EMJ HEPATOLOGY

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+ THE DIGITAL ILC 2020

Reviewed

+ INTERVIEW

EASL Ethics Committee Chairperson, Prof Christian Trautwein, discusses his role and why the committee is crucial.

+ ABSTRACT REVIEWS

Engrossing reviews of abstracts presented at The Digital ILC 2020 with topics including liver fibrosis, hepatocellular carcinoma, hepatitis B and C, plus more.

Contents

"The following pages are brimmed with trailblazing breakthroughs in the field that were presented and discussed at The Digital ILC to bring you up to date with the latest in hepatology."

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EMJ Hepatology ILC Congress Supplement

Welcome

Respected Readers and Friends,

I am delighted to present to you the eagerly awaited supplement to *EMJ Hepatology 8.1*, including our comprehensive Congress Review of The Digital International Liver Congress (ILC) 2020. The following pages are brimmed with trailblazing breakthroughs in the field that were presented and discussed at The Digital ILC to bring you up to date with the latest in hepatology.

The Digital ILC was a captivating experience providing over a thousand poster and abstract presentations reporting on the latest advances and findings. In this edition of *EMJ Hepatology*, you will find a fine assortment of abstract summaries written by the presenters themselves, providing insight on topics such as the diagnostic potential of presepsin in patients with cirrhosis, the fibrosis-4 score in the assessment of liver fibrosis, and the hepatitis C elimination programme, plus more.

Precision medicine, the emerging approach for disease treatment and prevention that accounts for individual variability in genes, environment, and lifestyle, was a highly discussed topic for the treatment of nonalcoholic fatty liver disease at this year's congress. Because EMJ is always up to date with the newest hot topics, we have summarised The Digital ILC session 'Precision medicine for the management of NAFLD - Are we there yet?' for your review.

We have also provided a summary of the topical 'COVID-19 and the Liver' session, which is a must read for any hepatologist intrigued by the association of the coronavirus disease (COVID-19) pandemic and hepatic disorders.

Additionally, we invite you to read our interview with Prof Christian Trautwein, European Association for the Study of the Liver (EASL) Ethics Committee Chairperson, who discusses his role at the society and justifies the importance of incorporating an ethics committee in every society and board.

Finally, I would like to thank all Editorial Board members, collaborators, contributors, and EMJ's diligent publishing team who have made this all-inclusive Congress Review possible. We hope you enjoy this supplement to *EMJ Hepatology 8.1*, and we look forward to seeing you at ILC next year.

Spencer Gore

Chief Executive Officer, EMG-Health

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EMJ Hepatology 8.1

Editor's Pick

+ Targeting Raised von Willebrand Factor Levels in Liver Diseases: Opening Up Newer Therapeutic Avenues

Articles

+ Liver Disorders in Inflammatory Bowel Disease
+ Rethink Your Transjugular Intrahepatic Portosystemic Shunt (TIPS): Pre-TIPS Infection Predicts Post-TIPS Infection and Post-TIPS Portosystemic Encephalopathy
+ Cholangioscopy and its Role in Primary Sclerosing Cholangitis

Interviews

+ Prof Markus Peck-Radosavljevic
+ Prof Ashwani Singal

And even more...

EMJ Hepatology 8.1 provides influential articles, including an in-depth review on raised von Willebrand factor levels in liver diseases.

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Congress Review

Review of The Digital International Liver Congress (ILC) 2020

Location: The Digital ILC 2020

Date: 27th–29th August 2020

Citation: EMJ Hepatol. 2020;8[Suppl 2]:10-22. Congress Review.

LONDON, UK, is considered to be one of the world's most influential cities, with a significant impact on arts, commerce, and finance, but also on education, healthcare, and research. The city was the home of Robert Hooke, who was the first to visualise a micro-organism under a microscope and coined the term 'cell' in 1665; it also houses St Mary's Hospital where Sir Alexander Fleming first discovered penicillin in 1928. The city has served as a major global hub for innovation and scientific advancements and continually attracts experts across various disciplines. These qualities, against a backdrop of London's historic scenery, has made the UK's capital a popular destination to host world-leading congresses such as the International Liver Congress (ILC), which attracted 8,560 participants from 117 countries in 2019.

2020 marks the 55th European Association for the Study of the Liver (EASL) ILC; however, "2020 has been a year like no other in recent memory, and coronavirus disease (COVID-19) continues to be a major societal challenge," reflected Prof Newsome, EASL Secretary General, host of this year's ILC Opening Ceremony. Although many advances have been made during the global COVID-19 pandemic, Prof Newsome underlined an accompanying consequence: the widespread cancellation of face-to-face congresses, including the flagship ILC, which was due to be held in London in April. However, this did not encourage EASL to cancel ILC. "Necessity is the mother of invention," Prof Newsome confidently stated as he welcomed everyone to the first ever virtual 3-day event: The Digital ILC. In the live broadcast, he continued to thank the delegates and EASL's industry partners for their continued support throughout these difficult times. This appreciation was extended to the efforts and innovation of the EASL Governing Board, EASL committees, and the EASL Office for their "herculean" efforts to organise the digital congress in such a short time frame.

The Digital ILC offered a plethora of stimulating content, both live and on-demand, to explore new ways to engage with the community and reach a global

"We have worked hard to ensure that this year's Digital ILC is an immersive experience, to learn all about the latest in science"

audience. Prof Newsome asserted: "We have worked hard to ensure that this year's Digital ILC is an immersive experience, to learn all about the latest in science, education, and advances in liver disease therapy." A key component distinguishing The Digital ILC was the EASL Studio: the main meeting room of the EASL Governing Board and the Editorial Team in Geneva, Switzerland, was transformed into a live hub and platform where top experts of the field could converse, recap, and disseminate the events of the day.

Comprising hundreds of hours of content, including >90 sessions, >200 fully live posters, >1,500 ePosters with video presentations, and 46 abstracts with live question and answer sessions, The Digital ILC was a fascinating experience. The content covered all liver specialities, categorised into six disease tracks: general hepatology; metabolism, alcoholism, and toxicity; liver tumours; viral hepatitis; cirrhosis and complications; and immune-mediated and cholestatic diseases.

The EASL Community Hub featured live virtual booths for networking and opportunities to learn from, or participate in, EASL initiatives on science, education, and advocacy. It was impossible to miss the latest news, videos, and updates as EASL's Newsroom was always up to date. After a long day at the digital congress, the EASL Lounge provided a space to relax and network; source new, healthy recipes; take a virtual trip through London; or, for those that needed to get blood circulating after sitting all day, try the 15-minute live yoga sessions.

Jumping between the live format and prerecorded videos, the Opening Ceremony included special guests Honorary President Prof Jaime Bosch; Michelle Clayton, Head of EASL Nurses and Allied Health Professionals Task Force; and Martine Walmsley, Chair of Trustees for Primary Sclerosing Cholangitis Support. The ceremony also paid special tribute to valued members of the community, including the recent passing of Prof Rodger Williams, "a true pioneer in liver disease and an inspiration to the world of hepatology," who was due to receive a Lifetime Achievement Award at the ILC in London. Awards presented at The Digital ILC included the EASL Emerging Leaders Award, dedicated to young, distinguished fellows <40 years old and active EASL members who have achieved important accomplishments in liver research; the 2020 awards were presented to Dr Thomas Reiberger and Dr Prakash Ramachandran. The winners of this year's EASL Recognition Award were Prof Giovanna Fattovich and Prof Patrick Marcellin, and the International Recognition Awards were presented to Prof Michael Trauner and Prof James L. Boyer.

The Digital ILC provided the audience with an abundance of breakthroughs in the field. We have compiled some of this trailblazing research in the following pages, with topics ranging from the function of the enzyme monoacylglycerol lipase in liver regeneration, to new guidelines on hepatic encephalopathy in transjugular intrahepatic portosystemic shunt use, and the hidden population living with advanced liver disease. We have also recruited some of the presenting abstract authors to write a summary of their research; these provide a first-hand account of the progress made in hepatitis C testing as part of the Hepatitis C Elimination Programme in Georgia, the diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection, and much more.

During the Opening Ceremony, co-host Prof Thomas Berg, EASL Vice Secretary, hoped that the congress would have "the maximum interaction, something which we all have missed over the past 6 months"; after the 3-day official event, the congress continued with a series of Digital Takeaways, providing a series of open-access expert discussions and debates, and eight 30-minute thematic webcasts throughout September and October. This spirit of supporting engagement, embracing digital connectedness, and maximising opportunities to share in liver research was on brilliant display throughout the congress, and we look forward to the continuation of this spirit in next year's ILC, planned for Amsterdam, the Netherlands, in June.

ILC 2020 REVIEWED →

The Function of Monoacylglycerol Lipase in Liver Regeneration

REGENERATIVE properties of the enzyme monoacylglycerol lipase (MAGL) were highlighted in new data presented at The Digital ILC as a press release on 28th August and may pave the way forward towards understanding the mechanisms of liver regeneration.

Currently, the only treatment for end-stage liver disease or acute liver failure is liver transplantation. However, obtaining donors is extremely challenging and therefore the capability of the liver to regenerate and repair itself has received increased attention, in the hope of finding alternatives to transplantation.

The proinflammatory enzyme MAGL reprogrammes lipid metabolism by converting monoacylglycerols into free fatty acids. Previously, both genetic (*MAGL-/-*) and pharmacological (MJN110 inhibitor) invalidation have benn shown to reduce inflammation and slow fibrosis progression in mice. In their study, the researchers assessed whether inhibition of MAGL could affect liver regeneration and found that MAGL-invalidated mice with liver damage had impaired liver regeneration compared with wild-type counterparts. Furthermore, MAGL deficiency was linked to a decreased production of inflammatory mediators (PGE2) and reduced mRNA expression of TGF-α, IL-17, and hepatocyte growth factor after liver injury. Impairment in liver regeneration was also seen in mice where MAGL was specifically inactivated in hepatocytes or myeloid cells.

Dr Manon Allaire, Center for Inflammation Research, Paris, France, summarised: "Inhibition of MAGL is associated with compromised liver regeneration, that results both from a direct effect on hepatocytes and an indirect effect on macrophages. Thus, while being profibrogenic, MAGL displays proregenerative capacities in the liver." Ideally, therapies for end-stage liver disease or acute liver failure would both target fibrosis and promote liver regeneration, and the data presented here highlighted that MAGL could be a therapeutic target for chronic liver disease and potentially other therapeutic lipid metabolism targets.

"Thus, while being profibrogenic, MAGL displays proregenerative capacities in the liver"

Fecal Microbial Transplant for Treatment of Alcoholic Liver Disease and Hepatocarcinogenesis

TECHNIQUES highlighting the significant effect of microbial biodiversity in the gut may be effective in improving aspects of alcoholic liver disease. The fecal microbial transplant could serve as an intervention to alleviate adverse symptoms of the disease. This is according to the results of two new studies which were presented as part of a press release dated 27th August 2020 at The Digital ILC 2020.

