Review

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Acute-on-chronic liver failure: A distinct clinical syndrome

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Summary

There are different operating definitions for acute-on-chronic liver failure (ACLF) in different geographic regions. Consortia in Western countries have developed definitions that apply to patients with cirrhosis, while consortia in Asia have developed definitions that apply to patients with chronic liver diseases with or without cirrhosis. Investigators of the Chinese and Western Consortia believe that ACLF can be precipitated by acute insults that are intrahepatic (*e.g.* alcoholic hepatitis) or extrahepatic (*e.g.* bacterial infection, gastrointestinal haemorrhage), and that extrahepatic organ system failures can be used to define ACLF. In contrast, the Asia Pacific consortium believe that ACLF is only defined by an acute onset of liver failure in response to an acute hepatic insult. Of note, although ACLF has received different operating definitions, every definition recognises that ACLF is a distinct clinical entity. This article provides an updated overview of the distinctive features of ACLF according to the definitions used to characterise it. In addition, we discuss future directions for research aimed at identifying the hallmarks of ACLF.

Keywords: Decompensated cirrhosis; Organ system failures; Prognostication; ACLF; EASL; APASL; NACSELD.

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Background

The terms "acutely decompensated cirrhosis or acute decompensation of cirrhosis" which characterise patients with cirrhosis who are non-electively admitted to the hospital for recent onset ascites, gastrointestinal haemorrhage, newly developed hepatic encephalopathy, or any combination of these disorders, are universally accepted.[1–6] The term "acute-on-chronic liver failure" (ACLF) has been proposed to define a distinct syndrome which is observed among patients with acutely decompensated chronic liver disease and is characterised by an intense systemic inflammatory response, single- or multiple organ system failures, and high 28-day mortality.[5,6] With the exception of some investigators,[4] most investigators consider ACLF a severe form of acutely decompensated cirrhosis.[5,6] The distinctive features of ACLF have been discussed in several review articles in recent years.[5–11] Since then, new results have been published suggesting the existence of a unique clinical trajectory for patients who are developing ACLF[12,13] and of distinctive molecular features that are associated with ACLF.[14–18] This article provides an updated summary of the current evidence suggesting that ACLF is a distinct clinical entity, according to the operating definitions of this syndrome. In addition, we discuss future directions for research aimed at identifying the hallmarks of ACLF.

Distinctive features of ACLF according to the operating definitions

Table 1 summarises the definitions of ACLF that have been developed by international consortia.[1–4,19]

European definition of ACLF

In 2013, the European Association for the Study of the Liver - Chronic Liver Failure consortium (CLIF-C) developed a definition using the results of the CANONIC study, which was a prospective, observational study conducted in 1,343 European patients non-electively admitted to hospital for acutely decompensated cirrhosis[1] (Table S1). In the European definition, the diagnosis of organ failures is based on the CLIF-C organ failure (CLIF-C OF) scoring system which assesses 6 organ systems (liver, kidney, brain, coagulation, circulation, and respiration)[20] (Table 1). According to this definition, precipitating events can be intrahepatic or extrahepatic, or both. Patients with ACLF have a single kidney failure (ACLF grade 1); a single, non-kidney organ system failure if it is associated with kidney or brain dysfunction (ACLF grade 1); or ≥2 organ failures (ACLF grade 2 or 3) (Table 1). The European definition also defines a population of patients with acutely decompensated cirrhosis without ACLF; this population comprises patients with no organ system failure; those with a single, non-kidney organ system failure without kidney or brain dysfunction; and those with a single organ brain failure who do not have kidney dysfunction (Table 1).

Using this definition in European patients, the prevalence of ACLF was 23% among patients with acutely decompensated cirrhosis at presentation.[1] Patients with ACLF were different from those without ACLF, not only based on the presence of organ system failure(s), but also on mortality rate (33.9% *vs.* 4.7% in patients without ACLF).[1] Other distinctive features of ACLF were younger age; greater

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Key point

There are different operating definitions for ACLF in different geographic regions, although every definition recognises that ACLF is a distinct clinical entity.

