243 (OS-295)
- El Saghire, Houssein, S196 (GS-2069), S247 (OS-2190)
- El Saghire, Hussein, S212 (OS-1491)
- El-Sayed, Manal Hamdy, S293 (OS-2306)
- Elsharkawy, Ahmed, S194 (GS-1997), S209 (OS-2060), S342 (PO-2851)
- Elson, Greg, S196 (GS-2069), S247 (OS-2190)
- Elvevi, Alessandra, S495 (PO-2799)
- Elwir, Saleh, S193 (GS-1213)
- El-Zainy, Shreen, S293 (OS-2306)
- Emamaullee, Juliet, S471 (PO-1773)
- Embade, Nieves, S564 (PO-916)
- Emir, Birol, S314 (PO-832), S538 (PO-819), S539 (PO-825)
- Emmanuelle, Deraucourt, S197 (GS-613)
- Emmerich, Florian, S454 (PO-1983)
- Emmett, Amanda, S794 (PO-815)
- Emre Yildirim, Abdullah, S472 (PO-2001)
- Enea, Marco, S540 (PO-831)
- Engel, Bastian, S423 (PO-60), S464 (PO-841), S473 (PO-2821)
- Engleitner, Thomas, S498 (PO-336), S703 (PO-1711), S754 (PO-2243)
- Englisch, Cornelia, S589 (PO-716)
- Engsig, Frederik, S276 (OS-2202)
- Enkhold, Chinbold, S241 (OS-699), S499 (PO-541)
- Enns, Edwin, S368 (PO-1064)
- Enyedi, Judit, S655 (PO-1572)
- Erard-Poinsot, Domitille, S461 (PO-351), S462 (PO-353)
- Erasmus, Hans-Peter, S332 (PO-2358)
- Erconi, Veronica, S600 (PO-2033)
- Erden Er, Ramazan, S549 (PO-1865)
- Ergenç, İlkay, S472 (PO-2001)
- Erhardtsen, Elisabeth, S573 (PO-1336)
- Eric, Trépo, S327 (PO-1161)
- Erika, Graf, S661 (PO-1903)
- Erion, Derek, S393 (PO-938)
- Erken, Robin, S705 (PO-1980)
- Ermler, Megan, S455 (PO-2173)
- Ermolova, Tatiana, S612 (PO-435)
- Ersoy, Baran, S603 (PO-2161)
- Ertl, Hildegund, S290 (OS-2478)
- Escudero, Adriana, S591 (PO-1037)
- Escudero-Garcia, Desamparados, S788 (PO-1919)
- Escudero-García, Desamparados, S335 (PO-698), S335 (PO-709), S338 (PO-1761)
- Eslem, Mohamed, S239 (OS-2686)
- Eslem, Mohammed, S253 (OS-635), S490 (PO-2070), S540 (PO-831), S541 (PO-1030)
- Eslick, GUY, S551 (PO-2074)
- Esli, Medina-Morales, S226 (OS-894)
- Esmael, Hossam El-deen, S803 (PO-2320)
- Esmaili, Saeed, S607 (PO-2732)
- Esmat, Gamal, S655 (PO-1551)
- Esmat, Gammal, S669 (PO-2108)
- Espérance, Claire, S352 (PO-1712)
- Espina, Silvia, S337 (PO-1643)
- Espinosa-Escudero, Ricardo A., S631 (PO-1668)
- Espinosa, Jorge Simón, S243 (OS-1948), S320 (PO-2043), S502 (PO-1752), S624 (PO-2192)
- Esplugues, Juan V., S401 (PO-1935), S595 (PO-1626)
- Esposito, Daina, S566 (PO-980)
- Esposito, DainaDr., S577 (PO-1588)
- Esposito, Irene, S589 (PO-716)
- Esteban, Juan Ignacio, S802 (PO-2295)
- Esteban, Rafael, S651 (PO-1341), S654 (PO-1431), S663 (PO-2014), S696 (PO-469), S732 (PO-2637), S732 (PO-2834), S747 (PO-1661)
- Estep, James M., S395 (PO-1505), S592 (PO-1235)
- Estes, Chris, S295 (LBP-2814), S532 (PO-19)
- Esteve, Maria, S723 (PO-1622)
- Etzion, Ohad, S637 (PO-2936), S801 (PO-2240)
- Eun Chon, Young, S549 (PO-1823)
- Eun Yeon, Jong, S345 (PO-714)
- Eurich, Dennis, S235 (OS-213)
- Evanhcik, Marc, S290 (OS-2299)
- Evans, Alex, S207 (OS-2158)
- Evans, Amy, S273 (OS-199)
- Evitt, Lee, S724 (PO-1725)
- Eyal, Yehezkel, S226 (OS-894)
- Eysackers, Nathalie, S527 (PO-608)
- Ezzat, Sameera, S803 (PO-2320)
- Ezz Eldin, Azza M., S803 (PO-2320)
- Fabeni, Lavinia, S704 (PO-1928)
- Fabrellas, Nùria, S311 (PO-345), S319 (PO-1932)
- Fabre, Monique, S242 (OS-906)
- Facchetti, Floriana, S492 (PO-2364), S713 (PO-408), S722 (PO-1519)
- Fagan, Andrew, S207 (OS-2158), S220 (OS-119), S309 (PO-117), S403 (PO-418)
- Fagiolino, Sveva, S395 (PO-1441)
- Fagioli, Stefano, S513 (PO-574), S654 (PO-1426)
- Failli, Mario, S689 (PO-2090)
- Fairclough, Sarah, S207 (OS-2158)

Author Index

- Faitot, François, S461 (PO-351), S462 (PO-353)
- Fajardo, Emmanuel, S768 (PO-908)
- Falcon-Perez, Juan, S334 (PO-624)
- Faleo, Gaetano, S476 (PO-982)
- Falgà, M. Àngels, S694 (PO-2902)
- Falk, Christine, S473 (PO-2821)
- Fallowfield, Jonathan, S359 (PO-2688)
- Fanciulli, Chiara, S785 (PO-1404)
- Fanetti, Ilaria, S782 (PO-697), S782 (PO-717)
- Fang, Chengwen, S368 (PO-1094)
- Fanget, Marie C., S733 (PO-43)
- Fang, Haiming, S368 (PO-1094)
- Fang, Kuangnan, S483 (PO-1147)
- Fang, Yanfei, S368 (PO-1094)
- Faniaha Dimby, Solohaja, S198 (GS-945)
- Fania, Michele, S769 (PO-951)
- Fan, Jian-Gao, S259 (OS-1592)
- Fan, Jiagao, S709 (PO-218)
- Fan, Kristi, S281 (OS-595)
- Fan, Xiude, S316 (PO-1215)
- Fan, Zhenhua, S680 (PO-996), S681 (PO-1108)
- Farag, Mina, S755 (PO-2269)
- Farges, Olivier, S238 (OS-1704)
- Fargion, Silvia, S785 (PO-1247), S786 (PO-1542)
- Farhat, Rayan, S703 (PO-1711), S754 (PO-2243)
- Farid, Gaouar, S226 (OS-894)
- Farina, Elisa, S722 (PO-1519)
- Farin-Glattacker, Erik, S661 (PO-1903)
- Färkkilä, Martti, S227 (OS-1088), S229 (OS-2096), S437 (PO-2230), S444 (PO-2830)
- Faron, Anton, S213 (OS-513)
- Farooq, Muhammad, S307 (PO-2888)
- Farooq, Umer, S322 (PO-2389)
- Farquhar, Ronald, S739 (PO-853)
- Fasullo, Matthew, S460 (PO-212)
- Fatourou, Evangelia, S435 (PO-1790)
- Fatta, Erika, S785 (PO-1247)
- Faulkes, Rosemary, S464 (PO-594)
- Faure-Dupuy, Suzanne, S703 (PO-1711), S752 (PO-2089), S754 (PO-2243)
- Faure, Frederic, S647 (PO-785)
- Faure, Stéphanie, S352 (PO-1712), S461 (PO-351), S462 (PO-353)
- Fayyad, Rana, S563 (PO-836)
- Fear, Corrina, S233 (OS-2656)
- Federico, Alessandro, S261 (OS-297)
- Feierbach, Becket, S284 (OS-654), S716 (PO-665), S725 (PO-1789)
- Feigh, Michael, S223 (OS-1847), S399 (PO-1831), S509 (PO-2828), S597 (PO-1849), S622 (PO-2006)
- Feld, Jordan, S446 (PO-216), S447 (PO-240), S448 (PO-846), S455 (PO-2307), S659 (PO-1817), S749 (PO-1791), S751 (PO-1841), S755 (PO-2269), S770 (PO-983), S794 (PO-815), S798 (PO-1962)
- Feldman, Alexandra, S570 (PO-1195)
- Feldt-Rasmussen, Ulla, S482 (PO-707)
- Felipo, Vicente, S335 (PO-698), S335 (PO-709), S338 (PO-1761)
- Felix, Sean, S395 (PO-1505), S592 (PO-1235), S655 (PO-1551)
- Felli, Emanuele, S196 (GS-2069), S247 (OS-2190), S392 (PO-692), S780 (PO-602)
- Feltracco, Paolo, S466 (PO-935), S488 (PO-1238), S668 (PO-2097)
- Feltrin, Alessandra, S466 (PO-935)
- Fenaux, Martijn, S523 (PO-1856)
- Feng, Bo, S629 (PO-1091)
- Feng, Hao, S410 (PO-738)
- Feng, Sophie, S508 (PO-2742)
- Feng, Ying-Hua, S740 (PO-990)
- Feray, Cyrille, S482 (PO-750)
- Ferdousi, Sapphire, S512 (PO-75)
- Ferenci, Peter, S681 (PO-1244), S683 (PO-1500), S746 (PO-1448)
- Ferguson, James, S235 (OS-213), S367 (PO-1040)
- Ferlitsch, Arnulf, S307 (PO-48)
- Fernandes, Gail, S671 (PO-2152)
- Fernandes, Gwen, S273 (OS-183)
- Fernández-Ares, Larraitz, S497 (PO-133)
- Fernández-Arroyo, Salvador, S598 (PO-1897)
- Fernández-Checa, José, S217 (OS-888)
- Fernandez-Codina, Andreu, S229 (OS-1728)
- Fernández-Fernández, Maria, S217 (OS-888)
- Fernandez Fondevila, Marcos, S389 (PO-477), S391 (PO-479)
- Fernandez, Javier, S194 (GS-1997), S209 (OS-2060), S325 (PO-552), S329 (PO-2058)
- Fernández, Javier, S354 (PO-1930)
- Fernández-Palanca, Paula, S504 (PO-1949), S505 (PO-1957)
- Fernández Paz, Uxia, S249 (OS-1355)
- Fernández Ramos, David, S502 (PO-1752), S564 (PO-916)
- Fernández-Rodríguez, Carmen, S301 (PO-1185), S320 (PO-2043), S612 (PO-627)
- Fernández-Rodríguez, Conrado, S746 (PO-1449)
- Fernandez, Roman Perez, S249 (OS-1355)
- Fernandez, Tatiana, S537 (PO-685)
- Fernandez, Uxia, S391 (PO-479)
- Fernández, Uxia, S389 (PO-477), S591 (PO-1037)
- Fernando, Raymond, S236 (OS-2792)
- Ferrarese, Alberto, S668 (PO-2097), S787 (PO-1561)
- Ferrari, Carlo, S289 (OS-1430)
- Ferreccio, Caterina, S199 (GS-2309)
- Ferreira-Cornwell, M. Celeste, S434 (PO-1748)
- Ferreira, João Pedro Sousa, S296 (LBP-2891)
- Ferreira, Lorena Carneiro, S408 (PO-301)
- Ferreira, Rosa, S794 (PO-815)
- Ferreira, Vítor, S250 (OS-1414)
- Ferrer-Costa, Roser Maria, S737 (PO-774)
- Ferrer-Orta, Cristina, S802 (PO-2295)
- Ferrigno, Luigina, S654 (PO-1480), S767 (PO-694)
- Ferri, Silvia, S533 (PO-441)
- Ferronato, Marco, S428 (PO-1017)
- Ferstl, Philip, S332 (PO-2358)
- Fessas, Petros, S448 (PO-718)
- Festag, Julia, S753 (PO-2106)
- Festi, Davide, S377 (PO-1474), S787 (PO-1561)
- Fetrow, Lelani, S540 (PO-969)
- Fiaschetti, Katia, S604 (PO-2210)
- Fidalgo, Miguel, S391 (PO-479), S591 (PO-1037)
- Fidan, Sami, S671 (PO-2288)
- Fidouh, Nadhira, S678 (PO-561)
- Filho, João Martins Cortez, S408 (PO-301)
- Filippov, Yaroslav, S640 (PO-1221)
- Fillipas-Ntekouan, Sempastien, S204 (LBO-2765), S360 (PO-2867)
- Filpe, Pamela, S262 (OS-584)
- Finch, Peter, S670 (PO-2131)
- Fine, Nick, S342 (PO-2851)
- Finkelmeier, Fabian, S236 (OS-498), S521 (PO-1420)
- Finn, Richard, S246 (OS-1674), S521 (PO-1420)
- Fiorella Murillo Perez, Carla, S387 (PO-2938)
- Fiorillo, Alessandra, S335 (PO-698), S335 (PO-709), S338 (PO-1761)
- Fisher, Trevor, S312 (PO-442)
- Fiumara, Mariasole, S353 (PO-1767)
- Flack, Steven, S420 (PO-1578)
- Flaherty, John, S720 (PO-1309)
- Flaherty, John F., S199 (GS-2283), S287 (OS-2225), S755 (PO-2338), S756 (PO-2395)
- Fleming, Kate, S316 (PO-1375)
- Fleming, Kenneth, S403 (PO-2790)
- Flemming, Jennifer, S228 (OS-1586), S435 (PO-1755), S658 (PO-1713)
- Fletcher, Russell, S198 (GS-1645)
- Fletcher, Simon, S231 (OS-1299)
- Flint, Emilio, S306 (PO-2178)
- Fliiss Isakov, Naomi, S546 (PO-1436)
- Floreani, Annarosa, S193 (GS-1213), S227 (OS-1088), S387 (PO-2938), S425 (PO-376)
- Florent, Artru, S679 (PO-570)
- Flores-Costa, Roger, S325 (PO-552)
- Florez Díez, Pablo, S516 (PO-1010)
- Florian Ulmer, Tom, S517 (PO-1046)
- Florian, Veyre, S352 (PO-1730)
- Flynn, Sean, S460 (PO-212)
- Foca, Adrien, S698 (PO-700)
- Folkers, Colleen, S540 (PO-969)
- Folseraas, Trine, S421 (PO-2285), S432 (PO-1512)
- Fondevila, Constantino, S334 (PO-624)
- Fondevila, Constatino, S277 (OS-1172)
- Fondevila, Flavia, S504 (PO-1949), S505 (PO-1957)

- Fondevila, Marcos Fernandez, S249 (OS-1355)
- Fondevila, Marcos Fernández, S591 (PO-1037)
- Fong, Erica, S204 (LBO-2800), S618 (PO-1314)
- Fontaine, Helene, S191 (GS-1065), S194 (GS-1587), S793 (PO-468)
- Fontaine, Hélène, S291 (OS-2717), S292 (OS-728)
- Foquet, Lander, S603 (PO-2161)
- Forlani, Greta, S246 (OS-1399)
- Forlano, Roberta, S309 (PO-94), S537 (PO-711), S540 (PO-950), S558 (PO-565)
- Forman, Lisa, S424 (PO-210), S433 (PO-1644), S686 (PO-1809), S690 (PO-2120)
- Forne, Montserrat, S723 (PO-1622)
- Forner, Alejandro, S448 (PO-718), S495 (PO-2799), S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
- Forns, Xavier, S252 (OS-571), S499 (PO-541), S640 (PO-1193), S699 (PO-820), S749 (PO-1791), S751 (PO-1841), S786 (PO-1415), S795 (PO-1307)
- Forrest, Ewan, S211 (OS-2779), S317 (PO-1563), S318 (PO-1623), S319 (PO-1654), S489 (PO-1729), S611 (PO-337)
- Fortea, Jose Ignacio, S252 (OS-571), S694 (PO-2902)
- Fortunato, Francesco, S600 (PO-2033)
- Forza, Giovanni, S466 (PO-935)
- Fossdal, Guri, S432 (PO-1512)
- Foster, Graham, S292 (OS-795), S790 (PO-2946)
- Foster, Murray, S317 (PO-1563)
- Fotiou, Anastasios, S653 (PO-1421)
- Fouad, Faysoil, S766 (PO-649)
- Fouchard, Isabelle, S566 (PO-944)
- Foucher, Juliette, S559 (PO-569), S583 (PO-1981), S647 (PO-785), S648 (PO-821)
- Foucquier, Julie, S257 (OS-555)
- Fouqueray, Pascale, S267 (OS-427), S609 (PO-159)
- Fournier, Celine, S259 (OS-1592)
- Fournier, Céline, S257 (OS-555)
- Fournier, Claire, S755 (PO-2338), S756 (PO-2395)
- Fowell, Andrew, S677 (PO-299)
- Fox, Naomi, S676 (PO-2904)
- Fox, Rena, S558 (PO-454)
- Fracanzani, Anna Ludovica, S253 (OS-635), S261 (OS-297), S600 (PO-1986), S600 (PO-2033), S601 (PO-2055), S785 (PO-1247)
- França, Alex Vianey Callado, S495 (PO-2799)
- Franca, Maria, S764 (PO-388)
- Francesca, Sarocchi, S592 (PO-1369)
- Francés, Rubén, S342 (PO-2420)
- Francione, Paolo, S253 (OS-635), S785 (PO-1247)
- Francoz, Claire, S461 (PO-351), S462 (PO-353)
- Franque, Sven, S246 (OS-1399), S252 (OS-571), S268 (OS-1034), S268 (OS-1044), S581 (PO-1895), S609 (PO-230)
- Franey, Bridgette Boggess, S627 (PO-2297)
- Franke, Annegret, S429 (PO-1294)
- Franque, Sven, S255 (OS-243), S568 (PO-1056)
- Franqu, Sven, S564 (PO-919)
- Frantz, Stefan, S636 (PO-2386)
- Fraquelli, Mirella, S642 (PO-251)
- Fraser, Chris, S798 (PO-2020)
- Fraser, David A., S297 (LBP-2907), S622 (PO-2006)
- Frazzoni, Leonardo, S518 (PO-1124)
- Frederiksen, Peder, S573 (PO-1336)
- Freeman, Elliot, S512 (PO-75)
- Freemantle, Nicholas, S211 (OS-2779), S452 (PO-1598)
- Freilich, Bradley, S204 (LBO-2800), S619 (PO-1762), S686 (PO-1809)
- Fremer, Carolin, S682 (PO-1354)
- French, Jeremy, S493 (PO-2687)
- Frenicks, Nicola, S697 (PO-611)
- Fresneau, Brice, S242 (OS-906)
- Fresquet, Judith, S695 (PO-258)
- Frias, Francisco Rodriguez, S651 (PO-1341), S696 (PO-469)
- Frias, Juan, S410 (PO-985), S616 (PO-981), S617 (PO-1082), S627 (PO-2297)
- Fridriksdottir, Ragnheidur H., S670 (PO-2127)
- Friedman, Scott, S241 (OS-699), S623 (PO-2163)
- Fried, Michael W., S798 (PO-1962)
- Friedrich-Rust, Mireen, S306 (PO-2203)
- Friesland, Martina, S703 (PO-1907)
- Fromme, Malin, S677 (PO-323)
- Fronek, Jiri, S473 (PO-2211)
- Frugbeck, Gema, S249 (OS-1355)
- Fründt, Thorben, S351 (PO-1701), S506 (PO-2227), S522 (PO-1745)
- Fry, John, S741 (PO-1004)
- Fuccio, Lorenzo, S518 (PO-1124)
- Fuchs, Bryan C., S196 (GS-2069), S212 (OS-1491)
- Fuchs, Michael, S581 (PO-1808)
- Fuentes, Ana, S765 (PO-525)
- Fuentes-López, Eduardo, S199 (GS-2309)
- Fujishiro, Mitsuhiro, S787 (PO-1918)
- Fujiwara, Naoto, S212 (OS-1491), S695 (PO-175)
- Fukumitsu, Ken, S415 (PO-2531)
- Fukuyoshi, Jun, S646 (PO-539)
- Fulden Yumuk, Perran, S491 (PO-2223)
- Fu, Lei, S759 (PO-2738)
- Fulmer, Clifton, S603 (PO-2161)
- Fu, Mingui, S417 (PO-899), S587 (PO-195)
- Fundo, Michelle Reina Do, S589 (PO-716)
- Fung, Scott, S287 (OS-2225), S446 (PO-216), S447 (PO-240), S448 (PO-846), S736 (PO-482), S755 (PO-2269), S757 (PO-2429)
- Funuyet-Salas, Jesús, S533 (PO-381)
- Furrie, Elizabeth, S292 (OS-1390)
- Fuster, Carla, S640 (PO-1193)
- Fuster-Martínez, Isabel, S595 (PO-1626)
- Gabernet, Gisela, S219 (OS-2754)
- Gabriele Gambino, Carmine, S355 (PO-2273), S469 (PO-1496)
- Gabunia, Tamar, S797 (PO-1553)
- Gacs, Judit, S655 (PO-1572)
- Gadipudi, Laila lavanya, S598 (PO-1916)
- Gaggar, Anuj, S283 (OS-2826), S284 (OS-654), S287 (OS-2225), S446 (PO-216), S447 (PO-240), S448 (PO-846), S720 (PO-1309), S725 (PO-1789), S755 (PO-2338), S756 (PO-2395), S757 (PO-2422), S757 (PO-2429)
- Gaia, Silvia, S259 (OS-1592)
- Gaio Castro Nery, Filipe, S216 (OS-1544)
- Gaisa, Nadine, S677 (PO-323)
- Galal, Shereen, S293 (OS-2306)
- Galanaud, Damien, S355 (PO-2194)
- Galaris, Georgios, S623 (PO-2099)
- Gallacher, Jenny, S266 (OS-2831)
- Gallagher, Kerrin, S566 (PO-980), S577 (PO-1588)
- Gallay, Philippe, S708 (PO-2474)
- Gallego-Durán, Rocío, S342 (PO-2420)
- Gallego, Isabel, S802 (PO-2295)
- Gallegos-Orozco, Juan, S327 (PO-968)
- Galle, Peter, S246 (OS-1674), S501 (PO-1304), S521 (PO-1420), S556 (PO-167), S560 (PO-632), S599 (PO-1942)
- Gallez, Bernard, S477 (PO-1207)
- Galli, Claudio, S652 (PO-1374)
- Gallinger, Steven, S508 (PO-2742)
- Galloway, David Rodríguez, S674 (PO-2596)
- Gálvez, Mont, S786 (PO-1415), S795 (PO-1307)
- Gambato, Martina, S521 (PO-1351), S668 (PO-2097)
- Gamkrelidze, Amiran, S274 (OS-551), S643 (PO-504), S773 (PO-1691), S797 (PO-1553)
- Ganchua, Sharie C., S761 (PO-2823)
- Gándara, Julián-Gonzalo, S533 (PO-445)
- Gander, Amir, S194 (GS-1997), S209 (OS-2060), S347 (PO-1045), S451 (PO-1460)
- Gane, Ed, S287 (OS-2225)
- Gane, Edward, S203 (LBO-2764), S287 (OS-44), S288 (OS-211), S289 (OS-1430), S294 (LBP-2580), S733 (PO-43), S736 (PO-482), S738 (PO-824), S741 (PO-1004), S756 (PO-2395), S760 (PO-2822), S761 (PO-2823), S762 (PO-2879)

Author Index

- Ganne-Carrié, Nathalie, S239 (OS-2686), S312 (PO-433), S377 (PO-1474), S520 (PO-1263)
- Ganne, Nathalie, S487 (PO-1153), S518 (PO-1209)
- Gan, Weiqiang, S283 (OS-2482)
- Ganz, Michal, S594 (PO-1547)
- Gao, Bing, S757 (PO-2422)
- Gao, Feng, S567 (PO-1020), S569 (PO-1106)
- Gao, Hainv, S795 (PO-987)
- Gao, Jing, S372 (PO-1152), S382 (PO-2298), S510 (PO-2919)
- Gao, Min, S368 (PO-1094), S372 (PO-1152)
- Gao, Na, S283 (OS-2482)
- Gao, Youfang, S629 (PO-1091)
- Gao, Zhi-liang, S759 (PO-2738)
- Gao, Zhiliang, S283 (OS-2482)
- Garcia, Agustin, S537 (PO-685)
- García-Altare, María, S250 (OS-1414)
- Garcia-Bravo, Maria, S680 (PO-891)
- García-Buey, Luisa, S746 (PO-1449)
- García-Cáceres, Cristina, S262 (OS-584)
- García, Carmelo, S591 (PO-1037)
- García-Cehic, Damir, S802 (PO-2295)
- García Cortes, Miren, S302 (PO-1335), S303 (PO-1389), S304 (PO-1406)
- García-Crespo, Carlos, S802 (PO-2295)
- García-Criado, María Ángeles, S640 (PO-1193)
- García-Escudero, Ramon, S680 (PO-891)
- Garcia, Federico Garcia, S765 (PO-525)
- Garcia-Garcia, Selene, S706 (PO-2145), S737 (PO-774)
- García Juárez, Ignacio, S495 (PO-2799)
- García-López, Mireia, S499 (PO-541), S699 (PO-820), S732 (PO-2637)
- García, María, S591 (PO-1037)
- García-Martinez, Irma, S250 (OS-1414)
- Garcia, Mary, S358 (PO-2683), S386 (PO-2685)
- García-Monzón, Carmelo, S389 (PO-477)
- García-Mulas, Seila, S784 (PO-1176)
- García-Pras, Ester, S699 (PO-820)
- Garcia-Retortillo, Montserrat, S280 (OS-1921), S734 (PO-247), S799 (PO-2021)
- García-Retortillo, Montserrat, S431 (PO-1484), S746 (PO-1449)
- García-Ruiz, Carmen, S217 (OS-888)
- Garcia, Selene, S696 (PO-469)
- García-Torralba, Aida, S680 (PO-891)
- Gardini, Andrea Casadei, S495 (PO-2799)
- Gardini, Ivan, S654 (PO-1426)
- Garg, Pranay, S567 (PO-1001)
- Garner, Will, S440 (PO-2657), S682 (PO-1285)
- Garrido, Esther, S280 (OS-1921), S734 (PO-247), S799 (PO-2021)
- Garrido, Marta, S689 (PO-2090)
- Garteiser, Philippe, S572 (PO-1217)
- Gaspar, Rui, S628 (PO-818), S677 (PO-323)
- Gastaldelli, Amalia, S600 (PO-2033)
- Gatselis, Nikolaos, S226 (OS-894), S387 (PO-2938), S422 (PO-2681), S737 (PO-715), S747 (PO-1661)
- Gaublomme, Djoere, S453 (PO-1649)
- Gaudet-Blavignac, Christophe, S548 (PO-1772)
- Gaudy, Allison, S391 (PO-663), S392 (PO-733)
- Gautheron, Jérémie, S604 (PO-2276)
- Gautier, Jean-François, S555 (PO-2692)
- Gavis, Edith, S220 (OS-119), S403 (PO-418)
- Gay, Suzanne, S518 (PO-1209)
- Gaztambide, Sonia, S497 (PO-133)
- Geerts, Anja, S257 (OS-1556), S437 (PO-2230), S576 (PO-1575)
- Ge, Guohong, S359 (PO-2688), S629 (PO-1091), S650 (PO-1330)
- Geh, Daniel, S493 (PO-2687)
- Gehring, Adam, S446 (PO-216), S447 (PO-240), S448 (PO-846), S455 (PO-2307)
- Gehrke, Nadine, S599 (PO-1942)
- Geier, Andreas, S255 (OS-243), S259 (OS-1592), S547 (PO-1667), S564 (PO-919), S568 (PO-1056), S636 (PO-2386)
- Geisler, Fabian, S219 (OS-2754), S278 (OS-1396)
- Gelson, Will, S235 (OS-213)
- Gelson, William, S233 (OS-2656)
- Gencdal, Genco, S472 (PO-2001), S671 (PO-2288)
- Gencer, Selin, S406 (PO-1763)
- Genesca, Joan, S307 (PO-48), S677 (PO-323)
- Geng, Dawei, S256 (OS-538), S579 (PO-1777)
- Geng, Jiawei, S759 (PO-2738)
- Gentile, Carmine, S722 (PO-1519)
- Gentilucci, Umberto Vespasiani, S261 (OS-297)
- Genyk, Yuri, S471 (PO-1773)
- George, Jacob, S253 (OS-635), S257 (OS-1556), S490 (PO-2070), S515 (PO-767), S540 (PO-831), S541 (PO-1030), S576 (PO-1575), S607 (PO-2732), S669 (PO-2108)
- Georgiou, Alexandra, S350 (PO-1471)
- Georgiou, Chrysanthos, S657 (PO-1624)
- Gérard, Claude, S509 (PO-2839)
- Géraud, Cyril, S393 (PO-793)
- Gerbes, Alexander, S389 (PO-410)
- Geremia, Alessandra, S418 (PO-1026)
- Geretti, Anna Maria, S670 (PO-2131)
- Gerhardt, Florian, S544 (PO-1296)
- Gerhart-Hines, Zach, S593 (PO-1407)
- Gerlach, Brennan, S607 (PO-2653)
- Germani, Giacomo, S466 (PO-935), S668 (PO-2097)
- Germanova, Desislava, S327 (PO-1161)
- Gerstoff, Jan, S276 (OS-2202)
- Gerussi, Alessio, S425 (PO-376)
- Gervain, Judit, S655 (PO-1572)
- Getia, Vladimer, S274 (OS-551), S643 (PO-504)
- Geyvandova, Natalia, S294 (LBP-2730)
- Ghalib, Reem, S578 (PO-1689)
- Ghataore, Lea, S306 (PO-2178)
- Ghazal, Awaisa, S240 (OS-179)
- Ghemtio, Leo, S596 (PO-1753)
- Gheorghe, Cristian, S477 (PO-1119)
- Gheorghe, Liana, S686 (PO-1809)
- Gheorghe, Liliana Simona, S477 (PO-1119)
- Gherlan, George Sebastian, S291 (OS-2717)
- Ghezzi, Catherine, S582 (PO-1927)
- Ghicavii, Nelli, S742 (PO-1240), S743 (PO-1251)
- Ghirardi, Arianna, S513 (PO-574)
- Ghoneem, Elsayed, S494 (PO-2786), S497 (PO-2893)
- Ghose, Sampa, S388 (PO-89)
- Ghoshal, Sarani, S212 (OS-1491)
- Gianatti, Andrea, S513 (PO-574)
- Gianello, Pierre, S477 (PO-1207)
- Giannakeas, Nikolaos, S309 (PO-94)
- Giannini, Edoardo G., S448 (PO-718)
- Gibbs, Paul, S233 (OS-2656)
- Gibilaro, Gerlando, S785 (PO-1247)
- Gielen, Vera, S724 (PO-1725)
- Giersch, Katja, S702 (PO-1631), S702 (PO-1707)
- Gigliotti, Luca Casimiro, S598 (PO-1916)
- Giles, Benjamin, S677 (PO-299)
- Gil-Gomez, Antonio, S342 (PO-2420)
- Gil-Ibanez, Ines, S522 (PO-1745)
- Giljaca, Vanja, S491 (PO-2181)
- Gillard, Justine, S588 (PO-470)
- Gillberg, Per-Goran, S688 (PO-1843)
- Gilleron, Véronique, S648 (PO-821)
- Gillespie-Akar, Liane, S553 (PO-2343)
- Gillet, Nicolas, S754 (PO-2243)
- Gillevet, Patrick, S220 (OS-119), S309 (PO-117), S403 (PO-418)
- Gil, Montserrat, S345 (PO-835)
- Gil Park, Jung, S550 (PO-1904)
- Gil-Pitarch, Claudia, S301 (PO-1185), S320 (PO-2043)
- Gil-Redondo, Rubén, S564 (PO-916)
- Gimenez-Garzo, Carla, S338 (PO-1761)
- Giménez-Garzó, Carla, S335 (PO-698), S335 (PO-709)
- Gimenez-Mascarell, Paula, S612 (PO-627)
- Gindin, Yevgeniy, S265 (OS-1746), S575 (PO-1568)
- Ginès, Pere, S207 (OS-2028), S252 (OS-571), S311 (PO-345), S319 (PO-1932), S329 (PO-2058), S347 (PO-1045)
- Gineste, Paul, S707 (PO-2293)
- Gioia, Stefania, S383 (PO-2381)
- Giorgini, Alessia, S767 (PO-694)
- Giostra, Emiliano, S461 (PO-351), S462 (PO-353)
- Giovannelli, Silvia, S746 (PO-1448)
- Giovanna, Scoazec, S197 (GS-613)
- Giraldez-Gallego, Alvaro, S307 (PO-48)
- Girard, Muriel, S193 (GS-1213)
- Giraud, Guillaume, S695 (PO-258)
- Girleanu, Irina, S216 (OS-1544)
- Girma, Hugo, S761 (PO-2844)

- Gish, Robert G., S289 (OS-1430), S424 (PO-254)
- Giudicelli-Lett, Heloïse, S277 (OS-1172)
- Giuly, Nathalie, S708 (PO-2684)
- Giuseppe Di Costanzo, Giovan, S514 (PO-591)
- Given, Bruce, S201 (LBO-2592), S289 (OS-1430)
- Gkoufa, Kyriaki, S548 (PO-1772)
- Glebe, Dieter, S702 (PO-1707)
- Gleeson, Dermot, S423 (PO-127)
- Glusman Bendersky, Ahinoam, S556 (PO-2791)
- Gluud, Lise Lotte, S593 (PO-1407)
- Glynn, Paul, S394 (PO-1125)
- Gnad-Vogt, Ulrike, S246 (OS-1399)
- Gnemmi, Viviane, S318 (PO-1651)
- Göcebe, Deniz, S607 (PO-2623)
- Gödecke, Natascha, S697 (PO-611)
- Godfrey, Edmund, S233 (OS-2656)
- Goel, Aparna, S193 (GS-1213), S686 (PO-1809), S690 (PO-2120)
- Goel, Ashish, S277 (OS-1172), S438 (PO-2280)
- Goenaga-Infante, Heidi, S692 (PO-2628), S693 (PO-2697)
- Goerd, Sergij, S393 (PO-793)
- Goerg, Boris, S339 (PO-2098)
- Goetze, Oliver, S636 (PO-2386)
- Gohil, Vikrant, S741 (PO-1004)
- Goikoetxea, Naroa, S320 (PO-2043), S497 (PO-133), S502 (PO-1752), S612 (PO-627), S624 (PO-2192)
- Goikoetxea-Usandizaga, Naroa, S243 (OS-1948), S301 (PO-1185)
- Gokcan, Hale, S549 (PO-1865)
- Gokcan Sumer, Hale, S472 (PO-2001)
- Gokturk, Huseyin Savas, S671 (PO-2288)
- Golabi, Pegah, S395 (PO-1505), S592 (PO-1235)
- Goldbeck, Cameron, S471 (PO-1773)
- Goldberg, David, S800 (PO-2205)
- Goldberg, Marcel, S253 (OS-612), S536 (PO-614)
- Goldenberg, Simon, S220 (OS-1167)
- Goldin, Robert, S309 (PO-94)
- Goldin, Robert D., S208 (OS-638), S224 (OS-1946), S245 (OS-1145), S448 (PO-718), S558 (PO-565)
- Goldman, Ellie, S434 (PO-1664)
- Goldmann, Nora, S702 (PO-1707)
- Goldschmidt, Imeke, S682 (PO-1354)
- Goldsmith, Chloe, S695 (PO-258)
- Golfieri, Rita, S244 (OS-777)
- Goli, Karthik, S323 (PO-2417)
- Golsaz-Shirazi, Forough, S753 (PO-2106)
- Golse, Nicolas, S525 (PO-2408)
- Gomes, Catarina, S677 (PO-323)
- Gomes da Fonseca, Leonardo, S495 (PO-2799)
- Gomes, Pedro, S591 (PO-1037)
- Gómez-Camarero, Judith, S778 (PO-2359)
- Gómez, Jordi, S802 (PO-2295)
- Gómez, Julián, S781 (PO-689)
- Gómez-Manero, Noemi, S778 (PO-2359)
- Gomez, Manuel Romero, S253 (OS-635), S269 (OS-1769), S342 (PO-2420), S495 (PO-2799), S610 (PO-231), S669 (PO-2108), S746 (PO-1449)
- Gomez, Marta Campos, S639 (PO-511), S641 (PO-1525)
- Gómez, Raquel Muñoz, S788 (PO-1919)
- Gong, Jun, S496 (PO-2812)
- Goñi, Javier Juampérez, S271 (OS-1954)
- Gonzales, Emmanuel, S242 (OS-906), S687 (PO-1811), S688 (PO-1833)
- González, Agueda, S591 (PO-1037)
- González, Águeda, S389 (PO-477)
- González-Aseguinolaza, Gloria, S694 (PO-2770), S696 (PO-469)
- González-Gállego, Javier, S504 (PO-1949), S505 (PO-1957)
- González-García, Juan, S781 (PO-689)
- González-Grande, Rocio, S302 (PO-1335), S304 (PO-1406)
- González-Guerra, Rosa Lidia, S674 (PO-2596)
- Gonzalez, Juan, S785 (PO-1404)
- González, Lorena Mosteiro, S497 (PO-133)
- González, María Jesús, S591 (PO-1037)
- González, María Sarai, S686 (PO-1809)
- Gonzalez-Motos, Victor, S196 (GS-2069)
- Gonzalez, Noemi, S786 (PO-1415), S795 (PO-1307)
- González-Recio, Irene, S243 (OS-1948), S301 (PO-1185), S320 (PO-2043), S502 (PO-1752), S612 (PO-627)
- Gonzalez-Rellan, Maria J., S391 (PO-479)
- González Rellán, María J., S249 (OS-1355), S389 (PO-477)
- Gonzalez-Romero, Francisco, S497 (PO-133)
- Gonzalo-Benito, Hugo, S255 (OS-2337), S584 (PO-2369)
- Goodman, Zachary, S395 (PO-1505), S578 (PO-1689), S579 (PO-1714), S592 (PO-1235), S633 (PO-1899)
- Goodman, Zack, S593 (PO-1504)
- Goodwin, Bryan, S740 (PO-942)
- Gooptu, Bibek, S677 (PO-323)
- Goossens, Nicolas, S548 (PO-1772)
- Gopi, Srikanth, S378 (PO-1705)
- Gordon, David, S395 (PO-1505), S587 (PO-283), S592 (PO-1235)
- Gordon, Fiona, S273 (OS-183)
- Gordon, Melita, S670 (PO-2131)
- Gordon, Stuart C., S686 (PO-1809)
- Gore, Martin, S224 (OS-1946)
- Gores, Gregory, S499 (PO-677)
- Görg, Boris, S528 (PO-1357), S530 (PO-1615)
- Gorgoglione, Franco, S769 (PO-951)
- Gorgoglione, Leonardo, S769 (PO-951)
- Goria, Odile, S197 (GS-613), S678 (PO-561), S694 (PO-2902)
- Gori, Stefania, S246 (OS-1399)
- Gorka-Dynysiewicz, Joanna, S347 (PO-974)
- Górnicka, Barbara, S432 (PO-1574)
- Gorodin, Vladimir, S291 (OS-2717)
- Gorospe, Myriam, S502 (PO-1752)
- Gostick, Emma, S454 (PO-1983)
- Goswami, Hardik, S671 (PO-2152)
- Gottfredsson, Magnús, S670 (PO-2127)
- Gottwald, Mildred, S410 (PO-985), S616 (PO-981), S617 (PO-1082)
- Goulis, Ioannis, S286 (OS-1892), S544 (PO-1334), S737 (PO-715), S747 (PO-1661)
- Gountas, Ilias, S653 (PO-1421), S657 (PO-1624)
- Gournay, Jérôme, S291 (OS-2717), S312 (PO-433), S647 (PO-785)
- Gournopanos, Kostas, S248 (OS-387), S250 (OS-2934)
- Gouttefangeas, Cecile, S246 (OS-1399)
- Goutte, Nathalie, S238 (OS-1704)
- Gouw, Annette, S318 (PO-1651)
- Govaere, Olivier, S253 (OS-635), S256 (OS-538), S266 (OS-2831), S579 (PO-1777)
- Gow, Paul, S471 (PO-1971)
- Goyal, Omesh, S438 (PO-2280)
- Gozlan, Yael, S730 (PO-2366)
- Grabar, Sophie, S790 (PO-2836)
- Gracia-Sancho, Jordi, S334 (PO-624)
- Graf, Christiana, S332 (PO-2358), S771 (PO-1029), S792 (PO-153)
- Graf, Samantha, S681 (PO-1244)
- Grajales, Diana, S250 (OS-1414)
- Grajkowska, Wieslawa, S634 (PO-2094)
- Grammatikopoulos, Tassos, S687 (PO-1811)
- Granel, Núria, S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
- Granito, Alessandro, S514 (PO-591)
- Granston, Tanya, S625 (PO-2290)
- Grasso, Marco, S488 (PO-1238)
- Gratacós-Gines, Jordi, S311 (PO-345), S319 (PO-1932), S329 (PO-2058)
- Graupera, Isabel, S252 (OS-571), S311 (PO-345), S319 (PO-1932), S329 (PO-2058), S423 (PO-60)
- Graus, Javier, S269 (OS-1769)
- Graves, Ingrid, S281 (OS-595)
- Gray, Kevin, S203 (LBO-2764), S762 (PO-2879)
- Grazia Lucà, Maria, S513 (PO-574)
- Grazie Valsecchi, Maria, S425 (PO-376)
- Grbic, Dusanka, S228 (OS-1586)
- Greaves, William, S677 (PO-106)
- Grebely, Jason, S515 (PO-767), S661 (PO-1936)
- Greco, Antonio, S769 (PO-951)
- Green, Daniel, S194 (GS-1997), S209 (OS-2060), S347 (PO-1045)
- Green, Ilan, S730 (PO-2366)
- Green, Kile, S419 (PO-1364)
- Gregori, Josep, S696 (PO-469), S706 (PO-2145), S802 (PO-2295)
- Gregory, Stephen, S343 (PO-187)
- Greig, Carolyn, S342 (PO-2851)
- Greinert, Robin, S337 (PO-1222)
- Grgurevic, Ivica, S636 (PO-2370)
- Griffin, Julian, S263 (OS-1028)

Author Index

- Grillo, Federica, S448 (PO-718)
Grimmer, Katharine, S617 (PO-1112)
Gripon, Philippe, S696 (PO-526)
Groenbaek, Lisbet, S436 (PO-1799)
Groenendaels, Yoni, S581 (PO-1895)
Grompe, Markus, S603 (PO-2161)
Grønbaek, Henning, S307 (PO-48),
S384 (PO-2529), S432 (PO-1512)
Große, Karsten, S226 (OS-894)
Grove, Jane, S303 (PO-1379)
Grover, Gagandeep Singh, S647 (PO-739)
Grubeck-Loebenstien, Beatrix,
S446 (PO-147)
Gruben, Nanda, S591 (PO-1150)
Gruber, Tim, S262 (OS-584)
Gruevska, Aleksandra, S401 (PO-1935),
S595 (PO-1626)
Grünberger, Thomas, S213 (OS-925)
Gruneau, Lina, S554 (PO-2583)
Grünewaldt, Achim, S332 (PO-2358)
Gruskos, Jessica, S612 (PO-627)
Grzebyk, Ewa, S347 (PO-974)
Gschwantler, Michael, S800 (PO-2191)
Gschwend, Sarah G., S466 (PO-1126)
Guallar, Diana, S591 (PO-1037)
Guan, Yujuan, S759 (PO-2738),
S795 (PO-987)
Guarino, Maria, S495 (PO-2799)
Guccione, Ernesto, S240 (OS-615)
Guckenbiehl, Sabrina, S448 (PO-262)
Gudd, Cathrin L.C., S224 (OS-1946)
Guendogdu, Mehtap, S793 (PO-377),
S794 (PO-773)
Guenther, Rainer, S429 (PO-1294)
Guerin, Florent, S242 (OS-906)
Gu, Er-li, S231 (OS-687)
Guerra, Javier Abad, S269 (OS-1769)
Guerra, Laura, S689 (PO-2090)
Guerrero, Antonio, S216 (OS-1544)
Guettier, Catherine, S242 (OS-906),
S482 (PO-750)
Gugenheim, Jean, S461 (PO-351),
S462 (PO-353)
Guha, Neil, S562 (PO-775)
Guido, Maria, S318 (PO-1651)
Guillaume, Lassailly, S206 (OS-1619),
S461 (PO-351), S462 (PO-353)
Guillebaud, Julia, S289 (OS-865)
Guillemard, Catherine, S647 (PO-785)
Guillen, Maria, S250 (OS-1414)
Guillén, Santiago Moreno, S746 (PO-1449)
Guillot, Adrien, S262 (OS-584),
S401 (PO-2415)
Guimarães, Lenon Liberdade Alvares,
S408 (PO-301)
Guinard-Azadian, Carine, S745 (PO-1416)
Guiu, Boris, S198 (OS-945), S352 (PO-1712)
Gu, Jessie, S534 (PO-534)
Gu, Jie, S523 (PO-1883)
Gulab, Muraduddin, S776 (PO-2193)
Gulamhusein, Aliya, S228 (OS-1586),
S387 (PO-2938), S427 (PO-860),
S435 (PO-1755), S686 (PO-1809),
S690 (PO-2120)
Guldager Kring Rasmussen, Daniel,
S573 (PO-1336)
Gu, Lin, S283 (OS-2482)
Gulzar, Ghulam M., S796 (PO-1533)
Gulzar, Reem, S383 (PO-2305)
Gumrukcu, Serhat, S708 (PO-2474)
Gumussoy, Mesut, S549 (PO-1865)
Gunduz, FEYZA, S491 (PO-2223),
S671 (PO-2288)
Gündüz, Feyza, S472 (PO-2001)
Gunjan, Deepak, S212 (OS-31),
S371 (PO-1151), S378 (PO-1705)
Gunn, Nadege T., S297 (LBP-2907),
S410 (PO-985), S424 (PO-210),
S578 (PO-1689), S616 (PO-981),
S617 (PO-1082)
Günsar, Fulya, S472 (PO-2001),
S671 (PO-2288)
Günther, Georgia, S219 (OS-2754)
Guntipalli, Prathima, S383 (PO-2305)
Guo, Chang, S730 (PO-2484)
Guo, Grace, S529 (PO-1606)
Guo, Jiaqi, S589 (PO-550)
Guo, Ju-Tao, S281 (OS-595)
Guo, Wenwei, S368 (PO-1094)
Guo, Wen-zhi, S231 (OS-687)
Guo, Ying, S759 (PO-2738)
Gupta, Deepak, S382 (PO-2298)
Gupta, Ekta, S666 (PO-2081)
Gupta, Kusum, S742 (PO-1196)
Gupta, Ruchi, S401 (PO-2415)
Gupta, Samir, S214 (OS-1266)
Gupta, Sneha V., S288 (OS-211),
S733 (PO-43), S738 (PO-824)
Gupta, Suhani, S198 (OS-1645)
Gupte, Girish, S687 (PO-1811)
Gurney-Champion, Oliver J.,
S585 (PO-2485)
Gustot, Thierry, S327 (PO-1161),
S385 (PO-2621)
Gute, Peter, S771 (PO-1029)
Gutfraind, Alexander, S768 (PO-745)
Gutic, Enisa, S800 (PO-2191)
Gutierrez Atemis, Alejandro,
S533 (PO-445)
Gutiérrez de Juan, Virginia, S497 (PO-133)
Gutiérrez, Luz Goretta Santiago,
S674 (PO-2596)
Gutierrez, Maria Luisa, S788 (PO-1919)
Guttenberg, Georg, S332 (PO-2358)
Guven, Sirin, S691 (PO-2392)
Gu, Wenyi, S332 (PO-2358)
Guyader, Dominique, S696 (PO-526),
S793 (PO-468)
Guy, Cynthia, S410 (PO-985),
S593 (PO-1504), S616 (PO-981),
S617 (PO-1082)
Gu, Ye, S359 (PO-2688), S368 (PO-1094),
S629 (PO-1091), S650 (PO-1330),
S759 (PO-2738)
Guyon, Joris, S502 (PO-1752)
Gvinjilia, Lia, S274 (OS-551),
S643 (PO-504), S773 (PO-1691),
S797 (PO-1553)
Gyu Hwang, Seong, S526 (PO-2712),
S549 (PO-1823), S585 (PO-2710)
Gyune Kim, Sang, S369 (PO-1103)
Haas, Joel, S608 (PO-2883)
Haber, Philipp, S240 (OS-615),
S241 (OS-699), S499 (PO-541),
S521 (PO-1420)
Habes, Sarah, S423 (PO-60)
Habtemariam, Zebib, S314 (PO-607)
Habtesion, Abeba, S329 (PO-1585),
S330 (PO-2147), S338 (PO-1684)
Haciyev, Ferid, S671 (PO-2288)
Hackling, Melissa, S534 (PO-534)
Haddad, Marwan, S763 (PO-72)
Hadzhiolova, Tanya, S207 (OS-2158)
Hadziyannis, Emilia, S328 (PO-1501)
Haele, Matthias Van, S266 (OS-2831)
Hagström, Hannes, S251 (OS-293),
S269 (OS-1627), S488 (PO-1164),
S554 (PO-2583), S557 (PO-313),
S692 (PO-2667)
Haimowitz, Tom, S748 (PO-1699)
Hai, Suping, S300 (PO-712)
Hajarizadeh, Behzad, S515 (PO-767)
Hajduk, Jovana, S501 (PO-1304)
Hajji, Yacine, S586 (PO-2739)
Hakim, Aaron, S334 (PO-134)
Hakimian, David, S220 (OS-2854)
Haktanyan, Busra, S671 (PO-2288)
Halabi, Atef, S745 (PO-1416)
Halder, Georg, S509 (PO-2839),
S527 (PO-375)
Halford, Rachel, S292 (OS-795),
S766 (PO-637)
Halim, Tim, S230 (OS-1171)
Hallager, Sofie, S276 (OS-2202)
Haller, Dirk, S262 (OS-584)
Halliday, Neil, S236 (OS-2792),
S426 (PO-770), S474 (PO-2842)
Hallimond Brindley, James, S536 (PO-630)
Hallsworth, Kate, S552 (PO-2326)
Hall, Zoe, S263 (OS-1028)
Halonen, Juha, S356 (PO-2524)
Haltmayer, Hans, S800 (PO-2191)
Hamatake, Robert, S731 (PO-2575)
Hamberg, Marie Louise Sjoedin,
S638 (PO-190)
Hamdane, Nourdine, S780 (PO-602)
Hameed, Huma, S307 (PO-2888)
Hamesch, Karim, S677 (PO-323)
Hamid, Saeed Sadiq, S655 (PO-1551),
S776 (PO-2193)
Hamilton, Aaron, S701 (PO-1450),
S701 (PO-1451), S713 (PO-408)
Hamilton, Elizabeth, S642 (PO-260)
Hamilton, James, S201 (LBO-2592),
S289 (OS-1430), S294 (LBP-2580)
Hammam, Olfat, S407 (PO-2363),
S606 (PO-2412)
Hammond, John, S386 (PO-2788),
S493 (PO-2687)
Hammond, Kyle, S489 (PO-1289),
S770 (PO-983)

