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From the Editor's Desk…

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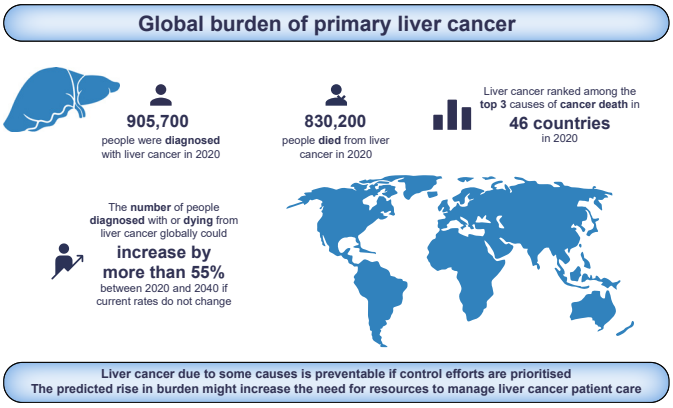
SELECTION OF THE MONTH

Global burden of primary liver cancer in 2020 and predictions for 2040

To understand how the burden of liver cancer varies across the world, **Rumgay *et al.*** have extracted data on primary liver cancer cases and deaths from the GLOBOCAN 2020 database for 185 countries. **An estimated 905,700 persons were diagnosed with, and 830,200 died from, liver cancer in 2020.** Age-standardised incidence and mortality rates per 100,000 person-years were highest in Eastern Asia (17.8 new cases, 16.1 deaths), Northern Africa (15.2 new cases, 14.5 deaths), and South-Eastern Asia (13.7 new cases, 13.2 deaths). Liver cancer was among the top five causes of cancer death in 90 countries. Cases and deaths for 2040 were then predicted based on current rates and global demographic projections for 2040. In 2040, a predicted 1.4 million people could be diagnosed (55% increase), and 1.3 million people could die (56.4% increase) from liver cancer. **Such a predicted rise in cases may have an important socio-economic impact in healthcare systems and, more importantly, can to a large extent be prevented.**



Rumgay *et al.*, 2022.
Global burden of primary liver cancer in 2020 and predictions for 2040.

EXPERIMENTAL AND TRANSLATIONAL HEPATOLOGY

Chromatin remodeller MRG15 promotes transition from simple steatosis to NASH

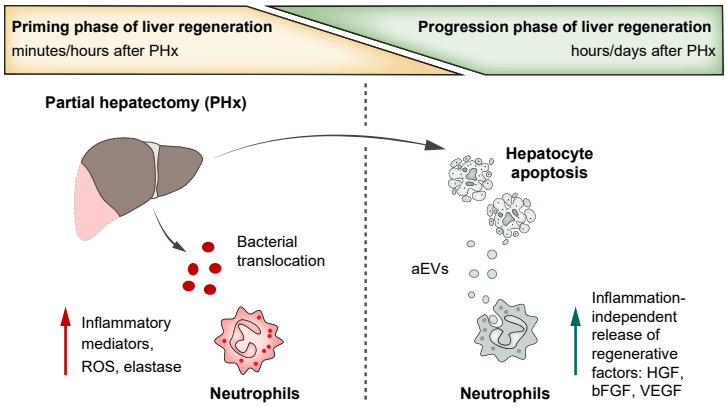
The exact molecular pathways mediating the transition from relatively benign steatosis to progressive non-alcoholic steatohepatitis (NASH) are incompletely understood. **Tian *et al.*** uncover an unexpected role of mortality factor 4-like protein 1 (MORF4L1, also called MRG15) – previously identified as a nuclear chromatin remodeller in the rhythmic regulation of genes involved in hepatic lipid synthesis – in this transition. Using two NASH mouse models, patient samples and primary cells, they demonstrate that MRG15 partly localises at the mitochondrial membrane, where MRG15 deacetylates the mitochondrial Tu translation elongation factor and impairs mitophagy. **Blocking hepatic MRG15 expression could thereby represent a new strategy to ameliorate NASH progression.**