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prevalence of certain precipitating events (including proven acute bacterial infection, severe alcoholic hepatitis, variceal haemorrhage with hypovolemic shock, drug-induced encephalopathy).[1,12,13] ACLF was also characterised by a higher prevalence of cases with one precipitating and of cases with ≥2 precipitating events[1,13]; higher model for end-stage liver disease (MELD) score at enrolment and greater prevalence of each of the 5 non-kidney organ system failures.[1] Moreover, the prevalence of severe forms of infection, such as pneumonia, secondary bacterial peritonitis, and infections caused by multidrug-resistant bacteria, was significantly higher among patients with ACLF than among those without.[21] Finally, different responses to therapy may be a hallmark of ACLF. For example, among patients with severe alcoholic hepatitis, the response to prednisolone was negatively correlated with the number of organ system failures at baseline.[22] Among patients with type 1 hepatorenal syndrome, the probability of an improvement in renal function with vasoconstrictor therapy was inversely related to the number of organ system failures at baseline.[23] Of note, findings from the CANONIC study suggesting that the proportion of patients who improved was greater among those who had ACLF grade 1 at presentation than among those who had ACLF grade 3 at presentation[10] may be explained, at least in part, by the fact that responses to therapy depend on the number of organ system failures present at the time of treatment initiation.[24]

The CANONIC study revealed that patients with ACLF had more intense systemic inflammation, indicated by significantly greater white blood-cell counts, and C-reactive protein (CRP) levels.[1] In addition, studies have shown that blood levels of cytokines linked to the cytokine release syndrome, including interleukin (IL)-6, IL-10, IL-8, tumour necrosis factor-α, were higher in patients with ACLF than in those without ACLF.[14,16,25] Metabolomics comparing blood from patients with ACLF to blood from those without ACLF found that ACLF was characterised by an increase in a broad variety of metabolites, some indicating inhibition of mitochondrial ATP production in peripheral tissues[17] while others probably reflected gut dysbiosis.[18] Collectively these findings strongly suggest that ACLF is a distinct entity not only because of its different clinical features but also because of distinct blood molecular features related to its pathophysiology.

Key point

Most definitions consider ACLF as a severe form of acutely decompensated cirrhosis.

Key point

There is evidence that ACLF is the result of a clinical course that is distinct from the course of other forms of acutely decompensated cirrhosis.

Of note, the PREDICT study has provided information on the natural history of patients with acutely decompensated cirrhosis who were free of ACLF at presentation and were followed-up for 3 months[12] (Box 1). Among these patients, the trajectory of those who rapidly developed ACLF was totally distinct from the trajectories of patients who did not develop ACLF within 3 months follow-up (Box 1). These findings suggest that patients who were on the way to developing ACLF were already distinct from other patients with acutely decompensated cirrhosis who followed a different trajectory.

The European criteria of ACLF have been used extensively outside Europe[5] (Table S1). A study using European criteria in a large number of US patients with decompensated cirrhosis admitted to 127 Veteran Affairs hospitals[26] has shown an ACLF prevalence of 26.4%. Patients with ACLF had a higher 28-day mortality rate than those without ACLF (25.5% *vs.* 10.4%). This study also reported distinctive features of ACLF that were not observed in the European population, and therefore were unique to the area (US) or context (Veteran Affairs hospitals): patients with ACLF were older, more frequently male and African American, and more often had cirrhosis unrelated to alcohol or HCV compared to patients without ACLF.

The European criteria have also been used to distinguish ACLF in cohorts of patients with acutely decompensated cirrhosis in Asia (Table S1), including China (where chronic HBV infection is the most common cause of cirrhosis),[27–30] Korea,[31] and India.[32]