- Hammond, Rachel, S283 (OS-2826), S739 (PO-853)
- Hamoudi, Waseem, S636 (PO-2476)
- Hampton, Helen, S771 (PO-1339)
- Handler, Eric, S676 (PO-2904)
- Han, Dong, S284 (OS-654)
- Hanemaaijer, Roeland, S623 (PO-2099)
- Han, Guohong, S216 (OS-1544)
- Han, Guorong, S738 (PO-797)
- Han, Kyungdo, S549 (PO-1823)
- Han, Ling, S254 (OS-1611), S265 (OS-1746), S578 (PO-1689)
- Hanly, Louise, S493 (PO-2612)
- Han, Meifang, S714 (PO-415)
- Han Ng, Cheng, S376 (PO-1278)
- Hann, Hie-Won, S736 (PO-482)
- Han, Ping, S368 (PO-1094)
- Hansdottir, Ingunn, S670 (PO-2127)
- Hansen, Bettina, S193 (GS-1213), S226 (OS-894), S228 (OS-1586), S387 (PO-2938), S425 (PO-376), S427 (PO-860), S435 (PO-1755), S439 (PO-2327), S718 (PO-915), S733 (PO-80), S749 (PO-1791), S751 (PO-1841), S755 (PO-2269), S798 (PO-1962)
- Hansen, Henrik B., S509 (PO-2828)
- Hansen, Torben, S313 (PO-487), S593 (PO-1407)
- Han, Steven-Huy B., S736 (PO-482)
- Han, Tao, S629 (PO-1091)
- Han, Xueji, S795 (PO-987)
- Han, Ying, S762 (PO-2853)
- Haque, Nazneen, S434 (PO-1748)
- Harasym, Troy O., S281 (OS-595)
- Harber, Mark, S236 (OS-2792)
- Hardikar, Winita, S683 (PO-1641)
- Hardtke-Wolenski, Matthias, S706 (PO-2105)
- Hardwigsen, Jean, S461 (PO-351), S462 (PO-353)
- Hardy, Timothy, S266 (OS-2831)
- Harif, Yael, S272 (OS-798)
- Harlow, Chris, S537 (PO-711)
- Harman, David, S562 (PO-775)
- Harms, Maren, S430 (PO-1428), S431 (PO-1486)
- Harputluoglu, Murat, S193 (GS-1213), S472 (PO-2001), S671 (PO-2288)
- Harring, Michael, S597 (PO-1839)
- Harrington, Claire, S382 (PO-2298)
- Harris, Nicola, S321 (PO-2185)
- Harrison, Bryce, S623 (PO-2163)
- Harrison, Stephen, S200 (GS-2563), S204 (LBO-2800), S255 (OS-243), S257 (OS-555), S259 (OS-1592), S267 (OS-427), S294 (LBP-2580), S297 (LBP-2907), S410 (PO-985), S424 (PO-210), S564 (PO-919), S568 (PO-1056), S575 (PO-1568), S579 (PO-1714), S593 (PO-1504), S609 (PO-159), S609 (PO-230), S614 (PO-849), S616 (PO-981), S617 (PO-1082), S618 (PO-1314), S619 (PO-1762), S622 (PO-2006), S686 (PO-1809)
- Harris, Rebecca, S562 (PO-775)
- Harrod, Elizabeth, S241 (OS-699)
- Harshit, Garg, S259 (OS-1592)
- Hartig-Lavie, Kerstin, S350 (PO-1549)
- Harting, Eliza, S613 (PO-757)
- Hartleben, Björn, S464 (PO-841)
- Hartl, Johannes, S408 (PO-629), S430 (PO-1418)
- Hartl, Lukas, S213 (OS-925), S270 (OS-507), S364 (PO-532), S365 (PO-560), S374 (PO-1249), S376 (PO-1316), S377 (PO-1613), S383 (PO-2403), S645 (PO-533)
- Hartlova, Anetta S., S266 (OS-2831)
- Hartmann, Daniel, S262 (OS-584), S393 (PO-793)
- Hartmann, Heinz, S778 (PO-52)
- Hart, Susan Emeigh, S748 (PO-1699)
- Harzandi, Azadeh, S222 (OS-2044)
- Hasanpourghadi, Mohadeseh, S290 (OS-2478)
- Hashim, Mahmoud, S234 (OS-161)
- Hassan Bhat, Mohsin, S221 (OS-1979)
- Hassanein, Tarek, S561 (PO-756), S578 (PO-1689), S618 (PO-1198), S736 (PO-482)
- Hassan, Manal, S234 (OS-161), S239 (OS-2686)
- Hassan, Muhammad Radzi Abu, S660 (PO-1877), S672 (PO-2424)
- Hassany, Sahar M., S803 (PO-2320)
- Hassouneh, Ramzi, S460 (PO-212)
- Hatano, Etsuro, S415 (PO-2531)
- Hatzakis, Angelos, S653 (PO-1421), S768 (PO-908)
- Häussinger, Dieter, S339 (PO-2098), S528 (PO-1357), S530 (PO-1615)
- Havervall, Sebastian, S339 (PO-1787)
- Havinga, Rick, S591 (PO-1150)
- Hayashi, Jun, S780 (PO-666)
- Hayde, Brandy, S193 (GS-1213)
- Ha, Yeonjung, S526 (PO-2712), S549 (PO-1823), S585 (PO-2710)
- Hayes, Peter, S378 (PO-1987)
- Hay, Iain, S611 (PO-337)
- Hayward, Kelly, S353 (PO-1766)
- Hazou, Wadi, S220 (OS-2854)
- Heaton, Nigel, S321 (PO-2185), S343 (PO-187), S503 (PO-1771)
- Hebditch, Vanessa, S663 (PO-2032)
- He, Chaohui, S368 (PO-1094), S629 (PO-1091)
- Hee Choi, Dae, S305 (PO-1947)
- Hee Kim, In, S305 (PO-1947)
- Heeren, Ron M.A., S262 (OS-584)
- Hees, Stijn Van, S749 (PO-1791)
- He, Fuliang, S680 (PO-996), S681 (PO-1108)
- Hegade, Vinod, S420 (PO-1578)
- Hegenbarth, Silke, S262 (OS-584)
- Heggelund, Lars, S734 (PO-111)
- He, Guochang, S629 (PO-1091)
- He, Haiying, S748 (PO-1775)
- He, Handan, S620 (PO-1851), S620 (PO-1908), S621 (PO-1961), S703 (PO-1917)
- Heiberg, Ida, S231 (OS-1299)
- Heida, Andries, S591 (PO-1150)
- Heide, Danijela, S262 (OS-584), S752 (PO-2089)
- Heidenreich, Regina, S246 (OS-1399)
- Heidt, Sebastiaan, S428 (PO-872)
- Heikenwälder, Mathias, S196 (GS-2069), S219 (OS-2754), S262 (OS-584), S278 (OS-1396), S703 (PO-1711), S752 (PO-2089), S753 (PO-2106), S754 (PO-2243)
- Heil, Franz Josef, S661 (PO-1903)
- Heil, Marantha, S701 (PO-1450), S701 (PO-1451), S713 (PO-408)
- Heimers, Philipp, S530 (PO-1615)
- Heimisdottir, Maria, S670 (PO-2127)
- Heim, Markus, S628 (PO-2377)
- Heinemann, Melina, S473 (PO-2211)
- Hellard, Margaret, S358 (PO-2683), S386 (PO-2685), S658 (PO-1813), S797 (PO-1872)
- Hellings, Samuel, S395 (PO-1505), S592 (PO-1235)
- Helmsberger, Thomas, S244 (OS-777)
- Hemming Karlsens, Tom, S432 (PO-1512)
- Henderson, Andrew, S348 (PO-1102)
- Henderson, James, S373 (PO-1236)
- Henderson, Neil C., S232 (OS-943)
- Hendifar, Andrew, S496 (PO-2812)
- Hendricks, Lennart, S702 (PO-1707)
- Heneghan, Michael, S193 (GS-1213), S306 (PO-2178), S441 (PO-2719), S473 (PO-2211)
- Hengstler, Jan G., S219 (OS-2754), S248 (OS-334)
- Henquell, Cécile, S647 (PO-785)
- Henriksson, Martin, S554 (PO-2583)
- Henrion, Jean, S313 (PO-488)
- Heo, Jeong, S294 (LBP-2580), S755 (PO-2338), S756 (PO-2395), S761 (PO-2844)
- He, Qibin, S629 (PO-1091)
- Heras, Violeta, S391 (PO-479)
- Herkel, Johannes, S451 (PO-1472)
- Hermabessiere, Paul, S648 (PO-821)
- Hermanussen, Lennart, S702 (PO-1707)
- Hernández-Aguilera, Anna, S598 (PO-1897)
- Hernández, Candido, S770 (PO-983), S798 (PO-2020)
- Hernández, Francisco Andrés Pérez, S492 (PO-2594), S674 (PO-2596)
- Hernandez-Gea, Virginia, S252 (OS-571), S277 (OS-1172), S307 (PO-48), S694 (PO-2902)
- Hernandez-Guerra, Manuel, S307 (PO-48)
- Hernandez, Juana Maria, S723 (PO-1622)
- Hernandez, Juan-Jose, S734 (PO-247)
- Hernandez, Nélia, S199 (GS-2309)
- Hernandez, Rocio Munoz, S342 (PO-2420)
- Hernandez, Sairy, S246 (OS-1674)
- Hernández-Tejero, M., S194 (GS-1997)

Author Index

- Hernández-Tejero, Maria, S209 (OS-2060)
Hernández-Tejero, María, S325 (PO-552)
Hernandez, Ubaldo Benitez, S670 (PO-2127)
Hernandez-Vargas, Hector, S695 (PO-258)
Hernansaiz, Rosa, S689 (PO-2090)
Heron, Jon, S273 (OS-183)
Herranz, Jose Maria, S320 (PO-2043)
Herring, Michael, S468 (PO-1169)
Herring, Robert Jr., S561 (PO-756)
Herrmann, Eva, S306 (PO-2203)
Herro, Rana, S686 (PO-1758)
Hershkovich, Leor, S750 (PO-1837)
He, Ruiling, S372 (PO-1152)
Herzig, Stephan, S249 (OS-1355)
Herzog, Katharina, S780 (PO-602)
He, Sichan, S515 (PO-767)
He, Song, S368 (PO-1094)
Hessheimer, Amelia, S334 (PO-624)
Hessling, Bernd, S752 (PO-2089)
He, Wei, S248 (OS-334)
He, Wen-Qiang, S673 (PO-2483)
Heydmann, Laura, S392 (PO-692), S695 (PO-175)
Heyens, Leen, S581 (PO-1895)
Heyne, Renate, S764 (PO-131)
He, Yongfeng, S368 (PO-1094)
He, Yulong, S389 (PO-410)
He, Yuqian, S629 (PO-1091)
Hezode, Christophe, S769 (PO-955)
He, Zonglin, S650 (PO-1330)
Hickey, Raymond, S476 (PO-982)
Hickman, Matthew, S273 (OS-183), S800 (PO-2205)
Hidalgo, Nuria Cañete, S734 (PO-247)
Higgins, Victoria, S552 (PO-2326), S553 (PO-2343)
Hilgard, Gudrun, S294 (LBP-2730)
Hillaire, Sophie, S277 (OS-1172)
Hilleret, Marie-Noëlle, S291 (OS-2717), S461 (PO-351), S462 (PO-353)
Hiller, Karsten, S248 (OS-334)
Hinde, Richard, S356 (PO-2524)
Hin Ko, Hin, S228 (OS-1586)
Hinkson, Alexander, S394 (PO-1125)
Hintz, Andreas, S793 (PO-377), S794 (PO-773)
Hinz, Michael, S194 (GS-1997), S209 (OS-2060)
Hiraoka, Atsushi, S239 (OS-2686)
Hirode, Grishma, S749 (PO-1791), S751 (PO-1841)
Hirschfield, Gideon, S193 (GS-1213), S226 (OS-894), S228 (OS-1586), S387 (PO-2938), S420 (PO-1578), S424 (PO-210), S425 (PO-376), S427 (PO-770), S427 (PO-860), S429 (PO-1074), S435 (PO-1755), S439 (PO-2327)
Hirsch, Theo, S242 (OS-906)
Hizir, Zoheir, S752 (PO-2089), S754 (PO-2243)
Hjorth, Maria, S271 (OS-686)
Hoare, Matthew, S230 (OS-1171)
Hobbs, Brian, S334 (PO-134)
Hobbs, Helen, S588 (PO-475)
Ho Choe, Yon, S199 (GS-2283)
Hocquelet, Arnaud, S679 (PO-570)
Hodson, David, S342 (PO-2851)
Hoentjen, Frank, S437 (PO-2230)
Hoepfer, Marius M., S473 (PO-2821)
Hofer, Benedikt S., S383 (PO-2403), S645 (PO-533), S681 (PO-1243)
Hoffman, Sara, S254 (OS-1611), S602 (PO-2123)
Hofmann, Maike, S281 (OS-1021), S453 (PO-1929), S454 (PO-1983)
Høgdall, Dan, S240 (OS-179)
Ho, George, S531 (PO-2627)
Hogh, Birthe, S231 (OS-1299)
Hohenester, Simon, S389 (PO-410), S535 (PO-566)
Ho, Joan, S739 (PO-853)
Ho Lee, Joo, S585 (PO-2710)
Ho Lee, Ju, S549 (PO-1823)
Holleboom, Adriaan G., S585 (PO-2485)
Hollenbach, Stanley, S476 (PO-982)
Holmer, Magnus, S269 (OS-1627)
Holmes, Elaine, S404 (PO-799)
Holmes, Jacinta, S203 (LBO-2764), S775 (PO-2048), S780 (PO-602)
Holmes, Michael, S476 (PO-982)
Holzmann, Heidemarie, S746 (PO-1448)
Honcharova-Biletska, Hanna, S278 (OS-1396)
Honda, Takashi, S787 (PO-1918)
Honerlaw, Jackie, S254 (OS-1611), S602 (PO-2123)
Hong, Jin, S700 (PO-1305), S720 (PO-1257), S742 (PO-1196)
Hong Loo, Jing, S349 (PO-1462)
Hong, Mei-Zhu, S483 (PO-1147), S709 (PO-1844)
Hong Park, Jae, S199 (GS-2283)
Honnet, Geraldine, S202 (LBO-2647)
Hontañón, Victor, S785 (PO-1404)
Hontañón, Víctor, S781 (PO-689)
Hood, Gillian, S536 (PO-630)
Hoogerland, Joanne, S531 (PO-2793)
Hookey, Lawrence, S658 (PO-1713)
Hoon Kim, Ji, S345 (PO-714)
Hoon Yoon, Jai, S402 (PO-2695)
Hoorens, Anne, S450 (PO-1333)
Hoover, Katherine, S314 (PO-832), S538 (PO-819), S539 (PO-825)
Horhat, Adelina, S318 (PO-1651)
Horia, Stefanescu, S252 (OS-571)
Horn, Patrick, S279 (OS-1554), S597 (PO-1849), S683 (PO-1641), S684 (PO-1665), S687 (PO-1811), S688 (PO-1833), S688 (PO-1843)
Horrillo, Raquel, S354 (PO-1930)
Horta, Diana, S723 (PO-1622)
Horvath, Gabor, S655 (PO-1572)
Horvatits, Thomas, S351 (PO-1701)
Hoshida, Yujin, S196 (GS-2069), S212 (OS-1491), S695 (PO-175)
Ho, Shinn-Ying, S523 (PO-1801)
Hosmane, Suneil, S586 (PO-2739)
Hosur Ananthashayana, Venkatesh, S381 (PO-2238)
Houben, Inge, S581 (PO-1895)
Hou, Jingyu, S247 (OS-2679)
Houlihan, Diarmaid, S493 (PO-2612)
Hou, Ming-Chih, S483 (PO-1090), S518 (PO-1142)
Ho Um, Soon, S345 (PO-714)
Hourmand, Isabelle Ollivier, S678 (PO-561)
Houssel-Debry, Pauline, S197 (GS-613), S461 (PO-351), S462 (PO-353)
Housset, Chantal, S191 (GS-1065)
Hout, Kay, S289 (OS-865)
Houwen, Roderick H.J., S684 (PO-1665)
Hou, Yuchen, S410 (PO-738)
Hou, Zhiyun, S359 (PO-2688)
Hov, Johannes R., S421 (PO-2285)
Howard, Rob, S637 (PO-2936)
Howell, Jess, S658 (PO-1813)
Howell, Jessica, S358 (PO-2683), S386 (PO-2685)
Howell, Scott, S559 (PO-580)
Hoyas, Elena, S746 (PO-1449)
Hsieh, Sen-Yung, S695 (PO-175)
Hsieh, Yi-Chung, S788 (PO-2008)
Hsu, Chao-Wei, S761 (PO-2844)
Hsu, Yao-Chun, S749 (PO-1791), S751 (PO-1841), S780 (PO-666)
Htun Oo, Ye, S423 (PO-60)
Huang, Chenlu, S726 (PO-1810), S742 (PO-1109)
Huang, Chung-Feng, S780 (PO-666)
Huang, Emily, S316 (PO-1215)
Huang, Erjiong, S368 (PO-1094)
Huang, Guangyu, S759 (PO-2738)
Huang, Janet, S453 (PO-1653)
Huang, Jee-Fu, S780 (PO-666)
Huang, Jonathan, S686 (PO-1809)
Huang, Jo-Yu, S523 (PO-1801)
Huang, Julia, S471 (PO-1773)
Huang, Kuo-Wei, S483 (PO-1090), S518 (PO-1142)
Huang, Leyi, S507 (PO-2694)
Huang, Ou-Yang, S538 (PO-719)
Huang, Pinzhu, S499 (PO-677)
Huang, Qi, S290 (OS-2299)
Huang, Rui, S400 (PO-1857), S728 (PO-2134)
Huang, Stephen, S287 (OS-44)
Huang, Xiaohong, S208 (OS-638), S406 (PO-1763)
Huang, Xuanhui, S368 (PO-1094)
Huang, Yan, S795 (PO-987)
Huang, Yifei, S359 (PO-2688), S368 (PO-1094), S372 (PO-1152)
Huang, Yi-Hsiang, S483 (PO-1090), S518 (PO-1142), S523 (PO-1801), S756 (PO-2395)
Huang, Yuxian, S726 (PO-1810), S742 (PO-1109)
Huang, Zhenlin, S503 (PO-1771)
Hua, Peng, S629 (PO-1091)
Hua, Rui, S795 (PO-987)

- Huber, Samuel, S351 (PO-1701)
 Hubers, Lowiek, S225 (OS-706)
 Hubert, Aurélie, S202 (LBO-2647)
 Hu, Chen, S204 (LBO-2800),
 S618 (PO-1314), S619 (PO-1762)
 Huckle, Florian, S236 (OS-498),
 S380 (PO-2162)
 Hu, Doudou, S629 (PO-1091)
 Hudson, Mark, S386 (PO-2788),
 S470 (PO-1523)
 Hwei Lee, Guan, S438 (PO-2280)
 Hueser, Norbert, S262 (OS-584)
 Hüffner, Lucas, S282 (OS-1062)
 Hughes, Gareth, S273 (OS-199)
 Huguet, Jade, S742 (PO-1240)
 Huguet, Mathilde, S647 (PO-785)
 Hu, Hao, S629 (PO-1091)
 Hu Hu, Jinhua, S438 (PO-2280)
 Hui, Aric J., S757 (PO-2422)
 Hui, Aric Josun, S755 (PO-2338),
 S756 (PO-2395)
 Hui, Cynthia, S773 (PO-1871)
 Huijckman, Nicolette, S691 (PO-2204)
 Huiling, Xiang, S368 (PO-1094),
 S629 (PO-1091)
 Hui, Vicki Wing-Ki, S268 (OS-931),
 S727 (PO-1876)
 Hu, Jianping, S368 (PO-1094)
 Hu, Junjian, S300 (PO-712)
 Hulse, Jason, S476 (PO-982)
 Hung, Chao-Hung, S747 (PO-1628)
 Hunyady, Peter, S306 (PO-2203)
 Huot-Marchand, Philippe, S268 (OS-1034),
 S268 (OS-1044)
 Hupa-Breier, Katharina Luise, S423 (PO-60)
 Hu, Peng, S770 (PO-1007)
 Hüppe, Dietrich, S778 (PO-52)
 Hu, Qiankun, S726 (PO-1810),
 S742 (PO-1109)
 Hurst, John R., S677 (PO-323)
 Husbyn, Hannah, S208 (OS-638)
 Husebye, Eystein, S432 (PO-1512)
 Hu, Shengjuan, S368 (PO-1094),
 S629 (PO-1091)
 Husi, Kathrin, S347 (PO-1045)
 Hussain, Nabeel, S383 (PO-2305)
 Huss, Anke, S225 (OS-706)
 Huss, Ryan, S254 (OS-1611), S257 (OS-555),
 S265 (OS-1746), S561 (PO-756),
 S575 (PO-1568), S578 (PO-1689),
 S579 (PO-1714), S613 (PO-757)
 Hust, Michael, S423 (PO-60)
 Hutchinon, Sharon, S800 (PO-2205)
 Hutin, Yvan, S276 (OS-2750)
 Hutsch, Tomasz, S417 (PO-899)
 Hu, Tsung-Hui, S668 (PO-2103),
 S718 (PO-947), S747 (PO-1628),
 S761 (PO-2844)
 Hu, Xiao-Yu, S709 (PO-218)
 Hu, Yanbin, S735 (PO-397)
 Huynh, Thao, S283 (OS-2826)
 Hu, Zhanying, S281 (OS-595)
 Hvidbjerg Gantzel, Rasmus,
 S384 (PO-2529)
 Hyakumura, Michiko, S739 (PO-853)
 Hyde, Sarah, S435 (PO-1790)
 Hyeon Choi, Gwang, S305 (PO-1947)
 Hylemon, Phillip, S309 (PO-117)
 Hyötyläinen, Tuulia, S256 (OS-538),
 S579 (PO-1777), S605 (PO-2322)
 Hyuk Oh, Chi, S550 (PO-1880)
 Hyun Bae, Si, S488 (PO-1275)
 Hyung Kim, Tae, S345 (PO-714)
 Hyun Park, Su, S402 (PO-2695)
 Hyun Shim, Ju, S500 (PO-920)
 Hyunsoon, Kang, S720 (PO-1257),
 S742 (PO-1196)
 Iacob, Razvan, S477 (PO-1119)
 Iacob, Speranta, S477 (PO-1119)
 Iacone, Roberto, S196 (GS-2069),
 S247 (OS-2190)
 Iakovleva, Viktoriia, S233 (OS-1290)
 Iapadre, Nerio, S704 (PO-1928)
 Iarovoi, Liviu, S750 (PO-1837)
 Iavarone, Massimo, S492 (PO-2364),
 S495 (PO-2799), S521 (PO-1351),
 S524 (PO-2401), S782 (PO-697),
 S784 (PO-921)
 Ibañez, Luis, S194 (GS-1997),
 S252 (OS-571), S307 (PO-48),
 S784 (PO-1176)
 Ibañez-Samaniego, Luis, S781 (PO-689)
 Ibrahim Alabsawy, Eman, S194 (GS-1997)
 Ichai, Philippe, S717 (PO-813)
 Ichai, Phillippe, S194 (GS-1997),
 S209 (OS-2060)
 Ichikawa, Takeshi, S335 (PO-994)
 Idalsoaga, Francisco, S199 (GS-2309),
 S323 (PO-2704)
 Idilman, Ramazan, S286 (OS-1892),
 S472 (PO-2001), S549 (PO-1865),
 S671 (PO-2288), S747 (PO-1661)
 Ielasi, Luca, S514 (PO-591)
 Ieluzzi, Donatella, S767 (PO-694)
 Ierardi, Anna Maria, S492 (PO-2364)
 Iesari, Samuele, S477 (PO-1207)
 Iglesias, Ainhoa, S497 (PO-133)
 Iglesias, Anabel Fernández, S334 (PO-624)
 Iglesias, Cristina, S249 (OS-1355)
 Ignasi, Olivas, S226 (OS-894)
 Ihne, Sandra, S636 (PO-2386)
 Iida, Yuki, S267 (OS-681)
 Iio, Etsuko, S715 (PO-529)
 Ijssennagger, Noortje, S457 (PO-279)
 Ijzermans, Jan, S245 (OS-972),
 S418 (PO-903)
 Ikegami, Toru, S193 (GS-1213)
 Iliopoulos, Panos, S768 (PO-908)
 Il Lee, Jung, S294 (LBP-2580)
 Imai, Hirohiko, S415 (PO-2531)
 Imai, Norihiro, S787 (PO-1918)
 Imajo, Kento, S267 (OS-681)
 Imamura, Michio, S780 (PO-602)
 Immer, Franz, S466 (PO-1126),
 S467 (PO-1133)
 Inao, Mie, S425 (PO-376)
 Iñarrairaegui, Mercedes, S246 (OS-1399)
 Incicco, Simone, S355 (PO-2273),
 S469 (PO-1496)
 Indolfi, Giuseppe, S673 (PO-2586)
 Inglis, Sarah, S800 (PO-2205)
 Inoue, Takako, S715 (PO-529)
 Inukai, Yosuke, S787 (PO-1918)
 Invernizzi, Federica, S521 (PO-1351)
 Invernizzi, Pietro, S226 (OS-894),
 S387 (PO-2938), S425 (PO-376),
 S690 (PO-2120)
 Inverso, Donato, S262 (OS-584)
 Ioannou, Maria, S422 (PO-2681)
 Ioannou, Stephanie, S437 (PO-2230)
 Iorio, Raffaele, S683 (PO-1522)
 Ipiens, Cristina, S335 (PO-698),
 S338 (PO-1761)
 Iqbal, Shahed, S720 (PO-1309)
 Irazabal, Yolanda Gonzalez, S337 (PO-1643)
 Ireuzubieta, Paula, S255 (OS-2337),
 S584 (PO-2369)
 Iriberrri, Rafael Artuch, S271 (OS-1954)
 Irlés-Depe, Marie, S559 (PO-569),
 S583 (PO-1981), S648 (PO-821)
 Iruarrizaga-Lejarreta, Marta, S564 (PO-916)
 Iruretagoyena, Begoña Rodriguez,
 S243 (OS-1948), S612 (PO-627)
 Iruzubieta, Paula, S269 (OS-1769),
 S497 (PO-133), S537 (PO-685),
 S574 (PO-1518), S612 (PO-627),
 S624 (PO-2192)
 Irvine, Katharine, S266 (OS-2831),
 S348 (PO-1102), S353 (PO-1766)
 Isabel Lucena, Maria, S301 (PO-1185),
 S302 (PO-1335), S303 (PO-1389),
 S304 (PO-1406)
 Isabel, Nuñez, S640 (PO-1193)
 Iserte, Gemma, S639 (PO-511),
 S640 (PO-1193), S641 (PO-1525)
 Isfordink, Cas J., S664 (PO-2039),
 S774 (PO-1966)
 Ishigami, Masatoshi, S787 (PO-1918)
 Ishii, Takamichi, S415 (PO-2531)
 Ishikawa, Toru, S239 (OS-2686)
 Ishizu, Yoji, S787 (PO-1918)
 Islam, Kendall, S558 (PO-454)
 Islam, Mojahidul, S330 (PO-2313)
 Islam, Tawhidul, S604 (PO-2276)
 Ismail, Marwa, S427 (PO-860)
 Ismail, Mohamed, S234 (OS-161)
 Isoniemi, Helena, S227 (OS-1088)
 Israelsen, Mads, S207 (OS-1726),
 S313 (PO-487), S321 (PO-2331)
 Issachar, Assaf, S272 (OS-798)
 Issad, Tarik, S528 (PO-1027)
 Itoh, Yoshito, S243 (OS-295)
 Ito, Takanori, S787 (PO-1918)
 Ito, Takashi, S415 (PO-2531)
 Iuculano, Federica, S785 (PO-1247),
 S786 (PO-1542)
 Ivancovsky Wajcman, Dana,
 S546 (PO-1436)
 Ivanova, Elena, S768 (PO-908),
 S776 (PO-2218)
 Iyer, Rajalakshmi, S578 (PO-1689)

Author Index

- Izzo, Francesco, S246 (OS-1399)
Izzy, Manhal, S382 (PO-2298),
S463 (PO-530), S472 (PO-2121)
- Jachs, Mathias, S213 (OS-925),
S270 (OS-507), S364 (PO-532),
S365 (PO-560), S376 (PO-1316),
S377 (PO-1613), S383 (PO-2403),
S645 (PO-533)
- Jackson, Jessica, S552 (PO-2326),
S553 (PO-2343)
- Jackson, Kathy, S289 (OS-1430)
- Jacobson, Ira, S736 (PO-482)
- Jacquemin, Emmanuel, S242 (OS-906)
- Jacquemin, Patrick, S509 (PO-2839)
- Jacquet, Maxime, S449 (PO-896)
- Jae Chon, Hong, S526 (PO-2712)
- Jaekel, Elmar, S235 (OS-213),
S423 (PO-60), S464 (PO-841),
S473 (PO-2821)
- Jaeger, Tina, S449 (PO-896)
- Jae Lee, Youn, S305 (PO-1947)
- Jafri, Syed-Mohammed, S193 (GS-1213),
S756 (PO-2395)
- Jafri, Wasim, S438 (PO-2280)
- Jagas, Jacek, S347 (PO-974)
- Jagdish, Rakesh Kumar, S330 (PO-2313)
- Jäger, Burkhard, S764 (PO-131)
- Jäger, Johannes, S661 (PO-1903)
- Jager, Marion, S318 (PO-1651)
- Jain, Shuchi, S581 (PO-1808)
- Jain, Vandana, S677 (PO-106)
- Jalal, Prasun, S234 (OS-161),
S239 (OS-2686)
- Jalan, Rajiv, S194 (GS-1997),
S209 (OS-2060), S329 (PO-1585),
S330 (PO-2147), S338 (PO-1684),
S347 (PO-1045), S349 (PO-1165),
S465 (PO-922)
- Jamal-Allial, Aziza, S566 (PO-980),
S577 (PO-1588)
- James, Fiona, S464 (PO-594)
- Jamieson, Brian D., S357 (PO-2634)
- Jamieson, Thomas, S508 (PO-2787)
- Jamil, Khurram, S208 (OS-845),
S326 (PO-675), S327 (PO-968)
- Janardhan, Sujit, S540 (PO-969)
- Janciauskiene, Sabina, S677 (PO-323)
- Jancsik, Viktor, S655 (PO-1572)
- Jang, Byoung Kuk, S757 (PO-2422)
- Jang, Eun Sun, S286 (OS-1892)
- Jang, Jae Young, S743 (PO-1270)
- Jang, Jeong Won, S504 (PO-1825),
S743 (PO-1270)
- Jang, Jeong-Won, S757 (PO-2422)
- Janick, Selves, S487 (PO-1153)
- Janik, Maciej K., S193 (GS-1213),
S423 (PO-60), S432 (PO-1574)
- Janjua, Naveed, S782 (PO-862),
S789 (PO-2708)
- Jankowska, Irena, S193 (GS-1213)
- Janovitz, Evan, S529 (PO-1606)
- Janowski, Kamil, S634 (PO-2094)
- Jansakun, Chutima, S607 (PO-2623)
- Jansen, Christian, S213 (OS-513),
S307 (PO-48)
- Jansen, Lauren, S453 (PO-1653)
- Janssen, Harry, S228 (OS-1586),
S286 (OS-1892), S387 (PO-2938),
S435 (PO-1755), S446 (PO-216),
S447 (PO-240), S448 (PO-846),
S455 (PO-2307), S659 (PO-1817),
S718 (PO-915), S733 (PO-80),
S747 (PO-1661), S749 (PO-1791),
S751 (PO-1841), S755 (PO-2269),
S798 (PO-1962)
- Janssen, Harry L.A., S755 (PO-2338),
S757 (PO-2429)
- Janssen, Harry LA, S756 (PO-2395)
- Jäntti, Sirkku, S605 (PO-2322)
- Janvier, Paul, S691 (PO-2324)
- Japaridze, Maia, S643 (PO-504),
S773 (PO-1691)
- Jasmins, Luís, S677 (PO-323)
- Jassem, Wayer, S503 (PO-1771)
- Jaształ, Agnieszka, S342 (PO-2833),
S417 (PO-899), S587 (PO-195)
- Jaubert, Laura, S352 (PO-1712)
- Jayaswal, Arjun, S259 (OS-1592)
- Jean-Baptiste, HIRIART, S461 (PO-351),
S462 (PO-353), S559 (PO-569),
S583 (PO-1981)
- Jean Damascene, Makuza, S789 (PO-2708)
- Jean Marie, Dubertrand, S394 (PO-1069),
S396 (PO-1580)
- Jedrysiak, Katrin, S763 (PO-68),
S764 (PO-131)
- Jeffers, Thomas, S395 (PO-1505),
S592 (PO-1235)
- Jeffery-Smith, Anna, S231 (OS-1299)
- Jekle, Andreas, S744 (PO-1386)
- Jeng, Darren, S539 (PO-825)
- Jeng, Rachel Wen-Juei, S715 (PO-460),
S725 (PO-1788), S747 (PO-1628),
S749 (PO-1781), S749 (PO-1791),
S751 (PO-1841), S788 (PO-2008)
- Jensen, Peter, S646 (PO-640)
- Jeong, Dahn, S782 (PO-862),
S789 (PO-2708)
- Jeong, Jinseon, S265 (OS-2450)
- Jeong, Sook-Hyang, S305 (PO-1947),
S686 (PO-1809)
- Jepsen, Peter, S316 (PO-1375),
S344 (PO-342), S384 (PO-2529),
S436 (PO-1799), S482 (PO-707),
S675 (PO-2861)
- Jeremie, Corneille, S394 (PO-1069),
S396 (PO-1580)
- Jeremy, BOMO, S696 (PO-526)
- Jessica, Azzi, S239 (OS-2686)
- Jezequel, Caroline, S696 (PO-526)
- Jia, Catherine, S265 (OS-1746),
S578 (PO-1689), S579 (PO-1714),
S613 (PO-757)
- Jia, Ji-Dong, S680 (PO-996), S681 (PO-1108),
S731 (PO-2575)
- Jiang, Jiaji, S759 (PO-2738)
- Jiang, Li, S709 (PO-218)
- Jiang, Pan, S368 (PO-1094)
- Jiang, Pei-Ying, S629 (PO-1047)
- Jiang, Su'e, S738 (PO-797)
- Jiang, Wei, S629 (PO-1091)
- Jiang, Wentao, S523 (PO-1883)
- Jiang, Xuhua, S726 (PO-1810),
S742 (PO-1109)
- Jiang, Yongfang, S759 (PO-2738),
S795 (PO-987)
- Jiang, Yu, S589 (PO-550)
- Jiang, Yuyong, S506 (PO-2601)
- Jiang, Z. Gordon, S334 (PO-134)
- Jiang, Zicheng, S629 (PO-1091),
S758 (PO-2735), S759 (PO-2759)
- Jia, Xiaoli, S758 (PO-2735),
S759 (PO-2759)
- Ji Choi, Seong, S402 (PO-2695)
- Ji, Dong, S300 (PO-679), S629 (PO-1091),
S730 (PO-2484), S738 (PO-811)
- Ji, Jiansong, S359 (PO-2688),
S629 (PO-1091)
- Ji, Jingjing, S589 (PO-550)
- Jimbei, Pavlina, S750 (PO-1837)
- Jimenez, Cesar, S347 (PO-1045)
- Jiménez, Miguel, S302 (PO-1335),
S304 (PO-1406)
- Jiménez Sousa, María Ángeles,
S785 (PO-1404)
- Jiménez, Wladimiro, S218 (OS-1478)
- Jin Chung, Woo, S305 (PO-1947)
- Jindal, Ankur, S371 (PO-1151),
S378 (PO-1987), S380 (PO-2136),
S381 (PO-2294), S635 (PO-2319)
- Jing, Wang, S709 (PO-218)
- Jin, Hua, S478 (PO-1346)
- Jin Jung, Su, S550 (PO-1880)
- Jin, Wei-lin, S510 (PO-2919)
- Jin, Yi, S562 (PO-769)
- Ji, Rui, S368 (PO-1094)
- Jith, Jithin, S676 (PO-2872)
- Ji, Xiaolin, S359 (PO-2688)
- Ji, Yun, S731 (PO-2575)
- Jochmans, Ina, S475 (PO-2910)
- Joekes, Elizabeth, S670 (PO-2131)
- Joensson, Marthe Forbord Huss,
S638 (PO-190)
- Johanna Nußbaumer, Rosa, S376 (PO-1316),
S377 (PO-1613)
- Johannes, Chang, S252 (OS-571)
- Johannessen, Asgeir, S734 (PO-111)
- Johannsson, Birgir, S670 (PO-2127)
- Johansen, Stine, S207 (OS-1726),
S313 (PO-487), S321 (PO-2331)
- Johnson, Amy, S348 (PO-1102)
- Johnson, Jeff, S596 (PO-1797)
- Johnstone, Ben, S471 (PO-1971)
- Jo, Hyeim, S263 (OS-768)
- Jokelainen, Kalle, S229 (OS-2096)
- Jonas, Jan Philipp, S213 (OS-925)
- Jonel, Trebicka, S307 (PO-48)
- Jones, Andrew, S766 (PO-637),
S775 (PO-2095)
- Jones, Christopher, S523 (PO-1856)
- Jones, Daryl, S471 (PO-1971)

- Jones, David, S404 (PO-799),
S419 (PO-1364), S420 (PO-1578),
S427 (PO-770), S434 (PO-1748)
- Jones-Hughes, Tracey, S685 (PO-1722)
- Jones, Rebecca, S464 (PO-594)
- Jones, Rebecca L., S367 (PO-1040),
S394 (PO-1125), S420 (PO-1578),
S427 (PO-770)
- Jonigk, Danny, S423 (PO-60)
- Jonkers, Daisy, S554 (PO-2673)
- Joon Kim, Dong, S438 (PO-2280)
- Joon Yim, Hyung, S345 (PO-714)
- Jopson, Laura, S420 (PO-1578)
- Jordan, William, S455 (PO-2173)
- Jördens, Markus, S339 (PO-2098)
- Jorgensen, Kristin, S227 (OS-1088)
- Joris, Katrien, S581 (PO-1895)
- Jorquera, Francisco, S778 (PO-2359)
- Jörs, Simone, S219 (OS-2754)
- José Aragonés, Juan, S194 (GS-1997),
S209 (OS-2060)
- José Gallego, Juan, S335 (PO-698),
S338 (PO-1761)
- José Gallego Roig, Juan, S335 (PO-709)
- José Lozano, Juan, S401 (PO-2113)
- Joshi, Deepak, S227 (OS-1088),
S437 (PO-2230), S441 (PO-2719)
- Joshi, Shilpy, S455 (PO-2173)
- Jothimani, Dinesh, S438 (PO-2280)
- Joudiou, Nicolas, S477 (PO-1207)
- Jouihan, Hani, S531 (PO-2627)
- Joung, Chanmin, S619 (PO-1819)
- Joven, Jorge, S598 (PO-1897)
- Joyes, S., S438 (PO-2280)
- Juang, Charity, S476 (PO-982)
- Juanola, Adria, S311 (PO-345),
S319 (PO-1932), S329 (PO-2058)
- Juanola, Oriol, S221 (OS-1979)
- Jubran, Bellal, S427 (PO-860)
- Jucov, Alina, S203 (LBO-2764),
S741 (PO-1004), S742 (PO-1240),
S743 (PO-1251), S750 (PO-1837)
- Judd, Ali, S643 (PO-425)
- Jugnarain, Davina, S292 (OS-795)
- Jühling, Frank, S196 (GS-2069),
S247 (OS-2190), S695 (PO-175),
S780 (PO-602)
- Juhl, Pernille, S313 (PO-487)
- Julé, Yvon, S582 (PO-1927)
- Julia Brosnan, M., S255 (OS-243),
S259 (OS-1592)
- Julian, Luetkens, S213 (OS-513)
- Julien, Céline, S510 (PO-2865)
- Jun, Baek Gyu, S332 (PO-2547)
- Jun, Dae Won, S675 (PO-2689),
S780 (PO-666)
- Juneja, Pinky, S459 (PO-2234)
- Junge, Norman, S202 (LBO-2647),
S682 (PO-1354)
- Jung, Jinho, S577 (PO-1648)
- Jung, Jin Woo, S263 (OS-768)
- Jung, Kyu-Won, S479 (PO-409)
- Jung, Young Kul, S720 (PO-1115)
- Junien, Jean-Louis, S595 (PO-1727)
- Jura, Jolanta, S417 (PO-899), S587 (PO-195)
- Jurkiewicz, Elżbieta, S634 (PO-2094)
- Juul Nielsen, Mette, S313 (PO-487)
- Juuti, Anne, S260 (OS-2362),
S605 (PO-2322)
- Juyal, Dinkar, S254 (OS-1611),
S602 (PO-2123)
- Ju, Young Cheol, S675 (PO-2689)
- Kabaçam, Gökhan, S193 (GS-1213),
S472 (PO-2001)
- Kabahizi, Jules, S768 (PO-908)
- Kabat, Agnieszka, S262 (OS-584)
- Kabbani, Mohammad, S603 (PO-2161)
- Kabbara, Khaled, S468 (PO-1169)
- Kabbara, Khalid W., S597 (PO-1839)
- Kabil, KhaledDr, S293 (OS-2306)
- Kachala, Rabson, S670 (PO-2131)
- Kaczara, Patrycja, S342 (PO-2833)
- Kaeser, Rafael, S262 (OS-584)
- Kahlon, Nikhil, S567 (PO-1001)
- Kainov, Denis, S281 (OS-1024)
- Kakalou, Christine, S665 (PO-2059)
- Kakiyama, Genta, S309 (PO-117)
- Kakuda, Thomas, S745 (PO-1416)
- Kalambokis, Georgios, S204 (LBO-2765),
S360 (PO-2867)
- Kallis, Yiannis, S211 (OS-2779)
- Kallis, YiannisDr, S426 (PO-770)
- Kalmeijer, Ronald, S289 (OS-1430)
- Kamal, Dalia T., S803 (PO-2320)
- Kamar, Nassim, S461 (PO-351),
S462 (PO-353)
- Kamath, Binita M., S279 (OS-1554)
- Kaminsky, Elenor, S271 (OS-686)
- Kamlin, C. Omar, S280 (OS-2590),
S692 (PO-2628), S693 (PO-2697)
- Kamzolas, Ioannis, S263 (OS-1028)
- Kaneko, Atsushi, S715 (PO-529)
- Kaneko, Takahiro, S448 (PO-718)
- Kane, Pauline, S343 (PO-187)
- Kang, Ning, S372 (PO-1152)
- Kang, Seong Hee, S327 (PO-984),
S332 (PO-2547), S721 (PO-1340)
- Kann, Anna, S316 (PO-1375)
- Kantala, Shrika, S567 (PO-1001)
- Kanto, Tatsuya, S646 (PO-539)
- Kanwal, Fasiha, S323 (PO-2417)
- Kao, Cheng, S700 (PO-1305),
S742 (PO-1196)
- Kao, Jia-Horng, S629 (PO-1047),
S749 (PO-1791), S751 (PO-1841),
S757 (PO-2429)
- Kapatais, ANDREAS, S737 (PO-715)
- Kaplowitz, Neil, S593 (PO-1504)
- Karababa, Ayse, S528 (PO-1357)
- Karabulut, Umit, S671 (PO-2288)
- Karademir, Sedat, S472 (PO-2001)
- Karakaya, Fatih, S549 (PO-1865)
- Karam-Allah, Haidi, S803 (PO-2320)
- Karam, Alvina, S383 (PO-2305)
- Karamanidou, Christina, S665 (PO-2059)
- Karam, Vincent, S473 (PO-2211)
- Karaoulani, Theofanie, S737 (PO-715)
- Karapatanis, Stylianos, S737 (PO-715)
- Karapet, Artin, S761 (PO-2844)
- Karasu, Abdullah Zeki, S671 (PO-2288)
- Karasu, Zeki, S472 (PO-2001)
- Karatas, Gokturk, S549 (PO-1865)
- Karatay, Eylem, S671 (PO-2288)
- Kardashian, Ani, S191 (GS-1072)
- Karim, Md. Fazal, S438 (PO-2280)
- Karim, Mohammad Ehsanul,
S789 (PO-2708)
- Kariv, Revital, S546 (PO-1436)
- Karlas, Thomas, S259 (OS-1592),
S544 (PO-1296), S560 (PO-751)
- Karl Kadler, Benjamin, S536 (PO-630)
- Karlsen, Lars Normann, S734 (PO-111)
- Karlsen, Tom Hemming, S421 (PO-2285)
- Karnel, Franz, S213 (OS-925)
- Karner, Josef, S213 (OS-925)
- Karns, Rebekah, S686 (PO-1758)
- Karpen, Saul, S688 (PO-1833)
- Karrar, Azza, S395 (PO-1505),
S592 (PO-1235)
- Karsdal, Morten, S313 (PO-487),
S362 (PO-309), S363 (PO-310),
S564 (PO-919), S568 (PO-1056),
S573 (PO-1336), S633 (PO-1899)
- Karsdal, Morton, S255 (OS-243)
- Kartal, Aysun, S472 (PO-2001)
- Kaseb, Ahmed, S494 (PO-2786),
S497 (PO-2893)
- Kassas, Mohamed El, S803 (PO-2320)
- Kasztelan-Szczerbinska, Beata,
S319 (PO-1708)
- Katapur, Preetishirin, S666 (PO-2081)
- Katharina Baumann, Anna, S464 (PO-841)
- Katja, Füssel, S226 (OS-894)
- Katsioloudes, Petros, S657 (PO-1624)
- Katzarov, Krum, S207 (OS-2158)
- Kaur, Impreet, S459 (PO-2234)
- Kaur, Kanudeep, S647 (PO-739)
- Kaur, Savneet, S459 (PO-2234)
- Kaushal, Kanav, S371 (PO-1151),
S378 (PO-1705)
- Kautiainen, Hannu, S229 (OS-2096),
S444 (PO-2830)
- Kautz, Achim, S429 (PO-1294),
S663 (PO-2032)
- Kavnoudias, Helen, S512 (PO-75)
- Kayali, Zeid, S561 (PO-756)
- Kaymakoglu, Sabahattin, S671 (PO-2288)
- Kazankov, Konstantin, S349 (PO-1165)
- Kaze, Edeline, S313 (PO-488)
- Kazemzadeh Dastjerd, Mina, S527 (PO-375)
- Kearney, Orla, S215 (OS-1864)
- Kechagias, Stergios, S227 (OS-1088),
S260 (OS-2362)
- Kefeli, Ayse, S671 (PO-2288)
- Keitel, Verena, S339 (PO-2098)
- Keklikkiran, Caglayan, S671 (PO-2288)
- Kelleher, Charles, S314 (PO-607)
- Kelly, Matt, S634 (PO-2094)
- Kemble, George, S617 (PO-1112)
- Ke, Mengyun, S298 (PO-537)
- Kemming, Janine, S454 (PO-1983)

Author Index

- Kemos, Polychronis, S790 (PO-2946)
Kemp, Tracey, S771 (PO-1339)
Kemp, William, S358 (PO-2683), S386 (PO-2685), S512 (PO-75)
Kendall, Tim, S508 (PO-2787)
Kendre, Gajanan, S249 (OS-901)
Kendrick, Stuart, S419 (PO-1364), S724 (PO-1725)
Kenton, Nate, S740 (PO-942)
Kerashvili, Vakhtang, S797 (PO-1553)
Kerbert, Annarein, S338 (PO-1684), S347 (PO-1045)
Kersey, Kathryn, S489 (PO-1289)
Keskin, Hülya, S640 (PO-1353)
Kessler, Linda, S393 (PO-793)
Keun, Hector, S245 (OS-1145)
Kew Yoon, Seung, S460 (PO-186), S488 (PO-1275)
Khac, Eric Nguyen, S201 (LBO-2631)
Khakoo, Salim, S796 (PO-1508)
Khalilova, Fidan, S691 (PO-2392)
Khamri, Wafa, S208 (OS-638), S224 (OS-1946)
Khamseh, Ava, S248 (OS-387)
Khan, Mushtaq, S796 (PO-1533)
Kheloufi, Lyes, S355 (PO-2194)
Khonelidze, Irma, S773 (PO-1691)
Khorsandi, Shirin Elizabeth, S503 (PO-1771)
Kieling, Carlos, S442 (PO-2761)
Ki, Han Seul, S721 (PO-1340)
Kij, Agnieszka, S342 (PO-2833), S417 (PO-899)
Killmer, Saskia, S245 (OS-1145)
Kim, Adam, S317 (PO-1541)
Kim, Beom Kyung, S717 (PO-676)
Kim, Bo Hyun, S479 (PO-409)
Kim, Byung Seok, S743 (PO-1270)
Kim, Chang Wook, S743 (PO-1270)
Kim, Dae Jin, S614 (PO-787), S615 (PO-851)
Kim, Donghee, S532 (PO-33)
Kim, Dong Joon, S332 (PO-2547)
Kim, Dong-Kyu, S263 (OS-768)
Kim, Doohyun, S701 (PO-1450), S701 (PO-1451)
Kim, Do Young, S717 (PO-676)
Kim, Gi-Ae, S550 (PO-1880)
Kim, Hwi Young, S286 (OS-1892)
Kim, Hyoung Su, S743 (PO-1270)
Kim, Hyung Joon, S757 (PO-2429)
Kim, In Hee, S743 (PO-1270)
Kim, Irene, S496 (PO-2812)
Kim, Jae Wha, S265 (OS-2450)
Kim, Janice, S476 (PO-982)
Kim, Ji Hoon, S720 (PO-1115), S743 (PO-1270)
Kim, Ji Hyun, S332 (PO-2547)
Kim, Jin-Wook, S713 (PO-266)
Kim, Jung Kuk, S417 (PO-855), S614 (PO-787), S615 (PO-851)
Kim, Kang Mo, S721 (PO-1385)
Kim, Kilyoung, S296 (LBP-2886), S624 (PO-2287), S628 (PO-2329)
kim, Kyung-ah, S305 (PO-1947)
Kim, Kyung Mo, S199 (GS-2283)
Kim, Misook, S288 (OS-691)
Kim, Moon Young, S327 (PO-984), S332 (PO-2547), S721 (PO-1340), S743 (PO-1270)
Kim, Sam, S446 (PO-216), S447 (PO-240), S448 (PO-846), S725 (PO-1789)
Kim, Sang Geon, S619 (PO-1819)
Kim, Sang Gyune, S238 (OS-1101)
Kim, Seung Up, S286 (OS-1892), S686 (PO-1809), S717 (PO-676)
Kim, Sumi, S713 (PO-266)
Kim, Sungeun, S619 (PO-1819)
Kim, Tae Hyung, S720 (PO-1115)
Kim, Tae Suk, S332 (PO-2547)
Kimura, Hirokazu, S689 (PO-2090)
Kim, Won, S259 (OS-1592), S567 (PO-1020), S743 (PO-1270), S757 (PO-2422)
Kim, Won-Ki, S619 (PO-1819)
Kim, Wonkyung, S500 (PO-920), S528 (PO-895)
Kim, Yohan, S417 (PO-855)
Kim, Yoon Jun, S286 (OS-1892), S288 (OS-691), S757 (PO-2429)
Kim, Young Don, S332 (PO-2547)
Kim, Young Hoon, S614 (PO-787)
Kim, Young Seok, S238 (OS-1101)
Kim, Yun Jin, S675 (PO-2689)
Kim, Yun Soo, S743 (PO-1270)
Kinast, Volker, S705 (PO-1950)
King, Dominic, S435 (PO-1790)
King, Mauricio Larrarte, S271 (OS-1954)
Kiraithe, Muthamia M., S454 (PO-1983)
Kirby, John, S420 (PO-1578)
Kirchner, Theresa, S423 (PO-60), S464 (PO-841), S473 (PO-2821)
Kirchner, Varvara, S472 (PO-2121)
Kirstein, Martha M., S236 (OS-498)
Kith, Óscar Brochado, S783 (PO-881)
Kitrinos, Katie, S744 (PO-1286)
Kiyici, Murat, S472 (PO-2001)
Kjærgaard, Maria, S207 (OS-1726), S321 (PO-2331)
Kjaer, Mette, S257 (OS-1556), S561 (PO-756), S576 (PO-1575), S609 (PO-230)
Kjems, Lise, S279 (OS-1554), S683 (PO-1641), S684 (PO-1665), S687 (PO-1811), S688 (PO-1833), S688 (PO-1843)
Kleemann, Robert, S564 (PO-916)
Kleiner, David E., S593 (PO-1504)
Kleinjans, Moritz, S405 (PO-1558)
Klein, Samuel, S564 (PO-916)
Klinker, Hartwig, S778 (PO-52), S791 (PO-51)
Kloosterhuis, Niels, S591 (PO-1150), S691 (PO-2204)
Klopp, Alexandre, S736 (PO-655)
Klucher, Kevin, S523 (PO-1856)
Kluwe, Johannes, S351 (PO-1701)
Knappe, Olivia, S528 (PO-1357)
Knecht, Gaby, S771 (PO-1029)
Knegendorf, Leonard, S703 (PO-1907)
Knegt, Robert De, S664 (PO-2039), S718 (PO-915), S733 (PO-80)
Knight, James, S317 (PO-1563)
Knolle, Percy, S446 (PO-147)
Knolle, Percy A., S262 (OS-584)
Knop, Stefan, S636 (PO-2386)
Knox, Jennifer, S508 (PO-2742)
Knox, Steven J., S736 (PO-482)
Knuchel-Legendre, Nathalie, S202 (LBO-2647)
Koay, Tsin Shue, S321 (PO-2185)
Koball, Sebastian, S194 (GS-1997), S209 (OS-2060)
Koch, Philipp-Sebastian, S393 (PO-793)
Koch, Sandra, S236 (OS-498)
Kockerling, David, S354 (PO-1998)
Koc, Ozge, S549 (PO-1865)
Kodela, Elisavet, S235 (OS-213)
Ko, Dong-hyun, S263 (OS-768)
Koehorst, Martijn, S591 (PO-1150)
Koek, Ger, S554 (PO-2673), S581 (PO-1895)
Koestler, Devin, S489 (PO-1289)
Köhler, Daniel, S506 (PO-2227)
Kohli, Anita, S297 (LBP-2907), S410 (PO-985), S424 (PO-210), S561 (PO-756), S567 (PO-1001), S578 (PO-1689), S613 (PO-757), S616 (PO-981), S617 (PO-1082)
Kohli, Rohit, S471 (PO-1773)
Ko, KL, S773 (PO-1871)
Ko, Ko, S532 (PO-19)
Koksal, Aydin, S671 (PO-2288)
Koller, Tomáš, S547 (PO-1693)
Kolligs, Frank, S244 (OS-777)
Komolmit, Piyawat, S719 (PO-1000)
Komori, Atsumasa, S425 (PO-376)
Komuta, Mina, S477 (PO-1207), S509 (PO-2839)
Kondili, Loreta, S652 (PO-1374), S654 (PO-1480), S767 (PO-694), S792 (PO-81)
Kong, Bo, S529 (PO-1606)
Kong, Fei, S795 (PO-987)
Kong, Kristine, S315 (PO-1099)
König, Daniel, S681 (PO-1244)
Königshofer, Philipp, S362 (PO-309)
Königsrainer, Alfred, S246 (OS-1399)
Konobrocka, Katarzyna, S509 (PO-2839)
Kontogianni, Meropi, S350 (PO-1471)
Koonen, Debby, S591 (PO-1150)
Koot, Bart, S547 (PO-1526)
Kootstra, Neeltje, S705 (PO-1980), S728 (PO-1982)
Koppe, Christiane, S278 (OS-1396)
Körber, Nina, S446 (PO-147)
Kordis, Manja, S667 (PO-2093)
Korenaga, Keiko, S646 (PO-539)
Korenaga, Masaaki, S646 (PO-539)
Kornek, Miroslaw, S476 (PO-246)
Kornyejev, Dmytro, S725 (PO-1789)
Kosari, Kambiz, S496 (PO-2812)
Koskinas, John, S511 (PO-2920)
Kostadinova, Radina, S604 (PO-2210)

