Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

JOURNAL OF HEPATOLOGY

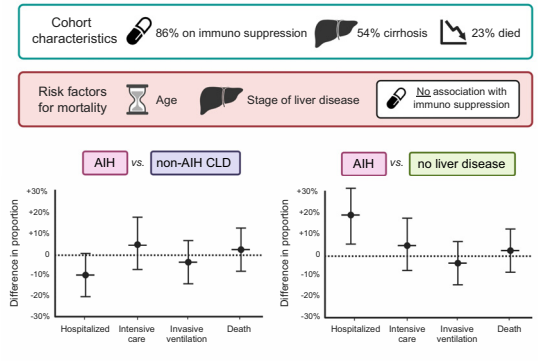
From the Editor's Desk…

Patrizia Burra*, Frank Tacke, Vlad Ratziu, Stefan Zeuzem, Bruno Sangro, Paolo Angeli

SELECTION OF THE MONTH

SARS-CoV-2 infection in patients with autoimmune hepatitis

It has not been well established if patients with autoimmune hepatitis (AIH) treated with immunosuppressive drugs are at higher risk of severe COVID-19 infection. The current study by Marjot and coworkers reports the course of SARS CoV-2 infection in 70 patients with AIH on immunosuppressive therapy and compares it with that of 862 patients with non-AIH chronic liver disease (CLD), all from 3 international large-scale reporting registries, and also with 769 consecutive non-CLD controls. There were **no differences between AIH and non-AIH CLD patients for rate of hospitalisation, intensive care unit requirement, invasive ventilation or death.** Sixteen patients with AIH died with no excess liver-related death compared to non-AIH CLD. When considering the whole cohort, the diagnosis of AIH did not place the patient at higher risk of death, which was confirmed in a propensity score matched analysis. Patients with AIH had a higher rate of hospitalization than non-CLD controls but not of any other major outcome, including ICU admission or death. In conclusion, AIH does not confer additional susceptibility to adverse outcomes and the use of immunosuppression had no negative impact following SARS-COV-2 infection.



Marjot *et al.*, 2021.
SARS-CoV-2 infection in patients with autoimmune hepatitis

EXPERIMENTAL AND TRANSLATIONAL HEPATOLOGY

The specific metabolic profile of cholangiocarcinoma stem cells reveals new therapeutic targets

The biological features of cholangiocarcinoma (CCA) are linked to their cancer stem cell (CSC) compartment, but little is known about CSC's metabolic features in CCA. By using human CCA spheroid cultures, patient material and xenograft mouse models, Raggi and coworkers demonstrate that mitochondrial oxidative metabolism contributes to maintain stemness features in CCA, conferring *in vivo* tumorigenic capacity and drug-resistance. Intriguingly, they also identify that PGC-1α, a molecule which regulates mitochondrial biology, can be pharmacologically targeted by metformin, PGC-1α silencing or an inhibitor (SR-18292), **suggesting that at least a subset of patients with CCA and unfavourable CSC characteristics could benefit from a new treatment strategy**. The next step of translating the basic findings into preclinical models and clinical development is eagerly awaited.

The role of alternative bile acid synthesis in fatty liver-associated hepatocellular carcinoma

The mechanisms of hepatocellular carcinoma (HCC) development in non-alcoholic fatty liver disease (NAFLD) are incompletely understood, but bile acids (BAs) are increasingly recognised as important signalling molecules in NAFLD and HCC. Conde de la Rosa and coworkers uncover a key role of steroidogenic acute regulatory protein 1 (STARD1) in NAFLD-driven HCC, wherein it stimulates the alternative, mitochondrial BA synthesis pathway. STARD1 overexpression promoted, while its deletion reduced, tumour formation in mouse models. Mechanistically, **STARD1-dependent BAs stimulate tumour-initiating cells and primary hepatocytes for pluripotency, self-renewal and inflammation**. The clinical implications of these findings, including the role of BA-modifying NAFLD treatments for HCC development, require further studies.

