# The current issue of JHEP Reports

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Hepatology has evolved from a small subdiscipline to a major domain of clinical interest. Research in hepatology has accordingly taken "ampleur" and the quality and quantity of research papers in hepatology has exponentially increased over the years, with specialty journals like the *Journal of Hepatology*, the first journal of EASL, now ranking amongst the top journals in medicine. The current issue of *JHEP Reports*, EASL's new journal, not surprisingly contains equally important papers that fuel our knowledge in several areas of hepatology with findings of high interest to the field. Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease in countries with a Western lifestyle characterised by high calorie intake and relative sedentarism. Although many knowledge gaps exist in terms of the pathophysiology, epidemiology and natural course of the disease, a large pipeline of drugs to treat this condition is already under development. The disease is often quoted as asymptomatic. The insight is, however, growing that, although usually no specific symptoms are present, the impact on health and well-being of the patients is not restricted to the advanced stages of the disease. Recent reports on patient-related outcomes in the context of clinical trials already suggested this[1] but little data exist outside the setting of clinical trials. In this issue, Balp *et al.*[2] report on the analysis of a patient survey across 5 European countries, coming from the 2016 National Health and Wellness Survey. This is a nationally representative patient-reported outcomes survey, including mental and physical health but also data on absenteeism and use of health care resources. Even after correction for several covariates, including the presence of diabetes, patients with non-alcoholic steatohepatitis (NASH) had significantly lower quality of life and mental status, lower work productivity and higher use of health care resources. These data clearly show that the disease is not asymptomatic and without consequence for patients affected, also warning us that the societal impact is more far reaching than we thought. The kind of data provided by Balp *et al.*[2] are important to incorporate in the modelling of costs and cost-benefit analyses of preventive and therapeutic strategies that urgently need to be developed to tackle this epidemic.

Another important aspect of NAFLD is its diagnosis, for which biopsy is currently the gold standard. Besides the fact that biopsy is an imperfect standard due to sampling error and inter- and intra-observer variability, it is not suited for screening or frequently repeated follow-up assessments because of its inherent risks and lack of the experienced personnel to perform and analyse the biopsy. This explains the ongoing huge effort in biomarker development in NASH. Type III collagen neo-epitope (PRO-C3) has gained considerable interest as a marker for fibrosis in NASH, but data so far have come mainly from small series and mostly in the context of clinical trials, and have been poorly validated. Boyle *et al.*[3] have collected the largest series to date, showing a high accuracy of PRO-C3 for the diagnosis of advanced fibrosis. A score with 5 variables (age, body mass index, the presence of type 2 diabetes, platelet count and PRO-C3) reached an AUROC of 0.89 and 0.83 in design and validation cohorts, respectively. Taking into account that an AUROC of 0.9 is considered the maximum accuracy a non-invasive test can obtain compared to an imperfect gold standard like the liver biopsy,[4] this combined score has an excellent performance. Moreover, it outperforms current fibrosis scores. Even if these findings are based on a fairly large patient series, further validation is warranted. Furthermore, the performance was only tested to identify dichotomously the presence of advanced (*i.e.* F3) fibrosis in a diagnostic setting. As for any biomarker, the context of use is critical to assess performance. As the patients who are currently considered most at risk of disease progression and hence are the target for more intensive treatments, including drugs, are patients with significant (*i.e.* F2) fibrosis and active steatohepatitis,[5] PRO-C3 and the 5-parameter score proposed by Boyle *et al.*[3] do not provide that comprehensive information, for which a biopsy is still required. Nevertheless, this and other biomarkers may prove to be of value in a sequential approach and patient path that can help distinguish patients with and without indices of more severe disease, the latter needing more intensive treatment and more in-depth diagnosis. Also, its value in monitoring patients and assessing treatment response requires further study.