North American definition of ACLF

The North American Consortium for the Study of End-stage Liver Disease (NACSELD)'s definition of ACLF is based on the analysis of the NACSELD database that included observational data obtained in 507 North American patients with acutely decompensated cirrhosis non-electively hospitalised for infection[2] (Table 1). The North American definition considers 4 organ systems (circulation, respiration, kidney, brain) and among each of these the most severe form of organ system failure. Indeed, the definition uses standard definitions of shock, the need for mechanical ventilation, the need for renal replacement therapy and West Haven grade III or IV hepatic encephalopathy to diagnose organ system failures (Table 1). Of note, the definition does not include changes in liver function and coagulation. ACLF is defined by the presence of ≥2 extrahepatic organ system failures. A second study by the NACSELD has validated the definition of ACLF in a cohort of 2,675 patients with acutely decompensated cirrhosis related or not to an acute infection.[19] In this study, the prevalence of ACLF was 10% and, not surprisingly, the 30-day mortality rate was significantly higher among patients with ACLF than among those without ACLF (41% *vs.* 7%).[19] When these findings are compared to European results, it appears that the prevalence of ACLF depends on the definition used. Because the NACSELD definition is based on the patients' management (use of mechanical ventilation, RRT, vasopressors), and because medical strategies depend on centres, this definition may induce a bias in the estimation of the burden of the syndrome.

The definition of ACLF by the Chinese Group on the Study of Severe Hepatitis B (COSSH)

The COSSH use a definition for HBV-related ACLF which has been developed in a prospective cohort

Table 1. Definitions of ACLF used by each of the 4 major international consortia.*

Characteristics	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium	North American Consortium for the Study of End-stage Liver Disease (NACSELD)	Chinese Group on the Study of Severe Hepatitis B (COSSH)	Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)
Patients' population to which the definition of ACLF applies	Patients with acutely decompensated cirrhosis,[a] with or without prior episode(s) of decompensation	Patients with acutely decompensated cirrhosis,[a] with or without prior episode(s) of decompensation[a]	Patients with acute decompensation of HBV-related chronic liver disease,[a] with or without cirrhosis	Patients with compensated cirrhosis (diagnosed or undiagnosed) or non-cirrhotic chronic liver disease, who have a first episode of acute liver deterioration due to an acute insult directed to the liver.
Precipitating events	Intrahepatic (alcoholic hepatitis), extrahepatic (infection, gastrointestinal haemorrhage), or both	Intrahepatic, extrahepatic, or both	Intrahepatic (HBV reactivation), extrahepatic (bacterial infection) or both	Intrahepatic
Definition of organ system failures	6 organ systems are considered whose function is assessed using the CLIC-C OF score[b]	4 organ systems are considered (see below)	6 organ systems are considered whose function is assessed using the CLIC-C OF score[b]	Only the liver and eventually the brain are considered; other extrahe patic organ system failures may sub sequently develop but are not included in the definition (see below)
Criteria of organ system failures used to define ACLF	Liver: Total bilirubin ≥12 mg/dl; Kidney: Creatinine ≥2 mg/dl or use of renal replacement therapy; Coagulation: INR ≥2.5; Brain: HE Grade 3–4 in the West Haven classification or use of mechanical ventilation because of HE; Circulation: Use of vasopressors including terlipressin; Lung: PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214, or use of mechanical ventilation for reason other than HE	Kidney: Use of dialysis or other form of renal replacement therapy; Brain: HE Grade 3–4 in the West Haven classification; Circulation: Shock defined by MAP <60 mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output; Lung: Use of mechanical ventilation	Same criteria as those used by the EASL-CLIF Consortium	Liver: Total bilirubin levels ≥5 mg/dl Brain: clinical HE
Criteria for the presence of ACLF and ACLF stratification	ACLF is divided into 3 grades of increasing severity. - ACLF grade 1 includes 3 subgroups: (1) patients with single kidney failure (2) patients with single liver, coagulation, circulatory or lung failure that is associated with either kidney dysfunction, brain dysfunction,[c] or both; (3) patients with single brain failure and kidney dysfunction;[c] - ACLF grade 2 includes patients with 2 organ failures; - ACLF grade 3 includes patients with 3 organ failures or more had ACLF grade 3	Patients are stratified according to the number of organ failures 2, 3, or all 4 organ failures	ACLF is divided into 3 grades of increasing severity. - ACLF grade 1 includes 4 subgroups: (1) patients with single kidney failure; (2) patients with single liver failure and either INR ≥1.5, kidney dysfunction, brain dysfunction,[c] or any combination of these alterations; (3) patients with single type of failure of the coagulation, circulatory or respiratory systems and either kidney dysfunction, brain dysfunction,[c] or both; (4) patients with cerebral failure alone plus kidney dysfunction; - ACLF grade 2 includes patients with 2 organ failures - ACLF grade 3 includes patients with 3 organ failures or more	Acute hepatic insult manifesting as jaundice (total bilirubin levels of 5 mg/dl or more) and coagulopathy (INR ≥1.5, or prothrombin activity <40%) complicated within 4 weeks by clinical ascites, HE, or both. The severity of ACLF is assessed using the AARC score.[d] The grading system, defines Grade 1 by scores of 5–7, Grade 2 by scores 8–10 and Grade 3 for 11–15.