Proof-of-concept for synthetic mRNA therapy in genetic cholestatic liver disease

Liposomal delivery of synthetic mRNA has recently gained attention as a basis for COVID-19 vaccines. Wei and coworkers now employed this principle to develop a novel strategy to treat progressive familial intrahepatic cholestasis type 3 (PFIC3), a rare lethal autosomal recessive liver disorder caused by loss-of-function variations of a phosphatidylcholine transporter (ABCB4/MDR3). After screening different chemically- and genetically modified mRNA variants for human *ABCB4* (h*ABCB4*), they examined a hepatocyte-delivered codon-optimised h*ABCB4* mRNA in cell-based and *in vivo* mouse models of human PFIC3. Repeated injections of the h*ABCB4* mRNA construct effectively rescued the severe liver disease phenotype in a genetic model of PFIC3 in mice, **including proper liver regeneration and normalisation of inflammation and fibrosis.** This novel concept holds promise for the treatment of PFIC3, and other genetic liver diseases in the near future.

COVID-19

Association of liver abnormalities with in-hospital mortality of patients with COVID-19

COVID-19 caused by SARS-CoV-2 infections has spread rapidly worldwide. As a new, highly contagious disease, COVID-19 was first reported with characteristics of viral pneumonia, such as fever, dry cough, and lymphopenia. In addition, alterations in liver function tests were observed. In a large retrospective cohort study, Ze-yang Ding and coworkers conducted longitudinal liver function tests and determined their associated clinical factors and mortality risk. Of the 2,073

patients with COVID-19, 61.8% had abnormal liver chemistries, and 14.3% had a liver injury. The mean levels of aspartate aminotransferase (AST) and direct bilirubin increased early after symptom onset in deceased patients and showed disparity compared with those in discharged patients throughout the clinical course of the disease**. Abnormal admission AST and direct bilirubin levels were independent risk factors for mortality due to COVID-19.** Concomitant HBV infection in patients, however, did not increase the risk of poor COVID-19-associated outcomes.

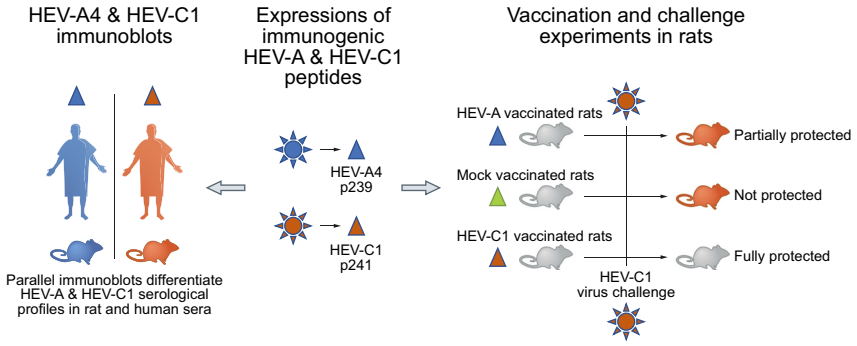
VIRAL HEPATITIS

Role of core protein mutations in the development of occult HBV infection

Occult HBV infection is defined as the presence of HBV DNA in liver and/or in serum of individuals negative for the surface antigen (HBsAg) by currently available assays. Occult HBV infection is not only associated with transmission through blood transfusion, organ transplantation and dialysis, but also appears closely associated with cirrhosis and HCC. Jingna Chen and coworkers selected a strain carrying 9 amino acid substitutions in the core protein/capsid by sequence alignment and western blot analysis and explored the impact of mutations on viral antigen production *in vitro* and *in vivo*. The expression of HBcAg, HBeAg and HBsAg and viral RNA was quantified from mutant replicons in transfected Huh7 cells or infected mice, respectively. They observed that a W62R mutation in the core protein/capsid had a critical impact on reduction of HBcAg and HBeAg production during HBV replication, while its combined mutations with P50H or/and S74G played a limited role in influencing viral protein production *in vivo*. The authors conclude that W62R and its combination mutations in the HBV core protein/capsid might massively affect HBcAg and HBeAg production during viral replication, which, in turn, **might contribute to the occurrence of occult hepatitis B infection**.