- Koster, Mirjam, S591 (PO-1150), S691 (PO-2204)
- Kotha, Sreelakshmi, S214 (OS-1266), S441 (PO-2719)
- Kotlinowski, Jerzy, S417 (PO-899), S587 (PO-195)
- Kotski, Sylvain, S238 (OS-1704)
- Kotsoros, Barbara, S640 (PO-1221)
- Kounis, Ilias, S482 (PO-750), S717 (PO-813)
- Kouroufexi, Andri, S657 (PO-1624)
- Koustenis, Kanellos, S544 (PO-1334)
- Koustousi, Christina, S204 (LBO-2765), S360 (PO-2867)
- Koutsopoulos, Olga, S196 (GS-2069)
- Kowalik, Marta Anna, S627 (PO-2312)
- Kowalski, Rose, S281 (OS-595)
- Kowdley, Kris, S265 (OS-1746), S424 (PO-210), S433 (PO-1644), S578 (PO-1689), S690 (PO-2120)
- Kowdley, Kris V., S387 (PO-2938)
- Ko, Young Eun, S265 (OS-2450)
- Kozbial, Karin, S681 (PO-1244), S683 (PO-1500)
- Koziel, Joanna, S417 (PO-899), S587 (PO-195)
- Kozlov, Oleksandr, S385 (PO-2655)
- Kozlov, Sergii, S385 (PO-2655)
- Krabb, Eva, S800 (PO-2191)
- Kraczik, Jenny, S522 (PO-1745)
- Kraft, Anke, S454 (PO-2154), S456 (PO-2339)
- Krag, Aleksander, S207 (OS-1726), S307 (PO-48), S313 (PO-487), S321 (PO-2331), S677 (PO-323)
- Kraglund, Frederik, S482 (PO-707)
- Krajden, Mel, S782 (PO-862), S789 (PO-2708)
- Kramer, Fritz, S531 (PO-2627)
- Kramer, Jan, S763 (PO-68), S764 (PO-131)
- Kranidioti, Hariklia, S737 (PO-715)
- Krassenburg, Lisette, S798 (PO-1962)
- Krause, Jenny, S522 (PO-1745)
- Krause, Linda, S506 (PO-2227)
- Krawczyk, Marcin, S337 (PO-1222), S432 (PO-1574), S476 (PO-246), S547 (PO-1667)
- Kremer, Andreas E., S193 (GS-1213), S227 (OS-1088), S429 (PO-1294)
- Kremer, Anna, S450 (PO-1333)
- Kreter, Bruce, S770 (PO-983)
- Kreuels, Benno, S670 (PO-2131)
- Krey, Thomas, S282 (OS-1062)
- Krishan Dhiman, Radha, S360 (PO-2832)
- Krishnakumar, Arathi, S592 (PO-1235)
- Kriss, Stephanie, S801 (PO-2240)
- Kristian Aagaard, Niels, S344 (PO-342), S384 (PO-2529)
- Kristian Muff Aagaard, Niels, S209 (OS-2060)
- Kristiansen, Viggo Bjerregaard, S593 (PO-1407)
- Kroll, Claudia, S430 (PO-1418)
- Kronsten, Victoria, S220 (OS-1167)
- Kruk, Beata, S432 (PO-1574)
- Krupinski, John, S529 (PO-1606)
- Krzikalla, Daria, S451 (PO-1472)
- Krzysztof, Simon, S347 (PO-974)
- Ksiazek, Elea, S469 (PO-1459)
- Kuballa, Lilith, S351 (PO-1701)
- Kübra Dindar Demiray, Emine, S472 (PO-2001)
- Kuchta, Alison, S732 (PO-2637)
- Kuchuloria, Tinatin, S274 (OS-551), S643 (PO-504)
- Kucykowicz, Stephanie, S451 (PO-1460)
- Kudo, Masatoshi, S243 (OS-295)
- Kühn, Jens-Peter, S535 (PO-566)
- Kuipers, Folkert, S457 (PO-279), S591 (PO-1150), S688 (PO-1843)
- Kuiper, Adrian, S446 (PO-216)
- Kul Jung, Young, S345 (PO-714)
- Kulkarni, Anand, S438 (PO-2280)
- Kultgen, Steven G., S281 (OS-595)
- Kumar, Anupa, S548 (PO-1747)
- Kumar, Anupam, S330 (PO-2313)
- Kumar, Ashish, S632 (PO-1696)
- Kumar, Guresh, S380 (PO-2136), S406 (PO-2010)
- Kumari, Anupama, S340 (PO-2213), S406 (PO-2010)
- Kumari Gara, Sirisha, S383 (PO-2305)
- Kumar Jagdish, Rakesh, S371 (PO-1151)
- Kumar, Mandhir, S632 (PO-1696)
- Kumar, Manoj, S239 (OS-2686), S378 (PO-1705), S380 (PO-2136), S381 (PO-2294), S635 (PO-2319)
- Kumar Nidamarthy, Prasanna, S534 (PO-534)
- Kumar, Pavitra, S603 (PO-2186)
- Kumar, Rahul, S194 (GS-1997), S209 (OS-2060), S765 (PO-453)
- Kumar, Ravi, S349 (PO-1165)
- Kumar, Renuka, S290 (OS-2299)
- Kumar Sarin, Shiv, S210 (OS-2142), S371 (PO-1151), S378 (PO-1705), S378 (PO-1987), S380 (PO-2136), S381 (PO-2238), S381 (PO-2294), S438 (PO-2280)
- Kum, Dieudonné B., S744 (PO-1386)
- Kummen, Martin, S421 (PO-2285)
- Kung-Hao, Liang, S718 (PO-947)
- Kunihiko, Tsuji, S239 (OS-2686)
- Kunta, Jeevan, S281 (OS-595)
- Kuo, Alexander, S361 (PO-2951), S496 (PO-2812)
- Kuo-Liang, Wei, S718 (PO-947)
- Kuo, Yong-Fang, S465 (PO-922)
- Kurisu, Akemi, S532 (PO-19)
- Kurnaz, Canan, S351 (PO-1701)
- Kuromatsu, Ryoko, S243 (OS-295)
- Kurtz, Ira, S327 (PO-968)
- Kus, Edyta, S587 (PO-195)
- Kusters, Meeike, S547 (PO-1526)
- Kusumoto, Shigeru, S715 (PO-529)
- Kütting, Fabian, S236 (OS-498)
- Kutz, Alexander, S628 (PO-2377)
- Kuypers, Dirk, S475 (PO-2910)
- Kwanten, Wilhelmus, S252 (OS-571)
- Kwon, Hyunjoo, S417 (PO-855), S614 (PO-787), S615 (PO-851)
- Kwon, Jung Hyun, S743 (PO-1270)
- Kwo, Paul Yien, S736 (PO-482)
- Kyprianou, Evi, S657 (PO-1624)
- Kyriazidou, Anastasia, S737 (PO-715)
- Kyu Kang, Min, S550 (PO-1904)
- Kyu Lee, Soon, S488 (PO-1275)
- Kyun Na, Seong, S305 (PO-1947)
- Labenz, Christian, S259 (OS-1592), S556 (PO-167)
- Labгаа, Ismail, S521 (PO-1420)
- Laborante, Antonio, S769 (PO-951)
- Labreuche, Julien, S201 (LBO-2631)
- Labrune, Philippe, S202 (LBO-2647)
- Lacaille, Florence, S193 (GS-1213), S684 (PO-1665)
- Laccabue, Diletta, S767 (PO-694)
- Lachaux, Alain, S687 (PO-1811)
- Lachenmayer, Anja, S495 (PO-2799)
- Lachiondo-Ortega, Sofia, S243 (OS-1948), S301 (PO-1185), S320 (PO-2043), S502 (PO-1752), S612 (PO-627), S624 (PO-2192)
- Lackner, Carolin, S318 (PO-1651), S592 (PO-1369)
- Lacombe, Benoît, S698 (PO-700)
- Lacombe, Jean-Marc, S191 (GS-1065)
- Lacombe, Karine, S253 (OS-612), S536 (PO-614), S790 (PO-2836)
- La, Danie, S455 (PO-2307)
- Lada, Oliver, S769 (PO-955)
- Lada, Olivier, S766 (PO-649)
- Ladelund, Steen, S257 (OS-1556), S576 (PO-1575), S609 (PO-230), S610 (PO-231)
- Ladero, Iraia, S243 (OS-1948)
- Laffers, Lukas, S547 (PO-1693)
- Lafuente-Barquero, Juan, S240 (OS-179)
- Lagrou, Katrien, S475 (PO-2910)
- Laguna de la Vera, Anna-Lena, S332 (PO-2358)
- Lai, Ching Lung, S289 (OS-1430)
- Lai, Michelle, S659 (PO-1862), S672 (PO-2387)
- Lai, Ming-Wei, S758 (PO-2619)
- Lainka, Elke, S683 (PO-1641)
- Laithier, Véronique, S242 (OS-906)
- Lai, Yu-Chiang, S342 (PO-2851)
- Lake, John, S686 (PO-1809)
- Lakkas, Lampros, S204 (LBO-2765), S360 (PO-2867)
- Lak Lee, Hang, S402 (PO-2695)
- Lalanne, Claudine, S423 (PO-60)
- Lalazar, Gadi, S603 (PO-2161)
- Laleman, Wim, S252 (OS-571), S307 (PO-48)
- Lalezari, Jacob, S736 (PO-482)
- Lalor, Patricia, S393 (PO-938)
- Lam, Angela M., S281 (OS-595), S760 (PO-2822), S761 (PO-2823)
- Lambert Tergast, Tammo, S370 (PO-1146)

Author Index

- Lamblin, Géraldine, S647 (PO-785), S793 (PO-468)
- Lam, Brian, S395 (PO-1505), S592 (PO-1235), S655 (PO-1551)
- Lam, Elina, S327 (PO-1161)
- Lamle, Sophie, S615 (PO-889)
- Lam, Marnix, S245 (OS-972)
- Lammers, Willem J., S387 (PO-2938)
- Lammert, Frank, S337 (PO-1222), S432 (PO-1574), S661 (PO-1903), S677 (PO-323)
- Lamolone, Florence, S509 (PO-2839)
- Lamoury, Francois, S768 (PO-908)
- Lampertico, Pietro, S286 (OS-1892), S294 (LBP-2730), S353 (PO-1767), S492 (PO-2364), S521 (PO-1351), S524 (PO-2401), S637 (PO-2936), S713 (PO-408), S722 (PO-1519), S746 (PO-1448), S747 (PO-1661), S756 (PO-2395), S782 (PO-697), S782 (PO-717), S784 (PO-921), S786 (PO-1542)
- Lam, Simon, S686 (PO-1758)
- La Mura, Vincenzo, S216 (OS-1544)
- Lancaster, Graeme, S622 (PO-1992)
- Landis, Charles, S424 (PO-210), S780 (PO-666)
- Lange, Christian M., S448 (PO-262)
- Langer, Mona-May, S448 (PO-262)
- Langholm, Lasse, S633 (PO-1899)
- Lang, Julia, S454 (PO-1983)
- Langley, Joanne, S714 (PO-420)
- Lang, Tobias, S800 (PO-2191)
- Lang, Wensheng, S531 (PO-2627)
- Lanzillotta, Marco, S229 (OS-1728)
- Laouenan, Cedric, S555 (PO-2692)
- Lapidus, Nathanaël, S253 (OS-612), S536 (PO-614)
- Lapitz, Ainhoa, S634 (PO-2184)
- Laquerriere, Patrice, S247 (OS-2190)
- Lara, Magdalena, S674 (PO-2596)
- Larger, Etienne, S555 (PO-2692)
- Larkin, James, S224 (OS-1946)
- Laroyenne, Alexia, S252 (OS-571)
- Larrey, Dominique, S292 (OS-728), S793 (PO-468), S798 (PO-2020)
- Larrubia, Juan Ramón, S447 (PO-235), S735 (PO-430)
- Larrue, Hélène, S252 (OS-571), S277 (OS-1172)
- Larsen, Steen, S593 (PO-1407)
- Larsson, Simon B., S284 (OS-2864)
- Lasanta, Grisell Ortiz, S627 (PO-2297)
- Laschinger, Melanie, S262 (OS-584)
- Latasa, Maria U., S301 (PO-1185)
- Latib, Mushida Binte Abdul, S450 (PO-1333), S453 (PO-1649)
- Latournerie, Marianne, S461 (PO-351), S462 (PO-353), S469 (PO-1459)
- Lattanzi, Barbara, S353 (PO-1767), S466 (PO-935)
- Latysheva, Inga, S673 (PO-2586)
- Lau, Cathrine, S316 (PO-1375)
- Laurent, Alexis, S518 (PO-1209)
- Laurent, Denis, S289 (OS-865)
- Laurenzano, John, S382 (PO-2298)
- Lauzon, Marie, S496 (PO-2812)
- Lavery, Gareth, S342 (PO-2851)
- Law, Amy, S424 (PO-254), S434 (PO-1664), S566 (PO-980), S577 (PO-1588)
- Lawitz, Eric, S575 (PO-1568), S579 (PO-1714), S613 (PO-757), S618 (PO-1198), S627 (PO-2297)
- Lawlor, Deborah, S273 (OS-183)
- Law, Matthew, S515 (PO-767)
- Law, Ngai Moh, S765 (PO-453)
- Layton, Michelle, S272 (OS-1756)
- Lazar, Stefan, S291 (OS-2717)
- Lazarus, Jeffrey, S646 (PO-640), S661 (PO-1936), S662 (PO-1990), S663 (PO-2032), S665 (PO-2059), S667 (PO-2093), S669 (PO-2108), S675 (PO-2861), S765 (PO-525), S771 (PO-1186)
- Lazcano, Ana Lopez, S319 (PO-1932)
- Lazo, Mariana, S199 (GS-2309)
- Leal, Cassia Regina Guedes, S495 (PO-2799)
- Leandro, Gioacchino, S215 (OS-1864)
- Le Bail, Brigitte, S583 (PO-1981)
- Lebiedzińska-Arciszewska, Magdalena, S432 (PO-1574)
- Lebossé, Fanny, S350 (PO-1549), S352 (PO-1730)
- Lechel, André, S498 (PO-196)
- Lechler, Christian, S498 (PO-336)
- Lech, Maciej, S417 (PO-899)
- Leclercq, Isabelle, S458 (PO-1356), S477 (PO-1207), S572 (PO-1217), S588 (PO-470)
- Leclercq, Isabelle A., S582 (PO-1927)
- Lee, Amy C.H., S281 (OS-595), S761 (PO-2823)
- Lee, BYUNG SEOK, S743 (PO-1270)
- Lee, Chee Leng, S739 (PO-853)
- Lee, Chien-Nan, S758 (PO-2619)
- Lee, Dahhay, S479 (PO-409)
- Lee, Danbi, S721 (PO-1385)
- Lee, Donghyeon, S288 (OS-691), S567 (PO-1020)
- Lee, Han Ah, S286 (OS-1892)
- Lee, Han Chu, S721 (PO-1385)
- Lee, Hannah, S403 (PO-418)
- Lee, Hye Won, S717 (PO-676)
- Lee, Hyung-Chul, S286 (OS-1892)
- Lee, HYUN WOONG, S743 (PO-1270)
- Lee, I-Cheng, S523 (PO-1801)
- Lee, Jae Seung, S717 (PO-676)
- Lee, Jenny, S255 (OS-243), S259 (OS-1592), S564 (PO-919), S568 (PO-1056)
- Lee, Jeong-Hoon, S743 (PO-1270)
- Lee, Jeonghoon, S286 (OS-1892), S288 (OS-691), S294 (LBP-2580)
- Lee, Jonathan, S611 (PO-393)
- Lee, Jong Soo, S417 (PO-855), S615 (PO-851)
- Lee, Jong Suk, S417 (PO-855), S614 (PO-787), S615 (PO-851)
- Lee, Kwan Sik, S757 (PO-2422)
- Lee, Kyoung-Jin, S611 (PO-393)
- Lee, Mei-Hsuan, S715 (PO-460), S725 (PO-1788)
- Leeming, Diana, S313 (PO-487), S362 (PO-309), S363 (PO-310), S564 (PO-919), S568 (PO-1056), S573 (PO-1336), S633 (PO-1899)
- Leeming, Diana Julie, S255 (OS-243)
- Lee, Minjong, S332 (PO-2547)
- Lee, Myoung Seok, S259 (OS-1592)
- Lee, Pei-Chang, S483 (PO-1090), S518 (PO-1142)
- Lee, Peter, S476 (PO-982)
- Leerapun, Apinya, S203 (LBO-2764), S731 (PO-2575)
- Lee, Rheun-Chuan, S523 (PO-1801)
- Lee, Sae Hwan, S743 (PO-1270)
- Lee, Samuel, S315 (PO-1099)
- Lee, Sang Gil, S619 (PO-1819)
- Lee, Sang Hyun, S417 (PO-855), S615 (PO-851)
- Lee, Seon Myeong, S614 (PO-787), S615 (PO-851)
- Lee, Seung-chul, S263 (OS-768)
- Lee, Sunjae, S222 (OS-2044), S406 (PO-1763)
- Lee, Young-Sun, S345 (PO-714), S720 (PO-1115)
- Lee, Yun Bin, S286 (OS-1892), S288 (OS-691)
- Lee, Yu Rim, S717 (PO-676)
- Lefort, Agnes, S691 (PO-2324)
- Legal, Victor, S648 (PO-821)
- Legrand, Anne-Flore, S698 (PO-700), S703 (PO-1711)
- Legros, Ludivine, S201 (LBO-2631)
- Leidal, Kenneth, S254 (OS-1611), S602 (PO-2123)
- Leite, Jean Michel Rocha Sampaio, S408 (PO-301)
- Leithead, Joanna, S235 (OS-213)
- Leitner, Isabella, S542 (PO-1205)
- Leiva, Magdalena, S591 (PO-1037)
- Lei, Yu, S531 (PO-2793)
- Lei, Ziyang, S283 (OS-2482)
- Le, Kha, S741 (PO-1004)
- Leleu, Henri, S769 (PO-955)
- Lelli, Filippo, S356 (PO-2608)
- Lemaigre, Frédéric, S509 (PO-2839)
- Lemaître, Elise, S206 (OS-1619)
- Lemaître, Magali, S766 (PO-649)
- Lemmers, Arnaud, S385 (PO-2621)
- Lemoine, Maud, S354 (PO-1998)
- Lempp, Florian, S282 (OS-1742), S698 (PO-626)
- Lenoir, Veronique, S604 (PO-2276)
- Lens, Sabela, S231 (OS-1299), S252 (OS-571), S640 (PO-1193), S699 (PO-820), S746 (PO-1449), S749 (PO-1791), S751 (PO-1841), S786 (PO-1415), S795 (PO-1307)
- Lenzen, Henrike, S227 (OS-1088)
- Lenzi, Marco, S428 (PO-1017)
- Lenz, Oliver, S289 (OS-1430)
- Leo, Carlin, S508 (PO-2787)

- Leonel, Thais, S431 (PO-1484),
 S499 (PO-541), S699 (PO-820),
 S732 (PO-2637)
 Leone, Maurizio, S769 (PO-951)
 Leone, Valentina, S262 (OS-584)
 Leong, Jennifer, S780 (PO-666)
 Leoni, Simona, S533 (PO-441)
 Leow, Wei Qiang, S241 (OS-699),
 S499 (PO-541)
 Le, Phuc, S567 (PO-1001)
 Lepida, Antonia, S327 (PO-1161)
 Le, Quang, S254 (OS-1611), S602 (PO-2123)
 Lerosey, Lea, S469 (PO-1459)
 Lesch, Miklos, S655 (PO-1572)
 Le-seyec, Jacques, S307 (PO-2888)
 Leslie, Jack, S263 (OS-1028)
 Lesmana, Laurentius A., S438 (PO-2280)
 Lestavel, Sophie, S608 (PO-2858),
 S608 (PO-2883)
 Le, Tiep, S312 (PO-442)
 Letouzé, Eric, S242 (OS-906), S499 (PO-541)
 Lett, Martin, S449 (PO-896)
 Leuchtenberger, Corinna, S752 (PO-2089),
 S754 (PO-2243)
 Leung, Daniel Hao Bin, S199 (GS-2283)
 Levacher, Anita, S696 (PO-526)
 Levi, Ana, S596 (PO-1753)
 Levina, Nataliia, S673 (PO-2586)
 Levrero, Massimo, S350 (PO-1549),
 S574 (PO-1453), S701 (PO-1450),
 S701 (PO-1451), S713 (PO-408)
 Levy, Cynthia, S193 (GS-1213),
 S227 (OS-1088), S424 (PO-210),
 S433 (PO-1644), S434 (PO-1748),
 S437 (PO-2230), S686 (PO-1809)
 Lewin, Maite, S482 (PO-750)
 Lewinska, Monika, S240 (OS-179)
 Lewis, Heather, S314 (PO-607),
 S354 (PO-1998)
 Lewis, Matthew, S490 (PO-2070)
 Lheureux, Oliver, S209 (OS-2060)
 Lheurex, Oliver, S194 (GS-1997)
 Li Adams, Huyen, S207 (OS-2158)
 Liang, Chen, S709 (PO-218)
 Liang, Mingkai, S372 (PO-1152)
 Liang, Po-Cheng, S780 (PO-666)
 Liang, Yan, S268 (OS-931)
 Liang, Yunxiao, S368 (PO-1094)
 Liang, Yupu, S603 (PO-2161)
 Lian, Jia, S368 (PO-1094)
 Lian, Jianqi, S795 (PO-987)
 Liao, Jingyuan, S368 (PO-1094)
 Liao, Weijia, S479 (PO-250), S531 (PO-1887)
 Liaw, Yun-Fan, S749 (PO-1781)
 Li, Cheng, S795 (PO-987)
 Lichtner, Miriam, S704 (PO-1928)
 Li, Chuan-xing, S510 (PO-2919)
 Li, Chunming, S731 (PO-2575)
 Lickei, Helena, S454 (PO-2154),
 S456 (PO-2339)
 Li, Dawei, S779 (PO-404)
 Li, Dong, S731 (PO-2575)
 Li, Dongliang, S795 (PO-987)
 Lie Berntsen, Natalie, S233 (OS-2656)
 Lieu, Hsiao, S410 (PO-985),
 S429 (PO-1074), S616 (PO-981),
 S617 (PO-1082)
 Li, Fan, S358 (PO-2683), S386 (PO-2685)
 Li, Fenxiang, S359 (PO-2688)
 Li, Gang, S538 (PO-719), S541 (PO-1030)
 Ligat, Gaëtan, S695 (PO-175)
 Ligocka, Joanna, S476 (PO-246)
 Li, Guangming, S740 (PO-990),
 S795 (PO-987)
 Li, Guanlin, S268 (OS-931)
 Li, Guojun, S759 (PO-2738)
 Liguori, Antonio, S253 (OS-635)
 Li, Guozhong, S727 (PO-1876)
 Li, Hai, S629 (PO-1091)
 Li, Hongjiang, S368 (PO-1094)
 Li, Jia, S368 (PO-1094), S372 (PO-1152),
 S629 (PO-1091), S759 (PO-2738)
 Li, Jiabin, S759 (PO-2738)
 Li, Jian, S748 (PO-1775)
 Li, Jia-Wei, S629 (PO-1047)
 Li, Jie, S453 (PO-1653)
 Li, Jing-Mao, S483 (PO-1147),
 S709 (PO-1844)
 Li, Jingzhi, S772 (PO-1397)
 Li, Jun, S629 (PO-1091)
 Li, Ka Kit, S676 (PO-2872)
 Li, Lei, S629 (PO-1091), S762 (PO-2853)
 Li, Li, S284 (OS-654), S629 (PO-1091),
 S716 (PO-665), S725 (PO-1789)
 Li, Lu, S396 (PO-1579), S723 (PO-1605)
 Lima, Natalia, S249 (OS-1355),
 S391 (PO-479)
 Lim, Andy, S471 (PO-1971)
 Lim, Chetana, S518 (PO-1209)
 Li, Mei, S758 (PO-2735), S759 (PO-2759)
 Li, Mengmeng, S368 (PO-1094)
 Li, Mengyu, S368 (PO-1094)
 Li, Ming, S772 (PO-1397)
 Li, Minghui, S629 (PO-1091)
 Li, Mingyang, S478 (PO-1346)
 Lim, Seng-Gee, S700 (PO-861)
 Lim, Tien Huey, S289 (OS-1430),
 S731 (PO-2575)
 Li, Musong, S629 (PO-1091)
 Lim, Wei Jin, S676 (PO-2872)
 Lim, Young-Suk, S286 (OS-1892),
 S287 (OS-44), S721 (PO-1385),
 S731 (PO-2575), S738 (PO-824),
 S755 (PO-2338), S756 (PO-2395),
 S757 (PO-2422), S757 (PO-2429)
 Lin, Chun-yen, S755 (PO-2338),
 S788 (PO-2008)
 Linde Mak, Anne, S585 (PO-2485)
 Lindén, Daniel, S263 (OS-1028)
 Lindh, Magnus, S284 (OS-2864)
 Lindor, Keith D., S387 (PO-2938),
 S425 (PO-376)
 Lindqvist, Catarina, S269 (OS-1627)
 Lindström, Erik, S223 (OS-1847),
 S597 (PO-1849)
 Lindvig, Katrine Prier, S321 (PO-2331)
 Lin, Gaoyang, S368 (PO-1094)
 Lingdi, Liu, S723 (PO-1605)
 Ling, Lei, S410 (PO-985), S429 (PO-1074),
 S616 (PO-981), S617 (PO-1082)
 Ling Macrina Lam, Wai, S219 (OS-2754)
 Lingohr-Smith, Melissa, S424 (PO-254)
 Lin, Hsin-Che, S715 (PO-460)
 Lin, Huapeng, S268 (OS-931)
 Lin, Jay, S424 (PO-254)
 Lin, Kai, S740 (PO-942)
 Lin, MInghua, S759 (PO-2738)
 Lin, Shanshan, S650 (PO-1330)
 Lin Tan, Jin, S524 (PO-2075)
 Lin, Tse-i, S741 (PO-1004)
 Lin, WeiQi, S613 (PO-668), S618 (PO-1198)
 Lin, Yu-Shuang, S718 (PO-947)
 Liotta, Francesco, S506 (PO-2375)
 Lioudmila, Bogatyreva, S661 (PO-1903)
 Li, Peng, S681 (PO-1108)
 Li, Pengfei, S281 (OS-1024)
 Li, Ping, S629 (PO-1091)
 Lipka, Daniel, S754 (PO-2243)
 Lippens, Saskia, S450 (PO-1333)
 Li, Qiang, S726 (PO-1810), S742 (PO-1109)
 Li, Qin, S709 (PO-218)
 Li, Ruidong, S287 (OS-2225),
 S720 (PO-1309)
 Li, Shen, S212 (OS-1491)
 Li, Shiwen, S727 (PO-1876)
 Li, Shuang, S368 (PO-1094), S629 (PO-1091)
 Lisman, Ton, S343 (PO-187),
 S374 (PO-1249), S376 (PO-1316)
 Li, Tinghong, S629 (PO-1091)
 Little, Derek, S427 (PO-860)
 Littler, Peter, S493 (PO-2687)
 Liu, Aimin, S368 (PO-1094)
 Liu, Bin, S748 (PO-1699)
 Liu, Boya, S281 (OS-595)
 Liu, Chang'en, S368 (PO-1094)
 Liu, Chao, S359 (PO-2688), S629 (PO-1091)
 Liu, Cheng, S744 (PO-1386)
 Liu, Chuan, S359 (PO-2688),
 S368 (PO-1094), S629 (PO-1091),
 S650 (PO-1330)
 Liu, Chun-Jen, S758 (PO-2619),
 S761 (PO-2844)
 Liu, Dengxiang, S359 (PO-2688),
 S629 (PO-1091)
 Liu, Feng, S400 (PO-1857)
 Liu, Fuquan, S680 (PO-996),
 S681 (PO-1108)
 Liu, Geoffrey, S508 (PO-2742)
 Liu, Huabao, S709 (PO-218)
 Liu, Huan, S629 (PO-1091)
 Liu, Hui, S680 (PO-996), S681 (PO-1108)
 Liu, Jessica, S715 (PO-460),
 S725 (PO-1788)
 Liu, Jiangyuan, S334 (PO-134)
 Liu, Jianxin, S359 (PO-2688)
 Liu, Jianyong, S523 (PO-1883)
 Liu, Jiaye, S281 (OS-1024)
 Liu, JyanWei, S741 (PO-1004)
 Liu, Kevin, S773 (PO-1871)
 Liu, Kun, S562 (PO-769)
 Liu, Liangang, S392 (PO-733)
 Liu, Ping, S772 (PO-1397)

Author Index

- Liu, Tian, S523 (PO-1883)
Liu, Wen-yue, S541 (PO-1030),
S569 (PO-1106)
Liu, Xiangyu, S433 (PO-1644)
Liu, Xiaoli, S506 (PO-2601), S525 (PO-2666)
Liu, Xiaoguo, S742 (PO-1109)
Liu, Xing, S359 (PO-2688)
Liu, Yang, S199 (GS-2283)
Liu, Yanmin, S762 (PO-2853)
Liu, Yen-Chun, S747 (PO-1628),
S749 (PO-1781), S788 (PO-2008)
Liu, Yixin, S758 (PO-2735), S759 (PO-2759)
Liu, Yunhui, S299 (PO-559)
Liu, Zhenbei, S368 (PO-1094)
Liu, Zhu, S772 (PO-1397)
Livingstone, Callum, S292 (OS-1390)
Livingston, Sherry, S581 (PO-1826)
Li, Wang, S523 (PO-1883)
Li, Wei, S740 (PO-990)
Li, Wenhao, S536 (PO-630)
Liowski, Timur, S473 (PO-2211)
Li, Xiaodong, S620 (PO-1908),
S621 (PO-1961), S703 (PO-1917)
Li, Xiaoguo, S359 (PO-2688),
S372 (PO-1152)
Li, Xiao-Kang, S231 (OS-687)
Li, Xinyan, S726 (PO-1810), S742 (PO-1109)
Li, Xitang, S300 (PO-712)
Li, Xue, S359 (PO-2688)
Li, Xue Mei, S758 (PO-2735),
S759 (PO-2759)
Li, Xun, S510 (PO-2919)
Li, Yang, S198 (GS-1645), S281 (OS-1024)
Li, Yaping, S758 (PO-2735),
S759 (PO-2759)
Li, Yunlong, S281 (OS-1024)
Li, Zhi-Qin, S740 (PO-990)
Li, Zhong-bin, S300 (PO-679)
Llaneras, Jordi, S663 (PO-2014)
Llarch, Neus, S639 (PO-511),
S640 (PO-1193), S641 (PO-1525)
Lleo, Ana, S387 (PO-2938)
Lleshi, Ermira, S232 (OS-943)
Lligoña, Anna, S319 (PO-1932)
Llop, Elba, S252 (OS-571), S269 (OS-1769),
S277 (OS-1172), S307 (PO-48),
S694 (PO-2902)
Llop, Elva, S781 (PO-689)
Llorens-Revull, Meritxell, S802 (PO-2295)
Llovet, Josep M., S240 (OS-615),
S241 (OS-699), S499 (PO-541),
S521 (PO-1420)
Llovet, Laura Patricia, S193 (GS-1213)
Lluch, Paloma, S335 (PO-698),
S335 (PO-709)
Lobo-Vega, Rebeca, S802 (PO-2295)
Locarnini, Stephen, S283 (OS-2826),
S289 (OS-1430), S739 (PO-853),
S744 (PO-1286)
Locatelli, Maelle, S695 (PO-258)
Lodge, Peter, S473 (PO-2211)
Loeffler, Juergen, S615 (PO-889)
Loeffler, Markus, S246 (OS-1399)
Loffredo-Verde, Eva, S753 (PO-2106)
Loglio, Alessandro, S713 (PO-408),
S722 (PO-1519), S746 (PO-1448),
S747 (PO-1661)
Lohse, Ansgar, S230 (OS-2782),
S408 (PO-629), S430 (PO-1418),
S451 (PO-1472), S702 (PO-1707)
Lohse, Ansgar W., S193 (GS-1213),
S351 (PO-1701), S423 (PO-60),
S473 (PO-2211), S506 (PO-2227),
S522 (PO-1745)
Lollivier, Julien, S206 (OS-1619)
Lomas, David, S677 (PO-323)
Lombardi, Rosa, S601 (PO-2055),
S785 (PO-1247), S786 (PO-1542)
Lombay, Bela, S655 (PO-1572)
Londoño, Maria Carlota, S788 (PO-1919)
Longerich, Thomas, S278 (OS-1396)
Longo, Francesco, S769 (PO-951)
Longo, Miriam, S600 (PO-1986),
S600 (PO-2033), S601 (PO-2055)
Long, Qing-Hua, S709 (PO-218)
Lomba, Rohan, S577 (PO-1648)
Lomba, Rohit, S201 (LBO-2592),
S254 (OS-1611), S265 (OS-1746),
S267 (OS-681), S294 (LBP-2580),
S429 (PO-1074), S561 (PO-756),
S577 (PO-1648), S578 (PO-1689),
S579 (PO-1714), S613 (PO-757),
S617 (PO-1112), S618 (PO-1314),
S625 (PO-2290), S627 (PO-2297)
Loomes, Kathleen, S688 (PO-1833)
Loosen, Sven H., S517 (PO-1046)
Lopez, David, S401 (PO-2415)
López-Gómez, Marta, S747 (PO-1661)
Lopez, Hugo, S319 (PO-1932)
López-Larrubia, Pilar, S250 (OS-1414)
López-Manzaneda, Sergio, S694 (PO-2770)
Lopez, Martin, S752 (PO-2089)
Lopez, Miguel, S391 (PO-479)
López, Miguel, S591 (PO-1037)
Lopez, Patricia, S615 (PO-889)
Lopez-Santamaria, Manuel,
S690 (PO-2090)
Lopez, Sonia Alonso, S239 (OS-2686)
López-Vicario, Cristina, S325 (PO-552)
Lopitz Otsoa, Fernando, S564 (PO-916)
Lorbeer, Roberto, S535 (PO-566)
Lorca, Rebeca, S516 (PO-1010)
Lord, Janet, S342 (PO-2851)
Lori, Giulia, S606 (PO-2411)
Loriot, Axelle, S509 (PO-2839)
Lorz, Georgina, S249 (OS-901)
Losa-Garcia, Juan E., S788 (PO-1919)
Losic, Bojan, S240 (OS-615)
Loste, Maria Teresa Arias, S255 (OS-2337)
Loste, María Teresa Arias, S269 (OS-1769)
Lotteau, Vincent, S698 (PO-700)
Lotte Gluud, Lise, S307 (PO-48),
S384 (PO-2529)
Loudianos, Georgios, S683 (PO-1522)
Louisa, Ruhl, S473 (PO-2821)
Louis, Junien Jean, S268 (OS-1034),
S268 (OS-1044)
Louis, Tanya, S649 (PO-1035)
Loukachov, Vladimir, S705 (PO-1980),
S728 (PO-1982)
Loureiro, Dimitri, S708 (PO-2684)
Loustaud-Ratti, Veronique, S647 (PO-785),
S793 (PO-468)
Louvet, Alexandre, S201 (LBO-2631),
S206 (OS-1619), S312 (PO-433)
Louyot, Marie, S574 (PO-1453)
Löve, Arthur, S670 (PO-2127)
Lovendoski, James, S314 (PO-607)
Löve, Thorvardur J., S670 (PO-2127)
Lovis, Christian, S548 (PO-1772)
Low, Vyechi, S440 (PO-2657)
Lozano, Elisa, S631 (PO-1668)
Lozano, Juanjo, S207 (OS-2028),
S334 (PO-624)
Lubel, John, S358 (PO-2683),
S386 (PO-2685)
Luber, Andrew, S290 (OS-2478)
Luca, Angelo, S216 (OS-1544)
Lucantoni, Federico, S401 (PO-1935),
S595 (PO-1626)
Lucena, Ana, S255 (OS-2337),
S584 (PO-2369)
Lu, Chenggang, S198 (GS-1645)
Luciani, Alain, S518 (PO-1209)
Lucidi, Valerio, S327 (PO-1161)
Lucifora, Julie, S698 (PO-700),
S702 (PO-1688), S703 (PO-1711),
S752 (PO-2089), S754 (PO-2243)
Luciw, Michael, S272 (OS-1756)
Lüdde, Tom, S339 (PO-2098)
Ludovica Fracanzani, Anna, S540 (PO-831),
S786 (PO-1542)
Ludwig, Joerg, S246 (OS-1399)
Luedde, Tom, S278 (OS-1396),
S517 (PO-1046), S528 (PO-1357),
S530 (PO-1615)
Luetgehetmann, Marc, S351 (PO-1701)
Lu, Fei, S510 (PO-2919)
Lu, Haonan, S490 (PO-2070)
Lui, Chung Yan Grace, S285 (OS-900)
Lui, Eric, S214 (OS-1266)
Luisa Gonzalez Dieguez, Maria,
S516 (PO-1010)
Luis Calleja, Jose, S584 (PO-2369)
Luis Calleja, José, S277 (OS-1172)
Luis Calleja Panero, José, S307 (PO-48),
S537 (PO-685)
Luis Mundi, Jose, S307 (PO-48)
Luis, Tellez, S216 (OS-1544), S252 (OS-571),
S347 (PO-1045), S694 (PO-2902)
Luiz dos Santos, Jorge, S442 (PO-2761)
Lujambio, Amaia, S502 (PO-1752)
Lu, Junyu, S368 (PO-1094)
Lukacs-Kornek, Veronika, S476 (PO-246)
Lukasic, Agnes, S263 (OS-1028)
Lu, Lin, S368 (PO-1094)
Lu, Min, S623 (PO-2163)
Lu, Ming, S629 (PO-1091)
Lun, Aaron, S230 (OS-1171)
Luna, Joseph, S603 (PO-2161)
Lundin, Pal, S223 (OS-1847),
S597 (PO-1849)

- Lundin, Rebecca, S673 (PO-2586)
Luo, Fei, S588 (PO-475)
Luo, Shanshan, S753 (PO-2106)
Luo, Xiaoping, S714 (PO-415)
Luo, Xiucui, S738 (PO-797)
Luo, Xuefeng, S384 (PO-2572)
Luo, Xufeng, S706 (PO-2105)
Luo, Yang, S510 (PO-2919)
Luo, Yi, S395 (PO-1505), S587 (PO-283), S592 (PO-1235)
Lupberger, Joachim, S196 (GS-2069), S212 (OS-1491), S247 (OS-2190), S392 (PO-692)
Lupsor-Platon, Monica, S259 (OS-1592)
Lu, Rui, S758 (PO-2735), S759 (PO-2759)
Lu, Shelly C., S564 (PO-916)
Lu, Sheng-Nan, S715 (PO-460), S725 (PO-1788), S747 (PO-1628)
Lutgehetmann, Marc, S702 (PO-1631), S702 (PO-1707)
Lüttgau, Sandra, S753 (PO-2106)
Lutz, Katrin, S745 (PO-1419)
Lutz, Philipp, S351 (PO-1670)
Luukkonen, Panu, S260 (OS-2362), S605 (PO-2322)
Luu, Michael, S496 (PO-2812)
Luus, Lia, S623 (PO-2163)
Lu, WEI, S523 (PO-1883), S709 (PO-218)
Lu, Xiaomin, S433 (PO-1644)
Luzano, Jonathan, S305 (PO-2122)
Luz Martinez-Chantar, Maria, S391 (PO-479)
Luz Martínez-Chantar, María, S301 (PO-1185), S389 (PO-477), S502 (PO-1752)
Lv, Cheng, S359 (PO-2688)
Lv, Jiayu, S523 (PO-1883)
Lv, Min-Zhi, S541 (PO-1030)
Lv, Muhan, S368 (PO-1094)
Lyberopoulou, Angeliki, S422 (PO-2681)
Lynch, Kate, S418 (PO-1026)
Lytyyak, Ellina, S193 (GS-1213), S226 (OS-894), S227 (OS-1088), S228 (OS-1586)
Maalej, Nadia Hachicha, S643 (PO-425)
Ma, Ann, S311 (PO-345), S319 (PO-1932)
Maan, Raoel, S798 (PO-1962)
Maasoumy, Benjamin, S370 (PO-1146), S423 (PO-60), S456 (PO-2339), S707 (PO-2293)
Mabe, Jon, S320 (PO-2043)
Mabrouk, Mai, S636 (PO-2476)
Macchi, Chiara, S600 (PO-2033)
MacConell, Leigh, S439 (PO-2327)
MacDougall, Louise, S470 (PO-1523), S493 (PO-2687)
Macé, Aurélien, S768 (PO-908)
Macedo, Guilherme, S296 (LBP-2891), S440 (PO-2701), S443 (PO-2801), S445 (PO-2887), S445 (PO-2898), S628 (PO-818)
Machluf, Nathalie, S714 (PO-420)
Macias, Rocio IR, S634 (PO-2184)
MacIsaac, Michael, S775 (PO-2048)
Mack, Cara, S683 (PO-1641), S688 (PO-1833)
Mackenzie, Andrew, S559 (PO-580)
Mackesy-Amiti, Mary-Ellen, S768 (PO-745)
MacKey, William, S318 (PO-1623), S319 (PO-1654)
Macmaster, Stephanie, S248 (OS-387)
Macnaughtan, Jane, S329 (PO-1585), S347 (PO-1045)
MacNicholas, Ross, S493 (PO-2612)
Macpherson, Iain, S292 (OS-1390)
Maddrey, Willis, S593 (PO-1504)
Madejón, Antonio, S746 (PO-1449)
Ma, Deqiang, S629 (PO-1091)
Madley-Dowd, Paul, S273 (OS-183)
Madsbad, Sten, S593 (PO-1407)
Madsen, Lone, S316 (PO-1375)
Madsen, Martin Rønn, S509 (PO-2828)
Maeda, Miho, S241 (OS-699), S499 (PO-541), S521 (PO-1420)
Maeglin, John, S571 (PO-1202)
Magaz, Marta, S216 (OS-1544), S277 (OS-1172), S694 (PO-2902)
Maggi, Daniela, S799 (PO-2138)
Maggioni, Marco, S261 (OS-297), S600 (PO-1986)
Maggiore, Giuseppe, S193 (GS-1213), S683 (PO-1522)
Maggi, Paolo, S656 (PO-1593)
Magini, Giulia, S514 (PO-591)
Maglott-Roth, Anne, S695 (PO-175)
Magnanensi, Jeremy, S586 (PO-2739)
Magnúsdóttir, Stefánía, S457 (PO-279)
Magnusson, Maria, S339 (PO-1787)
Magowan, Colin, S290 (OS-2478)
Magro, Bianca, S513 (PO-574)
Mahadevan, Sangeetha, S401 (PO-2415)
Mahadeva, Sanjiv, S259 (OS-1592), S569 (PO-1106)
Ma, Haiyan, S731 (PO-2575)
Mahajan, Ujjwal M., S389 (PO-410)
Mahamed, Deeqa, S446 (PO-216), S447 (PO-240), S448 (PO-846)
Mahubani, Krishna, S233 (OS-2656)
Maheshwari, Deepanshu, S330 (PO-2313)
Mahfouz, Amel, S293 (OS-2306)
Mahgoub, Sara, S467 (PO-1168)
Mahmud, Nadim, S463 (PO-364)
Ma, Hong, S795 (PO-987)
Ma, Hong-Lei, S538 (PO-719), S541 (PO-1030)
Maibach, Rudolf, S690 (PO-2090)
Maida, Valeria, S356 (PO-2608)
Maiello, Evaristo, S769 (PO-951)
Maieron, Andreas, S798 (PO-2020)
Maily, Laurent, S196 (GS-2069), S247 (OS-2190), S780 (PO-602)
Maimone, Sergio, S353 (PO-1767)
Mainar, Jose M. Arbones, S337 (PO-1643)
Maini, Alexander, S452 (PO-1598)
Maini, Mala, S231 (OS-1299)
Maini, Mala K., S451 (PO-1460)
Mainz, Dagmar, S661 (PO-1903)
Maira, Giovanni Di, S606 (PO-2411)
Maiwall, Rakhi, S210 (OS-2142), S330 (PO-2313), S340 (PO-2213)
Major, Marian, S768 (PO-745)
Major, Xavier, S786 (PO-1415), S795 (PO-1307)
Ma, Julie, S736 (PO-482)
Majumdar, Avik, S358 (PO-2683), S386 (PO-2685)
Makara, Michael, S655 (PO-1572)
Makino, Kenta, S415 (PO-2531)
Mak, Lung Yi Loey, S773 (PO-1871)
Ma, Kuai, S231 (OS-687)
Malagnino, Vincenzo, S728 (PO-1996)
Malaspina, Gemma, S601 (PO-2055)
Maleux, Geert, S244 (OS-777)
Malhotra, Deepa, S314 (PO-832), S538 (PO-819), S539 (PO-825)
Malik, Abdullah, S386 (PO-2788)
Malik, Adnan, S322 (OS-2389)
Malik, Astha, S225 (OS-2274), S422 (PO-2388), S686 (PO-1758)
Malik, Fariha, S673 (PO-2586)
Malik, Muhammad, S322 (PO-2389)
Malinn, Brian, S659 (PO-1862), S672 (PO-2387)
Malkov, Vlad, S720 (PO-1309)
Mallet, Vincent, S194 (GS-1587), S438 (PO-2259)
Mallewa, Jane, S670 (PO-2131)
Mallm, Jan-Philipp, S262 (OS-584)
Malobela, Agnes, S768 (PO-908)
Mamonova, Nina, S291 (OS-2717), S294 (LBP-2730)
Manas, Derek, S386 (PO-2788), S493 (PO-2687)
Mancebo, Antonio, S746 (PO-1449)
Manchon, Pauline, S555 (PO-2692)
Mancina, Rosellina Margherita, S261 (OS-297)
Mancuso, Gaia, S229 (OS-1728)
Mandel, Erin, S659 (PO-1817)
Mandorfer, Mattias, S201 (LBO-2592), S213 (OS-925), S252 (OS-571), S270 (OS-507), S362 (PO-309), S363 (PO-310), S364 (PO-532), S365 (PO-560), S374 (PO-1249), S376 (PO-1316), S377 (PO-1613), S383 (PO-2403), S521 (PO-1312), S645 (PO-533), S677 (PO-323), S681 (PO-1243)
Manea, Ioana, S477 (PO-1119)
Manesis, Emmanouil, S737 (PO-715)
Mangia, Alessandra, S654 (PO-1426), S764 (PO-388), S769 (PO-951), S770 (PO-983)
Manicardi, Nicolò, S334 (PO-624)
Manichon, Anne-Frederique, S518 (PO-1209), S520 (PO-1263)
Mani, Ilianna, S328 (PO-1501), S350 (PO-1471)
Mani, Nagraj, S281 (OS-595)
Manmadhan, Saumya, S498 (PO-336)

