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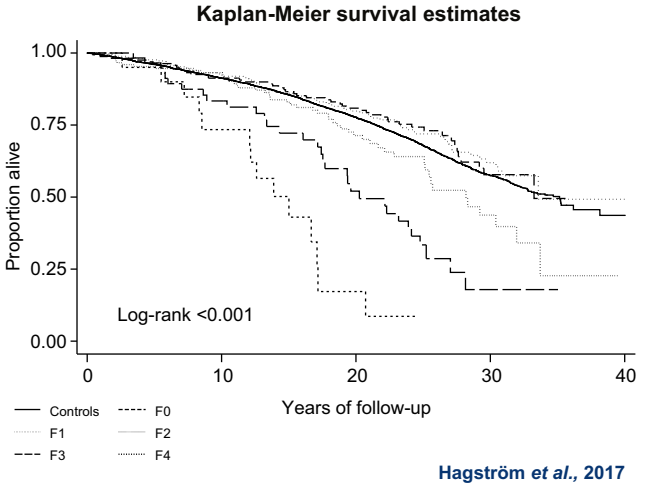
From the Editor's desk...

Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucman-Rossi, Rajiv Jalan

SELECTION OF THE MONTH

Fibrosis stage predicts mortality in patients with non-alcoholic fatty liver disease (NAFLD)

NAFLD is a growing cause of chronic liver disease worldwide. Identifying patients with NAFLD who are at an increased risk of mortality and liver-specific morbidity is crucial. In this issue, Hagström *et al.* conducted a retrospective cohort study of 646 biopsy-proven patients with NAFLD and matched controls. During a follow-up of 20 years, 12% of patients with NAFLD developed severe liver disease (only 2.2% in controls). **The risk of severe liver disease increased per stage of fibrosis** (HR ranging from 1.9 in F0 to 104.9 in F4). **Similar results were seen for overall mortality**. **Importantly, the presence of NASH did not change these estimates significantly**. This important study strongly suggests that all patients with NAFLD should undergo non-invasive assessment of fibrosis stage. Preventive and therapeutic manoeuvers aimed at attenuating the progression of liver fibrosis in patients with NAFLD should be implemented.

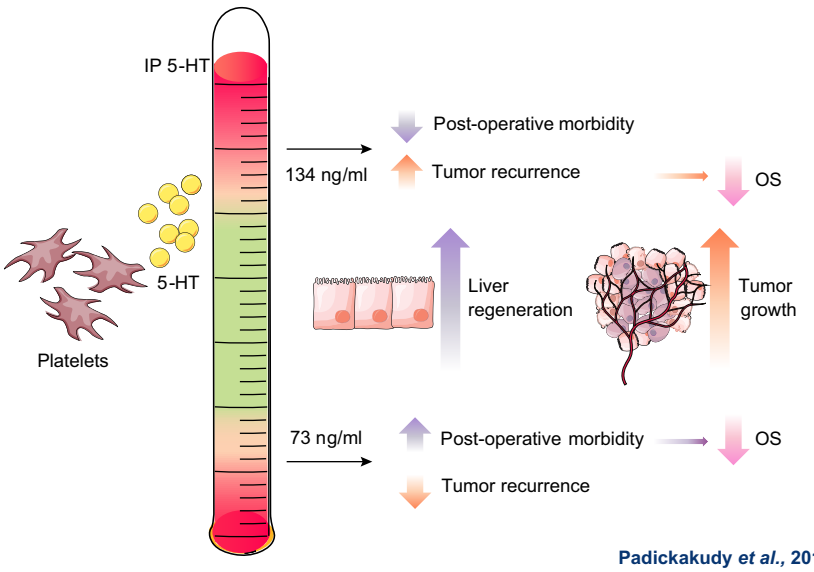


Hagström *et al.*, 2017
Fibrosis stage predicts mortality in patients with NAFLD

LIVER INJURY

Sterile inflammation in hepatic ischaemia-reperfusion injury (IRI)

Hepatic IRI, which is characterised by local inflammation and hepatocellular death, represents a risk factor for acute and chronic rejection in liver transplantation. To gain new insights into mechanisms underlying hepatic IRI, Nakamura *et al.* performed elegant translational research in human liver transplants and primary murine macrophage cultures. They reveal that, **in macrophages, a signalling axis involving heme oxygenase 1, NAD-dependent protein deacetylase sirtuin-1, and p53 plays a crucial role in the development of hepatic sterile inflammation.** This may lead to novel therapeutic approaches in patients receiving a liver transplant.



Padickakudy *et al.*, 2017
Serotonin: friend of foe?

LIVER REGENERATION

Serotonin: friend or foe?

