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Review article

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Interaction of inflammation and portal hypertension in cirrhosis progression

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Abstract

Decompensated cirrhosis describes an advanced clinical stage with clinical complications, such as ascites, variceal bleeding or hepatic encephalopathy, associated with considerable mortality. Portal hypertension is the main risk factor for developing decompensation in patients with compensated cirrhosis, whereas systemic inflammation is the key driving force for organ failure, that is, for acute-on-chronic liver failure in later stages of cirrhosis. As portal hypertension and systemic inflammation coexist in patients with cirrhosis, an improved understanding of their interaction and dynamic role in distinct stages of cirrhosis is an important step forward towards the development of urgently needed therapeutic interventions. Based on emerging evidence from clinical and translational studies, a novel concept of different predominant pathomechanisms of decompensated cirrhosis is presented, which includes portal hypertension-predominant, systemic inflammmation-predominant and mixed portal hypertension–systemic inflammation phenotypes. A comprehensive set of biomarkers and surrogates of portal hypertension and systemic inflammation might assist clinicians in identifying a predominance of one over the other cirrhosis phenotype. As survival rates of patients with decompensated cirrhosis have remained detrimental without liver transplantation over the past decades, future studies should build on this knowledge to develop effective portal hypertension and systemic inflammation-directed therapies for this underserved population.

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Key points

- Cirrhosis decompensation is defined by the development of ascites, variceal bleeding, hepatic encephalopathy, or jaundice and is linked to a considerable increase in the risk for mortality.
- In compensated cirrhosis, the magnitude of portal hypertension is the key determinant of the risk for developing decompensation.
- Inflammation, and particularly the severity of systemic inflammation, is particularly pronounced in advanced stages of cirrhosis, that is, in patients with further decompensated cirrhosis or acute-on-chronic liver failure.
- We propose a concept of 'pathophysiological' phenotypes of decompensated cirrhosis by predominance of portal hypertension, systemic inflammation, or even mixed systemic inflammation and portal hypertension.
- The evidence for the interaction of portal hypertension and systemic inflammation in the key pathomechanism driving cirrhosis decompensation and end-organ dysfunction or failure is presented.
- A summary of promising therapeutic approaches targeting portal hypertension and systemic inflammation for which translational or clinical studies have been or are being conducted is presented.

We dedicate this article, which provides an integrated view on the pathogenesis of cirrhosis complications, to the memory of Professor Jaume Bosch – a great teacher, mentor, colleague and dear friend to all of us, whose pioneering efforts in developing new concepts and therapies in the field of portal hypertension are immeasurable. Jaume was more than a brilliant clinician–scientist; he was a source of inspiration, wisdom, generosity and warmth for everyone privileged to work with him. His passion for advancing knowledge in the field of cirrhosis was matched only by his zest for life and love for his friends and family. Many of us owe our careers – and our love for hepatology – to his guidance and example. This article stands as a small tribute to a remarkable man whose legacy will continue to shape and inspire us.

Introduction

The natural history of cirrhosis is characterized by a long asymptomatic course known as compensated cirrhosis[1]. Decompensated cirrhosis describes an advanced clinical stage at which complications related to portal hypertension, such as ascites, variceal bleeding and hepatic encephalopathy, have occurred. Furthermore, each stage can be further divided into substages of cirrhosis, each of which has different prognostic implications[2] (Table 1). Instead, an alternative classification has been proposed based on the clinical urgency of events (and the need for hospitalization) with discrimination between acute decompensation[3,4] and non-acute decompensation (NAD)[5,6]. Even though the molecular pathomechanisms involved in decompensation and cirrhosis progression remain incompletely understood, portal hypertension has been shown to be a prerequisite for the development of decompensation[7,8]. In the decompensated phase, systemic inflammation drives the course of the disease, with a pronounced pro-inflammatory cytokine profile being observed in patients with acute-on-chronic liver failure (ACLF)[4,9–11]. This traditional, rigid concept of dissociating portal hypertension and systemic inflammation has been challenged by past and current evidence[12–14] on the dynamic interplay of both central pathomechanisms across the spectrum of cirrhosis, that is, from compensation to decompensation towards ACLF and liver-related death (Fig. 1). It has become evident that portal hypertension[7,8,15–18] and systemic inflammation[4,10,13,19,20] as drivers for complications and decompensating events in cirrhosis are not mutually exclusive pathomechanisms but in fact occur – albeit to a different extent – simultaneously in most patients with cirrhosis. With improved knowledge of molecular surrogates of portal hypertension and systemic inflammation, a novel pathomechanistic concept is presented in this Review encompassing a portal hypertension-predominant phenotype, a systemic inflammation-predominant phenotype and, importantly, a mixed phenotype of cirrhosis (Table 2). Moreover, a growing understanding of systemic inflammation has led to novel insights into cirrhosis-associated immune dysfunction (CAID)[21] and organ immunopathology that affect essential cellular and metabolic homeostatic pathways and predispose patients to infection[22–24] and end-organ failure[9,25]. We provide an in-depth review of the mechanistic, translational and clinical studies on which we based the development of this novel concept about drivers of disease progression in patients with decompensated cirrhosis. Improved knowledge of the molecular link between portal hypertension and inflammation in the liver (that is, hepatic inflammation) and extrahepatic sites will facilitate the development of novel pathophysiology-oriented therapeutic strategies for patients with decompensated cirrhosis and for the prevention or treatment of ACLF. This timely Review aims to summarize the evidence for the dynamic interplay between portal hypertension and systemic inflammation in mediating organ dysfunction across the whole spectrum of cirrhosis and to put it into a clinical perspective.

Pathomechanistic concepts of portal hypertension

Decompensation was traditionally regarded as the consequence of progressive portal hypertension[7,8]. Portal hypertension initially arises due to increased intrahepatic vascular resistance (IHVR) caused by architectural distortion and sinusoidal vasoconstriction. Increased IHVR leads to portal venous congestion and subsequently to splanchnic vasodilation, central hypovolaemia and activation of compensatory mechanisms – ultimately further increasing splanchnic blood flow and, thereby, portal venous blood inflow[26]. Under homeostatic conditions, hepatic stellate cell (HSC) quiescence is regulated by liver sinusoidal endothelial cells (LSECs) through vascular endothelial growth factor (VEGF)-stimulated nitric oxide-dependent and nitric oxide-independent pathways[27,28]. During liver injury, LSECs become dysfunctional and undergo capillarization (loss of fenestration and build-up of a basement membrane), providing HSCs with pro-inflammatory signals. Sinusoidal capillarization and HSC transdifferentiation to myofibroblasts impair metabolic exchange between the sinusoidal blood and the perihepatocellular interstitium as well as oxygenation, triggering further HSC activation by inducing hypoxia-inducible factor 1α expression[29] and the synthesis of Hedgehog molecules[30], together with other profibrotic factors (such as transforming growth factor-β (TGFβ) and platelet-derived growth factor (PDGF))[28] in in vitro studies. In a vicious cycle, HSCs also influence the phenotype of LSECs by expressing pro-angiogenic mediators (that is, angiopoietin and VEGF) and increasing Hedgehog signalling in LSECs, further driving fibrosis[28,29]. LSEC dysfunction is further aggravated by an imbalance

Table 1 | Definition of stages and concepts in cirrhosis

Concept	Definition	Particularities	Prognostic implications
Compensated cirrhosis	Cirrhosis without current or previous decompensation as defined by absence of clinically overt ascites, hepatic encephalopathy or variceal bleeding	Nowadays, it is mainly diagnosed non-invasively via elastography (liver stiffness measurement) and included in broader entity of cACLD	Median survival >10 years[153]
First decompensation	Cirrhosis with clinical decompensation (ascites, variceal bleeding, hepatic encephalopathy)	Longitudinal view of the disease	5-year mortality rate: 20–30%; 5-year incidence of further decompensation: 45–48%[153]
Further decompensation	Patient with decompensated cirrhosis who has either developed a second decompensating event (ascites, hepatic encephalopathy, variceal bleeding) and/or jaundice, or had recurrent variceal bleeding or hepatic encephalopathy, recurrent ascites or complications of ascites (SBP, HRS-AKI)	First defined by Baveno VII consensus	5-year cumulative incidence of death or liver transplantation after further decompensation: 52%[227]
Recompensation	Patients with previous decompensation who had achieved all the following criteria: removal or suppression or cure of the primary aetiology of cirrhosis, resolution of ascites and hepatic encephalopathy (both off treatment), and absence of variceal haemorrhage for ≥1 year, stable improvement of liver function tests (albumin, INR, bilirubin)	Novel concept introduced by Baveno VII consensus based on expert opinion Aetiological cure and/or treatment of the underlying liver disease is essential, and a certain degree of regression of fibrosis is expected Resolution of clinically significant portal hypertension and removal of β-blockers is not required	Data on long-term outcomes and survival after recompensation are limited (ALD recompensation[177]; no liver-related mortality for 3 years; *n*=37) (hepatitis B virus recompensation[172]; *n*=265; 89.3% 5-year TFS)
Acute decompensation	Patients who are hospitalized with first or recurrent grade 2 or 3 ascites within 2 weeks; first or recurrent acute hepatic encephalopathy; acute gastrointestinal bleeding; bacterial infections; progressive jaundice	Starts with and requires hospitalization; independent from a prior course of the disease; inclusion criteria of the CANONIC[9] and PREDICT[4] study	28-day mortality rate: 5–7%; 1-year mortality: 20–30%[4,9]
Non-acute decompensation	Patients who have slow ascites formation, low-grade hepatic encephalopathy managed in an outpatient setting or (slowly) progressive jaundice	Patients in outpatient setting and do not need hospitalization; independent from a prior course of the disease	1-year mortality rate: 25–30%[6]
SDC	Patients who developed acute decompensation but are not again hospitalized for liver-related complications during 90 days of follow-up	SDC cannot be defined at the moment of acute decompensation or admission (but only after 90 days without admission); low intensity of systemic inflammation	1-year mortality rate: 10%[4,9]
UDC	Patients who develop acute decompensation and require re-admission for repeat acute decompensation but not ACLF during 90 days of follow-up	UDC cannot be defined at the moment of acute decompensation or admission (but only after re-admission within 90 days); higher intensity of systemic inflammation than SDC, but lower than pre-ACLF	1-year mortality rate: 36%[4,9]
Pre-ACLF	Patients who develop acute decompensation and then develop ACLF during 90 days follow-up	Pre-ACLF cannot be defined at the moment of acute decompensation or admission (but only after ACLD development within 90 days); higher intensity of systemic inflammation than SDC and UDC	1-year mortality rate: 67%[4,9]
ACLF	Patients with acute decompensation and organ failure	ACLF is defined by EF CLIF criteria based on dysfunction or failure of liver or extrahepatic organs	28-day mortality rate: 22–77%, depending on ACLF grade[9]

ACLF, acute-on-chronic liver failure; ALD, alcohol-associated liver disease; cACLD, compensated advanced chronic liver disease; EF CLIF, European Foundation for the Study of Chronic Liver Failure; HRS-AKI, hepatorenal syndrome-type acute kidney injury; INR, international normalized ratio; SBP, spontaneous bacterial peritonitis; SDC, stable decompensated cirrhosis; TFS, transplant-free survival; UDC, unstable decompensated cirrhosis.

between decreased endogenous vasodilators and increased vasoconstrictors. The bioavailability of the vasodilator nitric oxide in LSECs is markedly decreased owing to low production (decreased endothelial nitric oxide synthase (eNOS) expression[31] and enzymatic activity[32]) and high scavenging due to elevated amounts of reactive oxygen species (ROS) in the cirrhotic rat liver[33]. On the other hand, there is an increase in vasoconstrictor molecules in LSECs (upregulation of endothelin and cyclooxygenase 1 (COX1)–thromboxane synthase pathways leading to increased endothelin 1 (ET1) (ref. 34) and thromboxane A2 (ref. 35), respectively) in the cirrhotic rat liver.