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Table 1. (*continued*)

Characteristics	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium	North American Consortium for the Study of End-stage Liver Disease (NACSELD)	Chinese Group on the Study of Severe Hepatitis B (COSSH)	Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)
Criteria for the absence of ACLF	(1) Patients with no organ system failure (2) Patients with single failure (affecting any of the following: liver, coagulation, circulation, respiration) who do not have kidney or brain dysfunction; (3) Patients with single cerebral failure who do not have kidney dysfunction	(1) None of the 4 organ system failures used to define ACLF (2) Presence of a single organ system failure	(1) Patients with no organ system failure (2) Patients with single liver failure and INR <1.5, who do not have kidney or brain dysfunction; (3) Patients with single failure (affecting any of the following: coagulation, circulation, respiration) who do not have kidney or brain dysfunction; (4) Patients with single cerebral failure who do not have kidney dysfunction	Presence of acutely decompensated cirrhosis[a]
Short-term mortality rate of ACLF	By 28 days: Grade 1: 20% Grade 2: 30% Grade 3: 80%	By 30 days: 2 organ failures: 49% 3 organ failures: 64% 4 organ failures: 77%	By 28 days: Grade 1: 23% Grade 2: 61% Grade 3: 93%	By 30 days: Grade 1: 13% Grade 2: 45% Grade 3: 86%
Short-term mortality rate in the absence of ACLF	By 28 days: 4.7%	By 30 days: 7%	By 28 days: 4%	By 30 days: 20%:

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy; INR, international normalised ratio; MAP, mean arterial pressure.
*Adapted from refs. 5 and 6.
[a]Acute decompensation is defined by recent onset ascites, gastrointestinal haemorrhage, newly developed HE, or any combination of these disorders, as a cause of nonelective admission to the hospital. In addition, the EASL-CLIF, NACSELD, and COSSH definitions, but not the AARC definition, include bacterial infection as a feature of acute decompensation.
[b]The EASL-CLIF Consortium diagnoses organ system failures by using the CLIF-C OF score. This score includes sub-scores ranging from 1 to 3 for each of 6 components (liver, kidneys, brain, coagulation, circulation, and lungs), with higher scores indicating more severe organ system impairment. Aggregated scores range from 6 to 18 and provide information on overall severity.[20]
[c]Kidney dysfunction is defined by serum creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl and brain dysfunction by grade 1 or grade 2 HE.
[d]The AARC score includes sub-scores ranging from 1 to 3 for each of 5 components (total bilirubin, hepatic encephalopathy grade, INR, creatinine levels, blood lactate levels). Aggregated scores range from 5 to 15, with higher scores indicating more severe ACLF.[4]

of 1,202 Chinese patients with acutely decompensated HBV-related chronic liver disease (with or without cirrhosis)[3] (Table 1; Table S1). The Chinese investigators use the CLIF-C OF scoring system for the diagnosis of organ system failures and distinguish 3 grades of ACLF, very similar to those defined by the European investigators. However, ACLF grade 1 in the Chinese classification includes an additional subgroup comprising patients with single liver failure who have an international normalised ratio (INR) of ≥1.5 (Table 1).

