Review

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The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis

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Summary

Acute decompensation (AD) of cirrhosis is defined by the development of ascites, hepatic encephalopathy and/or variceal bleeding. Ascites is traditionally attributed to splanchnic arterial vasodilation and left ventricular dysfunction, hepatic encephalopathy to hyperammonaemia, and variceal haemorrhage to portal hypertension. Recent large-scale European observational studies have shown that systemic inflammation is a hallmark of AD. Here we present a working hypothesis, the systemic inflammation hypothesis, suggesting that systemic inflammation through an impairment of the functions of one or more of the major organ systems may be a common theme and act synergistically with the traditional mechanisms involved in the development of AD. Systemic inflammation may impair organ system function through mechanisms which are not mutually exclusive. The first mechanism is a nitric oxide-mediated accentuation of the preexisting splanchnic vasodilation, resulting in the overactivation of the endogenous vasoconstrictor systems which elicit intense vasoconstriction and hypoperfusion in certain vascular beds, in particular the renal circulation. Second, systemic inflammation may cause immune-mediated tissue damage, a process called immunopathology. Finally, systemic inflammation may induce important metabolic changes. Indeed, systemic inflammatory responses are energetically expensive processes, requiring reallocation of nutrients (glucose, amino acids and lipids) to fuel immune activation. Systemic inflammation also inhibits nutrient consumption in peripheral (non-immune) organs, an effect that may provide one mechanism of reallocation and prioritisation of metabolic fuels for inflammatory responses. However, the decrease in nutrient consumption in peripheral organs may result in decreased mitochondrial production of ATP (energy) and subsequently impaired organ function.

Keywords: Acute-on-chronic liver failure; ACLF; Stable decompensated cirrhosis; Unstable decompensated cirrhosis; Bacterial infections; Pre-ACLF; Systemic inflammation; Metabolism.

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Introduction

Cirrhosis is among the most complex chronic diseases in humans. Its clinical course is dominated by 3 major complications (also known as decompensations): ascites, hepatic encephalopathy and gastrointestinal haemorrhage. Moreover, it seriously affects the function of the kidneys, brain, heart, lungs, systemic circulation, intestines, immune system, adrenal glands, thyroid, reproductive organs and skeletal muscles.

The course of cirrhosis is classically divided into 2 major periods, compensated (asymptomatic) and decompensated cirrhosis. The term acute decompensation (AD) defines the acute development of one or more major complication(s). The first episode of AD signals the transition from compensated to decompensated cirrhosis. The course of decompensated cirrhosis is characterised by repeated episodes of AD. During AD, patients are extremely prone to developing bacterial infections, to the point that infections have been proposed as the fourth major complication of the disease. Finally, the recently recognised syndrome of acute-on-chronic liver failure (ACLF), which is characterised by single or multiple organ system failure and elevated short-term mortality, always occurs in the setting of an episode of AD. However, the current paradigm of decompensated cirrhosis does not consider AD as a specific clinical entity. Instead, this paradigm considers that ascites, hepatic encephalopathy and gastrointestinal haemorrhage develop through different pathophysiological pathways in the setting an acute aggravation of portal hypertension or liver failure.

Systemic inflammation is a well-recognised feature of decompensated cirrhosis. The aim of the current article is to present a new hypothesis, the systemic inflammation hypothesis, which, instead of supporting specific and relatively independent pathophysiological mechanisms for each of the major complications and organ failures of

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AD, proposes systemic inflammation as the common driver of all these events. Systemic inflammation, either acting alone or in concert with organ-specific mechanisms (*e.g.* the effects of hyperammonaemia on the brain), and depending on its severity, would give rise to a wide array of clinical forms, ranging from a relatively stable decompensated cirrhosis with good quality of life and prolonged survival to a rapidly evolving multiorgan ACLF syndrome that may lead to death withing days of hospital admission.

The systemic inflammation hypothesis proposes systemic inflammation as the key mechanism in the progression of compensated to decompensated cirrhosis, and the development of episodes of acute decompensation of cirrhosis that are associated with either a generalised extrahepatic organ system dysfunction or organ system failure.

Current paradigm of AD

Modern concepts on the pathophysiology of ascites, hepatic encephalopathy and gastrointestinal haemorrhage in cirrhosis were introduced at the end of the 19th century by Ernest Starling in London, Ivan Pavlov in Saint Petersburg, and Augustin Gilbert in Paris. Starling was first to demonstrate that ascites develops due to an increased hepatic lymph production secondary to high hydrostatic and low oncotic pressures at the sinusoidal capillaries, with a significant proportion of lymph escaping from subcapsular lymphatics directly into the peritoneal cavity.[1] Renal fluid retention was subsequently proposed as the natural consequence of a reduction in circulating blood volume. Pavlov *et al.* went even further in their investigations on the pathogenesis of hepatic encephalopathy. They demonstrated that dogs with side-to-side portacaval anastomosis (Eck's fistula) developed hepatic encephalopathy only a few weeks after surgery in association with a marked increase in the urinary excretion of ammonium salts, and that this feature could be reproduced by oral administration of this molecule.[2–4] Finally, portal hypertension was first suggested by Gilbert in his book "Les Fonctions Hépatiques". He hypothesised that cirrhosis could bring about a condition of hypertension in the portal system, with enlargement of the natural collaterals between the portal and the systemic venous circulation and subsequent development of oesophageal varices.[5]

The current paradigm of AD was developed during the last century and consisted in a modification of principles proposed in the 19th century. Among the new concepts introduced, 3 are of special interest for the systemic inflammation hypothesis. The first relates to the functional component of portal hypertension, which consists of an imbalance between the local activity of vasodilators (*i.e.*, nitric oxide [NO] and hydrogen sulphide) and vasoconstrictors (*i.e.*, angiotensin II and endothelin) molecules leading to increased intrahepatic vascular resistance .[6–10] Portal hypertension is therefore not only the result of distortion of the hepatic histological architecture due to fibrosis and the formation of regenerative nodules, but also to an intense dysregulation of intrahepatic vasoactive mechanisms. An additional functional mechanism of portal hypertension is the increased local release of NO in the splanchnic microcirculation with subsequent vasodilation and increased inflow of blood into the portal venous system.[10–12] The second concept is that, despite numerous attempts to identify potential alternative mechanisms, hyperammonaemia is still considered a key factor in the development of hepatic encephalopathy. Thus, identification of new pathophysiological mechanisms related to hyperammonaemia, new pathways of ammonia entry into the brain, and new processes by which ammonia impairs neuronal function, emphasised the major role of hyperammonaemia in the development of hepatic encephalopathy.[13–22] Finally, the pathophysiology of ascites was reformulated in 1988 by an international group of investigators according to the new concept of portal hypertension and in line with studies showing that decompensated cirrhosis develops in the setting of decreased vascular resistance in the splanchnic circulation, decreased cardiac output, and homeostatic activation of the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone to maintain arterial pressure (peripheral arterial vasodilation hypothesis of ascites).[23] Accordingly, splanchnic arterial vasodilation and left ventricular dysfunction are considered the initial events of ascites formation, while homeostatic activation of endogenous vasoconstrictor systems is seen as the intermediate process, and renal fluid retention forming ascites the final consequence.

Fig. 1 illustrates the complexity of AD. At the time of admission to hospital, patients with AD presented 15 different combinations of major complications;[24,25] approximately 1 in every 3 of these patients presented ACLF at admission or developed the syndrome during early follow-up (1–3 months); also, the number of failing organ systems (liver, kidney, brain, coagulation, circulation and respiration) in these patients ranged between 1 and 6. Therefore, stratification of patients with AD is a major challenge.