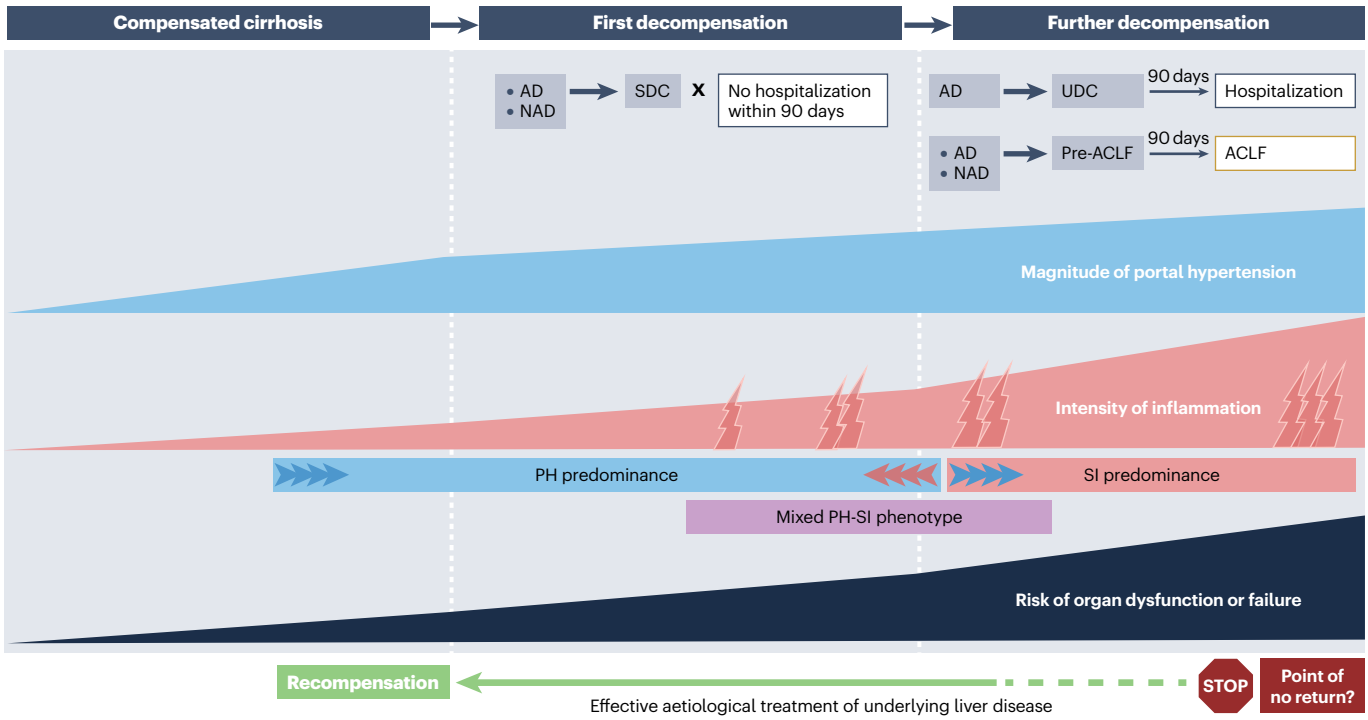


Fig. 1 | Clinico-pathophysiological correlates in patients with different cirrhosis phenotypes. Clinical staging traditionally defines decompensated cirrhosis as first decompensation and further decompensation. Patients with acute decompensation (AD) might take different clinical courses: stable decompensated cirrhosis (SDC) or unstable decompensated cirrhosis (UDC), initially defined based on their subsequent (90 days) risk of hospitalization and, mechanistically, their systemic inflammatory and portal hypertension (PH) profiles are distinct. Patients with AD develop organ failures and progress to acute-on-chronic liver failure (ACLF) with pronounced systemic inflammation (SI). A proportion of patients with decompensated cirrhosis might recover after an aetiological cure and behave clinically similarly to patients with compensated cirrhosis, a condition defined as recompensation. When patients with cirrhosis progress from compensated cirrhosis towards non-acute decompensation (NAD), AD and/or ACLF, the severity of PH tends to plateau while there is a progressive SI severity linked to increased risk of organ dysfunction or failure.

Upon injury, HSCs are activated and adopt a profibrogenic phenotype via multiple pathways (for example, Rho-kinase[36] or cannabinoid receptors[37]), upregulating the synthesis of extracellular matrix proteins that sustains tissue remodelling and progressive fibrosis in human liver. Contraction of HSCs contributes to the dynamic part of hepatic resistance and is mainly regulated by myosin regulatory light chain phosphatase, which is inhibited by the RhoA–Rho-kinase pathway[36]. These vascular-fibrotic events distort the normal architecture of the liver and generate a pro-contractile, pro-thrombotic and pro-inflammatory sinusoidal milieu, which further increases IHVR. Secondary to increased IHVR, abnormalities in the splanchnic vascular bed contribute to and aggravate portal hypertension by further increasing portal flow[38]. VEGF-driven angiogenesis and the increased release of nitric oxide, mainly derived from eNOS in the human splanchnic microcirculation, contribute to the progressive vasodilation of mesenteric arterioles[39]. In addition, endocannabinoids[40] and carbon monoxide[41] were demonstrated in rats to exert vasodilatory effects in cirrhosis. Moreover, the formation of portal-systemic collaterals, including oesophageal and gastric varices, predisposes patients to severe gastrointestinal bleeding[42,43]. In parallel to the increased splanchnic vasodilation mainly mediated by nitric oxide in human, the vasoconstriction response in the mesenteric arteries is also impaired (for example, a defective RhoA–Rho-kinase pathway[44,45], desensitization of angiotensin II receptor type 1 and activation of the angiotensin-converting enzyme 2–MAS receptor axis in the splanchnic vessels[46,47]), suggesting that splanchnic vascular dysfunction is mainly functional and not structural and, therefore, presumably reversible, for example, when local inflammation recedes.

Progressive portal hypertension-mediated vascular changes, including splanchnic blood pooling, lead to a relative systemic underfilling and subsequent activation of neurohumoral pathways (that is, renin–angiotensin–aldosterone system (RAAS)[46], activation of the sympathetic nervous system (SNS)[46] and antidiuretic hormone[48]) to sustain cardiocirculatory function in humans. In pre-ascitic cirrhosis, a moderate circulatory dysfunction can be compensated by increased plasma volume and cardiac output. However, as vasodilation intensifies with disease progression, continuous retention of sodium leads to ascites formation and enhanced water reabsorption, which is responsible for dilutional hyponatraemia[48]. Increasing vasodilation culminates in a hyperdynamic state with microvascular dysfunction and reduced organ perfusion, which might be one link between cardiovascular dysfunction, disease progression to ACLF and extrahepatic organ failure[49].

Pathomechanistic concepts of local and systemic inflammation

Next to the traditional pathophysiological concept of portal hypertension-mediated haemodynamic and vascular abnormalities as central mechanisms in the process of decompensation, the importance

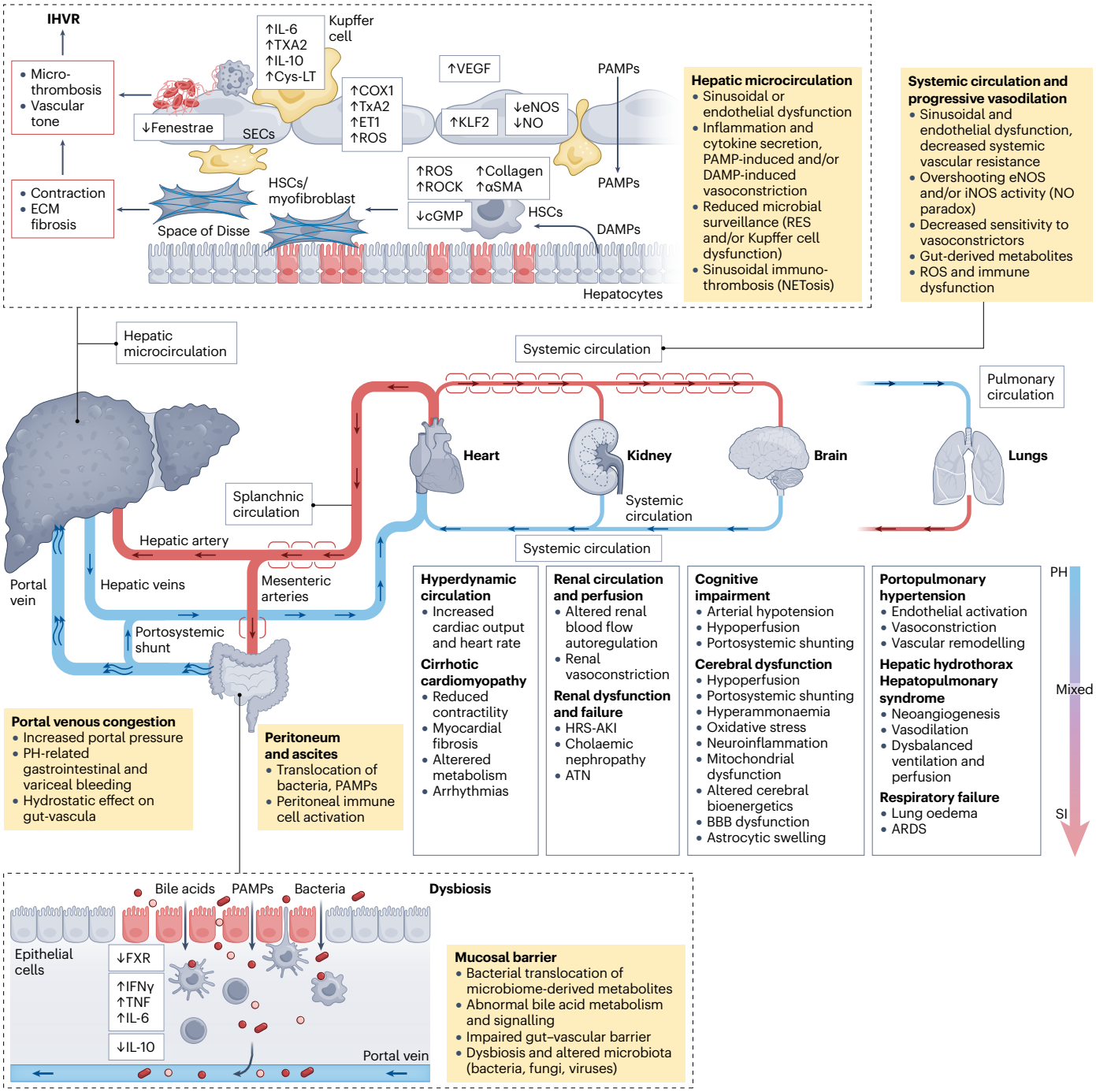
of systemic inflammation, combined with mitochondrial dysfunction, oxidative stress and metabolic changes, has been highlighted in the development of multiorgan failure and linked to a high risk of short-term mortality[9].