When the Chinese definition was applied to patients with acutely decompensated HBV-related cirrhosis, the prevalence of ACLF was 30.2%. Patients with ACLF were distinct from those without ACLF based on a higher 28-day mortality rate (52.1% *vs.* 4.5%).[3] Patients with ACLF differed significantly from those without ACLF as follows: they were younger; had a higher MELD score, transaminase levels, white blood-cell count and CRP levels; a greater prevalence of bacterial infection as a precipitating event (combined with HBV-flare or acting as a single precipitating event); and a greater prevalence of liver failure, coagulation failure, brain failure, and respiratory failure.[3] Kidney and brain dysfunctions were more prevalent in patients with ACLF. Although the European and Chinese definitions of ACLF were very similar, the clinical phenotypes of patients with ACLF differed between the continents, because of the higher prevalence of intrahepatic insults as a trigger of ACLF in China relative to Europe.

Definition of ACLF by the Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)

Based on expert opinion, APASL published a definition of ACLF in 2009[33] which was subsequently updated in 2014[34] and 2019.[4] The last update used the results of an internal review of the AARC database, which at that time had collected data on 5,228 patients. The AARC definition markedly differs from the definitions developed by other consortia (Table 1). Indeed, the only precipitating events considered by the AARC definition are primary intrahepatic insults.[4] The investigators of the AARC consider extrahepatic disorders, such as bacterial infections or variceal haemorrhage as complications, but not triggers, of ACLF.[4] Moreover, the AARC definition encompasses patients with compensated cirrhosis (diagnosed or undiagnosed) and those with non-cirrhotic chronic liver disease, who have a first episode of acute liver deterioration due to an acute insult directed to the liver. The acute hepatic insult is defined by jaundice (total bilirubin levels of ≥5 mg/dl) and coagulopathy (INR of ≥1.5, or prothrombin activity of less than 40%) complicated within 4 weeks by clinical ascites, hepatic encephalopathy, or both.[4] The "Asia Pacific ACLF" is reversible in 50% of cases and the mortality rate at 1 month is 30%.

Box 1. The 3 groups of patients with acutely decompensated cirrhosis without ACLF, identified according to their respective clinical course.*

1. Patients with pre-ACLF, are those who develop ACLF and have 3-month and 1-year mortality rates of 53.7% and 67.4%, respectively.
2. Patients with unstable decompensated cirrhosis are those who require ≥1 readmission but not developing ACLF and had 21.0% and 35.6% mortality rates.
3. Patients with stable decompensated cirrhosis are those who are neither readmitted, nor develop ACLF and show a 1-year mortality of only 9.5%.

*The 3 groups have been identified by analysing the results of the PREDICT study.[12] ACLF, acute-on-chronic liver failure.

The experts of the AARC consider ACLF to be totally distinct from acutely decompensated cirrhosis.[4] Indeed, for Asia Pacific investigators, acutely decompensated cirrhosis develops in patients with cirrhosis, with or without prior decompensation.[4] The presentation is either hepatic (jaundice, ascites, hepatic encephalopathy) or extrahepatic (variceal haemorrhage, acute kidney injury or sepsis), and the time from insult to presentation is up to 3 months. Ascites, hepatic encephalopathy and variceal haemorrhage may precede jaundice. Serum bilirubin is below 5 mg/dl at presentation. According to the AARC criteria, acutely decompensated cirrhosis is associated with an estimated 1-month mortality rate of 20%.[4] One of the statements in the last document updating the Asian Pacific definition of ACLF was that distinctive features between presentations of acutely decompensated cirrhosis and ACLF need to be studied by expanding the AARC database.[4]

Key point

ACLF also has characteristic molecular features.

