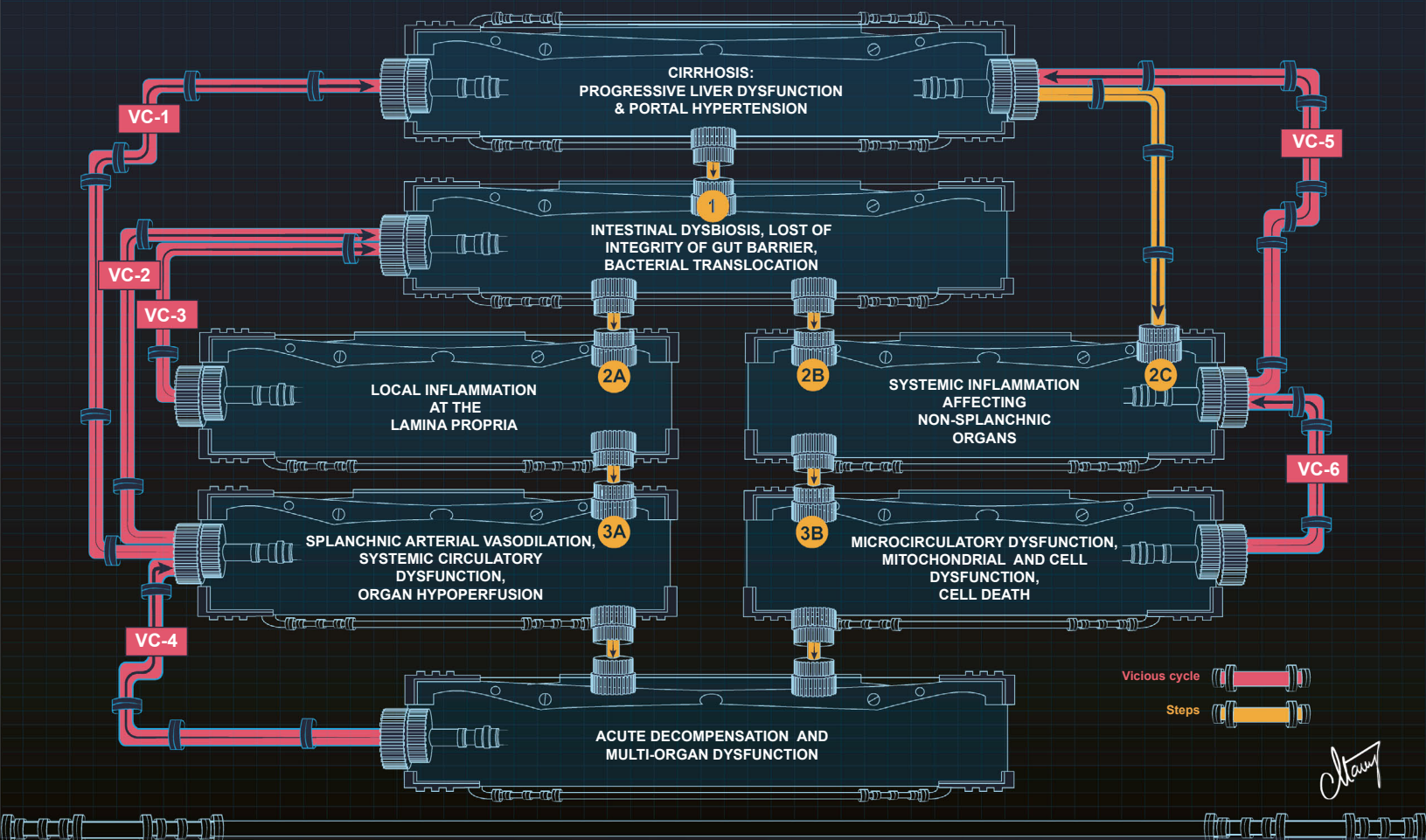# Hepatology Snapshot:
Diagnosis and prognosis of acute on chronic liver failure (ACLF) in cirrhosis

Vicente Arroyo[1,2,*], Richard Moreau[1,3-5]