Mystery solved? On the origin of cHCC-CCA

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare and poorly understood type of primary liver cancer. Using the well-characterised *Mdr2*-KO mice with persistent cholestatic inflammation, **Rosenberg *et al.*** characterised the role of hepatic progenitor cells (HPCs) in carcinogenesis. These mice develop either only HCC (54%), only cHCC-CCA (4%) or both (42%) at 14-18 months. Throughout a series of models and experiments including single-cell RNA sequencing analyses, the authors show that cHCC-CCA tumours, but not HCC, arise from HPCs. Mechanistically, IL6, which derives in part from senescent parenchymal and immune cells, drives the development of cHCC-CCA. This fundamental insight hints at the potential clinical utility of **either inhibiting IL6 trans-signalling or using senolytic agents** for this aggressive type of liver cancer.

Hepatectomy-induced aEVs stimulate neutrophils to secrete regenerative growth factors

Surgical resection of the cancerous tissue represents one of the few curative treatment options for neoplastic liver disease. Such partial hepatectomy (PHx) induces hepatocyte hyperplasia to restore liver function. PHx is associated with bacterial translocation, leading to an immediate immune response involving neutrophils and macrophages, which are indispensable for the priming phase of liver regeneration. **Brandel, Schimek *et al.*** investigated the effect of apoptotic extracellular vesicles (aEVs) on neutrophil function and their role in this later phase of liver regeneration. Blood levels of the apoptosis marker caspase-cleaved cytokeratin-18 (M30) and circulating aEVs were analysed pre-operatively and on the first and fifth post-operative days. Circulating aEVs increased at the first postoperative day and were associated with higher concentrations of M30, which was only observed in patients with complete liver recovery. Classical inflammatory responses such as NETosis, respiratory burst, degranulation, or secretion of pro-inflammatory cytokines could not be observed. Instead, efferocytosing neutrophils released various growth factors including fibroblast growth factor-2 and hepatocyte growth factor. **These data suggest that the clearance of PHx-induced aEVs leads to a population of non-inflammatory, but regenerative neutrophils, which may support human liver regeneration.**



Brandel, Schimek *et al.*, 2022.
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VIRAL HEPATITIS

Entecavir plus Biejia-Ruangan compound reduces the risk of HCC in Chinese patients with CHB

Chronic hepatitis B (CHB) and liver fibrosis are risk factors for hepatocellular carcinoma (HCC). **Ji, Chen, Bi, *et al.*** assessed in a double-blind randomised placebo-controlled trial whether entecavir (ETV) plus Biejia-Ruangan compound (BRC) can reduce the risk of HCC in treatment-naïve Chinese patients with CHB and an Ishak fibrosis score of ≥3 points. BRC is approved by the China Food and Drug Administration as an anti-fibrotic drug. After a 72-week comparison between ETV+BRC and ETV+placebo treatment, participants were eligible to enter an open-label treatment phase and were followed up every 6 months. A total of 1,000 patients were recruited: the median age was 42.0 years, 69.9% were male, 58.3% had positive HBeAg. **In the modified intention-to-treat population, the 7-year cumulative incidence of HCC was 4.7% for ETV+BRC, which was significantly lower than the 9.3% for ETV+placebo.** Multivariable Cox proportional regression analysis, including the treatment allocation as a parameter, also demonstrated that ETV+BRC treatment reduced the incidence of HCC.

CHOLESTATIC DISEASE

Inflammatory type 2 conventional DCs contribute to murine and human cholangitis

In primary sclerosing cholangitis (PSC) the portal tracts display an expanded population of dendritic cells (DCs). **Müller *et al.*** have investigated the role of DCs in orchestrating the immune response to bile duct injury. DCs are sentinel cells residing in portal tracts that are able to recruit other inflammatory cells and act as antigen-presenting cells, effectively activating the adaptive immune system. Distinct DC subsets (type 1, type 2 and plasmocytoid cells) may contribute differently to liver injury in various disease models. The authors studied DC numbers and subtypes in different mouse models of cholangitis and in liver samples from patients with PSC. They found that DCs are expanded in the portal fields of human PSC samples and in mouse models of acute and persistent cholangitis. In both species, the expansion concerned type 2 DCs. These cells acquire monocyte features and inflammatory activity, upregulate inflammatory genes and promote TH17 expression. Thus, **the expansion of this particular population of DCs promotes inflammation and increases antigen presentation.** DCs could potentially represent a future therapeutic target but the specificity of these findings to PSC rather than other inflammatory hepatic diseases needs to be further studied.