Background of systemic inflammation in cirrhosis

Bacterial translocation, as defined by the passage of viable bacteria or bacterial byproducts (pathogen-associated molecular patterns [PAMPs], *e.g.* lipopolysaccharide [LPS]) through the gut mucosa to the systemic circulation (Fig. 2A), and the secondary systemic inflammation, have been well-known features of decompensated cirrhosis for many

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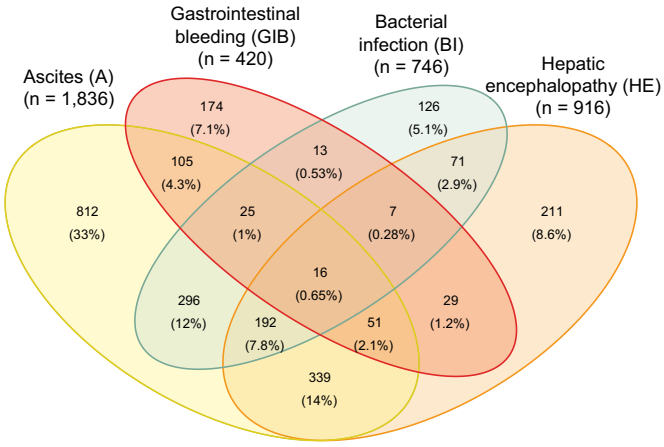

Fig. 1. Combinations of major complications at AD development. The four-ellipse Venn's diagram was constructed merging data from the CANONIC and PREDICT studies (2,467 patients).

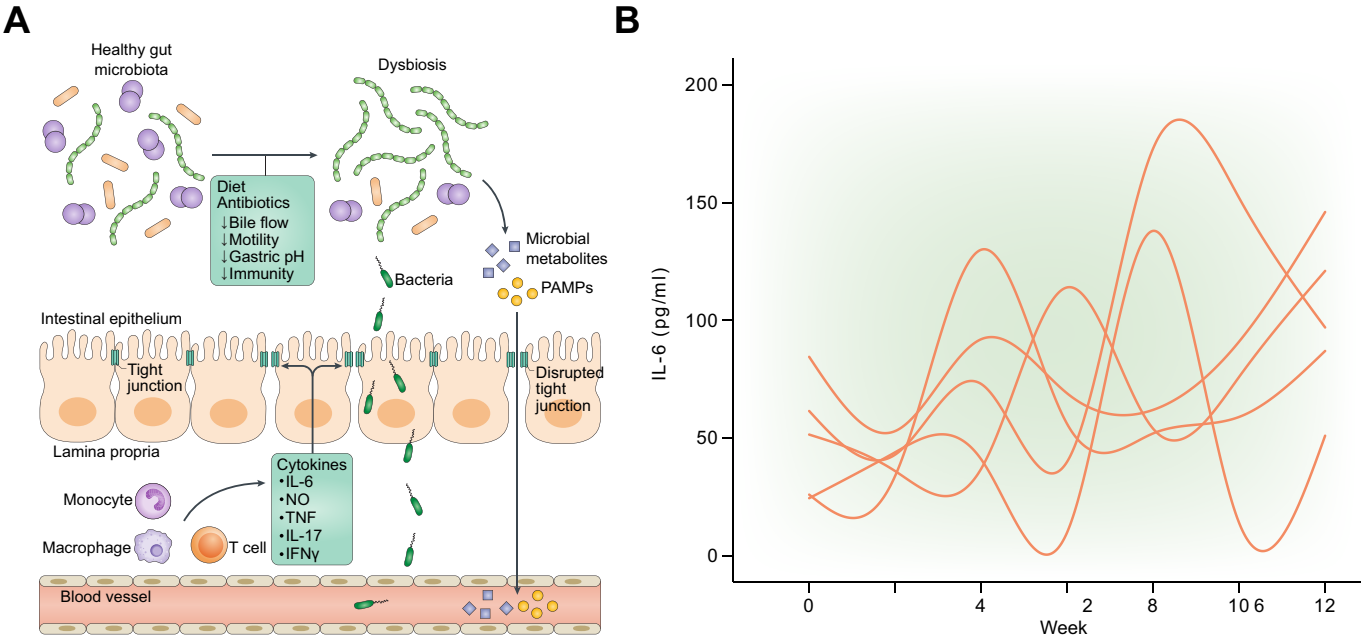

Fig. 2. Bacterial translocation. (A) Intestinal dysbiosis and bacterial translocation. Cirrhosis is associated with bacterial overgrowth and qualitative changes in the intestinal microbiota. A second important feature of cirrhosis is the translocation of bacteria or bacterial products from the intestinal lumen to the systemic circulation. Disruption of the tight junctions allows PAMPs and other microbial products to use the paracellular route between adjacent intestinal epithelial cells for translocation. Viable bacteria use a transcellular route (transcytosis). PAMPs activate immune cells in the lamina propria of the intestines, leading to release of inflammatory mediators and NO, which contributes to further dysfunction of tight junctions and to splanchnic arterial vasodilation that characterises portal hypertension (Arroyo V. *et al., Nat Rev Dis Primers* (2016) PM10. ID: 27277335 DOI 1038/nrdp.2016.41). (B) Instability of bacterial translocation. Sequential measurement of the plasma IL-6 levels (ELISA, normal upper value <5 pg/ml), as marker of systemic inflammation, in 5 selected patients hospitalised for the treatment of an episode of AD. The study was performed during a follow-up period of 14 weeks after discharge. Since patients did not present bacterial infections or any other significant event during this period, the peaks of the circulating levels of IL-6 were interpreted as secondary to transient bursts of translocation of PAMPs (Fernandez J. *et al., Gastroenterology* 2019; 157:149-162). IFN, interferon; IL-, interleukin-; NO, nitric oxide; PAMPs, pathogen-assocated molecular patterns; TNF, tumour necrosis factor.

years. In the 1950s, among the standard laboratory tests routinely used for the assessment of patients with cirrhosis, the plasma concentration of gamma-globulin became an important component. Hypergammaglobulinemia, which is common in decompensated cirrhosis, was considered a signal of the escape of intestinal antigens into the systemic circulation and correlated with prognosis. In the 1960s, spontaneous bacterial peritonitis was recognised as a specific infection of decompensated cirrhosis secondary to translocation of viable bacteria to the systemic circulation and

ascites.[26] Wilkinson *et al.*, Tarao *et al.*, and Triger *et al.*, first reported in the 1970s that circulating levels of LPS are increased in patients with acute liver failure or with cirrhosis and AD in association with renal failure and poor prognosis.[27–29] In 1998 and 2003, Navasa *et al.* and Albillos *et al.* presented data suggesting for the first time that bacterial translocation and systemic inflammation are chronically present in non-infected patients with decompensated cirrhosis.[30,31] For decades intestinal bacterial overgrowth and increased permeability of the mucosal barrier to bacteria and bacterial products were considered the main mechanism of chronic bacterial translocation and systemic inflammation in cirrhosis .[32,33] This has recently been confirmed by metagenomics studies showing that an altered profile of human gut microbiota is associated with complications of cirrhosis .[34,35] Finally, Fernández *et al.* have shown that chronic systemic inflammation in cirrhosis, as estimated by the sequential measurement of plasma interleukin (IL)-6, is not a steady process. Indeed, in some patients, plasma IL-6 levels displayed a waxing and waning profile, with extremely high peaks, the duration of which ranging from days to weeks[36] (Fig. 2B). These peaks likely relate to transient episodes of massive translocation of PAMPs.

Systemic inflammation in decompensated cirrhosis is a chronic condition related to sustained translocation of bacterial products from the intestinal lumen to the systemic circulation. Bursts of systemic inflammation related to episodic aggravations of bacterial translocation or to proinflammatory precipitants (mainly bacterial infections, alcoholic hepatitis, and hepatitis B reactivation) are the mechanisms by which organ system dysfunctions or failures develop.

Interest in systemic inflammation in decompensated cirrhosis increased after the pioneering observational study by Rolando *et al.* of 887 patients admitted to hospital with acute liver failure.[37] Patients were investigated by sequential assessment of the systemic inflammatory response syndrome (SIRS), which was present in 56% of patients irrespective of whether the patients had bacterial infections or not. Severity of SIRS was associated with a more critical illness, progression of encephalopathy, multiorgan failure and death. Following this publication, the number of studies investigating systemic inflammation as a potential mechanism of AD increased markedly (reviewed in detail in references 38–41).

