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CONFERENCE

CROATIAN SOCIETY OF GASTROENTEROLOGY

SVEUČILIŠTE U SPLITU MEDICINSKI FAKULTET

KLINIČKI BOLNIČKI CENTAR SPLIT

EASL
European Association for the Study of the Liver

September 25th 2020

6th Adriatic Liver Forum

Cirrhosis and portal hypertension: from guidelines to individualized approach

Dear colleagues and friends,

It is our great pleasure to welcoming you to the 6th Adriatic Liver Forum (ALF) conference. Following great success achieved by the previous five ALF conferences in Zagreb, thanks to great support of domestic and foreign speakers and attendees from Croatia, wider Adriatic and Central European region, as well as from distant European centres of excellence, our intention was to move across the region in order to come closer to the people working with the patients with liver diseases, and initially chosen destination was beautiful and ancient town of Split at the Adriatic coast. However, the development of epidemiological situation has forced us to organize on-line meeting, in line with the practice of almost all similar events. Still, we keep the organisational structure as previously planned, so the organizers of this year conference are Croatian society of gastroenterology, University of Split School of medicine and University hospital centre Split.

The main topic of this ALF conference will be **Cirrhosis and portal hypertension: from guidelines to the individualised approach**. This subject was selected for several reasons. First, we are witnessing increase in the incidence of liver cirrhosis and its complications, with portal hypertension being the main driving force for the most prominent clinical complications and prognosis to these patients. Considering the fact that from the last Baveno VI conference in 2015 important scientific facts have emerged establishing thus a ground for more precise and individualised approach we have decided to put forward this everlasting topic in hepatology. The aims of ALF conference are to bring the state-of-the art knowledge and leading experts to the practicing hepatologists in this part of Europe, to improve their knowledge and the way of practice, as well as to establish connections and collaboration among local and international network of hepatologists. ALF 2020 conference comes in the dawn of Baveno VII, the most important international meeting on portal hypertension to set the future guidelines on this topic, and we are especially proud to have among the ALF 2020 Faculty some of the leading experts that will take decisive role at the upcoming Baveno meeting.

Our special thanks go to the organisations that have endorsed this conference: European Association for the Study of the Liver (EASL) and Croatian Society for Ultrasound in Medicine and Biology of the Croatian Medical Association. We are grateful to all the sponsors for recognising the importance of this topic and for giving their support to make this conference possible.

Best regards,

Ivica Grgurevic and Zeljko Puljiz,
ALF 2020 CONFERENCE CO-PRESIDENTS

Friday, September 25th 2020

08:30-09:00 OPENING CEREMONY (Ljubičić N, Ostojić R, Tonkić A, Dolic K, Flisiak R, Puljiz Z, Grgurević I)

09:00-10:35 RECOGNIZING THE PROBLEM (Ostojic R, Puljiz Z)

09:00-09:20 Noninvasive tests for fibrosis and cirrhosis: are we ready for screening? [Gines P, ES]

09:25-09:45 What about steatosis and NAFLD? [Mikolasevic I, HR]

09:50-10:10 Noninvasive diagnosis of portal hypertension by elastography [Grgurevic I, HR]

10:15-10:35 How close we are to HCV elimination: data from Central Europe [Flisiak R, PL]

11:00-12:35 PREVENTING THE COMPLICATIONS (Flisiak R, Tonkic A)

11:00-11:20 Primary prevention of variceal bleeding and decompensation [Bosch J, ES]

11:25-11:45 Gut microbioma in progression of cirrhosis and portal hypertension [Papp M, HU]

11:50-12:10 Treatment of hepatitis C in patients with cirrhosis [Filipec KT, HR]

12:15-12:35 Treatment of PBC [Jarcuska P, SK]

13:30-15:05 PATIENT WITH ADVANCED CIRRHOSIS AND PH 1 (Villanueva C, Milic S)

13:30-13:50 Endoscopic treatment of acute variceal bleeding [Puljiz Z, HR]

13:55-14:15 Secondary prevention of variceal bleeding: guided or blinded? [Alvarado T, E]

14:20-14:40 The role of TIPS [Patch D/Potts J, UK]

14:45-15:05 Renal injury in cirrhosis [Knezevic SI, HR]

15:30-17:05 **PATIENT WITH ADVANCED CIRRHOSIS AND PH 2** (Hrstic I, Sperl I)

15:30-15:50 Frailty in cirrhosis [Skladany L, SK]

15:55-16:15 Severe alcoholic hepatitis [Virovic Jukic L, HR]

16:20-16:40 Long-term outcome of patients with alcoholic liver cirrhosis [Stauber R, AT]

16:45-17:05 Impact of outpatient care on survival in alcoholic cirrhosis [Tepes B, SI]

17:30-19:05 **PERSONALIZED MEDICINE IN CIRRHOSIS AND PH** (Bonacin D, Graupera I)

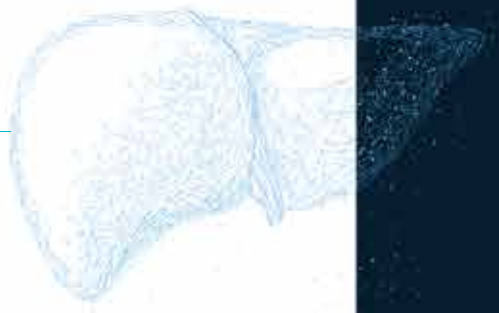
17:30-17:50 Genetic determinants for progression of cirrhosis and portal hypertension [Tsochatzis E, UK]

17:55-18:15 A new prognostic algorithm to improve risk-stratification after variceal bleeding [La Mura, IT]

18:20-18:40 Artificial neural network prognostic modeling in cirrhosis [Salkic N, BA]

18:45-19:05 Screening for HCC [Milovanovic T, RS]

19:05 **CLOSING REMARKS**



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ABSTRACTS

Non-invasive tests for fibrosis and cirrhosis: are we ready for screening?

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Chronic liver diseases (CLD) are very common worldwide and have become a major global health issue. It has been estimated that cirrhosis represents the 12th cause of death overall and 2.2% of all deaths worldwide. Remarkably, the incidence of CLD worldwide is increasing due to the raise in non-alcoholic fatty liver disease (NAFLD) in most countries and also alcohol-related liver disease (ALD) in some countries. If deaths due to hepatocellular carcinoma (HCC), which in most cases occurs with an underlying cirrhosis, are added to those of cirrhosis, the number of deaths increases and CLD becomes the 5th leading cause of death worldwide.

Cirrhosis is the final consequence of CLD that may be caused by several etiological factors, including hepatitis B or C virus, alcohol abuse, and metabolic syndrome or a combination of these factors. The major histological consequence of CLD is the unrelenting deposition of collagen fibers due to activation of hepatic stellate cells that causes progressive liver fibrosis and, eventually, cirrhosis. Although this process occurs very slowly, over decades, the disease is rarely diagnosed in the pre-cirrhotic stage or in early cirrhosis because patients do not seek medical attention due to the lack of symptoms. Currently, diagnosis most commonly occurs once the disease has reached the later stages with decompensated cirrhosis or when HCC develops.

Given its high prevalence in many countries and high mortality rate, CLD should ideally be diagnosed before cirrhosis has developed or at the stage of early cirrhosis. This would allow identification of etiological factor(s) responsible for liver inflammation and subsequent application of specific targeted interventions. The elimination of the etiological factor halts hepatic inflammation and leads to fibrosis regression. However, the identification of patients in early stages of chronic liver diseases raises two critical issues that are discussed below: 1/ are there accurate methods for early diagnosis?; and 2/ could these methods be used for screening in the general population?.

Liver fibrosis is the most important event in the natural history of CLD in terms of determining disease progression to cirrhosis and clinically-relevant outcomes, including liver-related complications and mortality. Therefore, the assessment of a patient with CLD ease requires the evaluation of fibrosis. In the past, the only available method to assess fibrosis was liver biopsy. However, liver biopsy is invasive, expensive, prone to sampling error, and may be associated with rare but potentially life-threatening complications, such as bleeding. Over the last decade, liver biopsy has been challenged by the development of non-invasive methodologies, which

rely on two different but complementary approaches: a biological approach based on surrogate markers, and a physical approach based on the measurement of liver stiffness. Most serum biomarkers have been developed for hepatitis C, but some like the NAFLD fibrosis score, have been developed and validated for NAFLD. The advantages of the serum biomarkers are wide availability and relatively low costs; however, despite high negative predictive values, the accuracy of the NAFLD fibrosis score is moderate because almost one third of patients cannot be correctly classified and a liver biopsy may still be required to assess fibrosis. Among physical methods available to evaluate liver stiffness, the most commonly used worldwide is transient elastography (TE). Several studies and meta-analyses have confirmed the excellent performance of TE for diagnosing cirrhosis in patients with CLD, with mean area under the ROC curve values of 0.94 and a suggested optimal cut-off of 14 kPa, but which may vary according to etiology of CLD.