[1]European Foundation for the Study of Chronic Liver Failure (EF-CLIF); [2]University of Barcelona; [3]INSERM, Université Paris Diderot, Centre de Recherche sur l'inflammation, Paris, France;
[4]DHU UNITY, Service d'hépatologie, Hôpital Beaujon, APHP, Clichy, France; [5]Lbex Inflamex, COMUE Sorbonne Paris Cité, Paris, France
*Corresponding author: European Foundation for the Study of Chronic Liver Failure, Travesera de Gracia 11, 7th Floor, 08021 Barcelona, Spain.
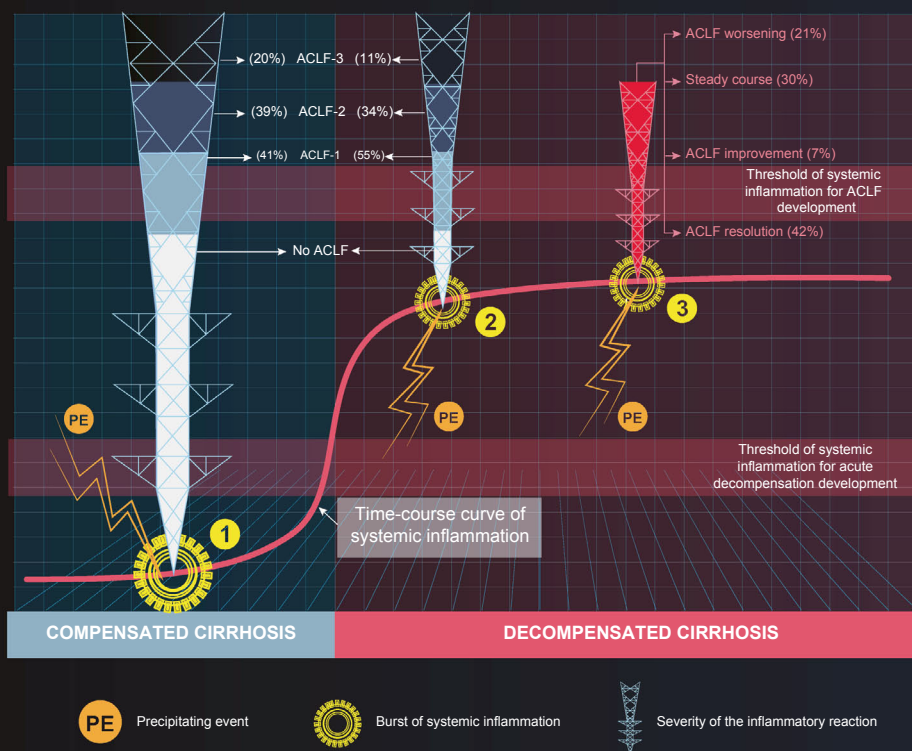
VC-1 · **VC-2** · **VC-3** · **VC-4** · **VC-5** · **VC-6**

CIRRHOSIS: PROGRESSIVE LIVER DYSFUNCTION & PORTAL HYPERTENSION

1 — INTESTINAL DYSBIOSIS, LOST OF INTEGRITY OF GUT BARRIER, BACTERIAL TRANSLOCATION

2A — LOCAL INFLAMMATION AT THE LAMINA PROPRIA

2B · 2C — SYSTEMIC INFLAMMATION AFFECTING NON-SPLANCHNIC ORGANS

3A — SPLANCHNIC ARTERIAL VASODILATION, SYSTEMIC CIRCULATORY DYSFUNCTION, ORGAN HYPOPERFUSION

3B — MICROCIRCULATORY DYSFUNCTION, MITOCHONDRIAL AND CELL DYSFUNCTION, CELL DEATH

ACUTE DECOMPENSATION AND MULTI-ORGAN DYSFUNCTION

Vicious cycle — Steps

Top panel: Mechanism of acute decompensation and multi-organ dysfunction in cirrhosis.