Infections are well-known precipitants of encephalopathy. Indeed, 1 in every 3 patients hospitalised with encephalopathy also have bacterial infections at admission, whereas the prevalence of infections in patients with gastrointestinal haemorrhage is less than 2% [24,25] (Fig. 1). Moreover, patients with decompensated cirrhosis and infections challenged with a dose of oral amino acids mimicking haemoglobin composition, had significant impairment in neuropsychological scores associated not only with hyperammonemia but also SIRS, suggesting that inflammation modulates the cerebral effect of ammonia.[42] This synergy probably relates to the effect of cytokines and reactive molecules on blood-brain barrier permeability, entry of ammonia and inflammatory mediators into the brain, secondary activation of microglia and neuroinflammation .[40,41,43,44]

There is also evidence that systemic inflammation is involved in the acute development of ascites and renal failure. In fact, ascites and bacterial infections occur concurrently in 30% of patients hospitalised with AD (Fig. 1). Moreover, bacterial infections are well-recognised precipitants of hepatorenal syndrome (HRS).[45] Finally, as observed in sepsis, systemic inflammation related to bacterial infections in decompensated cirrhosis may worsen liver failure, impair left ventricular contractibility, and reduce vascular resistance in the splanchnic and systemic circulation.[38,39]

Clinical studies on the potential role of systemic inflammation in gastrointestinal haemorrhage in cirrhosis are scarce .[46,47] In contrast, there are many experimental studies indicating that systemic inflammation may exacerbate portal hypertension (reviewed in detail by Mehta *et al.* in reference 39). Serum bacterial DNA levels, an inducer of inflammation, as well as the severity of systemic inflammation correlate with the severity of portal hypertension in patients with cirrhosis.[46] Moreover, in patients with spontaneous bacterial peritonitis, those with higher plasma levels of tumour necrosis factor (TNF)-α had higher portal pressures .[47] Systemic inflammation activates Toll-like receptors on hepatic stellate cells making them responsive to the increased circulating levels or local release of vasoconstrictors (endothelin, norepinephrine, angiotensin II, leukotrienes and thromboxane A2). These activated cells cover the sinusoidal network through cellular extensions and can modulate intrahepatic vascular resistance through contractibility .[9,48] Moreover, Kupffer cells, the resident macrophages in the liver, are activated in the setting of systemic inflammation, increasing the production of proinflammatory cytokines and reactive oxygen species (ROS) .[49,50] Next, oxidative stress decreases local NO bioavailability and activity through several mechanisms, including direct interaction of ROS with NO, which leads to the formation of peroxynitrite and other ROS ,[51] and inhibition of endothelial NO synthase (eNOS) via increased formation of eNOS inhibitors .[51] Therefore, systemic inflammation may induce a disequilibrium between vasoconstrictor and vasodilator mechanisms within the liver, leading to increased vascular resistance .[39] This concept is supported by the observation that high-density lipoprotein administration, which has an anti-inflammatory effect by neutralising circulating

LPS, attenuates the liver proinflammatory response, restores liver eNOS activity and lowers portal pressure in rats with experimental cirrhosis challenged with LPS.[52]

Systemic inflammation is the common mechanism for major complications and organ failures in AD

Most of the concepts included in this section largely derive from the CANONIC and PREDICT studies. Both studies were observational prospective investigations in large cohorts of non-selected patients hospitalised with AD.[24,25] The aim of these studies was to characterise the ACLF syndrome at hospital admission (CANONIC study) and to explore the critical periods prior to and within 3 months after admission (early follow-up period) in patients with AD without ACLF (PREDICT study).

Considering the complexity of AD, patient stratification (for prognostic classification) was the initial analytical process in both studies. This was relatively simple in patients with ACLF (AD-ACLF phenotype, CANONIC study), since stratification according to the number of organ system failures at admission resulted in 3 clearly distinct subgroups (ACLF-1, 1 organ system failure; ACLF-2, 2 organ system failures; and ACLF-3, 3 to 6 organ system failures), with different clinical courses and prognoses (Box1, Fig. 3A).[24] However, this was less easy

