Regenerating research and life

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The eleventh issue of JHEP Reports falls into a time where the COVID-19 pandemic is still growing, infecting the highest worldwide number of patients ever. COVID-19 numbers are currently controlled at mostly low and stable levels in Europe, the home of EASL, whereas Southeast Asia as well as North and South America continue to experience high numbers of infections and deaths. With most places switching from strict lockdowns to other means of restricting spread, the world and the research community are nonetheless starting to see light at the end of the tunnel. Accordingly, our professional and private lives have started slowly regaining some normalcy, even though many things will remain changed, possibly permanently. Like the liver, humankind is a master of regeneration and regrowth. Even during the pandemic, critical clinical management could be maintained as discussed in the letter by Garrido *et al.,* who described cirrhosis management in a major hepatology referral center in Porto during COVID-19.[1] Many of us have returned to work, and clinical operations and research are regaining strength. Our community, clinical operations and research have suffered from many months of lockdown, and many of our international meetings that propel key advances in the field have been cancelled or gone virtual. Nonetheless, scientific publications have remained strong and many of us have reached out to our colleagues and started exciting interactions, collaborations and research pipelines through new platforms, which we hope will continue to increase international collaborations in academia and industry even after the pandemic. JHEP Reports has continued to grow during the pandemic and it is my pleasure to highlight the wide range of clinical, translational and basic liver research papers published in this issue, while not forgetting the effects that the pandemic has had on the lives of many.

Two studies in this issue investigated non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty steatohepatitis (NASH). O'Hara and colleagues explored the socio-economic burden of NASH in a retrospective, cross-sectional study, in which physicians provided demographic, clinical and economic patient information via an online survey.[2] The Global Assessment of the Impact of NASH (GAIN) determined the mean total annual per patient cost of NASH across major European countries and the United States at €2,763, €4,917 and €5,509 for direct medical, direct non-medical and indirect costs. National per patient cost was highest in the United States and lowest in France. These data revealed a substantial burden of NASH for health services and affected individuals. Sinha *et al.* used "volatomics" to analyze volatile organic compounds in exhaled breath as a means to discover non-invasive biomarkers and novel mechanistic insights in NAFLD.[3] Comparing breath samples from participants with NAFLD with or without cirrhosis to those of healthy volunteers, the authors found that terpinene and dimethyl sulfide could discriminate between groups and thus represent promising volatomic markers for stratifying NAFLD.

A meta-analysis led by Marot *et al.* evaluated the effects of granulocyte colony-stimulating factor (G-CSF) in patients with alcoholic hepatitis.[4] The authors included seven studies from Asia and Europe with nearly 400 patients. While the overall meta-analysis revealed significantly reduced risk of death at 90 days in patients receiving G-CSF, Asian and European studies revealed conflicting data, with Asian studies showing reduced risk of death with G-CSF, whereas European studies showed a numerically higher but not significantly different risk of death in patients receiving G-CSF compared to controls. The authors discuss whether these differences are explained by ethnic differences or by disparities in patient selection.

Two studies in this issue investigated viral hepatitis. Itakura and colleagues investigated viral escape mutation patterns in patients who had failed treatment with direct-acting antiviral treatment.[5] The authors described specific mutational patterns in NS3 and NS5 with select drugs as well as a significantly increased prevalence of some mutations, specifically resistance-associated substitutions in either NS3 or NS5, according to the number of failed regimens. Together, these data suggest that specific mutations contribute to viral resistance and should be considered during decision making for treatment of chronic hepatitis C. Cohen *et al.* uncovered hepatitis B variants with PreS2 deletions between nucleotides 38-55 (PreS2Δ38-55) as a new risk factor for hepatocellular carcinoma in The Gambia, West Africa.[6] The authors found surface gene variants that were more frequent in cirrhotic and HCC cases than in controls, with PreS2Δ38 representing the main detected genetic variant. While PreS2Δ38 was only marginally associated with risk of cirrhosis, it significantly increased HCC risk, with a further multiplicative effect between PreS2Δ38-55 and AFB1 exposure.

Souhami *et al.* follow-up on the topic of cirrhosis and HCC, where they investigated the performance and feasibility of liver surface nodularity for the detection of clinically significant portal hypertension in comparison to liver stiffness measurements.[7] In patients with cirrhosis and hepatocellular carcinoma, liver surface nodularity correlated strongly (and to a similar degree as liver stiffness measurement) with hepatic venous pressure gradient. Based on this, integration of liver surface nodularity into current workflows could be useful in centers where the hepatic venous pressure gradient measurement is unavailable.

Finally, two basic papers investigated the role constitutive androstane receptor signaling in cholestasis as well as nuclear deformation and mechanosensing in cirrhosis. Analysis of

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high-throughput RNA sequencing data from mouse livers with diverse types of injuries, Mathur *et al.* found significant overlap in the expression of inflammatory and proliferation-related genes across liver diseases, but noticed a unique pattern in cholestatic livers, displaying robustly induced genes regulating drug metabolism.[8] As such, they found constitutive androstane receptor (CAR) activation was crucial for the induction of this metabolic gene program in cholestasis. Accordingly, cholestatic mice were protected against the effects of zoxazolamine and acetaminophen due to altered drug metabolism, while protective effects were diminished upon inhibition of CAR activity. Together, these findings demonstrate that CAR activation may lead to variations in drug metabolism and clinical outcomes in cholestasis. Guixé-Muntet *et al.* investigated the effect of matrix stiffness on the phenotype of cirrhotic liver cells, demonstrating a significant phenotype amelioration in low stiffness compared to high stiffness.[9] High stiffness induced nuclei deformation in all cell types, including human livers, and disconnected the nucleus from the cytoskeleton by cytoskeleton disruption or a defective form of nesprin1. These studies may point towards novel approaches to ameliorate cellular functions and halt progression in advanced liver disease.

The editorial team at JHEP Reports hopes you will enjoy the issue and consider submitting your studies to JHEP Reports in the near future.

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