LSM by vibration-controlled transient elastography improves outcome prediction in PBC

The prognostic scores currently used for primary biliary cholangitis (PBC) are imperfect predictors of clinical events. **Corpechot *et al.*** from the Global PBC Study Group intended to study the added value of elastography (liver stiffness measurement [LSM]) in a derivation cohort of 2,740 patients and a validation cohort of 568 patients with both vibration-controlled transient elastography and blood tests available. The mean follow-up was 5 years in both cohorts. Clinical outcomes of interest were death, liver transplantation or complications of cirrhosis, which occurred in 10% and 14% of individuals in the two cohorts, respectively. LSM was associated with clinical outcomes, with a 6% increase for any additional kPa and a monotonic increase between 5 and 30 kPa. LSM measurements significantly added to the performance of other prognostic scores (GLOBE, UK-PBC, MELD) or of fibrosis markers (FIB-4 and APRI), with an independent predictive value compared to each predictor. Patients could be separated at baseline into low- (below 8 kPa), medium-, and high-risk groups (above 15 kPa). **The authors further provided heat-maps of the interaction between LSM and Globe score values in order to predict clinical outcomes at 1, 3, 5 and 10 years**, which they made freely available online.

NAFLD

Head-to-head comparison between MEFIB, MAST, and FAST for detecting stage 2 fibrosis or higher among patients with NAFLD

In NASH, the two main diagnostic factors associated with clinical outcomes are significant fibrosis (stage 2 or higher) and at-risk NASH (active steatohepatitis with significant fibrosis). **Kim, Tamaki *et al.*** studied a bicentric population (USA and Japan) of 563 patients with biopsy-proven NAFLD with a prevalence of significant fibrosis of 51%. They compared the diagnostic performance of MEFIB (magnetic resonance elastography [MRE] plus FIB-4), MAST (magnetic resonance imaging [MRI]-aspartate aminotransferase [AST]), and FAST (FibroScan-AST). MEFIB outperformed both MAST and FAST for the diagnosis of significant fibrosis (AUROC of 0.90 for MEFIB). The negative predictive value of MEFIB (90.1%) was significantly higher than either MAST (69.6%) or FAST (71.8%). The positive predictive value was also higher (95%, 83% and 90%, respectively). MEFIB outperformed both MAST and FAST for the diagnosis of at-risk NASH (AUROCs of 0.768, 0.719 and 0.687, respectively). While MRE may not be

widely available for clinical use, **these results are important for future therapeutic trials that aim to reduce the burden of liver biopsy.**

Mitochondrial respiration is decreased in visceral but not subcutaneous adipose tissue in obese individuals with fatty liver disease

Adipose tissue dysfunction is a major pathogenic event in NASH as it determines insulin resistance, overflow of fatty acids to the liver and of soluble inflammatory mediators. **Pafili *et al.*** sought to determine if mitochondrial dysfunction is a feature of adipose tissue dysfunction both in the visceral (VAT) and subcutaneous (SAT) compartments. The authors analysed tissue-specific insulin sensitivity using stable isotope dilution and hyperinsulinemic-normoglycemic clamp tests, as well as mitochondrial respiration, mRNA and protein expression and tissue morphology in biopsies of SAT and VAT from obese humans without NAFL, with NAFL or with NASH (n = 22/group). They documented a 30% reduction in mitochondrial respiration in VAT but not SAT. This was associated with lower insulin sensitivity and a higher protein expression of TNF-alpha. The authors measured levels of oxidative stress and anti-oxidant defences in the two adipose tissue compartments. A salient difference between steatosis and steatohepatitis was lower oxidative phosphorylation complex IV activity and higher mRNA expression of CD68, a macrophage marker, in the VAT of patients with steatohepatitis. In fact, **mitochondrial respiration in VAT associated positively with adipose tissue insulin sensitivity, but negatively with inflammation of VAT**. These data indicate an important role of compartment-specific AT energy metabolism on insulin resistance and steatosis in the context of obesity.