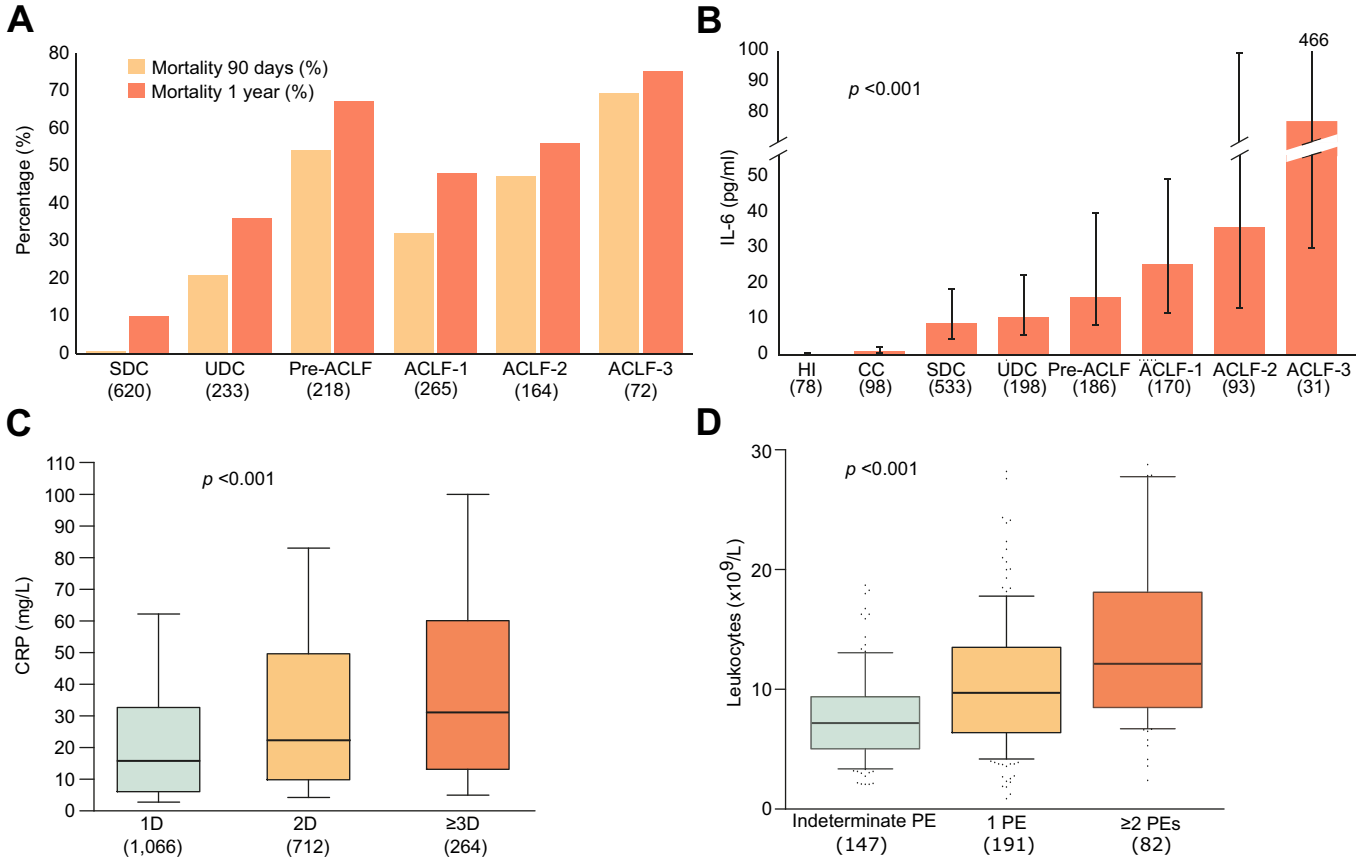

Fig. 3. Systemic inflammation, clinical course, decompensations and precipitating events. (A) Prognosis of patients with the different subtypes of AD. Patients with AD-No ACLF included in the PREDICT study were stratified into 3 subgroups according to the clinical course during the 3-month follow-up period after admission: SDC, UDC and pre-ACLF. Patients with AD-ACLF at hospital admission from an integrated cohort including patients from the CANONIC and PREDICT studies were stratified into 3 groups according to the number of organ failures at admission: ACLF-1, ACLF-2, ACLF-3 (see Box 1 for additional information). (B) Systemic inflammation across the stratified patient subgroups. The panel shows the plasma concentration of IL-6 (multiplex immunoassay, normal median value 0.5 pg/ml; IQR 0.2–0.7 pg/ml) in HIs and in patients with CC, patients with SDC, UDC and Pre-ACLF at admission included in the PREDICT study, and in patients with ACLF-1, ACLF-2 and ACLF-3 at admission included in an integrated cohort of patients from the CANONIC and PREDICT studies. The plasma concentrations of IL-6 were markedly elevated in patients with SDC compared to patients with CC, and steadily increased across the different groups of patients up to the ACLF-3 group, except for the UDC group, which showed similar values as the SDC group. *p* value was from a Kruskal Wallis test. (C) Association of systemic inflammation with the number of decompensations (ascites, encephalopathy, gastrointestinal hemorrhage or bacterial infections). The number of decompensations correlated directly with the severity of systemic inflammation, as estimated by the plasma levels of CRP. *p* value was from a Kruskal Wallis test. (D) Severity of systemic inflammation according to the number of PEs. The panel shows that the severity of systemic inflammation at admission in patients with AD, as estimated by the absolute white blood cell count, varied in parallel with the number of PEs. The analysis was performed in patients with and without ACLF included in the PREDICT study and indicates that the effects of PEs as inflammatory promoters are additive. *p* value was from a Kruskal Wallis test. ACLF, acute-on-chronic liver failure; AD, acute decompensation; D, decompensation; CC, compensated cirrhosis; CRP, C-reactive protein; HIs, healthy individuals; IL-6, interleukin-6; PEs, precipitating events; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

Box 1. Definitions proposed by the systemic inflammation hypothesis.

Acute decompensation-related definitions

Acute decompensation (AD): defines the acute development of ascites, encephalopathy, gastrointestinal bleeding, bacterial infection or any combination of these complications. Bacterial infection may precipitate and/or constitutes part of the AD process.

Classification of infections according to their role on AD (PREDICT study)

- Precipitant: proven infection cured within 48 hours prior to the onset of AD or diagnosed at the time of AD.
- Decompensation: infections diagnosed at the time of the first episode of AD or thereafter.
- Unrelated: isolated bacterial infections in patients with compensated cirrhosis.
- Decompensation: each of the individual major complications of cirrhosis (ascites, encephalopathy, gastrointestinal bleeding related to portal hypertension and infections).

Compensated cirrhosis: the disease phase prior to the first AD.
Decompensated cirrhosis: the disease phase after the first AD.
Acute-on-chronic liver failure (ACLF): AD associated with single or multiple (≥2) organ failure(s) and high risk (>15%) of short-term (28-day) mortality.

Stratification of AD (CANONIC and PREDICT studies)

AD-No ACLF phenotype or "mere" AD: AD without diagnostic criteria of ACLF

- Stable decompensated cirrhosis (SDC). AD No-ACLF episode, no death during hospitalisation, no rehospitalisation during early follow-up (3 months after admission).
- Unstable decompensated cirrhosis (UDC). AD No-ACLF episode, death during hospitalisation or early follow-up due to causes other than ACLF, or one or more rehospitalisation during early follow-up.
- Pre-ACLF. AD No-ACLF episode progressing to ACLF development during early follow-up.

AD-ACLF phenotype: AD with diagnostic criteria of ACLF.

- ACLF grade 1 (ACLF-1). AD episode associated with single renal failure, single brain failure associated with renal dysfunction, or single liver, coagulation, circulatory or respiratory failure associated with renal and/or brain dysfunction.
- ACLF grade 2 (ACLF-2). AD episode associated with 2 organ failures.
- ACLF grade 3 (ACLF-3). AD episode associated with 3–6 organ failures.

Clinical course of ACLD (CANONIC study)

Resolution of ACLF: evolution of AD-ACLF (any grade) to AD No-ACLF.
ACLF development: progression of AD No-ACLF to AD-ACLF (any grade).
Improvement of ACLF: decrease of ACLF severity by at least 1 grade.
Worsening of ACLF: increase of ACLF severity by at least 1 grade.
Steady ACLF: ACLF with no changes in grade.

in patients without ACLF (AD-No ACLF phenotype, PREDICT study) until we considered the clinical course during early follow-up as a stratification criterion;[25] this enabled us to identify the following prognostic subgroups (Box 1, Fig. 3A): stable decompensated cirrhosis (SDC, no death during hospitalisation and no re-hospitalisation during early follow-up), unstable decompensated cirrhosis (UDC, death by any cause other than ACLF during first hospitalisation or at least 1 re-admission during early follow-up), and pre-ACLF (ACLF development during the 3-month follow-up period). The 3-month and 1-year mortality rates after admission increased progressively and in parallel with the severity of AD in all 6 subgroups except for the pre-ACLF subgroup, which showed a distinctly higher mortality than the ACLF-1 and ACLF-2 subgroups (Fig. 3A).

The identification of clear clinical phenotypes of AD and ACLF enabled us to address key questions regarding the relationships between these phenotypes and systemic inflammation. These key questions and their respective answers are discussed in the following sections

Do all patients with AD exhibit systemic inflammation at hospital admission and during early follow-up? Is the severity of systemic inflammation correlated with the severity of AD?

The plasma levels of IL-6, a sensitive marker of systemic inflammation, and of other cytokines and chemokines were evaluated to address this question (PREDICT study database, unpublished observations). IL-6 plasma levels were normal at admission in only 40 (3.3%) of the 1,211 patients with AD included in the analysis (unpublished observation). Additionally, 37 of these patients showed high plasma levels of 2 or more other markers of systemic inflammation (TNFα, IL-8, IL-10, IL-1RA and C-reactive protein [CRP]). Therefore, only 3 patients (0.24%) showed no biological evidence of systemic inflammation at presentation. In contrast, of the 97 patients with compensated cirrhosis (*i.e.* out-patients with no history of AD) included in the analysis, 48 (49.4%) showed normal plasma levels of IL-6, and 24 (24.7%) showed normal plasma levels of all other markers of systemic inflammation. Moreover, while plasma levels

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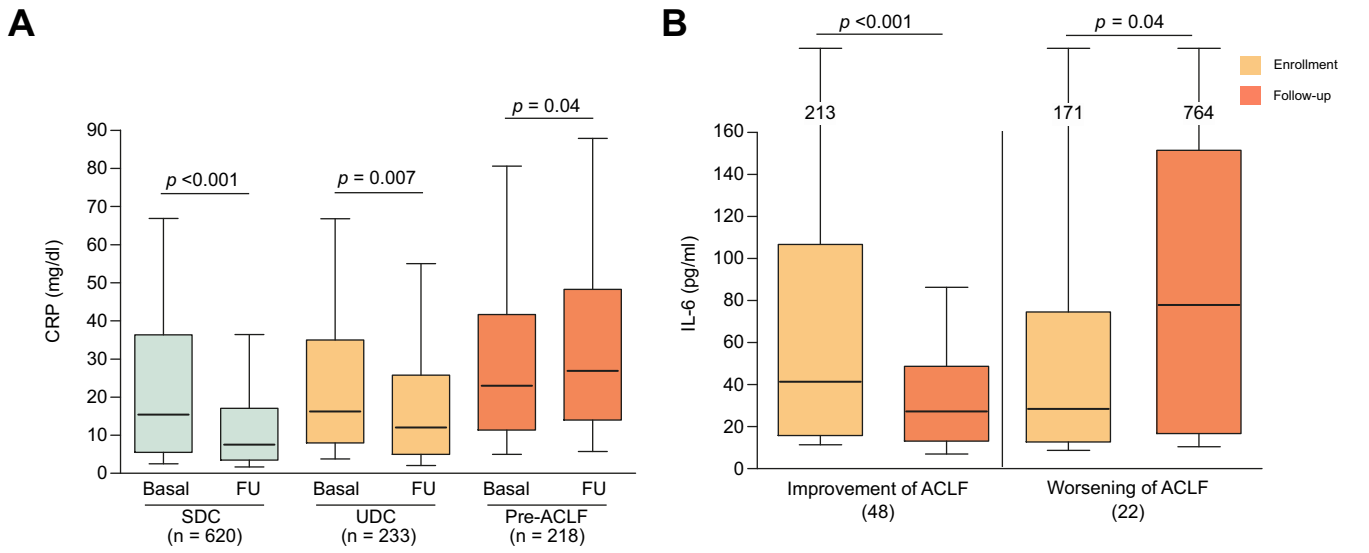

