



Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis

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Summary

Acute-on-chronic liver failure (ACLF) is a recently recognized syndrome characterized by acute decompensation (AD) of cirrhosis and organ/system failure(s) (organ failure: liver, kidney, brain, coagulation, circulation and/or respiration) and extremely poor survival (28-day mortality rate 30–40%). ACLF occurs in relatively young patients. It is especially frequent in alcoholic- and untreated hepatitis B associated-cirrhosis, in addition it is related to bacterial infections and active alcoholism, although in 40% of cases no precipitating event can be identified. It may develop at any time during the course of the disease in the patient (from compensated to long-standing cirrhosis). The development of ACLF occurs in the setting of a systemic inflammation, the severity of

which correlates with the number of organ failures and mortality. Systemic inflammation may cause ACLF through complex mechanisms including an exaggerated inflammatory response and systemic oxidative stress to pathogen- or danger/damage-associated molecular patterns (immunopathology) and/or alteration of tissue homeostasis to inflammation caused either by the pathogen itself or through a dysfunction of tissue tolerance. A scoring system composed of three scores (CLIF-C OFs, CLIF-C AD, and CLIF-C ACLFs) specifically designed for patients with AD, with and without ACLF, allows a step-wise algorithm for a rational indication of therapy. The management of ACLF should be carried out in enhanced or intensive care units. Current therapeutic measures comprise the treatment for associated complications, organ failures support and liver transplantation.

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Abbreviations: ACLF, Acute-on-Chronic Liver Failure; AD, Acute Decompensation; CANONIC Study, EASL-CLIF Acute-on-Chronic Liver Failure Study; CLIF, Chronic Liver Failure; CLIF-C ACLFs, CLIF Consortium ACLF score; CLIF-C ADs, CLIF Consortium AD score; CLIF-C OFs, CLIF Consortium Organ Failure score; CLIF-SOFAs, CLIF-Sequential Organ Failure Assessment score; CPs, Child-Pugh score; CRP, C-Reactive Protein; DAMPs, Danger/Damage-Associated Molecular Patterns; E, epinephrine; EASL, European Association for the Study of the Liver; ER, Endoplasmic Reticulum; FIO₂, fraction of inspired oxygen; HBV, hepatitis B virus; HE, hepatic encephalopathy; INR, International Normalized Ratio; LPS, Lipopolysaccharide; MAP, mean arterial pressure; MARS, Molecular Adsorbent Recirculating System; MELDs, Model of End-Stage Liver Disease; MELD-Nas, MELD-Sodium score; NE, norepinephrine; NO, Nitric Oxide; PAMPs, Pathogen-Associated Molecular Patterns; PaO₂, partial pressure of arterial oxygen; PMBC, Peripheral Blood Mononuclear Cells; PRRs, Pattern-recognition Receptors; SOFA, Sequential Organ Failure Assessment; SpO₂, pulse oximetric saturation; TLRs, Toll-like Receptors.

Introduction

Cirrhosis has long been recognized by the development of acute deterioration of liver and/or renal function, hepatic encephalopathy and high risk of hospital mortality in association to a precipitating event, commonly an infection [1–3]. During the last decade many experts have suggested that this array of symptoms may constitute the hallmark of a new specific entity. The term acute-on-chronic liver failure (ACLF) has gained popularity for this condition [4–6]. Since current diagnostic criteria of ACLF are based on personal opinions rather than on objective data, significant discrepancies between groups are apparent [7–9]. Due to these discrepancies, the first project of EASL-Chronic Liver Failure (CLIF) Consortium was to perform a prospective observational investigation (CANONIC Study) in a large series of patients with cirrhosis (1343 cases). These patients were consecutively admitted to 21 European hospitals for the treatment of an acute decompensation (AD). The aim was to assess the concept, prevalence, diagnostic criteria, precipitating events, natural course and prognosis of ACLF. The current review is largely based on this investigation [10,11].



Review

Key Points 1

- ACLF is a specific syndrome characterized by acute decompensation (AD), organ failure (OF) and high short-term mortality. AD means development of ascites, encephalopathy, gastrointestinal hemorrhage and/or bacterial infections. OFs (liver, kidney, brain, coagulation, respiration, circulation) are defined by the original CLIF-SOFA score or its simplified version CLIF-C OF score. High short-term mortality means a 28-day mortality rate $\geq 15\%$
- Patients with single OF have different 28-day mortality according to the type of OF and the presence of renal dysfunction (serum creatinine 1.5–1.9 mg/dl) and/or cerebral dysfunction (grade 1–2 hepatic encephalopathy). 1. Patients with liver, coagulation, respiration or circulation failure and no cerebral and/or renal dysfunction have low mortality rate (5–7%) and therefore no ACLF; 2. Patients with cerebral failure (grade 3–4 hepatic encephalopathy) but no renal dysfunction also have low mortality (8%) and no ACLF; 3. Finally, patients with renal failure (serum creatinine ≥ 2 mg/dl), those with cerebral failure and renal dysfunction, and those with liver, coagulation, respiration or circulation failure, and renal and/or cerebral dysfunction have a mortality rate of 16–30% and ACLF. The presence of one OF is, therefore, not a synonym of ACLF
- Mortality in ACLF correlates with the ACLF grade: ACLF-1 is associated to a 28-day mortality rate of 22%, ACLF-2 (2 OFs) of 32% and ACLF-3 (3–6 OFs) of 73%. Mortality rate in patients without ACLF is 4.9%
- The prevalence of ACLF in patients hospitalized with AD is 30%, being particularly prevalent in alcoholic and hepatitis B associated cirrhosis. ACLF may develop at any time during the course of cirrhosis and is especially severe in patients without prior history of AD. The most frequent precipitating events associated to ACLF are bacterial infections, active alcoholism or acute reactivation of hepatitis B, but in 40% of cases no precipitating event can be identified
- ACLF is very dynamic. It may improve (50%) or worsen (20%) within a short period of time. Not surprisingly, prognosis is more dependent on the early clinical course than of the initial ACLF grade

Definition, prevalence, clinical features and prognosis of ACLF according to the CANONIC study

Methodology used

The following features were pre-defined before the analysis of the CANONIC database:

1. ACLF was defined as a syndrome characterized by AD of cirrhosis associated to organ failure (OF) and high short-term mortality rate.

2. AD refers to the acute development of ascites, hemorrhage, encephalopathy and/or bacterial infections.
3. The sequential Organ Failure Assessment (SOFA) Scale [12] was the model selected for the diagnosis of organ failure because it is widely used in patients requiring intensive care treatment and is superior to the Child-Pugh and MELD scores [13–15] in predicting mortality in patients with cirrhosis and (OF(s)). Since components of the SOFA score (liver, renal, cerebral, coagulation, circulatory and respiratory function) do not take into account specific features of cirrhosis, the SOFA scale was modified establishing a new scale called the CLIF-SOFA score (CLIF-SOFAs) adapted for liver patients. A simplified CLIF-SOFA score (CLIF Consortium Organ Failure score, CLIF-C OFs) with identical diagnostic criteria for organ failure and similar prognosis was later designed (Fig. 1A) [16].
4. “Relatively high short-term mortality rate” was defined as a mortality rate equal or greater than 15% within a period of 28 days. This figure represents approximately 50% of the short-term mortality rate associated with severe sepsis in the general population [17]. The inclusion of a short-term mortality rate threshold in the definition of ACLF was considered important because it has major therapeutic implications. Fig. 1B shows that mortality rate in the CANONIC patients was clearly related to the presence and number of organ failures as defined by the CLIF-SOFA score or by the CLIF-C OFs. Also, renal dysfunction (as defined by a serum creatinine of 1.5–1.9 mg/dl) and/or moderate (grade 1–2) hepatic encephalopathy (cerebral dysfunction), when associated to single organ failure, were found to predict prognosis. Based on the presence of OF, renal and/or cerebral dysfunction, and short-term mortality rate, the following groups of patients were excluded and included from the diagnosis of ACLF:

1. Excluded: (a) No OF; (b) Single non-renal OF with serum creatinine < 1.5 mg/dl and no hepatic encephalopathy.
2. Included: (a) Single renal failure; (b) Single non-renal OF plus renal dysfunction and/or grade 1–2 hepatic encephalopathy; (c) 2 or more OFs.

Severity of ACLF was then graded according to the number of OFs: ACLF 1: 1 OF; ACLF 2: 2 OFs; ACLF 3: 3–6 OFs.