Meanwhile more sophisticated studies of human tissues and samples can help us to unravel the complex pathophysiology of the disease and help overcome the difficulties in translating data from rodent models to the complex human condition, particularly in this disease, which is so closely entwined with the derangements of the metabolic syndrome. Sandhu *et al.*[6] quantified adiponutrin (*PNPLA3*) and collagen 1α (*COL1α*) gene transcripts *in situ* at single cell resolution using RNAscope in 87 patients with NAFLD.[6] There findings need further exploration but indicate a path to further detailed analysis of the pathophysiology of NASH, in which mutations in the *PNPLA3* gene have shown to play an important role.[7]

The controversies regarding the role of the gut microbiome in NAFLD/NASH but also in other chronic liver diseases, are another illustration of how difficult it is to obtain high-quality clinical evidence that unequivocally confirms pre-clinical findings. Many extensive reviews summarise the knowledge on the role of the microbiome in liver diseases, but one often forgets that most of the data come from pre-clinical studies.[8] In this issue of *JHEP Reports* Schwenger *et al.*[9] focus their review solely on the clinical data that are available, summarising the methodological issues

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and caveats of this area of research and clearly demonstrating the paucity of good quality clinical data, as well as the need for further well-conducted research before firm conclusions can be drawn. They also summarise the results of the clinical trials that have used strategies to alter the gut microbiome to treat liver disease. This review, with its focus solely on clinical evidence, frames the microbiome discussion from the right perspective.

Despite numerous efforts, strategies to improve the outcome of patients with cirrhosis mostly yielded disappointing results. The holy grail of an antifibrotic therapy that significantly changes the natural course of cirrhosis still seems to be out of reach, as many recent trials failed both when surrogate markers, such as the hepatic venous pressure gradient, or hard clinical endpoints are considered. Of course, if the underlying aetiology is well-controlled, fibrosis is reversible, even in the cirrhotic stage. This has been most convincingly documented in the context of viral hepatitis, but even in that context, not all lesions appeared to be reversible[10] and even if the underlying disease is controlled, compensated cirrhosis can evolve to decompensation and death. Intriguingly, endothelial dysfunction and altered platelet function leading to microthrombotic events have been shown to play a role in fibrogenesis, distortion of vascular architecture and progression of cirrhosis towards decompensation.[11] It has become clear that, although gastrointestinal bleeding is obviously a major complication of cirrhosis, cirrhosis is a prothrombotic condition, explained by both reduced pro- and anticoagulant mechanisms with an imbalance towards a prothrombotic state. In a landmark investigator-driven clinical trial, E. Villa *et al.*[12] already in 2012 reported a significantly reduced rate of decompensation in cirrhotic patients treated with enoxaparin compared to controls. This pivotal study clearly demonstrated that endothelial-platelet interactions had the potential to strongly influence the natural history of cirrhosis and reduce the risk of or delay the occurrence of decompensation. This truly important finding, which is also important from a pathophysiological point of view (as it highlights the importance of microvascular derangements, endothelial dysfunction and altered platelet-endothelial interactions in the progression of cirrhosis to end-stage liver disease) has to date received too little attention, although it represents one of the rare approaches that (beyond the treatment of the underlying aetiology) does improve the outcome of patients with cirrhosis. In this issue, Turco *et al.*[13] provide the readers with an elegant overview of coagulation disturbances in cirrhosis, the correct interpretation of the cirrhosis-associated coagulant state, and the therapeutic potential of interfering with these mechanisms in order to improve the outcomes of patients with cirrhosis. These findings clearly support further evaluation of anticoagulant or antiaggregant treatment as an antifibrotic strategy or as a treatment to prevent cirrhosis decompensation. Nicely fitting with the review by Turco *et al.*,[13] Blasi *et al.*[14] report the original work from an international multicentric collaboration, confirming the state of hypercoagulability in acute-on-chronic liver failure (ACLF) and its relationship with poor outcomes. Intriguingly they could not find a clear role for neutrophil extracellular traps (NETs), web-like structures composed of neutrophil DNA and neutrophil-derived proteins. Pre-clinical data pointed towards an important role for these NETs in hypercoagulability and sepsis in cirrhosis, but this could not be confirmed in this reasonably large series that compared acutely decompensated, ACLF and control patients. Although these studies are hampered by small numbers and patient heterogeneity, they illustrate the difficulty of translating pre-clinical data into the complex environment of a patient with cirrhosis. Further study is warranted to clearly establish the role of NETs in end-stage liver disease, but the study by Blasi *et al.*[14] in this issue of *JHEP Reports* clearly argues against an important role for these mediators.