Fig. 4. Clinical course of patients with AD-No ACLF and AD-ACLF. (A) Association between systemic inflammation and clinical course in patients with AD-No ACLF. The plasma levels of CRP (normal range 0.8–3.0 mg/dl) increased during early follow-up in patients included in the PREDICT study with pre-ACLF and decreased in patients with SDC. (B) Association between systemic inflammation and clinical course in patients with AD-ACLF. The plasma levels of IL-6 (multiplex immunoassay, normal median value 0.5 pg/ml; IQR 0.2–0.7 pg/ml) decreased significantly in patients included in the CANONIC study who showed improvement of the ACLF grade and increased in patients who showed worsening of the ACLF grade during hospitalisation. *p* values were from a Wilcoxon signed ranks test. ACLF, acute-on-chronic liver failure; AD, acute decompensation; CRP, C-reactive protein; FU, follow-up; IL-6, interleukin-6; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

of these inflammation markers were only slightly increased in patients with compensated cirrhosis, they were markedly elevated in most patients with AD (Fig. 3B). Finally, elevated plasma levels of these inflammation markers were observed in all patients with AD during early follow-up. Therefore, the transition from compensated to decompensated cirrhosis and the recurrence of AD occur in the setting of severe systemic inflammation,[25,53] which persists following AD resolution.

In the patients with AD, the intensity of systemic inflammation at admission increases progressively from the best (UDC) to the worst (ACLF-3) prognostic subgroup (Fig. 3B) .[25,53] Systemic inflammation also correlated with the number of decompensations at admission, which is also a prognostic marker in AD (Fig. 3C) (unpublished observations). Therefore, the intensity of systemic inflammation at admission correlates with the clinical phenotypes of the AD syndrome as well as short- and long-term prognosis.

Do type and number of precipitants impact the severity of systemic inflammation at admission?

AD frequently follows a major clinical event that may act as a precipitating factor. In Europe, the most frequent precipitants are bacterial infections and acute alcoholic hepatitis, which are present, either as a single precipitant, pair of precipitants, or associated with other precipitants, in more than 90% of patients with identifiable precipitants. Patients with any precipitant represent 44% of AD-No ACLF patients and 70% of AD-ACLF patients.[54] Bacterial infections and acute alcoholic hepatitis are forceful inducers of systemic inflammation through the release of PAMPs by bacteria or damage-associated molecular patterns (DAMPs) from necrotic hepatocytes. Bursts of bacterial translocation are likely the precipitants of systemic inflammation and AD in more than half of the AD-No ACLF patients and in 30% of AD-ACLF patients. The number but not the type of precipitants impacts the severity of systemic inflammation (Fig. 3D), suggesting a synergetic effect between precipitating events .[54]

Does the evolution of systemic inflammation correlate with the patient's clinical course?

In addition to the clinical characteristics present at hospital admission, the second feature that marks the prognosis of patients with AD is the short-term clinical course, which may follow different trajectories within a few weeks after admission in patients with AD-No ACLF and within a few days in patients with AD-ACLF. As indicated, patients with AD-No ACLF may follow a distinct clinical course which can be benign (SDC), moderately severe (UDC), or extremely severe (pre-ACLF).[25] In patients with SDC, the benign course is associated with marked deactivation of systemic inflammation, while the progression to AD-ACLF observed in patients with pre-ACLF occurs in association with a significant increase in the grade of systemic inflammation, emphasising systemic inflammation as a key mechanism of ACLF (Fig. 4A). The clinical course of patients with UDC, which is characterised

by a higher prevalence of surrogates of severe portal hypertension, is predominantly related to the severity of portal hypertension, which is associated with systemic inflammation. In patients with AD-ACLF, the ACLF syndrome may improve or worsen within a few days after admission in the context of significant deactivation or overactivation of systemic inflammation, respectively (Fig. 4B) .[53] Therefore, in patients with AD-No ACLF as well as AD-ACLF, the clinical course is closely correlated with the evolution of systemic inflammation.

The systemic inflammation hypothesis proposes that clinical features of acutely decompensated cirrhosis, including ascites, encephalopathy, gastrointestinal haemorrhage, bacterial infections, and organ system dysfunction or failure, share a common pathophysiological mechanism which is systemic inflammation.

Which mechanisms underpin the link between systemic inflammation and multiorgan dysfunction or failure?

Systemic inflammation is traditionally thought to cause organ dysfunction and failure through 2 different mechanisms which are not mutually exclusive. First, systemic inflammation, by stimulating NO production in splanchnic arterioles may accentuate the preexisting systemic circulatory dysfunction resulting in a further decrease in effective arterial blood volume and overactivation of endogenous vasoconstrictor systems. This overactivation causes vasoconstriction in several vascular beds resulting in organ hypoperfusion and subsequently impaired organ function .[23,38] For example, intense renal vasoconstriction is a central mechanism in the development of type-1 HRS (an acute kidney injury that is specific to cirrhosis and a form of ACLF). Second, systemic inflammation may be associated with an activation of immune cells resulting in tissue damage and impaired organ function .[38] Recently, a third mechanism that involves metabolic alterations associated with systemic inflammation and may develop on top of the 2 other mechanisms has been suggested to play a role in the development of organ dysfunction and failure in patients with cirrhosis. Indeed, results of blood metabolomics obtained in a large series of patients with AD of cirrhosis (with and without ACLF) ,[55–57] along with data accumulated in the field of immunology of sepsis ,[58–63] suggest that activated innate immune cells, which have a high metabolic demand, are prioritised in the allocation of circulating nutrients (glucose, amino acids, fatty acids) [57,64] (Fig. 5A). Thus, activated innate immune cells are the site of an energy-consuming anabolic metabolism required to produce soluble inflammatory mediators (proteins and lipids), acute-phase response, respiratory burst, and cell proliferation (resulting in leukocytosis). One way in which systemic inflammation leads to the reallocation of nutrients to the immune system is by inhibiting nutrient consumption in peripheral organs, an effect that results in decreased mitochondrial O_2 consumption and ATP (energy) production. The cost of decreasing mitochondrial energy production may be peripheral organ dysfunction and, in extreme cases, multiorgan failure.

Connection between systemic inflammation hypothesis and the classical physiopathological concepts of ascites, encephalopathy and variceal bleeding

In patients with cirrhosis there is no ascites without sodium retention, encephalopathy without hyperammonaemia or variceal bleeding without significant portal hypertension. However, none of these complications develop without systemic inflammation. Therefore, systemic inflammation and these organ-specific mechanisms are likely to act synergistically in the development of major complications of cirrhosis. In fact, as indicated, systemic inflammation alone can affect brain function and effective arterial hypovolemia and increase portal hypertension in cirrhosis. It is also likely that the acute burst of systemic inflammation preceding AD may reduce the critical threshold level of cerebral ammonia, effective arterial blood volume or portal hypertension leading to the development of encephalopathy, ascites and/or variceal haemorrhage.