The prevalence of ACLF in the CANONIC Study patients was 30% (20% at admission and 10% during hospitalization) and the overall 28-day and 90-day mortality rates were 33% and 51%, respectively. Mortality rates in patients without ACLF were low (28-day: 1.9%; 90-day: 10%). The prevalence, 28-day and 90-day mortality rates associated with the different grades of ACLF were 15.8%, 22%, and 41% respectively in ACLF-1, 10.9%, 32%, and 55% in ACLF-2 and 4.4%, 73%, and 78% in ACLF-3.

Clinical features and precipitating events of ACLF

Patients with ACLF were significantly younger than those without ACLF and the main etiologies were alcoholism in 60%, hepatitis C in 13% and alcoholism plus hepatitis C in 10% (Table 1). In only 5% of patients was cirrhosis associated with hepatitis B virus (HBV) infection. The commonest OF in patients with ACLF was renal failure (56%), followed by liver,

A

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dl)	<6	6-12	>12
Kidney, creatinine (mg/dl)	<2	2-<3.5	≥3.5 or renal replacement
Brain, grade (West-Haven)	0	1-2	3-4
Coagulation, INR	<2.0	2.0-<2.5	≥2.5
Circulation, MAP (mmHg)	≥70	<70	Vasopressors
Respiratory PaO ₂ /FiO ₂	>300	≤300 and >200	≤200
or SpO ₂ /FiO ₂	>357	>214 and ≤357	≤214

B

Number and types of organ failures	No kidney dysfunction and no mild-to-moderate hepatic encephalopathy	Kidney dysfunction and/or mild-to-moderate hepatic encephalopathy
No organ failure	20/562 (3.6)	19/312 (6.2)
Single liver failure	4/68 (5.9)	10/33 (30.3)
Single cerebral failure	2/25 (8.0)	1/5 (20.0)
Single coagulation failure	1/19 (5.3)	2/9 (22.2)
Single circulation or single lung failure	1/15 (6.7)	2/7 (28.6)
Single kidney failure	9/57 (15.8)	7/29 (24.1)
Two organ failures	19/66 (28.8)	12/31 (38.7)
Three organ failures or more	25/59 (86.2)	8/13 (61.5)

Fig. 1. CLIF Consortium organ failure score and mortality according to type of organ failure. (A) CLIF Consortium Organ Failure Score. The highlighted area in light blue reflects the definition of each organ/system failure. (B) 28-day mortality in patients included in the CANONIC Study classified according to the number of organ failures and the presence or absence of kidney dysfunction and/or grade I-II hepatic encephalopathy. The highlighted area in light blue shows the subgroups of patients defined as having ACLF (with organ failure(s) and a 28-day mortality rate >15%). Kidney dysfunction: serum creatinine 1.5–1.9 mg/dl. In brackets: % of 28-day mortality. MAP, mean arterial pressure; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; SpO₂, pulse oximetric saturation.

coagulation, cerebral, circulatory and respiratory failures (44%, 28%, 24%, 17%, and 9%, respectively). The prevalence of circulatory and respiratory failure was significant only in patients with ACLF-3. Patients with ACLF showed systemic inflammation (high count of C-reactive protein and leukocyte concentration) which was independent on the presence or absence of recognized bacterial infections.

The traditional concept that OF(s) and, therefore, ACLF is the final event of a long-standing decompensated cirrhosis was not supported by the CANONIC Study, since almost half of patients with ACLF did not have a prior history of AD or had developed the first AD within the 3 months prior to diagnosis of ACLF (Table 1). Patients with no history of decompensated cirrhosis developed a more severe form of ACLF than patients with previous episodes of decompensation (28-day mortality of 42% vs. 29%).

The most common precipitating events were bacterial infections and active alcoholism (Table 1). Interestingly in

patients with ACLF the prevalence of alcoholic cirrhosis (60%) was higher than the prevalence of active alcoholism, indicating that alcoholic hepatitis accounts for only part of cases of ACLF associated with alcoholic cirrhosis. There was a small proportion of other precipitating events. As a trigger, gastrointestinal hemorrhage was less frequent in patients with ACLF than in patients without ACLF, suggesting that hemorrhage, if not associated to other complications (i.e. active drinking and/or bacterial infections), is not related to ACLF development. Finally, and of considerable interest is the significant proportion of patients developing ACLF in the absence of any identifiable trigger. Mortality was independent of the presence and type of precipitating events, indicating that although triggers are important in the development of ACLF, mortality depends of other factors, such as the clinical course (see below) and number of OFs.

Clinical course of ACLF

ACLF is an extraordinarily dynamic syndrome [11] and only one-third of ACLF patients grade had no change during hospitalization. In most cases ACLF either improved (50%) or worsened (20%). Resolution of ACLF (no OF) was observed in 40% of patients. The frequency of resolution was high (55%) in patients with ACLF-1, moderate (35%) in patients with ACLF-2 and low (15%) in patients with ACLF-3. Although the ACLF grade at diagnosis correlated with prognosis, the clinical course of the syndrome during hospitalization was the most important determinant of short-term mortality. In fact, 28-day survival in patients developing resolution of ACLF was similar than that in patients with AD without ACLF. Since changes in ACLF grade occurred very rapidly (1–2 days) or rapidly (3–7 days) in most patients, the early course of ACLF was a major determinant of prognosis.

ACLF in patients with cirrhosis associated to HBV infection

Li *et al.* have reported the characteristics of ACLF in 890 consecutive patients with HBV associated-cirrhosis and AD using the diagnostic criteria derived from the CANONIC Study [18]. Their results indicate that ACLF associated to HBV infection is similar to ACLF associated to alcoholism or chronic hepatitis C although with some specific characteristics. The prevalence of ACLF in the Chinese study was higher (40%) than in the CANONIC series, with ACLF-2 being the most frequent ACLF grade, followed by ACLF 1 and 3. Liver and coagulation failures were the most common OFs. The most frequent precipitating event was bacterial infections followed by reactivation of hepatitis B and active alcoholism. In half of patients no precipitating event could be identified. As in the CANONIC Study, patients with ACLF showed systemic inflammation independently on the type of precipitating event. Mortality rates (28-day and 90-day) in patients with no ACLF, ACLF and ACLF grades 1, 2, and 3 were similar to those in CANONIC series. Fifty-per-cent of patients had no prior AD episodes. Mortality was unrelated to the presence or type of precipitating events or prior history of AD.

Review

Table 1. Characteristics of patients with or without ACLF.

Characteristic	No ACLF ^a (N = 871)	ACLF (N = 417)	p value
Age (yr)	58.1 ± 12.3	55.8 ± 11.7	0.0011
Male sex	551 (63.3)	267 (64.0)	0.7887
Ascites	533 (61.4)	289 (80.7)	<0.001
Mean arterial pressure (mmHg)	84.8 ± 11.9	78.4 ± 13.1	<0.001
Cause of cirrhosis			
Alcohol	398 (48.5)	233 (58.4)	0.0011
Hepatitis C virus	182 (22.2)	59 (14.8)	0.0024
Alcohol plus hepatitis C virus	76 (9.3)	37 (9.3)	0.9927
Potential precipitating events of ACLF			
Bacterial infection	218 (25.2)	160 (39.1)	<0.001
Gastrointestinal hemorrhage	99 (15.6)	74 (17.8)	0.3505
Active alcoholism within the last 3 months ^b	115 (13.9)	89 (22.9)	<0.001
Other precipitating event ^c	31 (3.8)	38 (9.6)	<0.001
No precipitating event ^d	483 (64.8)	124 (43.1)	<0.001
More than one precipitating event ^e	41 (28.7)	25 (29.8)	0.8613
Organ failures			
Liver	51 (7.9)	156 (39.6)	<0.001
Kidney	0 (0)	196 (49.8)	<0.001
Cerebral	13 (2.0)	87 (22.1)	<0.001
Coagulation	14 (2.2)	122 (31.0)	<0.001
Circulation	10 (1.6)	89 (22.6)	<0.001
Lungs	3 (0.5)	50 (12.7)	<0.001
Kidney dysfunction ^f	68 (7.8)	69 (16.6)	<0.001
Mild-to-moderate hepatic encephalopathy ^g	221 (25.4)	173 (41.6)	<0.001
Laboratory data			
Hematocrit (%)	32 ± 6	28 ± 5	<0.001
Platelet count (x10 ⁹ /L)	110 ± 75	95 ± 71	0.0011
Serum bilirubin (mg/dl)	4.3 ± 5.0	11.7 ± 11.4	<0.001
International normalized ratio	1.5 ± 0.4	2.1 ± 0.9	<0.001
Alanine aminotransferase (U/L)	54 ± 130	72 ± 126	0.0326
Aspartate aminotransferase (U/L)	90 ± 141	198 ± 716	<0.001
γ-Glutamyltransferase (U/L)	174 ± 298	130 ± 158	0.0019
Serum creatinine (mg/dl)	0.9 ± 0.3	2.0 ± 1.4	<0.001
Serum sodium (mmol/L)	135.7 ± 5.3	134.5 ± 6.6	0.0013
Time from first previous decompensation			
No previous decompensation	237 (29.8)	98 (26.4)	0.2419
Less than 3 months	85 (10.7)	58 (15.6)	
From 3 to 12 months	139 (17.5)	62 (16.7)	0.0967
More than 12 months	334 (42.0)	153 (41.2)	

Data are means ± SD or number of patients (%).