Author Index

- Mannaerts, Inge, S527 (PO-375), S527 (PO-608)
- Mannini, Antonella, S505 (PO-1969)
- Mann, Jelena, S614 (PO-838)
- Manns, Michael P., S193 (GS-1213), S423 (PO-60), S433 (PO-1644)
- Manohar, Rohan, S393 (PO-938)
- Manolakopoulos, Spiliios, S286 (OS-1892), S544 (PO-1334), S737 (PO-715), S747 (PO-1661)
- Manon-Jensen, Tina, S573 (PO-1336)
- Manousou, Pinelopi, S309 (PO-94), S537 (PO-711), S540 (PO-950), S558 (PO-565)
- Man, Robert De, S718 (PO-915), S733 (PO-80), S798 (PO-1962)
- Mansbach, Hank, S627 (PO-2297)
- Manso, Andre, S475 (PO-2890)
- Mansouri, Abdel, S708 (PO-2684)
- Mansour, Sohaib, S385 (PO-2621)
- Mantero, Sara, S478 (PO-1422)
- Manzano-Nunez, Fatima, S509 (PO-2839)
- Manzhalii, Elina, S385 (PO-2655)
- Mao, Fuji, S629 (PO-1091)
- Mao, John, S735 (PO-397), S748 (PO-1775)
- Mao, Qing, S795 (PO-987)
- Mao, Tin, S476 (PO-982)
- Mao, Xiaorong, S795 (PO-987)
- Marafioti, Teresa, S245 (OS-1145), S448 (PO-718)
- Maramis, Christos, S665 (PO-2059)
- Marañon, Patricia, S591 (PO-1037)
- Marasco, Giovanni, S787 (PO-1561)
- Marcellin, Fabienne, S292 (OS-728), S662 (PO-1990), S663 (PO-2032)
- Marcellin, Patrick, S284 (OS-654), S287 (OS-2225), S725 (PO-1789)
- Marcellusi, Andrea, S652 (PO-1374), S792 (PO-81)
- Marchesi, Julian, S220 (OS-1167), S245 (OS-1145)
- Marcos-Fosch, Cristina, S651 (PO-1341), S746 (PO-1449)
- Marcos, Miguel, S389 (PO-477), S391 (PO-479)
- Marcotte, Suzanne, S640 (PO-1221)
- Marculescu, Rodrig, S362 (PO-309), S364 (PO-532)
- Mardinoglu, Adil, S222 (OS-2044)
- Margalit, Maya, S627 (PO-2297)
- Marget, Matthias, S454 (PO-1983)
- Margetts, Jane, S493 (PO-2687)
- Margotti, Marzia, S767 (PO-694)
- Marhenke, Silke, S248 (OS-334), S249 (OS-901)
- Maria Banales, Jesus, S223 (OS-1847), S564 (PO-916), S574 (PO-1518)
- Maria Battezzati, Pier, S387 (PO-2938)
- Maria, Guardascione, S307 (PO-48)
- Maria Ierardi, Anna, S524 (PO-2401)
- María Ortiz, Ana, S354 (PO-1930)
- María Palazon, Jose, S307 (PO-48)
- Mariappan, Lavanya, S493 (PO-2687)
- Marie Peron, Jean, S487 (PO-1153)
- Marignani, Massimo, S704 (PO-1928)
- Marijnissen, Camiel, S428 (PO-872)
- Marinelli, Sara, S514 (PO-591)
- Marinescu, Stefan, S281 (OS-1021)
- Marin, Jose, S547 (PO-1667), S624 (PO-2192), S631 (PO-1668), S634 (PO-2184)
- Marino, Mónica, S346 (PO-864)
- Mariño, Zoe, S271 (OS-1954), S640 (PO-1193), S699 (PO-820), S786 (PO-1415), S795 (PO-1307)
- Marin, Pedro, S329 (PO-2058)
- Marin, Silvia, S243 (OS-1948)
- Marion, Khaldi, S206 (OS-1619)
- Marjot, Thomas, S332 (PO-2609)
- Markby, Jessica, S660 (PO-1877), S666 (PO-2081), S773 (PO-1691)
- Mark, Henry, S669 (PO-2108)
- Mark Torres, John, S305 (PO-2122)
- Marquardt, Jens, S240 (OS-179), S498 (PO-336), S501 (PO-1304)
- Marquardt, Jens U., S521 (PO-1420)
- Marques, Joana Rita, S663 (PO-2014)
- Márquez, Andrea, S199 (GS-2309)
- Marquez, LAURA, S784 (PO-1176)
- Marra, Fabio, S505 (PO-1969), S506 (PO-2375), S606 (PO-2411)
- Marschall, Hanns-Ulrich, S193 (GS-1213)
- Marsden, Justin, S581 (PO-1826)
- Marshall, Aileen, S235 (OS-213), S677 (PO-323)
- Martásek, Pavel, S689 (PO-2040)
- Martel, Dominic, S640 (PO-1221)
- Martel-Laferrrière, Valérie, S640 (PO-1221)
- Martens, Joerg, S473 (PO-2821)
- Martens, Liesbet, S450 (PO-1333), S453 (PO-1649)
- Martin-Bermudo, Franz, S612 (PO-627)
- Martin, Cesar, S301 (PO-1185)
- Martín, Cesar Augusto, S502 (PO-1752), S612 (PO-627)
- Martin, Daniel, S194 (GS-1997), S209 (OS-2060)
- Martin de Carpi, Javier, S271 (OS-1954)
- Martin, Eleonora De, S717 (PO-813)
- Martin, Eric F., S193 (GS-1213)
- Martinez-Alcocer, Ana, S334 (PO-624)
- Martinez, Anthony, S798 (PO-2020)
- Martínez-Arranz, Ibon, S302 (PO-1335), S564 (PO-916), S574 (PO-1518)
- Martinez-Camprecios, Joan, S651 (PO-1341), S788 (PO-1919)
- Martínez-Chantar, María Luz, S243 (OS-1948), S320 (PO-2043), S497 (PO-133), S612 (PO-627), S624 (PO-2192)
- Martinez-Cruz, Luis Alfonso, S320 (PO-2043), S502 (PO-1752), S612 (PO-627)
- Martinez de la Piscina, Idoia, S497 (PO-133)
- Martinez Garcia de la Torre, Raquel A., S401 (PO-2113)
- Martinez-Gili, Laura, S404 (PO-799)
- Martínez-González, Brenda, S802 (PO-2295)
- Martínez, Isidoro, S781 (PO-689)
- Martinez, Javier, S307 (PO-48), S347 (PO-1045)
- Martínez, Javier, S781 (PO-689)
- Martínez, María, S591 (PO-1037)
- Martinez, Maria Guadalupe, S695 (PO-258), S701 (PO-1450)
- Martínez, Paula, S783 (PO-881)
- Martinez, Rita Garcia, S784 (PO-1176)
- Martinez, Sergio Muñoz, S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
- Martínez-Valle, Fernando, S229 (OS-1728)
- Martin-Fernández de Basoa, María Cecilia, S492 (PO-2594)
- Martin, Harry, S227 (OS-1088)
- Martini, Silvia, S234 (OS-116), S353 (PO-1767)
- Martin, Jennifer, S353 (PO-1766)
- Martin- Mateos, Rosa, S269 (OS-1769)
- Martín-Rodríguez, Agustín, S533 (PO-381)
- Martins, Maria, S596 (PO-1753)
- Martin Sprinkart, Alois, S213 (OS-513)
- Martí-Rodrigo, Alberto, S401 (PO-1935)
- Martró, Elisa, S786 (PO-1415), S795 (PO-1307)
- Martyn-St James, MARRISSA, S423 (PO-127)
- Maryam Ghufuran, Shaikh, S388 (PO-89)
- Mary Young, Anna, S245 (OS-1145)
- Marzioni, Marco, S227 (OS-1088), S425 (PO-376)
- Marzouk, Samir, S636 (PO-2476)
- Masarwa, Mohammad, S220 (OS-2854)
- Mascarenhas, Miguel, S296 (LBP-2891), S440 (PO-2701), S443 (PO-2801), S445 (PO-2887), S445 (PO-2898)
- Masclée, Ad, S554 (PO-2673)
- Masi, Gianluca, S521 (PO-1351)
- Maslen, Lynn, S490 (PO-2070)
- Masnou, Helena, S252 (OS-571), S307 (PO-48)
- Mason, Andrew L., S193 (GS-1213), S228 (OS-1586), S387 (PO-2938), S420 (PO-1822), S435 (PO-1755)
- Mason, Lisa, S464 (PO-594)
- Masoodi, Mojgan, S603 (PO-2186)
- Massari, Marco, S767 (PO-694)
- Masson, Steve, S464 (PO-594)
- Masson, Steven, S235 (OS-213), S301 (PO-1185), S386 (PO-2788), S493 (PO-2687)
- Mastrototaro, Lucia, S589 (PO-716)
- Matano, Alfredo, S656 (PO-1593)
- Matarazzo, Margherita, S683 (PO-1522)
- Matchett, Kylie, S232 (OS-943)
- Mateva, Lyudmila, S609 (PO-230)
- Mathes, Arthur, S393 (PO-793)
- Mathurin, Philippe, S191 (GS-1065), S201 (LBO-2631), S206 (OS-1619), S207 (OS-2028), S253 (OS-612), S536 (PO-614)
- Maticic, Mojca, S667 (PO-2093)
- Matilla, Ana, S243 (OS-295)

- Matje, Douglas, S476 (PO-982)
- Mato, José M., S389 (PO-477), S564 (PO-916), S574 (PO-1518)
- Mato, Jose Maria, S249 (OS-1355)
- Matsuda, Tetsuya, S415 (PO-2531)
- Matsuura, Kentaro, S239 (OS-2686), S715 (PO-529)
- Mattada, Umesh Tharehalli, S498 (PO-196)
- Matter, Matthias, S240 (OS-179)
- Matthews, Philippa, S649 (PO-1158)
- Matt, Kelly, S408 (PO-629)
- Mattsson, Jan, S223 (OS-1847), S597 (PO-1849), S688 (PO-1843)
- Matz-Soja, Madlen, S706 (PO-2135)
- Maud, Michelet, S698 (PO-700), S702 (PO-1688), S703 (PO-1711)
- Maulat, Charlotte, S487 (PO-1153)
- Mauri, Francesco A., S448 (PO-718)
- Mauriz-Barreiro, Maria-Violeta, S545 (PO-1429)
- Mauriz, José Luís, S504 (PO-1949), S505 (PO-1957)
- Maurrer, Lars, S281 (OS-1021)
- Mauss, Stefan, S778 (PO-52), S791 (PO-51)
- Ma, Xiaoli, S736 (PO-482)
- Ma, Xiayi, S214 (OS-1266)
- Maya, Douglas, S342 (PO-2420)
- Mayer, Andrea, S246 (OS-1399)
- Mayerle, Julia, S389 (PO-410)
- Mayers, Douglas, S742 (PO-1240), S743 (PO-1251)
- Ma, Ying, S372 (PO-1152)
- Ma, Yingjie, S795 (PO-987)
- Maynard, Marianne, S574 (PO-1453)
- Mayo, Marlyn J., S193 (GS-1213), S387 (PO-2938), S434 (PO-1748), S686 (PO-1809), S690 (PO-2120)
- Mayo, Rebeca, S564 (PO-916), S574 (PO-1518)
- Mayor, Ugo, S624 (PO-2192)
- May, Stephanie, S508 (PO-2787)
- Ma, Yuk Ting, S246 (OS-1399)
- Ma, Yukting, S303 (PO-1379)
- Ma, Yun, S306 (PO-2178), S503 (PO-1771)
- Ma, Zhongren, S281 (OS-1024)
- Mazumder, Nikhilesh, S382 (PO-2298)
- Mazzaferro, Vincenzo, S240 (OS-615), S241 (OS-699), S448 (PO-718), S521 (PO-1420)
- Mazza, Giuseppe, S596 (PO-1753)
- Mazzarelli, Chiara, S466 (PO-935)
- Mazzella, Giuseppe, S518 (PO-1124)
- Mazzone, Massimiliano, S500 (PO-1118)
- Mazzotta, Alessandro, S525 (PO-2408)
- Mbewe, Maurice, S670 (PO-2131)
- McCain, Misti, S301 (PO-1185), S490 (PO-2070), S493 (PO-2687)
- McCaughan, Geoff, S358 (PO-2683), S386 (PO-2685)
- McClure, Matthew, S741 (PO-1004)
- McConaghy, Lynda, S347 (PO-1045)
- McCulloch, Bill, S617 (PO-1112)
- McCune, Anne, S427 (PO-770)
- McDonald, Circe, S757 (PO-2422)
- McDonald, Lucy, S798 (PO-2020)
- McDougall, Stuart, S692 (PO-2628)
- McElvaney, Noel G., S677 (PO-323)
- McGarry, Lynn, S508 (PO-2787)
- McGilvray, Ian, S508 (PO-2742)
- McGlinchey, Aidan, S256 (OS-538), S579 (PO-1777)
- McKeating, Jane, S752 (PO-2089), S780 (PO-602)
- McKibben, Andrew, S440 (PO-2657)
- McKiernan, Patrick, S687 (PO-1811)
- McLaren, Joscelyne, S273 (OS-199)
- McLaughlin, Megan, S434 (PO-1748)
- McLeod, Euan, S314 (PO-832), S538 (PO-819), S539 (PO-825)
- McMullen, Megan, S316 (PO-1215), S317 (PO-1541)
- McNeil, Michael, S493 (PO-2687)
- McPhail, Mark, S306 (PO-2178)
- McPhail, Mark J. W., S406 (PO-1763)
- McPhail, Mark J.W., S208 (OS-638)
- McPherson, Stuart, S266 (OS-2831), S493 (PO-2687)
- McQuillin, Andrew, S207 (OS-2158)
- McQuitty, Claire, S478 (PO-1422)
- McWherter, Charles, S593 (PO-1504), S596 (PO-1797), S686 (PO-1809), S690 (PO-2120)
- Meador, Vincent, S298 (PO-443)
- Meaux, Virginie LE, S761 (PO-2844)
- Mecci, Jibrán, S790 (PO-2946)
- Medhat, Mohammed, S803 (PO-2320)
- Medina-Caliz, Inmaculada, S302 (PO-1335), S303 (PO-1389)
- Meglić, Jelka, S667 (PO-2093)
- Mehigan, Niamh, S493 (PO-2612)
- Mehraban, Shadi, S296 (LBP-2886)
- Mehrabi, Arianeb, S473 (PO-2211)
- Mehrotra, Aman, S446 (PO-216), S447 (PO-240), S448 (PO-846), S455 (PO-2307)
- Mehta, Gautam, S330 (PO-2147), S347 (PO-1045)
- Mehta, Rajiv, S199 (GS-2283)
- Mehta, Varun, S438 (PO-2280)
- Meikle, Peter, S622 (PO-1992)
- Meiring, James, S670 (PO-2131)
- Meischl, Tobias, S236 (OS-498), S521 (PO-1312)
- Meiser, Philippa, S262 (OS-584)
- Mélanie, Tremblay, S341 (PO-2382)
- Melara, Rebeca, S742 (PO-1240)
- Melekoğlu Elik, Zeynep, S472 (PO-2001)
- Melero, Ignacio, S243 (OS-295)
- Mello, Vivianne, S495 (PO-2799)
- Mells, George, S233 (OS-2656), S404 (PO-799), S420 (PO-1578), S427 (PO-770)
- Melum, Espen, S233 (OS-2656)
- Melvær Giil, Lasse, S432 (PO-1512)
- Ménard, Camille, S698 (PO-700)
- Menconi, Alessio, S606 (PO-2411)
- Méndez-Blanco, Carolina, S504 (PO-1949), S505 (PO-1957)
- Méndez-Sánchez, Nahum, S655 (PO-1551)
- Mendizabal, Manuel, S199 (GS-2309)
- Mendoza, Alan, S476 (PO-982)
- Mendrzyk, Regina, S246 (OS-1399)
- Menetrey, Caroline, S660 (PO-1877)
- Meng, Chenxin, S795 (PO-987)
- Mengers, Jan, S332 (PO-2358)
- Mennini, Francesco Saverio, S652 (PO-1374), S792 (PO-81)
- Menon, Krishna, S321 (PO-2185)
- Mensah, Kofi A, S392 (PO-733)
- Mensel, Birger, S535 (PO-566)
- Mensorio, Mario Massimo, S656 (PO-1593)
- Mercadal, Maria Margaret, S271 (OS-1954)
- Mercado-Gómez, Maria, S243 (OS-1948), S301 (PO-1185), S320 (PO-2043), S502 (PO-1752), S612 (PO-627), S624 (PO-2192)
- Merino, Lucía Ramos, S746 (PO-1449)
- Merle, Philippe, S198 (GS-945), S246 (OS-1674)
- Merle, Uta, S294 (LBP-2730), S607 (PO-2623), S791 (PO-51)
- Merli, Manuela, S353 (PO-1767), S466 (PO-935)
- Meroni, Marica, S600 (PO-1986), S600 (PO-2033), S601 (PO-2055)
- Mertens, Joachim C., S236 (OS-498), S391 (PO-567)
- Merz, Simon, S706 (PO-2105)
- Mesaros, Eugen, S281 (OS-595)
- Mesquita, Marta, S475 (PO-2890)
- Mesropian, Agavni, S241 (OS-699)
- Messina, Vincenzo, S656 (PO-1593)
- Mestre, Anna, S354 (PO-1930)
- Meszáros, Magdalena, S352 (PO-1712), S647 (PO-785)
- Metelli, Flavio, S518 (PO-1124)
- Metreveli, David, S797 (PO-1553)
- Metselaar, Herold, S430 (PO-1428), S431 (PO-1486)
- Meuleman, Philip, S603 (PO-2161)
- Meunier, Lea, S242 (OS-906)
- Meunier, Lucy, S352 (PO-1712), S717 (PO-813)
- Meyer, Markus, S196 (GS-2069), S247 (OS-2190)
- Meyer, Marten, S753 (PO-2106)
- Meyer, Tim, S521 (PO-1420)
- Meynert, Alison, S250 (OS-2934)
- Meza, Beatriz, S663 (PO-2014)
- Miaglia, Clothilde, S350 (PO-1549)
- Miailhes, Patrick, S352 (PO-1730)
- Miao, Yen, S676 (PO-2872)
- Micán, Rafael, S785 (PO-1404)
- Miceli, Francesca, S252 (OS-571)
- Michael, Galambos, S686 (PO-1809)
- Michael, Nagel, S661 (PO-1903)
- Michalak, Agata, S319 (PO-1708)
- Michel, Maurice, S560 (PO-632)
- Michel, Rivoire, S695 (PO-258), S702 (PO-1688), S703 (PO-1711)
- Michieli, Paolo, S217 (OS-874), S231 (OS-687)

Author Index

- Midha, Vandana, S438 (PO-2280)
Midttun, Øyvind, S421 (PO-2285)
Miekus, Katarzyna, S417 (PO-899)
Miele, Luca, S253 (OS-635), S261 (OS-297), S600 (PO-1986), S600 (PO-2033)
Miethke, Alexander, S225 (OS-2274), S422 (PO-2388), S686 (PO-1758)
Miette, Véronique, S257 (OS-555)
Migalni, Sandeep, S666 (PO-2081)
Miguens Blanco, Jesus, S245 (OS-1145), S540 (PO-950)
Miguez, Carlos, S346 (PO-864)
Mihm, Ulrike, S306 (PO-2203)
Mikami, Shigeru, S239 (OS-2686)
Mikesell, Glen, S476 (PO-982)
Mikhail, Nabil, S239 (OS-2686), S636 (PO-2476)
Miksztal, Andy, S618 (PO-1198)
Miletic, Damir, S491 (PO-2181)
Milgrom, Yael, S220 (OS-2854)
Milheiro, Adelaide, S475 (PO-2890)
Milionis, Chalampos, S204 (LBO-2765), S360 (PO-2867)
Milkiewicz, Piotr, S193 (GS-1213), S227 (OS-1088), S423 (PO-60), S432 (PO-1574), S476 (PO-246)
Millán, Laura, S617 (PO-1112)
Millar, Ben, S419 (PO-1364), S420 (PO-1578)
Millares, Daniel Valle, S783 (PO-881)
Mille, Gwenaëlle, S618 (PO-1198)
Miller, Crispin, S508 (PO-2787)
Miller, Julija, S695 (PO-175)
Miller, Michael, S292 (OS-1390)
Millet, Oscar, S249 (OS-1355), S564 (PO-916)
Mill, Pleasantine, S248 (OS-387)
Millwood, Iona, S642 (PO-260)
Milner, Andrew, S766 (PO-637), S775 (PO-2095)
Mimidis, Konstantinos, S737 (PO-715)
Mina, Christos, S657 (PO-1624)
Mincholé, Itziar, S564 (PO-916), S574 (PO-1518)
Minello Franza, Anne, S197 (GS-613), S201 (LBO-2631), S469 (PO-1459)
Miners, Alec, S273 (OS-199)
Mingozzi, Federico, S202 (LBO-2647)
Minguez, Beatriz, S521 (PO-1420)
Minguez, Beatriz, S448 (PO-718)
Ming, Wai-Kit, S650 (PO-1330)
Min Kim, Chang, S488 (PO-1275)
Minoves, Mélanie, S238 (OS-1704)
Minten, Jaak, S194 (GS-1997), S209 (OS-2060)
Miozzo, Monica, S261 (OS-297)
Miquel, Joaquin, S447 (PO-235), S735 (PO-430)
Miquel, Mireia, S345 (PO-835), S746 (PO-1449)
Miquel, Rosa, S235 (OS-213), S318 (PO-1651), S321 (PO-2185)
Miralpeix, Anna, S786 (PO-1415), S795 (PO-1307)
Miravittles, Marc, S677 (PO-323)
Mirella, Fraquelli, S491 (PO-2181)
Mirza, Darius F., S473 (PO-2211)
Mishra, Alita, S544 (PO-1227)
Misner, Dinah, S744 (PO-1386)
Mithieux, Gilles, S531 (PO-2793)
Mittra, Lalita, S210 (OS-2142)
Mittal, Ruchika, S724 (PO-1725)
Mitzner, Steffen, S194 (GS-1997), S209 (OS-2060)
Mix, Carola, S454 (PO-2154), S456 (PO-2339)
Miyata, Tatsunori, S316 (PO-1215)
Moaz, Inas, S803 (PO-2320)
Mocan, Tudor, S476 (PO-246), S495 (PO-2799)
Mochida, Satoshi, S425 (PO-376)
Mocroft, Amanda, S276 (OS-2202)
Moelker, Adriaan, S245 (OS-972)
Moeller, Nora, S703 (PO-1907)
Mogalian, Erik, S733 (PO-43)
Moga, Lucile, S252 (OS-571)
Moghadamrad, Sheida, S221 (OS-1979)
Mogler, Carolin, S393 (PO-793), S498 (PO-336)
Mohamed Ali, Mohamed A., S521 (PO-1420)
Mohamed, Islam, S234 (OS-161)
Mohamed, Sawsan Moniem, S494 (PO-2786)
Mohamed, Sayed Farouk, S784 (PO-975)
Mohiuddin, Sadaf, S768 (PO-908)
Mo, Hongmei, S284 (OS-654), S725 (PO-1789)
Mohta, Srikant, S212 (OS-31), S371 (PO-1151), S378 (PO-1705)
Moigboi, Christiana, S285 (OS-887), S721 (PO-1510)
Moirand, Romain, S312 (PO-433)
Moiseev, Sergey, S789 (PO-2418)
Mo Kim, Kang, S516 (PO-857)
Molcan, Pavol, S547 (PO-1693)
Moldenhauer, Gerhard, S753 (PO-2106)
Molendi-Coste, Olivier, S608 (PO-2858), S608 (PO-2883)
Moles, Anna, S217 (OS-888)
Molina, Elena, S243 (OS-1948)
Molina, Esther, S545 (PO-1429)
Molina, Israel, S664 (PO-2047)
Molina, Juan Carlos Fernández, S674 (PO-2596)
Molina, Laura, S242 (OS-906)
Molinari, Nicolas, S352 (PO-1712)
Molinos-Vicente, Andrea, S680 (PO-891)
Moller, David, S267 (OS-427), S609 (PO-159)
Möller, Hjordis, S764 (PO-131)
Møllerhøj, Mathias, S509 (PO-2828)
Moll, Matthew, S334 (PO-134)
Momburg, Frank, S753 (PO-2106)
Monajemi, Houshang, S585 (PO-2485)
Monbaliu, Diethard, S475 (PO-2910)
Moncsek, Anja, S391 (PO-567)
Monforte, Arnau, S663 (PO-2014)
Monge, Fanny, S395 (PO-1505)
Moniem Mohamed, Sawsan, S497 (PO-2893)
Montabord, Melanie, S528 (PO-1027)
Montalto, Michael, S254 (OS-1611), S433 (PO-1644), S602 (PO-2123)
Montanari, Noe, S716 (PO-665)
Montani, Matteo, S603 (PO-2186)
Montano-Loza, Aldo, S228 (OS-1586)
Montano-Loza, Aldo J., S193 (GS-1213), S226 (OS-894), S227 (OS-1088), S433 (PO-1644)
Monteiro, Benedict, S242 (OS-906)
Montejo Velazquez, Cesar, S533 (PO-445)
Montemagno, Christopher, S582 (PO-1927)
Monte, Maria, S547 (PO-1667)
Monterde, Vanesa Bernal, S337 (PO-1643), S746 (PO-1449)
Montero, Marta, S788 (PO-1919)
Montero, Saul Martinez, S742 (PO-1196)
Montero-Vallejo, Rocío, S342 (PO-2420)
Montes, Pedro, S199 (GS-2309)
Montironi, Carla, S240 (OS-615), S241 (OS-699), S499 (PO-541)
Montoliu, Carmina, S335 (PO-698), S335 (PO-709), S338 (PO-1761)
Montón, Cristina, S335 (PO-698), S335 (PO-709)
Mookerjee, Raj, S194 (GS-1997), S209 (OS-2060)
Mookerjee, Raj, S347 (PO-1045), S349 (PO-1165)
Moon, Andrew, S332 (PO-2609)
Moon, Christina, S716 (PO-665), S725 (PO-1789)
Moore, Chris, S761 (PO-2823)
Mor, Adi, S419 (PO-1311)
Moradpour, Darius, S679 (PO-570)
Moragrega, Ángela B., S401 (PO-1935), S595 (PO-1626)
Morales-Ruiz, Manuel, S218 (OS-1478)
Morcrette, Guillaume, S242 (OS-906)
Moreau, Clemence, S557 (PO-313)
Moreau, Richard, S708 (PO-2684)
Moreno, Virginia, S217 (OS-874)
Moreno, Christophe, S312 (PO-433), S327 (PO-1161), S385 (PO-2621), S792 (PO-153)
Moreno-Garcia, Juan, S271 (OS-1954)
Moreno, José Juan, S746 (PO-1449)
Morgan, Caroline, S347 (PO-1045)
Morgan, Carrie, S194 (GS-1997), S209 (OS-2060)
Morgan, James, S467 (PO-1168)
Morgan, Marsha Y., S207 (OS-2158)
Morillas, Rosa, S746 (PO-1449)
Morland, Bruce, S690 (PO-2090)
Morley, Timothy, S692 (PO-2628), S693 (PO-2697)
Morling, Joanne, S274 (OS-1381), S562 (PO-775)
Mor, Orna, S730 (PO-2366)
Morris, April, S581 (PO-1808)
Morris, Jude, S611 (PO-337)
Morris, Margaret, S264 (OS-1524)

- Morrison, Martine C., S564 (PO-916)
Morrow, Linda, S627 (PO-2297)
Morsica, Giulia, S767 (PO-694)
Mortimore, Gerri, S679 (PO-737)
Moscalu, Iruie, S750 (PO-1837)
Moschouri, Eleni, S679 (PO-570)
Moshtaghi-Svensson, John, S269 (OS-1627)
Mostafavi, Nahid, S225 (OS-706)
Mouillot, Thomas, S469 (PO-1459)
Moulin, Philippe, S574 (PO-1453)
Moulton, Carol-Anne, S508 (PO-2742)
Mountain, Victoria, S254 (OS-1611), S602 (PO-2123)
Mouri, Sarah, S355 (PO-2194), S551 (PO-2002)
Moussa, Sam, S616 (PO-981), S617 (PO-1082)
Moustafa, Ehab F., S803 (PO-2320)
Mozes, Ferenc, S259 (OS-1592)
Mo, Zhishuo, S283 (OS-2482)
Muckenthaler, Martina, S607 (PO-2623)
Mueller, Katrin, S278 (OS-1396)
Mugisha, Jean-Claude, S768 (PO-908)
Muir, Andrew, S433 (PO-1644), S579 (PO-1714)
Mujagic, Zlatan, S554 (PO-2673)
Mukherjee, Sucheta, S742 (PO-1196), S744 (PO-1386)
Mukherjee, Sujit, S208 (OS-638), S354 (PO-1998)
Mukherji, Atish, S695 (PO-175), S780 (PO-602)
Mukund, Amar, S381 (PO-2238)
Mulazzani, Lorenzo, S533 (PO-441)
Mulcahy, Victoria, S233 (OS-2656)
Müller, Christian, S236 (OS-498), S521 (PO-1312)
Muller, Marion, S247 (OS-2190)
Müller, Miryam, S508 (PO-2787)
Müller-Stich, Beat, S262 (OS-584)
Müller, Tobias, S437 (PO-2230), S521 (PO-1420)
Müller-Vahl, Kirsten, S682 (PO-1354)
Muller, Zsofia, S655 (PO-1572)
Müllhaupt, Beat, S792 (PO-153)
Mullish, Benjamin, S354 (PO-1998)
Mullish, Benjamin H., S220 (OS-1167), S537 (PO-711), S540 (PO-950), S558 (PO-565)
Munaganuru, Nagambika, S577 (PO-1648)
Munda, Petra, S681 (PO-1244), S683 (PO-1500)
Mungalpara, Disha, S451 (PO-1472)
Muñoz, Alberto, S346 (PO-864)
Muñoz, Beatriz Mateos, S746 (PO-1449)
Muñoz-Bellvis, Luis, S634 (PO-2184)
Muñoz-Couselo, Eva, S437 (PO-2015)
Muñoz, Francisco Bellido, S779 (PO-578)
Munoz-Garrido, Patricia, S240 (OS-179)
Muñoz-Gomez, Maria Jose, S771 (PO-1186)
Muñoz, María Muñoz, S783 (PO-881)
Muñoz, Mario Mayoral, S783 (PO-881)
Munoz-Martínez, Sergio, S495 (PO-2799)
Munteanu, Mona, S583 (PO-1981)
Mun Wang, Lai, S403 (PO-2790)
Muraro, Daniele, S233 (OS-2656)
Muratori, Luca, S533 (PO-441)
Muratori, Luigi, S423 (PO-60), S428 (PO-1017)
Murphy, Daniel, S508 (PO-2787)
Murray, Peter, S262 (OS-584)
Murray, Sam, S448 (PO-718)
Murya, Mugil, S666 (PO-2081)
Musabaev, Erkin, S642 (PO-424)
Muselli, Marco, S425 (PO-376)
Musteata, Tatiana, S750 (PO-1837)
Muthiah, Mark, S376 (PO-1278)
Muti, Leon, S647 (PO-785), S793 (PO-468)
Muvunyi, Claude, S768 (PO-908)
Myers, Robert, S254 (OS-1611), S257 (OS-555), S265 (OS-1746), S433 (PO-1644), S556 (PO-167), S561 (PO-756), S575 (PO-1568), S578 (PO-1689), S579 (PO-1714), S613 (PO-757)
Mylopoulou, Theodora, S737 (PO-715)
Naamneh, Rabab, S556 (PO-2791)
Nabatchikova, Ekaterina, S789 (PO-2418)
Nabi, Oumarou, S253 (OS-612), S536 (PO-614)
Nacht, Maxime, S572 (PO-1217), S582 (PO-1927)
Nadarevic, Tin, S491 (PO-2181)
Nadeem, Mahum, S322 (PO-2389)
Nader, Fatema, S395 (PO-1505), S592 (PO-1235), S655 (PO-1551), S671 (PO-2152)
Nagasami, Chandrasekaran, S343 (PO-187)
Nagpal, Neha, S735 (PO-397)
Nagy, Anna Nemes, S655 (PO-1572)
Nagy, Laura, S316 (PO-1215), S317 (PO-1541)
Nahass, Ronald, S736 (PO-482)
Nahnsen, Sven, S219 (OS-2754)
Nahon, Pierre, S198 (GS-945), S201 (LBO-2631), S377 (PO-1474), S520 (PO-1263), S646 (PO-640), S675 (PO-2861)
Nakajima, Atsushi, S259 (OS-1592), S267 (OS-681)
Nakamura, Atsushi, S335 (PO-994)
Nakamura, Masanori, S415 (PO-2531)
Na Kim, Mi, S549 (PO-1823)
Nakjang, Sirinitra, S513 (PO-573)
Nam, Hee Chul, S488 (PO-1275)
Namisaki, Tadashi, S425 (PO-376)
Nam, Joon Yeul, S286 (OS-1892), S288 (OS-691)
Nang, Boraneath, S289 (OS-865)
Nangosyah, Julius, S745 (PO-1416)
Nankya, Prossie Lindah, S282 (OS-1062)
Nano, Jana, S535 (PO-566)
Nan, Yuemin, S396 (PO-1579), S723 (PO-1605)
Naoumov, Nikolai V., S615 (PO-889)
Napoleone, Laura, S311 (PO-345), S319 (PO-1932)
Narasimman, Manasa, S227 (OS-1088)
Nardelli, Silvia, S383 (PO-2381)
Narguet, Stephanie, S708 (PO-2684)
Narita, Masashi, S230 (OS-1171)
Narmada, Balakrishnan Chakrapani, S699 (PO-852), S700 (PO-861)
Naseem, Khadija, S322 (PO-2389)
Nasir, Nazrila Hairizan Binti, S660 (PO-1877)
Nasr, Patrik, S251 (OS-293)
Nassal, Michael, S695 (PO-175)
Nassar, Noha, S407 (PO-2363)
Natal Jorge, Renato, S296 (LBP-2891), S440 (PO-2701), S443 (PO-2801), S445 (PO-2887), S445 (PO-2898)
Natarajan, Dipa, S395 (PO-1441), S478 (PO-1422)
Nathalie, Boyer, S708 (PO-2684)
Nathalie, Gault, S197 (GS-613), S555 (PO-2692)
Natha, Macky, S566 (PO-980), S577 (PO-1588)
Nathwani, Rooshi, S354 (PO-1998)
Natsiavas, Pantelis, S665 (PO-2059)
Nattermann, Jacob, S351 (PO-1670)
Naumann, Uwe, S429 (PO-1294)
Nava, Felice Alfonso, S654 (PO-1426)
Navarrete, Cristina, S784 (PO-1176)
Navarro, Alicia, S347 (PO-1045)
Navarro, Daniel, S765 (PO-525)
Navarro, Vincent, S355 (PO-2194)
Navasa, Miguel, S235 (OS-213)
Nawrocki, Andrea, S531 (PO-2627)
Nawrot, Margaux, S608 (PO-2858), S608 (PO-2883)
Nayagam, Jeremy, S227 (OS-1088), S437 (PO-2230)
Nayyar, Dhruv, S214 (OS-1266)
Ndegwa, Nelson, S488 (PO-1164)
Nebbia, Gabriella, S683 (PO-1522)
Nederveen, Aart, S547 (PO-1526), S585 (PO-2485)
Nedoschinsky, Katja, S745 (PO-1416)
Neely, Jaclyn, S241 (OS-699), S243 (OS-295), S499 (PO-541)
Neff, Guy, S200 (GS-2563), S204 (LBO-2800), S297 (LBP-2907), S578 (PO-1689), S614 (PO-849), S616 (PO-981), S617 (PO-1082), S619 (PO-1762), S686 (PO-1809), S690 (PO-2120)
Negi, Preeti, S340 (PO-2213)
Negro, Francesco, S276 (OS-2750), S548 (PO-1772), S646 (PO-640), S675 (PO-2861)
Neilson, Matthew, S508 (PO-2787)
Nelson, David R., S798 (PO-1962)
Nelson, Kristen, S410 (PO-985), S616 (PO-981), S617 (PO-1082)
Nem, Buntho Eun, S289 (OS-865)
Nemesi, Krisztina, S655 (PO-1572)
Nery, Filipe, S277 (OS-1172)

Author Index

- Ness, Erik, S254 (OS-1780), S434 (PO-1664), S439 (PO-2327), S566 (PO-980), S577 (PO-1588)
- Neßling, Michelle, S393 (PO-793)
- Netter, Hans, S739 (PO-853)
- Neubauer, Stefan, S259 (OS-1592), S403 (PO-2790)
- Neuhaus, Katharina, S754 (PO-2243)
- Neumann-Haefelin, Christoph, S281 (OS-1021), S453 (PO-1929), S454 (PO-1983)
- Neumann, Ulf, S517 (PO-1046)
- Nevens, Frederik, S226 (OS-894), S235 (OS-213), S277 (OS-1172), S307 (PO-48), S336 (PO-1051), S387 (PO-2938), S475 (PO-2910), S677 (PO-323), S690 (PO-2120)
- Nevola, Riccardo, S657 (PO-1666)
- Newberry, Elizabeth, S564 (PO-916)
- Newman, Maureen, S298 (PO-443), S311 (PO-302), S312 (PO-442)
- Newsome, Philip N., S257 (OS-1556), S257 (OS-555), S259 (OS-1592), S576 (PO-1575)
- Nezos, Andrianos, S511 (PO-2920)
- NF, Aehling, S194 (GS-1997), S209 (OS-2060)
- Ng, Irene Oi-Lin, S689 (PO-2090)
- Nguyen, Anh, S622 (PO-1992)
- Nguyen, Anh-Hoa, S199 (GS-2283), S757 (PO-2429)
- Nguyen Khac, Eric, S312 (PO-433)
- Nguyen, Mindie, S434 (PO-1664), S566 (PO-980), S577 (PO-1588), S675 (PO-2689), S780 (PO-666)
- Nguyen-Tat, Marc, S661 (PO-1903)
- Nguyen, Tuan, S736 (PO-482)
- Nguyen, Tung, S708 (PO-2474)
- Nhoueng, Sovann, S289 (OS-865)
- Nicholas, Alan, S246 (OS-1674)
- Nicoara-Farcau, Oana, S252 (OS-571), S377 (PO-1474)
- Nicoară-Farcău, Oana, S277 (OS-1172)
- Nicolas, Carine, S793 (PO-468)
- Niederseer, David, S542 (PO-1205), S552 (PO-2328), S570 (PO-1195), S573 (PO-1220)
- Nielsen, Mette Juul, S633 (PO-1899)
- Nie, Shengdan, S620 (PO-1851)
- Niess, Gero, S793 (PO-377), S794 (PO-773)
- Nieto-Romero, Virginia, S680 (PO-891)
- Nieuwdorp, Max, S585 (PO-2485)
- Nie, Yuchun, S700 (PO-1305), S720 (PO-1257), S742 (PO-1196)
- Nigel, Stace, S731 (PO-2575)
- Nijhawan, Sandeep, S199 (GS-2283)
- Nik Mustapha, Nik Raihan, S569 (PO-1106)
- Nikolopoulos, Georgios, S653 (PO-1421), S657 (PO-1624)
- Nikulkina, Elena, S789 (PO-2418)
- Ni, Liyun, S239 (OS-2686), S489 (PO-1289), S770 (PO-983)
- Nilsson, Emma, S227 (OS-1088)
- Ningarhari, Massih, S206 (OS-1619)
- Ning, Qin, S299 (PO-559), S300 (PO-712), S438 (PO-2280), S714 (PO-415)
- Ni, Quanhong, S279 (OS-1554), S683 (PO-1641), S684 (PO-1665), S688 (PO-1833), S688 (PO-1843)
- Nissen, Nicholas, S496 (PO-2812)
- Nitze, Louise, S257 (OS-1556), S576 (PO-1575)
- Niu, Hao, S303 (PO-1389)
- Niu, Junqi, S795 (PO-987)
- Nixon, Colin, S508 (PO-2787)
- Ni, Yen-Hsuan, S758 (PO-2619)
- Ni, Yi, S282 (OS-1742), S698 (PO-626)
- Njouom, Richard, S768 (PO-908)
- Nkongolo, Shirin, S446 (PO-216), S447 (PO-240), S448 (PO-846), S455 (PO-2307)
- Nobes, Jennifer, S292 (OS-1390)
- Nogueira, Lucas Salume Lima, S408 (PO-301)
- Nogueiras, Ruben, S389 (PO-477), S624 (PO-2192)
- Nogueiras, Rubén, S391 (PO-479), S591 (PO-1037)
- Nøhr-Meldgaard, Jacob, S622 (PO-2006)
- Nojima, Toshiaki, S267 (OS-681)
- Nolte-Koch, Friedrich, S262 (OS-584)
- Norder, Helène, S284 (OS-2864)
- Nordmann Winther, Thilde, S231 (OS-1299)
- Noronha Ferreira, Carlos, S307 (PO-48)
- Northall, Ellie, S393 (PO-938)
- North, Matthew, S215 (OS-1864)
- Nörz, Dominik, S351 (PO-1701)
- Not, Anna, S786 (PO-1415)
- Nother, Elizabeth, S777 (PO-2352)
- Noureddin, Mazen, S265 (OS-1746), S314 (PO-832), S361 (PO-2951), S496 (PO-2812), S538 (PO-819), S539 (PO-825), S559 (PO-580), S561 (PO-756), S563 (PO-836), S563 (PO-866), S564 (PO-916), S567 (PO-1001), S574 (PO-1518), S578 (PO-1689)
- Noureddin, Seham, S755 (PO-2269)
- Novak, KATJA, S669 (PO-2108)
- Nováková, Barbora, S689 (PO-2040)
- Novelli, Simone, S349 (PO-1165)
- Novikov, Nikolai, S231 (OS-1299)
- Novoa, Eva, S249 (OS-1355), S389 (PO-477), S391 (PO-479), S591 (PO-1037)
- Nozaki, Akito, S239 (OS-2686)
- Numata, Kazushi, S243 (OS-295)
- Núñez, Alexa, S677 (PO-323)
- Núñez, Maitane, S497 (PO-133)
- Núñez, Susana, S217 (OS-888)
- Nyeong Lee, Kang, S402 (PO-2695)
- Nyhlin, Nils, S227 (OS-1088)
- Oakley, Fiona, S263 (OS-1028)
- O'Beirne, James, S636 (PO-2370)
- Oberhardt, Valerie, S453 (PO-1929)
- Oberkofler, Hannes, S570 (PO-1195)
- Oberti, Frédéric, S198 (GS-945), S201 (LBO-2631), S312 (PO-433), S566 (PO-944)
- Oberti, Giovanna, S785 (PO-1247)
- O'Brien, Alastair, S211 (OS-2779), S328 (PO-1387), S452 (PO-1598)
- Ocama, Ponsiano, S669 (PO-2108)
- Ochoa-Sanchez, Rafael, S341 (PO-2279)
- Odenthal, Margarete, S501 (PO-1629)
- Odin, Joseph, S686 (PO-1809)
- Odoul, Marion, S761 (PO-2844)
- Oellerich, Michael, S464 (PO-841)
- Oettl, Karl, S194 (GS-1997), S209 (OS-2060)
- Oezdirik, Burcin, S521 (PO-1420)
- O'Farrell, Marie, S617 (PO-1112)
- Ofner, Andrea, S389 (PO-410)
- Ogawa, Eiichi, S780 (PO-666)
- Ogawa, Shintaro, S715 (PO-529)
- Ogilvie, Lauren, S742 (PO-1240), S743 (PO-1251)
- Ogiso, Satoshi, S415 (PO-2531)
- Ogle, Laura, S420 (PO-1578)
- Oh, Bora, S500 (PO-920), S528 (PO-895)
- Oh, In-Hwan, S550 (PO-1880)
- Oh, Ji-Hye, S500 (PO-920), S528 (PO-895)
- Ohk Sung, Chang, S500 (PO-920)
- Oh Kweon, Young, S294 (LBP-2580)
- Ohlendorf, Valerie, S707 (PO-2293)
- Ohrenstein, Daniel, S646 (PO-640)
- Oh, Yoo-Jin, S500 (PO-920), S528 (PO-895)
- Ojeda-Pérez, Isabel, S694 (PO-2770)
- Okajima, Akira, S259 (OS-1592)
- Okanoue, Takeshi, S259 (OS-1592), S575 (PO-1568), S579 (PO-1714), S609 (PO-230)
- Okovityi, Sergey, S590 (PO-725)
- Olafsson, Sigurdur, S670 (PO-2127)
- Olague, Cristina, S694 (PO-2770)
- Olando, Massimo, S356 (PO-2608)
- Olartekoetxea, Gaizka Errazti, S497 (PO-133)
- Oldak, Natalia, S193 (GS-1213)
- Olivas, Pol, S252 (OS-571), S694 (PO-2902)
- Oliveira, Brunna, S408 (PO-301)
- Oliveira, Mariana M., S341 (PO-2382)
- Oliveira, Paulo J., S604 (PO-2276)
- Oliveira, Rui, S442 (PO-2761)
- Oliveri, Filippo, S491 (PO-2223), S729 (PO-2261)
- Oliveros, Francisco Hernandez, S689 (PO-2090)
- Öllinger, Rupert, S262 (OS-584), S754 (PO-2243)
- Ollivier-Hourmand, Isabelle, S197 (GS-613)
- Olmo, Javier Fuentes, S337 (PO-1643)
- Olsen, Beth Hærstedt, S593 (PO-1407)
- Olson, Kristin, S425 (PO-344)
- Olveira, Antonio, S781 (PO-689)
- Ones, Tunc, S491 (PO-2223)
- Oneto, Gianfranco, S323 (PO-2704)
- Ong, Elaine, S394 (PO-1125)
- Ong, Janus, S301 (PO-1107), S305 (PO-2122), S597 (PO-1839)
- Ong, Nathalie, S648 (PO-821)

- Onofrio, Fernanda, S193 (GS-1213)
 Onorina, Bruno, S197 (GS-613)
 Ono, Suzane Kioko, S408 (PO-301)
 Ooi, Geraldine, S259 (OS-1592)
 Oosterveer, Maaik, S531 (PO-2793),
 S691 (PO-2204)
 Oo, Ye Htun, S193 (GS-1213),
 S303 (PO-1379)
 Orci, Lorenzo A., S492 (PO-2242)
 Orešič, Matej, S256 (OS-538),
 S579 (PO-1777), S605 (PO-2322)
 Ormeci, Asli Ciftcibasi, S671 (PO-2288)
 Ormeci, Necati, S636 (PO-2476)
 Orozco-Galvez, Olimpia, S229 (OS-1728)
 Orozco, Olimpia, S663 (PO-2014)
 Orrell, Michael, S418 (PO-1026),
 S427 (PO-770)
 Orr, James, S273 (OS-183)
 Orsini, Corinna, S492 (PO-2364),
 S784 (PO-921)
 Ortega-Alonso, Aida, S302 (PO-1335),
 S304 (PO-1406)
 Ortega, Lluisa, S319 (PO-1932)
 Ortega-Ribera, Martí, S317 (PO-1541)
 Ortiz, Pablo, S574 (PO-1518)
 Ortne, Julia, S661 (PO-1903)
 Orts, Lara, S277 (OS-1172), S694 (PO-2902)
 Oruncu, M. Berk, S671 (PO-2288)
 Or, Yat Sun, S740 (PO-942)
 Oshima, Yu, S415 (PO-2531)
 Osinusi, Anu, S239 (OS-2686)
 Osman, Karim, S226 (OS-894)
 Osman, Mohamed, S493 (PO-2612)
 Ossimi, Ashima'a I., S803 (PO-2320)
 Ostadreza, Mahnoosh, S261 (OS-297)
 Ostendorf, Robert, S623 (PO-2099)
 Ostyn, Tessa, S266 (OS-2831),
 S336 (PO-1051)
 Osuji, Immaculeta, S686 (PO-1758)
 O'Sullivan, Margaret, S798 (PO-2020)
 Otero-Sanchez, Lukas, S327 (PO-1161)
 Otsoa, Fernando Lopitz, S249 (OS-1355),
 S502 (PO-1752), S612 (PO-627),
 S624 (PO-2192)
 Ottobrelli, Antonio, S234 (OS-116)
 Ott, Peter, S280 (OS-2590)
 Oudot, Marine, S196 (GS-2069),
 S212 (OS-1491), S247 (OS-2190)
 Oukil, Sarra, S647 (PO-785)
 Ouyang, Lea, S744 (PO-1286)
 Ouzan, Denis, S394 (PO-1069),
 S396 (PO-1580)
 Owino, Collins Oduor, S699 (PO-852)
 Oxtrud, Evelin, S272 (OS-798)
 Ozdogan, Osman Cavit, S671 (PO-2288)
 Ozen, Hasan, S687 (PO-1811)
 Ozercan, Mubin, S549 (PO-1865)
 Ozer Demirtas, Coskun, S491 (PO-2223)
 Ozik, Jonathan, S768 (PO-745)
 Oztumer, Ceyhun, S442 (PO-2724)
- Paar, Margret, S194 (GS-1997),
 S209 (OS-2060)
 Pablo Roblero, Juan, S199 (GS-2309)
- Pacín, Beatriz, S696 (PO-469),
 S706 (PO-2145), S737 (PO-774)
 Pacurar, Daniela, S199 (GS-2283)
 Padaki, Nagaraja Rao, S438 (PO-2280)
 Páez, Antonio, S354 (PO-1930)
 Paff, Melanie, S455 (PO-2173)
 Pagan, Juan Carlos Garcia, S252 (OS-571),
 S277 (OS-1172), S334 (PO-624),
 S694 (PO-2902)
 Pagano, Giulia, S280 (OS-1921),
 S799 (PO-2021)
 Pageaux, Georges-Philippe,
 S201 (LBO-2631), S226 (OS-894),
 S352 (PO-1712), S461 (PO-351),
 S462 (PO-353)
 Page, Emma, S273 (OS-199)
 Page, Kimberly, S768 (PO-745)
 Pahk, Kisoo, S619 (PO-1819)
 Paik, James, S544 (PO-1227),
 S597 (PO-1839)
 Paisant, Anita, S520 (PO-1263)
 Pais, Raluca, S551 (PO-2002)
 Pajak, Agnieszka, S604 (PO-2210)
 Pakala, Ramya, S383 (PO-2305)
 Palaniyappan, Naaventhana,
 S259 (OS-1592)
 Palayew, Adam, S665 (PO-2059),
 S669 (PO-2108)
 Palazón, Asís, S243 (OS-1948),
 S502 (PO-1752)
 Palazzo, Vincenzo, S769 (PO-951)
 Pallett, Laura J., S451 (PO-1460)
 Palma, Elena, S321 (PO-2185)
 Palmer, Anna, S797 (PO-1872)
 Palmer, Jeremy, S266 (OS-2831),
 S420 (PO-1578)
 Palmer, Melissa, S620 (PO-1851)
 Palmisano, Maria, S391 (PO-663),
 S392 (PO-733)
 Palom, Adriana, S437 (PO-2015),
 S664 (PO-2047), S706 (PO-2145),
 S732 (PO-2637), S732 (PO-2834)
 Palomique, Juvelyn, S361 (PO-2951)
 Palomo-Irigoyen, Marta, S497 (PO-133)
 Panagiotou, Georgios, S511 (PO-2920)
 Panarese, Joe, S740 (PO-942)
 Panariello, Adelaide, S466 (PO-935)
 Pandak, William, S309 (PO-117)
 Panday, Priyanka, S383 (PO-2305)
 Pandey, Rajendra, S700 (PO-1305),
 S720 (PO-1257), S742 (PO-1196)
 Pandey, Rishabh, S724 (PO-1725)
 Panero, José Luis Calleja, S269 (OS-1769),
 S286 (OS-1892), S662 (PO-1990),
 S663 (PO-2032), S746 (PO-1449),
 S747 (PO-1661)
 Pang, Phil, S287 (OS-44), S288 (OS-211),
 S733 (PO-43), S738 (PO-824)
 Pang, Xiuqing, S283 (OS-2482)
 Pan, Hongduo, S368 (PO-1094)
 Pan, Jin-Shui, S483 (PO-1147),
 S709 (PO-1844)
 Pan, Mei-Hung, S725 (PO-1788)
 Panning, Marcus, S281 (OS-1021)
- Pan, Qiuwei, S281 (OS-1024),
 S550 (PO-1951)
 Pantaleón Martínez, Claudia, S533 (PO-445)
 Pantea, Victor, S291 (OS-2717)
 Pântea, Victor, S750 (PO-1837)
 Paola Anolli, Maria, S782 (PO-717)
 Paolini, Erika, S600 (PO-1986),
 S600 (PO-2033), S601 (PO-2055)
 Paolo Russo, Francesco, S226 (OS-894),
 S472 (PO-2121)
 Papaluca, Tim, S797 (PO-1872)
 Papangkorn, Kongnara, S624 (PO-2287),
 S628 (PO-2329)
 Papanorn, Kongnara, S296 (LBP-2886)
 Papa, Sophie, S441 (PO-2719)
 Papatheodoridi, Margarita, S544 (PO-1334),
 S737 (PO-715), S747 (PO-1661),
 S749 (PO-1791), S751 (PO-1841)
 Papatheodoridis, George, S255 (OS-243),
 S286 (OS-1892), S544 (PO-1334),
 S564 (PO-919), S568 (PO-1056),
 S737 (PO-715), S747 (PO-1661),
 S749 (PO-1791), S751 (PO-1841)
 Pape, Simon, S423 (PO-60)
 Pappas, Chris, S326 (PO-675)
 Pappas, S. Chris, S208 (OS-845),
 S327 (PO-968)
 Paradis, Valérie, S197 (GS-613),
 S318 (PO-1651), S487 (PO-1153),
 S555 (PO-2692), S572 (PO-1217),
 S708 (PO-2684)
 Paratala, Bhavna, S761 (PO-2823)
 Pardo, Albert, S746 (PO-1449)
 Paredes, Angelo, S410 (PO-985),
 S616 (PO-981), S617 (PO-1082)
 Parente, Marco, S296 (LBP-2891),
 S445 (PO-2887), S445 (PO-2898)
 Parent, Jocelyne, S640 (PO-1221)
 Parent, Romain, S754 (PO-2243)
 Pares, Albert, S193 (GS-1213),
 S226 (OS-894), S387 (PO-2938),
 S425 (PO-376)
 Parés, Albert, S431 (PO-1484)
 Paris, Alejandro Sanz, S337 (PO-1643)
 Park, Chanwoo, S263 (OS-768)
 Park, Dong Jun, S504 (PO-1825)
 Park, Enu Jin, S614 (PO-787)
 Parker, Lee, S273 (OS-199)
 Parker, Richard, S367 (PO-1040),
 S394 (PO-1125), S464 (PO-594)
 Parkes, Julie, S796 (PO-1508)
 Park, Eun Jin, S417 (PO-855), S615 (PO-851)
 Park, James, S736 (PO-482)
 Park, Jang-June, S761 (PO-2823)
 Park, Jiyeon, S263 (OS-768)
 Park, Jung Gil, S743 (PO-1270)
 Park, Jun Yong, S717 (PO-676)
 Park, Kaapjoo, S265 (OS-2450)
 Park, Key-Chung, S550 (PO-1880)
 Park, Somlee, S263 (OS-768)
 Park, Soo Young, S286 (OS-1892),
 S717 (PO-676)
 Parlatti, Lucia, S528 (PO-1027),
 S717 (PO-813)