Given the high prevalence of CLD and the importance of cirrhosis and HCC as major causes of death worldwide, it seems reasonable to consider the possibility of screening the population for liver fibrosis. So far, a limited number of studies reported results of screening for liver fibrosis in the general population. Most of these have used TE as screening tool or a combination of a serological marker and TE. In the first study performed in France as many as 7.5% of 1,190 subjects older than 45 years without previously known liver disease who attended a primary care center for a medical check-up had liver stiffness greater than 8 kPa, a value suggestive of significant liver fibrosis. In addition, 0.7% had a liver stiffness > 13 kPa, suggestive of cirrhosis. NAFLD was the most common etiology, followed by ALD. A liver biopsy was performed in almost one third of subjects with increased stiffness and significant fibrosis was found in 66%. Interestingly, cirrhosis was confirmed histologically in the 9 subjects with liver stiffness>13kPa (100% positive predictive value). Similar findings have been reported in a recent population-based study from Rotterdam including 3,041 subjects older than 45 years. The prevalence of liver stiffness greater than 8 kPa or 13 kPa was of 5.6% and 0.6%, respectively, and increased stiffness was associated with components of the metabolic syndrome, suggesting that NAFLD was the cause of liver disease in most subjects. The prevalence of increased liver stiffness among subjects with combined diabetes and steatosis at ultrasonography was 17%. Unfortunately, liver biopsy was not performed to confirm liver fibrosis. Finally, in another study in 3,076 subjects aged 18 to 75 years selected randomly from the general population in the Barcelona metropolitan area, the prevalence of increased liver stiffness (>8kPa) was of 6%. The prevalence of fibrosis (≥ F2) was confirmed by liver biopsy in 44% of subjects and was again related to NAFLD in most cases. Other studies in Asia and other parts of the world have reported similar results of screening for liver fibrosis in selected populations with risk factors for CLD, specifically NAFLD and ALD. Interestingly, in most of the studies mentioned, most subjects with significant liver fibrosis or cirrhosis had normal liver enzymes, indicating that the diagnosis of CLD would have been missed if subjects had been assessed with standard diagnostic algorithms currently used in primary care.

In summary, the high prevalence of CLD, their relevance in terms of mortality and use of medical resources, and the existence of effective screening methods to detect patients in presymptomatic stages supports the concept of designing and evaluating programs for screening of liver fibrosis in the general population. This approach may change completely the paradigm of how the fight against the current epidemics of CLD is addressed.

What about steatosis and NAFLD?

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In parallel to the growing global epidemic of obesity and diabetes mellitus type 2 (T2DM), non-alcoholic fatty liver diseases (NAFLD) is becoming the leading chronic liver disease (CLD) of the 21st century. It encompasses the entire spectrum of fatty liver diseases ranging from isolated steatosis to steatohepatitis and cirrhosis. It is in a bidirectional association with metabolic syndrome (MetS) and its individual components (central obesity, T2DM, insulin resistance, dyslipidemia, and hypertension). Increased liver tests (ALT, AST, GGT) are found in approximately half of all patients with NAFLD, some of NAFLD patients have hepatomegaly, but NAFLD often gives no symptomes. Liver biopsy is considered the "gold standard" for diagnosing and staging NAFLD; however, the invasiveness, the possible sampling errors and the potential acute complications of this procedure largely limit its routine clinical use. Therefore, several non-invasive diagnostic methods for NAFLD have been increasingly investigated over the last decade. US-B mode has been recommended as the preferred first-line diagnostic procedure for imaging of NAFLD in adults by the clinical practice guidelines of the EASL released together with the European Association for the Study of Diabetes and the European Association for the Study of Obesity. US B-mode imaging allows to subjectively estimate the degree of fatty infiltration in the liver. The grading of liver steatosis is usually obtained using some US features that include liver brightness, contrast between the liver and the kidney, US appearance of the intrahepatic vessels, liver parenchyma and diaphragma. According to data, the performance of US B-mode imaging for the detection of mild steatosis (fat content > 5%) is low, with reported sensitivity of 60.9%-65%. On the other hand, the performance of US-B mode imaging for the detection of moderate-severe fatty liver (> 20%-30% steatosis), B-mode US has a performance similar with CT or MRI. Compared to histology as reference standard, the overall sensitivity and specificity of B-mode US were, respectively, 84.8% and 93.6%, with 0.93 (0.91-0.95) area under the ROC curve (AUROC). Nowadays, in the world of hepatology the main role in non-invasive diagnostics has been taken over by elastography techniques. To date, although they are all relatively cheap, easy to obtain, quick and patient-friendly, the most widely used technique is the vibration-controlled transient elastography (TE). TE allows the simultaneous assessment of both the level of liver steatosis by using the controlled attenuation parameter (CAP) and the level of liver fibrosis by measuring liver stiffness (LSM). Thanks to the recent development of XL probes, TE may accurately assess liver steatosis and fibrosis even in obese patients with NAFLD. In particular, the failure rate of Fibroscan machine 502 Touch is currently

much lower than previous versions of TE machines, because this machine has a software with an automatic probe selection that determines the choice of the probe (M or XL) based on the skin liver capsule distance. Overall, it has been shown that TE has a high reliability (>95%), low failure (<5%) and high reproducibility for the estimation of CAP and LSM in patients with NAFLD. According to data, CAP correlate with the MetS and its individual components and is a good method for detection and quantification of steatosis.

Noninvasive diagnosis of portal hypertension by elastography

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Portal hypertension is the most important driving force for the development of complications from liver cirrhosis including decompensation and death. Reference diagnostic methods for portal hypertension and its complications (such as esophageal varices (EV)) are invasive and include measurement of hepatic venous pressure gradient (HVPG) requiring catheterisation of hepatic veins, and endoscopy to diagnose and treat gastro-esophageal varices (GEV). Due to invasiveness and limited availability (HVPG for example) there have been ongoing research efforts aiming to establish non-invasive methods that could reliably replace HVPG and endoscopy for diagnostic purposes. These can be divided into biochemical and physical approaches. Biochemical (serological) tests use circulating compounds of the blood such as Platelets, albumins, liver transaminases, components of the extracellular matrix and some others used either alone or combined according to mathematical algorithms tested in clinical studies. Physical tests mostly use elastography to measure liver and/or spleen stiffness as they are changed in the diseased liver and spleen. Among ultrasound based elastography methods most data have been accumulated by using transient elastography (TE), that resulted in Baveno VI recommendations. Accordingly, liver stiffness measurement (LSM) by TE <10 kPa reliably exclude compensated advanced chronic liver disease (cACLD), wheras LSM≥10 kPa is suggestive for this entity. TE might be used to rule-in clinically significant portal hypertension (CSPH) if LSM>20-25 kPa, and to rule out varices needing treatment (VNT) in patients with Plt count>150.000 and LSM<20 kPa. These recommendations have been extensively validated and according to the recent-meta analysis have sensitivity of 97% to rule-out VNT, with low specificity of 32% as expected, and AUROC 0.9. By applying these criteria to a hypothetical cohort of 1000 patients with cACLD and 20% prevalence of VNT it would be possible to avoid endoscopy in 26% of them, with the risk of missing

VNT in 0.6% of patients. In order to overcome limitations of LSM research interest has recently been directed to measuring spleen stiffness (SSM). In the sequential algorithm patients who did not fit into Baveno VI criteria were in the second step referred to SSM and those with SSM≤46 kPa had 98% negative predictive value for VNT. By using this algorithm it was possible to avoid endoscopy in 42% of patients with the 3% risk of missing VNT. The most recent and exciting development in the field is the attempt to evaluate the response to nonselective beta blockers by SSM, however only preliminary results have been published requiring validation in the independent cohort.

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How close are we to HCV elimination? Data from Central Europe.

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Despite of number of publications on the global burden of HCV infection and its worldwide elimination, we need more detailed description of current situation related to HCV elimination in central european countries. Data were obtained from HCV opinion leaders/experts working within Central European Hepatologic Collaboration involved in management of HCV infections, which participated in 9th Conference of the Central European Hepatologic Collaboration (Warsaw, 10-11 October 2019). Based on dedicated

questionnaire current informations from Bulgaria, Croatia, the Czech Republic, Hungary, Latvia, Lithuania, Poland and Slovakia were collected and analysed. The HCV prevalence rate in particular countries varied from 0.2% to 1.7%. In most central european countries all the HCV infected population is eligible for reimbursement of treatment. However, in some countries there are still some limitations related to the stage of the disease and people who inject drugs. Access to therapy for HCV is similar and the majority of patients in Central Europe can be treated according to the current guidelines. All countries have access to at least one pangenotypic regimen. The most common barrier to HCV elimination in all countries is insufficient political will to establish priority for HCV. None of the reporting countries has established a national screening programme. Depsite of optimistic opinions from some experts, according to collected data HCV elimination will not be possible in the region by 2030, which is a target established by World Health Organization.