This first study was a pilot, double-blind, placebo-controlled, randomised clinical trial that investigated cravings for alcohol following a fecal microbial transplant after fecal bacteria from a healthy person was transferred to a patient with alcohol use disorder and liver cirrhosis. The patients, who had made previous attempts to overcome their disorder but were unsuccessful in abstaining, were given a fecal microbial transplant or placebo. At Day 15 post-treatment, results from the 20 patients showed fecal microbial transplant reduced alcohol cravings and the psychosocial impact profile. Researchers found an abundance of microbiota diversity in patients who had a fecal microbial transplant including higher levels of *Odoribacter, Alistipes*, and *Roseburia*, compared to the placebo group at Day 15.

The second study presented as part of the same press release investigated the effect of gut microbiota on hepatocellular carcinoma in a study which incorporated mice that had been genetically engineered to develop steatohepatitis. The researchers crossed these mice with another group that had different gene expressions in their inflammatory responses and then treated them with antibiotics. The team showed that knocking out the NLRP6 receptor, a mediator of colonic homeostasis, led to more severe steatohepatitis and a higher tumour burden. The degree of intestinal barrier permeability was highly correlated with tumour burden and fecal microbial transplant was shown to successfully transfer this immune phenotype to other mice by fecal microbial transplant in a reversible process if the transplanted microbiota were depleted with broad-spectrum antibiotics. Dr Kai Markus Schneider, University Hospital RWTH Aachen, Aachen, Germany, commented on the therapeutic potential of these results: "This knowledge of how short-term changes to microbiota reshape the hepatic tumour microenvironment has the potential to reveal new therapeutic options for cancer prevention and therapy."

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New Guidelines on Hepatic Encephalopathy in Transjugular Intrahepatic Portosystemic Shunt Use

COMPLICATIONS of transjugular intrahepatic portosystemic shunt (TIPS) in patients with high-risk liver cirrhosis and acute variceal bleeding (AVB) have deterred attending physicians from performing the procedure, especially in patients with existing hepatic encephalopathy (HE). Through international collaboration, new evidence has been obtained to support the use of TIPS in this population of patients, according to a study presented at The Digital ILC 2020 and a press release dated 28th August 2020.

HE impairs brain function through the accumulation of toxic molecules in the bloodstream as a result of the liver being unable to remove them, and is a potential complication of TIPS, a therapeutic procedure for portal hypertension which has the life-threatening complication variceal bleeding. But, despite the Baveno VI recommendations on the management of portal hypertension suggesting performing early TIPS in high-risk cirrhotic patients with AVB, only 10% of those eligible undergo the procedure, a key reason being the concern for developing HE.

In the multicentre, observational study, the prevalence of HE on admission and the outcomes of early TIPS in high-risk patients with AVB were assessed, as well as the utility of HE at admission as an independent factor to predict death or HE progression in high-risk cirrhotic patients. Through the investigation of >2,000 patients across 34 centres, the study found that the frequency of HE presence at admission was significantly higher in high- versus low-risk patients with cirrhosis (38.1% versus 10.6%; p=0.008).

Investigation of the survival of patients with HE at admission highlighted an association between early-TIPS placement and significantly improved survival. Furthermore, there were less recurrent HE events compared to those who received endoscopic and drug treatment (hazard ratio: 0.453; 95% confidence interval: 0.218–0.940; p=0.003, 16.7% versus 27.3%; p=0.04, respectively). Dr Marika Rudler, Groupe Hospitalier Pitié-Salpêtrière-Charles, Paris, France, explained: "Although HE at admission is independently associated with poor survival in high-risk patients with AVB, early TIPS significantly improved survival, recovery of HE, and decreased the occurrence of new HE episodes after AVB."

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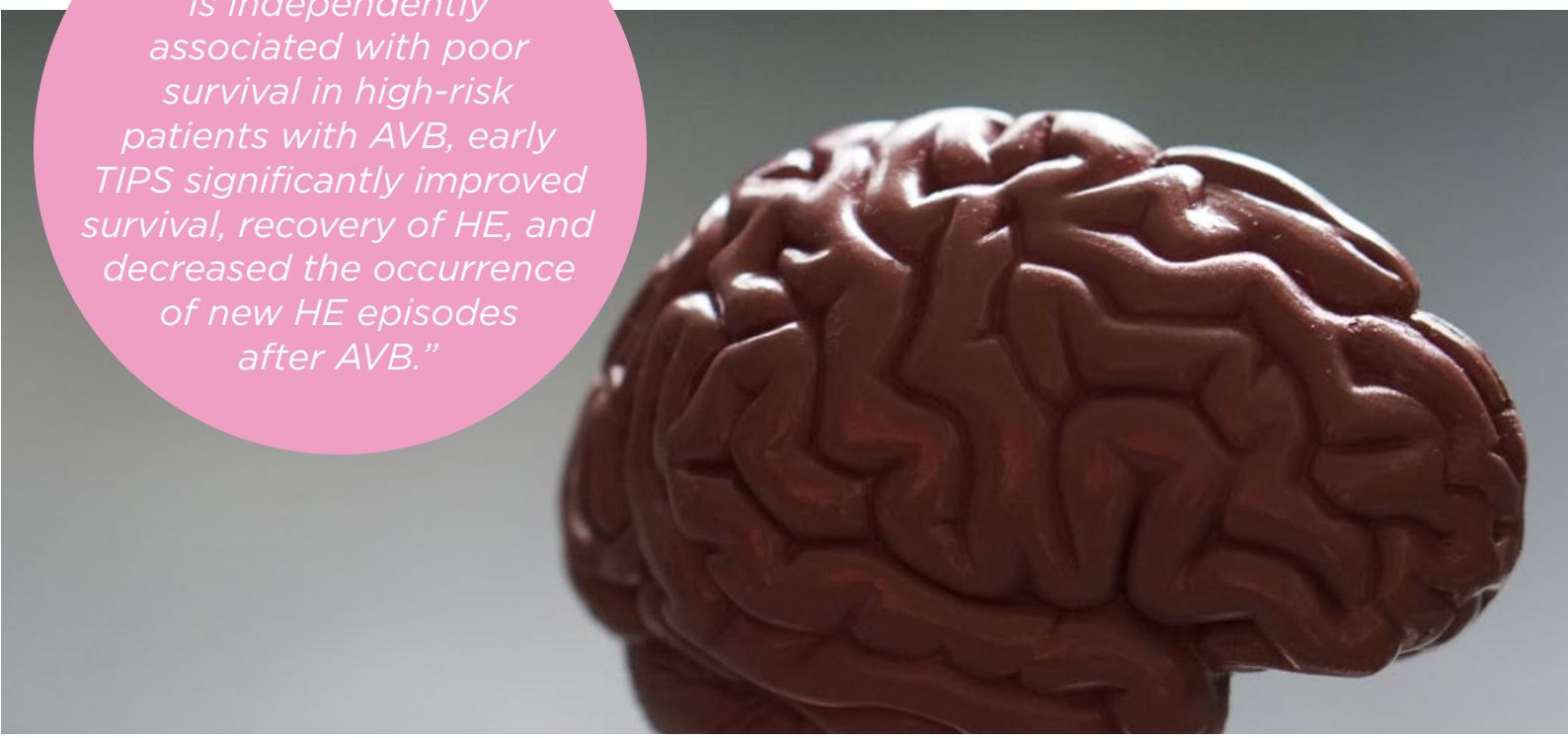


A Wide Field of Novel Treatments for Chronic Hepatitis B

NEW agents have shown promise for a functional cure for chronic hepatitis B virus (HBV) infection. The results of early trials for several novel agents were presented at The Digital ILC 2020 and in a press release dated 28th August 2020, with evidence of early progress in combatting this chronic liver disease discussed.

Current treatments for chronic HBV infection can suppress viral replication, but rarely result in a functional cure, defined by loss of detection of the hepatitis B surface antigen (HBsAg). The two currently approved treatments for chronic HBV infection are nucleos(t)ide reverse transcriptase inhibitors (NRTI) and interferon-α. The new agents discussed at The Digital ILC 2020 exploit different mechanisms to address HBV infection: disruption of viral proteins, including HBsAg; direct inhibition of the HBV core protein; and immune system targeting.

Four studies at The Digital ILC 2020 discussed trial results of agents that target the production of viral proteins, either by RNA interference (RNAi) or using antisense oligonucleotides.

A further study examined the impact of targeting the viral core protein directly in patients who were already virologically suppressed on NRTI therapy; this study found a greater percentage of patients went on to have HBV DNA <5 IU/mL compared to baseline in the treatment group versus placebo (63% at baseline to 94%, versus 80% to 70% with placebo). A final study considered the strategy of improving the innate immune response to chronic HBV infection; there were dose-proportional increases in cytokines, changes in immune cells, and 5% of patients receiving the new agent (a toll-like receptor 8 agonist) had a loss of HBsAg.

"The development of novel therapeutics for persistent HBV infection is currently one of the most vibrant fields in hepatology," outlined Dr Tobias Böttler, University Hospital Freiburg, Germany, and a member of the EASL Governing Board. "With so many different approaches that show promising results regarding HBsAg-decline, and even HBsAg-loss, we appear to be edging closer to the development of a functional cure."

"The development of novel therapeutics for persistent HBV infection is currently one of the most vibrant fields in hepatology"

Patients with Diabetes: A Hidden Population Living with Advanced Liver Disease?

TYPE 2 diabetes mellitus (T2DM) has been uncovered to be highly associated with liver fibrosis, according to a pilot study conducted in two primary care centres in North East England, UK. The results of the study were published in a press release at The Digital ILC 2020, dated 28th August 2020.

Up to 25% of adults worldwide are thought to be affected by nonalcoholic fatty liver disease (NAFLD), the liver manifestation of metabolic syndrome. NAFLD is progressive and leads to fibrosis through accumulation of fat deposits in the liver, which leads to inflammation and scarring. In severe conditions, it progresses to nonalcoholic steatohepatitis (NASH). Despite being a risk factor for NAFLD, patients with T2DM are not universally screened for NASH or fibrosis.

This pilot study assessed 477 successive patients with T2DM between April 2018 and September 2019. If older than 35 years, patients had their fibrosis-4 (FIB-4) score measured; 84 patients had a FIB-4 above their age-specific cut-off. If a patient had a liver stiffness measurement of ≤8 kPa they remained in primary care and were advised to repeat staging in 3 years; however, 24 patients had a measurement of >8 kPa, and therefore were referred to secondary care. If a patient was suspected of having advanced fibrosis, they were enrolled into a surveillance programme.

Overall, results showed that 4.8% of the participants had advanced liver fibrosis, a 7-fold increase compared to the centre's previous T2DM cases. Additionally, >50% of those who received a diagnosis of significant fibrosis or advanced liver disease would not have been diagnosed had national guidelines been followed, as they presented with normal alanine aminotransferase levels.