CIRRHOSIS

Non-invasive tests for clinically significant portal hypertension after HCV-cure – pooled analysis and validation

In this study, **Semmler, Lens *et al.*** aimed to determine the diagnostic/prognostic utility of non-invasive tests (NITs) for clinically significant portal hypertension (CSPH) in patients with advanced chronic liver disease (ACLD) after HCV cure. Among patients with ACLD, the pre- and post-treatment prevalence of CSPH was 80% and 54%, respectively. The correlation between LSM and hepatic venous pressure gradient (HVPG) increased from pre- to post-treatment (r = 0.45 *vs.* 0.60), while that of platelet count (PLT) and HVPG remained unchanged. Combining post-treatment-LSM/-PLT yielded a high diagnostic accuracy for post-treatment CSPH (AUC 0.884; 95% CI 0.843-0.926). Post-treatment-LSM <12 kPa & PLT >150 G/L excluded CSPH (sensitivity: 99.2%), while LSM ≥25 kPa was highly specific for CSPH (93.6%). The derived LSM/PLT-criteria were then validated against the direct endpoint decompensation in a validation cohort (n = 755). The 3-year decompensation risk was 0% in the 42.5% of patients who met the LSM <12 kPa & PLT >150 G/L criteria. In patients with post-treatment LSM ≥25 kPa, 3-year decompensation risk was 9.6%, while it was 1.3% in those meeting none of the above criteria. Thus, **NITs can estimate the probability of CSPH after HCV cure and predict clinical outcomes.** Patients with an LSM <12 kPa & PLT >150 G/L may be discharged from portal hypertension surveillance (NITs and/or endoscopy), if no co-factors are present.

Plasma ammonia levels predict hospitalisation with liver-related complications andmortality in clinically stable outpatients with cirrhosis

In this study, **Tranah, Ballester, Carbonell-Asins *et al.*** tested the hypothesis that severity of hyperammonaemia is a risk factor for liver-related complications in clinically stable outpatients with cirrhosis. Data from 754 clinically stable outpatients with cirrhosis from 3 independent liver units were collected. Baseline ammonia levels were corrected to the upper limit of normal for the reference laboratory (AMM-ULN). The primary endpoint was hospitalisation with liver-related complications (a composite endpoint of bacterial infection, variceal bleeding, overt hepatic encephalopathy, or new onset or worsening of ascites). Multivariable competing risk frailty analysis and fast unified random forests were performed in order to predict complications and mortality. External validation was carried out using prospective data from 130 patients with cirrhosis in an independent tertiary liver centre. Overall, 260 patients were hospitalised with liver-related complications. On multivariable analysis, AMM-ULN was an independent predictor of both liver-related complications and mortality. AUROC of AMM-ULN was 77.9% for 1-year complications, higher than traditional severity scores. Statistical differences in survival were found between high and low levels of AMM-ULN both for complications and mortality (p <0.001) using 1.4 as the optimal cut-off from the training set. AMM-ULN remained a key variable for the prediction of complications within the random forests model in the derivation cohort and upon external validation. Thus, **ammonia is an independent predictor of hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis,** performing better than traditional prognostic scores in predicting complications.

Validation of baveno VII criteria for recompensation in entecavir-treated hepatitis B patients with decompensated cirrhosis

