JOURNAL
OF HEPATOLOGY

From the Editor's desk. . .

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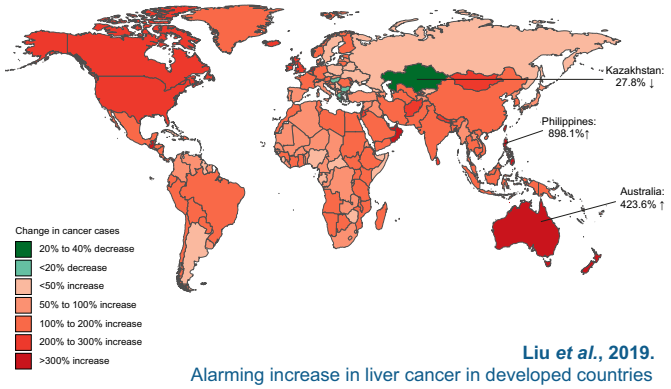
SELECTION OF THE MONTH

Alarming increase in liver cancer in developed countries

Liu *et al.* collected detailed information on liver cancer aetiology between 1990–2016, derived from the global burden of disease in 2016. In this issue of the Journal, they show that liver cancer remains a major public health concern globally, though control of hepatitis B virus and hepatitis C virus infections has contributed to the decrease in liver cancer incidence in some regions. **They report an unfavourable trend in countries with high socio-demographic index, including the Netherlands, the UK, and the USA**. They conclude that the "current prevention strategies in liver cancer should be reoriented, and much more targeted and specific strategies should be established in some countries to forestall the increase in liver cancer".



Liu *et al.*, 2019.
Alarming increase in liver cancer in developed countries

LIVER FIBROSIS

A hepatocyte-specific miRNA contributes to liver fibrosis

MicroRNAs (miRNAs) are short (19 to 25 nucleotides) noncoding RNA molecules that regulate gene expression both at the level of messenger RNA degradation and translation. Tsay *et al.* hypothesized a role of hepatocyte miRNAs in liver fibrosis. To address this question, they inhibited microRNAs using adeno-associated virus in the hepatocytes of mice with chemically induced liver fibrosis. Here, they show that blocking miRNA-221-3p function in hepatocytes during chronic liver injury facilitates recovery of the liver and faster resolution of the deposited extracellular matrix. Their experiments also reveal that inhibition of miRNA-221-3p results in increased hepatocyte expression of the Gnai2 gene product, guanine nucleotide-binding protein G(i) subunit alpha-2, an effect which reduces the secretion of C-C motif chemokine ligand 2 (also known as MCP-1), decreases hepatic stellate cell activation, and ultimately reduces liver fibrosis. **These findings suggest that hepatocyte miRNA-221-3p could be a target for therapeutic interventions in liver disease**.

NON-ALCOHOLIC STEATOHEPATITIS

Rosuvastatin improves lipid profile in patients treated with an FGF19 analogue

Fibroblast growth factor 19 (FGF19), has been shown to exert beneficial effects in non-alcoholic fatty liver disease including improving steatosis, inflammation and fibrosis. NGM282, an FGF19 analogue, is known to increase serum cholesterol levels by inhibiting CYP7A. In this issue of the *Journal*, Rinella *et al.* studied whether administration of an HMG-CoA reductase inhibitor (rosuvastatin) can manage the cholesterol increase seen in patients with non-alcoholic steatohepatitis treated with NGM282. From a previously multicentre clinical trial (Harrison SA, *et al.* The Lancet 2018;391), the authors noticed that administration of different doses of NGM282 resulted in elevated cholesterol levels. In the current study, initiation of rosuvastatin was well tolerated and resulted in rapid decline in plasma levels of total cholesterol and LDL-C as well as triglycerides. Importantly, a significant decrease in liver fat content was also observed. In this multicentre study, the NGM282-associated elevation of cholesterol was effectively managed with rosuvastatin. **This study suggests that co-administration of rosuvastatin with NGM282 is a promising strategy to optimize cardiovascular risk profile in patients with non-alcoholic fatty liver disease.**