^aAbsence or presence of ACLF at enrolment or during the post-enrolment hospitalization.

^bActive alcoholism was defined by more than 14 drinks per week in women and more than 21 drinks per week in men.

^cOther precipitating event was defined by the presence of one of the following: transjugular intrahepatic porto-systemic shunting, major surgery, therapeutic paracentesis without use of intravenous albumin, hepatitis, or alcoholic hepatitis (liver biopsy required for diagnosis).

^dNo precipitating event denotes the absence of bacterial infection, active alcoholism, or other precipitating event.

^eMore than one precipitating event denotes the presence of at least two of these: bacterial infection, active alcoholism, or other precipitating event.

^fKidney dysfunction was defined by serum creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl.

^gMild-to-moderate hepatic encephalopathy is grade I or II hepatic encephalopathy according to the West Haven classification.

Systemic inflammation as a cause of ACLF

As indicated, white cell count and plasma C-reactive protein (CRP) levels are higher in patients with ACLF than in those

without, indicating higher degree of systemic inflammation in the former patients [4]. Furthermore, the higher white cell count or CRP levels the higher the number of failing organs [4]. Together these findings suggest that OFs may result from

an excessive inflammatory response, for which the term immunopathology is used [19]. As shown by studies in type-1 hepatorenal syndrome, a special form of ACLF, and in severe sepsis, immunopathology may cause OF as a consequence of impairment in cardiocirculatory function leading to organ hypoperfusion and/or by direct specific effect of inflammatory mediators on cell function and death. An alternative view is that OFs develop mainly because of an impairment of mechanisms involved in tissue homeostasis. The distinction between these two arms of the alternative is crucial, for example in the context of infection. If an excessive immune response to the pathogen is the cause of OF, the use of anti-inflammatory therapies could be effective. In contrast, if the primary mechanism of OF is an alteration of tissue homeostasis caused directly by the pathogen, the use of anti-inflammatory therapies may decrease the immune response (which is in fact beneficial to reduce pathogen burden), fail to restore tissue homeostasis and finally worsen the outcome of the infection.

Key Points 2

- In 30% of cases of ACLF, inflammation develops in response to bacterial infection. Infection-related ACLF represents 30% of cases of ACLF. Whole bacteria exhibit different pathogen-associated molecular patterns (PAMPs) that are specifically recognized by pattern-recognition receptors (PRRs) expressed in innate immune cells. During the first hours of infection, recognition of PAMPs by PRRs results in the induction of hundreds of genes including those coding for pro-inflammatory cytokines. Induction of these cytokines is excessive in patients with ACLF resulting in the development of tissue damage (a process called immunopathology) and subsequent multiorgan failure
- Tissue damage in infection-related ACLF may involve mechanisms others than immunopathology. Bacteria may directly damage host tissue by altering a broad variety of cell functions. Tissue damage may also be related to failed tolerance; i.e. failure of "endurance" mechanisms that normally protect tissue against direct tissue damage by bacteria and immunopathology
- A significant number of cases of ACLF are not related to obvious bacterial infection. Nevertheless, in these cases an excessive immune host response probably causes tissue damage and OFs. The excessive immune response may be triggered by PAMPs released by bacteria that have been killed after their translocation from the intestinal lumen. Alternatively the excessive immune response may be a result of PRR activation by endogenous (non bacterial) molecules released by dying cells (e.g. the danger-associated molecular pattern called high-mobility group box 1, known as HMGB1). All these mechanisms are pro-inflammatory
- Studies are needed to decipher mechanisms of OFs in ACLF

The paradigm of bacterial infections. Bacterial infections in the general population

Early stage

Initiation of inflammation. Bacteria express molecular structures known as pathogen-associated molecular patterns (PAMPs) that are specifically recognized by germ line-encoded receptors called pattern-recognition receptors (PRRs) located at the surface or within innate immune cells (Table 2) [20,21]. Among PRRs there are toll-like receptors (TLRs), NOD-like receptors (NLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) (Table 2). The engagement of PRRs results in the activation of signaling cascades that activate transcription factors (e.g., nuclear factor (NF)-κB, AP-1, interferon (IFN)-regulator factor (IRF) 3, among others) [20,21]. These induce hundreds of genes including those encoding major inflammatory cytokines [7,22,23] (Fig. 2A and B). This inflammatory response is beneficial in that it plays a major role in host resistance to infection, i.e. the reduction of bacterial burden [19]. However, the inflammatory response to bacterial components may be excessive and associated with collateral tissue damage (immunopathology) resulting in OF [19].

Effects of an excessive inflammatory response. Patients with this excessive response have severe sepsis or septic shock [20]. Bacterial components and proinflammatory cytokines are known to induce the inducible nitric oxide (NO) synthase in arteriolar walls of the systemic circulation and on cardiac tissue resulting in increased production of the vaso-relaxant NO, impairment in cardiac inotropic function, arterial hypotension and decreased oxygen delivery to tissues [20,24]. Bacterial components and proinflammatory cytokines target the endothelium of microvasculature in vital organs favoring the formation of microthrombi (and tissue hypoxia) as well as adhesion and transendothelial migration of various circulating cells [25]. Influx of phagocytes in tissues may induce tissue damage (cell dysfunction, apoptosis or necrosis) via release of oxygen reactive species [25]. All these features contribute to OFs.

Late stage

A proportion of patients who survive the early stage of bacterial infections progress to an immune suppressed state [26]. Immune suppression is characterized by decreased production of inflammatory cytokines, decreased HLA-DR expression at the surface of antigen-presenting cells, high risk of hospital-acquired bacterial infections, and infections by reactivated viruses such as cytomegalovirus or herpes simplex virus and poor prognosis.

Bacterial infections in cirrhosis. Organ failures related to immunopathology

Early stage

Evidence for an excessive innate immune response in cirrhosis. During the first hours of bacterial infection, patients with cirrhosis have significantly higher plasma levels of proinflammatory cytokines than patients without cirrhosis [27]. Experimental studies investigated the *in vivo* effects of a challenge with lipopolysaccharide (LPS, a PAMP recognized by TLR4 (Table 2)) and found that LPS-induced plasma TNF-α levels were significantly higher in cirrhotic than in non-cirrhotic animals

Review

Table 2. Examples of pattern-recognition receptors (PRRs) and their ligands.*

PRRs	Localization	Ligand	Origin of the ligand
Toll-like receptor (TLRs)*			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasites, self
TLR3	Endolysosome	Double-stranded RNA	Virus
TLR4	Plasma membrane	Lipopolysaccharide	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7	Endolysosome	Single-stranded RNA	Virus, bacteria, self
TLR8	Endolysosome	Single-stranded RNA	Virus, bacteria
TLR9	Endolysosome	Unmethylated DNA with CpG motifs	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11**	Plasma membrane	Profilin-like molecule	Protozoa
TLR12**	Endolysosome	Profilin	Protozoa (<i>Toxoplasma gondii</i>)
TLR13**	Endolysosome	23S ribosomal RNA	Bacteria
Nucleotide binding oligomerization domain (NOD)-like receptors			
NOD1	Cytoplasm	g-D-glutamyl-mesodiaminopimelic acid (iE-DAP)	Bacteria
NOD2	Cytoplasm	Muramyl dipeptide (MDP)	Bacteria
NLRC4 (IPAF)	Cytoplasm	Flagellin	Bacteria
NAIP5	Cytoplasm	Flagellin	Bacteria
Retinoic acid-inducible gene (RIG)-I-like receptors			
RIG-I	Cytoplasm	Short double-stranded RNA, 5'triphosphate double-stranded RNA	RNA viruses, DNA virus, <i>Salmonella typhimurium</i> RNA
MDA5	Cytoplasm	Long double-stranded RNA	RNA viruses
LGP2	Cytoplasm	Unknown	RNA viruses
C-type lectin receptors			
Lectin-1	Plasma membrane	β -Glucan	Fungi
Lectin-2 (also known as CLEC6A)	Plasma membrane	β -Glucan	Fungi
MINCLE	Plasma membrane	Unknown	Fungi

*TLRs form homodimers except TLR2 that can heterodimerize with TLR1 or TLR6.