CAID[21] encompasses the distinct immune alterations seen in advanced liver disease. It is characterized by systemic inflammation and immune deficiency, affecting both the innate and adaptive immune systems. The severity of systemic inflammation in cirrhosis progresses with the disease, manifesting as either low-grade or high-grade inflammation that contributes to organ immunopathology. Among patients with compensated cirrhosis, the presence in the systemic circulation of low-grade inflammation (indicated by modest increases in the concentrations of IL-6, von Willebrand factor and CD163) associated with bacterial products characterizes patients with clinically significant portal hypertension (CSPH) relative to those without CSPH[13,50]. In addition, the worsening of systemic inflammation precedes the development of first decompensation[50]. In patients with ascites and stable decompensated cirrhosis, the intensity of systemic inflammation is higher among those who exhibit subclinical bacterial translocation[51]. In patients who present with acute-decompensated cirrhosis, the intensity of systemic inflammation depends on the patient's phenotype; although systemic inflammation intensity is low in patients without any organ dysfunction or failure, systemic inflammation is high among those with ACLF and intermediate among those with isolated kidney and/or cerebral dysfunction, organ dysfunction, and those with a single, isolated extrarenal organ failure[10,11]. Patients with ACLF present with full-blown systemic inflammation, including increases in white-cell and neutrophil counts[52], elevated serum levels of pro-inflammatory cytokines (IL-6, granulocyte colony-stimulating factor (G-CSF), IL-8 and TNF)[11], bioactive lipids[53], and acute-phase proteins (such as C-reactive protein (CRP))[9]. Features of systemic immune deficiency have been reported in patients with decompensated cirrhosis and systemic inflammation, which explains the increased risk of infection in patients with decompensated cirrhosis[54]. Even though the production of neutrophils is increased in advanced decompensated cirrhosis, they seem mostly immature[52] and exhibit defective effector functions (for example, impaired degranulation[55]). In addition, the monocyte compartment is enriched in subsets with an immunosuppressed phenotype (increased frequency of MER receptor tyrosine kinase (MERTK)-expressing cells[56] and of monocytic myeloid-derived suppressor cells[57]). A decrease in CD52 expression at the monocyte surface occurs when patients progress to acute decompensation and is associated with monocyte reprogramming from a pro-inflammatory phenotype to an immunosuppressive phenotype[58]. Moreover, there is a depletion in the blood of natural killer cells (which are group 1 innate lymphoid cells) and innate-like lymphocytes, that is, unconventional T cells such as mucosal-associated invariant T cells and γδ T cells[52]. Regarding adaptive immune cells, decreases in B cells and in most subsets of conventional $CD4^+$ and $CD8^+$ T cells have been reported[52]. A defect in thymopoiesis and poor peripheral homeostatic replenishment of T helper cells contribute to T cell lymphopenia in cirrhosis[59]. Finally, elevated blood levels of anti-inflammatory signals (such as IL-10, soluble CD163, IL-1 receptor antagonist (IL-1RA))[11] complete the landscape of immunosuppression. There are unsolved questions regarding immune deficiency in cirrhosis. An important gap in knowledge is that the underpinning mechanisms explaining the development of immune deficiency in cirrhosis are unknown. It is important to note that, in patients with severe sepsis but without cirrhosis, elevated levels of blood cytokines such as IL-6 and G-CSF induce emergency granulopoiesis, resulting in increased output of neutrophils, which exhibit immunosuppressive properties against T cells[60]. Further mechanistic and longitudinal studies in patients with decompensated cirrhosis are

Table 2 | Pathophysiological phenotypes of cirrhosis: a proposed concept

Summary phenotype	Portal hypertension predominant	Mixed portal hypertension and systemic inflammation phenotype	Systemic inflammation predominant	
Common clinical presentation	Compensated or recompensated cirrhosis	Non-acute decompensation	Acute decompensation	ACLF
Expected course after acute decompensation	Stable decompensated cirrhosis	Unstable decompensated cirrhosis	Pre-ACLF	NA
Portal hypertension				
Portal pressure	+[7,8,13,14,49,174]	+[13,14,49]	++[13,14,49]	+++[13,49,229]
Cardiac output	=[14,49,122]	+[14,122]	++ (or – –)[14,49,122]	++ (or––)[49,122,129]
Renal blood flow	=[49,129]	–[122,228]	–[122,228]	– – –[11,122]
Systemic inflammation				
Inflammatory markers	=[10]	+[4,6]	++[4,10,11,13,230]	++[4,10,11,13,230]
Immunodeficiency	=[22]	=[22]	+[10,22]	+++[10]
Organ immunopathology	=	=	+	+++
Effectors on organ function				
Endothelial dysfunction	+++[231,232]	+[231,232]	++[231]	+++
Mitochondrial dysfunction	=	=	+[230,233]	+++[230,233]
ER stress	=	=	+[234]	+++[234]
Cell death	NA	+[166]	++[166]	NA

The authors propose a novel pathomechanistic concept in which three pathophysiological phenotypes can be distinguished: a portal hypertension-predominant phenotype comprising mostly patients with compensated or recompensated cirrhosis; a mixed portal hypertension–systemic inflammation phenotype, commonly observed in patients with non-acute decompensation; and, finally, a systemic inflammation-predominant phenotype mostly comprising patients with acute decompensation, pre-ACLF and ACLF. The signs (=) indicate that the variable is relatively unchanged; (–) and (+) indicate that the respective variable is reduced or increased, respectively. The number of (-) and (+) indicate the intensity of change. Some conceptual aspects of our proposal remain without clinical evidence and, therefore, without reference. ACLF, acute-on-chronic liver failure; ER, endoplasmic reticulum; NA, non applicable.



warranted to confirm the temporal sequence and pathomechanistic link of systemic inflammation and CAID, as it remains unknown whether immune deficiency develops late in decompensated cirrhosis or even at an earlier stage of cirrhosis.

Regarding systemic inflammation, compelling evidence supports the occurrence of low-grade inflammation already in compensated cirrhosis, which marks the ordinal progression to CSPH and then towards decompensated cirrhosis without organ failure[50]. In contrast, the mechanisms underpinning low-grade inflammation in patients with compensated cirrhosis and those with decompensated cirrhosis without organ failures are unknown. The role of different inducers of inflammation that have been reported in other fields[61] remains to be specifically investigated in patients with cirrhosis. Intestinal dysbiosis and impaired intestinal barrier function — two hallmarks of decompensated cirrhosis — might result in the increased passage of pathogen-associated molecular patterns (PAMPs) from bacteria or fungi (such as lipopolysaccharide (LPS) from Gram-negative bacteria or β-glucan from fungi) and/or microbial metabolites (such as

Fig. 2 | Organ-level consequences of PH and inflammation in cirrhosis. Portal hypertension (PH) and inflammation can affect multiple organs and systems during the course of cirrhosis. Although the initial hit usually influences primarily the liver, in which different types of liver injury affect the hepatic and sinusoidal microcirculation and loco-hepatic inflammation, ultimately, hepatic vasoconstriction caused by both haemodynamic or vascular alterations and the pro-inflammatory hepatic microenvironment leads to increased portal pressure, that is, clinically significant PH (CSPH). CSPH, in turn, has a profound effect on the splanchnic circulation and the gut, particularly in decompensated cirrhosis, in which luminal dysbiosis and mucosal defence mechanisms become impaired, and translocation of viable bacteria and their products (PAMPs) ultimately affect the liver via the hepatic circulation and the splanchnic circulation (progressive vasodilation) as well as the systemic circulation. Although systemic vasodilation has been traditionally linked to CSPH-associated haemodynamic abnormalities, many of the vascular and endothelial alterations are actually mediated through pro-inflammatory molecular signals (such as IL-6, IL-10, IFNγ, TNF). In turn, dysfunction of the heart, kidneys, brain and lungs can only partly be explained by haemodynamic or systemic vasodilation effects alone, but systemic and regional pro-inflammation and immune processes are crucially involved in mediating organ damage and potential organ failure, as seen in acute-on-chronic liver failure. αSMA, α-smooth muscle actin; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; BBB, blood–brain barrier; COX1, cyclooxygenase 1; cGMP, cyclic guanosine monophosphate; Cys-LT, cysteinyl leukotrienes; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ET1, endothelin 1; FXR, farnesoid X receptor; HRS-AKI, hepatorenal syndrome-type acute kidney injury; HSC, hepatic stellate cells; IHVR, intrahepatic vascular resistance; iNOS, inducible nitric oxide synthase; KLF2, Kruppel-like factor 2; NETosis, neutrophil extracellular trap formation; NO, nitric oxide; RES, reticuloendothelial system; ROCK, Rho-associated coiled-coil containing protein kinase; ROS, reactive oxygen species; SECs, sinusoidal endothelial cells; SI, systemic inflammation; TXA2, thromboxane A2; VEGF, vascular endothelial growth factor.

bacteria-derived vitamin B metabolites) over the gut barrier, which might contribute to the induction of a low-grade pro-inflammatory environment that does not require the presence of an ongoing infection[62]. Recognition of microbial products by cells involved in innate immunity might trigger bursts of systemic inflammation, which can sustain a prolonged inflammatory response[23,63]. Next to gut-derived PAMPs, danger-associated molecular patterns (DAMPs) — released from damaged tissues or as soluble products of the extracellular matrix — might act as endogenous triggers of systemic inflammation[23,64].