HEPATITIS B VIRUS (HBV) INFECTION

A biomarker approach for a deeper view into the core of HBV replication

Hepatitis B core-related antigen (HBcrAg) is a relatively old HBV biomarker that gathered new attention as a potential endpoint marker for new treatment strategies targeting the intrahepatic HBV covalently closed circular DNA (cccDNA) pool. Indeed, compared to HBV surface antigen, this marker might better reflect the pool of transcriptionally active cccDNA and overall viral activity in the liver. However, in depth analyses regarding the correlation between HBcrAg serum levels and intrahepatic HBV replication activity markers as well as histological fibrosis and inflammatory activity scores have not been performed yet. Testoni *et al.* now investigated for the first time the relationship between circulating HBcrAg and markers of intrahepatic viral activity like total intrahepatic HBV-DNA, cccDNA, pgRNA, and the cccDNA transcriptional activity, in a cohort of untreated patients with chronic hepatitis B infected with several HBV genotypes. **Their results indicate that serum HBcrAg levels represents a valid surrogate of both intrahepatic cccDNA and its transcriptional activity that can be useful in the evaluation of new antiviral therapies aiming at a functional cure of HBV infection.**

HEPATITIS C VIRUS (HCV) INFECTION

Human serum components promote HCV lipidation and infectivity, a step forward towards an HCV vaccine, the role of lipid binding protein SEC14L2 for HCV replication

A unique feature of patient-derived HCV particles is the particularly low buoyant-

density of virions owing to their particular lipid composition (HCV lipoviroparticles). Virion lipidation of cell culture-grown HCV (HCVcc) particles, however, is incomplete, and this ccHCV-specific feature is the likely explanation for their poor specific *in vitro* infectivity. The lack of models fully mimicking the conformation of authentic HCV particles critically limits further structural and functional investigations of the HCV biology. In an elegant study, Denolly *et al.* developed simple and useful culture conditions to produce infectious HCV particles that resemble those retrieved from chronically infected patients. **They clearly demonstrate that specific human serum components promote extracellular maturation of HCV particles shifting their density and infectivity, hence indicating that a major determinant that imprints lipidation of particles is serum itself, likely after cell egress.** Moreover, the HCV hypervariable region 1 was found to be a major viral determinant that controls this process. These important findings may also have major implications for the rationale design of a much-needed vaccine.

The high variability of immunogenic regions of the HCV envelope proteins E1 and E2 is a major obstacle for HCV vaccine development as neutralizing antibodies against these regions rapidly select resistant viral variants of the quasispecies. The highest sequence variability occurs in N-terminus of E2, the hypervariable region 1 (HVR1). Khera *et al.* hypothesized that the HVR1 and specific protein glycosylations of the envelope protein limit the access to conserved viral epitopes which might be important for a neutralizing antibody response. To overcome these limitations, the elegantly combined targeted protein deglycosylation with deletion of HVR1 to create viruses and proteins with increased exposure of the crucial CD81 binding site and possibly superior immunogenicity. **Vaccination approaches with recombinant E2 proteins harbouring these combined modifications induced robust cross-binding antibody responses across all major HCV genotypes, a finding which can be taken as an important step forward in the search for a potent HCV vaccine.**

Efficient replication of patient-derived HCV particles in Huh-7.5 hepatoma cell lines, cell lines which are normally not permissive for HCV replication, can be achieved by overexpression of the lipid binding protein SEC14L2. Given this important role of SEC14L2 in HCV replication, Costa *et al.* aimed to identify viral factors associated with efficient replication in cell culture but also whether genetic variants (single nucleotide polymorphisms [SNPs]) of *SEC14L2* might impact replication of natural occurring HCV isolates. **Their data clearly indicate that homogenous expression of SEC14L2 in hepatoma cell lines is a reliable model to study patient-derived HCV isolates, and that SEC14L2 elicited HCV replication varies between HCV genotypes 1 to 4.** While all tested *SEC14L2* SNPs support HCV RNA replication *in vitro*, they identified one SNP that resulted in reduced protein expression and HCV replication *in vitro*.

CIRRHOSIS

Bedside test to identify cirrhosis patients at risk of accident, 25% hospitalized cirrhotics have ACLF in the US