Multimodal investigation of antigenicity of rat hepatitis E virus: Implications for infection, diagnostics, and vaccine efficacy

The family Hepeviridae, which encompasses all HEV variants, comprises 2 genera: Orthohepevirus and Piscihepevirus. The genus Orthohepevirus is further classified into 4 species: A – D. Orthohepevirus A (HEV-A) comprises 8 HEV genotypes, 4 of which commonly infect humans. HEV-A genotype 1 and genotype 2 are spread between humans via the faecal-oral route. HEV-A genotype 3 and genotype 4 circulate in swine and spread to humans via consumption of undercooked meat products. HEV-A3 circulates in Europe and the Americas while HEV-A4 circulates in China. Rat hepatitis E virus (Orthohepevirus species C; HEV-C1) is an emerging cause of viral hepatitis in humans. The study by Sridhar and colleagues assessed HEV-C1 antigenic divergence from HEV-A and investigated the impact of this divergence on infection susceptibility, serological test sensitivity, and vaccine efficacy. E2s sequence identity between HEV-A and HEV-C1 was found to be only 48%. There was a low conservation at E2s residues involved in monoclonal antibody binding. This divergence **reduces the capacity of existing tests to diagnose HEV-C1** and also indicates that prior exposure to HEV-A (via infection or vaccination) is not protective against HEV-C1.



Sridhar *et al.*, 2021.
Multimodal investigation of antigenicity of rat hepatitis E virus

detoxifying the bile, in addition to anti-inflammatory effects. In this randomized trial **by** Schattenberg and coworkers in non-cirrhotic patients with PBC, 2 doses of ELA, 80 and 120 mg were tested *vs.* placebo in patients resistant or intolerant to UDCA (15 patients per arm). There was a strong reduction in alkaline phosphatase (-48% for ELA 80, -41% for ELA 120, +3% for placebo) mirrored by higher efficacy of the 2 ELA doses (without dose response) for different composite outcomes, including 1 testing a more stringent response (>40% reduction of baseline alkaline phosphatase). GGT, IgM and select soluble inflammatory markers also declined on therapy, but aminotransferases did not change. Bile acid synthesis was reduced. There were no issues related to safety except a possible flare of autoimmune hepatitis. There was no pruritus in the ELA groups while lipid abnormalities typical of PBC were corrected. This is a **promising study which will be followed by a larger phase III trial** in what now becomes a crowded field of second-line therapy for PBC (obeticholic acid, bezafibrate, seladelpar, tropifexor, cilofexor, saroglitazar…)

CHOLESTATIC LIVER DISEASES

Elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA

A relatively small proportion of patients with primary biliary cholangitis (PBC) are resistant or intolerant to ursodeoxycholic acid (UDCA), which is the first-line therapy. **Elafibranor (ELA), a dual PPARα/δ agonist alleviates the toxicity of bile acids by inhibiting their synthesis**, increasing their hepatic elimination and

CIRRHOSIS

Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality

Data on the interaction between ACLF and MELD score in predicting waitlist (WL) mortality in patients with cirrhosis are scarce. Thus, Mohamed Abdallah and coworkers analysed the UNOS database, from 01/2002 to 06/2018, on liver transplantation (LT) listings for adult patients with cirrhosis and ACLF. In 18,416

candidates with ACLF at listing, 90-day WL mortality, defined as patient death or too sick for LT, was 21.6% (18%, 20%, 25%, and 39% for ACLF grades 1, 2, 3a, and 3b respectively). Using a Fine and Gray regression model, the authors identified an interaction between MELD and ACLF grade, with higher impact of ACLF at lower MELD score. A score, developed using parameter estimates from the interaction model on a derivation cohort (n = 9,181), was used to stratify a validation cohort (n = 9,235) into 4 quartiles: Q1 (score <10.42), Q2 (10.42–12.81), Q3 (12.82–15.50), and Q4 (>15.50). WL mortality increased with each quartile from 13%, 18%, 23%, and 36%, respectively. Observed *vs*. expected deciles on WL mortality in the validation cohort showed good calibration (goodness of fit $p = 0.98$) and correlation (r = 0.99). Thus, the authors concluded that, among selected candidates with ACLF at listing, **MELD score and ACLF interact in predicting cumulative risk of 90-day WL mortality**, with higher impact of ACLF grade at lower listing MELD score.