Prof Emmanuel Tsochatzis, University College London, London, UK, and EASL Governing Board member, emphasised the clinical importance of the study for patients with diabetes and missed NAFLD diagnoses: "We cannot rely on clinical judgment or abnormal liver tests for this and we do need staging pathways with noninvasive fibrosis assessment in primary care or diabetic clinics."

"We cannot rely on clinical judgment or abnormal liver tests for this and we do need staging pathways with noninvasive fibrosis assessment in primary care or diabetic clinics."

Novel Models to Predict Hepatocellular Carcinoma

IMPROVED understanding of who is most at risk of developing hepatocellular carcinoma (HCC) following hepatitis C virus infection could have an important impact on how screening programmes are implemented. This may now be easier than expected as two independent research teams have developed new predictive models for HCC in patients who achieved a sustained virological response (SVR) to direct-acting antiviral (DAA) therapy. These results were presented in a press release at The Digital ILC on 27th August 2020.

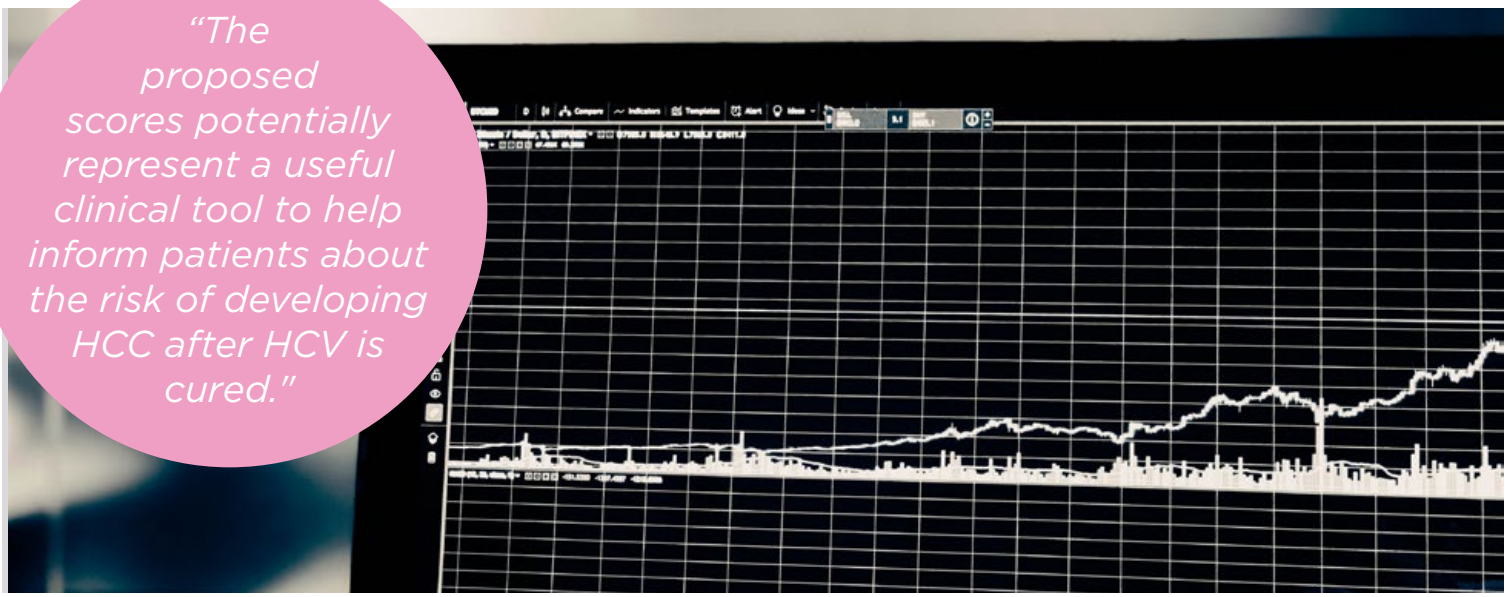
Although DAA therapy can achieve SVR in >95% of patients with chronic HCV infection, these patients continue to have a residual risk of HCC, particularly those with underlying liver disease or comorbidities. Prediction models and risk factors for HCC in HCV-infected patients prior to eradication is well understood; however, these have not yet been established in patients who achieve SVR with DAA therapy.

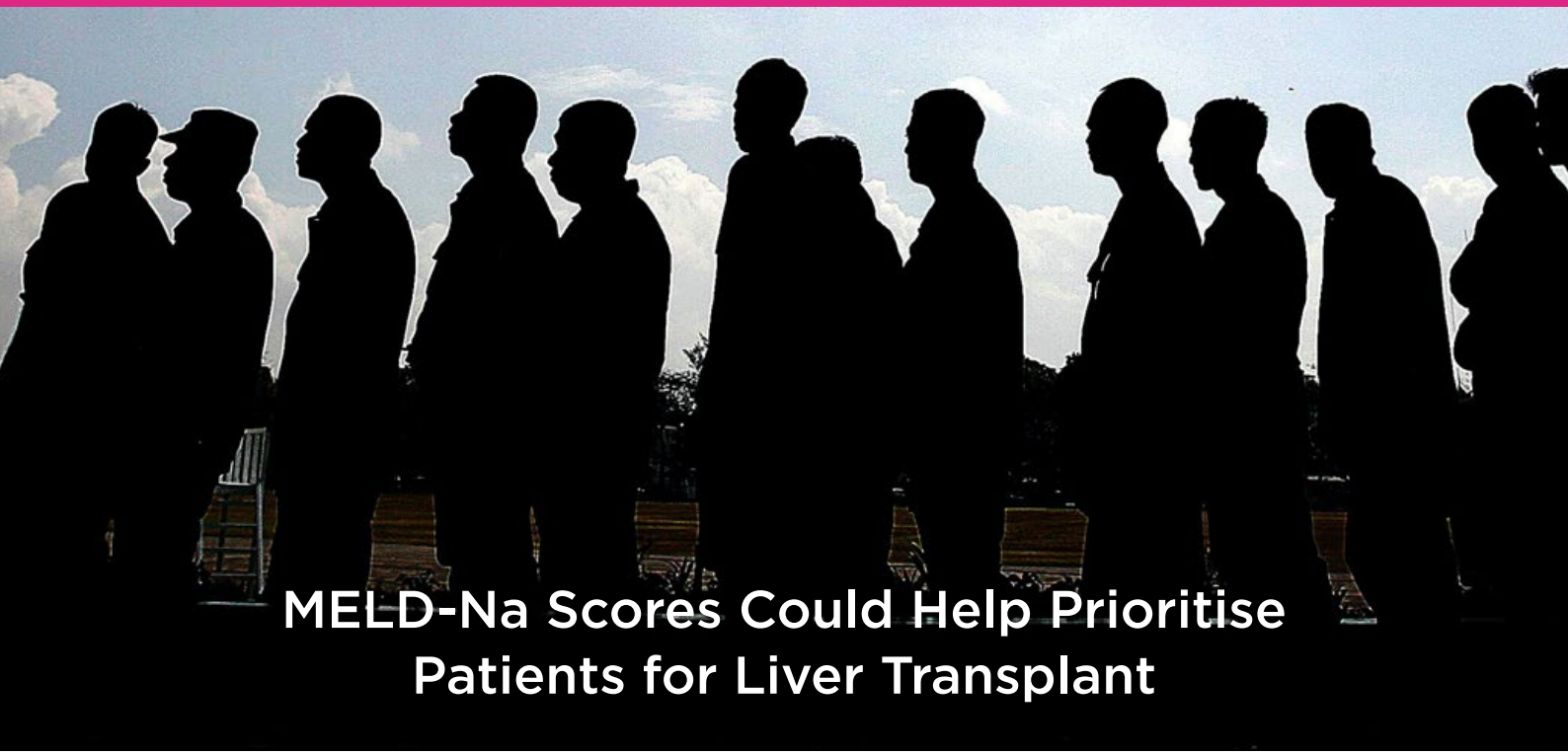
A French research team used data from patients with biopsy-proven compensated cirrhosis from the French ANRS CirVir prospective cohort. They aimed to identify characteristics associated with patients likely to develop HCC after HCV eradication according to serum alpha-fetoprotein and routine serum biomarkers. The cohort included 142 out of 717 patients with HCV at baseline and 47 out of 413 who achieved SVR developed HCC, over a median follow-up period of 74.2 months. Results identified that patients with elevated serum parameters (n=95; 13.7% HCC incidence) and with impaired liver function (n=109; 15.6% HCC incidence) had an elevated risk of developing HCC among those who achieved SVR.

In an Egyptian study, 2,326 patients with chronic HCV infection and advanced hepatic fibrosis or liver cirrhosis who achieved an SVR were followed for an average of 24 months. Here, 109 patients (4.7%) developed HCC during the follow-up period. Risk factors included age, sex, serum albumin, alpha-fetoprotein, and pretreatment fibrosis stage. These variables were used to develop a simple scoring system, which stratified patients into low-, medium-, and high-risk groups with a good predictive accuracy. Cumulative incidence of HCC in these groups after 2 years was 2.0%, 4.5%, and 10.3%, respectively. If validated, the simple scoring system could help to individualise HCC screening of HCV-infected patients after successful DAA treatment.

Dr Jordi Bruix, EASL Governing Board member, noted that: "The proposed scores potentially represent a useful clinical tool to help inform patients about the risk of developing HCC after HCV is cured. These data also reinforce the importance of implementing HCC screening programmes in DAA-treated patients and the need to reinforce research efforts to identify the causes of liver cancer development despite cure of HCV."

"The proposed scores potentially represent a useful clinical tool to help inform patients about the risk of developing HCC after HCV is cured."





MELD-Na Scores Could Help Prioritise Patients for Liver Transplant

"This study is an important step in introducing MELD-Na in the European liver transplant programmes, as it demonstrated an almost 5% improvement in 90-day waiting list mortality."

THE MODEL for End-stage Liver Disease-Sodium (MELD-Na) score, as opposed to the more commonly used MELD score, may be more optimised for prioritising patients for liver transplantation. This is according to a study, the results of which were announced in a press release dated 27th August 2020 at The Digital ILC 2020, conducted by researchers at Leiden University Medical Center, Leiden, the Netherlands, who used data from the Eurotransplant network.

More than 5,000 patients with chronic liver disease who were placed on the Eurotransplant liver transplant waiting list between 2007 and 2008 were included in the study. The MELD score had been used to determine the priority of each transplant, and the researchers of the study reclassified the patients retrospectively based on their MELD-Na score.

Results showed that 26.3% of patients who had died within 90 days of listing would have had a significantly higher chance of receiving a transplant if they had been classified by MELD-Na. Additionally, 40% of the patients had been diagnosed with hyponatraemia, which was associated with a 3-fold increased risk of mortality within 90 days of being listed.

Dr Ben Goudsmit, who presented the results at The Digital ILC 2020, stated: "We believe that MELD-Na-based allocation would help to prioritise patients on European liver transplant waiting lists and reduce the number of patients who die before they get the chance of receiving this life-saving treatment."