**Expressed in mice but not humans.

[28–30]. Interestingly in freshly isolated monocytes or peripheral blood mononuclear cells (PBMCs), the *ex vivo* LPS-stimulated production of proinflammatory cytokines and chemokines is higher in cells from patients with cirrhosis than in cells from healthy subjects [23,31–36]. The mechanisms of the “cytokine storm” associated with cirrhosis are poorly understood and need to be investigated further.

Is there a role for an excessive inflammatory response in the development of organ failures in cirrhosis? In patients with spontaneous bacterial peritonitis (SBP) higher levels of proinflammatory cytokines in the plasma and ascitic fluid are associated with an increased risk of renal failure [37]. The degree of the *ex vivo* LPS induction of proinflammatory genes in PBMCs from patients with decompensated cirrhosis is related to prognosis: the higher the gene induction the higher the risk of short-term death [23]. ACLF is the main cause of death in patients with cirrhosis [4]. Together these findings suggest that patients with cirrhosis who have innate immune cells with super-inducible proinflammatory genes are at risk of developing ACLF.

Late stage

Evidence of immune suppression has been reported in some patients with bacterial infection-induced ACLF [38].

Patients had decreases in monocyte HLA-DR expression and *ex vivo* TNF- α production by LPS-stimulated monocytes [38]. These findings suggest that patients were investigated several days or weeks after their admission to the hospital, and there is no clear information on the in-hospital risk of bacterial infection or viral reactivation in patients with ACLF.

Organ failures related to alterations in tissue homeostasis in the general population and cirrhosis

Direct tissue damage by bacteria

Bacterial virulence can be due to direct damage to host's tissues by toxins and virulence factors. Bacterial products alter tissue homeostasis through different inhibitory mechanisms affecting translation, electron transport chain (resulting in mitochondrial oxidative stress), protein folding in the endoplasmic reticulum (ER) lumen (resulting in ER stress), tRNA synthetases, actin cytoskeleton, among others (Table 3) [19].

There is currently no information on the direct tissue damage caused by bacteria as a mechanism for OFs in patients with cirrhosis.

Failed tolerance

As mentioned earlier, infection may be associated with two fitness costs: first, the immune response to infection can be excessive and cause tissue damage; second bacteria can directly damage tissues [19]. The host can reduce fitness costs through tolerance mechanisms that reduce tissue damage caused by the host immune response or directly by bacteria [19]. Some tolerance mechanisms are listed in Table 3.

These findings suggest that failed tolerance can play a role in the development of OF caused by bacterial infection. To address this hypothesis Medzhitov and colleagues used a mouse model of lethal viral (influenza virus)-bacterial (*L. pneumophila*) co-infection [6]. In this model, co-infection results in lung failure and death. The authors show that lung failure is related to marked downregulation of a battery of genes including genes

involved in tissue and cellular repair and lung development as well as genes involved in stress responses in lung tissue. Importantly, in this model there was no evidence for tissue damage caused by the immune response of the host [6]. This is an example of organ damage cause by failed tolerance.

Little is known about organ tolerance in the context of sepsis in cirrhosis. In a rat model of LPS-induced sepsis, LPS via TNF- α induced *in vivo* apoptosis of 30–40% of hepatocytes in cirrhotic livers, an effect not observed in normal rats [29]. TNF- α elicited hepatocyte apoptosis because the translation of NF- κ B-survival genes into proteins was inhibited in these cells [29]. The blockade of translation of NF- κ B-target genes was related to sustained phosphorylation of eukaryotic initiation factor α caused by chronic ER stress in cirrhotic hepatocytes [29]. Failed tolerance may therefore explain LPS-induced hepatocyte death in these cirrhotic livers (Fig. 2C).

Inflammation unrelated to infection

The trigger of ACLF is not related to an infection in 70% of cases [1]. In these cases inflammation is present and might be induced by PAMPs or endogenous ligands for TLRs.

Role of PAMPs

Patients with cirrhosis have translocation of intestinal Gram-negative bacteria [39]. In a proportion of patients whole bacteria do not reach the systemic circulation and infection does not

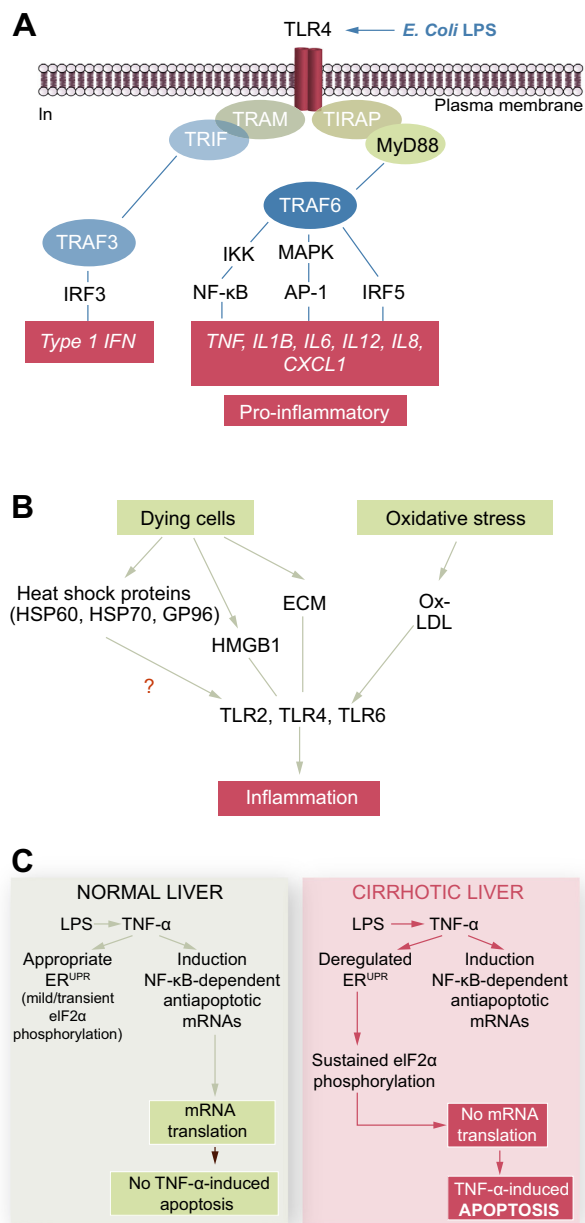


Fig. 2. Induction of inflammation and its consequences on hepatocyte survival in cirrhotic livers. (A) Induction of the innate immune response by *E. Coli* lipopolysaccharide (LPS). TLR4, an innate pattern-recognition receptor is expressed at the surface of immune cells such as monocytes/macrophages. TLR4 recognizes specifically LPS (a pathogen-associated molecular pattern) and this recognition results in the early-phase activation of the transcription factor NF- κ B by recruiting the TIR domain-containing adaptors TIRAP (Mal) and MyD88 (MyD88-dependent pathway). MyD88 recruits TRAF6 and induces inflammatory responses by activating NF- κ B, MAPK and IRF5. TRAF6 activates the IKK complex consisting of NEMO and IKK α β , which catalyze I κ B proteins for phosphorylation. TLR4 is then internalized and retained in the endosome, where it triggers signal transduction by recruiting TRAM and TRIF which recruits TRAF6 and TRAF3. TRAF6 activates MAPK and NF- κ B. TRAF3 (with RIP, not shown) activates the kinases TBK1 and IKKi (not shown), which phosphorylate and activate IRF3, the last of which controls transcription of type I interferons (IFN). (B) Endogenous ligands of cell surface TLRs. Molecules released by dying cells, such as high-mobility group box 1 (HMGB1), heat shock proteins (HSP) and extracellular matrix (ECM) components are recognized by cell surface TLR2, TLR4 or TLR2-TLR4. Oxidized low-density lipoproteins (Ox-LDL) are sensed by TLR4-TLR6. Recognition of these endogenous molecules by cell surface TLRs may lead to inflammation. (C) LPS causes *in vivo* hepatocyte apoptosis in cirrhotic rat livers. Left panel: Four hours after LPS challenge normal livers exhibit mild hepatocyte endoplasmic reticulum (ER) stress and unfolded protein response (ER^{UPR}) inducing transient phosphorylation of eukaryotic initiation factor (eIF2) α . LPS challenge also results in increased tumor necrosis factor (TNF)- α production. TNF- α engages its cognate receptors (TNF receptor R1, not shown) expressed at surface of hepatocytes. TNFR1 engagement activates NF- κ B which induces a broad variety of survival mRNAs that are translated into proteins. Hepatocyte accumulation of survival proteins inhibits pro-apoptotic signal encoded by TNF- α . Right panel: after LPS challenge cirrhotic livers have marked ER stress and ER^{UPR} resulting in sustained eIF2 α phosphorylation. This phosphorylation attenuates the translation into proteins of most cellular mRNAs, including translation of NF- κ B-dependent survival mRNAs into corresponding proteins. As a result there is no inhibition of the death signal encoded by TNF- α and hepatocyte apoptosis occurs. Adapted from reference [29]. TLR, Toll-like receptor; MyD88, Myeloid differentiation primary response protein MyD88; MAPK, mitogen-activated protein kinase; IRF, IFN-regulatory factor; TRAF, TNFR-associated factor; IKK, I κ B kinase; NEMO, NF-kappa-B essential modulator; TBK1, TANK-binding kinase 1; I κ B, NF-kappa-B inhibitor alpha.