Refining prediction of survival in TIPS patients: The Freiburg index of post-TIPS survival (FIPS)

TIPS implantation is an effective and safe treatment for complications of portal hypertension. Prediction of survival is important in these patients as they constitute a high-risk population. Therefore, the aim of Bettinger and coworkers in this retrospective study was to develop an alternative prognostic model to predict survival after planned TIPS implantation. Data from 1,871 patients with *de novo* TIPS implantation for ascites or secondary prophylaxis of variceal bleeding were analysed. A Cox regression model was performed to create an alternative prediction model, which includes significant prognostic factors. Age, bilirubin, albumin and creatinine were the most important prognostic factors. These parameters were included in a new score named the Freiburg index of post-TIPS survival (FIPS). The FIPS score was able to identify high-risk patients with significantly reduced survival (3.1–6.9 months) after TIPS in the training cohort. These results were confirmed in the validation cohort. The FIPS score showed better prognostic discrimination compared to the Child-Pugh-, MELD-, MELD-Na-score and the bilirubin-platelet model. However, **the FIPS score showed insufficient prognostic discrimination in patients with early TIPS implantation**. Thus, the authors stated that the FIPS score is superior to established scoring systems for identifying high-risk patients with a reduced prognosis in patients after elective TIPS implantation.

ALCOHOL-RELATED LIVER DISEASE

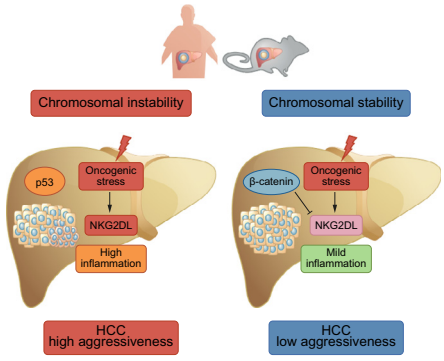
Cost-effectiveness of alcohol use treatments among patients with alcohol-related cirrhosis

Alcohol use treatment and counselling are available and effective in promoting alcohol abstinence. Avanceña and coworkers aimed to explore the cost-effectiveness of different alcohol use treatments among patients with compensated alcohol-related cirrhosis. The authors simulated a cohort of patients with compensated cirrhosis receiving care over their lifetimes and estimated costs and benefits in terms of quality-adjusted life years (QALYs) gained from healthcare and societal perspectives. The authors calculated incremental cost-effectiveness ratios (ICERs) to understand the impact of parameter uncertainty. Interestingly, when compared to a do-nothing scenario, medication-assisted therapies and counselling to treat alcohol use were found to be cost-saving from a healthcare perspective, which means that **they provide more benefits with less costs than no intervention.**

HEPATOCELLULAR CARCINOMA

NKG2D ligand expression is associated with HCC aggressiveness

Present in the membrane of natural killer (NK) cells and some effector T cells, **NKG2D is an activating receptor which contributes to cancer immunosurveillance by interacting with induced-self proteins** overexpressed on the surface of tumour cells. Cadoux *et al.* studied the expression of NKG2D ligands (MICA, MICB, ULBP1 and ULBP2) in human datasets of HCC and in 2 mouse models that replicate important molecular features of human HCC. Expression of all ligands was associated with worse patient outcome while CTNNB1-mutated HCCs expressed less ULBP1 and 2 and had lower levels of inflammation and a better prognosis. Indeed, expression of ULBP1 and 2 correlated inversely with the expression of β-catenin target genes and, in mice, β-catenin signalling downregulated the expression of NKG2D ligands. In this way, the authors have **highlighted a potential contribution of an immunological mechanism to the improved prognosis of patients with HCC tumours harbouring β-catenin mutations**.



Cadoux *et al.*, 2021.
NKG2D ligand expression is associated with HCC aggressiveness

LIVER TRANSPLANTATION

Safety and efficacy of *in vitro* fertilisation in patients with chronic liver disease and liver transplantation recipients