By identifying the patients most in need of treatment, and with the global shortage of liver grafts and the increasing prevalence of cirrhosis, Dr Goudsmit hopes that using MELD-Na-based allocation will reduce the mortality rate of patients on the transplant list.

Prof Emmanuel Tsochatzis, University College London, London, UK, and EASL Governing Board member, explained that use of the MELD score has been a breakthrough in chronic liver disease treatment, but it is becoming apparent that the addition of Na to the equation is vital for improving classification of patients. He praised the study: "This study is an important step in introducing MELD-Na in the European liver transplant programmes, as it demonstrated an almost 5% improvement in 90-day waiting list mortality."

New Treatments Improve Biomarkers in Fatty Liver Disease

NOVEL pharmacological therapies have shown promise in the treatment of nonalcoholic fatty liver disease (NAFLD). While there are no currently approved therapies for NAFLD, new treatments have demonstrated an ability to improve biomarkers of the disease, as highlighted in a press release from The Digital ILC 2020, dated 27th August 2020.

NAFLD, including nonalcoholic steatohepatitis (NASH), is thought to affect 25% of the world's population. It is the fastest-growing liver disease globally and can increase risk of hepatocellular carcinoma and cirrhosis. An estimated 37.3% of people with Type 2 diabetes mellitus (T2DM) have concurrent NASH; this overlap has led to investigation of lipid metabolism and inflammation pathways as potential treatment avenues.

"These clinical studies show that targeting FXR, GLP-1, and gastrointestinal hormone receptors are promising approaches for the treatment of NASH, which are worth being further evaluated."

The farnesoid X receptor (FXR) negatively regulates hepatic gluconeogenesis, lipogenesis, and steatosis. EDP-305, a novel FXR agonist, was studied in 132 patients with fibrotic NASH without cirrhosis. Those treated with 2.5 mg of EDP-305 saw significant reductions compared to placebo in alanine aminotransferase, fat percentage (measured by MRI-proton density fat fraction), γ-glutamyl transferase, C4 as a pharmacodynamic marker, and high-density lipoprotein. The most common treatment-emergent adverse event was pruritis, leading to discontinuation in 20.8% of patients receiving 2.5 mg and 1.8% of patients receiving 1 mg of EDP-305.

The glucagon-like peptide-1 (GLP-1) receptor decreases appetite, and influences hepatic lipid content and inflammation, to improve glucose control and reduce body weight. A second study explored the impact of the first-in-class GLP-1/glucagon dual-receptor agonist cotadutide on 834 patients with T2DM who were overweight or obese, over a period of 54 weeks of treatment. At the end of treatment, significant reductions in body weight and alanine aminotransferase were noted with cotadutide 300 µg compared to placebo and an open-label once-daily 1.8 mg dose of liraglutide. This was further confirmed by improvements in NAFLD fibrosis score and FIB-4 with cotadutide 300 µg versus placebo.

Representing the EASL Scientific Committee, Prof Luca Valenti, University of Milan, Italy, highlighted the value of these findings: "These clinical studies show that targeting FXR, GLP-1, and gastrointestinal hormone receptors are promising approaches for the treatment of NASH, which are worth being further evaluated."

Addition of Bezafibrate May Improve Primary Biliary Cholangitis Outcomes

"As response to UDCA can now be anticipated from pretreatment features, a new treatment approach may be to start bezafibrate combination therapy immediately in patients with a predicted poor response to UDCA"

BEZAFIBRATE, a hypolipidaemic fibrate, in combination with ursodeoxycholic acid (UDCA) has growing evidence for its use in treating primary biliary cholangitis (PBC). According to a study of a Japanese cohort, which was presented at The Digital ILC 2020 and reported in a press release dated 27th August 2020, this combination therapy improved transplant-free survival for patients with PBC when compared to UDCA monotherapy or no treatment.

Current evidence suggests that biochemical markers and long-term outcomes are both improved by the addition of bezafibrate to UDCA therapy for PBC, an immune-medicated liver disease. Progression of symptoms can lead to cirrhosis and liver failure, putting those with PBC at risk of requiring a liver transplantation. This risk is further increased if patients with PBC do not respond adequately to UDCA, which is the case for approximately 20% of patients, despite UDCA being the recommended first-line treatment for PBC in Europe.

In the large nationwide cohort (N=8,180), patients with PBC either received UDCA monotherapy (6,087; 74.4%), a combination of UDCA and bezafibrate (943; 11.5%), no treatment (1,133; 13.9%), or bezafibrate monotherapy (17; 0.2%). A significant decrease in the risk of all-cause mortality or liver transplantation was observed in those treated with UDCA monotherapy versus those who did not receive any treatment (adjusted hazard ratio: 0.55; 95% confidence interval: 0.47–0.65; $p<0.0001$). Compared to UDCA monotherapy, the combination of bezafibrate and UDCA further reduced this risk (adjusted hazard ratio: 0.23; 95% confidence interval: 0.15–0.35; $p<0.0001$).

"As response to UDCA can now be anticipated from pretreatment features, a new treatment approach may be to start bezafibrate combination therapy immediately in patients with a predicted poor response to UDCA," theorised Dr Atsushi Tanaka, Teikyo University School of Medicine, Tokyo, Japan, presenter of the study's findings. To confirm the long-term effectiveness of the addition of bezafibrate to routine UCDA treatment, Dr Tanaka acknowledged the need for prospective, randomised, placebo-controlled studies.

Treatment Option for Viral Hepatitis High-Dose Bulevirtide

Bulevirtide, a first-in-class entry inhibitor treatment for patients with hepatitis B virus (HBV)/hepatitis D virus (HDV) coinfection, has been proven to be safe and effective in a study focussed on high-dose regimens. This is according to the results of a new study that was presented as part of a press release dated 28th August 2020 at The Digital ILC 2020.

The potential new treatment option was investigated for safety and efficacy in both single-drug therapy and in combination with pegylated interferon α (PEG-IFNα), the only treatment option currently recommended for HDV. Over the 48-week treatment period, declines in HDV RNA were monitored. Patients with chronic HBV/HDV coinfection were randomised to either bulevirtide 10 mg once daily and PEG-IFNα 180 µg once weekly, or bulevirtide 5 mg twice daily with tenofovir disoproxil fumarate. Patients were treated for 48 weeks, followed by a 24-week period of either being treatment-free or having tenofovir disoproxil fumarate only.

The results at the end of the treatment period showed a decrease in serum HDV RNA levels: these were undetectable in 86.7% and 40.0% of the patients in the groups bulevirtide 10 mg once daily and PEG-IFNα 180 µg once weekly, and bulevirtide 5 mg twice daily with tenofovir disoproxil fumarate, respectively. Alanine aminotransferase was also shown to have decreased and 26.7% and 40.0% of patients achieved normalised levels of alanine aminotransferase after 48 weeks, in the groups bulevirtide 10 mg once daily and PEG-IFNα 180 µg once weekly, and bulevirtide 5 mg twice daily with tenofovir disoproxil fumarate, respectively. Notably, HBsAg, indicative of HBV infection, became undetectable in one patient in the treatment arm bulevirtide 10 mg once daily and PEG-IFNα 180 µg once weekly. These results suggested the patient achieved 'functional cure'. The researchers recorded 143 treatment-related nonserious adverse events. The study lead, Prof Heiner Wedemeyer, Hannover Medical School, Hannover, Germany, reflected on the importance of this data, explaining that the "high-dose administration of bulevirtide coadministered with PEG-IFNα or TDF for 48 weeks was safe and well tolerated in patients with HBV/HDV coinfection." He also commented on the prospects of the results: "This trial offers new treatment options for the most severe form of viral hepatitis."

"This trial offers new treatment options for the most severe form of viral hepatitis."

COVID-19 and the Liver

Rachel Donnison
Editorial Assistant

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IN THIS YEAR'S European Association for the Study of the Liver (EASL) Digital International Liver Congress (ILC) 2020, the session 'COVID-19 and the Liver' covered the essential information hepatologists need to know about the novel virus. Opening the session, Prof Sandra Ciesek gave the audience a background on the facts and figures of coronavirus disease (COVID-19). Coronaviruses were first identified in the 1960s, and before 2019 there were only six members of the viral family that were known to cause disease in humans. Four of these six known coronaviruses are responsible for 10–30% of all respiratory infection in adults, which results in the common cold. Though COVID-19 is well known for causing respiratory pathology, it can also result in several extrapulmonary manifestations, including hepatocellular injury.

RISK FACTORS FOR SEVERE COVID-19

Dr Johannes Hov, University of Oslo and Oslo University Hospital, Oslo, Norway, presented the known risk factors for severe COVID-19, which include hypertension, cardiovascular disease, obesity, and an immunocompromised state. He went on to analyse the data on pre-existing liver disease, a rarely mentioned factor in studies on comorbidities and risk factors for severe disease. Patients with chronic liver disease (CLD) had an increased risk of mortality from COVID-19 as reported by The UK OpenSAFELY National Health Service (NHS) study; however, this only totalled to 2% of deaths from CLD in the total study population.

There is conflicting evidence from several studies regarding smoking; while some studies have claimed it may play a protective role, a recent systematic review has declared smoking as a risk factor for severe disease and mortality.

"Genetically, it is impossible to define which of the genes is the culprit."

When discussing genetic factors, Dr Hov described the genome-wide association study he was involved in, which utilised single-nucleotide polymorphism comparisons between patients and healthy controls. The study compared patients with COVID-19 and respiratory failure to population controls using a Manhattan plot. Results demonstrated two distinct visible statistical associations: one at chromosome 9 and one at chromosome 3, though the strongest association was for the latter. The genetic variant identified at chromosome 3 was associated with respiratory failure in COVID-19, with an odds ratio of 1.77. There are at least six genes linked to the variant, including an immune-response gene and a gene linked to viral entry, but Dr Hov stated: "Genetically, it is impossible to define which of the genes is the culprit."

The chromosome 9 findings were also of interest; blood group A appeared to be associated with increased risk of COVID-19 respiratory failure and blood group O was associated with a protective role. These data are

"It emphasises the need for a very low threshold for viral testing in patients presenting with cirrhosis complications in the current era."

supported by data from the UK BioBank, but Dr Hov was cautious, and believed more data from larger studies are required to be able to draw conclusions.

COVID-19 AND CHRONIC LIVER DISEASE

Dr Thomas Marjot, University of Oxford, Oxford, UK then went on to explain the COVID-Hep and SECURE-cirrhosis registries and subsequent analyses. The online reporting registries are supported by EASL and the University of North Carolina, Chapel Hill, North Carolina, USA, respectively, and facilitate online submission of non-identifiable data with laboratory-proven COVID-19 and pre-existing CLD or individuals who are post-liver transplantation. A total of 1,000 cases from 35 countries were submitted to the registries from their initiation on the 25th March 2020 up until the 8th July 2020.