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occur. However these bacteria may release PAMPs that reach the liver and systemic circulation. PAMPs may thus be recognized by PRRs and trigger inflammation (Table 2). There is evidence of an LPS contribution to liver inflammation and injury in patients with severe alcoholic hepatitis [40]. The involvement of PAMP-induced inflammation in the development of extra-hepatic OFs deserves investigation.

Endogenous ligands for TLRs

The fact that TLRs are able to recognize not only PAMPs but also endogenous molecules (produced by the host) has been shown in experiments in non-cirrhotic individuals. These molecules can be released by dying cells and include the danger/damage-associated molecular pattern (DAMP) high-mobility group box 1 (HMGB1) and products of the extracellular matrix (such as biglycan, hyaluronic acid, versican, extracellular matrix A of fibronectin and surfactant protein A). These endogenous ligands may be recognized by cell surface TLRs (TLR2, TLR4) and induce “sterile” inflammation (Fig. 2B) [41]. Dying cells are also known to release heat shock proteins and some of these proteins have also been shown to induce inflammation through cell surface TLRs [41]. Finally there are examples of TLR-mediated recognition of self nucleic acids (Table 1). This recognition is inappropriate and may lead to inflammation [28]. Cell death or oxidative stresses are common findings in patients with ACLF. Therefore future studies performed in the context of ACLF should seek for endogenous ligands of TLRs and investigate their role in inflammation and the development of OFs.

ACLF is a complex syndrome because it is the result of a complex mechanism

The above discussion implies that systemic inflammation in ACLF has a complex pathogenesis. The release of PAMPs by bacteria is important but the syndrome occurs in the setting of bacterial infections in only one-third of patients [10]. Translocation of PAMPs without viable bacteria from the intestinal lumen to the systemic circulation or the release of DAMPs by dying cells during acute liver injury (i.e. acute alcoholic liver injury or reactivation of hepatitis B) or increased systemic oxidative stress are likely mechanisms of the “sterile inflammation” observed in most patients with ACLF. Finally, acute increase in systemic inflammation may not be the sole mechanism. It is important to note that ACLF develops in patients with AD, who already have moderate systemic inflammation and oxidative stress. Direct tissue damage caused by bacterial products or any process leading to a decrease in the tolerance to inflammation could enhance the effects of this moderate systemic inflammation and precipitate ACLF. These three mechanisms, which are not mutually exclusive but may operate simultaneously, could explain many features observed in patients with AD and ACLF such as the distinct predisposition to develop ACLF and severity of ACLF between patients in front of an identical precipitating event (i.e. higher ACLF severity in patients without prior AD) and the distinct clinical course (resolution, improvement, steady course or worsening) following an identical treatment. Also it could account for the effectiveness of human serum albumin in the prevention and treatment (in combination with terlipressin) of type-1 HRS, a special form of ACLF, owing to the capacity of albumin molecule to bind and decrease the biological effects of PAMPs, vasodilators released

in systemic inflammation (NO and prostaglandins) and reactive oxygen species.

Key Points 3

- The CLIF-SOFA and its simplified version CLIF-C OF scores, which are based in the stratification of the function of six organs (liver, kidney, brain, coagulation, circulation and respiration) in 5 (0-4) and 3 (1-3) subscores, respectively, (aggregated scores 0-24 and 3-9, respectively) were initially designed for the diagnosis of OF in cirrhotic patients with AD
- Two other specific prognostic scores, one for patients with ACLF (CLIF-C ACLF score) and a second for patients with AD cirrhosis without ACLF (CLIF-C AD score) that improve the prediction accuracy of the CLIF-C OF score and CLIF-SOFA, MELD, MELD-Na and Child-Pugh scores were subsequently designed. The CLIF-C ACLF score includes the CLIF-C OF score, age and white cell count. The CLIF-C AD score includes age, white cell count, serum sodium, serum creatinine and INR. Variables in each score were combined to generate a score system ranging from 0 to 100. The CLIF-C OF score, the CLIF-C ACLF score and the CLIF-C AD score allow a step-wise algorithm for a rational management of patients with decompensated cirrhosis
- The general management of ACLF includes a rapid identification and treatment of potential triggers, the application of measures that prevent progression of the syndrome and the use of specific organ support systems. In general, patients with ACLF should be treated in an ICU environment and potential candidates for liver transplantation should be transferred to a transplant center. Liver transplantation is treatment of choice. One year survival after transplantation is of approximately 80%
- Extracorporeal liver support systems based on albumin dialysis have been widely used in patients with ACLF. They have been shown to be effective in supporting organ function in patients with cerebral and renal failure. However they did not improve survival. Plasma exchange, which increases survival in patients with acute liver failure, is being explored in patients with ACLF. Finally, studies on the role of bioartificial livers using hepatocytes are underway. ACLF represents a unique condition to explore the potential effectiveness of new treatments such as granulocyte colony-stimulating factor or cell (hepatocytes or stem cells) transplantation

Prognostic assessment of patients with AD of cirrhosis with and without ACLF. Therapeutic implications

To develop management strategies for AD patients with or without ACLF, a validated clinical scoring system that can be used at the bed-side is required that can be updated on a daily basis to allow on-going stratification of patients for intensive care, fast-track listing for liver transplantation, early hospital discharge or determination of futility of further intensive care [9,10,15,42].

Table 3. Stresses during infections, their origin and tolerance responses they elicit.

Stress	Origin	Tolerance response
Fever	Host	Heat shock factor 1 program
TNF- α -induced cell death	Host	NF- κ B-dependent survival genes
Oxidative stress	Host, pathogens	NRF2-mediated antioxidant program
Endoplasmic reticulum stress	Host, pathogens	Unfolded protein response (UPR)
Mitochondrial stress (inhibition of electron chain transport)	Pathogens	Mitochondrial UPR
Inhibition of translation		
Ribotoxic stress	Pathogens	Unknown
tRNA synthetases	Pathogens	Unknown
Inhibition of actin cytoskeleton	Pathogens	Serum response factor-mediated program
Tissue hypoxia	Host, pathogens	Hypoxia inducible factor-1-mediated program
Cell death	Host, pathogens	Tissue repair program

Many previous studies have defined potential prognostic markers in the cirrhotic patients with OF but for the most part these studies have not been conducted with a view to defining prognostic variables, are retrospective, have performed studies in specific groups of patients or are not validated in independent cohorts [15,43–46]. Despite limitations, these previous studies have pointed to the importance of OF in defining the prognosis of the sick cirrhotic patients and suggested the importance of systemic inflammation. In order to overcome these limitations, one of the major objectives of the CANONIC Study was to develop a scoring system for patients with AD of cirrhosis with and without ACLF and a step-wise algorithm for a rational indication of therapy.

Development of a scoring system for patients diagnosed as having ACLF

The approach used was to perform statistical analysis of clinical and biochemical factors in the CANONIC patients with ACLF that were independently associated with mortality and then to mathematically develop a prognostic model [17]. The factors independently associated with mortality were the CLIF-C OF score, age and white cell count. The final model including these three variables was developed to generate a new score (CLIF Consortium ACLF score, CLIF-C ACLFs), which ranged from 0 to 100. The concordance index as well as the AUC of the ROC curve showed that this score was significantly better at predicting the

Table 4. Predictive ability of CLIF-C ACLF score (upper panel) and CLIF-C AD score (lower panel) as compared with MELD, MELD-Sodium and Child-Pugh in the CANONIC patients with and without Acute-on-Chronic Liver Failure (ACLF), respectively.

