Celebrating the third year of JHEP Reports in the COVID-19 era

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When I celebrated the second year of JHEP Reports in the editorial of the first 2020 issue,[1] I could not imagine the year we would go through. But the 14th issue of the journal is now associated with new hopes arising from vaccines that were developed at an unprecedented speed, thanks to previous solid research on related viruses and technologies, and huge financial investment. During this strange period, JHEP Reports has continued to expand, as illustrated in this issue gathering 11 basic, translational and clinical articles and 4 reviews covering liver cancer, autoimmune liver diseases, liver transplantation, non-alcoholic fatty liver disease (NAFLD) and viral hepatitis.

Amaddeo *et al.*,[2] studied the impact of the COVID-19 pandemic on the management of hepatocellular carcinoma (HCC) in Paris, in a multicentric cross-sectional study comparing the COVID-19 period to the same period in 2019. The study showed that COVID-19 clearly impacted the care of patients with liver diseases, especially those with HCC, with less patients being discussed in multidisciplinary tumor boards, especially newly diagnosed patients, and longer treatment delays. These data highlight the negative impact of the COVID-19 pandemic on HCC management. Moreover, although additional data on survival are needed to appreciate the impact of COVID-19 on liver disease progression, maintaining the usual care of patients in a pandemic is a major issue. A study by Azoulay *et al.*[3] aimed to reevaluate the fate of liver resection for HCC in patients with cirrhosis and significant portal hypertension, performed in highly specialized liver centers. They show that these patients can undergo liver resection with acceptable mortality, morbidity, and liver decompensation rates. The laparoscopic approach was the sole predictor of a textbook outcome. Finally, Gregory *et al.*[4] assessed the proportion of registered randomized controlled trials (RCTs) among RCTs on transarterial chemoembolization (TACE) for the treatment of HCC published between 2007 and 2018, using data from MEDLINE and EMBASE. The analysis shows that registration and outcome reporting in RCTs on TACE for HCC are often inadequate. The study clearly indicates that, although the registration of all RCTs before enrollment of participants is mandatory for publication by the International Committee of Medical Journal Editors, registration should be reinforced because it is key to transparency in trial reporting. Finally, in a review focusing on rare primary liver cancers (PLCs), Gigante *et al.*[5] provide an update on the management of hepatocholangiocarcinoma, fibrolamellar carcinoma, hepatic hemangioendothelioma and hepatic sarcoma. The authors describe several advances in terms of pathophysiology, genetic profile and diagnosis but also discuss the limited data on PLC treatment. Future guidelines about the management of such PLCs are needed and studies in large international cohorts are required to better understand the pathophysiology of PLCs and propose future clinical trials.

Three studies in this issue are related to cholestatic liver diseases. In the first study, Harms *et al.*[6] show that obeticholic acid (OCA) treatment is associated with a reduction in the predicted risk of liver-related complications in patients with primary biliary cholangitis (PBC). Ursodeoxycholic acid (UDCA) is the standard first-line therapy and is associated with reduced mortality. However, UDCA does not prevent progression to cirrhosis and liver failure in all patients, and those with an incomplete biochemical response to UDCA are most at risk of an unfavorable outcome. The POISE trial was a randomized, double-blind, placebo-controlled, pivotal phase III trial evaluating the efficacy, safety and tolerability of the farnesoid X receptor agonist OCA as a monotherapy in patients who were intolerant to UDCA, or combined with UDCA, in patients with PBC who had an incomplete response to UDCA. Compared with placebo, OCA treatment was associated with a significant improvement in liver biochemistry in patients with PBC and an inadequate response to UDCA. Harms *et al.* show that OCA treatment was associated with a reduction in the predicted risk of liver-related complications in

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patients with PBC, using data from the POISE trial to calculate GLOBE score and APRI. These findings strongly suggest that the biochemical effects of OCA may translate into clinical benefit. In another study, Vesterhus *et al.*[7] provide a comprehensive assessment of extracellular matrix (ECM) turnover profiles, establishing PBC as a high-turnover autoimmune liver disease. In a case-control retrospective study, they quantified the serum levels of a panel of ECM and fibrosis remodeling markers across different autoimmune liver diseases (primary sclerosing cholangitis [PSC], PBC, and autoimmune hepatitis [AIH]), in a test cohort from the UK and a validation cohort from Norway. Although small-sized subgroups were studied, the data show that the levels of ECM markers were associated with disease stage and were higher in PBC than in PSC or AIH, suggesting a higher ECM turnover in PBC than in PSC or AIH. A third study by Dyson *et al.*[8] explores the impact of potential environmental contributors to cholestatic disease and investigates whether the geo-epidemiology of PBC and PSC are disease-specific or pertain to cholestatic autoimmune liver diseases in general. The study, performed in a population-based cohort in north England, shows that PBC was prevalent in the urban, post-industrial area with coal-mine heritage and associated with cadmium levels, whereas PSC was more common in the rural, sheep farming west and inversely associated with social deprivation. The study is welcomed since in contrast to genetic studies, the role of environmental factors in cholestatic diseases has been poorly explored.