High-grade inflammation, driven by infections or non-infectious factors (for example, liver inflammation in the context of acute alcohol-related liver injury, alcohol) can directly damage tissues by activating pro-inflammatory pathways, including those involving canonical inflammasomes (which are composed of an activated pattern-recognition receptor (such as a member of the NLRP family), an adaptor protein ASC, and caspase 1 to induce cell death and IL-1β or IL-18 release) and non-canonical inflammasomes (that is, caspases such as caspase 4 or 5 in humans and caspase 11 in mice that are directly activated by intracellular LPS to cause cell death)[19,65]. This immune-driven tissue damage (immunopathology) indicates that organ abnormalities are not just functional impairments but also include leukocyte infiltration[66,67], microvascular clots, cell death[68,69], mitochondrial damage[70] and structural injury[66] — factors that together heighten the risk of organ failure. Furthermore, systemic inflammation is a process that considerably increases energy expenditure and requires certain metabolites and nutrients (that is, glucose, amino acids, fatty acids) for effective immune cell functioning (immunometabolism), which is often impaired in cirrhosis due to associated conditions such as anorexia, fatigue and somnolence. As a result, inflammatory signals, such as TNF and IL-6, together with the activation of the hypothalamic–pituitary axis, which governs adrenal secretion of glucocorticoids, trigger the mobilization of stored fuels, that is, glucose from the liver, amino acids from skeletal muscles and fatty acids from adipocytes[70]. In addition, inflammatory signals decrease nutrient consumption in peripheral organs[70]. For example, systemic inflammation, probably through the mediation of certain areas in the brainstem[71], results in markedly reduced mitochondrial fatty acid β-oxidation in peripheral organs[70]. This mechanism enables fatty acid reallocation to the immune system but also causes decreases in energy (ATP) production and increases in ROS production in peripheral organs, effects that can contribute to organ dysfunction and failure[70,72].

The systemic inflammation hypothesis underscores a complex interplay of direct immunopathology, inflammation-driven mitochondrial dysfunction and metabolic imbalance as key drivers of acute decompensation, particularly in ACLF[70]. However, this hypothesis acknowledges traditional organ-specific mechanisms (that is, portal hypertension and effective arterial blood volume). Indeed, these mechanisms are complementary and can act synergistically in the development of complications such as ascites, hepatic encephalopathy, risk of infection and variceal bleeding.

Evidence for interaction between portal hypertension and inflammation

There is a profound effect of hepatic inflammation on sinusoidal vasoconstriction (that is, the functional components of IHVR), neoangiogenesis and fibrogenesis (key drivers of the structural portal hypertension component via capillarization and fibrosis; reviewed in ref. 73). In turn, portal hypertension-mediated splanchnic and intestinal congestion related to increased portal venous pressure, in addition to the immunological (defensins, inflammatory cells) and microenvironmental (such as bile acids and gut microbiota) changes, fuel the local inflammation in intestinal mucosa and the gut–vascular barrier, which might facilitate the vasodilation of mesenteric arteries, thereby causing a further increase in portal venous blood flow, aggravating portal hypertension (reviewed in ref. 74) (Fig. 2). Portal hypertensive gastropathy is a typical feature of portal hypertension, but mucosal pathologies are not strictly correlated to portal pressure (that is, hepatic venous–portal pressure gradient (HVPG)) but are also driven by gastric mucosal inflammation and angiogenesis[75]. The abovementioned pathomechanisms suggest an intercausal relationship between portal hypertension and inflammation within the splanchnic region.

Ultimately, the profound effect of portal hypertension on splanchnic perfusion (reviewed in ref. 76) and the cirrhosis-associated mucosal inflammation (reviewed in ref. 74) facilitate the translocation of bacteria and PAMPs[77,78]. Bacterial translocation and PAMPs, in turn, aggravate portal hypertension by sinusoidal vasoconstriction (by increasing IHVR) as they are recognized by hepatic immune cells (such as LSECs and Kupffer cells), which respond by secretion of pro-inflammatory cytokines (such as TNF and IL-6) to limit systemic exposure to pathogens (reviewed in ref. 73). At some point, this bacterial translocation–PAMP-driven hepatic inflammation also leads to systemic inflammation when liver injury is pronounced and/or

there is a transhepatic 'spill-over' of bacterial translocation (such as *Enterobacteriaceae* and *Streptococcaceae*) to the systemic circulation as shown in patients with decompensated cirrhosis receiving a transjugular intrahepatic portosystemic shunt (TIPS)[77,79]. Although a systemic pro-inflammatory state has been traditionally recognized as a feature of decompensated cirrhosis and ACLF, there is evidence that bacterial translocation and systemic inflammation might also occur in some patients with compensated cirrhosis[13,50,80]. The exact chronological relationship between systemic inflammation and decompensation remains a subject of debate. However, the concept that systemic inflammation is more pronounced in decompensated cirrhosis than in compensated cirrhosis and that systemic inflammation drives further progression once decompensation has occurred is widely accepted[4,81].

Intrahepatic interplay of systemic inflammation and portal hypertension

From a mechanistic perspective, portal hypertension initially results from the capillarization of LSECs lining hepatic sinusoids and vasoconstrictive HSCs that transdifferentiate into extracellular matrix-producing myofibroblasts[73]. The liver injury-related release of pro-inflammatory cytokines and chemokines (such as TNF, IL-6 and CC-chemokine ligand 2 (CCL2)) results in endothelial–LSEC dysfunction, polarization of hepatic macrophages (Kupffer cells) and recruitment of pro-inflammatory immune cells (monocytes, neutrophils and lymphocytes) into the liver. This shift of the cellular landscape and their functional phenotypes in cirrhosis is mediated by intricate cellular crosstalk via direct interactions and soluble factors such as cytokines, growth factors and other soluble signalling molecules (reviewed in ref. 73). In cirrhosis, the dysfunctional sinusoids will eventually lead to impaired microbial clearance and/or surveillance, generating a pro-thrombotic and pro-inflammatory sinusoidal milieu, which contributes to structural and functional components of IHVR and, therefore, to the progression of portal hypertension[82]. Additionally, resident immune cells are activated (such as LSECs and Kupffer cells), and neutrophils and monocytes are readily recruited from circulation[83]. Pattern-recognition receptors of the innate immune system, such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors, are activated by PAMPs and DAMPs, triggering canonical and non-canonical inflammasome activation[10,84]. During ongoing liver injury, neutrophils and pro-inflammatory (M1) macrophages persistently release inflammatory cytokines (such as TNF, IL-6 and IL-1β), which perpetuate local inflammation[10,19,85]. Clinically, this also explains why liver stiffness in patients with active liver disease is significantly higher at similar levels of fibrosis than in patients with cured or controlled underlying aetiology[86,87].

Importantly, M1 macrophages promote angiogenesis (secretion of ROS, TNF, PDGF) and directly activate HSCs via TGFβ, stimulating their contractility and fibrogenesis, which ultimately drives portal hypertension progression[88]. Interestingly, when incorporating a macrophage activation marker (soluble CD163) into an established fibrosis test (such as the Enhanced Liver Fibrosis test), the accuracy of non-invasive portal hypertension assessment is improved (that is, correlation to HVPG)[89]. Further cirrhosis-related abnormalities in macrophage functions, for example, as reflected by a decreased M2 macrophage polarization (which is an oversimplified categorization of the multidirectional dynamics of macrophages), result in reduced anti-inflammatory cytokine secretion and impaired tissue repair in mice[90]. Overall, defects in their pathogen phagocytic function contribute to the increased susceptibility to infections in cirrhosis[91].

Hepatic microvascular thrombosis has been reported to contribute to cirrhosis and portal hypertension progression in mice by causing (sinusoidal) vascular obstruction and areas of parenchymal extinction and collapse, leading to further tissue injury[82,92]. Platelets can be rapidly recruited and aggregated by a damaged, pro-inflammatory and dysfunctional endothelium through von Willebrand factor-dependent mechanisms, to which Kupffer cells contribute by serving as 'landing pads' for platelet adhesion in humans[93]. Neutrophils also seem to recruit platelets, and the aggregation of both has been shown to induce the release of neutrophil extracellular traps (NETs; a sticky web of decondensed nuclear DNA released into the extracellular environment)[94] in human liver. Consequently, intrahepatic clot generation (involving sinusoidal immunothrombosis) facilitates cirrhosis progression by occluding small veins and sinusoids, leading to parenchymal cell death and increasing IHVR and, thereby, portal hypertension[88]. Platelet activation occurs due to serum LPS-linked inflammation in the portal venous vascular bed, as suggested by increased levels of LPS and high oxidative stress levels (that is, NADPH oxidase 2 activation) in the portal vein[78]. Interestingly, the transcription factor Kruppel-like factor 2, highly and early expressed in the vascular endothelium of the cirrhotic liver, confers endothelial protection against inflammation, thrombosis and vasoconstriction (that is, it attenuates cytokine-mediated induction of pro-inflammatory molecules, induces thrombomodulin gene and protein expression, and induces eNOS), delaying or attenuating vascular occlusion and subsequent parenchymal extinction lesions in cirrhotic rat liver[31]. The involvement of inflammation in sinusoidal remodelling and vascular resistance, leading to portal hypertension, and the subsequent portal hypertension-induced shear stress, LSEC dysfunction, hepatic necroinflammation, translocation of bacteria or bacterial products, and immune dysfunction, provide striking evidence for the underlying interlinked pathomechanisms involved in cirrhosis progression.