Author Index

- Paroni, Giulia, S769 (PO-951)
Parruti, Giustino, S704 (PO-1928)
Parveen, Shaheena, S796 (PO-1533)
Pascale, Alina, S482 (PO-750),
S525 (PO-2408)
Pascual, Sonia, S495 (PO-2799)
Pasqualetti, Patrizio, S654 (PO-1426)
Pasquazzi, Caterina, S704 (PO-1928)
Pastore, Mirella, S505 (PO-1969)
Patai, Arpad, S655 (PO-1572)
Patanwala, Imran, S426 (PO-770)
Patel, Anjali, S446 (PO-216), S447 (PO-240),
S448 (PO-846), S455 (PO-2307)
Patel, Keyur, S578 (PO-1689),
S633 (PO-1899), S718 (PO-915)
Patel, Mahesh, S296 (LBP-2886),
S624 (PO-2287), S628 (PO-2329)
Patel, Mehaben, S198 (GS-1645),
S298 (PO-443), S312 (PO-442)
Patel, Poulam, S303 (PO-1379)
Patel, Pratiksha, S670 (PO-2131)
Patel, Preya, S353 (PO-1766),
S470 (PO-1523), S493 (PO-2687)
Patel, Priyanka, S670 (PO-2131)
Patel, Samartha, S460 (PO-212)
Patel, Vaishali, S460 (PO-212)
Patel, Vishal C., S220 (OS-1167),
S222 (OS-2044), S306 (PO-2178),
S330 (PO-2147), S333 (PO-2870),
S406 (PO-1763)
Patel, Yuval, S434 (PO-1664),
S566 (PO-980), S577 (PO-1588)
Paternostro, Rafael, S252 (OS-571),
S270 (OS-507), S362 (PO-309),
S363 (PO-310), S364 (PO-532),
S365 (PO-560), S376 (PO-1316),
S377 (PO-1613), S383 (PO-2403)
Pathak, Vai, S317 (PO-1541)
Pathil, Anita, S306 (PO-2203)
Patil, Rashmee, S204 (LBO-2800),
S567 (PO-1001), S619 (PO-1762)
Patkowski, Waldemar, S476 (PO-246)
Patricia Llovet, Laura, S431 (PO-1484)
Patrizia, Carrieri, S292 (OS-728),
S662 (PO-1990), S663 (PO-2032),
S665 (PO-2059), S669 (PO-2108)
Patten, Daniel, S230 (OS-1171)
Pattrick, Melanie, S536 (PO-630)
Paturel, Alexia, S701 (PO-1450),
S701 (PO-1451)
Patwardhan, Vilas, S193 (GS-1213),
S226 (OS-894)
Paul, Andreas, S473 (PO-2211)
Paul Cervoni, Jean, S197 (GS-613),
S584 (PO-2030)
Paulin Mendoza, Yuly, S373 (PO-1230),
S540 (PO-831)
Paul Reiter, Florian, S389 (PO-410)
Paul, Sudip, S622 (PO-1992)
Paulweber, Bernhard, S570 (PO-1195)
Paupard, Thierry, S201 (LBO-2631)
Pavesi, Marco, S194 (GS-1997),
S209 (OS-2060), S347 (PO-1045)
Pavie, Benjamin, S450 (PO-1333)
Pavlidis, Michael, S255 (OS-243),
S259 (OS-1592), S403 (PO-2790),
S418 (PO-1026), S564 (PO-919),
S568 (PO-1056)
Pavlova, Slava, S207 (OS-2158)
Pavlyuk, Mariya, S202 (LBO-2647)
Pavone, Luigi M., S217 (OS-888)
Pawliszak, Piotr, S634 (PO-2094)
Payawal, Diana, S438 (PO-2280)
Pazgan-Simon, Monika, S347 (PO-974)
Pazmiño, Galo, S199 (GS-2309)
Pearce, Edward, S262 (OS-584),
S450 (PO-1333)
Pearce, Margo, S782 (PO-862),
S789 (PO-2708)
Pečavar, Blaž, S667 (PO-2093)
Pechlivanis, Alexandros, S404 (PO-799)
Pech, Sothy, S289 (OS-865)
Peci, Adriana, S659 (PO-1817)
Peck-Radosavljevic, Markus, S236 (OS-498),
S364 (PO-532), S380 (PO-2162),
S495 (PO-2799)
Pedawi, Aryan, S254 (OS-1611),
S602 (PO-2123)
Pedersen, Julie Steen, S593 (PO-1407)
Pedersen, Mark, S193 (GS-1213)
Pedra, Gabriel, S398 (PO-1589),
S399 (PO-1609)
Pedrana, Alisa, S797 (PO-1872)
Pedro Sousa Ferreira, João, S440 (PO-2701),
S443 (PO-2801), S445 (PO-2887),
S445 (PO-2898)
Peiffer, Kai Hendrik, S332 (PO-2358)
Peiffer, Kai-Henrik, S771 (PO-1029),
S792 (PO-153)
Peixoto, Gabriel, S476 (PO-982)
Pellegata, Alessandro, S478 (PO-1422)
Pellicciari, Roberto, S457 (PO-279)
Pellone, Monica, S668 (PO-2097)
Peltekian, Kevork, S228 (OS-1586)
Pelusi, Serena, S260 (OS-2362),
S261 (OS-297), S642 (PO-251)
Pemberton, David, S775 (PO-2048)
Pembroke, Tom, S494 (PO-2755)
Penaranda, Guillaume, S394 (PO-1069),
S396 (PO-1580)
Peñaranda, Nicolás, S335 (PO-698),
S338 (PO-1761)
Pencek, Richard, S611 (PO-393)
Pendem, Swetha, S401 (PO-2415)
Peng, Cheng-Yuan, S718 (PO-947)
Peng, Chien-Wei, S749 (PO-1781)
Peng, Lijun, S368 (PO-1094)
Peng, Yanzhong, S759 (PO-2738)
Pen, Jérémie Le, S603 (PO-2161)
Pennisi, Grazia, S253 (OS-635),
S540 (PO-831)
Penn, Matthew, S775 (PO-2048)
Penttilä, Anne, S260 (OS-2362)
Peppelenbosch, Maikel, S281 (OS-1024)
Perales, Celia, S802 (PO-2295)
Pera, Teresa Le, S657 (PO-1666)
Pe, Rautou, S318 (PO-1651), S678 (PO-561),
S694 (PO-2902)
Perbellini, Riccardo, S492 (PO-2364),
S722 (PO-1519), S746 (PO-1448),
S782 (PO-697), S782 (PO-717),
S784 (PO-921)
Perdigoto, Rui, S475 (PO-2890)
Perdikis, Konstantinos-Cédric,
S548 (PO-1772)
Perego, Alberto, S492 (PO-2364),
S784 (PO-921)
Pereira, Joana Patrícia Ventura,
S339 (PO-2098)
Pereira-Leal, Jose, S475 (PO-2890)
Pereira, Pedro, S296 (LBP-2891),
S440 (PO-2701), S443 (PO-2801),
S445 (PO-2887), S445 (PO-2898)
Pereira, Sara, S765 (PO-525)
Pereira, Sharon, S501 (PO-1304)
Pereira, Vítor, S677 (PO-323)
Perelló, Christie, S495 (PO-2799)
Perera, Thamara, S467 (PO-1168)
Pérez, Alba, S354 (PO-1930)
Pérez, Alicia Isabel Pascual, S271 (OS-1954)
Perez, Angelina Rodriguez, S674 (PO-2596)
Pérez-del-Pulgar, Sofía, S499 (PO-541),
S699 (PO-820), S732 (PO-2637)
Pérez-Latorre, Leire, S781 (PO-689)
Pérez, María Dolores, S784 (PO-1176)
Pérez, MARIA JOSE, S799 (PO-2021)
Perez, Martina, S311 (PO-345),
S319 (PO-1932)
Perez-Melero, Concepcion, S631 (PO-1668)
Perez, Miguel Lopez, S249 (OS-1355)
Perez-Valdes, Zeus, S303 (PO-1389)
Perez, Valeria, S694 (PO-2902)
Perillo, Pasquale, S657 (PO-1666)
Peritt, David, S453 (PO-1653)
Periyasamy, Giridharan, S699 (PO-852),
S700 (PO-861)
Permtersin, Chalermsein, S513 (PO-573)
Perno, Carlo Federico, S728 (PO-1996)
Perra, Andrea, S627 (PO-2312)
Perren, Aurel, S603 (PO-2186)
Perret, Pascale, S582 (PO-1927)
Persona, Paolo, S668 (PO-2097)
Personeni, Nicola, S236 (OS-498)
Perugorria, María Jesús, S497 (PO-133)
Peschard, Simon, S608 (PO-2858),
S608 (PO-2883)
Pessaux, Patrick, S196 (GS-2069),
S247 (OS-2190), S392 (PO-692),
S695 (PO-175), S780 (PO-602)
Pesta, Dominik, S589 (PO-716)
Peta, Valentina, S191 (GS-1065)
Peterfi, Zoltán, S655 (PO-1572)
Peter Hofmann, Wolf, S429 (PO-1294)
Peter, Joy, S798 (PO-1962)
Peter R., Galle, S661 (PO-1903)
Peters, Annette, S535 (PO-566)
Petersen, Jörg, S702 (PO-1707)
Peter, Simon, S248 (OS-334)
Peterson, Jorg, S287 (OS-2225)
Peters, Rory, S418 (PO-1026)
Petersson, Sven, S269 (OS-1627)
Petitjean, Mathieu, S499 (PO-677)

- Petroff, David, S544 (PO-1296), S560 (PO-751), S763 (PO-68), S764 (PO-131)
- Petrov, Petar, S320 (PO-2043)
- Petrov-Sanchez, Ventzislava, S292 (OS-728)
- Petrtyl, Jaromir, S689 (PO-2040)
- Petruzzello, Arnolfo, S656 (PO-1593)
- Petsalaki, Evangelia, S263 (OS-1028)
- Petta, Salvatore, S253 (OS-635), S255 (OS-243), S259 (OS-1592), S261 (OS-297), S377 (PO-1474), S540 (PO-831), S564 (PO-919), S568 (PO-1056), S785 (PO-1247)
- Pevear, Daniel, S748 (PO-1699)
- Peynircioglu, Bora, S244 (OS-777)
- Peyvandi, Flora, S786 (PO-1542)
- Pfammatter, Thomas, S244 (OS-777)
- Pfefferkorn, Maria, S706 (PO-2135), S732 (PO-2834)
- Pfister, Dominik, S262 (OS-584)
- Pfister, Eva, S682 (PO-1354)
- Pham, Minh, S358 (PO-2683), S386 (PO-2685)
- Philip Åstrand, Claus, S313 (PO-487)
- Philip, George, S658 (PO-1713)
- Philippe, Sultanik, S355 (PO-2194)
- Philipp, Stoffers, S332 (PO-2358)
- Phillips, Alexandra, S349 (PO-1165)
- Phillips, Sandra, S321 (PO-2185)
- Phipps, Jacqueline, S198 (GS-1645)
- Phyu, Khine, S273 (OS-199)
- Piano, Salvatore, S346 (PO-918), S346 (PO-932), S355 (PO-2273), S469 (PO-1496)
- Piao, Hongxin, S629 (PO-1091)
- Piazzolla, Valeria, S764 (PO-388), S769 (PO-951)
- Picchio, Camila, S661 (PO-1936), S665 (PO-2059), S765 (PO-525)
- Picchio, Gaston, S203 (LBO-2764), S760 (PO-2822), S761 (PO-2823), S762 (PO-2879)
- Pierce, Glenn, S476 (PO-982)
- Piermatteo, Lorenzo, S704 (PO-1928), S728 (PO-1996)
- Pierre Ripault, Marie, S352 (PO-1712)
- Pieterman, Elsbet, S623 (PO-2099)
- Pietschmann, Thomas, S282 (OS-1062), S697 (PO-611)
- Pihlajamaki, Jussi, S261 (OS-297)
- Pike, James, S552 (PO-2326)
- Pilar Ballester, María, S338 (PO-1761)
- Pilar Ríos, María, S335 (PO-709)
- Pilet, Jill, S242 (OS-906)
- Pilger, Alexander, S683 (PO-1500)
- Pinato, David J., S236 (OS-498), S245 (OS-1145), S448 (PO-718), S495 (PO-2799)
- Pinazo Bandera, Jose, S302 (PO-1335), S304 (PO-1406)
- Pineau, Laurent, S608 (PO-2858), S608 (PO-2883)
- Pinelli, Domenico, S513 (PO-574)
- Pinero, Federico, S495 (PO-2799), S521 (PO-1351)
- Pink, Isabell, S473 (PO-2821)
- Pinter, Matthias, S236 (OS-498), S270 (OS-507), S362 (PO-309), S363 (PO-310), S365 (PO-560), S374 (PO-1249), S376 (PO-1316), S377 (PO-1613), S521 (PO-1312), S521 (PO-1351), S645 (PO-533), S681 (PO-1243)
- Pinto Marques, Hugo, S475 (PO-2890)
- Pinyol, Roser, S240 (OS-615), S241 (OS-699)
- Pinzani, Massimo, S451 (PO-1460), S596 (PO-1753)
- Piombanti, Benedetta, S505 (PO-1969), S606 (PO-2411)
- Piotrowski, Katja, S429 (PO-1294)
- Piquet Pellorce, Claire, S307 (PO-2888)
- Pirenne, Jacques, S475 (PO-2910)
- Pirenne, Sophie, S509 (PO-2839)
- Pirker, Roxana, S800 (PO-2191)
- Pirlot, Boris, S458 (PO-1356)
- Pirnat, Zala, S667 (PO-2093)
- Pisani, Francesco, S477 (PO-1207)
- Pisano, Giuseppina, S600 (PO-1986), S785 (PO-1247), S786 (PO-1542)
- Piscaglia, Fabio, S216 (OS-1544), S514 (PO-591), S521 (PO-1351), S533 (PO-441)
- Pistorio, Valeria, S217 (OS-888)
- Pita-Juarez, Yered, S334 (PO-134)
- Pittaluga, Fabrizia, S234 (OS-116)
- Pittman, Meredith, S603 (PO-2161)
- Pittol, Jose Miguel Ramos, S527 (PO-778)
- Pizzirani, Enrico, S488 (PO-1238)
- Pla, Anna, S640 (PO-1193)
- Placinta, George, S750 (PO-1837)
- Placinta, Gheorghe, S291 (OS-2717)
- Plagiannakos, Christina, S435 (PO-1755)
- Pla, Iris, S459 (PO-2234)
- Plata-Bello, Julio, S492 (PO-2594)
- Plesko, Maja, S667 (PO-2093)
- Plessier, Aurélie, S197 (GS-613), S355 (PO-2194), S678 (PO-561), S694 (PO-2902)
- Plissonnier, Marie-Laure, S350 (PO-1549), S701 (PO-1451), S713 (PO-408)
- Pocai, Alessandro, S531 (PO-2627)
- Pochet, Nathalie, S212 (OS-1491)
- Podrug, Kristian, S636 (PO-2370)
- Pohl, Laureen, S446 (PO-147)
- Pöhlmann, Stefan, S697 (PO-611)
- Poikola, Anni, S260 (OS-2362)
- Poincloux, Laurent, S793 (PO-468)
- Poinsot, Domitille, S350 (PO-1549)
- Pokkalla, Harsha, S254 (OS-1611), S602 (PO-2123)
- Polak, Wojciech, S472 (PO-2121)
- Polanco, Prido, S567 (PO-1001)
- Polat, Esra, S691 (PO-2392)
- Poli, Edoardo, S482 (PO-750), S717 (PO-813)
- Poljak, Mario, S667 (PO-2093)
- Pollarsky, Florencia, S346 (PO-864)
- Pollok, Joerg-Matthias, S474 (PO-2842)
- Pol, Stanislas, S191 (GS-1065), S194 (GS-1587), S292 (OS-728), S555 (PO-2692), S766 (PO-649)
- Polveche, Hélène, S695 (PO-258)
- Polychronopoulou, Efstathia, S234 (OS-161)
- Pomej, Katharina, S236 (OS-498), S374 (PO-1249), S377 (PO-1613), S521 (PO-1312), S645 (PO-533), S681 (PO-1243)
- Poniachik, Jaime, S323 (PO-2704)
- Pons, Caroline, S702 (PO-1688), S703 (PO-1711)
- Ponsioen, Cyriel, S387 (PO-2938)
- Pons-Kerjean, Nathalie, S708 (PO-2684)
- Ponsolles, Clara, S212 (OS-1491), S247 (OS-2190), S780 (PO-602)
- Pontisso, Patrizia, S355 (PO-2273)
- Popa, Alexandru, S398 (PO-1582)
- Popa, Codruta, S477 (PO-1119)
- Popescu, Alina, S398 (PO-1582)
- Popescu, Irinel, S477 (PO-1119)
- Popescu, Mihai, S194 (GS-1997), S209 (OS-2060)
- Popovic, Vlad, S714 (PO-420)
- Popov, Yury, S499 (PO-677)
- Porras, José Luis Martínez, S269 (OS-1769)
- Porretti, Laura, S746 (PO-1448)
- Portal, Isabelle, S647 (PO-785)
- Porta-Pardo, Eduard, S689 (PO-2090)
- Porteiro, Begoña, S249 (OS-1355), S391 (PO-479)
- Porte, Robert J., S343 (PO-187)
- Portero-Navarro, Julian, S492 (PO-2594)
- Porthan, Kimmo, S260 (OS-2362)
- Portincasa, Piero, S359 (PO-2753)
- Port, Kerstin, S792 (PO-153)
- Portolés, Irene, S218 (OS-1478)
- Pose, Elisa, S207 (OS-2028), S311 (PO-345), S319 (PO-1932), S329 (PO-2058)
- Po[?]piech, Ewelina, S417 (PO-899)
- Possamai, Lucia, S208 (OS-638), S354 (PO-1998)
- Possamai, Lucia A., S224 (OS-1946)
- Postic, Catherine, S528 (PO-1027)
- Potapova, Anna, S233 (OS-1290)
- Potes, Yaiza, S432 (PO-1574)
- Potey, Camille, S201 (LBO-2631)
- Poth, Tanja, S219 (OS-2754)
- Pou, Diana, S664 (PO-2047)
- Poujois, Aurelia, S280 (OS-2590)
- Poujol-Robert, Armelle, S197 (GS-613)
- Poulos, John, S578 (PO-1689)
- Pouryahya, Maryam, S254 (OS-1611), S602 (PO-2123)
- Powell, Elizabeth, S348 (PO-1102), S353 (PO-1766)
- Powell, James, S464 (PO-594)
- Poynard, Thierry, S191 (GS-1065), S555 (PO-2692)
- Pozo, Katherine, S613 (PO-668)
- Pozo, Ruben Nogueiras, S249 (OS-1355)
- Prachalias, Andreas, S321 (PO-2185)

Author Index

- Pradat, Pierre, S352 (PO-1730)
Prado, Verónica, S329 (PO-2058)
Praetorius, Alejandro González, S447 (PO-235), S735 (PO-430)
Prager, Gerhard, S592 (PO-1369)
Prakash, Aaditya, S433 (PO-1644)
Prakash, Kasthuri, S284 (OS-2864)
Praktiknjo, Michael, S213 (OS-513)
Prasad Tripathy, Tara, S381 (PO-2238)
Prati, Daniele, S261 (OS-297), S642 (PO-251), S746 (PO-1448)
Prat, Laura Iogna, S215 (OS-1864), S642 (PO-251)
Pratschke, Johann, S473 (PO-2211)
Premkumar, Madhumita, S360 (PO-2832)
Present, Luc, S581 (PO-1895)
Pressiani, Tiziana, S236 (OS-498), S514 (PO-591)
Preston, Johanna, S536 (PO-630)
Preziosi, Melissa, S321 (PO-2185)
Price, David, S454 (PO-1983)
Price, Jillian, S655 (PO-1551)
Priebe, Maximilian, S522 (PO-1745)
Prier Lindvig, Katrine, S207 (OS-1726)
Priest, Matthew, S489 (PO-1729), S611 (PO-337)
Prieto, Martín, S788 (PO-1919)
Prieto, Paula Ortega, S528 (PO-1027)
Prikhodko, Veronika, S590 (PO-725)
Primignani, Massimo, S216 (OS-1544), S252 (OS-571), S307 (PO-48), S722 (PO-1519)
Prince, William, S534 (PO-534)
Prip-Buus, Carina, S604 (PO-2276)
Probert, Fay, S418 (PO-1026)
Procopet, Bogdan, S252 (OS-571), S307 (PO-48)
Proctor, Gordon, S222 (OS-2044)
Prokosch, Sandra, S752 (PO-2089), S754 (PO-2243)
Pronicki, Maciej, S634 (PO-2094)
Pronier, Charlotte, S696 (PO-526)
Pronina, Nina, S352 (PO-1730)
Prost, Ardavan, S352 (PO-1712)
Protopopescu, Camelia, S292 (OS-728), S662 (PO-1990)
Protzer, Ulrike, S446 (PO-147), S736 (PO-655), S752 (PO-2089), S753 (PO-2106), S754 (PO-2243)
Provera, Alessia, S598 (PO-1916)
Puchades, Laura, S788 (PO-1919)
Pu, Chunwen, S629 (PO-1091)
Puente, Angela, S252 (OS-571), S694 (PO-2902)
Puget, Eric, S767 (PO-690)
Puigvehí, Marc, S240 (OS-615), S241 (OS-699), S280 (OS-1921), S499 (PO-541), S521 (PO-1420), S734 (PO-247), S799 (PO-2021)
Pule, Martin, S736 (PO-655)
Punia, Pankaj, S303 (PO-1379)
Puri, Puneet, S581 (PO-1808)
Putera, Martin, S344 (PO-485)
Putignano, Antonella, S327 (PO-1161)
Pydyn, Natalia, S417 (PO-899), S587 (PO-195)
Qadri, Sami, S260 (OS-2362)
Qamar, Sumaira, S212 (OS-31)
Qas Yonan, Aed, S577 (PO-1648)
Qian, Linglin, S589 (PO-550)
Qian, Tongqi, S212 (OS-1491)
Qiao, Jinggui, S368 (PO-1094)
Qiao, Linlan, S298 (PO-537)
Qi, Hailong, S629 (PO-1091)
Qi, Shenglin, S368 (PO-1094)
Qiu, Yibo, S523 (PO-1883)
Qiu, Yuanwang, S359 (PO-2688)
Qi, Xiaolong, S359 (PO-2688), S368 (PO-1094), S372 (PO-1152), S631 (PO-1091), S650 (PO-1330)
Qi, Xingsi, S368 (PO-1094)
Qi, Xun, S726 (PO-1810), S742 (PO-1109)
Quadri, Sami, S605 (PO-2322)
Quaranta, Maria Giovanna, S654 (PO-1480), S767 (PO-694)
Queck, Alexander, S332 (PO-2358)
Quehenberger, Peter, S270 (OS-507)
Quehenberger, Prof. PeterMD, S363 (PO-310), S365 (PO-560), S374 (PO-1249), S376 (PO-1316), S377 (PO-1613)
Quelhas, Patricia, S442 (PO-2761)
Quer, Josep, S696 (PO-469), S802 (PO-2295)
Que, Weitao, S231 (OS-687)
Quiambao, Ronald, S583 (PO-1981)
Quidant, Romain, S218 (OS-1478)
Quinlan, Jonathan, S342 (PO-2851)
Quiñones, Raisa, S778 (PO-2359)
Quirk, Corrine, S603 (PO-2161)
Quitt, Oliver, S753 (PO-2106)
Qumosani, Karim, S228 (OS-1586), S435 (PO-1755)
Rabea, Mohamed, S293 (OS-2306)
Raboisson, Pierre, S744 (PO-1386)
Racila, Andrei, S655 (PO-1551)
Rada, Patricia, S250 (OS-1414)
Radford-Smith, Daniel E., S418 (PO-1026)
Radley, Andrew, S800 (PO-2205)
Rad, Roland, S262 (OS-584), S498 (PO-336), S754 (PO-2243)
Radu, Iuliana Pompilia, S236 (OS-498)
Radu, Pompilia, S521 (PO-1420)
Raffi, Francois, S291 (OS-2717)
Rafiqi, Umara, S603 (PO-2186)
Raga, Agnés, S723 (PO-1622)
Raggi, Chiara, S505 (PO-1969)
Raghupathy, Narayanan, S587 (PO-283)
Ragnarsdottir, Oddny, S605 (PO-2322)
Rahbari, Mandana, S420 (PO-1822)
Rahbari, Nuh N., S236 (OS-498)
Raja, Maruthi, S349 (PO-1165)
Rajani, Rupesh, S692 (PO-2667)
Rajan, Vijayraghavan, S330 (PO-2313), S381 (PO-2238)
Rajas, Fabienne, S531 (PO-2793)
Raj Bhandari, Bal, S578 (PO-1689)
Rajicic, Natasa, S201 (LBO-2592), S294 (LBP-2580)
Rajoriya, Neil, S277 (OS-1172)
Rajout, Bijal, S592 (PO-1235)
Rajput, Bijal, S395 (PO-1505)
Rajwal, Sanjay, S687 (PO-1811)
Rajwanshi, Vivek, S720 (PO-1257), S742 (PO-1196)
Rakhimov, Anvarjon, S532 (PO-19)
Raluca, Lupusoru, S398 (PO-1582)
Ramachandran, Babu Entoor, S666 (PO-2081)
Ramadori, Pierluigi, S262 (OS-584)
Ramakrishna, Gayatri, S330 (PO-2313)
Raman, Rakesh, S682 (PO-1285)
Ramanuj, DasGupta, S699 (PO-852)
Ramaswami, Ramya, S490 (PO-2070)
Ramavath, Naresh Naik, S598 (PO-1916)
Ramière, Christophe, S698 (PO-700)
Ramirez, Carolina A., S199 (GS-2309)
Ramirez, Giuseppe A., S229 (OS-1728)
Ramirez, Jaime, S687 (PO-1828)
Ramirez, Ricardo, S284 (OS-654), S716 (PO-665), S725 (PO-1789)
Ramirez-Valle, Francisco, S392 (PO-733), S587 (PO-283)
Ramji, Alnoor, S736 (PO-482), S798 (PO-1962)
Rammensee, Hans-Georg, S246 (OS-1399)
Rammohan, Ashwin, S472 (PO-2121)
Ramos, Ana Laserna, S674 (PO-2596)
Ramos, David Fernandez, S249 (OS-1355)
Ramos, David Fernández, S612 (PO-627), S624 (PO-2192)
Ramos Pittol, José M., S457 (PO-279)
Ramsoekh, Dewkoemar, S585 (PO-2485)
Rana, Abbas, S323 (PO-2417)
Randhawa, Amarita, S566 (PO-980), S577 (PO-1588)
Rando, Ariadna, S651 (PO-1341), S696 (PO-469), S706 (PO-2145), S732 (PO-2637)
Rang, Limaocai, S368 (PO-1094)
Ranjan, Piyush, S632 (PO-1696)
Rao, Ankit, S303 (PO-1379)
Rao, Huiying, S400 (PO-1857), S795 (PO-987)
Rapado, Marta, S784 (PO-1176)
Rapposelli, Simona, S627 (PO-2312)
Raquel Terrabuio, Debora, S193 (GS-1213)
Rasines, Laura, S537 (PO-685)
Rasmussen, Ditlev, S207 (OS-1726), S321 (PO-2331)
Rastovic, Archana, S406 (PO-2010)
Rastovic, Una, S321 (PO-2185)
Rathmann, Wolfgang, S535 (PO-566)
Ratnasekera, Isanka, S348 (PO-1102)

- Ratziu, Vlad, S191 (GS-1065),
 S255 (OS-243), S256 (OS-538),
 S257 (OS-1556), S266 (OS-2831),
 S267 (OS-427), S291 (OS-2717),
 S551 (PO-2002), S564 (PO-919),
 S568 (PO-1056), S576 (PO-1575),
 S579 (PO-1777), S586 (PO-2739),
 S604 (PO-2276), S609 (PO-159),
 S625 (PO-2290), S669 (PO-2108)
- Rau, Monika, S547 (PO-1667)
- Rautou, Pierre-Emmanuel, S197 (GS-613),
 S252 (OS-571), S277 (OS-1172),
 S679 (PO-570)
- Ravaioli, Federico, S377 (PO-1474),
 S787 (PO-1561)
- Ravendhran, Natarajan, S736 (PO-482)
- Raventós, Aida, S354 (PO-1930)
- Rawal, Preety, S459 (PO-2234)
- Ray, Adrian, S623 (PO-2163)
- Raymenants, Karlien, S277 (OS-1172)
- Raymond, Anne-Aurélié, S510 (PO-2865)
- Razavi, Homie, S295 (LBP-2814),
 S532 (PO-19), S642 (PO-424),
 S669 (PO-2108)
- Razavi-Shearer, Kathryn, S642 (PO-424)
- Razooky, Brandon, S603 (PO-2161)
- Razpotnik, Marcel, S380 (PO-2162)
- Reau, Nancy S., S540 (PO-969),
 S770 (PO-983)
- Rebouissou, Sandra, S242 (OS-906)
- Reddy, Rajender, S326 (PO-675),
 S433 (PO-1644), S463 (PO-364)
- Reesink, Henk, S728 (PO-1982)
- Reeves, Helen, S261 (OS-297)
- Reeves, Helen L., S301 (PO-1185),
 S490 (PO-2070), S495 (PO-2799),
 S513 (PO-573)
- Reeves, Helen Louise, S493 (PO-2687)
- Rega, Dalia, S335 (PO-698), S338 (PO-1761)
- Reggiani, Giulio Marchesini,
 S669 (PO-2108), S756 (PO-2395)
- Reiberger, Thomas, S213 (OS-925),
 S216 (OS-1544), S236 (OS-498),
 S252 (OS-571), S270 (OS-507),
 S362 (PO-309), S363 (PO-310),
 S364 (PO-532), S365 (PO-560),
 S374 (PO-1249), S376 (PO-1316),
 S377 (PO-1613), S383 (PO-2403),
 S521 (PO-1312), S645 (PO-533),
 S681 (PO-1243), S800 (PO-2191)
- Reichert, Matthias, S337 (PO-1222),
 S661 (PO-1903)
- Reichert, Matthias C., S677 (PO-323)
- Reider, Simon, S262 (OS-584)
- Reig, María, S243 (OS-295),
 S492 (PO-2242), S495 (PO-2799),
 S639 (PO-511), S640 (PO-1193),
 S641 (PO-1525)
- Reikvam, Dag Henrik, S734 (PO-111)
- Reinders-Hut, Margot, S245 (OS-972)
- Reinhardt, Carsten, S246 (OS-1399)
- Reisinger, Florian, S754 (PO-2243)
- Rela, Mohd., S438 (PO-2280)
- Rellán, María J. González, S624 (PO-2192)
- Remingler, Katja, S455 (PO-2173)
- Remmen, Roy, S581 (PO-1895)
- Remmerie, Anneleen, S450 (PO-1333),
 S453 (PO-1649), S456 (PO-2456)
- Remouchamps, Caroline,
 S754 (PO-2243)
- Remy, André-Jean, S767 (PO-690),
 S798 (PO-2020)
- Renand, Amédée, S423 (PO-60)
- Renaudineau, Yves, S422 (PO-2681)
- Renault, Victor, S242 (OS-906)
- Rendina, Maria Grazia, S353 (PO-1767)
- Rendon, Adriana, S257 (OS-1556),
 S576 (PO-1575)
- Ren, Hong, S770 (PO-1007)
- Ren, Limei, S368 (PO-1094)
- Ren, Liying, S479 (PO-250), S531 (PO-1887)
- Ren, Suping, S700 (PO-1305)
- Ren, Tao, S359 (PO-2688)
- Renteria, Sara Colonia Uceda,
 S492 (PO-2364), S722 (PO-1519),
 S746 (PO-1448), S784 (PO-921)
- Ren, Yan-Dan, S483 (PO-1147)
- Ren, Yayun, S400 (PO-1857), S615 (PO-889)
- Repking, Sarah, S540 (PO-969)
- Requena, Maria, S790 (PO-2836)
- Resino-García, Salvador, S771 (PO-1186),
 S785 (PO-1404)
- Resino García, Salvador, S783 (PO-881)
- Resino, Salvador, S781 (PO-689)
- Resner, Kathrin, S703 (PO-1907)
- Resnick, Murray, S254 (OS-1611),
 S433 (PO-1644), S602 (PO-2123)
- Ress, Claudia, S589 (PO-716)
- Resteu, Anastasia, S419 (PO-1364)
- Retat, Lise, S646 (PO-640), S675 (PO-2861)
- Reuten, Philipp, S429 (PO-1294)
- Reverter, Enric, S329 (PO-2058)
- Revill, Peter, S283 (OS-2826),
 S744 (PO-1286)
- Reyes, Eira Cerda, S533 (PO-445),
 S694 (PO-2902)
- Reyes, Juliana, S795 (PO-1307)
- Reyes-Ureña, Juliana, S786 (PO-1415)
- Rey, Francisco Javier García-Samaniego,
 S788 (PO-1919)
- Reymond, Maud, S647 (PO-785),
 S793 (PO-468)
- Reynaert, Hendrik, S388 (PO-223),
 S527 (PO-375), S527 (PO-608)
- Rhead, Camilla, S328 (PO-1387)
- Rhodes, Freya, S324 (PO-2749)
- Rialdi, Alex, S240 (OS-615)
- Riaz, Zeshan, S677 (PO-299)
- Ribeiro, Tiago, S296 (LBP-2891),
 S440 (PO-2701), S443 (PO-2801),
 S445 (PO-2887), S445 (PO-2898)
- Ribera, Jordi, S218 (OS-1478)
- Ribera, Martí Ortega, S334 (PO-624)
- Ricardo-Lax, Inna, S603 (PO-2161)
- Ricco, Gabriele, S491 (PO-2223),
 S729 (PO-2261)
- Rice, Charles, S603 (PO-2161)
- Richardson, Harriet, S658 (PO-1713)
- Rich, Nicole, S496 (PO-2812)
- Richou, Carine, S584 (PO-2030)
- Richter, Maria L., S232 (OS-943)
- Richwien, Paula, S592 (PO-1369)
- Ridder, Filip De, S289 (OS-1430)
- Ridola, Lorenzo, S383 (PO-2381)
- Riedl, Tobias, S703 (PO-1711),
 S752 (PO-2089), S754 (PO-2243)
- Riggio, Oliviero, S383 (PO-2381)
- Rigopoulou, Eirini, S227 (OS-1088)
- Rijnbrand, Cornelis, S281 (OS-595)
- Rimassa, Lorenza, S236 (OS-498),
 S495 (PO-2799)
- Rimini, Margherita, S514 (PO-591)
- Rimola, Jordi, S640 (PO-1193)
- Rimondi, Alessandro, S492 (PO-2364),
 S784 (PO-921)
- Rincon, Adalberto, S269 (OS-1769)
- Rincón, Mercedes, S243 (OS-1948)
- Rinella, Mary, S624 (PO-2287),
 S625 (PO-2290)
- Ringlander, Johan, S284 (OS-2864)
- Ríos, María Pilar, S335 (PO-698)
- Rios, Rafael, S538 (PO-719), S541 (PO-1030),
 S562 (PO-769)
- Ripoll, Cristina, S337 (PO-1222)
- Rippe, Karsten, S754 (PO-2243)
- Rita De Caro, Emilia, S600 (PO-2033)
- Riva, Antonio, S207 (OS-2158),
 S321 (PO-2185)
- Riveiro Barciela, Mar, S431 (PO-1484),
 S437 (PO-2015)
- Riveiro-Barciela, Mar, S651 (PO-1341)
- Rivera, Jesús, S255 (OS-2337),
 S584 (PO-2369)
- Rivera, Stephanie, S531 (PO-2627)
- Roade, Luisa, S437 (PO-2015),
 S664 (PO-2047), S732 (PO-2637),
 S732 (PO-2834)
- Roayaie, Sasan, S241 (OS-699),
 S499 (PO-541)
- Robaey, Anneleen, S581 (PO-1895)
- Robaey, Geert, S581 (PO-1895)
- Robert Latta, Markus, S399 (PO-1831)
- Roberts, Lewis, S496 (PO-2812),
 S521 (PO-1420)
- Robertson, Marcus, S471 (PO-1971)
- Roberts, Stuart K., S512 (PO-75)
- Roberts, Surain, S228 (OS-1586),
 S435 (PO-1755)
- Robic, Marie-Angèle, S307 (PO-48)
- Robinson, Emma, S800 (PO-2205)
- Robinson, Sharayne, S233 (OS-2656)
- Robinson, Stuart, S386 (PO-2788),
 S493 (PO-2687)
- Roblero, Juan Pablo, S323 (PO-2704)
- Roblero, Pablo, S323 (PO-2704)
- Robles-Díaz, M., S302 (PO-1335),
 S304 (PO-1406)
- Robles-Díaz, Mercedes, S303 (PO-1389)
- Roccarina, Davide, S215 (OS-1864),
 S226 (OS-894)
- Rocha, Bruno Aragão, S408 (PO-301)
- Rocha, Filipa, S694 (PO-2902)

Author Index

- Roche, Bruno, S717 (PO-813)
Rockey, Don, S359 (PO-2688),
S631 (PO-1091)
Rocque, Brittany, S471 (PO-1773)
Rode, Agnès, S198 (GS-945),
S518 (PO-1209), S520 (PO-1263)
Roden, Michael, S535 (PO-566),
S589 (PO-716)
Roderburg, Christoph, S339 (PO-2098),
S495 (PO-2799), S517 (PO-1046)
Rodger, Alison, S324 (PO-2749)
Rodica Tomescu, Dana, S194 (GS-1997),
S209 (OS-2060)
Rodrigo-Velásquez, Fernando,
S663 (PO-2014)
Rodrigues, Cecília M. P., S604 (PO-2276),
S634 (PO-2184)
Rodrigues, Clara, S475 (PO-2890)
Rodrigues, Pedro Miguel, S634 (PO-2184)
Rodrigues, Susana G., S307 (PO-48),
S378 (PO-1987)
Rodríguez Agudo, Rubén, S301 (PO-1185),
S502 (PO-1752)
Rodríguez, Amaia, S249 (OS-1355)
Rodríguez, Amanda Fernández,
S783 (PO-881), S785 (PO-1404)
Rodríguez, Antonio González,
S492 (PO-2594), S674 (PO-2596)
Rodríguez, Beatriz García, S337 (PO-1643)
Rodríguez, Carlos, S531 (PO-2627)
Rodríguez de Lope, Carlos, S495 (PO-2799)
Rodríguez, Diego Rincón, S784 (PO-1176)
Rodríguez-Frías, Francisco, S663 (PO-2014),
S664 (PO-2047), S699 (PO-820),
S706 (PO-2145), S732 (PO-2637),
S732 (PO-2834), S737 (PO-774),
S802 (PO-2295)
Rodríguez-Gandía, Miguel Ángel,
S347 (PO-1045)
Rodríguez, Ingrid, S766 (PO-649),
S769 (PO-955)
Rodríguez, Juan Luis García, S497 (PO-133)
Rodríguez-Madoz, Juan R., S694 (PO-2770)
Rodríguez, Manuel, S516 (PO-1010),
S746 (PO-1449), S788 (PO-1919)
Rodríguez, Manuel S., S502 (PO-1752)
Rodríguez, Maria, S193 (GS-1213)
Rodríguez, Prof. Dr. Manuel, S307 (PO-48)
Rodríguez-Santiago, Enrique,
S746 (PO-1449)
Rodríguez-Tajes, Sergio, S699 (PO-820),
S746 (PO-1449), S786 (PO-1415),
S795 (PO-1307)
Rodríguez-Tomás, Elisabet, S598 (PO-1897)
Roehlen, Natascha, S196 (GS-2069),
S247 (OS-2190)
Roehrig, Amélie, S242 (OS-906)
Roels, Joris, S450 (PO-1333)
Rogers, Bruce, S623 (PO-2163)
Roget, Mercé, S431 (PO-1484),
S788 (PO-1919)
Roggendorf, Hedwig, S446 (PO-147)
Rohde, Gernot, S332 (PO-2358)
Rohilla, Sumati, S459 (PO-2234)
Roinard, Morganer, S708 (PO-2684)
Rojas, Cyd Castro, S686 (PO-1758)
Rojo, David, S785 (PO-1404)
Roksund Hov, Johannes, S432 (PO-1512)
Rolinski, Jacek, S319 (PO-1708)
Rolland, Maude, S752 (PO-2089),
S754 (PO-2243)
Rolph, Tim, S204 (LBO-2800),
S618 (PO-1314), S619 (PO-1762)
Romagnoli, Renato, S234 (OS-116)
Romagnoli, Veronica, S729 (PO-2261)
Romano, Roberta, S202 (LBO-2647)
Rombouts, Krista, S596 (PO-1753)
Romeo, Stefano, S261 (OS-297)
Romero Gomez, Manuel, S307 (PO-48),
S398 (PO-1589), S399 (PO-1609),
S533 (PO-381), S540 (PO-831),
S556 (PO-167), S557 (PO-313),
S564 (PO-916), S564 (PO-919),
S568 (PO-1056), S574 (PO-1518),
S579 (PO-1714)
Romero-Gomez, Manuel, S255 (OS-2337),
S255 (OS-243), S575 (PO-1568),
S584 (PO-2369)
Romero, Gustavo, S346 (PO-864)
Romero, Judit, S280 (OS-1921),
S734 (PO-247), S799 (PO-2021)
Romero, Marta, S631 (PO-1668)
Ronca, Vincenzo, S193 (GS-1213)
Ronchi, Dario, S600 (PO-2033)
Ronot, Maxime, S244 (OS-777),
S487 (PO-1153)
Ronzan, Andrea, S466 (PO-935)
Ronzitti, Giuseppe, S202 (LBO-2647)
Root, David E., S695 (PO-175)
Roque-Afonso, Anne Marie, S717 (PO-813)
Roquelaure, Bertrand, S687 (PO-1811)
Rorsman, Fredrik, S227 (OS-1088),
S271 (OS-686)
Rosa, Abel De La, S743 (PO-1251)
Rosa, Isabelle, S647 (PO-785)
Rosato, Valerio, S657 (PO-1666)
Rösch, Thomas, S230 (OS-2782)
Rose, Christopher F., S341 (PO-2279),
S341 (PO-2382)
Rosenau, Jens, S798 (PO-2020)
Rosenberg, William, S324 (PO-2749)
Rosenquist, Christian, S586 (PO-2739)
Rosenthal, Philip, S199 (GS-2283)
Roskams, Tania, S266 (OS-2831),
S336 (PO-1051)
Rosler, Elen, S742 (PO-1196)
Rosmorduc, Olivier, S482 (PO-750),
S525 (PO-2408)
Rösner, Thomas, S498 (PO-336)
Ros, Oliva, S694 (PO-2902)
Rospleszcz, Susanne, S535 (PO-566)
Rossi, Geoffrey, S691 (PO-2324)
Rossi, Giorgio, S524 (PO-2401)
Rossi, Luca, S217 (OS-874)
Rossi, Simona, S466 (PO-1126)
Rossi, Stephen, S297 (LBP-2907)
Rosso, Chiara, S253 (OS-635)
Rosso, Natalia, S619 (PO-1359)
Ross, Paul, S245 (OS-1145)
Rother, Karen, S755 (PO-2269)
Roth, Nitzan, S649 (PO-1035)
Roth, Sofia, S306 (PO-2178)
Roth, Susanne, S262 (OS-584)
Roudot-Thoraval, Françoise, S766 (PO-649)
Roulot, Dominique, S291 (OS-2717),
S312 (PO-433), S555 (PO-2692)
Round, Patrick, S297 (LBP-2907)
Rourke, Colm O., S240 (OS-179),
S497 (PO-133)
Roux, Marine, S565 (PO-941),
S566 (PO-944)
Roux, Olivier, S691 (PO-2324)
Rovida, Elisabetta, S505 (PO-1969),
S606 (PO-2411)
Rowe, Ian, S367 (PO-1040), S394 (PO-1125),
S464 (PO-594)
Roxburgh, Sarah, S611 (PO-337)
Rox, Katharina, S697 (PO-611)
Roy, Carine, S197 (GS-613)
Royo, Félix, S334 (PO-624)
Royo, Laura, S240 (OS-615), S689 (PO-2090)
Rozina, Teona, S789 (PO-2418)
Ruane, Peter, S204 (LBO-2800),
S578 (PO-1689), S613 (PO-757),
S619 (PO-1762)
Rubens, Eva, S581 (PO-1895)
Rubio, Aileen, S739 (PO-853)
Rubio, Teresa, S335 (PO-709)
Rudler, Marika, S307 (PO-48),
S355 (PO-2194), S551 (PO-2002)
Rudraraju, Madhavi, S297 (LBP-2907)
Ruf, Murad, S273 (OS-199), S652 (PO-1374)
Ruiz-Blázquez, Paloma, S217 (OS-888)
Ruiz Casas, Leonardo, S398 (PO-1589),
S399 (PO-1609)
Ruiz, Isaac, S717 (PO-813)
Ruiz, Lourdes, S663 (PO-2014)
Ruiz-Ortiz, Estibaliz, S431 (PO-1484)
Ruiz, Pablo, S235 (OS-213)
Ruiz, Patricia Cordero, S779 (PO-578)
Ruiz, Pilar Díaz, S674 (PO-2596)
Ruiz-Ramirez, Pablo, S723 (PO-1622)
Ruiz, Sandra Díez, S778 (PO-2359)
Rumi, Maria Grazia, S722 (PO-1519)
Runarsdottir, Valgerdur, S670 (PO-2127)
Runfola, Massimiliano, S627 (PO-2312)
Runge, Jurgen, S585 (PO-2485)
Rupp, Carina, S498 (PO-336)
Rupp, Christian, S227 (OS-1088),
S421 (PO-2285)
Rupp, Jana, S604 (PO-2210)
Ruscica, Massimiliano, S600 (PO-2033)
Rushbrook, Simon, S420 (PO-1578),
S435 (PO-1790)
Rushton, Steve, S420 (PO-1578)
Russo, Francesco Paolo, S668 (PO-2097),
S767 (PO-694)
Rustøen Braadland, Peder, S432 (PO-1512)
Rusu, Ioana, S318 (PO-1651)
Rutten, Martijn, S531 (PO-2793),
S691 (PO-2204)
Rutter, Karoline, S351 (PO-1701)