	CLIF-C ACLF score C-index (95% CI)	Child-Pugh score C-index (95% CI)	MELD score C-index (95% CI)	MELD-Sodium score C-index (95% CI)
CANONIC patients with ACLF (N = 275)				
28-day mortality	0.760 (0.715-0.805)	0.668 (0.610-0.726)	0.687 (0.635-0.738)	0.684 (0.632-0.736)
<i>p</i> value vs. CLIF-C ACLF score		<0.001	<0.001	<0.001
90-day mortality	0.732 (0.691-0.773)	0.655 (0.605-0.705)	0.659 (0.615-0.710)	0.663 (0.617-0.709)
<i>p</i> value vs. CLIF-C ACLF score		<0.001	<0.001	<0.001
180-day mortality	0.723 (0.683-0.763)	0.642 (0.593-0.691)	0.652 (0.607-0.697)	0.654 (0.609-0.699)
<i>p</i> value vs. CLIF-C ACLF score		<0.001	<0.001	<0.001
365-day mortality	0.707 (0.668-0.746)	0.636 (0.588-0.683)	0.638 (0.595-0.682)	0.640 (0.597-0.683)
<i>p</i> value vs. CLIF-C ACLF score		<0.001	<0.001	<0.001
	CLIF-C AD score C-index (95% CI)	Child-Pugh score C-index (95% CI)	MELD score C-index (95% CI)	MELD-Sodium score C-index (95% CI)
CANONIC patients without ACLF (N = 1016)				
90-day mortality	0.743 (0.704-0.783)	0.651 (0.601-0.701)	0.649 (0.602-0.697)	0.681 (0.633-0.728)
<i>p</i> value vs. CLIF-C ADs*		<0.001	<0.001	<0.001
180-day mortality	0.711 (0.675-0.747)	0.635 (0.593-0.677)	0.625 (0.585-0.665)	0.655 (0.615-0.695)
<i>p</i> value vs. CLIF-C ADs*		<0.001	<0.001	<0.001
365-day mortality	0.670 (0.639-0.702)	0.613 (0.578-0.648)	0.593 (0.560-0.627)	0.618 (0.584-0.652)
<i>p</i> value vs. CLIF-C ADs*		<0.001	<0.001	<0.001

Concordance index (C-index) estimates between the observed and predicted mortality probabilities.
**p* values from the IDI statistics test.

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28-day, 90-day, 180-day and 365-day mortality compared with the current gold-standards; the Model for End-Stage Liver Disease score (MELDs) [47], MELD-Sodium score (MELD-Nas) [48], and the Child-Pugh score (CPs) [49] (Table 4 upper panel, Fig. 3A and B). The CLIF-C ACLFs was then tested and validated for sequential use with data obtained from patients at 48-h, between day 3 and 7 and beyond. The performance of the score improved significantly at predicting 28-day and 3-month mortality of patients when measured at 48 h compared with the measurements at the time of admission suggesting that the CLIF-C ACLF score can be updated on a daily basis taking into account the effect of interventions.

Development of a scoring system for patients diagnosed as having AD but no ACLF

Using a similar approach, the CLIF-C Acute Decompensation score (CLIF-C ADs) was developed for hospitalized cirrhotic patients without ACLF using the CANONIC data [50]. The reason for undertaking this analysis was based on the hypothesis that within the

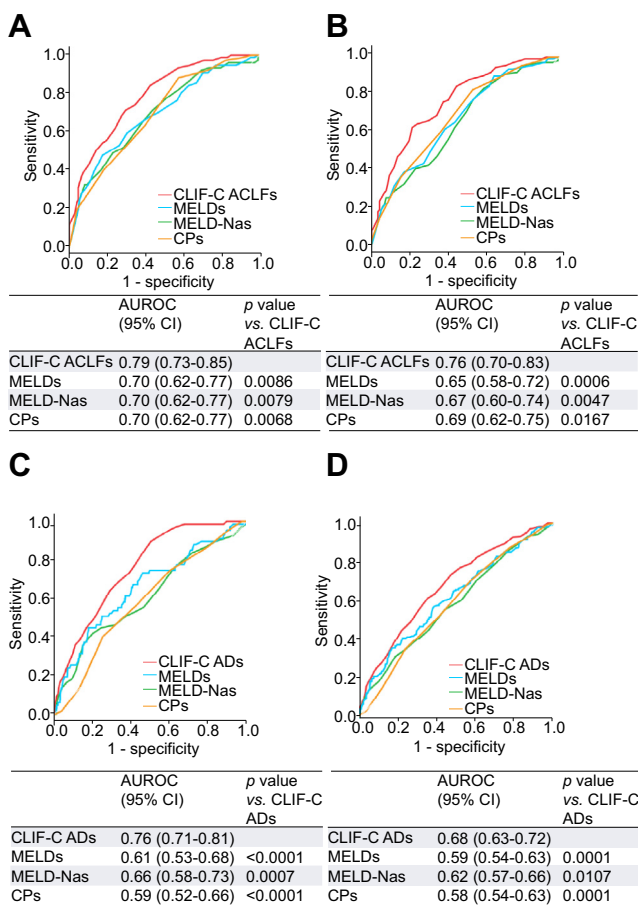


Fig. 3. Accuracy of CLIF-C ACLFs and CLIF-C ADs as compared to that of MELDs, MELD-Nas and CPs in predicting mortality in patients with decompensated cirrhosis. (A and B) Compares the accuracy of CLIF-C ACLFs with the other scores in predicting 28-day and 90-day mortality in patients with ACLF. (C and D) Compares the accuracy of CLIF-C ADs with the other scores in predicting 90-day and 1 year mortality in patients with acute decompensation of cirrhosis without ACLF. Accuracy was assessed by estimating the area under the ROC curve (AUROC) corresponding to each score.

no ACLF patients with AD, there is likely to be a very low risk group that should be discharged and there may be a high risk group that will progress to develop full-blown ACLF and therefore have a high mortality. The analysis revealed five independent variables including age, serum sodium, white cell count, creatinine and INR. Depending upon the relative weights, they were combined into a score ranging from 0 to 100. The CLIF-C ADs performed significantly better than the MELDs, MELD-Nas, and the Child-Pugh scores in predicting 3-month and 12-month mortality (Table 4 lower panel, Fig. 3C and D). In real terms, the CLIF-C ADs improved prediction of mortality by 10–20% over these other scoring systems. Additionally, discrete cut-offs were developed for CLIF-C ADs such that a score of less than or equal to 45 was associated with a 3-month mortality of 1.8% identifying a very low risk group. The score also identified a high risk group that had a score 60 or above that had a 3-month mortality of about 31%. The intermediate risk group was identified by a CLIF-C AD score of greater than 45 but less than 60.

Development of a step-wise algorithm to determine the prognosis of all hospitalized patients with AD

These three scores specifically designed for patients with and without ACLF can be combined into an algorithm that should be useful in defining the prognosis of cirrhotic patients admitted to the hospital on a daily basis [50]. CLIF-C OFs scores should be applied to the patient admitted acutely to the hospital if they have developed a complication of cirrhosis such as encephalopathy, bleeding, infection or ascites. If the score suggests they have ACLF, they should be managed in an enhanced care or intensive care environment. Their prognosis can be determined using the CLIF-C ACLFs, which can be updated daily. The score can be used to gauge the effectiveness of intervention or futility within 3–7 days. On the other hand if they do not have ACLF, then the CLIF-C ADs should be applied. At the outset, those with CLIF-C ADs of less than or equal to 45 may be discharged early from the hospital, those with a score above 60 are at high risk of progressing to ACLF and should therefore be managed in enhanced or intensive care, and those with a score greater than 45 but less than 60 need to be managed in the hospital (Fig. 4). Although these scores are important to allow future studies, there is a scope

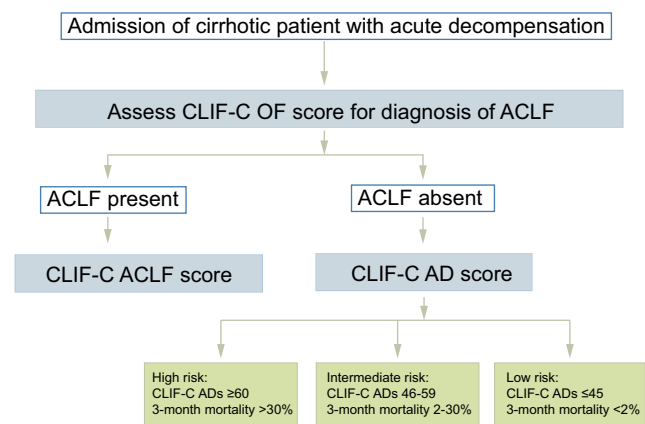


Fig. 4. Algorithm for the sequential use of the EASL-CLIF Consortium predictive scores in patients with cirrhosis admitted to hospital with acute decompensation.

for improvement as the best predictability reached is a C-index in the range of 0.75.