Extrahepatic interplay of portal hypertension and systemic inflammation

In cirrhosis, both portal hypertension and systemic inflammation are associated with profound changes and adaptive mechanisms involving the whole organism and not limited to the liver. The gut, especially, has an important role in this context due to the tight evolutionary and functional link with the liver (previously reviewed in ref. 74). The concept of the gut–liver axis is central towards a modern understanding of the pathomechanistic interplay between portal hypertension and local splanchnic and systemic inflammation[95–97], driving the progression towards decompensation[98,99]. The intestinal barrier dysfunction is associated with damage to physical (congestion, mucus) and immunological (defensins, inflammatory cells) layers and the local (micro) environment (such as bile acids and microbiota) that is associated with increased intestinal permeability[74]. The impaired gut–vascular barrier and mucosal integrity by portal hypertension and its consequences might, in turn, facilitate the translocation of viable bacteria and/or PAMPs, which further aggravates hepatic and systemic inflammation and compromises the anti-inflammatory response[77,78,100]. Notably, in the absence of both local and systemic inflammation, the mechanical increase in portal pressure is not associated with increased disruption of the mucosal barrier[101]. Ineffective splanchnic perfusion and altered microperfusion, along with impaired bile acid signalling, further compromise intestinal function and promote gut-derived inflammation in humans[102]. The hepatic release and 'unfiltered' passing of pro-inflammatory cytokines, DAMPs and PAMPs in the systemic

circulation is further aggravated by portal hypertension-driven collateral formation and associated perihepatic shunting. This might lead to chronic systemic inflammation, which can take place at multiple sites: in the liver, promoting inflammation and fibrosis; in the portal circulation, predisposing to splanchnic thrombosis; and in extrahepatic organs, such as the pulmonary capillary bed and the kidneys (affecting glomerular and tubular function), thereby eventually promoting end-organ dysfunction or failure[103].

There is indirect evidence for gut-derived bacteria exacerbating systemic circulatory dysfunction in cirrhosis. Portal venous endotoxin influx induces TNF expression in hepatic and circulating immune cells, triggering systemic inflammation[104] and aggravating portal hypertension by induction of splanchnic and systemic vasodilation through an increased inducible nitric oxide synthase (iNOS) activity[105]. Accordingly, antimicrobial interventions (for example, norfloxacin) in patients with cirrhosis have been associated with the downregulation of TNF and IL-6 expression by inhibiting nuclear factor-κB (NF-κB) signalling, blunting systemic vasodilatation[106]. Moreover, inflammation-associated vascular dysfunction and oxidative stress promote tissue hypoxia and pathological angiogenesis (as prominently elicited by VEGF and PDGF). Thus, the splanchnic inflammation-mediated increase in portal blood inflow aggravates portal hypertension, and the associated increase in bacterial translocation with DAMP and/or PAMP signalling further contributes to the progression of cirrhosis, particularly in the setting of decompensation[77,100].

Changes in the gut microbiota[107] (such as a decrease of beneficial bacteria *Lachnospiraceae* and *Ruminococcaceae*, and an increase of pathogenic bacteria *Enterobacteriaceae* and *Streptococcaceae*) have been described in patients with cirrhosis[77] and might also affect the circulating microbiota (predominantly Proteobacteria) and their derived metabolites (such as LPS), which are postulated to modulate hepatic and systemic inflammation. Specifically, some microbial members have been shown to aggravate hepatic inflammation and, thereby, probably hepatic resistance[108]. Luminal bile acids are metabolized by the intestinal microbiota in rats, leading to a decreased potential to activate intestinal and hepatic farnesoid X receptor, which might, in turn, increase the contractility of HSCs and thereby promote portal hypertension[109]. Reduced intraluminal levels of bile acids in rats with decompensated cirrhosis might also contribute to bacterial translocation, predisposing to endotoxaemia, triggering cytokine release and, thereby, inflammation[110].

Cirrhosis is associated with an activation of the SNS. Non-selective β-adrenergic blockers (NSBBs) counteract the SNS-mediated increase in hyperdynamic cardiac output and increase splanchnic blood flow, decrease portal hypertension, and prevent variceal bleeding. Additionally, NSBBs exert non-haemodynamic beneficial effects on gut motility and intestinal permeability[111,112] and modulate systemic inflammation in patients with cirrhosis and ACLF[113]. Studies have reported an amelioration of gastroduodenal and intestinal permeability upon NSBB therapy — partially mediated via non-haemodynamic effects — that explains the stronger efficacy in preventing portal hypertension-related complications, as would be expected from haemodynamic response rates to NSBBs[112].

Additionally, treatment of portal hypertension by TIPS cannot only control variceal bleeding and/or ascites but also substantially decreases biomarkers of chronic systemic inflammation (that is, CXC-chemokine ligand 9 (CXCL9) (ref. 114) and CXCL10 (ref. 115)) in most patients, particularly in those who show a favourable clinical outcome and a lower risk of ACLF[114,115]. Additionally, increased levels of inflammatory markers are found in the hepatic veins compared with the portal veins, suggesting that it is mainly liver-derived systemic inflammation (IL-6) that predisposes patients receiving TIPS to developing organ failure and ACLF[86]. In turn, pronounced systemic inflammation — as found in ACLF — considerably increases portal pressure and IHVR[116], resulting in an almost doubled risk of portal hypertension-related variceal bleeding[117].

Organ-specific interplay of portal hypertension and systemic inflammation

The systemic interaction between portal hypertension-derived haemodynamic and vascular abnormalities and inflammation-mediated pathomechanisms in driving cirrhosis progression is most evident at the end-organ level (Fig. 2), compromising tissue integrity and disrupting metabolic balance to sustain immune activation[118]. A pro-inflammatory state might persist after successful management of portal hypertension (indicating a systemic inflammation-predominant phenotype)[4]. Conversely, inflammation might be largely absent despite severe, persistent portal hypertension, as sometimes seen in patients with cured or controlled viral hepatitis (a portal hypertension-predominant phenotype)[119].

Kidneys are commonly affected in patients with ascites (for example, in hepatorenal syndrome-type acute kidney injury (HRS-AKI)) as the most common extrahepatic organ dysfunction or failure in ACLF[9]. The traditional pathomechanistic concept focusing solely on renal hypoperfusion related to portal hypertension-mediated systemic vasodilation has been challenged by novel results in patients with cirrhosis[66,118,120]. Still, evidence holds true that progressive splanchnic vasodilatation and splanchnic hyperaemia lead to relative systemic hypovolaemia and potentially ineffective compensatory activation of antidiuretic hormone and the RAAS system as potent endogenous vasoconstrictors, favouring HRS-AKI[121]. However, systemic and, subsequently, renal inflammation might accelerate or promote the development of acute renal tubular necrosis through capillary leukocyte infiltration, microthrombosis and mitochondrial injury, substantially increasing the risk of kidney failure in ACLF[66,120]. The pronounced systemic inflammation-mediated effects on kidney dysfunction are reflected by the reduced efficacy of terlipressin and albumin in treating kidney injury in ACLF[118]. Patients with decompensated cirrhosis are prone to developing repeated episodes of HRS-AKI and often develop irreversible chronic kidney disease[121]. Moreover, enhanced tubular and endothelial injury, along with monocyte-macrophage infiltration and mitochondrial dysfunction, are linked to an increased risk of renal fibrosis[66], contributing to the clinical challenge of estimating the reversibility of kidney damage in cirrhosis. Vascular or tubulointerstitial renal lesions are often found in patients with cirrhosis, and particularly vascular renal lesions seem to increase the risk of acute tubular necrosis[66]. Systemic inflammation in patients with cirrhosis is associated with tubular injury and apoptosis and is accompanied by increased renal expression and urinary excretion of TLR4 (ref. 120), suggesting that T cell-induced innate immune activation contributes to renal injury as an example of organ immunopathology in cirrhosis.

Cirrhotic cardiomyopathy represents another end-organ manifestation of cirrhosis that is pathomechanistically affected by both portal hypertension and systemic inflammation. Alongside the haemodynamic imbalance driven by peripheral arterial vasodilation, the initial compensation by enhanced cardiac output becomes inadequate to meet the demands of systemic circulation, leading to hyperdynamic circulation that is insufficient to maintain an adequate mean arterial pressure[103,122]. Cardiac dysfunction is not only affected

by portal hypertension via volume overload and increased dromotropy but also via pro-inflammatory, profibrogenic and pro-arrhythmogenic mediators that might cause both functional and structural changes, summarized as cirrhotic cardiomyopathy[123]. The pathophysiology of cardiac dysfunction is linked to an inflammatory phenotype driven by intestinal congestion secondary to portal hypertension[124]. Cardiac monocyte or macrophage infiltration is associated with decreased myocardial contractility and systolic dysfunction in cirrhotic rats. Pro-inflammatory cytokines (such as TNF, IL-1β and IL-6) induce disturbance of calcium transients in the hearts of rats with cirrhosis[125–127], promote tissue injury directly by activating cell death pathways (especially TNF), and contribute to diastolic and systolic dysfunction (TNF-induced activation of the NF-κB–iNOS pathway)[126–128]. An altered cardiodynamic state and reduced heart rate variability are strongly associated with systemic inflammation (circulating levels of IL-6, IL-8 and soluble IL-33 receptor); patients with hyperdynamic and hypodynamic circulation have an increased risk of fatal ACLF[116,129,130].

In brain dysfunction, portosystemic shunting, in addition to liver insufficiency, contributes to hyperammonaemia, which is the central mechanism underlying the development of hepatic encephalopathy[131]. However, in severe cases with brain failure — as observed in patients with cirrhosis and ACLF — hepatic encephalopathy is caused by a combination of factors such as hyperammonaemia, abnormalities in cerebral bioenergetics, mitochondrial dysfunction, oxidative stress and neuroinflammation[132–134]. In the brains of patients with cirrhosis, particularly in the cerebral cortex of those with hepatic encephalopathy, there is evidence of increased oxidative stress, altered zinc homeostasis and microglia activation, and interestingly, an anti-inflammatory gene response (such as IL-4 and IL-10 receptors) to counteract pro-inflammatory signalling (such as CXCL2, CXCL8, IL-1R and TLR2)[135]. Experimental studies reveal evidence of astrocytic swelling and cerebral hypoperfusion[21,136] (that is, microvascular damage and a decreased ability for autoregulation[137] with increased expression of iNOS). It is hypothesized that a combination of systemic oxidative stress and inflammation sensitizes the brain to the harmful effects of hyperammonaemia, producing blood–brain barrier dysfunction and worsening neuroinflammation. Notably, astrocyte senescence, as well as neuronal cell death, might be key features of irreversible hepatic encephalopathy[138–141].

The lungs are affected by portal hypertension-associated haemodynamics changes, as evident in portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS)[142,143]. In HPS, both pulmonary vasodilatation (mediated by nitric oxide derived from endothelial and inducible synthase) and vasoconstriction (for example, mediated by hepatic production of ET1 (refs. 144,145) and pulmonary neoangiogenesis mediated by CX3CL1, VEGF[146]) have a crucial role in the mismatch between increased perfusion and unaltered alveolar ventilation, leading to intrapulmonary shunting and hypoxaemia. Lung inflammation, as reflected by pulmonary intravascular sequestration of monocytes and monocyte-derived macrophages, is also critically involved in HPS development in a rat model[144,146]. PoPH, resulting from excessive pulmonary vasoconstriction and vascular remodelling, is driven by an imbalance of vasoregulators (increased expression of ET1 and serotonin; reduced nitric oxide and prostacyclin synthase), proliferation of smooth muscle cells, endothelial activation, platelet aggregation and in situ thrombosis[147]. The hyperdynamic circulation inducing shear stress was reported as a potential trigger for the development PoPH[148]. Notably, portosystemic shunting and the gut–liver–lung axis play a pivotal role in the pathophysiology of both HPS and PoPH in patients with cirrhosis[149,150].