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Primary Prevention of Variceal Bleeding

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Aim of Therapy: Prevention of First Variceal Bleeding Vs Prevention of First Decompensation

Variceal bleeding is one of the major complications of portal hypertension in patients with cirrhosis and despite a marked progress in recent years is still associated with a high 6-week mortality, of about 15-20%. Traditionally, prophylactic treatments for portal hypertension were mostly devoted at preventing variceal bleeding. However, it is now recognized that ascites represents the more common complication of portal hypertension in cirrhosis. Moreover, it has been shown than the incidence of ascites is markedly

decreased after and effective reduction of portal pressure, achieved either by pharmacological therapy or after transjugular intrahepatic portal-systemic shunt (TIPS) placement. Also, it is well known that the prognosis of variceal bleeding is much more severe in patients with ascites than in those without other complications of portal hypertension. Because of this, at the past Baveno VI meeting (held in 2015), it was proposed that we should no longer talk about prevention of first variceal bleeding but on prevention of the decompensation of cirrhosis, would that be ascites, bleeding or hepatic encephalopathy. Therefore, what before was covered under "Primary Prophylaxis of Variceal Hemorrhage" is now included under two different categories: Prevention of the Decompensation of Cirrhosis (a low-risk scenario) and Prevention of First Variceal Bleeding in Patients with Decompensated Cirrhosis (a high-risk scenario).

Therapies for Primary Prophylaxis

Potential therapeutic modalities include the use of pharmacological agents, endoscopic therapy and TIPS.

TIPS. TIPS shall never be used for primary prophylaxis since we know from the era of prophylactic surgical portacaval shunts that although the procedure is highly effective in preventing bleeding and ascites, it may cause invalidating encephalopathy and decreases the survival probability. Therefore, this type of therapy is formally contraindicated and unethical in compensated asymptomatic patients. Whether is some circumstances it might be justified is something that should be first proved by very well designed, supervised and conducted randomized controlled trials.

Endoscopic therapy. Endoscopic therapy, mainly using endoscopic band ligation (EBL) of esophageal varices or endoscopic obturation of gastric varices with tissue adhesives have become popular because they are highly effective to control acute variceal bleeding. These therapies are less effective in "eradicating" the varices, the success rate being about 65-70% after multiple sessions of EBL. Furthermore, recurrence of varices approaches 80% at 1-year of its "eradication", which calls for continued endoscopic surveillance and re-treatment. In addition, treatment is very frequently associated with transient dysphagia and esophageal ulcers, and results in acute bleeding in 6-9% of patients. It can lead less frequently to other complications such as esophageal strictures, and it has not been adequately evaluated whether it can facilitate portal vein thrombosis. However, its main limitation in primary prophylaxis is that it does not decrease portal pressure (there are even reports of increased portal pressure after EBL), so they have no potential at all to prevent the formation of ascites.

Pharmacological therapy. The continued administration of non-selective beta-blockers continues to be the mainstem of the treatment of portal hypertension.

Although any non-selective beta-blocker can theoretically be used, those better assessed in RCTs are propranolol and nadolol. More recently carvedilol has emerged as the beta-blocker of choice for primary prophylaxis in compensated patients. Its main advantages over propranolol are: a) it allows a greater reduction of portal pressure (measured as the hepatic vein pressure gradient or HVPG, that decreases about 17-20% with carvedilol Vs 12-15% with propranolol) and in a higher proportion of patients (60-85% "responders" Vs 40-55% with propranolol, using a definition of response of a fall in HVPG of at least 20% from baseline); b) carvedilol is much easier to dose and better tolerated. Only 2 dose steps are used in practice, therapy starting by 6.25 mg per day (divided in two doses), and if tolerated is increased to 12.5 mg per day. This dose, in my experience, causes less side effects such as exertion dyspnea, fatigue, and impotence than propranolol, which increases acceptability and compliance to therapy. Limitations of beta-blockers (including carvedilol) is that they are of very little potential in patients without clinically significant portal hypertension (CSPH), defined by an HVPG of at least 10 mmHg. This makes that too early treatment (before developing CSPH) would probably be futile. Assessing whether a patient has already CSPH requires up to now measuring the HVPG. However, a number of different non-invasive tests are being developed that allow detecting patients with CSPH with a quite high specificity, although sensitivity is not yet optimal.

Comparison of EBL Vs Propranolol

Many studies have compared these two therapies up to now. The results are well known, showing that overall, there was a slight advantage for EBL in preventing first variceal bleeding. However, on meta-analysis this was only evident when including either low quality studies, or studies grossly underpowered (with less than 100 patients overall when sample size calculation indicates that an adequately sized trial shall include at least 400 patients), or trials presented only as abstracts and that have never been published in full in the subsequent 5 years.

The more recent studies show a change in tendency, with equal or better results with drug therapy than with EBL. Most of these studies are using carvedilol. Unfortunately, these studies did not assess other outcomes such as ascites, and the length of follow-up was not adequate to assess potential effects on survival. The issue will probably be settled by a large cooperative study being conducted in Scotland.

Prevention of first decompensation

The low time elapsed since Baveno VI has not allowed to perform many prospective studies and randomized controlled trials (RCTs) on prevention of first decompensation. Therefore, most evidence comes from the recently published PREDESCI (Prevention of the Decompensation of Cirrhosis) Study. This was a cooperative, multicenter, double-blind, randomized controlled trial conducted in

Spain independently from any drug company, sponsored by competitive grants from the Spain Ministry of Health. The study included patients with compensated cirrhosis of the liver, without varices needing treatment (VNT, those at high-risk of bleeding as assessed by being large or with red-whale marks). All patients had baseline measurements of HVPG and of the acute decrease in HVPG achieved after intravenous propranolol administration. Patients with HVPG of at least 10 mmHg and without varices needing therapy were randomized to receive propranolol or identical placebo if the response to IV propranolol was a fall in HVPG of at least 10% of baseline, and to carvedilol Vs identical placebo if they were not acute propranolol "responders". Patients developing varices needing treatment received EBL in addition to their randomized therapy. 210 patients were included, as per the sample size calculation. Follow-up was continued for a median of 4 years.

The study showed that beta-blockers, compared to placebo administration decreased significantly the incidence of first decompensation of cirrhosis, by approximately 40%. This was mainly due to a marked reduction in the incidence of ascites, that was cut by circa 50%. There were no differences in the incidence of bleeding, that was similar and very low in both treatment arms, probably because patients developing large varices or varices with red whales being treated with EBL and continued in the study. Treatment was well tolerated. Noteworthy, patients treated with carvedilol, despite being the worse candidates as demonstrated by the lack of HVPG decrease after IV propranolol, performed at least as well as those receiving propranolol.

The study is of great importance as it shows for the first time than it is possible to prevent ascites with such a simple and inexpensive therapy as the use of beta-blockers. This study establishes a new indication for beta-blockers in cirrhosis.

Clinical hemodynamic correlations

Patients in the PREDESCI study had yearly measurements of HVPG. This allowed to examine how much should the HVPG decrease to prevent the decompensation of cirrhosis. The results showed that the only independent predictors of lack of decompensation on follow up were being treated with beta-blockers and achieving a decrease in HVPG of at least 10% of baseline or to values below 10 mmHg.

It would be interesting to verify if non-invasive investigations could allow to predict either the response to beta-blockers or the occurrence of decompensation, in order to predict the best candidates and/or the effectivity of therapy.

The role of gut microbiome in progression of cirrhosis and portal hypertension

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Inhabitants of human gut, the so-called gut microbiota perform several important and beneficial functions for the host. However it has been more and more recognized as a new important player in the pathophysiology of many intestinal and extraintestinal diseases. Interest about the of link of the gut microbiota to liver diseases dates back to 1960s. Currently it has been attracting accentuated attention in liver cirrhosis.

The liver is the organ, which is in the closest contact with the intestinal tract, and is exposed to a substantial amount of bacterial components and metabolites. Accordingly, liver is affected by gut microbiome and its changes in many ways. At the same time, progression of the liver disease has significant impact on gut microbiome as well. Increasing disease severity is characterized by profound dysbiosis marked reductions in gene richness, especially in acute-on chronic liver failure (ACLF). Recent technological developments and culture-independent technics (16S rRNA gene amplicon and whole metagenome shotgun sequencing) made it possible the more precise characterization of the structural and functional changes of gut microbiome. First metagenomics studies show that in cirrhosis oral flora dominates in the intestine and profound salivary dysbiosis is a typical feature. In the end-stage liver disease (ESLD), the microbiome-liver interaction is largely etiology independent. Dysbiotic microbiome can affect the gut epithelial barrier as well resulting in poorly controlled translocation of viable gut bacteria or antigens from the gut tract to the liver and beyond ("leaky gut"). Bacterial translocation is highly associated to disease progression and characteristic feature of the advanced liver disease. It is still to be revealed whether gut microbial changes precede, coincide with or follow the development of complications in cirrhosis. More recently, several studies clearly support a major role for the gut microbiome in the progression of liver disease to decompensated cirrhosis and ACLF syndrome.