Eventually, after exclusions, 745 patients with COVID-19 and CLD remained, of which 359 had CLD without cirrhosis and 186 had cirrhosis. The most common causes of liver disease were nonalcoholic fatty liver disease (NAFLD), alcohol, and chronic viral hepatitis. Dr Marjot presented the major outcome according to liver disease stage: "With each liver disease stage there was a stepwise increase in rates of major adverse outcomes, including death."

Looking at the cause of death of patients with cirrhosis, the overwhelming majority (71%) died of COVID-19 lung disease, followed by liver- (19%) and cardiac-related complications (5%). "The chances of recovery worsened as the patient moves through hospitalisation, intensive care unit admission, and need for invasive ventilation," explained Dr Marjot. The diminishing chances of recovery were associated with heightened severity of baseline liver disease. For example, patients with Child–Pugh B cirrhosis who required invasive ventilation had a 26% chance of survival, which fell to 10% for those with Child–Pugh C cirrhosis.

Dr Marjot expressed his belief that these results "highlight the need for close monitoring of cirrhosis patients during the hospital stay, and this data may also help with escalation decisions in terms of providing treatment in the intensive care setting."

Another finding from the analysis of the registries was that, when looking at case fatality by 10-year age groups, those with cirrhosis were dying of COVID-19 significantly younger. Within the patients with cirrhosis, 46% experienced acute hepatitis decompensation following diagnosis of COVID-19, of which 22% had no typical respiratory symptoms of COVID-19. Dr Marjot stressed the importance of this: "It emphasises the need for a very low threshold for viral testing in patients presenting with cirrhosis complications in the current era."

COVID-19 AND LIVER TRANSPLANTATION

Solid organ transplantation activity trends during the COVID-19 outbreak in Europe and the USA were presented by Prof Ellie Barnes, University of Oxford, Oxford, UK. When considering the abrupt reduction in transplant activity observed in all countries, particularly Spain and Italy, in the month of April, Prof Barnes stated that: "There is a need to modify and develop a strategic plan to adapt transplantation programme activity and reduce the risk of transmission."

Prof Barnes went on to clarify that the action plan will require donor and recipient screening, via the clinic and the laboratory, to minimise the risk of transmission; resource planning for blood supplies, hospital capacity, and staff; and a staged approach to transplant volume considerations to weigh up the risk–benefit, risk tolerance, hospital capacity, and degree of local transmission.

Understanding that this is an evolving situation, the infectious risk to the recipient, availability of resources, daily evaluation of risk–benefit, and patient prioritisation must all be considered by the physician. In areas where the virus is heavily circulating, Prof Barnes suggested that: "Despite the risk of negative consequences, temporary cessation of transplantation may be necessary."

Prof Barnes then offered the current suggestions for modifying transplant programmes in instances where there is a 25% reduction in transplant activity, when elective cases could be pursued; urgent cases could be pursued when there is a 50% reduction in activity; and only emergency cases should be pursued in cases of 75% transplant activity reduction.

There are three pillars to minimising transmission of the virus during transplantation: epidemiological screening, clinical screening, and PCR testing of the donor and recipient. "If the donor or recipient are positive, we should not proceed with liver transplantation," cautioned Prof Barnes. She continued: "If the donor is positive, we should discard the organ, and in the setting of live donor liver transplant, this should be delayed by 28 days."

The discussion of a recent multicentre study on the incidence of COVID-19 in liver transplant patients led to two major conclusions: the standardised incidence ratio was significantly increased, suggesting the transplant population was at an increased risk of infection compared to the general population, and the standardised mortality ratio was similar between the two populations, signifying that disease severity was not worse in the transplant, immunosuppressed population.

Despite the apparent similar severity of disease among the populations, Prof Barnes also wanted to note that: "We may anticipate a more prolonged shedding of the virus in the immunosuppressed state, thus potentially increasing the risk of transmission to contacts including healthcare workers." Interestingly, immunosuppression has been likened to a double-edged sword for patients with COVID-19, as it can beneficially reduce hyperinflammation on the one hand, but on the other it leads to deleterious impairment of antimicrobial immunity and can delay viral clearance.

Summarising the international guidelines and recommendations for liver transplantation, Prof Barnes concluded: "The vast majority of recommendations advise against reduction of immunosuppression, particularly in patients who are asymptomatic."

"The vast majority of recommendations advise against reduction of immunosuppression, particularly in patients who are asymptomatic."

Precision Medicine in NAFLD: Are We There Yet?

Katherine Colvin
Editorial Assistant

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PRESENTING at an interactive session entitled 'Precision medicine for the management of NAFLD - Are we there yet?' at The Digital International Liver Congress 2020 on 29th August 2020, a number of experts shared their insights into current genetic understandings of nonalcoholic fatty liver disease (NAFLD) and how heterogeneity of phenotypes provides opportunities for precision medicine approaches.

PRECISION MEDICINE

In his opening presentation, Dr Salvatore Petta, University of Palermo, Palermo, Italy, discussed the concept of precision medicine and the features of NAFLD that make it an excellent candidate for a precision medicine approach. "We can define precision medicine as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations," he explained. Precision medicine approaches rely upon the presence of heterogeneous disease for targeted, individualised care; diagnostic tests that allow for refined disease classification or prognostication to create subtypes within the same disease; and therapeutic targets that allow for specific treatments of different phenotypes of the same disease.

NAFLD is a heterogeneous disease in that prevalence of progressive complications, including fibrosis and hepatocellular carcinoma (HCC), is varied, and associated comorbid conditions also vary across affected individuals. The phenotypes of NAFLD, according to Dr Petta, include multiple types of subgroups: metabolic syndrome-associated NAFLD, in patients with associated obesity and Type 2 diabetes mellitus (T2DM); lean NAFLD in patients without other features of obesity; lipid disorder-associated NAFLD in patients with increased rates of cardiovascular disease; patients who progress rapidly versus those who are slow to progress; and those patients with cardiovascular or extrahepatic complications of NAFLD versus those with hepatic complications. This variation in phenotypic expression allows for subgroup typing of individuals, which is of great importance in the development and application of precision medicine; however, diagnostic capabilities are not yet developed to be able to completely classify these subtypes.

Prognostic variation between subgroups in NAFLD allows for some classification of these groups and has led to the identification of some genetic markers and variants. Dr Petta highlighted that comorbid metabolic factors can

"the most specific classifications currently available, with the greatest hope for development of precision medicine for NAFLD, are the identified genetic variants associated with different NAFLD phenotypes"

discriminate fibrosis risk in known NAFLD, with arterial hypertension, a definite risk factor for rapid progression of liver fibrosis. The presence of T2DM predicts an increased risk of liver fibrosis over time, but the metabolic risk factors of T2DM, hypertension, dyslipidaemia, and obesity have a combined impact on the time to development of cirrhosis greater than each of their cumulative impacts on cirrhosis risk. However, the most specific classifications currently available, with the greatest hope for development of precision medicine for NAFLD, are the identified genetic variants associated with different NAFLD phenotypes.

GENETIC VARIANTS

In the second presentation, Prof Elizabeth Speliotes, University of Michigan, Ann Arbor, Michigan, USA, outlined the current understanding of genetic variants across heterogeneous phenotypes of NAFLD. In seeking to better understand this heterogeneity, genome-wide association studies have identified seven loci that account for approximately 15% of the heritability of NAFLD. Variants across these gene loci have differing effects on heritability or liver disease phenotypes and have differing associations with markers of dyslipidaemia and metabolic syndrome. Prof Speliotes highlighted the research and clinical value of these findings: "This is actually very exciting because it shows that genetics can dissociate epidemiologically correlated traits," which can then potentially be used as markers to identify subgroups of NAFLD for prognostic understanding and therapeutic targets: the basis of precision medicine.

To assess the value of testing for genetic variants to identify these subgroup patients, Prof Speliotes described population studies of thousands of patients that considered the interaction of these genetic variants with environmental factors. These studies found that the genetic variant PNPLA3 I148M, when combined with elevated serum insulin, glucose, triglycerides, and BMI, multiplied the risk of developing hepatic steatosis beyond the cumulative risk of each individual risk factor. A further study assessed the value of intervening in these genetically at-risk subgroups by comparing the impact of lowering insulin resistance; it found a greater reduction in risk of NAFLD following lowering of insulin resistance in those patients with the PNPLA3 genotype compared to those without the genetic variant. This magnified benefit of intervention was also seen in shorter-term interventional studies, including a study where patients with the higher risk genetic variant lost a greater amount of liver fat during a 6-day hypocaloric diet compared to those without the genetic variant, even with identical weight loss.

LIVER LIPIDOME

In her closing presentation, Prof Hannele Yki-Järvinen, University of Helsinki, Helsinki, Finland discussed the genetic variants of phenotypic subtypes of NAFLD, and how they impact lipid metabolism and expression in the liver (i.e., the liver lipidome). Multiple genetic variants predispose to progressive NAFLD, but several other genetic variants protect against progression of steatosis to more advanced forms of liver disease, or protect against development of cardiovascular disease or T2DM. To illustrate the impact of genetic variants on lipid metabolism in NAFLD, Prof Yki-Järvinen described her research identifying hepatic lipid expression by genetic variant subtype. "To our surprise, the human liver lipidome was markedly different in metabolic NAFLD and PNPLA3 NAFLD," she explained. She found that metabolic phenotypes had a predominance of saturated or monounsaturated fatty acids, whilst those individuals with PNPLA3 NAFLD had almost no triglycerides and a greater predominance of highly polyunsaturated fatty acids. Ceramides, which are known to contribute to insulin resistance, T2DM, and cardiovascular disease, were found to be markedly increased in metabolic NAFLD but not in those carrying

the PNPLA3 gene variant, which Prof Yki-Järvinen indicated is potentially the reason for the association of metabolic NAFLD with these comorbidities but not of PNPLA3 NAFLD.

In protective genetic variants in NAFLD, those that protect against the development of cardiovascular disease, T2DM, or liver malignancy, there were also subtype-specific alterations in the liver lipidome. HSD17B13, a lipid droplet protein expressed in the liver, has a protective variant HSD17B13 rs72613567 that decreases the risk of alcoholic and nonalcoholic cirrhosis, fibrosis, and HCC in NAFLD, but does not affect steatosis. The lipidome in this variant was associated with increased liver phosphatidylcholines and phosphatidylethanolamines. MARC1, an enzyme of unknown function located in the outer mitochondrial membrane, has a protective variant MARC1 rs2642438 that shields against steatosis and cirrhosis and is associated with decreased low-density lipid cholesterol. Study of the lipidome of this variant found it to be associated with increased hepatic phosphatidylcholines, and less inflammation and fibrosis. The significance and underlying mechanism of the changes in lipidome with these protective variants, particularly the increase in hepatic phosphatidylcholines, is currently being investigated.