- Ryan, Jennifer M, S207 (OS-2158)
 Ryan, John, S215 (OS-1864)
 Ryan, Pablo, S771 (PO-1186), S783 (PO-881), S798 (PO-2020)
 Rycyk, Anna, S319 (PO-1708)
 Rydell, Gustaf, S284 (OS-2864)
 Ryder, Stephen, S274 (OS-1381), S420 (PO-1578), S755 (PO-2338)
 Rygg, Marte Opseth, S593 (PO-1407)
- Saade, George, S440 (PO-2657)
 Saandi, Thoueiba, S509 (PO-2839)
 Sabatini, Silvia, S600 (PO-2033)
 Sabat, Mark, S393 (PO-938)
 Sabillon-Mendoza, Alejandra Marisela, S687 (PO-1828)
 Sabio, Guadalupe, S391 (PO-479), S591 (PO-1037), S612 (PO-627)
 Saborowski, Anna, S248 (OS-334), S249 (OS-901)
 Saborowski, Michael, S248 (OS-334), S249 (OS-901)
 Saccani, Andrea, S619 (PO-1359)
 Sacco, Rodolfo, S514 (PO-591)
 Sachdeva, Munish, S632 (PO-1696)
 Sacks-Davis, Rachel, S796 (PO-1508)
 Sacleux, Sophie-Caroline, S194 (GS-1997), S209 (OS-2060)
 Sa Cunha, Antonio, S482 (PO-750), S525 (PO-2408)
 Sadalla, Sinan, S518 (PO-1124)
 Sadiq Hamid, Saeed, S438 (PO-2280)
 Sadirova, Shakhlo, S642 (PO-424)
 Sadler, Matthew, S315 (PO-1099)
 Saeb-Parsy, Kouros, S233 (OS-2656)
 Saenz de Urturi, Diego, S497 (PO-133)
 Saey, Yvan, S450 (PO-1333)
 Saez-Rodriguez, Julio, S690 (PO-2090)
 Safadi, Rifaat, S220 (OS-2854)
 Safdar, Nawaz, S464 (PO-594)
 Saffers, Pierre, S206 (OS-1619)
 Saffioti, Francesca, S226 (OS-894), S272 (OS-1756)
 Sagalova, Olga, S291 (OS-2717), S294 (LBP-2730)
 Saghire, Hussein El, S695 (PO-175)
 Sahney, Amrishi, S210 (OS-2142)
 Sahoo, Manoj, S438 (PO-2280)
 Saigal, Sanjiv, S438 (PO-2280)
 Saini, Monika, S228 (OS-1586), S435 (PO-1755)
 Salama, Marwa, S803 (PO-2320)
 Sala, Margarita, S495 (PO-2799), S690 (PO-2090)
 Salamé, Ephrem, S518 (PO-1209)
 Salehi, Shayon, S771 (PO-1339)
 Salem, Riad, S246 (OS-1674)
 Salgado, Pablo, S346 (PO-864)
 Saliba, Faouzi, S194 (GS-1997), S209 (OS-2060), S461 (PO-351), S462 (PO-353)
 Salido, Eduardo, S680 (PO-891), S694 (PO-2770)
 Sallahuddin, Sultan, S776 (PO-2193)
- Salpini, Romina, S704 (PO-1928), S728 (PO-1996)
 Saltel, Frederic, S510 (PO-2865)
 Saludes, Veronica, S795 (PO-1307)
 Saludes, Verónica, S786 (PO-1415)
 Salvador, Fernando, S664 (PO-2047)
 Salvati, Antonio, S729 (PO-2261)
 Salvatori, Mauro, S769 (PO-951)
 Salvetti, Anna, S702 (PO-1688), S703 (PO-1711)
 Salvoza, Noel, S619 (PO-1359)
 Samakidou, ANNA, S747 (PO-1661)
 Samartsidis, Pantelis, S292 (OS-795)
 Samiotaki, Martina, S511 (PO-2920)
 Samji, Hasina, S782 (PO-862), S789 (PO-2708)
 Sannalkorpi, Henna, S260 (OS-2362)
 Samonakis, Demetrios N., S544 (PO-1334), S737 (PO-715)
 Sampaziotis, Fotis, S233 (OS-2656)
 Samson, Michel, S307 (PO-2888)
 Samuel, Didier, S191 (GS-1065), S194 (GS-1997), S291 (OS-2717), S461 (PO-351), S462 (PO-353), S482 (PO-750), S525 (PO-2408), S717 (PO-813)
 Samyn, Marianne, S677 (PO-106)
 Sanabria-Cabrera, J., S302 (PO-1335), S304 (PO-1406)
 Sanabria-Cabrera, Judith, S303 (PO-1389)
 Sanai, Faisal, S636 (PO-2476)
 Sancez, Moises, S209 (OS-2060)
 Sanchez, Abel Acosta, S744 (PO-1386)
 Sanchez, Antonio, S208 (OS-845)
 Sánchez-Delgado, Jordi, S345 (PO-835)
 Sánchez, Fabián Betancourt, S694 (PO-2902)
 Sanchez-Fueyo, Alberto, S235 (OS-213), S431 (PO-1484)
 Sanchez, Juan Diego, S448 (PO-846)
 Sanchez, Katarzyna, S604 (PO-2210)
 Sanchez, Moises, S194 (GS-1997)
 Sanchez-Romero, Natalia, S459 (PO-2234)
 Sanchez, Yolanda, S255 (OS-2337), S584 (PO-2369)
 Sancho-Bru, Pau, S207 (OS-2028), S320 (PO-2043), S401 (PO-2113)
 Sandeman, Susan, S347 (PO-1045)
 Sandford, Richard, S685 (PO-1718)
 Sandford, Richard N., S420 (PO-1578)
 Sandrin, Laurent, S257 (OS-555)
 Sands, Caroline, S490 (PO-2070)
 Sanduzzi Zamparelli, Marco, S492 (PO-2242), S495 (PO-2799)
 Sanfiz, Anthony, S395 (PO-1505)
 Sangiovanni, Angelo, S492 (PO-2364), S524 (PO-2401), S782 (PO-697), S784 (PO-921)
 Sangro, Bruno, S243 (OS-295), S244 (OS-777), S246 (OS-1399)
 San Lee, Jin, S550 (PO-1880)
 San Martin, Javier, S201 (LBO-2592), S294 (LBP-2580)
 Sansom, Owen, S508 (PO-2787)
- Sansone, Vito, S514 (PO-591)
 Santamaria, Diego Burgos, S269 (OS-1769)
 Santamaria, Eva, S243 (OS-1948)
 Santiago, Antoine, S355 (PO-2194)
 Santiago, Jesús González, S495 (PO-2799), S746 (PO-1449)
 Santis, Adriano De, S799 (PO-2138)
 Santisteve, Sara Sopena, S732 (PO-2834)
 Santoro, Armando, S243 (OS-295)
 Santos, Ana, S443 (PO-2801)
 Santos, Beatriz Gómez, S497 (PO-133), S612 (PO-627)
 Santos-Laso, Álvaro, S269 (OS-1769), S537 (PO-685)
 Santos, Melina, S292 (OS-728)
 Sanyal, Arun, S254 (OS-1611), S257 (OS-555), S297 (LBP-2907), S326 (PO-675), S574 (PO-1518), S579 (PO-1714), S586 (PO-2739), S597 (PO-1849), S610 (PO-231), S615 (PO-889), S616 (PO-981), S624 (PO-2287), S625 (PO-2290), S628 (PO-2329)
 Sanz, Alicia Gómez, S783 (PO-881)
 Sanz, Jesús Sanz, S783 (PO-881)
 Sanz, Vanesa, S218 (OS-1478)
 Sapena, Víctor, S492 (PO-2242), S495 (PO-2799), S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
 Sapisochin, Gonzalo, S508 (PO-2742)
 Saracco, Margherita, S234 (OS-116)
 Saracino, Annalisa, S767 (PO-694)
 Saraya, Anoop, S212 (OS-31), S371 (PO-1151), S378 (PO-1705), S381 (PO-2294), S438 (PO-2280), S635 (PO-2319)
 Sarin, Sanjay, S647 (PO-739), S666 (PO-2081)
 Sarin, Shiv, S406 (PO-2010), S459 (PO-2234)
 Sarin, Shiv K., S666 (PO-2081)
 Sarin, Shiv Kumar, S239 (OS-2686), S330 (PO-2313), S340 (PO-2213), S635 (PO-2319)
 Sarmati, Loredana, S704 (PO-1928), S728 (PO-1996)
 Sarowar, Arif, S751 (PO-1841), S755 (PO-2269)
 Sar, Polinn, S289 (OS-865)
 Sarrazin, Christoph, S771 (PO-1029), S778 (PO-52), S791 (PO-51), S792 (PO-153)
 Sarrias, Maria-Rosa, S690 (PO-2090)
 Sassatelli, Romano, S307 (PO-48)
 Sassi, Lisa, S478 (PO-1422)
 Sastre, Lydia, S431 (PO-1484)
 Satapathy, Sanjaya, S357 (PO-2634), S649 (PO-1035)
 Sator-Schmitt, Melanie, S219 (OS-2754)
 Satoskar, Rohit S., S208 (OS-845)
 Satriano, Letizia, S240 (OS-179)
 Sattanino, Damiana, S217 (OS-874)
 Saueressig, Camila, S639 (PO-205)
 Sauer, Hagen, S473 (PO-2821)

Author Index

- Sauerzopf, Kristen, S508 (PO-2742)
Saunders, Emily, S423 (PO-60),
S464 (PO-841), S473 (PO-2821)
Saur, Dieter, S509 (PO-2798)
Saverio Belli, Luca, S466 (PO-935),
S472 (PO-2121)
Saviano, Antonio, S196 (GS-2069),
S247 (OS-2190)
Savvidou, Savvoula, S544 (PO-1334),
S747 (PO-1661)
Sawhney, Rohit, S358 (PO-2683),
S386 (PO-2685)
Sawiak, Stephen, S233 (OS-2656)
Sayed, Anwar A., S245 (OS-1145)
Sayed, Hamdy, S803 (PO-2320)
Scalfaro, Pietro, S761 (PO-2844)
Scatton, Olivier, S518 (PO-1209)
Schaapman, Jelte, S336 (PO-1051)
Schaefer, Benedikt, S677 (PO-323)
Schaefer, Heidi, S463 (PO-530)
Schaefer, Niklaus, S244 (OS-777)
Schaeffer, Eugénie, S212 (OS-1491)
Schaeper, Ute, S301 (PO-1185),
S612 (PO-627)
Schafer, Peter, S587 (PO-283)
Schattenberg, Jörn, S256 (OS-538),
S259 (OS-1592), S266 (OS-2831),
S398 (PO-1589), S399 (PO-1609),
S564 (PO-919), S573 (PO-1336),
S599 (PO-1942)
Schattenberg, Jörn M., S255 (OS-243),
S556 (PO-167), S560 (PO-632),
S568 (PO-1056), S579 (PO-1777)
Schauffler, Dunja, S364 (PO-532)
Schefczyk, Stefan, S706 (PO-2105)
Scheiner, Bernhard, S216 (OS-1544),
S236 (OS-498), S270 (OS-507),
S362 (PO-309), S363 (PO-310),
S364 (PO-532), S365 (PO-560),
S374 (PO-1249), S376 (PO-1316),
S377 (PO-1613), S383 (PO-2403),
S521 (PO-1312), S645 (PO-533),
S681 (PO-1243)
Schepis, Filippo, S252 (OS-571)
Scherbakovsky, Stacey, S770 (PO-983)
Schiano, Thomas, S193 (GS-1213)
Schiff, Eugene R., S736 (PO-482)
Schilcher, Gernot, S194 (GS-1997),
S209 (OS-2060)
Schilsky, Michael, S280 (OS-2590)
Schinazi, Raymond F., S744 (PO-1386)
Schirmacher, Peter, S318 (PO-1651),
S752 (PO-2089)
Schirmbeck, Reinhold, S498 (PO-196)
Schirwani, Nawa, S645 (PO-533)
Schledzewski, Kai, S393 (PO-793)
Schleinitz, Nicolas, S229 (OS-1728)
Schlett, Christopher, S535 (PO-566)
Schlupe, Thomas, S289 (OS-1430)
Schlund, Franziska, S698 (PO-626)
Schmelzle, Moritz, S521 (PO-1420)
Schmidbauer, Caroline, S800 (PO-2191)
Schmid, Christian, S393 (PO-793)
Schmid, Roland M., S498 (PO-336)
Schmidt, Nathalie M., S451 (PO-1460)
Schmiel, Marcel, S501 (PO-1629)
Schminke, Ulf, S535 (PO-566)
Schmitt, Jennifer, S501 (PO-1304)
Schmitt, Theresa, S547 (PO-1667)
Schneider, Anne, S278 (OS-1396)
Schneider, Annika, S262 (OS-584)
Schneider, Carolin Victoria, S405 (PO-1558),
S677 (PO-323)
Schneider, Ferenc, S655 (PO-1572)
Schneider, Kai Markus, S677 (PO-323)
Schneider, Martin, S752 (PO-2089)
Schneider, William M., S603 (PO-2161)
Schneller, Doris, S219 (OS-2754)
Schoder, Maria, S213 (OS-925)
Schoenhofer, Katharina, S213 (OS-925)
Schoenmakers, Birgitte, S581 (PO-1895)
Schöler, Ulrike, S522 (PO-1745)
Scholtes, Caroline, S695 (PO-258),
S713 (PO-408)
Schönhaber, Hiltrud, S393 (PO-793)
Schönung, Maximilian, S754 (PO-2243)
Schrader, Jil Alexandra, S705 (PO-1950)
Schramm, Christoph, S193 (GS-1213),
S226 (OS-894), S227 (OS-1088),
S230 (OS-2782), S408 (PO-629),
S423 (PO-60), S430 (PO-1418),
S437 (PO-2230), S451 (PO-1472),
S473 (PO-2211)
Schregel, Ida, S437 (PO-2230)
Schreiner, Andrew, S581 (PO-1826)
Schrimpf, Alina, S528 (PO-1357)
Schropp, Jonas, S466 (PO-1126)
Schubert, Maren, S423 (PO-60)
Schubert, Raphael, S800 (PO-2191)
Schuehle, Svenja, S752 (PO-2089),
S754 (PO-2243)
Schuetz, Ekkehard, S464 (PO-841)
Schuijs, Martijn, S230 (OS-1171)
Schultalbers, Marie, S370 (PO-1146)
Schulte, Benjamin, S370 (PO-1146)
Schulte, Lina, S351 (PO-1670)
Schulze, Kornelius, S236 (OS-498),
S506 (PO-2227), S522 (PO-1745)
Schulze zur Wiesch, Julian,
S294 (LBP-2730), S351 (PO-1701)
Schulz, Martin, S332 (PO-2358)
Schumacher, Justin, S529 (PO-1606)
Schuppan, Detlef, S633 (PO-1899)
Schuster, Catherine, S196 (GS-2069),
S247 (OS-2190), S392 (PO-692),
S695 (PO-175), S780 (PO-602)
Schuster, Heiko, S246 (OS-1399)
Schuster, Linda, S754 (PO-2243)
Schütz, Angelika, S800 (PO-2191)
Schuurman, Alex, S225 (OS-706)
Schwabe, Christian, S289 (OS-1430),
S294 (LBP-2580), S741 (PO-1004)
Schwabl, Philipp, S362 (PO-309),
S363 (PO-310), S364 (PO-532),
S365 (PO-560), S383 (PO-2403)
Schwanke, Cornelia, S800 (PO-2191)
Schwartz, Myron, S241 (OS-699)
Schwarzenbach, Heidi, S506 (PO-2227)
Schwarz, Lilian, S518 (PO-1209)
Schwarz, Michael, S800 (PO-2191)
Schwarz, Tatjana, S454 (PO-1983)
Schweighoffer, Tamas, S196 (GS-2069),
S247 (OS-2190)
Schwenke, Julia, S498 (PO-336)
Schwinge, Dorothee, S451 (PO-1472)
Sciannamè, Natale, S769 (PO-951)
Sciveres, Marco, S193 (GS-1213)
Sclair, Seth, S208 (OS-845)
Scott, Beth, S713 (PO-408)
Scott, Charlotte L., S450 (PO-1333),
S453 (PO-1649), S456 (PO-2456)
Scott, Deborah, S613 (PO-668),
S618 (PO-1198)
Scott, John, S493 (PO-2687)
Scott, Karen, S643 (PO-425)
Scott, Nick, S658 (PO-1813), S797 (PO-1872)
Scott, Russell, S294 (LBP-2580)
Scutari, Rossana, S704 (PO-1928)
Seabright, Alex, S342 (PO-2851)
Sebastiani, Giada, S373 (PO-1230),
S540 (PO-831)
Sebode, Marcial, S262 (OS-584),
S423 (PO-60), S430 (PO-1418)
Secchi, Maria Francesca, S193 (GS-1213)
Secher, Thomas, S223 (OS-1847)
Sedki, Mai, S193 (GS-1213)
Seeger, John D., S254 (OS-1780),
S434 (PO-1664)
Segal, Michal, S419 (PO-1311)
Segeal, Olivier, S289 (OS-865)
Segovia, Jose, S680 (PO-891),
S694 (PO-2770)
Segura, Ariadna Rando, S663 (PO-2014),
S664 (PO-2047)
Sehgal, Rashi, S330 (PO-2313)
Seifert, Gabriel, S262 (OS-584)
Sejling, Anne-Sophie, S610 (PO-231)
Selec, Muharrem, S451 (PO-1472)
Selvapatt, Nowlan, S354 (PO-1998)
Selvaraj, Emmanuel, S259 (OS-1592),
S418 (PO-1026)
Selzner, Nazia, S228 (OS-1586)
Semmler, Georg, S252 (OS-571),
S270 (OS-507), S364 (PO-532),
S374 (PO-1249), S376 (PO-1316),
S377 (PO-1613), S542 (PO-1205),
S552 (PO-2328), S570 (PO-1195),
S573 (PO-1220), S645 (PO-533),
S681 (PO-1243)
Semmler, Marie, S542 (PO-1205),
S552 (PO-2328), S573 (PO-1220)
Sempoux, Christine, S588 (PO-470),
S679 (PO-570)
Sem, Xiaohui, S660 (PO-1877)
Sen, Gourab, S386 (PO-2788),
S493 (PO-2687)
Sen, Partho, S256 (OS-538), S605 (PO-2322)
Senra, Ana, S391 (PO-479)
Senzolo, Marco, S216 (OS-1544),
S307 (PO-48), S488 (PO-1238),
S668 (PO-2097)
Seoane, Samuel, S249 (OS-1355)

- Seo, Gi Hyen, S720 (PO-1115)
- Seok Kim, Young, S305 (PO-1947), S369 (PO-1103)
- Seok Lee, Byung, S305 (PO-1947)
- Seok Seo, Yeon, S345 (PO-714)
- Seon Kim, Hye, S488 (PO-1275)
- Seoub Kim, Jin, S488 (PO-1275)
- Seo, Yeon Seok, S286 (OS-1892), S720 (PO-1115), S743 (PO-1270)
- Sepúlveda-Crespo, Daniel, S781 (PO-689)
- Serfaty, Lawrence, S253 (OS-612), S536 (PO-614)
- Serfert, Yvonne, S778 (PO-52), S791 (PO-51)
- Serisawa, Reza, S593 (PO-1407)
- Seronde, Marie-France, S584 (PO-2030)
- Seror, Olivier, S198 (GS-945), S518 (PO-1209), S520 (PO-1263)
- Serra, Eugenio, S668 (PO-2097)
- Serra, Margarida, S457 (PO-1154)
- Serra, Marina, S500 (PO-1118), S627 (PO-2312)
- Serra, Miguel, S788 (PO-1919)
- Serrano-Macia, Marina, S243 (OS-1948), S301 (PO-1185), S320 (PO-2043), S502 (PO-1752), S612 (PO-627), S624 (PO-2192)
- Serrano, Maria José, S694 (PO-2902)
- Serrano, Sandra, S209 (OS-2060)
- Serrano, Sandro, S194 (GS-1997)
- Serre, Nuria, S664 (PO-2047)
- Seto, Wai-Kay, S368 (PO-1094), S749 (PO-1791), S751 (PO-1841), S761 (PO-2844), S773 (PO-1871)
- Sette, Alessandro, S454 (PO-1983)
- Seubnooch, Patcharamon, S603 (PO-2186)
- Seul ki, Han, S327 (PO-984)
- Seurinck, Ruth, S450 (PO-1333)
- Sevastianos, Vasilis, S737 (PO-715)
- Sevdali, Eirini, S422 (PO-2681)
- Sevinsky, Heather, S203 (LBO-2764), S760 (PO-2822), S761 (PO-2823), S762 (PO-2879)
- Sezgin, Gulden Can, S671 (PO-2288)
- Sezgin, Orhan, S671 (PO-2288)
- Sgueglia, Tommaso, S656 (PO-1593)
- Shadab Siddiqui, Mohammad, S460 (PO-212)
- Shadaker, Shaun, S274 (OS-551), S643 (PO-504), S773 (PO-1691), S797 (PO-1553)
- Shafie, Ahmad Al, S803 (PO-2320)
- Shafi, Syed Mushfiq, S796 (PO-1533)
- Shafir, Asher, S220 (OS-2854)
- Shah, Altaf, S796 (PO-1533)
- Shah, Bharti, S534 (PO-534)
- Shah, Darshini, S198 (GS-1645)
- Shaheen, Abdel-Aziz, S315 (PO-1099), S368 (PO-1064)
- Shah, Hasnain A., S378 (PO-1987)
- Shah, Jaymin, S613 (PO-668)
- Shah, Rajiv, S670 (PO-2131)
- Shah, Samir, S438 (PO-2280)
- Shah, Sujal, S593 (PO-1504)
- Shah, Vicki, S540 (PO-969)
- Shaikh, Anum, S398 (PO-1589), S399 (PO-1609)
- Shakhin, Victoria, S471 (PO-1773)
- Shalaby, Sarah, S488 (PO-1238), S668 (PO-2097)
- Shamsaddini, Amirhossein, S220 (OS-119), S403 (PO-418)
- Shamseldeen, Ahmed, S803 (PO-2320)
- Shanahan, William, S493 (PO-2612)
- Shang, Jia, S759 (PO-2738)
- Shang, Qing-Hua, S709 (PO-218)
- Shang, Xiaojuan, S772 (PO-1397)
- Shang, Ying, S251 (OS-293)
- Shanis, Zahil, S254 (OS-1611), S602 (PO-2123)
- Shao, Chuxiao, S629 (PO-1091)
- Shao, Jianbo, S359 (PO-2688), S368 (PO-1094), S629 (PO-1091), S650 (PO-1330)
- Sharara, Alaa, S636 (PO-2476)
- Sharma, Divya, S686 (PO-1758)
- Sharma, Prativa, S476 (PO-982)
- Sharma, Praveen, S632 (PO-1696)
- Sharma, Rohini, S245 (OS-1145), S490 (PO-2070)
- Sharma, Sachin, S388 (PO-89)
- Sharma, Sanchit, S212 (OS-31), S371 (PO-1151), S378 (PO-1705), S381 (PO-2294), S438 (PO-2280), S635 (PO-2319)
- Sharma, Shvetank, S406 (PO-2010)
- Sharvadze, Lali, S797 (PO-1553)
- Shawa, Isaac T., S670 (PO-2131)
- Shawcross, Debbie L., S207 (OS-2158), S220 (OS-1167), S406 (PO-1763)
- Shaw, Robin, S508 (PO-2787)
- Shaw, Tim, S283 (OS-2826)
- Shearer, Jessica, S367 (PO-1040)
- Sheehan, Julia, S766 (PO-637)
- Sheen, I-Shyan, S788 (PO-2008)
- Sheikh, Aasim, S578 (PO-1689)
- Sheikh, Mohammed, S194 (GS-1997), S209 (OS-2060)
- Sheikh, Muhammad Y., S297 (LBP-2907)
- Shkhtman, Louis, S750 (PO-1837)
- Sheldon, Julie, S697 (PO-611)
- Shen, Anna, S718 (PO-947)
- Shen, Feng, S259 (OS-1592)
- Shengir, Mohamed, S373 (PO-1230)
- Shen, Ling, S287 (OS-44), S288 (OS-211), S733 (PO-43), S738 (PO-824)
- Shen, Steve, S460 (PO-212)
- Shen, Xian, S795 (PO-987)
- Shen, Yefeng, S501 (PO-1629)
- Shen, Yun, S243 (OS-295)
- Shepherd, Emma, S393 (PO-938)
- Sheron, Nick, S646 (PO-640), S675 (PO-2861)
- Sheth, Abhishek, S274 (OS-1381)
- Shetty, Shishir, S230 (OS-1171), S464 (PO-594)
- Shevell, Diane, S573 (PO-1336)
- Shibolet, Oren, S437 (PO-2230), S546 (PO-1436)
- Shiffman, Mitchell, S433 (PO-1644), S578 (PO-1689)
- Shiha, Gamal, S239 (OS-2686), S636 (PO-2476)
- Shi, Hongxue, S607 (PO-2653)
- Shi, Juanjuan, S758 (PO-2735)
- Shilton, Sonjelle, S643 (PO-504), S647 (PO-739), S660 (PO-1877), S666 (PO-2081), S672 (PO-2424), S773 (PO-1691), S776 (PO-2218)
- Shima, Toshihide, S259 (OS-1592)
- Shim, Jae-Jun, S550 (PO-1880), S743 (PO-1270)
- Shim, Ju Hyun, S528 (PO-895), S721 (PO-1385)
- Shingina, Alexandra, S463 (PO-530)
- Shin, Su-Hyun, S265 (OS-2450)
- Shirgaonkar, Niranjan, S700 (PO-861)
- Shirin, Dor, S556 (PO-2791)
- Shi, Shaojun, S418 (PO-903)
- Shi, Tiffany, S422 (PO-2388)
- Shivakumar, Pranavkumar, S442 (PO-2761)
- Shi, Yiwen, S709 (PO-218)
- Shlomain, Amir, S272 (OS-798), S556 (PO-2791), S801 (PO-2240)
- Shoae, Saeed, S222 (OS-2044), S406 (PO-1763)
- Sho, Eiketsu, S620 (PO-1908), S621 (PO-1961)
- Shokoohi, Pooya, S498 (PO-336)
- Shokri, Fazel, S753 (PO-2106)
- Shoukat, Bilal, S493 (PO-2612)
- Shrestha, Ichhya, S609 (PO-230), S610 (PO-231)
- Shringarpure, Reshma, S204 (LBO-2800), S618 (PO-1314), S619 (PO-1762)
- Shteyer, Eyal, S279 (OS-1554)
- Shukla, Akash, S277 (OS-1172), S438 (PO-2280)
- Shukla, Ruchi, S513 (PO-573)
- Shumbayawonda, Elizabeth, S408 (PO-629), S634 (PO-2094)
- Sia, Daniela, S240 (OS-615), S241 (OS-699), S499 (PO-541), S521 (PO-1420)
- Siddique, Shafiq, S802 (PO-2275)
- Siddiqui, Kashif, S356 (PO-2608)
- Sidhu-Brar, Sandeep, S524 (PO-2075)
- Sidney, John, S454 (PO-1983)
- Siebenhüner, Alexander, S236 (OS-498)
- Siederdisen, Christoph Hoener zu, S707 (PO-2293)
- Siegele, Martin, S796 (PO-1508)
- Siegerink, Sebastiaan, S359 (PO-2753)
- Siena, Riccardo Rayan, S478 (PO-1422)
- Sievert, William, S289 (OS-1430)
- Sigal, Samuel, S208 (OS-845)
- Sigon, Giordano, S785 (PO-1247), S786 (PO-1542)
- Sigurdardottir, Bryndis, S670 (PO-2127)
- Sikandar, Usama, S518 (PO-1124)
- Sikaroodi, Masoumeh, S220 (OS-119), S309 (PO-117), S403 (PO-418)
- Silberstein, Francesca Ceccherini, S704 (PO-1928), S728 (PO-1996)

Author Index

- Silungwe, Niza, S670 (PO-2131)
Silva, Joel, S628 (PO-818)
Silva-Junior, Gilberto, S307 (PO-48)
Silva, Marcelo, S669 (PO-2108)
Silva, Silvia, S475 (PO-2890)
Silverman, Edwin, S334 (PO-134)
Simão, André L., S634 (PO-2184)
Simbrunner, Benedikt, S270 (OS-507),
S362 (PO-309), S363 (PO-310),
S364 (PO-532), S365 (PO-560),
S374 (PO-1249), S376 (PO-1316),
S377 (PO-1613), S383 (PO-2403),
S645 (PO-533), S681 (PO-1243)
Sim, Hao-Wen, S508 (PO-2742)
Simoesegenio, Melanie, S307 (PO-2888)
Simões, Inês C.M., S432 (PO-1574)
Simon-Coma, Marina, S689 (PO-2090)
Simonelli, Claudia, S792 (PO-81)
Simone, Loredana, S353 (PO-1767)
Simón Espinosa, Jorge, S301 (PO-1185)
Simón, Jorge, S612 (PO-627)
Simon, Karl-Georg, S778 (PO-52),
S791 (PO-51)
Simón, Miguel Angel, S746 (PO-1449)
Simonova, Marieta, S207 (OS-2158),
S646 (PO-640), S675 (PO-2861)
Simon Schiergens, Tobias, S389 (PO-410)
Simonsen, Hans Erling, S734 (PO-111)
Simpson, Kenneth J., S235 (OS-213)
Simsek, Cem, S671 (PO-2288)
Sims, Karen, S203 (LBO-2764),
S760 (PO-2822), S761 (PO-2823),
S762 (PO-2879)
Singal, Amit, S246 (OS-1674),
S496 (PO-2812)
Singal, Ashwani, S199 (GS-2309),
S465 (PO-922), S655 (PO-1551)
Singanayagam, Arjuna, S306 (PO-2178)
Singh, Jaswinder, S406 (PO-2010),
S796 (PO-1533)
Singh, Jennifer, S455 (PO-2173)
Singh, Namrata, S212 (OS-31)
Singh, Ruchi, S686 (PO-1758)
Singh, Surender, S360 (PO-2832)
Singh, Sushrut, S371 (PO-1151)
Singh, Virendra, S360 (PO-2832),
S438 (PO-2280), S647 (PO-739)
Sinha, Praveen Kumar, S647 (PO-739)
Sinioja, Tim, S256 (OS-538)
Sinkus, Ralph, S585 (PO-2485)
Sinnreich, Magdalena Filipowicz,
S449 (PO-896)
Sirlin, Claude, S577 (PO-1648)
Sirli, Roxana, S398 (PO-1582)
Siskos, Alexandros, S245 (OS-1145)
Si, Tengfei, S503 (PO-1771)
Siu, Gordon, S539 (PO-825)
Siva, Sasikala, S660 (PO-1877)
Sjöberg, Daniel, S271 (OS-686)
Sjöblom, Nelli, S444 (PO-2830)
Skibsted Kornerup, Linda, S482 (PO-707)
Skjaeret, Tore, S622 (PO-2006)
Skladany, Lubomir, S547 (PO-1693)
Skoglund, Catarina, S284 (OS-2864)
Slaughter, James, S463 (PO-530)
Sleiman, Ahmad, S708 (PO-2684)
Smagris, Eriks, S588 (PO-475)
Smesnoi, Valentina, S750 (PO-1837)
Smethurst, Peter, S771 (PO-1339)
Smets, Lena, S277 (OS-1172)
Smith, Aaron, S763 (PO-72)
Smith, Belinda, S426 (PO-770)
Smith, David, S720 (PO-1257),
S742 (PO-1196), S744 (PO-1386)
Smith, Graham, S420 (PO-1578)
Smith, Helen, S434 (PO-1748)
Smith, John, S222 (OS-2044)
Smith, Loren, S229 (OS-1728)
Smith, Stacey, S771 (PO-1339)
Smith, Stuart, S292 (OS-795)
Smith, Susan, S455 (PO-2173),
S571 (PO-1202)
Smits, Maarten, S245 (OS-972)
Smoot Malecha, Elizabeth, S439 (PO-2327)
Smout, Ayla, S527 (PO-608)
Smout, Elizabeth, S273 (OS-199)
Smyk, Wiktor, S432 (PO-1574)
Soardo, Giorgio, S261 (OS-297),
S600 (PO-1986), S600 (PO-2033)
Sobesky, Rodolphe, S355 (PO-2194),
S717 (PO-813)
Sobral, Mafalda, S475 (PO-2890)
Sobreviela, Maria Pilar García,
S337 (PO-1643)
Socha, Piotr, S193 (GS-1213),
S634 (PO-2094)
Söderling, Jonas, S227 (OS-1088)
Soffientini, Ugo, S330 (PO-2147)
Soffredini, Roberta, S782 (PO-697),
S782 (PO-717)
Sofia, Michael J., S203 (LBO-2764),
S281 (OS-595), S760 (PO-2822),
S761 (PO-2823), S762 (PO-2879)
Sogni, Philippe, S194 (GS-1587),
S678 (PO-561)
Sohn, Ki -Young, S265 (OS-2450)
Soholt Larsen, Magnus, S223 (OS-1847)
Soin, Arvinder Singh, S438 (PO-2280)
Sojoodi, Mozhdeh, S212 (OS-1491)
Solà, Eulàlia, S799 (PO-2021)
Solé, Cristina, S345 (PO-835)
Solé, Gemma, S345 (PO-835)
Soliman, Reham, S239 (OS-2686),
S636 (PO-2476)
Sologashvili, Manana, S768 (PO-908)
Song, Chuan, S629 (PO-1091)
Song, Do Seon, S743 (PO-1270)
Song, Jianguo, S596 (PO-1797)
Song, Jie, S726 (PO-1810)
Song, Tianqiang, S523 (PO-1883)
Song, Ying, S368 (PO-1094)
Soni, Divya, S666 (PO-2081)
Sonneveld, Milan, S718 (PO-915),
S733 (PO-80), S747 (PO-1661),
S749 (PO-1791), S751 (PO-1841)
Soo Byun, Kwan, S345 (PO-714)
Sood, AJIT, S438 (PO-2280)
Soon Choi, Ho, S402 (PO-2695)
Soo Sung, Pil, S460 (PO-186),
S488 (PO-1275)
Sophie, METIVIER, S793 (PO-468)
Soppe, Sally, S283 (OS-2826)
Soria, Isabel Carmona, S779 (PO-578)
Soria, Maria Eugenia, S802 (PO-2295)
Soriano, German, S342 (PO-2420)
Soubrane, Olivier, S518 (PO-1209)
Soufi, Nisreen, S279 (OS-1554)
Soulayrac, Cathy, S352 (PO-1712)
Soulette, Cameron, S284 (OS-654),
S725 (PO-1789)
Souliotis, Kyriakos, S653 (PO-1421)
Soumelis, Vassili, S708 (PO-2684)
Sousa, María Ángeles Jiménez,
S783 (PO-881)
Soussan, Patrick, S708 (PO-2684)
Sovann, Saren, S289 (OS-865)
Spaans, Johanna, S714 (PO-420)
Spahn, Stephan, S236 (OS-498)
Spann, Ashley, S463 (PO-530)
Spataro, Joseph, S581 (PO-1808)
Speletas, Matthaios, S422 (PO-2681)
Spelman, Tim, S358 (PO-2683),
S386 (PO-2685)
Spires, Thomas, S395 (PO-1505)
Spittaels, Kurt, S718 (PO-947)
Spooren, Corinne, S554 (PO-2673)
Sporea, Ioan, S398 (PO-1582)
Sprengers, Dave, S245 (OS-972)
Sprinzl, Martin, S560 (PO-632)
Squillante, Maria, S764 (PO-388),
S769 (PO-951)
Squires, Katherine, S742 (PO-1240),
S743 (PO-1251)
Srikanth, Akshaya, S498 (PO-196)
Srinivas, Jay, S801 (PO-2240)
Sriphoosanaphan, Supachaya,
S719 (PO-1000)
Srivastava, Dhyanes, S455 (PO-2173)
Ssebyatika, George, S282 (OS-1062)
Stach, Jesse, S368 (PO-1064)
Stadlbauer, Vanessa, S194 (GS-1997),
S209 (OS-2060)
Stadler, Daniela, S753 (PO-2106)
Stadler, Mira, S754 (PO-2243)
Stæhr Madsen, Bjørn, S313 (PO-487)
Staels, Bart, S588 (PO-470), S608 (PO-2858),
S608 (PO-2883)
Staettermayer, Albert, S683 (PO-1500)
Staffer, Simone, S607 (PO-2623)
Stahl, Felix, S430 (PO-1418)
Stalke, Amelie, S682 (PO-1354)
Stal, Per, S269 (OS-1627), S339 (PO-1787)
Stamatakis, Georgios, S511 (PO-2920)
Stamm, Luisa, S290 (OS-2299),
S736 (PO-482)
Stamouli, Marilena, S333 (PO-2870)
Stanca, Carmen, S686 (PO-1809),
S690 (PO-2120)
Stanciu, Carol, S216 (OS-1544)
Stange, Jan, S194 (GS-1997),
S209 (OS-2060)
Stangel, Martin, S423 (PO-60)

- Staniczek, Theresa, S393 (PO-793)
 Stanley, Adrian, S489 (PO-1729)
 Stathis, Peter, S311 (PO-302)
 Stättermayer, Albert, S270 (OS-507),
 S362 (PO-309), S363 (PO-310),
 S365 (PO-560), S376 (PO-1316),
 S377 (PO-1613), S383 (PO-2403),
 S681 (PO-1244)
 Stauber, Rudolf, S259 (OS-1592)
 Stauber, Rudolf E., S318 (PO-1651)
 Stauffer, Katharina, S259 (OS-1592),
 S592 (PO-1369)
 Stebbins, Jeffrey, S596 (PO-1797)
 Steen Petersen, Pia, S399 (PO-1831)
 Steensels, Sandra, S603 (PO-2161)
 Stefanescu, Horia, S216 (OS-1544),
 S318 (PO-1651), S377 (PO-1474)
 Stefanini, Bernardo, S533 (PO-441)
 Stege, Paul B., S457 (PO-279)
 Steiger, Katja, S498 (PO-336)
 Steinbach, Bettina, S506 (PO-2227)
 Steinberg, Alexandra (Sasha),
 S686 (PO-1809), S690 (PO-2120)
 Stein, Kerstin, S429 (PO-1294)
 Steinmann, Eike, S703 (PO-1907),
 S705 (PO-1950)
 Stein, Maya, S427 (PO-860)
 Stein, Philip, S684 (PO-1665)
 Stenzel, Ansgar, S603 (PO-2161)
 Stepanova, Maria, S395 (PO-1505),
 S468 (PO-1169), S592 (PO-1235),
 S655 (PO-1551)
 Stepanova, Tatyana, S291 (OS-2717),
 S294 (LBP-2730)
 Stephan, Christoph, S771 (PO-1029)
 Stephens, Camilla, S304 (PO-1406)
 Sterling, Richard, S403 (PO-418)
 Stern, Christiane, S291 (OS-2717),
 S551 (PO-2002)
 Sterneck, Martina, S193 (GS-1213)
 Steuer, Holly M., S281 (OS-595)
 Stever, Kim, S281 (OS-595)
 Sticht, Carsten, S393 (PO-793)
 Stichtenoth, Dirk O., S370 (PO-1146)
 Stickel, Felix, S570 (PO-1195)
 Stimac, Davor, S491 (PO-2181)
 Stirrup, Tracey, S777 (PO-2352)
 Stockdale, Alexander, S670 (PO-2131)
 Stoehr, Albrecht, S778 (PO-52),
 S791 (PO-51)
 Stoerk, Stefan, S636 (PO-2386)
 Stoica, Luminita, S477 (PO-1119)
 Stokman, Geurt, S623 (PO-2099)
 Stols-Gonçalves, Daniela, S585 (PO-2485)
 Stooove, Mark, S797 (PO-1872)
 Storz, Corinna, S535 (PO-566)
 Stottmeier, Benjamin, S752 (PO-2089)
 Støy, Sidsel, S406 (PO-1763)
 St-Pierre, Marie V., S603 (PO-2186)
 Straniero, Sara, S223 (OS-1847),
 S597 (PO-1849)
 Strassburg, Christian, S213 (OS-513),
 S227 (OS-1088), S351 (PO-1670)
 Strassburg, Christian P., S476 (PO-246)
 Strasser, Michael, S570 (PO-1195)
 Strasser, Simone, S203 (LBO-2764),
 S265 (OS-1746), S289 (OS-1430),
 S578 (PO-1689), S731 (PO-2575)
 Strathdee, Gordon, S513 (PO-573)
 Strathie, Kirstin, S314 (PO-607)
 Straub, Beate, S599 (PO-1942)
 Streinu-Cercel, Adrian, S291 (OS-2717)
 Stringer, Rowan, S534 (PO-534)
 Strnad, Pavel, S201 (LBO-2592),
 S405 (PO-1558), S570 (PO-1195),
 S677 (PO-323)
 Ströbel, Simon, S604 (PO-2210)
 Ströh, Luisa J., S282 (OS-1062)
 Stroh, Plamena, S338 (PO-1684)
 Stroumpouli, Evangelia, S350 (PO-1471)
 Stuart, Katherine, S353 (PO-1766)
 Sturm, Ekkehard, S687 (PO-1811)
 Sturm, Nathalie, S565 (PO-941)
 Stvilia, Ketevan, S773 (PO-1691)
 Subhan, Amna, S438 (PO-2280)
 Subhani, Mohsan, S274 (OS-1381)
 Subhanová, Iva, S689 (PO-2040)
 Subic-Levrero, Miroslava, S350 (PO-1549)
 Subudhi, P. Debishree, S340 (PO-2213)
 Su, Chien-Wei, S483 (PO-1090),
 S518 (PO-1142)
 Suemizu, Hiroshi, S603 (PO-2161)
 Sukanami, Hideki, S267 (OS-681)
 Sugiyama, Aya, S532 (PO-19)
 Sühs, Kurt-Wolfram, S423 (PO-60)
 Su, Jessica, S334 (PO-134)
 Sukeepaisarnjaroen, Wattana,
 S203 (LBO-2764), S731 (PO-2575)
 Suk, Ki Tae, S332 (PO-2547)
 Sukriti, Sukriti, S330 (PO-2147),
 S330 (PO-2313), S340 (PO-2213)
 Suksawatamnuay, Sirinporn,
 S719 (PO-1000)
 Sulkowski, Mark, S736 (PO-482),
 S744 (PO-1286), S770 (PO-983)
 Sulpice, Thierry, S582 (PO-1927),
 S595 (PO-1727)
 Sultan, Ahmed, S494 (PO-2786),
 S497 (PO-2893)
 Sultanik, Philippe, S551 (PO-2002)
 Sumida, Yoshio, S259 (OS-1592)
 Su, Minghua, S795 (PO-987)
 Sundaram, Vinay, S361 (PO-2951),
 S424 (PO-210), S465 (PO-922),
 S496 (PO-2812)
 Sun, Fei, S735 (PO-397)
 Sung, Chang Ohk, S528 (PO-895)
 Sung, Pil Soo, S504 (PO-1825)
 Sun, Guangyong, S478 (PO-1346)
 Sun Jang, Eun, S305 (PO-1947)
 Sun, Jingwei, S359 (PO-2688)
 Sun, Lihui, S368 (PO-1094)
 Sun, Tong, S738 (PO-797), S795 (PO-987)
 Sun, Yameng, S400 (PO-1857)
 Suo, Yuhong, S523 (PO-1883)
 Sura, Asmiti, S198 (GS-1645)
 Surace, Lorenzo, S353 (PO-1767)
 Surdacka, Agata, S319 (PO-1708)
 Surguladze, Sophia, S274 (OS-551)
 Suri, Vithika, S239 (OS-2686),
 S284 (OS-654), S287 (OS-2225),
 S720 (PO-1309), S725 (PO-1789),
 S755 (PO-2338), S756 (PO-2395),
 S770 (PO-983)
 Susan, Davies, S318 (PO-1651)
 Sustarsic, Elahu Gosny, S593 (PO-1407)
 Sutcliffe, Caroline, S536 (PO-630)
 Sutherland, James D., S624 (PO-2192)
 Su, Ting, S529 (PO-1606)
 Sutter, Olivier, S487 (PO-1153),
 S520 (PO-1263)
 Sutti, Salvatore, S598 (PO-1916)
 Su, Tung-Hung, S629 (PO-1047),
 S749 (PO-1791), S751 (PO-1841)
 Su, Wei-Wen, S668 (PO-2103),
 S718 (PO-947)
 Suzuki, Takanori, S715 (PO-529)
 Svanberg, Ann Karin, S271 (OS-686)
 Svegliati-Baroni, Gianluca,
 S353 (PO-1767)
 Svendsen, Jan, S734 (PO-111)
 Svicher, Valentina, S704 (PO-1928),
 S728 (PO-1996)
 Swadling, Leo, S451 (PO-1460)
 Swain, Mark G., S228 (OS-1586),
 S315 (PO-1099), S368 (PO-1064)
 Swift, Lisa, S233 (OS-2656)
 Syed, Hussain, S420 (PO-1822)
 Syed, Taseen, S460 (PO-212)
 Symons, Julian, S700 (PO-1305),
 S720 (PO-1257), S742 (PO-1196),
 S744 (PO-1386)
 Syn, Wing-kin, S536 (PO-630)
 Sypsa, Vana, S286 (OS-1892),
 S747 (PO-1661)
 Syssoev, Yuriy, S590 (PO-725)
 Syutkin, Vladimir, S291 (OS-2717)
 Szabo, Gyongyi, S205 (OS-1293),
 S206 (OS-1663), S594 (PO-1547)
 Szabo, Olga, S655 (PO-1572)
 Szczepankiewicz, Benedykt,
 S432 (PO-1574)
 Szczerbinski, Mariusz, S319 (PO-1708)
 Szekeres, Thomas, S364 (PO-532)
 Szlavik, Janos, S655 (PO-1572)
 Taanman, Jan-Willem, S596 (PO-1753)
 Tabas, Ira, S607 (PO-2653)
 Taberner, David, S696 (PO-469),
 S706 (PO-2145), S732 (PO-2637),
 S732 (PO-2834), S737 (PO-774)
 Tachtatzis, Phaedra, S235 (OS-213)
 Tacke, Frank, S262 (OS-584),
 S266 (OS-2831), S401 (PO-2415),
 S495 (PO-2799), S563 (PO-836),
 S669 (PO-2108), S745 (PO-1419),
 S793 (PO-377), S794 (PO-773)
 Taddei, Maria Letizia, S606 (PO-2411)
 Tae Yoon, Ki, S294 (LBP-2580)
 Tagliamonte, Maria, S246 (OS-1399)
 Tai, Dean, S400 (PO-1857), S615 (PO-889)
 Taik, Patricia, S241 (OS-699), S499 (PO-541)

Author Index

- Tailleux, Anne, S588 (PO-470), S608 (PO-2858)
- Tait, Paul, S245 (OS-1145)
- Taivanbaatar, Erdenebileg, S241 (OS-699), S499 (PO-541)
- Takaguchi, Koichi, S239 (OS-2686)
- Takahara, Terumi, S231 (OS-687)
- Tak, Hyoseon, S701 (PO-1451)
- Takkenberg, Bart, S248 (OS-138), S705 (PO-1980), S728 (PO-1982)
- Tak, Won Young, S686 (PO-1809)
- Tak, Won-Young, S757 (PO-2422)
- Talbot, Thomas, S245 (OS-1145)
- Talib, Zohra, S198 (GS-945)
- Tallis, Caroline, S353 (PO-1766)
- Tamaki, Nobuharu, S267 (OS-681), S577 (PO-1648)
- Tamayo-Caro, Miguel, S497 (PO-133)
- Tamayo, Ibon, S694 (PO-2770)
- Tamayo, Laura, S694 (PO-2770)
- Tampaki, Maria, S511 (PO-2920)
- Tampi, Radhika, S671 (PO-2152)
- Tam, Steve Yew-chong, S349 (PO-1462)
- Tanabe, Kenneth K., S212 (OS-1491)
- Tanaka, Atsushi, S193 (GS-1213), S425 (PO-376)
- Tanaka, Junko, S532 (PO-19)
- Tanaka, Yasuhito, S715 (PO-529), S780 (PO-666)
- Tan, Albert, S395 (PO-1505)
- Tanashchuk, Elena, S789 (PO-2418)
- Tan, Darren, S376 (PO-1278)
- Tandoi, Francesco, S234 (OS-116)
- Taneja, Sunil, S360 (PO-2832), S438 (PO-2280)
- Taner Gulsen, Murat, S472 (PO-2001)
- Tang, Juan, S629 (PO-1091)
- Tangkijvanich, Pisit, S203 (LBO-2764), S731 (PO-2575)
- Tang, Liangjie, S538 (PO-719), S541 (PO-1030)
- Tang, Shanghong, S629 (PO-1091)
- Tang, Sunny, S281 (OS-595)
- Tan, Hua, S720 (PO-1257), S742 (PO-1196)
- Tan, Huey, S322 (PO-2341)
- Tanigawa, Ryohei, S267 (OS-681)
- Tanios, Fady, S314 (PO-832), S538 (PO-819), S539 (PO-825), S563 (PO-836)
- Tan, Jessica, S765 (PO-453)
- Tan, Lin, S709 (PO-218)
- Tan, Soek-Siam, S438 (PO-2280)
- Tan, Susanna, S755 (PO-2338), S756 (PO-2395), S757 (PO-2429)
- Tantau, Marcel, S307 (PO-48)
- Tanwar, Sudeep, S324 (PO-2749)
- Tan, Xiaoyan, S368 (PO-1094)
- Tan, Youwen, S795 (PO-987)
- Tao, Shuai, S726 (PO-1810), S742 (PO-1109)
- Tapper, Elliot, S373 (PO-1236)
- Taque, Sophie, S242 (OS-906)
- Tarazona, Sonia, S335 (PO-709)
- Tardelli, Matteo, S603 (PO-2161)
- Targher, Giovanni, S538 (PO-719), S541 (PO-1030), S562 (PO-769), S567 (PO-1020)
- Tarli, Claudia, S466 (PO-935)
- Tassy, Barbara, S352 (PO-1712)
- Tatara, Eric, S768 (PO-745)
- Tata, Xhimi, S654 (PO-1480), S767 (PO-694)
- Taubert, Richard, S193 (GS-1213), S235 (OS-213), S423 (PO-60), S464 (PO-841), S473 (PO-2821)
- Taub, Rebecca, S200 (GS-2563), S614 (PO-849)
- Taurchini, Marco, S769 (PO-951)
- Tavaglione, Federica, S261 (OS-297)
- Tawfiq, Rasha, S407 (PO-2363), S606 (PO-2412)
- Tay, Chin, S288 (OS-211), S733 (PO-43), S738 (PO-824)
- Taylor, Adam, S455 (PO-2173)
- Taylor, David R., S306 (PO-2178)
- Taylor, Michael, S676 (PO-2872)
- Taylor, Rhiannon, S474 (PO-2842)
- Taylor-Weiner, Amaro, S254 (OS-1611), S602 (PO-2123)
- Teckman, Jeffrey, S201 (LBO-2592)
- Tedjokusumo, Raindy, S753 (PO-2106)
- Teh, Francis, S344 (PO-485), S349 (PO-1462)
- Teichmann, Sarah, S233 (OS-2656)
- Teisner, Ane Soegaard, S638 (PO-190)
- Tejaswi, Sooraj, S425 (PO-344)
- Télliez, Luis, S277 (OS-1172)
- Telliam, Charlene, S574 (PO-1453)
- Tempany-Afdhal, Clare, S433 (PO-1644)
- Temprano, Alvaro, S631 (PO-1668)
- Tenca, Andrea, S229 (OS-2096)
- Teng, Xiaowei, S281 (OS-595)
- Tenta, Roxani, S350 (PO-1471)
- ten Wolde, Marije, S585 (PO-2485)
- Teo, Eng Kiong, S765 (PO-453)
- Teresa Arias Loste, Maria, S584 (PO-2369)
- Teresa Arias Loste, Maria, S537 (PO-685)
- Teresa Salcedo, Maria, S437 (PO-2015)
- Terracciano, Luigi Maria, S318 (PO-1651)
- Terrada, Natalia Ramos, S788 (PO-1919)
- Terrault, Norah, S191 (GS-1072)
- Terris, Benoit, S555 (PO-2692)
- Tessema, Yabetse G., S699 (PO-820)
- Tessier, Mary Elizabeth, S684 (PO-1665)
- Testoni, Barbara, S695 (PO-258), S699 (PO-820), S701 (PO-1450), S701 (PO-1451), S713 (PO-408)
- Tetri, Brent, S294 (LBP-2580)
- Teuber, Gerlinde, S778 (PO-52), S791 (PO-51)
- Teufel, Andreas, S236 (OS-498)
- Tewatia, Navneet, S666 (PO-2081)
- Thabut, Dominique, S191 (GS-1065), S307 (PO-48), S355 (PO-2194), S356 (PO-2608), S551 (PO-2002), S793 (PO-468)
- Thaimai, Panarat, S719 (PO-1000)
- Thälin, Charlotte, S339 (PO-1787)
- Tham, Christine Y.L., S746 (PO-1448)
- Thanapirom, Kessarinn, S596 (PO-1753), S719 (PO-1000)
- Thanawala, Vaidehi, S738 (PO-824)
- Thangariyal, Swati, S340 (PO-2213)
- Thapa, Kajal, S724 (PO-1725)
- Tharwa, Elsayed, S636 (PO-2476)
- Theise, Neil, S603 (PO-2161)
- The, Kok Ban, S631 (PO-1091)
- Theo Brehm, Thomas, S351 (PO-1701)
- Theodore, Dickens, S455 (PO-2173)
- Theodoro, Carmem Ferguson, S495 (PO-2799)
- Thévenot, Thierry, S201 (LBO-2631), S584 (PO-2030)
- Thevis, Mario, S423 (PO-60)
- Thibault, Vincent, S696 (PO-526)
- Thiele, Maja, S207 (OS-1726), S321 (PO-2331)
- Thi, Emily P., S203 (LBO-2764), S281 (OS-595), S760 (PO-2822), S761 (PO-2823), S762 (PO-2879)
- Thimme, Robert, S262 (OS-584), S281 (OS-1021), S453 (PO-1929), S454 (PO-1983)
- Thindwa, Deus, S670 (PO-2131)
- Thi, Viet Loan Dao, S281 (OS-1021)
- Thoma, Eva, S604 (PO-2210)
- Thomaides-Brears, Helena, S634 (PO-2094)
- Thomas, Lutz, S771 (PO-1029)
- Thomas, Rachel, S531 (PO-2793), S691 (PO-2204)
- Thomas, Robert, S245 (OS-1145)
- Thompson, Alexander, S283 (OS-2826), S289 (OS-1430), S358 (PO-2683), S386 (PO-2685), S658 (PO-1813), S744 (PO-1286), S775 (PO-2048), S797 (PO-1872)
- Thompson, April, S434 (PO-1748)
- Thompson, Carrie, S684 (PO-1665)
- Thompson, John, S395 (PO-1505), S592 (PO-1235)
- Thompson, Richard, S279 (OS-1554), S683 (PO-1641), S684 (PO-1665), S687 (PO-1811), S688 (PO-1833)
- Thomson, Emma, S670 (PO-2131)
- Thoné, Tinne, S450 (PO-1333), S453 (PO-1649)
- Thorand, Barbara, S535 (PO-566)
- Thorburn, Douglas, S226 (OS-894), S387 (PO-2938), S419 (PO-1311), S420 (PO-1578), S426 (PO-770), S435 (PO-1790), S474 (PO-2842), S677 (PO-323), S686 (PO-1809)
- Thorgeirsson, Snorri, S501 (PO-1304)
- Thorhauge, Kathrine, S207 (OS-1726), S321 (PO-2331)
- Thorhauge, Katrine, S677 (PO-323)
- Thorne, Claire, S673 (PO-2586)
- Thornton, Karla, S797 (PO-1553)
- Thuluvath, Paul J., S208 (OS-845), S365 (PO-1032), S366 (PO-1038)
- Thumann, Christine, S196 (GS-2069)
- Thu Nga Nguyen, Thi, S520 (PO-1263)