Chronic liver disease and liver transplantation can reduce the ability of women to conceive. With increased awareness and availability of *in vitro* fertilisation, the need for accurate counselling is paramount. To date, **minimal data exists regarding outcomes of *in vitro* fertilisation in patients with chronic liver disease, cirrhosis or in liver transplant recipients**. Rahim and coworkers reported the largest experience of *in vitro* fertilisation in 42 women with liver disease and liver transplantation. They had undergone 57 *in vitro* fertilisation cycles (9 cycles in 6 women with cirrhosis, 14 cycles in 11 women after transplant and 34 cycles in 25 women without cirrhosis). Eight (2 transplanted, 3 cirrhotic, 4 non-cirrhotic) patients experienced a miscarriage. The live birth rate was reported in 74% of cases. 2/9 (22%) cirrhotics, 4/14 (29%) transplanted and 6/34 (18%) non-cirrhotics had unsuccessful attempts. 9/57 (16%) cycles resulted in new liver enzyme derangement during therapy, which improved after treatment completion. Six pregnancies (2 liver transplant recipients, 4 non-cirrhotic) were complicated by obstetric cholestasis. One patient with AIH-related cirrhosis decompensated after initiating therapy, warranting discontinuation of therapy. There were no maternal

deaths. Half the pregnancies resulted in premature deliveries (range 27–36 weeks). The final message is that in selected cases, ***in vitro*** **fertilisation in patients with liver disease can be successful.**

Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: the SURFASA score

In acute severe autoimmune hepatitis (AS-AIH), the optimal timing for liver transplantation remains controversial. De Martin and coworkers aimed to evaluate early predictive factors for a non-response to corticosteroids and to propose a score to identify patients in whom liver transplantation is urgently needed. The steroid-treatment response was defined as liver transplant-free survival at 90 days; 128 patients were included, 72% were female, 115 patients received corticosteroids with a 66% liver transplant-free survival rate at 90 days. The SURFASA score, including INR and bilirubin, was highly predictive of transplant or death (AUC = 0.93; 88% specificity; 84% sensitivity) with a cut-off point of <–0.9. Below this cut-off, the chance of responding was 75%, with a score higher than 1.75, the risk of dying or being transplanted was between 85% and 100%. **Within 3 days of initiating steroids, the SURFASA score can identify non-responders who require a referral for liver transplant.**

Predicting survival after liver transplantation for patients with HCC using the LiTES-HCC score

Liver transplant priority in the US and Europe follows the 'sickest-first 'principle. However, for patients with HCC, priority is based on tumour criteria (*e.g.* Milan or University California San Francisco [UCSF] criteria) or on biological markers (alpha-fetoprotein). Newer risk scores (*e.g.*, Metroticket, HALT-HCC) focus on HCC-related pre-transplant variables. Goldberg and coworkes aimed to develop a risk score to predict post-transplant survival for patients using HCC- and non-HCC related variables such as age and chronic kidney disease. They identified a retrospective cohort using national registry data of liver transplant recipients with HCC from 2002 to 2018. They used Cox regression models focused on 5- and 10-year survival to estimate beta coefficients for a risk score, using manual variable selection, and calculated absolute predicted survival time and compared it to available risk scores. In the final model, called LiTES-HCC score, the authors selected 11 variables, among 6,502 liver transplant recipients. The AUCs at 5- and 10-years were: 0.62, 95% CI 0.57-0.67 and 0.65, 95% CI 0.58-0.72, which were not significantly different to those achieved with the Metroticket and HALT-HCC scores. **The LiTES-HCC score was able to discriminate patients based on post-transplant survival among those meeting Milan and UCSF.** This score could be integrated into survival benefit-based models to lead to improvements in life-years at the population-level.

Patrizia Burra* at Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy.
* Corresponding author: Patrizia Burra, Multivisceral Transplant Unit-Gastroenterology, University Hospital of Padova, Via Giustiniani 2, 35128, Padova, Italy. *E-mail address: burra@unipd.it.*
Frank Tacke at Department of Hepatology and Gastroenterology, Charité Universitätsmedizin Berlin, Berlin, Germany.
Vlad Ratziu at Insitute for Cardiometabolism and Nutrition, Sorbonne Université and Hospital Pitié Salpêtrière, Paris, France.
Stefan Zeuzem at Department of Medicine I, Goethe University Hospital, Frankfurt, Germany.
Bruno Sangro at Liver Unit, Clinica Universidad Navarra and CIBEREHD, Pamplona, Spain.
Paolo Angeli at Unit of Internal Medicine and Hepatology, University of Padua, Padua, Italy.