ROLE OF EPIGENETICS

Epigenetic modifications also influence the heterogeneity of phenotypes in NAFLD, as outlined by Dr Sookoian, University of Buenos Aires, Buenos Aires, Argentina, in her presentation. "Epigenetics is the interface between the environment, fetal life, and the genome," clarified Dr Sookoian, before briefly providing an overview of the three major processes of epigenetics that may play a role in NAFLD phenotypes. Gene methylation is usually associated with gene repression and usually occurs at the gene promoter region. Histone modification is generally associated with gene expression and involves many post-translational modifications. Another mechanism of epigenetics is noncoding RNA-mediated gene silencing, which involves regulation of chromatin structure, co-operation with methylases, and effects RNA stability.

Epigenetic changes found in NAFLD include hypermethylation of the promoter of PGC1α, a master metabolic regulator, in patients with NAFLD (47.9% of alleles methylated), which is associated with decreased mitochondrial copy number and increased insulin resistance. In advanced NAFLD, epigenetic changes are found in tissue repair genes (hypomethylated and overexpressed), which leads to the accumulation of scar tissue, and in metabolic genes (hypermethylated and under-expressed), which leads to metabolic dysregulation.

FUTURE APPLICATIONS AND RESEARCH DIRECTIONS

Although progress in refined diagnostic testing and further scientific understanding of the pathophysiology of genetic variant-specific subtypes is needed, the presenters highlighted a few approaches for precision medicine in NAFLD already underway. Studies of environmental modifications in PNPLA3 NAFLD suggest that dietary or surgical interventions to reverse obesity will have a more pronounced reduction in risk of NAFLD development or progression in individuals carrying this variant. Another

"This is actually very exciting because it shows that genetics can dissociate epidemiologically correlated traits"

potential strategy in this subgroup is to directly address the genetic variant itself. PNPLA3 I148M is a 'gain-of-function' variant, Prof Speliotes explained, where the presence of the variant gives a new deleterious phenotype, while the absence of the variant has no known effect. It is thought that the action of this variant reduces triglyceride hydrolysis in lipid droplets in cells. A study in mice using antisense oligonucleotides for gene editing of this variant found a reduction in steatosis and fibrosis, and protection against diet-induced obesity. Prof Speliotes discussed a case example of gene editing in sickle cell disease as a suggestion that gene editing for NAFLD could be a future valuable intervention. For the other genetic variants, the complex protective interplay with other conditions including cardiovascular disease, metabolic syndrome, and diabetes, mean that more context-specific considerations are needed, and further research is required before genotype-specific recommendations can be developed.

Epigenetic modifications can also potentially be utilised in the management of NAFLD. Dr Sookoian discussed a study of patients following bariatric surgery that found that their methylation pattern demonstrated epigenetic remodelling post-treatment. This suggests that epigenetic changes are potentially modifiable or partially reversible. Another study of a biomarker present in NAFLD, miR-122, found it to be upregulated in the circulation and downregulated within the liver of patients with NAFLD; miR-122 was found to have a regulatory role in serum levels of alanine (ALT), and downregulation of the miR-122 gene was associated with loss of the hepatic phenotype in NAFLD and features associated with cancer. Dr Sookoian discussed that targeted downregulation of this noncoding microRNA could be a potential future target of precision medicine, before discussing other identified noncoding RNA and epigenetic components with associations to NAFLD subtypes, prognosis, and complications.

Prof Speliotes expects that NAFLD will be the leading cause of liver disease worldwide "within a year or so," highlighting that this means it is "one of the biggest unmet medical needs of our time" because of the lack of effective medical treatments currently available. Given this unavailability of successful treatment and the growing prevalence, improved understanding and rapid translation to clinical practice is a priority. In closing the session, chair Prof Stefano Romeo, University of Gothenburg, Gothenburg, Sweden, articulated the value of addressing progress in precision medicine in NAFLD: "I think this is the key question for the next decade: on whether we'll be able to implement precision diagnosis and therapy for our patients."

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Abstract Reviews

The following pages provide summaries of commendable abstract presentations presented at The Digital International Liver Congress (ILC) this year.

Diagnostic and Prognostic Role of Presepsin in Patients with Cirrhosis and Bacterial Infection

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Keywords: Acute-on-chronic liver failure, cirrhosis, liver transplantation, sepsis.

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BACKGROUND AND AIMS

Bacterial infection (BI) is a common event in the natural history of cirrhosis, often requiring hospitalisation due to hepatic and extra-hepatic organ dysfunction. Diagnostic criteria for severe infection and sepsis currently adopted in the general population display suboptimal accuracy in patients with cirrhosis.[1] Common serum biomarkers such as C-reactive protein (CRP), white blood cells (WBC), and procalcitonin (PCT) are often inaccurate in the early diagnosis of BI in cirrhosis. Presepsin (PSP), a 13 kDa fragment of CD14, is released into the blood upon the activation of monocytes in response to BI and has been evaluated as a promising diagnostic sepsis biomarker and prognostic tool in different populations.[2,3] This study aimed to prospectively evaluate PSP in a cohort of hospitalised patients with cirrhosis, with and without BI, to investigate its diagnostic accuracy in comparison with other commonly used biomarkers (i.e., CRP, PCT, and WBC); and to evaluate its prognostic role in short-term mortality.

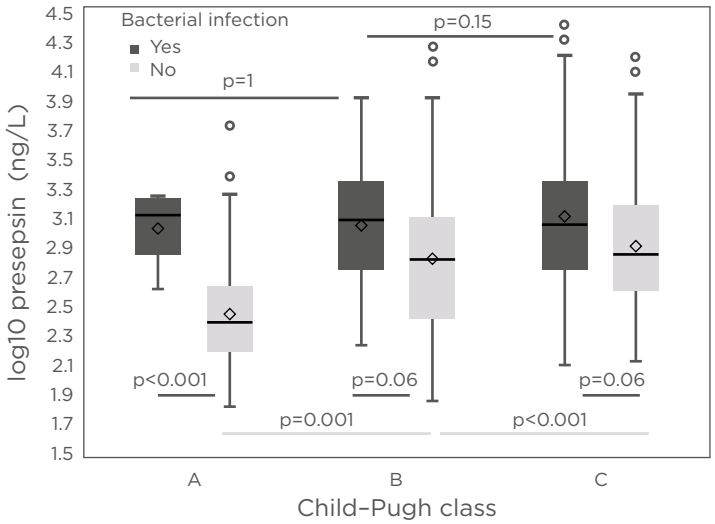

Figure 1: Presepsin values according to severity of underlying liver disease and bacterial infection.

MATERIALS AND METHODS

All cirrhotic patients admitted at Padua University Hospital between 2016 and 2019 were consecutively enrolled. Patients aged <18 or >80 years and with a prior solid organ transplant were excluded. For each patient, PSP was measured at hospitalisation by Pathfast™ technique (chemiluminescent enzyme immune assay) and its diagnostic accuracy was compared with that of CRP, PCT, and WBC. The 28-day outcome of each patient was evaluated considering liver transplantation as a competing event. Predictors of mortality were assessed with multivariable analysis.

RESULTS

Two-hundred and seventy-eight patients with cirrhosis were prospectively enrolled (males: 179; females: 99; mean±standard deviation [SD] age: 56±11 years; alcohol-related disease: 47.5%), for a total of 448 hospitalisations. The mean±SD Child–Pugh and Model for End-Stage Liver Disease (MELD) score at admission was 9.3±2.5 and 18±8, respectively, whereas 22.5% patients fulfilled criteria of acute-on-chronic liver failure. BI occurred in 28.3% of cases at hospitalisation, with the lower respiratory tract and blood being the most common sources (24% and 19%, respectively). In the whole cohort, the mean±SD PSP value was 1,620±3,014 ng/L. There was a correlation between serum PSP values and severity of underlying liver disease according to Child–Pugh class (p=0.001). Furthermore, serum PSP values were significantly higher in patients with BI than in those without (p=0.001). When comparing patients with similar underlying liver dysfunction, PSP significantly varied according to infectious status in those belonging to Child–Pugh A class (p<0.001), but not among patients with Child–Pugh B and C class (each p=0.06; Figure 1). A PSP cut-off value of 752 ng/L was able to retrieve the best diagnostic accuracy for BI, displaying an area under the curve–receiver operating characteristic equal to 0.685 (95% confidence interval [CI]: 0.63–0.73), with a sensitivity and specificity equal to 66.1% (95% CI: 57.2–74.4) and 63.2% (95% CI: 57.7–68.5), respectively. The diagnostic accuracy of PSP was lower than that of CRP (p=0.002), similar to that of PCT (p=0.18), and better than that of WBC (p=0.006). The short-term mortality was 13.8% in the whole cohort and was significantly higher among patients with BI at hospitalisation than in those without at competing risks analysis (p<0.001). At multivariate analysis, age, acute-on-chronic liver failure at hospitalisation, PSP (hazard ratio: 2.37; 95% CI: 1.29–4.34), but not CRP nor BI, were independent predictors of short-term mortality.

CONCLUSION

Hospitalised patients with cirrhosis had high values of serum PSP. It seemed to be influenced by the severity of underlying liver disease and displayed a diagnostic accuracy lower than that of CRP, but equal to PCT, suggesting a possible role in infection monitoring. PSP was an independent predictor of short-term mortality, reinforcing the role of a proinflammatory state in decompensated cirrhosis.

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Fibrosis-4 Score for Assessment of Liver Fibrosis is Useful in General Practice

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Keywords: Fibrosis-4 (FIB-4) score, general practitioner (GP), liver fibrosis, screening.

Citation: EMJ Hepatol. 2020;8[Suppl 2]: 33-34. Abstract Review No: AR2.

BACKGROUND AND AIM

Early recognition of liver fibrosis will be a challenge that continues in the coming years and should be performed by general practitioners (GP). The fibrosis-4 (FIB-4) test is one of the simplest, free-of-charge, noninvasive scoring tests based on age and routine laboratory parameters that has been shown to rule in/out significant fibrosis.[1] The authors of this study aimed to prospectively measure, using FIB-4 scores, the prevalence of significant liver fibrosis in adults without known liver disease who had consulted a GP. The authors compared this test with two others: nonalcholic fatty liver disease fibrosis score (NFS) and the Fibrometer^{V3G} test. The prevalence of the main risk factors (obesity, diabetes, alcohol consumption, and hypertension) and their link with fibrosis scores was then explored, as well as a reconsideration of a possible cause of liver disease in patients who tested FIB-4 positive.

METHODS

Over a 6-month period, 40 GP from the French Alpes Maritimes area offered all of their 45–79-year-old primary care patients, without known liver pathology, liver fibrosis screening via a simple blood test to allow for calculation of three noninvasive fibrosis scores.