Specific microbiome patterns are found to be diagnostic and predictive for certain complications of cirrhosis, mainly hepatic encephalopathy. Analyzing the gut microbiome is an attractive future diagnostic tool however its implementation into the routine clinical practice needs future studies and also have difficulties. It is clearly proved that stool and colonic mucosa associated microbiome are different. Moreover microbiome obtained from different part of gastrointestinal tract are diverse and samples are not easy to get.

Evaluation of microbiome signature in the saliva is one exception and indeed hold future promise. Salivary microbiome is, however, very different from stool microbiome. Salivary dysbiosis was able to predict hospitalization independently of cirrhosis severity.

Being amenable for changes, gut microbiome is increasingly an attractive therapeutic target. Currently practiced treatments for cirrhosis, such as probiotics, diet, rifaximin or prophylactic antibiotics, are already targeting the gut-microbiome-liver axis. Albumin is widely used in cirrhosis but its link to microbiome has not been studies so far. It is appealing to hypothesize that albumin leaking into the gut lumen might influence and be metabolized by the gut microbiome, that backfire to the host. New approaches are already taken in place, such as fecal microbiome transplantation (FMT). In a pilot study, FMT from a rational stool donor improved dysbiosis and so recurrent hepatic encephalopathy.

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Treatment of hepatitis C in patients with liver cirrhosis

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Chronic HCV infection is a slowly progressive disease which can lead to cirrhosis in 20–30 years. Once cirrhosis has developed, the risk of hepatic decompensation is approximately 3–6%/year. Successful HCV treatment results in lower risk of hepatic failure, hepatocellular carcinoma (HCC), liver-related deaths, and all-cause mortality. In the era of safe and effective direct-acting antiviral drugs (DAAs) therapy, in patients with compensated cirrhosis (CTP A), HCV treatment is intuitively indicated in order to improve hepatic function and avoid liver transplantation (LT), while the definitive treatment for patients with decompensated cirrhosis (CTP B/C) is transplantation. Patients with decompensated liver cirrhosis (CTP B/C) - LT candidates, belong to a group of patients who have priority in the treatment of HCV infection with the aim of reducing the risk of worsening underlying liver disease and/or developing

of HCC. Successful HCV eradication enable in selected patients (20-60%) liver function recovery and possibly for some patients (5-35%) delay of LT procedure with preventing liver graft infection after transplantation by achieving viral clearance. However, the risk of progressive liver disease and HCC still remains.

Treatment of HCV infection in transplant medicine may be performed before or after LT. DAAs are treatment of choice because of their high efficacy and a favourable side effect profile. The optimal approach is not uniquely defined, further to the fact that it is a special group of patients in which a multitude of factors are affecting antiviral or underlying liver disease treatment success: the severity of the underlying disease before LT, different waiting times on transplant list, complications of transplant surgery and immunosuppressive (IS) treatment.

The treatment of LT candidates (decompensated liver cirrhosis or HCC) is related to:

1. average 10-20% lower expected sustained virological response (SVR12)
2. longer expected treatment duration (12-24 weeks) and / or need for ribavirin (RV)
3. a higher risk of side effects and interaction of DAA with other drugs prescribed to patients with decompensated cirrhosis
4. limited therapeutic options in patients with decompensated cirrhosis (protease inhibitors (PI) are contraindicated)
5. the potential risk of HCC despite or associated with DAA treatment
6. in case of failure of antiviral treatment, patients enter LT with positive viremia and resistance associated mutations (RAS) of the virus
7. MELD "purgatory" which decreases their chances of achieving a LT.

The 2018 European Hepatological Association (EASL) Guidelines recommend LT first and then treatment with DAA drugs in patients with decompensated cirrhosis (CTP B / C) and MELD score ≥18-20 or patients with HCC and expected waiting time on the list <3-6 months. If the patient does not meet the above criteria, it is recommended that the DAA treatment should be considered first, followed by the LT procedure.

In viraemic patients, graft reinfection after LT is universal and, if untreated, associated with reduced recipient and graft survival. Therefore, all viremic LT recipients should be considered for initiation of treatment after surgery. An urgent indication for antiviral treatment is early severe recurrence of HCV infection after LT - fibrosing cholestatic hepatitis or the onset of high-grade fibrosis (F2-4) in the first year after LT. In other situations, it is considered optimal to start antiviral treatment after the first 3 months from LT, when the patient is in a stable phase of immunosuppressive treatment and at a lower risk of complications of surgery.

Compared to the pre-transplant period, the benefits of applying antiviral treatment in post-transplant period are:

1. avoidance of therapy in the advanced stage of decompensated liver disease or with HCC consequently with the possibility of achieving higher levels of SVR12
2. shorter duration of therapy and avoidance of RV.

The challenge of treating DAA drugs after LT is the possible interaction of IS drugs (calcineurin inhibitors, antimetabolites, and m-TOR (mammalian target of rapamycin) inhibitors) with DAA drugs. This applies in particular to combination of NS3/4A inhibitors (PI) and calcineurin inhibitors or everolimus and NS5A inhibitors (velpatasvir and ledipasvir) requiring IS drugs dose adjustments. Transplanted patients should be treated in centres with experience in IS treatment and the ability to control the level of exposure to IS.

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Treatment of primary biliary cholangitis

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Primary biliary cholangitis (PBC) is a chronic inflammatory autoimmune liver disease that is characterized by chronic non-suppurative inflammation and progressive cholestasis accompanied by fibrosis. PBC can progress to liver cirrhosis in some patients and hepatocellular cancer can develop in liver cirrhosis.

The treatment aims are: to slow down or completely stop PBC progression, to reduce mortality and to improve health-related quality of life. Ursodeoxycholic acid (UDCA) is the gold standard therapy, daily dose is 13 - 15 mg/kg. UDCA is a safe and well-tolerated. The treatment slows down or even completely stops the disease progression and liver fibrosis when treatment response is achieved. There are several definitions of response to UDCA, most frequently used criteria to define treatment response are Toronto criteria., response is defined: ALP ≤ 1.67 ULN and bilirubine ≤ 2 ULN) after UDCA treatment. Approximatly 2/3 patients achieve response to

UDCA. Those who achieve biochemical response to UDCA have similar estimated survival as healthy controls, nonresponders have shorter transplantation-free survival.

Second line therapy in nonresponders is the addition of obeticholic acid (OCA) to the UDCA. Approximately 50% noresponders to UDCA treated with UDCA and OCA achieve therapy response. Alternative option are fibrates, particularly bezafibrate, although this treatment option is still not licensed for PBC treatment.

Secondary prevention of variceal bleeding: guided or blinded?

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Cirrhosis is a heterogeneous disease that cannot be studied or managed as a single entity, and is classified in two main prognostic stages according the progression of the portal hypertension and the presence of decompensations. The 2 main prognostics stages are: compensated and decompensated cirrhosis. Those, with very different management and prognosis. In compensated patients the portal hypertension treatment is focus to avoid decompensation, unlike treatment in patients with decompensated cirrhosis, which is aimed at preventing further decompensations and death. Variceal bleeding is one of the most feared complications of portal hypertension, because of its deleterious impact in the liver function and prognosis because the high risk of death, the adequate management of those patients included the treatment of the acute episode of variceal bleeding and rebleeding, and is crucial in modifying prognosis. The gold standard method for evaluating portal hypertension is to measure the hepatic venous pressure gradient (HVPG) by hepatic catheterization. The presence of clinically significant portal hypertension is the main factor determining the risk of development of varices, other liver-related decompensations, for that reason it should be carefully screened and monitored. The evaluation of the HVPG and liver function (Child-Pugh score/MELD score), can stratify patients according to their risk of bleeding (in the setting of primary prophylaxis), and in the setting of secondary prophylaxis, the risk of failure and rebleeding which can improve survival in appropriate candidates. Patients surviving a first acute variceal bleeding (AVB) episode are at high risk of rebleeding during follow-up (60% in the first year) if no treatment is given. Therapy to prevent rebleeding is mandatory in all patients surviving an AVB episode.