Management of ACLF

General management

The main principle of the general management of patients with ACLF is an early identification of the syndrome and its potential triggering factors. Although not proven, it is likely that an early identification and treatment of, for example, a SBP in a patient with cirrhosis and ACLF may have a beneficial impact on patient's outcome by preventing/slowing a further progression of ACLF. In general, patients with ACLF should be treated in enhanced care or intensive care units for best monitoring and management [42,51]. Potential candidates for transplantation should be transferred to a transplant centre. Organ function should be monitored frequently and treatment should be given according to each specific dysfunction. Circulatory and lung support should be provided if there is significant reduction in arterial pressure and arterial oxygenation, respectively. Kidney function should be monitored by means of urine volume and daily serum creatinine concentration. In case of circulatory failure or kidney failure, fluid resuscitation should be performed cautiously to avoid problems related to an excessive fluid administration such as peripheral edema or, more importantly pulmonary, edema. A trial of plasma expansion with albumin or crystalloids should be made for a limited period of time and then stopped if there is no beneficial effect in terms of improvement of circulatory or kidney function. It is important to remark that most patients with cirrhosis and ACLF have impaired sodium excretion and the fluid administered is usually retained and may cause significant edema and dilutional hyponatremia. Brain function should be evaluated frequently and hepatic encephalopathy should be treated promptly. Intubation should be performed in patients with hepatic encephalopathy grades III or IV to prevent aspiration. Finally, liver function tests, particularly serum bilirubin and prothrombin time should be measured daily.

Specific management

In this section, the potential usefulness of some therapeutic options is discussed in the light of the available evidence.

Liver transplantation

Liver transplantation is a useful method for treating patients with ACLF [52–54]. Nonetheless, it should be noted that not all patients with ACLF are transplant candidates for a number of reasons, which may include advanced age, active alcoholism, or concomitant diseases, and that the presence of associated OFs, particularly if the number is high or they are severe, may preclude transplantation, at least for a certain period of time until multiorgan dysfunction has improved. Available information on liver transplantation for ACLF patients' is limited [52–54]. One year survival after transplantation is of approximately 80%, slightly lower but not significantly different from that of patients transplanted without ACLF. However, published studies are retrospective, have a limited sample size, and have used variable definitions of ACLF. Most importantly, only one study used intention-to-treat analysis and showed that some potential candidates

are not even listed for transplantation and out of those listed mortality is of 50% [54]. Overall, only one-third of potential candidates reach liver transplantation according to this report. There is therefore a clear need for effective therapeutic methods that can “bridge” patients with ACLF to liver transplantation.

Extracorporeal liver support systems

In recent years, several extracorporeal liver support systems have been assessed in the management of ACLF [6,55–57]. These systems are based on dialysis techniques aimed at removing a number of substances thought to participate in the pathogenesis of ACLF, such as NO, prostaglandins, PAMPs and reactive oxygen species. The most extensively used system, is the extracorporeal albumin dialysis by the molecular adsorbent recirculating system (MARS). Besides reducing the plasma levels of a number of substances, it has been shown that MARS is effective in improving systemic hemodynamics and severe hepatic encephalopathy. However, a randomized multicentre European study of MARS vs. standard therapy in 189 patients with ACLF did not show differences in survival [57]. Another randomized study using a different system, Prometheus, also showed no improvement on survival [58]. Therefore, although these systems have some beneficial effects in patients with ACLF, their overall usefulness in this setting is uncertain. Along the lines of dialysis systems, plasma exchange has also been proposed as a therapeutic method in patients with acute liver failure and ACLF. A randomized study in patients with acute liver failure showed improved survival in patients treated with plasma exchange compared to a control group receiving standard therapy [59]. A study in patients with ACLF organized by the EASL-CLIF Consortium is underway.

Other methods

A few recent studies have focused their attention on the potential effectiveness of granulocyte colony-stimulating factor (G-CSF) in patients with ACLF [60–62]. Two randomized studies, one performed mainly in alcoholic patients and the other exclusively in patients with chronic HBV infection, have shown that administration of G-CSF to patients with ACLF reduces the risk of developing kidney and brain failure, and sepsis and improves short-term survival [60,61]. It is important to note that patients with sepsis, multiorgan failure and/or grade 3 or 4 hepatic encephalopathy were excluded from these studies, which indicates that most of the treated patients had “early” ACLF. Potential treatment effectiveness may be related to the mobilization of CD34+ cells from bone marrow to the liver, improvement of neutrophil function, or some other yet unknown factors.

Finally, cell transplantation, either using hepatocytes or stem cells, has also been proposed as potential therapy for patients with ACLF with the aim of improving liver function by causing cell repopulation of the diseased liver [63–68]. Moreover, mesenchymal stem cells have a number of other potentially beneficial effects, including anti-inflammatory actions. So far, however, the available information is limited and a definite conclusion about its potential efficacy in clinical practice cannot be made.

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Conflict of interest

Rajiv Jalan received research funding from Vital Therapies, has served on Scientific Advisory Board for Conatus Pharma, has on-going research collaboration with Gambro, Grifols and is the Principal Investigator of an Industry sponsored study (Sequana Medical). He is also the inventor of a drug, L-ornithine phenylacetate which UCL has licensed to Ocera Therapeutics. Pere Ginès has received research funding from Grifols, served on the scientific advisory board for Ferring and Sequana and received research funding from Sequana. Vicente Arroyo has received grant and research support from Grifols. Richard Moreau declares that he has no conflicts of interest.

The EASL-CLIF Consortium

It is a network of 63 European university hospitals, aimed at stimulating research on pathophysiology, diagnostic and treatment on Chronic Liver Failure. The EASL-CLIF Consortium has an unrestricted grant from Grifols for the period 2013–2016. The Fundació Clinic, a foundation ruled by the Hospital Clinic and University of Barcelona, administers the EASL-CLIF Consortium grants. Vicente Arroyo (Chairman), Mauro Bernardi (Vice-Chairman), and members of the Steering Committee have no relationship with Grifols other than conferences at international meetings (from which they may receive an honorarium) or as investigators on specific projects unrelated to the consortium. Up to now the EASL-CLIF Consortium has not performed any study promoted by pharmaceutical companies. The scientific agenda of the EASL-CLIF Consortium and the specific research protocols are made exclusively by the Steering Committee members without participation of pharmaceutical companies.