ACLF prevalence according to the definition used

The prevalence of ACLF differs across the studies, depending on the definition used.[5,6] For example, a study using the European and North American definitions in 72,316 American patients with decompensated cirrhosis, has shown that the prevalence of ACLF was 26.4% with the European criteria and 9.8% with the North American definition.[26] Another study performed in 80,383 American patients with decompensated cirrhosis has shown that the incidence rate of newly developed ACLF was 20.1 cases per 1,000 person-years (95% CI 19.5–20.6) with the European criteria and 5.7 per 1,000 person-years (95% CI 5.4–6.0) with the Asia Pacific criteria.[35]

Prognostication of patients with ACLF

Because ACLF is a distinct clinical entity and because patients with ACLF may be considered for urgent liver transplantation, prognostic scores have been developed by different consortia. An ideal survival model

Key point

Future research should aim to improve prognostication and identify new therapies.

should be based only on objective continuous variables without a "floor" or "ceiling" effect. It is important to emphasise that the organ failure models that are currently used for diagnosis are strictly speaking prognostic models. Outcome in patients with ACLF is related to severity of liver disease as well as severity and numbers of extrahepatic organ failures and the interaction between the two. The AARC score developed by APASL utilises 5 variables at baseline: serum total bilirubin, creatinine, serum lactate, INR and hepatic encephalopathy. The 'c' statistic in derivation and validation cohorts was 0.80 and 0.78, respectively. The AARC-ACLF score ranges from 5–15 (similar to the Child-Pugh score) and was found to be superior to MELD and CLIF-sequential organ failure assessment scores in predicting mortality in their cohort.[36] Of note, there is a subjective element in the determination of hepatic encephalopathy. In addition, there is a ceiling effect with the AARC-ACLF score. For example, patients with serum lactate of 2.5 or 10 mmol/L, and patients with serum creatinine of 1.6 mg/dl or 4.0 mg/dl are given the same score, though it is almost certain that patients with the higher serum lactate and higher serum creatinine levels will do less well.

The NACSELD organ failure score has the advantage of simplicity. However, the criteria used are representative of advanced circulatory, renal, brain and ventilatory failure. The NACSELD organ failure score is best used to determine futility of care.[37] The CLIF-C ACLF score has the advantage of capturing both hepatic and extrahepatic organ failures. However, it does have a subjective element in the scoring of hepatic encephalopathy, recognising that even experienced clinicians find it difficult to differentiate grade 1 from grade 0 hepatic encephalopathy. The measures of serum bilirubin, INR, and serum creatinine are all associated with a ceiling effect. For example, a patient with serum bilirubin of 25 mg/dl is considered to have the same prognosis as a patient with serum bilirubin of 12 mg/dl; and a patient with an INR of 4 the same as a patient with INR of 2.5. Because of the subjective variability in determining which patient should be placed on vasopressors, a patient with a mean arterial pressure of 70 mm Hg on vasopressors is given a higher score indicative of greater risk of dying than a patient with unrecordable pressures who is near death but not on vasopressors. None of the organ failure scores have consistently been associated with a 'c' statistic of ≥0.8 indicative of being an excellent model. Thus, all ACLF models can be considered to be only "clinically useful" and require improvement using only objective, verifiable and continuous variables. Serial assessment of scores at 3–7 days may be used to determine which patients require early liver transplantation, and in whom further treatment is futile.[24]

Future directions

The ACLF concept was first described by Jalan and Williams based on the clinical observation that insertion of a transjugular intrahepatic portosystemic shunt in 4 patients with uncontrolled variceal bleeding led to the development of a syndrome that resembled acute liver failure with severe intracranial hypertension. Thus, the term acute-on-chronic liver failure was used. The potential for reversibility was also considered part of ACLF.[38] The current definitions do not recognise the importance of either raised intracranial pressure (which is the pathophysiologic basis of brain dysfunction in acute liver failure) or potential for reversibility. Therefore, every patient with cirrhosis who dies of liver failure and has multiple organ failure potentially meets the criteria for ACLF. A critical future direction is that ACLF needs to be defined based on a set of signs and symptoms, definite pathophysiology, confirmatory tests, and specific interventions. Other research priorities are summarised in Box 2.

Because ACLF is a life-threatening complication, preventing its development is of the utmost importance. Until now, only the use of intravenous albumin combined with large-spectrum antibiotics has been shown to prevent the development of hepatorenal syndrome (an acute kidney injury which is specific to cirrhosis and a form of ACLF) among patients with spontaneous bacterial peritonitis.[39] Recently, results of the PREDICT study, a prospective observational multicentre, European study conducted in 1,071 patients non-electively admitted for acutely decompensated cirrhosis without ACLF, revealed that these patients could be divided into 3 distinct groups according to their short-term clinical course[12] (Box 1). As mentioned earlier, one of these groups (the pre-ACLF group) included patients who rapidly developed ACLF. However, investigators of the PREDICT study were disappointed because, although there were clear between-group differences (in particular, a more intense systemic inflammation) at enrolment, they failed to identify accurate clinical and biological markers able to predict the onset of ACLF[12]; findings which indicate that future research should address this unmet medical need.