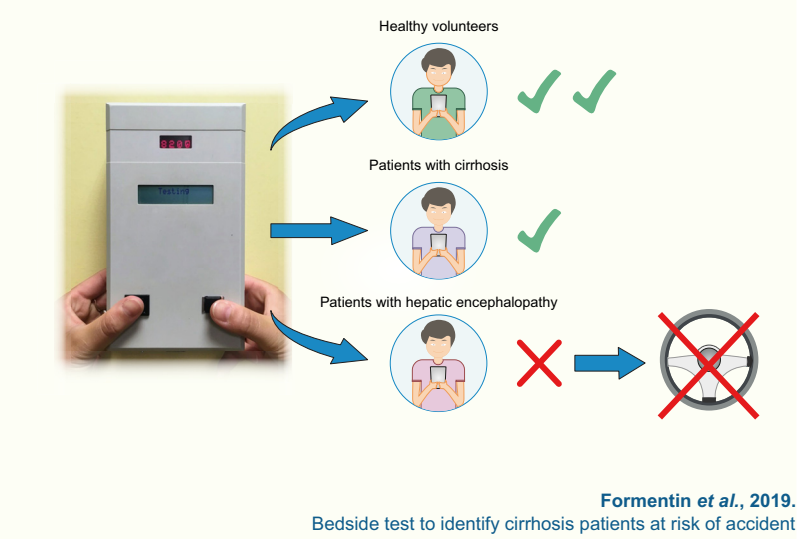
Patients with cirrhosis are known to have reduced driving ability and are at increased risk of accidents. However, there is a lack of validated tests to identify these patients. Formentin *et al.* describe the results of an important prospective study, which evaluated the performance of a hand-held vigilance test that takes about 10 minutes to perform. They assessed its ability to discriminate patients at risk of driving accidents. **Although the study did not confirm that the vigilance test predicted the risk of accidents, the severity of the abnormality was associated with those not driving and those likely to have increased risk of accidents independent of their model for end-stage liver disease scores and age.** If this test can be further improved and validated, it could be introduced into clinical practice to identify those at risk of harming themselves and the community.

Acute-on-chronic liver failure (ACLF) is a newly defined syndrome characterized by distinct diagnostic, prognostic and pathophysiological features. Consortia in Asia-Pacific, US and Europe consider different definitions of this syndrome. The paper by Hernaez *et al.* is hugely important as it applied the best validated diagnostic criteria developed by the EASL-CLIF Consortium in about 72,000 US patients**. Their data provide validation of the concept that ACLF is indeed a distinct clinical syndrome that can be diagnosed and categorized into risk groups using the EASL-CLIF criteria. Alarmingly, they found that about 25% of hospitalized cirrhotic patients have ACLF and their 28-day and 90-day mortality are about 25% and 40%, respectively.** These data support the urgent need for harmonization of definitions and the development of novel therapies for patients with ACLF.

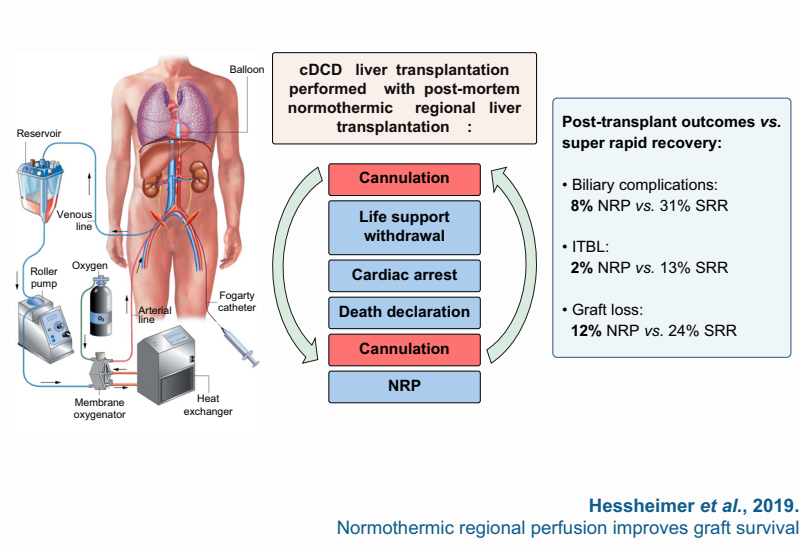
LIVER TRANSPLANTATION

Normothermic regional perfusion improves graft survival, HCC outcomes are better if they have potential living donors

In order to reduce the deaths of patients on the waiting list, liver transplantation is increasingly being performed with organs obtained from deceased donors (DCD). It is well-documented that transplantation using these organs leads to worse outcomes than when transplanting organs obtained from brain dead donors. Hessheimer *et al.* describe the results of an important study where they compared the transplant outcomes of patients receiving



Formentin *et al.*, 2019.
Bedside test to identify cirrhosis patients at risk of accident



Hessheimer *et al.*, 2019.
Normothermic regional perfusion improves graft survival