Step 1: Increased translocation of bacteria and pathogen-associated molecular patterns (PAMPs) from the intestinal lumen to the mucosa and the systemic circulation. Step 2A: Initially, the inflammation caused by bacterial translocation is predominantly located at the lamina propria. Step 2B: As the disease progresses, inflammation extends systemically, affecting the extra-splanchnic organs. Step 2C: Systemic inflammation from the release of damage-associated molecular patterns (DAMPs) from the diseased liver (e.g., in the case of acute liver injury in cirrhosis). Steps 3A and 3B: Organ hypoperfusion related to circulatory dysfunction and direct effects of inflammatory mediators are predominant mechanisms for multi-organ dysfunction/failure in cirrhosis. Vicious cycles (VC) contribute to disease progression. (VC-1) Splanchnic arterial vasodilation increases portal venous inflow and portal hypertension. (VC-2) Homeostatic activation of the sympathetic nervous system increases intestinal dysbiosis. (VC-3) Inflammation at the lamina propria impairs the enterocyte tight junctions. (VC-4) Cardiac and adrenal dysfunction impairs systemic circulatory dysfunction. (VC-5) Circulatory dysfunction and systemic inflammation aggravate liver dysfunction. (VC-6) The release of DAMPs from injured extra-hepatic organs contributes to local and systemic inflammation.

Bottom panel: Time-course of systemic inflammation and ACLF development in cirrhosis.

Moderately raised systemic inflammation in compensated cirrhosis, rises during transition to decompensated cirrhosis. ACLF develops after a burst of systemic inflammation after a precipitating event (PE). Inflammatory **Bursts 1 and 2** cause ACLF in compensated and decompensated cirrhosis, respectively. There is a threshold of systemic inflammation for ACLF development; more inflammation is required for ACLF development in compensated cirrhosis compared to decompensated cirrhosis. Compensated cirrhosis is therefore associated with more severe ACLF (percentages of patients developing ACLF-1, -2 and -3) and mortality. **Burst 3** illustrates the short-term (3–7 day) course of ACLF after diagnosis, which correlates closely with the evolution of systemic inflammation and prognosis.

(20%) ACLF-3 (11%)
(39%) ACLF-2 (34%)
(41%) ACLF-1 (55%)
No ACLF

ACLF worsening (21%)
Steady course (30%)
ACLF improvement (7%)
Threshold of systemic inflammation for ACLF development
ACLF resolution (42%)

Time-course curve of systemic inflammation

Threshold of systemic inflammation for acute decompensation development

PE

COMPENSATED CIRRHOSIS — DECOMPENSATED CIRRHOSIS

PE Precipitating event · Burst of systemic inflammation · Severity of the inflammatory reaction

Hepatology Snapshot

Acute-on-chronic liver failure (ALCF) is characterized by three major features:

1) Acute decompensation (AD: ascites, gastrointestinal bleeding and/or encephalopathy)
2) One or more organ failures (OFs)
3) Poor short-term prognosis [1]

The diagnostic criteria of ACLF described in this snapshot were proposed by the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium, after a pragmatic assessment of the CANONIC study, a prospective observational one-year follow-up study in 1343 patients admitted to hospital for AD [1].

The CLIF-SOFA score and its simplified version, the CLIF-C OF score [1–3], which have identical criteria for the diagnosis of OFs, and similar prognostic accuracy, were developed for sequential assessment of organ function and ACLF diagnosis. The cut-off values that limit organ function sub-scores (six in CLIF-SOFA score and three in CLIF-C OF scores) were established based on a 28-day mortality criteria [2]. Definitions of OFs were: liver failure: a serum bilirubin ≥12 mg/dl; renal failure: serum creatinine ≥2 mg/dl or renal replacement therapy; brain failure: West-Haven hepatic encephalopathy grade 3–4; coagulation failure: international normalized ratio (INR) ≥2.5; circulatory failure: use of vasoconstrictors for circulatory support; respiratory failure: PaO_2/FiO_2 ≤200 or SPO_2/FiO_2 ≤214 or mechanical ventilation for respiratory support. Impairment of organ function not fulfilling OF criteria were defined as organ dysfunction (i.e., renal dysfunction: serum creatinine 1–5–1.9 mg/dl; brain dysfunction: West-Haven hepatic encephalopathy grade 1–2). The mean mortality rate reported for severe sepsis in the general population (15% within 28 days) was selected as a cut-off value to define poor short-term prognosis in ACLF.