Portal hypertension and systemic inflammation in different stages of cirrhosis

In compensated cirrhosis, the progressive architectural hepatic distortion eventually progresses towards CSPH as defined by the presence of an HVPG ≥10 mmHg (refs. 7,151). The risk for first decompensation is reflected by portal hypertension severity and increases by 11–12% with every 1-mmHg increase in HVPG[7,8]. This is also reflected by a progressive increase of HVPG observed across the compensated substages of cirrhosis[13,14]. Although patients in the compensated cirrhosis stages typically display normal (as compared to healthy individuals[10]) or borderline levels of systemic inflammation[10,13,14], some compensated patients might already present a clinically relevant pro-inflammatory state that puts them at particular risk for first decompensation[50,152]. Indeed, the presence of systemic inflammation in patients with compensated cirrhosis is linked to ACLF development as the first acute decompensation[19] (Fig. 1).

The first decompensation event is the most important stratification variable for predicting mortality risk in cirrhosis[1,9,153], mostly frequent ascites (64–78%), followed by variceal bleeding (9.5–18%) and hepatic encephalopathy (2–7%)[13,154]. The last Baveno consensus conference also introduced the concept of further decompensation if a patient has either developed a second decompensating event and/or jaundice or had recurrent variceal bleeding or hepatic encephalopathy, recurrent ascites, or complications of ascites (spontaneous bacterial peritonitis, HRS-AKI)[2]. Although portal hypertension (that is, HVPG) considerably worsens along substages of compensated cirrhosis towards decompensation, HVPG levels tend to reach a certain plateau in further decompensation[13]. Conversely, systemic inflammation surrogates[155,156] reveal an exponential increase, with substantially increased values in patients with further decompensation[13]. Interestingly, patients with decompensated cirrhosis defined by (past) variceal bleeding[4] showed lower levels of systemic inflammation (that is, decreased levels of circulating IL-6 (ref. 4), CXCL9 (ref. 114), CXCL10 (ref. 115)) compared to those with ascites. Decreased circulating levels of systemic inflammation surrogates were also linked to improved survival[13,14], suggesting pronounced gut-barrier dysfunction, bacterial translocation and systemic inflammation in ascites decompensation[114,115,157]. This suggestion supports the idea that ascites might represent a more advanced stage of decompensation than variceal bleeding.

Once acute decompensation develops, as defined by CANONIC (n = 1,343)[9], systemic inflammation is usually pronounced but might be punctuated by intermittent pro-inflammatory flares[158] (cytokine storms), often triggered by precipitants like bacterial infections, severe alcoholic hepatitis and variceal bleeding[159]. Notably, the incidence of bacterial infections in the CANONIC[9] and PREDICT[4,160] (n = 1,071) studies was 65% and 53%, respectively, which strongly suggests immunoparesis. Patients with acute decompensation can follow distinct clinical courses paralleled by an increase in systemic inflammation[4,161] (Fig. 1). The stable decompensated cirrhosis (SDC) sub-phenotype follows an excellent clinical course, not requiring further hospital re-admission. Although plasma IL-6 concentrations are notably higher in patients with SDC compared to those with compensated cirrhosis, its benign course is linked to a substantial decrease in systemic inflammation during follow-up[4]. In the unstable decompensated cirrhosis (UDC) sub-phenotype, patients require hospital re-admissions for

repeat acute decompensation during 90 days of follow-up[4]. It follows a complicated course with relatively high mortality, ongoing systemic inflammation and pronounced portal hypertension (as suggested by surrogates)[3]; therefore, UDC seems to reflect a cirrhosis stage of a mixed or combined portal hypertension and systemic inflammation phenotype.

ACLF is defined by hepatic and/or extrahepatic organ failures and might develop in patients with an episode of first or subsequent acute decompensation. A prospective cohort of 388 patients revealed a high short-term mortality of up to 80% depending on ACLF grade (1–3)[12]. Although systemic inflammation is the predominant factor identified in ACLF, most patients still show pronounced portal hypertension, and IHVR might be further aggravated by both hepatic inflammation and circulating mediators of systemic inflammation[116] involving both pro-inflammatory (such as TNF, IL-6 and IL-8) and anti-inflammatory (such as IL-10 and IL-1RA) cytokines[21]. The intensity of the inflammatory response in ACLF parallels its clinical severity, as indicated by increased IL-6 blood levels across the three grades[12]. The past few years have seen the emergence of several prognostic biomarkers (Tables 3 and 4) in acute decompensation (such as IL-6 (refs. 13,14), IL-8 (ref. 10), TNF[20] and IL-1RA[10]) but integrating them into clinical practice remains challenging given unclear evidence of their superiority over established scores such as the Child–Turcotte–Pugh score or the Model for End-Stage Liver Disease (MELD).

Table 3 | Selected clinical biomarkers of portal hypertension in cirrhosis

Biomarker	Source or location	Pathophysiological role	Clinical importance
HVPG[7,8] Diagnostic, prognostic, therapeutic target and surrogate for treatment response	Invasive haemodynamic measurement	Indirect measure of portal pressure	HVPG ≥10 mmHg: CSPH (indicates risk of decompensation and mortality) HVPG ≥12 mmHg: risk of VB HVPG ≥16 mmHg: pronounced risk of decompensation HVPG ≥20 mmHg: indicates high risk for rebleeding after acute VB and suggests benefit of TIPS placement
LSM[172,235] Diagnostic and prognostic	Non-invasive imaging	Reflects mostly the amount of liver fibrosis but also hepatic injury and/or inflammation; correlates with portal pressure	LSM correlates with HVPG, risk of varices and decompensation Rule of 5 for LSM (10–15–20–25 kPa) indicates (simplified) categories with increasing risk of decompensation and mortality
SSM[236] Diagnostic and prognostic	Non-invasive imaging	Integrative (reflecting both congestive and backward pressure, and dynamic and inflow components) and dynamic measure of PH	Elevated spleen stiffness predicts the presence of CSPH, varices and risk for decompensation SSM >40–50 kPa rules in CSPH
vWF[16,237] Diagnostic and prognostic	Released from activated or dysfunctional endothelial cells in response to injury	Reflects endothelial activation or dysfunction and microvascular changes	Elevated vWF levels are associated with CSPH and increased risk for VB, decompensation and mortality (>315%)[38]
VEGF[38,238]	Released from macrophages, hypoxic tissue and endothelial cells	Reflects neoangiogenesis and vascular remodelling, collateral formation	Associated with mesenteric angiogenesis and splanchnic hyperaemia; considerable increase in ACLF
ET1 (ref. 185)	Released from activated endothelial cells and hepatic stellate cells	Causes (hepatic sinusoidal) vasoconstriction and thereby increases portal hypertension	Reflecting dynamic component of portal hypertension that could be targeted by ET1 receptor blockers
Renin[228,239] Prognostic	Released in response to decreased renal perfusion	Activates RAS	Reflecting the severity of portal hypertension, associated with risk of renal dysfunction and first or further decompensation and mortality
Copeptin[240,241] Prognostic	A vasopressin-release biomarker	Reflects hyperdynamic circulation and activates the vasopressin pathway	Correlated with risk of developing AKI or ACLF and of mortality
ICG-r15 test[242] Diagnostic and prognostic	Intravenous ICG injection clearance	Quantitative assessment of liver function that assesses hepatic perfusion and capacity for extraction and metabolism	ICG-r15 identifies CSPH (ICG-r15 ≥16.7%) and predicts decompensation events (ICG-r15 ≥23%)
Ammonia[243–246] Diagnostic, prognostic, therapeutic target and surrogate for response to therapy	Accumulates because of dysfunction of the urea cycle in advanced liver disease	Neurotoxicity exerting direct effects on the astrocytes, neurons and microglia; hepatotoxicity, hepatic fibrosis, PH through stellate cell activation; impairs function of immune cells (neutrophils, monocytes); involved in sarcopenia development	Elevated levels are needed to diagnose HE; ammonia >80 μmol/l indicates increased risk of death in patients with AD In stable outpatients with cirrhosis, levels of ammonia >1.4× ULN defines risk of overt HE Changes in ammonia levels in AD reflect mortality risk

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AKI, acute kidney injury; CSPH, clinically significant portal hypertension; ET1, endothelin 1; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ICG-r15, indocyanine green 15-minute retention test; LSM, liver stiffness measure; PH, portal hypertension; RAS, renin–angiotensin system; SSM, spleen stiffness measurement; TIPS, transjugular intrahepatic portosystemic shunt; ULN, upper limit normal; VB, variceal bleeding; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