- Thung, Swan N., S241 (OS-699), S499 (PO-541), S521 (PO-1420)
- Thurairajah, Prem Harichander, S765 (PO-453)
- Thursz, Mark, S207 (OS-2158), S208 (OS-638), S309 (PO-94), S324 (PO-2749), S537 (PO-711), S540 (PO-950), S558 (PO-565)
- Thursz, Mark R., S224 (OS-1946)
- Tian, Shuni, S368 (PO-1094)
- Tian, Yan, S758 (PO-2735), S759 (PO-2759)
- Tian, Zibin, S368 (PO-1094)
- Tibbitts, Jay, S198 (GS-1645), S298 (PO-443), S311 (PO-302), S312 (PO-442)
- Tibi, Annick, S198 (GS-945)
- Tilg, Herbert, S262 (OS-584)
- Tillander, Veronika, S269 (OS-1627)
- Tillman, Erik, S204 (LBO-2800), S618 (PO-1314), S619 (PO-1762)
- Timelthaler, Gerald, S362 (PO-309)
- Timm, Jörg, S454 (PO-1983)
- Ting Wu, Cheuk, S391 (PO-567)
- Tiniakos, Dina, S255 (OS-243), S266 (OS-2831), S318 (PO-1651), S564 (PO-919), S568 (PO-1056)
- Tiribelli, Claudio, S619 (PO-1359)
- Tirona, Kattleya, S228 (OS-1586)
- Titievsky, Lina, S254 (OS-1780), S434 (PO-1664), S439 (PO-2327), S566 (PO-980), S577 (PO-1588)
- Tittanegro, Thais H., S328 (PO-1387), S452 (PO-1598)
- Tiv, Say, S289 (OS-865)
- Tiwari, Avinash, S796 (PO-1533)
- Toapanta, David, S325 (PO-552)
- Tobar, Ana, S556 (PO-2791)
- Tobias, Hillel, S686 (PO-1809)
- Todo, Tsuyoshi, S496 (PO-2812)
- Todt, Daniel, S703 (PO-1907)
- Toenges, Gerrit, S556 (PO-167)
- Toet, Karin, S623 (PO-2099)
- Tojo, Marta, S389 (PO-477)
- Toka, Bilal, S671 (PO-2288)
- Tokat, Yaman, S473 (PO-2211)
- Tølbøl, Kirstine, S597 (PO-1849)
- Toledo, Catalina, S347 (PO-1045)
- Tomar, Arvind, S340 (PO-2213)
- Tomás, André F., S634 (PO-2184)
- Tomažic, Janez, S667 (PO-2093)
- Tomofuji, Katsuhiko, S415 (PO-2531)
- Tong, Jing, S631 (PO-1091)
- Tong, Lily, S670 (PO-2131)
- Tong, Xin, S728 (PO-2134)
- Toniutto, Pierluigi, S448 (PO-718)
- Tonon, Marta, S355 (PO-2273), S469 (PO-1496)
- Topal, Baki, S266 (OS-2831)
- Topp, Andrew, S794 (PO-815)
- Tornai, David, S205 (OS-1293)
- Toro, Luis, S199 (GS-2309)
- Torp, Nikkolaj Christian, S321 (PO-2331)
- Torp, Nikolaj, S313 (PO-487)
- Torralba, Miguel, S447 (PO-235), S735 (PO-430)
- Torrecilla, Sara, S499 (PO-541)
- Torrens, Laura, S240 (OS-615), S499 (PO-541)
- Torres, Ferran, S378 (PO-1987), S492 (PO-2242), S640 (PO-1193)
- Torres, Juan, S771 (PO-1186)
- Torres-Martín, Miguel, S240 (OS-615), S241 (OS-699), S499 (PO-541), S521 (PO-1420)
- Torres, Mireia, S354 (PO-1930)
- Torstenson, Richard, S255 (OS-243), S564 (PO-919), S568 (PO-1056)
- Tortora, Raffaella, S514 (PO-591)
- Tosca, Joan, S335 (PO-698), S338 (PO-1761)
- Tosca, Juan, S335 (PO-709)
- Tosetti, Giulia, S252 (OS-571), S722 (PO-1519), S782 (PO-697)
- Toso, Christian, S466 (PO-1126), S467 (PO-1133), S492 (PO-2242), S548 (PO-1772)
- Tóth, Tamás, S655 (PO-1572)
- Touloumi, Giota, S653 (PO-1421)
- Tourna, Aikaterini, S264 (OS-1524), S333 (PO-2870)
- Tournier, Cathy, S606 (PO-2411)
- Tout, Issam, S708 (PO-2684)
- Tovar, Sulay, S391 (PO-479)
- Tovoli, Francesco, S514 (PO-591), S521 (PO-1351), S533 (PO-441)
- To, Wai Pan, S773 (PO-1871)
- Toyoda, Hidenori, S239 (OS-2686), S636 (PO-2476)
- Tozlu, Mukaddes, S671 (PO-2288)
- Trabut, Jean-Baptiste, S769 (PO-955)
- Tranah, Thomas, S220 (OS-1167), S406 (PO-1763)
- Tran, Chy-Anh, S476 (PO-982)
- Tran, Qua, S659 (PO-1862), S672 (PO-2387)
- Tran, Vanessa, S659 (PO-1817)
- Trauner, Michael, S213 (OS-925), S236 (OS-498), S259 (OS-1592), S270 (OS-507), S362 (PO-309), S363 (PO-310), S364 (PO-532), S365 (PO-560), S374 (PO-1249), S376 (PO-1316), S377 (PO-1613), S383 (PO-2403), S433 (PO-1644), S521 (PO-1312), S575 (PO-1568), S579 (PO-1714), S645 (PO-533), S677 (PO-323), S681 (PO-1243), S683 (PO-1500)
- Trautwein, Christian, S201 (LBO-2592), S405 (PO-1558), S429 (PO-1294), S677 (PO-323)
- Trebicka, Jonel, S213 (OS-513), S252 (OS-571), S332 (PO-2358)
- Treeprasertsuk, Sombat, S438 (PO-2280)
- Trehanpati, Nirupma, S330 (PO-2313)
- Tremblay, Mélanie, S341 (PO-2279)
- Tremblay, Michel L., S301 (PO-1185)
- Trepo, Eric, S385 (PO-2621)
- Trépo, Eric, S242 (OS-906)
- Trevaskis, James, S399 (PO-1831)
- Trevaskis, James L., S614 (PO-838)
- Treviño, Begonia, S664 (PO-2047)
- Trevisani, Franco, S514 (PO-591)
- Triantafyllou, Evangelos, S208 (OS-638), S224 (OS-1946), S306 (PO-2178)
- Triantos, Christos, S544 (PO-1334), S737 (PO-715)
- Trillaud, Hervé, S198 (GS-945), S518 (PO-1209), S520 (PO-1263)
- Trinh, Huy, S755 (PO-2338)
- Tripaldelli, Elena, S656 (PO-1593)
- Tripathi, Dhiraj, S277 (OS-1172), S378 (PO-1987), S467 (PO-1168)
- Tripathi, Dinesh Mani, S459 (PO-2234)
- Tripodi, Armando, S786 (PO-1542)
- Trippler, Martin, S706 (PO-2105)
- Trivedi, Palak, S387 (PO-2938), S427 (PO-770), S435 (PO-1790), S686 (PO-1809)
- Trkulja, Vladimir, S636 (PO-2370)
- Troelstra, Marian, S547 (PO-1526), S585 (PO-2485)
- Trojan, Jörg, S236 (OS-498), S521 (PO-1420)
- Troke, Phil, S766 (PO-637), S775 (PO-2095)
- Trombetta, Elena, S746 (PO-1448)
- Trøseid, Marius, S421 (PO-2285)
- Trotter, James F., S410 (PO-985), S616 (PO-981), S617 (PO-1082)
- Trotti, Roberta, S642 (PO-251)
- Trouw, Leendert, S428 (PO-872)
- Trovato, Francesca, S208 (OS-638)
- Troya, Jesús, S771 (PO-1186), S783 (PO-881)
- Trylesinski, Aldo, S557 (PO-313), S625 (PO-2290), S662 (PO-1990), S663 (PO-2032)
- Tsai, Ming-Chieh, S758 (PO-2619)
- Tsai, Pei-Chien, S780 (PO-666)
- Tsai, Wen-Wei, S614 (PO-838)
- Tsang, Tak Yin Owen, S755 (PO-2338), S756 (PO-2395), S757 (PO-2422)
- Tschaharganeh, Darjus, S754 (PO-2243)
- Tschaika, Marina, S243 (OS-295)
- Tseng, Cheng-Hao, S757 (PO-2429), S780 (PO-666)
- Tseng, Leo, S627 (PO-2297)
- Tsereteli, Maia, S773 (PO-1691)
- Tsertsvadze, Tengiz, S797 (PO-1553)
- Tse, Tiffany, S476 (PO-982)
- Tse, Yee-Kit, S268 (OS-931), S285 (OS-900), S727 (PO-1876)
- Tsiakas, Ilias, S204 (LBO-2765), S683 (PO-2867)
- Tsien, Cynthia, S228 (OS-1586), S435 (PO-1755)
- Tsiouris, Spyridon, S204 (LBO-2765), S360 (PO-2867)
- Tskhomelidze, Irina, S274 (OS-551), S643 (PO-504)
- Tsochatzis, Emmanuel, S215 (OS-1864), S236 (OS-2792), S642 (PO-251), S669 (PO-2108)
- Tsoi, Andrew, S471 (PO-1971)
- Tsolova, Dayana, S509 (PO-2798)
- Tsoulas, Christos, S544 (PO-1334)

Author Index

- Tsreteli, Maia, S274 (OS-551),
S643 (PO-504)
- Tsui, Wai Man Vivien, S773 (PO-1871)
- Tucker, Ed, S682 (PO-1285)
- Tudor, Andrada, S194 (GS-1997),
S209 (OS-2060)
- Tuefferd, Marianne, S718 (PO-947)
- Tuma-Kellner, Sabine, S607 (PO-2623)
- Tunill, Theresa, S259 (OS-1592)
- Tunkelrott, Michael, S559 (PO-580)
- Tuo, Biguang, S501 (PO-1352)
- Turajlic, Samra, S224 (OS-1946)
- Turan Gokce, Dilara, S549 (PO-1865)
- Turan Gökçe, Dilara, S472 (PO-2001)
- Turan, Ilker, S472 (PO-2001),
S671 (PO-2288)
- Turco, Laura, S252 (OS-571)
- Turdziladze, Alexander, S274 (OS-551),
S643 (PO-504)
- Turel, Gabriele, S667 (PO-2093)
- Türeyen, Aynur, S640 (PO-1353)
- Turkova, Anna, S673 (PO-2586)
- Turner, Alice, S677 (PO-323)
- Turner, Nigel, S264 (OS-1524)
- Turner, Paul, S493 (PO-2687)
- Turner, Scott, S716 (PO-665),
S725 (PO-1789)
- Turnés, Juan, S746 (PO-1449)
- Turon, Fanny, S277 (OS-1172),
S694 (PO-2902)
- Tussy, Pablo Fernández, S320 (PO-2043),
S612 (PO-627)
- Tyrfingsson, Thorarinn, S670 (PO-2127)
- Tyshkovskiy, Alex, S666 (PO-2081)
- Tysoe, Olivia C., S233 (OS-2656)
- Tyson, Luke, S207 (OS-2158)
- Tyson, Luke D., S309 (PO-94), S314 (PO-607)
- Tzallas, Alexandros, S309 (PO-94)
- Ucbilek, Enver, S671 (PO-2288)
- Ueda, Yoshihide, S193 (GS-1213)
- Ueland, Per, S421 (PO-2285)
- Uhlen, Mathias, S222 (OS-2044)
- Ujhelyi, Eszter, S655 (PO-1572)
- Ulcár, Barbara Kokosar, S667 (PO-2093)
- Ulrich, Angelika, S509 (PO-2798)
- Ulucay, Edagul, S309 (PO-94)
- Ulvik, Arve, S421 (PO-2285)
- Umland, Tim, S793 (PO-377),
S794 (PO-773)
- Um, Soon Ho, S720 (PO-1115)
- Unger, Kristian, S754 (PO-2243)
- Unitt, Stuart, S274 (OS-1381)
- Uojima, Haruki, S239 (OS-2686)
- Upponi, Sara, S233 (OS-2656)
- Urak, Christian, S380 (PO-2162)
- Urbani, Luca, S395 (PO-1441),
S478 (PO-1422)
- Urban, Sabine K., S476 (PO-246)
- Urban, Stephan, S282 (OS-1742),
S698 (PO-626)
- Ure, Daren, S321 (PO-2185)
- Uriel Vázquez Medina, Martín,
S533 (PO-445)
- Urios, Amparo, S335 (PO-698),
S335 (PO-709), S338 (PO-1761)
- Urs, Fichtner, S661 (PO-1903)
- Ursic-Bedoya, José, S352 (PO-1712)
- Urschner, Frank, S332 (PO-2358)
- Uta, Mihaela, S477 (PO-1119)
- Utomo, Elaine, S430 (PO-1428),
S431 (PO-1486)
- Uvarovskii, Alexey, S393 (PO-793)
- Uyanikoglu, Ahmet, S671 (PO-2288)
- Uzel, Ali, S671 (PO-2288)
- Uziel, Asher, S801 (PO-2240)
- Uzilov, Andrew, S241 (OS-699),
S499 (PO-541)
- Uzun, Sinan, S491 (PO-2223)
- Vacca, Michele, S263 (OS-1028),
S266 (OS-2831), S596 (PO-1753)
- Vaidya, Hrisheekesh, S677 (PO-106)
- Vaillant, Andrew, S750 (PO-1837)
- Vaine, Michael, S740 (PO-942)
- Valasek, Mark, S577 (PO-1648)
- Valcheva, Velichka, S685 (PO-1722),
S688 (PO-1843)
- Valencia, Alfonso, S690 (PO-2090)
- Valencia, Jorge, S771 (PO-1186)
- Valenti, Luca, S253 (OS-635),
S260 (OS-2362), S261 (OS-297),
S333 (PO-2870), S600 (PO-1986),
S600 (PO-2033), S607 (PO-2653),
S624 (PO-2192), S642 (PO-251)
- Valero, Oliver, S345 (PO-835)
- Valery, Patricia, S348 (PO-1102),
S353 (PO-1766)
- Vales, África, S694 (PO-2770)
- Vali, Yasaman, S255 (OS-243),
S564 (PO-919), S568 (PO-1056)
- Valla, Dominique, S197 (GS-613),
S216 (OS-1544), S555 (PO-2692),
S678 (PO-561)
- Vallejos, Catalina, S232 (OS-943)
- Vallejo-Senra, Nicolau, S545 (PO-1429)
- Vallet Pichard, Anais, S194 (GS-1587),
S555 (PO-2692)
- Vallez, Emmanuelle, S608 (PO-2858)
- Vallier, Ludovic, S233 (OS-2656)
- Vallverdú, Julia, S401 (PO-2113)
- Valmori, Danila, S246 (OS-1399)
- Valverde, Angela Martinez, S250 (OS-1414)
- Van Beers, Bernard E., S572 (PO-1217)
- van Bömmel, Florian, S544 (PO-1296),
S706 (PO-2135), S732 (PO-2834),
S733 (PO-80), S747 (PO-1661),
S755 (PO-2269)
- Vanbrabant, Lisa, S581 (PO-1895)
- Van Buuren, Henk, S225 (OS-706)
- Van Buuren, Nicholas, S725 (PO-1789)
- van Campenhout, Margo J.H., S733 (PO-80)
- Vandamme, Niels, S450 (PO-1333)
- van de Kolk, Kees, S691 (PO-2204)
- Van De Laan, Luc, S281 (OS-1024)
- van Delden, Otto, S585 (PO-2485)
- van den heuvel, Marius C., S343 (PO-187)
- van den Hurk, Anne, S705 (PO-1980)
- Van der Eijk, Annemiek, S428 (PO-872)
- van der Helm, Danny, S336 (PO-1051)
- van der Laan, Luc J.W., S418 (PO-903)
- Van der Meer, Adriaan, S226 (OS-894),
S387 (PO-2938), S428 (PO-872),
S430 (PO-1428), S431 (PO-1486)
- van der Reijden, Johannes, S336 (PO-1051)
- van der Valk, Marc, S664 (PO-2039),
S774 (PO-1966)
- van der Veen, Suzanne, S527 (PO-778)
- van de Sluis, Bart, S531 (PO-2793),
S591 (PO-1150), S691 (PO-2204)
- van de Steeg, Evita, S623 (PO-2099)
- van de Water, Bob, S623 (PO-2099)
- van Dijk, Anne, S359 (PO-2753)
- van Dijk, Anne-Marieke, S585 (PO-2485)
- van Dijk, Marleen, S664 (PO-2039),
S774 (PO-1966)
- van Dijk, Theo, S591 (PO-1150)
- van Dort, Karel, S705 (PO-1980),
S728 (PO-1982)
- van Erpecum, Karel J., S245 (OS-972),
S359 (PO-2753)
- Vanessa, Banz, S466 (PO-1126),
S467 (PO-1133)
- van Ewijk, Reyn, S661 (PO-1903)
- van Grunsven, Leo, S527 (PO-608)
- van Grunsven, Leo A., S388 (PO-223),
S527 (PO-375)
- Van Haele, Matthias, S336 (PO-1051)
- Vanhalewyn, Tineke, S453 (PO-1649),
S456 (PO-2456)
- Van Hees, Stijn, S751 (PO-1841)
- Vanhockerhout, Mathias, S450 (PO-1333),
S453 (PO-1649), S456 (PO-2456)
- Van Hoek, Bart, S193 (GS-1213),
S428 (PO-872)
- van Hooff, Maria, S430 (PO-1428),
S431 (PO-1486)
- Vanhove, Trudy, S198 (GS-1645),
S298 (PO-443), S311 (PO-302),
S312 (PO-442)
- Van, Huy, S358 (PO-2683), S386 (PO-2685)
- van Kleef, Laurens, S550 (PO-1951),
S718 (PO-915)
- Vanlemmens, Claire, S461 (PO-351),
S462 (PO-353), S584 (PO-2030)
- van Loo, Geert, S591 (PO-1150)
- van Mil, Saskia, S248 (OS-138),
S457 (PO-279), S527 (PO-778)
- Vanneste, Bavo, S450 (PO-1333),
S453 (PO-1649), S456 (PO-2456)
- van Pelt, Jos, S504 (PO-1949),
S505 (PO-1957)
- Van Renne, Nicolaas, S212 (OS-1491)
- van Rooijen, Kristel, S457 (PO-279)
- Vanrusselt, Hannah, S744 (PO-1386)
- Van Steenkiste, Christophe, S581 (PO-1895)
- Vanstraelen, Frederik, S581 (PO-1895)
- Vanstraelen, Kim, S770 (PO-983)
- Van Vlierberghe, Hans, S450 (PO-1333)
- VanWagner, Lisa, S382 (PO-2298)
- Vanwolleghe, Thomas, S252 (OS-571),
S749 (PO-1791), S751 (PO-1841)

- Vaquero, Javier, S334 (PO-624)
 Varadarajan, Ajay Ramakrishnan, S499 (PO-541)
 Varela, Maria, S495 (PO-2799), S516 (PO-1010)
 Varela, Marta, S591 (PO-1037)
 Varela Rey, Marta, S249 (OS-1355)
 Varela-Rey, Marta, S389 (PO-477), S497 (PO-133), S612 (PO-627)
 Varga, Marta, S655 (PO-1572)
 Vargas Blasco, Víctor Manuel, S347 (PO-1045)
 Vargas-de León, Cruz, S533 (PO-445)
 Vargas, Hugo E., S326 (PO-675), S327 (PO-968)
 Vartak, Nachiket, S219 (OS-2754), S415 (PO-1023)
 Vashistha, Chitranshu, S340 (PO-2213)
 Vasileiadis, Themistoklis, S737 (PO-715)
 Vasileva, Larisa, S328 (PO-1501), S350 (PO-1471)
 Vasques, João, S347 (PO-1045)
 Vasudevan, Ashwini, S459 (PO-2234)
 Vázquez, Horacio, S346 (PO-864)
 Vázquez, Inmaculada Fernández, S746 (PO-1449)
 Vázquez-Morón, Sonia, S771 (PO-1186)
 Vázquez-Sirvent, Lucía, S802 (PO-2295)
 Vecchio, Ferdinando Del, S657 (PO-1666)
 Vega, Laura Alcoba, S778 (PO-2359)
 Vegt, Erik, S245 (OS-972)
 Veidal, Sanne, S399 (PO-1831), S509 (PO-2828), S597 (PO-1849), S622 (PO-2006)
 Velasquez, Hector, S782 (PO-862), S789 (PO-2708)
 Velázquez-Cruz, Alejandro, S502 (PO-1752)
 Velez, Juan Carlos Q., S208 (OS-845), S327 (PO-968)
 Velez, Rubén Peña, S687 (PO-1828)
 Veloz, María Guerra, S779 (PO-578)
 Velthuis, Louis, S661 (PO-1903)
 Vendeville, Sandrine, S744 (PO-1386)
 Vendeville, Sophie, S584 (PO-2030)
 Venishetty, Shantan, S378 (PO-1705)
 Ventura-Cots, Meritxell, S307 (PO-48)
 Verbeek, Jef, S475 (PO-2910), S554 (PO-2673), S677 (PO-323)
 Verboven, Peter, S745 (PO-1416)
 Vercoulen, Yvonne, S457 (PO-279)
 Verda, Damiano, S425 (PO-376)
 Verdager, Nuria, S802 (PO-2295)
 Verde, Ignacio, S442 (PO-2761)
 Vergara Gómez, Mercedes, S495 (PO-2799)
 Vergara, Mercedes, S345 (PO-835)
 Vergis, Nikhil, S309 (PO-94), S324 (PO-2749)
 Vergunst, Manon, S428 (PO-872)
 Verhaegh, Pauline, S554 (PO-2673)
 Verheij, Joanne, S585 (PO-2485)
 Verhelst, Xavier, S227 (OS-1088), S277 (OS-1172)
 Verhulst, Stefaan, S527 (PO-375), S527 (PO-608)
 Verkade, Henkjan, S215 (OS-755), S687 (PO-1811), S688 (PO-1833), S688 (PO-1843)
 Verma, AbhinavDr, S210 (OS-2142)
 Verma, Manisha, S655 (PO-1551)
 Verma, Nipun, S360 (PO-2832)
 Vermeersch, Pieter, S475 (PO-2910)
 Vermeulen, Michiel, S527 (PO-778)
 Vermeulen, Roel, S225 (OS-706)
 Vernijns, Liesbeth, S581 (PO-1895)
 Veron, Philippe, S202 (LBO-2647)
 Verret, Wendy, S246 (OS-1674)
 Verrier, Eloi, S392 (PO-692), S695 (PO-175)
 Verslype, Chris, S504 (PO-1949), S505 (PO-1957), S521 (PO-1420)
 Verspaget, H.W., S336 (PO-1051)
 Verstegen, Monique, S281 (OS-1024)
 Verstegen, Monique M.A., S418 (PO-903)
 Verstraete, Carina, S359 (PO-2753)
 Verucchi, Gabriella, S767 (PO-694)
 Vesikari, Timo, S714 (PO-420)
 Vespasiani Gentilucci, Umberto, S425 (PO-376)
 Vesterhus, Mette, S227 (OS-1088), S421 (PO-2285), S432 (PO-1512)
 Vets, Sofie, S475 (PO-2910)
 Viacheslav, Morozov, S291 (OS-2717), S294 (LBP-2730)
 Vianna, Luis Gustavo Rocha, S408 (PO-301)
 Vibert, Eric, S482 (PO-750), S525 (PO-2408)
 Vicaut, Eric, S198 (GS-945), S518 (PO-1209)
 Vicente, Pedro, S457 (PO-1154)
 Victorio, Rut, S338 (PO-1761)
 Vidal-Puig, Antonio, S256 (OS-538), S263 (OS-1028)
 Vidal-Trecan, Tiphaine, S555 (PO-2692)
 Vieira, Sandra, S442 (PO-2761)
 Vierling, John M., S327 (PO-968), S593 (PO-1504), S686 (PO-1809)
 Vietti-Violi, Naik, S679 (PO-570)
 Viganò, Mauro, S540 (PO-831), S722 (PO-1519)
 Vig, Pamela, S682 (PO-1285)
 Vijayakumar, Archana, S399 (PO-1831)
 Vijay, Godhev Manakkat, S406 (PO-1763)
 Vila, Joan, S347 (PO-1045)
 Vila, Marta, S696 (PO-469), S706 (PO-2145)
 Vilana, Ramón, S640 (PO-1193)
 Vilarinho, Silvia, S334 (PO-134)
 Vilas Boas, Filipe, S443 (PO-2801)
 Vilas-Boas, Filipe, S296 (LBP-2891), S440 (PO-2701), S445 (PO-2887), S445 (PO-2898)
 Vilches, Clara, S218 (OS-1478)
 Vilgrain, Valerie, S197 (GS-613), S572 (PO-1217)
 Villa, Erica, S624 (PO-2192)
 Villagrasa, Ares, S307 (PO-48)
 Villani, Rosanna, S495 (PO-2799)
 Villanueva, Amiel, S305 (PO-2122)
 Villanueva, Augusto, S241 (OS-699), S490 (PO-2070), S499 (PO-541), S521 (PO-1420)
 Villanueva, Candid, S252 (OS-571), S307 (PO-48), S378 (PO-1987)
 Villeret, Francois, S350 (PO-1549)
 Villeret, François, S461 (PO-351), S462 (PO-353), S713 (PO-408)
 Villesen, Ida, S313 (PO-487), S362 (PO-309), S363 (PO-310), S633 (PO-1899)
 Villota, Marcela, S665 (PO-2059), S669 (PO-2108)
 Vilstrup, Hendrik, S344 (PO-342), S436 (PO-1799), S482 (PO-707)
 Vinaixa, Carmen, S717 (PO-813)
 Viñas, Odette, S431 (PO-1484)
 Vincent, Catherine, S228 (OS-1586), S435 (PO-1755)
 Vincent, Leroy, S201 (LBO-2631)
 Vincent, Royce P., S306 (PO-2178)
 Vinuesa, Raquel, S778 (PO-2359)
 Violi, Francesco, S216 (OS-1544)
 Vionnet, Julien, S235 (OS-213)
 Vipani, Aarshi, S496 (PO-2812)
 Virseda, Ana, S785 (PO-1404)
 Virtue, Samuel, S263 (OS-1028)
 Virzi, Alessia, S392 (PO-692)
 Visaggi, Egidio, S764 (PO-388)
 Visvanathan, Kumar, S358 (PO-2683), S386 (PO-2685)
 Vitale, Alessandro, S473 (PO-2425), S488 (PO-1238)
 Vitek, Libor, S564 (PO-916), S574 (PO-1518), S689 (PO-2040)
 Vittorio, Jennifer, S684 (PO-1665)
 Viu, Ana, S280 (OS-1921), S734 (PO-247), S799 (PO-2021)
 Vivaldi, Caterina, S521 (PO-1351)
 Vives Moreno, Jordi, S345 (PO-835)
 Vizcarra, Pamela, S694 (PO-2902)
 Vlachos, Ioannis, S334 (PO-134)
 Vleggaar, Frank, S359 (PO-2753)
 Vnencakova, Janka, S547 (PO-1693)
 Vogel, Arndt, S236 (OS-498), S248 (OS-334), S249 (OS-901), S521 (PO-1420)
 Voigt, Robert, S421 (PO-2285)
 Völzke, Henry, S535 (PO-566)
 Volz, Tassilo, S702 (PO-1631), S702 (PO-1707)
 vom Hofe, Annika Yang, S422 (PO-2388), S686 (PO-1758)
 Vonderscher, Jacky, S761 (PO-2844)
 Vondran, Florian, S697 (PO-611), S705 (PO-1950)
 von Felden, Johann, S506 (PO-2227), S522 (PO-1745)
 von Figura, Guido, S393 (PO-793)
 Vong, Chanlina, S289 (OS-865)
 Vonghia, Luisa, S246 (OS-1399)
 von Maltzahn, Robyn, S434 (PO-1748)
 von Meijenfeldt, Fien, S343 (PO-187)
 von Seth, Erik, S227 (OS-1088)
 Voorhoeve, Maaike, S547 (PO-1526)
 Voronin, Evgeny, S673 (PO-2586)
 Voss, Jessica, S405 (PO-1558)
 Vos, Valerie, S581 (PO-1895)

Author Index

- Vo, Tiffany, S453 (PO-1653)
Voulgaris, Theodoros, S544 (PO-1334)
Vovko, Tomaz, S667 (PO-2093)
Vrbova, Petra, S547 (PO-1693)
Vrij, Casper, S475 (PO-2910)
Vucur, Mihael, S278 (OS-1396)
Vuille-Lessard, Elise, S252 (OS-571)
Vuong, Jennifer, S741 (PO-1004)
Vuppalachchi, Raj, S433 (PO-1644)
Vyssocki, Benjamin, S681 (PO-1244)
- Wack, Katy, S254 (OS-1611),
S602 (PO-2123)
Waddell, Scott, S248 (OS-387)
Wadd, Nick, S493 (PO-2687)
Wadowska, Marta, S417 (PO-899)
Wagner, Brandee, S225 (OS-2274),
S422 (PO-2388)
Wagstaff, Johanna, S637 (PO-2936)
Wahl, Alica, S560 (PO-632)
Waidmann, Oliver, S236 (OS-498)
Waiss, Erika, S272 (OS-798)
Wai-Sun Wong, Vincent, S540 (PO-831),
S575 (PO-1568), S576 (PO-1575),
S578 (PO-1689), S579 (PO-1714)
Wakama, Satoshi, S415 (PO-2531)
Waldschmidt, Dirk-Thomas, S236 (OS-498)
Walker, Lucy, S493 (PO-2687)
Wallin, Jeffrey, S287 (OS-2225),
S446 (PO-216), S447 (PO-240),
S448 (PO-846), S720 (PO-1309),
S725 (PO-1789), S757 (PO-2429)
Wall, Jurate, S235 (OS-213)
Walmsley, Martine, S435 (PO-1790)
Walsh, Alice, S587 (PO-283)
Walsh, Renae, S283 (OS-2826),
S739 (PO-853)
Walter, Lisa, S698 (PO-626)
Walther, Tobias, S282 (OS-1742)
Wang, Bingduo, S476 (PO-246)
Wang, Bingqiong, S629 (PO-1091)
Wang, Bo, S285 (OS-887), S721 (PO-1510)
Wang, Chenxu, S738 (PO-797)
Wang, Chun Yan, S372 (PO-1152)
Wang, Chun-yan, S730 (PO-2484)
Wang, ChunYan, S629 (PO-1091)
Wang, Feng, S772 (PO-1397)
Wang, Fengmei, S368 (PO-1094),
S372 (PO-1152), S629 (PO-1091)
Wang, Fengxiang, S359 (PO-2688)
Wang, Guiyang, S728 (PO-2134)
Wang, Hongwu, S300 (PO-712)
Wang, Huan, S241 (OS-699), S499 (PO-541)
Wang, Jason, S602 (PO-2123)
Wang, Jian, S400 (PO-1857), S728 (PO-2134)
Wang, Jianbo, S368 (PO-1094)
Wang, Jie, S501 (PO-1629)
Wang, Jiefei, S795 (PO-987)
Wang, Jing-Houng, S747 (PO-1628)
Wang, Jitao, S359 (PO-2688)
Wang, Kewei, S772 (PO-1397)
Wang, Lifeng, S531 (PO-2627)
Wang, Ling, S713 (PO-408)
Wang, Lingyu, S501 (PO-1629)
- Wang, Li-Yu, S715 (PO-460), S725 (PO-1788)
Wang, Lulu, S575 (PO-1568)
Wang, Mei, S772 (PO-1397)
Wang, Peng, S506 (PO-2601),
S525 (PO-2666)
Wang, Qianqian, S726 (PO-1810),
S742 (PO-1109)
Wang, Ruixu, S359 (PO-2688)
Wang, Sheng-Ping, S531 (PO-2627)
Wang, Shuai, S523 (PO-1883)
Wang, Shu-Chi, S780 (PO-602),
S780 (PO-666)
Wang, Su, S676 (PO-2904)
Wang, Tingyan, S649 (PO-1158)
Wang, Wenjuan, S629 (PO-1091),
S650 (PO-1330)
Wang, Wenjun, S759 (PO-2759)
Wang, Wenshi, S698 (PO-626)
Wang, Xian-bo, S525 (PO-2666)
Wang, Xiaobo, S607 (PO-2653)
Wang, Xiao-Dong, S541 (PO-1030),
S567 (PO-1020), S569 (PO-1106)
Wang, Xiaodong, S538 (PO-719)
Wang, Xiaohui, S247 (OS-2679)
Wang, Xiaojing, S300 (PO-712)
Wang, Xiaoze, S384 (PO-2572)
Wang, Xiaozhong, S629 (PO-1091),
S795 (PO-987)
Wang, Xing, S368 (PO-1094),
S650 (PO-1330)
Wang, Xinhui, S506 (PO-2601),
S525 (PO-2666)
Wang, Xin-Xin, S538 (PO-719)
Wang, Yan, S359 (PO-2688),
S368 (PO-1094), S629 (PO-1091),
S650 (PO-1330)
Wang, Yanling, S368 (PO-1094)
Wang, Yifei, S795 (PO-987)
Wang, Yijin, S281 (OS-1024)
Wang, Yikai, S758 (PO-2735),
S759 (PO-2759)
Wang, Yining, S281 (OS-1024)
Wang, Yu, S680 (PO-996), S681 (PO-1108)
Wang, Zeyu, S523 (PO-1883)
Wang, Zhiqiang, S795 (PO-987)
Wani, Muzafar Maqsood, S796 (PO-1533)
Wan, Xiaoyang, S714 (PO-415)
Wapinski, Ilan, S254 (OS-1611),
S433 (PO-1644), S602 (PO-2123)
Ward, Caroline, S245 (OS-1145),
S490 (PO-2070)
Ward, John, S661 (PO-1936)
Warner, Nadia, S283 (OS-2826)
Wartel, Faustine, S201 (LBO-2631)
Wartelle-Bladou, Claire, S640 (PO-1221)
Watanabe, Tsunamasa, S239 (OS-2686)
Waters, Michael, S618 (PO-1198)
Waterstradt, Katja, S194 (GS-1997),
S209 (OS-2060)
Watkins, Paul, S593 (PO-1504)
Watson, Adam, S403 (PO-2790)
Watson, Chris, S233 (OS-2656)
Watson, Hugh, S384 (PO-2529)
Watson, Robyn, S493 (PO-2687)
- Wattamwar, Tosh, S203 (LBO-2764),
S762 (PO-2879)
Wawer, Andrea, S446 (PO-147)
Weaver, Carly, S471 (PO-1773)
Webber, Laura, S646 (PO-640),
S675 (PO-2861)
Webb, Gwilym, S332 (PO-2609)
Webb, Muriel, S546 (PO-1436)
Weber, Achim, S278 (OS-1396)
Weber, Anna-Lena, S193 (GS-1213)
Weber, Susanne N., S432 (PO-1574)
Wedemeyer, Heiner, S227 (OS-1088),
S282 (OS-1062), S288 (OS-211),
S294 (LBP-2730), S370 (PO-1146),
S423 (PO-60), S438 (PO-2259),
S454 (PO-2154), S456 (PO-2339),
S473 (PO-2821), S703 (PO-1907),
S707 (PO-2293), S778 (PO-52),
S798 (PO-1962)
Wee, Aileen, S400 (PO-1857)
Wefer, Agnes, S227 (OS-1088)
Wege, Henning, S236 (OS-498),
S351 (PO-1701), S506 (PO-2227),
S522 (PO-1745)
Wei, Alice, S508 (PO-2742)
Weidtkamp-Peters, Stefanie,
S339 (PO-2098)
Wei, Guangyan, S499 (PO-677)
Wei, Jia, S759 (PO-2738)
Wei, Lai, S395 (PO-1441), S400 (PO-1857)
Weiler-Normann, Christina, S193 (GS-1213)
Weil-Verhoeven, Delphine, S584 (PO-2030)
Weinberger, Birgit, S446 (PO-147)
Weinberg, Ethan, S463 (PO-364)
Weinmann, Arndt, S236 (OS-498)
Weinman, Steven, S489 (PO-1289)
Weinschenk, Toni, S246 (OS-1399)
Weinzierl, Johanna, S376 (PO-1316),
S377 (PO-1613)
Wei, Qin, S629 (PO-1091)
Weisel, John W., S343 (PO-187)
Weismüller, Tobias, S227 (OS-1088),
S437 (PO-2230)
Weis, Nina, S276 (OS-2202),
S734 (PO-111)
Weiss, Julius, S466 (PO-1126)
Weiss, Karl Heinz, S280 (OS-2590)
Weiss, Nicolas, S355 (PO-2194)
Wei, Wei, S368 (PO-1094)
Welker, Martin-Walter, S332 (PO-2358)
Wellens, Judith, S581 (PO-1895)
Welsch, Christoph, S332 (PO-2358)
Weltman, Martin, S294 (LBP-2580),
S551 (PO-2074), S731 (PO-2575)
Wendon, Julia, S208 (OS-638),
S306 (PO-2178), S406 (PO-1763)
Wen, Wan-Hsin, S758 (PO-2619)
Wen, Xiaofeng, S795 (PO-987)
Werling, Klara, S655 (PO-1572)
Werner, Märten, S227 (OS-1088)
Wernly, Sarah, S542 (PO-1205),
S552 (PO-2328), S573 (PO-1220)
Wesley, Brandon, S233 (OS-2656)
Wessbecher, Isabel, S752 (PO-2089)

- Westbrook, Rachel, S236 (OS-2792), S324 (PO-2749)
- West, Joe, S316 (PO-1375)
- Wetten, Aaron, S420 (PO-1578), S470 (PO-1523)
- Wettengel, Jochen, S752 (PO-2089), S754 (PO-2243)
- Wettstein, Guillaume, S595 (PO-1727)
- Wheeler, Darren, S424 (PO-254), S434 (PO-1664)
- White, Steven, S493 (PO-2687)
- White, Trenton, S661 (PO-1936)
- Whitsey, Heidi, S676 (PO-2872)
- Whitton, Bradley, S775 (PO-2048)
- Widman, Linnea, S251 (OS-293), S554 (PO-2583), S692 (PO-2667)
- Więckowski, Mariusz, S432 (PO-1574)
- Wiegand, Johannes, S259 (OS-1592), S429 (PO-1294), S544 (PO-1296), S560 (PO-751), S763 (PO-68), S764 (PO-131)
- Wiencke, Kristine, S227 (OS-1088)
- Wienhold, Tobias, S554 (PO-2673)
- Wiesel, Philippe, S217 (OS-874)
- Wiestler, Miriam, S227 (OS-1088)
- Wiest, Reiner, S347 (PO-1045)
- Wietje Kürschner, Sina, S393 (PO-793)
- Wigger, Jennifer, S262 (OS-584)
- Wijarnpreecha, Karn, S532 (PO-33)
- Wild, Katharina, S281 (OS-1021)
- Wilkinson, Rebecca, S777 (PO-2352)
- Willemse, José, S430 (PO-1428), S431 (PO-1486)
- Willemsen, Ellen, S527 (PO-778)
- Willemsen, Ellen C.L., S457 (PO-279)
- Willemse, Sophie, S664 (PO-2039), S705 (PO-1980)
- Williams, Felicity, S342 (PO-2851)
- Williams, Jack, S273 (OS-199)
- Williamson, Catherine, S440 (PO-2657)
- Williams, Roger, S207 (OS-2158), S222 (OS-2044), S321 (PO-2185), S330 (PO-2147)
- Willis, Todd, S354 (PO-1930)
- Willms, Arnulf G., S476 (PO-246)
- Willoughby, Catherine E., S240 (OS-615)
- Wilson, David, S797 (PO-1872)
- Wilson, Elizabeth, S476 (PO-982)
- Wilson, Mollie, S250 (OS-2934)
- Wilton, James, S782 (PO-862), S789 (PO-2708)
- Wimmer, Ralf, S389 (PO-410)
- Windelinckx, Tessa, S798 (PO-2020)
- Winkler, Manuel, S393 (PO-793)
- Winkler, Melina, S697 (PO-611)
- Winston Li, Henry, S301 (PO-1107)
- Winter, Rebecca, S797 (PO-1872)
- Wirth, Dagmar, S697 (PO-611)
- Wise, Craig, S476 (PO-982)
- Wisskirchen, Karin, S736 (PO-655)
- Witek, Rafal, S476 (PO-982)
- Witherden, Elizabeth, S222 (OS-2044), S406 (PO-1763)
- Witjes, Julia, S585 (PO-2485)
- Witte, Torsten, S423 (PO-60)
- Woditsch, Vivien, S677 (PO-323)
- Woessner, Ralph, S534 (PO-534)
- Wojnar-Lason, Kamila, S587 (PO-195)
- Wojnar-Lasoń, Kamila, S342 (PO-2833)
- Wolf, Armin, S604 (PO-2210)
- Wolf, Florian, S213 (OS-925)
- Wolffram, Ingmar, S763 (PO-68)
- Wolters, Karin, S691 (PO-2204)
- Wong, Danny Ka-Ho, S289 (OS-1430)
- Wong, Darren, S283 (OS-2826)
- Wong, David, S455 (PO-2307), S755 (PO-2269)
- Wong, Florence, S326 (PO-675)
- Wong, Grace Lai-Hung, S268 (OS-931), S285 (OS-900), S569 (PO-1106), S727 (PO-1876), S749 (PO-1791), S751 (PO-1841)
- Wong, Kowk, S420 (PO-1578)
- Wong, Lin Lee, S419 (PO-1364)
- Wong, Michael, S476 (PO-982)
- Wong, Robert, S465 (PO-922)
- Wong, Siu Yin, S773 (PO-1871)
- Wong, Stanley, S782 (PO-862), S789 (PO-2708)
- Wong, Vincent Wai-Sun, S257 (OS-1556), S257 (OS-555), S259 (OS-1592), S265 (OS-1746), S268 (OS-931), S285 (OS-900), S569 (PO-1106), S709 (PO-218), S727 (PO-1876)
- Wong, Yu Jun, S344 (PO-485), S349 (PO-1462), S629 (PO-1091), S765 (PO-453)
- Won Han, Ji, S460 (PO-186)
- Won Jang, Jeong, S460 (PO-186), S488 (PO-1275)
- Won Jun, Dae, S402 (PO-2695)
- Won, Young-Joo, S479 (PO-409)
- Woodhoo, Ashwin, S249 (OS-1355), S497 (PO-133)
- Woodhouse, Charlotte, S220 (OS-1167)
- Woodman, Richard, S524 (PO-2075)
- Woodward, Amelia, S679 (PO-737)
- Wook Kim, Jung, S550 (PO-1880)
- Woollard, Kevin J., S224 (OS-1946)
- Wootton, Grace, S303 (PO-1379)
- Wöran, Katharina, S362 (PO-309)
- Wörns, Marcus-Alexander, S501 (PO-1304), S560 (PO-632), S599 (PO-1942), S661 (PO-1903)
- Worobetz, Lawrence, S228 (OS-1586), S435 (PO-1755)
- Wouters, Jasper, S266 (OS-2831)
- Woźniak, Małgorzata, S634 (PO-2094)
- Wright, Gavin, S194 (OS-1997), S207 (OS-2158), S209 (OS-2060), S211 (OS-2779), S347 (PO-1045)
- Wright, Mark, S796 (PO-1508)
- Wright, Penny, S353 (PO-1766)
- Wu, Bin, S368 (PO-1094), S650 (PO-1330)
- Wu, Chao, S728 (PO-2134)
- Wu, Di, S714 (PO-415)
- Wuebbolding, Maximillian, S707 (PO-2293)
- Wuestefeld, Torsten, S233 (OS-1290)
- Wu, Fazong, S359 (PO-2688)
- Wu, Feng-ping, S758 (PO-2735), S759 (PO-2759)
- Wu, Jinzi, S620 (PO-1908), S703 (PO-1917)
- Wu, Jinzi J., S620 (PO-1851), S621 (PO-1961)
- Wu, Jun, S629 (PO-1091)
- Wunsch, Ewa, S227 (OS-1088)
- Wu, Qiong, S795 (PO-987)
- Wu, Suhua, S368 (PO-1094)
- Wu, Wei, S368 (PO-1094)
- Wu, Wenqiang, S735 (PO-397), S748 (PO-1775)
- Wu, Wenyu, S714 (PO-415)
- Wu, Xiaoli, S368 (PO-1094), S629 (PO-1091)
- Wu, Xiaoqin, S316 (PO-1215)
- Wu, Xi-Xi, S567 (PO-1020)
- Wu, Ya, S589 (PO-550)
- Wu, Ying, S523 (PO-1883)
- Wu, Yunhai, S368 (PO-1094)
- Wu, Yunhong, S359 (PO-2688)
- Wu, Ze-Qian, S759 (PO-2738)
- Xavier, Verhelst, S387 (PO-2938)
- Xenofontos, Elena, S657 (PO-1624)
- Xia, Dong, S596 (PO-1753)
- Xia, Dongli, S368 (PO-1094)
- Xiao, Guang-Ming, S709 (PO-218)
- Xiao, Huanming, S562 (PO-769)
- Xiao, Jueling, S376 (PO-1278)
- Xiao, Qing, S592 (PO-1235)
- Xiao, Yinzong, S658 (PO-1813)
- Xia, Qiang, S410 (PO-738)
- Xi, Dong, S714 (PO-415)
- Xie, Dong-Ying, S759 (PO-2738)
- Xie, Qing, S359 (PO-2688), S631 (PO-1091)
- Xie, Rui, S501 (PO-1352)
- Xie, Wen, S629 (PO-1091), S795 (PO-987)
- Xie, Xingwang, S531 (PO-1887)
- Xie, Yan, S523 (PO-1883)
- Xie, Zhe, S753 (PO-2106)
- Xing, Qing-Qing, S483 (PO-1147)
- Xin, Kefeng, S772 (PO-1397)
- Xin, Shaojie, S438 (PO-2280)
- Xin, Yongning, S629 (PO-1091), S795 (PO-987)
- Xiong, Qingfang, S795 (PO-987)
- Xiong, Yali, S728 (PO-2134)
- Xirodimas, Dimitris, S624 (PO-2192)
- Xourgia, Xanthi, S204 (LBO-2765), S360 (PO-2867)
- Xu, BIN, S762 (PO-2853), S795 (PO-987)
- Xu, Binghong, S676 (PO-2904)
- Xu, Dan, S359 (PO-2688), S372 (PO-1152)
- Xu, Hangfei, S680 (PO-996), S681 (PO-1108)
- Xu, Hui, S283 (OS-2826)
- Xu, Jiang-Hai, S740 (PO-990)
- Xu, Jingyu, S501 (PO-1352)
- Xu, Jinxia, S738 (PO-797)
- Xu, Li, S247 (OS-2679)
- Xu, Mingyi, S629 (PO-1091)
- Xu, Ren-Ai, S538 (PO-719)
- Xu, Tingfeng, S479 (PO-250)
- Xu, Wei, S726 (PO-1810), S742 (PO-1109)