It is critical to have good experimental models of ACLF in order to explore its pathogenesis and potential treatment. Several published models have aimed to combine chronic liver injury (using chronic

carbon tetrachloride or bile-duct ligation), acute injury/inflammation (injection of carbon tetrachloride, lipopolysaccharide), and induction of bacterial infection.[40,41] These models recapitulate some but not all features of ACLF. There is an urgent need to develop a model(s) that can recapitulate more features of ACLF, including precipitating events, sepsis, and multi-organ failure.

The pathogenesis of ACLF needs to be better understood in order to identify therapeutic targets. Hepatocyte damage occurs in ACLF, but damaged hepatocytes cannot be efficiently regenerated.[40] Hepatic and systemic inflammation accelerate ACLF and could be important therapeutic targets,[11] while bacterial infection is a major cause of mortality in ACLF.[42] Gut dysbiosis has also been implicated in the progression of ACLF.[18,43] All of these factors may contribute to the pathogenesis of ACLF; hence a combination therapy or a therapeutic option that targets multiple aspects should be explored in preclinical models and clinical trials. Statins have beneficial effects on the intrahepatic circulation and decrease portal hypertension. Rifaximin may prevent bacterial translocation in patients with cirrhosis by modulating the gut microbiome. A combination of rifaximin and simvastatin (NCT03780673), and atorvastatin alone (NCT04072601) are currently being studied as potential therapies to prevent the development of ACLF. IL-22 has been found to promote hepatocyte survival and regeneration, as well as control of bacterial infection, in a preclinical model of ACLF.[40] IL-22 also protects against acute kidney injury[44] and improves gut dysbiosis,[45] and may be of potential benefit in the management of ACLF. A recent open-label, cohort, dose-escalation phase IIa trial to assess the safety and efficacy of IL-22 in patients with alcohol-related ACLF (alcoholic hepatitis) reported promising results with improved clinical manifestations,[46] supporting the need for a randomised placebo-controlled trial to evaluate the efficacy of IL-22Fc in alcohol-related ACLF and maybe in ACLF caused by other aetiologies.

Box 2. Future directions.

- Develop better animal models of ACLF to study pathophysiology and identify therapeutic targets
- Prospective data collection to arrive at uniform definition of ACLF that is acceptable worldwide
- Standardisation of management protocols for investigation and treatment of precipitating events
- Biomarkers to diagnose chronic liver disease and ACLF sub-types
- Uniform criteria to define need and type of support for failing organs
- Development of more accurate prognostic scores
- Role of liver assist devices
- Role of hepatic regenerative therapies
- Conduct more clinical trials for the treatment of ACLF

Conclusions

ACLF is a recently recognised entity in which patients with chronic liver disease, with or without cirrhosis, develop hepatic and extrahepatic organ failure. It is associated with high mortality risk irrespective of the operating definition used. The pathophysiology of ACLF is still unclear but very likely involves inflammation. Specific diagnostic tests reflecting the pathophysiology of ACLF are urgently required. Because ACLF is a potentially reversible condition, there may be a role for bio-artificial liver support, while selected patients may benefit from liver transplantation.

Abbreviations

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; COSSH, Chinese Group on the Study of Severe Hepatitis; CRP, C-reactive protein; CLIF-C, European Association for the Study of the Liver – Chronic Liver Failure Consortium; IL-, interleukin; INR, international normalised ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NACSELD, North American Consortium for the Study of End-stage Liver Disease; OF, organ failure.

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Conflict of interests

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

Authors' contributions

All authors participated in drafting of the manuscript and were involved in critical revision of the manuscript for important intellectual content.

Supplementary data

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