Editorial

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Hepatic and cardiac hemodynamics and systemic inflammation in cirrhosis: It takes three to tango

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In this issue, Turco *et al.*[1] present a single center study wherein they comprehensively assessed hepatic and cardiac haemodynamics and C-reactive protein (CRP) to analyse their interrelationship and to explore their prognostic relevance, in a cohort of cirrhotic patients. Cirrhosis has for many decades been classified into two main prognostic stages: compensated and decompensated stage. Decompensation is characterized by the presence of clinically evident decompensating events, with ascites and complications, such as spontaneous bacterial peritonitis, hepatorenal syndrome and variceal haemorrhage being the most frequent events, while hepatic encephalopathy and jaundice occur less frequently.[2] Development of decompensated cirrhosis is a milestone, as median survival is significantly lower in decompensated patients, especially in patients with more than one decompensating event, irrespective of the type of event.[2]

Portal hypertension is responsible for the majority of decompensating events. Hepatic venous pressure gradient (HVPG) values >5 mmHg indicate postsinusoidal portal hypertension and the relationship between HVPG and decompensating events, like variceal haemorrhage has long been recognized.[3] The term clinically significant portal hypertension (CSPH) was defined as a hepatic venous pressure gradient >10 mmHg in the most recent Baveno consensus workshop.[4] Compensated cirrhosis was further divided in the recent AASLD guideline into those with mild PH (HVPG >5 but <10 mmHg); those with CSPH without gastroesophageal varices (GEV) and those with CSPH with GEV.[5] This substaging is prognostically important and the therapeutic approach is different. However, in clinical practice, invasive measurement of HVPG, although a simple technique, is not available in every center. Liver stiffness by transient elastography, which is widely available nowadays, can be used to identify compensated advanced chronic liver disease,[4] and in combination with platelet count to identify up to 40% of patients with compensated cirrhosis, who can safely avoid screening endoscopy for gastroesophageal varices.[6]

The 'peripheral arterial vasodilation hypothesis' was proposed in 1988 by Schrier *et al.*[7] and is still accepted nowadays.[8] Peripheral and splanchnic arterial vasodilation occurs as early as the compensated stage and is progressive in the decompensated stage and in hepatorenal syndrome, where it is accompanied by activation of vasoconstrictor systems, such as the renin-angiotensin-aldosterone system, the vasopressin system and the sympathetic nervous system. Renal sodium and water retention occurs, because of decreased arterial vascular filling. Increased cardiac output (CO) is a common feature of cirrhosis.[7] Cardiac dysfunction in advanced cirrhosis may contribute to the decreased effective circulating volume, especially when the heart fails to compensate for the arterial vasodilation.[9] This may lead to a systolic dysfunction as reflected by a lower CO, which may precipitate development of hepatorenal syndrome and early death.

Recently, it has become clear that bacterial translocation, as well as a storm of pro-inflammatory cytokines, and reactive oxygen and nitrogen species, in response to pathogen-associated molecular patterns, appear to be the primary event in the pathogenesis of decompensated liver cirrhosis and associated liver failure.[10,11] Therefore the syndrome of decompensated cirrhosis is not solely explained by the peripheral arterial vasodilation hypothesis, but is a complex interplay between inflammation and vasodilation, with systemic inflammation being the primary event in decompensated cirrhosis and associated organ failure (Fig. 1).[11,12] The concept of acute on chronic liver failure (ACLF) has recently been introduced with clear diagnostic criteria.[13] ACLF is a syndrome distinct from 'mere' decompensated cirrhosis, as it is characterized by acute decompensation, the presence of organ failure and associated with a very high short-term mortality rate. Remarkably, previous episodes of acute decompensation were absent in 23% of patients with ACLF, which did not confirm the generally accepted paradigm that organ failure in cirrhosis is a terminal event that develops at the latest phase in the course of cirrhosis.[13] Inflammatory markers, white blood cell count (WBC) and CRP were significantly higher in patients with ACLF than the group without ACLF, even when patients with infection were excluded from the analysis. Moreover, mortality in ACLF was related to