Bacterial infections in AD may be caused by immunoparesis

Immunoparesis was first described as a mechanism of primary or secondary infection in patients with sepsis .[65–67] Among 407 patients with AD-ACLF enrolled in the CANONIC study, the incidence of infections at admission and during a 28-day follow-up period was 65%.[68] The corresponding incidence of infections in the 1,071 patients with AD-No ACLF from the PREDICT study was 53%.[25,54] Such extremely high incidences of infections strongly suggest immunoparesis. In addition, many of our patients had severe alcoholic hepatitis and some received corticosteroids, which may induce immunosuppression, contributing to their susceptibility to bacterial infections.[69,70]

There are results suggesting mechanisms by which immunoparesis may develop in patients with AD. The blood levels of soluble molecules known to induce immunoparesis, including the anti-inflammatory cytokines IL-10 and IL-1RA, and the tryptophan catabolite quinolinate are markedly increased in patients with AD-No ACLF and even more so in those with AD-ACLF.[53,71] Moreover, in patients with AD, subsets of circulating monocytes exhibit features of immune incompetence. These cells are present in patients with AD-No ACLF and their number increases in patients with AD-ACLF.[72–75] Patients with severe alcoholic hepatitis have reduced frequencies of myeloid mononuclear

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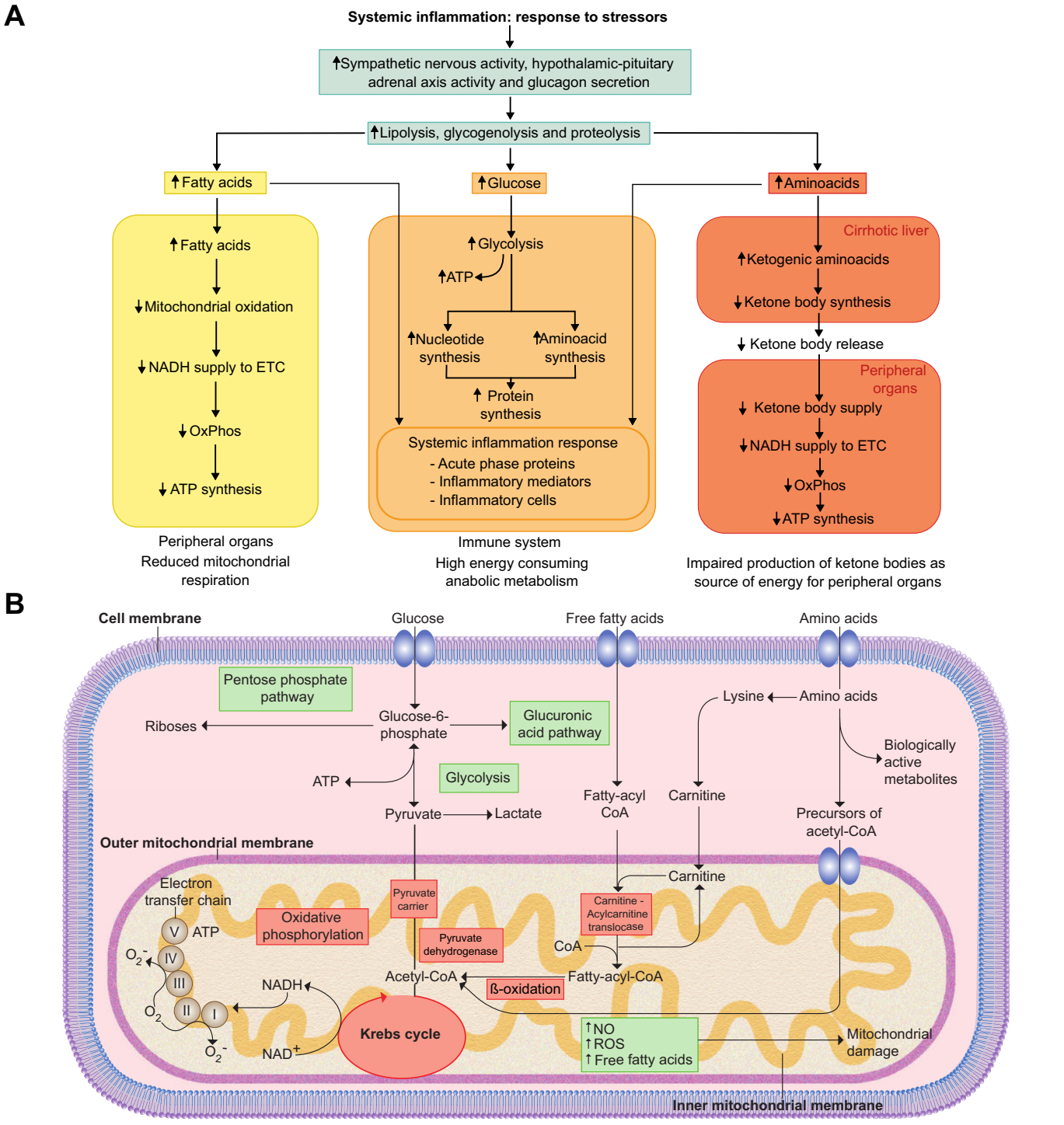

Fig. 5. Metabolic abnormalities and energy production in AD. (A) Schematic of the metabolism of glucose, fatty acids and amino acids. The panel shows the 3 major disorders of energetic metabolism in patients with AD: i) The increased systemic catabolic metabolism in response to systemic inflammation (upper part of the panel), which leads to intense lipolysis, glycogenolysis and proteolysis and release of fatty acids, glucose and amino acids to the immune system and peripheral organs; ii) the anabolic and increased energetic metabolism (ATP synthesis) by the innate immune cells (central box); iii) the reduced mitochondrial respiration and energy production by peripheral (non-immune) cells (lateral boxes). (B) Major abnormalities of cell metabolism in AD. In cytosol, there is activation of aerobic glycolysis, pentose phosphate and glucuronic pathways, and ATP and lactate synthesis. As indicated in Panel A (central box), glucose metabolism occurs predominantly in the immune cells. In the mitochondria, there is downregulation of carnitine-acylcarnitine translocase, and inhibition of β-oxidation, leading to fatty acid hypometabolism by the Krebs cycle and impaired oxidative phosphorylation and ATP synthesis. There is also increased mitochondrial oxidative stress and protein damage, which further impairs mitochondrial function. As indicated in Panel A (left box), these features occur in the cells of peripheral organs. The net effect of the whole process is an increased production of energy by the immune system and hypometabolism and decreased energy production by peripheral organs. In addition, there is a marked reduction in the hepatic production by the cirrhotic liver of ketone bodies (right-upper box), thus depriving the peripheral organs for another source of acetyl-CoA (right-lower box). These changes explain the widespread dysfunction of peripheral organs in non-severe cases (AD-No ACLF clinical phenotype) and multiorgan failure (AD-ACLF clinical phenotype) in cases with extreme mitochondrial dysfunction. Overexpressed and underexpressed mechanisms represented in green and red colour, respectively. (Modified from Arroyo *et al.*, *N Engl J Med* 2020; 382:2137-2145). ACLF, acute-on-chronic liver failure; AD, acute decompensation; ETC, electron transport chain; NO, nitric oxide; OxPhos, oxidative phosphorylation; ROS, reactive oxygen species.

cells, including conventional and plasmacytoid dendritic cells.[76] Moreover, in these patients, circulating $CD14^+$ monocytes exhibit transcriptional alterations characterised by downregulation of major innate immune and metabolic pathways and upregulation of important genes known to induce immunoparesis .[76] These changes in gene expression were closely associated with corresponding changes in chromatin accessibility at the gene promoter level, suggesting that epigenetic regulation plays a crucial role in the development of monocyte immunoparesis in the context of severe alcoholic hepatitis. In patients with decompensated cirrhosis, the ability of circulating neutrophils to migrate, recognise bacteria, and kill bacteria (by engulfment, phagocytosis, degranulation, rapid production of large amounts of ROS [respiratory burst] and neutrophil extracellular trap [NET] formation) is defective.[77] A defect in respiratory burst is a hallmark of neutrophils and monocytes in severe alcoholic hepatitis .[77] Of note, alterations in T cells and natural killer cells have been shown to be involved in immunoparesis and the development of secondary infections in patients with protracted sepsis .[67] Because little is known about T cells and natural killer cells in the context of AD, these cells should be investigated in this context. In sum, simultaneous increases in plasma levels of soluble proinflammatory signals, immunosuppressive molecules, and immune-incompetent myeloid cells, strongly suggest that immunoparesis occurs early, as a compensatory mechanism in AD, to limit the vigorous proinflammatory response seen in affected patients. Based on these data, bacterial infections present at admission, or that develop thereafter, can be considered as likely complications of immunoparesis within the framework of the systemic inflammation hypothesis.