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References

- Toledo C, Salmerón JM, Rimola A, Navasa M, Arroyo V, Llach J, et al. Spontaneous bacterial peritonitis in cirrhosis: predictive factors of infection resolution and survival in patients treated by cefotaxime. *Hepatology* 1993;17:257.
- Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, et al. Renal impairment following spontaneous bacterial peritonitis in cirrhosis. Incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495–1501.
- Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164–176.
- Jalan R, Williams R. Acute-on-Chronic liver failure: Pathophysiological basis and therapeutic options. *Blood Purif* 2002;20:252–261.
- Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. *JAMA* 2003;289:217–222.
- Khuroo MS, Khuroo MS, Farahat KL. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. *Liver Transpl* 2004;10:99–1106.
- Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Grag H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009;3:269–282.
- Bajaj JS. Defining acute-on-chronic liver failure: will East and West ever meet? *Gastroenterology* 2013;144:1337–1339.
- Jalan R, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014;147:4–10.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Córdoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–1437.
- Gustot T, Fernandez J, García E, Ginès P, Moreau R, Jalan R, et al. Short-term (28-day) clinical course and transplant-free mortality in acute-on-chronic liver failure (ACLF): evidence for reversibility of ACLF (a study from the CANONIC database). *J Hepatol* 2014;60:S228.
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendoca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–710.
- Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R, et al. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology* 2001;34:255–261.
- Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. *Crit Care Med* 2010;38:2108–2116.
- Levesque E, Hoti E, Azoulay D, Guidet B, Maury E, Carbonell R, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. *J Hepatol* 2012 Jan;56:95–102.
- Agnus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:840–851.
- Jalan R, Saliba F, Pavesi M, Amorós A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014;61:1038–1047.
- Li H, Pavesi M, Zeng B, Chen LY, Li ST, Qiu DK, et al. "Eastern" type of acute-on-chronic liver failure (ACLF) is similar in pathophysiologic, diagnostic and prognostic criteria to the "Western" type: A comparison of Chinese hospitalized patients with hepatitis B with CANONIC data (abstract). *Hepatology* 2014;60:480A–481A.
- Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. *Science* 2012;335:936–941.
- Gustot T, Durand F, Lebrech D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009;50:2022–2033.
- Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011;34:637–650.
- Foster SL, Hargreaves DC, Medzhitov R. Gene-specific control of inflammation by TLR-induced chromatin modifications. *Nature* 2007;447:972–978.
- Gandoura S, Weiss E, Rautou PE, Fasseu M, Gustot T, Lemoine F, et al. Gene- and exon-expression profiling reveals an extensive LPS-induced response in immune cells in patients with cirrhosis. *J Hepatol* 2013;58:936–948.
- MacMicking JD, Nathan C, Hom G, Chartrain N, Fletcher DS, Trumbauer M, et al. Altered responses to bacterial infection and endotoxin shock in mice lacking inducible nitric oxide synthase. *Cell* 1995;81:641–650.
- Russell JA. Management of sepsis. *N Engl J Med* 2006;355:1699–1713.
- Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013;13:862–874.
- Byl B, Roucloux I, Crusiaux A, Dupont E, Devière J. Tumor necrosis factor alpha and interleukin 6 plasma levels in infected cirrhotic patients. *Gastroenterology* 1993;104:1492–1497.
- Moreau R, Barrière E, Tazi KA, Lardeux B, Dargère D, Urbanowicz W, et al. Terlipressin inhibits in vivo aortic iNOS expression induced by lipopolysaccharide in rats with biliary cirrhosis. *Hepatology* 2002;36:1070–1078.
- Tazi KA, Bièche I, Paradis V, Guichard C, Laurendeau I, Dargère D, et al. In vivo altered unfolded protein response and apoptosis in livers from lipopolysaccharide-challenged cirrhotic rats. *J Hepatol* 2007;46:1075–1088.
- Thabut D, Tazi KA, Bonnefont-Rousselot D, Aller M, Farges O, Guimont MC, et al. HDL administration attenuates liver proinflammatory response, restores liver eNOS activity and lowers portal pressure in cirrhotic rats. *Hepatology* 2007;46:1893–1906.

- [31] Devière J, Content J, Denys C, Vandenbussche P, Schandene L, Wybran J, et al. Excessive in vitro bacterial lipopolysaccharide-induced production of monokines in cirrhosis. *Hepatology* 1990;11:628–634.
- [32] Le Moine O, Marchant A, De Groote D, Azar C, Goldman M, Devière J. Role of defective monocyte interleukin-10 release in tumor necrosis factor- α overproduction in alcoholic cirrhosis. *Hepatology* 1995;22:1436–1439.
- [33] Tazi KA, Quioc JJ, Saada V, Bezeaud A, Lebrec D, Moreau R. Upregulation of TNF- α production signaling pathways in monocytes from patients with advanced cirrhosis: possible role of Akt and IRAK-M. *J Hepatol* 2006;45:280–289.
- [34] Tazi KA, Quioc JJ, Abdel-Razek W, Tellier Z, Guichard C, Ogier-Denis E, et al. Protein array technology to investigate cytokine production by monocytes from patients with advanced alcoholic cirrhosis: an ex vivo pilot study. *Hepatol Res* 2009;39:706–715.
- [35] Galbois A, Thabut D, Tazi KA, Rudler M, Mohammadi MS, Bonnefont-Rousselot D, et al. Ex vivo effects of high-density lipoprotein exposure on the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. *Hepatology* 2009;49:175–184.
- [36] Coant N, Simon-Rudler M, Gustot T, Fasseu M, Gandoura S, Ragot K, et al. Glycogen synthase kinase 3 involvement in the excessive proinflammatory response to LPS in patients with decompensated cirrhosis. *J Hepatol* 2011;55:784–793.
- [37] Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;27:1227–1232.
- [38] Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display “sepsis-like” immune paralysis. *J Hepatol* 2005;42:195–201.
- [39] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014;60:1310–1324.
- [40] Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009;360:2758–2769.
- [41] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010;140:805–820.
- [42] Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, García-Tsao G, et al. Acute-on chronic liver failure. *J Hepatol* 2012;57:1336–1348.
- [43] Schepke M, Roth F, Fimmers R, Brensing KA, Sudhop T, Schild HH, et al. Comparison of MELD, Child-Pugh, and Emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting. *Am J Gastroenterol* 2003;98:1167–1174.
- [44] Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl* 2006;12:1049–1061.
- [45] Bajaj JS, O’Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014;60:250–256.
- [46] Theodoridou E, Pieri G, Mohammad AO, Cheung M, Cholongitas E, Agarwal B, et al. The Royal Free Hospital score: a calibrated prognostic model for patients with cirrhosis admitted to intensive care unit. Comparison with current models and CLIF-SOFA score. *Am J Gastroenterol* 2014;109:554–562. <http://dx.doi.org/10.1038/ajg.2013.466>.
- [47] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). *Hepatology* 2007;45:797–805.
- [48] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008;359:1018–1026.
- [49] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–649.
- [50] Jalan R, Pavesi M, Saliba F, Amorós A, Fernandez J, Holland-Fischer P, et al. The CLIF Consortium acute decompensation score (CLIF-C ADs) for prognosis of hospitalized cirrhotic patients without acute-on-chronic liver failure. *J Hepatol* 2015;62:831–840.
- [51] Ginès P, Fernández J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. *J Hepatol* 2012;56:S13–S24.
- [52] Bahirwani R, Shaked O, Bewtra M, Forde K, Reddy KR. Acute-on-chronic liver failure before liver transplantation: impact on posttransplant outcomes. *Transplantation* 2011;92:952–957.
- [53] Duan BW, Lu SC, Wang ML, Liu JN, Chi P, Lai W, et al. Liver transplantation in acute-on-chronic liver failure patients with high model for end-stage liver disease (MELD) scores: a single center experience of 100 consecutive cases. *J Surg Res* 2013;183:936–943.
- [54] Finkenstedt A, Nachbaur K, Zoller H, Joannidis M, Pratschke J, Graziadei IW, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. *Liver Transpl* 2013;19:879–886.
- [55] Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. *Curr Opin Crit Care* 2011;17:195–203; Vaid A, Chweich H, Balk EM, Jaber BL. Molecular adsorbent recirculating system as artificial support therapy for liver failure: a meta-analysis. *ASAIO J* 2012;58:51–59.
- [56] Xu X, Liu X, Ling Q, Wei Q, Liu Z, Xu X, et al. Artificial liver support system combined with liver transplantation in the treatment of patients with acute-on-chronic liver failure. *PLoS One* 2013;8:e58738.
- [57] Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. RELIEF study group. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology* 2013;57:1153–1162.
- [58] Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al. HELIOS Study Group. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology* 2012;142:782–789.
- [59] Larsen FS, Schmidt LE, Wendon J, et al. Liver assisting with high volume plasma exchange in patients with acute liver failure. *Hepatology* 2010;52:88A.
- [60] Garg V, Garg H, Khan A, Trehanpati N, Kumar A, Sharma BC, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology* 2012;142:505–512.
- [61] Duan XZ, Liu FF, Tong JJ, Yang HZ, Chen J, Liu XY, et al. Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure. *World J Gastroenterol* 2013;19:1104–1110.
- [62] Khanam A, Trehanpati N, Garg V, Kumar C, Garg H, Sharma BC, et al. Altered frequencies of dendritic cells and IFN- γ -secreting T cells with granulocyte colony-stimulating factor (G-CSF) therapy in acute-on-chronic liver failure. *Liver Int* 2014;34:505–513.
- [63] Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl Med* 2012;1:725–731.
- [64] Yuan SF, Jiang T, Sun LH, Zheng RJ, Cao GQ, Ahat NZ, et al. Use of bone mesenchymal stem cells to treat rats with acute liver failure. *Genet Mol Res* 2014;30:6962–6980.
- [65] Tögel FE, Westenfelder C. Mesenchymal stem cells: a new therapeutic tool for AKI. *Nat Rev Nephrol* 2010;6:179–183.
- [66] Huebert RC, Rakela J. Cellular therapy for liver disease. *Mayo Clin Proc* 2014;89:414–424.
- [67] Wang F, Zhou L, Ma X, Ma W, Wang C, Lu Y, et al. Monitoring of intrasplenic hepatocyte transplantation for acute-on-chronic liver failure: a prospective five-year follow-up study. *Transplant Proc* 2014;46:192–198.
- [68] Zhang Y, Chen XM, Sun DL. Effects of coencapsulation of hepatocytes with adipose-derived stem cells in the treatment of rats with acute-on-chronic liver failure. *Int J Artif Organs* 2014;37:133–141.