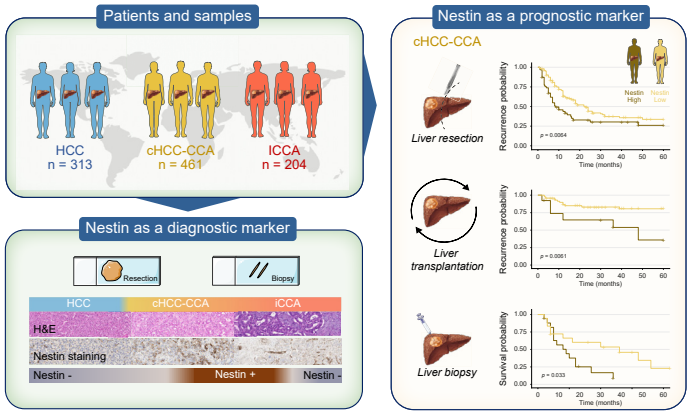
In this study, **Wang, Zhao, Deng *et al.*** aimed to explore the criteria to define a stable improvement of liver function tests as required for the Baveno VII definition of recompensation in entecavir-treated patients with CHB and decompensated cirrhosis. This multicentre prospective study enrolled decompensated patients with ascites and provided entecavir for 120 weeks. The patients were followed up for clinical events, viral and biochemical tests, and ultrasonography every 6 months. Multivariate regression models were used in order to identify the predictors of recompensation. Finally, the criteria for stable improvement of liver function tests were explored. Among the 320 recruited patients, 283 completed the 120-week study, with 261/283 (92.2%) achieving HBV DNA levels <20 IU/ml and 171/283 (60.4%) achieving resolution of ascites, encephalopathy, and absence of recurrent variceal haemorrhage for at least 12 months. MELD <10 and/or liver function tests within Child-Pugh class A (albumin >35 g/L & international normalised ratio <1.50 & total bilirubin <34 μmol/L) were identified as the criteria for stable improvement of liver function tests. Accordingly, 56.2% (159/283) of the patients fulfilled the BAVENO VII definition of recompensation with a stable improvement of liver function tests as defined by the current study. **These criteria to define a stable improvement of liver function tests required by the Baveno VII definition of**

recompensation can be applied in patients with CHB and decompensated cirrhosis on antiviral therapy. However, these criteria warrant further validation in patients with cirrhosis of other aetiologies.

HEPATIC AND BILIARY CANCER

Nestin, a new biomarker for cHCC-CCA

cHCC-CCA is an uncommon type of primary liver cancer which shows a dual phenotype and entails significant challenges in terms of pathogenesis, diagnosis, treatment and prognosis. Nestin, an intermediate filament expressed by liver progenitor cells, may enable the transdifferentiation of neoplastic cells. **Calderaro *et al.*** have studied the potential diagnostic and prognostic value of Nestin immunohistochemistry in a large series of patients (461 cHCC-CCA, 368 HCC, 221 intrahepatic CCA) from 32 different European, American and Asian centres. In samples from resected tumours, **Nestin expression (usually cytoplasmic) was detected in 75% of HCC-CCA, 7% of HCCs and 59% of iCCAs.** Among HCC-CCAs, Nestin expression was more often observed in equivocal or intermediate cases. For the distinction between HCC and cHCC-CCA, Nestin showed an AUC of 0.85, a sensitivity of 0.75 and a specificity of 0.93. Similar data were observed when biopsy samples were studied. In addition, **tumours with high (>30% neoplastic cells) Nestin expression showed shorter disease-free and overall survival after resection and transplantation**. Therefore, Nestin immunohistochemistry may help in the diagnosis and prognostication of cHCC-CCA.



Calderaro *et al.*, 2022.
Nestin, a new biomarker for cHCC-CCA.

LIVER TRANSPLANTATION

Low utilisation of adult-to-adult LDLT in western countries despite excellent outcomes

Adult-to-adult living donor liver transplantation (LDLT) offers an opportunity to decrease the liver transplant waitlist and reduce waitlist mortality. **Ivanics *et al.*** retrospectively compared donor and recipient characteristics and post-transplant outcomes after LDLT in the US, UK, and Canada. A total of 2,954 LDLTs were performed (US: n = 2,328; Canada: n = 529; UK: n = 97). Canada has maintained the highest proportion of LDLT utilisation over time (proportion of LDLT 2008: US: 3.3%; Canada: 19.5%; UK: 1.7%; p <0.001; 2018: US: 5.0%; Canada: 13.6%; UK: 0.4%; p <0.001). The 1-, 5-, and 10-year patient survival was 92.6%, 82.8%, and 70.0% in the US *vs.* 96.1%, 89.9%, and 82.2% in Canada *vs.* 91.4%, 85.4%, and 66.7% in the UK. After adjustment for characteristics of donors, recipients, transplant year, and treating transplant centre as a random effect, all countries had a non-statistically significantly different mortality hazard post-LDLT. **The use of LDLT has remained low in the US, UK and Canada**, despite long-term survival being excellent. Continued efforts to increase LDLT in these countries may be warranted due to the growing waitlist and differences in allocation that may disadvantage patients currently awaiting LT.

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