Combination therapy with non-selective beta-blockers (NSBBs) and endoscopic banding ligation (EBL) is significantly more effective than either EBL or drug therapy alone in preventing recurrent AVB. However, despite correctly applying combination therapy, 21% of patients rebleed and 24% die during the first 6 weeks. HVPG and Child-Pugh score are the main reported prognostic factors that enable risk-based approach and stratification of patients according to their probability of rebleeding. For that reason, the general recommendation of NSBBS+EBL for all patients undergoing secondary prophylaxis should be re-evaluated. On the other hand, the implantation of pre-emptive TIPS may change the characteristics of the population requiring secondary prophylaxis. Recent studies have explored the effect of combination therapy vs. monotherapy depending on Child-Pugh class (A vs B/C), the overall results reinforce the concept that NSBBs are the key element of secondary prophylaxis. Regarding HVPG-guided therapy, several studies have demonstrated that in secondary prophylaxis, achieving HVPG response (decrease of HVPG>20% or HVPG<12mmhg) is associated with a very low residual risk of bleeding, better survival and lower risk of developing other complications of portal hypertension. The non-responders to NSBBs after adding or changing the drug treatment can finally achieve an adequate hemodynamic response with similar survival and rebleeding rates as acute responders to propranolol/nadolol. The use of hemodynamic criteria to individualise treatment of portal hypertension, using optimizes therapy and may avoid unnecessary procedures. Stratifying the risk of recurrent variceal bleeding based on liver function and hemodynamic response to non-selective beta-blockers allows for tailored treatment, thereby increasing survival and avoiding adverse events.

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Renal injury in cirrhosis

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Patients with decompensated cirrhosis frequently have chronic kidney disease (CKD) caused by certain comorbidities (i.e. diabetes, arterial hypertension) and/or specific causes (i.e. IgA nephropathy, virus-induced glomerulopathy), but the real prevalence is not known. On the other hand, acute renal injury (AKI) is a common complication of advanced cirrhosis. Beyond the usual types of AKI, namely, prerenal, intrarenal/intrinsic, and postrenal, patients with cirrhosis can develop a specific type called hepatorenal syndrome (HRS).

Hyperdynamic circulation due to arterial vasodilation in splanchnic pool reduces volume in systemic circulation with consequence of organ hypoperfusion, dominantly kidneys. Renal hypoperfusion is the leading cause of acute kidney injury in cirrhosis, and could also lead to chronic kidney disease. Beside significant circulatory changes there is also a chronic inflammatory milieu which plays a significant role in circulatory and kidney dysfunction.

In a few recent years, definition, classification and grading of renal disfunction and injury, is considerably changed, so today we are using definitions proposed from International ascites club (ICA), based on Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine (SCr) criteria. The term acute renal failure is changed to acute renal injury (AKI) which is, irrespectively of its different types defined as either an absolute increase in SCr of more than or equal to 0.3 mg/dl (≥26.4 mmol/L) in less than 48 h, or by a percentage increase in SCr of more or equal to 50% (1.5-fold from baseline) in less than seven days. A new staging system was also introduced, mainly based on the percentage increase of SCr from baseline.

HRS is also redefined, but the criteria for diagnosing HRS are still exclusion of shock, use of nephrotoxic drugs, absence of parenchymal disease, no response to withdrawal of diuretics and volume expansion in the presence of cirrhosis, acute or acute on chronic liver disease. Type I HRS previously represented acute form of HRS and Type II was considered as chronic form. Today we recognize HRS-AKI which represents AKI of stage 2 or 3, or progression of initial stage despite all standard therapy measures in patients who fulfil criteria for hepatorenal syndrome regardless of initial serum creatinine value at diagnosis.

HRS-chronic kidney disease (HRS-CKD), previously known as HRS typ II, applies to patients who have criteria for HRS but not for AKI. It is essential to start treatment as soon as possible in order to prevent further damage since higher SCr values reduce chance of response to treatment.

Once the diagnosis of HRS-AKI is established therapy with vasoconstrictors (preferably terlipressin) and albumin should be started, with expected response in >50% of cases. Terlipresin could be administered by iv boluses of 0,5- 1 mg every 4-6 hours with an escalation of a dose up to 2 mg every 4-6 hours if there is no response to initial treatment (meaning reduction of more than 25% of initial SCr within the 3 days). Administration of terplipressin as a continuous i.v. infusion is also possible (from 2-12 mg/day) with a significantly lower incidence of severe side effects (diarrhoea, ischaemia, circulatory overload). Albumin in a dose of 1g/kg B.W. should be administered with terlipressin at day 1, and 20-40 g/day after, during the treatment which should not last for more than 14 days.

Non-pharmacological treatments of HRS include renal replacement therapy in patient with irreversible HRS with no response to pharmacological treatment, molecular adsorbent recirculating system (MARS) in patients with HRS on acute on chronic liver failure (ACLF) and transjugular intrahepatic portosystemic shunting.

Orthotopic liver transplantation (OLT) represents the best therapeutic option in patients with HRS- AKI, regardless of their response to pharmacological therapy. Still there are some unsolved issues like need for simultaneous liver-kidney transplantation since there are no good predictors for the estimation of the extent of renal recovery following OLT.

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Physical frailty in liver cirrhosis

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Frailty is the concept introduced 20 years ago in geriatrics in an attempt to give name and form to old man's evaporating physiologic reserve. It is the usually unrecognized predeccessor of disability, which thereupon comes as a surprise although we could have known. Since liver cirrhosis drains physiologic reserve akin to aging, researchers – after showing that frailty is not captured by MELD - attempted to translate the concept to hepatology; they have proven its construct validity, and accuracy of copypasted diagnostic tools. Frailty has been shown to predict wide spectrum of bad outcomes from patient-reported to mortality. In our high-flux, low-resources liver unit, frailty was immediate match: it illuminated grey zone imposed by the prognostic limits of MELD and, importantly, adopting diagnostic tools turned up to be feasible. There are only two unmet needs: too many diagnostic instruments, and too few studies in inpatients with liver cirrhosis.

Therefore, we focused on the prognostic performance of the diagnostic toolkit in the cohort of inpatients hospitalized with liver cirrhosis. Particularly, we aimed to see the performance of the reportedly eclectic Liver frailty index, appreciated for its being fast, easy to perform, objective, reproducible, and a continuous digit.

To maximally approximate frailty to our dailty routine, we removed as many exclusion criteria used in previous studies, as possible. We included patients irrespective of their LTx candidacy, patients with hepatic encephalopathy (HE), and excluded only malignancies outside Milan criteria, and ICU patients. Of the shrunken diagnostic toolkit proposed recently by AST, we provide the data on frailty as diagnosed by the Liver frailty index (LFI) - measured and uploaded by trained nurse according to recommendations on the UCSF website.

Our cohort consisted of 200 consecutive adults aged 58 years, one third females, hospitalized over 6 months with liver cirrhosis due mostly to alcohol-associated liver disease, with MELD 16. We measured LFI on admission, and defined frailty as LFI>4.5. Frequency of the specific complications of cirrhosis was 23 - 30%, 13% of pts were transplanted, and one quarter died. Median LFI was 4,4 – with 45% patients being frail. When we compared the results according to the presence of frailty, frail patients were older, more decompensated, had more complications, and much higher mortality from them. Of interest, contrary to infections, *ascites and HE*

had the licence to kill only in the presence of frailty. Increasing LFI was inversely associated with quality of life.

In conclusion, our results suggest that

- LFI reproduced its behaviour in complete different setting from the FrAILt Study in which it has been developed,
- Measured at admission, LFI predicts 6-month mortality,
- In combination with HE, ascites, and infection, LFI has considerable additive prognostic value.

Summary statistics							
	Non frail (LFI≤4.5)			Frail (LFI>4.5)			P
	N=109	Median %	25 - 75 P	N=91	Median %	25 - 75 P	
Age (y)		55.7	48.5 to 61.8		61.4	50.65 to 65.6	0.004
Female gender (%)		30.3			39.6		0.17
Etiology alcohol (%)		70.6			73.6		0.64
Etiology viral (%)		10.1			6.59		0.38
Etiology NAFLD (%)		14.7			14.3		0.94
Etiology autoimmune (%)		10.1			4.4		0.13
BMI_baseline		27.0	23.6 to 30.1		25.7	23.87 to 29.7	0.56
MELD_baseline		15.0	11.0 to 20.0		17.0	12.0 to 23.0	0.04
Child-Pugh-Turcotte baseline		9.0	7.0 to 10.0		9.0	8.0 to 11.5	0.0012
Refractory ascites (%)		23.9			38.5		0.026
Ref. Ascites D180 mortality (%)		7.7			60.0		0.0001
Hepatic encephalopaty (%)		8.3			41.8		0.0001
HE D180 mortality (%)		11.1			68.4		0.002
Infection_baseline (%)		15.6			40.7		0.0001
Infection D180 mortality (%)		23.5			73.0		0.0007
Days of follow-up		229.0	166.0 to 369.3		167.0	34.0 to 260.8	0.0001

Severe alcoholic hepatitis

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Alcoholic hepatitis is a distinct manifestation of alcoholic liver disease characterized by jaundice and liver failure, which affects individuals with prolonged and excessive alcohol consumption. The diagnosis should be suspected in patients with history of alcohol abuse and a recent development of jaundice with other signs of liver decompensation such as ascites and/or encephalopathy. It is often accompanied by fever, malaise, weight loss and malnutrition. Underlying this clinical syndrome is steatohepatitis, histologically characterized by steatosis, hepatocyte ballooning with presence of Mallory-Denk bodies, inflammatory infiltrate with predominant polymorphonuclear neutrophils, and progressive fibrosis. Although diagnosis is often established based on clinical presentation and laboratory findings, liver biopsy may be performed in order to confirm the diagnosis, exclude competing aetiologies that can be found in 10%–20% of patients and to determine the severity of the disease. Different prognostic models are used in practice to establish the severity of the disease and to identify patients at high risk of adverse outcome. Most commonly used are the Maddrey discriminant function (DF), model for end-stage liver disease (MELD) score, Glasgow alcoholic hepatitis score (GAHS), ABIC score (age, bilirubin, INR, creatinine) and Lille model. Alcohol abstinence is the mainstay of treatment for patients with alcoholic hepatitis, together with adequate nutrition (intake of 35–40 kcal/kg and protein intake of 1.2–1.5 g/kg of body weight, supplementation of B-complex vitamins), treatment of complications like hepatic encephalopathy, ascites, or infections, and prevention of renal injury.