Hepatocellular carcinoma (HCC) is another complication of chronic liver disease, mostly restricted to the cirrhotic stage. Liver cancer is the fastest growing cancer in the United States, and the study by Pinheiro *et al.*[15] in this issue shows that it has become the leading cause of cancer-related death in Mexican American men. Intriguingly, across several ethnic groups and populations examined, the highest rates are seen in men born in the United States and in the period 1945-1965, the so-called baby boom generation. This is probably driven mainly by hepatitis C, which is highly prevalent in this cohort, at least in the United States. These differential population patterns represent important information that might help us to anticipate the growing impact of HCC on health care resources. In another paper, Verna *et al.*[16] review the impact of the opioid epidemic on liver disease, with, amongst other effects, a shift of incident hepatitis C to women and to younger individuals.

Primary biliary cholangitis (PBC) is in many ways a challenging disease. As it is rare and the patient population heterogenous, it is hard to collect high-quality evidence on disease pathophysiology and to prove the efficacy of therapeutic regimens. In this issue, Corpechot *et al.*[17] provide us with a comprehensive overview of the current treatment strategies, already tested or in development, anchored to the most recent insights in disease pathophysiology. The bicarbonate umbrella theory[18] as a basis for drugs that increase the biliary pH, and the role of the altered bile acid composition as a basis for drugs that impact bile acid metabolism, give a strong rationale for recent trials that, not without success, tested the efficacy of drugs like nor-ursodeoxycholic acid (norUDCA), farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor (PPAR) agonists and other compounds. Bezafibrate, a PPARα agonist, and obeticholic acid, an FXR agonist, have recently shown positive results in properly conducted clinical trials, which have drastically changed PBC treatment. Interestingly, although disease presentation and pathophysiology substantially differ, drugs like obeticholic acid, but also PPAR agonists like elafibranor and seladelpar, are in development for both PBC and NASH. Shedding further light on the pathophysiology of PBC, Arenas *et al.*[19] show that epigenetic changes, namely hypermethylation of the *AE2* promoter regions (*AE2* encodes a $Cl^-/HCO^{3-}$ exchanger involved in biliary bicarbonate secretion) and subsequent downregulation of *AE2*-gene expression occur in both the liver and peripheral bone marrow-derived cells of patients with PBC to a greater extent than in patients with other aetiologies of chronic liver disease or those with normal livers. This study not only further supports the bicarbonate umbrella theory but also increases our knowledge of the role of hypermethylation and other epigenetic changes, that potentially applies to many diseases.

To complete the spectrum of liver diseases covered in this issue of *JHEP Reports*, the study of Ferrando-Martinez *et al.*[20] explores the potential of interfering with the PD-1:PD-L1/PD-L2 axis in the treatment of chronic hepatitis B (HBV). HBV-specific T-cell immunity is impaired in chronic hepatitis B and has recently emerged as a potential therapeutic target[21] Ferrando-Martinez *et al.*[20] show different levels of expression of PD-1 in the T-cell compartment and PD-L1 on myeloid dendritic cells, as well as differences in HBV reactivity according to the disease stage in 65 patients with different disease and treatment status. Anti-PDL1 had a beneficial effect, leading the authors to suggest that PD-L1 blockage should be explored in the treatment of chronic HBV.

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