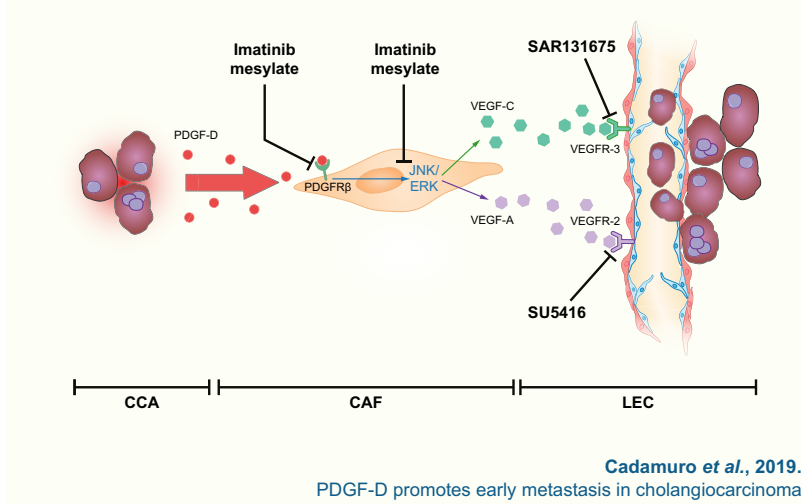
standard DCD transplantation, a procedure referred to as super rapid recovery and compared it with normothermic regional perfusion (NRP). **The data reveal striking findings and show that the patients receiving NRP organs had significantly lower rates of biliary complications and improved graft survival. Although the study is a 'non-randomized' study, these real-world data provide compelling information that may lead to a change in clinical practice.**

Many patients with hepatocellular carcinoma (HCC) are disadvantaged because they have less severe liver disease and living donor liver transplantation is a potential strategy to reduce their risk of death on the transplant waiting list. However, the outcomes of living donor liver transplantation for patients with HCC are variable. Goldaracena *et al.* describe the results of an intriguing study assessing the results of liver transplantation in patients listed with potential living donors compared with those listed without a potential living donor. **Based on intention-to-treat analysis they clearly show that patients with a potential living donor graft have a significantly better survival than those without, due to shorter waiting times and lower dropout rates. It is important to note that this benefit was noted despite only about 50% actually receiving a living donor.** These data suggest that where possible, patients with HCC should be encouraged to bring forward a potential living donor.

CHOLANGIOCARCINOMA – BASIC

PDGF-D promotes early metastasis in cholangiocarcinoma

In cholangiocarcinoma, early metastatic spread via lymphatic vessels often precludes curative therapies. Cholangiocarcinoma invasiveness is fostered by an extensive stromal reaction, enriched in cancer-associated fibroblasts (CAFs) and lymphatic endothelial cells. Cholangiocarcinoma cells recruit and activate CAFs by secreting platelet-derived growth factor D (PDGF-D). Cadamuro *et al.* investigated the role of PDGF-D and liver myofibroblasts in promoting lymphangiogenesis in cholangiocarcinoma. **They reveal that PDGF-D stimulates the fibroblast production of vascular endothelial growth factors, A and C, resulting in expansion of the lymphatic vasculature and tumour cell invasion.** This process, critical for the early metastasis process of cholangiocarcinoma, may be blocked by inducing CAF apoptosis or by inhibiting PDGF-D-induced axis.



Cadamuro *et al.*, 2019.
PDGF-D promotes early metastasis in cholangiocarcinoma

LIVER CANCER – CLINICAL

Interest of MRI in assessing IPNB, a trial of sorafenib with or without transarterial chemoembolization in patients with advanced HCC

Imaging characteristics that identify the malignant potential of intraductal papillary neoplasm of the bile duct (IPNB) are unclear. Lee *et al.* performed a retrospective study in 120 patients with surgically resected IPNB who underwent preoperative magnetic resonance (MR) imaging with MR cholangiography before surgery to see whether MR imaging findings could help to differentiate IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. In addition, they correlated MRI findings with clinically relevant outcomes. **Here, they show that MR imaging with MR cholangiography may be helpful in differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. Significant MR imaging findings of IPNB with an associated invasive carcinoma have a negative impact on recurrence-free survival rates.**

Park *et al.* performed an investigator-initiated, randomized, open-label, parallel, multicentre, phase III trial comparing sorafenib combined with conventional transarterial chemoembolization (cTACE) with sorafenib alone in 339 patients with advanced HCC (ClinicalTrial.gov ID: NCT01829035). **They now show no improvement of overall survival with sorafenib plus cTACE therapy compared with sorafenib alone.** However, the combination therapy significantly resulted in

longer time-to-progression and progression-free survival, and higher tumour response rate. They conclude that "sorafenib alone treatment remains the first-line standard care for patients with advanced HCC".

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