Since the results of the STOPAH trial were published, corticosteroids (prednisolone 40 mg or methylprednisolone 32 mg per day for 28 days) are recommended for the treatment of patients with severe alcoholic hepatitis, defined as mDF ≥32 and GAHS ≥9, although only modest reduction in short-term mortality was shown with treatment. Recently published studies have shown that newer scores like GAHS, ABIC and MELD, and baseline neutrophil-to-lymphocyte ratio were superior to DF in predicting the outcome and identifying patients who would benefit most from treatment.

Because of the increased risk of infections with corticosteroid therapy, careful evaluation of patients for infections prior to treatment is necessary. The Lille score is a dynamic model used to predict poor response to corticosteroid treatment after 7 days, in which case therapy should be discontinued. Adding N-acetylcysteine (intravenously for 5 days) to prednisolone may be beneficial, while other treatments including pentoxiphylline and anti-TNF agents failed to show benefit or even increased risk of serious infections and

death. Among alternative therapies that are being explored, granulocyte-colony stimulating factor (G-CSF) and cell replacement therapy with human induced pluripotent stems cells offer promising results. In case of non-response to corticosteroids, early liver transplantation may be considered as an option in selected cases where available.

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The impact of outpatient clinical care on the survival and hospitalisation rate in patients with alcoholic liver cirrhosis

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The harmful use of alcohol has been estimated to cause approximately 3.3 million deaths every year, what represents 6% of all deaths globally. Therefore, the effective management and treatment of alcoholic liver disease is a pertinent public health issue.

In the study that was conducted in General hospital Murska Sobota between 2006 and 2011 we aimed to determine whether regular outpatient controls in patients with alcoholic liver cirrhosis have an impact on their survival and hospitalisation rates. We included patients with alcoholic liver cirrhosis and regular outpatient controls as a prospective study group and patients with liver cirrhosis who were admitted to hospital only in cases of complications as a retrospective control group.

We included 98 patients in the study group and 101 patients in the control group. There were more outpatient controls in the study group than in the control group (5.54 examinations vs. 2.27 examinations, p = 0.000). Patients in the study group had 25 fewer hospitalisations (10.2%; p = 0.612). The median survival rate was 4.6 years in the study group and 2.9 years in the control group (p = 0.021). Patients with Child A classification had an average survival of one year longer in the study group (p = 0.035). No significant difference was found for Child B patients. Patients with Child C classification had longer survival by 1.6 years in the study group (p = 0.006). Alcohol consumption was lower in the study group than in the control group (p = 0.018).

We confirmed that patients with regular outpatient controls had lower alcohol consumption, a lower hospitalisation rate and significantly prolonged survival time. We confirmed the necessity for the establishment of regular outpatient controls in patients with alcoholic liver cirrhosis.

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Article: "A new prognostic algorithm based on stage of cirrhosis and HVPG to improve risk-stratification after variceal bleeding" – Hepatology in press

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Prognosis of cirrhosis is based on the stage of the disease. The development of at least one complication among ascites, variceal bleeding or hepatic encephalopathy (HE) defines the passage from compensated to decompensated cirrhosis and marks a turning

point for mortality (1). Of note, prognosis is worse if the decompensation is due to variceal bleeding on top of ascites and/or HE in comparison with variceal bleeding alone. Therefore, it has been proposed a survival model based on an additive effect of any episode of decompensation on survival (1,2).

Current standard of care for the prevention of variceal rebleeding is the combination of non-selective beta-blockers (NSBBs) plus endoscopic band ligation (EBL) (3). However, making an earlier decision for TIPS, instead of using it as rescue therapy after failure of standard treatment, may be lifesaving and this has been demonstrated promising for acute bleeding (4) as well as recurrent ascites (5). Moreover, survival may ameliorate by the addition of simvastatin to NSBBs plus EBL in candidates to rebleeding prophylaxis (6) although collateral effects can develope in Child C patients and liver transplantation remains the only option to improve survival in these high-risk cases. Altogether these observations suggest the need of an accurate system of risk stratification in order to allocate patients into the most appropriate pharmacological/invasive treatment and improve survival (7).

In candidates to recurrent variceal bleeding prophylaxis, the hepatic venous pressure gradient (HVPG) provides valuable prognostic information (8). Indeed, several clinical studies and meta-analysis have consistently shown that the HVPG response to NSBBs is associated with a reduced risk of recurrent variceal bleeding, other portal hypertension related complications and mortality. However, the need of repeated measurements of HVPG, which is demanding and costly, the fact that up to 48% of HVPG non-responders to NSBBs do not rebleed during the follow-up (grey-zone problem) have hampered the cost-effectiveness of HVPG-guided therapy in this clinical setting (9). Several studies have shown that a baseline HVPG over 16 mmHg can be an independent predictor of survival (8). However, none of these studies investigated its prognostic value in the context of the medical treatment of portal hypertension.

All these observations were the premise to plan the observational study this brief report is based on. The aim was testing and validating a new algorithm to stratify patients in accordance to the presence/absence of ascites and/or HE and by adding the finding of a baseline HVPG below or over 16mmHg to the traditional criteria of hemodynamic response in order to improve risk stratification and simplify the use of HVPG-based therapeutic decisions.

The study included, retrospectively, a training set of candidates to rebleeding prophylaxis with NSBBs and EBL (n=193). All patients had two HVPG measurements, the first before starting NSBBs after the acute variceal bleeding episode, the second after 1-3 months of treatment. The endpoints were: rebleeding and rebleeding/transplantation-free survival up to 4-years. An independent cohort (n=231) served as validation set.

Main findings: During the follow-up n=45 patients had variceal bleeding and n=61 died. Seventy-one patients were HVPG-responders and had lower rebleeding-risk (10% vs 34%, p=0.001) and better survival than 122 non-responders (61% vs 39%, p=0.001). One-hundred and twenty patients (62% of the series) had ascites/HE on top of bleeding. They had lower survival than patients without ascites/HE (40% vs 63%, p=0.005). Inside the group of patients with ascites/HE, a low rebleeding-risk (13%) was registered in patients with baseline HVPG≤16mmHg (n=16). On the contrary, inside the group of patients with ascites/HE and baseline HVPG>16mmHg, those HVPG-responders (n=32) had lower rebleeding-risk (7% vs 39%,p=0.018) and better survival than HVPG non-responders (n=72) (56% vs 30% p=0.010). Therefore, it was tested the accuracy of an algorithm in which HVPG-response was only measured in patients with ascites and/or HE and baseline HVPG>16mmHg. This algorithm had a high accuracy, reduced the grey-zone (high-risk patients not dying on follow-up) from 46% to 35% and decreased by 42% the HVPG measurements required for risk-stratification. These results were confirmed in the independent cohort of n=231 patients included for validation.

Conclusions: In candidates to rebleeding prophylaxis with the standard of care, it can be proposed the following strategy for risk-stratification:

1. patients without ascites/HE on top of bleeding: start NSBBs+EBL, no HVPG measurement is needed
2. patients with ascites/HE on top of bleeding: measure HVPG before starting NSBBs. If HVPG≤16mmHg start NSBBs and EBL. If HVPG>16mmHg, then measure the HVPG-response to NSBBs.

Final Comment: At today, high-risk patients are already referred to tertiary care centres to be considered for TIPS, liver transplantation or experimental therapies. It is likely that a stratification strategy based on the combination of clinical data with HVPG would be easily adopted and successful, however the final application of this new algorithm in the clinical decision-making process needs to be addressed by an adequately designed randomized controlled trial.