Table 4 | Selected clinical biomarkers of systemic inflammation in cirrhosis

Biomarker	Source or location	Pathophysiological role	Clinical significance
CRP[9,156] Prognostic	Hepatocytes (stimulated by IL-6)	Acute-phase protein indicating systemic inflammation	Elevated CRP is linked to disease severity, risk of decompensation and higher mortality Sustained CRP levels >1 mg/dl are associated with worse prognosis
Modified albumin[208,247,248] Prognostic and therapeutic target	Produced by hepatocytes	In cirrhosis, both albumin quantity and functional status are changed at three main domains: cysteine-34 domain is oxidized (HNA); metal-binding domain is altered (IMA); detoxification and transport function are affected	Elevation of HNA, IMA and reduced function of the binding function are associated with risk of mortality in patients with AD No specific cutoffs established
IL-6 (refs. 11,13) Prognostic	Kupffer cells, immune cells	Central pro-inflammatory mediator; reflects acute-phase response and immune activation	IL-6 blood levels correlate with the risk of first decompensation, ACLF, AKI development and mortality IL-6 blood levels >14 pg/ml associated with worse prognosis in dACLD
TNF[249,250] Prognostic	Activated macrophages and Kupffer cells	Potent pro-inflammatory cytokine; promotes hepatocyte injury and immune activation	Elevated TNF blood levels are associated with decompensation and worse outcomes, predictor of AKI development No specific cutoffs established
IL-8 (refs. 10,11) Prognostic	Macrophages, neutrophils, endothelial cells	Chemokine-recruiting neutrophils, reinforcing inflammation	Strongly related with the frequency and severity of ACLF and correlates with mortality No specific cutoffs established
IL1 gene cluster (encodes IL-1β)[19,249] Prognostic	Activated macrophages and monocytes	Inflammasome-driving interleukin associated with hepatocellular injury, activation of stellate cells and fibrosis	Strongly related with the frequency and severity of ACLF and correlates with mortality No specific cutoffs established
IL-25 (ref. 251)	Intestinal tuft cells	Activation of type 2 immune responses in gut mucosa; involved in mucosal barrier homeostasis	Associated with the progression of acutely decompensated cirrhosis towards ACLF No specific cutoffs established
IL-22 (ref. 251) Prognostic	T helper 22 cells, T helper 17, group 3 innate lymphoid cells	Effector type 3 cytokine involved in intestinal epithelium homeostasis and repair	Associated with the progression of acutely decompensated cirrhosis towards ACLF No specific cutoffs established
LPS and/or LBP[51] Prognostic and therapeutic target	Gut microbiota (LPS), more stable serum marker (LBP)	Reflect bacterial translocation due to gut-barrier dysfunction, fuelling SI	Elevated LPS blood levels (reflected by LBP) in patients with ascites drive immune and haemodynamic disturbances, correlate with worse clinical outcomes and are linked to severe bacterial infections No specific cutoffs established
sCD163[20,252] Prognostic	Released from activated macrophages	Macrophage activation; associated with inflammation, disruption of gut barrier, fibrosis and portal hypertension	Elevated sCD163 blood levels reflect worsening liver disease, peak in ACLF and correlate with mortality Combining sCD163 with Enhanced Liver Fibrosis test improves non-invasive CSPH diagnosis sCD163 blood levels >5.9 mg/l are associated with reduced survival
NGAL[253,254] Prognostic	NGAL is expressed in response to injury (kidney, liver, leukocytes)	Overexpression of the *LCN2* gene (and *NGAL*) in hepatocytes induced by toxins and/or pro-inflammatory cytokines (IL-6)	Urine NGAL is an independent predictor of ACLF and mortality Correlates with liver failure and SI No specific cutoffs established
Cytokeratin 18 (refs. 69,255) Prognostic and therapeutic target	Cell death is associated with the release of cytokeratin 18 in the circulation	Fragments of cytokeratin 18 identify mode of cell death; M30 fragment indicates apoptosis and M65 fragment indicates necrosis	Elevated blood levels of cytokeratin are noted in patients with AD Predominant cell death changes from apoptosis to non-apoptotic mechanisms, with progression from AD to ACLF No specific cutoffs established

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AKI, acute kidney injury; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; dACLD, decompensated advanced chronic liver disease; HNA, nonmercaptalbumin or oxidized albumin; IMA, ischaemia-modified albumin; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; NGAL, neutrophil gelatinase-associated lipocalin; sCD163, soluble CD163; SI, systemic inflammation.

A novel concept of NAD has recently been introduced, though there is no established consensus on defining criteria, underlying pathophysiology and limited long-term outcome data. NAD was described as slow ascites formation, mild hepatic encephalopathy or progressive jaundice, with no imminent need for hospitalization[5,6]. Although the gradual onset of ascites and hepatic encephalopathy[162–164] seems to mirror slowly progressive portal hypertension, patients still also exhibit elevated levels of systemic inflammation compared with compensated cirrhosis[163]. NAD might eventually progress to acute decompensation and ACLF[165,166] or, mainly when systemic inflammation is mild or its severity is decreasing, NAD might take a course of SDC with similar clinical management implications[4].

Finally, the presence of comorbidities and the activity of the underlying liver disease might have an impact on systemic inflammation and portal hypertension as well as on their severity and interaction. Indeed, obesity and type 2 diabetes mellitus have been associated with systemic inflammation (independent of liver disease)[167–170]. Further studies are warranted to investigate the specific effect of comorbidities and liver disease aetiologies on the interplay between systemic inflammation and portal hypertension in cirrhosis. Furthermore, the cure or control of the underlying liver disease aetiology represents the most effective treatment for patients with (decompensated) cirrhosis, as this might even result in cirrhosis recompensation, as defined by the 2022 Baveno consensus. Next to aetiological cure, recompensation requires control of all decompensating episodes of cirrhosis without ongoing treatment (that is, diuretics and hepatic encephalopathy medication) and restoration of liver function[171,172]. The prognosis of patients with recompensated cirrhosis seems favourable[173–176]; however, more long-term outcomes are required. Recompensation is associated with an amelioration of both portal hypertension[177] and systemic inflammation[19]. Although patients with recompensated and compensated cirrhosis might seem clinically similar, varices and collaterals can often persist[174–176] and a distinct inflammatory profile predisposes to higher rates of further decompensation and mortality[19].

Following a comprehensive review on the molecular pathomechanisms involved in the dynamic interplay between systemic inflammation and portal hypertension across the spectrum of cirrhosis, we propose a novel pathomechanistic concept of portal hypertension-predominant phenotype (that is, compensated cirrhosis and SDC phenotype), systemic inflammation-predominant phenotype (as mostly seen in ACLF) and a mixed phenotype of systemic inflammation–portal hypertension (as mostly seen in UDC) (Table 2). Although the inflammatory profile of patients with acute decompensation and NAD might be similar[6], most of the available data support our hypothesis.

Pathophysiological basis of novel therapeutic approaches

In patients with compensated cirrhosis, CSPH is the key driver of decompensation[7,8]; in turn, effective treatment of CSPH through reduction of portal pressure by NSBBs (such as carvedilol), reduces the risk of first decompensation and mortality[178,179]. Moreover, NSBBs exert beneficial non-haemodynamic effects such as reducing intestinal permeability and, thereby, systemic inflammation[112]. Other drugs that modulate portal hypertension include statins[180] and angiotensin-receptor blockers[181] (Fig. 3). Anti-diabetic drugs, such as metformin, GLP1 receptor agonists[182] or sodium–glucose transporter 2 inhibitors[183], can improve glucose homeostasis and induce weight loss, whereas thyroid-hormone receptor-β agonists (MAESTRO clinical programme[184]) improve metabolic dysfunction-associated steatohepatitis fibrosis; therefore, these aetiological therapies might benefit both portal hypertension and systemic inflammation. Antagonizing sinusoidal vasoconstriction by endothelin A receptor blockade (proof-of-concept study; $n = 14$)[185] or promoting sinusoidal vasodilation by soluble guanylyl cyclase activation ($n = 64$)[186,187] represent promising treatment options for portal hypertension. Intriguingly, inhibition of the coagulation cascade, for example, by enoxaparin, not only prevented the development of portal vein thrombosis but also resulted in a lower risk for decompensating events and improved survival[188]. Although in patients with compensated cirrhosis and CSPH there might be some degree of systemic inflammation[13], there have been no clinical studies that have evaluated whether targeting systemic inflammation and/or immune dysfunction reduces the incidence of first decompensation in this patient population.

In decompensated cirrhosis, portal pressure still has a role in determining the course of the disease; however, systemic inflammation gains increasing relevance. Reduction of portal pressure with NSBBs reduces the incidence of acute decompensation and further decompensation. Furthermore, the introduction of NSBBs leads to a reduction in white blood cell count[189], underlining the interaction between portal hypertension and systemic inflammation. Indeed, in ACLF, which is characterized by massive systemic inflammation, patients on β-blockers seem to have a less severe course with lower white blood cell count[113]. Despite some prior reports, there are no concerns about the use of NSBBs as long as patients maintain an adequate mean arterial blood pressure[190]. Although beneficial effects of statins and rifaximin have been repeatedly reported in patients with cirrhosis, the LIVERHOPE trial ($n = 237$)[191,192] published in 2024 demonstrated no significant benefit of the combination of rifaximin and statins in patients with decompensated cirrhosis. Thus, as of now, both drugs cannot be routinely recommended in patients with decompensated cirrhosis outside of their specific label use. In the setting of hospitalized patients, reduction of portal pressure by means of terlipressin (or somatostatin or octreotide) is part of the standard of care. Reduction of portal pressure by means of TIPS placement leads to a reduction in the incidence of further decompensation and improvement in survival[193]. TIPS placement leads to a reduction in systemic inflammation[114,115,194] (Fig. 3).

Immunomodulatory therapies for decompensated cirrhosis should address both harmful systemic inflammation and compromised antibacterial defenses[195]. The ongoing passage of PAMPs from a dysfunctional intestinal barrier, worsened by dysbiosis, perpetuates a chronic state of systemic inflammation, eventually leading to a loss of antigen tolerance[21]. Non-absorbable antibiotics (rifaximin[196] or norfloxacin[197]), non-antibiotic gut decontaminating agents (activated charcoal[198]) and faecal microbial transplantation[199] follow this principle. The randomized, placebo-controlled phase II, THEMATIC trial ($n = 60$)[200,201] published in 2024 demonstrated the safety of faecal microbial transplantation in patients with decompensated cirrhosis and its efficacy to prevent hepatic encephalopathy recurrence. Emerging evidence suggests that non-apoptotic cell death (necroptosis and pyroptosis) is highly prevalent in ACLF. Pyroptosis, characterized by gasdermin-induced pore formation, results in cell rupture and DAMP release, which further intensifies systemic inflammation[21]. The role of necroptosis in ACLF was studied in two rodent (mouse and rat) models, in which inhibitors of RIPK1 (necrostatin 1 and SML2100) successfully prevented ACLF development in rodents[68,202]. Additionally, a phase IIa trial is under way to evaluate disulfiram[203], an inhibitor of gasdermin D aggregation, in patients at high risk with acute decompensation and grade 1 ACLF.

The role of TLR4 in the mediation of systemic inflammation is well documented as evidenced by its upregulation and the increased circulation levels of its ligands (PAMPs and DAMPs)[202]. Inhibition of TLR4 has been shown to improve survival in animal models[204]. The G-TAK therapy, which combines a TLR4 inhibitor with G-CSF, has effectively prevented inflammation and promoted regeneration in mice[205]. This approach will be further evaluated in the multicentre European phase II study A-TANGO ($n = 100$ estimated; not yet recruiting)[206].