Liver failure and acute kidney injury in AD as seen by the systemic inflammation hypothesis

The liver is a component of the innate immune system. PAMPs and proinflammatory cytokines induce sustained synthesis of positive acute-phase proteins, including CRP, serum amyloid protein and mannose-binding protein, which promotes pathogen clearance through complement activation and phagocytosis .[78] Another acute-phase protein is hepcidin, whose role is to limit the availability of iron, which is vital for invading microbes .[79] The liver is, therefore, a site of an extensive energy-consuming anabolic metabolism during systemic inflammation. To cope with the high cost of the synthesis of positive acute-phase proteins, repression of the synthesis of negative acute-phase proteins, such as albumin and transferrin, occurs.[78] It is plausible that the *de novo* synthesis of other hepatic proteins (*e.g.* coagulation proteins) decreases in order to "spare" oxygen. Indeed, systemic inflammation also inhibits hepatic biotransformation,[80] the enzymatic transformation of lipophilic molecules (*i.e.* bilirubin) into water soluble molecules, which is an important energy-consuming process. The inhibition of hepatic biotransformation in sepsis is induced by proinflammatory cytokines and results in hyperbilirubinemia and jaundice .[80] Collectively, these findings suggest that systemic inflammation in AD elicits an energetic trade-off between the synthesis of acute-phase proteins and other biosynthetic processes, resulting in the progressive decline of liver function and, ultimately, liver failure.

Patients with cirrhosis are prone to develop acute kidney injury, which is traditionally thought to be functional and related to renal hypoperfusion. Acute kidney injury, which also commonly develops in the general population of patients with sepsis, is traditionally attributed to renal tubular cell death (necrosis or apoptosis) secondary to renal ischaemia. However, these traditional views are challenged by recent findings. Acute kidney injury associated with sepsis may develop in the setting of normal or even increased total renal perfusion, it commonly occurs in the absence of significant histological signs of tubular necrosis or apoptosis, and is characterised by heterogeneous dysfunction in the microcirculation and downregulation of energy production by the tubular epithelial cells.[81–83] That said, in the only study published to date assessing renal lesions in biopsies from patients with decompensated cirrhosis, Trawalé *et al.* observed fibrosis and interstitial inflammation by mononuclear and polymorphonuclear leukocytes as the most obvious features .[84] Inflammation was closely associated with renal failure. Overexpression of Toll-like receptors by epithelial tubular cells was also reported in another study on kidney biopsies.[85] Therefore, the following 4 major steps proposed to explain the development of acute kidney injury during sepsis[86,87] may also be applied to acute kidney injury in cirrhosis: i) Damage of the glycocalyx covering the microvascular endothelium by PAMPs, DAMPs and cytokines, exposing adhesion molecules and facilitating the transmigration of activated leukocytes to the peritubular interstitium. ii) Extension of inflammation to the epithelial tubular cells, either via interaction of circulating PAMPs, DAMPs and inflammatory cytokines with luminal Toll-like receptors on epithelial tubular cells, or via the extension of interstitial inflammation to the tubules, or both. iii) Induction of tubular cell hypometabolism by the inflammatory milieu enabling nutrients to be reallocated to activated immune cells. iv) Downregulation of tubular function, leading to increased sodium release to the macula densa, activation of the glomerulus-tubular feedback mechanism, massive intrarenal release of angiotensin II, vasoconstriction of the afferent

arteries and reduction of the glomerular filtration rate.

This new pathophysiological concept is also supported by the recent observation of Piano *et al.* that the renal response to terlipressin and albumin in patients with type-1 HRS is highly dependent on the grade of ACLF .[88] Resolution of HRS (normalisation of serum creatinine) was obtained in 60% of patients with ACLF-1, in 42% of patients with ACLF-2, and in only 29% of patients with ACLF-3. It appears as if both renal vasoconstriction secondary to effective arterial hypovolemia and intrarenal mechanisms secondary to renal inflammation operate simultaneously in patients with HRS. When systemic inflammation, and probably also renal inflammation, is not extreme, as in patients with ACLF-1, HRS likely responds to improvement in systemic haemodynamics by plasma volume expansion and vasoconstrictors. However, this is not the case in patients with ACLF-3, in whom HRS would be predominantly related to renal inflammation.

Albumin treatment downregulates systemic inflammation in decompensated cirrhosis

Prevention of circulatory dysfunction after therapeutic paracentesis and prophylaxis and treatment of HRS are well-recognised indications for albumin treatment in cirrhosis .[89] Moreover, long-term albumin treatment has recently been shown to reduce the number of episodes of AD and to increase survival in patients with cirrhosis and AD-No ACLF.[90] A recent study in patients with AD suggests that these beneficial effects are related to downregulation of systemic inflammation since both acute and long-term (14 weeks) albumin administration at high dosages significantly reduced the plasma levels of CRP and cytokines [36].

Systemic inflammation causes multiorgan dysfunction (AD No-ACLF) or failure (AD-ACLF) through 3 different mechanisms: first, synergy with organ-specific pathophysiological pathways; second, immunopathology (direct tissue damage by the inflammatory process); and third, reduction of mitochondrial respiration (hypometabolism) in the non-immune organs as a metabolic regulation reallocating nutrients to the activated immune system.

The molecular mechanisms underlying the immunomodulatory properties of albumin were also recently identified .[91] Experiments in isolated leukocytes from patients with AD-No ACLF and AD-ACLF demonstrated that albumin abolishes cytokine expression and release induced by bacterial DNA rich in unmethylated CpG-DNA (Fig. 6A,B). The immunomodulatory actions of albumin were related to its internalisation into the cytosol of leukocytes (Fig. 6C) and, specifically, to the endosomal compartment (Fig. 6D), where CpG-DNA binds Toll-like receptor 9, its cognate receptor.[92] These findings suggest that albumin modulates responses to PAMPs through interaction with intracellular Toll-like receptor signalling pathways.

Main proposals of the systemic inflammation hypothesis

The proposals presented here are based on data from clinical studies in patients with decompensated cirrhosis, the authors' clinical experience, and concepts derived from studies of other diseases associated with systemic inflammation and multiorgan failure.

1. The term AD is used to define the acute development of one or more of the major complications of cirrhosis. These complications are traditionally thought to develop due to different pathophysiological mechanisms. Acute worsening of portal hypertension and/or liver failure are considered the initial triggers of AD. In contrast, the systemic inflammation hypothesis proposes that AD is a specific clinical entity and that all major complications, including organ system failures, share a common pathophysiological mechanism.
2. Systemic inflammation is the major driver of progression from compensated to decompensated cirrhosis, the recurrence of AD during the clinical course of the disease, and the development of single or multiple organ system failures.
3. Once the first episode of AD develops, systemic inflammation follows a chronic course, with transient episodes of reactivation due to identifiable proinflammatory precipitants, or to bursts of translocation of viable intestinal bacteria or bacterial products. The repeated episodes of AD during the clinical course of decompensated cirrhosis develop in the setting of these reactivations of the immune system.
4. ACLF is the extreme expression of severe systemic inflammation and is associated with a very high risk of short-term mortality. When systemic inflammation progresses rapidly, major decompensations and organ failures coincide leading to the AD-ACLF phenotype which, depending on the intensity of the inflammatory reaction, may evolve to ACLF-1, ACLF-2 or ACLF-3. However, if the progression of systemic inflammation is slower, as it is in patients with pre-ACLF, the AD-No ACLF phenotype precedes ACLF development by days or some weeks. Unfortunately, at present, patients with pre-ACLF cannot be differentiated from patients with UDC and SDC at hospital admission based on standard clinical and laboratory parameters. Once ACLF develops, a patient's clinical course critically depends on the evolution of systemic inflammation.