Besides its critical role during liver regeneration, serotonin (5-hydroxytryptamine, 5-HT) is known to be a mitogenic factor in several cancers. Padickakudy *et al.* evaluated whether intra-platelet 5-HT was associated with oncological outcome after liver resection and evaluated its ability to serve as a therapeutic target to promote liver regeneration. **Their results show for the first time that intra-platelet 5-HT is associated with early disease recurrence after liver resection in**

humans. Thus, pharmacological intervention aimed to promote 5-HT-mediated liver regeneration should be considered with caution. A careful definition of indications and timing is needed to promote liver regeneration without inducing deleterious effects.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD increases the risk of chronic kidney disease (CKD)

In another article in this issue of the *Journal*, Sinn *et al.* studied the association between NAFLD and CKD a frequent co-morbidity in patients with metabolic syndrome. The authors performed a retrospective cohort study of 41,430 adult men and women without CKD at baseline, who underwent repeated health check-up examinations. During a median follow-up of 4.15 years, they identified 691 incident CKD cases. **The risk of CKD increased progressively with increased NAFLD severity**. The multivariable-adjusted hazard ratios for CKD of participants with a NAFLD Fibrosis Score (NFS) ≥−1.4 was 1.58, suggesting that the existence of advanced stages of NAFLD predisposes patients to CKD. This clinically relevant study suggests that **NAFLD may adversely affect renal function** and close attention should be paid to patients regarding the risk of CKD.

HEPATITIS C VIRUS (HCV) INFECTION

Impact of coffee consumption on all-cause mortality in HIV-HCV coinfection, the long-term sequelae of the Irish single source HCV outbreak, clinical outcomes after delisting from the liver transplant waiting list, the negative liaison between monocytes and natural killer (NK) cells

Polyphenols and caffeine in coffee have several well described hepato-protective properties, but coffee consumption has also been associated with a 14% risk reduction in all-cause mortality in the general population. The study by Carrieri *et al.* is the first to investigate the relationship between coffee consumption and all-cause mortality risk in patients co-infected with HIV and HCV, by using data from a large five-year longitudinal follow-up study in the ANRS CO13-HEPAVIH French national cohort. **Drinking three or more cups of coffee per day halved all-cause mortality risk in patients co-infected with HIV-HCV, and this association remained significant even after adjustment for relevant co-factors** like severe liver fibrosis, and smoking status. Further research will help to elucidate the causal mechanisms of this relationship; but in the meantime, certain at-risk populations like patients co-infected with HIV-HCV should be aware of these results to adapt their coffee drinking behaviour individually.

Between 1977–1979, over 800 women were infected in Ireland with HCV genotype 1b via contaminated anti-D immunoglobulin from a single donor. Initially, after 17 years, a quite benign course with a low rate of cirrhosis development (2%) was reported in this group, but almost 20 years have elapsed since then. **Now, approximately 36 years after infection, Garvey *et al.* demonstrated a substantial increase in cirrhosis, hepatocellular carcinoma (HCC) and liver-related death, which doubled in the last five years of follow-up**. Although the overall progression rate remains relatively slow in this cohort, nearly one in five patients has now reached a disease state that is probably irreversible with treatment, and harbours a significant life-time risk of HCC development. This happened despite regular medical supervision, highlighting once more the limited effect of our previous interferon-based treatment strategies in altering the population-based HCV-associated morbidity and mortality – a finding that will hopefully change when follow-up data is collected after the introduction of direct-acting antivirals.

Treating patients with HCV-induced decompensated cirrhosis while on the liver transplant waiting list offers the chance for delisting because of improvements in liver function. However, the long-term efficiency of this strategy in terms of clinical outcomes remains largely unclear. Pascasio *et al.* further expanded on this important issue by following the course of patients treated on the liver transplant waiting list. **They confirmed that approximately a quarter of the treated patients with decompensated disease presented a significant improvement in liver function that allowed delisting, and 80% of them remained stable after a median follow-up of 88 weeks**. These results are of great importance as they imply that delisting because of improved liver function is a safe strategy that can save organs for those with the highest transplantation need. However, close monitoring of the delisted patients is mandatory given the significant risk of HCC development in this particular group.

Coordination and collaboration between immune cells are essential to fight pathogens. The interplay between NK cells and monocytes represents a first-line of protection from pathogens and takes place during the early stages of innate immune responses against them. The authors of the current study have previously shown that peripheral blood NK cells from patients infected with HCV fail to upregulate TRAIL expression after exposure to HCV, a process accompanied by impaired cytolytic potential and Extracellular Signal-Related Kinase 1 (ERK) activity. Now, **Mele *et al.* demonstrated that during HCV infection monocytes secrete interleukin (IL)-18 and IL-36 inhibitory proteins, reducing NK cell activation, and consequently inhibiting their ability to express TRAIL and kill target cells**. This important study confirms the essential role of monocytes as negative regulators of NK cell activation in HCV infection, and of cellular cross-talk in NK cell activation in general.

CIRRHOSIS

Identification of factors associated with development of acute on chronic liver failure (ACLF) in outpatients, declining mortality of patients with cirrhosis admitted to the intensive care units

Hospitalised patients with cirrhosis who develop ACLF have high mortality rates.