RESULTS

Of the 2,121 patients included, 39% had a BMI >25; 13% consumed >100 g of alcohol per week; 10%

had diabetes; and 29% had hypertension. The prevalence of significant liver fibrosis, according to age,[2] was 19.1% (95% confidence interval [CI]: 17.5–20.9%) by FIB-4. By comparison, prevalence was 16.8% (CI: 15.0–18.5%) by the NFS and 8.2% (CI: 6.9–9.6%) by the Fibrometer^{V3G} test. Univariate analyses showed that all risk factors (obesity, diabetes, alcohol consumption, and hypertension) were significantly associated with significant fibrosis, independent of the test scores, except for diabetes using FIB-4 testing. Information on a possible cause of liver disease was obtained from 295/406 FIB-4-positive patients. GP reconsidered a cause of liver damage in 65% of cases: 97 of these were nonalcholic fatty liver disease cases, 48 were linked to alcohol consumption, 24 were linked to both, and 24 had other related causes. Specialist advice was requested for 65/406 patients. Among the 62 patients with interpretable liver stiffness measurements, 13 (21%) had a measurement of >7 kPa. The percentage of significant fibrosis, according to the 7 kPa threshold, was significantly higher in patients with a FIB-4 >2.67 and in those with a cause of liver disease, who need to be confirmed in priority.

CONCLUSION

Liver fibrosis was suspected by FIB-4 scores in 19.1% of patients who had consulted a GP and were without known hepatic pathology. The detection of significant fibrosis by a simple blood test such as the FIB-4 allowed the GP to suspect a chronic liver disease, and to define its cause, in two-thirds of cases. Widespread FIB-4 testing could be automatically generated as soon as the transaminase and platelet levels are measured, which should allow earlier detection of chronic liver diseases.

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FIB-4 and APRI Scores Revalidation in a Cohort Study of 69,106 Chronic Hepatitis C Patients

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Keywords: Aspartate aminotransferase (AST) to platelet ratio index (APRI), attribute reduction, fibrosis-4 index (FIB-4), hepatitis C virus, liver fibrosis, machine learning, METAVIR score.

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INTRODUCTION

Assessment of liver fibrosis is vital for enabling therapeutic decisions and prognostic evaluation of chronic hepatitis. The fibrosis-4 index (FIB-4) and aspartate aminotransferase (AST) to platelet ratio index (APRI) are simple, noninvasive, inexpensive scores.[1]

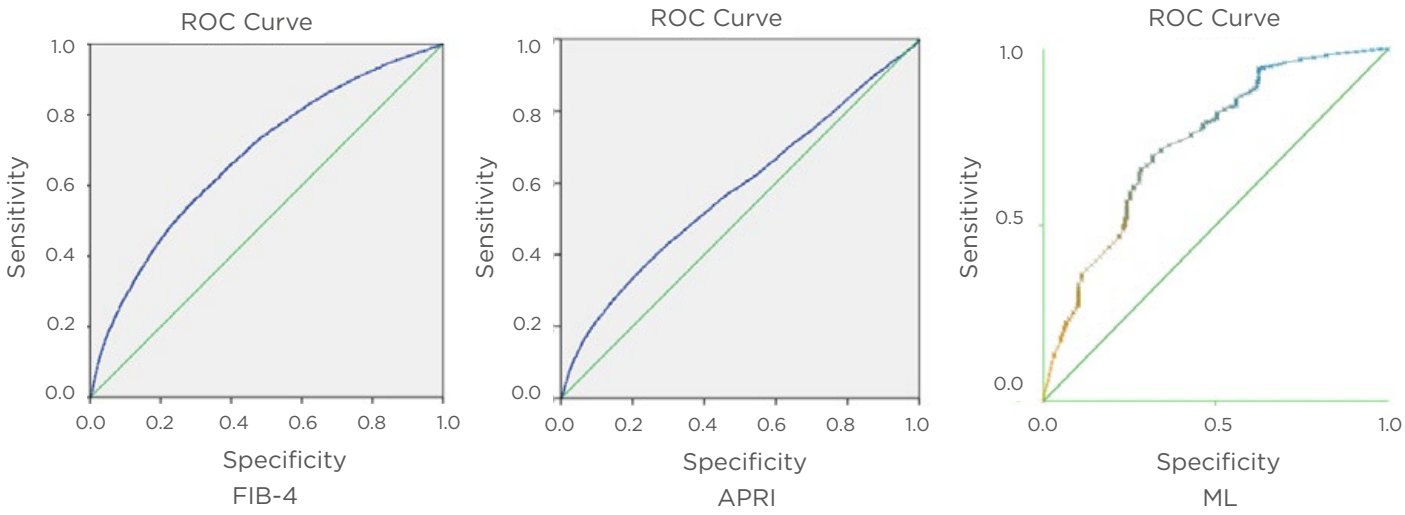

Figure 1: Receiver operating characteristic area of fibrosis-4 index (FIB-4), aspartate aminotransferase to platelet ratio index, and machine learning approach for prediction of F3-F4.

APRI: aspartate aminotransferase to platelet ratio index; FIB-4: fibrosis-4 index; ML: machine learning; ROC: receiver operating characteristic.

However, their accuracy is questioned because studies of the scores are based on a few hundred patients, and did not exclude decompensated cirrhosis that is easy to diagnose.[1,2] The Egyptian National Committee for Control of Viral Hepatitis has provided a rich pool of electronic patients' records with liver biopsy results.

This chance will not be repeated or available in the future, with the new era of directly acting antiviral therapy which does not necessitate liver biopsy. The authors were motivated by the opportunity to revise and validate the accuracy of FIB-4 and APRI scores, and to further explore the potential for developing an accurate prediction method using a machine learning (ML) approach.

METHODS

This retrospective, multicentre study included 69,106 Egyptian patients with hepatitis C viral infection (HCV) for interferon-based antiviral therapy from 2010–2014, where liver biopsy was mandatory for fibrosis assessment. FIB-4 and APRI scores were calculated and performance analysis of these scores was assessed and compared to the METAVIR scoring system (F0–F4) as a gold standard for liver fibrosis diagnosis. ML was used for feature selection and reduction to the most relevant attributes (CfsSubsetEval and best first).

RESULTS

In this study, 57,492 (83.2%) patients had F0–F2, and 11,615 (16.8%) patients had F3–F4 METAVIR scores. Score validation involved the evaluation of discrimination represented by the area under the curve (AUC), and calibration to assess agreement between predicted and observed risks (correctly classified). The revalidation of FIB-4 and APRI showed low accuracy and high disagreement with biopsy results, with overall AUC 0.68 and 0.58 respectively (Figure 1). FIB-4 diagnosed few cases (14%) of F3–F4 patients; the high specificity and negative predictive values of FIB-4 and APRI reflect the low prevalence of F3–F4 in the study population.

Recent guidelines recommend screening high-risk patients for liver cirrhosis. The high disagreement between APRI, FIB-4, and biopsy motivated the authors to develop a ML approach. Of 15 attributes, ML selected age >35 years, fetoprotein (AFP) >6.5, and platelet count <150,000 as the most relevant risk attributes, at these cut-off values. Any patient with one or more of these risk factors was considered as a possible F3–F4, with a classification accuracy of up to 92.0% and receiver operating characteristic (ROC) area 0.74 (Figure 1). High sensitivity ensures that high-risk F3–F4 patients will not be missed and will be assessed appropriately, and fibrosis screening will be reduced by 40%: the percentage of patients with no risk factors.

CONCLUSION

To the authors' knowledge, this study enrolled the largest studied sample size of 69,106 patients with chronic hepatitis C with available histopathological results. This study represents a multidisciplinary approach between hepatologists and health informatics researchers. This revalidation study showed that the two popular FIB-4 and APRI scores are not accurate, and missed the diagnosis of most of the F3–F4 patients studied. ML implementation helps empower medical decisions, and minimises the dimensionality of clinical data to three risk factors. This approach does not need any calculation and provides an accurate F3–F4 diagnosis, superior to APRI and FIB-4 scores.

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Progress in Hepatitis C Testing as Part of the Hepatitis C Elimination Programme in Georgia

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Keywords: Elimination, Georgia, hepatitis C virus (HCV), national data, prevalence, programme, progress, screening, testing.

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INTRODUCTION

In April 2015, the country of Georgia, with a high prevalence of hepatitis C virus (HCV) infection (5.4% of the adult population, approximately 150,000 persons), embarked on the world's first national HCV Elimination programme.[1-4] The overall goal of the programme was to achieve a 90% reduction in HCV prevalence by 2020. Currently, the hepatitis testing, diagnostics, and medication are available free of charge to all citizens. The aim of this analysis was to describe progress in HCV testing as part of the elimination programme.

MATERIAL AND METHODS

The study merged data from the national hepatitis C screening registry and the treatment database and census data from 2014 using a unique national ID.

RESULTS

As of 10th November 2019, 1,628,452 adults were tested for HCV (56.9% of the adult population), of whom 125,016 (7.7%) were anti-HCV positive. By the end of 2015, the positivity rate was 27.0%,

which was reduced to 3.8% in 2019. Overall, 98,134 individuals received viraemia testing, of whom 80,074 (81.6%) tested positive.

Screening rates were similar for males and females (55.9% versus 57.9%, respectively). Among males, screening rates were highest among those aged ≥60 years (64.2%) and lowest among those aged 18–29 years (51.7%). The overall positivity rate for adult males was 12.4%, with highest positivity among those aged 30–59 years (18.6%).

Screening rates were highest among females aged 18–29 years (60.7%) and lowest among those aged 30–59 years (56.4%). The overall positivity rate for adult females was 3.7%, with the highest positivity rate among those aged ≥60 (5.3%).

CONCLUSION

The overall anti-HCV prevalence was higher in males and among those aged 30–59 years. The anti-HCV positivity rate among those being screened has declined since the launch of the HCV Elimination Program in April 2015. Although significant progress has been made, a substantial proportion of infected people need to be identified through screening, testing for viraemia, and linking to care.

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Multivariant Surface Quasispecies in a Hepatitis B Virus Chronically Infected Individual with Concomitant and Continually Positive Surface Antigen and Anti-Hbs Biomarkers

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Keywords: Hepatitis B virus (HBV), hepatitis B virus surface antigen (HBsAg), next-generation sequencing.

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Table 1: Surface gene sites with amino acids identified with GATACA Assembly Tool (GATACA, Newport, Virginia, USA).

Surface gene site	Stop codons	Amino acid variants
Y100STOP/Y/N*/S/F/H/C/N*	1	7
S114T/S*/I/P/K/T*/Q*	0	6
P120P/T*/S*/A*/L*/R*/G/H*	0	7
C121STOP/C*/F/L/S*/R/V/T*	1	7
C123T/P/S/N/A*	0	5
L127P/T*/H*/S*	0	4
Q129Q/P*/H/K/T/S/Y*	0	7
G130G/V*/E/D/A*/R*/C*/S/P*/F/STOP*	1	10
M133L/T*/I*/Q/F/K*	0	6
F134F/S*/Y*/C/L**	0	4
D144D/A*/N/T*	0	3
G145G/STOP/V*	1	2
E164E/D*/G*/A*/R*/V**	0	5
W172L/R/C*/G/S/STOP*	1	7
W172L/R/C*/G/S/STOP*	1	7
I915I/M/L*/V*/T*/R*/K**	0	6
W196L/C*/F*/R/G/S/V/STOP*	1	8
L216L/V*/S/STOP**	1	3

*Amino acid with different nucleotides.