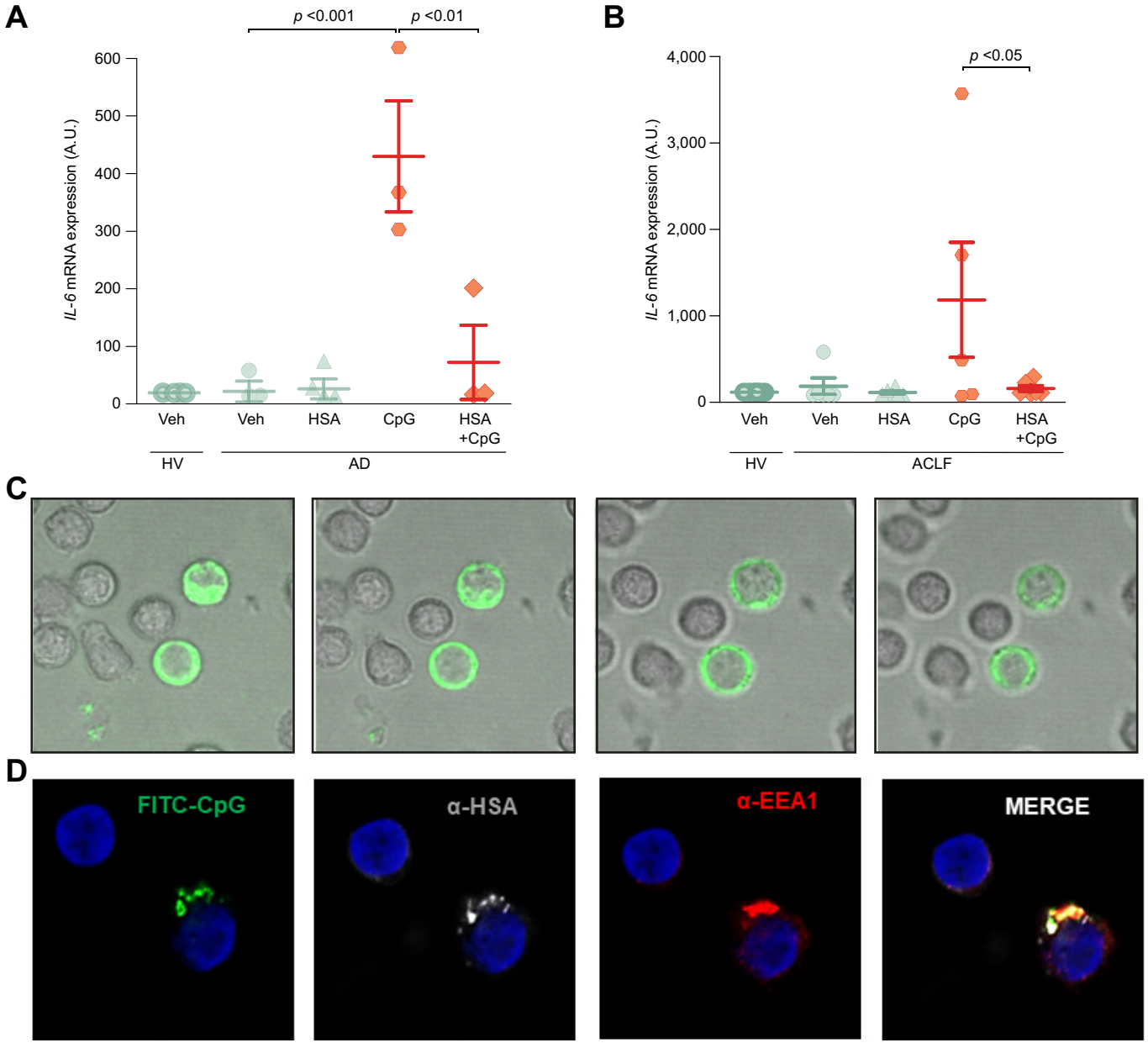

Fig. 6. Immunomodulatory effect of HSA in patients with cirrhosis and its mechanism of action. (A and B) show the ability of albumin to prevent CpG-DNA-induced IL-6 expression in leukocytes isolated from patients with AD-No ACLF (A) and from patients with AD-ACLF (B). *p* values were One-way analysis of variance and paired Student's *t* tests with Welch's correction. (C) Shows representative images segmented in different Z-stacks from the top to the bottom of the plate captured with confocal microscopy of leukocytes incubated with FITC-labelled HSA (green) in combination with CpG-DNA. These data demonstrate that HSA is internalized into the cytoplasm of the leukocytes. (D) shows representative confocal images of triple colocalization of FITC-labelled CpG-DNA (green), HSA (grey) and EEA1 (a marker of early endosomes, red) in human leukocytes. Nuclei are stained with Hoechst 33342 (blue). These data demonstrate that HSA colocalises with CpG-DNA in early endosomes, the cytosolic compartment where CpG-DNA binds its cognate TLR9. (Modified from Casulleras M. *et al., Sci Trans Med,* 2020 Oct 21;12(566): eaax5135. https://doi.org/10.1126/scitranslmed.aax5135). ACLF, acute-on-chronic liver failure; AD, acute decompensation; HAS, human serum albumin; HV, leukocytes from healthy volunteers; Veh, vehicle.

5. The clinical course of patients with AD associated with moderate, non-progressive systemic inflammation depends on the grade of portal hypertension. Patients with severe portal hypertension frequently develop an unstable clinical course (UDC), requiring frequent hospital readmission, and significant short- and long-term mortality. In contrast, if portal hypertension is moderate, systemic inflammation improves after the episode of AD, patients develop a benign stable course (SDC), and long-term mortality is low.

6. Re-compensation of decompensated cirrhosis following successful aetiological treatment (*i.e.* antiviral treatment or sustained alcohol withdrawal) eliminates the risk of AD by improving the diseased liver, which is the primary cause of systemic inflammation.
7. Systemic inflammation perturbs organ function or causes organ failure (AD-ACLF) through 3 different pathways:
   - acting in synergy with organ-specific mechanisms (hyperammonaemia in hepatic encephalopathy, portal hypertension in variceal haemorrhage and effective arterial hypovolemia in ascites).
   - through immune pathology (damage of endothelial glycocalyx, migration of inflammatory cells, and direct tissue damage by cytotoxic mediators).
   - through metabolic dysregulation. This is a major mechanism of AD. Systemic inflammatory responses are energetically expensive processes requiring reallocation of nutrients to the immune system. Therefore, immunity competes with other maintenance programmes (including peripheral organ function homeostasis). The systemic inflammation hypothesis postulates that immune activation in AD causes an energetic trade-off with mechanisms of organ function homeostasis, resulting in peripheral organ hypometabolism and organ dysfunction (AD-No ACLF) or organ failure (AD-ACLF).
8. Systemic inflammation hypothesis and the traditional organ-specific mechanisms of AD (portal hypertension, effective arterial blood volume, and hyperammonaemia) are not mutually exclusive, but rather complementary, since they may act synergistically in the development of ascites and HRS, encephalopathy and gastrointestinal haemorrhage. The systemic inflammation hypothesis offers a rational explanation for the development of multiorgan dysfunction/failure that characterises decompensated cirrhosis.

Final remarks

The systemic inflammation hypothesis shows better agreement with the clinical features of decompensated cirrhosis than the traditional pathophysiological paradigm of the disease. Moreover, the hypothesis is supported by the close relationship between intensity and course of systemic inflammation, and features of decompensated cirrhosis, including severity of AD, clinical course and patient survival. Finally, the identification of an intense metabolic dysregulation, with hypometabolism in peripheral organs, as observed in patients with severe sepsis and other conditions associated with systemic inflammation, offers a rational explanation for the multiorgan dysfunction/failure associated with advanced cirrhosis. We are aware that many aspects proposed here require further investigation. In particular, investigations should address the potential role of bacterial translocation in the chronic systemic inflammation of decompensated cirrhosis and the question of whether acute increases in translocation can explain the frequent AD episodes not associated with identifiable precipitants. The main objective of proposing the systemic inflammation hypothesis for cirrhosis is to provide a new perspective for research that will hopefully facilitate the development of new pathophysiological concepts and improved targeted treatments.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; eNOS, endothelial NO synthase; IL-, interleukin-; LPS, lipopolysaccharide; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; SDC, stable decompensated cirrhosis; SIRS, systemic inflammatory response syndrome; TNF, tumour necrosis factor; UDC, unstable decompensated cirrhosis.

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Conflict of interest

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Ltd. (a spin-out company from University College London), Thoeris GmbH, Cyberliver Ltd. and Hepyx Ltd. None of the other authors have conflicts of interest in relation to the reported study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

VA, PA, RM and RJ elaborated the hypothesis. PA, RM, RJ are co-first authors of the article. VA, PA, RM, RJ and JC wrote the article. JC, JT and JF selected

the data from the CANONIC and PREDICT studies in support of the hypothesis and designed the figures. JC, JT, JF, TG, PC and MB participated in the final discussion of the hypothesis and the critical revision of the manuscript.

Data availability statement

Data used to write this review article were mostly obtained from studies listed in the References section. Unpublished data presented here will be available upon request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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