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Artificial neural network prognostic modeling in cirrhosis

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Mortality of patients with liver cirrhosis is very important for timely listing of patients for liver transplantation. Despite the fact that Child-Pugh scoring system and recently Model for End-Stage Liver Disease (MELD) score have become popular for prediction of short-term mortality for organ allocation, there are numerous drawbacks associated with their use that impair their prognostic potential.

In any type of biological system, it is not feasible to try to describe it with any linear prognostic method, which is why artificial neural networks are much better alternative due to their inherent capabilities to predict outcomes in nonlinear and sometimes fuzzy logic fashion. ANN as a predictive method are gaining momentum in many areas of human knowledge and medicine seems to be almost ideal field for their application with a huge potential waiting to be harvested.

There are not many studies that evaluated artificial neural network (ANN)-based models for prediction of outcome of cirrhosis of liver in terms of mortality. However, most of them have consistently shown it to be superior to Child–Pugh scoring and logistic regression-based models; it is worth noting that MELD score is also derived using the logistic regression model.

More studies are needed on ANN-based models for prediction of mortality of patients with cirrhosis of liver and its value in prioritization of organ allocation for treatment of patients with cirrhosis of liver.

Keywords: cirrhosis, prognosis, artificial neural networks, deep learning, artificial intelligence.

Screening for HCC: current recommendations

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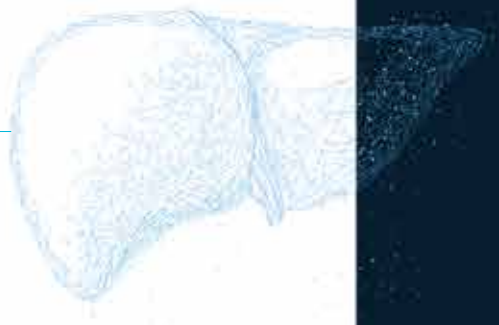
Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem. Chronic liver disease is the most significant risk factor for HCC with 80%-90% of new cases occurring in the background of cirrhosis. Studies have shown that early diagnosis of HCC through surveillance programs improve prognosis and availability of curative therapies. The rising incidence of HCC in most European countries suggests an insufficient awareness of liver disease in general, calling for public health policies aiming to prevent, detect and treat liver disease – not only for HCC prevention. To make surveillance cost-effective tools need to be developed to stratify patients at high, intermediate and low risk for hepatocellular carcinoma and to adjust surveillance strategies accordingly. Surveillance or secondary prevention needs to be complemented by primary prevention and the development and the utilization of chemo-preventive strategies is strongly encouraged. The recommended surveillance modality is abdominal ultrasound (US) given that it is cost effective and noninvasive with good sensitivity. However, US is limited in obese patients and those with non-alcoholic fatty liver disease (NAFLD). With the current obesity epidemic and rise in the prevalence of NAFLD, abdominal computed tomography or magnetic resonance imaging may be indicated as the primary screening modality in these patients. Further investigation of serum biomarkers is needed. Semiannual screening is the suggested surveillance interval.



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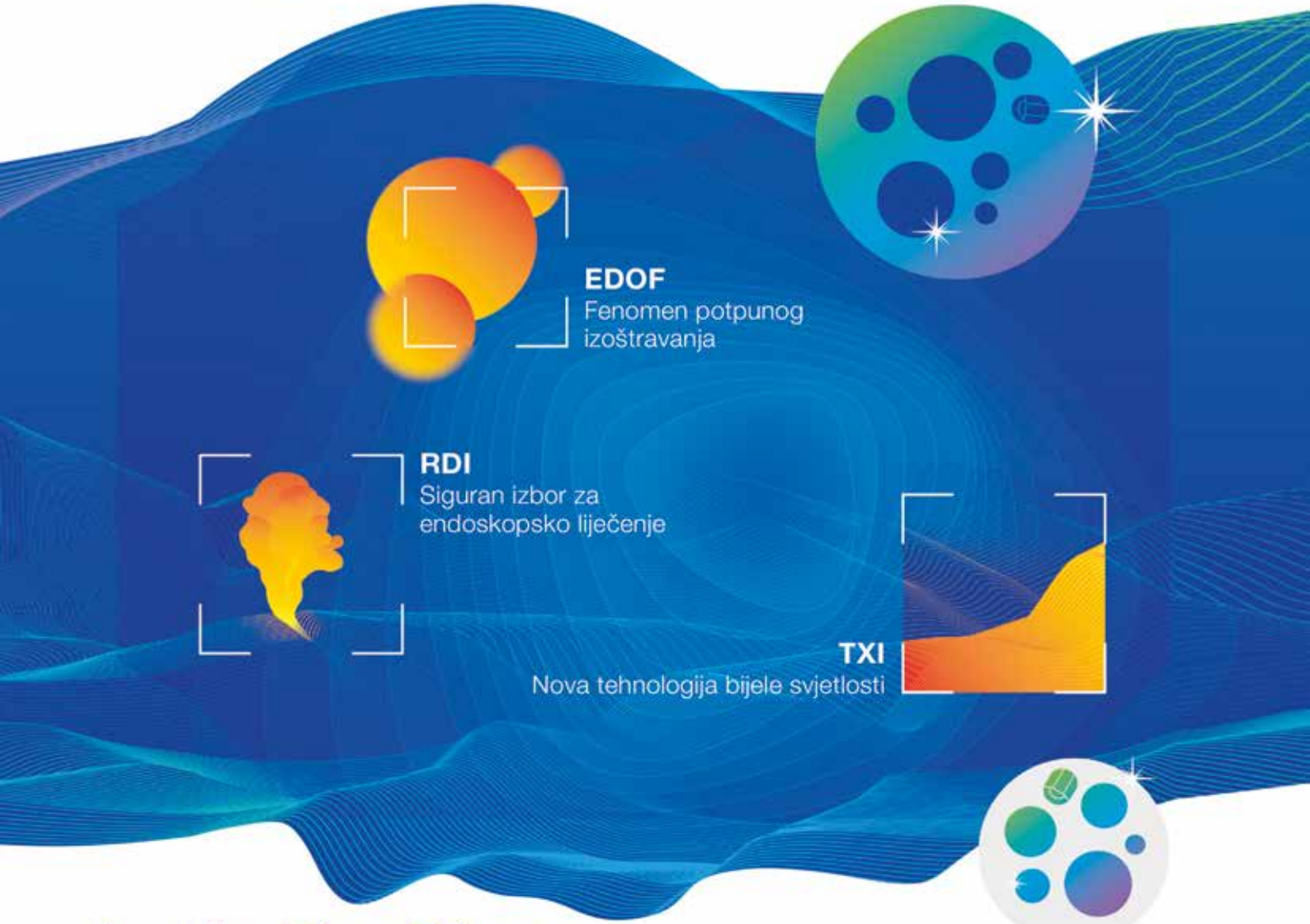

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▼ Ovaj je lijek pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave sveku sumnju na nuspojavu za ovaj lijek. Za postupak prijavljivanja nuspojava vidjeti dio 4.8.

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EPCLUSA – izliječite svoje bolesnike s kompenziranim virusom hepatitisa C u samo 12 tjedana s pangenotipskim jednotabletnim režimom[1,a]

12 tjedana

JEDNA
Jedna tableta, jednom dnevno 12 tjedana[1]

IZLJEČENJE
95-100% izliječeno u HCV GT 1–6[1,b]

STR

JEDNOSTAVNO
Jedini bez RBV-a, bez PI-a, STR-opcija za skoro svakog HCV-bolesnika[1,4]

Izrađen od lijeka SOVALDI®,▼ dokazanom temelju liječenja HCV-a[1-12]

Kratice: GT = genotip; HCV = virus hepatitisa C; RBV = ribavirin; STR = Jednotabletni režim (*Single-Tablet Regimen*); SmPC = Sažetak opisa svojstava lijeka (*Summary of Product Characteristics*).

Bilješke: a EPCLUSA pruža opciju jednotabletnog režima bez RBV-a za većinu HCV-bolesnika, isključujući one s dekompenziranom cirozom. Za dalnje informacije o ograničenjima, pogledajte SmPC. RBV se preporučuje za liječenje bolesnika s dekompenziranom cirozom, a može biti uzet u obzir za liječenje HCV GT3 bolesnika s kompenziranom cirozom i preporučuje se za liječenje bolesnika s dekompenziranom cirozom - pogledajte RBV SmPC za potpunu informaciju.[1] **b** U ASTRAL-1, -2 i -3 studijama kod bolesnika s kompenziranim monoinfektivnim virusom hepatitisa C primarni ishod SVR-omjera bio je 99%, 99% i 95%. Kroz sve genotipove, omjer izliječenja bio je 95-100% u bolesnika koji su liječeni lijekom Epclusa tijekom 12 tjedana.[1]

SAŽETAK OPISA SVOJSTAVA LIJEKA EPCLUSA:

▼ Ovaj je lijek pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave sveku sumnju na nuspojavu za ovaj lijek. Za postupak prijavljivanja nuspojava vidjeti dio 4.8.