Albumin also has an important role as standard medical therapy of patients with decompensated cirrhosis; specifically, it is used after

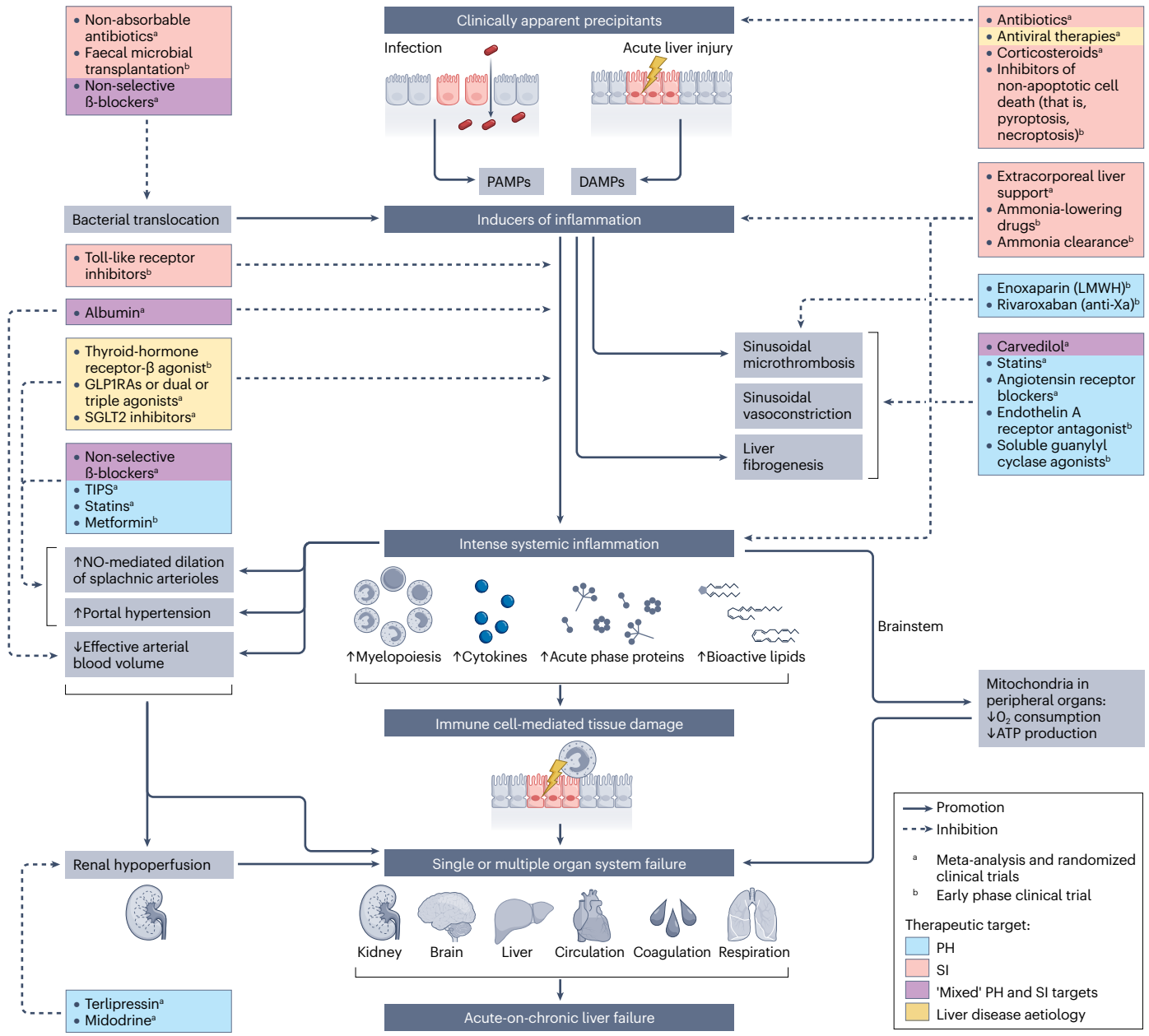


Fig. 3 | Model for the role of SI and PH in accentuating cirrhosis progression and acute-on-chronic liver failure development, including therapeutic approaches targeting the presented pathomechanisms. In patients with cirrhosis, the recognition of microbial byproducts (that is, pathogen-associated molecular patterns (PAMPs)) by pattern-recognition receptors of the innate immune system triggers the systemic inflammatory response. In patients with ongoing liver injury, damaged and/or dying hepatocytes release damage-associated molecular patterns (DAMPs), which engage pattern-recognition receptors to trigger systemic inflammation (SI). In patients with gastrointestinal haemorrhage, liver ischaemia might cause hepatocyte death and subsequent DAMP-induced inflammation. In patients who develop acute-on-chronic liver failure in the absence of any clinically apparent precipitant, SI might be a result of PAMP translocation from the gut lumen. Intense SI can cause organ failure through different mechanisms that are not mutually exclusive. First, accentuation of splanchnic and systemic nitric oxide (NO)-mediated vasodilation, which enhances portal hypertension (PH) and causes regional (for example, renal) hypoperfusion. Second, PAMPs and cytokines stimulate myelopoiesis, resulting in the release of neutrophils, which can cause and aggravate tissue damage. Third, intense SI stimulates the brainstem to induce hypometabolism and decreased ATP production in peripheral organs. This Figure summarizes therapies targeting SI, the consequences of intense SI on PH and peripheral organ function. Solid lines indicate promotion and dashed lines indicate inhibition. GLP1RAs, glucagon-like peptide 1 receptor agonists; LMWH, low-molecular-weight heparin; SGLT2, sodium–glucose co-transporter 2; TIPS, transjugular intrahepatic portosystemic shunt.

large-volume paracentesis to prevent paracentesis-induced circulatory dysfunction, and for the treatment of HRS-AKI[121] and spontaneous bacterial peritonitis. Next to the established plasma-expanding role of albumin in cirrhosis, its immunomodulatory effects are tested for their potential in preventing and treating acute decompensation and ACLF[207,208]. The ANSWER study ($n = 440$)[209,210] demonstrated substantial benefits for albumin, whereas the MACHT ($n = 196$)[211,212] and ATTIRE ($n = 777$)[213] trials did not detect a survival benefit with the use of albumin in decompensated cirrhosis. In the ANSWER ($n = 440$)[209,210] study, albumin therapy reduced the risk of developing refractory ascites by 57% and of mortality by 38%, respectively. The completed PRECIOSA study[214] (410 patients with cirrhosis and decompensation with ascites) did not meet the primary end point of improved transplant-free survival after 1 year but demonstrated numerically longer survival and a substantially lower risk of spontaneous bacterial peritonitis and HRS-AKI as compared to placebo[215]. These benefits of albumin seem linked to reduced systemic inflammation as both acute and long-term (14 weeks) high-dose albumin administration substantially lowered plasma levels of CRP and cytokines[165]. In the setting of ACLF, a small study including 10 patients with ACLF demonstrated that plasma exchange using replacement with albumin improved albumin function and organ dysfunction[215]. The therapeutic concept of plasma exchange using predominantly albumin replacement is further evaluated by the APACHE trial[216]; the study results are awaited after the trial has been stopped (due to corporate business reasons) after recruitment of 275 patients).

In the ongoing ALB-TRIAL (inclusion target: 240 patients)[217,218] conducted by the MICROB-PREDICT consortium, two metabolite biomarkers guide the stratification of this randomized, placebo-controlled trial investigating the response to albumin. Currently, the definition of the population of patients with cirrhosis who will benefit from repeated, long-term albumin infusion is still debated.

DIALIVE[219] is a novel device designed to address the pathomechanisms of ACLF more effectively than previous devices like MARS[220] and Prometheus[221]. It combines a renal dialysis machine with a dual-filtration system: the first filter ultrafilters albumin (replaced in similar quantities) and cytokines, while the second adsorbs PAMPs and DAMPs. In a randomized controlled trial[219,222] involving 32 patients with ACLF, DIALIVE substantially reduced endotoxaemia severity and improved albumin function, resulting in improved clinical outcomes, providing circumstantial evidence of a cause–effect relationship[21].

Hyperammonaemia is also associated with increased infection risk and organ failure, pointing out the need for effective ammonia-lowering strategies[223]. Although lactulose and rifaximin are well-established options for preventing hepatic encephalopathy, L-ornithine phenylacetate has demonstrated efficacy with an excellent safety profile in a phase IIb study (231 patients)[224]. Furthermore, VS-01, a new treatment using pH-gradient liposomes to adsorb ammonia and other metabolic toxins, is under evaluation in a phase II multicentre, randomized controlled, open-label study with patients with ACLF and ascites (UNVEIL-IT)[225,226].

Conclusions

This Review presents a novel concept of clinical phenotypes of decompensated cirrhosis based on the crosstalk between portal hypertension and systemic inflammation as two essential pathomechanisms driving advanced liver disease and the development of complications of cirrhosis and liver failure. A further degree of complexity is introduced by recently introduced cirrhosis disease states such as NAD, recompensation and pre-ACLF that require further clinical validation and mechanistic studies. With increasing knowledge on cirrhosis-driving (molecular) mechanisms, we sought to provide a clinico-pathophysiological framework for cirrhosis classification with 'portal hypertension-predominant', 'systemic inflammation-predominant' and 'mixed' phenotypes. To offer more granular insight, longitudinal studies that track the clinical course of cirrhosis and its association with portal hypertension and systemic inflammation are needed to substantiate and confirm our proposed phenotyping of cirrhosis based on the leading underlying pathophysiological drivers. A better understanding of the differential contribution of systemic inflammation and portal hypertension in the various aetiologies of underlying cirrhosis, the effect of precipitating factors, and the host responses to injury and organ dysfunction should be the focus of future mechanistic investigations. Future investigations are required to define the clinical course and pathophysiological basis of organ dysfunction and failure, and assess their potential for reversibility.

Given the heterogeneity of decompensated cirrhosis, three pathophysiological phenotypes and representative biomarkers are suggested that could help transition this conceptual framework into therapeutic developments and clinical practice. Such biomarkers should ideally provide insights into the severity of portal hypertension, systemic inflammation, and organ dysfunction and support each of the described predominant clinical phenotypes of decompensated cirrhosis. Further research should focus on validating pathomechanistic biomarkers for the different cirrhosis phenotypes and identifying therapeutic targets and clinically-relevant surrogate end points for patients with decompensated cirrhosis.

This Review also offers an integrated perspective on the wide range of potential therapeutic approaches aimed at modifying the disease course, from primary prophylaxis to treatment of acute decompensation and ACLF, as well as secondary prophylaxis. It describes the numerous (ongoing) early-phase clinical trials of novel agents currently under way. The main challenges in bringing innovative approaches to patients with cirrhosis who have a large unmet need for effective therapeutics include harmonization of nomenclature, accepted diagnostic criteria for the different clinical states, regulatory alignment on end points, the use of surrogate biomarkers, and broader stakeholder engagement.

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Author contributions
The authors contributed equally to all aspects of the article.

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