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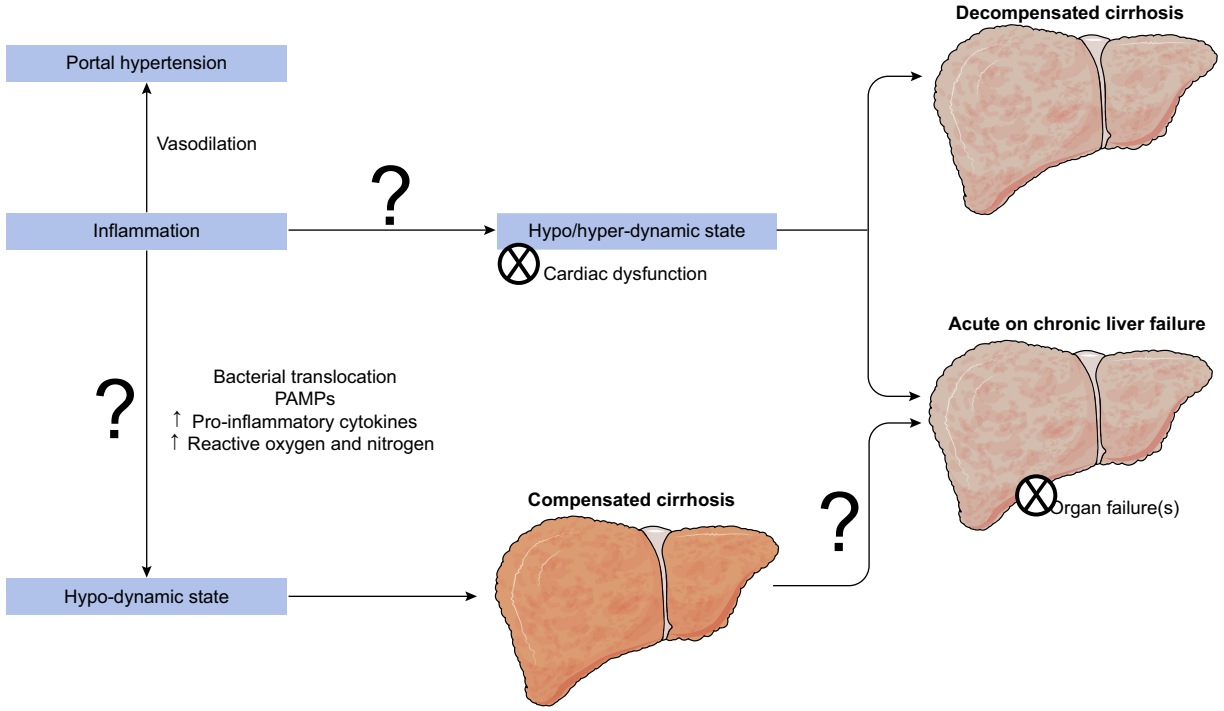

Fig. 1. The hypothesis of the roles of inflammation, portal hypertension and cardiodynamic state in the pathogenesis of compensated and decompensated cirrhosis, and acute on chronic liver failure. Question marks represent areas of uncertainty which need further exploration. PAMPs, pathogen-associated molecular patterns.

WBC.[13] Systemic inflammation, which is already present in acute decompensation of cirrhosis, appears to be the primary driver of ACLF and the course of systemic inflammation is associated with the course of ACLF.[12]

Turco *et al.*[1] integrate the acquired knowledge in a comprehensive exploratory study of hepatic and systemic hemodynamics, and inflammation by CRP, in a cohort of 238 patients among the different substages of cirrhosis, assessing their interrelationship and prognostic relevance. The authors adhered to the classical stages of compensated and decompensated cirrhosis, although these stages were subdivided into five substages, according to the recent guidelines, dependent on the presence and severity of portal hypertension, presence of varices and decompensation. The novelty of the study was that data were analysed using different cardiodynamic states defined as hyperdynamic, normodynamic and hypodynamic. Thorough hepatic and cardiac hemodynamic investigations were performed in patients and CRP was measured as a marker of inflammation. The main findings are that CRP and a relatively hypo- or hyperdynamic circulatory state are, next to known prognostic factors, predictive of the development of decompensation in compensated cirrhosis and of death or liver transplantation in decompensated cirrhosis. This study contributes to the understanding of the heterogeneity of cirrhosis and the roles of hepatic and cardiocirculatory factors and inflammation at the different stages of cirrhosis, as well as their prognostic relevance.

Many eligibility criteria were applied, significantly impacting on the number of patients included and the generalisability of the results. For example, compensated patients who were treated with non-selective beta-blockers and patients with ACLF or active infections were excluded from the study. The effect of disease-modifying treatments, such as use of direct-acting antivirals, or liver transplantation were adequately accounted for in the analysis. However, given the number of events per variable in the study, there is still a risk that the proposed model could over-fit the data, as rightly discussed by the authors. Moreover, calibration plots showed some under/overestimation of the probability of event at the extreme, especially for compensated cirrhosis. Therefore, studies are needed to externally validate the proposed prognostic models. The authors explain that the results of their study do not provide insight to the sequential interaction between bacterial translocation, inflammation and hemodynamic alterations at different stages of cirrhosis and that this should be further explored. Indeed, there is a need for better understanding of the drivers of the different stages of cirrhosis, in order to identify patients at higher risk of poor outcome or to predict the response to a given therapy and move towards individualizing patient care in cirrhosis using therapies directly targeting the driver.

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Conflict of interest

MC and RP have nothing to disclose; FB Ferring Pharmaceuticals A/S, consultant.

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Authors' contributions

MC wrote the manuscript, RP and FB revised the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.02.007.

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