Author Index

- Xu, Wen, S738 (PO-797)
Xu, Wentao, S479 (PO-250)
- Yadav, Pushpa, S330 (PO-2313)
Yagi, Shintaro, S715 (PO-529)
Yalcin, Kendal, S671 (PO-2288)
Yale, Kitty, S204 (LBO-2800),
S618 (PO-1314), S619 (PO-1762)
Yamamoto, Kenta, S787 (PO-1918)
Yan, Andrew, S410 (PO-985), S616 (PO-981),
S617 (PO-1082)
Yan, Fengna, S506 (PO-2601),
S525 (PO-2666)
Yang, Bailing, S620 (PO-1908)
Yang, Boram, S288 (OS-691)
Yang, Chi-Chao, S668 (PO-2103)
Yang, Chi-Chieh, S668 (PO-2103)
Yang, Dongliang, S795 (PO-987)
Yang, Hwai-I, S715 (PO-460),
S725 (PO-1788)
Yang, Jenny, S757 (PO-2422),
S757 (PO-2429)
Yang, Jiahong, S759 (PO-2738)
Yang, Joe, S671 (PO-2152)
Yang, Ju Dong, S496 (PO-2812)
Yang, Ke, S686 (PO-1809), S690 (PO-2120)
Yang, Li, S384 (PO-2572), S629 (PO-1091)
Yang, Ling, S642 (PO-260)
Yang, Ming, S368 (PO-1094)
Yang, Jaymie, S676 (PO-2904)
Yang, Qing, S650 (PO-1330)
Yang, Shiyang, S359 (PO-2688)
Yang vom Hofe, Annika, S225 (OS-2274)
Yang, Xiaocui, S368 (PO-1094)
Yang, Xiaosong, S629 (PO-1091)
Yang, Xingxiang, S795 (PO-987)
Yang, Yang, S368 (PO-1094)
Yang, Yongping, S680 (PO-996),
S681 (PO-1108), S709 (PO-218),
S738 (PO-811)
Yangzhen, Bianba, S629 (PO-1091)
Yang, ZhiYun, S506 (PO-2601),
S525 (PO-2666)
Yang, Zhongyuan, S299 (PO-559)
Yan, Huiwen, S525 (PO-2666)
Yan, Li, S731 (PO-2575)
Yanni, George, S471 (PO-1773)
Yan, Ran, S290 (OS-2299), S736 (PO-482),
S744 (PO-1286)
Yan, Stephanie, S425 (PO-344)
Yan, Wei, S368 (PO-1094)
Yan, Weiming, S299 (PO-559),
S714 (PO-415)
Yan, Xiaomin, S728 (PO-2134)
Yan, Xuebing, S795 (PO-987)
Yan, Yan, S359 (PO-2688)
Yan, Zhihan, S562 (PO-769)
Yan, Zhongfang, S372 (PO-1152)
Yao, Jiangchao, S748 (PO-1699)
Yao, Jin, S243 (OS-295)
Yao, Kefang, S728 (PO-2134)
Yao, Yuelin, S248 (OS-387)
Yao, Yuyu, S589 (PO-550)
Yaras, Serkan, S671 (PO-2288)
- Yarde, Melissa, S395 (PO-1505)
Yardeni, David, S637 (PO-2936)
Yasay, Eric, S305 (PO-2122)
Yashiro, Hiroaki, S393 (PO-938)
Yassin-Rajkumar, Bebi, S714 (PO-420)
Yates, Euan, S322 (PO-2341)
Yay, Chantana, S289 (OS-865)
Yazdanpanah, Yazdan, S643 (PO-425),
S678 (PO-561)
Ye, Bin, S368 (PO-1094)
Yee, Michael, S537 (PO-711), S558 (PO-565)
Yeh, Chau-Ting, S718 (PO-947)
Yeh, Ming-Lun, S780 (PO-666)
Yeh, Wen-Chen, S198 (GS-1645),
S298 (PO-443), S312 (PO-442)
Yeh, Yen-Po, S668 (PO-2103)
Ye, Jay, S198 (GS-1645), S311 (PO-302)
Yekkala, Krishna, S531 (PO-2627)
Yélamos, María Belén, S781 (PO-689)
Ye, Liangtao, S389 (PO-410)
Yeon, Jong Eun, S720 (PO-1115)
Yerbolat, Amankyeldi, S499 (PO-541)
Ye, Xinjian, S562 (PO-769)
Ye, Ying, S391 (PO-663), S392 (PO-733)
Ye, Yinong, S795 (PO-987)
Yiasemi, Ioanna, S657 (PO-1624)
Yi, FEI, S476 (PO-982)
Yilan, Zeng, S759 (PO-2738)
Yilmaz, Nimet, S671 (PO-2288)
Yilmaz, Sezai, S473 (PO-2211)
Yi Loey Mak, Lung, S294 (LBP-2580)
Yim, Colina, S755 (PO-2269)
Yim, Hyung Joon, S720 (PO-1115),
S743 (PO-1270), S757 (PO-2422)
Yim, Sun Young, S720 (PO-1115)
Yin, Kelvin, S230 (OS-1171), S232 (OS-943)
Yin, Shengxia, S728 (PO-2134)
Yin, Song, S289 (OS-865)
Yip, Terry Cheuk-Fung, S268 (OS-931),
S285 (OS-900), S727 (PO-1876)
Yi, Yiling, S631 (PO-1091)
Yıldırım, Abdullah Emre, S671 (PO-2288)
Yılmaz, Yusuf, S257 (OS-555),
S259 (OS-1592), S655 (PO-1551),
S669 (PO-2108)
Yki-Järvinen, Hannele, S260 (OS-2362),
S605 (PO-2322)
Yogaradnam, Jeysen, S741 (PO-1004)
Yogun, Yasar, S671 (PO-2288)
Yolacan, Ramazan, S671 (PO-2288)
Yoneda, Masato, S259 (OS-1592)
Yong, Xin, S368 (PO-1094)
Yoo, Jeong-Ju, S238 (OS-1101),
S369 (PO-1103)
Yoo, Juhwan, S549 (PO-1823)
Yoon, Eileen, S402 (PO-2695),
S675 (PO-2689), S743 (PO-1270)
Yoon, Jaehyun, S305 (PO-1947)
Yoon, Jung-Hwan, S286 (OS-1892),
S288 (OS-691), S731 (PO-2575)
Yoon Kim, Ji, S516 (PO-857)
Yoon, Seung Kew, S504 (PO-1825)
Yoon, Sun Young, S265 (OS-2450)
Yoo, Sun, S721 (PO-1385)
- Yoshiji, Hitoshi, S425 (PO-376)
You, Hong, S400 (PO-1857), S629 (PO-1091)
You, Jia, S709 (PO-1844)
Younes, Ramy, S253 (OS-635),
S259 (OS-1592), S266 (OS-2831)
Younes, Ziad H., S200 (GS-2563),
S410 (PO-985), S578 (PO-1689),
S616 (PO-981), S617 (PO-1082)
Young, Andrew, S230 (OS-1171)
Young Choi, Jong, S460 (PO-186),
S488 (PO-1275)
Young Dan, Yock, S233 (OS-1290)
Younger, Nicholas, S250 (OS-2934)
Young Lee, Oh, S402 (PO-2695)
Young Park, Jin, S488 (PO-1275)
Youngson, Neil, S264 (OS-1524),
S333 (PO-2870)
Young Yim, Sun, S345 (PO-714)
Younossi, Elena, S655 (PO-1551)
Younossi, Issah, S655 (PO-1551)
Younossi, Zobair, S257 (OS-555),
S395 (PO-1505), S468 (PO-1169),
S544 (PO-1227), S575 (PO-1568),
S579 (PO-1714), S592 (PO-1235),
S597 (PO-1839), S625 (PO-2290),
S655 (PO-1551), S669 (PO-2108),
S671 (PO-2152)
You, San-Lin, S715 (PO-460)
You, Shihyun, S455 (PO-2173)
Yu, Amanda, S789 (PO-2708)
Yuan, Baoying, S304 (PO-1885)
Yuan, Lili, S368 (PO-1094)
Yuan, Qingong, S697 (PO-611)
Yuan, Xiaodong, S779 (PO-404)
Yuen, Man-Fung, S203 (LBO-2764),
S287 (OS-44), S288 (OS-211),
S289 (OS-1430), S294 (LBP-2580),
S731 (PO-2575), S736 (PO-482),
S738 (PO-824), S741 (PO-1004),
S744 (PO-1286), S749 (PO-1791),
S751 (PO-1841), S760 (PO-2822),
S761 (PO-2823), S762 (PO-2879),
S773 (PO-1871)
Yu, Jingjing, S772 (PO-1397)
Yu, Lihua, S506 (PO-2601), S525 (PO-2666)
Yu, Ming-Lung, S780 (PO-602),
S780 (PO-666), S798 (PO-2020)
Yu, Qifeng, S687 (PO-1811)
Yurci, Mustafa Alper, S671 (PO-2288)
Yurdagül, Arif, S607 (PO-2653)
Yurdaydin, Cihan, S747 (PO-1661)
Yu, Rosa L., S659 (PO-1862), S672 (PO-2387)
Yu, Su Jong, S286 (OS-1892), S288 (OS-691)
Yuswan, Fazidah Binti, S660 (PO-1877)
Yu, Xiaojie, S501 (PO-1629)
Yu, Yue, S538 (PO-719)
Yu, Yuehua, S368 (PO-1094)
Yu, Zhou, S735 (PO-397), S748 (PO-1775)
Yu, Zu-Jiang, S709 (PO-218), S740 (PO-990)
- Zabaleta, Nerea, S694 (PO-2770)
Zaccherini, Giacomo, S347 (PO-1045)
Zachou, Kalliopi, S422 (PO-2681),
S423 (PO-60)

- Zago, Alessandra, S226 (PO-894)
 Záhorková, Daniela, S689 (PO-2040)
 Zain, Rozainanee Binti Mohd, S660 (PO-1877)
 Zakeri, Nekisa, S451 (PO-1460)
 Zaky, Samy, S636 (PO-2476)
 Zalaznik, Mateja, S667 (PO-2093)
 Zaldana, Aaron, S471 (PO-1773)
 Zamalloa, Ane, S220 (OS-1167), S222 (OS-2044), S406 (PO-1763)
 Zambrano, Sheila Gato, S342 (PO-2420)
 Zamora, Javier, S216 (OS-1544)
 Zamparelli, Marco Sanduzzi, S639 (PO-511), S640 (PO-1193), S641 (PO-1525)
 Zandanell, Stephan, S570 (PO-1195)
 Zanetto, Alberto, S488 (PO-1238), S668 (PO-2097)
 Zapatero, ANA, S799 (PO-2021)
 Zarate, Flora, S687 (PO-1828)
 Zech, Christoph, S449 (PO-896)
 Zecher, Britta, S230 (OS-2782)
 Zeck, Briana, S603 (PO-2161)
 Zehn, Dietmar, S262 (OS-584)
 Zeina, Walid Al-Akkad Abu, S596 (PO-1753)
 Zeisel, Mirjam, S196 (OS-2069)
 Zekrini, Kamal, S678 (PO-561)
 Zelba-Sagi, Shira, S646 (PO-640)
 Zelber-Sagi, Shira, S546 (PO-1436), S665 (PO-2059), S669 (PO-2108), S675 (PO-2861)
 Zeldin, Sharon, S607 (PO-2653)
 Zelenika, Marko, S636 (PO-2370)
 Zeng, Dan-Yi, S483 (PO-1147), S709 (PO-1844)
 Zeng, Jing, S368 (PO-1094)
 Zeng, Qing-Lei, S629 (PO-1091), S740 (PO-990)
 Zeng, Zhaochong, S304 (PO-1885)
 Zenlander, Robin, S339 (PO-1787)
 Zenouzi, Roman, S227 (OS-1088), S408 (PO-629)
 Zen, Yoh, S343 (PO-187), S441 (PO-2719)
 Zeriuoh, Mohamed, S327 (PO-1161)
 Zeuge, Ulf, S508 (PO-2742)
 Zeuzem, Stefan, S294 (LBP-2730), S306 (PO-2203), S332 (PO-2358), S771 (PO-1029), S778 (PO-52), S792 (PO-153), S797 (PO-1553)
 Zhai, Song, S759 (PO-2759)
 Zhang, Aiguo, S359 (PO-2688)
 Zhang, Changhua, S389 (PO-410)
 Zhang, Chunpan, S478 (PO-1346)
 Zhang, Dazhi, S770 (PO-1007)
 Zhang, Dong, S478 (PO-1346), S748 (PO-1775)
 Zhang, Guo, S368 (PO-1094), S629 (PO-1091), S650 (PO-1330)
 Zhang, Guofan, S740 (PO-990)
 Zhang, Guoxin, S631 (PO-1091)
 Zhang, Haijun, S372 (PO-1152)
 Zhang, Haili, S298 (PO-443)
 Zhang, Ingrid Wei, S325 (PO-552)
 Zhang, Jie, S507 (PO-2694)
 Zhang, Jingwen, S581 (PO-1826)
 Zhang, Li, S523 (PO-1883)
 Zhang, Liao, S757 (PO-2422)
 Zhang, Lijiu, S368 (PO-1094)
 Zhang, Liting, S359 (PO-2688), S629 (PO-1091)
 Zhang, Liyao, S368 (PO-1094)
 Zhang, Ming, S779 (PO-404)
 Zhang, Mingxin, S629 (PO-1091)
 Zhang, Nina, S359 (PO-2688)
 Zhang, Ningning, S523 (PO-1883)
 Zhang, Qingling, S744 (PO-1386)
 Zhang, Ruyi, S281 (OS-1024)
 Zhang, Shiliang, S359 (PO-2688)
 Zhang, Shuwen, S523 (PO-1883)
 Zhang, Talan, S365 (PO-1032), S366 (PO-1038)
 Zhang, Wei, S523 (PO-1883)
 Zhang, Wenhong, S359 (PO-2688)
 Zhang, Wenhua, S759 (PO-2738)
 Zhang, Wenhui, S368 (PO-1094)
 Zhang, Wen-jiang, S508 (PO-2742)
 Zhang, Xian, S795 (PO-987)
 Zhang, Xin, S758 (PO-2735), S759 (PO-2759)
 Zhang, Xinrong, S268 (OS-931)
 Zhang, Xiuping, S368 (PO-1094)
 Zhang, Xuehong, S334 (PO-134)
 Zhang, Xue-jun, S393 (PO-793)
 Zhang, Xueyun, S742 (PO-1109)
 Zhang, Yamin, S523 (PO-1883)
 Zhang, Yanmin, S368 (PO-1094)
 Zhang, Yao, S731 (PO-2575)
 Zhang, Yaojun, S247 (OS-2679)
 Zhang, Yi, S726 (PO-1810), S742 (PO-1109)
 Zhang, Yong, S629 (PO-1091)
 Zhang, Yudi, S697 (PO-611)
 Zhang, Yuening, S368 (PO-1094), S681 (PO-1108)
 Zhang, Yuexin, S795 (PO-987)
 Zhang, Yuqing, S720 (PO-1309)
 Zhang, Zhenfeng, S282 (OS-1742), S698 (PO-626)
 Zhang, Zhongwei, S299 (PO-559)
 Zhan, Luna, S508 (PO-2742)
 Zhan, Tiannan, S672 (PO-2424)
 Zhao, Dandan, S396 (PO-1579), S723 (PO-1605)
 Zhao, Elaine, S559 (PO-580)
 Zhao, Hui, S772 (PO-1397)
 Zhao, Junzhou, S298 (PO-537)
 Zhao, Lei, S395 (PO-1505), S587 (PO-283), S592 (PO-1235)
 Zhao, Lili, S368 (PO-1094), S372 (PO-1152), S629 (PO-1091), S753 (PO-2106)
 Zhao, Liwen, S795 (PO-987)
 Zhao, Qianqian, S304 (PO-1885)
 Zhao, Qianwen, S329 (PO-1585)
 Zhao, Shuangshuang, S499 (PO-677)
 Zhao, Taiyun, S629 (PO-1091)
 Zhao, Wen, S396 (PO-1579), S723 (PO-1605)
 Zhaoxi, Pingcui, S629 (PO-1091)
 Zhao, Xun, S214 (OS-1266)
 Zhao, Yang, S755 (PO-2338), S756 (PO-2395)
 Zhao, Yingren, S795 (PO-987)
 Zhao, Yue, S501 (PO-1629)
 Zhao, Zhe, S373 (PO-1236)
 Zhao, Zhongwei, S359 (PO-2688)
 Zheng, Jian, S523 (PO-1883)
 Zheng, Jiao, S620 (PO-1851)
 Zheng, Kenneth I., S538 (PO-719), S541 (PO-1030), S562 (PO-769), S567 (PO-1020)
 Zheng, Ming-Hua, S257 (OS-555), S359 (PO-2688), S538 (PO-719), S541 (PO-1030), S556 (PO-167), S562 (PO-769), S567 (PO-1020), S569 (PO-1106), S629 (PO-1091)
 Zheng, Xiao-Yong, S538 (PO-719)
 Zhigan, Jiang, S748 (PO-1775)
 Zhong, Huaiyang, S776 (PO-2218)
 Zhong, Liang, S231 (OS-687)
 Zhong, Weidong, S523 (PO-1856)
 Zhou, Dongdong, S525 (PO-2666)
 Zhou, Guanlun, S738 (PO-797)
 Zhou, Huiping, S309 (PO-117)
 Zhou, Jiajia, S507 (PO-2694)
 Zhou, Li, S372 (PO-1152)
 Zhou, Qiong, S703 (PO-1917), S735 (PO-397)
 Zhou, Shengqiang, S359 (PO-2688), S629 (PO-1091), S650 (PO-1330)
 Zhou, Taotao, S227 (OS-1088), S437 (PO-2230)
 Zhou, Xiang, S290 (OS-2478)
 Zhou, Xiqiao, S368 (PO-1094), S629 (PO-1091)
 Zhou, Yi, S629 (PO-1091)
 Zhou, Yi-Hua, S740 (PO-990)
 Zhou, Yixin, S735 (PO-397)
 Zhou, Yonghe, S523 (PO-1883)
 Zhou, Yu-Jie, S569 (PO-1106)
 Zhou, Zhongguo, S247 (OS-2679)
 Zhu, Andrew, S246 (OS-1674)
 Zhuang, Shaoyong, S779 (PO-404)
 Zhuang, Xiaodong, S752 (PO-2089), S780 (PO-602)
 Zhuang, Yuan, S594 (PO-1547)
 Zhu, Liying, S795 (PO-987)
 Zhuo, Yueran, S672 (PO-2424), S776 (PO-2218)
 Zhu, Pei-Wu, S541 (PO-1030)
 Zhu, Qing, S731 (PO-2575)
 Zhu, Shijia, S212 (OS-1491)
 Zhu, Xiao-Ning, S709 (PO-218)
 Zhu, Yanni, S561 (PO-756)
 Zhu, Yueyong, S709 (PO-1844)
 Ziegler, Milinda, S529 (PO-1606)
 Zieniewicz, Krzysztof, S476 (PO-246)
 Zieniewicz, Krzysztof, S473 (PO-2211)
 Ziesch, Andreas, S389 (PO-410)
 Zigmund, Ehud, S226 (OS-894), S230 (OS-2782), S437 (PO-2230), S690 (PO-2120)
 Zimny, Sebastian, S429 (PO-1294)
 Zimper, Gudula, S661 (PO-1903)

Author Index

- Zins, Marie, S253 (OS-612), S536 (PO-614)
Ziol, Marianne, S198 (GS-945),
S259 (OS-1592), S487 (PO-1153)
Zipprich, Alexander, S252 (OS-571),
S307 (PO-48), S337 (PO-1222)
Zisimopoulos, Konstaninos,
S544 (PO-1334), S737 (PO-715)
Zivehe, Fariba, S589 (PO-716)
Ziv, Tomer, S230 (OS-2782)
Zohra Mokrane, Fatima, S487 (PO-1153)
Zoldan, Katharina, S281 (OS-1021)
Zoller, Heinz, S677 (PO-323)
Zöllner, Caroline, S745 (PO-1419)
- Zong, Yuhua, S290 (OS-2299)
Zotov, Sergey, S294 (LBP-2730)
Zou, Chenhui, S603 (PO-2161)
Zou, JUN, S239 (OS-2686)
Zoulim, Fabien, S191 (GS-1065),
S291 (OS-2717), S350 (PO-1549),
S352 (PO-1730), S574 (PO-1453),
S695 (PO-258), S699 (PO-820),
S701 (PO-1450), S701 (PO-1451),
S703 (PO-1711), S713 (PO-408),
S744 (PO-1286)
Zou, Zi-Yuan, S709 (PO-218)
Zubiaga, Ana, S497 (PO-133)
- Zucculo, Luisa, S273 (OS-183)
Zuckerman, Eli, S690 (PO-2120)
Zucman-Rossi, Jessica, S242 (OS-906),
S487 (PO-1153), S499 (PO-541)
Zuhair, Mohamed, S215 (OS-1864)
Zuin, Massimo, S683 (PO-1522)
Zuin, Massimo Giovanni, S280 (OS-2590)
Zurawek, Dariusz, S587 (PO-195)
Zuwała-Jagiełło, Jolanta, S347 (PO-974)
Zwerenz, Burkhard, S661 (PO-1903)
Zwicker, Christian, S456 (PO-2456)
Zwinderman, Aeilko, S585 (PO-2485)
Zwirs, Diona, S585 (PO-2485)

Disclosures: no commercial relationships

The following abstract submitters have indicated that they have no relationships with commercial entities that might be perceived as having a connection with their presentation:

Luise Aamann	Octavi Bassegoda	Jasna Cernosa
Javier Abad Guerra	Ramon Bataller	Maurizio Cesari
Aminah Abdul Razzack	Anna Katharina Baumann	Annalisa Cespiati
Armand Abergel	Chiara Becchetti	Devon Y. Chang
Kushala Abeysekera	Merjem Begic	Mei-Hwei Chang
Zain Ul Abideen	Amine Benmassaoud	Michael Charlton
Hiatem Abofayed	Marina Berenguer Haym	Sudrishti Chaudhary
Jordi Abril-Fornaguera	Annika M Bergquist	Sardar Chaudhary
Fadi Abu Baker	Philip Berry	Chien-Hung Chen
Silvia Acosta-López	Antonio Bertolotti	Tao Chen
David Adams	Annalisa Berzigotti	Huey-Ling Chen
Giovanni Addolorato	Ulrich Beuers	Dongbo Chen
Madeline Adee	Meha Bhuvu	Ruoyang Chen
Marta B. Afonso	Cristiana Bianca	Genwen Chen
João Afonso	Kilian Bock	Zhongwei Chen
Samagra Agarwal	Albrecht Boehlig	Louise China
Banwari Agarwal	Adrian Alick Bonghanoy	Yeonhee Cho
Beatriz Aguilar-Bravo	Angel Borisov	Won-Mook Choi
Catharina Alberts	Piter Bosma	Gwang Hyeon Choi
Agustin Albillos	Patrick Bossuyt	Hannah S.J. Choi
Emma Alexander	Tobias Böttler	George Cholankeril
Theodoros Alexopoulos	Marc Bourliere	Yasmina Chouik
Elmira Aliabadi	Delphine Bousquet	Conan Chua
Mohammad Alkhatib	Amber Bozward	Sungwon Chung
Sophie Allen	Peder Rustøen Braadland	Alex Cole
Joseph Alukal	Chiara Braconi	Massimo Colombo
Bruna Cherubini Alves	Teresa Brevini	Christophe Corpechot
Jihyun An	Christopher Bricogne	Maria Francesca Cortese
Prooksa Ananchuensook	Óscar Brochado-Kith	João Martins Cortez Filho
Raul J. Andrade	Teresa Broquetas	Sean Cox
Paolo Angeli	ryan buchanan	Antonio Craxi
Quentin Anstee	Anna Bujko	Emilie Crouchet
Bethlehem Arefaine	Luigi Buonaguro	Benedikt Csernalabics
Josepmaria Argemi	Thomas Burkard	Jiawei Cui
Cigdem Arıkan	Patrizia Burra	William Cunliffe
Athanasios Armakolas	Christopher Byrne	Chris Curran
Angelo Armandi	Natalia Bystrianska	Harel Dahari
Matthew Armstrong	Tessa Cacciottolo	Elton Dajti
Aadil Ashraf	Xinting Cai	Olav Dalgard
Tarik Asselah	Julien Calderaro	Chloé De Broucker
David N. Assis	Paul Cales	Marcelle de Carvalho Ribeiro
Hanne Åström	José Luis Calleja Panero	Maxime De Rudder
Yasmeen Attia	Claudia Campani	Rozanne de Veer
Emma Avitabile	Cori Campbell	Marie Decraecker
Vian Azzu	Sara Campinoti	Emanuel Della Torre
Mrigya Babuta	Lidia Canillas	Coskun Ozer Demirtas
Gerard Baiges	Elisabetta Caon	Alix Demory
Anna Baiges	Paolo Caraceni	Stijn Aaron den Daas
Lorenz Balcar	Joana Cardoso	Shari Dermer
Victor Baldea	Ivana Carey	Manon Desmares
Rafael Bañares	Rui Castro	Liza Dewyse
Rafael Bañares Cañizares	Darko Castven	Simone Di Cola
Jeevan Barn	francois cauchy	Daniel E. Di Zeo-Sánchez

Disclosures

Luis Antonio Diaz
John Dillon
Jlanhong Ding
Katja Dinkelborg
Selena Dixon
Alexander Doyle
Laura Draijer
Nicolas Drilhon
Michael Dudek
François Durand
Geoffrey Dusheiko
Sanne Suzan Duursma
Lea Duwe
Jessica Dyson
Philippa Easterbrook
Lindsey A Edwards
Cumali Efe
Hydar El Jamaly
Mohamed Elnadry
Bastian Engel
Cornelius Engelmann
Tatiana Ermolova
Mohammed Eslam
Saeed Esmaili
Silvia Espina
Elisa Farina
Martti Färkkilä
Evangelia Fatourou
Suzanne Faure-Dupuy
Sean Felix
Uxía Fernández
Paula Fernandez Alvarez
Marcos Fernandez Fondevila
Paula Fernández-Palanca
Vitor Ferreira
Marco Ferronato
Yaroslav Filippov
Artru Florent
Constantino Fondevila
Roberta Forlano
Ewan Forrest
Guri Fossdal
Mirella Fraquelli
Leonardo Frazzoni
Elliot Freeman
Malin Fromme
Thorben Fründt
Jesús Funuyet-Salas
Laila lavanya Gadipudi
Amiran Gamkrelidze
Weiqiang Gan
Rasmus Hvidbjerg Gantzel
Feng Gao
Carlos García-Crespo
Ester García-Pras
Amalia Gastaldelli
Daniel Geh
Nadine Gehrke
Giacomo Germani
Alessio Gerussi
Benjamin Giles
Antonio Gil-Gomez
Upkar Gill
Justine Gillard
Pere Ginès
Stefania Gioia
Guillaume Giraud
Lise Lotte Gluud

Deniz Göcebe
Naroa Goikoetxea-Usandizaga
Judith Gómez- Camarero
María J González Rellán
Gloria González-Aseguinolaza
Irene González-Recio
Francisco Gonzalez-Romero
Nicolas Goossens
Stuart C Gordon
Ilias Gountas
Olivier Govaere
Jordi Gracia-Sancho
Christiana Graf
Jordi Gratacós-Gines
Isabel Graupera
Cathrin L.C. Gudd
Antonio Guerrero
Aliya Gulamhusein
mesut gumussoy
Yeonjung Ha
Philipp Haber
Nadia Hachicha Maalej
david hakimian
Neil Halliday
Marie Louise Sjoedin Hamberg
Huma Hameed
Guorong Han
Ying Han
Louise Hanly
Claire Harrington
Rebecca Harris
Lukas Hartl
Ramzi Hassouneh
Dieter Häussinger
Iain Hay
Kelly Hayward
Sichan He
Ruiling He
Wen-Qiang He
Andries Heida
Philipp Heimers
Leen Heyens
Victoria Higgins
Alexander Hinkson
Grishma Hirode
Theo Hirsch
Gideon Hirschfield
Maria Hjorth
Benedikt S Hofer
Diana Horta
yuchen hou
Chantal Housset
Tsung-Hui Hu
Qiankun Hu
Pinzhu Huang
Yifei Huang
Kuo-Wei Huang
Vicki Wing-Ki Hui
Peter Hunyady
Sharon Hutchinson
Razvan Iacob
Viktoria Iakovleva
Massimo Iavarone
Luis Ibañez
Samuele Iesari
Simone Incicco
Yosuke Inukai
Federica Invernizzi

Gemma Iserte
Tawhidul Islam
Kendall Islam
Dana Ivancovsky Wajcman
Mathias Jachs
Maciej K. Janik
Naveed Janjua
Maia Japaridze
Thomas Jeffers
Rachel Wen-Juei Jeng
Morten Daniel Jensen
Peter Jepsen
Dong Ji
Hua Jin
Ankur Jindal
Asgeir Johannessen
Amy Johnson
Oriol Juanola
Bellal Jubran
Davina Jugnarain
Frank Jühling
Young Kul Jung
Gökhan Kabaçam
Mohammad Kabbani
Seong Hee Kang
Anna Kann
Ani Kardashian
Tom Hemming Karlsen
Savneet Kaur
Kanudeep kaur
Edeline Kaze
Verena Keitel
Gajanan Kendre
Annarein Kerbert
Hülya Keskin
Gi-Ae Kim
Hwi Young Kim
Mi Na Kim
Tae Hyung Kim
Doohyun Kim
Jin Seoub Kim
Theresa Kirchner
David E Kleiner
Alexandre Klopp
Olivia Knappe
Mina Komuta
Masaaki Korenaga
Linda Skibsted Kornerup
Radina Kostadinova
Jerzy Kotlinowski
Karin Kozbial
Sergii Kozlov
Aleksander Krag
Lisette Krassenburg
Lilith Kuballa
Patrizia Kuenzler
Adrian Kuiper
Ashish Kumar
Christian Labenz
Sofia Lachiondo-Ortega
Carolin Lackner
Simon Lam
Elina Lam
Wai Ling Macrina Lam
Mona-May Langer
Marianne Latournerie
Michelle Layton
Fanny Lebossé

Minjong Lee
 Pei-Chang Lee
 Hye Won Lee
 Jenny Lee
 changhyun lee
 Martin Lett
 Massimo Levrero
 Wenhao Li
 Xitang Li
 pengfei li
 Henry Winston Li
 Ming Li
 Gaëtan Ligat
 Wei Jin Lim
 Hsin-Che Lin
 Shanshan Lin
 Yen-Chun Liu
 Feng Liu
 Wen-yue Liu
 Chuan Liu
 Callum Livingstone
 Timur Liwinski
 Jordi Llaneras
 Alessandro Loglio
 Maria Carlota Londoño
 Miriam Longo
 Sven H Loosen
 Giulia Lori
 Dimitri Loureiro
 Alexandre Louvet
 Fei Lu
 Rui Lu
 Federico Lucantoni
 Maria Isabel Lucena
 Julie Lucifora
 Tom Luedde
 Fei Luo
 Mariana M. Oliveira
 Hong-Lei Ma
 Marta Magaz
 Daniela Maggi
 Bianca Magro
 Rakhi Maiwall
 Lung Yi Loey Mak
 Fariyah Malik
 Astha Malik
 Adnan Malik
 Abdullah Malik
 Vincent Mallet
 Agnes Malobela
 Erin Mandel
 Sohaib Mansour
 Silke Marhenke
 Jose Marin
 Raquel A. Martinez Garcia de la Torre
 Joan Martinez-Camprecios
 Laura Martinez-Gili
 Miguel Mascarenhas
 Beatriz Mateos Muñoz
 Philippe Mathurin
 Mojca Maticic
 José M. Mato
 Aidan McGlinchey
 Jane McKeating
 Jibran mecci
 Espen Melum
 Carolina Méndez-Blanco
 Nahum Méndez-Sánchez
 Yuly Paulin Mendoza
 Philippe Merle
 Marica Meroni
 Tim Meyer
 Nagel Michael
 Maurice Michel
 Beatriz Minguez
 Fraquelli Mirella
 Islam Mohamed
 Srikant Mohta
 Cristina Molera Busoms
 Diethard Monbaliu
 Aldo J Montano-Loza
 Carmina Montoliu
 Ángela B. Moragrega
 James Morgan
 Ferenc Mozes
 Katrin Mueller
 Atish Mukherji
 Amar Mukund
 Miryam Müller
 Alberto Muñoz
 Sam Murray
 Erkin Musabaev
 Mark Muthiah
 Ekaterina Nabatchikova
 Oumarou Nabi
 Maxime Nachit
 Atsushi Nakamura
 Balakrishnan Chakrapani Narmada
 Margaux Nawrot
 Francesco Negro
 Christoph Neumann-Haefelin
 Thi Thu Nga Nguyen
 Hao Niu
 Shirin Nkongolo
 Eva Novoa
 Line Carolle Ntandja Wandji
 Valerie Oberhardt
 Alastair O'Brien
 Rafael Ochoa-Sanchez
 Valerie Ohlendorf
 Matej Orešič
 Marti Ortega-Ribera
 Yu Oshima
 Denis Ouzan
 Collins Oduor Owino
 Evelin Oxtrud
 Ceyhun Oztumer
 Beatriz Pacín
 Giulia Pagano
 Georges-Philippe Pageaux
 Kisoo Park
 James Paik
 Elena Palma
 Anna Palmer
 Adriana Palom
 Juvelyn Palomique
 Jin-Shui Pan
 Erika Paolini
 Valérie Paradis
 Lucia Parlati
 Alina Pascale
 Patrizio Pasqualetti
 Mirella Pastore
 Carrieri Patrizia
 Sudip Paul
 Serena Pelusi
 Julia Peña Asensio
 Grazia Pennisi
 Chalermsein Permtersin
 Andrea Perra
 Simon Peschard
 Salvatore Petta
 Maria Pfefferkorn
 Eva-Doreen Pfister
 George Philip
 Sultanik Philippe
 Salvatore Piano
 Sophie Pirenne
 Fabio Piscaglia
 Christina Plagiannakos
 Aurélie Plessier
 Patricia Pochelon
 Kristian Podrug
 Laureen Pohl
 Prido Polanco
 Edoardo Poli
 Katharina Pomej
 Yury Popov
 Elisa Pose
 Michael Praktknjo
 Veronika Prikhodko
 Charlotte Pronier
 Natalia Pydyn
 Sami Qadri
 Xiaolong Qi
 linglin qian
 Linlan Qiao
 Oliver Quitt
 Jose Miguel Ramos Pittol
 Ditlev Rasmussen
 Monika Rau
 Anne-Aurélie Raymond
 Dalia Rega
 Anneleen Remmerie
 Liying Ren
 Lise Retat
 Enric Reverter
 Freya Rhodes
 Tiago Ribeiro
 Jordi Ribera
 Gabriele Ricco
 Paula Richwien
 Tobias Riedl
 Oliviero Riggio
 Lorenza Rimassa
 Mary Rinella
 Antonio Riva
 Mar Riveiro Barciela
 Jesús Rivera
 Luisa Roade
 Surain Roberts
 Marcus Robertson
 Juan Pablo Roblero
 Brittany Rocque
 Michael Roden
 Cecília M. P. Rodrigues
 Rubén Rodríguez Agudo
 Natascha Roehlen
 Valerio Rosato
 Sofia Roth
 Marika Rudler
 Paloma Ruiz-Blázquez
 Carina Rupp
 Francesco Paolo Russo

Disclosures

Martijn Rutten
Anna Rycyk
Gustaf Rydell
Alejandra Marisela Sabillon-Mendoza
Anna Saborowski
Nawaz Safdar
Niloufar Safinia
Elahe Salimi Alizei
Didier Samuel
Pau Sancho-Bru
Vito Sansone
Álvaro Santos-Laso
Gonzalo Sapisochin
Margherita Saracco
Shiv Kumar Sarin
Arif Sarowar
Jelte Schaapman
Stefan Schefczyk
Jil Alexandra Schrader
Christoph Schramm
Ida Schregel
Lina Schulte
Martin Schulz
Olivier Segeral
Emmanuel Selvaraj
Xiaohui Sem
Georg Semmler
Christine Sempoux
Partho Sen
Daniel Sepúlveda-Crespo
Lawrence Serfaty
Marina Serra
Marina Serrano-Macia
Patcharamon Seubnooch
Han Seul ki
Vicki Shah
Sarah Shalaby
Ying Shang
Sachin Sharma
Sanchit Sharma
Jessica Shearer
julie sheldon
Emma Shepherd
Nick Sheron
Shaojun Shi
Hongxue Shi
Yiwen Shi
Gamal Shiha
Sonjelle Shilton
Dor Shirin
Giordano Sigon
Joel Silva
Milessa Silva Afonso
André L. Simão
Benedikt Simbrunner
Jorge Simón
Claudia Simonelli
Surender Singh
Lubomir Skladany
Aaron Smith
Elizabeth Smout
Akshaya Srikanth
Jesse Stach
Bernardo Stefanini
Maria Stepanova
Maria Stepanova
Tracey Stirrup
Alexander Stockdale
Geurt Stokman
Mohsan Subhani
Sukriti Sukriti
Ahmed Sultan
Pil Soo Sung
Thomas Talbot
Nobuharu Tamaki
Huey Tan
Jin Lin Tan
Junko Tanaka
Giovanni Targher
Xhimi Tata
Ryosuke Tateishi
Richard Taubert
Rasha Tawfiq
Francis Teh
Sarah Teichmann
Barbara Testoni
Dominique Thabut
Thierry Thévenot
Mark Thursz
Thais H. Tittanegro
Marta Tonon
Laura Torella
Nikolaj Torp
Laura Torrens
Christian Toso
Aikaterini Tournia
Jonel Trebicka
Evangelos Triantafyllou
Tengiz Tsertsvadze
Ilias Tsiakas
Emmanuel Tsochatzis
Dayana Tsolova
Marianne Tuefferd
Luke D. Tyson
Enver Ucbilek
Luca Valenti
Yasaman Vali
Daniel Valle Millares
Nicolau Vallejo-Sentra
Karel J. van Erpecum
Maria van Hooff
Laurens van Kleef
Saskia van Mil
Elise Anne van Os
Nachiket Vartak
Martín Uriel Vázquez Medina
Joana Patrícia Ventura Pereira
Jef Verbeek
Umberto Vespasiani Gentilucci
Ares Villagrasa
François Villeret
Julien Vionnet
Aarshi Vipani
Alessia Virzi
Alessandro Vitale
Jordi Vives Moreno
Ioannis Vlachos
Luisa Vonghia
Jessica Voss
Scott Waddell
Martine Walmsley
Wenshi Wang
xiaoze wang
Su Wang
Jie Wang
Bingduo Wang
Peng Wang
Nadia Warner
Paul Watkins
Adam Watson
Klara Werling
Johannes Wiegand
Karn Wijarnpreecha
Felicity Williams
Mollie Wilson
Manuel Winkler
Julia Witjes
Kamila Wojnar-Lasoń
Yu Jun Wong
Ze-Qian Wu
Xiaoqin Wu
wenyu wu
Feng-ping Wu
Yinzong Xiao
Hangfei Xu
Li Xu
Pushpa Yadav
Stephanie Yan
Annika Yang vom Hofe
Kefang Yao
Liangtao Ye
Ming-Lun Yeh
Hyung Joon Yim
Kelvin Yin
Hannele Yki-Järvinen
Jeong-Ju Yoo
Sun Yoo
Eileen Yoon
Jia You
Ramy Younes
Neil Youngson
Lihua Yu
Nekisa Zakeri
Shira Zelber-Sagi
Qing-Lei Zeng
Robin Zenlander
Ulf Zeuge
Zhenfeng Zhang
Xinrong Zhang
Xun Zhao
Dandan Zhao
Qianwen Zhao
Wen Zhao
Yu-Jie Zhou
Ehud Zigmond
Caroline Zöllner
Jessica Zucman-Rossi
Jolanta Zuwała-Jagiełło
Christian Zwicker

Disclosures: commercial relationships

The following abstract submitters have indicated that they have relationships with commercial entities that might be perceived as having a connection with their presentation:

Nadir Abbas	Lorenzo d'Antiga	Raymond Hickey
Manal Abdelmalek	Victor de Lédighen	Magnus Holmer
Kosh Agarwal	Toon De Munck	Jin Hong
Arnon Aharon	Vincent De Smet	Raquel Horrillo
Peter Akerblad	Koos de Wit	Jessica Howell
Naim Alkhouri	Yannick Debing	Rui Hua
Naim Alkhouri	Elisabetta Degasperi	Zhenlin Huang
Joana Inês Almeida	William Delaney	Lowiek Hubers
Quentin Anstee	Münevver Demir	Sandra Ihne
Carolina Armengol	Marie Destro	Takako Inoue
Jasmohan S Bajaj	Bedair Dewidar	Shahed Iqbal
Pedro Baptista	Francisco Diaz-Mitoma	Rajiv Jalan
Eleanor Barnes	Julia Dietz	Harry Janssen
Ana Barreira	Melisa Dirchwolf	Dahn Jeong
Mustafa Bashir	Ellen Driever	David Jones
Thomas Baumert	Jean-François Dufour	Andrew Jones
Thomas Berg	Winston Dunn	Hani Jouihan
David Bernstein	Christina Ebert	Thomas Kakuda
Dipankar Bhattacharya	Manal Hamdy El-Sayed	Min Kyu Kang
Vadim Bichko	Birol Emir	Cheng Kao
Maaïke Biewenga	Elisabeth Erhardtson	Konstantin Kazankov
Therese Bittermann	Robin Erken	Jung Kuk Kim
Sarah Blach	Hildegund Ertl	Bo Hyun Kim
Valentin Blank	Rafael Esteban	Kilyoung Kim
Jan-Hendrik Bockmann	Michael Feigh	Kevin Klucher
Signe Bollerup	Trevor Fisher	Jennifer Knox
Simona Bota	Russell Fletcher	Frank Kolligs
Jerome Boursier	Xavier Fornis	Loreta Kondili
Sylvia Brakenhoff	Faysoil Fouad	Kris Kowdley
Sofia Brites Boss	Céline Fournier	Marcin Krawczyk
Ruth Brogden	Sven Francque	Daria Krzikalla
Robert BROWN	David A. Fraser	Karine Lacombe
Maurizia Brunetto	Ragnheidur H. Fridriksdottir	Pietro Lampertico
Benjamin Bruno	Scott Friedman	Amy Law
Theresa Bucsecs	Peter Galle	Eric Lawitz
Elisabetta Bugianesi	Edward Gane	Jeffrey Lazarus
Joaquín Cabezas	Federico Garcia Garcia	I-Cheng Lee
Dachuan Cai	Juan Carlos Garcia Pagan	Sabela Lens
Lorena Carballo Folgoso	Jacob George	Young-Suk Lim
Oscar Carrasco-Zevallos	Vera Gielen	Lei Ling
Cyrielle Caussy	Katja Giersch	Neus Llarch
Henry LY Chan	Núria Granel	Ana Lleo
Elaine Chien	Serhat Gumrukcu	Josep M. Llovet
In Young Choi	Sneha V. Gupta	Ansgar Lohse
Stefan Christensen	Thierry Gustot	Rohit Loomba
Jay Chuang	Hannes Hagström	Rohit Loomba
Glen Coburn	Aaron Hakim	Vladimir Loukachov
Charlotte Costentin	Juha Halonen	Michael MacIsaac
Emma Culver	Saeed Sadiq Hamid	Jane Macnaughtan
Kenneth Cusi	Elizabeth Hamilton	Mala Maini
George Dalekos	Stephen Harrison	Alessandra Mangia
Roberta D'Ambrosio	Johannes Hartl	Nagraj Mani
Maura Dandri	Virginia Hernandez-Gea	Michael P. Manns

Disclosures

Giulio Marchesini Reggiani
Thomas Marjot
Elisa Martró
Douglas Mayers
Charles McWherter
Mohammed Medhat
Shadi Mehraban
Kofi A Mensah
Joachim C. Mertens
Vincenzo Messina
Paolo Michieli
Anja Moncsek
Carla Montironi
Virginia Morello
Christophe Moreno
Timothy Morley
Gerri Mortimore
Sergio Munoz-Martínez
Mona Munteanu
Carla Fiorella Murillo Perez
Pierre Nahon
Nikolai V. Naoumov
Philip N Newsome
Virginia Nieto-Romero
Mazen Noureddin
Barbora Nováková
Marie O'Farrell
Pablo Ortiz
George Papatheodoridis
Mehaben Patel
Richard Pencek
Lorenzo Piermatteo
Massimo Pinzani
Cyril Ponsioen
Francesca Ponziani
Maryam Pouryahya
Thierry Poynard
Aaditya Prakash
Ulrike Protzer
Puneet Puri
Patricia Quelhas
Rakesh Raman
Christophe Ramière
Ricardo Ramirez
Vlad Ratziu
Rajender Reddy

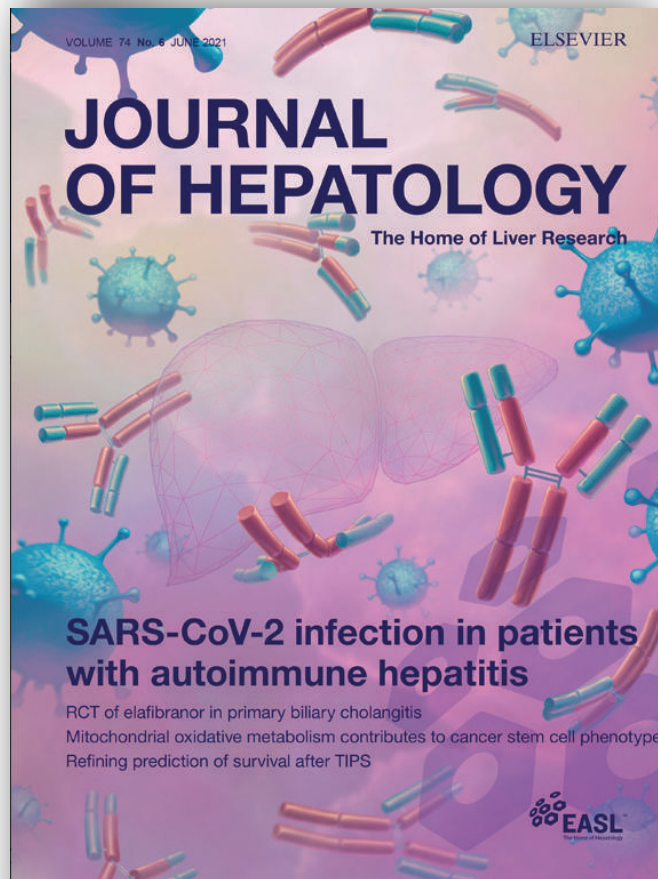
Helen Louise Reeves
Thomas Reiberger
María Reig
Margot Reinders-Hut
André-Jean Remy
Maria Requena
Peter Revill
Krista Rombouts
Manuel Romero Gomez
Leonardo Ruiz Casas
Pablo Ryan
Stephen Ryder
Shayon Salehi
Riad Salem
Noel Salvoza
Fotis Sampaziotis
Juan Diego Sanchez
Marco Sanduzzi Zamparelli
Bruno Sangro
Arun Sanyal
Sanjaya Satapathy
Savvoula Savvidou
Pietro Scalfaro
Jörn M. Schattenberg
Bernhard Scheiner
Michael Schilsky
Andrew Schreiner
Justin Schumacher
Michael Schwarz
Jaymin Shah
Abdel-Aziz Shaheen
rohini sharma
Debbie L. Shawcross
Elizabeth Shumbayawonda
Kashif Siddiqui
Ashwani Singal
Nelli Sjöblom
Cameron Soulette
Katherine Squires
Rowan Stringer
Pavel Strnad
Ekkehard Sturm
Tung-Hung Su
Mark Sulkowski
Vithika Suri
Nadege T. Gunn

Frank Tacke
Hua Tan
Elliot Tapper
Tammo Lambert Tergast
Emily P. Thi
Maja Thiele
Richard Thompson
Jay Tibbitts
Lina Titievsky
Palak Trivedi
Wen-Wei Tsai
Stephan Urban
José Ursic-Bedoya
Michele Vacca
Michael Vaine
Velichka Valcheva
Ludovic Vallier
Florian van Bömmel
Nicholas Van Buuren
Marleen van Dijk
Juan Carlos Q. Velez
Henkjan Verkade
Joana Vieira Barbosa
Archana Vijayakumar
Candid Villanueva
Ida Villesen
Arndt Vogel
Renae Walsh
Heiner Wedemeyer
Karl Heinz Weiss
Guillaume Wettstein
Florence Wong
Vincent Wai-Sun Wong
Jinzi Wu
Jenny Yang
Ying Ye
Terry Cheuk-Fung Yip
Jeysen Yogaratnam
Shihyun You
Zobair Younossi
Man-Fung Yuen
Kalliopi Zachou
Ingrid Wei Zhang
Ningning Zhang
jjajia zhou
Fabien Zoulim

Reviewers list

We express our deepest appreciation to the following people, who have given us generous and invaluable help as abstract reviewers for the ILC 2021.

Alazawi William	Gill Upkar	Raggi Chiara
Aleman Soo	Gonzales Emmanuel	Ramachandran Prakash
Alisi Anna	Gracia-Sancho Jordi	Ratziu Vlad
Andersson Emma	Graupera Isabel	Rautou Pierre-Emmanuel
Armstrong Matthew	Grebely Jason	Reiberger Thomas
Asselah Tarik	Gual Philippe	Reig María
Bansal Ruchi	Gustot Thierry	Rimassa Lorenza
Behrendt Patrick	Hagström Hannes	Ripoll Cristina
Berg Thomas	Hatzakis Angelos	Roman Eva
Bernal William	Hoener zu Siederdisen Christoph	Romeo Stefano
Berzigotti Annalisa	Hofmann Maïke	Romero Gomez Manuel
Beuers Ulrich	Housset Chantal	Ronot Maxime
Björnsson Einar S.	Huch Meritxell	Sällberg Chen Margaret
Boni Carolina	Hydes Theresa	Sarobe Pablo
Böttler Tobias	Iavarone Massimo	Schulze zur Wiesch Julian
Buti Maria	Jack Kathryn	Schwabl Philipp
Cabezas Joaquin	Jeng Rachel Wen-Juei	Scorletti Eleonora
Cabibbo Giuseppe	Komuta Mina	Seehofer Daniel
Calderaro Julien	Kuenzler Patrizia	Semmler Georg
Calvaruso Vincenza	Lachenmayer Anja	Serfaty Lawrence
Childs Kate	Laleman Wim	Shiri-Sverdlov Ronit
Ciesek Sandra	Lammers Twan	Solà Elsa
Clayton Michelle	Lemoine Maud	Spaan Michelle
Coll Mar	Lemoïne Sara	Spee Bart
Conti Filomena	Line Pål Dag	Spengler Ulrich
Corpechot Christophe	Leo Ana	Sperl Jan
D'Ambrosio Roberta	Long Michelle	Sposito Carlo
Dao Thi Viet Loan	Longerich Thomas	Stal Per
de Lédinghen Victor	Louvet Alexandre	Steinmann Eike
De Martin Eleonora	Makara Michael	Stickel Felix
Deuffic-Burban Sylvie	Manolakopoulos Spilios	Strick-Marchand Helene
Devisscher Lindsey	Marschall Hanns-Ulrich	Strnad Pavel
Dietz Julia	Marzioni Marco	Taubert Richard
Durand François	Mas Valeria	Thomsen Karen Louise
Elkrief Laure	Maticic Mojca	Thorburn Douglas
Engelmann Cornelius	Mauss Stefan	Tomasiewicz Krzysztof
Faivre Sandrine	McPhail Mark J W	Tonitutto Pierluigi
Ferraioli Giovanna	Merle Uta	Trebicka Jonel
Fischler Björn	Meuleman Philip	Trepo Eric
Flisiak Robert	Minguez Beatriz	Triantos Christos
Floreani Annarosa	Montagnese Sara	Tsochatzis Emmanuel
Forner Alejandro	Moreau Richard	Vacca Michele
Forrest Ewan	Moschetta Antonio	Valenti Luca
Fraga Christinet Montserrat	Negro Francesco	van de Graaf Stan
Franca Maria Manuela	Newsome Philip N	van Mil Saskia
Francoz Claire	Oude Elferink Ronald	Vesterhus Mette
Friedman Scott	Papatheodoridis George	Vonghia Luisa
Fuchs Claudia	Pérez-del-Pulgar Sofia	Wagner Martin
Galle Peter	Petta Salvatore	Waidmann Oliver
Gastaldelli Amalia	Piano Salvatore	Webb Glynn
Gastaminza Pablo	Pietrangelo Antonello	Weiland Ola
Gerbes Alexander	Pons Monica	Weiss Emmanuel
Gilgenkrantz Hélène	Ponziani Francesca	Yki-Järvinen Hannele



- **Fast decision**
Only 15 days for first decision
- **Expertise**
Clinical and basic science
- **Recommended reads in each issue**
From the Editor's desk...

2019 Impact Factor*

20.582

*Journal Citation Reports
(Clarivate Analytics, 2019)



EASLTM
The Home of Hepatology

THE

INTERNATIONAL

LIVER

CONGRESSTM

6-10 April 2022

Savour the science *together*

easl.eu/ilc2022
#ILC2022