NAZIV LIJEKA: Epclusa 400 mg/100 mg filmom obložene tablete. **BROJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** EU/1/16/1116/001 **NAČIN IZDAVANJA:** Lijek se izdaje na ograničeni recept. **NOSITELJ ODOBRENJA ZA STAVLJANJE LIJEKA U PROMET:** Gilead Sciences Ireland UC, Carrigtohill, County Cork, T45 DP77, Irska. **DJELATNA TVAR:** Jedna filmom obložena tableta sadrži 400 mg sofosbuvira i 100 mg velpatasvira. **TERAPIJSKE INDIKACIJE:** Epclusa je indicirana za liječenje kronične infekcije virusom hepatitisa C (HCV) u odraslih. **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. KONTRAINDIKACIJE:** Preosjetljivost na djelatne tvari ili neku od pomoćnih tvari navedenih u dijelu 6.1. Primjena s jakim induktorima P-gp-a i jakim induktorima CYP-a: Lijekovi koji su jaki induktori P-glikoproteina (P-gp) ili jaki induktori citokroma P450 (CYP) (rifampicin, rifabutin, gospina trava (Hypericum perforatum), karbamazepin, fenobarbital i fenitoin): istodobna primjena značajno će smanjiti koncentraciju sofosbuvira ili velpatasvira u plazmi i tako može dovesti do gubitka djelotvornosti lijeka Epclusa. **POSEBNA UPOZORENJA I MJERE OPREZA PRI UPORABI:** Epclusa se ne smije primjenjivati istodobno s drugim lijekovima koji sadrže sofosbuvir. Teška bradikardija i srčani blok: Slučajevi teške bradikardije i srčanog bloka uočeni su kada se sofosbuvir primijenjen u kombinaciji s drugim antivirotičima koji djeluju direktno primjenjivao istodobno s amiodaronom sa ili bez drugih lijekova koji snižavaju srčanu frekvenciju. Mehanizam nije ustanovljen. Istodobna primjena amiodarona bila je ograničena tijekom kliničkog razvoja sofosbuvira uz antivirotike koji djeluju direktno. Slučajevi su potencijalno opasni po život, stoga se amiodaron smije primjenjivati samo u pacijenata koji primaju lijek Epclusa u slučajevima kada se drugi alternativni antiaritmici ne podnose ili su kontraindicirani. Bolesnici u kojih je prethodna terapija režimom koji sadrži inhibitor NS5A bila neuspješna: Nema kliničkih podataka koji bi poduprli djelotvornost sofosbuvira/velpatasvira za liječenje bolesnika u kojih je liječenje režimom koji sadrži drugi inhibitor NS5A bilo neuspješno. Oštećenje bubrega: Nije potrebna prilagodba doze lijeka Epclusa u pacijenata s blagim ili umjerenim oštećenjem bubrega. Sigurnost lijeka Epclusa nije procijenjena u bolesnika s teškim oštećenjem bubrega (eGFR < 30 ml/min/1,73 m²) ili završnim stadijem bolesti bubrega koji zahtijeva hemodijalizu. Primjena s umjerenim induktorima P-gp-a ili umjerenim induktorima CYP-a: Lijekovi koji su umjereni induktori P-gp-a ili umjereni induktori CYP-a (npr. okskarbazepin, modafinil ili efavirenz) mogu smanjiti koncentracije sofosbuvira ili velpatasvira u plazmi što dovodi do smanjenog terapijskog učinka lijeka Epclusa. Istodobna primjena takvih lijekova s lijekom Epclusa se ne preporučuje. Upotreba s određenim antiretrovirusnim režimima za HIV: Pokazalo se da Epclusa povećava izloženost tenofoviru, naročito kada se koristi zajedno s režimom za HIV koji sadrži tenofovirdisoproksilfumarat i farmakokinetički pojačivač (ritonavir ili kobicistat). Primjena u bolesnika s dijabetesom: Nakon uvođenja liječenja HCV infekcije direktno djelujućim antivirotikom, bolesnici s dijabetesom mogu imati bolju kontrolu glukoze u krvi, što može dovesti do simptomatske hipoglikemije. Koinfekcija HCV-om/HBV-om (virusom hepatitisa B): Tijekom ili nakon liječenja antivirotičima koji djeluju izravno, zabilježeni su slučajevi reaktivacije virusa hepatitisa B (HBV), neki od njih sa smrtnim ishodom. Probir na HBV mora se provesti u svih bolesnika prije početka liječenja. Bolesnici istodobno zaraženi HBV-om/HCV-om izloženi su riziku od reaktivacije HBV-a te ih stoga treba pratiti i liječiti sukladno važećim kliničkim smjernicama. Ciroza jetre CPT stadija C: Sigurnost i djelotvornost lijeka Epclusa nije procijenjena u bolesnika s cirozom jetre CPT stadija C (vidjeti dijelove 4.8 i 5.1). Bolesnici s transplantiranom jetrom: Sigurnost i djelotvornost lijeka Epclusa u liječenju infekcije HCV-om u bolesnika u kojih je transplantirana jetra nisu procijenjene. **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. NUSPOJAVE:** Sažetak sigurnosnog profila: Procjena sigurnosti primjene lijeka Epclusa temeljila se na objedinjenim podacima iz kliničkog ispitivanja faze 3 bolesnika s infekcijom HCV-a genotipa 1, 2, 3, 4, 5 ili 6 (sa ili bez kompenzirane ciroze) uključujući 1035 bolesnika koji su primali lijek Epclusa tijekom 12 tjedana. Bolesnici s dekompenziranom cirozom: Sigurnosni profil lijeka Epclusa procijenjen je u otvorenom ispitivanju u kojem su bolesnici s cirozom CPT stadija B primali lijek Epclusa tijekom 12 tjedana (n = 90), lijek Epclusa + RBV tijekom 12 tjedana (n = 87) ili lijek Epclusa tijekom 24 tjedna (n = 90). Opaženi štetni događaji bili su konzistentni s očekivanim kliničkim posljedicama bolesti dekompenzirane jetre ili poznatim profilom toksičnosti ribavirina za bolesnike koji su primali lijek Epclusa u kombinaciji s ribavirinom. Opis odabranih nuspojava: Srčane aritmije: Slučajevi teške bradikardije i srčanog bloka uočeni su kada se sofosbuvir u kombinaciji s drugim antivirotikom koji djeluje direktno primjenjivao istodobno s amiodaronom (vili lijekovima koji snižavaju srčanu frekvenciju (vidjeti dijelove 4.4 i 4.5). *Poremećaji kože:* Nepoznata učestalost: Stevens-Johnsonov sindrom. **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. DOZIRANJE I NAČIN PRIMJENE:** Liječenje lijekom Epclusa treba započeti i nadzirati liječnik iskusan u liječenju bolesnika s infekcijom HCVa. Preporučena doza lijeka Epclusa je jedna tableta, peroralno, jedanput na dan s hranom ili bez nje (vidjeti dio 5.2). **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. PRIJAVLJIVANJE SUMNJI NA NUSPOJAVU:** Nakon dobivanja odobrenja lijeka važno je prijavljivanje sumnji na njegove nuspojave. Time se omogućuje kontinuirano praćenje omjera koristi i rizika lijeka. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu lijeka putem nacionalnog sustava prijave nuspojava: *Agencija za lijekove i medicinske proizvode (HALMED) Internetske stranice: www.halmed.hr ili potražite HALMED aplikaciju putem Google Play ili Apple App Store trgovine* **UPUTA ZDRAVSTVENIMA RADNICIMA:** Za dodatne informacije pogledati odobreni sažetak opise svojstava lijeka. **DATUM REVIZIJE TEKSTA:** Detaljnije informacije o ovom lijeku dostupne su na internetskoj stranici Europske agencije za lijekove http://www.ema.europa.eu.

SAMO ZA ZDRAVSTVENE RADNIKE.
DATUM PRIPREME: rujan 2020. EPC-011-2020
PREDSTAVNIK NOSITELJA ODOBRENJA U HRVATSKOJ: Medicopharmacia d.o.o., Ulica Pere Budmanija 5, 10 000 Zagreb, Hrvatska

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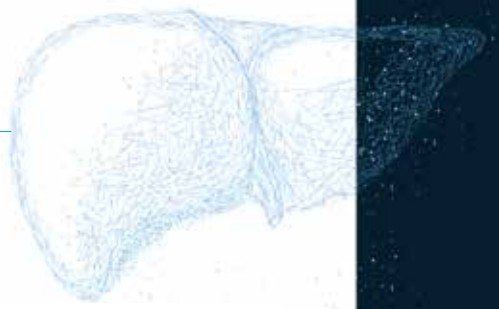

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