BACKGROUND AND AIMS

Coexistence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies (anti-HBs) can be found in 2.3–5.2% of chronic HBV (CHB) infected individuals. Recent reports have indicated that the presence of both biomarkers is associated with a high risk of hepatocellular carcinoma.[1,2] However, previous studies with clinical samples presenting both biomarkers have demonstrated that the presence of variants in the *HBsAg surface* (*S*) gene and anti-HBs subtype can non-specifically contribute to the coexistence of these two biomarkers in CHB.[3]

METHODS

In this study, HBsAg variants were analysed in a clinical sample from a 43-year-old female with CHB, with prolonged (>7 years) coexistence of HBsAg and anti-HBs, HBV e-antigen-negative, and treatment with tenofovir disoproxil fumarate. Total DNA was purified from plasma and HBV DNA was amplified. Next-generation sequencing and a novel HBV-specific assembly/machine-learning tool for quasispecies were applied for the analysis of the *S* gene (GATACA Assembly Tool [GAT], Newport, Virginia, USA).

RESULTS

The authors determined the frequency of 17 site variants in the *S* gene (Table 1). Variants *Y100S* and *L127P* occurred together in the same haplotypes and eight of the sites studied presented with a variant with a stop codon. Additionally, several quasispecies of the same amino acid variation in the variants' pool were found within this clinical sample. In addition, the study demonstrated that defective HBsAg variants can coexist with the wild type and other functional variants. Seven site variants were found in the 'a' determinant amino acid region of HBsAg, which could explain its persistence despite the presence of anti-HBs.

CONCLUSION

Considering that the *HBsAg S* gene is a potential target for antiviral development and HBsAg seroconversion is a potential outcome for a functional cure, understanding the dynamics of these variants can help identify strategies of use for the novel direct-acting antiviral agents.

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Contrast-Enhanced Ultrasound Algorithms for the Noninvasive Diagnosis of Hepatocellular Carcinoma in High-Risk Patients - A Prospective Multicentre Study (DEGUM CEUS HCC Trial)

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Keywords: Contrast-enhanced ultrasound (CEUS), CEUS algorithms, CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS®), Erlanger Synopsis for Contrast-enhanced Ultrasound for Liver lesion Assessment in Patients at risk (ESCULAP) guidelines, hepatocellular carcinoma (HCC), imaging, noninvasive diagnosis.

Citation: EMJ Hepatol. 2020;8[Suppl 2]:39-40. Abstract Review No: AR6.

INTRODUCTION

Hepatocellular carcinoma (HCC) can be diagnosed noninvasively in high-risk patients by means of contrast-enhanced imaging. The enhancement pattern considered typical of HCC is defined as arterial phase hyperenhancement, followed by contrast washout in the portal venous or late phase.[1] More recent studies suggest that washout in HCC is of mild intensity and often occurs in the late phase (after 4–6 minutes); in particular, well-differentiated HCC may show no washout at all. Contrast-enhanced ultrasound (CEUS) has a high diagnostic accuracy for the differential diagnosis of HCC.[2-5] However, standardisation of the CEUS examination procedure is insufficient, and CEUS-based diagnosis is often accused of

being subjective. Recently, standardised CEUS-algorithms (Erlanger Synopsis of Contrast-enhanced Ultrasound for Liver lesion Assessment in Patients at risk [ESCULAP], Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System [CEUS LI-RADS®]) have been developed to improve the interpretation and reporting of CEUS in HCC-suspect lesions.[6-8] However, these algorithms have not yet been validated prospectively in a clinical setting.

BACKGROUND AND AIMS

Here the authors initiated a prospective, nation-wide, multicentre study, funded by the German Society for Ultrasound in Medicine (DEGUM), intended to improve the standardisation of the CEUS examination procedure, and assess the diagnostic value of CEUS and the new standardised CEUS-algorithms for the noninvasive diagnosis of HCC.

MATERIALS AND METHODS

Patients at risk for HCC, with histologically proven focal liver lesions, upon B-mode ultrasound imaging were prospectively assessed with CEUS following standardised examination protocols in 43 German centres. Clinical data, findings from B-mode ultrasound, CEUS, categorisation according to the CEUS algorithms ESCULAP and CEUS LI-RADS, and histology were entered into online entry forms. CEUS-based diagnosis was compared to histology as the reference standard.

RESULTS

The study prospectively enrolled 395 patients (male/female: 329/66; mean age: 67.2±10.5 years; liver cirrhosis: 76.5%). Mean tumour size was 57.6 mm (range: 5–200 mm; <2 cm, n=42; 61.3% solitary). Histological diagnosis showed HCC in 316 cases and intrahepatic cholangiocellular carcinoma in 26 cases; 34 lesions (8.6%) were benign. Of the cases with HCC, 271 (85.8%) displayed arterial phase hyperenhancement and 255 (80.7%) showed contrast washout. The typical 'hyper–hypo' pattern was found in 72.2% of HCC (positive predictive value: 87.4%), and the 'hyper–iso' pattern in 13.6% (positive predictive value: 86%). Furthermore, 33 HCC (10.4%) showed late onset of washout after 4–6 minutes. The highest sensitivity for the diagnosis of HCC was reached with the ESCULAP algorithm (94.2%) and subjective on-site interpretation of CEUS (90.2%). The CEUS LI-RADS algorithm yielded the highest specificity (81.8%), but poorest sensitivity (61.8%) and negative predictive value (35.3%). The algorithms showed consensus in 67.1% of cases and one-third of the HCC were correctly identified with ESCULAP alone.

CONCLUSION

Arterial phase hyperenhancement is the key diagnostic feature of HCC in CEUS. The positive predictive value of the hyper–iso pattern is similar to that of the hyper–hypo pattern. The standardised CEUS algorithms add little diagnostic benefit to conventional on-site interpretation of CEUS. Additional late-phase assessment of washout after 4–6 minutes increases the diagnostic accuracy of CEUS for HCC and should be routinely performed.

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Congress Interview

Prof Christian Trautwein

European Association for the Study of the Liver (EASL) Ethics Committee Chairperson
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Q1 Becoming a doctor is a long training process; at what point did you decide to specialise in hepatology?

Actually, I decided to go into hepatology quite early when I put together my Doctor of Medicine thesis with Professor Michael Manns at the Department of Internal Medicine in Mainz, Germany (Prof Dr Karl-Hermann Meyer zum Büschenfelde). It then became clear to me to continue this topic and therefore I started my training in gastroenterology. Here, hepatology was always my favoured topic. I would like to mention that in Germany there is no specialisation for hepatology as it is part of gastroenterology.

Q2 How has your research focus on endoscopic examination methods aided your clinical work on diagnostic and therapeutic endoscopic procedures?

Right from the beginning, during my education, I had a strong interest in endoscopy, especially for endoscopic retrograde cholangiopancreatography (ERCP). Up until now, ERCP is something I perform very frequently as diagnostic and therapeutic procedures are very important for the field of hepatology. The relevance of the biliary system, due to my ERCP activity, also made it important for me to scientifically focus on the gut–liver axis.

Q3 You are familiar with the transjugular intrahepatic portosystemic shunt (TIPS) procedure and have carried out the surgery yourself. A lot of the literature describes risks of complications following the procedure; therefore, how important do you believe patient selection to be?

In Aachen, Germany, where I am right now, we do this together with the radiology department. It's not a procedure which we do ourselves. We do it in combination with other departments, as we are very closely linked to radiology, and therefore the potential problems we have are not very frequent. But of course, I also tell this to the patients. Patient selection is absolutely important because of these risks. I mean in the last years, because of an increase in the number of publications, we have incorporated a very

"Meanwhile it has become obvious to everyone that it is a very important risk factor for the progression of liver diseases."

specific selection criterion. However, we also know that TIPS have a very good impact on further follow-up clinically; therefore, TIPS is currently a standard procedure in the clinic, and we do this very frequently.

Q4 Could you tell our readers the key take-home message(s) of your recent publication: "Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis."

We started this some years ago with the help of the EASL and started to better understand what alpha1-antitrypsin is doing and how important it is. We realise right now that this is a very important genetic risk factor and because of this I think it is becoming clear worldwide that alpha1-antitrypsin was underestimated until now. Meanwhile it has become obvious to everyone that it is a very important risk factor for the progression of liver diseases.

Q5 As the European Association for the Study of the Liver (EASL) Ethics Committee Chairperson, what is your societal role?

We are very strongly involved in any potential conflicts of interest (COI) of any individual involved in the EASL. Therefore, we try to standardise it so that everybody has the same chances to have a COI or no COI. We have also developed thresholds that indicate when a person cannot take a job at the EASL to ensure that the industrial connection to the EASL is as low as possible. I think it's very important to have a clear standard of care for therapy and diagnostics and therefore we are very careful about potential COI. During my time as the Chairperson of the Ethics Committee, I want to establish absolute transparency concerning financial disclosures so that we can attain a clear separation between industry and academic societies. This is one of the main goals I have.

Q6 Not all medical associations have an ethics committee; how large a threat do you believe real or perceived bias to be to the integrity of medical guidelines?

I would suggest that every society and every board have an ethics committee to ensure that there is an independent surveillance of all the things which are ongoing. Therefore, I very much appreciate that the EASL has a very strong focus on this. I think it is very dangerous not to have an ethics committee. The clear line between industry, and especially academic research, should be made because if there was a close connection, industry-driven interests might take too much influence.

"I would suggest that every society and every board have an ethics committee to ensure that there is an independent surveillance of all the things which are ongoing."

Q7 The Digital International Liver Congress (ILC) 2020 scientific programme has been adapted to incorporate sessions relating to coronavirus disease (COVID-19). Could you tell us how the disease is thought to impact the liver?

It was a physical congress originally and was supposed to take place in London, UK, before it was postponed. The format was completely changed into digital sessions. The relationship between COVID-19 and the liver lies in the angiotensin-converting enzyme 2 (ACE2) receptor. Obviously, the ACE2 receptor is also in liver cells and because of that, the liver is also directly involved. We also know that some patients only display liver complications but no other problems or symptoms and therefore the liver plays an essential role in the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Q8 Which of the numerous sessions at The Digital ILC 2020 did you enjoy the most?

I only sat in for two sessions where I was involved. Nonetheless, it is discovering the newest trends in research that I always enjoy the most. This involves the newest research topics and where novel advances might take us; especially the work on the gut–liver axis, which is my focus topic. I think this is a very important research topic for the future.

Q9 What would your advice be to the younger generation that are following the same path and just beginning their career?

I think the important thing is that people have a clear leadership concept; they need to be supported and guided by somebody who is really interested in research and likes to invest in their career. I personally think this is the most essential component for young people, who are smart and willing to work hard and make a career.