One clinical and one basic article are related to NAFLD. The study by Linge *et al.*[9] provides a comprehensive assessment of the potential role of sarcopenia and myosteatosis in NAFLD. Sarcopenia (progressive and generalized loss of skeletal muscle mass, strength, and/or physical performance) is strongly associated with cirrhosis and commonly observed in end-stage liver disease. However, studies reporting associations between sarcopenia and NAFLD/NASH are not yet fully understood. Using data from a large UK Biobank imaging study, the authors investigate the associations of MRI-measured adverse muscle composition (*i.e* low muscle volume and high muscle fat) with poor function, sarcopenia and metabolic comorbidity within NAFLD. The study shows that measuring muscle health could be included in the assessment of liver disease and could help identify the more vulnerable patients and enable early prevention of severe liver disease. In a preclinical study, Gwag *et al.*[10] investigate the role of the immunoregulatory protein thrombospondin 1 (TSP1) in NASH. They show that the hepatic expression of TSP1 is upregulated in patients and with NASH and in animal models. They demonstrate the crucial role of macrophages in NASH and NASH-related liver fibrosis, owing to the use of mice with specific deletion of TSP1 in myeloid cells exposed to a NASH diet. Mechanistically, they show that macrophage-derived TSP1 suppresses sphingomyelin phosphodiesterase acid-like 3B (SMPDL3B) expression in the liver, a negative regulator of the Toll-like receptor-4 signaling pathway. Although previous data argued for a role of TSP1 in NASH, the current study provides novel insights into the role of TSP1 and SMPDL3B in the regulation of macrophages' inflammatory phenotype.

Additional articles in this issue include a study on inequalities in acute liver failure patients who underwent a liver transplant and a report of the role of *de novo* HBc synthesis in the maintenance and transcriptional regulation of HBV covalently closed circular DNA (cccDNA). Nephew *et al.*[11] used the US Scientific Registry of Transplant Recipient Database to assess whether potential sex differences could be identified in waitlist mortality, liver transplant and post-transplant 1-year survival in patients with acute liver failure. On multivariate analysis, women were not more likely to die on the waiting list than men and their chances of undergoing liver transplant were similar to those of men. In another study, Tu *et al.*[12] investigated the role of *de novo* nucleocapsid formation on cccDNA maintenance and transcriptional regulation, taking advantage of an HBc defective virus. They report that *de novo* HBV core protein produced from cccDNA is not required to maintain cccDNA copy numbers during long-term *in vitro* infection. Furthermore, HBc plays a minor role in transcriptional regulation of cccDNA.

In addition to the review on rare liver cancers, 3 additional reviews are included in this issue, covering different topics, the landscape of acute-on-chronic liver failure (ACLF) worldwide, long non-coding RNA (lncRNAs) in liver diseases and organoids to model liver disease. The review by Zaccherini *et al.*[13] focuses on ACLF, a syndrome characterized by the abrupt development of systemic inflammation and organ failure(s) in patients with chronic liver disease, with definitions and diagnostic criteria differing from one continent to another. They analyze all the operating definitions of ACLF and highlight the differences between these definitions. They also provide an update on the latest knowledge regarding the pathophysiology of this syndrome and discuss therapeutic approaches for organ support as well as the place of liver transplantation. The review by Mahpour and Mullen[14] focuses on lncRNAs which play essential roles in liver development, liver physiology, fibrosis and malignancy, including HCC and cholangiocarcinoma. The authors summarize the current understanding of the function of lncRNAs in the liver in health and disease and discuss approaches that could be used to target these non-coding transcripts for therapeutic purposes. Finally, Nuciforo and Heim[15] provide an updated review on liver organoids and specifically their use to model liver diseases. The liver is probably the most paradigmatic organ for the development of organoids with multiple functions depending on a specific complex organization. Retracing the history of liver organoids from the first reported organoid system based on Lgr-5 positive biliary cells until recent developments, the authors compare so-called Chol-orgs (cholangiocyte-derived organoids) to Hep-orgs (adult and foetal hepatocyte-derived organoids) and organoids derived from induced pluripotent stem cells. They also summarize the current knowledge on various liver diseases that have been modelled using this experimental approach, with a particular focus on monogenic diseases.

The first issue of 2021 is a fantastic vintage. I wish a long life to *JHEP Reports*, and our readers and all the team a happy, COVID-19-free and successful new year!

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