Four groups of patients were identified according to the number of OFs and 28-day mortality rate (≥ or <15%) [1,2]: 1. ACLF-1 (16% of the patients): includes patients with single renal failure (mortality: 19%) or with single non-renal OF associated with renal or cerebral dysfunction (mortality: 27%). Overall mortality of ACLF-1 patients 22%; 2. ACLF-2 patients (11%): includes patients with two OFs (mortality rate: 32%); 3. ACLF-3 patients (4%): 3-6 OFs (mortality: 78%, ranging from 53% in patients with three OFs to 87% in patients with six OFs); 4. No ACLF patients (59%): No OF (mortality: 4.5%) or single non-renal OF without renal or cerebral dysfunction (mortality: 6.2%). Overall mortality rate of patients with no ACLF: 4.5%.

AD of cirrhosis in patients without ACLF is probably related to translocation of bacteria and pathogen-associated molecular patterns (PAMPs) [2,4,5] and inflammation (Top panel) due to qualitative and quantitative changes of the microbiota and loss of integrity of the intestinal mucosal barrier. Impairment of biliary and gastric acid secretion, intestinal immunity, enterocyte tight junction integrity, Kupffer cell function and intestinal motility are involved in this process. At early phases, when the inflammatory process is predominantly located in the intestinal mucosa, the increase local release of inflammatory mediators, including nitric oxide and other vasodilator molecules, causes splanchnic arterial vasodilation which is compensated by homeostatic increase in cardiac output [6]. With the progression of the disease, however, inflammation extends to the systemic circulation and causes multi-organ dysfunction mainly by two different mechanisms. 1) Organ hypo-perfusion due to progression of splanchnic vasodilation and development of left ventricular dysfunction (cirrhotic cardiomyopathy) [7,8]; 2) Direct deleterious effects of inflammatory mediators in organ microcirculation, cell function and apoptosis [8,9]. Several vicious circles, including the release of damage-associated molecular patterns (DAMPs) by the liver and other dysfunctional organs [10], contribute to progression of AD.

In contrast to AD, which occurs in the setting of a progressive chronic systemic inflammation, ACLF develops as a consequence of an acute burst of systemic inflammation in response to precipitating events (PE: sepsis, acute liver injury due to ischemic, alcoholic, toxic or viral hepatitis, major surgery and others) [1,11,12] (Bottom panel). In 40% of patients in whom no PE is identified, the trigger of the inflammatory burst might be an acute increase of PAMPs translocation without viable bacteria translocation [1,2]. Since the magnitude of chronic systemic inflammation in patients with compensated cirrhosis is low, development of ACLF in these patients is infrequent and requires a severe precipitating event and inflammatory burst. In contrast, patients with decompensated cirrhosis are prone to develop ACLF even in the setting of a non-severe PE (i.e., spontaneous bacterial peritonitis).

Prognosis of ACLF at diagnosis is closely associated with the severity of systemic inflammation and number of organ failures [1]. Two prognostic scores specific for patients with AD (CLIF-C AD score) and with ACLF (CLIF-C ACLF score) [3,13], which provide a significantly better estimate of the risk of death compared with model for end-stage liver disease (MELD), MELD-sodium and Child-Pugh score, were designed with the CANONIC data and validated [2,4]. Since ACLF frequently resolves (evolution to no ACLF), improves (decrease in the number of OFs) or worsens within a short time-period (3-7 days), in parallel with changes in the grade of systemic inflammation [9, 12] and these features markedly influence the outcome, sequential assessment of ACLF grade and CLIF-C ACLF score after admission is essential for accurate prognostication.

Conflict of interest

Financial support

Authors' contributions

VA and RM equally contributed to the manuscript and to the figure.

Acknowledgements

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Author names in bold designate shared co-first authorship

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